PREPARATIVE ORGANIC CHEMISTRY

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PREPARATIVE ORGANIC CHEMISTRY

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Foreword to the 4th Edition

The first edition of "Organisch-chemische Experimentierkunst" by Professor Conrad Weygand was published some 30 years ago. He divided the book into three parts, corresponding to the natural course of an organic-chemical experiment, namely, construction of an apparatus, performance of the chemical reaction, and finally analysis and physical characterization of the product.

For arrangement of the actual chemical part, dealing with reactions, Weygand chose a particularly clear and satisfying division, which was then new, based on the formation of the various carbon bonds. The first section of this part contained the reactions on the pre-formed carbon skeleton, the second contained the formation of C—C bonds, the third the cleavage of C—C bonds, and the last the rearrangements of carbon compounds. This "Weygand key" has since been taken over as organizational principle in the Theilheimer series. Division according to reaction type has also been adopted recently in textbooks, for example, in "Cahiers de Synthèse Organique — Méthodes et Tableaux d'Application".

After the tragic death of Professor Weygand in April 1945 preparation of the second edition was continued by his pupil and collaborator, Dr. Theo Siebenmark.

The third edition, which appeared in 1964, was made possible by a number of specialist chemists, mostly colleagues at the Institut für Organische Chemie der Deutschen Akademie der Wissenschaften zu Berlin, who declared themselves ready to revise the book completely. The subdivision into "Materials and Operations", "Reactions", and "Chemical and Physical Characterization" was retained in that edition.

The present fourth edition consists only of the previous second part, "Reactions". Except for the chapters "Preparative Work with Small Quantities" and "Solvents and Gases" (a new section) which are retained as Appendices, the previous first part, "Materials and Operations" has been omitted since in the meanwhile monographs have appeared that treat this subject in greater detail. The previous third part, "Chemical and Physical Characterization", has also not been retained; it was too brief to provide a satisfactory guide and we agree with various critics of the third edition that it is better to consult detailed specialist books for chemical and physical analysis.

The fourth edition has been expanded by a chapter on the "Formation of Carbon-Phosphorus Bonds" and by another on the "Formation of Carbon-Deuterium Bonds". The chapter on "Alteration of Nitrogen Groups in Carbon-Nitrogen Compounds" has been substantially expanded, but the remaining parts of the book have merely been completed by inclusion of preparative processes discovered in recent years.

As the contributors handled their chapters more or less contemporaneously, the literature throughout this edition has been taken into account up to 1967.

I am most grateful to the contributors for their rapid and conscientious revision or re-working of their chapters.

Berlin, 1968 G. Hilgetag

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Part A. Reactions on the Intact Carbon Skeleton

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Part D. Rearrangement of Carbon Compounds

Contents

Introduction: Organization of the Material

The very large number of preparatively useful reactions of organic chemistry can be classified systematically and clearly by using the common characteristic of all organic compounds, namely, the carbon skeleton. The following cases can then be differentiated:

1. The carbon skeleton is preformed in the starting material.

   Examples: benozoic acid from toluene; acetaldehyde from ethanol.

2. The carbon skeleton is built up from two or more molecules with formation of a carbon–carbon bond.

   Examples: acetophenone from benzene and acetic anhydride (2 molecules); Michler's ketone from dimethylaniline and phosgene (3 molecules); caoutchouc from isoprene (many molecules).

3. The carbon skeleton is a residue obtained by partial degradation of a structure containing more carbon atoms.

   Examples: Enanthol from castor oil; phthalic acid from naphthalene.

4. The carbon skeleton is obtained from a pre-existing one by rearrangement.

   Example: pinacolin from pinacone.

We call these four types of reaction:

1. Alteration to the molecule without change of the carbon skeleton.
2. Construction of a carbon skeleton.
3. Degradation of a carbon skeleton.
4. Rearrangement of a carbon skeleton.

Ring closures do not require a position of their own. They usually result from reactions analogous to those between two reactants and are therefore treated together with them. Ring closures can also be assigned to four fundamental types:

1. Formation of phthalic anhydride from phthalic acid does not change any part of the carbon skeleton, any more than does formation of pyrroles from 1,4-diketones and ammonia.

2. Formation of mesitylene from acetone corresponds to that of mesityl oxide from acetone.
3. Formation of cyclopentanone from calcium adipate corresponds exactly to that of acetone from calcium acetate.
4. Formation of isobornyl chloride from camphene hydrochloride corresponds to that of pinacolin from pinacone.

A very satisfactory picture emerges if one considers the typical chemical processes that are brought together by this classification. Into group 1 (alteration) fall all those reactions such as hydrogenation, chlorination, nitration, oxidation, reduction, etc., that previous custom has always systematized together. The second group (construction) comprises all those that lead to expansion of the carbon skeleton by C—C linkage, including addition to multiple bonds, condensations (*e.g.*, Wurtz–Fittig reactions, Friedel–Crafts syntheses, Mannich reactions), and polymerization. Separation of group 3 (degradation) from group 4 (rearrangement) is new, but is clearly organic in sense.

It is true that, for instance, one does not find under the keyword 'aldehyde' the preparation of benzaldehyde (*a*) from toluene by way of benzyl chloride or benzaldehyde dichloride, (*b*) from benzene and hydrogen cyanide–hydrogen chloride (Gattermann–Koch) or from bromobenzene by way of phenylmagnesium bromide and formic ester (Grignard), and (*c*) from stilbene and ozone or from 1,2-diphenyl-1,2-ethanediol and lead tetraacetate; but such a collection of syntheses is to be found in the systematic textbooks and reference works of organic chemistry, and the compass of the large reactions remains nevertheless substantially intact in our treatment.

Subdivision of the very large first group (alteration) arises naturally from the fact one has to consider only the bonding of carbon to hydrogen, oxygen, nitrogen, sulfur, phosphorus, and metals; but formation of a carbon–carbon multiple bond is also included in this group. The resulting sections of group 1 are then further subdivided between two types of reaction that can be classified as addition and exchange. This subdivision into addition and exchange recations is also effected in group 2.

PART A

Reactions on the Intact Carbon Skeleton

CHAPTER 1

Formation of Carbon–Hydrogen Bonds

Compiled by
*Ch. Bischoff, P.-G. Dietrich, E. Höft, and D. Murawski**

1.1. Formation of the carbon–hydrogen by addition

Industrial hydrogenation of multiple C—C bonds is nowadays effected to a preponderating extent by catalytic methods. Because of the many variations possible they have also become a regular part of preparative and analytical work in the laboratory. Nevertheless, particularly in chemical research, other reducing agents have established their place, and the more so because they supplement catalytic procedures in the most satisfactory manner and even exceed them in selectivity.

For instance, hydrogenation of an acetylenic bond on a suitable catalyst gives almost exclusively *cis*-ethylenic compounds, whereas the corresponding *trans*-compounds can be obtained by reduction with complex metallic hydrides or with sodium in liquid ammonia.[1] Similar results are found for addition of hydrogen to unsaturated compounds containing fused ring systems.[2] Reduction of C=O groups is carried out in the laboratory almost exclusively by chemical reducing agents.

I. Addition of hydrogen to C=C bonds and aromatic systems

1. Chemical reducing agents

The most important processes for addition of hydrogen to the ethylenic bond and to aromatic and heterocyclic systems comprise reduction by non-noble metals in suitable solvents. All other reducing agents, such as tin(II) chloride, hydrogen iodide, and even complex metal hydrides, are much less important for reduction of multiple C—C bonds.

Although the reducing action of the first-named systems was earlier ascribed to so-called "nascent hydrogen," it is now known, particularly through the work of Willstätter,[3] Hückel,[4]

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* We are grateful to Dr. R. Philippson for extensive preliminary work on this Section.

[1] L. Crombie, *Quart. Rev. (London)*, **6**, 128 (1952); K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, **63**, (a) 216, (b) 2683 (1941).

[2] W. S. Johnson *et al.*, *J. Amer. Chem. Soc.*, (a) **78**, 6302 (1956); (b) **82**, 3409 (1960); (c) R. H. Jaeger, *Tetrahedron*, **2**, 326 (1958).

[3] R. Willstätter, F. Seitz, and E. Bumm, *Ber. Deut. Chem. Ges.*, **61**, 871 (1928).

[4] W. Hückel and H. Bretschneider, *Ann. Chem.*, **540**, 157 (1939).

and Birch[5] and their collaborators, that easy electron-transfer from the metal to the electrophilic system is the prerequisite for this reduction and that discharge of a proton by the resulting carbanion follows as a secondary reaction. Variously high reduction potentials are achieved according to the choice of metal, solvent, and pH, thus affording the possibility of reducing compounds of variously strong electron affinity.

However, Hückel[6] returned to the "nascent hydrogen" hypothesis in order to explain the reduction of isolated aromatic nuclei by the system alkali-metal–liquid ammonia–alcohol.[5,7] Since this system contains no metal surface to catalyse the recombination of H atoms ($2H \rightarrow H_2$), it may be the resulting concentration of free hydrogen atoms that triggers the primary process.

a. Reduction by non-noble metals

i, Reduction by sodium and alcohols

Although isolated double bonds and monocyclic aromatic compounds are usually not attacked by sodium and alcohols, it is fairly easy to reduce activated double bonds such as those in styrene or cinnamic acid. Thus, in compounds of the type $Ar—CH{=}CH—[CH_2]_n—CH{=}CH—R$ it is possible to hydrogenate only the double bond that is conjugated to the nucleus.[8] Conjugated dienes are occasionally converted into olefins by addition of two H atoms; condensed aromatic systems are also partially hydrogenated, as described by Bamberger. For instance, anthracene and its derivatives afford the 9,10-dihydro compounds,[9,10] and phenanthrene and acenaphthene give tetrahydro derivatives;[9] naphthalene gives dihydronaphthalene in ethanol but tetrahydronaphthalene in pentyl alcohol. Hydrogenation of nitrogen-containing heterocycles is fairly successful,[11] and naphthols and naphthylamines are reduced to the tretrahydro stage still more easily. It is interesting that attack is on the substituted ring of β-naphthylamine,[12] but mainly on the unsubstituted ring of α-naphthylamine. Cyclic ketones can be prepared from naphthyl ethers in good yield[13] if the reaction is carried only to the dihydro stage and the resulting enol ethers are then hydrolysed.

The technique of such reductions with sodium and alcohols is the same as that for Bouveault–Blanc reduction of esters (see page 76). Ethanol is usually used, although higher alcohols are preferable because of their higher boiling points. Large quantities of vapor are usually evolved and can badly overload condensers of the normal type, so it is advantageous to use condensers with large bulbs which can accomodate large amounts of condensate without too greatly decreasing the cross-section of the tube. Use of metal condensers is

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[5] A. J. Birch, *Quart. Rev.* (*London*), **4**, 69 (1950).

[6] W. Hückel, B. Graf, and D. Münkner, *Ann. Chem.*, **614**, 47 (1958).

[7] (a) C. B. Wooster, U.S. Pat. 2.182.242; *Chem. Abstr.*, **34**, 1993 (1940); (b) J. P. Wibaut and F. A. Haak, *Rec. Trav. Chim.*, **67**, 85 (1948).

[8] B. Loev and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 1180 (1956).

[9] E. Bamberger and W. Lodter, *Ber. Deut. Chem. Ges.*, **20**, 3077 (1887).

[10] G. H. Daub and W. C. Doyle, *J. Amer. Chem. Soc.*, **74**, 4449 (1952).

[11] D. Papa, E. Schwenk, and E. Klingsberg, *J. Amer. Chem. Soc.*, **73**, 253 (1951); O. Neunhoeffer and H. Ulrich, *Chem. Ber.*, **88**, 1123 (1955).

[12] E. B. H. Waser and H. Möllering, *Org. Syn.*, **9**, 84 (1929).

[13] J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, **1949**, 1855; M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson, and E. A. Bowler, *J. Amer. Chem. Soc.*, **72**, 3704 (1950).

often recommended. For safety the reaction vessel should be placed on a sand-bath and not on a water-bath or Babo funnel.

Ladenburg's preparation of **piperidine** from pyridine[14] will be described as an example: Pyridine (20 g) in anhydrous ethanol (150 g) is placed in a round-bottomed flask under a reflux condenser and warmed on the water-bath. Then sodium pieces (75 g) are added not too slowly. As soon as the reaction slackens or sodium ethoxide separates, more ethanol is added and the reaction is brought to conclusion as fast as possible. When all the sodium has been consumed, the mixture is allowed to cool, treated with an equal volume of water, and distilled in steam. The distillate is neutralized with hydrochloric acid and evaporated to dryness. Piperidine hydrochloride is obtained as residue in almost quantitative yield and can be recrystallized from ethanol.

ii, Reduction with sodium amalgam

The reducing action of sodium amalgam is similar to that of sodium and alcohol. Double bonds are resistant when isolated but reactive when conjugated. According to Kuhn and Hoffer,[15] polyenes always add the hydrogen at the ends of the conjugated system.

The necessary conditions of reduction seem in general to be somewhat milder. Thus the reagent is inferior to the combination of sodium and alcohol for hydrogenation of cyclic systems, but now selective reduction of unsaturated carboxylic acids containing a furan[16] or a thiophen ring[17] is possible. Anthracene and its derivatives,[18] acridine,[19] and also resorcinol are converted into dihydro derivatives; according to the conditions, terephthalic acid gives di- or tetra-hydroterephthalic acid or *p*-toluic acid.[20] Sodium amalgam has been repeatedly recommended for selective hydrogenation of a C=C bond in α,β-unsaturated nitriles,[21] ketones,[22] lactams,[23] and carboxylic acids.[24]

The amalgam can be prepared according to a prescription in *Organic Syntheses*.[25] It is used in water, in anhydrous ethanol,[23] in alkali hydroxide solutions,[24] or even in glacial acetic acid.[22] It is sometimes advisable to buffer the resulting sodium hydroxide by adding CO_2. The process is barely practicable for reduction of large quantities of unsaturated compounds. If one considers the necessity to regenerate the mercury and the inconvenience of work with large amounts of mercury, it is evident that catalytic methods will often be preferable.

For the preparation of **3-phenylpropionic acid** (hydrocinnamic acid), as described by Henle,[26] cinnamic acid (15 g) is dissolved in 5% sodium hydroxide solution (75 ml) with warming, the solution is cooled, and freshly prepared 2.5% sodium amalgam is added slowly

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[14] A. Ladenburg, *Ann. Chem.*, **247**, 51 (1888).

[15] R. Kuhn and M. Hoffer, *Ber. Deut. Chem. Ges.*, **65**, 170 (1932).

[16] A. S. Carter, *J. Amer. Chem. Soc.*, **50**, 2303 (1928).

[17] L. J. Owen and F. F. Nord, *J. Org. Chem.*, **15**, 988 (1950).

[18] E. L. May and E. Mosettig, *J. Amer. Chem. Soc.*, **70**, 688, 1077 (1948).

[19] R. R. Burtner and J. W. Cusic, *J. Amer. Chem. Soc.*, **65**, 1583 (1943).

[20] R. Willstätter, F. Seitz, and E. Bumm, *Ber. Deut. Chem. Ges.*, **61**, 871 (1928).

[21] S. Widequist, *Ark. Kemi*, **26 A**, No. 16, 10 (1948).

[22] J. F. J. Dippy and R. H. Lewis, *Rec. Trav. Chim.*, **56**, 1000 (1937); A. A. Challis and G. R. Clemo, *J. Chem. Soc.*, **1947**, 1692.

[23] G. R. Clemo and L. K. Mishra, *J. Chem. Soc.*, **1953**, 192.

[24] W. E. Bachmann and R. E. Holmen, *J. Amer. Chem. Soc.*, **73**, 3660 (1951).

[25] W. R. Brasen and C. R. Hauser, *Org. Syn.*, **34**, 56 (1954).

[26] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Walter de Gruyter and Co., Berlin, 1947.

in small pieces with efficient stirring. After consumption of about 300–350 g of alloy, a sample of the solution is treated with hydrochloric acid and then again with sodium hydroxide solution. If this no longer decolorizes permanganate, the whole liquid is decanted from the mercury, which is then washed with a little water. The solution and washings are neutralized with hydrochloric acid, filtered again if necessary, treated with concentrated hydrochloric acid (15 ml), and extracted with ether. The extract is dried with sodium sulfate and the ether is distilled off. The residual oil solidifies when rubbed. The yield amounts to about 12 g, corresponding to 79%. Recrystallization from not too little warm water gives the pure acid, which melts at 48.7°.

iii, Reduction with aluminum amalgam

A number of sensitive substances can be advantageously reduced by aluminum amalgam since the reaction medium can in this case easily be kept exactly neutral. It is often possible to reduce only one of the conjugated double bonds of fulvenes and indene and fluorene derivatives of analogous structure.[27] The process is particularly suitable for hydrogenation of unsaturated esters[28,29] that might be hydrolysed in alkaline solution.

Aluminum amalgam, prepared by Wislicenus' method,[28] and moist ether are usually used, being allowed to react with the unsaturated compound for 1–2 days with occasional addition of a little water.

Benzylindene. 1-Benzylideneindene (5 g) is dissolved in ether and treated, until decolorized, with freshly prepared aluminum amalgam (15 g) with occasional addition of a little water. This requires 6–24 h. The mixture is filtered, the residue is well washed with ether, the solution is dried and freed from ether by distillation, and the residue is fractionated. The resulting benzylindene distils between 183° and 185° at 13 mm.

Benzylidenefluorene, furfurylidenefluorene, and other derivatives can be similarly reduced.[27]

iv, Reduction by solutions of alkali or alkaline-earth metals in liquid ammonia

Solutions of alkali metals in liquid ammonia constitute strongly nucleophilic reagents, but nevertheless their efficiency for reduction of unsaturated hydrocarbons barely surpasses that of the systems described above.

Apart from exceptional cases,[30] isolated double bonds and monocyclic aromatic systems are not attacked. Conjugated double bonds,[4,31] however, aryl-substituted ethylenes,[32] and polycyclic aromatic compounds[4,33] can be partially hydrogenated with considerable success. Dimerization or further chain-formation of the starting material often occurs as a side reaction.

An excess of sodium is usually used, at −70° or −33° (carbon dioxide bath or boiling point of ammonia). Ether, tetrahydrofuran, and benzene and its

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[27] J. Thiele *et al.*, *Ann. Chem.*, **347**, 249, 275, 290 (1906).

[28] H. Wislicenus, *J. Prakt. Chem.*, **54**, 18 (1896).

[29] N. A. Milas and D. Fleš, *J. Amer. Chem. Soc.*, **78**, 5903 (1956).

[30] N. A. Nelson and J. C. Wollensak, *J. Amer. Chem. Soc.*, **80**, 6626 (1958).

[31] R. Ya. Levina, V. R. Skvarchenko, V. N. Kosstin, E. G. Treshchova, and A. S. Okunevich, *Sbornik Stateĭ Obshch. Khim., Akad. Nauk SSSR,* **1**, 355 (1953); *Chem. Abstr.*, **49**, 829 (1955).

[32] K. Ziegler, H. Colonius, and O. Schäfer, *Ann. Chem.*, **473**, 36 (1929); C. B. Wooster and J. F. Ryan, *J. Amer. Chem. Soc.*, **56**, 1133 (1934); H. Gilman and J. C. Bailie, *J. Amer. Chem. Soc.*, **65**, 267 (1943); W. F. Erman and T. F. Flautt, *J. Org. Chem.*, **27**, 1526 (1962).

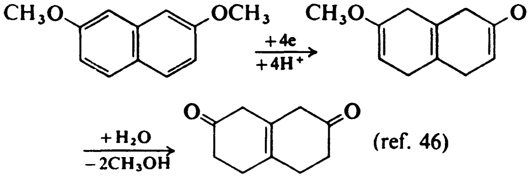
[33] P. Lebeau and M. Picon, *C. R. Hebd. Séances Acad. Sci.*, **158**, 1514 (1914); **173**, 84 (1921); C. B. Wooster and F. B. Smith, *J. Amer. Chem. Soc.*, **53**, 179 (1931).

homologs have been recommended as solvents. Subsequent addition of ammonium salts or alcohols removes the excess of metal and simultaneously protonizes the carbanions that are formed as primary product. Free carboxylic acids react only with difficulty under the above conditions and are advantageously neutralized beforehand with sodium amide. The following directions have been given for preparation of **9,10-dihydro-9-phenanthroic acid**:[34]

9-Phenanthroic acid (5.69 g), sodium amide (1 g), and liquid ammonia (90 ml) are placed in a reaction vessel fitted with a reflux condenser that can be cooled to −70° by alcohol–Dry Ice and with a magnetic stirrer. The mixture is stirred until the sodium amide is wholly dissolved (ca. 4 h) and thereafter freshly cut, small pieces of sodium (1.2 g) are added during 1 h. The dark red mixture is stirred for a further 1.5 h and then slowly decolorized by ethanol (10 ml). The ammonia is then allowed to evaporate, the residue dissolved in water and acidified with hydrochloric acid, and the thick brown oil is extracted in ether (two 25-ml portions). The united extracts are washed with water, dried over anhydrous sodium sulfate, and treated with Norite. Evaporation of the ether yields the dihydro acid of m.p. 122–124°.

Solutions of the more active metals lithium and potassium have been valuable for hydrogenation of C=C bonds of α,β-unsaturated ketones[2a,35,36] and aryl ethers.[37]

A striking improvement in technique was found in the addition of alcohols. This procedure, discovered by Wooster[7a] and developed chiefly by Birch,[38] reduces isolated aromatic rings. Benzene and its homologs are reduced to 1,4-dihydro derivatives,[39] which can be rearranged by $NaNH_2$ in liquid ammonia[40] to the corresponding conjugated dienes and then further transformed into cyclohexene derivatives. Condensed aromatic systems are, of course, also attacked: for instance, 1,4,5,8-tetrahydronaphthalene is obtained from naphthalene[6,39] 3,8-dihydropyrene from pyrene,[41] and hexahydrophenanthrene in 94% yield from tetrahydrophenanthrene;[42] 1-naphthol is converted into 5,8-dihydro-1-naphthol in 97% yield.[43] The method has found particularly wide application for partial hydrogenation of aryl ethers[44] which, without the



(ref. 46)

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[34] H. de Köning *et al.*, *Rec. Trav. Chim.*, **83**, 364 (1964).

[35] G. L. Chetty *et al.*, *Tetrahedron*, **22**, 2311 (1966); R. H. Jäger, *Tetrahedron*, **2**, 326 (1958).

[36] F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, **1958**, 1248; D. H. R. Barton *et al.*, *J. Chem. Soc.*, **1954**, 903; R. E. Schaub and M. J. Weiss, *Chem. & Ind.* (*London*), **1961**, 2003; R. Vilotti and A. Bowers, *Gazz. Chim. Ital.*, **93**, 1695 (1963); P. Westerhof, *Rec. Trav. Chim.*, **83**, 1069 (1964).

[37] A. Sandoval *et al.*, *J. Amer. Chem. Soc.*, **77**, 148 (1955); J. A. Barltrop and N. A. J. Rogers, *J. Chem. Soc.*, **1958**, 2566.

[38] A. J. Birch *et al.*, *J. Chem. Soc.*, **1944**, 430; **1946**, 593; **1951**, 1945.

[39] W. Hückel *et al.*, *Chem. Ber.*, **88**, 388, 346 (1955); C. A. Grob and P. W. Schiess, *Helv. Chim. Acta*, **43**, 1546 (1960).

[40] A. J. Birch, *J. Chem. Soc.*, **1950**, 1551.

[41] O. Neunhoeffer, H. Woggon, and S. Dähne, *Ann. Chem.*, **612**, 98 (1958).

[42] S. Mejer, *Bull. Acad. Polon. Sci.*, *Sér. Sci. Chim.*, **10**, 463 (1962).

[43] C. D. Gutsche and H. H. Peter, *Org. Syn.*, **37**, 80 (1957).

[44] R. Grewe, E. Nolte, and R.-H. Rotzoll, *Chem. Ber.*, **89**, 600 (1956).

addition of alcohol, are usually merely dealkylated; hydrolysis of the 2,5-dihydrogenated enol ethers formed as primary products gives unsaturated cyclic ketones.[38,45] Similar products can be prepared from corresponding aniline derivatives.[47] Aromatic carboxylic acids can also be reduced in the ring, hydrogenation being almost wholly at the 1,4-positions;[48] a convenient synthesis of 1,4-dihydrobenzoic acid is described in *Organic Syntheses*.[49]

The procedure has been variously adapted to advantage. Wooster[7a] and Birch[38, 40] generally add an alcoholic solution of the substance to a solution of sodium in liquid ammonia. Wibaut and Haak[7b] add sodium to a solution or suspension of the substance in liquid ammonia and alcohol. Wilds and Nelson[50] recommend solutions of lithium and add the alcohol last to the reaction medium. Lithium has recently been recommended also by other authors[51] as a powerful reagent. On the other hand, magnesium in ammonia and alcohols is said to be a reducing agent of specific activity.[52]

For the preparation of **1,2-dimethyl-1,4-cyclohexadiene** from *o*-xylene Hückel and Worffel[39] recommend the Birch method:

Apparatus: Reductions in liquid ammonia are carried out in a cylindrical vessel of 1 l capacity and 8 cm diameter. This vessel is fitted with two ground necks at the top to take a dropping funnel and a stirrer, two glass tubes with taps for introduction and removal of ammonia, and a position for insertion of a cold-reading thermometer. Ammonia, pre-dried by soda lime and potassium hydroxide, is introduced with cooling by methanol and solid carbon dioxide and evacuation of the vessel and, whilst in the liquid state, freed from the last traces of moisture by small pieces of sodium.

A mixture of *o*-xylene (54 g) and anhydrous methanol (51 g) is dropped slowly into a solution of sodium (30 g) in liquid ammonia (400 ml) at −70° to −65°, and the whole is stirred until the blue color is discharged. The ammonia is then evaporated, the residue is treated with water, and the hydrocarbon mixture is separated. The dihydro-*o*-xylene can be purified by way of the di- or the tetra-bromide; however, it is advantageous to submit the mixed product once more to reduction; the desired hydrocarbon is then obtained in 91% yield.

A reducing agent similar to the above solutions of metals was found in solid hexaamminecalcium, $Ca(NH_3)_6$. This can be used at room temperature in ethereal suspension, *i.e.*, it avoids the use of liquid ammonia. The unsubstituted ring of 1-methylnaphthalene is hydrogenated specifically by this reagent.[53]

Reviews by Watt[54] and Birch[54] should be consulted for more detailed accounts of reduction by metals in liquid ammonia.

v, Reduction by lithium in organic amines

When compared with the corresponding solutions in ammonia, solutions of lithium in amines appear as stronger but less selective reducing agents.

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[45] S. M. Mukherji and N. K. Bhattacharyya, *J. Amer. Chem. Soc.*, **75**, 4698 (1953); J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, **80**, 6118 (1958).

[46] B. Weinstein and A. Fenselau, *J. Org. Chem.*, **30**, 3209 (1965).

[47] G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).

[48] M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959).

[49] M. E. Kuehne and B. F. Lambert, *Org. Syn.*, **43**, 22 (1963).

[50] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953).

[51] B. A. Lewis and R. A. Raphael, *J. Chem. Soc.*, **1962**, 4263; R. E. Juday *et al.*, *J. Med. Chem.*, **7**, 519 (1964).

[52] P. Markoff and Ch. Iwanoff, *Tetrahedron Lett.*, **1962**, 1139.

[53] H. Boer and P. M. Duinker, *Rec. Trav. Chim.*, **77**, 346 (1958).

[54] G. W. Watt, *Chem. Rev.*, **46**, 316 (1950); A. J. Birch, *Quart. Rev.* (*London*), **4**, 69 (1950).

[55] R. A. Benkeser *et al.*, *J. Amer. Chem. Soc.*, **77**, 3230, 6042 (1955).

Amines are better solvents than ammonia for most organic substances, and their higher boiling points permit higher working temperatures. Thus, on reduction of aromatic compounds, not only is the initial step (1,4-addition) facilitated, but so also are isomerization of the primary product to the conjugated diene and then further reduction to the singly unsaturated dihydroaromatic derivative. In fact, isolation of the dihydro derivative is rarely described when this process is used; on the other hand, 1-ethylcyclohexene is obtained in good yield from ethylbenzene;[55] also, conjugated dienes are converted satisfactorily into sterically homogeneous olefins.[56]

Sometimes even isolated double bonds are attacked,[57,58] wherefore cyclohexane derivatives usually appear as by-products on hydrogenation of aromatic compounds by this method.

The reaction can be effected at low temperature or at the boiling point of the amine. Methylamine or a lower homolog, ethylenediamine,[58] or an alkylaniline[56] is usually used. They often act simultaneously as proton donors, but in other cases ammonium salts must be added after termination of the reaction. In reductions of abietic acid derivatives it was shown that reaction of lithium in ethylamine is milder than in presence of *tert*-pentyl alcohol.[59] A review of these reactions is given by Birch and Smith.[60]

The reduction of phenethyl alcohol to **1-(2-hydroxyethyl)-cyclohexene**[55] will be described as an example: Lithium wire (14 g) and anhydrous ethylamine (500 ml) are placed in a 500-ml three-necked flask fitted with a stirrer, a dropping funnel, and a reflux condenser with dry-ice cooling. Phenethyl alcohol (48.8 g) is added with stirring in 8–10 h. The initial blue color disappears fairly quickly and other color changes occur. All operations are conducted under an atmosphere of nitrogen. At the end of the reaction time, the ecxess of lithium is removed with a tongs, and the mixture is decomposed by cautious addition of ammonium chloride to decoloration. The ethylamine is then distilled off and the residue is treated dropwise with water whilst cooling. The organic phase is removed in ether and dried over magnesium sulfate. Distillation of the ethereal solution affords the 1-(2-hydroxyethyl)-cyclohexene (b.p. 74–75°/2 mm) in 67% yield.

vi, *Reduction with zinc, tin, or aluminum*

It is rare today that reduction of ethylenic compounds by zinc and acids has advantages over catalytic hydrogenation; however, it is still used for selective reduction of steroids,[61,62] unsaturated diketones,[62-64] and ethylenic derivatives containing sensitive functional groups.[65] The normal method is to use zinc

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[56] K. Ziegler *et al., Ann. Chem.*, **528**, 101 (1937); **567**, 1 (1950).

[57] G. Ohloff, H. Farnow, and G. Schade, *Chem. Ber.*, **89**, 1549 (1956); E. J. Corey and E. W. Cantrall, *J. Amer. Chem. Soc.*, **81**, 1745 (1959).

[58] L. Reggel, R. A. Friedel, and I. Wender, *J. Org. Chem.*, **22**, 891 (1957).

[59] A. W. Burgstahler and L. R. Warden, *J. Amer. Chem. Soc.*, **86**, 96 (1964); A. Tahara and O. Hoshino, *Tetrahedron Lett.*, **1966**, 3825.

[60] A. J. Birch and H. Smith, *Quart. Rev. (London)*, **12**, 17 (1958).

[61] L. F. Fieser, S. Rajagopalan, E. Wilson, and M. Tishler, *J. Amer. Chem. Soc.*, **73**, 4133 (1951).

[62] E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler, *J. Amer. Chem. Soc.*, **75**, 3477 (1953).

[63] P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **32**, 1934 (1949); R. Ramassent and A. Rassat, *Bull. Soc. Chim. France*, **1963**, 2214.

[64] H. B. Henbest, M. Smith, and A. Thomas, *J. Chem. Soc.*, **1958**, 3293.

[65] F. Bergel and J. A. Stock, *J. Chem. Soc.*, **1957**, 4563; E. A. Fehnel and M. Carnack, *J. Amer. Chem. Soc.*, **70**, 1813 (1948).

dust in glacial acetic acid or, as described by Kuhn and Winterstein,[66] in pyridine and glacial acetic acid; the advantage of the latter combination, which has been used for mild reduction of polyenes[67] and cyanine dyes, is connected with the presence of small amounts of water or alcohol. Reductions have also been carried out with zinc and mineral acid in aqueous medium, in which case use of coppered zinc dust is recommended. Tin and hydrochloric acid have recently been applied for reduction of isoquinolinium salts.[68]

As example may be chosen the reduction of pyrrole, which can be interrupted relatively successfully at the dihydro stage. Andrews and McElvain[69] give the following variation of the original prescription by Knorr and Rabe:[69]

20% Hydrochloric acid (500 ml) in a not too small flask is cooled (ice-salt) to 0°; zinc dust (200 g) is added with vigorous stirring and then pyrrole (50 g) slowly from a dropping funnel. If the temperature at the beginning of the reaction is above about 10° the reaction becomes so fast as to be uncontrollable. After all the pyrrole has been added, during about 1 h, the mixture is treated with concentrated hydrochloric acid (300 ml), stirred for a further 2 h whilst the temperature is kept between 15° and 25°, removed from the cooling bath, stirred at room temperature for a further 4.5 h, and filtered from unchanged zinc which is then washed with a little water. Alkali is added to the filtrate until the zinc hydroxide is redissolved and the whole is distilled in steam until the distillate is no longer alkaline to litmus. Next, the distillate is acidified with hydrochloric acid and evaporated to dryness on a steam-bath, and the sticky residue is treated with 40% sodium hydroxide solution and extracted twice with ether. These extracts are dried with sodium sulfate and distilled, affording **pyrroline** (28.5 g) which boils between 89° and 92° and gives a crystalline hydrochloride, m.p. 162–163°. The yield thus amounts to 56%, by-products being mainly in the higher-boiling fractions.

Kekulé[70] recommended zinc and alkali hydroxide solutions for preparation of the so-called "nascent hydrogen". Somewhat similarly, Raney nickel alloys in aqueous alkali have been used repeatedly for reductions. The aluminium that goes into solution in these reactions reduces naphthalene and its substitution products,[71] cyclooctatetraene,[72] and in particular 3-arylacrylic acids[73] in good yield.

b. Electrolytic reduction

Electrolytic methods have been applied for reduction of C—C multiple bonds more widely than is generally appreciated. Addition of hydrogen is often accompanied by simultaneous reduction of other functional groups, as when α,β-unsaturated nitro compounds are converted into saturated amines;[74] nevertheless, the method has also been recently used to convert unsaturated into saturated nitriles.[75] Heterocyclic compounds can in many cases be converted into either partially or wholly saturated derivatives. For instance, 1,2,3,4-

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[66] R. Kuhn and A. Winterstein, *Ber. Deut. Chem. Ges.*, **65**, 1737 (1932).

[67] H. I. Kabbe, E. Truscheit, and K. Eiter, *Ann. Chem.*, **684**, 14 (1965).

[68] G. Wittig, and H. Streib, *Ann. Chem.*, **584**, 1 (1953).

[69] L. H. Andrews, and S. M. McElvain, *J. Amer. Chem. Soc.*, **51**, 889 (1929); L. Knorr and P. Rabe, *Ber. Deut. Chem. Ges.*, **34**, 3491 (1901).

[70] A. Kekulé, *Ann. Chem.* (*Suppl.*), **2**, 85 (1862).

[71] D. Papa, E. Schwenk, and H. Breiger, *J. Org. Chem.*, **14**, 366 (1949).

[72] W. O. Jones, *J. Chem. Soc.*, **1954**, 1808.

[73] G. A. Page and D. S. Tarbell, *Org. Syn.*, **34**, 8 (1954); G. M. Badger, *J. Chem. Soc.*, **1948**, 999.

[74] K. H. Slotta and R. Kethur, *Ber. Deut. Chem. Ges.*, **71**, 62 (1938).

[75] A. P. Tomilov, L. V. Kaabak, and S. L. Varshavskii, *Zh. Obshch. Khim.*, **33**, 2811 (1963); *Chem. Abstr.*, **60**, 1584 (1964).

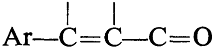
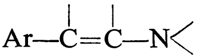
tetrahydro-8-quinolinol is obtained in 95% yield from 8-quinolinol[76] but as early as 1896 Ahrens[77] used electrolytic reduction to convert pyridine into piperidine.

In spite of the good yields obtained, the electrolytic process has never become truly popular in laboratory practice; it is probably not merely the apparatus but also experience in the electrochemical field that are lacking. A review by Swann[78] may be consulted for further references to the literature.

c. Reduction by lithium aluminum hydride or similar compounds

The applicability of lithium aluminum hydride to reduction of C=C bonds is strongly dependent on their position in the molecule, on the reaction temperature, and on the solvent.

When the usual method of operation is used, namely, in boiling ether, addition of hydrogen is limited to special circumstances. Isolated as well as conjugated olefinic bonds, and aromatic systems, are normally resistant; fulvenes are exceptional, being converted relatively well into alkylcyclopentadienes. Nitrogen heterocycles are attacked more easily at the C=N than at the C=C bond, wherefore, for instance, pyridine and quinoline afford their 1,2-dihydro derivatives.[79]

Even ethylenic bonds in α,β-position to polar groups are not always reduced. As a general rule, applicability of the reaction is confined to the groups  $\mathrm{Ar{-}\overset{|}{C}{=}\overset{|}{C}{-}C{=}O}$ (cinnamic acid derivatives,[80,81] chalcones[82]) and  $\mathrm{Ar{-}\overset{|}{C}{=}\overset{|}{C}{-}N}\!<$ (β-nitrostyrenes,[83] 1-methylindoles[84]); however, bicyclic nitroalkenes are smoothly converted into the saturated amines by lithium aluminum hydride[85] although their reduction by Raney nickel is incomplete; salo α,β-unsaturated cyanoacetic esters[86] and occasional vinyl ketones[87] can be reduced in good yield.

Normally the ethereal solution of the substance is added to the solution of the hydride in ether; other reducible groups are then attacked in addition to the olefinic bond. If, however, the lithium aluminum hydride is added gradually to the substance (the so-called "inverse reduction"), then saturation of the C=C bond can generally be avoided. For instance, cinnamaldehyde affords 3-phenyl-l-propanol by one method and cinnamyl alcohol by the other, both

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[76] S. Szmaragd and E. Briner, *Helv. Chim. Acta*, **32**, 1278 (1949).

[77] F. Ahrens, *Z. Elektrochem. Angew. Phys. Chem.*, **2**, 577 (1896).

[78] S. Swann Jr. in "Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N.Y., 1956, Vol. II, p. 385.

[79] F. Bohlmann, *Chem. Ber.*, **85**, 390 (1952).

[80] P. Karrer and P. Banerjea, *Helv. Chim. Acta*, **32**, 1962 (1949); A. R. Katritzky, *J. Chem. Soc.*, **1955**, 2586.

[81] F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3484 (1948).

[82] C. S. Rondestvedt Jr., *J. Amer. Chem. Soc.*, **73**, 4509 (1951).

[83] J. M. Bobbitt and T.-T. Chou, *J. Org. Chem.*, **24**, 1106 (1959); M. Erne and F. Ramirez, *Helv. Chim. Acta*, **33**, 912 (1950); J. Finkelstein, *J. Amer. Chem. Soc.*, **73**, 550 (1951).

[84] P. L. Julian and H. C. Printy, *J. Amer. Chem. Soc.*, **71**, 3206 (1949).

[85] E. Profft and F. Kaspar, *Ann. Chem.*, **647**, 61 (1961).

[86] A. Dornow, G. Messwarb, and H. H. Frey, *Chem. Ber.*, **83**, 445 (1950).

[87] J. R. Catch and E. A. Evans, *J. Chem. Soc.*, **1957**, 2796.

in good yield.[81] Low temperatures and avoidance of an excess of hydride favor exclusive reduction of the functional groups; on the other hand, in some cases it was possible to attack only the ethylenic bond, *e.g.*, in the conversion of 1-phenyl-2-nitro-1-propene into 1-phenyl-2-nitropropane[88] and the preparation of diphenylacetaldehyde from diphenylketene.[89]

Appreciably more severe conditions and thus generally shorter reaction times can be achieved by working in higher-boiling solvents, mainly homologous ethers, tetrahydrofuran, or dioxan. For instance, in di-*n*-butyl ether small amounts of piperidine are obtained from pyridine,[90] and allyl alcohol is at least partly converted into l-propanol.[81] Ether–benzene mixtures have been recommended for preparation of dihydro derivatives of acridine and similar heterocyclic compounds,[79] and quinoline has been reduced by diethylhydridoaluminum in benzene to di- and tetra-hydroquinoline.[91] A very powerful, but not generally applicable, reducing agent is a solution of lithium aluminum hydride in diethylene glycol monoethyl ether; it is thermally stable up to 200° and has the advantage that it moderates the violence of the hydrolysis that is necessary in all cases; even acenaphthylene is reduced to acenaphthene quantitatively by this method.[92]

At elevated temperature, if necessary under pressure, and in absence of a solvent, aluminum–hydrogen compounds add to ethylenes, monosubstituted ethylenes ($R—CH=CH_2$), and asymmetrically disubstituted ethylenes ($R_2C=CH_2$).[93] Under more severe conditions this reaction can be applied also to cycloolefins, except for cyclohexene. AlH reacts at 70°, but $LiAlH_4$ is better used at 110–120°. Symmetrically disubstituted ethylenes ($R—CH=CH—R$) react only under conditions where AlH_3 and $LiAlH_4$ are no longer stable, but in isolated cases the reaction can be carried through with dialkylhydridoaluminums, which are thermally more stable. Hydrolysis of the organoaluminum compounds that are first formed affords the saturated hydrocarbons. The much lower capacity for addition makes selective reductions possible, as, for instance, the ready conversion of 4-vinylcyclohexene into 4-ethylcyclohexene.

A selective reduction that can be readily carried out is involved in the preparation of **isopropylcyclopentadiene**:[94] Dimethylfulvene (53 g) in anhydrous ether (200 ml) is dropped slowly into a solution of $LiAlH_4$ (18 g) in ether (200 ml). The mixture becomes warm, the yellow color of the fulvene disappears, and a colorless precipitate is formed. At the end of the reaction (about 2 h) the addition compound is decomposed by methanol (100 ml) with cooling, and sufficient 2N hydrochloric acid is added to give a clear solution. The ethereal layer is separated, washed with dilute sodium carbonate solution, and dried over sodium sulfate. Then the ether is removed and the residue is fractionated in a vacuum. Isopropylcyclopentadiene (38.4 g, 71%) is obtained as a colorless liquid of b.p. 32–34°/23 mm.

Substances that are very sparingly soluble in ether are best reduced by the so-called Soxhlet extraction technique. The following directions are recorded for the preparation of **tryptamine**:[95]

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[88] R. T. Gilsdorf and F. F. Nord, *J. Amer. Chem. Soc.*, **74**, 1837 (1952).

[89] V. M. Mićović, M. M. Rogić, and M. Lj. Mihailović, *Tetrahedron*, **1**, 340 (1957).

[90] P. de Mayo and W. Rigby, *Nature*, **166**, 1075 (1950).

[91] W. P. Neumann, *Ann. Chem.*, **618**, 90 (1958).

[92] I. Goodman, *J. Chem. Soc.*, **1951**, 2209.

[93] K. Ziegler, H.-G. Gellert, H. Martin, K. Nagel, and J. Schneider, *Ann. Chem.*, **589**, 91 (1954).

[94] K. Hafner, *Ann. Chem.*, **606**, 79 (1957).

[95] E. H. P. Young, *J. Chem. Soc.*, **1958**, 3493.

3-(2-Nitrovinyl)indole (15 g) is extracted during 8 h from a Soxhlet thimble into a flask containing $LiAlH_4$ (15 g) in anhydrous ether (300 ml). The mixture is then treated with water (80 ml), slowly and with cooling, and filtered. The ether solution is separated, dried over sodium sulfate, and saturated with hydrogen chloride. Tryptamine hydrochloride (12.7 g) is thus obtained, melting at 249–250° (decomp.) after recrystallization from methanol–ethyl acetate.

Other complex metal hydrides can only rarely be applied to reduction of C=C bonds. Sodium borohydride, which can be used in aqueous-alcoholic solution, seems not normally to attack ethylenic bonds. A few cases only of partial reduction of cyclic iminum salts[96] and of selective reduction of unusually activated ethylenic bonds[97] have been reported. However, some polynitro aromatic compounds, *e.g.*, 1,3,5-trinitrobenzene, can be converted in high yield with saturation of the aromatic system into nitrocyclohexanes or nitrocyclohexenes.[98] Sodium hydridotrimethoxyborate has proved valuable as a mild reducing agent for preparation of a series of nitroparaffins from nitroalkenes.[99]

Monographs[100] should be consulted for comprehensive studies of these reductions.

d. Reduction by diimine

An increasingly important place in recent literature is being taken by papers on the reduction of olefinic double bonds by hydrazine in conjunction with oxidizing agents such as oxygen, peroxides (particularly in the presence of catalytic amounts of Cu^{2+}), mercuric oxide, hexacyanoferrate, iodine, etc.[101,102] This process saturates not only conjugated but also isolated double bonds. **Diimine** is formed as the actual hydrogenating agent; it is a short-lived species which can be obtained for this purpose also from other sources.[101,102] The following methods of obtaining it are important, as well as the oxidation of hydrazine: thermal decomposition of arenesulfonohydrazides[103,104] and 9,10-anthracenediimine;[105] spontaneous decarboxylation of azodicarboxylic acids on acidification of their salts;[103,104,106] and alkaline fission of chlor-

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[96] W. Awe, H. Wichmann, and R. Buerhop, *Chem. Ber.*, **90**, 1997 (1957); R. E. Lyle, R. E. Adel, and G. G. Lyle, *J. Org. Chem.*, **24**, 342 (1954); N. Kinoshita, M. Hamana, and T. Kawasaki, *Chem. & Pharm. Bull. (Tokyo)*, **10**, 753 (1962).

[97] J. Fajkos, *Collect. Czech. Chem. Commun.*, **23**, 2155 (1958); M. Miyano and M.Matsui, *Chem. Ber.*, **91**, 2044 (1958); J. Knabe, P. Herbort, and N. Ruppentahl, *Arch. Pharm.*, **299**, 534 (1966).

[98] T. Severin and R. Schmitz, *Chem. Ber.*, **95**, 1417 (1962).

[99] H. Shechter, D. E. Ley, and E. B. Robertson, Jr., *J. Amer. Chem. Soc.*, **78**, 4984 (1956).

[100] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956; (b) A. Hajós, "Komplexe Hydride und ihre Anwendung in der organischen Chemie," VEB Verlag der Wissenschaften, Berlin, 1966.

[101] Review: S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem.*, **77**, 368 (1965).

[102] (a) A. Fürst, R. C. Berlo, and S. Hooton, *Chem. Rev.*, **65**, 51 (1965); (b) B. F. Aylward and M. Sawistowska, *Chem. & Ind. (London)*, **1962**, 484.

[103] E. E. van Tamelen, *J. Amer. Chem. Soc.*, **83**, 3725, 3729 (1961).

[104] S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem. Int. Ed. Engl.*, **2**, 214 (1963); *Tetrahedron Lett.*, **1961**, 353.

[105] E. J. Corey and W. L. Mock, *J. Amer. Chem. Soc.*, **84**, 685 (1962).

[106] E. J. Corey *et al.*, *Tetrahedron Lett.*, **1961**, 347; *J. Amer. Chem. Soc.*, **83**, 2957 (1961)

amine[107] or chloroacetohydrazide hydrochloride.[108] Particular importance attaches to this hydrogenation because, in contrast to other chemical reducing agents, diimine effects stereospecific *cis*-addition of the hydrogen; this is evident, *inter alia*, in the partial reduction of carbon–carbon triple bonds (giving *cis*-olefins) and in the formation of homogeneous *meso*-2,3-dideuteriosuccinic acid from maleic acid and deuterated diimine.[106] Unlike catalytic hydrogenation, which also leads to predominatingly *cis*-addition products, diimine causes neither shift of the double bond nor stereoisomerization.[109] From results to date, the following rules have been set up for these hydrogenations:[161]

1. Unsymmetrical double bonds, as in NO_2, $-N{=}C$, $>S{=}O$, also $-C{\equiv}N$, are hardly attacked at all, nor are bonds that are susceptible to other reducing agents. For instance, diallyl sulfide can be converted into dipropyl sulfide without fission of the S—S linkage.[110] Carbonyl groups are, however, reducible (see page 62).

2. *trans*-Olefins are reduced faster than *cis*-olefins. For example, under standard conditions fumaric acid reacts ten times as fast as maleic acid.[101] In some special cases these differences are so great as to control completely the course of the reaction. *cis-trans-trans*-cyclododecatriene affords a mixture of 95% of *cis*-dodecene and 5% of dodecane without a detectable trace of *trans*-dodecene.[111]

3. The rate of reaction decreases with increase in the number of substituents on the doubly bonded atoms. However, not all substituents have the same influence. Terminal double bonds react faster than those in the interior of a chain;[112] and with further increase in the number of substituents on the double bond there may be no reduction at all. Relative rates of reaction measured by Hünig *et al.*[106] are: maleic acid 10, methylmaleic acid 0.7, dimethylmaleic acid 0, and ethylenetetracarboxylic acid (dicarboxymaleic acid 0.3). Nevertheless, under other conditions dimethylmaleic acid also can be reduced.[109]

4. *para*-Substituents in the benzene ring of cinnamic acid have practically no influence on the rate of reduction.

For **hydrogenation with hydrazine** Asinger and his collaborators[112] passed a stream of oxygen (60 ml/min) into a mixture of hydrazine monohydrate (145 mmoles), anhydrous ethanol (60 ml), and glacial acetic acid (63 mmoles) and after 30 seconds added the unsaturated hydrocarbon (34 mmoles); the course of reduction was then followed by gas chromatography.

For **reduction by potassium azodicarboxylate** Hamersma and Snyder[113] give the following prescription:

A solution of glacial acetic acid (1.3 g) in dioxan (5 ml) is dropped in 30 min into a mixture of potassium azodicarboxylate (5 g), dioxan (50 ml), and methyl cinnamate (2 g) with stirring under nitrogen. After 9 hours a further equal amount of acid is added, and after a total of 19 hours the mixture is worked up. Gas chromatography showed the product to contain 93% of 3-phenylpropionic acid.

Reduction by sodium hydrazide is a variant of hydrazine reduction for which the possible occurrence of diimine is not yet decided.[102,114] This reagent does

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[107] E. Schmitz and R. Ohme, *Angew. Chem.*, **73**, 807 (1961).

[108] R. Buyle, A. van Overstraeten, and F. Eloy, *Chem. & Ind. (London)*, **1964**, 839.

[109] T. Takagi, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **85**, 345 (1964) (English abstract p. A 27).

[110] E. E. van Tamelen *et al.*, *J. Amer. Chem. Soc.*, **83**, 4302 (1961); **84**, 1067 (1962).

[111] M. Ohno and M. Okamoto, *Tetrahedron Lett.*, **1964**, 2423.

[112] F. Asinger *et al.*, *Chem. Ber.*, **97**, 1568 (1964).

[113] J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).

[114] T. Kaufmann, C. Kosel, and W. Schoeneck, *Chem. Ber.*, **96**, 999 (1963).

not attack isolated double bonds, but fused aromatic rings are reduced, as are double bonds that are conjugated to aromatic rings. For example, *p*-diphenethylbenzene can be obtained in 93% yield from *p*-distyrylbenzene.

e. Other reducing agents

Tin(II) chloride, phosphonium iodide, sodium dithionite, and hydrogen iodide were previously much used as reducing agents for carbon–carbon multiple bonds but are nowadays seldom of practical interest. As examples, certain γ-keto carboxyamides were obtained from the corresponding benzoylacrylamides by use of $SnCl_2$.[115] The ethylene bonds in benzylideneindanediones were reduced by $Na_2S_2O_4$,[116] and substituted γ-diketones were prepared from 1,2-dibenzoylethylenes.[117] Carbazole, which is difficult to reduce, was converted into hexahydrocarbazole by hydrogen iodide,[118] and 3-(3-pyridyl)propionic acid was obtained from 3-(3-pyridyl)acrylic acid by means of phosphorus and hydrogen iodide.[119]

Other reagents have been used for reduction of C=C bonds in individual cases. For instance, benzylidenequinaldine and similar compounds could be reduced by *p*-thiocresol,[120] and benzyl alcohol in alkaline solution has been recommended for reduction of strongly activated ethylene bonds such as that in α-cyanostilbene.[121] In carotene chemistry some intermediates containing cumulated double bonds were converted into ethylene derivatives in good yield by means of chromium(II) acetate,[122] and tetracarbonylhydridocobalt $HCo(CO)_4$ has been used for reduction of α,β-unsaturated aldehydes.[123] This carbonyl occurs as homogeneous catalyst in the hydroformylation of olefins[124] and its solution in hexane converts unsaturated aldehydes at 25° into the saturated analogs in almost quantitative yield.

Finally, formic acid may be mentioned, for it was used to convert cyclic imonium compounds into saturated tertiary amines[125,126] and 1,2-dihydroquinolines into **1,2,3,4-tetrahydroquinolines**:[127]

A mixture of 1,2-dihydro-2,2,4-trimethylquinoline (20.94 g) and 85% formic acid (50 g) was boiled under reflux for 6–8 hours. After cooling, the whole was made alkaline, the oil that separated was extracted with ether, and the extract was dried over potassium carbonate.

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[115] R. E. Lutz and G. W. Scott, *J. Org. Chem.*, **13**, 284 (1948).

[116] G. Ja. Vanags and T. T. Dumpis, *Dokl. Akad. Nauk SSSR*, **125**, 549 (1959); *Chem. Abstr.*, **53**, 19991 (1959).

[117] R. E. Lutz and S. M. King, *J. Org. Chem.*, **17**, 1519 (1952).

[118] J. Schmidt and A. Sigwart, *Ber. Deut. Chem. Ges.*, **45**, 1779 (1912).

[119] R. S. Livshits *et al.*, *Zh. Obshch. Khim.*, **21**, 1354, 1360 (1951); *Chem. Abstr.*, **46**, 5050, 5051 (1952).

[120] H. Gilman, J. L. Towle, and R. K. Ingham, *J. Amer. Chem. Soc.*, **76**, 2920 (1954).

[121] M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 493 (1958).

[122] W. Oroshnik, *J. Amer. Chem. Soc.*, **76**, 5499 (1954).

[123] R. W. Goetz and M. Orchin, *J. Amer. Chem. Soc.*, **85**, 2782 (1963).

[124] J. A. Osborn, *Endeavour*, **26**, 144 (1967).

[125] A. N. Kost and L. G. Judin, *Zh. Obshch. Khim.*, **26**, 1720 (1956); *Chem. Abstr.*, **51**, 1958 (1957).

[126] S. Durand, X. Lusinchi, and R. C. Moreau, *Bull. Soc., of Chim. France.* **1961**, 270.

[127] L. Zalukajevs and T. I. Zheltukhina, *Izv. Vysshikh uchebn. Zavedenii, Khim. i Khim. Tekhnol.*, **6** (3), 521 (1963); *Chem. Abstr.*, **59**, 13947 (1963).

The solvent was then evaporated off and the residue was distilled in a vacuum. The tetrahydro product was thus obtained in 74% yield as a liquid of b.p. 132–138°/12–13 mm, and on recrystallization from ether melted at 39–40°.

The use of formic acid for **reduction of enamines** is so characteristic that this reaction can be used for detection of the enamine group.[128,129] Even enamines that are resistant to catalytic hydrogenation with Raney nickel or palladium can be reduced smoothly by formic acid.[130]

2. Catalytic hydrogenation

Catalytic hydrogenation, which usually proceeds easily and in a clear-cut manner, is very suitable for addition of hydrogen to C=C bonds. At higher temperatures, the reverse reaction, dehydrogenation, may occur, in which case dehydrogenation products accompany the hydrogenation products in accordance with the position of the particular equilibrium involved.

Poisoning of the catalyst often endangers the success of a hydrogenation, so that such reactions should be carried out only with pure substances. This precaution applies equally to the substances to be hydrogenated and to the materials used for preparation of the catalyst, as well as to the solvent. Further, it is advisable to carry out hydrogenations in rooms that are free from poisonous impurities. Horner and his co-workers[131] have studied the relation between the structure of a large number of organic compounds and their poisoning effect on Raney nickel used as hydrogenation catalyst.

Hydrogen from steel bottles can often be used without special purification. Its suitability is best tested by hydrogenation of a known substance. Such hydrogen, if impure, and hydrogen generated from zinc and sulfuric acid in a Kipp apparatus, should be washed with potassium permanganate and silver nitrate solutions. If it interferes, oxygen in electrolytic hydrogen can be removed by copper in a heated combustion tube. For complete purification of hydrogen see page 1104.

a. Catalysts

The choice and properties of a suitable catalyst are of greatest importance for success of a hydrogenation. Those considered are mainly noble metals and nickel, copper, cobalt, and iron, but also mixed catalysts and oxide or sulfide catalysts. Finely divided metal catalysts are prepared by reduction of salts of the metal. The noble metals can be prepared from their compounds by organic reducing agents such as formaldehyde and formic acid, or by reducing them with hydrogen at room temperature. Non-noble metals can be prepared by reducing their oxides, hydroxides, basic carbonates, formates, acetates, or oxalates in a stream of hydrogen at higher temperatures.

Skeletal alloy catalysts are prepared by Raney's method, namely, by dissolving the inactive metal out from an alloy of a catalytically active and a catalytically inactive metal, usually by means of an alkali hydroxide but often by acid, whereupon the catalyst remains as solid residue.

Raney nickel and cobalt, like the noble-metal catalysts, are very efficient for hydrogenation and can be used at room temperature.

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[128] P. L. De Benneville and J. H. Macartney, *J. Amer. Chem. Soc.*, **72**, 3073 (1950).

[129] N. J. Leonard and F. P. Hauck Jr., *J. Amer. Chem. Soc*, **79**, 5279 (1957); F. Asinger, F. J. Schmitz, and S. Reichel, *Ann. Chem.*, **652**, 50 (1962).

[130] G. Opitz, H. Mildenberger, and H. Suhr, *Ann. Chem.*, **649**, 47 (1961).

[131] L. Horner, H. Reuter, and E. Herrmann, *Ann. Chem.*, **660**, 1 (1962).

i, Noble-metal catalysts (Adams catalysts)

Noble-metal catalysts are highly efficient and permit hydrogenations to be carried out at room temperature. That is especially important when the starting materials or the products are unstable at higher temperatures. A further advantage is the insensitivity of platinum and palladium catalysts to acids, wherefore hydrogenations can also be effected in acid solution (glacial acetic acid). Alcohols, ethyl acetate, ether, and water are also used as solvent.

Elemental platinum metal catalysts: Willstätter and Waldschmidt-Leitz[132] prepared **platinum black** by the following modification of Loew's classical procedure:[133]

A solution of hydrogen chloroplatinate (80 ml) containing 20 g of platinum and a slight excess of hydrochloric acid is treated with 33% of formaldehyde solution (150 ml) and cooled to −10°; 50% potassium hydroxide solution is then dropped in with good stirring, the temperature not being allowed to rise above 6°. Later the mixture is warmed at 55–60° for 30 min with vigorous stirring. The precipitated platinum black is washed with water by decantation until all the chloride ions are removed and the wash-water no longer reacts alkaline. The product is then placed on a filter, with care that it remains continuously covered with water; it is rapidly sucked dry and pressed between filter papers, and placed in a desiccator which is evacuated to a high vacuum. After several days the product is bone dry. Carbon dioxide is allowed into the desiccator, releasing the vacuum, and the catalyst is stored under carbon dioxide. If the platinum black is not degassed in the high vacuum for a considerable time, then, according to Willstätter and Bommer,[134] when it is kept for a few days water is formed from the occluded hydrogen and oxygen.

The preparation of palladium black by reduction with formic acid has been described by Wieland.[135] For preparation of he Brown catalyst see Brown and Brown (p. 40).

Catalysts are often used on carriers. According to Ott and Schröter[136] **palladized charcoal** is prepared as follows:

Charcoal is shaken in an aqueous solution of palladium(II) chloride under hydrogen. After the reduction, the catalyst is filtered off and washed with water, alcohol, and finally ether.

Other possible carriers for catalysts are asbestos, pumice, kieselgur, silica gel, silica, active charcoal, and oxides, carbonates, and sulfates of magnesium, calcium, barium, zinc, aluminum, iron, chromium, and zirconium. Details for the preparation of palladium catalysts on barium sulfate have been recorded by Mozingo.[137]

For special purposes, *e.g.*, for partial reduction of triple to double bonds[138] or of cumulenes to polyenes,[139] the catalyst may be deactivated by partial poisoning. Double bonds are not hydrogenated in presence of these catalysts. Lindlar[138] gives the following directions for preparation of a **palladium catalyst deactivated** by lead acetate and supported on calcium carbonate:

Very pure precipitated calcium carbonate (50 g) is stirred into distilled water (400 ml). Palladium chloride solution (50 ml, containing 5% of palladium) is added and the mixture is stirred first for 5 min at room temperature and then for 10 min at 80°. The hot suspension

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[132] R. Willstätter and E. Waldschmidt-Leitz, *Ber. Deut. Chem. Ges.*, **54**, 113 (1921).

[133] O. Loew, *Ber. Deut. Chem. Ges.*, **23**, 289 (1890).

[134] R. Willstätter and M. Bommer, *Ber. Deut. Chem. Ges.*, **51**, 770 (1918).

[135] H. Wieland, *Ber. Deut. Chem. Ges.*, **45**, 489 (1912).

[136] E. Ott and R. Schröter, *Ber. Deut. Chem. Ges.*, **60**, 633 (1927).

[137] R. Mozingo, *Org. Syn.*, **26**, 77 (1946).

[138] H. Lindlar, *Helv. Chim. Acta*, **35**, 450 (1952).

[139] R. Kuhn and H. Fischer, *Chem. Ber.*, **93**, 2285 (1960).

is placed in a vessel for hydrogenation and shaken with hydrogen until no more hydrogen is absorbed, then filtered off under suction and washed thoroughly with distilled water. The filter cake is then stirred vigorously with distilled water (500 ml). As soon as all the material is in suspension, a solution of lead(II) acetate (5 g) is added in distilled water (100 ml) and stirring is continued for 10 min at 20° and for 40 min on a boiling water-bath. The catalyst is filtered off under suction, washed thoroughly with distilled water, and dried in a vacuum at 40–45°.

Similar deactivation is observed with bismuth and copper salts. A palladium catalyst poisoned with quinoline–sulfur and support on barium sulfate is used in the Rosenmund–Saytzeff reaction (p. 67).

Zelinsky and Borisoff give the following directions for preparation of **platinized or palladized asbestos catalysts**:[140]

Pure short-fibre asbestos is washed with acid and heated to red heat, then soaked in a concentrated, weakly acid solution of platinum or palladium chloride. Absorption is accelerated heating on the water-bath. Then the fibres are treated in the cold with 35–40% formaldehyde solution — 2.5–3 ml per gram of platinum or 4.5–5 ml per gram of palladium. After cooling, 40–50% sodium hydroxide solution is slowly added (1.5 times by weight that of formaldehyde solution). The metal is precipitated in the cold, but reaction is completed by warming on the water-bath. Then much water is added and the mass of asbestos is washed until as free as possible from salts and alkali; thereafter, the black asbestos fibres are placed in very dilute acetic acid, to remove the last traces of alkali. Finally they are filtered off under suction and washed until the washings are neutral, then dried for a short time in a drying oven. The black asbestos obtained in this way is a useful, very active catalyst for both hydrogenation and dehydrogenation.

Zelinsky and Turowa-Pollak[141] describe the specific properties of an osmium catalyst. Hydrogenation on osmium catalysts usually occurs at lower temperatures than on platinum, palladium, or nickel catalysts. Osmium asbestos is a very resistant catalyst that can be used for months on end without loss in activity; disadvantages are that osmium catalysts that are not supported on carriers must be frequently regenerated and that when the temperature exceeds 150° osmium tends to decompose the material under hydrogenation.

Noble-metal oxide or hydroxide catalysts: Elemental platinum-metal catalysts such as platinum black and palladium black, which were earlier used with great success, have now been replaced in practice by the oxides which are more easily prepared. The oxide or hydroxide catalysts are first shaken with hydrogen, being reduced to very finely divided metal that forms the actual catalyst. The time required for this pre-reduction varies from a few seconds to some minutes. If only the solvent is present this reduction is usually fast; if the catalyst and the substance to be hydrogenated are reduced together, the time depends on the nature of the latter and can be 10–15 min.

Adams and his collaborators[142] describe the preparation of a **platinum oxide catalyst** (known as Adams catalyst) that is very convenient to use and exceedingly active:

Sodium nitrate (20 g) is mixed in a porcelain dish with platinum(IV) chloride (equivalent to 1 g of platinum) dissolved in water (5 ml). The mixture is heated gently with stirring by a glass rod, until the water is driven off. Heating is then continued until the mass is molten and brown fumes of nitrogen oxides are evolved. The temperature of the melt amounts to about 400–500°. When evolution of oxides of nitrogen stops, the mass is cooled and extracted with

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[140] N. D. Zelinsky and P. Borisoff, *Ber. Deut. Chem. Ges.*, **57**, 150 (1924).

[141] N. D. Zelinsky and M. B. Turowa-Pollak, *Ber. Deut. Chem. Ges.*, **62**, 2865 (1929).

[142] R. Adams, V. Voorhees, and R. L. Shriner, *Org. Syn.*, **8**, 92 (1928).

water (50 ml). The resulting brown precipitate is washed, first by decantation and then on a filter, until the filtrate shows no reaction for nitrate. It is, however, difficult to obtain a product wholly free from alkali; the normal alkali content is about 2% for a melt temperature of 400–500° but may be more after higher melt temperatures. The brown platinum oxide is dried in a vacuum or over sulfuric acid.

Bruce uses ammonium chloroplatinate for preparation of platinum oxide.[143] According to Shriner and Adams[144] palladium oxide is prepared in the same way as the platinum catalyst, but as it peptizes readily it must be washed only with 1% sodium carbonate or sodium nitrate solution.

As shown in the following method of preparing **platinum hydroxide on magnesium oxide**, hydrolysis of platinum(II) chloride by carrier magnesium oxide, may yield a platinum oxide catalyst:[145]

Magnesium oxide (100 parts) is suspended in water (500 parts) and digested with an aqueous solution (400 parts) of platinum(II) chloride (2.9 parts). The platinum(II) hydroxide formed separates on the magnesium oxide. After being washed, the catalyst is dried at 100°.

Ruthenium catalysts[146] consist of the finely divided metal or of their oxides or salts which may be suspended on carriers (wood charcoal, silica gel, and the like). A useful method is to melt ruthenium metal or its oxide with sodium peroxide and to place the solution of the salt obtained on to the carrier.

Used catalysts must on occasions be reactivated by air or oxygen. This must sometimes be done even during a hydrogenation in order to complete the reaction or to raise the decreasing rate of uptake of hydrogen. Nevertheless, this procedure often results in the catalyst's being totally inactivated. If, during the hydrogenation, the catalyst agglomerates it must be worked up again. If the catalyst settles down spontaneously when shaking stops, it is not necessarily spoilt — provided, that is, that it is readily resuspended on shaking. Portions of used catalyst are dissolved in aqua regia and, after evaporation of the excess of acid, are precipitated in aqueous solution by ammonia. Wichers[147] gives an efficient but complex method for working up platinum that has become unusable, that is, that has become too contaminated with poisons.

Colloidal noble metals: Colloidal hydrogenation catalysts have only slight practical importance. They can be prepared by reducing noble-metal chlorides with hydrazine hydrate in weakly alkaline solution. Albumin or its hydrolysates are suitable protective colloids. Dunworth and Nord[148] recently prepared colloidal iridium with polyvinyl alcohol as protective colloid. Paal and Amberger[149] used platinum and palladium colloids with sodium protabinate and lysalbinate; Skita *et al.*[150] used gum arabic as protective colloid. An acid-resistant colloid with degraded glutin as protective colloid is described by Kelber and Schwarz.[151] Skita and his co-workers[150a] describe the preparation of colloidal platinum hydroxide and palladium hydroxide.

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[143] W. F. Bruce, *J. Amer. Chem. Soc.*, **58**, 687 (1936); cf. *Org. Syn.*, **17**, 98.

[144] R. L. Shriner and R. Adams, *J. Amer. Chem. Soc.*, **46**, 1685 (1924); **47**, 1147 (1925).

[145] Ger. Pat. 256,500 (1911; Friedländer, **11**, 101.

[146] U.S. Pat. 2,494,563 (1947); *Chem. Abstr.* **44**, 4498 (1950).

[147] E. Wichers, *J. Amer. Chem. Soc.*, **43**, 1268 (1921).

[148] W. P. Dunworth and F. F. Nord, *J. Amer. Chem. Soc.*, **72**, 4197 (1950).

[149] C. Paal and C. Amberger, *Ber. Deut. Chem. Ges.*, **37**, 131 (1904); see also **35**, 2197 (1902).

[150] A. Skita and co-workers, *Ber. Deut. Chem. Ges.*, (a) **45**, 3584 (1912); (b) **57**, 1977 (1924).

[151] C. Kelber and A. Schwarz, *Ber. Deut. Chem. Ges.*, **45**, 1946 (1912).

Colloidal platinum (cf. Paal and Amberger[152]): Sodium lysalbinate (1 g) is dissolved in 30 times its weight of water, and slightly more sodium hydroxide solution is added than is necessary for bonding with all the chlorine that is to be added as hydrogen chloroplatinate. To the alkaline solution is added next a solution of hydrogen chloroplatinate (2 g) in a little water. The clear dark brown solution is treated with a slight excess of hydrazine hydrate. The solution darkens and gas is evolved; the resulting black liquid appears clear and dark brown when viewed in thin layers in transmitted light; it is subjected to dialysis against water. By repeated change of the external water, it is possible to remove from the colloidal solution the excess of sodium hydroxide, the unchanged hydrazine hydrate, and the sodium chloride formed in the reduction. The dialysed solution is filtered and evaporated carefully on a water-bath and finally to dryness in an evacuated desiccator. The preparation forms dark, very shiny, brittle laminae that dissolve readily and completely in water to a black, non-transparent liquid.

Colloidal palladium can be prepared similarly by use of hydrogen as reducing agent.[152]

ii, *Skeletal alloy catalysts* (*Raney metals*)

In Raney's method a catalytically active metal is alloyed with a catalytically inactive one and then treated with a reagent that dissolves out the inactive metal. The catalytically inactive component that is to be dissolved out may be aluminum, silicon, magnesium, or zinc. The catalytically active metal is usually nickel, cobalt, copper, or iron. Noble-metal catalysts can, however, also be produced by Raney's method if an aluminum–platinum alloy (40% of platinum) or a zinc–palladium alloy (40% of palladium) is decomposed by hydrochloric acid.[153]

As advantages of Raney metals, in particular of Raney nickel, it is stated that, as with noble-metal catalysts, it is possible to work under mild conditions. One is warned against hydrogenation with Raney nickel at high temperatures because explosive reactions can occur. In general it is possible to work with Raney nickel at temperatures 20–40° below those needed for the other nickel catalysts described on page 24. However, Raney nickel loses its superior activity at 100–150°, so that at higher temperatures the older nickel catalysts can be used with equal success.[154]

According to Paul and Hilly[155] **Raney nickel** is prepared as follows:

Aluminum (400 g) is melted and heated to 1200°. Cubes of nickel (300 g) are added to the melt all at once (cubic nickel is more suitable than compact, mechanically worked metal for preparation of the alloys). The nickel dissolves in a lively reaction, the temperature rising to about 1500°. After cooling, the alloy is broken and powdered. The alloy (250 g) is added in small portions to an ice-cold, approximately 25% sodium hydroxide solution (100 ml), whereupon decomposition sets in exothermally with lively evolution of hydrogen (foaming and spitting). When all the alloy has been added, the temperature is raised to 90–100° and kept there until evolution of hydrogen ceases. The metal is allowed to settle and is then decanted, and the treatment with alkali is repeated twice (1 l of fresh solution each time). After decantation of the last alkali the precipitated nickel is washed with water by suspension, settling, and decantation until the wash-water reacts neutral to phenolphthalein. The water is then replaced by alcohol. The catalyst is stored under alcohol in bottles.

Raney nickel is kept under alcohol since it is highly pyrophoric, owing, presumably, to the nickel hydride contained in the catalyst.[156]

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[152] C. Paal and C. Amberger, *Ber. Deut. Chem. Ges.*, **37**, 126 (1904); **38**, 1398 (1905).

[153] U.S. Pat. 2,384,501 (1945); *Chem. Abstr.*, **39**, 5422 (1945).

[154] E. B. Maxted and R. A. Titt, *J. Soc. Chem. Ind.* (*London*), **57**, 197 (1938).

[155] R. Paul and G. Hilly, *Bull. Soc. Chim. France*, [v], 3, 2330 (1936); see also R. Mozingo, *Org. Syn.*, **21**, 15 (1941); H. R. Billica and H. Adkins, *Org. Syn.*, **29**, 24 (1949); *J. Amer. Chem. Soc.*, **70**, 695 (1948).

[156] U.S. Pat. 2,461,396 (1945); *Chem. Abstr.*, **43**, 3340 (1949).

Formation of the alloy is accompanied by evolution of much heat. Because of the increase in temperature higher-melting alloys can often be obtained with a greater content of active metal. In the presence of atmospheric oxygen an aluminothermic reaction may lead to a further rise in temperature. **Care** is therefore necessary! The melt can be protected against attack by atmospheric oxygen by covering it with a layer of salt or by means of an inert gas.

Alloys ready for use can now be obtained commercially.

After decomposition of the aluminum alloys there is still residual aluminum in the metal, and this residue seems to be in part responsible for the activity of the catalyst. If this residue is largely removed by continued extraction, the catalyst becomes inactive.[157] Alloys containing more than 75% of nickel are only partly attacked by aqueous sodium hydroxide, or are not attacked at all; then decomposition has to be undertaken with very concentrated sodium hydroxide solution or by adding solid sodium hydroxide to the molten mass.[158] Alloys containing between 30% and 50% of active metal are most suitable for preparation of active metal catalysts.

The activity of Raney nickel can be increased by means of activators, for which purpose noble metals in the form of their chlorides, chloro acids, or salts of chloro acids are added after decomposition of the alloy or during the washing process.[159]

To increase the activity, Paul[160] added chromium, molybdenum, or cobalt in amounts of 3–10% (calculated on the amount of nickel) during preparation of the alloy. Hydrogenation in the presence of alkali or of organic bases is stated to effect a still further increase in activity.

The efficiency of a Raney nickel catalyst for hydrogenation of carbonyl groups is much diminished if the catalyst is treated with 0.1% acetic acid or an amino acid, particularly dibasic amino acids or L-phenylalanine; but the efficiency for hydrogenation of C=C double bonds remains unaffected. Thus mesityl oxide was hydrogenated to isobutyl methyl ketone selectively and in good yield; but cinnamaldehyde could not be reduced in this way.[161] For asymmetric hydrogenation with Raney nickel modified by optically active 2-hydroxy carboxylic acids see Tatsumi *et al.*[162]

Raney cobalt,[163] iron,[164] and copper catalysts[164] can be prepared in precisely analogous manner. They are, however, not so versatile in their application as Raney nickel.

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[157] J. Aubry, *Bull. Soc. Chim. France.* [v], **5**, 1333 (1938).

[158] Brit. Pat. 282,112 (1927) (I. G. Farbenindustrie); *Chem. Abstr.*, **22**, 3625 (1928).

[159] M. Delépine and A. Horeau, *Bull. Soc. Chim. France*, [v], **4**, 31 (1937); E. Lieber, *J. Amer. Chem. Soc.*, **72**, 1190 (1950).

[160] R. Paul, *Bull. Soc. Chim. France*, [v], **13**, 208 (1946); see also J. Ishikawa, *J. Chem. Soc. Japan, Pure Chem. Sect.* [*Nippon Kagaku Zasshi*], **81**, 1179 (1960) (cited from *Chem. Zentralbl.*, **1963**, 19,566).

[161] H. Fukawa, Y. Izumi, S. Komatsu, and S. Akabori, *Bull. Chem. Soc. Japan*, **35**, **1703** (1962) (cited from *Chem. Zentralbl.*, **1964**, 16-0821).

[162] S. Tatsumi, M. Imaida, Y. Fukuda, Y. Izumi, and S. Akabori, *Bull. Chem. Soc. Japan*, **37**, 846 (1964) (cited from *Chem. Zentralbl.*, **1966**, 19-0820).

[163] U.S. Pat. 2,166,183 (1938); *Chem. Abstr.*, **33**, 8219 (1939); see also Brit. Pat. 628,407 (1949); *Chem. Abstr.*, **44**, 2675e (1950).

[164] L. Faucounau, *Bull. Soc. Chim. France*, [v], **4**, 58 (1937).

For discontinuous hydrogenations the active metal is generally used as a fine powder. For continuous hydrogenation it is advantageously used in granules or lumps.[165]

iii, Metal catalysts

The preparation of nickel catalysts is usually carried out in two stages. First, suitable nickel compounds are prepared, such as the oxide, hydroxide, basic carbonate, acetate, formate, or oxalate, sometimes with addition of an activator or carrier, and these salts are then reduced.

Sulfur-free catalyst is generally obtained by treating nickel nitrate with alkali carbonate, hydroxide, or hydrogen carbonate. The alkali salts formed during the precipitation must be removed so far as possible from the product. The nickel hydroxide or basic carbonate is then reduced, without prior conversion into the oxide. Nickel oxide is usually prepared by decomposition of nickel acetate or nitrate.

Nickel formate decomposes at 200° with formation of metallic nickel. A method of obtaining very finely divided nickel is to suspend nickel formate in its own weight of liquid paraffin and to heat the mixture to 260° with stirring whilst introducing carbon dioxide or hydrogen. The nickel formed is filtered off, washed with light petroleum by decantation, and stored under light petroleum. This material is a particularly active catalyst for pressure hydrogenations.

Nickel oxide is reduced in a combustion tube by a stream of hydrogen at 350°.[166] The material is allowed to cool in a stream of hydrogen after the reaction has penetrated the interior. Then the hydrogen is replaced by a stream of nitrogen. It is advisable to have an atmosphere of inert gas present when adding the catalyst to the substance to be hydrogenated. Freshly reduced nickel loses its activity if exposed to air and therefore, if not used at once, must be kept in an indifferent atmosphere or in a vacuum; alternatively it can be stored in methanol, ethanol, or benzene.

Covert, Connor, and Adkins[167] recommend the following procedure for preparation of a **nickel catalyst on kieselguhr:**

Nickel nitrate hexahydrate (58 g) is dissolved in distilled water (80 ml) and rubbed in a mortar with kieselguhr (previously extracted with hydrochloric acid) until, after 30–60 min the mixture flows like a heavy oil. It is then added slowly to a solution of ammonium carbonate monohydrate (34 g) in distilled water (200 ml); the precipitate is filtered off under suction, washed in two portions with water (100 ml), and dried at 110°. Shortly before use, this material is reduced at 450° for 1 hour in a stream of hydrogen (10–15 ml/min).

The nickel content of carrier catalysts is usually 10–40%. Nickel catalysts are generally reduced at 300–500°; but nickel mixed catalysts, containing metals nobler than nickel, can be reduced at lower temperatures, *e.g.*, copper–nickel mixed catalysts[168] as low as 200–300°.

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[165] U.S. Pat. 2,094,117; *Chem. Abstr.*, **31**, 7884 (1937); Brit. Pat. 628,405, 628,407, 629,405; *Chem. Abstr.*, **44**, 2675d, e (1950); **44**, 4498f (1950).

[166] G. M. Schwab and L. Rudolph, *Z. Phys. Chem.*, *B*, **12**, 427 (1931).

[167] L. Covert, R. Connor, and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 1651 (1932).

[168] G. Rienäcker and R. Burmann, *J. Prakt. Chem.*, [ii], **158**, 100 (1941).

The following nickel-carrier catalysts have been described: nickel–kieselguhr,[169] nickel–pumice,[170] nickel–kieselguhr containing thorium oxide,[171] nickel on magnesium oxide, barium oxide, or beryllium oxide,[172] nickel on aluminum oxide,[173] and nickel–zinc oxide–barium oxide–chromium oxide.[174] Other carriers for nickel catalysts are active charcoal, silica, fuller's earth, and oxides such as magnesia, alumina, and bauxite.

For many hydrogenations the carrier catalyst is stirred into the substance to be hydrogenated and the mixture is hydrogenated; the catalyst must then be reduced before hydrogenation of the compound can occur.

Copper can also be used as a catalyst, like nickel, alone, on carriers, or as a mixed catalyst with metals of the first to the eighth Group of the Periodic Table. The temperature needed for reduction of the catalyst, usually containing the copper as oxide, hydroxide, or basic carbonate, is 150–300°. Preparation of a copper–kieselguhr catalyst is similar to that of a nickel–kieselguhr catalyst.[175]

Cobalt catalysts are obtained by reducing the basic carbonate, hydroxide, or oxide in a stream of hydrogen. Howk prepared a cobalt–kieselguhr catalyst.[176] Cobalt–barium oxide–aluminum oxide,[177] cobalt–thorium oxide–kieselguhr,[178] and cobalt–thorium oxide–magnesium oxide–kieselguhr[179] may be mentioned as further examples.

The precipitate of nickel obtained on adding zinc dust to a solution of nickel chloride can be activated by treatment with aqueous ammonia (Urushibara Ni—NH_3). This nickel catalyst contains appreciable amounts of residual ammonia and is suitable for reduction of nitriles to amines. Treating the nickel precipitate with sodium hydroxide solution gives the Urushibara Ni—B catalyst; Urushibara Co—B catalyst is obtained analogously from cobalt chloride.[180]

Langenbeck[181] prepared "mixed salt catalysts" by decomposing salts in the form of mixed crystals in a stream of hydrogen. A particularly fine distribution of the starting components, down to the ions themselves, exists in mixed crystals. The charge and the ionic radius of the cations must be the same, and the anions must be chemically identical in the two components. To facilitate decomposi-

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[169] "Ullmann's Enzyklopädie der technischen Chemie," 2nd ed. Verlag Urban & Schwarzerberg, Berlin–Vienna, 1932, Vol. 5, pp. 171–172.

[170] BIOS Final Rep. 755, pp. 14–15, I. G., Höchst; Ger. Pat. 352,439 (cited from Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 178).

[171] Ger. Pat. 571,898 (1930); *Chem. Abstr.*, **27**, 4239 (1933).

[172] Ger. Pat. 307,580 (1913); Friedländer, **13**, 174.

[173] CIOS Rep. 30, XXXII-107, p. 118, I. G. Leuna (cited from Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 180).

[174] FIAT Final Rep. 1313, I, pp. 335–336.

[175] Ger. Pat. 594, 481 (1930); *Chem. Abstr.*, **28**, 3416 (1934).

[176] U.S. Pat. 2,166,152 (1938); *Chem. Abstr.*, **33**, 8211 (1939).

[177] Ger. Pat. 599,103 (1932); *Chem. Abstr.*, **28**, 5833 (1934); see also French Pat. 761,952; *Chem. Abstr.*, **28**, 4432 (1934).

[178] F. Fischer and H. Koch, *Brennstoff-Chem.*, **13**, 62, (1932).

[179] CIOS Rep. 30, XXVII-69, pp. 24–27 (cited from Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 185.

[180] S. Nishimura and A. Sugimori, *J. Chem. Soc. Japan, Pure Chem. Sect.* [*Nippon Kagaku Zasshi*], **81**, 314 (1960) (cited from *Chem. Zentralbl.*, **1964**, 45-0770).

[181] W. Langenbeck, *Angew. Chem.*, **68**, 453 (1956).

tion, oxalate or formate ions are used, since these are themselves reducing. Two different materials must be formed on decomposition, and not a new set of mixed crystals; to achieve this, either one component must remain unchanged while the other is reduced, or the two components must react in different directions. In this way, a nickel–magnesium oxide catalyst, for instance, is formed on decomposition of nickel formate–magnesium formate mixed crystals in a stream of hydrogen. The mixed-crystal systems cobalt–zinc oxalate and copper–calcium oxalate, as well as the pairs of formates, have been similarly studied.

A further possibility of preparing mixed-salt catalysts is provided by decomposition of complex salts of the type $A_n[BX_m]$,[181] where A is a non-noble metal cation and B is a noble metal present in a complex anion; an example is the oxalate complex $Li_2[Cu(Ox)_2]$. In all cases, highly active catalysts result; they are usually more efficient than other catalysts containing the metal in question, and maximum activity is found with a molar ratio of, *e.g.*, nickel oxalate: magnesium oxalate = 1 : 1.

iv, Copper oxide–chromium oxide catalysts (Adkins catalysts)

Copper oxide–chromium oxide catalysts[182] have assumed great importance. According to Adkins the catalyst is not used with various proportions of the oxides but as copper–chromium spinel $CuO{\cdot}Cr_2O_3$ (often called copper chromite). In contrast to the catalysts described above, the copper chromite catalyst is an oxide catalyst which is not reduced to the metal during the hydrogenation. Care must be taken that the black catalyst is not converted into the reduced, red, inactive form. The chromium oxide protects the copper against reduction;[183c] addition of an alkaline-earth oxide serves the same purpose.[184]

In contradiction thereto, Rabes and Schenk[185] assume that metallic copper and activating chromium oxide are the effective constituents of the reduced catalyst.

Instead of these catalysts that are very rich in chromium, others containing less chromium are often used; the latter, however, are cautiously reduced before use.[186]

Adkins and his co-workers[187] prepared very active copper chromite catalysts by decomposing copper ammonium chromate at a low temperature (100°) and reducing the product in methanol by a stream of hydrogen at 100–200 atm.

Hydrogenation with copper chromite requires increased pressures (40 to 200 atm) and elevated temperatures (100–280°). The activity of copper chromite equals that of palladium, platinum, or active nickel.

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[182] O. Schmidt, *Ber. Deut. Chem. Ges.*, **64**, 2051 (1931).

[183] W. Foerst (ed.), "Neuere Methoden der präparativen organischen Chemie," 3rd ed., Verlag Chemie, Weinheim/Bergstraße, Vol. 1, pp. (a) 98 (R. Schröter), (b) 117 (C. Grundmann), (c) 118 (C. Grundmann), (d) 137 (T. Bersin); Vol. 4 (1966), pp. (e) 173 (E. Schenker), (f) 198 (E. Schenker).

[184] R. Connor, K. Folkers, and H. Adkins, *J. Amer. Chem. Soc.*, **53**, 2012 (1931).

[185] I. Rabes and R. Schenk, *Z. Elektrochem.*, **52**, 37 (1948).

[186] W. Normann, *Z. Angew. Chem.*, **44**, 714 (1931).

[187] H. Adkins, E. E. Bourgoyne, and H. J. Schneider, *J. Amer. Chem. Soc.*, **72**, 2626 (1950).

A copper chromite catalyst can be prepared merely by mechanically mixing copper oxide and chromium oxide or by thermal treatment of such mixtures.[188] However, the best method for laboratory practice has proved to be thermal decomposition of copper ammonium chromate.

Preparation of a **copper oxide–chromium oxide catalyst containing barium oxide** according to Connor, Folkers, and Adkins:[188]

A hot (80°) solution (900 ml) containing hydrated copper nitrate [$Cu(NO_3)_2 \cdot 3H_2O$; 260 g) and barium nitrate (31 g) is poured into a warm (25°) solution (900 ml) containing ammonium bichromate (151 g) and 28% ammonia solution (225 ml). The resulting precipitate is filtered off and the filter cake is pressed with a spatula and sucked very dry. The product is dried in an oven at 75–80° for 12 h and then powdered. Thermal decomposition is effected by heating it in three portions in a large porcelain dish (15 cm in diameter) with a free flame. The material is stirred continuously with a steel spatula during the decomposition and the flame is regulated so that evolution of gas is not too violent. Decomposition should take place at as low a temperature as possible; this is best achieved by heating only one side of the dish and increasing the stirring as soon as the decomposition begins to spread through the whole mass. During this process the color of the powder changes from orange to brown and finally to black. When the mass has become uniformly black and gas evolution has ceased, the powder is allowed to cool. The three portions are reunited and stirred for 30 min with 10% acetic acid (600 ml) to dissolve out the excess of copper oxide; the residue is sucked off and washed with water (six portions, each of 100 ml), dried for 12 h at 125°, and powdered. The yield amounts to 170 g. It is not necessary to reduce the catalyst before use.

Lazier and Arnold,[189] also Riener,[190] describe other methods of preparing this catalyst. According to Riener, more active catalysts are obtained by decomposition at low than at high temperatures. Frazer and Jackson[191] prepared a nickel–chromium oxide catalyst of the composition $2NiO{\cdot}Cr_2O_3$ but reduced it with hydrogen before use. Sauer and Adkins[192] described a zinc chromite catalyst whose preparation paralleled that of the copper chromite catalyst. A zinc oxide–calcium chromite–silver catalyst was prepared by Grundmann.[193]

v, Sulfide catalysts

In contrast to the sensitive metal catalysts, sulfide catalysts are not poisoned by sulfur. They are therefore used for hydrogenation of substances that contain sulfur as impurity (high-pressure hydrogenation or treatment of coal), in synthesis of sulfur-containing organic compounds, and in destructive hydrogenation of organic sulfur compounds (*e.g.*, hydrogenation of thiophene with loss of hydrogen sulfide).

Pier, Jacob, and Simon[194] prepared an **iron sulfide** or **cobalt sulfide catalyst** as follows: Iron sulfide, obtained by precipitation from a solution of an iron salt by ammonium sulfide solution, is heated dry with hydrogen sulfide at 10 atm and 430° for 3 h. In the case of cobalt sulfide obtained by precipitation the subsequent treatment with a stream of hydrogen sulfide is for 12 h at 200°.

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[188] R. Connor, K. Folkers, and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 1138 (1932); see also H. Adkins and R. Connor, *J. Amer. Chem. Soc.*, **53**, 1091 (1931).

[189] W. A. Lazier and H. Arnold, (a) U.S. Pat. 1,964,000; *Chem. Abstr.*, **28**, 5076 (1934); (b) *Org. Syn.*, **19**, 31 (1939).

[190] T. W. Riener, *J. Amer. Chem. Soc.*, **71**, 1130 (1949).

[191] J. C. W. Frazer and C. B. Jackson, *J. Amer. Chem. Soc.*, **58**, 950 (1936).

[192] (a) J. Sauer and H. Adkins, *J. Amer. Chem. Soc.*, **59**, 1 (1937); see also (b) H. H. Storch, *J. Phys. Chem.*, **32**, 1744 (1928).

[193] C. Grundmann, *Angew. Chem.*, **62**, 558 (1950).

[194] U.S. Pat. 2,127,383 (1936); *Chem. Abstr.*, **32**, 8127 (1938); see also French Pat. 728,913; *Chem. Abstr.*, **26**, 6080 (1932).

According to Farlow, Lazier, and Signaigo[195] a cobalt polysulfide catalyst is useful for synthesis of thiols from aldehydes by means of hydrogen sulfide under hydrogenating conditions; the catalyst is obtained by treating a cobalt–aluminum alloy with sodium sulfide.

Farlow and Signaigo[196] describe the preparation of a **molybdenum sulfide catalyst** from a molybdenum–aluminum alloy:

To a suspension of a molybdenum–aluminum alloy (1 : 1; 36.5 g) in boiling water (300 ml) is slowly added a solution of sulfuric acid (130 g) in water (100 ml). The suspension is stirred for 4 h at 100°. The decomposition product is washed with water until free from acid and then placed in methanol. The mixture is then saturated with hydrogen sulfide, and the suspension is set aside for two weeks. The product is then washed again with methanol. The resulting catalyst is kept under methanol.

b. Apparatus and procedure for hydrogenation

i, Hydrogenation on a shaking machine

In the laboratory small amounts of compound are usually hydrogenated in presence of a noble-metal or a Raney catalyst on a shaking machine. The nature of the vessel used is of minor importance. Rapid shaking is essential. The hydrogenation vessel is usually shaken horizontally, but sometimes vertically.[197] The apparatus sketched in Figure 1 usually suffices for work at atmospheric pressure.

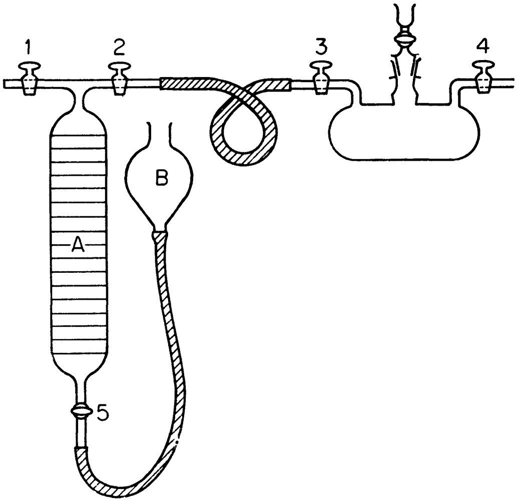

Figure 1. Apparatus for hydrogenation at atmospheric pressure.

The cylindrical vessel A, fitted with taps 1 and 2, is connected by a rubber tube to the levelling funnel B. The vessel A contains 1 litre or more between two marks, with subdivisions sufficing for the required purpose. For calibration it usually suffices to fill the vessel with

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[195] M. W. Farlow, W. A. Lazier, and F. K. Signaigo, *Ind. Eng. Chem.*, **42**, 2547 (1950).

[196] U.S. Pat. 2,402,613 (1939); *Chem. Abstr.*, **40**, 5758 (1946).

[197] E. B. Maxted in "Handbuch der Katalyse," Springer-Verlag, Vienna, 1943, Vol. 7, Part I, p. 654; see also E. B. Maxted, *Trans. Faraday Soc.*, **13**, 36 (1917).

water, draw off 50-ml portions into a measuring cylinder, and follow the subdivisions graphically in 10-ml units. Higher accuracy is never needed for preparative work. At the start, vessel A is filled with water by raising B, until the water is just below the horizontal part of the T piece above it. Taps 1–5 are then opened and the air displaced by hydrogen. Tap 4 and then tap 2 are closed, the funnel B is lowered, hydrogen is admitted until the water is at the lower mark under slight overpressure, and taps 1 and 5 are closed. To obtain atmospheric pressure in the whole system, taps 2 and 3 can be opened, and the excess of hydrogen allowed to escape through tap 4 for a short time. Then tap 5 is opened, the funnel B is raised to 10–20 cm above the level of water in vessel A, and reaction is carried out by shaking. If the gas in A is all consumed, taps 2 and 3 are shut, shaking is stopped, atmospheric pressure is restored by means of B, and the level of water is read off. Then A is refilled with hydrogen. If, for convenience, it is desired to fill A again to the starting mark, then tap B should have been fitted as a three-way tap; the vessel is filled to the mark, taps 1 and 5 are closed, and atmospheric pressure obtained by releasing the excess of gas through the neck of tap 2. Otherwise, tap 1 is closed again, atmospheric pressure obtained by moving B, and the water level noted. The amount of hydrogen used is measured volumetrically.

Some care is needed when bringing the catalyst into contact with hydrogen. Some oxidic and hydroxidic catalysts must be reduced under a protecting liquid because they heat up so much in dry hydrogen that an oxygen–hydrogen explosion can occur when hydrogen replaces the air in the hydrogenation vessel. Therefore the catalyst is reduced under the solvent to be used in the hydrogenation; alternatively, the catalyst is covered with ether, the air is displaced from the vessel without shaking, then shaking is undertaken until reduction is complete, the ether is blown off in a stream of hydrogen, and, without interruption of the hydrogen flow, the solution to be reduced is added from a funnel attached to the hydrogenation vessel.

A certain amount of water is always formed when oxide or hydroxide catalysts are used. If additional catalyst has to be added or the previous batch regenerated by oxygen, the hydrogen in the vessel must, of course, be previously removed by evacuation; and before hydrogen is readmitted the vessel must be re-evacuated to avoid a hydrogen–oxygen explosion.

For larger batches and moderate overpressure (up to about 3 atm) the apparatus illustrated in Fig. 2 is suitable.

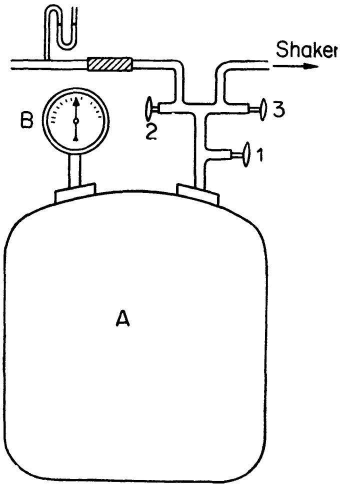

Figure 2. Apparatus for hydrogenation at moderate over pressure.

An iron tank A of 20-l capacity, and tested to 6 atm carries a manometer B and needle valves 1–3. The hydrogen bomb is securely attached to the tank by a "Tombak" or an armoured rubber tube.

For the first filling, the tank is evacuated through valves 1 and 2, with valve 3 closed, by means of an oil pump, then hydrogen is admitted from the bomb to a pressure of 3 atm; of course, the leads must have been previously cleared with hydrogen. If the tank is tight, which is tested on the manometer, valve 3 is connected to the shaking apparatus.

As hydrogenation vessel a strong-walled, tested pressure flask is used, which is closed by purified rubber stoppers made safe for pressure work in the usual way. Thick-walled pressure tubing, in perfect condition, is used for connection to the outlet valve 3. The tubing and stoppers should have been boiled several times with 20% sodium hydroxide solution, until the liquid is no longer colored yellow, and then washed carefully and repeatedly with hot distilled water.

The shaking vessel is attached, valve 1 is closed, valves 2 and 3 are opened, and the whole is evacuated. Then valve 2 is closed, valves 1 and 3 are opened, the pressure is read, and the shaker operated for 6–8 h; if the manometer reading does not fall by more than 0.02–0.03 atm during this time, the apparatus can be considered ready for operation. A reduction is carried out with a test substance, and the pressure fall is noted, whence the fall corresponding to one mole of hydrogen at the reigning temperature is calculated.

Maleic acid is a suitable test substance. 0.1 mole (11.6 g) is dissolved in 150 ml of ordinary ethanol and 0.1 g of platinum oxide is added. If the apparatus and reagents are in order, the time from beginning of shaking to the end of hydrogen uptake will be 20–30 minutes.

ii, High-pressure hydrogenation

Although most hydrogenations can be effected at atmospheric pressure with the usual shaking apparatus, it is sometimes necessary to work at higher pressure. Hydrogenation of aromatic rings is usually best carried out at 100 to 150 atm. Pressures of 300 atm suffice for reduction of carboxylic esters and carboxamides with copper chromite catalysts; but pressures of 700–1000 atm are required in some cases, *e.g.*, for hydrogenation with sulfide catalysts. All other hydrogenations can be carried out at pressures between 10 and 100 atm.

Laboratory high-pressure autoclaves can be filled to 100 atm with hydrogen from pressure bottles containing a maximum pressure of 125 atm; this corresponds to a pressure of about 175 atm at 250°. In general, hydrogen pressures of 40–200 atm can be obtained in the autoclave by normal methods; greater hydrogen pressures can be obtained by use of a compressor. The course of hydrogenation can be followed by the drop in pressure. A graphical presentation (see Houben–Weyl, Vol. 4/2, page 260) permits the amount of hydrogen added or the amount within the gas space of the autoclave to be determined from the pressure and temperature reigning at any time during a reaction.

Since at elevated pressures considerable quantities of hydrogen dissolve in the solutions or substances to be hydrogenated, shaking need not be so violent as at normal pressure. So it often suffices to use a shaking autoclave, which is simpler than a stirring autoclave to service and maintain.

The autoclave must be made of an indifferent material and must not influence the reaction unfavorably. This is achieved by coating the inside with copper, silver, or other suitable material; but autoclaves are also available in chrome–nickel steel.

A hydrogenation autoclave must be fitted with a manometer, a safety valve, and a valve through which additional hydrogen can be pressed in during an experiment. The temperature must be measured in the interior of the autoclave, either by a built in thermoelement or by a thermometer placed in a sheath that reaches into the interior.

It should be noted that protection may be legally required for work with pressure vessels of a certain size; their installation and supervision may be subject to official control.

For hydrogenations under pressure the autoclave is closed after the substance and catalyst have been introduced, and it is then washed out by repeated filling with, and release of, nitrogen; or the air is removed by evacuation. The test for tightness is to leave the autoclave under pressure for some time. After release of the nitrogen, the autoclave is filled with hydrogen, the initial pressure being chosen such that heating does not raise it higher than permissible. At the end of the hydrogenation the autoclave is first allowed to cool and then to come to atmospheric pressure through the valve; only after that may it be opened, Care is required when emptying the autoclave because certain catalysts, *e.g.*. Raney nickel, are pyrophoric and so must always remain under a layer of liquid. In such cases a stout-walled glass liner may be inserted, although this fulfils its purpose only partly when the substance volatilizes during the reaction.

iii, Hydrogenation in a catalyst tube

Gases, and substances that are readily volatilized, can be hydrogenated in the vapor phase over nickel or copper carrier catalysts. A flow apparatus is generally used, in which a vertical catalyst tube of high-melting glass contains pieces or fibres of catalyst filling its whole cross-section. The catalyst tube is heated electrically from outside. It must be possible to measure the temperature in the interior of the catalyst layer; a protective sheath running through the tube permits a thermoelement to be inserted by means of which the temperature can be measured at any desired height in the catalyst tube. When heating baths are used, the catalyst tube may be a U tube, or similar tube, with the entry and exit for the gas at the top.

Reduction with metal oxide catalysts may also be effected in tubes, 3–6 cm in diameter, of high-melting glass, quartz, or porcelain, that slope gently downwards (see Figure 3).

The temperature in the interior of the tube is measured by a moveable thermoelement. A pre-heat zone in the tube is left empty so that the hydrogen can attain the desired temperature before it reaches the catalyst. The course of the reduction can be recognized by the change in color of the catalyst or by the formation of water. If the reduced catalyst must be prevented from coming into contact with air, then, after cooling, the hydrogen is replaced by pure nitrogen or sulfur-free carbon dioxide; it can then be emptied directly into liquid to be reduced or can be stored under an inert gas or inert liquid.

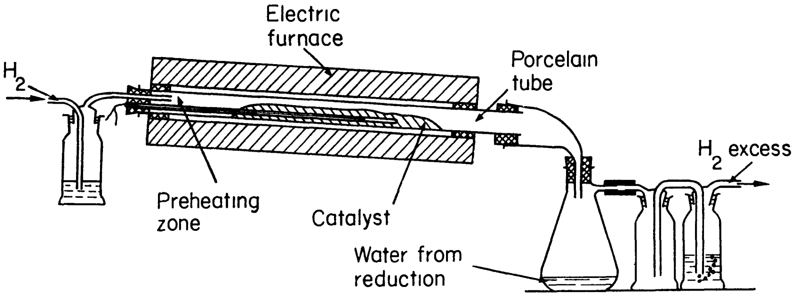

Figure 3. Apparatus for reduction of catalysts. (From Houben-Weyl, "Methoden der organischen Chemie," 4th ed., Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 262.)

c. Examples of catalytic hydrogenation

i, Choice of catalyst

No universally valid rules are available for the choice of catalysts suitable for hydrogenation of the various types of unsaturated compound; but certain catalysts have been proved valuable for specific cases.

Platinum, palladium, and nickel are useful for hydrogenation of gaseous and easily volatilized olefins in the vapor phase. Liquid olefins, unsaturated alcohols, and cycloalkenes can be hydrogenated in a shaking apparatus with noble-metal catalysts (in ethanol, glacial acetic acid, or ethyl acetate) or with Raney nickel, or in autoclaves with other nickel catalysts. Unsaturated acids can be hydrogenated over nickel catalysts when presented as esters or, for acids of low molecular weight, as sodium salts in aqueous or aqueous-alcoholic solution, or in the melt as free acids; noble-metal catalysts can, however, also be used for hydrogenation of unsaturated acids.

Hydrogenation of unsaturated side chains of aromatic compounds can be achieved in the liquid phase with Raney nickel or platinum and in the gas phase with copper catalysts. In most cases the differing rates of hydrogenation of olefinic and aromatic double bonds permits selective saturation of the side chain.

For selective saturation of one of several double bonds, palladium or Raney nickel can be used. Platinum is less selective but can nevertheless sometimes be used. The reaction is interrupted after consumption of the calculated amount of hydrogen. Sulfur must be completely absent during hydrogenation of aromatic rings with platinum metals; derivatives of benzene such as benzoic acid and phenol, also naphthalene, are more easily hydrogenated than benzene itself; but for such cases it is often advantageous to use nickel catalysts in an autoclave.

ii, Hydrogenation of olefinic double bonds

It is generally unnecessary to use particularly active catalysts for hydrogenation of olefinic double bonds, although according to Schuster[198] the rate of hydrogenation decreases with longer chains. Terminal double bonds react faster than those in the interior of a chain, and the latter faster than those at a branch point.[199] Thus, for instance, the olefinic double bond in triphenylethylene is hydrogenated in the presence of noble-metal catalysts at one-tenth of the rate for the double bond in styrene; tetraphenylethylene can be hydrogenated only at 100° and 125 atm.[200] Compounds of type $R_2C{=}CR_2$ and $R_2C{=}CHR$ can, in general, not be hydrogenated with Raney nickel, whereas those of type $R_2C{=}CH_2$ can: an ethylene can be the more easily hydrogenated the less the substitution (Lebedew's rule). When several reducible groups in one molecule compete for catalytically activated hydrogen, then, generally speaking, a definite series of priorities applies: double bonds and nitro groups are attacked approximately simultaneously, then follow seriatim

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[198] C. Schuster, *Z. Elektrochem.*, **38**, 614 (1932).

[199] G. Vavon and D. Ivanoff, *C. R. Hebd. Séances Acad. Sci.*, **177**, 453 (1923).

[200] W. H. Zartman and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 1668 (1932).

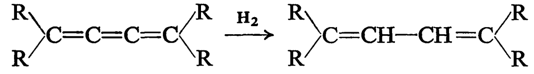
carbonyl groups, cyano groups, hydroxyl groups, aromatic systems, heterocycles, and the very resistant carboxyl group. *cis*-Compounds are hydrogenated more easily than their *trans*-isomers: under the same conditions maleic acid is hydrogenated three times faster than fumaric acid;[201] of the pair *cis*/*trans*-cinnamic acid the *cis*-acid is hydrogenated at twice the rate.[201] According to Weygand, Werner, and Lanzendorf,[206] this rule, set up by Paal and Schiedewitz,[201] is, however, not without exceptions; for instance, certain *trans*-dibenzoylethylenes are hydrogenated appreciably faster than the *cis*-isomers.

Addition of hydrogen always occurs in the *cis*-sense.

iii, Selective hydrogenation

Cyclohexane is the only product obtained on catalytic hydrogenation of benzene, and the two intermediates cyclohexadiene and cyclohexene are not isolated because they are hydrogenated faster than the aromatic system. However, hydrogenation of non-aromatic conjugated double bonds takes a totally different course. According to studies by Rieche, Grimm, and Albrecht,[203] hydrogenation of 1,3-butadiene with a palladium catalyst occurs by stepwise saturation of the double bonds: only butenes, and no butane, are formed until all the butadiene has been consumed, and only then are the butenes hydrogenated to butane; in contrast to other additions, catalytic hydrogenation of 1,3-butadiene occurs mainly by 1,2-addition.

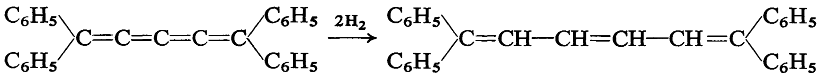
Partial hydrogenation of cumulenes affords *cis*-polyenes selectively in the presence of the Lindlar catalyst (a palladium–calcium catalyst deactivated by lead acetate; see p. 19); hydrogenation ceases almost entirely after a rapid absorption of $(n - 1)/2$ moles of hydrogen (n = number of double bonds). According to Kuhn and Fischer,[139] tetraphenylbutatriene absorbs one equivalent of hydrogen, yielding **1,1,4,4-tetraphenyl-1,3-butadiene**:



$$R_2C{=}C{=}C{=}CR_2 \xrightarrow{H_2} R_2C{=}CH{-}CH{=}CR_2$$

To a pre-reduced suspension of 800 mg of Lindlar catalyst in 50 ml of tetrahydrofuran (distilled over KOH) are added 500 mg of tetraphenylbutatriene, and the mixture is shaken at 21°. In 15 min 35 ml (31.5 ml at NTP) corresponding to 1 equivalent of H_2 are absorbed. Only a further 3 ml are consumed in a further hour's shaking. The mixture is filtered and the solvent removed. The residue, recrystallized from cyclohexane, constitutes 420 mg (84%) of colorless rhombs, m.p. 201°.

Tetraphenylhexapentaene absorbs 2 equivalents of hydrogen with formation of the corresponding *cis*-polyene:



$$(C_6H_5)_2C{=}C{=}C{=}C{=}C(C_6H_5)_2 \xrightarrow{2H_2} (C_6H_5)_2C{=}CH{-}CH{=}CH{-}CH{=}C(C_6H_5)_2$$

According to Natta, Rigamonti, and Tono,[204] butadiene and 1,3-pentadiene are hydrogenated to the corresponding monoalkenes quantitatively in the

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[201] C. Paul and H. Schiedewitz, *Ber. Deut. Chem. Ges.*, **60**, 1221 (1927); **63**, 766 (1930).

[202] C. Weygand, A. Werner, and W. Lanzendorf, *J. Prakt. Chem.*, **151**, 231 (1938).

[203] A. Rieche, A. Grimm, and H. Albrecht, *Brennstoff-Chem.*, **42**, 177 (1961).

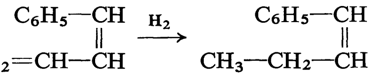
[204] G. Natta, R. Rigamonti, and P. Tono, *Chim. Ind. (Milan)*, **29**, 235 (1947).

vapor phase at atmospheric pressure in the presence of a nickel–zinc chromite catalyst.

When, owing to differing substitution, conjugated double bonds are not equivalent, the substituted double bond is more difficult to hydrogenate than the unsubstituted one:[205]

$$CH_2{=}CH{-}CH{=}CH{-}COOH \xrightarrow{H_2} CH_3{-}CH_2{-}CH{=}CH{-}COOH$$

Hydrogenation of phenylbutadiene proceeds analogously:[205]



$$\begin{array}{c} C_6H_5{-}CH \\ \| \\ CH_2{=}CH{-}CH \end{array} \xrightarrow{H_2} \begin{array}{c} C_6H_5{-}CH \\ \| \\ CH_3{-}CH_2{-}CH \end{array}$$

Hydrogenation of the isomeric *trans*-compound gives the corresponding ***trans*-phenylbutene**:

cis-Phenylbutadiene (17.2 g) was dissolved in glacial acetic acid (100 ml) in a shaking apparatus, and Adams catalyst (PtO_2) (0.15 g) was added. One equivalent of hydrogen was absorbed in 15 minutes' hydrogenation. The reaction was then interrupted. After removal of the catalyst the solution was distilled under diminished pressure. The phenylbutene obtained from the *cis*-phenylbutadiene distilled at 73–74.5°/12 mm. The phenylbutene from *trans*-phenylbutadiene distilled at 76–78°/12 mm. The yields were almost quantitative. The authors do not state the pressure at which hydrogenation was carried out; but they used the apparatus shown in Figure 2.

Hydrogenation of 2,4-pentadienoic acid was carried out analogously: The acid (29.5 g) was dissolved in purified methanol (100 ml), and Adams catalyst (0.25 g) was added. 3-Pentenoic acid distilled at 93°/15 mm. The yield was almost quantitative. In this hydrogenation, also, the reaction was interrupted after absorption of 1 equivalent (0.602 g) of hydrogen in 20 min.

On hydrogenation of citral

$$(CH_3)_2C{=}CH{-}CH_2{-}CH_2{-}C(CH_3){=}CH{-}CHO$$

with a platinum oxide–platinum black catalyst, the double bond next to the aldehyde group was reduced first, then the aldehyde group, and finally the second ethylenic bond. If, however, iron(II) sulfate and zinc acetate were added to the catalyst, the aldehyde group was reduced first and, after absorption of one equivalent of hydrogen, mainly geraniol

$$(CH_3)_2C{=}CH{-}CH_2{-}CH_2{-}C(CH_3){=}CH{-}CH_2OH$$

was obtained; absorption of a further one equivalent gave citronellol

$$(CH_3)_2{=}CH{-}CH_2{-}CH_2CH(CH_3){-}CH_2{-}CH_2OH$$

and further hydrogenation gave tetrahydrogeraniol.[206]

Analogously, Tuley and Adams[207] converted cinnamaldehyde smoothly into cinnamyl alcohol by addition of one equivalent of hydrogen in the presence of platinum black to which 0.01–0.02 milliequivalent of iron(II) chloride had been added; on further hydrogenation 3-phenyl-1-propanol was formed. If, however, iron(II) sulfate and zinc acetate were added, hydrogenation ceased

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[205] I. E. Muskat and B. Knapp, *Ber. Deut. Chem. Ges.*, **64**, 779 (1931).

[206] R. Adams and B. S. Garvey, *J. Amer. Chem. Soc.*, **48**, 477 (1926).

[207] W. F. Tuley and R. Adams, *J. Amer. Chem. Soc.*, **47**, 3061 (1925).

after absorption of one equivalent of hydrogen and cinnamyl alcohol was obtained almost exclusively.

Adams and his collaborators[208] observed similar behavior on hydrogenation of 3-(2-furyl)acraldehyde. In the presence of iron(II) sulfate and zinc acetate hydrogenation gave first 3-(2-furyl)allyl alcohol, with retention of the double bond; the alcohol absorbed a further equivalent of hydrogen and yielded 3-(2-furyl)-1-propanol. In the presence of iron(II) sulfate alone attack was mainly on the furan ring, and 3-(2-furyl)allyl alcohol was obtained, this being finally hydrogenated to 3-(tetrahydro-2-furyl)-1-propanol. In the presence of zinc acetate alone, 3-(2-furyl)allyl alcohol is not further hydrogenated.

On hydrogenation of unsaturated acids the double bond is usually saturated preferentially. For instance, Maxted and Stone[209] reduced crotonic to butyric acid by using Adams catalyst (PtO_2); and undecenoic acid was reduced to undecanoic acid, also in the presence of PtO_2.[210] Sorbic acid can be hydrogenated, in ethanol in presence of Raney nickel or, better, palladium at room temperature and atmospheric pressure, yielding 2-hexenoic acid (containing also some 3-hexenoic, sorbic, and hexanoic acid);[211] thus in sorbic acid the double bond next to the carboxyl group is the harder to hydrogenate, as in 2,4-pentadienoic acid. Wojcik and Adkins[212] reduced α-alkylidene-β-keto carboxylic esters which they obtained by loss of water between aldehydes and ethyl acetoacetate or diethyl malonate; in the presence of Raney nickel (10–15% of the weight of the ester) at room temperature and 100–200 atm, with ether as solvent, yields in excess of 90% of α-alkyl-β-keto carboxylic esters were obtained. Horning and his co-workers[213] used palladium–charcoal for hydrogenation of the ethylenic double bond of ethyl 2-acetyl-3-(2,3-dimethoxyphenyl)acrylate, which was prepared from 2,3-dimethoxybenzaldehyde and acetoacetic ester.

When platinum or palladium is used as catalyst, the acids themselves can be hydrogenated. When nickel is used it is advantageous to hydrogenate the esters. Allen and his colleagues hydrogenated the alkali salts of some unsaturated acids at high pressure.[214]

Succinic acid: In an autoclave (325 ml capacity), 58 g of maleic acid, dissolved in 100 ml of water containing 5 g of sodium hydroxide more than needed for neutralization, were treated with 5–8 g of Raney nickel.[215] Hydrogen was added to a pressure of 170 atm and heating then commenced. The pressure at first rose, but it decreased as reaction began (at 100°). This temperature of 100° was maintained until the end of the reaction; after 26 min there was no further fall in pressure. After removal of the catalyst (care: pyrophoric!), the mixture was acidified and the water removed in a vacuum. The succinic acid was extracted with absolute ethanol and the ethanol was then evaporated. 57 g (98%) of succinic acid were obtained; when recrystallized from water it melted at 184–185°.

Although the carboxyl group was unaffected in the hydrogenations of unsaturated acids and esters described above, Sauer and Adkins[192a] succeeded in

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[208] R. H. Bray and R. Adams, *J. Amer. Chem. Soc.*, **49**, 2101 (1927).
[209] E. B. Maxted and V. Stone, *J. Chem. Soc.*, **1934**, 26.
[210] J. W. Kern, R. L. Shriner, and R. Adams, *J. Amer. Chem. Soc.*, **47**, 1147 (1923).
[211] E. H. Farmer and L. A. Hughes, *J. Chem. Soc.*, **1934**, 1929.
[212] B. Wojcik and H. Adkins, *J. Amer. Chem. Soc.*, **56**, 2424 (1934).
[213] E. C. Horning, J. Koo, M. S. Fisch, and G. N. Walker, *Org. Syn.*, **31**, 56 (1951).
[214] B. B. Allen, B. W. Wyatt, and H. R. Henze, *J. Amer. Chem. Soc.*, **61**, 843 (1939).
[215] W. Covert and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 4116 (1932).

reducing unsaturated esters to unsaturated alcohols by using a zinc oxide–chromium oxide catalyst. The unsaturated alcohols could then be simply hydrogenated to the saturated alcohols, in the same way as olefins are reduced, *e.g.*, with platinum or palladium on the shaker; at higher temperatures the corresponding olefins can be formed by loss of water from the alcohols.

iv, Hydrogenation of aromatic compounds

Although the hydrogenation of aromatic systems requires more energetic conditions than does that of olefinic double bonds, the difficulties involved in hydrogenating aromatic systems have usually been exaggerated in the earlier literature. At any rate, aromatic systems were later hydrogenated just like other unsaturated centers; only hydroxyl and carboxyl groups provided exceptions. With modern catalysts, such as platinum oxide, hydrogenation is often successful even at room temperature.

Adams and Marshall[216] hydrogenated benzene (15.6 g) quantitatively to **cyclohexane** in glacial acetic acid at room temperature and 2–3 atm hydrogen pressure within 2 h in the presence of PtO_2 (0.2 g).

Only if absolutely free from sulfur can aromatic compounds be hydrogenated with platinum metals at low temperatures. Willstätter and Hatt[217] hydrogenated twelve times recrystallized naphthalene in glacial acetic acid quantitatively to decalin in presence of platinum black at room temperature and atmospheric pressure. Schroeter[218] hydrogenated naphthalene to decalin in precence of nickel catalysts at 40 atm and about 200°, and to **tetralin** at 15 atm and about 200°:

The naphthalene used must be pure and free from sulfur-containing, poisonous impurities. Repeated melting with sodium and subsequent vacuum distillation proved the most successful method of purification. Naphthalene (512 g) is melted in a stirring autoclave (capacity 4 l) with a suitable nickel compound (basic carbonate or oxide; 15–20 g), the autoclave is closed, pure hydrogen admitted to a pressure of 12–15 atm, the autoclave tested for tightness, and the temperature raised, with stirring, to 180–200°. The pressure first rises, then falls (by 1 atm in 45–60 sec). When the pressure has fallen to 5–8 atm more hydrogen is admitted, until the required amount (178 l) has been absorbed. That point can be recognized by a slackening in the rate of decrease of pressure. When the end of the reaction can be seen to approach the hydrogen supply is turned off and reduction allowed to continue until all the hydrogen present has been completely absorbed. The total time for the experiment amounts to an hour or somewhat longer. The tetralin formed can be distilled out of the autoclave under a vacuum, leaving the catalyst, and a second equal amount of naphthalene can be reduced on the same catalyst. Schroeter was able to carry through up to 25 batches without opening the autoclave; he allowed the new charge to flow in the molten state into the autoclave whilst it was still evacuated from the preceding distillation.

Like benzoic acid, phenol, and other benzene derivatives, naphthalene can be hydrogenated more easily than benzene.

Durland and Adkins[219] were able to hydrogenate phenanthrene to **9,10-dihydrophenanthrene** by using copper–chromium oxide:

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[216] R. Adams and J. R. Marshall, *J. Amer. Chem. Soc.*, **50**, 1970 (1928).

[217] R. Willstätter and D. Hatt, *Ber. Deut. Chem. Ges.*, **45**, 1471 (1912).

[218] G. Schroeter, *Ann. Chem.*, **426**, 1 (1922); cf. L. Palfray, *C. R. Hebd. Séances Acad. Sci.*, **206**, 1976 (1938), and M. Pier, *Z. Elektrochem.*, **53**, 297 (1949).

[219] J. R. Durland and H. Adkins, *J. Amer. Chem. Soc.*, **59**, 135 (1937); A. Burger and E. Mosettig, *J. Amer. Chem. Soc.*, **58**, 1857 (1936).

Phenanthrene (40 g) is hydrogenated with copper chromite (4 g) in ethanol (100 ml) at 150° with a hydrogen pressure of 150–200 atm. The reaction lasts about 3 h. After the hydrogenation the mixture is fractionated through a Widmer column, the fraction distilling at 176–178°/20 mm being collected. The yield amounts to 87%. When recrystallized from methanol, the dihydrophenanthrene melts at 33.8–34.4°. Further hydrogenation of 9,10-dihydrophenanthrene with copper chromite requires a temperature higher by 50–70°, so it is better to use nickel catalysts for complete hydrogenation of phenanthrene.

The preparation of 4-aminocyclohexanecarboxylic acid[220] will be described as an example of hydrogenation of aromatic compounds. The technique has the advantage that an aqueous suspension is used, without an organic solvent.

4-Aminocyclohexanecarboxylic acid:[221] *p*-Aminobenzoic acid (10 g; twice recrystallized from water) is suspended in water (800 ml) in a shaking flask, and platinum oxide (0.5 g; freshly prepared) is added. Hydrogenation requires 14.5 h, somewhat more than the theoretical amount of hydrogen being absorbed. The end of the hydrogenation is best recognized by flocculation of the catalyst. On completion of the hydrogenation the mixture is filtered, the filtrate is evaporated to dryness, and the brown crystal cake is recrystallized from a little water with addition of charcoal. The yield amounts to 6–7 g, corresponding to 60–70% of theory. The colorless needles of 4-aminocyclohexanecarboxylic acid contain 0.5 mole of water of crystallization and melt at 275–280° in a closed tube. Melting points between 260° and 330° are recorded in the literature. For separation of *cis*- and *trans*-isomers of 4-aminocyclohexanecarboxylic acid see reference 220).

It is possible also to start from the nitro compounds and to reduce these in aqueous solution in one step to the corresponding amino acids.

Cyclohexanecarboxylic acid: Ipatiev and Rasuwajev[222] hydrogenated sodium benzoate (50 g) in water (75 ml) in the presence of NiO (7 g) at an initial pressure of 92 atm of hydrogen. At a temperature of 300° the authors obtained 40% of cyclohexanecarboxylic acid of b.p. 235–238° and 9 g of cyclohexane.

Decarboxylation usually occurs on hydrogenation of aromatic hydroxy acids; their salts also can be only partly reduced without decarboxylation. On hydrogenation of 65 g of methyl salicylate in 65 g of methanol containing NiO, Ipatiev and Rasuwajev[223] obtained 40 g of cyclohexanol.

Hydrogenation of phenol also leads to cyclohexanol. It can be carried out in the vapor phase[224] or under pressure with nickel catalysts.[225]

Dihydroresorcinol is obtained in 85–95% yield from resorcinol by means of Raney nickel or 'Universal Oil Products Ni-SiO_2 catalyst' under pressure at 50° in 10–12 h.[226] Grewe, Nolte, and Rotzoll[44] used alkali-treated Raney nickel. Stetter and Dierichs[227] simplified the process by hydrogenating with freshly activated Raney nickel at atmospheric pressure and 50°, the duration being 24 h and the yield of dihydroresorcinol 98%.

On hydrogenation of 3,5-dihydroxybenzoic acid with Raney nickel catalyst W 1 (see Billica and Adkins[155]), 3,5-dioxocyclohexanecarboxylic acid is obtained.[228] Hydrogenation of 3-ethylphenol with Raney nickel leads to 3-ethylcyclohexanol.[229]

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[220] E. Ferber and H. Brückner, *Ber. Deut. Chem. Ges.*, **76**, 1022 (1943).

[221] R. Gabler, personal communication; see also ref. 226.

[222] W. Ipatiev and G. Rasuwajev, *Ber. Deut. Chem. Ges.*, **59**, 306, 2028 (1926).

[223] W. Ipatiev and G. Rasuwajev, *Ber. Deut. Chem. Ges.*, **59**, 2031 (1926).

[224] P. Sabatier and J. B. Senderens, *C. R. Hebd. Séances Acad. Sci.*, **137**, 1025 (1903).

[225] A. Brochet, *Bull. Soc. Chim. France.* [iv], **31**, 1270 (1922).

[226] R. B. Thompson, *Org. Syn.*, **27**, 21 (1947).

[227] H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 61 (1952).

[228] E. E. van Tamelen and G. T. Hildahl, *J. Amer. Chem. Soc.*, **78**, 4405 (1956).

[229] C. V. Banks, D. T. Hooker, and J. J. Richard, *J. Org. Chem.*, **21**, 547 (1956).

β-Naphthol can be hydrogenated selectively, either the oxygenated or the non-oxygenated ring being reduced. Use of Raney nickel catalyst W 4 at 65° in the presence of NaOH leads to saturation of the phenolic ring and a 65% yield of 1,2,3,4-tetrahydro-2-naphthol within 1.5 h; in the absence of NaOH, the non-oxygenated ring is saturated with formation of a 87% yield of 5,6,7,8-tetrahydro-2-naphthol.[230] McKusick[231] hydrogenated 2-naphthols to 1,2,3,4-tetrahydronaphthols in the presence of copper chromite; phenols, cresols, and thymols can also be hydrogenated with copper chromite under pressure and at high temperatures.[232]

Oxide catalysts such as cobalt oxide and nickel oxide[233] are recommended for hydrogenation of primary aromatic amines to saturated primary amines; the formation of secondary and tertiary amines, and of deaminated products, is avoided by use of these catalysts. Secondary and tertiary amines can be hydrogenated with Raney nickel. Addition of concentrated hydrochloric acid during hydrogenation of primary unsaturated amines with platinum metals leads predominantly to primary amines.

Cyclohexylamine is obtained, according to Skita and Berendt[234], by hydrogenating aniline in hydrochloric–acetic acid in presence of colloidal platinum:

A mixture of a 10% solution (30 ml) of hydrogen hexachloroplatinate and a 2% solution of gum arabic (75 ml) was seeded with a colloidal platinum solution (15 ml). The seeding solution was prepared by reducing colloidal platinum(II) hydroxide and contained 0.03 g of platinum per ml. The colloidal platinum solution was formed after 0.5 hour's shaking with hydrogen at 1 atm pressure; it contained 1.5 g of platinum. Aniline (8.37 g) was dissolved in glacial acetic acid (110 ml) and added to the colloidal platinum solution; then 36% hydrochloric acid (10 ml) was added. The hydrogenation vessel was evacuated and then connected to the hydrogen reservoir. After 2.5 h the calculated amount of hydrogen has been absorbed. Most of the acetic acid was then distilled off in a vacuum, the residue made alkaline with sodium hydroxide solution, and a liquid with a basic smell was driven over with steam. This liquid was taken up in ether, dried, recovered by evaporation of the ether, and distilled. It constituted cyclohexylamine (8 g), b.p. 135°.

Ruthenium dioxide has also been recommended[235] as catalyst for hydrogenation of the ring of amines.

v, Hydrogenation of heterocycles

Catalytic hydrogenation of furan can be effected by Sabatier's method with nickel at 170°. Cloke and Ayers[236] effected it at 50° with Raney nickel. Starr and Hixon[237] hydrogenated 120 g of furan in absence of solvent in about 20 h at 7 atm, obtaining a 96% yield by using palladium oxide as catalyst.

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[230] H. Adkins and G. Krsek, *J. Amer. Chem. Soc.*, **70**, 412 (1948).

[231] B. C. McKusick, *J. Amer. Chem. Soc.*, **70**, 2196 (1948).

[232] W. R. Brode and R. W. van Dolah, *Ind. Eng. Chem.*, **39**, 1157 (1947).

[233] Ger. Pat. 528,465 (1931); *Chem. Abstr.*, **25**, 4556 (1931).

[234] A. Skita and W. Berendt, *Ber. Deut. Chem. Ges.*, **52**, 1519 (1919).

[235] L. C. Behr, J. E. Kerby, R. N. MacDonald, and C. W. Todd, *J. Amer. Chem. Soc.*, **68**, 1296 (1946); A. E. Barkdoll, D. C. England, H. W. Gray, W. Kirk Jr., and G. M. Whitman, *J. Amer. Chem. Soc.*, **75**, 1156 (1953).

[236] J. B. Cloke and O. Ayers, *J. Amer. Chem. Soc.*, **56**, 2144 (1934).

[237] D. Starr and R. M. Hixon, *J. Amer. Chem. Soc.*, **56**, 1595; see also *Org. Syn.*, **16**, 78.

The aldehyde group of furfuraldehyde is easier to hydrogenate than the ring. Copper–chromium oxide[238] and copper–barium chromite[239, 193b] have each been recommended as catalyst for hydrogenation of furfuraldehyde to furfuryl alcohol; further hydrogenation affords tetrahydrofurfuryl alcohol, which is obtained directly from furfuraldehyde by using platinum and iron(II) chloride. More severe conditions lead to rupture of the ring with formation of pentanediols.

Hydrogenation of pyrrole is very difficult. Platinum in glacial acetic acid,[240] and rhodium or palladium on asbestos,[241] should be considered. Andrews and McElvain used platinum oxide.[69]

Pyrrolidine:[69] Pyrrole (18 g; twice distilled from sodium) was dissolved in glacial acetic acid (60 ml) and hydrogenated with platinum oxide (0.5 g). Absorption of hydrogen was throughout very slow and occasionally ceased completely, but the catalyst could be reactivated by shaking the reaction mixture with oxygen. Fresh platinum oxide (0.3 g) was added after 45 h, and after 96–100 h the theoretical amount of hydrogen had been absorbed. After the platinum had settled, the dark solution was decanted, the acetic acid was neutralized with concentrated sodium hydroxide (under a reflux condenser to avoid loss of the volatile pyrrolidine), an excess of sodium hydroxide was added, and the mixture was distilled in steam until the distillate no longer reacted alkaline to litmus. The distillate (about 1 l) was acidified with hydrochloric acid and evaporated to dryness on the water-bath. The dark, viscous residue was treated with 40% sodium hydroxide solution and extracted with ether. After the ethereal solution had been dried with sodium sulfate, fractionation afforded 63% (12 g) of pyrrolidine of b.p. 85–88°.

De Jong and Wibaut[240] hydrogenated pyrrole in glacial acetic acid with a platinum catalyst (from PtO_2) at 20° and 1.8 atm pressure of hydrogen and obtained ca. 80% of pyrrolidine within 4 h. Craig and Hixon[242] hydrogenated pyrrole in alcohol with PtO_2 at 6 atm.

In general, pyrroles are appreciably more easily reduced when substituted on nitrogen than when unsubstituted. For instance, 1-phenylpyrrole can be smoothly reduced to 1-cyclohexylpyrrolidine;[242] Rainey and Adkins[243] used Raney nickel for hydrogenation of ethyl 1-pyrrolecarboxylate.

The pyridine ring can be hydrogenated analogously to the benzene ring, but the pyridine ring of, for example, quinoline or isoquinoline is hydrogenated before the benzene ring. Platinum,[150b, 244] nickel at high pressure,[245] and osmium–cerium catalysts[246] have been used for hydrogenation of these compounds. Hydrogenation of 2-methylpyrrole is effective with platinum at 2–3 atm.[247] Adkins and Cramer[248] hydrogenated pyridine derivatives under pressure with a nickel–kieselguhr catalyst. 2-Methylpyridine can be hydrogenated to 2-methylpiperidine in 90% yield with Raney nickel at 200° and 150–300 atm pressure of hydrogen.[249]

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[238] H. D. Brown and R. M. Hixon, *Ind. Eng. Chem.*, **41**, 1382 (1949).

[239] R. Schröter, personal communication (see Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 307).

[240] M. De Jong and J. P. Wibaut, *Rec. Trav. Chim.*, **49**, 237 (1930).

[241] N. D. Zelinskii and Yu. K. Jur'ev, *Ber. Deut. Chem. Ges.*, **64**, 101 (1931).

[242] L. C. Craig and R. M. Hixon, *J. Amer. Chem. Soc.*, **52**, 804 (1930).

[243] J. L. Rainey and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 1104 (1939).

[244] A. Skita and W. A. Meyer, *Ber. Deut. Chem. Ges.*, **45**, 3593 (1912); see also *Chem. Ztg.*, **38**, 605 (1914); J. Overhoff and J. P. Wibaut, *Rec. Trav. Chim.*, **50**, 957 (1930).

[245] V. Ipatiev, *Ber. Deut. Chem. Ges.*, **41**., 991 (1908); J. von Braun, A. Petzold, and J. Seeman, *Ber. Deut. Chem. Ges.*, **55**, 3779 (1922).

[246] V. S. Sadikov and A. K. Mikhailov, *Ber. Deut. Chem. Ges.*, **61**, 1800 (1928).

[247] A. Skita and W. Brunner, *Ber. Deut. Chem. Ges.*, **49**, 1597 (1916).

[248] H. Adkins and H. I. Cramer, *J. Amer. Chem. Soc.*, **52**, 4349 (1930).

[249] H. Adkins, L. F. Knick, M. Farlow, and B. Wojcik, *J. Amer. Chem. Soc.*, **56**, 2427 (1934).

vi, Catalytic hydrogenation by bonded hydrogen

Instead of molecular hydrogen, Kindler and Peschke[250] used the readily dehydrogenated tetralin for hydrogenations. They achieved selective action in this way; for instance; cinnamonitrile was reduced almost quantitatively to 3-phenylpropionic acid, the cyano group remaining unaffected. 4-Chlorocinnamic acid afforded 3-(*p*-chlorophenyl)propionic acid without the chlorine atom being attacked. According to these results the use of tetralin as solvent in catalytic hydrogenations can achieve special results.

3-(*p*-Chlorophenyl)propionic acid: A solution of 4-chlorocinnamic acid (5 g) in tetralin (180 ml) containing palladium black (1 g) is heated at the boiling point for 1.5 h in a Kjeldahl flask under an air condenser. The side chain is then completely reduced. The catalyst is filtered off, the acid components are removed from the filtrate in sodium carbonate solution, adhering tetralin is removed from the alkaline solution by ether, the alkaline solution is acidified by hydrochloric acid, and the 3-(*p*-chlorophenyl)propionic acid that separates is taken up in ether. On evaporation, the pure 3-(*p*-chlorophenyl)propionic acid of m.p. 123° is obtained.

The tetralin used is purified by extraction with dilute hydrochloric acid, washing, and drying with calcium chloride and is then distilled.

II. Addition of hydrogen to C≡C bonds

Complete hydrogenation of the C≡C bond presents few peculiarities compared with that of the C=C bond beyond those due to the special nature of acetylene compounds, such as the possibility of forming explosive heavy-metal acetylides and the larger consumption of hydrogen due to the greater degree of unsaturation. Addition of the first equivalent of hydrogen is usually easier than further hydrogenation to the saturated compound, because adsorption of acetylenes on the catalyst surface is evidently much favored. Thus the methods discussed in the preceding Section can almost always be used for complete hydrogenation of a triple bond. For work with particularly sensitive substances that require unusually rapid handling it is advisable to use the platinum catalysts described by Brown and Brown.[251] Use, under mild conditions, of catalysts having higher sensitivity than usual represses disturbing side reactions that occur simultaneously.

However, conversion of the acetylenic into the olefinic bond makes special preparative demands. This half-reduction can be effected by chemical reagents as well as by catalytically activated hydrogen; the stable *trans*-ethylenic stereoisomers are usually obtained by the first method, whereas the second of these methods gives predominantly the metastable *cis*-isomers of higher energy content.

A review of hydrogenations leading to total or partial saturation can be obtained from relevant monographs.[252]

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[250] K. Kindler and W. Peschke, *Ann. Chem.*, **497**, 193 (1932).

[251] H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 1493, 1495, 2827, 2829 (1962).

[252] F. Zymalkowski, "Katalytische Hydrierungen im organisch-chemischen Laboratorium," Ferdinand Encke-Verlag, Stuttgart, 1965, pp. 42 *et seq.*; R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N.Y., 1965, pp. 69 *et seq.*

1. Chemical methods

There is a relatively meagre choice of methods suitable for partial reduction of acetylene and its derivatives. In individual cases partial reduction can be effected with sodium and alcohols, zinc and glacial acetic acid, or the zinc–copper couple (cf. a review by Campbell and Campbell[253]). Partial reduction of the triple bond in acetylene itself was described as early as 1916 by Traube and Passarge[254] who used chromium(II) chloride. A variation of this process, in which chromium(II) sulfate is used in water or aqueous dimethylformamide, has been used recently with considerable success for preparation of *trans*-olefins from various compounds containing C≡C bonds;[255] formation of by-products or conversion into *cis*-ethylenes was not observed with this method.

The following details have been given for the preparation of **allyl alcohol:**

400 ml of a 0.71N chromium(II) sulfate solution are treated in a 500-ml three-necked flask with 7.28 g (0.13 mole) of propargyl alcohol, with continuous stirring and introduction of nitrogen. About 250 mmoles of the bivalent chromium are consumed in approximately 5 min. Stirring is continued overnight, then the dark green solution is saturated with ammonium sulfate and extracted four times with ether. After being dried over anhydrous sodium sulfate the ethereal extracts are concentrated and the residue is distilled, whereby 4 g of allyl alcohol of b.p. 95–97° are obtained. A further amount of allyl alcohol, providing a total yield of 89%, can be obtained as aqueous solution by distilling the extraction residue.

From among the common chemical reducing agents lithium aluminum hydride and similar compounds, and alkali metals in liquid ammonia, are the most usually used for saturation of acetylenic bonds.

Isolated triple bonds are normally not attacked by $LiAlH_4$. However, α,β-acetylenic carboxylic acids and their derivatives are reduced, for instance, propiolic acid and acetylenedicarboxylic acid[256] as well as 3-phenyl-2-propynal;[257] attack probably occurs first at the functional group, the end result being *trans*-allylic alcohols. As expected, the isolated triple bond of 1,5-hexadiyne-1-carboxylic acid is resistant and 2-hepten-6-yn-1-ol is obtained in good yield:[258]

$$HC{\equiv}C{-}CH_2{-}CH_2{-}C{\equiv}C{-}COOC_2H_5 \xrightarrow{LiAlH_4} HC{\equiv}C{-}CH_2{-}CH_2{-}CH{=}CH{-}CH_2OH$$

Moreover, presence of neighboring hydroxyl groups[259–263] or conjugation to double bonds[260] permits $LiAlH_4$ to be used for partial reduction of the acetylenic bond; if a conjugated double bond and a neighboring hydroxyl

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[253] K. N. Campbell and B. K. Campbell, *Chem. Rev.*, **31**, 77 (1942).

[254] W. Traube and W. Passarge, *Ber. Deut. Chem. Ges.*, **49**, 1692 (1916).

[255] C. E. Castro and R. D. Stephens, *L. Amer. Chem. Soc.*, **86**, 4358 (1964).

[256] G. E. Benedict and R. R. Russell, *J. Amer. Chem. Soc.*, **73**, 5444 (1951).

[257] F. Wille and F. Knörr, *Chem. Ber.*, **85**, 841 (1952).

[258] B. L. Shaw and M. C. Whiting, *J. Chem. Soc.*, **1954**, 3217.

[259] (a) C. A. Grob and F. Gadient, *Helv. Chim. Acta*, **40**, 1145 (1957); (b) E. F. Jenny and J. Druey, *Helv. Chim. Acta*, **42**, 401 (1959).

[260] E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, **1954**, 1854; H. J. Kubbe, E. Truscheit, and K. Eiter, *Ann. Chem.*, **684**, 14 (1965).

[261] W. Oroshnik and A. D. Mebane, *J. Amer. Chem. Soc.*, **76**, 5719 (1954).

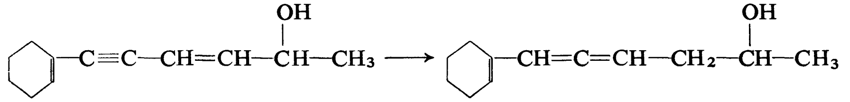
[262] R. Ahmad and B. C. L. Weedon, *J. Chem. Soc.*, **1953**, 2125.

[263] K. R. Bharucha and B. C. L. Weedon, *J. Chem. Soc.*, **1953**, 1584.

group are both present, conjugated olefinic alcohols are accessible by this route.[122,263]

According to Bharucha and Weedon[263] ***trans*-crotyl alcohol** is formed when $LiAlH_4$ (2 g) in anhydrous ether (150 ml) is dropped in 0.5–1 h into a stirred solution of 2-butyn-1-ol (3 g) in anhydrous ether (25 ml), and the mixture is then boiled under reflux for a further 3 h. After cooling, the excess of hydride is decomposed with ethyl acetate (14 ml), and saturated ammonium chloride solution (24 ml) is added. The mixture is then filtered and the ethereal layer is washed with water and dried (Na_2SO_4 plus some K_2CO_3). After removal of the ether the residue is distilled in a vacuum, yielding *trans*-crotyl alcohol (1.6 g) of b.p. 122° and n_D^{23} 1.4278.

In most cases, 1,2-addition of hydrogen to the C≡C bond forms the end result. However, 1,4-addition has been observed to some conjugated enyne systems,[260,263,264] whereby, it is interesting to note, compounds with cumulated double bonds result; *e.g.*:



Further examples of conversion of triple into double bonds by lithium aluminum hydride can be obtained from published monographs.[100]

Reaction of dialkylboron hydrides[265] or dialkylaluminum hydrides[266,267] with compounds containing isolated triple bonds also lead to *cis*-addition, and hydrolysis of the resulting organometallic compounds affords *cis*-olefins:

Tolane (9.5 g) was mixed under nitrogen with diisobutylhydridoaluminum (17 g) and warmed at 45–50° for 12 h. The red product was then cooled in ice, treated cautiously with methanol and dilute sulfuric acid, and extracted with ether. The extract was washed with water and sodium hydrogen carbonate solution, dried over calcium chloride, and evaporated, yielding a residue whence distillation in a vacuum afforded ***cis*-stilbene** (7 g, 73%) of b.p. 147–148°/15 mm.

Using this method, Asinger and his co-workers[268] obtained all the isomeric *cis*-undecenes in sterically pure form; and by treating the same starting materials with sodium in liquid ammonia they obtained the corresponding *trans*-undecenes also in steric purity. Thus, in contrast to the analogous C=C bonds, isolated C≡C triple bonds are attacked by sodium or lithium in liquid ammonia.[1a,1b,54]

Dialkylacetylenes can be converted by such methods in high yield into *trans*-ethylenes that do not contain saturated hydrocarbons as impurity.[1a,b,270,271] However, acetylene[282] and monoalkylacetylenes[1a,b,270,272] are reduced only to one-third, the remainder forming alkali-metal acetylides which are resistant to the reducing agent.

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[264] H. A. M. Jacobs and co-workers, *Rev. Trav. Chim.*, **84**, 1113 (1965).

[265] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 1512 (1959); A. J. Huber, *J. Chem. Soc.*, **1965**, 6669.

[266] G. Wilke and H. Müller, *Chem. Ber.*, **89**, 444 (1956).

[267] A. E. G. Miller, J. W. Biss, and L. H. Schwartzman, *J. Org. Chem.*, **24**, 627 (1959); W. J. Gensler and J. J. Bruno, *J. Org. Chem.*, **28**, 1254 (1963).

[268] F. Asinger, B. Fell, and G. Steffan, *Chem. Ber.*, **97**, 1555 (1964).

[269] B. B. Elsner and P. F. M. Paul, *J. Chem. Soc.*, **1953**, 3156.

[270] A. L. Henne and K. W. Greenlee, *J. Amer. Chem. Soc.*, **65**, 2020 (1943).

[271] H. Moissan, *C. R. Hebd. Séances Acad. Sci.*, **136**, 1217 (1903).

[272] P. Lebeau and M. Picon, *C. R. Hebd. Séances Acad. Sci.*, **157**, 137 (1913).

Advantage can be taken of this behavior when, in a compound containing two C≡C bonds, only the bond in the interior of the chain is to be reduced. For instance, 1,7-undecadiyne is first converted into the acetylide by means of $NaNH_2$ in liquid ammonia and the acetylenic linkage at position 7 is then reduced by addition of sodium: 7-undecen-1-yne is obtained.[273]

Moreover, high yields of olefins or diolefins are obtainable from monoalkylacetylenes or diacetylenes, respectively, by decomposition of the acetylides in the reaction medium with ammonium salts (ammonium sulfate has proved particularly suitable).[270]

1,6-Heptadiene:[270] For apparatus and working up see p. 10. 1,6-Heptadiyne (101 g) and $(NH_4)_2SO_4$ (295 g) are added to ammonia (1 l) in a 3-l flask. Then sodium is added in portions through a side arm, with stirring, until a permanent blue coloration is obtained (about 102 g). The crude product is obtained in 87% yield by the usual working up. After purification by distillation there remain 61% (64.4 g) of 1,6-heptadiene, b.p. 90°, n_D^{20} 1.4142.

The partial reduction of C≡C bonds by alkali metals in liquid ammonia can be applied also to ethynylcarbinols[274] and acetylenic compounds that contain hydroxyl[275] or acid groups[276] in the molecule.

However, difficulties arise if the acetylenic compounds contain also halogen[277] or if the products are olefins that are attacked by sodium and liquid ammonia. For instance, only ethylbenzene and the acetylide are formed from phenylacetylene.[278] Also, the conjugated dienes formed from the corresponding diynes or enynes are further reduced (see page 8); in such cases reduction by a zinc–copper couple in powder form[279] has proved valuable, but diphenylbutatriene is then formed by 1,4-addition to diphenyldiacetylene.[280]

2. Catalytic hydrogenation

Conversion of acetylene into ethylene bonds is preferably effected by catalytic methods,[253,281] since these usually involve mild conditions and give high yields. The *cis*-ethylenes which then form the predominant product can often be conveniently rearranged to the stable *trans*-isomers.[122,261,282,283]

Although the rates of hydrogenation of acetylenes and olefins barely differ or, as work with homogeneous catalysts has shown, are actually greater for C=C double bonds,[124] partial reduction of the acetylenic bond is relatively easy. The reason for the selectivity is the preferential adsorption of acetylene derivatives on the catalyst surface; it is therefore recommended that relatively small amounts of catalyst (sometimes 1–2% of the weight of the substrate)

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[273] N. A. Dobson and R. A. Raphael, *J. Chem. Soc.*, **1955**, 3558.

[274] G. F. Hennion, W. A. Schroeder, R. P. Lu, and W. B. Scanlon, *J. Org. Chem.*, **21**, 1142 (1956).

[275] F. Sondheimer, *J. Chem. Soc.*, **1950**, 877.

[276] D. R. Howton and R. H. Davis, *J. Org. Chem.*, **16**, 1405 (1951).

[277] R. E. A. Dear and F. L. M. Pattison, *J. Amer. Chem. Soc.*, **85**, 622 (1963).

[278] P. Lebeau and M. Picon, *C. R. Hebd. Séances Acad. Sci.*, **157**, 223 (1913); **175**, 223 (1922).

[279] F. Straus, *Ann. Chem.*, **342**, 190 (1905); I. G. Farbenindustrie, French Pat. 837,196; *Chem. Abstr.*, **33**, 6872 (1939).

[280] V. Grignard and Tchéoufaki, *C. R. Hebd. Séances Acad. Sci.*, **188**, 1531 (1929).

[281] G. Schiller in Houben-Weyl "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 291.

[282] W. D. Celmer and I. A. Solomons, *J. Amer. Chem. Soc.*, **75**, 3430 (1953).

[283] M. G. Ettlinger and J. E. Hodgkins, *J. Amer. Chem. Soc.*, **77**, 1831 (1955).

should be used in order to restrict reduction so far as possible to the triple bond; naturally, also, the use of particularly active catalysts should be avoided.

Because of their low selectivity platinum black and palladium black catalysts are unsuitable; after absorption of the calculated amount of hydrogen the product contains substantial amounts of the starting material and of the saturated compound alongside the olefin.

Considerable selective hydrogenation of the C≡C bond can be achieved with colloidal palladium or, less well, with Adams platinum catalysts[284] (see page 20); after one equivalent of hydrogen the product consists mainly of olefin although on further exposure to hydrogen the reaction leads to the saturated compound. Raney nickel catalysts have similar selectivity.[1a,b,122,261,276,285,286]

There is, however, a marked decrease in the rate of hydrogenation after absorption of the first equivalent of hydrogen if Raney iron[287] or suitably prepared palladium catalysts are used. The former are, however, significantly less active, so that higher temperatures and pressures are required and under such conditions isomerization to *trans*-ethylene derivatives can occur. The catalysts used in most procedures therefore consist of colloidal palladium that has been deposited on carriers such as $BaCO_3$,[274] $BaSO_4$,[203,288,289] $CaCO_3$,[262,275,290] or Al_2O_3,[291] and, often, treated with small amounts of catalyst poison (pyridine[292] or quinoline[289,293-295]). The more recent literature describes predominantly the use of the Pd–Pb–$CaCO_3$ catalyst as described by Lindlar (see page 19.[138,259a,283,294-297] A Pd–$BaSO_4$ catalyst deactivated by pure quinoline is said to have still better properties in that the results are more reproducible.

Selective hydrogenation is apparently best realized for dialkyl-[1a,b,203,298] and diaryl-acetylenes,[286] and for compounds in which the triple bond is endocyclic,[299] since in such cases further hydrogenation of the resulting olefins is markedly slower; for instance, cyclodecene is obtained in 96% yield from cyclodecyne.[296] The ethylene derivatives formed from monosubstituted

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[284] P. Karrer and H. Rentschler, *Helv. Chim. Acta*, **27**, 1297 (1944).

[285] S. Bance, H. J. Barber, and A. M. Woolman , *J. Chem. Soc.*, **1943**, 1.

[286] K. N. Campbell and M. J. O'Connor, *J. Amer. Chem. Soc.*, **61**, 2897 (1941); M. Bourguel, *Bull. Soc. Chim. France*, [iv], **45**, 1067 (1929).

[287] R. Paul and G. Hilly, *Bull. Soc. Chim. France*, [v], **6**, 218 (1939); A. F. Thompson Jr. and S. B. Wyatt, *J. Amer. Chem. Soc.*, **62**, 2555 (1940).

[288] C. Paal and co-workers, *Ber. Deut. Chem. Ges.*, **42**, 3930 (1909).

[289] D. J. Cram and N. L. Allinger, *J. Amer. Chem. Soc.*, **78**, 2518 (1956).

[290] R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, (a) **1950**, 3185; (b) **1950**, 120; (c) **1950**, 115; (d) **1951**, 2693.

[291] I. Marszak and M. Olomucki, *Bull. Soc. Chim. France*, **1959**, 182.

[292] H. Heusser, K. Eichenberger, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 370 (1950).

[293] H. Inhoffen, F. Bohlmann, K. Bartram, G. Rummert, and H. Pommer, *Ann. Chem.*, **570**, 54 (1950).

[294] W. Kimel and co-workers, *J. Org. Chem.*, (a) **22**, 1611 (1957); (b) **23**, 153 (1958).

[295] R. Rüegg, U. Gloor, R. N. Goel, G. Ryser, O. Wiss, and O. Isler, *Helv. Chim. Acta*, **42**, 2616 (1959); J. Weichet, L. Bláha, and V. Kvita, *Collect. Czech. Chem. Commun.*, **25**, 1914 (1960).

[296] V. Prelog, K. Schenker, and H. H. Günthard, *Helv. Chim. Acta*, **35**, 1598 (1952).

[297] A. S. Bailey, V. G. Kendall, P. B. Lumb, J. C. Smith, and C. H. Walker, *J. Chem. Soc.*, **1957**, 3027.

[298] W. Ziegenbein, *Chem. Ber.*, **98**, 1427 (1965).

[299] R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **82**, 4918 (1960).

acetylenes,[203,300] ethynylcarbinols,[138,274,284,294,295] and other alkynols[122,259a,261,262,275,290a,294] are hydrogenated at least as fast as the starting material; nevertheless, here too partial hydrogenation can be well achieved by working with selective catalysts and carefully measured quantities of hydrogen.

Even if other double bonds are present—whether isolated[292] or conjugated[122,261,290a]—the reaction can be so conducted that predominantly the triple bond is attacked. For instance, 1,3-butadiene is obtained in 69% yield from vinylacetylene by means of Pd–$BaSO_4$.[203] Catalytic hydrogenation has therefore been used to a large extent in syntheses of polyenes;[122,138,261,284,293,295] and also diolefin derivatives are obtained from the corresponding compounds containing two acetylenic linkages.[289,290b,c,d]

Addition of hydrogen is made really difficult or even impossible by accumulation of aryl substituents, as in tetraphenylbutynediol or hexaphenyl-2-butyne. In all other cases, even, for example, when there are amino groups in the molecule,[259,291,300] catalytic hydrogenation gives good results.

Acetylenecarboxylic acids,[276,288,290c,d,291] and their derivatives such as amides[283,290b] and esters,[274,282,289] can be converted into ethylene derivatives without change in the functional groups, which contrasts with the result of reduction by $LiAlH_4$. The conditions can be kept so mild that even the readily reducible nitrile group,[285] the sensitive acetal group,[285,299] or terminal fluorine atoms[301] are retained; even ynol ethers[292] can be converted into enol ethers.

2-Methyl-3-buten-2-ol:[294] A solution of 2-methyl-3-butyn-2-ol (336 g, 4 moles) in an equal volume of light petroleum is treated with quinoline (16.8 g) and Lindlar catalyst (30 g); the mixture is cooled to 10° and shaken in an atmosphere of hydrogen until 4moles of hydrogen are absorbed. After about 3–5 h the absorption slackens markedly and the catalyst is then filtered off and the product purified by distillation through a filled column. 94% (323 g) of 2-methyl-3-buten-2-ol is obtained, having m.p. 97–98° and n_D^{25} 1.4141.

***N*-(*cis*-2-Butenyl)phthalimide:**[283] A suspension of *N*-(2-butynyl)phthalimide (20 g) in ethyl acetate (1100 ml) is hydrogenated at atmospheric pressure in the presence of Lindlar catalyst (1 g) and quinoline (1 ml), until, after about 3.5 h, the consumption of hydrogen slackens (about 1.03 equivalents of hydrogen have been absorbed). The solution is filtered and concentrated in a vacuum. On recrystallization of the residue from 50% ethanol, *N*-(*cis*-2-butenyl)phthalimide (19.3 g, 96%) of m.p. 66–66.5° is obtained.

The product can be converted by NO_2 into the *trans*-isomer. *cis*-2-Butenylamine is obtained in 67% yield by hydrazinolysis.

III. Addition of hydrogen to C=O bonds

1. Reduction by non-noble metals

Aliphatic aldehydes can, in general, be very smoothly reduced to primary alcohols by non-noble metals. Zinc powder or iron powder in glacial acetic acid can be used for this purpose, although the acetates of the resulting alcohols are often formed in a side reaction. Hill and Nason[302] studied the effect of various metals in combination with glacial acetic acid in the reduction of

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[300] M. Bourguel, *Bull. Soc. Chim. France*, [iv], **51**, 253 (1932).

[301] R. E. A. Dear and F. L. M. Pattison, *Can. J. Chem.*, **41**, 2600 (1963).

[302] A. J. Hill and E. H. Nason, *J. Amer. Chem. Soc.*, **46**, 2236 (1924).

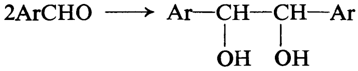
cinnamaldehyde; they found that use of iron repressed the formation of glycol that occurred as side reaction and also protected the ethylenic bond. A detailed prescription for preparation of *n*-heptyl alcohol[303] is based on the work of these authors.

Here the preparation of **2-(1-naphthyl)-1-propanol**[304] will be described as an example of reduction by iron powder:

A mixture of 2-(1-naphthyl)propionaldehyde (83.5 g), acetic acid (300 ml), water (300 ml), and iron powder (200 g) is heated for 7 h on the steam-bath. The solution is then filtered and the filter-cake is washed with water and then with ether. The filtrate and wash-water are diluted with water and then extracted with ether. The oil remaining after evaporation of the ether is boiled with a solution of NaOH (15 g) in water (30 ml) and alcohol (50 ml) to cleave the acetate that has been formed. The alcohol is then washed, dried in ethereal solution, and distilled. 2-(1-Naphthyl)-1-propanol is obtained as a yellowish viscous oil of b.p. 144–147°/3 mm, in 78.5% yield (66.3 g).

Aluminum amalgam is also often used as reducing agent; sodium amalgam is not recommended for reduction of aldehydes because of its basicity.

Aromatic aldehydes have a stronger tendency than have aliphatic aldehydes to form glycols on reduction:



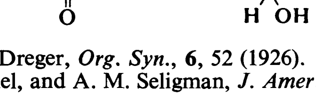
$$2\text{ArCHO} \longrightarrow \text{Ar}-\underset{\text{OH}}{\text{CH}}-\underset{\text{OH}}{\text{CH}}-\text{Ar}$$

The conditions can be so chosen that the hydrobenzoins are formed almost exclusively, and in many cases these are the only isolable product.[305] Aromatic alcohols are often prepared by the Cannizzaro reaction (see page 334) more conveniently than by reduction.

Alkaline reducing agents are usually recommended for reduction of ketones to secondary alcohols since pinacones are formed preferentially in an acid medium. Sodium in alcohol or in moist ether or benzene, sodium amalgam, and zinc dust in sodium hydroxide solution, etc., are often used for this purpose. 2-Heptanol, for example, is formed in good yield on addition of sodium to an aqueous-alcoholic solution of methyl *n*-pentyl ketone.[306] Reduction is also often carried out by adding sodium to an aqueous-ethereal suspension; but by this method the double bond of unsaturated ketones is also partially reduced.

3-Methyl-2-heptanol:[307] A solution of 3-methyl-2-heptanone (64 g) in ether (300 ml) is added to a suspension of $NaHCO_3$ (100 g) in water (300 ml). The mixture is treated, with cooling, with small portions of sodium (40 g in all), the whole being vigorously shaken after each fresh addition. The ethereal solution is separated and dried and the ether is evaporated. The residue is distilled in a vacuum; it boils at 172–173° and the yield is 77% (50 g).

For reduction of spiro[3.4]octan-5-one, Vogel[308] placed a layer of saturated sodium carbonate solution under its ethereal solution and, on addition of sodium, obtained the corresponding spiro alcohol in 79% yield:



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[303] H. T. Clarke and E. E. Dreger, *Org. Syn.*, **6**, 52 (1926).

[304] L. F. Fieser, L. M. Joshel, and A. M. Seligman, *J. Amer. Chem. Soc.*, **61**, 2137 (1939).

[305] S. Danilov, *Ber. Deut. Chem. Ges.*, **60**, 2393 (1927).

[306] F. C. Whitmore and T. Otterbacher, *Org. Syn.*, Coll. Vol. II, 317 (1943).

[307] S. G. Powell, *J. Amer. Chem. Soc.*, **46**, 2514 (1924); S. G. Powell and F. Hagemann, *J. Amer. Chem. Soc.*, **66**, 372 (1944).

[308] E. Vogel, *Chem. Ber.*, **85**, 25 (1952).

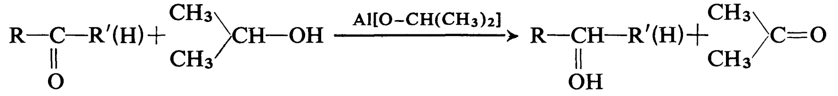
Bachmann[309] studied closely the reduction of ketones by sodium amalgam. Fluorenone, and benzophenone and its substitution products, were converted into the corresponding alcohols almost quantitatively by 2% sodium amalgam; metal ketyl radicals were shown to be intermediates in these reactions. Relevant also are the published detailed descriptions for reduction of xanthone[310] and thioxanthone[311] by sodium amalgam.

Reactions of alcoholic solutions of ketones with zinc and sodium hydroxide solution or with zinc and concentrated ammonia solutions also lead to good results.[312] In the reduction of 9-oxo-2-fluorenecarboxylic acid better yields are obtained in a shorter time by using zinc in aqueous potassium hydroxide to which a small amount of copper sulfate has been added.[313] Yields were appreciably lower when 9-oxo-1-fluorenecarboxylic acid was reduced with magnesium in methanol,[314] but Zechmeister and Rom[315] obtained excellent yields on reducing benzophenone and 1,3-diphenylacetone by this method.

Reduction of various aldehydes and ketones by Raney nickel alloy in aqueous sodium hydroxide below 20° was recommended by Cook;[316] this gave good yields of the corresponding alcohols from salicylaldehyde, vanillin, acetophenone, and other carbonyl compounds.

2. Meerwein–Ponndorf–Verley reduction

One of the mildest methods of reduction that are specific for the CO group is that of Meerwein–Ponndorf–Verley.[183d] In 1925 Meerwein and Schmidt[317] and Verley[318] independently discovered that aldehydes and certain ketones were reduced to the corresponding alcohols by aluminum ethoxide in the presence of ethanol. The same method was discovered by Ponndorf[319] at almost the same time; and in some cases he used aluminum isopropoxide in place of the ethoxide, a modification that was later recognized by Young, Hartung, and Crossley[320] and by Lund[321] to be advantageous for general application also to ketones:



$$R-\underset{\underset{O}{\|}}{C}-R'(H)+\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH-OH \xrightarrow{Al[O-CH(CH_3)_2]} R-\underset{\underset{OH}{\|}}{CH}-R'(H)+\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C=O$$

The reaction of aldehydes and ketones with aluminum isopropoxide is an equilibrium reaction which can be steered entirely in the desired direction by continuous removal of one of the products, *e.g.*, acetone, from the reaction

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[309] W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 770 (1933).

[310] A. F. Holleman, *Org. Syn.*, **7**, 88 (1927).

[311] H. F. Oehlschlaeger and I. R. MacGregor, *J. Amer. Chem. Soc.*, **72**, 5332 (1950).

[312] H. R. Frank and D. S. Tarbell, *J. Amer. Chem. Soc.*, **70**, 1276 (1948).

[313] F. E. Ray, E. K. Weisburger, and J. H. Weisburger, *J. Org. Chem.*, **13**, 655 (1948).

[314] J. Forrest and S. H. Tucker, *J. Chem. Soc.*, **1948**, 1137.

[315] L. Zechmeister and P. Rom, *Ann. Chem.*, **468**, 117 (1929).

[316] P. L. Cook, *J. Org. Chem.*, **27**, 3873 (1962).

[317] H. Meerwein and R. Schmidt, *Ann. Chem.*, **444**, 221 (1925).

[318] A. Verley, *Bull. Soc. Chim. France*, [iv], **37**, 537, 871 (1925); **41**, 788 (1927).

[319] W. Ponndorf, *Angew. Chem.*, **39**, 138 (1926).

[320] W. G. Young, W. H. Hartung, and F. S. Crossley, *J. Amer. Chem. Soc.*, **58**, 100 (1936).

[321] H. Lund, *Ber. Deut. Chem. Ges.*, **70**, 1520 (1937).

mixture. Aluminum salts of other secondary alcohols can also be used with success in place of aluminum isopropoxide. The reverse reaction is known as Oppenauer oxidation (see page 000).

The aluminum isopropoxide is not only a catalyst but is actually the reducing agent.[322] Experiments with aluminum alkoxides derived from alcohols deuterated on carbon[323] showed that the hydrogen is transferred to the carbonyl group directly from the alkoxide without participation of the solvent; thus the reaction can be carried out also in the absence of 2-propanol, by using aluminum isopropoxide in the molten state or in toluene or other hydrocarbon.

Carbon–carbon double bonds α, β to the carbonyl group are not attacked, which contrasts with the results of other methods of reduction. Nitro groups, ester groups, and even activated halogen are unaffected. And a further advantage of the method is the generally good yields obtained.

The Tishchenko reaction (see page 334) may take place as a side reaction to reduction of aldehydes, but for aliphatic aldehydes it is suppressed by using an excess of isopropoxide. Also the aldehyde may undergo an aldol condensation (see page 868) with itself or with the acetone produced. Recently the formation of 2-methyl-2,4-pentanediol as by-product was observed.[361] These side reactions, however, occur only occasionally and in no way detract from the value of this method of reduction.

The aluminum alkoxide is prepared by activating the surface of the metallic aluminum by $HgCl_2$ or iodine and then dissolving it in the appropriate alcohol.

As an example, here follows the preparation of **aluminum isopropoxide,**[325] which is the reagent most commonly used:

Aluminum wire (27 g, 1 mole) or foil is cleaned with emery paper, then with a cloth, and placed in a 1-l round-bottomed flask containing anhydrous 2-propanol (300 ml) and mercuric chloride (0.5 g). The flask is fitted with a reflux condenser and a calcium chloride tube. The mixture is then heated to the boiling point on a water-bath. When boiling begins, carbon tetrachloride (2 ml) is added through the condenser. The mixture becomes brown and in a few minutes vigorous evolution of hydrogen begins. Heating is then interrupted and the reaction is controlled by cooling in ice-water. When the reaction moderates, heating is continued until the aluminum is all dissolved (6–12 h). The hot solution is transferred to a distillation flask, the propanol is removed under slightly diminished pressure, and the aluminum isopropoxide is distilled in a vacuum (oil-bath temperature 180–190°). It is a colorless viscous liquid of b.p. 130–140°/7 mm, 140–150°/12 mm.

Aluminum isopropoxide can be kept in substance or in solution in glass-stoppered flasks sealed with paraffin. For many purposes it is unnecessary to distil the reagent, and the dark solution obtained on dissolution of the aluminum can be used directly.

Detailed directions for the preparation of aluminum ethoxide and butoxide are given in *Organic Syntheses*.[326,327]

Many aldehydes, *e.g.*, furfuraldehyde,[317] can be reduced even in the cold; in general, however, the reduction is carried out at elevated temperature in order that the usually volatile oxo compound may be removed by distillation.

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[322] L. Jackman and J. Mills, *Nature*, **164**, 789 (1949).

[323] E. D. Williams, K. A. Krieger, and A. R. Day, *J. Amer. Chem. Soc.*, **75**, 2404 (1953).

[324] C. H. Snyder, *J. Org. Chem.*, **32**, 2904 (1967).

[325] A. L. Wilds in "Organic Reactions," 1944, Vol. 2, p. 178.

[326] W. Chalmers, *Org. Syn.*, Coll. Vol. II, 598 (1943).

[327] W. Wayne and H. Adkins, *Org. Syn.*, **21**, 8 (1941).

2-Buten-1-ol:[319,325] Crotonaldehyde (210 g, 3 moles) and dry 2-propanol (1 l) are added to a solution of aluminum isopropoxide prepared in the usual way from aluminum (47 g, 1.74 moles) and 2-propanol (500 ml). The reaction is carried out in a 2-l round-bottomed flask fitted with a Vigreux column to which a descending condenser is attached. The mixture is heated in an oil-bath (bath temperature 110°), the acetone formed distilling slowly at 60–70°. When no more acetone can be detected in the distillate by 2,4-dinitrophenylhydrazine (after 8–9 h), the residual 2-propanol is removed under diminished pressure. The residue is cooled to 40° and hydrolysed, with cooling as necessary, by cold 6N sulfuric acid (900 ml; from 145 ml of concentrated acid and 790 ml of water). The organic phase is separated, washed with water, and distilled at 60–70° at a pressure decreasing gradually from 275 to 65 mm. Finally, distillation is completed at 100°/20 mm. A second fraction of 2-buten-1-ol is obtained by distillation of the aqueous phase and saturation of the distillate with potassium hydroxide. The crude 2-buten-1-ol is dried over potassium hydroxide and distilled through a column. It has b.p. 117–122° and the yield is 60% (130 g).

If reduction of the aldehyde takes a long time, or if the product is sensitive to air, a stream of nitrogen or hydrogen is passed through the reaction mixture. In general, a slight excess of aluminum alkoxide is recommended, but with aromatic aldehydes better yields are obtained by using a deficiency of alkoxide.

Piperonyl alcohol:[328] 2-Propanol is rendered anhydrous by 4 hours' boiling with calcium oxide, distillation, further boiling with aluminum isopropoxide, and renewed distillation. 50 g of piperonal in 500 ml of this alcohol are treated with 10 g of aluminum isopropoxide, and the whole is heated in an oil-bath at 95° under a Widmer column attached to a descending condenser. At the end of this time, 200 ml of distillate have passed over (b.p. 77–81°) and acetone is no longer detectable in a sample by means of 2,4-dinitrophenylhydrazine in N-hydrochloric acid. The residue is treated with water, made just acid with hydrochloric acid, and extracted with ether. The extract is dried and evaporated, and the residue is distilled in a vacuum, giving 45 g of a product of b.p. 151°/13 mm. This solidifies to crystals melting at 51°.

A detailed description of the reduction of chloral to 2,2,2-trichloroethanol is given in *Organic Syntheses.*[326]

Meerwein–Ponndorf–Verley reduction of ketones to secondary alcohols proceeds analogously to that of aldehydes, although usually more slowly. The method cannot, however, be used for ketones such as β-keto esters or β-diketones that have a strong tendency to enolize, since they form aluminum enolates which are not reduced; such compounds are preferably reduced by sodium borohydride, by potassium borohydride, or catalytically.

Treatment of lower-boiling ketones can be as given in the prescription for reduction of crotonaldehyde (see above).

The preparation of **benzhydrol** from benzophenone is described as an example of reduction of an aromatic ketone:[325]

Benzophenone (18.2 g, 0.1 mole) is treated with a solution of aluminum isopropoxide (20 g, 0.1 mole) in dry 2-propanol (100 ml) in a 200-ml round-bottomed flask. The flask is attached to a short reflux condenser through which, however, no water flows. A reflux condenser filled with methanol or a fractionating head of the type described by Hahn[329] may also be used. The upper end of the reflux condenser is fitted to a small, water-cooled, descending condenser. The solution is heated on a water-bath so that 5–10 drops pass over per minute (1–4 drops for difficultly reducible ketones). After 30–60 min no more acetone is detectable in a sample of the distillate. If more than 50 or 60 ml of 2-propanol distils over, fresh 2-propanol must be added to maintain the volume. Water is then passed through the condenser and the mixture is heated to vigorous refluxing for 5 ml. The water-cooling is then discontinued and the first five drops distilling are tested for acetone; if the test is positive, distillation is continued until it becomes negative. Then most of the 2-propanol is removed

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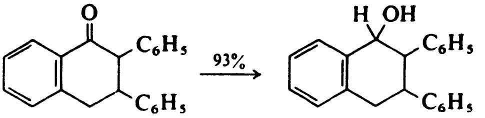
[328] C. Schöpf and W. Salzer, *Ann. Chem.*, **544**, 14 (1940).

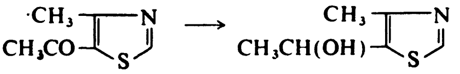
[329] A. Hahn, *Ber. Deut. Chem. Ges.*, **43**, 419 (1910).

under slightly reduced pressure. The cold residue is hydrolysed with dilute hydrochloric acid (35 ml of concentrated acid in 175 ml of water), and the aqueous suspension is shaken until hydrolysis is complete. The crystalline benzhydrol is filtered off and washed with cold dilute acid and with water, the crude yield being 18.4 g. For purification the product is dissolved in hot light petroleum (b.p. 60–70°; 50 ml). If this solution is not clear, benzene (20 ml) is added and the hot solution is filtered. The benzhydrol crystallizes, on cooling, as colorless needles (18.2 g, 99%), m.p. 67–69°.

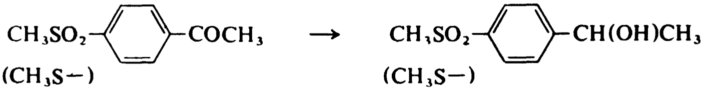
Cyclic ketones such as 1-decalone[321] and tetralone can also be reduced conveniently by this method. Crawford and Nelson[330] converted 2,3-diphenyl-2-tetralone into the corresponding alcohol in 93% yield by means of aluminum isopropoxide:



The furan[317] and the thiophene ring[331] are not attacked during Meerwein–Ponndorf–Verley reduction. Similarly, 4-methyl-5-(1-hydroxyethyl)thiazole can be prepared from the related acetylthiazole in 71% yield:[332]



Other sulfur-containing ketones such as keto sulfones and keto sulfides are also reduced by aluminum isopropoxide. Bachmann and Carlson[333] prepared 1-[*p*-(methylsulfonyl)phenyl]ethanol and 1-[*p*-(methylthio)phenyl]ethanol in good yield by this method:



Truett and Moulton[334] showed that in many cases it is unnecessary to remove the acetone and that purer products are obtained on reduction of benzophenone and benzosuberone if merely an excess of aluminum isopropoxide is used.

The reaction was modified by Macbeth and Mills[335] in that the carbonyl compound was introduced slowly as reaction proceeded, whereby its concentration remained low throughout and side reactions (see page 48) were reduced. This technique permitted, for instance, a yield of 96% to be obtained on reduction of benzylideneacetone although the yield was difficult to reproduce by the usual method.

Gál, Tokár, and Simonyi[336] found that the rate of Meerwein–Ponndorf–Verley reduction could be increased by using a mixture of aluminum isoprop-

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[330] H. M. Crawford and H. B. Nelson, *J. Amer. Chem. Soc.*, **68**, 134 (1946).

[331] E. Campaigne and J. L. Dietrich, *J. Amer. Chem. Soc.*, **70**, 391 (1948).

[332] P. Baumgarten, A. Dornow, K. Gutschmidt, and H. Krehl, *Ber. Deut. Chem. Ges.*, **75**, 442 (1942).

[333] G. B. Bachmann and C. L. Carlson, *J. Amer. Chem. Soc.*, **73**, 2857 (1951).

[334] W. L. Truett and W. N. Moulton, *J. Amer. Chem. Soc.*, **73**, 5913 (1951).

[335] A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, **1949**, 2646.

[336] G. Gál, G. Tokár, and I. Simonyi, *Magy. Kem. Foly.*, **61**, 268 (1955); G. Gál, I. Simonyi, and G. Tokár, *Acta Chim. Acad. Sci. Hung.*, **8**, 163 (1955); *Chem. Abstr.*, **51**, 14,606 (1957); **52**, 8084 (1958).

oxide 65–80% with the chloroisopropoxide 35–20%. This modified method proved admirable for preparation of bromohydrins from α-bromo ketones.

3. Reduction by lithium aluminum hydride[100,379]

Lithium aluminum hydride (lithium tetrahydridoaluminate), $LiAlH_4$, discovered by Finholt, Bond, and Schlesinger,[338] has recently found varied use as a reducing agent in preparative organic chemistry. The investigations by Nystrom and Brown[339] showed that a great number of functional groups are reduced extremely rapidly and smoothly whilst carbon–carbon multiple bonds are usually unattacked.

In the laboratory the ether-soluble $LiAlH_4$ is usually prepared by reaction of LiH with an aluminum halide in ether at 20°:

$$4\,LiH + AlX_3 \longrightarrow LiAlH_4 + 3\,LiX \qquad X = Cl \text{ or } Br$$

$AlCl_3$ was first used, but this was later replaced by $AlBr_3$ which offers appreciable advantages.[340] $LiAlH_4$ is stable up to about 100° provided that substances with which it reacts, including air and CO_2, are excluded. From 120° onwards it decomposes according to the reaction:

$$LiAlH_4 \longrightarrow LiH + Al + 1.5\,H_2$$

Lithium aluminum hydride is obtainable commercially as hard lumps, packed in metal boxes, and it is therefore unnecessary to describe its preparation. It is often very difficult to dissolve $LiAlH_4$ in ether; it must first be ground to a very fine powder under nitrogen with most careful exclusion of moisture, in which process local overheating must be avoided lest powerful explosion occurs.

Lithium aluminum hydride powder is best dissolved in ether by stirring the mixture in a flask fitted with a reflux condenser connected to a soda-lime tube. According to the nature of the material, stirring must be continued under gentle reflux for from several hours to two days. Technical products leave a grey, insoluble residue, wherefore it is advisable to start with an excess of 5–10% of hydride. It is advantageous to carry out the reduction in the same vessel.

To obtain a solution for storage, the liquid is decanted through a syphon by means of a nitrogen pressure; alternatively, it may be filtered under nitrogen. The filter residue and all the remaining $LiAlH_4$ are destroyed by covering with dioxan and addition of moist dioxan or methanol; when all the active hydride has been destroyed for certain, the apparatus is cleaned with dilute acid.

In many cases it is unnecessary to wait for complete dissolution of the $LiAlH_4$; the suspension can be used directly for the reduction.

The most convenient method of preparing a solution of $LiAlH_4$ is to use the commercially available ampoules into which calculated amounts of the two components LiH and $AlBr_3$ have been sealed. The ampoules are opened

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[337] (a) V. M. Mićović and M. Lj. Mihailović, "Lithium Aluminium Hydride in Organic Chemistry," Izdavačko Preduzeće, Belgrade, 1955; W. G. Brown, *Org. Reactions*, **6**, 469 (1951); U. Solms, *Chimia*, **5**, 25 (1951).

[338] A. E. Finholt, A. C. Bond, and H. I. Schlesinger, *J. Amer. Chem. Soc.*, **69**, 1199 (1947).

[339] R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **69**, (a) 1197, (b) 2548 (1947); (c) **70**, 3738 (1948).

[340] E. Wiberg and M. Schmidt, *Z. Naturforsch.*, **7b**, 59 (1952).

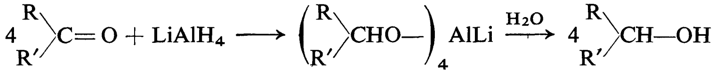
separately under ether, and the ethereal solutions are combined. The tedious dissolution of $LiAlH_4$ is thus avoided and a solution of exactly known hydride content is obtained.

Diethyl ether is usually used as solvent for the reduction, often tetrahydrofuran, more rarely dibutyl ether, diethylene glycol diethyl ether (Diethylcarbitol), or diethylene glycol dibutyl ether (Dibutylcarbitol).[341] 4-Ethylmorpholine is very suitable but is difficult to purify.[342] Pyridine has also proved a valuable solvent.[343] Solutions of the hydride in solvents other than ether are often prepared by adding the solvent to an ethereal solution of the hydride and then evaporating off the ether. All solvents used must be carefully purified.[344a]

The "normal" method of operation is to drop the oxo compound that is to be reduced into a solution of $LiAlH_4$ in one of the above-mentioned solvents. When the compound is difficult to reduce or when there is a danger of over-reduction, the inverse method has become customary, *i.e.*, the $LiAlH_4$ solution or suspension is dropped into the solution of the oxo compound.

The excess of $LiAlH_4$ can be decomposed with moist ether or, carefully, with sodium carbonate solution or water. For larger batches the decomposition is effected by a reagent that does not evolve hydrogen on reaction with $LiAlH_4$; ethyl acetate is very suitable, since its reduction product (ethanol) rarely interferes in subsequent working up.

Reduction of a carbonyl group by $LiAlH_4$ occurs according to the general equation



$$4\,\begin{matrix}R\\ R'\end{matrix}\!>\!C{=}O + LiAlH_4 \longrightarrow \left(\begin{matrix}R\\ R'\end{matrix}\!>\!CHO-\right)_4 AlLi \xrightarrow{H_2O} 4\,\begin{matrix}R\\ R'\end{matrix}\!>\!CH-OH$$

and has the advantage over Meerwein–Ponndorf–Verley reduction that reduction times are shorter and side reactions are absent: but they have the disadvantage that reduction is not specific for the carbonyl group. Yields are usually as good as in reduction with aluminum alkoxides. Directions for preparation of **1-heptanol**[339] will illustrate the procedure:

A solution of $LiAlH_4$ (19 g, 0.5 mole) in ether (600 ml) is placed in a 2-l three-necked flask fitted with a stirrer, reflux condenser, dropping funnel, and calcium chloride tube. *n*-Heptanal (200 g, 1.75 moles) is then added, with stirring, at such a rate that the mixture continues to boil. Whilst stirring is continued, water is dropped in, cautiously and with strong cooling, to decompose the excess of hydride. Then the mixture is poured into ice-water (200 ml) and treated with 10% H_2SO_4 (1 l). After removal of the ethereal layer, the aqueous solution is extracted with two portions (each 100 ml) of ether. The ethereal extracts are dried and evaporated and the 1-heptanol obtained as residue is distilled through a column. The yield is 86% and the b.p. 175–175.5 °C/750 mm.

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[341] L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 1675 (1949).

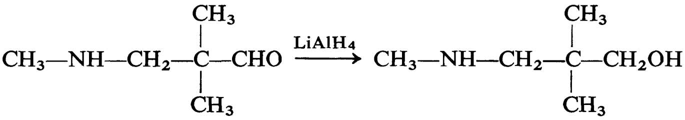
[342] F. A. Hochstein, *J. Amer. Chem. Soc.*, **71**, 305 (1949).

[343] P. T. Lansbury, *J. Amer. Chem. Soc.*, **83**, 429 (1961).

[344] Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, Vol. 1, Part 2 (W. Bunge; 1959), (a) p. 765; Vol. 4, Part 2 (G. Schiller; 1955), pp. (b) 307, (c) 318; Vol. 5, Part 3 (E. Forsche; 1954), (d) p. 497; Vol. 5, Part 4 (R. Stroh; 1960), (e) p. 761; Vol. 7, Part 1 (O. Baeyer; 1954), pp. (f) 285, (g) 291, (h) 297, (i) 491; Vol. 7, Part 4 (O. Baeyer; 1954), (j) p. 216; Vol. 11, Part 2 (F. Möller; 1958), (k) p. 216.

[345] K. Hayes and G. Drake, *J. Org. Chem.*, **15**, 873 (1950).

Amino aldehydes are also reduced by $LiAlH_4$. For instance, Hayes and Drake[345] describe the reduction of 2,2-dimethyl-3-(methylamino)propionaldehyde by an excess of $LiAlH_4$, obtaining the corresponding alcohol in 72% yield, whereas in this case Meerwein–Ponndorf–Verley reduction gave only a 27% yield:

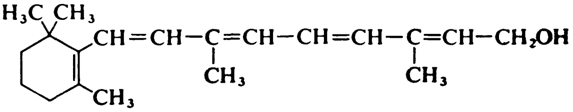


$$CH_3{-}NH{-}CH_2{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}{-}CHO \xrightarrow{LiAlH_4} CH_3{-}NH{-}CH_2{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}{-}CH_2OH$$

Aromatic aldehydes also react smoothly. Phenolic aldehydes can be similarly reduced but often do not give very good yields. Preparation of 3-hydroxybenzyl alcohol[346] is an example of a reduction that proceeds smoothly by the normal procedure, but on the other hand attempts to reduce vanillin and veratraldehyde failed.[347]

In very reactive systems the double bond is often attacked. Thus, if cinnamaldehyde is reduced under the usual conditions 3-phenyl-1-propanol is produced directly; but, if the temperature is lowered to −10°C and the hydride solution is dropped into the aldehyde solution, then cinnamyl alcohol is formed in a smooth reaction.[81]

If a carbonyl group in a side chain is not directly conjugated to an aromatic ring, the double bonds of a polyconjugated system are not attacked. This fact was used in the synthesis of vitamin A from the corresponding aldehyde.[348]



Vitamin A

Reduction by $LiAlH_4$ has found repeated use also in other cases in the carotenoid series.[100,337a]

This method of reduction is applicable also to heterocyclic aldehydes. For instance, 2-pyrrolemethanol can be prepared from 2-pyrrolecarbaldehyde in 59% yield by the inverse method;[349] but reduction of polysubstituted pyrrolecarbaldehydes is impossible or possible only with great difficulty.[350]

Ketones can be reduced by $LiAlH_4$ in the same way as aldehydes and provide a particular large number of examples for this method. Halohydrins are obtained from halo ketones. 1,3-Dichloroacetone is reduced by $LiAlH_4$ in good yield, whereas only 20–25% of 1,3-dichloro-2-propanol is obtained by use of aluminum alkoxides.[351] Even sterically hindered ketones such as 1,1-diphenylacetone

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[346] M. A. Karim, *J. Indian Chem. Soc.*, **37**, 244 (1960).

[347] E. Larsson, *Trans. Chalmers Univ. Technol. Gothenburg*, 1950, No. 94, p. 15; *Chem. Abstr.*, **45**, 1494 (1951).

[348] N. L. Wendler, C. Rosenblum, and M. Tishler, *J. Amer. Chem. Soc.*, **72**, 234 (1950); J. F. Arens and D. A. van Dorp, *Rec. Trav. Chim.*, **68**, 604 (1949).

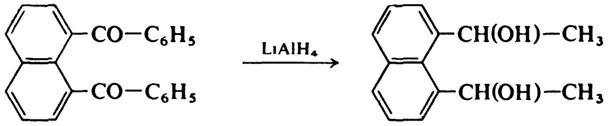
[349] R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *J. Amer. Chem. Soc.*, **76**, 4485, (1954).

[350] A. Treibs and H. Scherer, *Ann. Chem.*, **577**, 139 (1952); A. Treibs and H. Derra-Scherer, *Ann. Chem.*, **589**, 188 (1954).

[351] H. Schlenk and B. Lamp, *J. Amer. Chem. Soc.*, **73**, 5493 (1951).

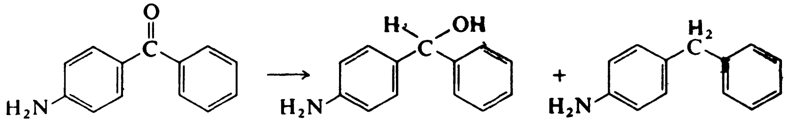
can be reduced to the corresponding alcohols in good yield;[352] dimesityl ketone provides dimesitylmethanol in 93% yield.[353]

A Soxhlet apparatus is used when the compound to be reduced is difficultly soluble in ether or difficult to reduce, but this technique is applicable only to small batches. As an example, 1,8-dibenzoylnaphthalene can be reduced in 96% yield by working in this way:[354]



Ketones of reduced ring systems are generally reduced in good yield. 9-Acetylanthracene affords 80% of the corresponding alcohol.[355]

Conover and Tarbell[356] demonstrated that using an excess of $LiAlH_4$ for the reduction of various aromatic ketones containing an amino group *ortho* or *para* to the oxo group gave the methylene compound as well as the alcohol, *e.g.*:

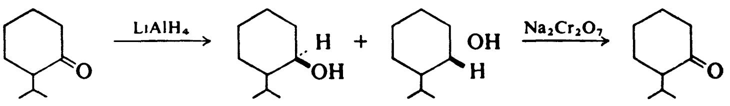


The larger the excess of $LiAlH_4$, the larger was the yield of 4-aminodiphenylmethane.

Similar results were observed with heterocyclic ketones. For instance, by the normal method of working, 2-acetylpyrrole gives small amounts of both 1-(2-pyrryl)ethanol and 2-ethylpyrrole; if the inverse method is used the alcohol (80% yield) is the sole product.[357]

1-(2-Thienyl)ethanol is formed on reduction of 2-acetylthiophen, whereas the thiophene ring is also reduced by catalytic hydrogenation.[358]

An asymmetric center next to a carbonyl group is not disturbed during the reduction. Thus from (−)-menthone a menthol mixture [71% of (−)-menthol and 29% of neomenthol (*cis*)] is obtained that can be reoxidized to (−)-menthone:[359]



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[352] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952).

[353] M. S. Newman and N. C. Deno, *J. Amer. Chem. Soc.*, **73**, 3644 (1951).

[354] R. L. Letsinger and P. T. Lansbury, *J. Amer. Chem. Soc.*, **81**, 935 (1959).

[355] E. L. May and E. Mosettig, *J. Amer. Chem. Soc.*, **73**, 1301 (1951).

[356] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.*, **72**, 3586 (1950).

[357] W. Herz and Ch. F. Courtney, *J. Amer. Chem. Soc.*, **76**, 576 (1954).

[358] T. L. Cairns and B. C. McKusick, *J. Org. Chem.*, **15**, 790 (1950).

[359] D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

The problem of the stereospecificity of the method arises when reduction of the keto group leads to formation of a new asymmetric carbon atom or of new cyclic *cis-trans*-isomers. Although a mixture of the epimeric *cis-trans*-isomers is obtained in many cases, one form is often favored or indeed may be formed exclusively. It transpires that the more stable isomer is usually formed from sterically unhindered ketones, and that hydrogen is usually added to the unhindered side of ketones that are strongly sterically hindered. Thus, on reduction of camphor a 94% yield is obtained of a mixture of borneol (10%) and isoborneol (90%) in which the *cis*-isomer patently preponderates.[359]

It is impossible to describe here in detail the stereochemistry of reduction by $LiAlH_4$, which plays an important part in, particularly, the stereoid field; it must suffice to indicate relevant reviews.[100,337]

Reduction of quinones proceeds analogously to that of ketones. Whereas *o*-benzoquinone gives pyrocatechol smoothly, a mixture of 1,2-naphthalenediol and *trans*-1,2-dihydro-1,2-naphthalenediol is formed from 1,2-naphthoquinone.[360] 3,4-Dihydro-4-hydroxy-1(2*H*)-naphthalenone is formed as well as 1,2,3,4-tetrahydro-1,4-naphthalenediol from 1,4-naphthoquinone.[361]

4. Reduction by complex boron hydrides

In addition to $LiAlH_4$, various complex boron hydrides have recently achieved importance as reducing agents in preparative organic chemistry.[183e,362,363] These are the borohydrides $Mt[BH_4]$, etc., of alkali and alkaline-earth metals, of zinc and aluminum, and sodium hydridotrimethoxyborate (sodium trimethoxyboron hydride) $Na[(CH_3O)_3HB]$; and finally diborane, B_2H_5, has recently also been applied for reducing purposes.[183e,363] The reducing power is weakest for those compounds having a truly ionic character, *e.g.*, the alkali boron hydrides; alkaline-earth boron hydrides occupy an intermediate position; and the reducing power is strongest for aluminum borohydride which has a typically covalent structure.

A large number of methods have recently been found for the preparation of complex boron hydrides. The alkali borohydrides and sodium hydridotrimethoxyborate can be obtained commercially; for preparation of the other compounds a few literature references must here suffice.[100,183e,362-364]

Reductions by complex boron hydrides have many features in common with those by $LiAlH_4$. A great advantage over the latter is that, because of their great stability, sodium and potassium boron hydride can be used also in aqueous or alcoholic solution; further, there is a minimum of side reactions with these reagents. The alkaline-earth boron hydrides, sodium hydridotrimethoxyborate, and $LiBH_4$ are brought into reaction in ether or tetrahydrofuran. $NaBH_4$ is insoluble in ether, since the sodium ion has only slight tendency to solvation there, but is dissolves in tetrahydrofuran, dioxan, or diglyme; dimethylforma-

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[360] J. Booth, E. Boyland, and E. E. Turner, *J. Chem. Soc.*, **1950**, 1188.

[361] E. Boyland and D. Manson, *J. Chem. Soc.*, **1951**, 1837.

[362] H. Hörmann, *Angew. Chem.*, **68**, 601 (1956).

[363] E. Schenker, *Angew. Chem.*, **73**, 81 (1961).

[364] E. Wiberg, *Angew. Chem.*, **65**, 16 (1953); F. G. A. Stone, *Quart. Rev.* (*London*), **9**, 174 (1955).

mide, still little used in reductions, is an exceedingly useful solvent for $NaBH_4$. Often reaction is effected between reactant and boron hydride initially in different solvents.

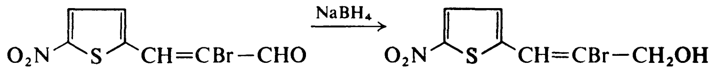
Reduction by quaternary ammonium boron hydrides containing long-chain alkyl groups, *e.g.*, hexadecyltrimethyl- and trioctylmethyl-ammonium boron hydride, can be carried out also in apolar solvents such as hydrocarbons.[365]

It is usually unnecessary to exclude moisture or atmospheric oxygen from reductions by complex boron hydrides. Also, for these reagents, unlike $LiAlH_4$, there is no need to prepare stock solutions since the commercial product is supplied as fine crystals. Usually the substance to be reduced is added to the hydride, but the inverse method has also come into use in which the reducing agent is added in portions. The normal process should be used to reduce substances that are sensitive to alkali, *e.g.*, aldehydes, since only a small amount of the starting material is then exposed to the alkaline solution. In general, an excess of the reducing agent is used, which must be destroyed at the end of the reaction by adding a little formic acid, dilute mineral acid, or acetone.[366] An advantageous method of destroying an excess of reducing agent consists in adding NaH_2PO_4.[367] Although complex boron hydrides are simpler to handle than is $LiAlH_4$, yet a certain amount of care is required. Decomposition of the excess of hydride by concentrated acid can cause a violent reaction, with formation of the explosive diborane; use of acetic acid for decomposition of the excess of hydride is particularly inadvisable after reduction of aliphatic aldehydes. Boric esters or boron complexes are often formed during the reaction, in particular from diols and some nitrogen bases; in such cases the reduction mixture should be worked up with, *e.g.*, carbon dioxide,[368] methanolic hydrochloric acid,[369] 1-butanol,[370] concentrated aqueous ammonia,[371] or aqueous alkali fluoride solution.[372]

The reduction of aliphatic and aromatic aldehydes by $NaBH_4$ was thoroughly studied by Chaikin and Brown.[373] The corresponding alcohols were formed in good yield and in most cases even at room temperature:

$$4\,R\text{—}CHO + NaBH_4 \longrightarrow NaB(OCH_2R)_4 \xrightarrow{H_2O} 4\,R\text{—}CH_2OH$$

Only in exceptional cases did nitro, ester, epoxy, acid, lactone, lactam, or amide groups react, so that $NaBH_4$ is particularly valuable as a selective reducing agent. An impressive example is the selective reduction of a heterocyclic-substituted 2-bromoacraldehyde:[374]



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[365] E. A. Sullivan and A. A. Hinckley, *J. Org. Chem.*, **27**, 3731 (1962).

[366] D. J. Cram and M. J. Hatch, *J. Amer. Chem. Soc.*, **75**, 38 (1953).

[367] E. S. Rothman and M. E. Wall, *J. Org. Chem.*, **25**, 1396 (1960).

[368] J. Defaye, *Bull. Soc. Chim. France*, **1964**, 2686.

[369] E. B. Reid and J. R. Siegel, *J. Chem. Soc.*, **1954**, 520.

[370] W. Grassmann, H. Hörmann, and H. Endres, *Chem. Ber.*, **88**, 102 (1955).

[371] L. J. Reed and Ching-I Niu, *J. Amer. Chem. Soc.*, **77**, 416 (1955).

[372] C. A. Buehler, J. W. Addleburg, and D. M. Glenn, *J. Org. Chem.*, **20**, 1350 (1955).

[373] S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949).

[374] G. Carrara, R. Ettore, F. Fava, E. Testa, and A. Vecchi, *J. Amer. Chem. Soc.*, **76**, 4391 (1954).

In this reaction the bromine atom, the nitro group, and the double bond are unaffected.

Because of its good solubility in water and methanol, $NaBH_4$ has found repeated use for reduction of sugars, and it does not cleave the glycosidic linkage. Deoxy sugars usually react more readily than the corresponding normal sugars.[375] Boron-containing complexes are often formed in reductions of sugars, hindering crystallization of the sugar alcohols, but this difficulty can be overcome by subsequent acetylation, whereby the fully acetylated derivatives can be obtained in good yield.[376]

General directions for **reduction of D-glucose, D-mannose, D-galactose, L-arabinose, D-xylose, and D-fructose:**

A solution of $NaBH_4$ (0.1 to 0.15 g) in water (10 ml) is added to one of the monosaccharide (1.0 g in 20 ml). The mixture, which becomes weakly alkaline, is set aside at 20–25° until, after acidification with acetic acid, a drop no longer reduces Fehling's solution or until the optical rotation reaches a constant value. Reduction is complete in 1 to 2 hours. The mixture is acidified with acetic acid, to destroy the excess of $NaBH_4$, and then evaporated in a vacuum. The dry residue is shaken with acetic anhydride (15 ml) containing H_2SO_4 (1 ml) until most of the solid product has dissolved and is then warmed at 50–60° for 10 min. After cooling, the mixture is poured, with stirring, into ice-water (50 ml). The acetate, which crystallizes well, is filtered off, washed with water, dried, and recrystallized in the usual way. Yields amount to between 75 and 87%.

The aldehyde group of cardioactive glycosides and aglycones can also be selectively reduced. Hunger and Reichstein[377] carried out such reactions with strophanthidin, convallatoxin, and similar compounds.

KBH_4 acts quite similarly to $NaBH_4$ but is less often used for reduction of aldehydes. Sodium hydridotrimethoxyborate has a more powerful reducing action; $LiBH_4$ is less selective than $NaBH_4$. An example of the use of sodium hydridotrimethoxyborate is the reduction of cinnamaldehyde effected by Brown and Mead:[378]

Cinnamyl alcohol:[363] Freshly distilled cinnamaldehyde (21.7 g, 0.165 mole) is added to a suspension of sodium hydridotrimethoxyborate (40 g) in ether (100 ml), whereupon the mixture begins to boil. The whole is heated for 4 h, under reflux, then the vessel is cooled and dilute sulfuric acid is added until evolution of hydrogen ceases. The ethereal solution is dried over sodium sulfate and the solvent is evaporated. Fractional distillation gives 80% (17.5 g) of cinnamyl alcohol, b.p. 134–135°/13 mm.

Still better yields are obtained in this reduction by using 1,2-ethanediaminoborane in tetrahydrofuran at a lower temperature.[379]

Lithium cyanotrihydridoborate reduces aldehydes in hot dioxan, *e.g.*, pyrenecarbaldehyde in 85% yield, but does not affect aliphatic or aromatic ketones.[380] Of the alkaline-earth boron hydrides, only calcium hydridotrimethoxyborate has been mentioned; it is prepared from calcium hydride and trimethyl borate and its preparative use for reduction of carbonyl compounds has been investigated by Hesse and Jäger.[381]

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[375] J. B. Lee, *Chem. & Ind. (London)*, **1959**, 1455.

[376] M. Abdel-Akher, J. K. Hamilton, and F. Smith, *J. Amer. Chem. Soc.*, **73**, 4691 (1951).

[377] A. Hunger and T. Reichstein, *Chem. Ber.*, **85**, 635 (1952); *Helv. Chim. Acta*, **35**, 1073 (1952).

[378] H. C. Brown and E. J. Mead, *J. Amer. Chem. Soc.* **75**, 6263 (1953).

[379] H. C. Kelly and J. O. Edwards, *J. Amer. Chem. Soc.*, **82**, 4842 (1960).

[380] G. Drefahl and E. Keil, *J. Prakt. Chem.*, [4], **6**, 80., (1958).

[381] G. Hesse and H. Jäger, *Chem. Ber.*, **92**, 2022 (1959).

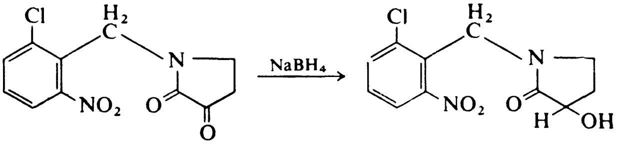
Compared with aldehydes, most ketones are reduced relatively slowly by complex boron hydrides, and a method of distinguishing aldehydes from ketones has been developed on the basis of these differing reaction velocities.[382] On the same principle, selective reduction of the aldehyde group can be effected without reduction of a keto group.[381] There are, however, numerous examples of the reduction of aliphatic, alicyclic, aromatic, and heterocyclic ketones by complex boron hydrides.

1,3-Dithian-5-ol:[384] A solution of $NaBH_4$ (4 g, 0.11 mole) in water (50 ml) is dropped into a stirred solution of 1,3-dithian-5-one[385] (30 g, 0.22 mole) in ether (300 ml) within 30 min, then the mixture is stirred at 20° for an hour, poured on ice, and neutralized with dilute sulfuric acid. The ethereal phase is separated, and the aqueous phase is extracted in a Steudel apparatus with ether. The united extracts are washed with water and dried over sodium sulfate, and the ether is removed; the residue affords colorless needles (25 g, 83%), m.p. 63–64°, from ether/light petroleum (b.p. 60–80°).

Use of complex boron hydrides in place of $LiAlH_4$ is particularly advisable when the molecule contains functional groups such as amide, carboxyl, epoxy, ester, lactone, mercapto, nitrile, or nitro groups.

5-Nitro-2-pentanol:[386] A solution of $NaBH_4$ (2.8 g, 0.075 mole) in water (50 ml) containing one drop of concentrated sodium hydroxide solution is dropped within 1 h into a mixture of 5-nitro-2-pentanone (19.7 g, 0.15 mole) and methanol (50 g) with gentle stirring. The temperature of the mixture is kept at 20–25° by cooling and its pH is kept at 3–4 by continuous addition of 3N sulfuric acid. The pH is measured by a pH-meter. Hydrogen is evolved during addition of the $NaBH_4$, and a white solid product is formed. At the end of the addition the mixture is set aside for 5 min and the excess of $NaBH_4$ is then destroyed by addition of concentrated sulfuric acid (1 ml). The mixture is diluted with water to 350 ml and neutralized with concentrated sodium hydroxide solution. The resulting homogeneous solution is extracted with ether. The united ethereal extracts are washed with saturated sodium hydrogen sulfite solution (3 × 150 ml, 5 min per portion) and with saturated sodium chloride solution, then filtered through anhydrous sodium sulfate. Benzene is added and the solvents are distilled off. After addition of a few crystals of boric acid, 5-nitro-2-pentanol distils in a vacuum as a colorless liquid, b.p. 101–102.5°/2 mm (yield, 11.3 g, 86.6%).

A typical example of selective reduction is the reaction of 1-(2-chloro-6-nitrobenzyl)pyrrolidine-2,3-dione with $NaBH_4$, in which only the keto group is reduced:[387]



Sodium hydridotrimethoxyborate reacts more stereospecifically with cyclic ketones than does $NaBH_4$: On reduction of 2- and 4-methylcyclohexanone the *trans*-isomers are obtained in, respectively, 99 and 88% yield.[388]

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[382] J. P. Critchley, J. Friend, and T. Swain, *Chem. & Ind.*, (*London*), **1958**, 596.

[383] P. Narasimha Rao and L. R. Axelrod, *J. Org. Chem.* **27**, 4694 (1962); F. Bohlmann, P. Herbst, and I. Dohrmann, *Chem. Ber.*, **96**, 226 (1963).

[384] A. Lüttringhaus, M. Mohr and N. Engelhard, *Ann. Chem.*, **661**, 84 (1963).

[385] A. Lüttringhaus and H. Prinzbach, *Ann. Chem.*, **624**, 79 (1959).

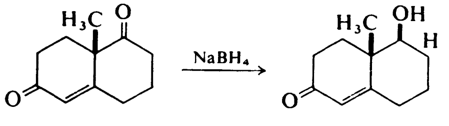
[386] H. Shechter, D. E. Ley, and L. Zeldin, *J. Amer. Chem. Soc.*, **74**, 3668 (1952).

[387] P. L. Southwick and S. E. Cremer, *J. Org. Chem.*, **24**, 753 (1959).

[388] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

[389] J. Dale, *J. Chem. Soc.*, **1961**, 910.

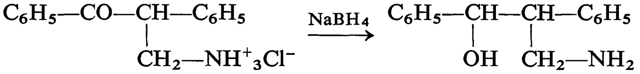
Equally smooth is the reduction of aliphatic, alicyclic, and aromatic diketones to diols by the equivalent amount of complex boron hydrides. For instance, excellent yields of, mainly, *meso*-diols are obtained from acyclic 1,3-diols.[389] The preparation of *trans*-5-hydroxy-4a-methyl-$\Delta^{1,8a}$-octalin-2-one from the corresponding dione by NaBN$_4$[390] is an example of selective reduction of one keto group of a dione:



The derived 1-ethoxycarbonyl compound is selectively reduced by NaBH$_4$ equally smoothly and with the same result.[391]

Quinones can be reduced successfully by NaBH$_4$ or by sodium hydridotrimethoxyborate in various solvents.[391]

Also, amino ketones can be readily converted into amino alcohols by alkali boron hydrides. For example, reduction of 3-amino-1,2-diphenyl-1-propanone hydrochloride by NaBH$_4$ in methanol and subsequent hydrolysis of the boric ester afford pure racemic *erythro*-3-amino-1,2-diphenyl-1-propanol in 70% yield:[392]



$$C_6H_5{-}CO{-}\underset{\textstyle CH_2{-}NH^{+}_{3}Cl^{-}}{\underset{|}{CH}}{-}C_6H_5 \xrightarrow{NaBH_4} C_6H_5{-}\underset{\textstyle OH}{\underset{|}{CH}}{-}\underset{\textstyle CH_2{-}NH_2}{\underset{|}{CH}}{-}C_6H_5$$

Racemic α-(dialkylamino)propiophenones, in which the dialkylamino group contained methyl, ethyl, propyl, and isopropyl groups in various combinations, have recently been reduced to the *erythro*-epimers of the related amino alcohols in good yield, whereas in these cases Meerwein–Ponndorf–Verley reduction does not afford satisfactory results.[393]

Use of NaBH$_4$ also has advantages over that of LiAlH$_4$ for reduction of certain amino ketones, as in the preparation of 3-[1-hydroxy-3-(dimethylamino)-propyl]indole.[394]

Further, alkali boron hydrides are very suitable for reduction of keto acids and their esters, because of the selectivity of these reagents (see refs. 193f. and 395).

5. Catalytic reduction[396]

The carbonyl group of aldehydes and ketones is hydrogenated catalytically to the carbinol group even under mild conditions, and in most cases the yield is almost quantitative.

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[390] J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, **1957**, 3441; C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, **1960**, 2680.

[391] T. A. Spencer, T. D. Weaver, and W. J. Greco Jr., *J. Org. Chem.*, **30**, 3333 (1965).

[392] G. Drefahl and H.-H. Hörhold, *Chem. Ber.*, **94**, 1641 (1961).

[393] H. K. Müller and E. Müller, *Ann. Chem.*, **689**, 134 (1965).

[394] J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **82**, 1180 (1960).

[395] E. Schenker, *Angew. Chem.*, **73**, 94 (1961).

[396] F. Zymalkowski, "Katalytische Hydrierungen im Organisch-chemischen Laboratorium," Enke Verlag, Stuttgart, 1965, p. 91.

Carothers and Adams[397] studied the catalytic hydrogenation of aldehydes in the presence of platinum oxide catalysts and found addition of iron salts to aid the reaction.

3-Methoxybenzyl alcohol:[398] *m*-Methoxybenzaldehyde (40 g), ethanol (200 ml), freshly prepared Adams platinum oxide catalyst (0.2 g), and 0.1M iron sulfate solution (2 ml) are placed in the flask of an Adams hydrogenation apparatus (see page 29). Shaking is begun at 3 atm; hydrogen uptake (0.294 mole) reaches the theoretical value in 10 min. The catalyst can be used for a second and third reduction, although absorption of hydrogen is then slower. The alcohol is removed under diminished pressure and the residual 3-methoxybenzyl alcohol is distilled in a vacuum under nitrogen. It has b.p. 150°/25 mm. The yield is quantitative.

Although acetone, for instance, is hydrogenated to 2-propanol in good yield in the presence of PtO_2, there is a whole series of ketones that cannot be reduced under these conditions, *e.g.*, isopropyl methyl ketone, methyl *n*-pentyl ketone, and 2-methyl-3-heptanone.[399] Rhodium/PtO_2 (3 : 1) is appreciably more active than PtO_2. In the presence of this catalyst, acetophenone in acetic acid is reduced to 1-cyclohexylethanol at room temperature and atmospheric pressure.[400]

Palladium–charcoal can also be used as catalyst for hydrogenation of carbonyl compounds: For instance, 5-methyl-11*H*-benzo[*a*]fluoren-11-one is reduced to the corresponding fluorenol in very good yield at room temperature, with absorption of one equivalent of hydrogen.[401]

Hydrogenation of carbonyl compounds in the presence of Raney nickel[183a] was investigated systematically by Delépine and Horeau.[159] They found the rate of uptake of hydrogen to vary greatly from one compound to another. Adding small amounts of alkali to the carbonyl compounds increased the rate of absorption three-fold to four-fold, or in occasional cases ten-fold; and the effect of alkali was even greater when the Raney nickel was activated by a noble metal (Pt or Pd). One factor responsible for Delépine and Horeau's good results is certainly that they worked with quite fresh Raney nickel which they prepared immediately before the experiment by decomposing an equivalent quantity of the alloy. It should be noted that side reactions may occur in reduction of aldehydes or sugars if alkali is used for activation of the catalyst.

According to Blance and Gibson,[402] Raney nickel is best activated for carbonyl reduction by platinizing it in the presence of triethylamine and then treating it with caustic soda.

As their hydrochlorides in acid solution (pH 3–6) Mannich bases of type $R_2NCH_2C(CH_3)_2CHO$ are hydrogenated in the presence of Raney nickel more successfuly than in the presence of noble metals; the corresponding amino alcohols are then formed in very good yields.[403]

The use of Raney nickel W 6 catalyst is particularly useful because hydrogenation can then be performed at low pressures and low temperature. There is a detailed description of its preparation.[155] The activity also of this is

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[397] W. H. Carothers and R. Adams, *J. Amer. Chem. Soc.*, **46**, 1675 (1924).

[398] R. B. Woodward, *J. Amer. Chem. Soc.*, **62**, 1480 (1940).

[399] F. C. Whitmore and P. A. Krueger, *J. Amer. Chem. Soc.*, **55**, 1531 (1933).

[400] S. Nishimura, *Bull. Chem. Soc. Japan*, **34**, 32 (1961).

[401] R. L. Letsinger and J. D. Jamison, *J. Amer. Chem. Soc.*, **83**, 193 (1961).

[402] R. B. Blance and D. T. Gibson, *J. Chem. Soc.*, **1954**, 2487.

[403] W. Wenner, *J. Org. Chem.*, **15**, 301 (1950).

increased by addition of triethylamine.[404] In the presence of Raney nickel W 7, adrenolone can be hydrogenated in 2N NaOH to D,L-adrenaline in good yield at 1.2 atm and room temperature.[405] Keto carboxylic esters can also be hydrogenated, giving hydroxy carboxylic esters, in the presence of Raney nickel to which triethylamine has been added; for instance, diethyl 3-hydroxyglutarate is obtained almost quantitatively from diethyl acetonedicarboxylate.[406] Sodium 2- and 3-oxo-1-alkanesulfonates can be smoothly converted into the corresponding hydroxyalkanesulfonates in the presence of Raney nickel at 100° with an initial hydrogen pressure of 180–200 atm.[407]

Further, aldehydes and ketones can be hydrogenated in the presence of a Raney nickel catalyst that has been prepared from the alloy by use of water without alkali.[408]

Catalytic reduction of sugars can also be effected in the presence of Raney nickel; however, aldoses and ketoses are more conveniently converted into the corresponding polyols by simply heating them with Raney nickel in boiling alcohol.[409]

Asinger and his co-workers[410] described the use of a cobalt catalyst for hydrogenation of long-chain ketones at about 200° and 200 atm.

When a copper–chromium oxide catalyst is used at 125–150° with pressures of about 100 atm carbonyl groups are reduced smoothly to alcohol groups. Adkins and Connor[188,411] name a series of aldehydes and ketones that can be hydrogenated in 100% yield under these conditions. Similarly, aldehydo and keto alcohols, as well as keto esters, are smoothly hydrogenated to the corresponding glycols and hydroxy esters. Olefinic double bonds present initially are hydrogenated simultaneously.

It is remarkable that furfuraldehyde can be converted into furfuryl alcohol in yields of up to 95% in presence of a copper chromite catalyst stabilized by barium,[344b] whereas it is hydrogenated simultaneously in the ring when the usual noble-metal catalysts are used.

Aromatic aldehydes and ketones that contain a hydroxyl group *ortho* or *para* to the carbonyl group are further hydrogenated to the hydrocarbons even at 110–130°.[412]

Mowry and his collaborators[413] prepared a series of arylmethylcarbinols by hydrogenating the corresponding ketones at 120–150° on a copper–chromium oxide catalyst. However, it is very difficult to hydrogenate 3,4-dichloroacetophenone or 1-acetyl-4-chloronaphthalene since these halogen compounds poison the catalyst. According to Ipatiev and Haensel[414] alkyl phenyl ketones

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[404] H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.*, **70**, 3118 (1948).

[405] A. L. Remisov, *Zh. Obshch. Khim.*, **28**, 2530 (1958).

[406] H. Stetter, O.-E. Bänder, and W. Neumann, *Chem. Ber.*, **89**, 1922 (1956).

[407] F. Püschel and C. Kaiser, *Chem. Ber.*, **97**, 2903, 2917 (1964).

[408] J. H. P. Tyman, *Chem. & Ind. (London)*, **1964**, 404.

[409] J. V. Karabinos and A. I. Ballun, *J. Amer. Chem. Soc.*, **75**, 4501 (1953).

[410] F. Asinger and H. Eckoldt, *Ber. Deut. Chem. Ges.*, **76**, 579 (1943); F. Asinger, *Ber. Deut. Chem. Ges.*, **77**, 73 (1944).

[411] R. Connor, K. Folkers, and H. Adkins, *J. Amer. Chem. Soc.*, **53**, 1091 (1931).

[412] D. Nightingale and H. D. Radford, *J. Org. Chem.*, **14**, 1089 (1949).

[413] D. T. Mowry, M. Renoll, and W. F. Huber, *J. Amer. Chem. Soc.*, **68**, 1105 (1946).

[414] V. N. Ipatiev and V. Haensel, *J. Amer. Chem. Soc.*, **64**, 520 (1942).

can be hydrogenated, without the benzene ring's being attacked, also in the presence of a copper oxide–aluminum oxide catalyst at 115°.

Reduction of cyclopropyl methyl ketone has been attempted by four different methods:[415] Only poor yields of the alcohol were obtained by use of sodium and alcohol; on use of $LiAlH_4$ difficulties were encountered for larger batches; and catalytic hydrogenation with Raney nickel caused partial cleavage of the cyclopropane ring; however, excellent yields of 1-cyclopropylethanol were obtained in the presence of a copper–chromium oxide catalyst activated by barium, at 100°.

6. Reduction by diimine

In recent years not only has the existence of diimine been proved for certain, but its formation as intermediate has also been used for non-catalytic hydrogenation of olefins[416] (see page 137). As first in the field, van Tamelen and his co-workers[417] described the reduction of benzaldehyde to benzyl alcohol by diimine; this reaction gave a 56% yield, but yields of alcohol were lower with some aliphatic and aromatic ketones.[417,418]

Recently some aromatic aldehydes have been treated with diimine under standardized conditions, the reagent being produced by decomposition of potassium azodicarboxylate in methanol; in almost all cases high yields of alcohol were obtained.[419]

1.2. Formation of the carbon–hydrogen bond by exchange

I. Replacement of halogen by hydrogen[344e]

In the series $F < Cl < Br < I$, iodine is the most easily replaced directly by hydrogen. This reaction is usually easier when the halogen is attached to tertiary than to secondary or primary carbon. Also exchange of the halogen is facilitated by neighboring substituents that, by electron-donor effect on the carbon atom, weaken the carbon–halogen bond.

The reducing agent used most often is the combination non-noble metal/acid (glacial acetic adic or hydrochloric acid). Catalytic processes are, however, also widely used, *e.g.*, those with Raney nickel, palladium, or platinum oxide.

Routes involving intermediates such as Grignard reagents are often of considerable preparative importance; and reduction of halides by complex metal hydrides such as $LiAlH_4$ and lithium tri-*tert*-butoxyhydridoaluminate also give good results.

Several methods are available for reduction of acid chlorides to the corresponding aldehydes, the Rosenmund–Saytzeff and the Reissert procedure being those most commonly used.

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[415] V. A. Slabey and P. H. Wise, *J. Amer. Chem. Soc.*, **71**, 3252 (1949).

[416] S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem. Int. Ed. Engl.*, **4**, 271 (1965).

[417] E. E. van Tamelen, M. Davis, and M. F. Deem, *Chem. Commun.*, **1965**, 71.

[418] J. J. Looker, *J. Org. Chem.*, **32**, 472 (1967).

[419] D. C. Curry, B. C. Uff, and N. D. Ward, *J. Chem. Soc., C*, **1967**, 1120.

1. Replacement of halogen on single C—C bonds

a. Direct replacement

Most of the reducing agents that consist of a non-noble metal and an acid are suitable for direct replacement of halogen by hydrogen. Zinc dust in combination with hydrochloric acid or with glacial acetic and hydrochloric acid has found widest use. Reduction is usually effected at the boiling point; but for very sensitive compounds replacement of halogen can be effected at room temperature, reaction then extending over several hours.[420]

Halogenomethyl ketones can be reduced to methyl ketones in very good yield by zinc dust in glacial acetic acid, without effect on the keto group.[421] Even the use of acid can be avoided for acid-senstitive substances, such as certain steroids,[422] replacement of halogen then being achieved by zinc dust in boiling alcohol. Further, substituted benzyl halides can be reduced to hydrocarbons by zinc dust in 10% sodium hydroxide solution.[423] In addition to zinc dust as in the above examples, sodium in alcohol,[424] stannous chloride and hydrochloric acid,[425] Raney nickel and Raney cobalt in sodium hydroxide solution,[426] potassium iodide and acid in acetone,[427] Arndt's alloy,[428] and aluminum amalgam[429] can be used for replacement of halogen.

The commonest method of reduction can be illustrated by the preparation of **n-hexadecane from hexadecyl iodide:**[430]

A mixture of glacial acetic acid (915 ml), zinc dust (327 g), and hexadecyl iodide (352 g) is saturated with dry hydrogen chloride in a round-bottomed flask (2 l) fitted with a stirrer and a gas inlet tube. The mixture is then heated, with stirring, on a steam-bath, saturated again with hydrogen chloride after 5 h, and after 25 h allowed to cool. The upper layer, consisting of hexadecane, is separated. The residual mixture is added to water (3 l), and the zinc dust is filtered off and washed with water (500 ml) and ether (250 ml). The united aqueous filtrates are washed with ether (2 × 500 ml), and the hexadecane previously separated is dissolved in these extracts. The total ethereal solution is shaken with 20% sodium hydroxide solution (2 × 250 ml), washed with water until free from alkali, dried with anhydrous sodium sulfate (150 g), and, after the ether has been distilled off, is fractionated in a vacuum through a column. *n*-Hexadecane, b.p. 156–158°/14 mm, m.p. 16–17°, is obtained in 85% yield (192 g).

Anhydrous chromium(II) chloride sometimes has advantages over other reagents for replacement of halogen by hydrogen. For some bromo keto steroids halogen exchange by zinc dust in glacial acetic acid gives very unsatisfactory yields, whereas the dehalogenated product is usually obtained in good yield by treating the halide for several hours with a solution of chromium

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[420] W. B. Whalley, *J. Chem. Soc.*, **1951**, 3229.

[421] O. Schnider, J.-P. Bourquin, and A. Grüssner, *Helv. Chim. Acta*, **28**, 510 (1945).

[422] H. H. Inhoffen, G. Kölling, and I. Nebel, *Chem. Ber.*, **84**, 361 (1951).

[423] R. C. Fuson, J. J. Denton, and J. W. Kneisery, *J. Amer. Chem. Soc.*, **63**, 2652 (1941).

[424] H. F. B. Hirschmann and M. A. Dans, *J. Biol. Chem.*, **178**, 751 (1949).

[425] R. E. Lutz and co-workers, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).

[426] N. P. Buu-Hoï, N. D. Xuong, and N. van Bac, *Bull. Soc. Chim. France*, **1963**, 2442.

[427] A. H. Blatt and E. W. Tristram, *J. Amer. Chem. Soc.*, **74**, 6273 (1952).

[428] F. Dallaker, *Ann. Chem.*, **633**, 14 (1960).

[429] T. Inoi, P. Gericke, and W. J. Horton, *J. Org. Chem.*, **27**, 4597 (1962).

[430] P. A. Levene, *Org. Syn.*, Coll. Vol. II, p. 320 (1943).

dichloride in acetone[431] under an atmosphere of carbon dioxide at 25–30°. α-Bromo ketones are also amenable to this exchange reaction.[432]

Lithium hydride containing some $LiAlH_4$ as catalyst provides a valuable reducing agent for some aliphatic and also benzyl halides, but it is not a general reagent, behaving particularly poorly with vinyl halides.[433]

The use of Raney nickel and of noble metals (palladium) may be singled out from the catalytic processes available in this field. For instance, Wessely and Sinwel[434] hydrogenated substituted benzyl halides with a 20% $Pd–BaSO_4$ catalyst in alcohol in presence of dimethylaniline. Addition of a base is essential to bind the acid formed which would otherwise poison the catalyst.

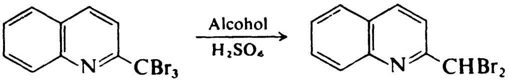
Aliphatically bound halogen can also be readily removed by reduction with hydrazine.[102a]

Stepwise substitution of hydrogen for halogen in polyhalides is important for preparation of halogen derivatives of the type $RCHX_2$. These compounds are, it is true, easily accessible from the corresponding aldehydes when the latter can be obtained conveniently; but their preparation by direct halogenation of terminal methyl group is not always simple because they are not easily separated from the intermediate stages. However, the trihalogenated products are readily prepared and in many cases replacement of one of their halogen atoms by hydrogen provides a superior method of obtaining the dihalogenated compounds. Sodium arsenite is one of the best reducing agents for this purpose; for instance, Hartman and Dreger[435] prepared **methylene bromide** from bromoform as follows:

540 g of commercial bromoform (containing alcohol; 88%; specific weight 2.59 at 25°) are placed in a three-necked flask (2 l) fitted with a stirrer, dropping funnel, and reflux condenser. To this are dropped in first only 10 ml of a solution of 230 g of arsenic trioxide and 440 g of sodium hydroxide (an excess of alkali) in 1.4 l of water and the reaction is started by gentle warming on the steam-bath. Then the remainder of the arsenite solution is dropped in, during about an hour, at a rate sufficient to keep the mixture boiling gently, after which the whole is heated for a further 4 h on the steam-bath. Next comes steam-distillation; the lower layer of the distillate is separated, and the aqueous layer is extracted with ether to collect the suspended droplets of methylene bromide. The extract is united with the bromide previously separated and is dried with 10 g of calcium chloride. On distillation, 290–300 g (88–90%) of pale yellowish methylene bromide are obtained that boils at 97–100°.

Methylene iodide can be obtained quite similarly from iodoform according to the directions of Adams and Marvel.[436]

However, trihalomethyl heterocycles are reduced to the corresponding dihalogeno compounds by 20% H_2SO_4 in hot alcohol or by tin(II) chloride.[437]



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[431] J. B. Conant and H. B. Cutter, *J. Amer. Chem. Soc.*, **48**, 1016 (1926).

[432] P. L. Julian, W. Cole, A. Magnani, and E. W. Meyer, *J. Amer. Chem. Soc.*, **67**, 1728 (1945).

[433] A. Hajós, "Komplexe Hydride," VEB Deutscher Verlag der Wissenschaften, Berlin, 1966, p. 219.

[434] F. Wessely, and F. Sinwel, *Monatsh. Chem.*, **81**, 1055 (1950).

[435] W. W. Hartman and E. E. Dreger, *Org. Syn.*, **9**, 56 (1929).

[436] R. Adams and C. Marvel, *Org. Syn.*, **1**, 57 (1941).

[437] L. K. Sharp, *J. Pharm. Pharmacol.*, **1**, 395 (1949).

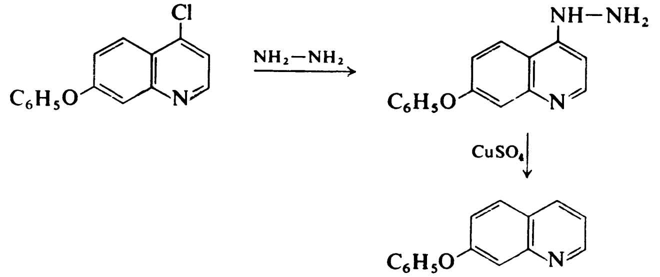
b. Replacement of halogen *via* intermediates

Hydrocarbons are formed on hydrolysis of Grignard compounds by water or hydroxyl-containing substances:[438]

$$\mathrm{RMgX + R'OH \longrightarrow RH + R'OMgX}$$

The reaction is well-known as the basis of Tchugaev and Zerewitinov's method of determining active hydrogen, but it is also of preparative importance for the preparation of hydrocarbons from halides. For instance, 2-(iodomethyl)-decalin gives 2-methyldecalin in good yield when its Grignard derivative is treated with dilute acetic acid.[439] Similarly cyclobutane is obtained in good yield when a solution of cyclobutylmagnesium bromide in di-*n*-butyl ether is treated with 1-butanol at about 50° for 30 min.[440]

Mobile chlorine attached to a heterocycle often reacts also with hydrazine and decomposition of the resulting hydrazine derivative by aqueous copper sulfate solution gives a product in which the original halogen has been replaced by hydrogen.[441]



A route involving reaction with *p*-toluenesulfonohydrazide and decomposition of that product with alkali has been described by Albert and Roger.[442]

Finally, aliphatically bound iodine may be replaced in a circuitous route in which reaction with thiourea gives a thiouronium salt that is cleaved reductively when shaken with Raney nickel.[443]

2. Replacement of halogen bound to olefinic or aromatic systems

Substitution of hydrogen for halogen in compounds containing the halogen attached to doubly or trebly bonded carbon can often be effected by aluminum amalgam,[444] lithium aluminum hydride,[445] zinc dust in pyridine and glacial

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[438] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N.Y., 1954.

[439] R. Ya. Levina and S. G. Kulikov, *Zh. Obshch. Khim.*, **16**, 117 (1946); *Chem. Abstr.*, **41**, 115 (1947).

[440] J. Cason and R. L. Way, *J. Org. Chem.*, **14**, 31 (1949).

[441] R. O. Clinton and C. M. Suter, *J. Amer. Chem. Soc.*, **69**, 704 (1947).

[442] A. Albert and R. Roger, *J. Chem. Soc.*, **1949**, 1148.

[443] E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

[444] T. I. Temnikova and Z. A. Baskova, *Zh. Obshch. Khim.*, **21**, 1823 (1951); *Chem. Abstr.* **46**, 6584.

[445] L. F. Hatch and R. H. Perry, *J. Amer. Chem. Soc.*, **71**, 3262 (1949).

acetic acid,[446] or butyllithium[447] in such a way that the carbon–carbon multiple bond is not attacked. When sodium amalgam is used, the primary action is usually reduction of the double bond, *e.g.*, in vinyl halides.

Halogen attached to an aromatic ring can be relatively easily exchanged for hydrogen only when made more reactive by presence of electron-attracting substituents in the *ortho*- and *para*-positions. The halogen in 1-chloro-2,4-dinitronaphthalene can be replaced by hydrogen when the compound is, for instance, heated with copper powder at 150–200° in the presence of an organic acid such as benzoic acid.[448] In other cases halogen exchange can be effected by means of copper(I) acetate in pyridine or copper(I) oxide in acetic anhydride[449] or, above all, by catalytic hydrogenation, suitable catalysts being palladium on charcoal or alkaline-earth carbonates and platinum oxide (Adams catalyst). That Raney nickel can also be used is shown by the fact that 2-chlorolepidine can be reduced in alcohol to **lepidine** by this catalyst in the presence of alkali.[450]

2-Chlorolepidine (20 g) and potassium hydroxide (6.3 g) are dissolved in alcohol (150 ml). Raney nickel (3 g) is added and hydrogenation (1 mole of hydrogen) is carried out at room temperature and atmospheric pressure. Reaction is complete in 16 h. The catalyst is filtered off and the alcohol is removed by distillation. The residue is extracted with ether, and the extracts are washed with water, dried, and evaporated. The crude lepidine is purified by distillation. Its boiling point is 126°/40 mm. The yield amounts to 94%.

However, using noble-metal catalysts for this hydrogenation of 2-chlorolepidine has the advantage that the reaction time is appreciably shorter, namely, 1.5–2 hours.[451]

Hydrogen replaces fluorine attached to an aromatic system only on catalytic hydrogenation of the aromatic ring.[344d]

3. Replacement of halogen in other surroundings (in acid chlorides)

Rosenmund–Saytzeff reduction permits replacement of halogen in carbonyl chlorides by hydrogen:[344b,452] aldehydes are obtained by selective hydrogenation of carbonyl halides in the presence of a suitable catalyst, usually palladium (5%) on barium sulfate (95%). The reduction is carried out by passing a stream of hydrogen into a hot or boiling solution of the acid chloride in which the catalyst is suspended, but water and oxygen must be completely excluded as otherwise acid anhydrides are formed.

This method is, however, successful only if further reduction of the resulting aldehyde to the alcohol or hydrocarbon is prevented. These limitations are achieved by Rosenmund and Zetsche's contact poison,[453] "quinoline S",

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[446] A. Roedig and H. Niedenbrück, *Chem. Ber.*, **90**, 682 (1957).

[447] W. Tochtermann, U. Walter, and A. Mannschreck, *Tetrahedron Lett.*, **1964**, 2981.

[448] E. V. Brown, *J. Amer. Chem. Soc.*, **76**, 3167 (1954).

[449] W. G. H. Edwards, and R. G. Stewart, *Chem. & Ind. (London)*, **1952**, 472.

[450] S. E. Krahler and A. Burger, *J. Amer. Chem. Soc.*, **63**, 2367 (1941).

[451] F. W. Neumann, N. B. Sommer, C. E. Kaslow, and R. L. Shriner, *Org. Syn.*, Coll. Vol. III, 519 (1955).

[452] E. Mosettig and R. Mozingo, *Org. Reactions*, **4**, 362 (1948).

[453] K. W. Rosenmund and F. Zetsche, *Ber. Deut. Chem. Ges.*, **54**, 425 (1921); **56**, 1481 (1923).

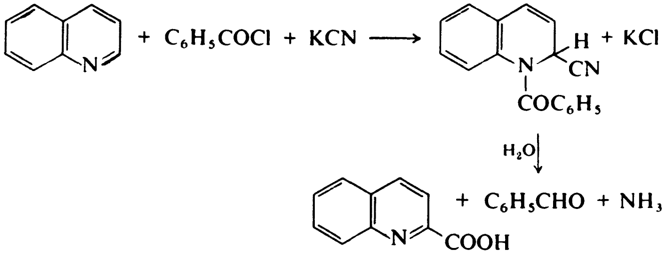
which is prepared from quinoline and sulfur. Weygand and Menzel[454] later found that thiourea could replace the indefinite material "quinoline S"; other suitable contact poisons are phenyl isothiocyanate and benzothiazole-2-thiol.

The reaction temperature has an appreciable effect on the yields of aldehyde. The best yields of aldehyde are obtained if the temperature is held at the point where formation of hydrogen chloride begins, whereas at higher temperatures these yields are decreased by formation of by-products.[455]

Readily reducible groups such as keto and nitro groups are not attacked by these methods of reduction. Also, hardly any exchange of aliphatically bound halogen occurs. Hydroxyl groups, however, must be protected by acetylation.

Quinoline S is prepared by heating 1 g of sulfur and 6 g of quinoline for 6 h under a reflux condenser and diluting the product with 70 ml of xylene that has been freed from poisons. Preparation of the palladium–barium sulfate catalyst has been described by Mozingo.[456]

Another procedure for converting carbonyl chlorides into aldehydes proceeds by way of Reissert compounds.[344g] Reissert found that 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile is formed in very good yield when benzoyl chloride reacts with quinoline in the presence of aqueous potassium cyanide, the technique being that of a Schotten–Baumann reaction; the nitrile can then be hydrolysed to benzaldehyde and quinaldic acid by acid.



The **Reissert compound** is best obtained by allowing 1 mole of the acid chloride to react with 1 mole of anhydrous hydrogen cyanide and 2 moles of quinoline in anhydrous benzene. The adduct (yield 65–95%) is hydrolysed by boiling 5–10N sulfuric acid, cleavage usually being quantitative.

Grundmann's aldehyde synthesis also starts from acid chlorides. The latter are converted by way of the diazo ketones or acetoxy ketones into the glycols, which are subjected to cleavage by lead tetraacetate. α,β-Unsaturated aldehydes cannot be obtained by this method.[457]

Sohn and Müller[458] have allowed ethereal hydrogen tetrachlorostannate(II) to react with imidoyl chlorides, obtaining thereby good yields of aldehydes in

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[454] C. Weygand and W. Menzel, *Ber. Deut. Chem. Ges.*, **76**, 503 (1943).

[455] T. Boehm, G. Schumann, and H. H. Hansen, *Arch. Pharm.*, **271**, 490 (1933).

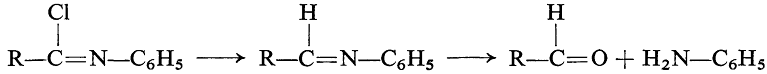
[456] R. Mozingo, *Org. Syn.*, Coll. Vol. III, 291 (1955).

[457] E. Mosettig, *Org. Reactions*, **8**, 225 (1954).

[458] A. Sonn and E. Müller, *Ber. Deut. Chem. Ges.*, **52**, 1929 (1919); cf. E. Mosettig, *Org. Reactions*, **8**, 240 (1954).

the aromatic series; but the method fails with imidoyl chlorides of aliphatic carboxylic acids.

By a similar process, von Braun and Rudolph[459] obtained α,β-unsaturated aldehydes from the imidoyl chlorides derived from anilides of α,β-unsaturated acids; the reaction proceeds by way of the Schiff bases, which are then hydrolysed to the aldehydes.



$$R{-}\overset{\overset{\textstyle Cl}{|}}{C}{=}N{-}C_6H_5 \longrightarrow R{-}\overset{\overset{\textstyle H}{|}}{C}{=}N{-}C_6H_5 \longrightarrow R{-}\overset{\overset{\textstyle H}{|}}{C}{=}O + H_2N{-}C_6H_5$$

According to more recent findings acid chlorides are also reduced to aldehydes by lithium tri-*tert*-butoxyhydridoaluminum in diethylene glycol dimethyl ether (diglyme) at −78°.[460] Reduction with $LiAlH_4$, however, gives the corresponding alcohol in 60–100% yield; unsaturated alcohols are obtained preferentially from α,β-unsaturated aliphatic acid chlorides,[339] but cinnamoyl chloride affords 3-phenyl-1-propanol. The action of sodium ethoxytrihydridoaluminate is somewhat milder than that of $LiAlH_4$, but even with this reagent cinnamyl alcohol is not formed from cinnamoyl chloride; the double bond is indeed retained, but cinnamyl alcohol is obtained in 70% yield after reaction for 4 h in tetrahydrofuran at 65°.[461]

tert-Butylaminoborane also reduces aroyl halides to the corresponding benzyl alcohols.[462]

II. Replacement of oxygen by hydrogen

1. Replacement of the hydroxyl group

It is only in some special, but nevertheless not unimportant, cases that direct replacement of hydroxyl by hydrogen is of preparative importance: for primary and secondary hydroxyl groups, in particular, detours are often more convenient. For primary groups the route is usually *via* halides, but for secondary groups also *via* the unsaturated compounds which are readily formed from secondary alcohols. Tertiary hydroxyl groups can usually be replaced directly by hydrogen with less difficulty, for which purpose a non-noble metal in alcohol or an acid (*e.g.*, sodium and alcohol or zinc and hydrochloric acid) or catalytic hydrogenation may be used.

In the route *via* the halides, the latter need not be obtained in the pure state when the substituting reagent has also reducing action, as in the case of hydrogen iodide. For that reason, reactions of alcohols with hydrogen iodide will here be considered as involving direct exchange of OH for H.

For economic reasons it is not usual to work with stoichiometric amounts of hydrogen iodide; instead, red phosphorus is added, which in the presence of water continuously regenerates hydrogen iodide from the elemental iodine formed. It often suffices to use a mixture of phosphorus and iodine to which

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[459] J. von Braun and W. Rudolph, *Ber. Deut. Chem. Ges.*, **67**, 269, 1735 (1934).

[460] H. C. Brown, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **80**, 5377 (1958).

[461] G. Hesse and R. Schrödel, *Ann. Chem.*, **607**, 24 (1957).

[462] H. Nöth and H. Beyer, *Chem. Ber.*, **93**, 1078 (1960).

small amounts of hydrogen iodide are sometimes added. For example, ***o*-ethylbenzoic acid** is best prepared from α-methylphthalide by the following modification of Giebe's directions:[463]

Glacial acetic acid (390 ml), red phosphorus (24 g), and iodine (8 g) are placed in a round-bottomed flask (1 l) and set aside for 20 min, whereupon reaction between the phosphorus and the iodine sets in slightly exothermally. Water (8 ml), constant-boiling hydriodic acid (2 ml), and α-methylphthalide (100 g) are then added and the whole is boiled under reflux for 160 h. The mixture is then filtered whilst hot from the phosphorus and poured, with stirring, into a solution of sodium hydrogen sulfite (35 g) in water (1.5 l); the brown color of the iodine disappears and *o*-ethylbenzoic acid separates as colorless crystals. After cooling, the mixture is filtered and the filtrate is concentrated, whereby a further small amount of *o*-ethylbenzoic acid is obtained (total, 80 g). A little (10 g) of the methylphthalide is recovered by ether-extraction of the concentrated filtrate, and the yield of acid calculated on phthalide consumed amounts to 90%. For purification, *o*-ethylbenzoic acid is recrystallized from water, being thus obtained completely colorless.

Hydroxy carboxylic acids are also reduced similarly to carboxylic acids. For instance, diphenylacetic acid is obtained in more than 90% yield from benzilic acid.[464]

Direct replacement of hydroxyl groups by hydrogen can be effected equally by combination of a non-noble metal with an acid or alcohol and by catalytic hydrogenation. The reaction is favored by neighboring unsaturated linkages, aromatic systems, or carbonyl groups, and is often only possible when such are present. An example—admittedly not one that is preparatively important—is the reaction cinnamyl alcohol with sodium and alcohol as described by Klages:[465] the product mixture contains mainly propylbenzene with a little propenylbenzene C_6H_5—CH=CH—CH_3. The propylbenzene could not have been formed from 3-phenyl-1-propanol $C_6H_5CH_2CH_2CH_2OH$ since the latter is completely unchanged in the reaction conditions. 4-Isopropylbenzyl alcohol $(CH_3)_2CH$—C_6H_4—CH_2OH, containing the aromatic system next to the alcoholic hydroxyl group, gives cymene when boiled for a long time even with zinc dust alone. And the alcoholic group of α-hydroxy ketones is readily eliminated, as shown by the fact that acetoins such as benzoin can be reduced to deoxyacetoins in good yield by zinc and alcoholic hydrochloric acid.[466] When α-hydroxy ketones esterified by acetic acid are boiled for several hours with zinc dust in glacial acetic acid the acetoxy group is replaced directly by hydrogen, the neighboring keto group remaining unaffected.[467]

A tertiary hydroxyl group is replaced appreciably more easily than a secondary or primary one. For instance, linaloöl $(CH_3)_2C{=}CHCH_2CH_2C(CH_3)\cdot(OH)$—$CH{=}CH_2$, whose tertiary hydroxyl group lies next to a double bond, is converted into the hydrocarbon diene even by zinc dust in a bomb tube.[468] In fact, it is often possible to decide from the occurrence or non-occurrence of this reaction whether a hydroxyl group is tertiary as opposed to secondary or primary.[469]

Naturally the reduction is more usually effected by combinations of zinc dust with hydrochloric acid, acetic acid, or sodium hydroxide solution. For

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[463] G. Giebe, *Ber. Deut. Chem. Ges.*, **29**, 2533 (1896).

[464] C. S. Marvel, F. D. Hager, and C. E. Candle, *Org. Syn.*, Coll. Vol. I, 224 (1947).

[465] A. Klages, *Ber. Deut. Chem. Ges.*, **39**, 2587 (1906).

[466] H. Stobbe, *Ber. Deut. Chem. Ges.*, **35**, 911 (1902).

[467] R. S. Rosenfeld and T. F. Gallagher, *J. Amer. Chem. Soc.*, **77**, 4367 (1955).

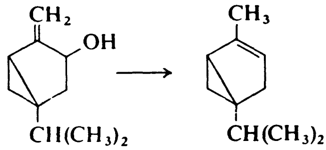
[468] F. W. Semmler, *Ber. Deut. Chem. Ges.*, **27**, 2520 (1894).

[469] F. W. Semmler, *Ber. Deut. Chem. Ges.*, **33**, 776 (1900).

instance, when a triarylmethanol is boiled with zinc in glacial acetic acid the hydroxyl group is readily replaced by hydrogen. According to Kauffmann,[470] methoxy derivatives of triphenylmethanol are reduced to triphenylmethanes even by warm alcohol in the presence of hydrochloric acid, though the reaction probably proceeds by way of a triarylmethyl chloride.

Enolic hydroxyl groups can be reduced by sodium amalgam, as shown by Vorländer and Apelt.[471] This reducing agent can be usefully applied in acid solution for substituting hydrogen in place of hydroxyl engaged in a lactone group. For example, valerolactone gives valeric acid, and 6-hexanolide gives hexanoic acid. Lactones of polyhydroxy carboxylic acids, particularly those in the carbohydrate series, are attacked by sodium amalgam first at the hydroxyl group engaged by the carboxyl.

According to Birch, allylic and other alcohols can be reduced at the hydroxyl group by sodium and alcohol. (−)-α-Thujene is formed from (+)-sabinol:



Benzyl and furfuryl alcohol are similarly converted into the corresponding hydrocarbons.[472]

Alcohols can also be reduced to hydrocarbons by catalytic hydrogenation. 2,2,3-Trimethylbutan-1-ol is hydrogenated to trimethylbutane (triptane) in 56% yield in presence of a cobalt–aluminum oxide catalyst at 300° within 18 h; this reduction cannot be effected with copper chromite.[473] Further, aliphatic alcohols can be converted into hydrocarbons on a vanadium pentoxide–aluminum oxide catalyst.[474] However, Raney nickel converts straight-chain primary alcohols into hydrocarbons containing one carbon atom less.[475]

According to Smith and Spillane,[476] **hemimellitol** is obtained from dimethylbenzyl alcohol in the following way:

2,3-Dimethylbenzyl alcohol (m.p. 65–66.5°; 61.5 g) is dissolved in ethanol (70 ml), and copper chromite catalyst (3 g) containing barium oxide is added. The mixture is hydrogenated in a stirring autoclave at 220–235° in 8.5 h. The initial hydrogen pressure, of 100 atm at 28°, rises to a maximum of 190 atm during the reaction. When hydrogenation is complete, the catalyst is filtered off and the filtrate is diluted with water (600 ml) and thoroughly extracted with ether. The ethereal solution is dried over sodium sulfate, the ether is distilled off, and the residue is distilled through a short column packed with pieces of glass. The fraction of b.p. 172–173° is collected, the yield being 50 g (92%).

For further information about use of copper-chromium oxide catalysts see the article by Grundmann.[183b]

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[470] H. Kauffmann, *Ber. Deut. Chem. Ges.*, **38**, 2702 (1950); **41**, 4423 (1908).

[471] D. Vorländer and O. Apelt, *Ber. Deut. Chem. Ges.*, **37**, 1134 (1904).

[472] A. J. Birch, *J. Chem. Soc.*, **1945**, 809.

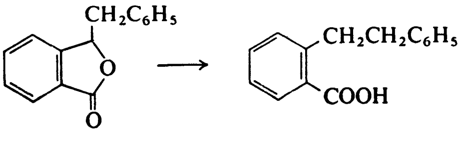
[473] T. A. Ford, H. W. Jacobson, and F. C. McGrew, *J. Amer. Chem. Soc.*, **70**, 3793 (1948).

[474] V. I. Komarewsky, C. F. Price, and J. R. Coley, *J. Amer. Chem. Soc.*, **69**, 238 (1947).

[475] H. Adkins, and R. E. Burks, *J. Amer. Chem. Soc.*, **70**, 4174 (1948).

[476] L. I. Smith and L. J. Spillane, *J. Amer. Chem. Soc.*, **62**, 2639 (1940).

Reductive hydrolysis of phthalides is achieved in good yield by catalytic hydrogenation on palladium–charcoal in presence of sodium hydroxide solution:[477]



Methanesulfonic esters[478] and benzoic esters[479] can be cleaved by hydrogenation over Raney nickel, acetic esters over platinum dioxide,[480] and carbonic ester over palladium on charcoal.[481]

Alcohols are rarely reduced by lithium aluminum hydride: the reaction occurs only in exceptional cases, such as that of benzyl alcohols containing an amino or methoxy group *ortho* or *para* to the CH_2OH group.[356] However, aliphatic and alicyclic sulfonic esters are more[482] or less easily[483] reduced by this reagent.

A phenolic hydroxyl group is removed by distillation with zinc dust, a process that has no preparative importance but can be useful for proof of structure. Phenanthrene is formed in 72% yield when 9-phenanthrol is distilled in hydrogen with zinc dust.[484]

2. Replacement of carbonyl-oxygen

a. Direct replacement[485]

There are three main processes for direct replacement of carbonyl-oxygen by hydrogen: Clemmensen reduction, catalytic hydrogenation, and reduction by metal hydrides.

Other reducing agents are also known for removing carbonyl groups from various oxo compounds. For instance, phenyl 2,4,5,6-tetramethylphenyl diketone in glacial acetic acid solution is partially reduced by a large excess of hydrogen iodide, with stirring at the boiling point, giving phenyl 2,4,5,6-tetramethylbenzyl ketone within 2 h.[486] Similarly, 2-bromobenzophenone is reduced by a mixture of hydriodic acid and red phosphorus to 2-bromodiphenylmethane in 82% yield, this process being more prolific than Clemmensen reduction in this case.[487] Further, Hewett *et al.*[488] describe the conversion of 2-aminobenzophenone in absolute alcohol into 2-aminodiphenylmethane in very good yield by an excess of sodium. Finally, similar reduction of the carbonyl group has been described on use of zinc dust in acid or

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[477] J. Kollonitsch, H. E. Mertel, and V. F. Verdi, *J. Org. Chem.*, **27**, 3362 (1962).

[478] A. S. Dreiding and A. J. Tomasewski, *J. Amer. Chem. Soc.*, **77**, 411 (1955).

[479] M. W. Cronyn, *J. Org. Chem.*, **14**, 1013 (1946).

[480] T. A. Geissman and E. Hinreiner, *J. Amer. Chem. Soc.*, **72**, 782 (1951).

[481] H. Kinder and K. Schrader, *Ann. Chem.*, **564**, 49 (1949).

[482] D. Gagnaire and A. Butt, *Bull. Soc. Chim. France*, **1961**, 312.

[483] H. van Bekkum, A. A. B. Kleis, A. A. Massier, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **80**, 588 (1961).

[484] A. Schönberg and F. L. Warren, *J. Chem. Soc.*, **1939**, 1838.

[485] O. H. Wheeler, in S. Patai, "The Chemistry of the Carbonyl Group," Interscience Publishers, Inc., London–New York–Sydney, 1966.

[486] R. C. Fuson and P. E. Hoch, *J. Amer. Chem. Soc.*, **71**, 1585 (1949).

[487] C. K. Bradsher and F. A. Vingiello, *J. Org. Chem.*, **13**, 786 (1948).

[488] C. L. Hewett, L. J. Lermit, H. T. Openshaw, A. R. Todd, A. H. Williams, and F. N. Woodward, *J. Chem. Soc.*, **1948**, 292.

alkaline solution, for example: loss of the 3-oxo group when 5α-pregnane-3,20-dione is converted in 71% yield by zinc dust in alcohol and concentrated hydrochloric acid into 5α-pregnan-20-one;[424] and the remarkable 95% yield when dibenz[*a*,*h*]anthraquinone-4,11-disulfonic acid is reduced by zinc dust in concentrated aqueous ammonia to the corresponding anthracene derivative.[489]

According to Clemmensen,[344*i*,490,491] amalgamated zinc in concentrated hydrochloric acid is a very general reagent for reduction of carbonyl compounds. Amalgamation of the metal leads to a hydrogen overpotential which raises the separation potential of the hydrogen. The strength of acid necessary for the reduction is said to be 20–40%, the reaction time at the boiling point then averaging 5–10 h. If the carbonyl compound is sensitive to acid the mixture may merely be kept at room temperature for several days. Yields of the desired reduction products are often mediocre. They depend not only on the substance to be reduced but also often on the reaction conditions. A prime requirement is a certain solubility of the carbonyl compound in the reaction medium; this solubility may be increased by addition of ethanol, acetic acid, or dioxan; but if the solubility of the compound is increased too much formation of resinous by-products is favored and these may coat the metal, rendering it inactive; this final mischance may be overcome by adding toluene.

The following types of compound can be reduced by the Clemmensen method:

(1) Aliphatic and aromatic aldehydes.

(2a) Aliphatic and alicyclic ketones. Only the carbonyl group of aliphatic hydroxy ketones is reduced, primary,[492] secondary,[493] or tertiary[495] hydroxyl groups remaining intact unless in α-position to the CO group. Partial reduction of diketones at one CO group is sometimes possible, but with cyclic β-diketones rearrangement of the ring system may occur.[495]

(2b) Mixed aliphatic-aromatic ketones.

(3) Keto acids or esters (α, β,[496] γ,[497] δ,[498] etc.). However, in α-keto acids the group —CO—COOH is reduced mainly to —CH(OH)—COOH.[496]

(4) α,β-Unsaturated carbonyl compounds. —CH=CH—CO— is reduced to $—CH_2—CH_2—CH_2—$,[496] but selective reduction of either the double bond or the carbonyl group is also possible.[499]

If a carbonyl compound cannot be reduced satisfactorily by the Clemmensen method, the Wolff–Kishner procedure usually gives better results (cf. page 74).

Clemmensen[500] has described the preparation of *n*-**undecane** from 2-undecanone as an example of the reduction of aliphatic ketones to straight-chain hydrocarbons:

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[489] J. Cason and L. F. Fieser, *J. Amer. Chem. Soc.*, **62**, 2681 (1941).

[490] E. L. Martin, *Org. Reactions*, **1**, 155 (1942).

[491] D. Staschewski, *Angew. Chem.*, **71**, 726 (1959).

[492] E. Clemmensen, *Ber. Deut. Chem. Ges.*, **47**, 681 (1914).

[493] R. E. Marker and E. J. Lawson, *J. Amer. Chem. Soc.*, **61**, 852 (1939).

[494] R. E. Lutz and L. Smale, *J. Org. Chem.*, **4**, 220 (1939).

[495] A. N. Dey and R. P. Linstead, *J. Chem. Soc.*, **1935**, 1063.

[496] W. Steinkopf and A. Wolfram, *Ann. Chem.*, **430**, 113 (1923).

[497] C. F. Koelsch, *J. Amer. Chem. Soc.*, **55**, 3885 (1923).

[498] L. Ruzicka, W. Buegger, C. F. Seidl, and H. Schinz, *Helv. Chim. Acta*, **11**, 496 (1928).

[499] R. Davis and P. D. Woodgate, *J. Chem. Soc.*, *C*, **1966**, 2006.

[500] E. Clemmensen, *Ber. Deut. Chem. Ges.*, **46**, 1841 (1913).

2-Undecanone (50 g; b.p. 224–226°) was boiled with amalgamated zinc (300 g) and a mixture (330 ml) of equal parts of water and concentrated hydrochloric acid for 24 h under reflux, concentrated (undiluted) acid being added periodically during this time to maintain brisk evolution of hydrogen. After cooling, the oily layer was separated from the aqueous solution, washed with water, and dried. Fractionation afforded 88% (40 g) of *n*-undecane, b.p. 193 to 195°.

The procedure for reducing mixed alkyl aryl ketones is very similar. For instance, propylbenzene is obtained as follows: Propiophenone (25 g) is warmed with amalgamated zinc (100 g) and a mixture of equal parts of water and concentrated hydrochloric acid. A lively reaction sets in after 5 min. Then heating is continued whilst concentrated acid is allowed to drop in during a further 4 h. On working up, 90% (20 g) of propylbenzene, b.p. 155–160°, is obtained.

The following directions for reducing substituted benzoylpropionic acids to the corresponding **arylbutyric acids** illustrates the technique devized by Martin[501] for effecting Clemmensen reduction in the presence of toluene.

Zinc foam (100 g) was shaken for 5 min with mercury(II) chloride (10 g), concentrated hydrochloric acid (5 ml), and water (150 ml), then the aqueous layer was poured off, and the amalgamated zinc was treated with water (75 ml), concentrated hydrochloric acid (175 ml), toluene (100 ml), and the carbonyl compound to be reduced (50 g). When necessary, glacial acetic acid (3–5 ml) may be added to increase the solubility in the aqueous layer. The mixture is heated to brisk ebullition under reflux. At each of three 6-hourly intervals hydrochloric acid (50 ml) is added, the total time of boiling being thus about 24 h. As examples, 3-oxo-3-phenyl-, -3-*m*-tolyl-, -3-*p*-tolyl-, -3-(1-naphthoyl)-, and -3-(2-naphthoyl)-propionic acid, benzoylnaphthalene, 2-acetylnaphthalene among other materials were reduced more satisfactorily than in absence of toluene. A comparison of the toluene method with the old method is provided, for instance, by Martin who obtained a 72–78% yield in a preparation by himself by the old method, compared with 90% by the new method.

An improvement in yield is observed when the Clemmensen reduction is carried out with acetic acid as solvent.[502]

Sometimes the Clemmensen reduction does not lead to unambiguous replacement of a carbonyl-oxygen by hydrogen. For instance, benzophenone gives about 70% of benzopinacone when reduced with amalgamated zinc turnings and aqueous hydrochloric acid; very little of the diphenylmethane expected is obtained on use of alcoholic hydrochloric acid, the main products being benzopinacolin and tetraphenylethylene.[496]

The carbonyl group can also be catalytically hydrogenated to a methylene group. Copper chromite and noble metals (Pd–C, Pd–$BaSO_4$, Pt, PtO_2) are used as catalysts. According to Nightingale,[412] aryl ketones are hydrogenated to alkylbenzenes in very good yield by means of copper chromite at 185–250°. *o*- and *p*-Hydroxybenzaldehyde are converted into the corresponding cresols at 110–130°, and *o*- and *p*-hydroxy ketones are reduced to alkylphenols.

Hydrogenation is effected in a steel shaking autoclave with a copper insert of 500 ml capacity. The ketone or aldehyde (0.25 mole) and copper chromite catalyst (4 g)[184] are introduced. For hydroxy aldehydes, anhydrous methanol (100 ml) is also added, to prevent formation of resinous products. For aromatic ketones the initial pressure of hydrogen is 300–340 atm, but for hydroxy aldehydes and hydroxy ketones 220–240 atm suffice. When alcohol is used, the temperature is kept at 200–250° until the pressure remains constant; when no alcohol is used, a temperature of 180–195° suffices for reduction to the hydrocarbon. When hydrogenation is complete, the mixture is washed from the vessel with methanol or benzene, filtered from the catalyst, and worked up as usual.

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[501] E. L. Martin, *J. Amer. Chem. Soc.*, **58**, 1438 (1936).

[502] G. E. Riesinger, and I. A. Thompson, *J. Appl. Chem.*, **13**, 346 (1963).

2-Methylfuran is obtained at atmospheric pressure when furfuraldehyde is led in a stream of hydrogen over a copper chromite catalyst finely spread over charcoal at 200–230°.[503]

Reduction with palladium catalysts (5% of Pd on $BaSO_4$ or charcoal) occurs under milder conditions. Suitable solvents are alcohols, ethyl acetate, or acetic acid containing a little sulfuric or perchloric acid which aids the hydrogenation. The pressure of hydrogen used ranges from atmospheric to 5 atm, the temperature from room temperature to 90°. The uptake of hydrogen should not exceed two moles per carbonyl-oxygen atom.

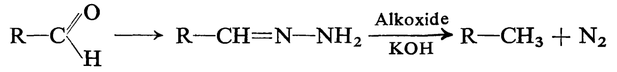
The carbonyl group in aldehydes or ketones can be reduced by complex metal hydrides to methyl or methylene only in exceptional cases. Aromatic aldehydes and ketones containing an amino or methoxy group *ortho* or *para* to the carbonyl group can be thus reduced under very drastic conditions. 4-Aminobenzophenone gives 57% of *p*-benzylaniline and 15% of 4-aminobenzhydrol when heated with a five-fold excess of $LiAlH_4$ in a mixture of diethyl and dibutyl ether at 80° for 1 hour.[356] These conditions lead to similar results with derivatives of acridone[504] and xanthone.[505] However, in the heterocyclic series the carbonyl group can sometimes be very readily reduced, as Treibs and Derra-Scherrer[350] have shown for the pyrrole series.

α,β-Diketones in methanol or dimethylformamide can be reduced quantitatively by hydrogen sulfide, to give monoketones in the presence of pyridine or β-hydroxy-α-ketones in the presence of piperidine.[506]

b. Replacement of carbonyl–oxygen *via* intermediates

i, Wolff–Kishner method

The Wolff–Kishner method is particularly suitable for reduction of most carbonyl compounds.[344i,507] It consists of converting the carbonyl compound into its hydrazone or, alternatively, its semicarbazone which is then decomposed by potassium hydroxide or alkoxide:



$$\mathrm{R{-}C}\Big\langle{}^{\mathrm{O}}_{\mathrm{H}} \longrightarrow \mathrm{R{-}CH{=}N{-}NH_2} \xrightarrow[\mathrm{KOH}]{\text{Alkoxide}} \mathrm{R{-}CH_3 + N_2}$$

Potassium hydroxide or alkoxide is not always necessary: the hydrazones of Michler's ketone, fluorenone, and benzophenone yield the corresponding hydrocarbons in the presence of hydrazine hydrate alone,[508] and so do the hydrazones of some ketones that contain a sulfo group, *e.g.*, 4-(methylsulfonyl)-acetophenone hydrazone.[509] Apparently these decompositions occur when the methylene group of the hydrazone contains mobile hydrogen atom.

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[503] L. W. Burnette, I. B. Johns, R. F. Holdren, and R. M. Hixon, *Ind. Eng. Chem.*, **40**, 502 (1948).

[504] G. M. Badger, J. H. Seidler, and B. Thomson, *J. Chem. Soc.*, **1951**, 3207.

[505] A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, **1952**, 1343.

[506] R. Mayer, G. Hiller, M. Nitzschke, and J. Jentzsch, *Angew. Chem., Int. Ed., Engl.*, **2**, 370 (1963).

[507] V. Franzen, "Reaktionsmechanismen," Dr. A. Hüthig-Verlag, Heidelberg, 1958, 1st Series, p. 140.

[508] H. Staudinger and O. Kupfer, *Ber. Deut. Chem. Ges.*, **44**, 2197 (1911).

[509] H. Klosterziel and H. J. Backer, *Rec. Trav. Chim.*, **71**, 361 (1952).

There are two side reactions, namely, formation of an azine and reduction of the carbonyl compound to the alcohol, that may, under certain circumstances, interfere with the decomposition of the hydrazone in Wolff–Kishner reduction. Both side reactions are favored by any water present. Part of the hydrazone can be cleaved by water to the carbonyl compound and hydrazine which then interact to yield the azine. Also the carbonyl compound liberated by hydrolysis of the hydrazone or semicarbazone can be reduced to the alcohol by the alkoxide anions present in the reaction medium, oxidation states being interchanged. Both side reactions can be suppressed by preventing hydrolysis of the hydrazone or semicarbazone, which can be effected either by using an excess of hydrazine or by removing the water liberated during formation of the hydrazone.

Reduction of heterocyclic or aromatic ketones containing reactive halogen atoms are accompanied by exchange of these halogens; nitro compounds, which are stabilized as *aci*-nitro compounds in alcoholic solution, are not reduced; and in certain circumstances ether groups may be cleaved.

According to Wolff the hydrazones are decomposed by alkoxide, but Kishner used solid potassium hydroxide.

Wolff[510] describes the reduction of camphor as follows:

Well-dried camphor hydrazone (10g) is heated with a solution of sodium (0.8 g) in alcohol (10 ml) for 18 h in a bomb tube at 190°. Crude crystalline **camphane** is then obtained on addition of water (750 ml) and is purified by distillation in steam. The camphane melts at 156–157° and boils at 161°/757 mm. The yield amounts to 7 g, *i.e.*, 84%.

As an example of Kishner's method, ***n*-propylcyclobutane** can be prepared from cyclobutyl ethyl ketone hydrazone as follows:[511]

For preparation of the hydrazone, the ketone (18 g), 90% hydrazine hydrate (18 g), and absolute alcohol (50 ml) are heated in an oil-bath at 110–130° for 3 h; the alcohol is then distilled off and the residue is dried with solid potassium hydroxide. The hydrazone is decanted from the alkali and is decomposed by addition, in small portions, through a dropping funnel into a Claisen flask maintained at 120–140° and containing solid potassium hydroxide (2 g) and two small fragments of porous plate that have been moistened with platinum–ammonium chloride and then roasted. The material that distils is treated with dilute acetic acid, and the hydrocarbon that separates is washed with water, dried over fused potassium carbonate, and redistilled twice from metallic sodium. In this way 44.5% (7 g) of the hydrocarbon, b.p. 99–100°/736 mm, are obtained.

Wolff–Kishner reduction without alkali can be exemplified by the preparation of **1-methylpyrene** from 1-pyrenecarbaldehyde:[512]

1-Pyrenecarbaldehyde (20 g) is heated with hydrazine hydrate (100 g) in a 1-l iron autoclave for 8 h at 200° (pressure about 100 atm). The pale, solid, crude product is washed, dried, and distilled in a vacuum, whereby almost pure 1-methylpyrene (17 g) of m.p. 70–71° is obtained.

By using high-boiling solvents and by removing completely the water formed in the reaction, Huang–Minlon[513] improved the older procedures so effectively that the reaction can be carried out at atmospheric pressure. For example,

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[510] L. Wolff, *Ann. Chem.*, **394**, 96 (1912).

[511] N. D. Zelinsky and B. A. Kasansky, *Ber. Deut. Chem. Ges.*, **60**, 1101 (1927).

[512] H. Vollmann, H. Becker, M. Corell, and H. Streeck, *Ann. Chem.*, **531**, 1 (1937).

[513] Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).

3-(*p*-phenoxybenzoyl)propionic acid is reduced to **4-(*p*-phenoxyphenyl)butyric acid** as follows:[514]

A mixture of the keto acid (500 g, 1.85 mole), potassium hydroxide (350 g), and 85% hydrazine hydrate (2500 ml) in tri- or di-ethylene glycol is heated under reflux for 1.5 h. The water formed is then distilled off through a descending condenser until the temperature of the reaction mixture has risen to 195°, whereafter the solution is heated for a further 4 h. After cooling, the solution is diluted with water (2.5 l) and poured slowly into 6N hydrochloric acid. The weight of dried product amounts to 95% of the theoretical (451 g), and the melting point is 64–66°. When recrystallized from ligroin–benzene, the pure 4-(*p*-phenyoxyphenyl)butyric acid has m.p. 71–72°.

Wolff–Kishner reduction occurs at room temperature if anhydrous dimethyl sulfoxide is used as solvent with potassium *tert*-butoxide, the hydrocarbons being obtained in 60–90% yield.[515]

The decomposition of a semicarbazone to the hydrocarbon has been described for the case of reduction of 2-pyrrolecarbaldehyde to 2-methylpyrrole.[516]

ii, Replacement of carbonyl-oxygen via mercaptals

The carbonyl group of α- and β-oxo carboxylic esters is readily converted into the corresponding mercaptal group by methanethiol in the presence of zinc chloride and sodium sulfate. The mercaptals are then heated under reflux with Raney nickel in alcohol for several hours, whereby the carboxylic esters are obtained in 70–80% yield.[517] In the sugar series some so-called 1-deoxy sugars are prepared in very good yield by boiling the mercaptals from the aldoses for 2 hours with a large excess of Raney nickel in alcohol.[518] D-xylose, for instance, being thus reduced to 1-deoxy-D-xylitol.

3. Replacement of oxygen in carboxyl or alkoxycarbonyl groups

Carboxylic acids and their esters are converted into the corresponding alcohols by reduction of their carbonyl group to a methylene group, and three methods are available for this purpose, namely:

(a) the Bouveault–Blanc reduction,
(b) catalytic hydrogenation over copper–chromium oxide, and
(c) reduction by complex metal hydrides.

The reduction of carboxylic esters by sodium and alcohol, discovered by Bouveault and Blanc in 1903, is carried out under very drastic conditions.[519] The usual procedure is to drop one mole of the ester in absolute alcohol directly on to six gram-atoms of sodium lumps and then to heat the mixture until all the sodium is dissolved, this requiring several hours under reflux. The whole is treated with water and worked up for the alcohol produced.

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[514] Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

[515] D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Amer. Chem. Soc.*, **84**, 1734 (1962).

[516] P. A. Cantor, R. Lancaster, and C. A. Vander Werf, *J. Org. Chem.*, **21**, 918 (1956).

[517] M. S. Newman and H. M. Walborsky, *J. Amer. Chem. Soc.*, **72**, 4296 (1950).

[518] E. Zissis and N. K. Richtmyer, *J. Amer. Chem. Soc.*, **75**, 129 (1953).

[519] L. Bouveault and H. G. Blanc, *Bull. Soc. Chim. France*, [iii], **29**, 787; **31**, 666 (1904); *C. R. Hebd. Séances Acad. Sci.*, **136**, 1676 (1903); **137**, 60 (1903).

Use of absolute alcohol is essential since otherwise substantial amounts of acid are formed by hydrolysis. Ethanol is generally used, but sometimes 1-butanol since this permits a higher reaction temperature.

The yields can be increased by adding substances such as CO_2 and NH_4Cl that destroy the alkoxide formed and by maintaining specific conditions.[520]

Reduction proceeds smoothly with fatty acid esters, but not with aromatic esters whose carboxylic ester group is attached directly to a benzene ring. α,β-Unsaturated esters give the related saturated alcohols, but double bonds that are not conjugated to the alkoxycarbonyl group are, in general, not reduced by this method.

An improved general method for reducing fatty acid esters by sodium was worked out by Hansley,[521] in which secondary alcohols serve best as the reducing alcohol. Only a small excess—about 5%— of sodium and reducing alcohol is used, but in addition an inert solvent in the form of an ether or hydrocarbon such as xylene. The ester and reducing alcohol are treated with sufficient of the solvent to keep the reaction mixture liquid, and finely divided sodium, in the solvent, is added with stirring at the boiling point. The yields amount to 80–95%. This method is particularly useful for preparation of unsaturated alcohols from unsaturated esters.

According to Adkins and Gillespie,[522] **oleyl alcohol** can be prepared from ethyl oleate in the following way:

Distilled ethyl oleate (200 g, 0.65 mole) and absolute alcohol (1.5 l) are placed in a 5-l round-bottomed flask under a wide reflux condenser. The alcohol has been previously dried over calcium and is distilled from aluminum *tert*-butoxide directly into the reaction flask. Sodium (to a total of 80 g, 3.5 gram-atoms) is added gradually through the reflux condenser at such a rate that vigorous reaction ensues, the flask being occasionally shaken. When the main reaction has ended, more absolute alcohol (200 ml) is added and the mixture is heated on the steam-bath until all the sodium is consumed. Then water (500 ml) is added and the heating continued for a further hour to hydrolyse unchanged ester. The unsaponifiable fraction is extracted with ether. The ether extract is washed with 1% potassium hydroxide solution and then with water until free from alkali (phenolphthalein) and is dried over sodium sulfate. The ether is distilled off and the residue is fractionally distilled. 49–51% (84–89 g) of oleyl alcohol are obtained at 150–152°/1 mm.

Catalytic reduction of a carboxylic ester to the corresponding alcohol can be effected by hydrogenation over copper–chromium oxide,[183b,344c] though very energetic conditions are required for this purpose, namely 200–300 atm pressure of hydrogen at 200–250°. Under these conditions fatty acid esters usually give the corresponding alcohols in more than 90% yield, and moreover dicarboxylic esters give the corresponding diols. Ethyl malonate and its substitution products constitute exceptions: the expected 1,3-glycols are further reduced, so that monohydric alcohols result.[523] The same is true for aromatic and heterocyclic carboxylic esters, for they are reduced to hydrocarbons: ethyl benzoate affords toluene quantitatively, and xylene is formed in 84% yield from ethyl phthalate.

The preparation of **1,6-hexanediol** from adipic ester may be cited to illustrate the procedure used in this method of reduction:[183b,344c,524]

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[520] L. Balfray and P. Anglaret, *C. R. Hebd. Séances Acad. Sci.*, **224**, 404 (1947).

[521] V. L. Hansley, *Ind. Eng. Chem.*, **39**, 55 (1947).

[522] H. Adkins and R. H. Gillespie, *Org. Syn.*, Coll. Vol. III, 671 (1955).

[523] R. Connor and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 4678 (1932).

[524] A. W. Ingersoll and S. H. Babcock, *Org. Syn.*, Coll. Vol. II, 328 (1943).

Ethyl adipate (252 g, 1.25 moles) and copper-chromium oxide catalyst[183b,344c,525] (20 g) are placed in a high-pressure autoclave of at least 400-ml capacity, which is then closed and fastened in a suitable shaking apparatus. Hydrogen is admitted to a pressure that is adjusted to the capability of the autoclave, whereby it must be noted that, because of the high temperature reached before reduction begins, the maximal pressure will be about 1.8 times that in the cold. For a highest working pressure of the autoclave of about 350 atm the initial pressure should not exceed 140 atm, but this may be increased to 200 atm if the autoclave has been tested to 650–700 atm.

Shaking is then begun and the temperature is raised as fast as possible to 255°, where it is maintained until the manometer shows no fall in pressure during 1 hour. Hydrogenation is complete in 6 to 12 hours according to the activity of the catalyst, the pressure, and the purity of the starting material. Unless a very high initial pressure is used or the autoclave has a capacity of at least 2 l further hydrogen must be introduced during the reaction so that the pressure does not fall below 100 atm.

When reaction is complete, the autoclave is allowed to cool, the pressure is released, and the contents of the autoclave are transferred to a 600-ml beaker, the autoclave being washed out with 96% alcohol (4 × 25 ml). The catalyst is filtered off or, better, centrifuged off, and washed with 96% alcohol (4 × 25 ml). 40% Sodium hydroxide solution (50 ml) is added and the whole is boiled under reflux for 2 h. Then the product is placed in a 1-l distillation flask, and the alcohol is distilled off until the temperature of the vapor reaches 95°. The residue is transferred, whilst still hot, to a continuous liquid-extraction apparatus, and the distillation flask is rinsed with water (50 ml). The liquid is then extracted exhaustively with ether or benzene, which requires 24 to 50 hours according to the efficiency of the apparatus. Finally, the solvent is distilled off and, after removal of alcohol and water, the diol is distilled in a vacuum from a Claisen flask. It has b.p. 143–144°/4 mm and m.p. 41–42°. The yield amounts to 125–132 g, corresponding to 85–90% of the theoretical.

A further method for reduction of carboxylic esters is the reductive cleavage of thioesters, which can be carried out under mild conditions and affords a thiol and the alcohol related to the carboxylic acid.[526]

Corey and Chaykovsky described the reduction of carboxylic esters to ketones by way of β-keto sulfoxides. The ester is treated in tetrahydrofuran with a solution of methylsulfinyl carbanions in a mixture of dimethyl sulfoxide and tetrahydrofuran at 0°. This yields a β-keto sulfoxide which is reduced with aluminum amalgam in 90% aqueous tetrahydrofuran.[527] The methylsulfinyl carbanions are formed by the action of sodium hydride on dimethyl sulfoxide under nitrogen at 65–70°.

Not only esters, but also free acids can be hydrogenated catalytically. For instance, 1-dodecanol is obtained in 94% yield in 90 min from dodecanoic acid by using copper oxide as catalyst at 250 atm pressure of hydrogen and 300°.[528]

According to Carnahan and his collaborators, ruthenium dioxide and ruthenium-charcoal (10% of ruthenium) serve well as catalysts for direct hydrogenation of carboxylic acids to alcohols. Working temperatures are around 150° at hydrogen pressures of 500–900 atm.[529]

α-Amino carboxylic esters can be reduced to the corresponding alcohol by a special Raney nickel catalyst at 50°, without racemization of the alcohol.[530]

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[525] W. A. Lazier and H. R. Arnold, *Org. Syn.*, Coll. Vol., II 142 (1943).

[526] O. Jeger, J. Noremberski, S. Szpilfogel, and V. Pregel, *Helv. Chim. Acta*, **29**, 684 (1946).

[527] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964).

[528] A. Guyer, A. Bieler, and K. Jaberg, *Helv. Chim. Acta*, **30**, 39 (1947).

[529] J. E. Carnahan, T. A. Ford, W. Gresham, W. E. Grigsby, and G. F. Hager, *J. Amer. Chem. Soc.*, **77**, 3766 (1955).

[530] H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.*, **70**, 695, 3118, 3121 (1948).

Of incalculable value, particularly for the chemistry of natural products, is the reduction of carboxylic acids and their derivatives by complex metal hydrides,[100a] especially lithium aluminum hydride.[337a,531] It is replacing the classical methods or reduction to an ever increasing extent. Free acids, and esters and anhydrides, can readily be reduced to the corresponding alcohols,[339b] and lactones are converted into diols.[532] The reaction proceeds very easily at room temperature. Ether, dioxan, and tetrahydrofuran are the principal solvents used, though methylal is often a better solvent, *e.g.*, for polycarboxylic acids and polycarbonyl compounds.[533] The cheaper $NaAlH_4$ may be used in place of $LiAlH_4$, tetrahydrofuran being a suitable solvent for its reactions; by its use aldehydes and hydroxy aldehydes can be obtained from carboxylic esters and lactones, respectively.[535]

From the numerous records in the literature the reduction of 2-methylacetoacetic ester to **2-methyl-1,3-butanediol**[536] is selected for detailed description here:

Lithium aluminum hydride (4.0 g) and dry ether (100 ml) are heated under reflux for 10 min in a 500-ml three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. Then the suspension of $LiAlH_4$ is cooled in ice, and a solution of 2-methylacetoacetic ester (14.4 g) in dry ether (50 ml) is dropped in slowly with continued cooling. The mixture is stirred for a further hour at 0°, after which water (20 ml) is dropped in cautiously with good ice-cooling. The resulting hydroxide sludge is filtered off and made into a slurry on the filter with a little ether and sucked dry eight times. The ethereal filtrate is dried over sodium sulfate, the solvent is evaporated, and the oily residue is distilled in a vacuum. A colorless oil of b.p. 111–112°/17 mm is obtained in 60% yield (6.2 g).

As well as $LiAlH_4$ the milder acting alkali boron hydrides are often used. Sodium tetrahydridoborate and lithium bromide in diglyme form together a reducing system that is intermediate between $NaBH_4$ and the more active $LiAlH_4$. This reagent permits a series of selective reductions. For instance, heating ethyl *p*-chlorobenzoate with a mixture of $NaBH_4$ and LiBr in diglyme for 3 hours on the water-bath affords 4-chlorobenzyl alcohol in 85–91% yield.[537]

$LiBH_4$ and dioxan form a complex which is less sensitive than the free hydride to moisture.[538]

Dialkylhydridoaluminums often have a more selective reducing action than $LiAlH_4$. Thus unsaturated aldehydes can be prepared in 60–95% yield by reducing the corresponding unsaturated fatty acid esters with diethyl- or diisobutyl-hydridoaluminum in benzene at 80°.[539]

4. Reduction of amides and lactams

Amides and lactams can be reduced in ways similar to those used for the acids and esters. Catalytic hydrogenation over copper–chromium oxide as

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[531] G. M. Brown, *Org. Reactions*, **6**, 469 (1951).

[532] A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, **26**, 2255 (1961).

[533] E. Bernatek, *Acta Chem. Scand.*, **8**, 874 (1954).

[534] H. Clasen, *Angew. Chem.*, **73**, 322 (1961).

[535] L. I. Zakharin, V. V. Gavrilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Lett.*, **1963**, 2087.

[536] E. Buchta and H. Bayer, *Ann. Chem.*, **573**, 227 (1951).

[537] H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **77**, 6209 (1955).

[538] R. Paul and N. Joseph, *Bull. Soc. Chim. France*, **1953**, 758.

[539] H. Reinheckel, *Oléagineux*, **20**, 31 (1965).

catalyst is carried out at 200–300 atm and 250–265°. To avoid side reactions the reaction must be made to proceed as fast as possible and dioxan (about 350 to 400 ml per mole of amide) must be added to take up the water formed which would otherwise hydrolyse the amide. In most cases the total yield of amines is satisfactory, hydrogenation of an unsubstituted amide always leads to a mixture of primary and sedondary amine in which the latter often predominates. In reactions of doubly substituted amides, where this side reaction is impossible, the tertiary amine forms the sole product and is obtained in good yield.[183b]

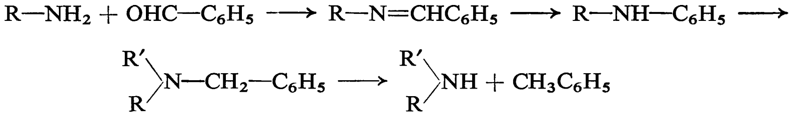
Reduction by lithium aluminum hydride proceeds very smoothly and gives very good yields.[100b] It is not accompanied by the side reactions that occur in catalytic hydrogenation over copper–chromium oxide catalysts. A 25–30% excess of $LiAlH_4$ suffices for disubstituted amides, but mono- and un-substituted amides should be boiled with a 200–250% excess for longer periods (12–20 h). Diethyl ether is used as solvent. It is usually more difficult to reduce aromatic than aliphatic amides, and for the former it is more effective to carry out the reduction in boiling tetrahydrofuran or dioxan.[540] Benzamide is not reduced by $LiAlH_4$, and hydrazides[541] are reduced only with much difficulty if at all.

Appreciably shorter times are needed for reduction of primary, secondary, and tertiary amides to amines by diborane in tetrahydrofuran under nitrogen, and other reducible groups are unaffected.[542]

Electrolytic reduction is also sometimes used. For instance, electrolysis of 1-butyl-3-pyrrolidone in 30% sulfuric acid at 60° and at a cadmium cathode with a current density of 0.053–0.073 A/cm^2 opens the ring, affording dibutylamine in 64% yield.[543]

III. Replacement of nitrogen by hydrogen

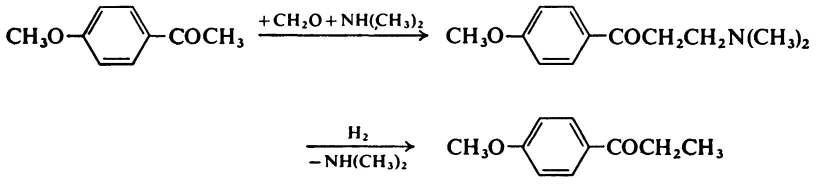
Direct replacement of an amino group by hydrogen is possible only in certain cases. Such reductive fissions are particularly well known for tertiary amines and quaternary ammonium compounds and occur especially readily with allyl- and benzyl-substituted amines. In the last-mentioned cases the benzyl group is removed as toluene, and this reaction route is used for preparation of secondary from primary aliphatic amines; the primary amine is first condensed with benzaldehyde, and the resulting Schiff base is reduced to the alkylbenzylamine; this is converted by alkylation into the dialkylbenzylamine, from which finally the benzyl group is removed by catalytic hydrogenation:[544]



$$R{-}NH_2 + OHC{-}C_6H_5 \longrightarrow R{-}N{=}CHC_6H_5 \longrightarrow R{-}NH{-}C_6H_5 \longrightarrow$$

$$\begin{matrix}R'\\R\end{matrix}\!\!>\!N{-}CH_2{-}C_6H_5 \longrightarrow \begin{matrix}R'\\R\end{matrix}\!\!>\!NH + CH_3C_6H_5$$

Some preparative importance attaches also to reductive deamination of tertiary Mannich bases, which are accessible by condensation of a CH-acidic compound with formaldehyde and a secondary aliphatic amine. By this route the active hydrogen of the CH-acidic starting material can be replaced by a methyl group, as in the following example:[545]



These reductive deaminations can be effected by hydrogenation over Raney nickel, palladium, or copper chromite catalysts, and also by means of sodium amalgam or zinc dust in aqueous-methanolic sodium hydroxide.[344k]

Substitution of hydrogen for a primary amino group attached to an aromatic nucleus is carried out almost exclusively by decomposing the derived diazonium compound with reducing agents such as alcohols, hypophosphorous acid, formaldehyde in alkaline solution, or tin(II) compounds.[546]

The usual procedure is to drop the freshly prepared diazonium salt solution at 0° into a cooled and stirred 50% hypophosphorous acid solution; the reaction mixture is set aside at 0–5° for several hours after evolution of the nitrogen and is then worked up.

If an aromatic and an aliphatic amino group are both contained in the molecule, as in 4-aminobenzylamine, the aromatic amino group can be replaced without affecting the primary aliphatic group: for this purpose an aqueous solution of sodium nitrite is dropped into a solution of the amine in hypophosphorous acid, primary aliphatic amines being indifferent to nitrous acid below pH 3.[547]

When an alcohol is used as the reducing agent, the yield of deaminated aromatic compound is often very unsatisfactory owing to extensive formation of aryl ethers. Use of lower alcohols favors ether formation, whereas use of higher alcohols favors formation of the hydrocarbons; for example, benzenediazonium chloride gives only anisole when methanol is used, a little benzene and much phenetole when ethanol is used, but much benzene and very little benzyl phenyl ether when benzyl alcohol is used.

Further, certain substituents, such as the nitro group and halogens, favor formation of the hydrocarbon. For instance, even with very dilute alcohol tribromobenzenediazonium chloride affords tribromobenzene almost exclusively, with only traces of tribromophenol; and the nitrated hydrocarbons are similarly obtained in very good yields from nitrated diazonium compounds.

When a suspension of cuprous oxide in alcohol is used for reduction of the diazonium salts, the deaminated products are formed immediately and without appreciable side reactions. This method seems to be generally applicable, but, in particular, compounds such as nitroanilines and aminoanthraquinones

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[540] M. Sander and D. Burmeister, *Chem. Ber.*, **95**, 964 (1962).

[541] R. L. Hinman, *J. Amer. Chem. Soc.*, **78**, 2463 (1956).

[542] H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).

[543] N. J. Leonard, S. Swann Jr., and H. L. Dryden Jr., *J. Amer. Chem. Soc.*, **74**, 2871 (1952).

[544] J. S. Buck and R. Baltzly, *J. Amer. Chem. Soc.*, **63**, 1964 (1941).

[545] B. Reichert and H. Posemann, *Arch. Pharm.*, **281**, 189 (1943).

[546] N. Kornblum, *Org. Reactions*, **2**, 262 (1944).

[547] N. Kornblum and D. C. Iffland, *J. Amer. Chem. Soc.*, **71**, 2137 (1949).

containing pronouncedly cationoid substituents give excellent yields.[548] Aminobenzoic acids are better deaminated by way of the diazonium hexafluorophosphates which decompose at room temperature in tetramethylurea.[549]

Replacing the amino group of amides by hydrogen leads to the corresponding aldehydes. According to Weygand and his co-workers,[550] *N*-methylcarboxyanilides can be reduced to aldehydes by lithium aluminium hydride in very good yield. A large number of aliphatic, aromatic, and heterocyclic mono- and di-aldehydes have been prepared in this way, the reaction not being disturbed by the presence in the molecule of phenolic or alcoholic hydroxyl groups, thiol or thioether groups, halogen, or heterocyclic nitrogen.

The practical procedure is as follows: The methylanilide is dissolved in dry tetrahydrofuran and treated at 0°, portionswise, with powdered lithium aluminum hydride (1/3 to 1/2 mole per anilide group) or with a solution of the hydride in ether. Much heat is evolved, this being countered by cooling in ice–salt mixture. At the end of the optimal time for reduction, the mixture is hydrolysed by dilute acid, with ice-cooling. According to its properties, the aldehyde is isolated by extraction or by distillation in steam.

Ried *et al.*[551] recently found a generally applicable aldehyde synthesis in the hydrogenolytic fission of 1-acyl-3,5-dimethylpyrazole by lithium aluminum hydride, a reaction that takes place with very good yields in ether at 0–20°. An appreciably better method still is to use the same hydride in ether or tetrahydrofuran to reduce the corresponding 1-acylimidazoles, which are readily obtained from the free acids and 1,1′-carbonyldiimidazole; with 0.25 mole of hydride per mole of acylimidazole the reduction is complete in 30–60 min at −20°,[552] and it is an advantage of the method that it can be carried out entirely in one vessel without isolation of the acylimidazole intermediate.

McFadyen and Stevens (cf. Bayer[344h]) obtained aldehydes from the corresponding carboxylic acids in yields of up to 60% by intramolecular disproportionation of aromatic and heterocyclic 1-acyl-2-(benzenesulfonyl)hydrazines induced by an alkali carbonate in ethylene glycol at 160°; but this method fails for aliphatic and α,β-unsaturated carboxylic acids.

Other possibilities for reduction of amides and hydrazides were found by Birch *et al.*[563] in the reduction of 1-benzoylpiperidine to benzaldehyde by sodium in liquid ammonia, and by Wingfield *et al.*[554] in the decomposition of nicotinoylhydrazine to give nicotinaldehyde by $NaIO_4$ in aqueous ammonia. The nitrogen of diazo ketones can be removed by tin(II) chloride in aqueous-alcoholic hydrochloric acid[425] or by hydriodic acid,[555] a methyl ketone being formed on both cases.

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[548] H. H. Hodgson and H. S. Turner, *J. Chem. Soc.*, **1942**, 748.

[549] K. G. Rutherford and W. A. Redmond, *J. Org. Chem.*, **28**, 568 (1963).

[550] F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).

[551] W. Ried, G. Derschel, and A. Koteiko, *Ann. Chem.*, **642**, 121 (1961).

[552] H. A. Staab and H. Bräunling, *Ann. Chem.*, **654**, 119 (1962).

[553] A. J. Birch, J. Cymerman-Craig, and M. Slayter, *Aust. J. Chem.*, **8**, 512 (1955).

[554] H. N. Wingfield, W. R. Harlan, and H. R. Hanmer, *J. Amer. Chem. Soc.*, **74**, 5796 (1952).

[555] M. L. Wolfrom and R. L. Brown, *J. Amer. Chem. Soc.*, **65**, 1516 (1943).

IV. Replacement of sulfur by hydrogen

An elimination reaction that is important for exchange of sulfur and hydrogen is the substitution of hydrogen for a sulfo group in aromatic compounds. This exchange has considerable importance both preparatively and technically. Sulfonic acids vary in stability under hydrolytic conditions from case to case, and this fact can be used for purification and separation of sulfonic acids prepared from hydrocarbon mixtures or of sulfonic acid mixtures, *e.g.*, for separation of the xylenes. The ability to remove sulfo groups can be utilized in another direction also, namely, for preparative purposes: if it is desired to introduce a substituent, such as a nitro group at a position other than that attacked on direct substitution, the favored position (or positions) may first be caused to be occupied by sulfo groups, then the desired substituent is introduced, and finally the sulfo group is removed hydrolytically. In this way 2,6-dinitroaniline can be prepared in good yield from chlorobenzene by way of *p*-chlorobenzenesulfonic acid, 4-chloro-2,6-dinitrobenzenesulfonic acid, and 1-amino-2,6-dinitrobenzenesulfonic acid.[556] The sulfo group introduced into polyalkylbenzenes often induces intramolecular and sometimes even intermolecular migration of alkyl groups when the sulfonic acid is heated in sulfuric acid at about 100°.[557]

In practice the sulfo group is replaced by hydrogen on hydrolysis by water or dilute sulfuric acid or hydrochloric acid under pressure at temperatures up to 200°.

Raney nickel has been widely used for reductive desulfurization.[558] The course of the reduction depends greatly on the hydrogen content of the metal; a deactivated catalyst gives considerable yields of dimerization products, whereas highly active Raney nickel favors hydrogenation. Since no solvent effect has been observed in this reductive desulfurization, the choice of solvent is unrestricted; *inter alia*, water, a lower alcohol, or dioxan is usually employed.

Aliphatic and aromatic thiols are reduced in good yield by boiling them with Raney nickel in alcohol containing sodium hydroxide or ammonia. According to Robins and Hitchings,[559] **6-methyl-7-phenylpyrido[2,3-*d*]pyrimidin-4-ol** is prepared as follows:

2-Mercapto-6-methyl-7-phenylpyrido[2,3-*d*]pyrimidin-4-ol (6 g; m.p. 240–242°) is dissolved in 95% ethanol (1.8 l) and concentrated aqueous ammonia (150 ml). Raney nickel (18–20 g) is added and the reaction mixture is boiled for 6 h under reflux on the water-bath. Then the catalyst is filtered off and washed with boiling 95% ethanol (300 ml). The united filtrates are concentrated in a vacuum to 100 ml and the pH is adjusted to 5 by dilute acetic acid. On cooling, white needles separate, having m.p. 245–248° which is raised to 248-250° by recrystallization from aqueous ethanol.

Thioesters can be similarly reduced to aldehydes;[560] further, the sulfur in heterocyclic rings, *e.g.*, in thiazole,[561] can be eliminated with ring fission; and examples are also known of reduction of sulfoxides[562] and sulfones.[663] Al-

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[556] H. P. Schultz, *Org. Syn.*, **31**, 45 (1951).

[557] L. I. Smith, *Org. Reactions*, **1**, 370 (1942).

[558] G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962).

[559] R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, **80**, 3449 (1958).

[560] H. J. Bestmann and H. Schulz, *Chem. Ber.*, **92**, 530 (1959).

[561] H. Behringer, E. Dillinger, H. Suter, and K. Kohl, *Chem. Ber.*, **91**, 2773 (1958).

[562] M. S. Kharasch, W. Nudenberg, and G. J. Mantell, *J. Org. Chem.*, **16**, 524 (1951).

[563] W. Davies and F. C. James, *J. Chem. Soc.*, **1955**, 314.

though sulfonic acids are inert towards the nickel catalysts so far prepared, these compounds can be desulfurized by the Schwenk–Papa method[564] which employs nickel–aluminum alloy in aqueous sodium hydroxide for the reduction. Truce and Perry[565] proposed the use of the less dangerous nickel boride in place of Raney nickel for selective, reductive desulfurization; this reagent permits selective desulfurization with retention of sulfone groups; but it is not suitable for disulfides. Di(1-naphthyl) sulfide is very smoothly (97% yield) desulfurized to naphthalene by 15 hours' heating with Raney cobalt W 7 in diethyl phthalate under nitrogen at 220°.[566]

Ketone mercaptals can be desulfurized by $NaBH_4$ (in excess) and nickel chloride in ethanol, the reaction proceding stepwise.[567]

On treatment with hydrogen peroxide or peroxyacetic acid, sulfur doubly bonded to a heterocycle as in a thiazolinethione[568] or a dithiolethione[560] is oxidatively replaced by hydrogen, with formation of a carbon–carbon double bond.

Aryl isothiocyanates are reduced to secondary arylmethylamines by lithium aluminum hydride.[570]

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[564] E. Schwenk, D. Papa, B. Whitman, and H. Ginsberg, *J. Org. Chem.*, **9**, 1 (1944).

[565] W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).

[566] G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.*, **1960**, 1658.

[567] W. E. Truce and F. E. Roberts, *J. Org. Chem.*, **28**, 961 (1963).

[568] S. Yamada and K. Achiwa, *Chem. & Pharm. Bull. (Tokyo)*, **9**, 119 (1961).

[569] E. Klingsberg, *J. Amer. Chem. Soc.*, **83**, 2934 (1961).

[570] W. Ried and F. Müller, *Chem. Ber.*, **85**, 470 (1952).

CHAPTER 2

Formation of Carbon-Deuterium Bonds

Compiled by
D. Murawski

Introduction

The labeling of organic compounds with stable or radioactive isotopes now constitutes an extremely important area of preparative chemistry. The number of publications in that field has grown to such an extent that it is almost impossible to find them all. This alone indicates the ever growing importance of labeled compounds in diverse branches of science; moreover, the work reactivates the experimental demands on preparative chemists because an extraordinarily large number of compounds of different isotopic composition are open to synthesis. For instance, even such a relatively simple molecule as propane can afford no less than twenty-nine different deuterium-labeled compounds with eight different molecular formulae.

Most of the reactions involved in this work, and particularly those with radioactive isotopes, require special laboratory installations and are now, and are likely to remain, the domain of specialists. It should be noted also that they rarely lead to truly homogeneous substances, but rather to mixtures of molecules containing the label at different places and in different proportions, either necessarily—because the pure isotope is not available as starting material or the labeling reaction is not wholly controllable—or intentionally, because economic factors, inconveniently high specific activities and the resulting difficulties of protection against radiation and autoradiolysis, or other considerations leave no other course open.

Considerations of this kind do not apply to labeling with deuterium, which is available cheaply as the almost pure isotope and is not dangerous. Deuterium-labeled compounds are, for instance, used in analysis, in studies of reaction mechanism, for investigation of isotope effects, and for research on the metabolism of biochemically important substances. They are of particular value for the determination of the structure of chemical substances both by means of chemical reactions and by means of mass spectroscopy or IR or NMR spectroscopy. Moreover, the perdeuterated compounds are important solvents for use in these physical measurements.

Deuterium-labeled compounds[1] are prepared almost exclusively by chemical methods. There is no physical method for deuterium-labeling similar to that

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[1] Reviews: G. P. Mikluchin, *Fortschr. Chem. Org. Naturst.*, **17**, 663 (1948); S. L. Thomas and H. S. Turner, *Quart. Rev.* (*London*), **7**, 407 (1953); A. Murray and D. L. Williams, "Organic Syntheses with Isotopes," Interscience Publishers, Inc., New York, N.Y., 1958, Vol. II.

used by Wilzback for tritium. Also biosynthetical and microbiological methods have only slight importance for deuteration, although they are still valuable for the preparation of ^{14}C- and ^{15}N-labeled compounds. The possibilities that remain can be divided into three groups:

1. Preparative methods in which previously labeled, simple organic compounds are used in conventional syntheses.
2. Preparative methods in which organic molecules are deuterated by means of gaseous deuterium or inorganic deuterium compounds.
3. Special methods of isotope exchange.

The first group of methods repeats, in principle, the whole variety of organic chemistry, with logical amendments and with due attention paid to isotope effects*. It suffices in this connection to refer to the series of articles by Leitch and his collaborators.[4]

It is noteworthy that labeling is often carried out by reactions that normally have only academic interest or that are preparatively unimportant because of their demands on money and labor. For example, one is hardly likely to prepare ethanol by reaction of diazoethane with carboxylic acid and subsequent hydrolysis of the resulting ester, yet this reaction has proved definitely useful[5] for the synthesis of deuterated ethanol, in the sense:

$$CH_3\text{—}\overset{-}{C}H\text{—}\overset{+}{N}{\equiv}N + DOOC\text{—}R \xrightarrow{-N_2} CH_3\text{—}CHD\text{—}O\text{—}CO\text{—}R \xrightarrow[-RCOOH]{+H_2O} CH_3\text{—}CHD\text{—}OH$$

To the second group belong the reactions that are treated in detail in Sections 2.1 and 2.2 of the this Chapter.

It is the reactions of the third group, treated in Section 2.3 below, that best characterize the special methods of working with isotopes. In contrast to other replacement reactions, there is here no exchange of one element for another, but only of one isotope for another isotope of the same elelment. Advantageis taken of the fact that a change in reaction conditions or in the bonding within a molecule to be labeled alters the mobility of the hydrogen or deuterium atoms contained therein. Also, for many labeling reactions, it is a favorable condition that a C–D bond is normally more stable than a C–H bond. Three types of hydrogen atom in organic compounds can be differentiated, according to the ease with which such an isotope exchange occurs, namely:

(a) inert hydrogen, as, for instance, that bonded to carbon in aliphatic hydrocarbons;

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* The isotope effect, denoted k_H/k_D, expresses the ratio of the reaction rates for a specific C–H bond and for the corresponding C–D bond. With deuterium, intramolecular isotope effects can assume extremely high values—up to 18—owing to the relatively large difference in mass (D : H = 2 : 1) (cf. Schütte[2] and Simon and Palm.[3]

[2] H. R. Schütte, "Radioaktive Isotope in der organischen Chemie und Biochemie," VEB Deutscher Verlag der Wissenschaften, Berlin, 1966, p. 10.

[3] H. Simon and D. Palm, *Angew. Chem. Int. Ed., Engl.*, **5**, 920 (1966).

[4] L. C. Leitch and co-workers, *Can. J. Chem.*, (a) **29**, 1034 (1951); (b) **30**, 924 (1952); **31**, 153, 385, 785 (1953); **32**, 500, (c) 813 (1954); (d) **34**, 98 (1956); (e) **35**, 345 (1957).

[5] G. L. Curran and D. Rittenberg, *J. Biol. Chem.*, **190**, 17 (1951).

(b) semilabile hydrogen, for example, the enolizable hydrogen in ketones; and

(c) labile hydrogen, as that bonded to a hetero atom by the free electron pair of the latter.

The last type causes subsidiary phenomena in many labeling reactions and for most purposes a label introduced in this way must be removed again in order to avoid false conclusions; this is done by repeated recrystallization from protonic solvents or by repeated dissolution in and recovery (by evaporation) from such solvents (see Section 2.3).

2.1. Formation of the carbon-deuterium bond by addition

I. Addition of D_2O or DX to carbon–carbon multiple bonds

The addition of water or hydrogen halide to carbon–carbon double bonds is normally almost valueless as a method for formation of new C–H bonds. However, for formation of carbon–deuterium bonds it is purposeful, as deuterium is a stable component of a molecule only when bonded to carbon whereas the deuterium of an OD group is labile and thus removable.

In principle, the methods of hydration described on pages 280 and 286 can be modified logically so as to be applicable also to addition of D_2O to carbon–carbon multiple bonds. An important example is the addition of heavy water to acetylene, catalyzed by $HgSO_4$ and H_3PO_4,[6,7] which leads to perdeuterioacetaldehyde if dideuterioacetylene is used:

$$DC{\equiv}CD + D_2O \longrightarrow D_3C{-}CDO$$

Starting materials that contain no C–H bond are particularly useful for the preparation of isotopically pure compounds by means of D_2O, as is exemplified by the synthesis of $[D_4]$malonic acid from carbon suboxide:[8,9]

$$C_3O_2 + 2\,D_2O \longrightarrow DOOC{-}CD_2{-}COOD$$

Wilson[8] gave the following directions for this reaction as early as 1935:

$[D_4]$Malonic acid: Carbon suboxide (6.3 ml) is distilled into a graduated tube that is cooled to −78°. Deuterium oxide (1 g), placed in a Pyrex tube (1.5 × 25 cm), is also cooled to −78°. An equivalent amount of the carbon suboxide (measured by the diminution in volume in the graduated tube; d_4^0 1.114) is distilled into the Pyrex tube, and carefully dried benzene (10 ml) is added. The tube is then closed and shaken for several days at room temperature, after which it is opened and the crystalline malonic acid is filtered off, washed with benzene, and dried over P_2O_5. It melts at 128–130°, and the yield is almost quantitative.

Addition of deuterium chloride to olefine double bonds[10] is often used for synthesis of labeled intermediates which, without isolation, can then be conv-

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[6] J. E. Zanetti and D. V. Sickmann, *J. Amer. Chem. Soc.*, **58**, 2034 (1936).

[7] K. Bloch and D. Rittenberg, *J. Biol. Chem.*, **155**, 243 (1944).

[8] C. L. Wilson, *J. Chem. Soc.*, **1935**, 492.

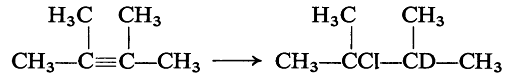
[9] E. R. Bissel and R. E. Spenger, *J. Org. Chem.*, **22**, 1713 (1957).

[10] L. C. Leitch and H. J. Bernstein, *Can. J. Res.*, **28 B**, 35 (1950); H. J. Bernstein, *Can. J. Res.*, **28 B**, 132 (1950).

erted into more complex compounds. An example is the addition of DCl to *p*-propenylanisole; *p*-([2-D]1-chloropropyl)anisole is formed, from which deuterated hexestrol is obtained in two further steps.[11]

Treatment of certain hydroaromatic compounds and steroids with DCl leads to the known rearrangements of the carbon skeleton,[12] which here occur with labeling although the chlorine is not retained in the molecule.[13]

The required deuterium chloride is prepared either outside the reaction medium by the action of deuterium oxide on phosphorus trichloride or thionyl chloride or by hydrolysis of an acid chloride in the reaction vessel. Shiner[14] gives an example of the latter method in the preparation of **1,1-dimethyl[2-D] isobutyl chloride:**



$$CH_3-\overset{H_3C}{\overset{|}{C}}\equiv\overset{CH_3}{\overset{|}{C}}-CH_3 \longrightarrow CH_3-\overset{H_3C}{\overset{|}{C}}Cl-\overset{CH_3}{\overset{|}{C}}D-CH_3$$

Deuterium oxide (2 g, 0.1 mole) is dropped during 48 h into a solution of 2,3-dimethyl-2-butene (7.3 g, 0.087 mole) in acetyl chloride (22 g, 0.28 mole). When the addition is complete the solution is boiled under reflux for 2 h and then poured on ice. The product is extracted with ether and dried over K_2CO_3. After removal of the ether, the product is distilled, whereby 1,1-dimethyl[2-D]isobutyl chloride, b.p. 109–110°/740 mm, is obtained in 72% yield (7.5 g).

Deuterium bromide is obtained from D_2O and thionyl bromide[15] in the same way (for preparation of liquid DBr from the elements see Kalinatchenko *et al.*[16]). Its addition to carbon–carbon multiple bonds has been used mainly for the preparation of various deuterium-labeled halogeno-ethanes and -ethylenes,[4a,17,18] for not only is the DBr readily added but also the bromine can be removed selectively from the products; *e.g.*:

$$Cl_2C{=}CHCl \xrightarrow{+DBr} Cl_2CD{-}CHClBr \xrightarrow[-BrCl]{Zn} CDCl{=}CHCl$$

II. Addition of deuterium* to carbon–carbon multiple bonds

The usual conditions of catalytic hydrogenation can be applied, with certain modifications, for the saturation of carbon–carbon double and triple bonds. Platinum and Raney nickel are the usual catalysts described. It is important that catalysts used for deuteration shall be pretreated with deuterium; noble-

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* D_2 is available commercially in steel bottles. Small amounts can be prepared as described in Brauer's book,[19] where also are to be found methods for preparation of the basic deuterium-containing reagents DF, DCl, DBr, DI, D_2S, D_2SO_4, and ND_3.

[11] A. Lacassagne, Ng.-Ph. Buu-Hoï, A. Chamorro, N. Dat-Xuong, and N. Hoan, *C. R. Hebd. Séances Acad. Sci.*, **231**, 1384 (1950).

[12] H. C. Brown and K. T. Liu, *J. Amer. Chem. Soc.*, **89**, 3900 (1967).

[13] D. H. R. Barton, J. E. Page, and E. W. Warnhoff, *J. Chem. Soc.*, **1954**, 2715.

[14] V. J. Shiner Jr., *J. Amer. Chem. Soc.*, **76**, 1603 (1954).

[15] R. C. Elderfield and co-workers, *J. Amer. Chem. Soc.*, **68**, 1579 (1946).

[16] V. R. Kalinachenko, Ya. M. Varshavskii, and A. I. Shatenstein, *Zh. Priklad. Khim.*, **30**, 1140 (1956); *Chem. Abstr.*, **50**, 16294 (1956).

[17] B. Bak and co-workers, *Acta Chem. Scand.*, **12**, 2021 (1958).

[18] J. C. Jungers, U. Verhulst, and J. Verhulst, *Acad. Roy. Belg.*, *Cl. Sci. Mem.*, **23**, 3 (1949); *Chem. Abstr.*, **45**, 4638 (1951).

[19] G. Brauer, "Handbuch der präparativen anorganischen Chemie," F. Enke-Verlag, Stuttgart, 1954, pp. 101 *et seq.*

metal catalysts are therefore reduced with deuterium or are saturated therewith by being stirred for a considerable time (30–60 min) in an aprotic solvent under an atmosphere of deuterium; Khan[20,21] gives a detailed prescription for the preparation of suitable Raney nickel catalysts, wherein, after decomposition of the alloy, dioxan is used as wash fluid in place of ethanol, a considerable part of the hydrogen dissolved in the nickel is removed by repeated partial distillation of pure dioxan, and the residual hydrogen is exchanged for deuterium by suspension of the catalyst in D_2O under a deuterium atmosphere.

Since a rapid exchange sets in on the catalyst between gaseous deuterium and the hydrogen of solvents that yield protons, dioxan, cyclohexane, and ethyl acetate are favored as solvents for deuteration. If it is essential to use alcohol or acetic acid, the hydrogen of the hydroxyl group must be previously exchanged for deuterium. Similarly it is advisable to replace labile hydrogen atoms by a protecting group before deuteration of the compound.

Catalytic hydrogenation of carbon–carbon multiple bonds would be an excellent method of preparing compounds labeled by deuterium at pre-determined positions were it not that unfortunately migration of the double bond and uncontrollable H → D exchange on the catalyst surface limits its applicability. Even under mild conditions a part of the deuterium introduced appears at other positions.[22,23] Relatively good results are obtained with the nickel catalysts mentioned above.

Catalytic deuteration of carbon–carbon multiple bonds is thus preferably restricted to small uncomplicated molecules or, as in the formation of [D_2]-dihydrouracil from uracil,[24] to such as contain a limited number of C–H bonds. Good results can also always be obtained when the substance to be reduced does not contain hydrogen in the allyl position, *e.g.*, with Δ^1-3-keto steroids,[25] and in partial reduction of carbon–carbon triple bonds. Khan[20] gives the following description of the last-mentioned reaction:

[9,10-D_2]-9-Octadecene: A solution of 9-octadecyne (5 g) in purified dioxan (125 ml) is deuterated in the presence of pretreated Raney nickel. The very selective reaction ceases after absorption of one equivalent of deuterium. The catalyst is then filtered off, the solution is evaporated, and the crude residue is dissolved in sufficient ether to give an approximately 10% solution. After cooling to ca. −45° for 2 h, the resulting crystals are removed; further cooling to ca. −50° gives a second fraction. On distillation of the two fractions at 2–3 mm the product of m.p. 140–142° is obtained.

Chemical methods are less often used for saturation of C=C bonds. Recently, however, dideuteriodiimine seems to have established a firm position for this reaction,[26] whereby *cis*-saturation of the carbon–carbon double bond results. Another, interesting reaction of the carbon–carbon double bond is that with B_2D_6, whose end result is an α-deuterated alcohol.[27]

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[20] N. A. Khan, *J. Amer. Chem. Soc.*, **74**, 3018 (1952).

[21] N. A. Khan, *Science*, **117**, 130 (1953).

[22] W. H. Pearlman, M. R. J. Pearlman, and S. Elsey, *J. Amer. Chem. Soc.*, **71**, 4126 (1949).

[23] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.*, **77**, 139 (1955); E. M. Hodnett and R. Gallagher, *J. Org. Chem.*, **24**, 564 (1959).

[24] C. Párkányi and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2491 (1963).

[25] H. J. Ringold, M. Gut, M. Hayano, and A. Turner, *Tetrahedron Lett.*, **1962**, 835.

[26] W. C. Baird, B. Franzus, and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).

[27] K. T. Finley and W. H. Saunders, *J. Amer. Chem. Soc.*, **89**, 898 (1967).

III. Addition of deuterium to carbonyl double bonds

Addition of deuterium to carbonyl double bonds and their nitrogen analogs is accomplished by complex metal hydrides in an increasing number of examples. In this reduction two deuterium atoms are transferred; of course, only the deuterium on carbon is firmly bound, and that attached to the hetero atom can be removed in the usual way. Since such reactions can in general be carried out with $LiAlD_4$ in aprotic solvents, the use of lithium aluminum deuteride, $LiAlH_4$, .offers no peculiarities. The necessary $LiAlD_4$, which is extremely sensitive to hydrolysis, is commercially available. It can be conveniently handled as a solution in a dry dialkyl ether or in tetrahydrofuran at temperatures up to ca. 130°.

Small quantities can be prepared by Wiberg's method:

$$4\,LiD + AlBr_3 \longrightarrow LiAlD_4 + 3\,LiBr$$

for which Holding and Ross[28] give a detailed prescription.

$LiAlD_4$ is often applied to the preparation of deuterium-labeled compounds by reduction of C=O bonds, for example, to the preparation of isobutyl alcohols labeled in the α-, β-, or γ-position[29,30] and to the reduction of biacetyl to [2,3-D_2]-2,3-butanediol.[31] Monodeuterated secondary alcohols are also formed by its action on alicyclic ketones,[27,32,33] on deuteration of camphor[34] formation of the 2-deuterated product is accompanied by that of [3-D_1]-isoborneol, which indicates that enolization occurs under the reaction conditions.

Dideuterated alcohols can be obtained by reducing carboxylic esters[34–37] or carbonyl chlorides[38,39] with lithium aluminum deuteride. The following description has been given of the preparation of [1,1-D_2]allyl alcohol from acryloyl chloride:[39]

Lithium aluminum deuteride (6 g) is made into a slurry with dry ether (300 ml), cooled in an ice-bath, and treated with stirring with acryloyl chloride (20 g) in ether (100 ml) at such a rate that the temperature does not rise above 5°. The mixture is stirred for 2 h at room temperature and then cooled again to 0°. The complex is decomposed by dropwise addition of water (7 ml), 15% sodium hydroxide solution (7 ml), and further water (7 ml), and the precipitate formed is filtered off and washed thoroughly with ether. The ethereal solutions are united, dried over Na_2SO_4, concentrated to 60 ml by distillation through a filled column, and again dried. Dibutyl ether (30 ml) is then added and the mixture is fractionated through a semimicro column containing glass fragments. The fraction of b.p. 95–98° (5.9 g) is IR-pure [1,1-D_2]allyl alcohol.

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[28] A. F. Holding and W. A. Ross, *J. Appl. Chem. (London)*, **8**, 321 (1958); *Chem. Abstr.*, **52**, 16961 (1958).

[29] F. E. Condon, *J. Amer. Chem. Soc.*, **73**, 4675 (1951).

[30] G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956).

[31] F. A. Loewus, F. W. Westheimer, and B. Vennesland, *J. Amer. Chem. Soc.*, **75**, 5018 (1953).

[32] G. S. Hammond and J. Warkentin, *J. Amer. Chem. Soc.*, **83**, 2554 (1961).

[33] S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235, 3244 (1961).

[34] A. Streitwieser and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **79**, 6233 (1957); **77**, 195 (1955).

[35] V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961).

[36] J. L. Kice and F. M. Parham, *J. Amer. Chem. Soc.*, **82**, 6168 (1960).

[37] R. O. Lindblom, R. M. Lemmon, and M. Calvin, *J. Amer. Chem. Soc.*, **83**, 2485 (1961).

[38] W. F. Edgell, and C. J. Ultee, *J. Chem. Phys.*, **22**, 1983 (1954).

[39] R. D. Schuetz and F. W. Millard, *J. Org. Chem.*, **24**, 297 (1959).

The use of other complex hydrides, such as $LiBD_4$ and $NaBD_4$, seems so far to play only a minor role for reduction of carbonyl bonds. Catalytic methods for reduction of carbonyl groups also have little importance. However, syntheses of labeled amino acids have been effected by reductive amination of α-keto acids on suitable catalysts.[40]

2.2. Formation of the carbon–deuterium bond by exchange

I. Replacement of metal by deuterium

One of the most important methods for specific incorporation of single deuterium atoms into both aliphatic and aromatic hydrocarbons employs compounds containing a carbon–metal bond. Most such substances are extremely sensitive to hydrolysis and it is thus a simple matter to label them by treatment with heavy water.

These organometallic compounds are usually prepared immediately before their hydrolysis by D_2O, generally from halogen compounds or ethers. Examples are the decomposition of phenyllithium[41] and (diphenylethyl)potassium.[42] However, Grignard compounds[43–46] must be cited as much the most important group, and the preparation of [1-D_1]butane[47] will be described here as example.

D_2O (11 g) is added slowly to a vigorously stirred Grignard solution from magnesium turnings (24 g) and butyl bromide (100 g) in dibutyl ether (400 ml). The mixture is then heated and the deuterated butane is collected in a cold trap at −78°. Distillation of the crude product through a Davis column, whose head is cooled with acetone/dry ice at −10°, affords **[1-D_1]-butane** (27.6 g, 85.2%), which boils at −0.5 to −0.2°/740 mm.

Decomposition of Grignard compounds with DCl is often recommended, particularly when they contain several aromatic groups: products with homogeneous isotopic distribution are thus formed.[48]

Decomposition of Grignard compounds is also used when halogen atoms are introduced as a kind of protecting group into an aromatic nucleus during isotope exchange, only to be removed again later by reaction of the organomagnesium compound with normal water; in this way, for instance, *p*-dibromobenzene can be converted into [1,2,4,5-D_4]benzene.[44]

An interesting method for the preparation of deuterated olefins starts with addition of a dialkylaluminum deuteride (or hydride) to an acetylenic bond. Hydrolysis of the unsaturated organoaluminum compound resulting from the

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[40] K. Bloch, and D. Rittenberg, *J. Biol. Chem.*, **159**, 45 (1945).

[41] K. B. Wiberg, *J. Amer. Chem. Soc.*, **77**, 5987 (1955).

[42] W. G. Brown, C. J. Mighton, and M. Senkus, *J. Org. Chem.*, **3**, 62 (1938).

[43] O. Redlich and W. Stricks, *Monatsh. Chem.*, **67**, 213 (1936).

[44] L. H. P. Weldon and C. L. Wilson, *J. Chem. Soc.*, **1946**, 235.

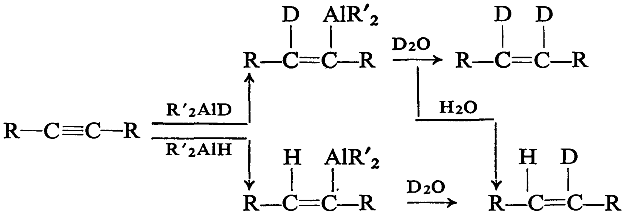
[45] A. P. Best and C. L. Wilson, *J. Chem. Soc.*, **1946**, 239.

[46] J. I. G. Cadogan, V. Gold, and D. P. N. Satchell, *J. Chem. Soc.*, **1955**, 561.

[47] B. S. Rabinovitch and F. S. Looney, *J. Amer. Chem. Soc.*, **75**, 2652 (1953).

[48] M. A. Langseth, "Le Isotope," Rapports et Discussions, Inst. Int. de Chimie Solvay, 1948, p. 242.

deuteride affords monodeuterated olefins, and a corresponding deuterolysis leads to dideuterioolefins.[49]



Further, hydrolysis of some carbides with D_2O leads to important fundamental compounds with deuterium labeling. For example, dideuterioacetylene is obtained from CaC_2,[50] tetradeuteriomethane from Al_4C_3,[51] and perdeuterated allene from Mg_2C_3 at about 350°:[52]

$$Mg_2C_3 \xrightarrow{D_2O} D_2C{=}C{=}CD_2$$

II. Replacement of halogen by deuterium

When deuterated compounds were being first prepared, the reduction of aliphatic halogen compounds to the corresponding deuterium compounds was effected mainly by potassium or aluminum amalgam in D_2O; the preparation of acetic acid from potassium trichloroacetate[53] and of methane from bromoform[54] may be cited as examples. Later, reduction by zinc in an acid medium was preferred;[4d,55] for instance, thymine was labelled in the methyl group by reduction of (chloromethyl)uracil with zinc and deuterium chloride:[24]

Zinc powder (1.75 g) was added within 10 min to a stirred suspension of 5-(chloromethyl)-uracil (0.2 g) in 6N-DCl (75 ml) at 60–75°C, and the mixture was stirred at that temperature for 2.5 h. The liquid was then decanted from the excess of metal powder, and the zinc was washed several times with water. After cooling, the aqueous solution was exactly neutralized with ammonia, freed from precipitated zinc hydroxide, and concentrated in a vacuum. The crystals that separated were collected. Recrystallization from water gave **[α-D_1]thymine** (0.04 g), m.p. 327–329°C (dec.).

However, catalytic hydrogenolysis with deuterium or tritium[56] can also be effective, particularly for arene-bonded halogen; thus 5-bromouracil in mixture of D_2O and [1-D]ethanol containing $Pd/BaSO_4$[56] was readily dehalogenated by gaseous deuterium, as also was 3-benzoyl-7-bromo-5-cholestene[57] in an aprotic medium containing Raney nickel (cf. Section 2.1, II above).

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[49] G. Wilke and H. Müller, *Ann. Chem.*, **618**, 267 (1958).

[50] F. W. Breuer, *J. Amer. Chem. Soc.*, **58**, 1289 (1936).

[51] F. S. Dainton and D. E. McElcheran, *Trans. Faraday Soc.*, **51**, 657 (1955).

[52] R. C. Lord and P. Venkateswarlu, *J. Chem. Phys.*, **20**, 1237 (1952).

[53] H. Erlenmeyer and H. Lobeck, *Helv. Chim. Acta*, **20**, 142 (1937).

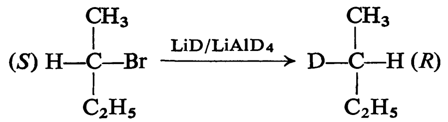
[54] G. E. MacWood and H. C. Urey, *J. Chem. Phys.*, **4**, 402 (1936).

[55] B. Bak, *J. Org. Chem.*, **21**, 797 (1956).

[56] M. Gut and M. Uskoković, *Naturwissenschaften*, **47**, 40 (1960).

[57] D. K. Fukushima, S. Lieberman, and B. Praetz, *J. Amer. Chem. Soc.*, **72**, 5205 (1950).

Reduction by lithium aluminum deuteride provides another method for direct replacement of halogen by deuterium, especially aliphatically bonded halogen; for example, methylene dibromide is converted into deuterated methane in 93% yield.[58] A mixture of LiD and $LiAlD_4$, usually in tetrahydrofuran, is recommended[59,60] especially for difficultly reducible compounds. This reduction is an S_N2 reaction, with the result that configuration is inverted at optically active centers, *e.g.*, (*R*)-(+)-[2-D]butane is obtained from (*S*)-(+)-2-bromobutane in 82% yield:[61]



$$(S)\ H{-}\underset{C_2H_5}{\overset{CH_3}{C}}{-}Br \xrightarrow{LiD/LiAlD_4} D{-}\underset{C_2H_5}{\overset{CH_3}{C}}{-}H\ (R)$$

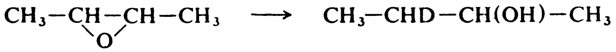
(+)-2-Bromobutane (8 g) was dropped into a boiling solution of $LiAlD_4$ (1 g) and LiD (0.9 g) in tetrahydrofuran (50 ml). The **(+)-(2-D_1)-butane** produced was passed through two wash-bottles containing 85% H_3PO_4, dried over NaOH pellets, and distilled (b.p. $-2°$ to $-1°/740$ mm; $[\alpha]^{25}_D$ $+0.50°$).

A formally similar reaction of α-amino nitriles—whose CN group is bonded to a tertiary carbon atom—also leads to labeled compounds on replacement of the CN group by deuterium.[62]

III. Replacement of oxygen by deuterium

Catalytic hydrogenolysis of C—O bonds of benzyl esters and similar compounds by deuterium has rarely been used for preparation of labeled compounds, whereas predeuterated Pd in D_2O is recommended for formation of deuterated alcohols from epoxides.[63]

This class of compound has been used repeatedly for preparation of labeled alcohols by means of $LiAlD_4$.[64,65] Only one D atom is introduced during this opening of the epoxide ring, namely, the one that is attached to the C of the C–O bond broken. For instance, boiling *trans*-2,3-epoxybutane for 2 hours under reflux with 0.25 mole of $LiAlD_4$ in ether gives *erythro*-[3-D_1]-2-butanol, whereas *cis*-2,3-epoxybutane furnishes *threo*-(3-D_1)-2-butanol analogously.



$$CH_3{-}\underbrace{CH{-}CH}_{O}{-}CH_3 \longrightarrow CH_3{-}CHD{-}CH(OH){-}CH_3$$

Since it is rarely satisfactory to reduce simple hydroxyl groups, the diversion by way of the bromide and Grignard reagent is usually chosen for replacement of OH by D (see Section 2.2, I), or the ester obtained by using a sulfonyl

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[58] V. H. Dibeler, and F. L. Mohler, *J. Res. Nat. Bur. Stand.*, **45**, 441 (1950).

[59] E. L. Eliel, *J. Amer. Chem. Soc.*, **71**, 3970 (1949), and later papers.

[60] W. H. McFadden and A. L. Wahrhaftig, *J. Amer. Chem. Soc.*, **78**, 1572 (1956).

[61] G. K. Helmkamp and co-workers, *J. Org. Chem.*, **21**, 844 (1956); **22**, 479 (1957); **24**, 529 (1959).

[62] E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, **82**, 1657 (1960).

[63] O. Gawron, T. P. Fondy, and D. J. Parker, *J. Org. Chem.*, **28**, 700 (1963).

[64] E. S. Lewis, W. C. Herndon, and D. C. Duffey, *J. Amer. Chem. Soc.*, **83**, 1959 (1961).

[65] A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *J. Amer. Chem. Soc.*, **82**, 6366 (1960).

chloride is reduced by $LiAlD_4$[62,66] or still better with additional LiD.[61] Walden inversion occurs at asymmetric centers, as in the corresponding reduction of halogen compounds: L-(−)-*erythro*-3-deuterio-2-(methanesulfonyloxy)butane thus affords L-(−)-*threo*-2,3-dideuteriobutane. It is interesting that such compounds are optically active although their asymmetry arises only from the hydrogen isotope introduced. The reaction conditions are the same as for reduction of halogen compounds.

A different complex metal hydride, namely, the water-soluble $NaBD_4$*, has been used for conversion of D-glucuronic acid δ-lactone in more than 90% yield into D-[1-D_1]glucose,[68a] a product that was previously synthesized by reduction of glucuronic acid γ-lactone by sodium amalgam and D_2O.[68b]

2.3. Isotope exchange methods

I. General

Isotope exchange, which is widely used for preparation of deuterated compounds, is usually effected in deuterium oxide but also—because of their improved solvent properties—in C_2H_5OD or CH_3COOD. Since all hydrogen atoms of the same type take part in this reaction, individual positions can be labeled selectively only if they are unique in the molecule. The occurrence of exchange of the hydrogen of an organic molecule for deuterium is extremely dependent on the nature of its bonding.

The exchange equilibrium is reached almost instantaneously with hydrogen atoms bonded to the oxygen or nitrogen of alcohols, carboxylic acids, amines, or similar compounds. The completeness of the reversible incorporation of deuterium depends in such cases only on the relative number of mobile H and D atoms. Clusius[69] derived an equation which gives the relative frequency of deuterium in a substance labeled by exchange; in its simplified form, with the equilibrium constant $K = 1$, it is given by the expression:

$$\%D = 100 \frac{n_L}{n_S + n_L}$$

where n_L and n_S are the moles of exchangeable hydrogen in the solvent and in the substance, respectively. This has the result, for instance, that one treatment of 0.001 mole of a carboxylic acid with 0.1 mole of pure D_2O causes replacement of 99% of the hydrogen of the COOH group, provided that there is complete establishment of equilibrium.

In principle, such consideration apply of course also to the reverse reaction. Indeed, labile deuterium atoms must be washed out of a labeled compound by water because use of such a compound requires that it can be purified to constant isotopic composition by distillation,

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* According to Davis *et al.*,[67] $NaBD_4$ is prepared from B_2D_6 and $NaB(OCH_3)_4$. It has a negative isotope effect, *i.e.*, it is hydrolysed faster than $NaBH_4$ by methanol.

[66] E. R. Alexander, *J. Amer. Chem. Soc.*, **72**, 3796 (1950).

[67] R. E. Davis *et al.*, *J. Amer. Chem. Soc.*, **82**, 5950 (1960); **84**, 885 (1962).

[68] M. Urquiza and N. N. Lichtin, *TAPPI*, **44**, 221 (1961); *Chem. Abstr.*, **55**, 16433 (1961).

[68a] Y. J. Topper and D. Stetten Jr., *J. Biol. Chem.*, **189**, 191 (1951).

[69] K. Clusius and H. Knopf, *Z. Naturforsch.*, **2b**, 169 (1947).

recrystallization, or chromatography; the washing-out is essential to avoid uncontrollable changes in isotopic distribution. The requirement has, in fact, sometimes not been met, owing to isotope effects or because exchange equilibria were not fully established.[3]

In contrast to the above, it is very difficult to replace hydrogen bound to carbon. It is possible only after complete or partial fission of a C–H bond — a process that naturally requires a considerable activation energy.[70,71]

Exceptions apart, isotopic exchange in C–H bonds, usually effected in the presence of bases, is sufficiently rapid only if some feature of the molecular structure weakens quite considerably the bond between carbon and hydrogen, *i.e.*, renders the hydrogen atom acidic (semilabile hydrogen atom). Exchange reactions of that type are often carried out in order to achieve semilabile labeling, e.g., at the α-position of a ketone, the material obtained in this way being later converted into stably labeled compounds by subsequent reactions, *e.g.*, reduction to secondary alcohols.

Hydrogen in the stable bonds of aliphatic and aromatic compounds can be exchanged only under particularly energetic conditions. It is favored, for instance, by solid catalysts*, by strong bases which ease the removal of protons in such cases, or by strong acids which act as effective deuteron-donors. An acid-base-catalysed ionic mechanism and an electrophilic substitution mechanism have both been discussed as explaining the formation of deuterated compounds.[70,71]

Summarizing it can be said that almost any class of compound can be deuterated by isotope exchange under suitable conditions. However, rules of general validity cannot by laid down. Finding reactions suitable for deuterium labeling by isotope exchange is always intimately connected with a study of the mobility of hydrogen atoms in relation to structure and reaction conditions.

II. Exchange of labile bonded hydrogen

As mentioned above, replacement of hydrogen by deuterium is easiest when the hydrogen atom to be labeled is bonded to a hetero atom that has free electron pairs. To label, for instance, the hydrogen of the hydroxyl group of an alcohol or phenol, of the carboxyl group of a carboxylic acid, or of the amino group of an aliphatic or aromatic amine it usually suffices to recrystallize the substance several times from D_2O. Exchange is particularly complete when a base is converted repeatedly into its salt with a deuterium acid in D_2O with regeneration of the base from the isolated salt. Similar success is achieved by liberation of carboxylic acids and alcohols from their alkali salts by deuterated acids in D_2O. Carboxylic acids labeled in the COOH group can be obtained almost isotopically pure also by hydrolysis of acid chlorides or anhydrides by deuterium oxide.

Such exchange reactions have preparative importance when the compound

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[70] A. E. Brodsky, "Isotopenchemie," Akademie-Verlag, Berlin, 1961, pp. 331 *et seq.*

[71] A. I. Shatenstein, "Isotopenaustausch und Substitution des Wasserstoffs," VEB Deutscher Verlag der Wissenschaften, Berlin, 1963.

* Cf. the preparation of [D_6]benzene from benzene and D_2O in the presence of platinum black.[4c]

with labile labeling is required for examination of its specific physicochemical properties, or when the labile deuterium atoms are to be stabilized by a simple subsequent reaction, *e.g.*, by treatment with a diazoalkane (see p. 86) or by decarboxylation.

Decarboxylation is, of course, easiest when the carboxyl group is 'loosened" by the influence of neighboring groups. Malonic acid[18] and suitable substitution products[73] can, after deuteration, be readily converted into deuterated acetic acid and its derivatives. Moreover, the simplest carboxylic acid, formic acid, has been obtained labeled in this way:[74,75]

$$(COOH)_2 \xrightarrow[-H_2O]{+D_2O} (COOD)_2 \xrightarrow{-CO_2} DCOOD \xrightarrow[-HDO]{+H_2O} DCOOH$$

Anhydrous oxalic acid (10 g) was recrystallized three times from D_2O (9 ml), the crystals being purified each time by sublimation at ca. 1 mm. The resulting **[D_2]oxalic acid** was pyrolysed by being sublimed at ca. 1 mm through a 10-inch column filled with glass pieces and heated at 220°. The **[D_2]formic acid** formed was collected in a dry box, the yield being 2.2 g from 8.8 g of [D_2]oxalic acid, *i.e.*, 98%; b.p. 44–44.5°C/58 mm; n^{20}_D 1.3692.

The [D_2]formic acid was treated twice with a ten-fold excess of distilled water. **[1-D_1]-Formic acid** was isolated from the aqueous phase by saturation with $CuSO_4$ and six extractions with anhydrous ether. The ether layer was dried over anhydrous $CuSO_4$ and distilled. B.p. 63°/145 mm; n^{20}_D 1.3674.

Analogous decarboxylations, sometimes in the presence of $Ca(OD)_2$, have been used for preparation of labeled aromatic hydrocarbons from the corresponding carboxylic acids,[76] *e.g.*, [D_6]benzene from mellitic acid,[77] deuteriochloroform from trichloroacetic acid,[78] and [6-D_1]uracil from orotic acid.[24]

III. Exchange reactions in alkaline media

1. Exchange in aqueous solution

Replacement of the hydrogen of hydrocarbons by deuterium is directly related to the acidity of the compounds. Accordingly exchange reactions are not observed for paraffins or most aromatic hydrocarbons in aqueous alkali. On the other hand, there are exceptions where such an exchange occurs even in the absence of a basic catalyst, *e.g.*, with fluoradene (indenofluorene) whose ionization constant pK is as high as 11 even in aqueous solution.[79] Pyrylium salts containing alkyl groups in the 2- or 4-position exchange hydrogen from the α-positions of side chains completely during 1 hour's heating in D_2O at

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[72] A. E. Potter and H. L. Ritter, *J. Phys. Chem.*, **58**, 1040 (1954).

[73] B. Nolin, *Can. J. Chem.*, **31**, 1257 (1953); D. J. G. Ives and M. R. Nettleton, *J. Chem. Soc.*, **1948**, 1085; C. C. Price and co-workers, *J. Org. Chem.*, **22**, 347 (1957).

[74] R. C. Herman and V. Z. Williams, *J. Chem. Phys.*, **8**, 447 (1940); D. W. G. Style and J. C. Ward, *J. Chem. Soc.*, **1952**, 2125.

[75] N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, **79**, 6210 (1957).

[76] N. Morita and T. Titani, *Bull. Chem. Soc. Japan*, **10**, 557 (1935); O. Redlich and W. Stricks, *Monatsh. Chem.*, **68**, 374 (1936).

[77] H. Erlenmeyer and H. Lobeck, *Helv. Chim. Acta*, **18**, 1464 (1935); H. Erlenmeyer, H. Lobeck, H. Gärtner, and A. Epprecht, *Helv. Chim. Acta*, **19**, 336 (1936).

[78] W. M. Boyer, R. B. Bernstein, T. L. Brown, and V. H. Dibeler, *J. Amer. Chem. Soc.*, **73**, 770 (1951).

[79] H. Rapoport and G. Smolinsky, *J. Amer. Chem. Soc.*, **80**, 2910 (1958); **82**, 1171 (1960).

90–100°, even without a catalyst. The last-mentioned reaction has been recommended for deuterium labeling[80] particularly, because the products can undergo a variety of reactions; for instance, reaction with aqueous ammonia affords collidine deuterated in the side chain there being no dedeuteration under these reaction conditions.

Other hydrocarbons related to fluoradene, such as indene,[81] fluorene, and cyclopentadiene,[82] exchange their mobile hydrogen atoms in D_2O only in the presence of a base. If, *e.g.*, indene is shaken with D_2O at 100°, hardly any exchange can be observed, but in 3N-potassium hydroxide both hydrogen atoms of the methylene group are exchanged within 1 hour. Similarly exchange occurs with acetylene and its monoalkyl and monoaryl derivatives in 0.5N-sodium hydroxide at as low as 0° and it is complete within a few days at room temperature.[83] Aromatic compounds can be labeled under more vigorous conditions although they are not normally attacked in this way; for instance, deuterium is incorporated when naphthalene is heated with $Ca(OD)_2$ and D_2O for 24 hours at 400°, and perdeuterionaphthalene can be isolated after seven repetitions of the treatment.[84]

When a molecule contains electronegative substituens isotope exchange is simpler than it is with hydrocarbons. It occurs relatively readily with nitroalkanes, alkyl cyanides, monochloroacetic acid, acetamide, and similar compounds. The following prescription has been given for the preparation of **[1,1-D_2]nitroethane:**[85]

A mixture of nitroethane (25 ml), D_2O (25 ml), and anhydrous sodium acetate (10 mg) was heated overnight in a sealed bomb-tube at 90°. After the tube had been opened, its contents were placed in a vacuum-distillation apparatus, which was cooled in an ice-bath and evacuated. The upper layer of [1,1-D_2]nitroethane distilled through an U tube filled with Drierite and was frozen into a U tube cooled to -78°C. The yield amounted to 19 ml. Repetition of the procedure gave 11 ml of [1,1-D_2]nitroethane. This product was then readily convertible into [1-D]acetaldehyde. [D_3]Nitromethane, similarly prepared,[86] is a convenient starting material for [D_3]methylamine.

Accumulation of electronegative groups within a molecule facilitates isotope exchange quite considerably. For example, with chloroform the exchange is complete in 10 minutes at 20°, being appreciably faster than the hydrolytic decomposition.[87]

A similar marked weakening of neighboring C–H bonds is observed also in sulfoxides[88] and sulfonium salts[89] and has been used for preparation of deuterium-labeled compounds; *e.g.*, the following method is recommended for

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[80] A. T. Balaban and co-workers, in "Preparation and Biomedical Applications of Labeled Molecules," Euratom 2200e, Brussels, 1964, p. 45.

[81] M. Koizumi, *Bull. Chem. Soc. Japan*, **14**, 491 (1939).

[82] D. N. Kursanov and S. N. Parnes, *Dokl. Akad. Nauk SSSR*, **109**, 315 (1956); *Chem. Abstr.*, **51**, 1944 (1957).

[83] L. H. Reyerson and B. Gillespie, *J. Amer. Chem. Soc.*, **57**, 2250 (1935).

[84] E. R. Lippincott and E. J. O'Reilly, *J. Chem. Phys.*, **23**, 238 (1955).

[85] L. C. Leitch, *Can. J. Chem.*, **33**, 400 (1955); L. C. Leitch, P. E. Gagnon, and A. Cambron, *Can. J. Res.*, **28B**, 256 (1950).

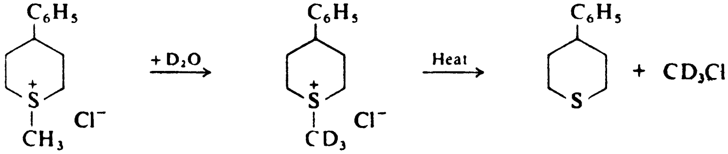
[86] H. D. Noether, *J. Chem. Phys.*, **10**, 664 (1942).

[87] J. Hine, R. C. Peek, and B. D. Oakes, *J. Amer. Chem. Soc.*, **76**, 827 (1954).

[88] F. A. Cotton, J. H. Fassnacht, W. D. Horrocks Jr., and N. A. Nelson, *J. Chem. Soc.*, **1959**, 4138.

[89] H. Dorn, *Angew. Chem. Int. Ed., Engl.*, **6**, 371 (1967).

synthesis of α-deuterated alkyl halides: When an *S*-alkylsulfonium halide derived from 4-phenylthiane is heated with D_2O containing a little NaOD at 35°, the α-hydrogen atoms of the *S*-alkyl group are replaced; when the deuterated product is heated alone at ca. 160° cleavage occurs, affording the deuterioalkyl halide in almost quantitative yield.



Also, all the α-situated hydrogen atoms of ketones are readily replaceable by deuterium in an aqueous alkaline medium, since these atoms take part one after the other in the reversible keto–enol tautomerism. This applies, for instance, to the four α-positions of cyclohexanone and to the one of 2,2,6-trimethylcyclohexanone, whereas no exchange occurs in camphor or camphorquinone which cannot enolize owing to the particular stereochemistry of the molecules.[90] Open-chain ketones and also steroidal ketones[91] that are not subject to this limitation are often used for exchange reactions. The following description of the preparation of **[D_6]acetone** illustrates the point:[29]

Deuterioacetone is prepared by twenty-one repetitions of the exchange reaction between acetone (0.66 mole) and 99.8% deuterium oxide (ca. 0.6 mole) in the presence of ca. 0.1 g of anhydrous potassium carbonate. Each exchange is carried out in a 100-ml flask that is attached to a filled fractionating column (30 × 0.7 cm). The acetone and a small amount of D_2O are distilled off until the temperature reaches 95°, and they are collected in a vessel that is used as reaction flask for the next exchange. The end product, obtained in 78% yield, has a deuterium content of 99.3%.

[D_6]-Acetone serves as starting material for the preparation of, *inter alia*, [1,3-D_6]-2-propanol by reduction with $LiAlH_4$ in aprotic solvents[29] or [D_2]ketene by pyrolysis.[92]

2. Exchange in liquid [D_3]ammonia

Labeling of hydrocarbons by base-catalysed exchange has received a considerable extension by the experiments of Shatenstein and his collaborators[93] with liquid [D_3]ammonia. It is true that working with pure ND_3 (prepared from D_2O and magnesium nitride) achieves substantially no more than does working with NaOH in D_2O; *e.g.*, three hydrogen atoms of indene can be replaced by deuterium. However, addition of deuterated potassium amide provides a reagent that decisively facilitates the transfer of deuterons. Under these extraordinarily basic conditions a large number of aromatic hydrocarbons can be labeled. For instance, with naphthalene exchange equilibrium is reached in 10–20 minutes at room temperature. Benzene and its homologs are also

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[90] A. N. Nesmeyanov and co-workers, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1949**, 592, 598.

[91] B. Nolin and R. N. Jones, *Can. J. Chem.*, **30**, 727 (1952).

[92] H. R. Johnson and M. W. Strandberg, *J. Chem. Phys.*, **20**, 687 (1952).

[93] Reviews: A. I. Shatenstein, *Fortschr. Chem. Org. Naturst.*, **24**, 377 (1955); **28**, 3 (1959).

readily converted into their perdeuterated derivatives at room temperature. The exchange rate is particular great for α-positions in side chains of alkylaromatic compounds; thus the α-hydrogen atoms of toluene are exchanged 300 times faster than the hydrogen atoms of benzene, and this fact can be utilized for selective deuteration of such positions, achieved by shortening the reaction period. On the other hand, increasing both the concentration of potassium amide and the temperature (to 120°) leads to exchange also of the β-hydrogen atoms of ethylbenzene.

ND_3 and KND_2 lead also to isotope exchange in olefins, though here appreciably more slowly. A small amount of replacement of hydrogen by deuterium has even been observed for some aliphatic hydrocarbons.

IV. Exchange reactions in acid media

Labeling in acid media is favored by substituents such as OH, OCH_3, NH_2, and NR_2, this being the reverse of the relations for base-catalyzed isotope exchange. The order of relative substitution rates and the directing effects of substituents for exchange of hydrogen follow the rules of normal electrophilic substitution. Accordingly, aniline is deuterated even by dilute deuterium chloride, giving 2,4,6-trideuterioaniline, which is used for preparation of [1,3,5-D_3]benzene by diazotization and reduction with sodium stannite.[45]

D_3O^+ ions are, however, normally insufficiently powerful deuteron-donors for labeling aromatic hydrocarbons; but as early as 1936 Ingold and his colleagues[94] found that deuterium sulfate constituted a suitable reagent for preparation of labeled compounds. A concentration of 65 mole-% of acid caused side reactions as well as exchange, and at a concentration of 40 mole-% exchange is very slow, so experiments are carried out at acid concentrations of 51–52 mole-% in D_2O.

Pure benzene is carefully dried over P_2O_5, then distilled into deuterium sulfate, and the mixture is shaken for 3–4 days, after which the benzene is distilled off in a vacuum into a fresh batch of D_2SO_4. After four repetitions of these operations the benzene is transferred to a flask containing roasted barium oxide, after 12 hours to a flask containing P_2O_5, and after a further 15 min to a storage flask. The [D_6]benzene obtained contains 99.8% of deuterium.

D_3PO_4 is less powerful, but correspondingly more selective, azulene, for instance, being labeled by it in the 1,3-positions.[95] One the other hand, DCl containing $AlCl_3$ is a more powerful reagent than D_2SO_4; equilibrium is established already after 3 hours at 25° if DCl is led into a suspension of $AlCl_3$ in benzene; 40 hours suffice for obtaining 36 ml of [D_6]benzene containing 99.3% of deuterium.[96]

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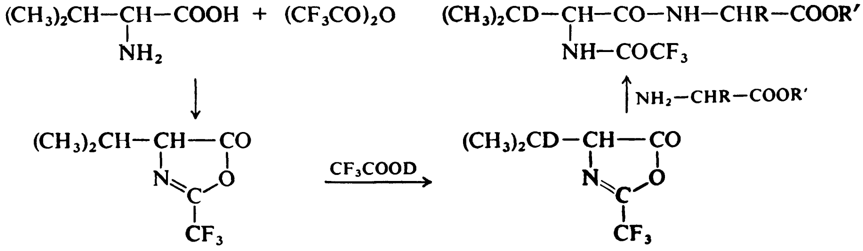
[94] C. K. Ingold and co-workers, *J. Chem. Soc.*, **1936**, 915, 1637; *Z. Elektrochem. Angew. Phys. Chem.*, **44**, 62 (1938).

[95] A. Bauder and H. H. Günthard, *Helv. Chim. Acta*, **41**, 889 (1958).

[96] M. Brüllmann, H.-J. Gerber, and D. Meier, *Helv. Chim. Acta*, **41**, 1831 (1958).

Experiments on isotope exchange with D_2SO_4 were later continued by other schools.[94,97–101] Fatty acids and amino acids[102,103] were labeled in this way, as well as other monocyclic and polycyclic aromatic compounds; but saturated aliphatic hydrocarbons are hardly attacked at all. Interesting exceptions to the last statement are provided by aliphatic hydrocarbons containing at least one tertiary carbon atom;[94,97,98] they undergo isotope exchange in presence of concentrated D_2SO_4 even at room temperature. It is assumed that the exchange is preceded by formation of a carbonium ion as a result of oxidation at the tertiary carbon atom by the sulfuric acid; this explanation is favored by the inability of the non-oxidizing phosphoric acid to cause the reaction, and by the finding of deuterium in all the positions in the molecule accessible by isomerization of a carbonium ion. Other acid systems have also been examined, primarily with a view to improving solubility, including deuteriotrifluoroacetic acid.[104] An interesting application of the last-mentioned acid as solvent is in the preparation of amino acids and dipeptides specifically deuterated at the *β*-position by isotope exchange carried out on 4-alkyl-2-(trifluoromethyl)-5(4*H*)-oxazolones as described by Weygand and his collaborators.[105]



Liquid deuterium bromide has proved a solvent well suited for isotope exchange and it is also a powerful deuteron-donor.[106] The hydrogen of polycyclic aromatic hydrocarbons is rapidly exchanged at 20°; the hydrogen of

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[97] J. W. Otvos, D. P. Stevenson, C. D. Wagner, and O. Beek, *J. Amer. Chem. Soc.*, **73**, 5741 (1951); D. P. Stevenson, C. D. Wagner, O. Beek, and J. W. Otvos, *J. Amer. Chem. Soc.*, **74**, 3269 (1952).

[98] R. L. Burwell Jr., L. G. Maury, and R. B. Scott, *J. Amer. Chem. Soc.*, **76**, 5828 (1954); R. L. Burwell Jr. and A. D. Shields, *J. Amer. Chem. Soc.*, **77**, 2766 (1955).

[99] V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, **1955**, 2743, 3619; **1965**, 3911.

[100] L. Melander and S. Olsson, *Acta Chem. Scand.*, **10**, 879 (1956); *Arkiv Kemi*, **14**, 85 (1959).

[101] C. Eaborn and R. Taylor, *J. Chem. Soc.*, **1960**, 3301.

[102] D. Rittenberg and co-workers, *J. Biol. Chem.*, **125**, 1, 495 (1938).

[103] V. N. Setkina and E. V. Bykova, *Dokl. Akad. Nauk SSSR*, **92**, 341 (1953); *Chem. Abstr.*, **49**, 164 (1955); E. V. Bykova and V. N. Setkina, *Dokl. Akad. Nauk SSSR*, **103**, 835 (1955); *Chem. Abstr.*, **50**, 9295 (1956).

[104] W. M. Lauer, G. W. Matson, and G. Stechman, *J. Amer. Chem. Soc.*, **80**, 6437 (1958).

[105] F. Weygand, D. Mayer, and W. Steglich, in "Prepaiation and Biomedical Application of Labeled Compounds," Euratom 2200e, Brussels, 1964, p. 57.

[106] A. I. Shatenshtein and Ya. N. Varshavskiĭ, *Dokl. Akad. Nauk SSSR*, **85**, 157 (1952); *Chem. Abstr.*, **46**, 9395 (1952); V. R. Kalinachenko, Ya. M. Varshavskiĭ, and A. I. Shatenshtein, *Dokl. Akad. Nauk SSSR*, **91**, 577 (1953); *Chem. Abstr.*, **49**, 12093 (1955); A. I. Shatenshtein, K. I. Zhdanova, L. N. Vinogradov, and V. R. Kalinachenko, *Dokl. Akad. Nauk SSSR*, **102**, 779 (1955); *Chem. Abstr.*, **50**, 3860 (1956).

benzene is, however, relatively slowly replaced by deuterium in that solvent, though reaction is instantaneous in the presence of $AlBr_3$.[107] The influence of substituents is the opposite to that for labeling by KND_2 inND_3. Electropositive groups such as CH_3, OCH_3, etc., which decelerate isotope exchange in ND_3, accelerate it in liquid DBr. The differing mobilities of the hydrogen atoms have greater influence in work with liquid DBr than in that with liquid ND_3, so that for a whole series of examples predetermined positions can be specifically labeled. For instance in the presence of $AlBr_3$ only six atoms of biphenyl are exchanged, so that 2,2′,4,4′,6,6′-hexadeuteriobiphenyl is formed. Deuteration of naphthalene provides a further example: since replacement of the α-hydrogen atoms is 40–50 times faster than that of the β-atoms, the reaction can be controlled to an optimum that affords pure 1,4,5,8-tetradeuterionaphthalene.[107]

The suitability of the system $DBr/AlBr_3$ for deuterium labeling is further underlined by the fact that even the C–H bonds of saturated aliphatic hydrocarbons are attacked: isotope exchange with cyclohexane reaches equilibrium in somewhat more than 10 hours.

Further acceleration of isotope exchange, by three to four powers of ten, can be achieved[116–118] by working in liquid deuterium fluoride, particularly if it contains BF_3.[108–110] The properties attaching to deuterium bromide apply also to this system. For toluene, equilibrium is reached in 15 minutes,[108] and, as in exchange in DBr, only the hydrogen atoms attached directly to the aromatic ring are replaced, even in presence of BF_3.

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[107] A. I. Shatenshtein, G. V. Peregudov, E. A. Izraelevich, and V. R. Kalinachenko, *Zh. Fiz. Khim.*, **32,** 146 (1958); *Chem. Abstr.*, **52,** 12554 (1958).

[108] Ya. M. Varshavskiĭ and A. I. Shatenshtein, *Dokl. Akad. Nauk SSSR*, **95,** 297 (1954); *Chem. Abstr.*, **49,** 15403 (1955); Ya. M. Varshavskiĭ, M. G. Ozhkina, and A. I. Shatenshtein, *Zh. Fiz. Khim.*, **31,** 1377 (1957); *Chem. Abstr.*, **52,** 3486 (1958).

[109] G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **80,** 6535 (1958).

[110] E. L. Mackor, P. J. Smit, and J. H. van der Waals, *Trans. Faraday Soc.*, **53,** 1309, 1957).

CHAPTER 3

Formation of Carbon-Halogen Bonds

Compiled by
H. Dorn

Halogenated organic compounds are important end products of organic syntheses in both academic research and industry, where they find use as solvents, plastics, drugs, dyestuffs, pesticides, and weedicides. Their role as intermediates is at least equally vital; they are stepping stones in very numerous procedures for the junction of C—N, C—O, and C—C bonds and for formation of C=O, C=C, and C≡C bonds.

In the following pages particular attention is paid to the bromination procedures that are most easily carried out on the laboratory scale, but most of the processes of fluorination, chlorination, iodination, and of formation of thiocyanates customarily used in the laboratory are also included (for detailed accounts of the preparation of organic fluorine and chlorine derivatives see reference, 1a, 1i and for bromine and iodine compounds see reference). The material is classified according to the type of reaction and the class of compound produced.

3.1. Formation of carbon-halogen bonds by addition

I. Addition of halogen or thiocyanogen to C–C multiple bonds

1. Properties and purification of halogens and thiocyanogen

Since the free halogens F_2, Cl_2, I_2, and $(SCN)_2$ are usually used for addition of halogen (X_2), a short description of their properties and purification opens this Chapter.

Fluorine, a yellowish-green gas, b.p. −188°, with an odor reminiscent of ozone and chlorine, is generally produced by electrolysis of KF·2HF; this salt solidifies at ca. 100° and can thus be electrolysed in a steam-heated cell. Iron is used as the cathode, and graphite or nickel as the anode. Many types of apparatus for preparation of fluorine in the laboratory have been de-

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[1] Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1962, (a) Vol. 5, Part 3, pp. (b) 1, (c) 213, (d) 552, (e) 616, (f) 624, (g) 654, 658, (h) 860, (i) Vol. 5, Part 4, pp. (j) 14, (k) 17, (l) 18, (m) 484, (n) 540–542, (o) 731–742, (p) Vol. 7, Part 1, p. 365, (q) Vol. 8, p. 73, (r) Vol. 10, Part 2, pp. 27, 764.

scribed.[2,3,4b,5a] In laboratory practice only so much fluorine is produced as will be consumed immediately. For details of filling of fluorine into steel or nickel bottles see reference 4i.

Fluorine attacks all organic compounds except CF_4. The inorganic compounds that react with fluorine include many, such as asbestos, that are relatively stable to the other halogens. Reaction with water often leads even to explosions. Metals react with fluorine at room temperature; some form an impermeable fluorine layer on the surface which protects them against further corrosion, in particular Monel metal, nickel, aluminum, magnesium, iron, and steel. Glass is not attacked by fluorine if it is free from HF and dry.

For the preparation of pure **chlorine**, b.p. −34.15°/760 mm., d^{-35} 1.565, d^{-30} 1.551, d^{-20} 1.524, see reference 4a. It usually suffices to pass chlorine through two wash-bottles containing concentrated sulfuric acid and, if necessary, through a CaO tube for removal of HCl and thereafter over phosphorus pentoxide to remove water. To provide measured amounts of chlorine it is convenient to liquify it in a calibrated vessel cooled in an acetone–CO_2 bath. Chlorine largely free from oxygen and oxides of chlorine can be obtained from manganese dioxide hydrate and concentrated hydrochloric acid.[5c]

The natural and artificial forms of mineral MnO_2 are unsuitable for the preparation of pure chlorine owing to their content of carbonates and sulfides. Pure chlorine can also be prepared as follows:

(*a*) Potassium dichromate is allowed to react with warm concentrated hydrochloric acid. The dichromate is placed in a flask that is set on a Babo funnel, hydrochloric acid (3 vol. of acid of *d* 1.19 plus 1 vol. of water) is added from a dropping funnel, and the mixture is heated as necessary.

(*b*) It is more convenient to use solid potassium permanganate and hydrochloric acid (*d* 1.16), with cooling if necessary, but chlorine prepared from permanganate always contains appreciable amounts of oxygen.

(*c*) Chlorine can be prepared in a Kipps apparatus from pieces of bleaching powder and hydrochloric acid.

Electrolytic chlorine from a steel bottle contains small amounts of oxygen, chlorine oxides, nitrogen, carbon monoxide, carbon dioxide, hydrogen chloride, chlorinated hydrocarbons, and moisture. For complete purification, chlorine washed with concentrated sulfuric acid is condensed into a receiver (preferably calibrated) cooled in ether/carbon dioxide, and a regular stream of chlorine is produced by placing the receiver in a bath of ice and water. A safety flask should be placed between the reaction flask and the chlorine supply. Chlorine bombs cool very considerably if chlorine is removed in a rapid stream; they should, if that happens, never be warmed above 30°C (vapor pressure of Cl_2 at 0° 3.76 atm, at +10° 5.14, at +20° 6.86, at +30° 8.97, and +40° 11.52 atm).

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[2] L. M. Dennis, J. M. Veeder, and E. G. Rochow, *J. Amer. Chem. Soc.*, **53**, 3263 (1931).

[3] A. L. Henne, *J. Amer. Chem. Soc.*, **60**, 96 (1938).

[4] M. Hudlicky, "Chemie der organischen Fluorverbindungen," Deutscher Verlag der Wissenschaften, Berlin, 1960, pp. (a) 22, (b) 28, (c) 35, (d) 45, (e) 47, (f) 49, (g) 50, (h) 60, (i) 81, (j) 93, (k) 126, (l) 167, (m) 296.

[5] G. Brauer, "Handbuch der präparativen anorganischen Chemie," F. Enke, Stuttgart, 2nd ed, 1960, Vol. 1, pp. (a) 144, (b) 145, (c) 249, (d) 251, (e) 253, (f) 254, (g) 257, (h) 258–259, (i) 263, 264, (j) 299.

The following are suitable solvents for chlorine: CCl_4 (8.5% of Cl_2), $CHCl_3$ (20% of Cl_2), acetic acid (11.6 g of Cl_2 per 100 ml), dimethylformamide, halobenzenes, and hexachlorobutadiene.

For preparative purposes it suffices to use commercial **bromine**, b.p. 58.8°/760 mm, d_4^{20} 3.119, which can be dried, if necessary, by being shaken with concentrated sulfuric acid, in which bromine is only slightly soluble. For data on pure bromine see references 1j, 5d, 6, 7. After bromination an excess of bromine can be removed by SO_2 or sodium hydrogen sulfite. CCl_4, $CHCl_3$, CH_2Cl_2, CS_2, light petroleum, glacial acetic acid, and nitrobenzene are suitable solvents; CCl_4, $CHCl_3$, and CH_2Cl_2 should be used only at low temperatures; diethyl ether can also be used at 0°.

Iodine, m.p. 113.6°, sublimes readily, a property that can be used for its purification. To remove chlorine or bromine present as impurity, sublimation is effected in presence of potassium iodide. Iodine is only slightly soluble in water (0.28 g/l at 20°), but readily so in mineral acids or aqueous potassium iodide (15.9 g/l in 0.12N-KI and 420 g/l in 1.9N-KI). At room temperature iodine dissolves readily in ether, methanol, ethanol, CS_2, or benzene, and moderately in acetic acid, $CHCl_3$, CCl_4, and light petroleum. Iodine can be dried in a desiccator over calcium chloride, concentrated sulfuric acid, or phosphorus pentoxide. It is not hygroscopic. For the preparation of very pure iodine see reference[1j].

When large batches are used, iodine can be recovered from the iodine mother-liquors, *e.g.*, by oxidation with oxygen in the presence of nitrogen oxides.[5f,8] A very simple method for recovery of iodine is described in *Organic Syntheses*:[9]

A mother-liquor containing about 1 mole of NaI and about 0.8 mole of $NaHCO_3$, from the preparation of *p*-iodoaniline, is treated with 100 ml of concentrated H_2SO_4 and 200 g of $Na_2Cr_2O_7$ in 200 ml of water. The iodine is allowed to settle, washed by decantation with water three times, filtered off, and dried on a watch-glass.

Thiocyanogen, $(SCN)_2$, is used in substantially the same way as the halogens.[10a] It is a liquid, freezing at −3 to −2°,[11] and polymerizes readily at room temperature to a red amorphous product. It is more stable in solution but polymerizes there too if reaction is slow, and particularly under the influence of light, heat, moisture, or oxygen. Separation of the organic thiocyanates is, however, easy, as polymerized thioxyanogen is insoluble in water and organic solvents.

A solution of thiocyanogen is obtained by adding somewhat less than the theoretical amount of bromine (as 10% solution) to a suspension of lead thiocyanate (from lead nitrate and NaSCN in cold water[10b]) in dry ether, light petroleum, CS_2, benzene, $CHCl_3$, CCl_4, or glacial acetic acid, with shaking and cooling to 5–10°. The resulting colorless and clear solution is decanted. Thiocyanogen should be prepared as shortly as possible before its use.

It is advantageous to use nascent thiocyanogen; for instance, bromine is added to a cooled solution of the organic compound and an alkali thiocyanate

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[6] O. Hönigschmidt and E. Zintl, *Ann. Chem.*, **433**, 201 (1923).

[7] O. H. Striebel and H. Striebel, *Z. Anorg. Allg. Chem.*, **194**, 294 (1930).

[8] F. Arndt, *Ber. Deut. Chem. Ges.*, **52**, 1131 (1919).

[9] R. Q. Brewster, *Org. Syn.*, Coll. Vol. II, 348 (1943).

[10] J. L. Wood, *Org. Reactions*, **3**, (a) 241, (b) 285 (1946).

[11] E. Söderbäck, *Ann. Chem.*, **419**, 217 (1919).

in methanol, acetone, methyl acetate, or glacial acetic acid.[12,13] The copper thiocyanate process[14] provides another method of working with nascent thiocyanogen: The organic compound is treated in an organic solvent (methanol, ethyl acetate, or glacial acetic acid) or in an aqueous acid with the black $Cu(SCH)_2$ which can be produced during the reaction from a copper(II) salt and an alkali or ammonium thiocyanate:

$$2\,Cu(SCN)_2 \rightleftarrows 2\,CuSCN + (SCN)_2$$

the thiocyanogen is continuously consumed and thus the reaction is driven to the right, as becomes recognizable by the decoloration to white CuSCN.

2. Addition of halogen to C=C bonds: general

The addition of halogens to compounds containing ethylenic linkages, which occurs spontaneously and at low temperatures, is so characteristic a reaction that these compounds were called olefins* as a result of it.

Addition of fluorine to a C=C bond is different from that of the other halogens in one important respect: the heat of reaction exceeds the dissociation energy of an aliphatic C–C bond (80 kcl/mole) quite appreciably. Addition and substitution reactions of fluorine are so exothermic that most organic substances burn or explode if brought into direct contact without special arrangements.[15] Addition of F_2 to olefins has no preparative importance;[4g] in the aromatic series addition and substitution result simultaneously. In electrophilic addition, *i.e.*, in most cases, chlorine reacts faster than bromine with olefins, but in nucleophilic addition bromine reacts faster than chlorine.[16]

Addition of halogen may involve either a radical or an ionic mechanism. The former predominates at elevated temperatures or under the influence of light. In an initial reaction halogen atoms X· are produced thermally, photochemically, or by an added radical-former and they then react further in a chain reaction, *e.g.*:

$$X^{\cdot} + H_2C{=}CH_2 \longrightarrow XCH_2{-}CH_2^{\cdot}$$

$$XCH_2{-}CH_2^{\cdot} + X_2 \longrightarrow XCH_2{-}CH_2X + X^{\cdot}$$

Radical halogen additions are effected without solvent or in apolar solvents such as light petroleum or CCl_4 (up to ca. 60°).

The π-complex **(1)** formed rapidly as primary product in electrophilic addition of halogen rearranges slowly to a carbonium ion **(2)**, an electrophilic reagent (polar solvent such as alcohol or water, halogen molecule X_2, or Lewis acid such as $AlCl_3$, $ZnCl_2$, BF_3) providing the necessary polarization of X_2. The subsequent rapid attack of a halogen anion (X^-) on **(3)** occurs on the rear side, so that finally *trans*-addition occurs, giving **(4)**. This is preparatively important, because it leads to two asymmetric carbon atoms. Other anions (Y = OH, Alkyl) can compete with X^-, yielding, *e.g.*, halohydrins or their

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* From the French, "gaz oléfiant" = oil-forming gas, because gaseous unsaturated hydrocarbons afforded oily products on reaction with chlorine.

[12] H. P. Kaufmann, *Ber. Deut. Chem. Ges.*, **62**, 390 (1929).

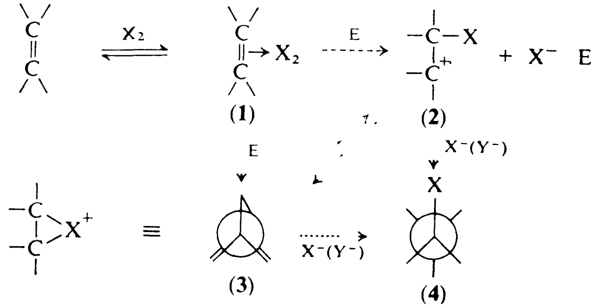
[13] H. P. Kaufmann and E. Weber, *Arch. Pharm.*, **267**, 201 (1929).

[14] H. P. Kaufmann and K. Küchler, *Ber. Deut. Chem. Ges.*, **67**, 944 (1934).

[15] A. L. Henne, *Org. Reactions*, **2**, 69 (1944).

[16] P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.*, **1939**, 1513; **1945**, 888.

ethers. Addition of X^- as, *e.g.*, NaCl or NaBr[17] depresses the formation of halohydrins, but removal of X^- by, *e.g.*, $AgNO_3$ favors it.



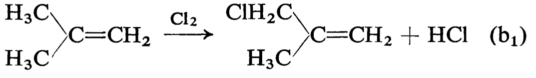
Some olefins, for instance, tetraphenylethylene, polyhaloolefins, and maleic anhydride, add halogen with difficulty or not at all. Completely dry ethylene does not add bromide at all in the dark. For further information on the theory of halogen addition and substitution see Gould[18] and de la Mare.[19]

Addition of bromine to C=C bonds does not begin with electrophilic addition of Br^+; nucleophilic mechanisms are possible. Thus, for instance, addition of bromine in glacial acetic acid to maleic or fumaric acid, stilbene, cinnamic acid, or tetrachloroethylene, which is normally slow, is catalysed by LiBr or KBr.[20]

3. Addition of halogen to simple unsaturated hydrocarbons

Straight-chain olefins of low molecular weight, namely, ethylene, propene, *n*-butenes, and *n*-pentenes, undergo addition of Cl_2 (a) on reaction therewith at room temperature; however, olefins whose chains branch at the double bond are substituted (b_1) even at room temperature, the double bond being retained as such. The former class can be substitutively chlorinated only at higher temperatures (400–500°) (b_2).[21]

$$CH_3—CH{=}CH_2 \xrightarrow{Cl_2} H_3C—CHCl—CH_2Cl \quad (a)$$



$$(H_3C)_2C{=}CH_2 \xrightarrow{Cl_2} (ClH_2C)(H_3C)C{=}CH_2 + HCl \quad (b_1)$$

$$CH_3—CH{=}CH_2 \xrightarrow{Cl_2} ClH_2C—CH{=}CH_2 + HCl \quad (b_2)$$

In the liquid phase addition of the resulting HCl occurs as a competing reaction to (b_1), but this addition is much suppressed in the gas phase. The large amount of energy liberated on addition of chlorine (about 40 kcal/mole) can induce substitution by chlorine of the primary chlorine-addition products unless strong

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[17] E. M. Terry and L. Eichelberger, *J. Amer. Chem. Soc.*, **47**, 1067 (1925).

[18] E. S. Gould, "Mechanismus und Struktur in der organischen Chemie," Verlag Chemie, Weinheim/Bergstraße, 2nd ed, 1964, pp. (a) 617, (b) 622, (c) 634, (d) 715, (e) 889.

[19] P. B. D. de la Mare, *Quart. Rev. (London)*, **3**, 126 (1949).

[20] R. A. Ogg, *J. Amer. Chem. Soc.*, **57**, 2728 (1935).

[21] H. P. A. Groll and G. Hearne, *Ind. Eng. Chem.*, **31**, 1530 (1939).

cooling is used (cf. Asinger[22]). This substitution by chlorine can be repressed by adding $FeCl_3$ (ca. 0.1–0.3 mole-%) which favorably influences the addition of chlorine.[23]

Ethylene adds chlorine only at low temperatures (−25°);[24] at 20° ca. 90% of more highly chlorinated products are formed. Dichloroethane is obtained in 90% yield[25] when chlorine and ethylene are led through a nozzle cooled to −30°. The reaction still occurs readily at −70°.

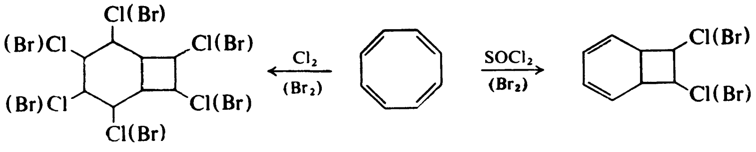
Iron, copper, and antimony chloride,[26] titanium chloride (in pentachloroethane as solvent),[27] and calcium chloride[28] have been used as catalysts favoring addition of Cl_2 to ethylene to yield dichloroethane at elevated temperatures. In the presence of iron-containing bauxite as powder on pumice (catalyst I) or of bauxite grains the size of a pea (catalyst II), a greater proportion of higher chlorination products is formed at low than at higher temperatures.[29]

CCl_4, $CHCl_3$, and CH_2Cl_2 are suitable solvents for addition reactions of chlorine to olefins. Liquid olefins are mostly chlorinated without a solvent.

Considerable heat of reaction must also be removed in additions of bromine, for otherwise substitution by bromine sets in as subsequent or side reaction; in the same way the hydrogen bromide formed can add to the C=C bond. It is thus important to provide cooling and to avoid an excess of bromine.

Addition of iodine to C=C bonds is of less preparative importance. It can be effected in ether, ethanol, CS_2, CCl_4, or aqueous KI, or without a solvent. Iodine-addition products are unstable and most of them lose I_2 even at room temperature. So the discussion that follows here is restricted to addition of chlorine and bromine.

For addition of chlorine the theoretical amount of chlorine is led into the unsaturated compound or a solution thereof, with good cooling, usually at 0° or less; it suffices if the unsaturated compound is only partly in solution. Or one can drop in a solution of chlorine in some suitable solvent. Sulfonyl chloride (SO_2Cl_2) is also very useful for adding chlorine and can be used without solvent or in CCl_4, $CHCl_3$, or CH_2Cl_2; the **addition of chlorine to cyclooctatetraene**[30] can be cited as example:



SO_2Cl_2 (140 g, ca. 1 mole) is allowed to flow into a mixture of cyclooctatetraene (104 g, 1 mole) and CH_2Cl_2 (208 g) at ca. 25°, with stirring, the cooling and rate of addition being adjusted so that the stated temperature is maintained. SO_2 is evolved. The mixture is then

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[22] F. Asinger, "Chemie und Technologie der Monoolefine," Akademie-Verlag, Berlin, 1957, pp. (a) 480, (b) 491.

[23] E. G. Galitzenstein and C. Woolf, *J. Soc. Chem. Ind.* (*London*), **69**, 292 (1950).

[24] H. Bahr and H. Zieler, *Angew. Chem.*, **43**, 233 (1930).

[25] *Ger. Pat.*, 529,524; *Chem. Abstr.*, **25**, 5178 (1931).

[26] *Brit. Pat.* 147,909; *Chem. Abstr.*, **15**, 97 (1921).

[27] *Fr. Pat.* 770,943; *Chem. Abstr.*, **29**, 817 (1935).

[28] U.S. Pat. 2,099,231; *Chem. Abstr.*, **32**, 190 (1938).

[29] I. Gavat, *Ber. Deut. Chem. Ges.*, **76**, 1115 (1943).

[30] W. Reppe and co-workers, *Ann. Chem.*, **560**, 18, 50 (1948).

stirred for a further 1 to 2 h at room temperature and the CH_2Cl_2 is distilled off in a vacuum. The residual brownish oil (175–180 g) is distilled twice in a good oil-pump vacuum, yielding 7,8-dichlorobicyclo[4.2.0]octa-2,4-diene as an almost colorless oil (120 g), b.p. 60°/0.1 mm, 67–68°/1.2 mm; this dimerizes on storage, as does the corresponding dibromo compound. If double the amount of SO_2Cl_2 is used at 0–5° then a tetrachlorobicyclo[4.2.0]octene, m.p. 111–112°, is formed.

If a stream of chlorine is led into a solution of cyclooctatetraene in ten times the quantity of chloroform at −30 to −25° until no more is absorbed and the mixture is left to react for some hours at the stated temperature and then for 8 hours at room temperature, then a hexachlorobicyclooctane, m.p. 126–127°, is obtained together with isomeric liquid hexachloro compounds.

Addition of 1 mole of bromine in twice the amount (by weight) of CH_2Cl_2 to 1 mole of cyclooctatetraene in twice the amount of CH_2Cl_2 at 0–5° gives 7,8-dibromobicyclo[4.2.0]octa-2,4-diene, b.p. 90–91°/1 mm. 2 Moles of bromine in twice its weight of CH_2Cl_2 reacts with 1 mole of cycloctatetraene in ten times the amount of CH_2Cl_2 at 0–5° to yield two tetrabromo compounds of m.p. 147–148° and 94° severally. 3 Moles of bromine in $CHCl_3$ at −20° afford a hexabromide of m.p. 150–151°.

In the addition of chlorine by means of SO_2Cl_2 it may be useful to initiate reaction by preliminary addition of about 3% of the SO_2Cl_2 and cautious warming, the reaction then being maintained by further additions and, if necessary, gentle warming. This method was used for the preparation of 1,2,3-trichloro-2-methylpropane from methallyl chloride.[31]

Addition of chlorine by means of SO_2Cl_2 must be considered as a radical chain reaction and it can be initiated by addition of radical-formers.

Into a solution of the unsaturated compound (0.2 mole) and dibenzoyl peroxide (0.002 mole) in CCl_4 or CH_2Cl_2 is dropped a mixture of about equal amounts of SO_2Cl_2 (ca. 0.15–0.3 mole) and CCl_4 at such a rate that the mixture boils gently; the whole is then boiled for a further hour.

Although, for instance, 1,2-dichloroethylene does not react when boiled for 3 hours with an excess of SO_2Cl_2, reaction sets in at once on addition of the peroxide. By this process one obtains, for instance, 90% of dichloro addition product from cyclohexene, 80–90% from allyl chloride, and 85% from 1,2-dichloroethylene; stilbene affords in this way 45% of the dichloride of m.p. 191–193° and 33% of that of m.p. 90–93°.[32]

For addition of bromine a gaseous unsaturated hydrocarbon can be led into cooled bromine; that is the process for, *e.g.*, synthesis of 1,2-dibromoethane in the laboratory[33] and the preparation of butadiene tetrabromide.[34] Usually, however, a solution of bromine in a suitable solvent (see page 104) is dropped into one of the olefin in the same solvent, with stirring and ice-cooling, until the bromine is no longer decolorized. Sensitive unsaturated compounds are preferably treated with the bromine addition product of a tertiary amine hydrobromide or of dioxane (see pages 112, 113).

Halogen addition to olefins is only slightly hindered when halogen is already attached to carbon other than the doubly bonded atoms; *e.g.*, 96–98% of 1,2,3-tribromopropane is obtained by addition of bromine to allyl bromide in CCl_4 at −5°.[35] Halogen substituents on doubly bonded carbon atoms hinder

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[31] A. Mooradian and J. B. Cloke, *J. Amer. Chem. Soc.*, **68**, 785 (1946).

[32] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **61**, 3432 (1939).

[33] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Verlag W. de Gruyter & Co., Berlin, 38th ed, 1958, pp. (a) 86, (b) 88, (c) 92, (d) 98, (e) 109, (f) 111, (g) 112, (h) 184, (i) 340.

[34] J. Thiele, *Ann. Chem.*, **308**, 337 (1899).

[35] J. R. Johnson and W. L. McEwen, "Organische Synthesen," F. Vieweg & Sohn, Brunswick (Germany), 1937, p. 522; *Org. Syn.*, Coll. Vol. 1, 2nd ed, p. 521.

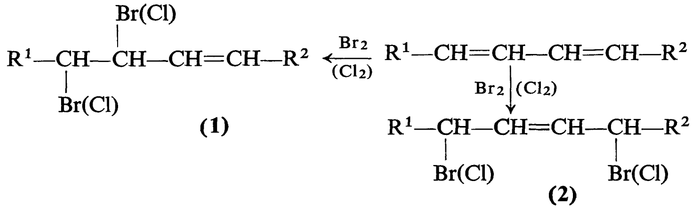
addition of halogen increasingly in the series —CH=CH⁻, —CH=CHX, CHX=CHX, $CHX=CX_2$, $CX_2=CX_2$;[36] the hindrance is least when X = F and greatest when X = Br. Iodoolefins exchange their iodine for another halogen even in the cold; *e.g.*, 1,1-diiodoethylene and bromine (or chlorine) in CCl_4 afford 1,1,1,2-tetra-bromo(or-chloro) ethane.[37] Addition of bromine or chlorine to polychloro- or polybromo-olefins is best achieved photochemically: in such reactions the calculated amount of bromine or chlorine is added to the liquid olefin, or to a solution of the olefin in CCl_4, under ultraviolet irradiation at not more than 25°. Addition of chlorine and bromine to fluorinated ethylenes occurs with very good yields, particularly in sunlight.[41a] Iodine is added to tetrafluoroethylene in a autoclave at 150°, again giving a good yield.[38]

Stilbene adds bromine relatively slowly. *trans*-Addition of bromine, which is usual with olefins, occurs with *cis*-stilbene in cold CS_2 in the dark, affording 83% of (±)-1,2-dibromo-1,2-diphenylethane (α,α'-dibromobibenzyl), m.p. 110–111°, together with a little of the *meso*-isomer, m.p. 236°. The former product is converted into the latter by, *e.g.*, bromine or iodine in CCl_4 in diffuse daylight.[39] The *meso*-compound arises as main product on bromination of *trans*-stilbene in CS_2[40] or ether.[41] (+)-m ,.p. 93–94°, and *meso*-1,2-dichloro-1,2-diphenylethane ($\alpha.\alpha'$-dichlorobibenzyl), m.p. 191–193°, are both formed in the reaction of *trans*-stilbene with a saturated solution of chlorine in anhydrous ether under the influence of ultraviolet or sun-light.[39,41]

1,1-Diphenyl- and 1,1,2-triphenyl-ethylene react very readily with bromine;[42] tetraphenylethylene still adds chlorine, but not bromine.[43] Styrene adds bromine easily.

Styrene dibromide [(1,2-dibromoethyl)benzene], pure enough for later conversion into phenylacetylene, is obtained by slowly dropping a solution of bromine (80 g) in CCl_4 (100ml) into one of styrene (52 g) in CCl_4 (50 ml) with vigorous stirring at −10 to −15°; towards the end of the reaction the mixture is cooled in water or ice to prevent its premature solidification. After a short time the product is filtered off and dried in the air (yield 90–95%).[44]

4. Addition of halogen to polyenes



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[36] B. E. Swedlund and P. W. Robertson, *J. Chem. Soc.*, **1947**, 630.

[37] H. P. Kaufmann, *Ber. Deut. Chem. Ges.*, **55**, 257 (1922).

[38] R. N. Haszeldine and K. Leedham, *J. Chem. Soc.*, **1953**, 1550.

[39] R. E. Buckles, W. E. Steinmetz, and N. G. Wheeler, *J. Amer. Chem. Soc.*, **72**, 2497 (1950).

[40] P. Pfeiffer, *Ber. Deut. Chem. Ges.*, **45**, 1817 (1912).

[41] L. I. Smith and M. M. Falkop, *Org. Syn.*, Coll. Vol. III, 350 (1955).

[42] J. Meisenheimer, *Ann. Chem.*, **456**, 141 (1927).

[43] J. F. Norris, P. Thomas, and B. M. Brown, *Ber. Deut. Chem. Ges.*, **43**, 2950 (1910).

[44] H. Fiesselmann and K. Sasse, *Chem. Ber.*, **89**, 1786 (1956).

Addition of 1 mole of bromine (or chlorine) to polyenes (for a discussion of the mechanism see Gould[18c]) generally leads to a mixture of α,β- **(1)** and α,δ-dibromo **(2)** (or -dichloro) compounds, the proportions of **(1)** and **(2)** depending on the solvent and the natures of R^1 and R^2. For example, exclusively 1,4-addition occurs when cyclopentadiene is brominated in light petroleum at −30 to −40°; this affords a mixture of *cis*- and *trans*-3,5-dibromocyclopentene;[45] of which the former is unstable at room temperature. The crystalline *cis*-3,5-dibromocyclopentene (m.p. 45°) rearranges partially, when distilled at 2 mm, to the 1,2-addition product (*trans*-3,4-dibromocyclopentene).[46] Similar rearrangements are also found[47] with, for instance, halogen adducts of butadiene, as is illustrated in the following preparative details.

If chlorine (150 g) in dry CCl_4 (750 ml) is added to butadiene (180 g) in dry CCl_4 (350 ml) during 45 min with stirring and cooling in dry ice–alcohol (the reaction temperature should be less than −5°), subsequent removal of the solvent and distillation of the residue through a column gives **3,4-dichloro-1-butene** (35 g), b.p. 123°/766 mm, and **1,4-dichloro-2-butene** (70 g), b.p. 159°/766 mm.[48] Leading butadiene and chlorine in the volume ratio 3 : 1 into CCl_4 or a mixture of CCl_4 and pyridine with cooling by dry ice–acetone yields only *trans*-1,4-dichloro-2-butene. The corresponding *cis*-compound[49] is obtained from *cis*-2-butene-1,4-diol in pyridine by PCl_3 at 0°.

If bromine (26 ml) in CCl_4 (200 ml) is dropped into a solution of butadiene (45 g) in CCl_4 (500 ml) at −20° with stirring during 45 min, removal of the solvent and recrystallization of the residue from light petroleum gives **1,4-dibromo-2-butene** (72 g), m.p. 54°,[48] which, analogously to the 1,4-dichloro compound, has the *trans*-configuration.[50] The same compound is obtained [51]on b;omination of butadiene by 1 mole of bromine in chloroform at −30°. A large amount (53.2%) of 3,4-dibromo-1-butene is obtained along with the 1,4-adduct (46.8%) if 1 mole of bromine is added during 2 h to 4 moles of butadiene in methylcyclopentane (125 ml) at −20°.[52]

Further information about the addition of halogen to butadiene is given in some earlier papers.[34,47]

The more C=C groups are present in a polyene, the more difficult it is to saturate all the C=C bonds with halogen and the greater is the tendency to loss of hydrogen halide. Addition of chlorine or bromine to the polyene occurs in such a way that the longest stretch of conjugation is retained; *e.g.*, the phenylvinyl conjugation on addition to phenylbutadiene, and the butadiene conjugation on addition to hexatriene.[53]

Polyenecarboxylic acids add bromine most easily at the C=C bond furthest removed from the COOH group.[54]

5. Addition of halogen to steroids

The products of addition of bromine to unsaturated steroids play a part, as intermediates, in steroid rearrangements. The reaction is carried out in glacial acetic acid, ether, or chloroform at temperatures below 20° and leads

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[45] G. W. Barber and J. English Jr., *J. Amer. Chem. Soc.*, **73**, 747 (1951).
[46] W. G. Young, H. K. Hall Jr., and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 4358 (1956).
[47] E. H. Farmer, C. D. Lawrence, and J. F. Thorpe, *J. Chem. Soc.*, **1928**, 730.
[48] L. N. Owen, *J. Chem. Soc.*, **1949**, 243.
[49] K. Mislow and H. M. Hellmann, *J. Amer. Chem. Soc.*, **73**, 244 (1951).
[50] K. Mislow, *J. Amer. Chem. Soc.*, **75**, 2512 (1953).
[51] E. M. Shantz, *J. Amer. Chem. Soc.*, **68**, 2557 (1946).
[52] J. C. Hillyer and C. H. Ice, U.S. Pat. 483,049 (1949); *Chem. Abstr.*, **44**, 652 (1950).
[53] P. B. D. de la Mare, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, **1948**, 21.
[54] O. Dann, *Chem. Ber.*, **80**, 427 (1947).

to the *trans*-addition that is customary in addition of bromine to C=C bonds. The *trans*-diaxial dibromides that are the primary products can be rearranged to the *trans*-diequatorial isomers. For discussion and references see Fieser and Fieser.[55a] It should, however, also be mentioned that iodobenzene dichloride, $C_6H_5ICl_2$, in chloroform is a useful reagent for adding chlorine to unsaturated steroids, *e.g.*, to cholesterol.[56]

6. Addition of halogen to unsaturated alcohols or ethers

It is usually possible to add bromine to unsaturated alcohols in dilute solution at 0–25° without replacement of the hydroxyl group.

Thus 2,3-dibromo-1-propanol is obtained[57] by treating allyl alcohol in ten times its volume of CCl_4 with a solution of the calculated amount of bromine in double its volume of CCl_4.

Addition of bromine to alkyl vinyl ethers is usually carried out in CCl_4 or $CHCl_3$ with cooling to $-5°$ to 0°. The preparation of 1,2-dibromoethyl methyl ether from methyl vinyl ether is described in detail in "Synthesen der organischen Verbindungen",[58] as also is the strongly exothermic addition of chlorine. 1,2-Dichloroethyl ethyl ether is obtained from ethyl vinyl ether below 30° (cooling with ice and salt).[59] This method, which has been studied with numerous examples,[60] is generally applicable, but its preparative importance in any one case depends on ready accessibility of the vinyl ether, *e.g.*, from acetylene, the alcohol, and KOH in an autoclave.[61] α,β-Dihalogeno ethers are interesting intermediates; *e.g.*, with alcoholic KOH they yield α-halogeno aldehyde acetals.[62]

1 mole of bromine is dropped, at first slowly and then rapidly, into a vigorously stirred solution of 1 mole of ethyl vinyl ether in 4 moles of $CHCl_3$ at $-15°$. When decoloration is complete, the chloroform is distilled off, and fractionation of the residue gives **1,2-dibromoethyl ethyl ether** (88.5%), b.p. 80°/20 mm.

1 mole of this product, dissolved in 3.5 moles of absolute ethanol, is dropped into a solution of 1.8 moles of KOH in 8.5 moles of absolute ethanol, at 0° with stirring. The mixture was boiled for 5 min (water-bath), then poured on ice, and the bromo acetal layer was separated. The aqueous layer was extracted with ether and the bromo acetal layer was combined with the ether and the whole dried over K_2CO_3. After removal of the ether and ethanol by distillation, fractionation in a vacuum gave **2-bromoacetaldehyde diethyl acetal** (83%), b.p. 63°/14 mm.[63]

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[55] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, pp. (a) 35–41, (b) 280–294, (c) 321–325.

[56] C. J. Berg and E. S. Wallis, *J. Biol. Chem.*, **162**, 683 (1946).

[57] W. G. H. Edwards and R. Hodges, *J. Chem. Soc.*, **1953**, 3428.

[58] M. F. Schostakowski and P. W. Tjupajew, "Synthesen der organischen Verbindungen," VEB Verlag Technik, Berlin, Porta-Verlag, Munich, 1956, Vol. 2, p. 81.

[59] M. F. Schostakowski and F. P. Sidelkowskaja, "Synthesen der organischen Verbindungen," VEB Verlag Technik, Berlin, 1959, Vol. 1, p. 69.

[60] M. F. Shostakovski, *Zh. Obshch. Khim.*, **13**, 1 (1943); *Dokl. Akad. Nauk S.S.S.R.*, **41**, 124 (1943); *Zh. Obshch. Khim.*, **14**, 102 (1944); **17**, 957 (1947); *Chem. Abstr.*, **38**, 330 (1944); **39**, 905 (1945); **42**, 4520 (1948).

[61] A. Je. Faworski and M. F. Schostakowski, "Synthesen der organischen Verbindungen," VEB Verlag Technik, Berlin, 1959, Vol. 1, p. 40.

[62] A. Je Favorski and M. N. Shchukina, *Chem. Abstr.*, **40**, 4347 (1946).

[63] H. Baganz and E. Brinckmann, *Chem. Ber.*, **86**, 1320 (1953).

1,2-Diacetoxy-1-alkoxyalkanes and 1,1,2-triacetoxyethane[64] are easily prepared by adding 1 mole of bromine to 1 mole of a vinyl ether or of vinyl acetate, respectively, in acetic anhydride containing 2 moles of anhydrous sodium acetate. This triacetate can be converted, without isolation, into DL-serine by a modified Strecker synthesis.[65]

It is not possible to add iodine to alkyl vinyl ethers as it causes polymerization.

Addition of halogens to enol acetates of aldehydes and ketones for preparation of α-halogeno aldehydes and ketones is described on page 187.

Particularly mild methods of bromination are often wanted for treatment of unsaturated alcohols and ethers. One such is the use of pyridine dibromide hydrobromide, which, for example, adds bromine selectively to the C=C bond in an unsaturated side chain of a phenyl ether such as safrole which is brominated in the benzene ring when treated with molecular bromine alone. This reagent may be prepared *in situ*, by adding the calculated amount of bromine to a solution of the substance to be brominated and a pyridine salt in glacial acetic acid.

Pyridine dibromide hydrobromide ($C_5H_5N \cdot HBr \cdot Br_2$):[66] Pure pyridine is treated with an excess of hydrochloric acid and saturated with bromine. A dark brown oil is formed. The aqueous layer is removed. The oil rapidly crystallizes when kept in a freezing mixture; and the oil sucked off from these crystals gives a second crop when cooled again. The solid products are washed with $CHCl_3$ and dissolved in alcohol at 40–50°, from which they crystallize on cooling.

A second method starts from pyridine hydrobromide: Bromine (1 mole) in glacial acetic acid (160 g) is added to a solution of pyridine hydrobromide (1 mole) in glacial acetic acid (240 g) with stirring at about 60°. On slow cooling of this mixture, red needles or prisms (about 300 g; m.p. 132–134°) crystallize; they are collected under suction and dried in a vacuum-desiccator.[67]

It is possible simply to add 1 mole of bromine to 1 mole of pyridine in 48% hydrobromic acid (2 moles).[68,69]

When α-vinylbenzyl alcohol reacts with bromine in dry $CHCl_3$, CCl_4, or CS_2, (1,2,3-tribromopropyl)benzene is formed exclusively; however, carrying out the reaction with pyridine hydrobromide dibromide in glacial acetic acid at 12–15° leads mainly to addition of bromine, which results in α-(1,2-dibromoethyl)benzyl alcohol.[70] Analogously, but without a solvent, allyl alcohol gives 2,3-dibromo-1-propanol.[71]

The **tetramethylammonium bromide–bromine adducts**[72] act similarly.

The eutectic of the two adducts $(CH_3)_4NBr_3$ and $(CH_3)_4NBr_9$ has the composition $(CH_3)_4NBr_{5.6}$ and melts at 15.8°. Between $Br_{5.1}$ and $Br_{6.2}$ the mixture is liquid above 25°.

Bromine (400 g, 2.5 moles) is added to a solution of $(CH_3)_4NBr$ (154 g, 1 mole) in water (500 ml) in 15 min with stirring and cooling to 20–30°. The dark red oil (*d* 2.33) that is formed is removed through a separatory funnel; the yield is 90%, but becomes about 100% if the aqueous layer is re-used.

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[64] H. Gross, K.-P. Hilgetag, J. Gloede, and H. Geipel, *Chem. Ber.*, **98**, 1673 (1965).

[65] H. Geipel, J. Gloede, K.-P. Hilgetag, and H. Gross, *Chem. Ber.*, **98**, 1677 (1965).

[66] K. W. Rosenmund and W. Kuhnhenn, *Ber. Deut. Chem. Ges.*, **56**, 1262 (1923); cf. S. M. E. Englert and S. M. McElvain, *J. Amer. Chem. Soc.*, **51**, 863 (1929).

[67] S. M. E. Englert and S. M. McElvain, *J. Amer. Chem. Soc.*, **51**, 865 (1929).

[68] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, **70**, 417 (1948).

[69] C. L. Arcus and H. E. Strauss, *J. Chem. Soc.*, **1952**, 2670.

[70] C. L. Arcus and H. E. Strauss, *J. Chem. Soc.*, **1952**, 2669.

[71] M. J. Frazer and W. Gerrard, *J. Chem. Soc.*, **1955**, 3628.

[72] L. Farkas and O. Schächter, *J. Amer. Chem. Soc.*, **71**, 2252 (1949).

The bromine reagent (222 g) is dropped into allyl alcohol (58 g, 1 mole) during 40 min with ice cooling and stirring at 40°. Tetramethylammonium bromide is precipitated; it is filtered off and washed with ether, being recovered almost quantitatively. The filtrate and the ether used for washing are united. Distillation then affords **2,3-dibromo-1-propanol** in 85% yield.

Dioxane dibromide, $C_4H_8O_2{\cdot}Br_2$, is also a mild brominating agent.

Gradually adding 25 g of dioxan dibromide to 10.4 g of styrene with cooling in running water and subsequently diluting the mixture with water affords 100% of **styrene dibromide** without any nuclear substitution.[73]

Dioxane dibromide (25 g) and 2,4-hexadiene (11.8 ml) give 86% of the 1,4-adduct, **2,5-dibromo-3-hexene.**

Similarly good yields of bromine adducts are obtained from acrolein, acrylic acid and its esters, acrylonitrile, and vinyl acetate.

7. Addition of thiocyanogen to unsaturated compounds

Thiocyanogen, $(SCN)_2$, adds at room temperature to a large number of unsaturated compounds such as ethylene, allyl alcohol, oleic acid, stilbene, styrene, anethole, and acetylene[74] in good yield, but not to, *e.g.*, α,β-unsaturated acids. Addition is, in general, slow (12 h) at room temperature. In many cases, as, for example, with ethylene, it does not occur without irradiation. Numerous references to the addition of thiocyanogen to isoprene, butadiene, terpenes, and fats have been recorded by Kaufmann.[75] Addition of thiocyanogen or thiocyanogen iodide (ISCN) to unsaturated compounds can be used for analytical determination of the latter[76,77] and has the advantage over determination by means of halogen addition (I_2, Br_2, ICl) that no substitution reaction occurs.

Anhydrous acetic acid containing some acetic anhydride provides the most **stable thiocyanogen solutions.** Very pure lead thiocyanate is shaken in the dark with bromine in a mixture of 6 parts by volume of acetic acid (distilled from 1% of chromic trioxide), 1 part by volume of acetic anhydride, and 3 parts by volume of pure anhydrous CCl_4, all contained in dry vessels that give up no alkali, *i.e.*, that have been previously boiled out with hydrochloric acid. Filtration of the mixture through a dry filter, with exclusion of moisture, gives clear thiocyanogen solutions that are stable for several weeks.

The $(SCN)_2$ content of the solutions is determined by treatment of a portion with an excess of 10% aqueous potassium iodide and titration of the liberated iodine with thiosulfate:

$$2\,KI + (SCN)_2 \longrightarrow 2\,KSCN + I_2$$

Addition of $(SCN)_2$ to unsaturated acids has a place in the analysis of fats and drying oils. Whereas iodine adds to all C=C bonds, $(SCN)_2$ is only partially added. From the differences between iodine numbers and thiocyanate numbers (see page 114) conclusions can be drawn about, *e.g.*, the composition of fatty acid mixtures containing oleic, linoleic, and linolenic acid. For details of the technique see Kaufmann.[78b]

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[73] A. W. Dombrovski, *Zh. Obshch. Khim.*, **24**, 610 (1954); *Chem. Abstr.*, **49**, 5484 (1955).

[74] H. P. Kaufmann and J. Liepe, *Arch. Pharm.*, **33**, 139 (1923).

[75] H. P. Kaufmann, "Neuere Methoden der präparativen organischen Chemie," Verlag Chemie, Berlin, 1944, Vol. 1, p. 241.

[76] H. P. Kaufmann and H. Grosse-Oetringhaus, *Ber. Deut. Chem. Ges.*, **70**, 911 (1937).

[77] H. P. Kaufmann, "Studien auf dem Fettgebiet," Verlag Chemie, Berlin, 1935, p. 73.

[78] H. P. Kaufmann, "Analyse der Fette und Fettprodukte," Springer-Verlag, Berlin–Göttingen–Heidelberg, 1958, Vol. 1, pp. (a) 570–584, (b) 589–595.

8. Addition of halogen to unsaturated carboxylic acids

The rate of addition of halogen to unsaturated fatty acids decreases in the order $Cl_2 > Br_2 > I_2$. Unsaturated acids and their esters and amides usually give good yields of bromine adducts at temperatures as low as −5 to −25° in the usual solvents — esters also without solvents — irradiation having considerable accelerating effect.

Crotonic acid adds bromine in CCl_4 under irradiation at 20°, finally at 40°, giving a 90% yield of **2,3-dibromobutyric acid.**[79]

When the theoretical amount of bromine is dropped into ethyl acrylate with stirring at 5–10° (ice cooling) and the reaction is allowed to proceed for 5 h at room temperature, 98% of **ethyl 2,3-dibromopropionate** is obtained.[80]

This ester, and also 2,3-dibromopropionitrile (obtained from acrylonitrile under similar conditions), exchange their 3-bromine atoms readily for alkoxyl groups, and the resulting α-bromo-β-alkoxy esters or nitriles are intermediates in the synthesis of α-amino-β-hydroxy acids — in the above cases for serine.[81]

Addition of bromine to multiply unsaturated fatty acids such as linoleic, linolenic, and arachidic acid, is used for quantitative or approximate analysis of fatty acid mixtures.[82]

In alcoholic solution free iodine adds hardly at all, or at most very slowly, to unsaturated fatty acids. The addition is accelerated by presence of mercuric chloride, a phenomenon that was used for the now outdated determination of iodine number (I no.).[83,84]

The addition of halogen to unsaturated acids is an important item in analysis of fats. The **iodine number** (I no.) denotes the mumber of parts of halogen, calculated as iodine, that are added to 100 parts of a fat under conditions that must be exactly maintained. In the method most used for determination of iodine numbers a stable solution of ICl in glacial acetic acid–CCl_4,[85] IBr in glacial acetic acid,[86] or NaBr and Br_2 in methanol[87] is allowed to react with a solution of the fat or oil in CCl_4 or $CHCl_3$ for 1–2 h, then 10% potassium iodide solution is added, and the iodine liberated by the excess of ICl, IBr, or Br_2 is back-titrated with thiosulfate. The (German) DGF Standard methods and various similar procedures have been collected by Kaufmann.[78a]

Bromine adds to unsaturated dicarboxylic acids in hot aqueous solution.

For instance, according to a description in *Organic Syntheses*,[88] 2,3-dibromosuccinic acid is obtained when the calculated amount of bromine is dropped into a boiling mixture of fumaric acid and double the amount of water.

Reaction of ordinary (*trans*-)cinnamic acid under the usual conditions, and also under irradiation, leads to *trans*-addition of bromine with formation of the high-melting 2,3-dibromo-3-phenylpropionic acid (m.p. ca. 200° with

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[79] P. Seifert and co-workers, *Helv. Chim. Acta*, **33**, 725 (1950).

[80] H. Bretschneider and co-workers, *Monatsh. Chem.*, **84**, 1087 (1953).

[81] H. Brockmann and H. Musso, *Chem. Ber.*, **87**, 590 (1954); J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

[82] G. Y. Shinowara and J. B. Brown, *J. Amer. Chem. Soc.*, **60**, 2734 (1938).

[83] (a) B. von Hübl, *Dinglers Polytech. J.*, **253**, 281 (1884); (b) J. Ephraim, *Z. Angew. Chem.*, **8**, 254 (1895).

[84] J. J. A. Wijs, *Z. angew. Chem.*, **11**, 291 (1898).

[85] J. J. A. Wijs, *Ber. Deut. Chem. Ges.*, **31**, 750 (1898).

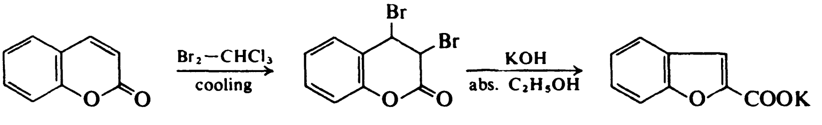
[86] J. Hanus, *Z Unters. Nahrungs- u. Genußmittel*, **4**, 913 (1901).

[87] H. P. Kaufmann, *Z. Unters. Lebensmittel*, **51**, 3 (1926).

[88] H. S. Rhinesmith, *Org. Syn.*, Coll. Vol. II, 177 (1943).

decomposition). *cis*-Cinnamic acid adds bromine in CS_2 in the dark, giving about 70% of the high-melting and about 30% of the diastereoisomeric lower-melting 2,3-dibromo-3-phenylpropionic acid.[89,90]

The preparation of coumarin dibromide from 1 mole of coumarin and 1 mole of bromine in chloroform at room temperature is described in detail in *Organic Syntheses*.[91] The dibromide is converted by alkali into coumarilic acid.



Whereas acrylonitrile adds bromine easily to give 2,3-dibromopropionitrile, it behaves completely differently towards chlorine. There is no reaction when chlorine is led into acrylonitrile unless the mixture is placed in direct sunlight, in which case a white polymeric mass is formed together with a liquid that has an inhomogeneous boiling point. If, however, acrylonitrile is chlorinated in solution in pyridine or some other heterocyclic base, smooth addition of chlorine occurs, giving an almost quantitative yield of **2,3-dichloropropionitrile**:

Chlorine is led into a water-cooled mixture of acrylonitrile (55 g) and pyridine (14 g) until the weight increase amounts to 71 g. The mixture is then shaken with water, dried over $CaCl_2$, and distilled, giving 2,3-dichloropropionitrile (118 g, 95%), b.p. 61°/13 mm. Further chlorination of this product in sunlight affords 2,2,3-trichloropropionitrile with some of the 2,3,3-trichloro isomer.

2-Chloroacrylonitrile is obtained by removal of HCl from 2,3-dichloropropionitrile by sodium acetate in methanol; it can be distilled at atmospheric pressure (b.p. 87–89°/736 mm) if a little hydroquinone is added to prevent polymerization.[92]

9. Addition of halogen to C≡C bonds

Acetylene–chlorine mixtures explode violently under even weak irradiation. The explosion limit lies at a 10% chlorine content. To minimise the danger of explosion chlorine must be added continuously and with cooling.

If chlorine and acetylene (molar ratio 2 : 1) are led over iron granules at 60°, 1,1,2,2-tetrachloroethane is formed almost quantitatively.[1d] Use of an excess of acetylene and active charcoal at 40–50° leads to a product composed of *cis*-1,2-dichloroethylene 90% and 1,1,2,2-tetrachloroethane 10%.[1d] 97% of *trans*-1,2-dichloroethylene is obtained if acetylene is led into a solution of $CuCl_2$ and Cu_2Cl_2 in 20% hydrochloric acid at 85°/250 mm.[93]

If *trans*-1,2-dichloroethylene (300 g) is allowed to react with a little (18 g) bromine for 24 h in the dark, an equilibrium mixture of the *trans*- and the *cis*-form is obtained from which the latter (b.p. 59.6°/768 mm) can be separated by fractional distillation.[94] To exclude oxidation it is recommended that such mixtures be fractionated under carbon dioxide.[95]

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[89] C. Liebermann, *Ber. Deut. Chem. Ges.*, **27**, 2039 (1894).

[90] E. Grovenstein Jr. and D. E. Lee, *J. Amer. Chem. Soc.*, **75**, 2640 (1953).

[91] R. C. Fuson, J. W. Kneisley, and E. W. Kaiser, *Org. Syn.*, Coll. Vol. III, 209 (1955).

[92] H. Brintzinger, K. Pfannstiel, and H. Koddebusch, *Angew. Chem.*, **60**, 311 (1948).

[93] A. Jacobowsky and K. Sennewald, Ger. Pat. 969,191; *Chem. Abstr.*, **54**, 18352 (1960).

[94] J. L. Jones and R. L. Taylor, *J. Amer. Chem. Soc.*, **62**, 3480 (1940).

[95] R. E. Wood and R. G. Dickinson, *J. Amer. Chem. Soc.*, **61**, 3259 (1939).

Adding bromine to a saturated solution of acetylene in anhydrous ethanol gives, *inter alia*, a mixture of *cis*- and *trans*-1,2-dibromoethylene.[96] 1,2-Dibromo- and 1,2-diiodo-, as well as 1,2-dichloro-ethylene (see above), are formed in very good yield if acetylene is led into a solution of Cu(II) salts in 20% aqueous HCl or 50% aqueous HBr at 60–100° and diminished pressure (300 mm).[97]

When acetylene is passed through, successively, concentrated nitric acid containing copper nitrate, sodium hydroxide solution, ice-cooled bromine, aqueous sodium hydrogen sulfite, and water and is then dried, 95% of 1,1,2,2-tetrabromoethane, b.p. 124–126°/15 mm, is obtained.[98-100]

Addition of iodine to C≡C bonds is often easier than to C=C bonds; for instance, *trans*-1,2-diiodoethylene, m.p. 73°, is readily obtained by leading acetylene into a solution of iodine in absolute alcohol at room temperature.[101,102] This product can be rearranged to the liquid *cis*-form, b.p. 185°, by heating it in a bomb-tube[103] or to 1,1-diiodoethylene by the action of finely divided sodium in ether for 21 days.[102]

1,2-Diodoethylene can be obtained by leading acetylene into a 0,2N-solution of iodine in aqueous potassium iodide. The mixture is kept under a slight over-pressure of acetylene for 2 days, at the end of which 96% of the iodine has reacted and 91% of crystalline *trans*-diiodoethylene can be isolated.[104]

Acetylenes react, in general, less readily than olefins with chlorine and bromine, but this difference in reaction rates is decreased by the presence of electron-attracting groups, *e.g.*, carboxyl, next to the C≡C bond. If two such groups are present, then addition of halogen to the C≡C bond is actually faster than to the C=C bond: thus diethyl acetylenedicarboxylate adds chlorine in acetic acid at 25° 60 times as fast as does diethyl fumarate. Whereas α,β-unsaturated carboxylic acids do not add iodine, propargylic acid is more reactive, adding iodine in boiling ethereal solution.[105] If bromine vapor is drawn in a stream of air slowly through a solution of acetylenedicarboxylic acid in twice the amount of water, with ice-cooling and exclusion of light, the main product obtained is dibromofumaric acid, together with some dibromomaleic acid.[106,107] Dibromomaleic and dichloromaleic acid are prepared[108] by nitric acid (*d* 1.52) oxidation of the 3-formyl-2,3-dihalogenoacrylic acid (HOOC—CX=CX—CHO) obtained from furfuraldehyde and the appropriate halogen.[109,110]

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[96] A. Sabanejeff, *Ann. Chem.*, **178**, 113 (1875).

[97] Brit. Pat. 736,375; *Chem. Abstr.* **50**, 8705 (1956).

[98] A. Sabanejeff, *Ann. Chem.*, **216**, 253 (1883).

[99] R. Anschütz, *Ann. Chem.*, **221**, 133 (1883).

[100] K. Elbs and J. Newman, *J. Prakt. Chem.*, [ii], **58**, 245 (1898).

[101] H. Biltz, *Ber. Deut. Chem. Ges.*, **30**, 1207 (1897).

[102] H. P. Kaufmann, *Ber. Deut. Chem. Ges.*, **55**, 254 (1922).

[103] H. P. Kaufmann, *Ber. Deut. Chem. Ges.*, **55**, 266 (1922).

[104] A. C. Pappas, *Acta Chem. Scand.*, **2**, 292 (1948).

[105] B. Homolka and F. Stolz, *Ber. Deut. Chem. Ges.*, **18**, 2284 (1885).

[106] E. Ott, *Ann. Chem.*, **392**, 267 (1912).

[107] R. E. Lutz, *J. Amer. Chem. Soc.*, **52**, 3416 (1930).

[108] A. Salmony and H. Simonis, *Ber. Deut. Chem. Ges.*, **38**, 2583, 2588 (1905).

[109] H. Simonis, *Ber. Deut. Chem. Ges.*, **32**, 2084 (1899).

[110] Y. Hachihama, T. Shono, and S. Ikeda, *J. Org. Chem.*, **29**, 1371 (1964).

Phenylacetylene adds 1 mole of bromine in strongly cooled chloroform, yielding 78% of α,β-dibromostyrene.[111] If bromine is added to the ice-cooled chloroform solution until a permanent bromine coloration is obtained, then there results a 92% yield of (1,1,2,2-tetrabromoethyl)benzene, m.p. 74–74.5°.[112] The silver salt of phenylacetylene is readily converted by iodine in potassium iodide solution into triiodostyrene.[113]

10. Addition of halogen to aromatic hydrocarbons

There are in principle three possibilities for reaction of halogens with aromatic hydrocarbons, namely, addition, substitution in the nucleus, and substitution in a side chain. The last of these is discussed on pages 152 and 157. Substitution of benzene by chlorine or bromine is an ionic reaction,[114] whereas photochemical or peroxide-catalyzed addition of these halogens involves a radical-chain mechanism.[115] Substitution in the side chain also proceeds by a radical mechanism,[116] addition rather than side-chain substitution being favored by higher chlorine concentrations.[115]

When pure naphthalene is treated in CCl_4 with bromine at room temperature, addition of bromine is greatly favored by light and peroxides;[117] the same is true for pure phenanthrene and bromine.[118]

Addition of fluorine to aromatic hydrocarbons is usually associated with simultaneous substitution. On fluorination of hexachlorobenzene in CCl_4 at 0° two crystalline adducts were isolated, namely, hexachlorotetrafluorocyclohexene and hexachlorohexafluorocyclohexane.[119]

Addition of 3 moles of chlorine to benzene leads to 1,2,3,4,5,6-hexachlorocyclohexanes. If the cyclohexane ring is in its more stable chair conformation eight isomers are possible, of which five have so far been isolated.[120,121] One of these, γ-hexachlorocyclohexane, has become a large-scale commercial insecticide.[122]

The addition is accelerated by irradiation (500-w lamp, UV) and radical-formers. Catalysts such as iron, iron chloride, antimony chloride, and iodine favor substitution by chlorine and so must be excluded. The reaction is exothermic and the temperature must be kept at 50–60° by cooling. The β-isomer is the predominant product; when it crystallizes out the reaction is broken off, unchanged benzene is removed, and the mixture of isomers is treated with about its own weight of methanol. The α- and β-isomer are relatively insoluble in methanol, and the γ-isomer crystallizes when the extract is concentrated.

Systematic attempts to improve the yield of γ-isomer have been reported.[123] Studies were made of the effect of adding compounds such as methyl chloride, chloroform, ethylene, and CS_2 that undergo a chain reaction with chlorine, and of adding radical-formers such as

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[111] J. V. Nef, *Ann. Chem.*, **308**, 273 (1899).

[112] M. S. Newman and H. E. Connor, *J. Amer. Chem. Soc.*, **72**, 4003 (1950).

[113] C. Liebermann and H. Sachse, *Ber. Deut. Chem. Ges.*, **24**, 4116 (1891).

[114] C. C. Price, *Chem. Rev.*, **29**, 37 (1941).

[115] M. S. Kharasch and M. G. Berkman, *J. Org. Chem.*, **6**, 810 (1941).

[116] M. S. Kharasch, P. C. White, and F. R. Mayo, *J. Org. Chem.*, **3**, 33 (1938).

[117] F. R. Mayo and W. B. Hardy, *J. Amer. Chem. Soc.*, **74**, 911 (1952).

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[119] L. A. Bigelow and J. H. Pearson, *J. Amer. Chem. Soc.*, **56**, 2773 (1934).

[120] T. van der Linden, *Ber. Deut. Chem. Ges.*, **45**, 236 (1912).

[121] K. C. Kauer, R. P. Du Vall, and F. N. Alquist, *Ind. Eng. Chem., Ind. Ed.*, **39**, 1335 (1947).

[122] R. Riemschneider, *Pharmazie*, 9th Beiheft, 1st Suppl. Vol., p. 728 (1950).

[123] W. Langenbeck, G. Losse, and H. Fürst, *Chem. Techn.*, **4**, 247 (1952).

perbenzoic acid, bis(hydroxycyclohexyl) peroxide, and tetraisopentyltin, all in weak diffuse daylight at 20°; the radical-formers gave increased addition of chlorine, even in the dark, and a slightly larger proportion of γ-isomer; both types of additive increased the rate of reaction. The proportion of γ-isomer could not be increased by adding inorganic substances; some, such as iodine and sodium iodate, hindered addition of chlorine, whereupon it became possible to isolate tetrachlorocyclohexene from the chlorination mixtures.[124] In experiments in the dark, at 20°, with reaction times and rate of passage of chlorine kept constant, di-*p*-toluoyl peroxide, bis(diphenylacetyl) peroxide, and bis(oxycyclohexyl) peroxide were particularly effective in accelerating addition of chlorine to benzene; and the content of γ-isomer in the hexachlorocyclohexane thus obtained was somewhat greater than was obtained by chlorination under illumination.[125] The various current technical processes, in which 12 to 17% of γ-isomer is formed, correspond in the main to the laboratory methods described by Matthews[126] in the 1890's.

Experimental details for separation of the isomers by fractional distillation and crystallization are given by Riemschneider[122] and by Schwabe *et al.*;[127] Fürst and Dietz[128] have recorded the evaluation of the almost always insecticidally less valuable isomers.

On reaction of liquid chlorine with benzene in a sealed tube under irradiation the most varied products of substitution and addition were found,[129] up to the fully chlorinated dodecachlorocyclohexane, C_6Cl_{12}.

In the absence of catalysts and in the dark, pure benzene does not react with bromine, as is the case also with chlorine. Photochemical addition of bromine, like that of chlorine, is a radical chain reaction.[130,131] Bromine has a more powerful substituting action than chlorine, and its rate of addition is slower.[132] At low temperatures light and addition of peroxides favor addition of bromine. To date, two isomeric hexabromocyclohexanes have been isolated, by very slow addition of bromine to benzene irradiated at 0°; 1% sodium hydroxide solution must be placed under the benzene and frequently renewed; even so, yields are poor.[126b,133]

Bromine adducts in which not all the C=C bonds are saturated are more easily prepared from polycyclic aromatic hydrocarbons. Thus 1,2,3,4-tetrabromo-1,2,3,4-tetrahydronaphthalene is obtained by brominating pure naphthalene in anhydrous CCl_4 at 0° with irradiation (30% yield)[134] or in CCl_4 at room temperature with irradiation and addition of peroxide (ascaridole) (12% yield).[135] Anthracene adds bromine in CS_2 at 0°, giving 9,10-dibromo-9,10-dihydroanthracene,[136,137] and phenanthrene in ether[138] or carbon disulfide[139] gives 9,10-dibromo-9,10-dihydrophenanthrene; when warmed, these two products pass into 9-monobromo derivatives by loss of HBr.

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[125] W. Langenbeck, G. Losse, and H. Fürst, *Chem. Techn.*, **5**, 561 (1953).

[126] F. E. Matthews, *J. Chem. Soc.*, (a) **1891**, 166; **1892**, 104; (b) **1898**, 243.

[127] K. Schwabe, H. Schmidt, and R. Kühnemann, *Angew. Chem.*, **61**, 482 (1949).

[128] H. Fürst and H.-J. Dietz, *Chem. Techn.*, **9**, 657 (1957).

[129] T. van der Linden, *Rec. Trav. Chim.*, **53**, 45 (1934); **55**, 282, 315, 421, 569 (1936); **57**, 217 (1938).

[130] E. Rabonowitsch, *Z. Phys. Chem.*, ***B***, **19**, 190 (1932).

[131] D. Ll. Hammick, J. M. Hutson, and G. I. Jenkins, *J. Chem. Soc.*, **1938**, 1959.

[132] T. van der Linden, *Rec. Trav. Chim.*, **55**, 291 (1936).

[133] S. B. Hendricks and C. Bilicke, *J. Amer. Chem. Soc.*, **48**, 3007 (1926).

[134] J. R. Sampey, J. M. Cox, and A. B. King, *J. Amer. Chem. Soc.*, **71**, 3697 (1949).

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[137] E. de B. Barnett and J. W. Cook, *J. Chem. Soc.*, **1924**, 1085.

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[139] M. Hayduck, *Ann. Chem.*, **167**, 180 (1873); H. Henstock, *J. Chem. Soc.*, **1921**, 57.

II. Addition of hydrogen halide to C–C multiple bonds

1. Preparation and properties of hydrogen halides

Hydrogen fluoride (HF), m.p. −83°, b.p. 19.4°, is prepared from CaF_2 and concentrated sulfuric acid in a rotating tube furnace, being absorbed in, *e.g.*, water to give 70% hydrofluoric acid from which almost dry HF is obtained by distillation. Volatile impurities (SiF_4, SO_2, and CO_2) can be removed by a second distillation.[4a] For removal of SO_4^{2-}, SiF_6^{2-}, and Cl^- commercial 35% HF can be distilled from NaF and a little $PbCO_3$.

Apparatus can be constructed in lead, copper, silver, or platinum, or, for more than 58% HF, from steel; paraffin-coated glass, polyethylene, celluloid, polychlorotrifluoroethylene, and polytetrafluoroethylene (Teflon) can also be used for reaction vessels. Glass dissolves rapidly in aqueous HF.

Hydrogen fluoride and water form an azeotropic mixture, b.p. 112°/750 mm, containing 38.26% of HF; for boiling points of aqueous hydrofluoric acids see Ullmann's Encyclopaedia.[140c] Almost anhydrous acid can be obtained from 48% acid by two distillations and from 70% acid by a single distillation. In the laboratory these distillations are best carried out in silver or platinum apparatus.

96–99.5% HF is commercially available in steel bottles, those containing 10–20 kg being most suitable for laboratory purposes.

HF may be allowed to flow as liquid out of the valve. Or it may be removed as gas, the bottle being heated in warm water; it is advisable to lead the gas first through a cooling condenser and to collect it in a cooled receiver. Although HF is very hygroscopic, anhydrous HF can be poured out in the air since entry of water is prevented by the high pressure of the evaporating acid. Small quantities of water in hydrogen fluoride are determined by conductivity measurement.[141]

Goggles, rubber gloves, and rubber aprons should be worn when working with HF! Skin damaged by HF or fluoride should be washed at once in 10% ammonium carbonate solution. A slurry of MgO in a little glycerol is also recommended for HF burns.

Fluorinated hydrocarbons of fatty consistency can be used for lubricating metal surfaces and taps, with an external seal of piceine. Packing rings of lead, soft iron, or copper are used when connecting metal apparatus. Litharge in glycerol is a suitable cement.

Very pure anhydrous hydrogen fluoride can be prepared in the laboratory by first drying KHF_2 at 220° and then heating it a 500–600° in a copper apparatus.[5b,142]

Hydrogen chloride (HCl), m.p. −114°, b.p. −85.0°, is prepared for practical purposes from hydrochloric acid (d^{15} 1.16, containing 31.5% of HCl, or d^{15} 1.19, containing 37.2% of HCl). At room temperature water dissolves about 450 times its volume of HCl gas; the acid is also readily soluble in ethanol and ether. Hydrogen chloride and water form an azeotrope (b.p. 110°) containing 20.24% of HCl. The solubility of HCl in ether is 35.60% at 0°, 30.35% at 10°, and 24.90% at 20°, but only 1.87% in dry benzene.

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[140] "Ullmanns Encyklopädie der Technischen Chemie," Verlag Urban & Schwarzenberg, Munich–Berlin, 3rd ed., Vol. 5, (1954) pp. (a) 319, (b) 428, Vol. 7 (1956), pp. (c) 585, (d) 605–641.

[141] K. Fredenhagen and G. Cadenbach, *Z. Phys. Chem.*, **146**, 251 (1930).

[142] J. H. Simons, *Inorg. Syn.*, **1**, 134 (1930).

To obtain a stream of HCl, concentrated sulfuric acid is placed in a flask and concentrated HCl (*d* 1.19) is dropped onto it through a capillary tube reaching almost to the bottom of the flask and previously filled with concentrated HCl. A connexion must be set up between the HCl exit tube and the dropping funnel so as to equalize pressure during addition of the concentrated HCl. Equal volumes of concentrated HCl and concentrated H_2SO_4 are used. 67.4 g of gaseous HCl are thus obtained from 200 ml of concentrated HCl.

To obtain continuous larger supplies of HCl, concentrated HCl and concentrated H_2SO_4 are dropped simultaneously into a tube about 25 cm in height and 5 cm in diameter, filled with chips or glass beads and fitted at the top with an HCl exit tube and at the bottom with a drainage tap.[5g] The hydrogen chloride from the exit tube is led through a wash-bottle containing concentrated H_2SO_4 and then through another containing glass wool. Calcium chloride or sulfuric acid can be used for drying it, but not phosphorus pentoxide as this reacts with it.

Hydrogen bromide (HBr), m.p. −86.9°, b.p. −66.8°, is required for preparative purposes as gas or as aqueous solution. There are several useful methods for preparing anhydrous hydrogen bromide.

(*a*) HBr from $H_2 + Br_2$:[5h] The apparatus consists of a round-bottomed flask *A* fitted with a dropping funnel, gas inlet tube *B*, and gas exit tube *C*. The flask *A* is placed in a water-bath at 25–35°; it serves as container for reacting bromine and must not be exposed to direct light; it is best to paint this flask black, leaving a window clear. The tube B through which H_2 is introduced must pass almost to the bottom of flask A and thus during the reaction extends below the surface of the bromine; a wash-bottle containing concentrated H_2SO_4 and then an empty wash-bottle are placed between the tube B and the hydrogen bomb. Before introduction to the reaction flask the hydrogen may also be passed over heated platinized asbestos and then, for drying, over $CaCl_2$ and P_2O_5.[143] A connexion must be established between the tube B and the dropping funnel so as to equalize the pressure. The exit tube *C* is connected to a tube *D* made of high-melting glass, 40–60 cm in length and 2–4 cm in diameter, placed horizontally but connected to a vertical tube *E* containing red phosphorus distributed over glass beads or Raschig rings. The tube D may also be attached to a receiver cooled in CO_2–ether. The tube E is connected to a wash-bottle containing water (to remove phosphorus compounds) and a drying tube containing $CaCl_2$ or $CaBr_2$.

Before the reaction is started the air in the apparatus is replaced by hydrogen, then tube D is heated to 350–380° though a final portion of it must be cooler to avoid dissociation of the HBr. Next 50 ml of bromine are placed in flask *A* and a hydrogen stream is passed through it—this stream must be rapid to ensure an excess of hydrogen. More bromine is added gradually to replace that used. If the reaction is too violent there is risk of an explosion! Further details are given by Rheinboldt,[144] Ruhoff *et al.*,[145] and Roedig.[1k]

For purification the hydrogen bromide is passed throguh CO_2–acetone-cooled traps, the HBr not being condensed. Bromine can be removed by finely divided red phosphorus (on glass wool or in concentrated hydrogen bromide solution). P_2O_5 and concentrated H_2SO_4 are not good drying agents for this gas; anhydrous $CaBr_2$ is best for work demanding high purity.[146]

(*b*) HBr from bromine and tetralin, $C_{10}H_{12} + 4Br_2 \rightarrow C_{10}H_8Br_4 + 4HBr$. This very convenient method has the disadvantage that only half the bromine consumed is converted into the desired product. Bromine is dropped on to tetralin (b.p. 270°; dried over H_2SO_4 and distilled) containing a few iron turnings. The reaction vessel is placed in a water-bath at room temperature but is warmed to about 40° as the reaction slackens. To remove entrained bromine the HBr is passed through a reflux condenser and then through a wash-bottle containing distilled tetralin. See also Houben *et al.*[147]

(*c*) Smaller amounts of gaseous HBr can also be obtained by reaction of bromine with red phosphorus in a slurry with saturated aqueous hydrobromic acid. Laboratory apparatus for this purpose is described by Fahr.[11]

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[143] C. P. Smyth and C. S. Hitchcock, *J. Amer. Chem. Soc.*, **55**, 1831 (1933).

[144] H. Rheinboldt, "Chemische Unterrichtsversuche," Verlag Steinkopff, Dresden–Leipzig, 4th ed, 1960, p. 107.

[145] J. R. Ruhoff, R. E. Burnett, and E. E. Reid, *Org. Syn.*, Coll. Vol. II, 338 (1943).

[146] G. P. Baxter and R. D. Warren, *J. Amer. Chem. Soc.*, **33**, 340 (1911).

[147] J. Houben, J. Boedler, and W. Fischer, *Ber. Deut. Chem. Ges.* **69**, 1772 (1936).

At 760 mm 100 g of water dissolve 221 g of HBr at 0°, 193 g at 25°, and 130 g at 100°. A solution of HBr saturated in glacial acetic acid at 11° contains 41% of HBr. Water and HBr form a constant-boiling mixture (b.p. 122.5/740 mm, 126°/760 mm) containing 47.8% of HBr; the HBr content can be raised to about 65% by passing HBr into this solution cooled in ice-salt.

Preparation of aqueous HBr:

(*a*) Concentrated sulfuric acid (90 ml) is added to a mixture of KBr (120 g) and water (200 ml) at such a rate that with water-cooling the temperature does not exceed 75°. After the whole has cooled to room temperature the $KHSO_4$ is filtered off through a glass sinter and the filtrate is distilled.

(*b*) A rapid stream of SO_2 is passed into bromine (1200 g, 377 ml), water (500 ml), and crushed ice (1500 g) through a tube passing into the lower, bromine layer. The rate of introduction of SO_2 is adjusted so that gas just does not pass through. At first the mixture is shaken frequently, to introduce reaction and to prevent accumulation of large amounts of SO_2 which would lead to vigorous reaction of the SO_2Br_2 formed with water. After about 2 hours the mixture becomes rapidly yellow and the procedure is then at once interrupted. The mixture then contains 2 moles of HBr per mole of H_2SO_4; it is distilled up to b.p. 130° and the distillate is redistilled, yielding 48% aqueous HBr (2400 g), b.p. 125–126°.[148]

Hydrogen iodide (HI), m.p. −50.7°, b.p. −35.4°, is usually prepared *in situ* for modern processes of adding HI to C=C bonds (see page 128) or replacing OH groups by I (see page 221). Anhydrous HI can be prepared, like HBr, from H_2 and I_2 over platinized asbestos at 500°.[5i]

Anhydrous HI can be obtained without much demand on apparatus as follows:[149] Sodium iodide (1 mole) is added to a solution of phosphorus pentoxide (0.35 mole) in 85% phosphoric acid (226 g, 2 moles) placed in a 500-ml round-bottomed flask connected *via* a reflux condenser to three cold traps (1, 0°; 2, −40°; 3, −80°). The flask is then warmed, whereupon about 50% of the calculated amount of HI collects in traps 2 and 3. When evolution of HI ceases, the connexion of trap 1 to trap 2 is sealed and the HI is distilled from trap 2 into trap 3 by allowing trap 2 to come to room temperature. In these operations care must be taken that tubes do not become choked with solid HI. The HI can be distilled from trap 3 into reaction solutions.

Aqueous hydriodic acid is formed when H_2S is led into a vigorously stirred suspension of iodine (120 g) in water (150 ml) until the iodine color is almost completely discharged. The solution is filtered from the sulfur formed, boiled for removal of H_2S, and distilled. Constant-boiling hydriodic acid (b.p. 126.5°/760 mm; *d* 1.70) contains 56.7% of HI. Aqueous HI that has become brown owing to liberation of iodine can be decolorized by treatment when hot with 50% hypophosphorous acid (H_3PO_2).[5i]

HI is decomposed by the action of atmospheric oxygen and light and it should be kept in brown, paraffin-coated bottles. For its stabilization 1 g of red phosphorus is added to 100 ml of hydriodic acid. One litre of water dissolves 12 moles of HI at 10°.

CH_2Cl_2, $CHCl_3$, and CCl_4 can be used as solvents for addition of HI at room temperature, and also for that of HCl or HBr; for the last two, benzene, toluene, xylene, nitrobenzene, light petroleum, hexane, heptane, nitromethane, glacial acetic acid, ether, and dioxan can also be used, but ether and dioxan decelerate ionic addition.

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[148] (a) O. Kamm and C. S. Marvel, *J. Amer. Chem. Soc.*, **42**, 304 (1920); (b) *Org. Syn.*, Coll. Vol. I, 29 (1941); 26 (1956, 2nd ed).

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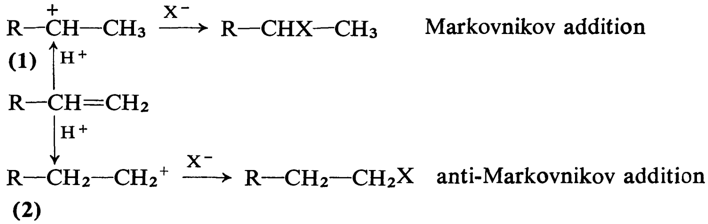
[150] W. Markovnikov, *Ann. Chem.*, **153**, 256 (1870).

2. Addition of hydrogen halide to C=C bonds: general

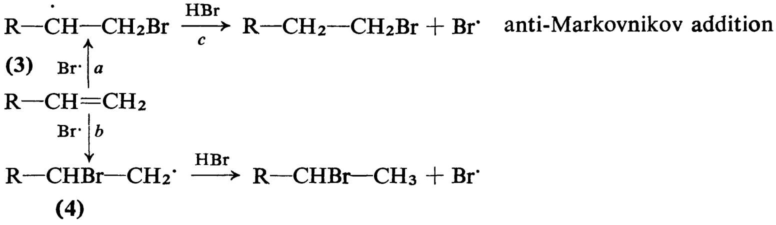
Compounds containing C=C bonds add HI the most easily, HBr easily, but HCl in absence of an catalyst less easily. HCl, HBr, and HI are added in ionic reactions, but HBr also readily by a radical mechanism. Of the carbonium ions assumed as intermediates in ionic addition the form **(1)** is usually the more stable (R = alkyl or phenyl), so that X^- adds to give the Markovnikov product.[150]



$$\begin{tikzcd}
R\text{—}\overset{+}{C}H\text{—}CH_3 \arrow[r, "X^-"] & R\text{—}CHX\text{—}CH_3 & \text{Markovnikov addition} \\
R\text{—}CH{=}CH_2 \arrow[u, "H^+"'] \arrow[d, "H^+"] & & \\
R\text{—}CH_2\text{—}CH_2^+ \arrow[r, "X^-"] & R\text{—}CH_2\text{—}CH_2X & \text{anti-Markovnikov addition}
\end{tikzcd}$$

However, if R is an electron-acceptor (*e.g.*, CF_3, R'_3N^+, CN, or COR′) the carbonium ion **(2)** is the more stable and anti-Markovnikov addition of HX results.[18a] Ionic addition is accelerated by polar solvents (*e.g.*, water, acetic acid[151]), strong acids, or polarizing catalysts (metal halides). Pure, freshly prepared allyl bromide adds bromine in 10 days in the dark in absence of oxygen to give 1,2-dibromopropane quantitatively; this addition is greatly accelerated by $ZnBr_2$, as is that to vinyl chloride by $FeBr_2$ or $FeCl_3$ in glacial acetic acid.

Anti-Markovnikov addition of HBr,[18e] induced by radical-formers or photochemically, is preparatively important.[152] An olefin and atomic bromine can, by reactions (*a*) and (*b*) form the radials **(3)** and **(4)** respectively, of which **(3)** is usually the more stable. **(3)** reacts with HBr to give the anti-Markovnikov adduct, together with a new bromine atom (radical chain reaction). Thus in the presence of small amounts of oxygen or peroxide (added specifically or already present in old preparations), allyl bromide affords the 'abnormal' (anti-Markovnikov) 1,3-dibromopropane within 30 minutes; and Mayo and Walling[153] have collected numerous other examples.



$$\begin{tikzcd}
R\text{—}\dot{C}H\text{—}CH_2Br \arrow[r, "HBr", "c"'] & R\text{—}CH_2\text{—}CH_2Br + Br^\cdot & \text{anti-Markovnikov addition} \\
R\text{—}CH{=}CH_2 \arrow[u, "Br^\cdot", "a"'] \arrow[d, "Br^\cdot"', "b"] & & \\
R\text{—}CHBr\text{—}CH_2^\cdot \arrow[r, "HBr"] & R\text{—}CHBr\text{—}CH_3 + Br^\cdot &
\end{tikzcd}$$

For HCl and HF the activation energies of reaction (*c*) are too great for it to occur; and HI does not provide sufficient iodine atoms.[153–155] If peroxide is

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[151] M. S. Kharasch, J. A. Hunckley Jr., and M. M. Gladstone, *J. Amer. Chem. Soc.*, **56**, 1643 (1934).

[152] W. E. Vaughan, F. F. Rust, and T. W. Evans, *J. Org. Chem.*, **7**, 477 (1942).

[153] F. R. Mayo and C. Walling, *Chem. Rev.*, **27**, 351 (1940).

[154] E. Müller, *Angew. Chem.*, **64**, 244 (1952).

[155] F. R. Mayo, *J. Amer. Chem. Soc.*, **76**, 5392 (1954).

added, it is reduced by the HI and the iodine formed catalyses ionic addition. For halogen-substituted olefins such as allyl bromide and vinyl chloride, finely divided metals that react with HBr yielding Br, also lead to anti-Markovnikov addition.

For example, when peroxide-free allyl bromide (one-twelfth of a mole) is shaken with HBr (1.3-twelfths of a mole) with exclusion of air but addition of 0.02–0.41 mole of freshly reduced iron, 1,3-dibromopropane is obtained in 94–97% yield.

Ionic addition of HBr is so fast for styrene, propene, and isobutene that anti-Markovnikov addition cannot be brought about by adding iron. Certain antioxidants, such as pyrocatechol and thiophenol,[156] completely suppress anti-Markovnikov addition also for halogen-substituted olefins.

Two further examples—of which the first is admittedly disputed—may be cited to show that it is not only peroxides, azoisobutyronitrile, and similar additions that catalyse anti-Markovnikov addition of HBr to olefins. It has been shown[157] that 1-bromopentane and 1-bromoheptane are formed exclusively when dry HBr is led at atmospheric pressure into a stirred solution of peroxide-free 1-pentene or 1-heptene, respectively, in CCl_4 or hexane at -10 to $-12°$ or in glacial acetic acid at 0–5° (1.5–3 h); but if these olefins are shaken with 48% aqueous HBr for 2 months at room temperature in the dark, then the addition gives exclusively 2-bromopentane and 2-bromoheptane. Also, addition of HBr to propene without a solvent gives 2-bromopropane,[158] but the reaction in *n*-pentane gives the anti-Markovnikov adduct 1-bromopropane even in absence of peroxides and air (dilution effect[159]).

The dilution effect has been used in conjunction with addition of a peroxide to force anti-Markovnikov addition.

In the absence of solvent, styrene adds HBr very rapidly, giving α-methylbenzyl bromide. In the presence of peroxide alone, only about 7% of the anti-Markovnikov product is formed, but if HBr is led for several hours into a solution of 1 mole of styrene in 6 moles of *n*-pentane containing 0.02 mole of lauroyl peroxide then the product contains 80% of phenethyl bromide.[160]

The dilution effect may also be used with photochemical addition of HBr to olefins.[161]

The following dilution effect is noteworthy, although it has been disputed. Contrary to a report by Sherrill *et al.*,[157] Kharasch *et al.*[162] found that addition of HBr to 1-pentene gave the anti-Markovnikov adduct 1-bromopentane only in the presence of peroxide (ascaridole), but in acetic acid leads mainly to 2-bromopentane even if ascaridole is present. Markovnikov addition in pentane is in this case achieved by adding diphenylamine as antioxidant,[162] again contrary to Sherrill *et al.*[157]

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[156] M. S. Kharasch, W. R. Haefele, and F. R. Mayo, *J. Amer. Chem. Soc.*, **62**, 2074 (1940).

[157] M. I. Sherrill, K. E. Mayer, and G. F. Walter, *J. Amer. Chem. Soc.*, **56**, 926 (1934).

[158] M. S. Kharasch, M. C. McNab, and F. R. Mayo, *J. Amer. Chem. Soc.*, **55**, 2531 (1933).

[159] F. R. Mayo and M. G. Savoy, *J. Amer. Chem. Soc.*, **69**, 1348 (1947).

[160] C. Walling, M. S. Kharasch, and F. R. Mayo, *J. Amer. Chem. Soc.*, **61**, 2693 (1939).

[161] U.S. Pat. 2,540,126, 2,540,127; *Chem. Abstr.*, **45**, 4143 (1951).

[162] M. S. Kharasch, J. A. Hinckley Jr., and M. M. Gladstone, *J. Amer. Chem. Soc.*, **56**, 1642 (1934).

Halogen substituents reduce the reactivity of C=C bonds in electrophilic additions quite generally, and thus including addition of hydrogen halide. The effect decreases in the order F > Cl > Br. Even when Markovnikov addition is hindered by halogen substituents, it is influenced favorably by working in glacial acetic acid or with an excess of HBr (liquid HBr under pressure), by dilution, or by addition of certain metal halides ($ZnBr_2$, $FeBr_2$, or $FeCl_3$). For instance, passing vinyl bromide and HBr over glass wool at 100–200° gives 1,2-dibromoethane; and 80–90% of 1,2-dibromoethane is obtained by using asbestos impregnated with $HgBr_2$.[163]

Ionic addition of HX to fluorinated olefins and to α,β-unsaturated carbonyl compounds and nitriles (see page 128) is, as expected (see above), an anti-Markovnikov addition. For instance, HCl and HBr in the presence of $AlCl_3$ and $AlBr_3$, respectively, add to CF_3—$CH{=}CH_2$ giving $CF_3CH_2CH_2Cl$ or $CF_3CH_2CH_2Br$;[164] ultraviolet irradiation improves the yield.[165]

α,β-Unsaturated carboxylic acids and esters add hydrogen halide so as to place the halogen in the β-position to the COOH or COOR group. For instance, addition of HI to acrylic acid gives 3-iodopropionic acid,[166] and of HBr or HI to ethyl crotonate gives the corresponding 3-halogenobutyric ester.[167] If an unsaturated compound contains both a CF_3 and an alkoxycarbonyl group, the influence of the latter predominates, as when ethyl 4,4,4-trifluorocrotonate adds HBr to give ethyl 3-bromo-4,4,4-trifluorobutyrate even after addition of $AlBr_3$ or benzoyl peroxide.[168]

3. Addition of hydrogen halide to simple unsaturated hydrocarbons

Olefins add hydrogen fluoride very readily, but polymerization of the olefins also occurs as a side reaction. Traces of acid and water, or temperatures of about 70°, lead to loss of HF from the alkyl fluorides produced. Preparative importance attaches to addition of HF to chlorinated olefins, whose tendency to polymerize in presence of HF is less the more Cl atoms are attached to the doubly bonded carbon atoms. HF adds readily to olefins with unsymmetrical halogen substitution, such as $CH_2{=}CHX$, $RCH{=}CX_2$, or $RCX{=}CH_2$, but with greater difficulty when halogen is attached to both the doubly bonded carbon atoms. BF_3, which assists removal of H^+ from HF by complex formation, accelerates the reaction but also the exchange of halogen for fluorine and the resin formation by polymerization that occur as parallel reactions.[169]

In general (exception: CF_3 next to C=C, see above), fluorine thus becomes attached to the carbon atom carrying the least hydrogen, according to Markovnikov's rule. This is true also for fluorinated olefins. If an olefin contains other halogen atoms besides fluorine, then on addition of hydrogen halide by either the ionic or the radical mechanism the halogen becomes attached to the carbon

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[163] J. P. Wibaut, *Z. Elektrochem.*, **35**, 602 (1929).

[164] A. L. Henne and S. Kaye, *J. Amer. Chem. Soc.*, **72**, 3369 (1950).

[165] A. L. Henne and M. Nager, *J. Amer. Chem. Soc.*, **73**, 5528 (1951).

[166] J. Wislicenus, *Ann. Chem.*, **166**, 1 (1873).

[167] W. Hemilian, *Ann. Chem.*, **174**, 324 (1874).

[168] H. M. Walborsky and M. Schwarz, *J. Amer. Chem. Soc.*, **75**, 3241 (1953).

[169] A. L. Henne and R. C. Arnold, *J. Amer. Chem. Soc.*, **70**, 758 (1948).

atom carrying the larger number of fluorine atoms; *e.g.*, addition of HBr to $CF_2{=}CFCl$ gives $CBrF_2$—CHClF.[170,171]

The olefin is added, when possible without a catalyst (BF_3), to liquid HF cooled to −40 to −60°; the mixture is allowed to warm gradually and finally kept at 75–90° for 1–2 h. The reaction vessel may be made of copper, Monel metal, stainless steel, platinum, magnesium, or nickel. Reactions giving low-boiling fluorides must be carried out in an autoclave. No addition can be achieved when concentrated aqueous HF is used.

1,2-Dichloro-2-fluoropropane:[4e] 1,2-Dichloro-2-propene (500 g) and anhydrous HF (90 g) are weighed into a 2-l steel bomb cooled in dry ice. The bomb is closed with a screwed-down lid carrying a manometer and valve and is heated for 18 h in a water-bath at 50°. The bomb is then cooled in dry ice, the valve is opened, the lid unscrewed, the reaction mixture is poured on ice and neutralized with dilute sodium hydroxide solution, and the organic layer is separated and distilled in steam. The crude product (450 g) is dried over $CaCl_2$ and distilled through a column, giving about 200 g each of 1,2-dichloro-2-fluoropropane, b.p. 85–90°, and a second fraction, b.p. 90–94°. The latter was treated again with HF as above and gave a further 75 g of 1,2-dichloro-2-fluoropropane.

For reactions with HF see also references 172–174.

In the following description of their addition reactions the other halogens will be treated as a group.

In the gas phase, olefins react very sluggishly with HCl alone, but nevertheless readily in the presence of $BiCl_3$[175] or $AlCl_3$.[175] HX adds more readily to the higher than to the lower gaseous normal olefins. In general, addition to terminal vinyl groups is harder than to non-terminal double bonds, so that sometimes a separation of isomers can be based thereon: 2-hexene, $C_3H_7CH{=}CHCH_3$, adds HCl from fuming hydrochloric acid at room temperature, but 1-hexene, $C_4H_9CH{=}CH_2$, is unaffected.[176] Of the two isomers $RCBr{=}CH_2$ and $RCH{=}CHBr$, the former absorbs HX much the more easily, so that in some cases mixtures can be separated in this way.

In the absence of a catalyst, ethylene reacts more slowly than any other olefin, but in the presence of $AlCl_3$ in the liquid phase (ethylene chloride solution) it adds HCl rapidly, even at −80°. In the absence of a catalyst ethylene does not react with HCl, HBr, or HI in the gas phase. Propene does not react with HCl or HBr, nor does 1-butene with HCl, but in the liquid phase there is addition.[177] In the presence of catalysts such as $BiCl_3$, $BiBr_3$, asbestos impregnated with $BiBr_3$, $FeCl_3$, $FeBr_3$, $AlCl_3$, or $ZnCl_2$, ethylene and propene add HCl or HBr in the gas phase, yielding ethyl and isopropyl chloride or bromide.[163]

The choice of solvent is important for addition in the liquid phase. For instance, propene adds HBr readily at room temperature in hexane but not

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[170] J. D. Park, M. L. Sharrah, and J. R. Lacher, *J. Amer. Chem. Soc.*, **71**, 2339 (1949).

[171] R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, **1954**, 3747.

[172] W. Bockemüller, "Neuere Methoden der präparativen organischen Chemie," Verlag Chemie, Berlin, 1944, Vol. 1, pp. 217–236.

[173] A. L. Henne, *Org. Reactions*, **2**, 67 (1944).

[174] J. H. Simons, "Fluorine Chemistry," Academic Press, Inc., New York, 1954, Vol. 2, pp. (a) 213, (b) 217, (c) 340.

[175] J. P. Wibaut, J. J. Diekmann, and A. R. Rutgers, *Rec. Trav. Chim.*, **47**, 477 (1928).

[176] Schorlemmer and Morgan, *Ann. Chem.*, **177**, 305 (1875).

[177] O. Maass, *Can. J. Res.*, **3**, 525 (1930); **5**, 48 (1931).

[178] V. N. Ipatieff, H. Pines, and R. C. Wackher, *J. Amer. Chem. Soc.*, **56**, 2398 (1934).

easily in glacial acetic acid[182]; yet 1-butene and HBr give *sec*-butyl bromide[179] in glacial acetic acid in a bomb tube at 5°. 1-Pentene adds HBr or HI, to give 2- bromo- or 2-iodo-pentane either in absence of a solvent or in water.[180]

Addition of HCl is easiest to tertiary olefins, such as isobutene and isopentene. Isobutene adds HCl in heptane at 0°, giving *tert*-butyl chloride only; traces of water accelerate the reaction.[181] In the presence of $AlCl_3$ 1-methylcyclohexane affords polymers, but the action of dry HCl in the presence of 5–10% of $SnCl_4$ at 5° yields 1-chloro-1-methylcyclohexane quantitatively.[182]

For the preparation of cyclohexyl chloride from cyclohexene and HCl $AlCl_3$ is again unsuitable as catalyst, but $SnCl_4$ and titanium chloride are effective.[183]

For reaction of a dry gaseous olefin with HBr the gas mixture is led through a wide tube, heated at 100° and filled with $AlCl_3$, $AlBr_3$, $BiCl_3$, $BiBr_3$, $ZnCl_2$, or $HgBr_2$ as catalyst; or this salt may be deposited on silica gel or asbestos; a laboratory apparatus for such experiments is described by Wibaut *et al.*[184] In laboratory practice addition of HBr is usually effected in glacial acetic acid at 0–15°, or HBr is led into the undiluted olefin or a solution thereof in $CHCl_3$ at about −20°. Volatile olefins are left for several days in a bomb-tube, higher-boiling ones for about 24 h in normal apparatus.

To promote ionic addition of HBr air must be excluded and the unsaturated compound and the solvent must be tested for peroxide which, if present, must be removed by some suitable method. Antioxidants, such as diphenylamine, thiophenol, or thiocresol, may be added, since they neutralize the effect of small amounts of peroxide.[185]

The following solvents generally contain peroxides: light petroleum, petrol (U.S. gas), decalin, aromatic hydrocarbons containing side chains (xylene, cumene), tetralin, all ethers.

For removal of hydroperoxides the solvent is shaken with potassium or sodium hydroxide, which precipitates the salts of the hydroperoxides (cooling, goggles!). A longer treatment with a solution of iron(II) sulfate in 50% H_2SO_4 is recommended for removal of trimeric and polymeric peroxides of aldehydes and ketones. Other methods are described in Houben-Weyl's " Methoden".[1q]

That polar solvents and metal halides favor ionic addition has already been discussed.

For radical addition of HBr peroxide is added or the solution is irradiated in ultraviolet light.

Volatile olefins are distilled into a suitably cooled bomb-tube containing 0.04–0.15% of a peroxide, then 1.2–1.5 moles of liquified HBr are added, the tube is sealed, and reaction is allowed to proceed for several days at 0–20°.[186] Volatile peroxides of greater molecular weight can be dissolved in pentane, hexane, or heptane and HBr can be led into such a solution after addition of a peroxide or with UV irradiation (quartz flasks are then used); examples are the behavior of 1-bromo- and 1-chloro-cyclohexene which add HBr to give, respectively,

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[179] H. J. Lucas, R. T. Dillon, and W. G. Young, *J. Amer. Chem. Soc.*, **52**, 1952 (1930).

[180] C. K. Ingold and E. Ramsden, *J. Chem. Soc.*, **1931**, 2746.

[181] F. R. Mayo and J. J. Katz, *J. Amer. Chem. Soc.*, **69**, 1339 (1947).

[182] M. Mousseron and G. Manon, *C. R. Hebd. Séances Acad. Sci.*, **227**, 533 (1948).

[183] M. Mousseron and G. Manon, *Bull. Soc. Chim. France*, **1949**, 392.

[184] J. P. Wibaut, J. J. Diekmann, and A. J. Rutgers, *Rec. Trav. Chim.*, **47**, 477 (1928).

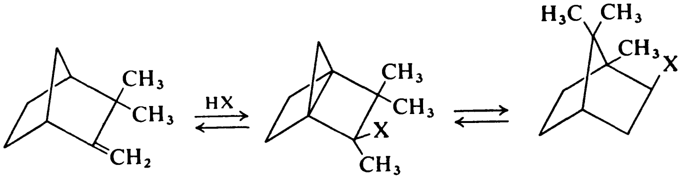
[185] M. S. Kharasch, M. C. McNab, and F. R. Mayo, *J. Amer. Chem. Soc.*, **55**, 2524 (1933).

[186] M. S. Kharasch and F. R. Mayo, *J. Amer. Chem. Soc.*, **55**, 2468 (1933).

cis-1,2-dibromocyclohexane under UV irradiation at room temperature[187] or 1-bromo-1-chlorocyclohexane in the presence of $FeCl_3$.[188]

Allylbenzene and various nuclear-substituted derivatives add dry HBr only in the presence of 3–8% of diacetyl or dibenzoyl peroxide (freezing mixture!); good yields of (3-bromopropyl)benzene and its derivatives are obtained.[194]

Rearrangement of the primary halide product (Wagner–Meerwein rearrangement) occurs when HCl or HBr is added to bicyclic terpenes, especially in solvents of high dielectric constant and when an excess of hydrogen halide is used. For the mechanism see Gould.[18d]



Camphene X = Cl or Br Isobornyl halide

About 90% of camphene hydrochloride is obtained when 1 mole of dry HCl is led, with exclusion of water, into a solution of camphene in half its volume of dry ether cooled in ice–salt.[190] About 70%-pure camphene hydrobromide is obtained when 85% of the calculated amount of HBr is led, with exclusion of moisture, into camphene in light petroleum cooled in ice–salt.[191] These products contain the isobornyl halide as impurity; since the secondary halide is much more firmly bound than the tertiary halogen of the camphene hydrohalide the purity of the product can be determined by titration with alcoholic potassium hydroxide.

Unsaturated hydrocarbons with conjugated C=C bonds can add HX at the 1,4- and the 1,2-position:

$$\underset{(1)}{CH_3—CHBr—CH=CH_2} \xleftarrow{HBr} CH_2=CH—CH=CH_2 \xrightarrow{HBr} \underset{(2)}{BrCH_2—CH=CH—CH_3}$$

If butadiene is led into 66% aqueous HBr at 30° and the upper layer of crude product is separated, washed until neutral, dried over $CaCl_2$, and fractionated, then a mixture, b.p. 101–104°, is obtained containing 80–85% of 1-bromo-2-butene (**2**) and 15–20% of 3-bromo-1-butene (**1**).[192] This mixture reacts at room temperature as if it consisted wholly of (**2**), which is important for, *e.g.*, the synthesis of 2-butenylethylbarbituric acid.[193] Analogously, leading butadiene into 57% aqueous HI at 20° affords a butenyl iodide, b.p. 35°/12 mm.[192]

1,4-Addition of HCl to cyclopentadiene, giving 3-chlorocyclopentene, also occurs when about 90% of the calculated amount of dry HCl is led rapidly, with stirring and cooling by CO_2 to below 0°, into freshly prepared cyclopentadiene.[194] Since 3-chlorocyclopentene soon polymerizes to a black tar, the apparatus must be dismantled and cleaned immediately after termination of the experiment.

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[187] H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Amer. Chem. Soc.*, **74**, 3591 (1952).

[188] H. L. Goering and L. L. Sims, *J. Amer. Chem. Soc.*, **79**, 6270 (1957).

[189] R. Durand-Dran, *Ann. Chim.*, [xiii], **4**, 43 (1959).

[190] H. Meerwein and K. van Emster, *Ber. Deut. Chem. Ges.*, **53**, 1824 (1920); **55**, 2500 (1922).

[191] H. Meerwein, *Ann. Chem.*, **453**, 36 (1927).

[192] R. Voigt, *J. Prakt. Chem.*, [ii], **151**, 309 (1938).

[193] H. Goldhahn, *Pharmazie*, **8**, 324 (1953).

[194] R. B. Moffett, *Org. Syn.*, **32**, 41 (1952).

With cycloheptatriene it is possible to saturate mainly just one of the C=C bonds: by using 40% hydrobromic–acetic acid in the cold one obtains, besides the dibromide, 65% of 6-bromo-1,3-cycloheptadiene which acts as intermediate in the first tropine synthesis.[195]

Addition of hydrogen iodide is less interesting from a preparative point of view. To achieve it, a gaseous olefin is led into iodine-free, constant-boiling, aqueous HI at 0–20° or allowed to react with a saturated solution of HI in glacial acetic acid. Alternatively, HI may be led into the olefin or its solution in benzene. In a newer method which has proved valuable also for converting alcohols and ethers into iodides (cf. pages 222 and 238), the olefin (0.5 mole) is added to a mixture of 95% phosphoric acid (2.14 moles and KI (1.5 moles) that is prepared from 85% phosphoric acid (102 ml), phosphorus pentoxide (47 g), and KI with cooling; the mixture is then heated for some hours under reflux.[196] An example is the preparation of iodocyclohexane from cyclohexene, which is described in detail in *Organic Syntheses.*[197] The process is also applicable to addition

$$\rangle C{=}C\langle + KI + H_3PO_4 \longrightarrow \rangle CH{-}CI\langle + KH_2PO_4$$

of HI to unsaturated acids.[198]

4. Addition of hydrogen halide to unsaturated alcohols, ethers, carbonyl compounds, and nitriles

The OH group is completely or partially replaced by halogen when HCl or HBr adds to an unsaturated alcohol unless that OH group is separated from the C=C unit by several carbon atoms. For example, the OH is replaced by Cl or Br when cinnamyl alcohol reacts with gaseous HCl at 0° or with HBr in glacial acetic acid.[199]

An intermediate esterification is required to achieve anti-Markovnikov addition of HBr to higher unsaturated alcohols. For instance, even when a peroxide is added, 10-undecen-1-ol and HBr afford 10-bromo-1-undecanol, whereas HBr adds to 10-undecenyl acetate in the presence of peroxides so that the bromine appears in the 11-position whereas in the presence of antioxidants (H_2 and diphenylamine) it appears in the 10-position.[200] The HBr adducts obtained from the acetates in the presence of dibenzoyl peroxide can be converted into the bromo alcohols by transesterification with methanol and *p*-toluenesulfonic acid.[201] 11-Bromo-1-undecanol, 13-bromo-1-tridecanol, and 15-bromo-1-pentadecanol can also be obtained by intermediate conversion of the corresponding ω-unsaturated alcohols into the boric esters.

HBr is led into a solution of the boric ester containing di-*tert*-butyl peroxide at 0–2°, then at least half of the solvent (toluene) is distilled off, and the ester is hydrolysed by addition of water and stirring for an hour at 50°.[202]

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[195] R. Willstätter, *Ann. Chem.*, **317**, 267 (1901).

[196] H. Stone and H. Shechter, *J. Org. Chem.*, **15**, 491 (1950).

[197] H. Stone and H. Shechter, *Org. Syn.*, **31**, 66 (1951).

[198] J. Corse and E. F. Jansen, *J. Amer. Chem. Soc.*, **77**, 6632 (1955).

[199] A. Klages and K. Klenk, *Ber. Deut. Chem. Ges.*, **39**, 2552 (1906).

[200] R. Ashton and J. C. Smith, *J. Chem. Soc.*, **1934**, 1308.

[201] F. L. M. Pattison and co-workers, *J. Org. Chem.*, **21**, 745 (1956).

[202] M. G. J. Beets and W. Meerburg, *Rec. Trav. Chim.*, **72**, 414 (1953).

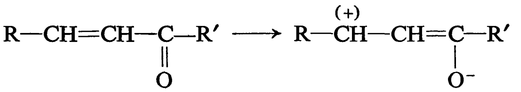
Addition of HCl or HBr to phenyl or alkyl vinyl ethers, leading to α-haloalkyl ethers, must be carried out at low temperatures (−5 to +5°), otherwise polymerization occurs.

The preparation of butyl 1-chloroethyl ether is described in detail in „Synthesen organischer Verbindungen".[203]

Addition of hydrogen halide to other unsaturated ethers must also be performed at low temperatures, since at higher temperatures the ether linkage is cleaved (see page 237).

If eugenol (7 g) is saturated at 0° with HBr, then saturated aqueous HBr is added at 0° shaking and ice-cooling and the whole is set aside for 3–4 days with occasional shaking, then **4-(2'-bromopropyl)vanillin** (7.7 g) is obtained. The 2'-chloro compound can be prepared similarly.[204]

The halogen appears at the β-position when HX is added to α,β-unsaturated aldehydes, ketones, acids, or nitriles whether the addition is electrophilic with addition of H^+ as primary step or nucleophilic with addition of X^- as primary step. The reaction is preparatively important for synthesis of β-halo acids, esters, and nitriles.



$$R{-}CH{=}CH{-}\underset{\underset{O}{\|}}{C}{-}R' \longrightarrow R{-}\overset{(+)}{CH}{-}CH{=}\underset{\underset{O^-}{|}}{C}{-}R'$$

HBr is led, with cooling in CO_2–acetone, into an α,β-unsaturated aldehyde or ketone (which may be diluted with benzene or CS_2) until HBr passes through. 4-Bromo-4-methyl-2-pentanone is thus obtained from mesityl oxide.[205]

When acrolein is allowed to react with HBr at −15° in the presence of methanol, the bromine adds primarily at the 3-position although the end-product is 1,3-dibromopropyl methyl ether; the latter affords 3-bromopropanal dimethyl acetal when kept in methanol for 12 hours.[206]

3-Chloro-3-phenylpropanal diethyl acetal (23 g) is similarly obtained when cinnamaldehyde (20 g) is dropped at −5 to 0° into a solution of HCl in anhydrous ethanol saturated at 0° and the whole is left to react for a further 30 min at 0°.[207]

Under certain conditions HCl or HBr and α,β-unsaturated ketones (other than β-halo ketones) give colored addition compounds.[208]

HCl or HBr can be added to unsaturated acids by leading the gas, with ice-cooling, into the undiluted liquid acid or into its solution in glacial acetic acid or ether. 3-Bromobutyric acid is thus obtained from crotonic acid.[209]

Addition to unsaturated carboxylic esters must be carried out at lower temperatures (−10 to 0°) with the neat ester or its solution in ether, light petroleum, or glacial acetic acid.

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[203] M. F. Schostakowski and A. W. Bogadnowa, "Synthesen organischer Verbindungen," VEB Verlag Technik, Berlin, 1959, Vol. 1, p. 46.

[204] G. R. Clemo and J. H. Turnbull, *J. Chem. Soc.*, **1945** 533.

[205] H. Rupe and S. Kessler, *Ber. Deut. Chem. Ges.*, **42**, 4715 (1909).

[206] R. Pineau, *J. Rech. Centre Nat. Rech. Sci., Lab. Bellevue (Paris)*, **1951**, 292.

[207] J. P. Fourneau and S. Chantalou, *Bull. Soc. Chim. France*, [v], **12**, 845 (1945).

[208] D. Vorländer, *Ber. Deut. Chem. Ges.*, **37**, 1644, 3364 (1904); *Ann. Chem.*, **341**, 1 (1905).

[209] H. Hunsdiecker, *Ber. Deut. Chem. Ges.*, **75**, 464 (1942).

The preparation of methyl 3-bromopropionate from methyl acrylate in dry ether is described in *Organic Syntheses*;[210] methyl 3-bromo-2-methylpropionate is formed similarly from methyl methacrylate and dry HBr without a solvent at −10 to −5°.[211]

If a rapid stream of HCl or HBr is led into an ice-cooled solution of 4-oxo-4-phenylbutenoic acid for 20 min and reaction is allowed to proceed for a further 3 h, 81% of 2-chloro-4-oxo-4-phenylbutyric acid or 90% of the 2-bromo acid are obtained,[212] in this case the β-directing effect of the keto group overcomes that of the COOH group.

In the reaction of α,β-unsaturated carboxylic acids and esters with HBr the addition of radical-formers is without effect on the entry of bromine at the β-position, but radical addition to give ω-bromo carboxylic acids and esters is possible with ω-unsaturated acids and esters that have CH_2 groups between the C=C and the COOH groups.

Bromine appears at the 10-position on addition of HBr to 10-undecanoic acid or its ethyl ester in benzene if the HBr is introduced under H_2, diphenylamine is added as antioxidant, or impurities (aldehydes) that form peroxides in air are previously removed.[200,213] However, in presence of peroxides (which may be specifically added or formed from adventitious aldehyde and atmospheric oxygen), radical addition of HBr occurs, leading to 11-bromoundecanoic acid or its ethyl ester.[200,213]

11-Bromoundecanoic acid is obtained in the presence of dibenzoyl peroxide if the HBr is prepared from bromine and tetralin but not if it is prepared from hydrogen and bromine.[214]

ω-Unsaturated acids $CH_2{=}CH{-}(CH_2)n{-}COOH$ (n = 1–3) add HBr in hexane in presence of peroxides to give ω-bromo acids, but in very pure hexane with exclusion of oxygen and addition of diphenylamine ionic addition of HBr supercedes.[215]

Dry HCl[216] and dry HBr[217] add to α,β-unsaturated nitriles in such a way that the halogen appears in the β-position to the nitrile group.

If acrylonitrile is allowed to react with HCl in ether for 3 h at room temperature, 80–85% of 3-chloropropionitrile are obtained, but only 40% are formed in absence of a solvent after 12 hours' boiling.[216]

5. Addition of hydrogen halide to C≡C bonds

Alkynes add hydrogen fluoride readily without a catalyst, in accordance with Markovnikov's rule. However, unlike the higher alkynes, acetylene does not react with HF between −70° and 0° at atmospheric pressure.

$$R{-}C{\equiv}C{-}R' \xrightarrow{HF} R{-}CF{=}CH{-}R' \xrightarrow{HF} R{-}CF_2{-}CH_2{-}R'$$

When acetylene reacted with HF for 72 h in a steel autoclave, with stirring, at room temperature and 8–12 atm, about 15% of it had been converted into vinyl fluoride (35 mole-%) and 1,1-difluoroethane (65 mole-%).[218]

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[210] R. Mozingo and L. A. Patterson, *Org. Syn.*, Coll. Vol. III, 576 (1955).
[211] H. L. Lochte, *J. Amer. Chem. Soc.*, **69**, 15 (1947).
[212] E. Buchta and S. Dauner, *Chem. Ber.*, **82**, 63 (1949).
[213] R. Ashton and J. C. Smith, *J. Chem. Soc.*, **1934**, 435.
[214] R. G. Jones, *J. Amer. Chem. Soc.*, **69**, 2352 (1947).
[215] A. Michael and H. S. Mason, *J. Amer. Chem. Soc.*, **65**, 683 (1943).
[216] C. C. Price and J. Zomlefer, *J. Org. Chem.*, **14**, 210 (1949).
[217] C. Moureau and R. L. Brown, *Bull. Soc. Chim. France*, [iv], **27**, 904 (1920).
[218] A. V. Grosse and C. B. Linn, *J. Amer. Chem. Soc.*, **64**, 2289 (1942).

Vinyl fluoride is obtained in the gas phase by using a $HgCl_2$–$BaCl_2$ catalyst on active charcoal at 83–109°; HF is separated from the crude gaseous product by sodium hydroxide solution, and unchanged acetylene by addition of ethane with which it forms an azeotrope that can be distilled off through a low-temperature column. Precise details for preparation of the catalyst and for the reactor are given by Newkirk.[219]

Addition of HF to acetylene homologs, giving difluoroalkanes, has been described both for small[218] and for large batches (5–10 moles).[220] In the latter case it is necessary to avoid formation of hot reaction zones (resinification) and decrease in temperature which can lead to dangerous accumulation of unchanged reagents. Propyne and 1-butyne are led as gas into liquid ice-cold anhydrous HF (2.5 moles per mole of alkyne); pentyne and hexyne are dropped into HF at −50° (copper vessels).

Higher-boiling alkynes are treated with a solution of 5 moles of HF in 1 mole of an ether or ketone; the resulting oxonium salts from 1 mole of solvent and 2 moles of HF are good solvents for both the reagents and the products.

2,2-Difluorooctane:[4f,220] 100 g of anhydrous HF in 74 g of ether or 56 g of acetone are introduced through a copper tube into an ice-cooled 500-ml copper flask, then 1 mole of 1-octyne is dropped in as slowly as possible. The mixture is allowed to warm to room temperature and after 1 h is poured on ice. The organic layer is separated and distilled (b.p. 137.5°). The yield is 70–90%.

Addition of hydrogen chloride to acetylene is technically a very important reaction and directions for it are laid down mainly in patents. Addition of HCl to alkynes follows Markovnikov's rule. Whether addition of the first or the second mole of HCl is the faster depends on the catalyst. The rate of reaction of acetylene and HCl in the

$$CH{\equiv}CH \xrightarrow{HCl} CH_2{=}CHCl \xrightarrow{HCl} CH_3{-}CHCl_2$$

gas phase is appreciable only if catalysts (metal halides) are present.

With $HgCl_2$ on silica gel at 25° and streaming velocities of 1.5 l/h for acetylene and 2.2 l/h for HCl there are formed 93% of vinyl chloride with less than 3% of 1,1-dichloroethane, and at 195° 98% and 1%, respectively.

$HgCl_2$ is a very active catalyst for the addition of HCl to acetylene leading to vinyl chloride, but it catalyses only slightly the addition of HCl to vinyl chloride. $ZnCl_2$ on the contrary catalyses specifically addition of HCl to vinyl chloride;[221] 1,1-dichloroethane is the only product when $HgCl_2$, $BiCl_3$, $FeCl_3$, or $ZnCl_2$ is used for this further addition between 55 and 200°.

In the gas phase vinyl bromide reacts with HBr much faster than vinyl chloride does and much faster than acetylene. In contrast to HCl, HBr reacts in the gas phase in accordance with or contrary to Markovnikov's rule, giving 1,1- or 1,2-dibromoethane according to the nature of the catalyst; use of $HgBr_2$ on asbestos, for example, leads mainly to 1,2-dibromoethane at 100 to 150°, and so does use of $FeBr_3$ on pumice at 200°; however, use of $FeBr_3$ on pumice at 100° leads to about 65% of 1,2- and 35% of 1,1-dibromoethane, and

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[219] A. E. Newkirk, *J. Amer. Chem. Soc.*, **68**, 2467 (1946).

[220] A. L. Henne and E. P. Plueddeman, *J. Amer. Chem. Soc.*, **65**, 587 (1943).

[221] J. P. Wibaut and J. van Dalfsen, *Rec. Trav. Chim.*, **51**, 636 (1932).

that of $SbBr_3$ on asbestos between 100 and 150° also leads to mixtures of isomers. Apparatus used for these gas-phase additions has been described in detail by Wibaut.[222]

Small amounts of vinyl bromide can be obtained readily in the laboratory by the action of alcoholic KOH or NaOH on 1,2-dibromoethane.[223,224] 1,1-Dibromoethane is formed from acetaldehyde and PCl_3Br_2.[228] As stabiliser against polymerization 0.1–0.2% of hydroquinone is added to vinyl bromide; phenol is added to vinyl chloride (b.p. −13.9°).

Vinyl chloride is prepared technically from acetylene and HCl at 140–200° in the presence of active charcoal soaked in $HgCl_2$ solution[225a] from 1,2-dichloroethane by removal of HCl either thermally (catalyst: SnO_2–$FeCl_2$[225b,226,227]) or by alcoholic alkali hydroxide.

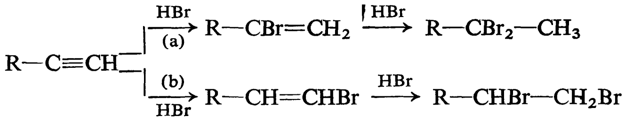
Vinyl chloride and bromide can also be obtained in the liquid phase: acetylene is led with stirring at 65–70° through a mixture of CuCl (250 g), NH_4Cl (100 g), and 15% HCl (300 ml) or at 60° through a solution of CuBr in aqueous hydrobromic acid.[228]

Preparative details have also been given for addition of HCl to vinylacetylene and its alkyl derivatives.[229,230]

2-Chloro-1,3-butadiene (chloroprene):[230] Crude vinylacetylene (45 g), concentrated hydrochloric acid (155 g), freshly precipitated CuCl (20 g), NH_4Cl (9 g), and pyrogallol (0.5 g) are mixed at 0°. When shaken at room temperature the mixture separates into two layers. The brown upper layer is washed with water, dried over $CaCl_2$ after addition of 1 g of pyrogallol, and distilled; this yields 12.5 g (20%) of 2-chloro-1,3-butadiene, b.p. 59–61°, and 12.5 g of material boiling at 61–75° and containing mostly chloroprene.

2-Chloro-3-methyl-1,3-butadiene, b.p. 35°, is obtained analogously, the yield being 75% after steam-distillation.

The addition of HBr to alkynes, as to alkenes, can be so directed that it leads (a) to 2-bromo-1-alkene or 2,2-dibromoalkane or (b) to 1-bromo-1-alkene or 1,2-dibromoalkane:



$$\begin{array}{l} R{-}C{\equiv}CH \xrightarrow[(a)]{HBr} R{-}CBr{=}CH_2 \xrightarrow{HBr} R{-}CBr_2{-}CH_3 \\ R{-}C{\equiv}CH \xrightarrow[HBr]{(b)} R{-}CH{=}CHBr \xrightarrow{HBr} R{-}CHBr{-}CH_2Br \end{array}$$

For instance, propyne and HBr at −35° give 2,2-dibromopropane, but on addition of ascaridole give 1,2-dibromopropane;[231] 1-hexyne and HBr at 15° give 2-bromo-1-hexene in the presence of catalytic amounts of hydroquinone and $FeBr_3$, but give 1-bromo-1-hexene if peroxides are added.[232]

For the theory of addition of halogen and hydrogen halides to the C≡C bond reference should be made to a paper by Bohlmann.[233]

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[222] J. P. Wibaut, *Rec. Trav. Chim.*, **50**, 318 (1931).

[223] J. P. Wibaut, *Rec. Trav. Chim.*, **50**, 313 (1931).

[224] F. R. Mayo and co-workers, *J. Amer. Chem. Soc.*, **70**, 1523 (1948).

[225] F. Asinger, "Einführung in die Petrolchemie," Akademie-Verlag, Berlin, 1959, pp. (a) 327, (b) 245.

[226] F. Kainer, *Kolloid-Z.*, **113**, 122 (1949).

[227] J. C. Ghosh and S. R. Das Guha, *Petroleum* (*London*), **14**, 261 (1951).

[228] N. S. Kozlov, *Zh. Prikl. Khim.*, **B**, 1n, 116 (1937); *Chem. Abstr.*, **31**, 4263 (1937).

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[230] H. J. Backer and T. A. H. Blaas, *Rec. Trav. Chim.*, **61**, 785 (1942).

[231] M. S. Kharasch, J. G. McNab, and M. C. McNab, *J. Amer. Chem. Soc.*, **57**, 2463 (1935).

[232] C. A. Young, R. R. Vogt, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **58**, 1807 (1936).

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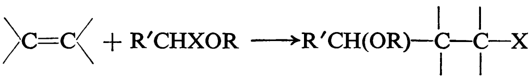
III. Addition of halogen to C–C multiple bonds with simultaneous formation of a C–C, C–O, or C–N bond

1. Addition of halogen to C—C multiple bonds with simultaneous formation of a C—C bond

a. Addition of α-halo ethers to C=C bonds



$$>C=C< + R'CHXOR \longrightarrow R'CH(OR)-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-X$$

α-Halo- and α,β-dihalo alkyl ethers can be added to C=C and C≡C bonds in the presence of $ZnCl_2$, $BiCl_3$, $HgCl_2$ or $AlCl_3$.[234,235] This reaction, whose numerous applications have been reviewed by Gross and Höft,[236] occurs at low temperatures, without a solvent or in CS_2, and is generally applicable and easy to carry out. As examples, chloromethyl methyl ether adds readily to isobutene,[235] cyclohexene,[237] and butadiene,[235,238] and also to vinylacetylene in the 1,2- and 1,4-positions.[234]

b. Meerwein reaction (interaction of diazonium halides and C—C multiple bonds)

In this reaction an acetone solution of a compound containing C=C or C≡C bonds is added at 0–40° to an aqueous solution of a diazonium chloride or bromide containing HCl or HBr or buffered with $(CaOH)_2$, MgO, $NaHCO_3$, or sodium acetate and containing also a catalytic amount of $CuCl_2$. The aryl group and the halogen atom add to the C=C or C≡C bond in competition with the Sandmeyer reaction (see page 259). The Cu^+ ion is a catalyst for both the Meerwein and the Sandmeyer reaction. Added Cu^{2+}, or Cu^{2+} formed from Cu^+ by atmospheric oxygen, is continuously reduced back to Cu^+ by the acetone:[239]

$$2\,CuCl_2 + CH_3COCH_3 \longrightarrow 2\,CuCl + ClCH_2COCH_3 + HCl$$

Thus adding acetone increases the preparative value of the Sandmeyer reaction. It is assumed[240] that the Sandmeyer and the Meerwein reaction occur by way of aryl radicals.

The Meerwein reaction was first observed for α,β-unsaturated carbonyl compounds.[241] In these cases, and for the corresponding nitriles, halogen (X) appears in the α-position to a group R^1 if the unsaturated compound had an alkyl group in the β-position to R^1 (reaction *a*); halogen (X) appeared in the

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[235] F. Strauss and W. Thiel, *Ann. Chem.*, **525**, 151 (1936).

[236] H. Gross and E. Höft, *Angew. Chem., Int. Ed., Engl.*, **6**, 335 (1967).

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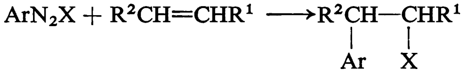
[239] J. K. Kochi, *J. Amer. Chem. Soc.*, **77**, 5090 (1955); **79**, 2944 (1957).

[240] J. K. Kochi, *J. Amer. Chem, Soc.*, **79**, 2942 (1957).

[241] H. Meerwein, E. Büchner, and K. van Emster, *J. Prakt. Chem.*, **152**, 237 (1939).

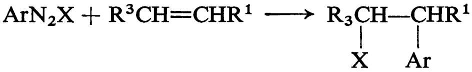
β-position to R^1 if the unsaturated compound had an aryl group in the β-position to R^1 (reaction *b*).



$$\mathrm{ArN_2X + R^2CH{=}CHR^1 \longrightarrow R^2\underset{\underset{\displaystyle Ar}{|}}{C}H{-}\underset{\underset{\displaystyle X}{|}}{C}HR^1} \qquad (a)$$

(*a*)

R^2 = H or alkyl; R^1 = COOH, $COOOH_3$, CN, or CHO



$$\mathrm{ArN_2X + R^3CH{=}CHR^1 \longrightarrow R_3\underset{\underset{\displaystyle X}{|}}{C}H{-}\underset{\underset{\displaystyle Ar}{|}}{C}HR^1} \qquad (b)$$

(*b*)

R^3 = aryl; R^1 as above.

There are many examples of reaction (*a*); *e.g.*, arenediazonium chlorides add to acrylic and methacrylic acids, esters, and nitriles giving β-aryl-α-chloropropionic acids, esters, and nitriles;[242–244] and α,β-unsaturated aldehydes afford 3-aryl-2-chloropropionaldehyde and the analogous 2-bromo aldehydes.[245,246] Butadiene undergoes 1,4-addition.[247–249] Phenylacetylene and a benzenediazonium chloride solution that has been neutralized with sodium carbonate solution gives, at 25–30°, a 46.5% yield of α-chlorostilbene.[250]

2-Chloro-3-(*p*-nitrophenyl)propionitrile:[247] *p*-Nitroaniline (4.2 kg) is dissolved in a hot mixture of concentrated HCl (9 l) and water (9 l), cooled to 30°, and treated with ice (24 kg). 30% Sodium nitrite solution (7.3 l) is run in within a few minutes with vigorous cooling. The diazonium salt solution is filtered and treated with a solution of acrylonitrile (1.76 kg) in acetone (15 l). $CuCl_2$ (600 g) is then added and a short time thereafter at ca. 18° evolution of nitrogen begins. The temperature is kept below 30° by ice-cooling. 2-Chloro-3-(*p*-nitrophenyl)propionitrile separates and after recrystallization from methanol has m.p. 110° (yield 5.3 kg).

2-Chloro-3-phenylpropionaldehyde:[245] $CuCl_2$ (10 g) and CaO (4 g) are suspended in a solution of acrolein (22.5 g) in acetone (200 ml); a solution of benzenediazonium chloride (0.4 mole) in water (350 ml) is neutralized with $NaHCO_3$ and added to the acetone solution at 0–2° at such a rate that only 2–3 bubbles of nitrogen are evolved per second. The mixture is finally extracted with ether, the ethereal layer is evaporated, and the residue is fractionated, giving a 52.8% yield of 2-chloro-3-phenylpropionaldehyde, b.p. 104–106°/12 mm.

c. Addition of acid chlorides to C=C bonds

If ethylene is led at 0–5° into a mixture of an aliphatic acid chloride and $AlCl_3$ prepared at 0°, the alkyl 2-chloroalkyl ketone is obtained:[251]

$$\mathrm{RCOCl + CH_2{=}CH_2 \longrightarrow RCOCH_2CH_2Cl}$$

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[242] G. H. Cleland, *J. Org. Chem.*, **26**, 3362 (1961).

[243] A. V. Dombrovskii, A. P. Terent'ev, and A. M. Jurkevich, *Zh. Obshch. Khim.*, **27**, 419 (1957); *Chem. Abstr.*, **51**, 15 454 (1957).

[244] A. V. Dombrovskii, A. P. Terent'ev, and A. M. Jurkevich, *Zh. Obshch. Khim.*, **26**, 3214 (1956); *Chem. Abstr.*, **51**, 8038 (1957).

[245] A. V. Dombrovskii, A. P. Terent'ev, and A. M. Jurkevich, *Zh. Obshch. Khim.*, **27**, 3047 (1957); *Chem. Abstr.*, **52**, 8087 (1958).

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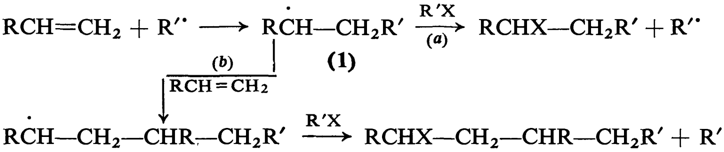
[250] A. V. Dombrovskii, *Zh. Obshch. Khim.*, **27**, 3050 (1957); *Chem. Abstr.*, **52**, 8087 (1958).

[251] J. Kenner and F. S. Statham, *Ber. Deut. Chem. Ges.*, **69**, 17 (1936).

2-Chloroethyl propyl ketone:[252] Freshly powdered $AlCl_3$ (158 g) is added in 30 min, with stirring, to butyryl chloride (126 g) cooled in ice–salt, and stirring is continued for 50 min thereafter. Then dry ethylene is led in to the mixture at 20° until the weight increase amounts to 33 g and the whole is stirred for a further 30 min at 20°. Working up is by addition of ice, extraction with $CHCl_3$, and distillation, giving an 80% yield of ketone, b.p. 67–68°/11 mm.

d. Addition of alkyl halides, etc., to C=C bonds

Polyhalomethanes (CCl_4 and CBr_4,[253] CCl_3Br[254]), and compounds that can form radicals stabilized by conjugation [$Cl_2CHCOOCH_3$, $BrCH(COOR)_2$[255]], can be added to C=C bonds in the presence of radical-forming agents (diacetyl or dibenzoyl peroxide, azo compounds). The unsaturated compound and the radical $R'^{\cdot}$ formed in the starting reaction (*e.g.*, $^{\cdot}CCl_3$ from CCl_4, CCl_3Br, or $CHCl_3$) give the radical (**1**) which attacks a second molecule R′X (route *a*) or a second molecule of the unsaturated compound (route *b*). The latter process may be repeated several times (telomerization[256]), particularly if R′X is not very reactive and if its concentration is low. The reaction is effected under nitrogen at 80–90°, with 0.05–0.1 mole of peroxide per mole of alkene.



$$\begin{tikzcd} \mathrm{RCH{=}CH_2 + R'^{\cdot}} \arrow[r] & \mathrm{R\dot{C}H{-}CH_2R'}\ (\mathbf{1}) \arrow[r, "\mathrm{R'X}", "(a)"'] \arrow[d, "(b)\ \mathrm{RCH{=}CH_2}"'] & \mathrm{RCHX{-}CH_2R' + R'^{\cdot}} \\ & \mathrm{R\dot{C}H{-}CH_2{-}CHR{-}CH_2R'} \arrow[r, "\mathrm{R'X}"] & \mathrm{RCHX{-}CH_2{-}CHR{-}CH_2R' + R'^{\cdot}} \end{tikzcd}$$

Alkyl chlorides or bromides with the halogen attached to a secondary or tertiary carbon atom can be added to olefins and chloroolefins in the presence of anhydrous $AlCl_3$ or $FeCl_3$. Such additions to ethylene are carried out by leading ethylene into, *e.g.*, *tert*-butyl chloride in pentane containing $AlCl_3$ or $FeCl_3$ at 0 to −30°:[257]

$$\mathrm{(CH_3)_3CCl + CH_2{=}CH_2 \longrightarrow (CH_3)_3C{-}CH_2{-}CH_2Cl}$$

2. Addition of halogen to C=C bonds with simultaneous formation of a C–O bond

The first step in this reaction is addition of X^+, by which the energy-poorer of the two possible carbonium ions is usually formed:[258]

$$\mathrm{CH_3{-}CH{=}CH_2 \xrightarrow{X^+} CH_3{-}\overset{+}{C}H{-}CH_2X \xrightarrow{HO^-} CH_3{-}CH(OH){-}CH_2X}$$

In this way addition of HOBr and HOCl to propene gives 1-bromo- and 1-chloro-2-propanol,[259] respectively, and to butene gives 1-bromo-2-butanol.[260]

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[252] K. Bowden and co-workers, *J. Chem. Soc.*, **1946**, 52.

[253] M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Amer. Chem. Soc.*, **69**, 1100 (1947).

[254] M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Amer. Chem. Soc.*, **65**, 1105 (1947).

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[257] L. Schmerling, *J. Amer. Chem. Soc.*, **67**, 1152 (1945).

[258] E. Müller, "Neuere Anschauungen der organischen Chemie," Springer-Verlag, Berlin–Göttingen–Heidelberg, 2nd ed., 1957, p. 174.

[259] E. Fourneau and J. Puyal, *Bull. Soc. Chim. France*, [iv], **31**, 427 (1922).

[260] M. de Montmollin and P. Matile, *Helv. Chim. Acta*, **7**, 108 (1924).

Halogen cations afford hypohalogen acids or $X_2 + H_2O$, or *N*-halo compounds. The HO^- is obtained from water, which must be present in sufficient amount.[261] The corresponding halohydrin ethers are formed when the reaction is carried out in an alcohol. Halogens and the silver salts of carboxylic acids in CCl_4 give acyl hypohalites RCOOX, which are added as X^+ and $RCOO^-$ to C=C bonds at low temperatures.[262–265]

$$X_2 + H_2O \rightleftharpoons HOX + H^+ + X^-$$

For addition of HOX in water the medium must be neutral or weakly acidic. In the presence of acid or chloride or bromide[17,266] the equilibrium above is shifted to the left, which favors formation of dihalides. In alkaline media epoxides are formed.

a. Addition of hypohalite to C=C bonds (halohydrins)

Addition of HOCl to olefins is technically very important. When chlorine and ethylene are passed into water (Gomberg's ethylene chlorohydrin synthesis[267]) the amount of chlorine added as such increases with increasing concentration of HCl. This undesirable side reaction is reinforced by the greater solubility of olefins and Cl_2 in the Cl_2-adduct than in water. The experiment must therefore be broken off at relatively low concentrations of chlorohydrin (for ethylene 8–10%), and the mixture must be worked up at that stage.[22b,268,269]

Ethylene chloride is not isolated directly since an azeotrope (b.p. 97.8°) of the chlorohydrin (42.5%) and water distils from the reaction mixture. Instead, calcium hydroxide is added, the resulting alkaline medium causing formation of ethylene oxide (b.p. 10.7°) which can be easily separated. This is then led, together with the equivalent amount of HCl, into preformed ethylene chlorohydrin, whereupon ethylene chlorohydrin (b.p. 128.7°/760 mm) is formed quantitatively. For a synthesis of ethylene bromohydrin see McDowell.[270]

The addition of Cl_2 increases rapidly with increasing molecular weight of the olefin. However, chlorohydrins are obtained in good yield from, *e.g.*, 2-pentene, 2-hexene, cyclohexene, butadiene, and pinene when a concentrated aqueous hypochlorite solution (10–15% bleaching powder solution) is added gradually, with cooling in ice and vigorous stirring, to an emulsion of the olefin in water at 0–30° whilst CO_2 is led in at a slight overpressure (0.35–3.5 atm).[271]

1-Chloro-3-buten-2-ol:[272] A 6 : 1 mixture of butadiene and CO_2 is led into a stirred 3.5% solution of calcium hypochloride (0.845 mole) at 0–3°. Reaction is complete after 1.8 hours

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[261] R. E. Buckles and J. E. Maurer, *J. Org. Chem.*, **18**, 1586 (1953).

[262] W. Bockemüller and F. W. Hoffmann, *Ann. Chem.*, **519**, 165 (1935).

[263] M. I. Uschakow and W. O. Tchistow, *Ber. Deut. Chem. Ges.*, **68**, 824 (1935).

[264] D. C. Abbott and C. L. Arcus, *J. Chem. Soc.*, **1952**, 1515.

[265] W. G. H. Edwards and R. Hodges, *J. Chem. Soc.*, **1954**, 762.

[266] A. W. Francis, *J. Amer. Chem. Soc.*, **47**, 2340 (1925).

[267] M. Gomberg, *J. Amer. Chem. Soc.*, **41**, 1414 (1919).

[268] W. G. Domask and K. A. Kobe, *Ind. Eng. Chem.*, **46**, 680 (1954).

[269] P. Ferrero, L. R. Flamme, and M. Fourez, *Ind. Chim. Belge*, **19**, 133 (1954)

[270] F. N. McDowell, *J. Chem. Soc.*, **1926**, 499.

[271] B. T. Brooks, U.S. Pat. 2,463,850; *Chem. Abstr.*, **43**, 4687 (1949).

[272] R. G. Kadesch, *J. Amer. Chem. Soc.*, **68**, 41 (1946).

as can be recognized by failure of a sample to oxidize KI. The $CaCO_3$ is filtered off and the solution saturated with NaCl and extracted with ether. The yield is 52% and the b.p. 64.0 to 64.8°/30 mm.

Bis-(3-chloro-2-hydroxypropyl) ether:[273] CO_2 is led into a mixture of diallyl ether (0.25 mole), water (2.5 l), and 35% calcium hypochlorite solution (102 g, 0.25 mole) at 3° with stirring and cooling. A dry-ice condenser is placed on the reaction flask to prevent loss of diallyl ether. The hypochlorite is consumed in 2 h, then a further amount (51 g) is added and CO_2 is passed in with stirring for a further 2 h. The solution is filtered from $CaCO_3$, saturated with NaCl, and extracted with ether. The yield is 94.4% and the b.p. is 150–165°/3 mm or, after a further distillation (138–139°/1 mm).

As well as these simple methods, there are others for preparation of hypochlorous acid solutions suitable for addition of HOCl, such as passage of Cl_2 into an ice-cold slurry of freshly precipitated HgO[274] or $NaHCO_3$ in ice-water[275] or of bleaching powder and K_2CO_3 in water.[276]

The following procedure may be used for preparing an approximately **20% hypochlorous acid solution** (HOCl) from chlorine hydrate and HgO:[277,278] Chlorine is passed to saturation into water that is stirred vigorously and cooled in ice-salt freezing mixture. The precipitated chlorine hydrate is filtered off and mixed, with stirring, with sufficient HgO (about 3/4 of its weight) to give an aqueous solution and remove the smell of chlorine. This solution is filtered and distilled at room temperature and 12 mm. The distillate, which contains up to 20% of HOCl, is kept in the dark in the frozen state; it is stable for several months at −10°.

For addition of HOCl the olefins are stirred with 0.125–0.5 m-HOCl at 10°. The yields of chlorohydrin from 1-alkenes of higher molecular weight are considerably increased by addition of pyridine and sulfuric acid (initial pH 6–6.5)[278]. Chlorohydrins of higher molecular weight are also accessible by reaction of alkyl hypochlorites with the olefin in an aqueous medium; *tert*-butyl hypochlorite (a yellow oil, b.p. 77–78°/760 mm) is suitable for this purpose; it is obtained by passage of chlorine into *tert*-butyl alcohol in aqueous sodium hydroxide at 0–20°.

tert-Butyl hypochlorite may decompose violently under the influence of intense light, rubber, or overheating! Its preparation (see above) is described in *Organic Syntheses*;[179] it is important that the temperature and rate of passage of chlorine be controlled; at temperatures above 20° there is danger of explosions.[280]

For addition of HOBr the unsaturated compound is usually stirred for some hours at room temperature with bromine water, then the excess of hypobromite is removed by sodium hydrogen sulfite, the solution is saturated with salt, and the bromohydrin is shaken out of the aqueous phase into ether or $CHCl_3$. A cold solution of hypobromite obtained from bromine and alkali carbonate may be used in place of bromine water.[281] The tendency of styrene to bromohydrin formation is so great that α-(bromomethyl)benzyl alcohol is obtained in excellent yield even in hot water (60–90°) by use of a bromine solution in the presence of KBr.[261,282]

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[273] J. R. Roach and S. E. Miller, *J. Amer. Chem. Soc.*, **71**, 2667 (1949).

[274] W. Markovnikov, *Ann. Chem.*, **336**, 314 (1904).

[275] A. Wohl and H. Schweitzer, *Ber. Deut. Chem. Ges.*, **40**, 94 (1907).

[276] E. Bamberger and W. Lodter, *Ann. Chem.*, **288**, 81 (1895).

[277] S. Goldschmidt, *Ber. Deut. Chem. Ges.*, **52**, 758 (1919).

[278] A. Guyer, A. Bieler, and E. Pedrazzelli, *Helv. Chim. Acta*, **39**, 423 (1956).

[279] H. M. Teeter and E. W. Bell, *Org. Syn.*, **32**, 20 (1952).

[280] C. P. C. Bradshaw and A. Nechvatal, *Proc. Chem. Soc.*, **1963**, 213; cf. *Org. Synth.*, **44**, 26 (1964).

[281] E. Berner and C. N. Riiber, *Ber. Deut. Chem. Ges.*, **54**, 1954 (1921).

[282] J. Read and W. G. Reid, *J. Chem. Soc.*, **1928**, 1487.

Addition of OH and I to C=C bonds can be effected with water-saturated ether as solvent if 0.5 mole of freshly prepared HgO is added per mole of olefin to remove the I^-. 1 Mole of iodine is added, in portions, with cooling and stirring, and the mixture is stirred until the color of the iodine has almost vanished.[1n,283] If this reaction is carried out in dry methanol, OCH_3 and I are added to the C=C bond. Iodohydrins and iodohydrin ethers are very unstable. α,β-Unsaturated carboxylic acids apparently do not add IOH, but they do add OCH_3 and I (see page 140).

HOCl and HOBr add to the C=C bond of α,β-unsaturated carboxylic acids in such a way that the halogen (X) appears at the α- and OH at the β-position to the carboxyl group.

2-Bromo-3-hydroxybutyric acid is obtained by passing a stream of air laden with bromine into a rapidly stirred aqueous 0.34m-solution of crotonic acid.[284]

2-Chloro-3-hydroxy-3-methylbutyric acid is obtained on addition of aqueous HOCl to a suspension of 3-methylcrotonic acid (β,β-dimethylacrylic acid).[285]

b. Formation of chlorohydrins by chromyl chloride

The direction (reaction *a*) of addition of HOCl to C=C bonds brought about by hypohalites[286] or *N*-halo amides can be reversed. If propene, 1-butene, or 1-hexene is treated in CCl_4 or $CHCl_3$ with CrO_2Cl_2 the end-result is addition according to reaction (*b*).[287] This is so also

$$R—CH=CH_2 \longrightarrow R—CH(OH)—CH_2Cl \qquad (a)$$

$$R—CH=CH_2 \longrightarrow R—CHCl—CH_2OH \qquad (b)$$

for compounds resembling steroids.[288]

2-Chloro-1-propanol: Propene is led into an ice-cooled, rapidly stirred solution of chromyl chloride (1 mole) in CCl_4 (300 ml) until the CrO_2Cl_2 color has disappeared (absorption 23 g). The solid product that separates is hydrolysed by sodium hydrogen sulfite solution. The aqueous solution is saturated with salt and extracted with ether. The ether layer is dried over Na_2SO_4 and distilled. The yield is 43%.

c. Formation of halohydrins by N-halo amides

N-Bromosuccinimide[289] and *N*-bromoacetamide[290,291] are very suitable Br^+-donors for addition of HOBr to C=C bonds.

The preparation and analysis of *N*-bromoacetamide is described in *Organic Syntheses*;[292] for *N*-bromosuccinimide see page 148.

1 mole of the unsaturated compound and 1 mole of the *N*-bromo amide are stirred together in water at room temperature until the bromo amide has dissolved, then the bromohydrin

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[283] L. Brunel, *C. R. Hebd. Séances Acad. Sci.*, **135**, 1055 (1902).

[284] H. E. Carter and C. I. Zirkle, *J. Biol. Chem.*, **178**, 711 (1949).

[285] E. Abderhalden and K. Heyns, *Ber. Deut. Chem. Ges.*, **67**, 537 (1934).

[286] A. Saytzeff, *J. Prakt. Chem.*, [ii], **3**, 88 (1871).

[287] S. J. Cristol and K. R. Eilar, *J. Amer. Chem. Soc.*, **72**, 4353 (1950).

[288] H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.*, **78**, 3751 (1956).

[289] C. O. Guss and R. Rosenthal, *J, Amer. Chem. Soc.*, **77**, 2549 (1955).

[290] S. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **61**, 1576 (1939); **64**, 2780 (1942).

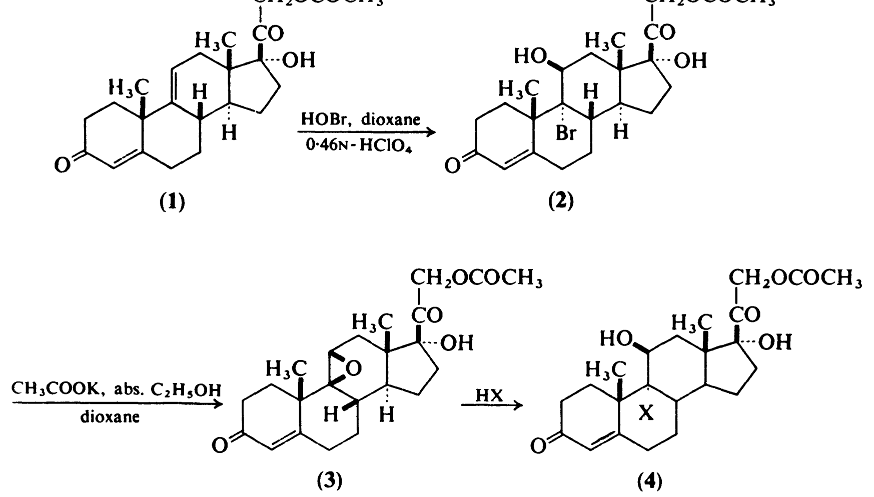
[291] E. Schmidt, W. Knilling, and A. Ascherl, *Ber. Deut. Chem. Ges.*, **59**, 1279 (1926).

[292] E. P. Oliveto and C. Gerold, *Org. Syn.*, **31**, 17 (1951).

is extracted with ether or benzene. The crude product can be converted by aqueous alkali directly in the epoxide, which can sometimes be distilled off continuously through a column; thus, for example, 2,3-epoxy-2-methylbutane (2,2,3-trimethyloxirane) is obtained in this way from 3-bromo-2-methyl-2-butanol.[293] A small amount of an acid (H_2SO_4 or acetic acid) accelerates the reaction.

Br^{14}CH$_2$–^{14}CH$_2$OH is obtained in 90% yield from [^{14}C]ethylene by use of *N*-bromoacetamide.[294]

Addition of HOX by means of *N*-halo amides is important for, *inter alia*, steroid syntheses. A 9(11)-double bond adds OH at position 11 (11β-OH) and Br at position 9 (9α-Br). Solvents used are mixtures of water with acetone, dioxane, pyridine, or *tert*-butyl alcohol. 0.46N-perchloric acid has proved particularly suitable as acid since it reduces any tendency to formation of halohydrin esters.[295]



(1) (2) (3) (4)

80% of 9α-bromohydrocortisone acetate **(2)** is obtained from 21-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione **(1)** and *N*-bromoacetamide. The 9β,11β-oxide **(3)** obtainable therefrom is converted by HI at −20° or by HCl or HF at 0° into the corresponding 9α-halohydrocortisone acetate **(4)** in good yield.[295] For further details of addition of HOBr to steroids by *N*-bromoacetamide or *N*-bromosuccinimide see, *inter alia*, references.[296–299]

Chlorourea can also be used to add HOCl to C=C bonds.[300] Chlorourea[301] [m.p. 71° (dec.)] dissolves in *ca.* 5 parts of water; it is best handled in solution; explosions can occur during chlorination of urea (formation of nitrogen trichloride).

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[293] S. Winstein and L. L. Ingraham. *J. Amer. Chem. Soc.*, **74**, 1163 (1952).

[294] D. E. Walz, M. Fields, and J. A. Gibbs, *J. Amer. Chem. Soc.*, **73**, 2968 (1951).

[295] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **79**, 1136 (1957).

[296] L. B. Barkley and co-workers, *J. Amer. Chem. Soc.*, **76**, 5017 (1954).

[297] J. A. Hogg and co-workers, *J. Amer. Chem. Soc.*, **77**, 6401 (1955).

[298] R. H. Lenhard and S. Bernstein, *J. Amer. Chem. Soc.*, **77**, 6665 (1955).

[299] H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.*, **78**, 3749 (1956).

[300] A. Detoeuf, *Bull. Soc. Chim. France*, [iv], **31**, 102, 171 (1922).

***trans*-2-Chlorocyclopentanol:** Monochlorourea is obtained by passing chlorine, with vigorous stirring, into an aqueous urea solution at 0–15° containing $CaCO_3$ to bind the hydrogen chloride formed. Acetic acid and the required olefin are added to the chlorourea solution with ice-cooling. Cyclopentene affords 52–56% of *trans*-2-chloro-1-cyclopentanol with some of the *cis*-isomer and 1,2-dichlorocyclopentane. The procedure for this example is described in *Organic Synthese.*[301]

Alkoxy bromides are obtained by treating a compound containing a C=C bond with *N*-bromoacetamide[297] or another bromo amides (*e.g.*, *N*,*N*-dibromobenzenesulfonamide[302,303]), not in an aqueous medium but in anhydrous methanol or ethanol at 0–20°; acyloxy bromides are obtained in glacial acetic acid.[297,304]

d. Alkoxyhalogenation

β-Alkoxy-*α*-bromo carboxylic esters are important intermediates for the synthesis of hydroxy amino acids in cases where the corresponding *α*,*β*-unsaturated acid is readily accessible. *α*-Bromo-*β*-methoxy carboxylic esters are obtained

$$R'R''C{=}CH{-}COOR \xrightarrow[CH_3OH]{Hg(OAc)_2} R'R''C(OCH_3){-}CH(HgOAc){-}COOR \xrightarrow{KBr}$$

$$R'R''C(OCH_3){-}CH(HgBr){-}COOR \xrightarrow{Br_2} R'R''C(OCH_3){-}CHBr{-}COOR + HgBr_2$$

in good yield by bromination, in chloroform or ethyl acetate, of the bromomercuri compounds which are readily accessible from the acetoxymercuri compounds and aqueous KBr.

Ethyl 3-methylcrotonate thus gives ethyl 2-bromo-3-methoxy-3-methylbutyrate,[305] ethyl crotonate gives ethyl 2-bromo-3-methoxybutyrate,[288,306] and ethyl acrylate gives ethyl 2-bromo-3-methoxypropionate,[307] these products being intermediates in the synthesis of, respectively, *β*,*β*-dimethylserine, DL-threonine, and DL-serine.[65]

Occasionally it is more profitable to treat the methoxy-bromomercuri or methoxyiodomercuri compound with iodine, which can be done in boiling methanol, aqueous methanol, or carbon tetrachloride, *e.g.*, in the conversion of *N*-allylphthalimide into the *N*-(3-halo-2-methoxypropyl)-phthalimide.

Adding mercuric acetate in boiling methanol to *N*-allylphthalimide and treating the product with KBr or KI in boiling aqueous methanol gives the *N*-(3-halomercuri-2-methoxypropyl)phthalimide (with smaller amounts of the isomer); this is not readily converted into the 3-bromopropyl derivative by bromine, but with iodine readily gives the 3-iodopropyl compound.[308] The whole reaction, starting from the allylphthalimide, can be carried out quickly without isolating the intermediates.[309]

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[301] H. B. Donahoe and C. A. Vanderwerf, *Org. Syn.*, **30**, 24 (1950).

[302] A. A. Petrov, *Zh. Obshch. Khim.*, **70**, 487 (1938); *Chem. Abstr.*, **32**, 7891 (1938).

[303] H. L. Holmes and K. M. Mann, *J. Amer. Chem. Soc.*, **69**, 2001 (1947).

[304] M. W. Likosherstov and A. A. Petrov, *Zh. Obshch. Khim.*, **9**, 2012 (1939); *Chem. Abstr.*, **34**, 4381 (1940).

[305] W. Schrauth and H. Geller, *Ber. Deut. Chem. Ges.*, **55**, 2788 (1922).

[306] H. E. Carter and H. D. West, *Org. Syn.*, Coll. Vol. III, 813 (1955).

[307] H. E. Carter and H. D. West, *Org. Syn.*, Coll. Vol. III, 774 (1955).

[308] D. E. Pearson, M. V. Sigal jr., and R. H. Krug, *J. Org. Chem.*, **15**, 1048 (1950).

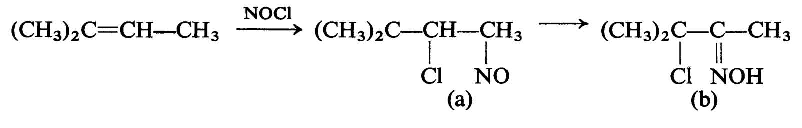
[309] B. R. Baker and co-workers, *J. Org. Chem.*, **17**, 74 (1952).

Methoxybromination can be effected directly by means of bromine. For example, when a current of air laden with bromine is passed with cooling through a methanolic solution of 3-methylcrotonic acid it affords 75% of 2-bromo-3-methoxy-3-methylbutyric acid;[310] MgO is added to the reactants to remove hydrogen bromide, but alternatively[311] $AgNO_3$ and $CaCO_3$ may be used.

β-Chloro-α-iodo carboxylic acids are readily available by addition of ICl (1.25 mole) in CCl_4 to α,β-unsaturated acids (1 mole). Treating these halo acids with alcohols at room temperature in the presence of freshly precipitated $CaCO_3$ gives β-alkoxy-α-iodo carboxylic acids together with an amount of the α,β-unsaturated acid that depends on the nature of the alcohol used. Alternatively $CaCO_3$ (7–15 g) is suspended in a solution of the unsaturated acid (5–10 g) in methanol (or 1- or 2-propanol), ICl (1.25 mole per mole of acid) is added, and the whole is stirred for about 20 h and then filtered. When this procedure is applied to cinnamic acid the products are precipitated as solids [yields in CH_3OH 88%, $C_2H_5CH_2OH$ 62%, $(CH_3)_2CHOH$ 22%] on pouring the filtrate into water. The reaction occurs by way of the alkyl hypoiodite ROI.[312]

3. Addition of halogen to C—C multiple bonds with simultaneous formation of a C—N bond*

Addition of nitrosyl chloride (NOCl) to compounds containing C=C or even C—C bonds has been studied for very many cases[313a] because it is a reaction of preparative importance in, *inter alia*, terpene chemistry (see, *e.g.*, references [314] and [315]). Olefins containing allyl units, as in $R{-}CH_2{-}CH{=}CH_2$, form nitrosochlorides (a) less easily than do olefins containing propenyl units as in $R{-}CH{=}CH{-}CH_3$ or those with terminal C=C bonds as in $C_6H_5CH{=}CH_2$



$$(CH_3)_2C{=}CH{-}CH_3 \xrightarrow{NOCl} \underset{\text{(a)}}{\underset{Cl\quad\ NO}{(CH_3)_2C{-}CH{-}CH_3}} \longrightarrow \underset{\text{(b)}}{\underset{Cl\quad NOH}{(CH_3)_2C{-}\overset{}{C}{-}CH_3}}$$

or $R{-}CH_2{-}C(CH_3){=}CH_2$. α,β-Unsaturated acids and nitro compounds do not give nitrosochlorides, but those unsaturated acids do that have several CH_2 groups between the C=C bond and the COOH group. Those olefins add nitrosyl chloride particularly readily that contain substituents decreasing the reactivity of the C=C bond to nucleophilic reagents and increasing it to electrophilic reagents. The primary step is addition of NO^+, this followed by

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[310] K. Rüfenacht, *Helv. Chim. Acta*, **35**, 764 (1952).

[311] K. Meinel, *Ann. Chem.*, **516**, 231 (1935).

[312] E. L. Jackson and L. Pasiut, *J. Amer. Chem. Soc.*, **50**, 2249 (1928).

[313] L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, (a) pp. 369–378, (b) 324 (1951).

[314] O. Wallach, *Ann. Chem.*, **245**, 241 (1888); **252**, 106 (1889); **253**, 249 (1889); **258**, 19 (1890); **345**, 127 (1906); **360**, 26–81 (1908); *Ber. Deut. Chem. Ges.*, **28**, 1308 (1895).

[315] A. Bayer, *Ber. Deut. Chem. Ges.*, **28**, 1586 (1895); **29**, 1078 (1896).

* Cf. page 415.

addition of Cl^- which occurs at the carbon atom carrying the smaller number of hydrogen atoms.[316]

Nitrosochlorides are usually obtained as colorless crystalline substances, which are dimers of (a). The blue monomeric forms (a) are formed on melting or on warming of solutions, but then the blue color generally soon disappears owing to rearrangement to the α-chloro oximes (b). For this isomerization it is, of course, necessary that the carbon atom carrying the NO group in (a) shall also carry a hydrogen atom; if the latter is not present, a stable blue monomer is obtained, as, for example, 2-chloro-2,3-dimethyl-3-nitrosobutane.[317]

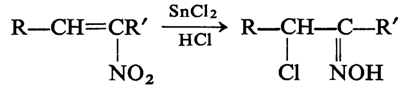
Yields obtained in additions of NOCl depend greatly on the reaction conditions, in particular temperature and solvent. If the olefins are sufficiently reactive, crystalline products are conveniently obtained by passing gaseous NOCl (b.p. −5.8°; from 2NO + Cl_2 in presence of activated Al_2O_3 at 40 to 50°[316b]) into the liquid unsaturated compound at 0°[316a] or into a solution thereof in glacial acetic acid at 5–10°. CCl_4, $CHCl_3$, CH_2Cl_2, nitromethane, and nitroethane are also suitable solvents, and Ni, $FeCl_3$, or CuCl may be used as catalysts.[313a,318]

For preparative purposes it is best to prepare the NOCl in the reaction mixture. Concentrated aqueous or ethanolic HCl is added to a mixture of the unsaturated compound and pentyl or ethyl nitrite at −15°; or concentrated $NaNO_2$ solution is dropped into a solution of the unsaturated compound in ethanolic HCl.

2-Chloro-2-methyl-3-nitrosobutane:[319,320] Ice-cold fuming hydrochloric acid (50 ml) is dropped during 1.5 h into a stirred mixture of 2-methyl-2-butene (30 g) and pentyl nitrite (50 ml) kept below 0° by ice-salt cooling. The mixture becomes blue at once and gradually solidifies to a mass of colorless crystals. These are left in the cold for 30 min and then filtered off under suction and washed with ice-cold ethanol. The yield is 29 g and the m.p. 76°.

Some (5 g) of this product is dissolved in ethanol (50 ml) and heated to the b.p. The solution then remains in ebullition for some minutes without further heating and the blue color changes to yellow. Removal of the alcohol yields **3-chloro-3-methyl-2-butanone oxime** (4.5 g), m.p. 50°.

A different, interesting method of preparing α-chloro oximes was discovered recently:[321] nitroolefins, dissolved in ethereal hydrogen chloride, are reduced with ice-salt cooling by ethereal stannous chloride containing HCl:



$$\underset{\displaystyle NO_2}{R\text{—}CH\text{=}CR'} \xrightarrow[HCl]{SnCl_2} R\text{—}\underset{\displaystyle Cl}{CH}\text{—}\underset{\displaystyle NOH}{\overset{}{C}}\text{—}R'$$

Nitrosyl chloride is also applied to the determination of C=C groups in fats, fatty acids, and unsaturated hydrocarbons (a review exists).[322]

Nitryl chloride (NO_2Cl) can also be added to C=C and C≡C bonds. α-Chloro-nitro compounds are obtained from halogenated ethylenes, styrene,

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[316] N. Thorne, *J. Chem. Soc.*, **1956**, 4271.

[317] J. Thiele, *Ber. Deut. Chem. Ges.*, **27**, 454 (1894).

[318] P. J. Gaylor, *Petrol. Process.*, **2**, 870 (1947).

[319] J. Schmidt, *Ber. Deut. Chem. Ges.*, **35**, 3730 (1902).

[320] N. Thorne, *J. Chem. Soc.*, **1956**, 2588.

[321] A. Dornow, H. D. Jordan, and A. Müller, *Chem. Ber.*, **94**, 67 (1961).

[322] H. P. Kaufmann and P. Rover, *Fette u. Seifen*, **47**, 103 (1940).

stilbene, cinnamic acid, cyclohexene, and phenylacetylene. Ethylene gives dichloroethane; ketene gives a poor yield of the unstable nitroacetyl chloride. Explosions can easily occur during work with NO_2Cl; for details see Steinkopf and Kühnel.[323]

3.2. Formation of carbon-halogen bonds by exchange

I. Replacement of hydrogen by halogen or thiocyanate

1. Replacement of hydrogen by halogen in aliphatic hydrocarbons

a. Replacement of hydrogen by halogen in alkanes

In the reaction, $>\!C{-}H + F_2 \rightarrow\ >\!C{-}F + HF$, 102.5 kcal/mole are liberated (+ Cl_2 22.9; + Br_2 6.2 kcal/mole). Thus it is very difficult to replace H atoms one-by-one by F. Usually several H atoms are replaced and C—C bonds are broken, so that CF_4 becomes the final product of such reactions. Monofluorides are mostly prepared by replacement of other halogens by fluorine (see page 204). The direct formation of polyfluoro and perfluoro compounds — in the latter all the H atoms are replaced by fluorine — is technically important.[174c] In this connexion electrolysis of organic compounds in anhydrous HF has particular significance; it is carried out at about 20° with a current density of 0.02 Amp/cm^2 and 5–6 V at nickel anodes and nickel or iron cathodes, reaction vessels being of iron or nickel and fitted with reflux condensers; for hydrocarbons KF or LiF is added to increase the conductivity; HF formed in the reaction returns continuously to the cycle.

Although exchange of hydrogen for chlorine is rarely used in the laboratory purely for the purpose of preparing chlorinated alkanes, chlorination of alkanes is of great technical importance. The large amounts of heat liberated can be removed in the gas phase by working with an excess of alkane or by admixture with an inert gas, and in the liquid phase by cooled solvents. Photochemical, catalytic, and thermal processes are all used. In all cases di- and poly-chlorination occur as competitors of the monochlorination that is usually desired.

Liquid alkanes, chloroalkanes, as well as liquified (*i.e.*, gaseous at room temperature) and molten (up to m.p. 7°) alkanes are chlorinated when chlorine is led through them with stirring and UV irradiation. Higher-melting alkanes and polyethylene are chlorinated in CCl_4 solution. Reference [324a] should be consulted for details of apparatus for photochemical chlorination of isobutane to isobutyl chloride and *tert*-butyl chloride, of CH_3Cl to CH_2Cl_2, of CH_2Cl_2 to $CHCl_3$, and of *n*-dodecane.

In homogeneous catalytic chlorination in the liquid phase, a chloride of I, P, S, Sb, Fe, or Sn (for patent literature see reference [324a]), or radical-formers such as tetraethyllead,[325] are added to the liquid or CCl_4 solution of the alkane. Olefins which may be present also act as catalysts.[326,327]

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[323] W. Steinkopf and M. Kühnel, *Ber. Deut. Chem. Ges.*, **75**, 1323 (1942).

[324] F. Asinger, "Chemie und Technologie der Paraffin-Kohlenwasserstoffe," Akademie-Verlag, Berlin, 1956, pp. (a) 157, (b) 164, (c) 169, (d) 177, (e) 191, (f) 611.

[325] W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **5**, 467 (1940).

[326] R. M. Deanesly, *J. Amer. Chem. Soc.*, **56**, 2505 (1934).

[327] H. P. A. Groll and G. Hearne, *Ind. Eng. Chem., Ind. Ed.*, **31**, 1239 (1939).

Homogeneous catalytic chlorination can also be effected in the gas phase, in presence of potassium, sodium, or $SbCl_5$ vapor. Heterogeneous catalysis in the gas phase occurs in the dark at higher temperatures over catalysts such as active charcoal, kieselguhr, pumice, clay, kaolin, silica gel, or bauxite which may have been soaked in solutions of metal salts and, in particular, copper salts.[324c] This reaction is cryptoionic and thus, unlike the photochemical and thermal chlorination which proceed by way of Cl radicals, it is insensitive to chain-breakers such as oxygen, to such an extent that air is actually added in order to convert the resulting hydrochloric acid into chlorine in analogy to the Deacon process.

In a technically valuable variant the gas mixture streaming into a conical reaction vessel maintains the suspended catalyst (active charcoal) in constant motion. This has the advantage of avoiding disturbances due to separation of carbon or tarry by-products such as occur in purely thermal or catalytic chlorination on fixed bed catalysts.[324e]

Thermal chlorination (400–500°) in the absence of catalysts and light is a chain reaction initiated by thermal dissociation of Cl_2.[328] Details of laboratory apparatus for this method of chlorination, which is particularly important for alkanes of lower molecular weight, are given in Asinger's book[324d] and by Hass.[329] The procedure can be used to convert alkanes into monochlorides and to chlorinate the latter further.

The amounts of the various isomers formed on monochlorination of alkanes depends on the relative rates at which the variously bound hydrogen atoms are replaced. Hydrogen atoms in CH_3—, —CH_2—, and $>$CH— are replaced at 300° in the proportions 1 :3.25 : 4.43.[324f] Above 300° the proportion of primary chloride increases; the cause of this is that dehydrochlorination, induced by chlorine, occurs preferentially at chlorinated methylene groups.[330] Catalysts and irradiation do not affect the above proportions and it follows from them that the amount of terminal chloride formed must decrease continuously with increasing chain length; thus, whereas propane gives 48% of 1-chloro compound, only 8.5% is formed from *n*-dodecane.

When radical formers are added, SO_2Cl_2 may replace Cl_2 as source of atomic chlorine ($Cl^\cdot$). SO_2Cl_2 alone provides only molecular chlorine (reaction e). Whilst radical chlorination by molecular chlorine (photochemical, thermal, or with addition of radical-formers) proceeds by the chain mechanism (a) and (b), the additional reactions (c) and (d) can be assumed to occur in chlorinations by SO_2Cl_2 and radical-formers (peroxides, azo compounds).[331-336]

$$\text{(a)}\ Cl^\cdot + RH \longrightarrow R^\cdot + HCl \qquad \text{(c)}\ R^\cdot + SO_2Cl_2 \longrightarrow RCl + SO_2Cl^\cdot$$

$$\text{(b)}\ R^\cdot + Cl_2 \longrightarrow RCl + Cl^\cdot \qquad \text{(d)}\quad SO_2Cl^\cdot \longrightarrow SO_2 + Cl^\cdot$$

$$\text{(e)}\ SO_2Cl_2 \rightleftarrows SO_2 + Cl_2$$

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[328] W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **5**, 449 (1940).

[329] H. B. Hass, *Ind. Eng. Chem.*, **27**, 1192 (1935); **29**, 1336 (1937).

[330] F. Asinger, G. Geiseler, and K. Schmiedel, *Chem. Ber.*, **92**, 3085 (1959).

[331] H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Amer. Chem. Soc.*, **62**, 3435 (1940).

[332] H.-J. Schumacher and J. Stauff, *Angew. Chem.*, **55**, 341 (1942).

[333] M. C. Ford and W. A. Waters, *J. Chem. Soc.*, **1951**, 1851.

When peroxides are added, alkanes can be chlorinated by SO_2Cl_2 even in the dark.[334] The time required for a mixture of 1 mole of SO_2Cl_2, 1–3 moles of hydrocarbon, and 0.02 mole of dibenzoyl peroxide is usually 1–2 hours. Secondary H atoms are more easily replaced by Cl than are primary ones in this process. Halogen substituents increase the difficulty of further halogenation, particularly on carbon that already carries halogen, the effect decreasing as the distance from the site of previous halogenation increases. Presence of two or three chlorine substituents on one carbon atom prevents further radical chlorination at that site, *e.g.*, for $CHCl_3$, $CHCl_2$—$CHCl_2$, or $C_6H_5CHCl_2$. Suitable solvents for radical SO_2Cl_2 chlorination of alkanes and side chains or aromatic hydrocarbons (see page 157) are, according to the necessary reaction temperature: CH_2Cl_2 (40°), $CHCl_3$ (61°), CCl_4 (77°), benzene (80°), chlorobenzene (132°), and *o*-dichlorobenzene (180°).

$$RH + SO_2Cl_2 \longrightarrow RCl + SO_2 + HCl$$

Bromination of alkanes is less interesting both preparatively and technically. Hydrogen is most difficult to replace by Br from methyl groups, and easiest from methine groups, so that, for instance, when 2,3-dimethylbutane and bromine are irradiated at room temperature 2,3-dibromo-2,3-dimethylbutane is easily obtained.[335] A paper by Kharasch *et al.*[336] should be consulted for the chain mechanism of thermal or photochemically initiated bromination.

Various other papers,[337–341] some of them old, are of interest for halogenation of alkanes.

b. Replacement of hydrogen by halogen in olefins

Replacement of hydrogen by halogen is, as we have shown, of relatively little importance for saturated hydrocarbons; the reaction is considerably more interesting for hydrocarbons containing C=C bonds.

Admittedly haloolefins in which the halogen is attached to doubly bonded carbon are prepared both in the laboratory and industrially by removing halogen (X_2) or hydrogen halide (HX) from polyhalogenated hydrocarbons.

Halogen (X_2) can be removed thermally or by use of metals (Fe, Mg, Zn, Al). *E.g.*, 1,2-dichloroethylene is obtained industrially from 1,1,2,2-tetrachloroethane by means of iron turnings and steam,[140c] and 1,2-dichloro-1,2-difluoroethylene from 1,2-difluoro-1,1,2,2-tetrachloroethane by means of Zn dust in ethanol.[342,343]

Removal of hydrogen halide (HX) in the preparation of haloolefins is governed by Saytzeff's rule that the proton is removed preferentially from the carbon carrying the smallest number of hydrogen atoms.[344] Removal of HX thermally or by aqueous-alcoholic alkali is important for laboratory work but particularly so on an industrial scale.[1o] Solid NaOH or KOH is used in the preparation of 2,3-dibromo-1-propene from 1,2,3-tribromopropane as described

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[334] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **61**, 2142 (1939).

[335] A. V. Grosse and V. N. Ipatieff, *J. Org. Chem.*, **8**, 440 (1943).

[336] M. S. Kharasch, W. S. Zimmt, and W. Nudenberg, *J. Org. Chem.*, **20**, 1430 (1955).

[337] A. D. Herzfelder, *Ber. Deut. Chem. Ges.*, **26**, 2432 (1893); **27**, 489 (1894).

[338] A. Michael, *Ber. Deut. Chem. Ges.*, **34**, 4037 (1901).

[339] H. Kronstein, *Ber. Deut. Chem. Ges.*, **54**, 1 (1921).

[340] P. Wertyporoch, *Ber. Deut. Chem. Ges.*, **66**, 732 (1933); *Ann. Chem.*, **493**, 153 (1932).

[341] F. Asinger, *Ber. Deut. Chem. Ges.*, **75**, 66 (1942).

[342] H. S. Booth and co-workers, *J. Amer. Chem. Soc.*, **55**, 2231 (1933).

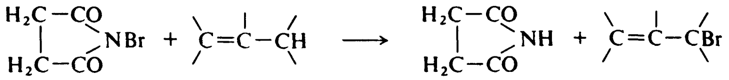
[343] J. C. Sauer, *Org. Syn.*, **36**, 19 (1956).

[344] A. Saytzeff, *Ann. Chem.*, **179**, 296 (1875).

in *Organic Syntheses*;[345] an inert solvent (light petroleum or a higher-boiling alkane) may be added in such cases.[346] The preparation of α-chlorostyrene in approximately 90% yield from α-chloro-α-(chloromethyl)benzyl chloride may be cited as an example of removal of HX by aqueous-ethanolic NaOH.[347] β-Halostyrenes can be obtained by removal of HX, with simultaneous decarboxylation, from 2,3-dihalo-3-phenylpropionic acids by an alkali acetate in boiling ethanol or by aqueous sodium carbonate.[348] Further, tertiary amines such as pyridine, collidine, quinoline, and dialkylanilines are other reagents for removal of HX.

Removal of HBr from bromosteroids under mild conditions is effected by leaving them in pyridine containing 5–10% of $AgNO_3$ at room temperature for 30–48 hours.[349,350]

Methods for direct halogenation of olefins at the carbon atom next to the C=C bond have been worked out mainly in the last 25 years. Allylic chlorination by Cl_2 has been noted above (page 106). Allylic bromination (the Wohl–Ziegler reaction) is of especial preparative importance. Wohl[351] was the first to give a process for this, treating olefins in ether or acetone with *N*-bromoacetamide, but *N*-bromosuccinimide (NBS), introduced by Ziegler,[352] is a substantially better reagent.



$$\mathrm{(H_2C{-}CO)_2NBr} + \mathrm{{>}C{=}C{-}CH{<}} \longrightarrow \mathrm{(H_2C{-}CO)_2NH} + \mathrm{{>}C{=}C{-}CBr{<}}$$

NBS is relatively stable, but it should be noted that *N*-halogenated carboxamides and carboximides such as 1,3-dichloro-5,5-dimethylhydantoin, *N*-chlorosuccinimide, and also NBS are thermally labile and may decompose **explosively.**[353]

Allylic bromination by NBS is a radical-chain reaction occurring on the surface of the NBS crystals. A solution of NBS in tetrachloroethane or nitromethane adds bromide to a C=C group;[354] solvents are therefore used in which NBS and, if possible, also the succinimide formed, are difficultly soluble; dry CCl_4 is usually chosen, but for reactive substances cyclohexane or benzene may also be used. The more polarized the N-halogen is, *i.e.*, the more positive the Br is rendered, the more easily does the *N*-halogenated compound cause addition to the C=C bond; NBS is particularly suitable for allylic bromination because of its steric structure and the almost apolar nature of its N–Br bond.

It should be noted that *N*-bromo compounds can act as oxidizing agents; *e.g.*, *N*-bromoacetamide and NBS oxidize secondary alcohols to ketones, and use of this has been made in steroid syntheses.[355] Aldehydes, semiacetals, and finally esters are formed from primary alcohols by NBS, and disulfides from thiols (for references see Horner and Winkelmann[354]). Iodine is liberated from acidified KI solution, a reaction that can be utilized for quantitative determination of NBS and for detection of unchanged NBS in a reaction.

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[345] R. Lespieau and M. Bourguel, *Org. Syn.*, Coll. Vol. I, 209 (1956).

[346] H. Baganz and co-workers, *Angew. Chem.*, **66**, 307 (1954); *Chem. Ber.*, **87**, 1622 (1954); **89**; 1560 (1956).

[347] W. S. Emerson and E. P. Agnew, *J. Amer. Chem. Soc.*, **67**, 520 (1945).

[348] F. Strauss, *Ber. Deut. Chem. Ges.*, **42**, 2878 (1909); H. Biltz, *Ann. Chem.*, **296**, 266 (1897).

[349] E. Dane, Y. Wang, and W. Schulte, *Z. Physiol. Chem.*, **245**, 80 (1936).

[350] A. Butenandt, G. Schramm, and H. Kudszus, *Ann. Chem.*, **531**, 205 (1937).

[351] A. Wohl, *Ber. Deut. Chem. Ges.*, **52**, 51 (1919); **54**, 476 (1921).

[352] K. Ziegler and co-workers, *Ann. Chem.*, **551**, 80 (1942).

[353] R. H. Martin, *Nature*, **168**, 32 (1951).

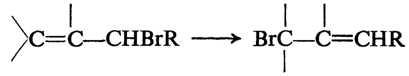
[354] L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

[355] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **72**, 5530 (1950).

There are also descriptions of chlorination in the allylic position by *N*-acyl-*N*-chloroanilines carrying halogen in the nucleus, but this process is inferior as a general method to allylic bromination by NBS.[352] Acyclic and cyclic olefins, also methyl-substituted aromatic compounds, are chlorinated in the allylic position in around 60% yield by *N*-chloro-*N*-cyclohexylbenzenesulfonamide, $C_6H_5SO_2—NCl—C_6H_{11}$, in boiling light petroleum (b.p. 80–110°) to which benzoyl peroxide has been added;[356] the *N*-cyclohexylbenzenesulfonamide produced is insoluble in light petroleum and separates gradually in a very pure state (90–100%). *N*-Chlorosuccinimide can be used for allylic chlorination only in a few special cases, such as the preparation of 5-(chloromethyl)uracil or 6-(chloromethyl)-2-methylthiouracil from 5-methyluracil or 2,6-dimethylthiouracil, respectively, in boiling chloroform containing 15 mole-% of benzoyl peroxide.[357] *tert*-Butyl hypochlorite usually chlorinates olefins in the allylic position by a photochemically induced radical-chain reaction; a paper by Walling and Thäler[358] should be consulted on the distribution and stereochemistry of isomers that can arise from mesomerism of the allyl radical $\cdot CH_2—CH{=}CHR \longleftrightarrow CH_2{=}CH—\dot{C}HR$.

An NBS reaction can be induced thermally, by UV irradiation,[359,360] by addition of radical-formers (dibenzoyl peroxide, 2,2′-azoisobutyronitrile, or dimethyl 2,2′-azoisobutyrate),[361,362] or by increasing the NBS suface (depositing it on neutral SiO_2).[354]

Attention must be paid to the side reactions that can occur in allylic bromination by NBS; they can be reduced by using lower temperatures and by activation, but they cannot be entirely avoided. Allylic rearrangement (cf. p. 1056) of



$$>C{=}\overset{|}{C}—CHBrR \longrightarrow BrC(—)—\overset{|}{C}{=}CHR$$

the primary bromination products is favored by the tendency to conjugation with neighboring multiple bonds in the group R, *e.g.*, when R is $>C{=}C<$, $—C{\equiv}C—$, $—C{\equiv}N$, $>C{=}O$, or $—C_5H_6$. It occurs particularly with olefins containing terminal C=C bonds and with diolefins containing isolated C=C bonds. The allylic bromination may then be followed by a second allylic bromination, or by loss of HBr if this leads to further conjugation or to aromatization; the HBr liberated then liberates bromine from the NBS and this may add to the C=C bond. Numerous references to this are given by Horner and Winkelmann.[354]

The following regularities have been observed in allylic bromination of mono-, di-, and alicyclic olefins by NBS.[352,354] In absence of activation methylene groups are brominated more easily than methyl groups, and these somewhat more easily than methine groups. Straight-chain and branched-chain olefins are brominated by NBS only once at each allyl position; two bromine

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[356] W. Theilacker and H. Wessel, *Ann. Chem.*, **703**, 34 (1967).

[357] R. A. West and H. W. Barrett, *J. Amer. Chem. Soc.*, **76**, 3146 (1954).

[358] C. Walling and W. Thäler, *J. Amer. Chem. Soc.*, **83**, 3877 (1961).

[359] M. S. Kharasch, R. Malec, and N. C. Yang, *J. Org. Chem.*, **22**, 1443 (1957).

[360] J. C. Martin and P. D. Bartlett, *J. Amer. Chem. Soc.*, **79**, 2533 (1957).

[361] H. Schmid and P. Karrer, *Helv. Chim. Acta*, **29**, 573, 1965 (1946).

[362] M. C. Ford and W. A. Waters, *J. Chem. Soc.*, **1952**, 2240.

atoms can be introduced at each allyl position of cyclic olefins but the products then undergo further reaction by allylic rearrangement or loss of HBr, *e.g.*, cyclohexene gives *m*- and *p*-dibromobenzene.[363] Also, if there are four allyl positions around a C=C bond, as in tetramethylethylene, then up to four allylic brominations may take place.

In polynuclear cyclic olefins a second bromination occurs always in the same ring as the first, namely, at the second allylic position if that is free; if that is substituted, allylic positions in other rings may be brominated.

The bromination is more difficult if the substance undergoing substitution dissolves NBS, if space-filling substituents shield the allylic position, if the angle between the C=C bond and the allylic position differs much from 120°, or if the allylic position is polarized by NO_2, CN, SO_2, or C≡C.

Allylic bromination by NBS can be applied with success not only to olefins but also to α,β-unsaturated ketones, carboxylic esters, nitriles, and lactones. Radical-formers must be added when NBS is used for allylic bromination of conjugated dienes, for side-chain bromination of aromatic or heterocyclic compounds (see p. 198), or for replacement of tertiary hydrogen atoms next to a C=C bond.

Preparation of **N-bromosuccinimide** (NBS)[354] (cf. ref. [352]): Succinimide (50 g) (m.p. 125 to 126°) is dissolved in a solution of NaOH (20 g) in water (100 ml) placed in a sulfonation flask cooled externally by ice-water or in a stout-walled, wide-necked flask fitted with mechanical stirring. Succinimide recovered from NBS should be first recrystallized from two parts of ethanol with active charcoal. Finely crushed ice (100 g) is added, and then bromine (27 ml) all at once with vigorous stirring. The mixture is stirred for a further 10 min and then filtered with good suction. The bromine must be distributed through the mixture almost instantaneously because the NBS is precipitated immediately as a crystalline mass. These crystals are made into a slurry with water once to three times, being filtered off each time—the last wash-water must run through without any color of bromine. The NBS is dried over NaOH and then over P_2O_5 in a desiccator. The yield is about 70 g of 98% NBS (44.9% of active bromine), and the m.p. is 174–175° (dec.).

NBS can be recrystallized without decomposition from nitromethane, or with only a little decomposition by dissolution in ten parts of water at 75–80°, rapid filtration, and cooling with ice (m.p. 176–177°). Recrystallized NBS is less reactive than the crude, washed product.

It has also been recommended[364] that the bromine should be dissolved in its own volume of CCl_4.

Allylic bromination with NBS: The usual procedure is to add dry NBS and an activator to a solution of the anhydrous olefin or alkyl-substituted aromatic compound in anhydrous CCl_4 and to heat the solution in a warm bath at about 80°, with occasional shaking, under an efficient reflux condenser carrying a drying tube. Particularly reactive substances are added, with stirring, to a suspension of NBS in CCl_4 at room temperature; readily volatile olefins can be brought into reaction at a lower temperature by UV irradiation. Photoactivation alone is not a good preparative technique because of the long reaction time needed. The materials, in particular the olefin, must be anhydrous; the latter can usually be first distilled over sodium; technical CCl_4 should be boiled for a day under reflux with P_2O_5, then distilled through a column. The proportion olefin: CCl_4 should be about 1 : 10 to 1 : 20, and the proportion

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[363] R. A. Barnes, *J. Amer. Chem. Soc.*, **70**, 145 (1948).

[364] E. Campaigne and B. F. Tullar, *Org. Syn.*, **33**, 97 (1953).

NBS : CCl_4 1 : 4; less CCl_4 is used with unreactive substances; liquid substances can also be brominated without a solvent.

Very reactive substances are treated with NBS alone, but in other cases a radical-former is added. The favored radical activator for bromination of olefins by NBS is 2,2′-azoisobutyronitrile, 1 part per 100–1000 parts of NBS. This nitrile is obtained by reaction of bromine water with 2,2′-hydrazoisobutyrodinitrile, which is prepared from acetone, KCN, and hydrazine sulfate in warm water[365] (see also Dox[366]). The decomposition temperature of dibenzoyl peroxide is higher than that of 2,2′-azoisobutyrodinitrile, and about 30° above the boiling point of CCl_4.

It is harder to induce reaction of NBS by means of dibenzoyl peroxide, for which reason it is recommended for use with less sensitive substances, and in particular with alkyl-substituted aromatic compounds. One part, or occasionally more, of the peroxide is taken per 100 parts of NBS. It is mixed with the NBS (not ground with it!) or added in a little chloroform; but substantial amounts of dibenzoyl peroxide should not be heated with chloroform (!).

Redox catalysts are particularly active.[354] A few drops of a 60% solution of *tert*-butyl hydroperoxide in dimethyl phthalate are added to the batch in the cold, followed at about 70° by 1–2 drops of a concentrated solution of cobalt(II) or copper(II) dodecanoate. The reaction then begins at once and continues smoothly.

Bromination by NBS, which is usually exothermic, generally begins when the temperature reaches about 80°. It then proceeds rapidly, but it can become strongly exothermic, so that it is advisable to have a bath of ice-water ready for a brief cooling in case of that eventuality. If the reaction is slow to start, the mixture may be heated at 80° for a few minutes or more activator may be added. If the reaction occupies more than an hour at 80° then side reactions must be expected, particularly with olefins. The end of the reaction is recognized when all the heavy NBS on the bottom flask has been replaced by the light succinimide at the surface of the liquid. At this stage heating is interrupted and if necessary, for concentrated solutions, some more CCl_4 is added. The mixture is then filtered, hot for multiply brominated compounds, otherwise after cooling. The succinimide is washed with CCl_4, and the solvent is removed from the filtrate in a vacuum; the residue is recrystallized or fractionated in a vacuum.

Attention is drawn to two reviews of NBS reactions.[354,367]

tert-Butyl hypobromite may be used, like *tert*-butyl hypochlorite, for radical halogenation at the allyl position.

$$(CH_3)_3C{-}O^\bullet + RH \longrightarrow (CH_3)_3C{-}OH + R^\bullet$$

$$R^\bullet + (CH_3)_3C{-}OX \longrightarrow RX + (CH_3)_3C{-}O^\bullet$$

$$X = Cl \quad \text{or} \quad Br$$

It is prepared by shaking a solution of *tert*-butyl alcohol in trichlorofluoromethane with a solution of HOBr obtained from bromine water and silver sulfate.[368]

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[365] J. Thiele and K. Heuser, *Ann. Chem.*, **290**, 30 (1896).

[366] A. W. Dox, *J. Amer. Chem. Soc.*, **47**, 1473 (1925).

[367] C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

[368] C. Walling and A. Padwa, *J. Org. Chem.*, **27**, 2976 (1962).

2. Replacement of hydrogen by halogen in aromatic compounds: general

Direct substitution of halogen for hydrogen on the C=C bond is an important preparative reaction in the aromatic series. The competition between addition of halogen and substitution of aromatic compounds has been discussed above (p. 117). Fluorine is best introduced into the nucleus or into a side chain by replacing a C—N bond by a C—F bond (p. 265) or by halogen exchange (p. 204). The following remarks therefore refer to chlorination, bromination, and iodination of aromatic compounds. Like nitration, nuclear halogenation is an electrophilic reaction; it is accelerated by using a solvent of high dielectric constant (*e.g.*, nitrobenzene or glacial acetic acid) and catalysts that have a polarizing action, such as Fe turnings, a halide of Fe, Al, Zn, Sn, or Sb, or iodine, so that alkyl-substituted aromatic compounds, which can also be halogenated in the side chain, are halogenated preferentially in the nucleus at low temperature (10–20°).

The ease with which aromatic compounds, and heterocyclic ones that resemble aromatic ones, are halogenated in the nucleus depends greatly on the substituents already attached to the ring. If these are halogen, COOH, SO_3H, or NO_2 a catalyst must usually be used, whereas OH, O-Alkyl, and NH_2, for instance, favor nuclear halogenation so much that it can be effected even without a catalyst.

In comparison with H, substituents of the first class, such as Br, Cl, F, CH_3, $NHCOCH_3$, OCH_3, OH, NH_2, and $N(CH_3)_2$, accelerate chlorination and bromination with an efficiency increasing from left to right in the above series, and they direct the entering group to the *ortho*- and preponderatingly the *para*-position; substituents of the second class, such as CHO, COR, $COOC_2H_5$, COOH, NO_2, SO_3H, and CF_3 direct the entering group to the *meta*-position and decrease the rate of halogenation.[369] However, in the gas phase at 400–450° upwards, fluoro-, chloro-, and bromo-benzene are no longer brominated mainly in *ortho*/*para*- but now in the *meta*-position; the temperature at which this reversal of substituion type occurs is lowered by addition of $FeBr_3$ and UV irradiation, whence it can be concluded that *meta*-bromination of halobenzenes involves a radical mechanism.[370]

Indirect routes must be used to introduce halogen into the *meta*-position of aromatic compounds containing substituents of the first class or into the *ortho*/*para*-positions of those with substituents of the second class.

Thus 1,3,5-tribromobenzene is prepared from 2,4,6-tribromoaniline, which is very easily obtained by leading a stream of air saturated with bromine vapor into an aqueous solution of aniline hydrochloride; the tribromoaniline is diazotized and boiled with ethanol, as described in detail in *Organic Syntheses*.[371]

2,4,6-Tribromobenzoic acid is similarly obtained from 3-amino-2,4,6-tribromobenzoic acid; the NH_2 group is replaced by H when the amino acid is diazotized in the presence of hypophosphorous acid. For details see *Organic Syntheses*.[372]

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[369] P. W. Robertson, P. B. D. de la Mare, and B. E. Swedlund, *J. Chem. Soc.*, **1953**, 782.

[370] J. P. Wibaut and co-workers, *Rec. Trav. Chim.*, **56**, 815 (1937); **69**, 1031 (1950).

[371] G. H. Coleman and W. T. Talbot, *Org. Syn.*, Coll. Vol. II, 592 (1943).

[372] M. M. Robison and B. L. Robison, *Org. Syn.*, **36**, 94 (1956).

The reaction (a) explains the effect of the above-mentioned catalysts in promoting electrophilic nuclear substitution by elemental halogen:

$$Br_2 + FeBr_3 \rightleftarrows Br^+[FeBr_4]^- \; \ldots \text{(a)}$$

The Birckenbach–Goubeau–Waters reaction[373–375] is another method of producing halogen cations: acyl hypohalites are produced as intermediates in the reaction mixture by treating iodine (or bromine) with a molar equivalent amount of mercury acetate or silver acetate, trichloroacetate, perchlorate, sulfate, or trifluoroacetate (reactions b and c):

$$\left.\begin{array}{l} AgClO_4 + I_2 \longrightarrow AgI + IClO_4 \\ RH + IClO_4 \longrightarrow RI + HClO_4 \end{array}\right\} \ldots \text{(b)}$$

$$\left.\begin{array}{l} CF_3COOAg + I_2 \longrightarrow AgI + CF_3COOI \\ RH + CF_3COOI \longrightarrow RI + CF_3COOH \end{array}\right\} \ldots \text{(c)}$$

Unsubstituted aromatic compounds (see p. 167) and those with *ortho/para*-directing (see p. 168) or, above all, *meta*-directing substituents (see p. 168) in the nucleus can be brominated and iodinated by this method; and some analogous chlorinations have also been described.[376] The reaction can be run in non-aqueous or in aqueous media; it is also often carried out without a solvent.

Silver perchlorate is used without a solvent or in ether or benzene, CaO, MgO, or $CaCO_3$ being added to trap the perchloric acid formed; an example is described on page 156.

Glacial acetic acid is a suitable solvent for use with silver acetate; and CCl_4 or, up to 150°, nitrobenzene for use with silver trifluoroacetate. The Hunsdiecker reaction (see p. 1005) may intervene as competing reaction:[377] trifluoroiodomethane, for example, may be formed when iodine, silver trifluoroacetate, and nitrobenzene are heated in the absence of a substance that can be iodinated:

$$CF_3COOAg + I_2 \longrightarrow CF_3I + AgI + CO_2$$

Preparation of silver trifluoroacetate from silver oxide and trifluoroacetic acid in water, and purification of the crude evaporation residue by extraction with ether, are described in *Organic Syntheses*.[378]

Silver trifluoroacetate has the advantages over the other salts[379] that it is the most soluble of them in organic solvents such as benzene and ether, and that the trifluoroacetic acid formed can be readily distilled off (b.p. 71.5°) in contrast to the somewhat dangerous perchloric acid. Examples are given on page 167.

If the compounds to be halogenated themselves contain COOH groups, their dry silver salts (0.05 mole) can be treated in dry CCl_4 with iodine or bromine (0.1 mole). Examples are benzoic[380] and aryl-substituted fatty acids.[381]

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[373] L. Birckenbach and J. Goubeau, *Ber. Deut. Chem. Ges.*, **65**, 395 (1932); **66**, 1280 (1933).

[374] D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, **1950**, (a) 573, (b) 3694.

[375] I. R. L. Barker and W. A. Waters, *J. Chem. Soc.*, **1952**, 151.

[376] J. H. Gorvin, *J. Chem. Soc.*, **1953**, 1237.

[377] C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).

[378] D. E. Janssen and C. V. Wilson, *Org. Syn.*, **36**, 46 (1956).

[379] R. N. Haszeldine and A. G. Sharpe, *J. Chem. Soc.*, **1952**, 993.

[380] K. Birnbaum and H. Reinherz, *Ber. Deut. Chem. Ges.*, **15**, 456 (1882).

[381] D. Papa, E. Schwenk, and E. Klingsberg, *J. Amer. Chem. Soc.*, **72**, 2623 (1950).

Only minute amounts of halogen cations are present in aqueous solutions of halogens. To shift the equilibrium (d) to the right, silver or mercury(II) salts, or $KBrO_3$ (f), are added, which remove the halogen a nion from the system.

$$H_2O + Br_2 \rightleftarrows HOBr + H^+ + Br^- \quad \text{... (d)}$$

$$H^+ + HOBr \rightleftarrows (H_2OBr)^+ \quad \text{... (e)}$$

$$5\,H^+ + 5\,Br^- + HBrO_3 \rightleftarrows 3\,H_2O + 3\,Br_2 \quad \text{... (f)}$$

If a mineral acid is also added — or 75% acetic acid may be used[382] — then HOBr becomes a powerful brominating agent (e); the same is true for iodination (for examples see pages 155 and 184).

Although the Birckenbach–Goubeau–Waters methods of nuclear bromination and iodination are applied under very similar conditions, most, though not all, of the other processes for nuclear iodination differ from the usual methods of chlorinating and brominating aromatic compounds. Since iodination by elemental iodine is reversible (g),

$$RH + I_2 \rightleftarrows RI + HI \quad \text{... (g)}$$

it is best to remove the hydrogen iodide formed either (a) by salt formation (alkali hydroxide, carbonate, or hydrogen carbonate, borax,[383] HgO, Hg acetate, NH_3, or an aliphatic amine) or (b) by an oxidizing agent (H_2O_2, $Na_2S_2O_8$, iodate or HIO_3, HNO_3, H_2SO_4, or oleum), which reconverts the HI into I_2.

At the end of the reaction the excess of iodine is removed by passing in SO_2 or by shaking the mixture with a solution of sodium hydrogen sulfite or thiosulfate, sometimes also with KI or mercury. Solvents used, besides water, are glacial acetic acid, alcohols, or benzene, more rarely ether or CCl_4. Iodination with added $Na_2S_2O_8$, HIO_3, or HNO_3 are quite generally applicable, but the methods (a) and the H_2O_2 procedure are used only for aromatic or heterocyclic compounds that are readily amenable to electrophilic substitution; numerous examples are cited on pages 155 and 182.

Radical side-chain halogenation competes with ionic nuclear halogenation for aromatic compounds that carry alkyl substituents. For radical side-chain chlorination or bromination the solvent used, if any, should be apolar (CS_2 or CCl_4; benzene is less suitable).

Even small amounts of sulfur in CS_2 or CCl_4 appreciably decelerate side-chain bromination of toluene under irradiation at 57°,[384] if CS_2 is shaken several times with mercury and redistilled, side-chain bromination in that solvent becomes substantially faster. $CHCl_3$ is not a suitable solvent for brominations; at 57° it reacts with bromine within a few minutes; however, if $CHCl_3$ (75 ml) is shaken ten times with water (50-ml portions), then dried and distilled, its stability towards bromine is increased.[384]

Side-chain halogenation is favored by heat with irradiation by sunlight, UV light, or powerful clear electric lamps (200–300 W), and also by addition of radical-formers. For instance, adding 0.03 mole of a peroxide (ascaridole or dibenzoyl peroxide) per mole of bromine leads to 85% bromination of

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[382] S. J. Branch and B. Jones, *J. Chem. Soc.*, **1954**, 2317.

[383] A. Classen and W. Löb, *Ber. Deut. Chem. Ges.*, **28**, 1605 (1895).

[384] J. R. Sampey and E. M. Hicks, *J. Amer. Chem. Soc.*, **62**, 3252 (1940); J. R. Sampey, F. S. Fawcett, and B. A. Morehead, *J. Amer. Chem. Soc.*, **62**, 1839 (1940).

toluene at 25° in the dark within 25 minutes, the product containing 98% of benzyl bromide.[385] Large concentrations of HCl or HBr in the reaction mixture are unfavorable.

For aromatic compounds having methyl or higher alkyl substituents side-chain halogenation at the α-carbon atom is analogous to allylic halogenation of olefins (see pp. 106 and 146), which explains why *N*-bromosuccinimide (NBS) can also be used for side-chain bromination. However, although all three H atoms of a methyl side chain can be replaced when elemental chlorine or bromine is used, only two atoms of bromine, at most, can be introduced into the side chain by NBS. To replace one α-H atom by bromine, at most 1 mole of NBS per methyl group is used, and for two α-H atoms 2 moles of NBS. Dibenzoyl peroxide is usually added as activator, reactions then requiring 5 to 60 minutes (see page 149).

For example, benzyl bromide is thus obtained from toluene,[361,385] and the corresponding bromomethyl compounds from 1- and 2-methylnaphthalene;[387,388] numerous other examples are given by Horner and Winkelmann.[354]

It should be noted that NBS can cause nuclear bromination when that reaction occurs readily. In the absence of a catalyst it can brominate the nucleus of condensed aromatic compounds such as naphthalene, anthracene, and phenanthrene,[399] veratrole, the dimethyl ethers of resorcinol and hydroquinone,[389] and pyrogallol trimethyl ether.[390] Pyrocatechol and 2 moles of NBS afford 4,5-dibromopyrocatechol; resorcinol and 3 moles of NBS afford 2,4,6-tribromoresorcinol;[391,392] and anthranilic or *o*- or *p*-hydroxybenzoic acid with 2 moles of NBS afford the 4,5- or 3,5-dibromo derivatives.[391-393] However, nuclear bromination of benzene and toluene is effected by NBS only if equimolar amounts of $AlCl_3$, $ZnCl_2$, $FeCl_3$, or H_2SO_4 are added.

3. Replacement of hydrogen by halogen in the nuclei of aromatic hydrocarbons

Elemental chlorine is usually used for nuclear chlorination, sometimes diluted with CO_2. For monochlorination ca. 0.8 mole of Cl_2 is passed into the liquid hydrocarbon with weight control (weighing of the chlorine reservoir or of the reaction mixture). The hydrocarbon may be diluted with, *e.g.*, CS_2, CCl_4, or glacial acetic or sulfuric acid. Water can also be used[1g] if 1–2% of an emulsifier is added, a C_{16}—C_{18}-alkane sulfonate being suitable as polar medium (100–250%) which also takes up the hydrogen chloride formed. The crude chlorination products are washed with water and sodium hydroxide solution. Chlorobenzene is obtained by using the customary carriers (I_2, $AlCl_3$, or $FeCl_3$). Chlorination of naphthalene affords mainly 1-chloronaph-

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[385] M. S. Kharasch, *J. Amer. Chem. Soc.*, **59**, 1405 (1937).

[386] H. Schmid, *Helv. Chim. Acta*, **29**, 1144 (1946).

[387] Ng. Ph. Buu-Hoï and J. Lecocq, *J. Chem. Soc.*, **1946**, 830.

[388] N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, **1952**, 5044.

[389] Ng. Ph. Buu-Hoï, *Ann. Chem.*, **556**, 1 (1944).

[390] Ng. Ph. Buu-Hoï. *Pec. Trav. Chim.* **73**, 197 (1954).

[391] W. J. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955).

[392] M. F. Abdel-Wahab and N. Z. Barakat, *Monatsh. Chem.*, **88**, 692 (1957).

[393] M. Z. Barakat and M. F. Abdel-Wahab, *J. Amer. Chem. Soc.*, **75**, 5731 (1953); **77**, 1670 (1955).

thalene, but this is difficult to separate from the 2-chloronaphthalene that is formed as by-product, so that the Sandmeyer synthesis from α-naphthylamine is preferable. Pure *o*- and *p*-halotoluenes are also best prepared from the corresponding toluidines.

SO_2Cl_2 can be used in place of chlorine (see page 162); or alternatively nascent chlorine which is obtained in the laboratory from HCl and H_2O_2 (see page 168) or industrially from HCl on a catalyst containing a copper salt. Dichloramine-T (p-CH_3—C_6H_4—SO_2NCl_2) in HCl/glacial acetic acid effects nuclear chlorination of, for example, 2-methyl-1*H*-benz[*de*]anthracene to the 3-chloro derivative.[394] Boiling 1,2,3-benzotriazole with aqua regia (3 vol-parts of concentrated HCl + 1 vol-part of concentrated HNO_3) for 3 hours under reflux yields 87% of 4,5,6,7-tetrachlorobenzotriazole.[395]

For monobromination it is usual to drop 0.8–1.1 mole of bromine with ice-cooling and stirring into 1 mole of the hydrocarbon to which a halogen carrier has been added, and to set the mixture aside for about 12 hours. The reaction may be completed at about 50° or the mixture may be washed at once with water and dilute alkali. When possible, the product is purified by steam-distillation. It is advantageous to pass dry HBr into the hydrocarbon before bromination is begun.[396]

As example may be cited the bromination of *o*-xylene by bromine in the presence of iron filings and/or iodine, giving 4-bromo-*o*-xylene, as described in detail in *Organic Syntheses*.[397]

A number of aromatic hydrocarbons are readily brominated in the nucleus by about a 10% excess of bromine, best in an indifferent solvent such as CCl_4 or CS_2, with warming but without a catalyst; examples are mesitylene,[398] naphthalene[399] (giving 1-bromonaphthalene), anthracene (giving 9-bromoanthracene[400] or 9,10-dibromoanthracene[401]), and phenanthrene [402] (giving 9-bromophenanthrene). Mesitylene, which can be attacked also in the side chain, is brominated in CCl_4 at 10–15°; the side-chain brominated product which is formed alongside the approximately 80% of bromomesitylene is removed by one hour's boiling of the crude product with ethanolic sodium ethoxide solution.

Chloromesitylene and other monochloropolyalkylbenzenes are similarly obtained without use of a carrier by means of Cl_2 in $CHCl_3$ at 0°.[403]

4,4′-Dibromobiphenyl can even be obtained (75–77% yield) if 0.1 mole of finely powdered biphenyl is kept in the presence of 0.24 mole of bromine for 8 hr in a desiccator whose tap is slightly opened to permit escape of HBr.[404]

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[394] D. H. Hey, R. I. Nicholls, and C. W. Pritchett, *J. Chem. Soc.*, **1944**, 97.

[395] R. H. Wiley, K. H. Hussung, and J. Moffat, *J. Amer. Chem. Soc.*,. **77**, 5105 (1955).

[396] U.S. Pat. 2,659,760; *Chem. Abstr.*, **49**, 1791 (1955).

[397] W. A. Wisansky and S. Ansbacher, *Org. Syn.*, Coll. Vol. III, 138 (1955).

[398] L. I. Smith and F. H. McDougall, *J. Amer. Chem. Soc.*, **51**, 3002 (1929); L. I. Smith, *Org. Syn.*, Coll. Vol. II, 95 (1943).

[399] F. F. Blicke, *J. Amer. Chem. Soc.*, **49**, 2846 (1927); H. T. Clarke and H. R. Brethen, *Org. Syn.*, **10**, 14 (1930); Coll. Vol. I, 121 (1941).

[400] E. de B. Barnett and J. W. Cook, *J. Chem. Soc.*, **1924**, 1086.

[401] I. M. Heilbron and J. S. Heaton, *Org. Syn.*, **3**, 41 (1923).

[402] C. A. Dornfield, J. E. Callen, and G. H. Coleman, *Org. Syn.*, Coll. Vol. III, 134 (1955).

[403] L. I. Smith and C. L. Moyle, *J. Amer. Chem. Soc.*, **58**, 7 (1936).

[404] R. E. Buckles and N. G. Wheeler, *Org. Syn.*, **31**, 29 (1951).

If 1 ml of an alkylbenzene is added during 1 h to 7 ml of bromine and 0.2 g of iron powder and the mixture is stirred for a further hour, polybromo compounds are obtained in which secondary and tertiary alkyl groups are replaced by bromine but primary alkyl groups are retained.[405]

An example of bromination of an aromatic hydrocarbon by Water's method is provided by the preparation of **bromobenzene**:[374a]

A solution of $AgNO_3$ (0.125 mole) in water (100 ml) is dropped during 90 min, in the dark, with stirring at room temperature, into an emulsion of benzene (0.25 mole), 2N-nitric acid (1 l), and bromine (20 g); the yield is 80%.

Dioxan · Br_2 (see page 166) can also be used for nuclear bromination:[406]

When toluene (9.5 g) is treated with dioxan · Br_2 (from 15.1 g of bromine) and heated at 35–40°, the mixture is rapidly decolorized; after dilution with 10% NaOH solution, ***p*-bromotoluene** (16.8 g) is obtained. Naphthalene can be similarly monobrominated at the 1-position, anthracene at the 9- and fluorene at the 2-position.

Iodine bromide (IBr) in glacial acetic acid, $CHCl_3$, or even nitrobenzene,[407] is a mild brominating agent and is recommended for the synthesis of 4-bromo-1-naphthol and 1-bromonaphthalene,[408] also of 1-bromo-4-methoxynaphthalene.[409] It is prepared from equimolar quantities of iodine and bromine in the solvent used for the reaction (glacial acetic acid or $CHCl_3$).

For direct introduction of iodine into the nucleus of aromatic hydrocarbons, usually only the most energetic of the methods mentioned on page 152 are useful. Iodination by iodine and HNO_3 (*d* 1.5)[410] is strongly exothermic and useful for benzene and alkylbenzenes, but phenols and nitrocompounds are formed as by-products; the phenols can be removed by shaking the crude product with 10% sodium hydroxide solution, and the nitro compounds by reduction of the crude product with iron filings and hydrochloric acid; then the crude solution is made acid to Congo Red and the iodinated aromatic compound is distilled off in steam.

When HNO_3 (*d* 1.5; 275 ml) is dropped during about 1 h into a mixture of I_2 (1.5 mole) and benzene (5.1 mole) stirred on a water-bath at about 50°, the whole gradually comes to the boiling point while considerable quantities of nitrogen oxides are evolved. Detailed descriptions of the preparation of iodobenzene[411] and 2-iodothiophen[412] can be found in *Organic Syntheses.*

A glacial acetic acid solution of the substance to be iodinated may also be treated with concentrated sulfuric acid, iodine (1 mole), and sodium nitrite, instead of with HNO_3;[413] success depends on the nature of the sodium nitrite; it is recommended that sintered sodium nitrite be ground in a mortar until the pieces have a volume of about 1 ml. Nitrosylsulfuric acid or nitrating acid may also be used in place of HNO_3.[414]

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[405] G. F. Hennion and J. G. Anderson, *J. Amer. Chem. Soc.*, **68**, 424 (1946).

[406] A. P. Terent'ev, L. I. Balen'ki, and L. A. Janovskaya, *Zh. Obsch. Khim.*, **24**, 1265 (1954); *Chem. Abstr.*, **49**, 12327 (1955).

[407] F. W. Bennett and A. G. Sharpe, *J. Chem. Soc.*, **1950**, 1383.

[408] W. Militzer, *J. Amer. Chem. Soc.*, **60**, 256 (1938).

[409] E. C. Spaeth, T. A. Geissman, and T. L. Jacobs, *J. Org. Chem.*, **11**, 399 (1946).

[410] R. L. Datta and N. R. Chatterjee, *J. Amer. Chem. Soc.*, **39**, 437 (1917); **41**, 292 (1919).

[411] F. B. Dains and R. Q. Brewster, *Org. Syn.*, **9**, 46 (1929); Coll. Vol. I, 323 (1947).

[412] H. Y. Lew and C. R. Noller, *Org. Syn.*, **30**, 53 (1950).

[413] J. T. Plati, W. H. Strain, and S. L. Warren, *J. Amer. Chem. Soc.*, **65**, 1274 (1943).

[414] P. S. Varma and co-workers, *J. Indian Chem. Soc.*, **12**, 343 (1935); **14**, 156 (1937); A. N. Novikov, *Zh. Obshch. Khim.*, **24**, 655 (1954); *Chem. Abstr.*, **49**, 5338 (1955).

Sodium peroxydisulfate can also be used to oxidize the hydrogen iodide formed on direct iodination of alkyl- and aryl-benzenes;[415] the solvent may by glacial acetic acid,

$$2C_6H_5R + I_2 + Na_2S_2O_8 \longrightarrow 2\,C_6H_4RI + 2\,NaHSO_4$$

to which 10–20 vol-% of water must be added for dissolution of the peroxy disulfate; the iodine and peroxydisulfate are used in stoichiometric proportions.[416a]

4-Iodobiphenyl:[416c] A solution of biphenyl (15.4 g) in glacial acetic acid (100 ml) is treated to turbidity with water (about 25 ml) at 80°, then iodine (12.7 g), sodium peroxydisulfate (12.5 g), and CCl_4 (8ml) are added, the last-mentioned to wash down the iodine that sublimes into the condenser. The whole is stirred vigorously until the iodine color has vanished (about 3 h), then water (300 ml) is added and the product that separates is filtered off and dried. The 4-iodobiphenyl forming the main product, together with unchanged biphenyl, is distilled off (b.p. 118–125°/0.05 mm) and, after recrystallization from methanol, has m.p. 112° (yield, 17.4 g, 62%).

Iodination by iodine and iodic acid or iodate[420b] is quite generally applicable.[416b] A suitable solvent is glacial acetic acid, for it is indifferent to iodic acid up to 80° although it is attacked at 100° with generation of CO_2; nitrobenzene, which is itself iodinated only at 120°, can be added to increase the solubility; to effect dissolution of the iodic acid, about 10 vol-% of water can be added. For each 2 moles of iodine 1.1–1.15 mole of iodic acid is used, *i.e.*, a 10–15% excess; the C_6H_5R is also used in slight excess.

$$5\,C_6H_5R + 2\,I_2 + HIO_3 \longrightarrow 5\,C_6H_4RI + 3\,H_2O$$

Iodination by I_2–HIO_3, as by I_2–$Na_2S_2O_8$, is catalysed by acid, so that 3 vol-% of concentrated H_2SO_4 is usually added. The reaction is exothermic and at 80–85° it should be complete in 2–3 hours.

Iodobenzene:[416d] A mixture of benzene (25 g), glacial acetic acid (80 ml), 50% sulfuric acid (15 ml), iodine (24.4 g), and iodic acid (9.5 g) is stirred for 1 h at 90°, and then at 95° until the iodine is consumed (2 h). The product that is precipitated by water is dissolved in $CHCl_3$ (50 ml), washed with $NaHSO_3$ solution, dried, and freed from $CHCl_3$ and benzene. This crude product (47.5 g) is diluted with light petroleum and passed through a column of alumina that has been pretreated dry with NH_3 (dried over KOH) until the initial warming ceases. Vacuum-distillation of the eluate affords 83% of iodobenzene.

53% of pure *p*-chloroiodobenzene, 65% of *p*-bromoiodobenzene, and 56% of *p*-diiodobenzene are obtained similarly.

The method of operating Birkenbach–Goubeau–Waters iodinations is illustrated by the following examples:

Finely powdered (!) iodine (0.22 mole) is added, in portions, during 2 h, to a rapidly stirred mixture of benzene (0.3 mole), Ag_2SO_4 (0.1 mole), concentrated HCl (200 ml), and water (200 ml). The whole is stirred for a further hour, then diluted with water (600 ml) and decanted from AgI and residual iodine. The solid product is treated with sodium hydrogen sulfite and extracted with ether. The ether extracts afford, after vacuum-distillation 78% of **iodobenzene.**[375]

Silver perchlorate (22 g) and $CaCO_3$ (10 g) are suspended in benzene (100 ml) and, with cooling, treated with iodine (25 g) during 15 min. The mixture is then filtered and the filtrate is washed three times with water, dried over calcium chloride, and distilled, giving 80% of **iodobenzene.**[373]

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[415] K. Elbs and A. Jaroslawzew, *J. Prakt. Chem.*, [ii], **88**, 92 (1913).

[416] H. O. Wirth, O. Königstein, and W. Kern, *Ann. Chem.*, **634**, (a) 84, (b) (d) 100 (1960).

4. Replacement of hydrogen by halogen in the side chain of aromatic hydrocarbons

Chlorination and bromination in the side chain of alkylaromatic compounds requires exclusion of the catalysts of ionic halogenation, *i.e.*, above all of metal salts. Thus it is recommended to add substances that form stable complexes with metal salts, *e.g.*, ethylenedinitrilotetraacetic acid (EDTA).[417] Side-chain halogenation requires conditions under which radicals can be formed, *i.e.*, illumination (100–200 household lamps or UV), high temperatures, and addition of radical formers. Discoloration occurring during side-chain chlorination, which inhibits light absorption, can be avoided by adding 0.1–5% of benzamide.[418]

Benzyl chloride (b.p. 179.3°/760 mm, 64°/12 mm)[33c,h] is prepared in the laboratory by passing chlorine into boiling dry toluene (exothermic reaction!) under irradiation (200 W lamp) until the temperature reaches 156° or the density is 1.05. The unchanged toluene is distilled off and the residue is fractionated in a vacuum. The product contains 60–70% of the calculated amount of benzyl chloride.

About 70% of **benzylidene chloride** (b.p. 207°/760 mm, 96–102°/5 mm), with 25% of benzotrichloride (b.p. 220.7°) and 5% of more highly chlorinated products, are obtained if the chlorine is led into the boiling toluene until the density at 135° amounts to 1.29–1.33.

Benzylidene chloride and its nuclear-substituted derivatives are important mainly as intermediates on the way to aldehydes, so that the difficulty of separating them from benzotrichlorides must be overcome. On hydrolysis they give benzoic acids, which are readily separable from the aldehydes. Phosphorus trichloride (ca. 2%) has been recommended as addition for side-chain chlorination of toluenes.

It is appropriate to add radical-formers for side-chain chlorination by sulfonyl chloride.

The mixture of SO_2Cl_2 and the compound to be chlorinated is treated with 0.001–0.005 mole of dibenzoyl peroxide or bisdodecanoyl peroxide per mole of SO_2Cl_2, and the mixture is warmed to gentle ebullition under an efficient reflux condenser until cessation of evolution of HCl and SO_2 signals the end of the reaction (15–30 min; 90 min for cumol). The product is worked up by direct fractional distillation. One mole of toluene with 1 mole (or less) of SO_2Cl_2 gives a very good yield of benzyl chloride, and with 2 moles (or more) of SO_2Cl_2 gives benzylidene chloride; this process does not give benzotrichloride.

Like radical side-chain bromination, side-chain chlorination by SO_2Cl_2 and a peroxide occurs mainly on the α-carbon atom: ethylbenzene gives mainly (1-chloroethyl)benzene; cumol gives 90% of the α- and 10% of the β-chloro product. Chlorine enters the β-position of *tert*-butylbenzene. *o*- and *p*-Nitrotoluene cannot be converted into the corresponding benzyl chlorides by SO_2Cl_2 and a peroxide.[419]

α,α'-Azoisobutyronitrile (R = CN) or dimethyl α,α'-azoisobutyrate (R = $COOCH_3$) may be used in place of a peroxide. These azo compounds decompose smoothly (reaction *a*) in solution at 80–120°, giving N_2 and a tertiary aliphatic radical that does not attack a solvent such as benzene, toluene, or CCl_4.

$$(CH_3)_2RC{-}N{=}N{-}CR(CH_3)_2 \longrightarrow 2\,(CH_3)_2RC^{\cdot} + N_2 \quad \ldots \text{(a)}$$

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[417] Ger. Pat. 855,105; *Chem. Abstr.*, **50**, 12,535 (1956).

[418] U.S. Pat. 2,695,873; *Chem. Abstr.*, **49**, 6364 (1955).

[419] M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **61**, 2144, 2148 (1939).

On addition of 0.3–0.5 mole-% of the azo compound to a boiling mixture of toluene or triphenylmethane with SO_2Cl_2, 70% of benzyl chloride or 77% of triphenylmethyl chloride was obtained.[333]

Triphenylmethyl chloride:[419] A mixture of triphenylmethane (8.4 g), SO_2Cl_2 (13.5 g), and bisdodecanoyl peroxide (0.1 g) is heated for 30 min under reflux. The residue left on removal of the excess of SO_2Cl_2 is recrystallized twice from light petroleum (b.p. 90–100°), giving triphenylmethyl chloride (5.7 g), m.p. 111–112°.

Benzyl chloride:[333] α,α′-Azoisobutyronitrile (0.2 g) is added to a mixture of dry toluene (0.8 mole) and SO_2Cl_2 (0.4 mole) boiling under reflux on the water-bath. A vigorous reaction sets in after a few seconds, with evolution of HCl and SO_2, and it is complete in 15 min. Two fractionations afford unchanged toluene and 70% of benzyl chloride.

The preparation of α′α′-azoisobutyronitrile by oxidation of the corresponding crude hydrazo compound with chlorine in aqueous solution is described in the Houben–Weyl compendium.[1r] α,α'-Hydrazoisobutyronitrile [*N,N*′-bis-(1-cyano-1-methylethyl)hydrazine] is readily accessible from hydrazine sulfate, NaCN, and acetone in water.[1r]

On side-chain chlorination of bromotoluenes by SO_2Cl_2 and benzoyl peroxide, exchange of nuclear bromine for chlorine occurs as side reaction.[420]

For the preparation of substituted benzyl bromides in quantity it is usual to drop 1.1 mole of bromine or its solution in CCl_4, during 1.5–2 h, with stirring and irradiation by UV light or by a 100–600 W lamp, to the appropriate toluene (1 mole) which is heated in an oil-bath at 120–160° or is dissolved in boiling CCl_4. When undiluted bromine is used it should be delivered from the dropping funnel below the surface of the liquid. An example of bromination by bromine at 145–150° is the preparation of 4-nitrobenzyl bromide from *p*-nitrotoluene that is detailed in *Organic Syntheses*.[421]

According to these directions, the bromine is dropped in during 2 h, and the mixture is left for a further 10 min, then worked up by being poured into hot light petroleum, from which, after treatment with charcoal, 4-nitrobenzyl bromide crystallizes. Kröhnke has given preparative data for a series of substituted benzyl halides, including 3-nitro-3-chloro-, 4-iodo-, 2,6-dichloro-,[422] and 4-chlorobenzyl bromide,[423] and he has reviewed briefly the methods available.[424] He has improved the direction given in *Organic Syntheses*: 4 g of mercury and 1 ml of water are added per 80 g of *p*-nitrotoluene, the product is poured into water, and the insoluble material is dissolved in 240 ml of hot ethanol, from which it crystallizes at 0°; the yield of **4-nitrobenzyl bromide** is then 80% instead of 59–66%.

The preparation of α,α′-dibromo-*o*-xylene from xylene, described in *Organic Syntheses*,[425] may be noted as a further example of this process.

It should be noted here that benzyl chlorides and bromides can be obtained also by replacement of OH by Cl or Br and by chloromethylation[426] or bromomethylation (see, *e.g.*, the Houben–Weyl compendium[1m]).

Side-chain halogenated aromatic compounds irritate the mucous membranes and are sensitive to moisture. They are not very stable thermally — the less so the less aromatic the nucleus. A simple method for **determination of side-chain bromine** is based on the mobility of the bromine in benzyl bromides:[384]

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[420] G. L. Goerner and R. C. Mametz, *J. Amer. Chem. Soc.*, **73**, 2940 (1951).

[421] G. H. Coleman and G. E. Honeywell, *Org. Syn.*, Coll. Vol. II, 443 (1943).

[422] F. Kröhnke, H. Schmeiss, and W. Gottstein, *Chem. Ber.*, **84**, 135 (1951).

[423] F. Kröhnke, *Chem. Ber.*, **83**, 43 (1950).

[424] F. Kröhnke and I. Vogt, *Chem. Ber.*, **85**, 373 (1952).

[425] E. F. M. Stephenson, *Org. Syn.*, **34**, 100 (1954).

[426] R. Adams, *Org. Reactions*, **1**, 63 (1947).

A weighed, dry sample is boiled with a large excess of anhydrous sodium acetate in absolute alcohol for 3 h and then acidified with 6N-HNO_3; a measured amount of $AgNO_3$ is added and the excess of Ag is back-titrated with NH_4SCN.

Benzylidene chlorides and bromides are of interest especially as intermediates in the synthesis of aldehydes. They are prepared in the same way as the monohalo compounds, except that 2 moles of halogen are used.

Detailed directions are given in *Organic Syntheses* for the preparation of crude 4-chlorobenzylidene chloride, which in concentrated H_2SO_4 affords *p*-chlorobenzaldehyde,[427] of crude 4-bromobenzylidene bromide, which with $CaCO_3$ and water affords *p*-bromobenzaldehyde,[428] of pure α,α,α′,α′-tetrabromo-*p*-xylene (starting material for terephthalaldehyde[429]), and of pure α,α,α′,α′-tetrabromo-*o*-xylene (starting material for phthalaldehyde[430]). Bromination of *m*-tolyl acetate in CCl_4 under irradiation by a 500 W lamp gives a 75% yield of 3-acetoxybenzylidene bromide, which is converted in 70% yield into *m*-hydroxybenzaldehyde by sodium formate in alcohol.[431]

5. Replacement of hydrogen by halogen in acetylenes

Replacement of hydrogen on triply bonded carbon by halogen can be effected directly or by way of a C≡C–metal compound which, without isolation, is converted into the halogen compound by a further reaction.

The procedure for chlorination, bromination, and iodination of acetylenes in alkaline hypohalite solution[432] is applicable to alkynes, alkynols, and acetylenemonocarboxylic acids with at least one hydrogen on the C≡C group.

$$RC{\equiv}CH + NaOX \longrightarrow RC{\equiv}CX + NaOH$$

Reactions with hypoiodite are the fastest, those with hypochlorite the slowest. Free hypohalous acid does not substitute alkynes but affords α,α-dihalo carbonyl compounds:

$$RC{\equiv}CH + 2\,HOX \longrightarrow [RC(OH)_2{-}CHX_2] \longrightarrow RCOCHX_2$$

Gaseous alkynes are passed into alkaline (up to 23% referred to KOH) hypohalite solution at 0°. Liquid alkynes or solutions of solid ones in light petroleum are shaken or stirred with the hypohalite solution at room temperature, sometimes with addition of an emulsifier. The necessary **hypohalite solutions** are prepared as follows:[432]

Bromine (25 ml) is dropped into a solution of KOH (180 g) in water (800 ml) with vigorous stirring, producing a solution that is about 0.55N in KOBr and 2N in free KOH.

Chlorine is passed into 12.5% aqueous KOH at 0° until the solution just bleaches litmus and it is then diluted with an equal volume of 25% KOH solution. The product is about 0.4–0.7N in KOCl and 2.2–1.7N in KOH.

Alkali hypoiodite solution is very unstable and is best prepared in the reaction mixture from KI and sodium hypochlorite solution (see below).

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[427] W. L. McEwen, *Org. Syn.*, **2**, 133 (1943).

[428] G. H. Coleman and G. E. Honeywell, *Org. Syn.*, Coll. Voll. II, 89 (1943).

[429] J. M. Snell and A. Weissberger, *Org. Syn.*, Coll. Vol. III, 788 (1955).

[430] J. C. Bill and D. S. Tarbell, *Org. Syn.*, **34**, 82 (1954).

[431] E. L. Eliel and K. W. Nelson, *J. Chem. Soc.*, **1955**, 1628.

[432] F. Straus, L. Kollek, and W. Heyn, *Ber. Deut. Chem. Ges.*, **63**, 1868 (1930).

The hypohalite process can also be used to prepare dichloroacetylene, the best starting material being acetylene evolved from calcium carbide; the original papers[432,433] must be consulted for technique. Dichloroacetylene (b.p. 29°/743 mm) is poisonous and extremely **explosive** when warmed or in contact with oxygen (the air dissolved in water suffices). Dibromoacetylene is also highly explosive. The stability of the haloacetylenes increases with the number of carbon atoms and with the molecular weight, but they are all thermally unstable and must all be handled with care. A simple lecture demonstration has been described, to illustrate the explosive tendency of dichloroacetylene,[433] and it also shows that a mixture of bleaching powder, carbide, and alkali is dangerous if moisture is present:

A cold solution of potassium hydroxide is prepared in a tall 250-ml beaker from 20 g of KOH and 50 g of well crushed ice; to this are added 15 g of bleaching powder. The mixture is stirred to give a thin slurry, the beaker is placed in an ice-bath, and 3–5 pea-sized pieces of calcium carbide are added during 20–30 min. At the end of this time the beaker is removed from the bath and it is observed that the glass gradually becomes warm owing to hydrolysis of the carbide, that the supernatant foam is self-flammatory when stirred, and that there is then a crackling noise due to partial explosions that can be nicely observed in the dark (fume cupboard!).

It is better to prepare dichloroacetylene by removal of HCl from trichloroethylene.[433,434] Ethereal solutions of dichloroacetylene (which forms a 1 : 1 ether adduct that is not autoxidizable) is best prepared by passing trichloroethylene vapor mixed with ether vapor over caustic alkali that is heated at 125° in a N_2 atmosphere; for preparative details see Riemschneider *et al.*[433]

1-Bromo-1-hexyne: 1-Hexyne (45 g) is added to the alkaline hypobromite solution described above and the whole is stirred for 18 h. The organic phase is taken up in light petroleum and dried over Na_2SO_4. Vacuum-distillation gives 72% of 1-bromo-1-hexyne, b.p. 40–41° 15 mm.[435]

Diiodoacetylene: Acetylene is passed into a solution of KI (20 g) in N-NaOH (100 ml) with stirring and ice-cooling, whilst simultaneously N-NaOCl solution (about 150 ml) is dropped in until the initial yellow color no longer appears. The precipitated white diiodoacetylene is collected, washed with water, drained well, and dried in a non-evacuated desiccator over P_2O_5 for 24 h, the product (96.5% yield) having m.p. 82°. It is volatile and must therefore not be dried in a vacuum. The acetylene is developed by dropping water on to CaC_2 (600 g); a pure white product is obtained from the unpurified acetylene derived from CaC_2, but very pure acetylene from a steel bottle gives yellow tetraiodoethylene. The hypochlorite solution is prepared by passing chlorine (12 g) into ice-cooled 2N-NaOH (200 ml).[436]

Diiodoacetylene is reported[436] to remain undecomposed for several months at room temperature in the dark, but, as a result of an accident, another author[437] states that the dry product (2 kg) decomposed **explosively**(!).

According to an older, less convenient procedure,[435] diiodoacetylene is obtained from acetylene and iodine in liquid ammonia.

For the preparation of iodoacetylenes the alkali hypoiodite may be replaced by an acyl hypoiodite in the form of a Simonini complex, $[(C_6H_5COO)_2Ag]I$.

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[433] R. Riemschneider and K. Brendel, *Ann. Chem.*, **640**, 8, 14 (1961).

[434] E. Ott, W. Ottemeyer, and K. Packendorff, *Ber. Deut. Chem. Ges.*, **63**, 1941 (1930); E. Ott and K. Packendorff, *Ber. Deut. Chem. Ges.*, **64**, 1324 (1931).

[435] K. E. Schulte and M. Goes, *Arch. Pharm.*, **290/62**, 124 (1957).

[436] V. Franzen, *Chem. Ber.*, **87**, 1148 (1954).

[437] H. Jaeschke, *Chem. Ber.*, **88**, 101 (1955).

[438] T. H. Vaughn and A. Nieuwland, *J. Amer. Chem. Soc.*, **54**, 787 (1932).

Silver benzoate and iodine are caused to react with the alkyne in benzene or CCl_4:[439]

$$R'COOAg + I_2 + RC{\equiv}CH \longrightarrow R'COOH + AgI + RC{\equiv}CI$$

1-Alkyn-3-ols (ethynylcarbinols) are chlorinated or brominated at the C≡C position in good yield by aqueous, alkaline hypohalites,[440,441] but routes *via* C≡C-metal compounds must be used for the corresponding iodinations.[440]

The last-mentioned procedure has advantages also for general halogenation of higher alkylacetylenes. First, the metal compound is prepared by reaction of the alkyne with C_2H_5MgBr in dry ether or with $NaNH_2$ or KNH_2 in liquid NH_3, and this is brought into further reaction without being isolated. Reaction of the Grignard compounds of the alkynes with bromine in dry ether at −32° gives good yields of the 1-bromoalkynes, the potassium compounds in dry ether with chlorine at −70° give 1-chloroalkynes,[442] and the sodium compounds in liquid NH_3 with iodine give 1-iodoalkynes.[443]

$$CH_3(CH_2)_nC{\equiv}CMgBr + Br_2 \longrightarrow CH_3(CH_2)_nC{\equiv}CBr + MgBr_2$$

$$CH_3(CH_2)_nC{\equiv}CK + Cl_2 \longrightarrow CH_3(CH_2)_nC{\equiv}CCl + KCl$$

1-Iodoalkynes may also be prepared in good yield by reaction of the acetylenic Grignard compound with iodine in dry ethereal solution at 0°.[444]

1-Bromo-1-heptyne:[442] 1-Heptyne (0.5 mole) is added slowly to a solution of ethylmagnesium bromide (0.5 mole) in anhydrous ether (500 ml), and the mixture is kept boiling under reflux until no more ethane is evolved (2–3 h). Then it is placed in a cooling-bath at −32° and bromine is slowly dropped in, this reacting at once with precipitation of $MgBr_2$. After ca. 75% of 0.5 mole of Br_2 has been added, the mixture suddenly becomes deep yellow; addition of bromine is then stopped and the mixture is allowed to warm to room temperature, whereupon the $MgBr_2$ dissolves and a lower layer of $MgBr_2$ etherate separates. Working up then consists of hydrolysis by dilute hydrochloric acid, washing with saturated sodium carbonate solution and water, drying over Na_2SO_4, and distillation. The yield is 70% of a product boiling at 69°/25 mm.

6. Replacement of hydrogen by halogen in phenols, hydroxyphenylalkanoic acids, aryl ethers, and aromatic amines

The preparation of mono- and di-halogenated derivatives of phenols and aromatic amines is of particular preparative interest. Mild conditions often suffice for introduction of, especially, chlorine or bromine, but also of iodine, at all the favored positions, even when that is not desired. Monochlorination or monobromination of phenols by Cl_2 or Br_2 occurs mainly at position 4 in the cold but mainly at position 2 at 150–180°.

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[439] C. Prevost, *C. R. Hebd. Séances Acad. Sci.*, **200**, 942 (1935); **204**, 989 (1937).

[440] A. Bavley, *J. Org. Chem.*, **19**, 570 (1954); **20**, 109 (1955).

[441] J. Colonge and L. Cumet, *Bull. Soc. Chim. France*, **1947**, 841.

[442] P. A. McCusker and R. R. Vogt, *J. Amer. Chem. Soc.*, **59**, 1307 (1937).

[443] T. H. Vaughn and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **55**, 2152 (1933).

[444] V. Grignard and H. Perrichon, *Ann. Chim. (Paris)*, [x], **5**, 5, (1926).

The bromination of phenol in CS_2 under cooling by ice–salt, described in detail in *Organic Syntheses*,[445] gives, first, a forerun and then a difficultly separable mixture of *o*- and *p*-bromophenol containing about 80% of the latter. The yield of *p*-bromophenol can be improved by using a 20% excess of phenol and adding the bromine dropwise in ethylene dichloride at 0°.[446]

***p*-Chlorophenol** is obtained by use of SO_2Cl_2 as follows:[447] Molar amounts of phenol and SO_2Cl_2 are mixed at room temperature and the mixture is set aside until reaction sets in with lively evolution of SO_2 and HCl. After this, the mixture is warmed on the water-bath until gas evolution ceases, then washed with sodium carbonate solution, dried by $CaCl_2$, and fractioned. The product, obtained in almost 100% yield, has b.p. 216–218° and m.p. 37°.

Phenols are chlorinated preferentially in the *ortho*-position if *tert*-butyl hypochlorite in CCl_4 is used.

ortho-Chlorination of phenols by tert-butyl hypochlorite:[448] *tert*-Butyl hypochlorite (0.5 mole) is dropped, with stirring, into a solution or suspension of the phenol (0.5 mole) in CCl_4 (150–300 ml), the temperature being allowed to rise to the boiling point of the solvent. The mixture is then boiled under reflux for a further 2 h, the CCl_4 and the *tert*-butyl alcohol are distilled off, and the residue is fractionated.

For preparation of *ortho*-halogenated phenols, SO_3H groups may be provisionally introduced at the positions that are not to be occupied by chlorine or bromine. The relevant hydroxy sulfonic acids are chlorinated or brominated without being isolated, and the SO_3H groups are then hydrolysed off by steam-distilling the reaction mixture after it has been acidified with sulfuric acid.

In this way, *o*-bromophenol is prepared in about 40% yield by brominating an alkaline aqueous solution of 4-hydroxy-1,3-benzenedisulfonic acid; detailed directions are in *Organic Syntheses*.[449]

Preferably, however, the crude hydroxy sulfonic acids are halogenated in nitrobenzene–sulfuric acid. This affords yields of about 70% of 2,6-dichloro- or 2,6-dibromo-phenol, 72% of *o*-chlorophenol, or 46.5% of *o*-bromophenol.[450]

It is also possible to halogenate a suitable hydroxy carboxylic acid and then to remove the COOH group.

2,6-Dichlorophenol: Ethyl *p*-hydroxybenzoate with, *e.g.*, SO_2Cl_2 (2.2 moles) in 1.5 h on the water-bath affords a yield of about 85% of ethyl 3,5-dichloro-4-hydroxybenzoate, which is hydrolysed by methanolic potassium hydroxide to 3,5-dichloro-4-hydroxybenzoic acid. This acid (1.2 moles) in dimethylaniline (575 g) is heated gradually to 190–200° and kept at this temperature until evolution of CO_2 ceases (about 2 h), giving 80–90% of 2,6-dichlorophenol. For details see *Organic Syntheses*.[451]

Certain bromine complexes are suitable for selective bromination of phenols and their ethers:

Dioxan · Br_2, alone or in ether or dioxan, can be used to monobrominate phenol, polyhydric phenols, aryl ethers, and salicyclic acid.[452]

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[445] R. Adams and C. S. Marvel, *Org. Syn.*, **1**, 39 (1921).

[446] H. E. Podall and W. E. Foster, *J. Org. Chem.*, **23**, 280 (1958).

[447] L. Vanino, "Handbuch der präparativen Chemie," F. Enke, Stuttgart, 1937, Vol. 2, p. 430.

[448] D. Ginsburg, *J. Amer. Chem. Soc.*, **73**, 2723 (1951).

[449] R. C. Huston and M. M. Ballard, *Org. Syn.*, Coll. Vol. II, 97 (1943).

[450] R. C. Huston and A. H. Neeley, *J. Amer. Chem. Soc.*, **57**, 2176 (1935).

[451] D. S. Tarbell, J. W. Wilson, and P. E. Fanta, *Org. Syn.*, **29**, 35 (1949); Coll. Vol. III, 268 (1955).

[452] L. A. Yanovskaya, A. P. Terent'ev, and L. I. Belen'kii, *Zh. Obshch. Khim.*, **22**, 1594 (1952); *Chem. Abstr.*, **47**, 8032 (1953).

p-Bromophenol: Dioxan · Br_2 (for preparation see page 169) (25 g) is added gradually to phenol (9.4 g) with water-cooling, then the mixture is poured into water and extracted with ether, yielding 88% of p-bromophenol, b.p. 115–117°/11–12 mm, m.p. 64–65°. If the cooling is omitted, appreciable amounts of o-bromophenol are formed.

Pyridine dibromide·HBr (pyridinium perbromide) can be used to monobrominate polyhydric phenols such as pyrocatechol, pyrogallol, and also aryl ethers at or below room temperature.[66–69,453] The solid reagent may be used (for preparation see page 112); alternatively glacial acetic acid containing a known amount of bromine is dropped into a mixture of the phenol or ether with pyridine hydrochloride (prepared by passing dry HCl into an ethereal solution of pyridine) or with quinoline sulfate.

Polyhydric phenols readily give di- and poly-bromo derivatives when treated with bromine. With 2 moles of Br_2 in glacial acetic acid pyrocatechol affords the 4,5-dibromo derivative, which is readily brominated to 3,4,5-tribromopyrocatechol in $CHCl_3$.[454] Similarly, resorcinol is first brominated at the *para*-positions to the two OH groups, giving 2,4-dibromoresorcinol, and then in the common *ortho*-position, giving 2,4,6-tribromoresorcinol.[455] According to a precise description in *Organic Syntheses*,[456] 4-bromoresorcinol is obtained by treating 2,4-dihydroxybenzoic acid (readily obtained from resorcinol[457]) with 1 mole of bromine in glacial acetic acid, the resulting 5-bromo-2,4-dihydroxybenzoic acid being decarboxylated when boiled with water for 24 hours.

2,4,6-Tribromophenol is easily prepared by adding bromine water to an aqueous solution of phenol until the former is no longer decolorized. An excess of bromine gives tribromophenol·bromine (for its preparation see Kohn and Sussmann[458]), which readily gives up one Br^+ and thus functions as a brominating agent. It liberates iodine from iodide,[459] so that tribromophenol is formed, with consumption of 6 atoms of Br per mole of phenol, when phenol is titrated with bromine (bromide–bromate), KI, and thiosulfate.

On bromination of o- or p-hydroxy- or o- or p-amino-benzoic acid, or the corresponding sulfonic acids, even at room temperature, bromine replaces the COOH or SO_3H group with liberation of CO_2 or H_2SO_4 as the case may be. At 40–45° the CHO group of o- or p-hydroxy- or o- or p-aminobenzaldehyde is also replaced by bromine, with evolution of CO. The end products are 2,4,6-tribromo-phenol or -aniline.[460] Thus p-hydroxybenzoic and sulfanilic acid, for example, can be determined quantitatively by means of 0.1N-bromide–bromate solution.

A series of mild processes, described under a) on page 152 for replacing H in the aromatic nucleus by I (see also page 198) are available for iodination of phenols and hydroxyphenylalkanoic acids, as is ICI iodination (see page 181) in an ammoniacal or alkaline medium.

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[453] K. Freudenberg, H. Fikentscher, and M. Harder, *Ann. Chem.*, **441**, 178 (1925).

[454] M. Kohn, *J. Amer. Chem. Soc.*, **73**, 480 (1951).

[455] M. Kohn and G. Löff, *Monatsh. Chem.*, **45**, 592 (1924).

[456] R. B. Sandin and R. A. McKee, *Org. Syn.*, Coll. Vol. II, 100 (1943).

[457] M. Nierenstein and D. A. Clibbens, *Org. Syn.*, Coll. Vol. II, 557 (1943).

[458] M. Kohn and S. Sussmann, *Monatsh. Chem.*, **46**, 578 (1925).

[459] P. Fresenius, *Angew. Chem.*, **64**, 473 (1952).

[460] A. W. Francis and A. J. Hill, *J. Amer. Chem. Soc.*, **46**, 2498 (1924).

Iodination by I_2 with addition of alkali or an amine is carried out by using solid iodine or solutions of iodine in aqueous NaI (NaI_3) or KI (KI_3), in methanol, or occasionally in ether. The procedure has the disadvantage that large amounts of iodide accumulate in the mother liquors, but these can be recovered from larger batches (see page 104). However, in the laboratory the method is often easy to carry out and gives good yields, and very many straight-chain and branched-chain ω-(*p*-hydroxyphenyl) fatty acids have been iodinated by I_2 in alkaline solution.[381,461]

4-Hydroxy-3,5-diiodophenylacetic acid: A solution of iodine (50.8 g) and KI (50.8 g) in water (250 ml) is dropped, with stirring, into a solution of *p*-hydroxyphenylacetic acid (0.1 mole) in 0.5N-NaOH (800 ml) at room temperature. The mixture is filtered and cooled to 0–5°, then SO_2 is led in slowly, with stirring, until the pH falls to 2–3. The crude acid that is precipitated is reprecipitated from sodium hydrogen carbonate solution and crystallized from aqueous ethanol. This 4-hydroxy-3,5-diiodophenylacetic acid, obtained in 92% yield, melts at 216.5 to 217.5°.

Iodination of phenols that have free *ortho*- and *para*-positions, in an alkaline medium, by iodine, leads not only to the desired iodo derivatives, but also to reddish-brown polymeric by-products, *e.g.*, "Lautemann's Red" from phenol[462,463] and aristol from thymol.[464] These unpleasant side reactions are reduced by working in methanolic alkali[465] or in concentrated aqueous or methanolic ammonia.[466] A nearly quantitative yield of 2,4,6-triiodophenol is obtained by slowly adding a concentrated solution of I_2 in KI to phenol in concentrated aqueous ammonia.[467]

Black, explosive nitrogen triiodide (NI_3) is formed as intermediate in this process. It can be used only for readily iodinated phenols (cf. Cassebaum[465]) which rapidly consume any NI_3 formed.

The reaction is carried out at room temperature, with rapid stirring, the iodine solution (in aqueous KI or methanol) being dropped in slowly, at a rate depending on the consumption. Then concentrated sodium hydrogen sulfite solution is added and the whole is stirred so as to remove any excess of NI_3.

Primary or secondary aliphatic amines in aqueous or methanolic solution may replace the ammonia, for these do not form explosive iodo derivatives.[468,469] This method can be recommended for preparative purposes and has proved very valuable in the preparation of thyroxine from 3,5-diiodothyronine in 20% aqueous ethylamine (KI_3), of thyroxine methyl ester from 3,5-diiodothyronine methyl ester in 1 : 2 butylamine–methanol (I_2)[469] and of 3,5-diiodotyrosine in 20% aqueous ethylamine (NaI_3),[470] as well as in iodination

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[461] D. Papa, H. Breiger, E. Schwenk, and V. Peterson, *J. Amer. Chem. Soc.*, **72**, 4907 (1950); M. G. Pratt, J. O. Hoppe, and S. Archer, *J. Org. Chem.*, **13**, 578 (1948).

[462] W. H. Hunter and G. H. Woollett, *J. Amer. Chem. Soc.*, **43**, 135 (1921).

[463] G. H. Woollett and co-workers, *J. Amer. Chem. Soc.*, **59**, 861 (1937).

[464] G. H. Woollett, *J. Amer. Chem. Soc.*, **43**, 553 (1921).

[465] H. Cassebaum, *J. Prakt. Chem.*, [iv], **13**, 141 (1961).

[466] J. C. Colbert and co-workers, *J. Amer. Chem. Soc.*, **66**, 122 (1944).

[467] R. I. Datta and N. Prosad, *J. Amer. Chem. Soc.*, **39**, 441 (1917).

[468] C. V. Bordeianu, *Ann. Sci. Univ. Jassy*, **20**, 131 (1935); *Chem. Abstr.*, **30**, 1760 (1936).

[469] J. C. Clayton and B. A. Hems, *J. Chem. Soc.*, **1950**, 842.

[470] J. H. Barnes, B. A. Hems, and co-workers, *J. Chem. Soc.*, **1950**, 2829.

(KI_3) of a series of aromatic amines and phenols in 60% aqueous ethylenediamine solution (0.5 mole per mole of substance to be iodinated).[471]

3-(4-Hydroxy-3,5-diiodophenyl)propionic acid:[470] A solution of iodine (50 g) and KI (48 g) in water (150 ml) is added slowly, with stirring, to a solution of 3-(*p*-hydroxyphenyl)propionic acid (16.2 g) in 20% aqueous methylamine (200 ml). The mixture is stirred for a further 10 min, then made acid to Congo Red by gradual addition of 2N-HCl. The crude white acid precipitated is washed with water and recrystallized from water, the yield being 90% and the m.p. 166–168°.

The accumulation of considerable amounts of iodide in the mother liquors, which is particularly undesirable with larger batches, can be avoided by using iodine chloride (ICl) in place of iodine. ICl has the further advantage that it dissolves in aqueous NaCl or KCl; for the preparation of ICl and its solutions see page 181. Phenols, *m*-C_6H_4ROH ($R = NH_2$ or OH), which are very readily iodinated, are triiodinated smoothly, even at room temperature by ICl in hydrochloric acid.[465,472]

NI_3 is formed as intermediate in iodination by ICl in an ammoniacal medium, just as with I_2. Although there has as yet been no report of an explosion due to this intermediary NI_3,[465] **care** is necessary (a protecting wall, goggles, use of phenols that react readily with NI_3). ICl can be used without danger and with equal success in methanolic methylamine or NaOH.

General **experimental details** for the **triiodination of phenol, and of phenols** *m*-C_6H_4ROH, by ICl in the presence of NH_3, CH_3NH_2, or NaOH:[465]

(a) The phenol (0.1 mole) is dissolved in 5–10% methanolic NH_3 (500 ml). 2M-$NaICl_2$ (155 ml) is run in, with stirring, during 20 min, then the mixture is stirred for a further 10 min, diluted with water (500 ml), and treated with concentrated $NaHSO_3$ solution (10–20 ml), and the product is precipitated by acidification with HCl or H_2SO_4. The consumption of ICl can be readily followed by disappearance of the dark NI_3. Yields are 80–95% when R = $NHCOC_3H_7$, $NHCOCH_3$, H, or NO_2. With *m*-nitrophenol ($R = NO_2$) the 2M-$NaICl_2$ is added in 50-ml portions, each in 10 min, and after each addition the mixture is stirred until the NI_3 color has disappeared, which requires about 15 min for the first portion, about 30 min for the second, and about 60 min for the third.

(b) 10–15% methanolic methylamine solution may be used instead of the 5–10% NH_3 solution, the procedure being otherwise as in (a). Yields are 80–95% when R = $NHCOC_3H_7$, $NHCOCH_3$, or H.

(c) The phenol (0.1 mole) and NaOH (18 g; 22 g for phenolic monocarboxylic acids) are dissolved in methanol (500 ml). 2M-$NaICl_2$ (155 ml) is run in during 20 min, then the precipitated sodium chloride is filtered off and washed with methanol (55 ml). The filtrate is treated with concentrated $NaHSO_3$ solution (10–20 ml) and diluted with water (500 ml), and the product is precipitated by acidification with concentrated HCl. Yields are 75–95% when R = $NHCOC_3H_7$, $NHCOCH_3$, H, COC_6H_5, COOH, or NO_2. Twice the above amount of 2M-$NaICl_2$ is required for smooth triiodination of *m*-nitrophenol ($R = NO_2$).

Iodine and H_2O_2 can be used to iodinate the ring of aromatic compounds carrying substituents that favor electrophilic substitution. Triiodophenol may be obtained by dropping 30% H_2O_2 (3.5–4.0 moles) slowly, with vigorous stirring, into a solution of phenol and iodine in ethanol at about 55° or methanol at about 45°, the yield being very good and the product nearly pure.[473] This procedure has the disadvantage that it may lead to violent decomposition; but

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[471] K. T. Potts, *J. Chem. Soc.*, **1953**, 3711.

[472] H. Cassebaum, *Pharmazie*, **15**, 313 (1960).

[473] J. E. Marsh, *J. Chem. Soc.*, **1927**, 3164.

this tendency can be reduced by adding a little MnO_2.[465] In the presence of traces of other heavy metals considerable amounts (30–40%) of tetraiodinated phenols may result.

The I_2–H_2O_2 procedure is also applicable to suitable heterocycles (see also page 199): 8-quinolinol, for example,[476] affords 89.4% of 5,7-diiodo-8-quinolinol; treating aniline in methanol at 45°, dropwise and slowly with stirring, with 30% H_2O_2 and 3 atoms of iodine per mole of aniline gives 2,4-diiodoaniline and with 4 atoms of iodine gives 2,4,6-triiodoaniline.[475] Aryl ethers can be iodinated by iodine and H_2O_2 only if a concentrated mineral acid (sulfuric, phosphoric, or nitric acid) is also added.[476–478] Iodination is considerably faster in an acidic medium, where, however, it is usually violent.

***p*-Iodoanisole:**[476] 30% H_2O_2 (10.0 ml) is added in small portions during 20 min to a mixture of anisole (5.93 g), powdered iodine (6.97 g), 95% ethanol (30 ml), and sulfuric acid (*d* 1.83; 1.0 ml). The mixture is warmed and stirred vigorously after each addition. When about 5 ml of the H_2O_2 solution have been added a violent reaction sets in, which is allowed to moderate before any further addition. On cooling of the solution and dilution with water a dark oil separates, which is collected in ether which is then washed with thiosulfate solution and water and dried over $CaCl_2$. The ether is removed, whereafter the residue crystallizes in a refrigerator (11.2 g, m.p. 49°) and after recrystallization from 90% ethanol has m.p. 50° (yield 80%, 10.18 g).

1-Iodo-2-methoxy- and 2-ethoxy-1-iodo-naphthalene are obtained similarly.

For nuclear iodinations it is also often advantageous first to convert a CH group into a C–metal group, later replacing the metal by iodine. Except in special cases where lithium compounds are used,[479] this metal is usually mercury. Acetoxymercuri and chloromercuri groups can be easily introduced into aromatic and similar heterocyclic compounds, but mixtures of isomers are usually formed that are not easily separated.

$$C_6H_5OH + Hg(OOCCH_3)_2 \longrightarrow o\text{—}CH_3COOHg\text{—}C_6H_4OH + CH_3COOH$$

$$o\text{—}CH_3COOHg\text{—}C_6H_4OH + NaCl \longrightarrow o\text{—}ClHg\text{—}C_6H_4OH + CH_3COONa$$

$$2\,o\text{—}ClHg\text{—}C_6H_4OH + 2\,I_2 \longrightarrow 2\,o\text{—}C_6H_4IOH + HgCl_2 + HgI_2$$

A detailed description of the preparation of *o*-chloromercuriphenol is given in *Organic Syntheses*.[480] This is stirred with iodine in chloroform for about 2 h, then filtered from $HgCl_2$ and HgI_2 and freed from most of the chloroform by distillation, and the residue is shaken with KI solution to remove dissolved HgI_2. *o*-Iodophenol (63%; m.p. 43°) is then distilled in a vacuum (b.p. 130°/18 mm). For details see *Organic Syntheses*.[481]

2,4-Diiodophenol is obtained in good yield by adding a solution of iodine (33 g) and KI (33 g) in water (300 ml) to a vigorously stirred suspension of 2,4-bis(acetoxymercuri)phenol[482] (20 g) in 10% KI solution.[483]

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[474] T. Nogradi, *Chem. Ber.*, **85**, 104 (1952).

[475] H. Dorn, *Chem. Ber.*, **90**, 464 (1957).

[476] L. Jurd, *Aust. J. Sci. Res.*, **2 A**, 595 (1949).

[477] L. Jurd, *Aust. J. Sci. Res.*, **3 A**, 587 (1950).

[478] L. Jurd, *J. Amer. Chem. Soc.*, **77**, 5747 (1955).

[479] H. Gilman and co-workers, *J. Amer. Chem. Soc.*, **67**, 1479 (1945); *J. Org. Chem.* **19**, 560 (1954).

[480] F. C. Whitmore and E. R. Hanson, *Org. Syn.*, **4**, 13 (1925).

[481] F. C. Whitmore and E. R. Hanson, *Org. Syn.*, **4**, 37 (1925).

[482] J. F. Caius and J. H. Wadia, *J. Indian Chem. Soc.*, **6**, 613 (1929).

[483] S. Wawzonek and S. C. Wang, *J. Org. Chem.*, **16**, 1271 (1951).

The chloromercuri compounds are so stable that they can be substantially modified before the HgCl is replaced by halogen. For instance, *p*-(chloromercuri)toluene (obtainable from toluene[484] or *p*-toluenesulfinic acid[485]) can be oxidized by alkaline $KMnO_4$ to *p*-(chloromercuri)benzoic acid[486] which, with iodine, affords *p*-iodobenzoic acid (for details see *Organic Syntheses*[487]). Other examples are cited on page 201.

Aryl ethers can be chlorinated in the ring by Cl_2, by a glacial acetic acid solution of SO_2Cl_2 (the amount of which is easily measured), or by PCl_5.

Phenoxyacetic acid with 2 moles of Cl_2 in acetic acid gives 75% of 2,4-dichlorophenoxyacetic acid or with an excess of Cl_2 gives the 2,4,6-trichloro acid. If phenoxyacetic acid is warmed with an excess of SO_2Cl_2 in glacial acetic acid gradually from 0° to 75° and kept at the latter temperature until gas evolution stops, 74% of 2,4-dichlorophenoxyacetic acid is obtained, but chlorination is not effected by SO_2Cl_2 in boiling CCl_4.[488]

The following mild procedure is recommended for nuclear bromination of aromatic compounds containing hydroxy, alkoxy, or amino groups: a stream of air, CO_2, or N_2 laden with bromine vapor is passed through an aqueous solution or suspension of the aromatic compound; this bromination can also be carried out in absence of water if $CaCl_2$ tubes are placed in front of and behind the reaction vessel.

***p*-Bromoanisole:**[489] A stream of air carrying bromine vapor is passed into a stirred and cooled solution of anisole (200 g) in glacial acetic acid (750 g). This solution is placed in a three-necked flask to which a stirrer is attached by a ground-glass joint (KPG) or in a two-necked flask fitted for magnetic stirring. The flask is fitted with a gas-inlet tube that dips into the solution. The other end of this tube is attached to a two-necked flask containing bromine (310 g) into which a wide capillary dips. The remaining neck of the reaction vessel is connected to a water-pump which, by creating a vacuum, draws a slow stream of air through the bromine supply. The pale yellow solution obtained in the reaction is poured into water (4 l), and the bromoanisole is separated. After distillation in a vacuum it has b.p. 120°/12 mm (yield, about 83%).

4-Bromoveratrole is obtained similarly in 80% yield.

Anisole also gives *p*-bromoanisole on use of PBr_5, [490]and *p*-chloroanisole is formed analogously on use of PCl_5.[491]

Aryl ethers can also be mono- or di-brominated in dry benzene or CCl_4 by adding *N*-bromosuccinimide (1 or 2 moles) (cf. pages 148 and 153) portionwise with stirring and cooling in ice-water.

Further, the Birckenbach–Goubeau–Waters method (see page 154) can be used to introduce Br or I into the ring of aryl ethers.

***p*-Iodoanisole:**[492] Anisole (20 ml) is heated to 100° with CF_3COOAg (4.40 g) and then cooled to room temperature. Adding finely powdered iodine (5.10 g) causes AgI to be pre-

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[484] O. Dimroth, *Ber. Deut. Chem. Ges.*, **32**, 761 (1899); W. Steinkopf, *Ann. Chem.*, **413**, 329 (1917).

[485] W. Peters, *Ber. Deut. Chem. Ges.*, **38**, 2569 (1905); F. C. Whitmore, F. H. Hamilton, and N. Thurman, *Org. Syn.*, **3**, 99 (1923).

[486] F. C. Whitmore and G. E. Woodward, *J. Amer. Chem. Soc.*, **48**, 534 (1926); *Org. Syn.*, **7**, 18 (1927).

[487] F. C. Whitmore and G. E. Woodward, *Org. Syn.*, **7**, 58 (1927).

[488] M. Fields, S. Rothchild, and M. A. Leaffer, *J. Amer. Chem. Soc.*, **74**, 2435 (1952).

[489] K. H. Slotta and H. Heller, *Ber. Deut. Chem. Ges.*, **63**, 3043 (1930).

[490] W. M. Whaley and C. White, *J. Org. Chem.*, **18**, 184 (1953).

[491] W. Authenrieth and P. Mühlinghaus, *Ber. Deut. Chem. Ges.*, **39**, 4098 (1906).

[492] R. N. Haszeldine and A. G. Sharpe, *J. Chem. Soc.*, **1952**, 1000.

cipitated. The mixture is heated at 100° for 15 min, then cooled, filtered, and distilled. The product, b.p. 235–237°, is obtained in 75% yield.

p-Bromoanisole, b.p. 110–115°/23 mm, is obtained analogously by use of bromine at 120°. Further, 51% of *p*-iodoaniline and 62% of *p*-bromoaniline are similarly prepared.

p-Iodoanisole is more conveniently accessible from anisole on use of ICl in glacial acetic acid, but the yield is not so good (46%).[493]

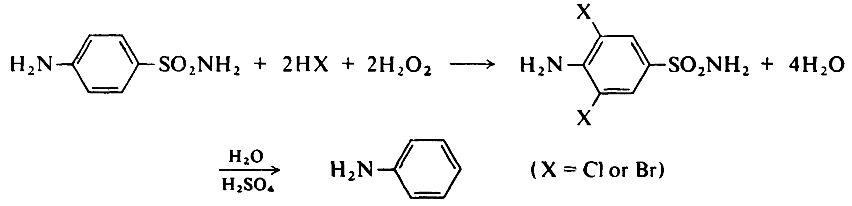
Iodination by iodine and HgO has been known for a long time and is discussed on page 198. Mercuric acetate in acetic acid may be used in place of HgO to trap the HI produced; in this way, for example, 3,3′-dimethoxybenzyl affords 93% of its 6,6′-derivative (2,2′-diiodo-5,5′-dimethoxybibenzyl).[494]

Preparation of phenoxymethyl chlorides is described on page 270.

The reactivity of aromatic amines towards halogens is reduced by salt formation (mineral acid medium), *N*-acylation, or *N*-alkylation. Aqueous solutions of the amine hydrohalide are treated with the halogen; or glacial acetic acid is used as solvent to which sodium acetate is added to bind the halogen acid formed. As with phenols, the formation of mono- and di-brominated amines is of especial interest.

p-Bromoaniline can be obtained by dropping somewhat less than one mole of bromine in glacial acetic acid into an ice-cold solution of 1 mole of aniline in the same solvent.[495]

Chlorination or bromination of both *ortho*-positions of aniline can be achieved by a device similar to that used for phenol: the *para*-position is substituted by a group that can be removed later. The preparation of **2,6-dichloro-** and **2,6-dibromo-aniline** can be cited as examples that also illustrate halogenation by HCl or HBr and H_2O_2 (for older papers see Leulier[496] and Zinke[497]):



30% H_2O_2 (2 moles) is added with rapid stirring to a solution of sulfanilamide (1 mole) in hydrochloric acid (about 6 moles) (conc. HCl : H_2O = 1 : 1) at 45° or in hydrobromic acid (about 2.3 moles) (40% HBr : H_2O = 1 : 8.5) at 70–75°. The exothermic reaction is allowed to proceed for about 30 min at not more than 60° or 85–90°, respectively. In both cases the 3,5-dihalosulfanilamide separates. The 2,6-dihaloanilines are isolated by steam-distillation after the corresponding amide has been heated with 70% H_2SO_4. For detailed directions see *Organic Syntheses*.[498]

Dioxan·Br_2 is suitable for mild bromination of aromatic amines.[499] This orange-yellow complex, m.p. 64°, is readily prepared by mixing equivalent amounts of dioxan and bromine and cooling the resulting warm mixture with

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[493] H. R. Frank, O. E. Fanta, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **70**, 2317 (1948).

[494] J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, **1942**, 684.

[495] W. Fuchs, *Monatsh. Chem.*, **36**, 113 (1915).

[496] A. Leulier, *Bull. Soc. Chim. France*, [iv], **35**, 1325 (1924).

[497] A. Zinke, *Ber. Deut. Chem. Ges.*, **58**, 330 (1925).

[498] M. K. Seikel, *Org. Syn.*, **24**, 47 (1944); Coll. Vol. III, 262 (1955).

[499] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3596 (1953).

ice-water. If a dioxan solution of the complex is to be used in the reaction, it suffices merely to add the desired amount of bromine to dioxan with stirring and cooling.

Dioxan · Br_2 can also be prepared as follows: (a) Bromine (990 g) is added rapidly, with cooling, to dioxan (500 g). The hot solution is poured into ice-water (2 l), and the orange precipitate is filtered off and dried on a porous plate (yield 94%). The product melts at 60° and is moderately soluble in dioxan, $CHCl_3$, 1,2-dichloroethane, or CCl_4, but less so in ether in which it gradually forms a two-layer system; it is less soluble in water by which it is hydrolysed at room temperature in several days, or more rapidly if heated.[451] Dioxan or ether is used as solvent for its reactions.

Dry bromine (320 g) is added with rapid stirring to dioxan (160 g) that has been distilled over sodium. The solution, which has warmed to 60°, is poured into light petroleum (b.p. below 40°; 2 l) at −20°. The yellow precipitate is filtered off and freed from adhering solvent in a vacuum as rapidly as possible (the appreciable volatility of dioxan · Br_2 causes losses!) The product, m.p. 60–61°, can be stored at 0°.[500]

Amines are brominated when a dioxan solution of dioxan · Br_2 is added with stirring and cooling to their solution in dioxan containing the calculated amount of concentrated alkali solution.

***p*-Bromoaniline:**[499] Bromine (16 g) in dioxan (160 ml) is dropped, with stirring, in 2 h into a solution of aniline (9.3 g) in dioxan (30 ml) and potassium hydroxide solution (from 5.6 g of KOH and 20 ml of water) at 5°. The organic layer is then washed with 40% KOH solution (15 ml), the solvent is distilled off in a vacuum, and the residue is recrystallized from diluted ethanol (yield 68%).

Nuclear iodination is generally carried out by using iodine in the presence of HI-acceptors (or of H_2O_2) or by using ICl in hydrochloric or acetic acid.

Thus, for example, 2,6-diiodo-4-nitroaniline[501] is obtained when a solution of ICl (2moles) in glacial acetic acid (100 ml) is dropped, with stirring, into one of p-nitroaniline (1 mole) in hot glacial acetic acid (370 ml) in 30 min (exothermic reaction!), with subsequent stirring for a further 2 h on a boiling water-bath. For details see *Organic Syntheses*.[502]

***p*-Iodoaniline:**[503,504] A solution of ICl (1 mole) is prepared from iodine (127 g) in glacial acetic acid (150 ml) (cf. page 182). When this is dropped, with stirring, into a solution of acetanilide (1 mole) in glacial acetic acid (150 ml) (exothermic reaction!) and the whole is stirred for a further few hours, *p*-iodoacetanilide is precipitated. After 12 h, the mixture is poured into water (2 l), and the product is collected and washed with water and dilute sodium hydroxide solution. Recrystallization of this crude material from ethanol gives a 90% yield of the amide, m.p. 184°, which is hydrolysed by concentrated hydrochloric acid to *p*-iodoaniline.

Preparation of *p*-iodoaniline by reaction of aniline (1.2 moles) with powdered iodine (1 mole) in water (1 l) containing $NaHCO_3$ (1.8 moles) is described in detail in *Organic Syntheses*.[505] The analogous iodination of *o*-toluidine in the position *para* to the NH_2 group is effected in a mixture of ether and water containing $CaCO_3$.[506]

7. Replacement of hydrogen by halogen in ethers

Ethers in which hydrogen atoms are replaced by halogen can be obtained by direct action of chlorine or bromine on the unhalogenated compounds. Other methods that start from aldehydes, hemiacetals, or acetals (see pages 232 and

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[500] J. D. Billimoria and N. F. Maclagan, *J. Chem. Soc.*, **1954**, 3259.

[501] A. Michael and L. M. Norton, *Ber. Deut. Chem. Ges.*, **11**, 113 (1878).

[502] R. B. Saudin, W. V. Drake, and F. Leger, *Org. Syn.*, Coll. Vol. II, 196 (1943).

[503] A. Michael and L. M. Norton, *Ber. Deut. Chem. Ges.*, **11**, 108 (1878).

[504] F. D. Chattaway and A. B. Constable, *J. Chem. Soc.*, **95**, 124 (1914).

[505] R. Q. Brewster, *Org. Syn.*, Coll. Vol. II, 347 (1943).

[506] A. A. Goldberg, *J. Chem. Soc.*, **1942**, 713.

240) are equally important but constitute, at least formally, a replacement of a C–O bond by a C–halogen bond. For reviews of methods of preparing halogenated ethers see Summers[507] and Gross and Höft.[508]

Direct replacement of hydrogen in ethers by halogen is of preparative importance only in the case of chloro ethers. The chlorination of diethyl ether, which is a radical reaction,[509] was first investigated a long time ago; for early reviews see Lieben[510] and Jacobsen.[511] At room temperature the chlorine enters diethyl ether successively in the 1-, 1,2-, 1,2,2-, and 1,2,2,2-positions presumably as a result of successive removals of HCl and additions of Cl_2. The removal of HCl is largely avoided on chlorination at −25° to −30° under irradiation, and 57% of the theoretical amount of 1,1′-dichlorodiethyl ether is then obtained if the starting material is dry.[512]

If less chlorine is used, this method gives 1-chloroethyl ethyl ether as main product, which is more easily separated from by-products by distillation than in the case of Henry synthesis (see page 232). Similarly chlorination of tetrahydrofuran under UV-irradiation at −30° to −40° gives 2-chloro- and 2,5-dichloro-tetrahydrofuran,[513] and that of dioxan in CCl_4 at −5° to −10° gives 2,5-dichlorodioxan.[514] However, no definite product was isolated on low-temperature chlorination of diisopropyl ether.[515]

In the preparation of 1,2-dichloroethyl ether from diethyl ether[516] care must be taken to cool the mixture in ice-water in the early stages and to introduce the chlorine slowly, since accumulation of chlorine easily leads to a violent reaction in which the mixture catches fire. As the reaction proceeds, the mixture becomes saturated with HCl, whereby the flammability is reduced. However, unless the stirring is rapid, the solution can become supersaturated with HCl which is then later released with violence. Chlorination of diethyl ether (800 g), first with ice-cooling (35 h; to a density of 0.785), then at temperatures rising gradually to room temperature (a further 47 h; to a density of 0.96), gave 24.2% of 1,2-dichloroethyl ethyl ether.

In the chlorination of dimethyl ether, which has no C-2 atom, hydrogen is replaced successively at the 1-, 1,1′-, 1,1,1′, and 1,1,1′,1′-positions.[517]

If dimethyl ether is to be further chlorinated it has been recommended[518] that dimethyl ether and chlorine should be passed simultaneously into previously prepared, liquid chloromethyl methyl ether with water-cooling (condenser in the liquid) and under intense UV irradiation; to avoid explosions the reaction must be carried out under N_2 until considerable amounts of HCl are being evolved.

Use of 1 mole of Cl_2 in the liquid phase (CCl_4 solution or chloromethyl methyl ether) leads to 1,1′-dichloro- and 1,1-dichloro-dimethyl ether in the

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[507] L. Summers, *Chem. Rev.*, **55**, 301 (1955).

[508] H. Gross and E. Höft, *Z. Chem.*, **4**, 401 (1964).

[509] L. Horner, B. Anders, and O. Basedow, *Ann. Chem.*, **635**, 46 (1960).

[510] A. Lieben, *Ann. Chem.*, **146**, 180 (1868).

[511] O. Jacobsen, *Ber. Deut. Chem. Ges.*, **4**, 215 (1871).

[512] G. E. Hall and F. M. Ubertini, *J. Org. Chem.*, **15**, 715 (1950).

[513] H. Gross, *Angew. Chem.*, **72**, 268 (1960); *Chem. Ber.*, **95**, 83 (1962).

[514] L. A. Bryan, W. M. Smedley, and R. K. Summerbell, *J. Amer. Chem. Soc.*, **72**, 2206 (1950).

[515] G. E. Hall and I. Sirel, *J. Amer. Chem. Soc.*, **74**, 836 (1952).

[516] E. A. Wildman and H. Gray, *J. Amer. Chem. Soc.*, **41**, 1122 (1919).

[517] L. R. Evans and R. A. Gray, *J. Org. Chem.*, **23**, 745 (1958).

[518] O. Neunhoeffer and G. Schmidt, *Chem. Tech.*, **10**, 103 (1958).

ratio ca. 3 : 1; the proportion of the latter is greater if chloromethyl methyl ether is chlorinated in the gas phase.[519] For rapid preparation of small amounts of dichloromethyl alkyl ethers in the laboratory a process is recommended in which a C=O group is converted into a CCl_2 group, namely, treatment of alkyl formates with PCl_5 (see page 252).

Gross[519] describes and illustrates an attachment placed on top of a column and consisting of a reflux tube A to the side of which is attached a wider reaction vessel B. Monochloromethyl methyl ether is treated in the gas phase at 90–95°, under UV irradiation, with a mixture of chlorine and nitrogen. The gas mixture obtained by chlorination in B is condensed in a reflux condenser that is so arranged that the condensate outside B flows back through A into the column which continuously delivers back the lowest-boiling constituent, namely, chloromethyl methyl ether (b.p. 60°). Bis(chloromethyl) ether (b.p. 101–103°) and dichloromethyl methyl ether (b.p. 84–86.5°), together with more highly chlorinated products collect in the distillation flask.

In discontinuous operation the reaction is continued until the vapor issuing from the column reaches a temperature of 64°. Fractionation of the products from 599 g of monochloromethyl methyl ether then gives 225 g of the 1,1- and 459 g of the 1,1'-dichloro ether. Monochloromethyl methyl ether is regenerated by passing the HCl produced into methanol and formaldehyde.[520]

Chlorination of dioxan affords a series of definite products that vary according to the reaction conditions (for a comprehensive review see Stumpf[52]). For instance, at 90° in the presence of iodine it affords up to 94% of 2,3-dichlorodioxan,[522] which is an important intermediate, *e.g.*, in the synthesis of glyoxal bisulfate;[523] and 2,3-dibromodioxan is obtained by brominating dioxan in CCl_4 which is a poor solvent for the resulting HBr that hinders the direct bromination.[524]

1,4-Addition of bromine to furan is used for preparation of 2,5-dibromotetrahydrofuran.[525] Like diethyl ether, dihydrofuran is chlorinated at room temperature[526] and at 0° in the presence of iodine[527] to give high yields of 2,3-dichlorotetrahydrofuran.

2,3-Dichlorodioxan:[528] SO_2Cl_2 (91.8 g) is dropped, with stirring, into dioxan (30 g) with UV irradiation and ice-cooling so that the internal temperature is kept at 30–35°. The gases evolved, which contain entrained SO_2Cl_2, are passed into ice-cooled dioxan (30 g) which is used in the next batch. The mixture is stirred for a further 5–6 h under UV irradiation, then distillation in a vacuum gives a 60% yield of the dichloro compound, b.p. 82–86°/12 mm.

Bromination of dialkyl ethers affords bromo aldehydes and acetals.[529,530] 1,2-Dibromoalkyl ethers are obtained from 1-chloroalkyl ethers and bromine, the HCl formed being finally removed in a vacuum in a stream of CO_2:

$$CH_3CHClOC_2H_5 + Br_2 \longrightarrow CH_2BrCHBrOC_2H_5 + HCl$$

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[519] H. Gross, *Chem. Techn.*, **10**, 659 (1958).

[520] C. S. Marvel and P. K. Porter, *Org. Syn.*, **9**, 58 (1929).

[521] H. Stumpf, "Chemie und Anwendungen des 1,4-Dioxans," Verlag Chemie, Weinheim, 1956.

[522] J. J. Kucera and P. C. Carpenter, *J. Amer. Chem. Soc.*, **57**, 2346 (1935).

[523] H. Gross, *J. Prakt. Chem.*, [iv], **21**, 99 (1963).

[524] H. C. Dehm, *J. Org. Chem.*, **23**, 147 (1958).

[525] C.-H. Schmidt, *Angew. Chem.*, **68**, 175 (1956).

[526] W. Reppe and co-workers, *Ann. Chem.*, **596**, 86, 113 (1955); L. Crombie and S. H. Harper, *J. Chem. Soc.*, **1950**, 1719.

[527] H. Normant, *C. R. Hebd. Séances Acad. Sci.*, **226**, 185 (1948).

[528] H. Gross, personal communication.

[529] C. Mauguin, *C. R. Hebd. Séances Acad. Sci.*, **147**, 747 (1908).

[530] K. Kratzl and K. Schubert, *Monatsh. Chem.*, **81**, 988 (1950).

1,2-Dibromoethyl ethyl ether:[531] Dry HCl is led cautiously into a mixture of paraldehyde (100 g) and ethanol (100 g) which is cooled in a freezing mixture. Two layers are formed, the upper of which is dried over $CaCl_2$ and fractionated (69%; b.p. 93–96°). To this 1-chloroethyl ethyl ether is added the theoretical quantity of bromine, portionwise (with time for decolorization in each case), with cooling in ice; HCl is evolved. When the crude dibromo product is distilled in a vacuum it has b.p. 92–95°/17 mm, the yield being 88–91%.

Treating glutardialdehyde at 30–40°, with stirring, with PCl_5 and brominating the resulting 1,5-dichloro-1,5-diethoxypentane at 0° give **1,2,4,5-tetrabromo-1,5-diethoxypentane.**[532]

1,2-Dibromo ethers are obtained still more simply on mixing bromine with equivalent amounts of an aldehyde and an alcohol; a 1-bromo ether is formed as intermediate by reaction of the aldehyde and alcohol with the HBr liberated in its bromination:

$$RCH_2CHO + R'OH + HBr \rightleftarrows CH_2RCHBrOR' + H_2O$$

$$CH_2RCHBrOR' + Br_2 \longrightarrow CHRBrCHBrOR' + HBr$$

Alkyl 1,2-dibromoalkyl ethers:[533] Bromine (0.1 mole) is dropped into a stirred and ice-cooled mixture of an aldehyde (0.1 mole) and an alcohol (0.1 mole) in benzene (20 ml) containing Na_2SO_4 (20 g). After 20 minutes' stirring at room temperature the hydrated sodium sulfate is filtered off and the filtrate is worked up by distillation in a vacuum. **1,2-Dibromoethyl ethyl ether,** b.p. 65–68°/12 mm (90%), **1,2-dibromopropyl ethyl ether,** b.p. 73–77°/12 mm (93%), and **1,2-dibromobutyl ethyl ether,** b.p. 89–91°/12 mm (91%), are thus obtained.

8. Replacement of hydrogen by halogen in carboxylic acids

a. Replacement of hydrogen by halogen in aliphatic monocarboxylic acids

The position for preferential substitution on chlorination of straight-chain alkanoic acids depends on whether an ionic or a radical mechanism predominates.[534,535] Ionic (electrophilic) substitution by chlorine occurs in the α-position to the carboxyl group and is favored by polarizing catalysts ($FeCl_3$, I_2) and exclusion of light. α-Chlorination is further favored by the inductive effect of COOH, ÇOOAlkyl (in esters), or COCl groups. This effect is considerably stronger for the COCl group than for the COOAlkyl or COOH group; thus chlorination of fatty acids gives only poor yields, but that of acid chlorides gives particularly good yields.

Preparation of 2-chlorobutyric acid by chlorination of the acid chloride at the b.p. in the presence of iodine has long been known.[536]

A systematic study[537] was devoted to α-chlorination of medium-chain fatty acids in the presence of polarizing catalysts that form acid chlorides as intermediates (I_2, S, or P with $SOCl_2$ or PCl_5): I_2/PCl_5 was the most effective combination. One mole of Cl_2 is used per mole of acid, with a streaming velocity of 25–50 l per hour at 100–160° for butyric but not more than 100 to 120° for hexanoic and longer-chain acids. Since side reactions are much favored

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[531] C. Swallen and C. E. Boord, *J. Amer. Chem. Soc.*, **52**, 654 (1930).
[532] P. Baudart, *Bull. Soc. Chim. France*, **11**, 336 (1944).
[533] H. Gross, K.-P. Hilgetag, J. Gloede, and H. Geipel, *Chem. Ber.*, **98**, 1673 (1965).
[534] M. S. Kharasch and H. C. Brown, *J. Amer. Chem, Soc.*, **62**, 925 (1940).
[535] H. Eistert, "Chemismus und Konstitution," F. Enke, Stuttgart, Vol. 1, 1948, p. 321.
[536] W. W. Markownikoff, *Ann. Chem.*, **153**, 241 (1869).

with acids of longer chain-length the concentration of the intermediate acid chloride should in these cases be as great as possible and that of the chlorine passed in should be kept as low as possible. It was found that ultraviolet irradiation favored side reactions more powerfully than did visible or infrared light. Although irradiation favors radical chlorination, which leads to chlorination at other than the α-position (see below), irradiation by visible light was in fact used in the two following cases of chlorination of acids or their acid chlorides; the dark reactions are reported[537] to give poorer yields; irradiation is, however, probably unnecessary if longer reaction times are allowed.

2-Chlorobutyric acid:[537] A mixture of butyric acid (1 mole) with iodine (0.005 mole), phosphorus (0.038 mole), and PCl_5 (0.006 mole) at 100° was treated with Cl_2 (1 mole; streaming velocity 50 l of Cl_2 per hour), with stirring and illumination by a 200-W lamp. The small amount of acid chloride produced was then hydrolysed by water (10 ml) during 30 min. A single distillation gave 71% of 2-chlorobutyric acid (calculated on acid that reacted). Later, refined fractionation (Destinorm filled column, filling length 1 m, ca. 18 theoretical plates) gave acid of b.p. 104.2°/20 mm.

Acid chlorides up to C_8 give good yields of α-chloro acid; too great concentrations of chlorine decrease the yields.[537]

The acid chloride (1 mole) is heated in a bath at 100° and chlorine (1.1 mole) is led in, with stirring, at a rate of 25 l per hour, the solution being irradiated throughout by a 200-W lamp. The various chlorination products must then be separated by distillation. Thus are obtained (yields based on acid that reacted) 92% of **2-chlorobutyryl chloride**, b.p. 130–131°, or 89% of **2-chloro-3-methylbutyryl chloride**, b.p. 155–156°.

Addition of a polarizing catalyst, *e.g.*, I_2, is recommended. Thus 2-chloro-propionyl or -butyryl chloride is prepared by passing dry Cl_2 into the boiling acid chloride (30 g) containing a little (0.5 g) iodine until the theoretical increase in weight is achieved.[538]

SO_2Cl_2 does not chlorinate aliphatic acids or acid chlorides appreciably in the dark and in the absence of catalysts; if, however, a halogen carrier is introduced, the α-chloro acids are formed.

If propionyl chloride (0.5 mole), SO_2Cl_2, and iodine (0.5 g) are boiled under reflux for 12 h, the pure 2-chloropropionyl chloride (22 g) and none of the 3-chloro isomer is obtained.[534]

6-(Benzoylamino)-2-chlorohexanoic acid:[539] 6-(Benzoylamino)hexanoic acid (35.3 g, 0.15 mole) and finely powdered iodine (0.5 g) are dissolved in SO_2Cl_2 (70 ml) and heated at 60–65° in a water-bath until the gas evolution slackens. The mixture is then brought slowly (60–90 min) to the b.p., after which the excess of SO_2Cl_2 is distilled off and the residual crude 6-(benzoylamino)-2-chlorohexanoic acid is washed with water. This material (yield 96–97.5%) can be used without further purification for the preparation of lysine.

The well-known method[33e] for monochlorination of acetic acid in the presence of red phosphorus in sunlight gives mixtures of homologous straight-chain compounds.[540] A tertiary α-hydrogen atom in an acid is smoothly replaceable by chlorine: isobutyric acid gives the α-chloro acid, but isovaleric acid, $(CH_3)_2CHCH_2COOH$, gives the β-chloro derivative.

Chloroacetic acid[1f] is most simply prepared by passing chlorine into a mixture of glacial acetic acid (300 g) and acetic anhydride at 105° until no more is absorbed (10–12 h); use of an efficient reflux condenser fed with ice-water is recommended. Distillation affords monochloroacetic acid, b.p. 185–187°, in 92–93% yield.

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[537] W. Criehl, W.-G. Schulze, and H. Fürst, *Chem. Ber.*, **91**, 1165 (1958).

[538] R. Wolffenstein and J. Rolle, *Ber. Deut. Chem. Ges.*, **41**, 735 (1908).

[539] A. Galat, *J. Amer. Chem. Soc.*, **69**, 86 (1947).

[540] H. H. Guest and C. M. Goddard Jr, *J. Amer. Chem. Soc.*, **66**, 2074 (1944).

If glacial acetic acid or chloroacetic acid is chlorinated at a temperature rising slowly from 80° to 110° until the density (at 20°) reaches 1.6, a product is obtained of which about two-thirds is dichloro- and about one-third trichloro-acetic acid, together with about 3% of monochloroacetic acid.[541] The trichloroacetic acid is removed by decarboxylation, achieved by heating the mixture (1500 g) with water (1 l) until no more chloroform distils. The water is distilled off and the residue fractionated in a vacuum, **dichloroacetic acid** distilling at 102°/20 mm (900 g).

An efficient laboratory process for obtaining dichloroacetic acid, from chloral and sodium cyanide, is described in *Organic Syntheses*.[542]

Radical substitution by chloride is favored by absence of polarizing catalysts, irradiation by direct sunlight or UV light, and working with SO_2Cl_2 containing added peroxides. Under these conditions chlorination gives a smaller proportion of α-chloro derivatives from fatty acids and fatty acid chlorides and correspondingly larger proportions of β- and γ-chloro derivatives.[543] Photochlorination of butyryl chloride in CCl_4 (sunlight, 0°) gives about 20% of 2-, 60% of 3-, and 20% of 4-chlorobutyryl chloride.[544]

In the presence of peroxides, SO_2Cl_2 converts fatty acids and their chlorides almost quantitatively into their chloro derivatives. Acetic acid is an exception — not more than 50% is converted into chloroacetic acid; acetyl chloride is not chlorinated by SO_2Cl_2 even in the presence of bisdodecanoyl or dibenzoyl peroxide. Peroxide-catalysed chlorination of (other) fatty acids by SO_2Cl_2 is a vigorous reaction, so that addition of a diluent (CCl_4 or chlorobenzene) is advisable: acid chlorides react less violently, so that there is no need to add a diluent for them.

The following examples show the proportions in which the isomers are formed on chlorination of some fatty acids by SO_2Cl_2 and peroxides.[534] The fatty acid (0.8 mole), SO_2Cl_2 (0.4 mole), CCl_4 (0.4 mole), and dibenzoyl peroxide (0.002 mole) are warmed gently under reflux in the dark until evolution of SO_2 and HCl ceases (60–90 min). The products are then converted into their acid chlorides by 4-hours' heating with $SOCl_2$ (1.6 moles). The excess of $SOCl_2$ and the CCl_4 are removed and the residue is fractionated. There result 45% of 2- and 55% of 3-chloropropionylchloride, 15% of 2- and 85% of 3-chloro-2-methylpropionyl chloride, or 10% of 2-, 45% of 3-, and 45% of 4-chlorobutyryl chloride.

α-Brominations are easier to carry out than α-chlorinations. Whereas it is difficult to exclude side reactions from α-chlorination of fatty acids or their chlorides, bromination gives only the α-bromo derivatives. Under ionic conditions the α-hydrogen atom, but not the tertiary α- or γ-hydrogen atom, of isovaleric or 4-methylvaleric acid, respectively, is replaced by bromine.[545] The usual syntheses of α-bromo fatty acids and their esters are direct substitutions or involve the acid halides as intermediates.

Electrophilic substitution of the α-CH_2 group of carbonyl compounds occurs the more easily the less the carbonyl group is stabilized by mesomerism. It is increasingly difficult in the series: ketone — acid chloride — acid anhydride — ester, carboxylic acid — carboxyamide.[546] This gradation can be illustrated by, for instance, the bromination of levulic acid (4-oxovaleric acid): with 2 moles

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[541] Ger. Pat. 852,997; *Chem. Abstr.*, **52**, 10152 (1958).

[542] A. C. Cope, J. R. Clark, and R. Connor, *Org. Syn.*, Coll. Vol. II, p. 181 (1943).

[543] N. O. V. Sonntag, *Chem. Rev.*, **52**, 359 (1953).

[544] A. Michael and W. W. Garner, *Ber. Deut. Chem. Ges.*, **34**, 4046 (1901).

[545] E. Fischer, *Ber. Deut. Chem. Ges.*, **36**, 2988 (1903).

[546] C. K. Ingold, C. W. Shoppee, and J. F. Thorpe, *J. Chem. Soc.*, **1926**, 1477.

of Br_2 in the presence of red phosphorus it occurs, not at the α-position to the COOH group, but on both the carbon atoms next to the CO group, for the product is 3,5-dibromolevulic acid.[547]

In the Hell–Volhard–Zelinsky procedure[548–550] the anhydrous acid is treated with red phosphorus and bromine. The red phosphorus should be washed with water until free from acid and dried at 100°, and the bromine should be rendered anhydrous by shaking with concentrated sulfuric acid. The reaction can be performed with 1 equivalent of red phosphorus or with catalytic amounts (ca. 3%); and catalytic amounts of PCl_3 may be used instead or red phosphorus. If the free α-bromo acid is required, 1 mole of a short- or medium-chain fatty acid is treated with ca. 1.1 mole of bromine and the resulting α-bromo acid is distilled from the reaction mixture in a vacuum; for higher fatty acids somewhat more than 2 moles of bromine are used and the crude α-bromo fatty acids are diluted with CCl_4 and decomposed with water.

The preparation of **ethyl α-bromophenylacetic acid**[551] illustrates the use of red phosphorus:

Phenylacetic acid (275 g) and red phosphorus (15 g) are ground together in a mortar, then dried for a few days over $CaCl_2$ in a desiccator. The mixture is placed in a 2-l flask and treated, with shaking, with bromine (200 g; dried by concentrated H_2SO_4). After cautious warming, this mixture is next treated on a boiling water-bath with a further amount (320 g) of bromine, heated for a further 2 h, and then cooled. Absolute ethanol (200 ml) is added and the mixture is left overnight, then boiled for 1 h under reflux and finally poured into water. The product is salted out and extracted with chloroform; it has b.p. 103–104°/2 mm and the yield is 75%.

Syntheses of the α-bromo derivatives of isovaleric,[552] 4-methylvaleric,[553] hexanoic,[554] and dodecanoic acid,[555] described in detail in *Organic Syntheses*, are examples of the bromination of medium- and long chain fatty acids.

2-Bromo-4-methylbutyric acid:[556] Isovaleric acid (8.6 moles; dehydrated by azeotropic distillation with benzene), bromine (1500 g; dried by shaking with 1 l of concentrated H_2SO_4), and PCl_3 (15 ml) are heated at 70–80° until the deep red color of bromine has disappeared from the condenser (10–20 h). More bromine (25 ml) is added and heating continued to disappearance of the red color, the oil bath temperature is raised slowly to 100–105° and kept there for 1.5–2 h, and the mixture is distilled in a vacuum. The fraction of b.p. 110–125°/15 mm (87.5–88.6%) is used for preparation of DL-valine.

63–66% of 2-bromo-4-methylvaleric acid is similarly obtained from 4.3 moles of acid, 4.65 moles of Br_2, and 10 ml of PCl_3. The fraction of b.p. 125–131°/12 mm was used for synthesis of DL-leucine.

At least two moles of Br_2 per mole of acid are used in the preparation of 2-bromododecanoic acid[555] in the presence of PCl_3.

Smaller quantities of bromine suffice, particularly for longer-chain acids, if the acids are first converted by $SOCl_2$ into the chlorides and these are brominated.[556] Adding a little iodine accelerates the reaction but is not absolutely

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[547] C. D. Hurd and J. R. Ferraro, *J. Org. Chem.*, **16**, 1640 (1951).

[548] C. Hell, *Ber. Deut. Chem. Ges.*, **14**, 891 (1881).

[549] J. Volhard, *Ann. Chem.*, **242**, 141 (1887).

[550] N. Zelinsky, *Ber. Deut. Chem. Ges.*, **20**, 2026 (1887).

[551] W. M. Rodionow, N. N. Ssuwowow, and K. S. Michailow, "Synthesen organischer Verbindungen," VEB Verlag Technik, Berlin, Porta-Verlag, Munich, 1956, Vol. 2, p. 158.

[552] C. S. Marvel, *Org. Syn.*, **20**, 106; Coll. Vol. III, 848 (1955).

[553] C. S. Marvel, *Org. Syn.*, **21**, 74 (1941); Coll. Vol. III, 523 (1955).

[554] H. T. Clarke and E. R. Taylor, *Org. Syn.*, Coll. Vol. I, 115 (1941).

[555] C. F. Allen and M. J. Kalm, *Org. Syn.*, **37**, 29 (1957).

[556] C. K. Ingold, *J. Chem. Soc.*, **119**, 316 (1921).

necessary. The α-bromo acid chlorides can be converted into the acids by water or into the esters by alcohols; ethyl 2-bromopropionate, for example, is easily accessible in this way.[557] **Methyl esters of straight-chain α-bromo C_4—C_{12}, C_{14}, C_{16}, and C_{18} fatty acids** can be prepared 'according to the following directions:[558]

The fatty acid (1mole) and $SOCl_2$ (150 g) are heated at 80–100° until gas evolution stops (3–4 h). A few crystals of iodine are added and then bromine (1.2 moles in ca. 4 h for the lower members; 1.4 moles in ca. 10 h for the higher members) at such a rate that no bromine can be seen in the upper part of the condenser. The mixture is then heated for a further 2–4 h on a boiling water-bath, next poured into boiling methanol (125 ml) (which gives two layers with the higher members), and finally the whole is poured into cold water where the bromo ester is precipitated. This ester is taken up in ether and washed successively with water, hydrogen sulfite solution, sodium carbonate solution (this must be omitted for the higher members because it forms emulsions therewith), and water, dried over Na_2SO_4, freed from ether, and fractionated in a vacuum (water-pump up to C_{12}, oil-pump for higher members). The refractive index is a good criterion of purity for the products.

The preparation of methyl 2-bromobutyrate will serve to illustrate how the process can be simplified by using a smaller excess of alcohol.[559]

Methyl 2-bromobutyrate: Butyric acid (70.4 g) is added to technical $SOCl_2$ (112 g) during 75 min, with stirring, at room temperature, then the mixture is heated on a boiling water-bath for 30 min, after which the $SOCl_2$ excess is distilled off. Bromine (135 g) is added to the residue at 80–90°, with stirring, and the whole is heated for 5 h on a boiling water-bath, then cooled. Methanol (46 ml) is added, and the solution is heated under reflux for 2 h. A small upper layer is formed and is separated in a separatory funnel and discarded. The remainder is distilled in a vacuum after a small forerun has been removed at 100° under atmospheric, pressure. The bromo ester (75–86%) has b.p. 70–75°/15 mm.

Preparation of 2-bromobutyric acid by hydrolysis of the crude bromide (obtained from butyric acid, bromine, and red phosphorus) by hot water is described by Fischer and Mouneyrat.[560]

The conversion of acetic acid (17.5 moles) by bromine (7.03 moles) in presence of acetic anhydride (200 ml) and pyridine (1 ml) into bromoacetic acid, and esterification of the bromo acid by benzene–ethanol with continuous removal of water, are detailed in *Organic Syntheses*.[561]

Carboxylic esters cannot be brominated by elemental bromine. However, mixtures of esters and acid chlorides in molar proportions 1 : 1 to 5 : 1 can be brominated, yields being the same as from 2–6 moles of acid chloride;[562] here the 2-bromo fatty acid chloride, formed as intermediate, reacts with the fatty acid ester in a transesterification that leads to the α-bromo ester and the unbrominated chloride.

$$CHRBr—COCl + CH_2RCOOCH_3 \rightleftarrows CHRBr—COOCH_3 + CH_2RCOCl$$

Ester chlorides of dicarboxylic acids, $ROOC(CH_2)_nCOCl$, which contain both an ester and an acid chloride group in the one molecule, thus give only poor yields of a crude α-bromo ester chloride $ROOC(CH_2)_{n-1}CHBrCOCl$, unless a special procedure is used (bromination in $SOCl_2$, see page 179); for, when

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[557] A. I. Vogel, *J. Chem. Soc.*, **1948**, 648.

[558] H. Reinheckel, *Chem. Ber.*, **93**, 2227 (1960).

[559] H. Cassebaum, *Arch. Pharm.*, **292**, 569, 570 (1959).

[560] E. Fischer and A. Mouneyrat, *Ber. Deut. Chem. Ges.*, **33**, 2387 (1900).

[561] S. Natelson and S. Gottfried, *Org. Syn.*, **23**, 37 (1943); Coll. Vol. III, 381 (1955).

[562] H. Reinheckel, *Chem. Ber.*, **93**, 2222 (1960); *J. Prakt. Chem.*, [iv], **15**, 260 (1962).

1 mole of Br_2 is used in this reaction, the monobrominated diester, the α,α′-dibromo diester, and the α,α′-dibromo dichloride are also formed, and when the mixed products are converted into diester a mixture of α-bromo and α,α′-dibromo esters is finally obtained.

The preparation of β-halo carboxylic acids and their esters by addition of HHal to the α,β-unsaturated acid or ester is discussed on page 129.

Preparative importance attaches also to γ-bromo α,β-unsaturated carboxylic acids and esters. They are prepared by bromination with *N*-bromosuccinimide (see page 146) at the b.p., the usual solvent being CCl_4, or occasionally thiophene-free benzene, with dibenzoyl peroxide as radical-former. This procedure has afforded, *e.g.*, methyl and ethyl 4-bromocrotonate,[352,563] ethyl 4-bromo-2-pentenoate,[564] ethyl 4-bromo-4-methyl-2-pentenoate[361] $(CH_3)_2CBrCH{=}CHCOOC_2H_5$, and ethyl 6-bromosorbate[565] $CH_2BrCH{=}CH{-}CH{=}CHCOOC_2H_5$.

Butyrolactone is brominated in the presence of red phosphorus[566] or phosphorus tribromide[567] to 2,4-dibromobutyryl bromide, the reaction occurring readily and requiring good cooling. Cautious addition of at least 1 mole of water at 80° converts the bromide into the dibromo acid, and by removal of HBr this yields 2-bromobutyrolactone which is important as an intermediate in the synthesis of methionine.[566]

The tendency for α-bromination is so strong that treating fatty acids with bromine in presence of halogen carriers (S, P, or I_2) in a bomb tube leads to α,α-dibromo acids; dibromoacetic acid, for instance, is obtained from glacial acetic acid and bromine in the presence of sulfur at 150°.[568]

Trichloro- and tribromo-acetic acid are obtained by oxidation of chloral and bromal, respectively, and α,α-dichloro fatty acids by reaction of α-keto acids with PCl_5.

b. Replacement of hydrogen by halogen in aliphatic dicarboxylic acids and nitriles

In principle, what has been said for halogenation of monocarboxylic acids applies also to that of dicarboxylic acids: there are preferential α-bromination, preferential α-chlorination under ionic reaction conditions, decrease in the proportion of α-chloro derivatives in radical chlorination, and in most cases direct or indirect reaction by way of the acid halides. There is, however, the additional complication that two diastereoisomers — the *meso*- and the racemic form — can usually arise, *e.g.*, with α,α′-dihalo dicarboxylic acids and their esters.

2,5-Dichloroadipic acid:[569] If chlorine is passed at 80°, with exclusion of light, into adipoyl dichloride containing $FeCl_3$ (5 g per mole of dichloride) or I_2 (2 g per mole of dichloride) until absorption reaches 2 atoms of Cl per mole of dichloride, subsequent esterification of

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[563] J. English Jr. and J. D. Gregory, *J. Amer. Chem. Soc.*, **69**, 2123 (1947); D. Todd and S. Teich, *J. Amer. Chem. Soc.*, **75**, 1895 (1953); R. D. Schuetz and W. H. Houff, *J. Amer. Chem. Soc.*, **77**, 1839 (1955).

[564] W. Herz, *J. Amer. Chem. Soc.*, **78**, 1488 (1956).

[565] H. E. Ungnade and T. R. Hopkins, *J. Amer. Chem. Soc.*, **73**, 3091 (1951).

[566] H. Plieninger, *Chem. Ber.*, **83**, 267 (1950).

[567] K. Folkers and co-workers, *J. Amer. Chem. Soc.*, **77**, 5142 (1955).

[568] A. Iliceto and E. Scoffone, *Gazz. Chim. Ital.*, **81**, 133 (1951); P. Genvresse, *Bull. Soc. Chim. France*, [iii], **7**, 365 (1892).

the product affords 55% ($FeCl_3$) or 69% (I_2) of dimethyl 2,5-dichloroadipates, b.p. 122–128° 0.6 mm. On cooling and seeding of the distillate 43% of these esters crystallize and these products are hydrolysed when boiled with concentrated HCl to complete dissolution (1 h). The resulting acids can be separated by recrystallization from water into the difficultly soluble *meso*-2,5-dichloroadipic acid, m.p. 186°, and the readily soluble racemic isomer, m.p. 145°.

3,4-Dichloroadipic acid: Under the preceding conditions but with UV-irradiation and exclusion of the polarizing catalyst, 61% of dimethyl dichloroadipates, b.p. 108–112°/0.6 mm, are obtained which on hydrolysis gives acids consisting to 94% of 3,4-dichloroadipic acid, m.p. 126°. In contrast to the two 2,5-dichloro acids, this is soluble in benzene; it is the main product of chlorination in the dark by SO_2Cl_2 and dibenzoyl peroxide (4 g per mole of dichloride).[569]

For the chlorination of glutaric acid see Treibs and Michaelis.[570]

Chlorination of nitriles RCH_2CN gives mainly α,α-dichloro nitriles, under ionic conditions and even under conditions (UV-irradiation) that favor radical reactions. Acetonitrile is readily chlorinated to trichloroacetonitrile since the chloro nitrilium salt that is first formed is chlorinated much faster than acetonitrile itself.

$$\mathrm{CH_3CN} \xrightarrow{\mathrm{Cl_2}} [\mathrm{CH_2Cl{-}C{\equiv}NH}]^+\,\mathrm{Cl^-} \xrightarrow{\mathrm{2Cl_2}}$$

$$[\mathrm{CCl_3{-}C{\equiv}NH}]^+\,\mathrm{Cl^-} \xrightarrow{\Delta H} \mathrm{CCl_3CN} + \mathrm{HCl}$$

It is therefore advantageous to pass in HCl (ca. 1 part per 10 parts of nitrile) below 36° and then to chlorinate at not too high a temperature (35–42°).[571] Monochloroacetonitrile is obtained from monochloroacetamide and P_4O_{10} in trimethylbenzene.[572]

Glutarodinitrile,[573] and also adipodinitrile, heptanedinitrile, and octanedinitrile,[574] are converted into the α,α,α'α'-tetrachloro dinitriles when chlorine is passed into them at 70 to 75°, and hydrolysis of these products by boiling concentrated HCl gives the corresponding tetrachloro dicarboxylic acids.

It is very easy to halogenate malonic acid and its esters and alkyl or arylalkyl derivatives. Chloromalonic acid is obtained by hydrolysis of diethyl chloromalonate, which is formed when chlorine is passed into the malonic ester at 70°.[575] Cloves[576] describes the preparation of 2-chlorobutyric acid by way of diethyl ethylmalonate.

When bromine (1 mole) is added to a suspension of malonic acid in ether, the acid dissolves whilst it is converted into bromomalonic acid;[575,576] use of 2 moles of bromine in formic acid leads to dibromomalonic acid, particularly rapidly if the mixture is irradiated.[578] If bromine is added to a dry ethereal solution of an alkyl- or arylalkyl-malonic acid at such a rate that the mixture

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[569] W. Treibs and H. Walther, *Chem. Ber.*, **88**, 396 (1955).

[570] W. Treibs and K. Michaelis, *Chem. Ber.*, **88**, 402 (1955).

[571] F. N. Stepanov and N. I. Shirokova, *Zh. Obshch. Khim.*, **25**, 941 (1955); *Chem. Abstr.*, **50**, 3209 (1956).

[572] D. B. Reisner and E. C. Horning, *Org. Syn.*, **30**, 22 (1950).

[573] W. Treibs, J. Herrmann, and G. Zimmermann, *Chem. Ber.*, **93**, 2198 (1960).

[574] W. Treibs and G. Zimmermann, *Chem. Ber.*, **90**, 1146 (1957).

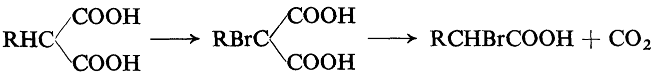
[575] M. Conrad and H. Reinbach, *Ber. Deut. Chem. Ges.*, **35**, 1816 (1902).

[576] A. M. Cloves, *Ann. Chem.*, **319**, 357 (1901).

[577] B. Teichmann, *Z. Chem.*, **5**, 106 (1965).

[578] R. Willstätter, *Ber. Deut. Chem. Ges.*, **35**, 1375 (1902).

just boils, very good yields of substituted bromomalonic acids are obtained whose hydrolysis has afforded a large number of α-bromo aliphatic acids and their aryl derivatives.



$$\mathrm{RHC}\genfrac{}{}{0pt}{}{\diagup \mathrm{COOH}}{\diagdown \mathrm{COOH}} \longrightarrow \mathrm{RBrC}\genfrac{}{}{0pt}{}{\diagup \mathrm{COOH}}{\diagdown \mathrm{COOH}} \longrightarrow \mathrm{RCHBrCOOH} + \mathrm{CO_2}$$

This method is exemplified in *Organic Syntheses*[579] by the synthesis of 2-bromo-3-phenylpropionic acid which is important for preparation of DL-phenylalanine.[580]

Higher dicarboxylic acids are brominated by the Hell–Volhard–Zelinsky procedure or as the crude dichlorides formed by $SOCl_2$.

It is advantageous to hydrolyse α,α′-dibromo dicarbonyl dibromides or dichlorides by formic acid; 50% formic acid has given good service for this purpose.[577]

α,α′-Dibromo derivatives of succinic,[548,581] glutaric,[582] adipic,[583] and pimelic acid[584] are examples of compounds prepared by these methods. To obtain the diesters the crude α,α′-dibromo dicarbonyl dihalides are treated with the required alcohol; the preparation of diethyl 2,5-dibromoadipate by way of the crude dichloride is described as a typical example in *Organic Syntheses.*[585]

Dimethyl 2,5-dibromoadipate[586–588] and 2,7-dibromosebacate,[588] which also are obtained by way of the brominated dicarbonyl dichlorides, are relatively easily isolated as the *meso*-forms, m.p. 77° and 52°, respectively; these crystallize from the mixture of isomers obtained on distillation in a vacuum. The liquid racemic dimethyl 2,5-dibromoadipate rearranges partially to the solid *meso*-form during the distillation and completely so on treatment with sodium methoxide solution.[587]

Since α-bromination is favored much more by a COCl group than by a COOAlkyl group, it would be expected that the ester chlorides of dicarboxylic acids would be brominated preferentially next to the COCl group by 1 mole of bromine. However, the yields are mostly poor: for example, 58% of diethyl 2-bromoglutarate,[589] 42% of dimethyl 2-bromoadipate,[590] 18.5% of dimethyl 2-bromoheptanedioate, and 11.5% of dimethyl 2-bromooctanedioate;[588] the reason for this is described on page 176. Considerably better yields are obtained by brominating the ester chlorides with $SOCl_2$ as solvent; then if one starts with the dicarboxylic acid monoester it is unnecessary to isolate the ester chloride.

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[579] C. S. Marvel, *Org. Syn.*, Voll. Col. III, 705 (1955).

[580] E. Fischer, *Ber. Deut. Chem. Ges.*, **37**, 3603 (1904).

[581] C. Hell and J. Gorodetzky, *Ber. Deut. Chem. Ges.*, **21**, 1731 (1888).

[582] J. M. van der Zanden, *Rec. Trav. Chim.*, **53**, 483 (1934).

[583] J. M. van der Zanden, *Rec. Trav. Chim.*, **63**, 113 (1944).

[584] E. A. Fehnel and G. C. Oppenlander, *J. Amer. Chem. Soc.*, **75**, 4660 (1953).

[585] P. C. Guha and D. K. Sankaran, *Org. Syn.*, Coll. Vol. III, 623 (1955).

[586] H. Stephen and C. Weizmann, *J. Chem. Soc.*, **103**, 271 (1913).

[587] A. Bernton, H. Ing, and W. Perkin, *J. Chem. Soc.*, **125**, 1500 (1924).

[588] W. Treibs and G. Leichsenring, *Chem. Ber.*, **84**, 54 (1951); W. Treibs and H. Reinheckel, *Chem. Ber.*, **89**, 51 (1956).

[589] P. Karrer and F. Kehrer, *Helv. Chim. Acta*, **27**, 142 (1944).

[590] H. Reinheckel, *Chem. Ber.*, **93**, 2554 (1960).

The dicarboxylic acid monoester (1 mole) is boiled under reflux with $SOCl_2$ (300 ml) for about 2 h, then Br_2 (1.05 mole) is dropped into the boiling solution during 2–3 h, and the mixture is set aside overnight before being poured carefully into ethanol (500 ml). Alternatively, the excess of $SOCl_2$ can be distilled off in a vacuum and only then is the crude α-bromo ester chloride treated with ethanol (200 ml). The whole is left at room temperature for 2–3 h, then poured into water, the crude bromo ester is taken up in ether (3 × 150 ml), and the ether extracts are washed successively with water, hydrogen sulfite solution, sodium carbonate solution, and again water, and dried over Na_2SO_4. The ether is distilled off and the residue is distilled through a 15–30 cm column in a good water-pump vacuum or in an oil-pump vacuum. Yields of **diethyl 2-bromo-glutarate, -adipate, and -octanedioate**[591] are around 90%.

This procedure is also useful for preparation of α-bromo monocarboxylic esters, *e.g.*, ethyl 2-bromo-2-cyclohexylacetate and -2-phenylacetate.

Using SO_2Cl_2 (450 ml) in place of bromine (1 mole) and removing the excess of $SOCl_2$ and SO_2Cl_2 in a vacuum before treating the crude α-chloro dicarboxylic ester chloride with absolute ethanol afford diethyl α-chloro dicarboxylates in good yield.[591]

$\alpha,\alpha,\alpha',\alpha'$-Tetrabromo dicarboxylic acids are formed on reaction of dicarboxylic acids or α,α'-dibromo dicarboxylic acids with bromine in the presence of a small amount of iodine in a bomb tube at 120–245° or on hydrolysis of nitriles of type $NC—CBr_2(CH_2)_nCBr_2—CN$.[592] Except when $n = 0$ or 1, these nitriles can be prepared by passing bromine vapor in a stream of nitrogen through the heated (80–125°) dinitrile containing a little iodine (0.3 g per mole of adipodinitrile) until absorption of bromine ceases (8 h); yields are about 40%. Only short- and medium-chain dicarbonitriles can be chlorinated at atmospheric pressure, but tetrabromination can be achieved at atmospheric pressure even with long-chain nitriles such as tetradecanedinitrile.[573]

Bromination of acetonitrile in the presence of $CaCO_3$ and red phosphorus at 50–60° gives 2,4,6-tris(dibromomethyl)-*s*-triazine.[593]

α-Bromo nitriles of the type $R(CH_2)/CHBrCN$ are unstable. They become discolored when kept at room temperature and cannot be distilled without decomposition, not even at, *e.g.*, 30° in a vacuum. Crude α-bromo nitriles are obtained[594] when Br_2 (1 mole) is dropped slowly into a nitrile (1 mole) containing about 1 g of PBr_3 at 70°; they are converted into α-bromo amides by the action of concentrated H_2SO_4 at 50° for about 3 minutes. α-Chloro and α-bromo nitriles of the type $R_2CHalCN$ are, however, stable and can be distilled in a water-pump vacuum; they are formed in good yield on interaction of the nitriles with PCl_5 or PBr_5.[595]

c. Replacement of hydrogen by halogen in aromatic carboxylic acids and hydroxy and amino carboxylic acids

Chlorine, bromine, and iodine can be introduced under mild conditions at free *ortho-* and *para*-positions to OH or NH_2 groups of aromatic hydroxy and amino carboxylic acids, also into similar sulfonic acids and esters. On reaction in water an excess of bromine replaces a COOH group (see page 163). The most easily accessible derivatives of *o-* and *p*-hydroxybenzoic acid are the dihalo derivatives in which the halogen atoms are in the *ortho-* and *para-*, or in the two *ortho*-positions, respectively, to the OH group. When treated in

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[591] E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

[592] W. Treibs, J. Herrmann, and W. Gerhardt, *Chem. Ber.*, **91**, 290 (1958).

[593] E. Ghigi, *Gazz. Chim. Ital.*, **71**, 641 (1941).

[594] C. L. Stevens and W. Holland, *J. Org. Chem.*, **18**, 1112 (1953).

[595] C. L. Stevens and T. H. Coffield, *J. Amer. Chem. Soc.*, **73**, 103 (1951).

glacial acetic acid with a little more than 2 moles of Cl_2, Br_2,[596] or ICl,[597] salicyclic acid gives the 3,5-dihalosalicylic acids, and *p*-hydroxybenzoic acid gives the 3,5-dihalo-4-hydroxybenzoic acids.

For the chlorination of ethyl *p*-hydroxybenzoate by SO_2Cl_2 see page 162. 3,5-Dibromo-4-hydroxybenzoic acid is readily available on addition of bromine (2 moles) in glacial acetic acid to *p*-hydroxybenzoic acid in the same solvent, with final heating on a steam-bath.

Anthranilic acid is converted into its 3,5-dibromo derivative by means of bromine in glacial acetic acid[598] or better by passing an air stream carrying 2 moles of bromine into a solution of anthranilic acid in hydrochloric acid;[599] 2-amino-3,5-dibromobenzoic acid (92%) is deposited from the acid solution, together with a little tribromoaniline. Analogously, passing about 2 moles of chlorine into a hydrochloric acid solution of anthranilic acid at not more than 30° gives 2-amino-3,5-dichlorobenzoic acid. For details see *Organic Syntheses.*[600]

Iodo derivatives are particularly interesting members of the halogenated aromatic hydroxy and amino carboxylic acids, for they are intermediates for the preparation of *X*-ray contrast media. They have been successfully prepared by iodination with ICl, which will therefore be treated in this Section (but see also page 165).

Iodine chloride (ICl): It is often recommended that ICl should be prepared by passing chlorine over powdered iodine until the theoretical increase in weight occurs and distilling the product, but this does not give pure ICl. If ICl is required in substance, the following procedure should be used:[601]

A weighed 1-l flask with a ground-glass neck is cooled in carbon dioxide–acetone. Gaseous chlorine is passed through three wash-bottles (1, empty; 2, concentrated H_2SO_4; 3, glass wool) into this flask, where it liquifies. When about 300 ml of chlorine (*d* 1.557) have been led in, slightly less than the equivalent amount of iodine is added; the contents of the flask then solidify. Next the flask is raised gradually from the cooling-bath (fume cupboard!), the excess of chlorine evaporating. The vessel is weighed, the small additional amount of iodine required for formation of ICl is added, and the crude liquid ICl is set aside for at least 24 h at a few degrees above room temperature, the flask being closed by its ground-glass stopper. The product, which is already almost pure, can be further purified as follows: the liquid ICl is cooled and when about 80% of it crystallized (m.p. 27.2°) the liquid residue is poured off.

The crude ICl suffices for preparative iodinations. The excess of iodine, which is generally innocuous, is determined by adding a weighed amount (1–2 ml) of the iodine chloride to a mixture of concentrated HCl (25 ml), water (25 ml), and $CHCl_3$ (5 ml) and titrating the mixture with KIO_3 solution (50 g of KIO_3 per litre of solution) until the violet color of the chloroform layer disappears; 1 ml of KIO_3 solution = 0.1188 g of iodine.[602] Overchlorination is determined by titration with KI solution (50 g of KI per liter of solution) until the iodine color appears in the chloroform layer; 1 ml of KI solution = 0.0766 g of missing iodine; the calculated total amount of missing iodine is added, as necessary, to the crude ICl or to its freshly prepared solution in hydrochloric or glacial acetic acid.

$$Cl_2 + KI \longrightarrow KCl + ICl$$

$$ICl + KI \longrightarrow KCl + I_2$$

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[596] R. B. Earle and H. L. Jackson, *J. Amer. Chem. Soc.*, **28**, 109 (1906).

[597] G. H. Woollett and W. W. Johnson, *Org. Syn.*, Coll. Vol. II, 343 (1943).

[598] A. S. Wheeler and W. M. Oates, *J. Amer. Chem. Soc.*, **32**, 771 (1910).

[599] F. Ullmann and E. Kopetschni, *Ber. Deut. Chem. Ges.*, **44**, 426 (1911).

[600] E. R. Atkinson, D. M. Murphy, and J. E. Lufkin, *Org. Syn.*, **31**, 96 (1951).

[601] J. Cornog and R. A. Karges, *J. Amer. Chem. Soc.*, **54**, 1882 (1932).

[602] V. H. Wallingford, H. G. Decker, and M. Kruty, *J. Amer. Chem. Soc.*, **74**, 4367 (1952).

ICl that is free from iodine and ICl_3 can be determined by addition of aqueous KI and titration with 0.1N-$Na_2S_2O_3$; 1 ml of 0.1N-$Na_2S_2O_3$ = 0.00812 g of ICl.

It is simpler not to prepare the ICl in substance but to prepare it directly in solution, which can be done in several ways:

(a) The calculated quantity of chlorine—in small batches from liquid chlorine contained in a calibrated vessel—is led on to iodine covered with glacial acetic acid and placed at 15° in the dark. During passage of the gas it is necessary to stir the acetic acid lying over the heavy iodine which finally dissolves entirely.[559,603]

(b) Dissolving 110.7 g of KI and 71.3 g of KIO_3 in 833 ml of 6N-HCl and making the solution up to 1 litre gives a 1M-solution of $KICl_2$ in hydrochloric acid.[604] Such a solution may, if required, be extracted with ether, the ethereal solution of ICl then being dried over $CaCl_2$.

(c) An ethereal solution of ICl may also be obtained from $HgCl_2$ (1 mole) and iodine (2 moles). Such solutions are used for addition of ICl to C=C bonds of fats (determination of the iodine number by von Hübl's method[83] (see page 114) and serve for addition of ICl to olefins.[605]

ICl decomposes in aqueous solution,[606] but this can be repressed by working in sufficiently concentrated HCl or by iodination with an aqueous solution of $KICl_2$ or $NaICl_2$ that contains an excess of KCl or NaCl; in this way the equilibrium is shifted to the left.[607]

$$5\,ICl_2^- + 3\,H_3O \rightleftharpoons 2\,I_2 + IO_3^- + 1\,OCl^- + 6\,H^+$$

Aqueous $KICl_2$ or $NaICl_2$ solutions can be obtained from previously prepared ICl or, more simply, directly.

(a) Direct preparation of a **2M-solution of $KICl_2$**:[608]

$$KIO_3 + 2\,KI + 6\,HCl \longrightarrow 3\,KICl_2 + 3\,H_2O$$

Concentrated HCl (*d* 1.19; 170 ml) and a solution of KI (111 g) in water (100 ml) are added simultaneously, with rapid stirring, to a mixture of KIO_3 (71 g), KCl (40 g), and concentrated HCl (5 ml) at such a rate that no chlorine is evolved. The solution is then made up to 500 ml.

(b) Direct preparation of a **2M-solution of $NaICl_2$** (from molar quantities of I_2 and Cl_2):[465] Powdered iodine (520 g) is suspended in a solution of NaCl (400 g) in water (1.2 l), and chlorine (142 g) is passed in with stirring at room temperature (3–5 h). The mixture is stirred for a further hour, the excess of iodine is filtered off and washed with a little water, and the $NaICl_2$ solution is made up to 2 l. 1 ml should consume 40 ml of 0.1N-$Na_2S_2O_3$ after addition of KI.

Non-acidic solutions of $KICl_2$ or $NaICl_2$ are particularly suitable for ICl-iodination of phenols in the presence of ammonia, amines, or alkali (see page 165); they are equally useful for ICl-iodination in a hydrochloric acid medium.[608]

Iodination by ICl is usually carried out in glacial acetic acid, but aromatic amines, amino carboxylic acids, and amino sulfonic acids[506] can also be iodinated by ICl in hydrochloric acid solution:

3-Amino-2,4,6-triiodobenzoic acid:[602] A mixture of ICl (290 g) and concentrated HCl (*d* 1.19 ; 290 ml) is run slowly into a stirred solution of *m*-aminobenzoic acid (68.5 g, 0.5 mole) in water (2 l) and concentrated HCl (*d* 1.19; 50 ml). The mixture is warmed gradually to

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[603] F. D. Chattaway and A. B. Constable, *J. Chem. Soc.*, **1914**, 125.

[604] K. Gleu and W. Jagemann, *J. Prakt. Chem.*, [ii], **145**, 260 (1936).

[605] S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 836 (1948).

[606] C. J. Klemme and J. H. Hunter, *J. Org. Chem.*, **5**, 232 (1940).

[607] H. W. Cremer and D. R. Duncan, *J. Chem. Soc.*, **1932**, 2031.

[608] J. O. Hoppe and co-workers, *J. Amer. Chem. Soc.*, **78**, 3214 (1956).

80–85° and stirred for a further 3 h at this temperature. The crude 3-amino-2,4,6-triiodobenzoic acid (about 92%) that is precipitated is purified by twice recrystallizing its sodium salt from about five times its weight of water with addition of a little hydrogen sulfite. A white acid, of m.p. 196.5–197.5° (dec.), is obtained in about 70% yield.

2- and 4-Amino-3,5-diiodobenzoic acid are obtained similarly from the corresponding aminobenzoic acids by use of 185 g of ICl per 0.5 mole of acid.

If anthranilic acid is treated in dilute HCl at 18–22° with 1 mole of ICl a good yield of 2-amino-5-iodobenzoic acid is obtained; a detailed prescription is given in *Organic Syntheses.*[609]

Three atoms of iodine can be introduced by $NaICl_2$ or $KICl_2$ into 3,5-diaminobenzoic acid as the NH_2 groups favor electrophilic substitution. However, only the 2,6-diiodo derivative is obtained on iodination of an aqueous suspension of 3-(acetylamino)-5-aminobenzoic acid by 2M-$KICl_2$; the medium becomes acidic in hydrochloric acid, and a third atom of iodine can be introduced into the ring if a little more NaOH (about 0.5 mole per mole of COOH in excess) is added than is necessary to neutralize both the COOH group and the hydrochloric acid formed. In neutral or weakly alkaline media, where the NH_2 group is free and the COOH group is present as anion, electrophilic substitution by iodine is easier than in an acid medium.[608]

For triiodination of *m*-hydroxybenzoic acid see page 165.

ICl acts as an iodinating agent only under conditions that favor dissociation into I^+ and Cl^-, *e.g.*, in glacial acetic acid or nitrobenzene. ICl vapor chlorinates solid salicylic acid.[407]

The introductions of halogen into aromatic hydroxy and amino carboxylic acids discussed so far occur in the *ortho* and/or the *para*-position, *i.e.*, in the positions favored in electrophilic substitution. Replacement of more than two hydrogen atoms of *o*- or *p*-hydroxybenzoic acid necessitates occupation of positions *meta* to the OH group and is thus possible only by energetic methods such as halogenation in a solution of SO_3 in concentrated sulfuric acid ("oleum"). In concentrated H_2SO_4 containing 60–70% of SO_3 two further bromine atoms can be introduced into 3,5-dibromosalicylic acid and one further Cl atom, or one Cl and one Br, into 3,5-dichlorosalicylic acid,[610] and also two further bromine atoms into 3,5-dibromo-4-hydroxybenzoic acid:[611]

A mixture of 3,5-dibromo-4-hydroxybenzoic acid (150 g) and 70% oleum (750 ml) is stirred vigorously for 30 min in a sulfonation flask fitted with a KPG stirrer (lubricated with concentrated H_2SO_4), a reflux condenser, and a dropping funnel whose tip just dips into the oleum, the flask being placed in a water-bath at 28–29°. Then five portions (6, 6, 6, 5, 5 ml) of bromine (dried by concentrated H_2SO_4) are added at 29°, each portion in 10 min at 45-min intervals. The mixture is set aside overnight and then poured slowly on ice with stirring by a glass rod. The precipitated crude **2,3,5,6-tetrabromo-4-hydroxybenzoic acid** is reprecipitated from ammonia. The yield is 76% and the m.p. is 222°, 228° after recrystallization from dilute ethanol.

When an excess of bromine is used in 30% acetic acid at about 60° the COOH group of such polyhalogenated hydroxybenzoic acids is replaced by Br with evolution of CO_2.

It is not possible to introduce further iodine atoms into 3,5-dihalo-2- or -4-hydroxybenzoic acid by the oleum method. However, in 60% oleum it is possible to halogenate *o*-sulfobenzoic anhydride and thus to obtain the 3,4,5,6-

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[609] V. H. Wallingford and P. A. Krueger, *Org. Syn.*, Coll. Vol. II, 349 (1943).

[610] L. H. Farinholt, A. P. Stuart, and D. Twiss, *J. Amer. Chem. Soc.*, **62**, 1237 (1940).

[611] H. Pfanz and H. Dorn, *Arch. Pharm.*, **61**, 657 (1956).

tetrachloro, -tetrabromo, and -tetraiodo derivatives and thence the corresponding acids.[612] This procedure was first used by Juvalta,[613] specifically for bromination of phthalic anhydride in 50% oleum to give, *inter alia*, tetrabromophthalic acid.[613,614]

The preparation of tetraiodophthalic anhydride by treatment of phthalic anhydride (1 mole) with iodine (2.12 mole) in 60% oleum (600 ml) at 65° and finally at 170° for 2 h is described in detail in *Organic Syntheses.*[615]

The Juvalta procedure can also be used for polybromination of heterocycles: 3,5-Dibromo-4-pyridone can be converted by bromine in 70% oleum at 80° in 85% yield into 2,3,5,6-tetrabromo-4-pyridone, from which pentabromopyridine is obtained in good yield by treatment with PBr_5 in a bomb tube at 180°.[611]

The procedure described so far for preparation of halogenated aromatic carboxylic acids concern such as carry substituents that make electrophilic substitution easier. When such groups are not present, and when an indirect synthesis such as the Sandmeyer reaction or oxidation of halogenated aldehydes or toluene derivatives is not preferred, the Birckenbach-Goubeau-Waters method (see page 151) provides for very elegant introduction of Br or I at the *meta*-position to a COOH group: benzoic acid reacts with bromine alone only in a bomb tube, and with bromine and iron filings only a 170-260°,[616] but it is rapidly brominated by halogen cations, *e.g.*, in acetic acid and nitric acid containing $AgNO_3$, in acetic acid and sulfuric acid containing $KBrO_3$, or as in the following examples.[374]

***m*-Bromobenzoic acid:** A solution of $KBrO_3$ (4 g) in water (150 ml) is added, with stirring, during 15 min to a solution of benzoic acid (0.1 mole) and bromine (2.1 ml) in a mixture of glacial acetic acid (250 ml) and concentrated HCl (150 ml) at 25° (cooling!). When the mixture is stirred for a further hour precipitation of *m*-bromobenzoic acid begins. Then a further amount (4 g) of $KBrO_3$ in water (50 ml) is dropped in during 30 min. The yield is 11 g.

***m*-Iodobenzoic acid:** A mixture of benzoic acid (0.1 mole), Ag_2SO_4 (0.05 mole; Ag_2SO_4 is soluble in 90% H_2SO_4), concentrated H_2SO_4 (240 ml), and water (30 ml) is stirred vigorously on a boiling water-bath, and finely powdered (!) iodine (0.11 mole) is added in portions. When the whole is stirred and heated for a further 80 min, AgI is continuously precipitated. The mixture is then cooled and diluted with water (2 l), the excess of iodine is removed by hydrogen sulfite, and the solution and the precipitated product are extracted with ether. Crude *m*-iodobenzoic acid obtained on removal of the ether is recrystallized from aqueous acetone, then having m.p. 185-186° (yield 75%).

9. Replacement of hydrogen by halogen in aromatic nitro compounds

The Waters procedure (see page 151) has proved its value also for preparation of ***m*-bromonitrobenzene**:[374]

Ag_2SO_4 (0.1 mole) is added to nitrobenzene (0.1 mole) and Br_2 (0.1 mole) in concentrated H_2SO_4 (90 ml) and water (10 ml), and the whole is shaken at room temperature for 16 h.

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[612] O. Twiss and L. H. Farinholt, *J. Amer. Chem. Soc.*, **58**, 1561 (1936).

[613] N. Juvalta, Ger. Pat. 50,177 (1899); Friedländer, **2**, 94, (1887-1890).

[614] D. S. Pratt and C. O. Young, *J. Amer. Chem. Soc.*, **40**, 1416 (1918).

[615] C. F. H. Allen, H. W. J. Cressman, and H. B. Johnson, *Org. Syn.*, **27**, 78 (1947); Coll. Vol. III, 796 (1955).

[616] H. L. Wheeler and B. W. McFarland, *Amer. Chem. J.*, **19**, 364 (1897).

Filtration from AgBr, dilution with water, and extraction with ether give the *m*-bromo compound, m.p. 55–56°, in 70% yield.

2-Bromo-4-nitrocumene, *inter alia*, is obtained similarly.[617] The classical bromination of nitrobenzene by bromine and iron powder is recorded in detail in *Organic Syntheses*.[618]

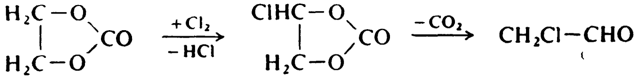
10. Replacement of hydrogen by halogen in aldehydes and ketones

Direct chlorination or bromination of aldehydes can occur at the C of the CHO group or at the C atom next to the CHO group. The latter reaction is much the more important. Reaction of the lower aldehydes with chlorine is highly exothermic and must therefore be carried out with good cooling or in a diluent such as methylene dichloride, chloroform, carbon tetrachloride, water, hydrochloric acid, or preformed chloro aldehyde.

Acetaldehyde derivatives chlorinated at the α-position are interesting intermediates. Chloroacetaldehyde, CH_2Cl—CHO, b.p. 85–85.5°/748 mm, can be obtained by chlorinating acetaldehyde in aqueous HCl at 18–20° [619] or by chlorinating anhydrous acetaldehyde below 10°;[140a,620] in the latter case there must be efficient cooling, particularly at the start, to avoid inflammation due to reaction of chlorine with the acetaldehyde vapor; only a small amount of acetaldehyde is used at first, and the remainder, cooled in Dry Ice, is added later in portions; the rate of chlorination (to *d* 1.37) is controlled by the rate at which the heat of reaction can be removed.

When dry chlorine is led into acetaldehyde with cooling at 16–18° a product of composition $2CH_2ClCHO$, $1CH_3CHO$, 1HCl is formed which affords 60% of chloroacetaldehyde on distillation; but if acetaldehyde is chlorinated whilst the temperature is raised gradually to about 80° di- and tri-chloroacetaldehyde are obtained according to the amount of chlorine introduced.[621]

Anhydrous **chloroacetaldehyde** can be obtained in good yield by the following laboratory procedure:[523]



A stream of chlorine is led into 3.44 moles of freshly distilled ethylene carbonate (1,3-dioxolan-2-one) under UV-irradiation at 63–70° until a weight increase of 119 g is attained (24 h). Fractional distillation at water-pump vacuum then gives 5.2% of 1,2-dichloroethylene carbonate (3,4-dichloro-1,3-dioxolan-2-one), b.p. 78–79°/19–20 mm, followed by 69% of the monochloro derivative, b.p. 106–107°/10–11 mm.[622] The latter product is treated with one drop of triethylamine and heated in a distillation apparatus slowly to 210° (oil-bath); CO_2 is split off and chloroacetaldehyde is formed, which collects in the receiver as a clear liquid with a green tinge; this reaction requires about 1 hour; redistillation through a short column gives the pure aldehyde (9 g), b.p. 84–86°.

On a manufacturing scale a continuous process is used. Chlorine is led into the chlorination mixture and acetaldehyde is run in at the same time under the surface of the liquid. UV-irradiation accelerates the reaction. The product is obtained as a polymer.

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[617] M. Crawford and F. H. C. Stewart, *J. Chem. Soc.*, **1952**, 4445.

[618] J. R. Johnson and C. G. Gauerke, *Org. Syn.*, **8**, 46 (1928).

[619] H. Guinot and I. Tabuteau, *C. R. Hebd. Séances Acad. Sci.*, **231**, 234 (1950).

[620] Ger. Pat. 844,595.

[621] M. N. Shchukina, *Zh. Obshch. Khim.*, **18**, 1653 (1948); *Chem. Abstr.*, **43**, 2575 (1949).

[622] M. S. Newman and R. W. Addor, *J. Amer. Chem. Soc.*, **75**, 1264 (1953); **77**, 3791 (1955).

Under certain conditions α,β-dichloro ethers (cf. page 170) react as a mixture of chloroacetaldehyde, alcohol, and HCl, *e.g.*, in the synthesis of 2-aminothiazole from 1,2-dichloroethyl ethyl ether and thiourea in water.

Dichloroacetaldehyde, b.p. 88°/760 mm, is obtained by two-stage chlorination (1st stage, 10–14°, 1.6–1.7 Cl; 2nd stage, 28–32°, 1.9–2.1 Cl) of a mixture of acetaldehyde or paraldehyde and water (molar ratio 1 : 3.5–4.5).[623]

Trichloroacetaldehyde (chloral), b.p. 97.8°/760 mm, is formed on chlorination of ethanol with irradiation and stirring. Absolute ethanol is no longer used, as in Liebig's procedure,[624] but, instead, aqueous 70–80% ethanol which leads directly to chloral hydrate:

$$C_2H_5OH + 4Cl_2 + H_2O \longrightarrow CCl_3CH(OH)_2 + 5HCl$$

Irradiation during chlorination reduces the reaction time (72 h) to one-third or one-quarter.[625]

Since ethanol vapor may react explosively with chlorine, it is best to introduce the chlorine and aqueous alcohol below the surface of the chlorination mixture which is removed continuously *via* an overflow. Reaction can be carried out, for example, in two consecutive reaction vessels, the second at a higher temperature, until the density reaches 1.44. Direct distillation then affords chloral hydrate, b.p. 97.5°, m.p. 53°, from which distillation with concentrated H_2SO_4 affords chloral containing 1 molar proportion of HCl. The HCl is removed by a further distillation from some $CaCO_3$.

Chloral can also be prepared by chlorinating aqueous acetaldehyde in preformed chloral[626] or acetaldehyde in 7N-hydrochloric acid.[627] In the latter case reaction is stopped after absorption of 1 mole of Cl_2 at 18–20°; at 35–40° chlorination leads to dichlorination and at 80–90° eventually to trichloroacetaldehyde.

In chlorination of aldehydes the nature of the product (α-chloro aldehyde or carboxylic acid) depends both on the concentration of the added acid and on the nature of its anion:[628] In 0.5N-hydrochloric acid at 10–15° chlorination of propionaldehyde gives 98% of propionic acid but in 4.5–6.3N-hydrochloric acid gives 90–92% of 2-chloropropionaldehyde. The concentration of acid is held constant by addition of water during the chlorination.

Whereas exhaustive chlorination of acetaldehyde dimethyl acetal (at not more than 60°) affords formaldehyde, 1-chloroethyl ethyl ether, trioxymethylene, and HCl as main products, exhaustive chlorination of the diethyl acetal (at 60–70°) gives a product that, on treatment with concentrated H_2SO_4, affords chloral in good yield.[629] The mixtures afforded by chlorination of acetals contain, *inter alia*, chloro ethers derived by reaction with the HCl formed; the chloro acetals are obtained by subsequent addition of ethoxide.

$$CH_3CH(OC_2H_5)_2 + Cl_2 \longrightarrow CH_2ClCH(OC_2H_5)Cl + C_2H_5OH$$

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[623] F. C. Potts, Brit. Pat. 644,914; *Chem. Abstr.*, **45**, 5176 (1951).

[624] J. von Liebig, *Ann. Chem.*, **1**, 189 (1832).

[625] O. W. Cass, U.S. Pat. 2,443,183 and 2,478,152; *Chem. Abstr.*, **42**, 7318 (1948) and **44**, 167 (1950).

[626] H. Petri and E. Mahler, Ger. Pat. 874,303; *Chem. Abstr.*, **52**, 7345 (1958).

[627] H. Guinot and I. Tabuteau, *C. R. Hebd. Séances Acad. Sci.*, **231**, 236 (1950).

[628] C. R. Dick, *J. Org. Chem.*, **27**, 272 (1962).

[629] J. S. Reichert, J. H. Bailey, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **45**, 1554 (1923).

If chlorine (1 mole) is led, with stirring and cooling, into pure acetaldehyde diethyl acetal (1 mole) at 40–45°, and then sodium ethoxide (1 mole) in anhydrous ethanol is added and the neutral mixture is fractionated, **chloroacetaldehyde diethyl acetal,** b.p. 157°, is formed in about 70% yield.[1p]

Meerwein's method of reducing chloral to trichloroethanol by aluminum ethoxide[630] is described in detail in *Organic Syntheses*.[631]

The old method[632] of making acid halides from aromatic aldehydes and a halogen can be of preparative value when the aldehyde is more accessible than the carboxylic acid; for instance, about 80% of *o*-chlorobenzoyl chloride is obtained when chlorine is led for about 15 h into vigorously stirred molten *o*-chlorobenzaldehyde (1 mole) at 140–160° (for details see *Organic Syntheses*).[633]

α-Bromo aldehydes can be prepared by direct action of bromine (1 mole) on aldehydes in $CHCl_3$ or CS_2 provided there is irradiation at a low temperature (−15°). The HBr formed may be trapped by added $CaCO_3$ but that is not essential. For example, 2,3-dibromosuccindialdehyde,[634] 2-bromovaleraldehyde,[635] and 2-bromo-2-phenylacetaldehyde[636] have been prepared in this way. If it is desired to store α-bromo aldehydes it is advisable to convert them into their acetals by adding an alcohol to the brominated reaction mixture; *e.g.*, the acetals of 2-bromovaleraldehyde,[637] 2-bromo-3-methylbutyraldehyde,[638] and 2,5-dibromoadipdialdehyde[639] have been thus obtained. If 2 moles of bromine are used α,α-dibromo acetals are formed.[640] Halogenation in methylene chlorine at −20° has led to, *e.g.*, 70% of 2-chloro- and 50% of 2-bromo-2-phenylacetaldehyde, also to 67% of 2-bromoheptanal.[641]

A series of alipatic aldehydes can be converted into the α-bromo aldehydes in 50–90% yield by use of dioxane·Br_2 (see page 168);[642] phenylacetaldehyde gives correspondingly a 40% yield.

A solution of dioxane · Br_2 (50 g) in ether is added to one of acetaldehyde (8.8 g) in ether (50 ml) at 5–10°. When the color has vanished the mixture is washed successively with water, sodium carbonate solution, and again water; this gives **bromoacetaldehyde,** CH_2BrCHO, b.p. 104–106° (7.5 g).

Paraldehydes are also useful starting materials for synthesis of α-bromo aldehydes. They are first brominated and then converted into their acetals by addition of alcohol.[643] High yields (85%) of bromoacetaldehyde diethyl acetal

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[630] H. Meerwein, *Ann. Chem.*, **444**, 221 (1925).

[631] W. Chalmers, *Org. Syn.*, Coll. Vol. II, 598 (1943).

[632] L. Wöhler and J. Liebig, *Ann. Chem.*, **3**, 262 (1832).

[633] H. T. Clarke and E. R. Taylor, *Org. Syn.*, **9**, 34 (1929).

[634] C. Harries and H. Krützfeld, *Ber. Deut. Chem. Ges.*, **39**, 3671 (1906).

[635] H. Erlenmeyer and J. P. Jung, *Helv. Chim. Acta*, **32**, 37 (1949).

[636] H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 2058 (1947).

[637] R. Kuhn and C. Grundmann, *Ber. Deut. Chem. Ges.*, **70**, 1898 (1937).

[638] F. G. Fischer and K. Löwenberg, *Ann. Chem.*, **494**, 272 (1932); *Ber. Deut. Chem. Ges.*, **64**, 31 (1931).

[639] F. G. Fischer and K. Löwenberg, *Ber. Deut. Chem. Ges.*, **66**, 667 (1933).

[640] S. M. McElvain and L. R. Morris, *J. Amer. Chem. Soc.*, **74**, 2659 (1952).

[641] J.-J. Riehl, *C. R. Hebd. Séances Acad. Sci.*, **245**, 1321 (1957).

[642] L. A. Yanovskaya and A. P. Terentiev, *Zh. Obshch. Khim.*, **22**, 1598 (1952); *Chem. Abstr.*, **47**, 9258 (1953).

[643] R. Dworzak and co-workers, *Monatsh. Chem.*, **46**, 253 (1925); **48**, 252 (1927); **50**, 467 (1928); **52**, 142 (1929); **53/54**, 588 (1929).

are obtained on brominating paraldehyde in the presence of peroxides[644] at −10° under irradiation, with subsequent addition of absolute ethanol to the reaction mixture.

A particularly simple method is to brominate (3 moles of Br_2 per mole of paraldehyde) paraldehyde in an alcohol, with vigorous stirring and water-cooling, this giving bromoacetaldehyde diethyl acetal (72.5%) and dipropyl acetal (65%),[645] also bromoacetaldhyde dibutyl acetal (65%) and diisopropyl acetal (22%).[646]

Br_2 is dropped during about 5 h into an alcoholic paraldehyde solution, then the HBr is neutralized by addition of a slurry of Na_2CO_3. The upper layer is dried over K_2CO_3, the lower-boiling fractions are distilled off through a column at water-pump vacuum, and the residue is fractionated.

Gradual addition of paraldehyde (0.5 mole) to Br_2 (4.5 moles) and sulfur (1.5 g) and warming at 60–80° for 2 h give bromal; for details see *Organic Syntheses*.[647]

Acetals are brominated by a solution of Br_2 in $CHCl_3$ to which $CaCO_3$ has been added.[648] The HBr may also be trapped by pyridine.[649]

2-Bromo-3-ethoxypropionaldehyde diethyl acetal:[650] When Br_2 (1 mole) is dropped into a stirred mixture of 3-ethoxypropionaldehyde diethyl acetal (1 mole) and pyridine (1 mole) and the mixture is held at 60–65° until the red color has disappeared (2–4 h), 83% of crude 2-bromo-3-ethoxypropionaldehyde diethyl acetal is formed. In this case the mild brominating agent pyridine dibromide · HBr is formed as intermediate.

The diethyl acetals of acetaldehyde, propionaldehyde, isobutyraldehyde, and butyraldehyde are converted into α-bromo acetals when treated at 25–40° in sunlight or under irradiation by a 60 W lamp with *N*-bromosuccinimide added portionwise;[651] the reaction being exothermic, cooling is required. This method gives purer products than do those described above, but the yields are no better.

A synthesis of α-halo aldehydes that is very generally applicable involves addition of halogen to a C=C group: the unhalogenated aldehyde is converted by 1 hour's boiling with acetic anhydride and potassium acetate into the enol acetate;

$$\mathrm{RCH_2CHO} \longrightarrow \mathrm{RCH{=}CHOAc} \xrightarrow{\mathrm{Br_2}} \mathrm{RCHBrCHBrOAc}$$

$$\longrightarrow \mathrm{RCHBrCH(OCH_3)_2} \longrightarrow \mathrm{RCHBrCHO}$$

bromine (1 mole) is added to this acetate (1 mole) in CCl_4 at 0–10°; the bromination mixture is set aside in 99.5–100% methanol for 2–3 days, giving the α-bromo dimethyl acetal from which the α-bromo aldehyde is obtained by distillation with concentrated HCl. This method gives 65–86% yields from acetaldehyde, isobutyraldehyde, and straight-chain aliphatic C_7—C_{12} al-

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[644] G. Darzens and M. Meyer, *C. R. Hebd. Séances Acad. Sci.*, **236**, 292 (1953).

[645] H. Baganz, K.-H. Dossow, and W. Hohmann, *Chem. Ber.*, **86**, 151 (1953).

[646] H. Baganz and C. Vitz, *Chem. Ber.*, **86**, 398 (1953).

[647] F. A. Long and J. W. Howard, *Org. Syn.*, Coll. Vol. II, 87 (1943).

[648] E. Fischer and K. Landsteiner, *Ber. Deut. Chem. Ges.*, **25**, 2549 (1892).

[649] S. M. McElvain and P. M. Walters, *J. Amer. Chem. Soc.*, **64**, 1963 (1942).

[650] W. T. Simpson, *J. Amer. Chem. Soc.*, **71**, 754 (1949).

[651] E. N. Marvell and M. J. Joncich, *J. Amer. Chem. Soc.*, **73**, 973 (1951).

dehydes, but only 25% from phenylacetaldehyde;[652] it is described in detail in *Organic Syntheses*[653] with 2-bromoheptanal as example.

Adding ICl in concentrated HCl (*d* 1.19) to a solution of vinyl acetate in CCl_4 below 5° gives, in 20 min, an almost theoretical yield of 1-chloro-2-iodoethyl acetate; and when a solution of this acetate in CCl_4 is treated with anhydrous ethanol and $CaCl_2$ and set aside at 10–15° for 3 days, about 80% of **iodoacetaldehyde diethyl acetal** is obtained.[654]

Free α-bromo aldehydes are obtained from their acetals by brief heating (1 min) in dioxane–water–concentrated HCl (10 : 5 : 1), immediate cooling, dilution with water, and extraction with ether.[655] For the preparation of α-halo acetals by way of α,β-dihalo ethers see also page 111.

Aromatic aldehydes and ketones containing halogen in the ring are rarely prepared by treating the aldehyde or ketone with elemental halogen. Usually one of the various aldehyde or ketone syntheses is applied to a halogenated starting material or the Sandmeyer synthesis is applied starting from a nitro aldehyde. Preparative access to *m*-bromo- and *m*-chloro-benzaldehyde and the corresponding acetophenones is provided by taking advantage of the "swamping catalyst effect":

A molten complex of the carbonyl compound (1 mole) and resublimed $AlCl_3$ (2.5 moles) is stirred in a sulfonation flask at 25–100° and treated with bromine (1.20 moles) or chlorine (1.25 moles; generated from chlorine liquified by an acetone–Dry Ice bath; led below the surface of the melt). The original paper[656] should be consulted for details.

Hydroxy, alkoxy, and amino aldehydes can, like phenols and aromatic amines, be halogenated under mild conditions. The possibility of loss of the aldehyde group has already been mentioned (page 163), and so will be (page 194) the competition between nuclear and side-chain halogenation in substituted alkyl-aromatic ketones.

Of all carbonyl compounds ketones are the most easily halogenated in the α-position. The halogenation of carbonyl compounds is preceded by an acid-catalysed unimolecular rearrangement into a more active molecule (the enolic form);[657-659] halogenation is therefore slow to start for as long as no acid is present. With large batches it is bad practice to add too much halogen initially, for an induction period during which hydrogen halide is formed in the initially slow reaction may be followed by a violent exothermic reaction. In brominations it is advisable to heat a few ml of the ketone with bromine and to add this mixture ("seed") to the bulk of the material to be halogenated.

To obtain α-monochloro ketones it is best to work in aqueous solution with a large excess of ketone and to add calcium carbonate.[1e,660] Chlorination (markedly exothermic!) of 1 mole of acetone with 1 mole of SO_2Cl_2 at 30–40° gives a mixture (total yield ca. 80%) containing 58% of 1,1,dichloro-2-pro-

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[652] P. Z. Bedoukian, *J. Amer. Chem. Soc.*, **66**, 651, 1325 (1944); **79**, 891 (1957).

[653] P. Z. Bedoukian, *Org. Syn.*, **29**, 14 (1949).

[654] S. Akiyoshi and K. Okuno, *J. Amer. Chem. Soc.*, **74**, 5759 (1952).

[655] E. R. Alexander, *J. Amer. Chem. Soc.*, **70**, 2592 (1948).

[656] D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).

[657] A. Lapworth, *J. Chem. Soc.*, **85**, 30 (1904); **93**, 2188 (1908).

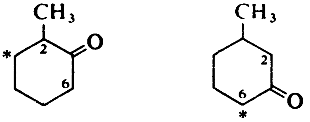
[658] F. Kröhnke, *Ber. Deut. Chem. Ges.*, **69**, 921 (1936).

[659] R. Huisgen and F. Jakob, *Ann. Chem.*, **590**, 40 (1955); O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **22**, 605 (1957).

[660] R. Justoni, *Chim. Ind. (Milan)*, **24**, 93 (1942).

panone and 41% of 1-chloro-2-propanone, and with 2 moles of SO_2Cl_2 gives 72% of 1,1-dichloro-, 6% of 1,3-dichloro-, and 20% of 1,1,3-trichloro-2-2-propanone.[661] Since 1-chloro- and 1,1-dichloro-2-propanone have approximately the same boiling point (118–120°),[662] monochloroacetone is best prepared from acetyl chloride and diazomethane by way of the diazo ketone.[663]

Mixtures of isomers are to be expected on monochlorination or monobromination of unsymmetrical ketones that have hydrogen atoms on each of the carbon atoms next to the carbonyl group. Since enolization is the rate-determining step in acid-catalysed halogenation of ketones, the preferred position of substitution in unsymmetrical saturated acyclic or cyclic ketones is determined by the preferred direction of enolization. For both types, with a few exceptions, the modified Saytzeff rule applies, namely, that halogen becomes attached to that carbon atom whose neighboring carbon atoms carry the largest number of hydrogen atoms.[664]



*= Preferred site of halogenation.

If the carbonyl group lies between a methyl and another alkyl group, the first hydrogen atom on the α-carbon atom of the latter is more easily replaced by halogen than is one in the methyl group. Further, in, *e.g.*, 2-methylcyclohexanone position 2 is halogenated preferentially, and in 3-methylcyclohexanone position 6. For the isomer distribution obtained on α-monobromination of dialkyl ketones carrying branched or unbranched alkyl groups see also a paper by Sacks and Aston.[665]

It is not possible to discuss here in detail the very complex results of brominating 3-keto steroids. It must suffice to mention, as examples, that, whereas 5α-cholestan-3-one is monobrominated in accord with the Saytzeff rule, 5β-cholestan-3-one derivatives such as methyl 12α-acetoxy-3-oxo-5β-cholanoate are monobrominated at position 4.[666] Numerous data from the literature of halogenation of steroids are cited by Fieser and Fieser.[566]

Bromination of carbonyl compounds is an equilibrium reaction. For most ketones the equilibrium (a) lies well to the right provided that the concentration of HBr is not too great or the bromine is not trapped.[667]

$$\text{RCOCHR}'\text{R}'' + \text{Br}_2 \rightleftharpoons \text{RCOCBrR}'\text{R}'' + \text{HBr} \quad \ldots \text{(a)}$$

Chloro ketones are not reduced by HCl. If R′ in (a) is an electron-attracting subsuent such as COOR or Br, the resulting α-bromo carbonyl compound is more easily reduced by HBr: α-bromoacetoacetic ester, which can

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[661] D. P. Wyman and P. R. Kaufman, *J. Org. Chem.*, **29**, 1956 (1964).
[662] E. R. Buchman and H. Sargent, *J. Amer. Chem. Soc.*, **67**, 401 (1945).
[663] R. E. Van Atta, H. D. Zook, and P. J. Elving, *J. Amer. Chem. Soc.*, **76**, 1185 (1954).
[664] H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, **1951**, 2430.
[665] A. A. Sacks and J. G. Aston, *J. Amer. Chem. Soc.*, **73**, 3902 (1951).
[666] H. H. Inhoffen, G. Kölling, and G. Koch, *Chem. Ber.*, **84**, 363 (1951).
[667] F. Kröhnke and H. Timmler, *Ber. Deut. Chem. Ges.*, **69**, 614 (1936).
[668] A. T. Blomquist and F. H. Baldwin, *J. Amer. Chem. Soc.*, **70**, 29 (1948).

be isolated only if HBr is excluded,[668] rearranges to γ-bromoacetoacetic ester in glacial acetic acid–HBr with intermediate liberation of bromine.

If 1 mole of a methyl ketone is treated in glacial acetic acid, CS_2, CCl_4, etc., with a mole of bromine in a pressure flask at 20–40°, then, provided that the mixture is worked up immediately on disappearance of the bromine color, mixtures of α-bromo and α,α-dibromo ketone are obtained in amounts that vary according to the nature of the solvent. If, however, the mixture is kept for 30–60 minutes at 20°, then, independently of the solvent, acetophenone, for example, presents 80% of the bromine in mono- and 20% in dibromoacetophenone, because time has been allowed for equilibration (a) to be followed by equilibration (b).[658]

$$2RCOCH_2Br \overset{(HBr)}{\rightleftarrows} RCOCH_3 + RCOCHBr_2 \quad \ldots \quad (b)$$

Thus introduction of one mole of Br_2 into a methyl ketone does not lead solely to the monobromo compound: to decrease the amount of dibromo compound produced, an excess of ketone must be used; the greater the excess the more equilibrium (b) lies to the right.

Bromination of acetone in glacial acetic acid in a pressure flask gives 1,3-dibromoacetone by way of 1,1-dibromoacetone, the proportion of the latter being increased if the HBr is trapped.[669]

2,2-Dibromo-3-keto steroids rearrange to 2,4-dibromo-3-keto steroids.[670]

Alicyclic ketones are chlorinated preferentially in the α-position. The hydrogen chloride formed may be trapped by addition of, *e.g.*, calcium carbonate so as to avoid aldol condensation.[671-673]

2-Chlorocyclopentanone:[673] A rapid stream of chlorine is led into a vigorously stirred mixture of cyclopentanone (500 g), $CaCO_3$ (290 g), water (320 ml), and 40% $CaCl_2$ solution (290 g). The temperature is kept at 40° by occasional cooling. After dissolution of the $CaCO_3$ the mixture is placed in an ice-chest, the hydrated calcium chloride that has crystallized is filtered off, and the filtrate is extracted with ether. The extract is dried over $CaCl_2$ and, after removal of the ether, repeatedly fractionated in a vacuum through a Widmer column. This gives recovered cyclopentanone (80 g), 2-chlorocyclopentanone (380 g, 64%), b.p. 73.5°/10 mm, and 2-chloro-2-cyclopentenone (70 g, 13%), b.p. 88°/10 mm.

Chlorination of cyclohexanone in water, to give 2-chlorocyclohexanone, is described in detail in *Organic Syntheses*,[674] but addition of an emulsifier is stated in a patent[675] to increase the yield. Methanol is a suitable solvent for α-monochlorination of cyclic ketones, 2-chlorocyclopentanone and 2,8-

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[669] F. Kröhnke and O. Lüderitz, *Chem. Ber.*, **83**, 60 (1950).

[670] H. H. Inhoffen and G. Zühlsdorff, *Ber. Deut. Chem. Ges.*, **76**, 233 (1943).

[671] P. Fritsch, *Ann. Chem.*, **279**, 313 (1894).

[672] A. Kötz, K. Blendermann, E. Kárpáti, and R. Rosenbusch, *Ann. Chem.*, **400**, 50 (1913).

[673] H.-W. Wanzlick, G. Gollmer, and H. Milz, *Chem. Ber.*, **88**, 69 (1955).

[674] M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syn.*, **25**, 22 (1945); Coll. Vol. III, 188 (1955).

[675] E. Henkel and H. Friederich, Ger. Pat. 954,694; *Chem. Abstr.*, **53**, 21191 (1959).

[676] G. Hesse, G. Krehbiel, and F. Rämisch, *Ann. Chem.*, **592**, 143 (1955).

dichlorocyclooctanone[677] having been thus obtained. Also, SO_2Cl_2 can be used as chlorinating agent.

2-Chloro-2-methylcyclohexanone: When SO_2Cl_2 (1.1 moles) in dry CCl_4 is added, during 1 h with stirring at room temperature (water-cooling!), to a solution of 2-methylcyclohexanone (1 mole) in dry CCl_4 and the solution is stirred for a further 2 h at room temperature, washed successively with water, aqueous $NaHCO_3$, and saturated NaCl solution, dried, and worked up by distillation, an 83–85% yield of 2-chloro-2-methylcyclohexanone is obtained. For details see *Organic Syntheses*.[678]

Steroid ketones can be α-chlorinated in very good yield by *tert*-butyl hypochlorite in glacial acetic acid; for example, 2-chloro-5α-cholestan-3-one is thus obtained.[679]

Acetic acid, CCl_4, CS_2, CH_2Cl_2, $CHCl_3$, and ether can be used as solvents for bromination of ketones, the last three solvents also at low temperatures. There are various methods of removing most of the HBr formed in the reaction: $CaCO_3$ or $NaHCO_3$ may be added to a solution of the ketone in CH_2Cl_2, $CHCl_3$, or CCl_4 although this may cause difficulty in getting the reaction started and subsequent too violent evolution of CO_2 unless a previously heated sample is added as seed.

Norris' method[680] is suitable for aliphatic ketones: the bromine is dropped into a solution of the ketone and $KClO_3$ in water at 35–40°:

$$6RCH_2COCH_2R' + 3Br_2 + KClO_3 \xrightarrow{H_2O} 6RCHBrCOCH_2R' + KCl + 3H_2O$$

Butane-2-one, for example, thus gives a mixture containing 3-bromo-2-butanone as main product (see substitution rules on page 190) with some 1-bromo-2-butanone, and the mixture can be separated by distillation at 150 mm through an efficient column with a reflux ratio of 6 : 1.[681] Monobromoacetone can also be prepared in this way.

Faworski's (Favorski's) procedure[682] is very simple: Bromine (1 mole) is dropped into the ketone, usually with cooling in ice-water, the HBr being removed by leading N_2 or CO_2 through the solution; or a stream of N_2 laden with bromine vapor may be passed into the ketone. In these cases also it is advisable to start the bromination by 'seeding' or by adding two drops of concentrated HBr solution (in water or acetic acid).

Adding a little HBr and a few small pieces of $AlCl_3$ has been recommended[683] for bromination of steroid ketones in glacial acetic acid by a solution of bromine in the same solvent.

Occasionally the HBr is removed only at the end of the reaction, *e.g.*, in the preparation of **bromoacetone**:

Bromine (7.3 moles) is added, at a rate such that it is continuously decolorized (1–2 h), to a stirred mixture of acetone (500 ml, 6.8 moles), glacial acetic acid (372 ml), and water (1.6 l) at 70–80°. The whole is then diluted with water (0.8 l), cooled to 10°, and neutralized

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[677] G. Hesse and F. Urbanek, *Chem. Ber.*, **91**, 2733 (1958).

[678] E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Syn.*, **37**, 8 (1957).

[679] J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 3503 (1953).

[680] J. F. Norris, *Ind. Eng. Chem.*, **11**, 828 (1919).

[681] J. R. Catch, D. F. Elliott, D. F. Hey, and E. R. H. Jones, *J. Chem. Soc.*, **1948**, 272.

[682] A. Faworski, *J. Prakt. Chem.*, [ii], **88**, 641 (1913).

[683] P. A. Plattner and co-workers, *Helv. Chim. Acta*, **30**, 385 (1947).

with solid Na_2CO_3. The product is separated, dried with $CaCl_2$, and fractionated, then having b.p. 40–42°/13 mm (yield 43–44%). For details see *Organic Syntheses*.[684]

Bromoacetone may also be obtained by drawing an air stream laden with bromine vapor through a mixture of acetone (4 parts) and marble (1 part) at 28–31° while water (2.5 parts) is gradually added.[685]

Bromo ketones irritate skin and mucous membranes (fume cupboard!). Samples that have not been distilled in a vacuum are impure and soon become discolored; addition of a little MgO is recommended.

If more highly brominated acetone is required the amount of bromine used should be increased.

When bromine (650 ml, 1.8 moles per mole of acetone) is slowly added dropwise to a mixture of acetone (500 ml), water (1.6 l), and glacial acetic acid (375 ml) at 70°, 1,1-dibromoacetone (20 g) and **1,3-dibromoacetone** (473 g), b.p. 97–98°/21–22 mm, are obtained as well as monobromoacetone (60 g).

Adding bromine (150 g) in glacial acetic acid (500 ml) dropwise to a solution of 1,3-dibromoacetone (210 g) in glacial acetic acid (500 ml) at 80–90° during one hour without additional heating, and removal of the acetic acid and a forerun in a vacuum afford **1,1,3-tribromoacetone** (180 g), b.p. 114–116°/14 mm, and 1,1,1,3-tetrabromoacetone (21 g), b.p. 132 to 133°/13 mm.[686]

Bromine complexes may be used instead of bromine for preparation of bromo ketones. Pyridine dibromide·HBr, which is crystalline and whose amount can therefore be easily measured, is useful for bromination of very small quantitites of substance, *e.g.*, of steroid ketones (see page 112); equimolar amounts of this complex and of the ketone are warmed together in glacial acetic acid or ethanol at 40–60°.[68]

Dioxan·Br_2 in ether is reported to give, *inter alia*, 83% of bromoacetone;[642] its suitability for the preparation of unstable cyclic bromo ketones has been disputed,[687] but it has been valuable for bromination of acetylcarbinols in ether.[500] The ether·Br_2 complex, a dark red oil obtained by adding dry ether to ice-cold bromine, has also been recommended for mild bromination of cyclic ketones in dry ether.[688]

Side reactions due to bromine or HBr are avoided by recourse to *N*-bromosuccinimide (for its preparation see page 148); 2-bromo-cyclohexanone[689] and -cycloheptanone,[690] for instance, have been obtained by its use.

The ketone (1 mole) and *N*-bromosuccinimide (1 mole) are heated for about 30 min under reflux in CCl_4 together with a small amount of a radical-former such as azoisobutyronitrile (0.1 g) or dibenzoyl peroxide (ca. 2 g). Then the succinimide is filtered off from the solution of the bromo ketone.

N-Bromosuccinimide introduces bromine at the allyl position of α,β-unsaturated ketones, for instance, at position 6 of testosterone acetate.[691] For

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[684] P. A. Levene, *Org. Syn.*, Coll. Vol. II, 88 (1943).

[685] R. Scholl and G. Matthaiopoulos, *Ber. Deut. Chem. Ges.*, **29**, 1555 (1896).

[686] F. Weygand and V. Schmied-Kowarzik, *Chem. Ber.*, **82**, 335 (1949).

[687] I. V. Mashinskaya and A. S. Podberezina, *Zh. Obshch. Khim.*, **28**, 1501 (1958); *Chem. Abstr.*, **53**, 1184 (1959).

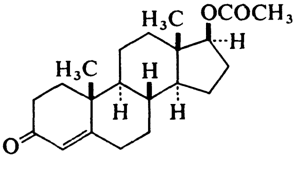
[688] N. R. Easton and S. J. Nelson, *J. Amer. Chem. Soc.*, **75**, 640 (1953).

[689] H. Schmid and P. Karrer, *Helv. Chim. Acta*, **29**, 579 (1946).

[690] E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 2303 (1953).

[691] C. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946).

further examples see Djerassi,[692] and for exceptions see Buu-Hoï,[693] also Karrer and Naik.[694]



Testosterone acetate

The preparation of α-bromo and α-iodo ketones by way of the enol acetates are mentioned on pages 195 and 196.

Unsubstituted alkyl aryl ketones, although susceptible to electrophilic halogenation in the ring, are readily brominated under mild conditions in the side chain at the position next to the CO group; normally the theoretical amount of bromine is used in glacial acetic acid, CH_2Cl_2, $CHCl_3$, CCl_4, or ether at room temperature, but sodium carbonate may be added in, *e.g.*, CH_2Cl_2 or benzene. Seeding (see above), UV-irradiation, or addition of catalytic amounts of $AlCl_3$ or $AlBr_3$ (about 1.2 g per mole of ketone) accelerate the reaction.

Treating acetophenone in dry ether at 0° with $AlCl_3$ and Br_2 (1 mole) and removing the HBr in a current of air give phenacyl bromide (ω-bromoacetophenone), m.p. 51°; for details see *Organic Syntheses*.[695] Using 2 moles of Br_2 leads equally easily to ω,ω-dibromoacetophenone.[696]

4-Bromophenacyl bromide, $p\text{-}C_6H_4Br\text{–}COCH_2Br$, m.p. 108–109°, separates in crystalline form when 1 mole of Br_2 is added to 4-bromoacetophenone dissolved in twice its amount of glacial acetic acid at 20°.[697] 4,α,α-Tribromoacetophenone, $p\text{-}C_6H_4Br\text{–}COCHBr_2$, is also readily formed on use of 2 moles of bromine.[698]

Adding an alcoholic solution of phenacyl or 4-bromophenacyl bromide to a solution of a carboxylic acid that has been neutralized with sodium carbonate gives an ester of ω-hydroxyacetophenone or of its 4-bromo derivative; these esters crystallize well from ethanol and are useful for characterization of liquid acids.

$$RCOONa + BrCH_2COC_6H_5 \longrightarrow RCOOCH_2COC_6H_5 + NaBr$$

Further, alkyl aryl ketones having substituents in the ring, although susceptible to halogenation in the ring under very mild conditions, can be brominated selectively either in the ring or in the side chain. To achieve the latter, advantage is taken of the observation that acid catalyses the conversion of the ketone into a more active (enolic) form. If, however, formation of the enol is repressed, *e.g.*, by removing the HBr with sodium or potassium acetate, then

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[692] C. Djerassi, *Chem. Rev.*, **43**, 282 (1948).
[693] Ng. Ph. Buu-Hoï, *Experientia*, **2**, 310 (1946).
[694] P. Karrer and A. R. Naik, *Helv. Chim. Acta*, **36**, 1527 (1953).
[695] R. M. Cowper and L. H. Davidson, *Org. Syn.*, Coll. Vol. II, 480 (1943).
[696] F. Kröhnke, *Chem. Ber.*, **83**, 56 (1950).
[697] W. D. Langley, *Org. Syn.*, **9**, 20 (1929).
[698] J. J. Klingenberg, *Org. Syn.*, **35**, 11 (1955).

bromination of, for example, 4-methoxyacetophenone in glacial acetic acid at 20° gives 3-bromo-4-methoxyacetophenone[699] and that of 4-hydroxyacetophenone gives 3,5-dibromo-4-hydroxyacetophenone.[700] Side-chain bromination is favored by seeding. 2- and 4-Hydroxy-acetophenone and -propiophenone are selectively brominated in the side chain in cold glacial acetic acid, but selectively in the ring in aqueous acetic acid.[701] Selective side-chain bromination of such hydroxy ketones can be achieved with high certainty by acylation and benzylation, followed by hydrolysis or catalytic hydrogenation of the resulting side-chain brominated ester or ether. An approximately 100% yield is claimed for side-chain bromination of 2-, 3-, or 4-hydroxyacetophenone by $CuBr_2$ in a boiling mixture of chloroform and ethyl acetate:[702]

$$HO{-}C_6H_4{-}COCH_3 + 2CuBr_2 \longrightarrow HO{-}C_6H_4{-}COCH_2Br + HBr + 2CuBr$$

Finally, α-bromo ketones, like α-bromo aldehydes, can also be obtained by way of the isolated enol acetates:[703] exactly the calculated amount of bromine is added, with ice-cooling, to the acetate in CCl_4 and the mixture is then mixed with dry methanol and set aside for two days. This method is valuable when the enol acetate required is readily accessible. A ketone $R'RCHCOCH_3$ can afford two isomeric enol acetates A or B; which of them is formed may depend on the natures of R and R′ but also on the reaction conditions.

$$\underset{(A)}{R'RCH{-}\underset{\substack{|\\ OCOCH_3}}{C}{=}CH_2} \longleftarrow R'RCHCOCH_3 \longrightarrow \underset{(B)}{R'RC{=}\underset{\substack{|\\ OCOCH_3}}{C}{-}CH_3}$$

Enol acetates are obtained in moderate yield by means of acetic anhydride containing *p*-toluenesulfonic acid[703] or, better, by passing ketene into the appropriate ketone containing 0.5% of sulfoacetic acid at 60–80°.[704,705] They are elegantly prepared by transesterification with isopropenyl acetate, $CH_2{=}CCH_3(OCOCH_3)$,[706] which is obtained from acetone and ketene at 55°.[704]

The isopropenyl acetate method yields, for example, 96% of isomer B from ethyl methyl ketone, but 92% of isomer A from isobutyl methyl ketone. With acetic anhydride and *p*-toluenesulfonic acid 20-oxo steroids give the enol acetates B,[707] but with isopropenyl acetate give the enol acetates A.[708]

To introduce a halogen atom at C-21 of a 20-oxo steroid that has a C=C group in ring A or B it is advantageous to treat the enol acetate with a halogenat-

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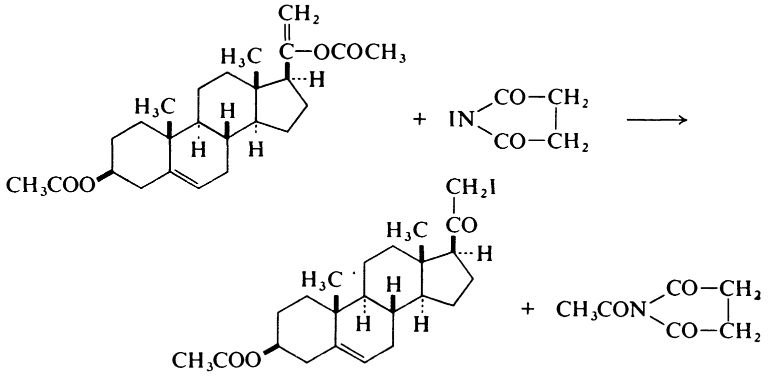
[699] F. Kröhnke and K. Ellegast, *Chem. Ber.*, **86**, 1562 (1953).
[700] K. W. Rosenmund and K. Pfroepffer, *Chem. Ber.*, **90**, 1922 (1957).
[701] Ng. Ph. Buu-Hoï, Ng. D. Xuong, and D. Lavit, *J. Chem. Soc.*, **1954**, 1034; **1955**, 18.
[702] L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).
[703] P. Z. Bedoukian, *J. Amer. Chem. Soc.*, **67**, 1430 (1945).
[704] B. H. Gwynn and E. F. Degering, *J. Amer. Chem. Soc.*, **64**, 2216 (1942).
[705] F. G. Young and co-workers, *J. Amer. Chem. Soc.*, **72**, 3635 (1950).
[706] H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).
[707] T. F. Gallagher and co-workers, *J. Amer. Chem. Soc.*, **70**, 1837 (1948).
[708] T. F. Gallagher and co-workers, *J. Amer. Chem. Soc.*, **74**, 2810 (1952).

ing agent that does not affect the C=C group; *N*-iodosuccinimide has been proposed for this purpose:[709]



5,20-Pregnadiene-3β,20-diyl diacetate (2.0 g), *N*-iodosuccinimide (1.18 g), and pure dioxan (2 ml) are heated at 85° for 45 min. The dark red solution is cooled and treated with KI solution and then with thiosulfate solution and much water. The precipitated crude product (2.1 g, m.p. 115–123°) is recrystallized from methanol–water (9 : 1), giving **3β-hydroxy-21-iodo-5,20-pregnadien-20-yl acetate** (1.31 g, m.p. 135–137°).

***N*-iodosuccinimide:**[709] Freshly precipitated silver oxide (510 g) is added to a solution of succinimide (392 g) in boiling water (12 l), and after filtration the silver salt of succinimide is allowed to crystallize, then filtered off and washed with water (yield 450 g). This salt (49.5 g) is finely powdered and added portionwise with stirring to a solution of iodine (50.8 g) in acetone (300 ml) at 5–10°. After decolorization (30 min) the AgI is filtered off, the acetone is driven off at room temperature in a vacuum, and the crude product is washed with ether (yield 43 g, m.p. 189–191°). Colorless needles, m.p. 200–201°, are obtained by dissolving this product in as little hot dioxan as possible and reprecipitating it with CCl_4. For iodination a reagent should be used that does not melt below 197°.

1,3-Diodo-5,5-dimethylhydantoin can be used with equal success.[710]

If enol acetates contain no extra C=C bond, α-iodo ketones can also be prepared by means of ICl in $CHCl_3$ if the acetyl chloride formed is simultaneously removed.[709]

21-Iodo 20-oxo steroids are important intermediates for synthesis of 21-hydroxy 20-oxo steroids, *e.g.*, dehydrocorticosterone and cortisone,[711] also deoxycorticosterone;[712] so the preparation of these α-iodo ketones by the following very interesting reaction with iodine should be noted:

$$\mathrm{RCOCH_3} \xrightarrow[\mathrm{C_2H_5ONa}]{(\mathrm{COOC_2H_5})_2} \mathrm{RCO{-}CH{=}C(ONa)COOC_2H_5}$$

$$\xrightarrow[\mathrm{I_2}]{(\mathrm{CH_3OH})} \mathrm{RCO{-}CHI{-}COCOOC_2H_5} \xrightarrow[(\mathrm{CH_3OH})]{\mathrm{NaOCH_3}} \mathrm{RCO{-}CH_2I}$$

3β-Hydroxy-21-iodo-5-pregnen-20-one:[713] A suspension of the sodium salt (0.1 mole) from the ethoxalyl derivative of 3β-hydroxy-5-pregnen-20-one in dry methanol is stirred at −15° while a solution of iodine (25.4 g) in methanol (600 ml) is run in during 15 min. After a further 30 min, sodium methoxide solution (2.5 g of sodium in 136 ml of methanol) is added

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[709] C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.*, **75**, 3493 (1953).

[710] O. O. Orazi, R. A. Corral, and H. E. Bertorello, *J. Org. Chem.*, **30**, 1101 (1965).

[711] L. H. Sarett and co-workers, *J. Amer. Chem. Soc.*, **74**, 4974 (1952).

[712] H. Ruschig, *Angew. Chem.*, **A**, **60**, 247 (1948).

[713] H. Ruschig, *Chem. Ber.*, **88**, 878 (1955).

slowly, and stirring is continued for a further hour. Then water (2 l) is added in portions during an hour, precipitating 3β-hydroxy-21-iodo-5-pregnen-20-one. The mixture is kept overnight, then the product is filtered off and washed with 30% methanol. The somewhat moist crude product is used for further reaction, namely, replacement of I by CH_3COO.

Alkali cleaves α,α,α-trihalomethyl ketones to trihalomethanes and carboxylic acids. This "haloform reaction"[714] also occurs directly if alkaline hypohalite solution is allowed to react with a methyl ketone and has preparative importance as a method of obtaining carboxylic acids from methyl ketones.

$$RCOCX_3 + NaOH \longrightarrow RCOONa + CHX_3$$

$$RCOCH_3 + 3X_2 + 4NaOH \longrightarrow RCOONa + CHX_3 + 3NaX + 3H_2O$$

When iodine is used the reaction serves for recognition of a group $RCOCH_3$ (R = H, alkyl, or aryl) or of a group such as ethanol that is oxidizable to $RCOCH_3$ by hypoiodite (Lieben's iodoform test):

0.1 g or 0.1 ml of the substance is dissolved in 5 ml of dioxan; 10% NaOH solution (1 ml) is added and then dropwise KI_3 solution (from 10 g of I_2, 20 g of KI, and 80 ml of water) until the dark color is just permanent. The mixture is heated at 60° for at most 2 min; if decolorization occurs, a little more KI_3 is added and the whole is warmed again briefly. Finally the solution is decolorized by a few drops of 10% NaOH solution and diluted with water. The test is positive if CHI_3 is precipitated in yellow crystals, m.p. 119° (from methanol).[715]

For the preparation of iodoform 4M-$NaICl_2$ can be added to, *e.g.*, an alkaline aqueous solution of acetone.[716]

11. Replacement of hydrogen by halogen in heterocycles

For the mechanism of halogenation of heterocycles and the influence of the medium (solvent, addition of acid to convert *N*-heterocycles into their conjugated acids, and addition of base for production of the anions from acidic heterocycles such as imidazole and pyrrole), as well as the influence of temperature a review by Eisch[717] should be consulted.

Oxygen heterocycles — furan,[718] benzo[*b*]furan,[719] and dibenzofuran[720] — are very readily brominated, the first two in the α-position to the heteroatom, bromine in CS_2, $CHCl_3$, CCl_4, or glacial acetic acid being usually used. Chroman and benzodioxan are brominated in the benzene ring, behaving as cyclic aryl ethers. Chlorination and bromination of isochroman and rearrangement of the 1-halo derivatives to *o*-(2-chloro- or 2-bromo-ethyl)benzaldehyde are described on page 1067.

Thiophene is readily brominated at positions 2 and 5. *N*-Bromosuccinimide gives a very poor yield of 2-bromothiophene,[721] but it is better when bromine is used.

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[714] R. C. Fuson and B. A. Bull, *Chem. Rev.*, **15**, 275 (1934).

[715] R. C. Fuson and C. W. Tullock, *J. Amer. Chem. Soc.*, **56**, 1638 (1934).

[716] A. I. A. I. Gengrinovich and N. G. Simkhaev, *Med. Prom. S.S.S.R.*, **12**, 27 (1958); *Chem. Abstr.*, **53**, 10005 (1959).

[717] J. J. Eisch, *Advan. Heterocycl. Chem.*, **7**, 1 (1966).

[718] H. Gilman and G. F. Wright, *Chem. Rev.*, **11**, 323 (1932).

[719] R. Stoermer and B. Kahlert, *Ber. Deut. Chem. Ges.*, **35**, 1633 (1902).

[720] H. Gilman, G. E. Brown, W. G. Bywater, and W. H. Kirkpatrick, *J. Amer. Chem. Soc.*, **56**, 2473 (1934).

[721] Ng. Ph. Buu-Hoï, *Ann. Chem.*, **556**, 9 (1944).

2-Bromothiophene:[722] Bromine (1.1 mole) in CCl_4 (300 ml) is dropped during 4 h into a stirred mixture of thiophene (1 mole) and CCl_4 (100 ml), cooled in an ice-bath. The residue left on removal of the solvent is heated with powdered NaOH (15 g) for 4 h on the steam-bath with occasional stirring. The solution is decanted from NaOH and the latter is washed with CCl_4. Distillation through a column affords 55% of 2-bromothiophene, b.p. 153–154°, and 29.2 g of 2,5-dibromothiophene, b.p. 95–98°/16 mm.

2,5-Dibromothiophene:[723] Bromine (950 g) is added to a mixture of thiophene (297 g) with an equal volume of benzene as quickly as is possible without escape of bromine vapor. When evolution of HBr has become slow, ethanol (700 ml) and NaOH (250 g) are added and the mixture is boiled under reflux for 16 h. Then, after dilution with water, the organic layer is separated and distilled through a column; it gives 2-bromothiophene (152 g), b.p. 158–162°, and 2,5-dibromothiophene (425 g), b.p. 200–210°.

2,3,5-Tribromo-[724] and tetrabromo-thiophene[725] are readily obtained by using larger amounts of bromine.

2-Chlorothiophene may be prepared by means of *N*-chloroacetamide[705] but better by treating thiophene in ether with SO_2Cl_2 in presence of a little $AlCl_3$.[727]

Furan and thiophene can be converted into their 2-bromo derivatives in good yield by dioxan·Br_2 in ice-cooled dioxan or ether, respectively.[406]

Of the methods of iodination described in section (a) on page 152, the old procedure with iodine and yellow HgO can, *inter alia*, be applied for iodination of heterocycles. The compound to be iodinated, or its solution in alcohol, glacial acetic acid, benzene, or light petroleum (b.p. 100–120°) is shaken or rapidly stirred with iodine (1 mole) and HgO (0.6–1.0 mole); the iodine and HgO are added in alternate small portions, and in most cases red HgI_2 is formed already at room temperature. A detailed description of the preparation of 2-iodothiophene is given in *Organic Syntheses*.[728] This derivative can also be obtained by treating thiophene with iodine and concentrated nitric acid.[729]

2- and 3-Methylthiophene are easily brominated in the ring. *N*-Bromosuccinimide (NBS) in CCl_4 gives mixtures of ring- and side-chain-brominated methylthiophenes. It is sometimes better not to work such solutions up by distillation but to use them directly in further reactions, for instance, with piperidine for the preparation of 2-(piperidinomethyl)thiophene or with hexamethylenetetramine for preparation of 3-thiophenecarbaldehyde.[730]

Side-chain bromination of 3-methylthiophene is described in detail in *Organic Syntheses*.[731] The rate of acid-catalysed decomposition of 3-(bromomethyl)thiophene, which sometimes leads to explosions, is decreased by addition of calcium carbonate or a tertiary amine.

2-(Chloromethyl)thiophene is best obtained by chloromethylation of thiophene.[732]

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[722] F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, **64**, 478 (1942).

[723] K. Folkers and co-workers, *J. Amer. Chem. Soc.*, **67**, 2094 (1945).

[724] C. Troyanovski, *Bull. Soc. Chim. France*, **1955**, 424.

[725] W. Steinkopf, H. Jacob, and H. Penz, *Ann. Chem.*, **512**, 136 (1934).

[726] W. Steinkopf and A. Otto, *Ann. Chem.*, **424**, 68 (1921).

[727] A. Töhl and O. Eberhard, *Ber. Deut. Chem. Ges.*, **26**, 2947 (1893).

[728] W. Minnis, *Org. Syn.*, Coll. Vol. II, 357 (1943).

[729] H. J. Lew and C. R. Noller, *Org. Syn.*, **30**, 53 (1950).

[730] T. W. Campbell and W. W. Kaeding, *J. Amer. Chem. Soc.*, **73**, 4018 (1951).

[731] E. Campaigne and B. F. Tullar, *Org. Syn.*, **33**, 96 (1953).

[732] F. F. Blicke and F. Leonard, *J. Amer. Chem. Soc.*, **68**, 1934 (1946).

All the hydrogen atoms of the CH groups of pyrrole and imidazole are very readily replaced by Cl, Br, or I. The preparation of 2,3,4,5-tetraiodopyrrole is a further example (see page 169) of the value of halogenation by HX and H_2O_2.

2,3,4,5-Tetraiodopyrrole:[733] Freshly distilled pyrrole (6.7 g) and KI (66 g) are dissolved in 25% ethanol (400 ml) at 30° and glacial acetic acid (28 ml), sodium acetate (10 g), and 10% H_2O_2 (38 ml) in water (50 ml) are added. The solution becomes warm and reddish-brown but the temperature should not be allowed to exceed 45°. The solution is kept for an hour at 45°, and after a further hour is diluted with twice its volume of water. The greyish-brown precipitate is recrystallized from ethanol, with addition of charcoal, giving an 80% yield of white needles, dec. 162–164°.

Electrophilic substitution of pyridine, pyrimidine, quinoline, and the like is difficult to effect, whereas nucleophilic introduction of NH_2 or OH at the α- and the γ-position to nitrogen, and ring-closure syntheses of *N*-heterocycles containing NH_2 or OH substituents, are relatively easy. Therefore, in laboratory work, those methods are when possible used in which a NH_2 or an OH group is replaced by halogen; examples are the preparation of 2- and 4-bromopyridine (see pages 264 and 241) and 2-chloropyrimidine (see pages 259 and 241).

Electrophilic substitution of pyridine by halogen occurs at the 3- and the 5-position; thus bromination of pyridinium chloride in the presence of $HgCl_2$ (10 g per 100 g of pyridine) in a metal bath at 212–215° gives 3-bromo- or 3,5-dibromopyridine as main product according to the amount of bromine used.[734,735] Raising the temperature at which pyridine is halogenated reverses the type of substitution, as in the bromination of halobenzenes.

2-Bromopyridine:[735] Pyridine (6 moles) and Br_2 (9 moles) are allowed to react in the vapor phase in a column of 3.5 cm diameter, heated electrically to 500° and filled for a height of 40 cm with high-melting glass tubes of 6 mm diameter. The bromine is dropped in through a glass spiral (12 cm) whose tip is 2 cm above the glass filling of the column. The pyridine is added simultaneously through a spiral (60 cm in length) placed on the top of the column and also heated to 500°. The additions require about 5 hours, the rate being adjusted so that no bromine vapor appears in the 1-l necked flask fitted with an air-condenser (evolution of HBr!) and on which the column is placed. The crude product is made alkaline with a solution of sodium hydroxide, then distilled in steam to give 3 l of distillate. The mixed products are taken up in benzene and fractionally distilled, giving 46% of 2-bromopyridine, b.p. 90–92°/25 mm, and 17% of 2,6-dibromopyridine, m.p. 118–119°.

Gas-phase chlorination of pyridine on pumice in the presence of nitrogen affords α-substitution at as low as 270°: 31% of 2-chloropyridine is obtained, but at higher temperatures (up to 400°) 2,6-dichloropyridine is the main product.[736] Chlorination of molten pyridinium chloride at 165–175° gives mainly 3,5-dichloropyridine.[735,736] Chlorination of the pyridine–$AlCl_3$ complex (swamping catalyst method) affords 3-chloropyridine in 30–35% yield;[737] for details of the apparatus see the preparation of 3-bromoaceto-

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[733] A. Treibs and H. G. Kolm, *Ann. Chem.*, **614**, 187 (1958).

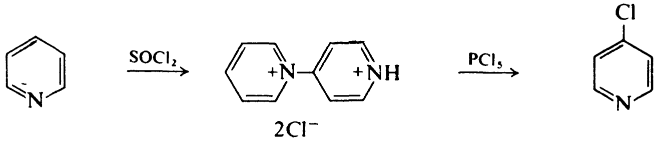
[734] H. Maier-Bode, *Ber. Deut. Chem. Ges.*, **69**, 1535 (1936).

[735] S. M. McElvain and M. A. Goese, *J. Amer. Chem. Soc.*, **65**, 2231 (1943).

[736] J. P. Wibaut and J. R. Nicolai, *Rec. Trav. Chim.*, **58**, 709 (1939).

[737] D. E. Pearson, W. W. Hargrove, J. K. T. Chow, and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).

phenone by way of the $AlCl_3$ complex as described in *Organic Syntheses.*[738] Since the salt $[C_5H_5NH]^+[AlCl_4]^-$ is not halogenated, the maximum yield is 50% calculated on pyridine. This process is also suitable for preparation of 3-chloro-, 3,5-dichloro-, and 3-bromo-4-picoline.[737] 4-Chloropyridine is best obtained directly from 1-(4-pyridinio)pyridinium dichloride (see formulae).[739,740]



Pyridine (200 g, dried over KOH) is dropped, with stirring and ice-cooling, into $SOCl_2$ (600 g) at 8–12°. The mixture is stirred for some hours while the inner temperature is allowed to rise slowly to 20° and then set aside at 20° for 3 days. The excess of $SOCl_2$, etc., is distilled off in a vacuum and the residue is heated for an hour on a boiling water-bath.The resulting greyish-brown crystalline mass is cooled to 0°, triturated with ice-cold dry ethanol (250 ml) (ice-cooling!), filtered off, washed with ice-cold dry ethanol (2 × 200 ml), dried in a vacuum, and dissolved in a mixture of water (100 ml) and 2N-HCl (300 ml). This solution is boiled for 5 min with active charcoal, concentrated at water-pump vacuum to 180 ml, and cooled to 0°. Pale yellow **1-(4-pyridyl) pyridinium dichloride hydrochloride** that separates is washed with dry ethanol and dried in a vacuum, then having m.p. 158–160° (yield 167 g).

The dichloride (120 g) is mixed with PCl_5 (110 g) and melted in an oil-bath at 130–140°. The melt soon solidifies but remelts as the temperature is raised to 150° during 10 min. It is then cooled, treated with ice-water, and made weakly alkaline with sodium carbonate solution. The whole is thoroughly extracted with ether, and the extracts are washed with water and dried over Na_2SO_4. The ether is removed through a column, and the residue is distilled in a vacuum. Water is added to the distillate, causing a heavy oil to separate, which is taken up in ether, dried, and distilled. This gives **4-chloropyridine** (30 g, 50%), b.p. 53 to 55°/20 mm.

4-Bromopyridine can be prepared similarly (PBr_5, 130°).[741]

Electrophilic substitution by halogen into a N-heterocycle to which a benzo ring is fused occurs first at the β-position; if, however, the conjugate acid is used, the benzo ring is preferentially substituted. Thus, for instance, bromination of quinoline by Derbyshire and Waters' method[374a] gives a mixture of 5- and 8-bromoquinoline or 5,8-dibromoquinoline according to the amount of bromine used,[742] and halogenation of the $AlCl_3$ complex of isoquinoline gives 5-chloro-, 5,8-dichloro-, or 5,8-dibromo-isoquinoline;[743] in both cases a third halogen atom may enter the benzo ring.

5,8-Dibromoquinoline:[742] A solution of quinoline (6.6 ml), Ag_2SO_4 (16.5 g), concentrated H_2SO_4 (60 ml), and bromine (5.2 ml) is shaken until the bromine is consumed (ca. 3 h) and then filtered from AgBr. The AgBr is washed with water, and the filtrate and washings are poured on ice and brought to pH 2–3. The colorless precipitate is recrystallized from acetone, then having m.p. 129–130° (yield 12.5 g).

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[738] D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Syn.*, **40**, 7 (1960).

[739] E. Koenigs and H. Greiner, *Ber. Deut. Chem. Ges.*, **64**, 1052 (1931).

[740] K. Bowden and P. N. Green, *J. Chem. Soc.*, **1954**, 1796.

[741] D. Jerchel, H. Fischer, and K. Thomas, *Chem. Ber.*, **89**, 2928 (1956).

[742] P. B. D. de la Mare, M. Kiamud-Din, and J. H. Ridd, *J. Chem. Soc.*, **1960**, 561.

[743] M. Gordon and D. E. Pearson, *J. Org. Chem.*, **29**, 329 (1964).

Pyrazole is preferentially chlorinated,[744] brominated,[745] and iodinated[746] at position 4. In aqueous akaline solution 1,2,4-triazole exchanges for bromine both the hydrogen atoms attached to carbon; however, in sodium hydroxide solution at 0° chlorine causes substitution on carbon and nitrogen, giving 1,3-dichloro-1,2,4-triazole (m.p. 87°), which is thus an easily accessible *N*-chloro compound.[747]

4-Chloropyrazole:[744] Dry chlorine (10 g) is led into a solution of pyrazole (2.72 g) in CCl_4 at 0° in 60 min. The precipitated hydrochloride (88%) is filtered off and dissolved in water. Adding Na_2CO_3 to weak alkalinity precipitates, 4-chloropyrazole, and the remainder is extracted in ether. The total yield is 55% and, after recrystallization from light petroleum the m.p. is 76–77°.

Hydrogen is considerably more easily replaced by halogen in those *N*-heterocycles that carry NH_2 or OH substituents. Procedures similar to those for aromatic amines and phenols are used (see page 161).

It is to be expected that bromination of 4(1*H*)-pyridone to 3,5-dibromo-4(1*H*)-pyridone even under mild conditions will be accompanied by oxidative degradation as a side reaction.[611] However, 3,5-diiodo-4(1*H*)-pyridone can be obtained by treating 4-pyridone with iodine in aqueous solution which is made alternately alkaline by sodium hydroxide solution and acid by hydrochloric acid,[748] and 5-iodo-2-pyridinamine has been similarly prepared.[749] The sodium derivative of 2-pyridone is converted by iodine in aqueous sodium carbonate into 3,5-diiodo-2(1*H*)-pyridone.[749]

The procedure described on page 166 for replacement of H by I by way of organomercury compounds has proved very suitable for preparation of 5-iodopyrimidine-2-amine.[750]

In this case the acetoxymercuri compound is obtained from the amine and $Hg(OCOCH_3)_2$ within a few minutes and a slurry of it is at once treated at 70° with iodine in hot dioxan. HgI_2 is removed from the product by aqueous KI. The yield is 70%.

2-(Chloromercuri)-3-methylthiophene is converted by aqueous iodine–potassium iodide solution into 2-iodo-3-methylthiophene in 92% yield,[751] and the readily accessible 2,5-bis-(chloromercuri)-3-methylthiophene[752] into 2,5-diiodo-3-methylthiophene in 70% yield.[751] The mono- and bis-(chloromercuri) derivatives of 2,5-dimethylfuran give analogously 3-iodo- and 3,4-diiodo-2,5-dimethylfuran, respectively.[753]

Two methods are available for direct side-chain halogenation of alkylated *N*-heterocycles: (a) halogenation in glacial acetic acid containing sodium or potassium acetate,[754,755] the mechanism of which is the same as that of bromination of ketones;[756] and (b) bromination by *N*-bromosuccinimide.

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[744] R. Hüttel, O. Schäfer, and G. Welzel, *Ann. Chem.*, **598**, 186 (1956).

[745] R. Hüttel, H. Wagner, and P. Jochum, *Ann. Chem.*, **593**, 179 (1955).

[746] R. Hüttel, O. Schäfer, and P. Jochum, *Ann. Chem.*, **593**, 200 (1955).

[747] R. Miethchen and C.-F. Kröger, *Z. Chem.*, **7**, 184 (1967).

[748] W. Baker and A. S. Briggs, *J. Soc. Chem. Ind.*, **62**, 189 (1943).

[749] W. T. Caldwell, F. T. Tyson, and L. Lauer, *J. Amer. Chem. Soc.*, **66**, 1481 (1944).

[750] R. G. Shepperd and C. E. Fellows, *J. Amer. Chem. Soc.*, **70**, 157 (1948).

[751] W. Steinkopf and W. Hanske, *Ann. Chem.*, **532**, 241 (1937).

[752] W. Steinkopf and A. Killingstad, *Ann. Chem.*, **532**, 292 (1937).

[753] C. D. Hurd and K. Wilkinson, *J. Amer. Chem. Soc.*, **70**, 741 (1948).

[754] W. Koenigs, *Ber. Deut. Chem. Ges.*, **31**, 2364 (1898).

[755] B. R. Brown, D. Ll. Hammick, and B. H. Thewlis, *J. Chem. Soc.*, **1951**, 1145.

[756] B. R. Brown, D. Ll. Hammick, B. H. Thewlis, and D. J. Walbridge, *J. Chem. Soc.*, **1953**, 1369.

Method (a) usually gives only trichloro or tribromo derivatives of N-heterocycles that contain active CH_3 groups; and it is not applicable to 3-methylpyridine, 3- or 4-methylquinoline, or 1-, 3-, or 4-methylisoquinoline; further, 2- and 4-methylpyridine cannot be brominated by this method, although they can be thus chlorinated.[755,757]

4-(Trichloromethyl)pyridine: Dry chlorine (50 g, 3 moles per mole of amine) is led into a mixture of 4-methylpyridine (21 ml), acetic anhydride (20 ml), sodium acetate (60 g), and acetic acid (250 ml) kept at 80°. The mixture is then poured on ice, made alkaline with ammonia, and extracted with ether. Two vacuum-fractionations of the oil obtained from the extract gives 4-(trichloromethyl)pyridine (15.4 g), b.p. 105–107°/18 mm. The product decomposes in a few days; it is converted by $AgNO_3$ in aqueous acetic acid into isonicotinic acid and by tin in acetone–hydrochloric acid into 4-(dichloromethyl)pyridine.

Method (b) affords, *inter alia*, **4-(bromomethyl)quinoline,** which cannot be obtained by method (a):[758]

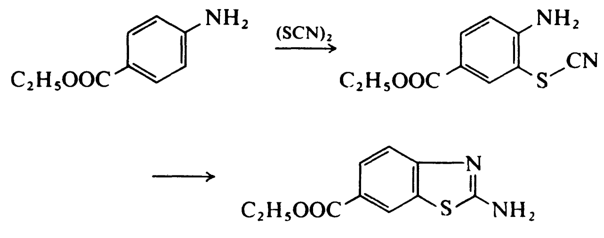
4-Methylquinoline (lepidine) (0.1 mole) is added to a stirred suspension of *N*-bromosuccinimide (0.08 mole) in CCl_4 at 60°. The mixture is boiled under reflux for 30 min, then filtered hot. The bromo product crystallizes from the filtrate in white crystals (10 g), from which adhering succinimide is removed by thorough washing with water. When dried in a vacuum, the product has m.p. 88–91°. It should be used as soon as possible because it decomposes after a few hours.

The literature for other reactions of N-heterocycles with *N*-bromosuccinimide has been reviewed by Horner and Winkelmann.[759]

Bromomethyl derivatives of N-heterocycles can also be obtained by oxidizing methylated N-heterocycles by SeO_2, then reducing the resulting aldehydes by formaldehyde and treating the alcohols formed with PBr_3 in benzene so as to replace their OH groups by bromine.[756]

12. Direct replacement of hydrogen by SCN in aromatic compounds

Phenols and primary, secondary, and tertiary aromatic amines with free *ortho-* and/or *para*-positions react readily with thiocyanogen, $(SCN)_2$. SCN enters the position *para* to the OH or NR_2 group, or, if that is occupied, into the *ortho*-position.[11,12] In the later case subsequent ring closure may be easy.[14,760] For instance, *p*-toluidine gives 6-methylbenzo[*b*]thiazole-2-amine, and etyhl *p*-aminobenzoate gives ethyl 2-aminobenzo[*b*]thiazole-6-carboxylate.



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[757] P. Dyson and D. Ll. Hammick, *J. Chem. Soc.*, **1939**, 781.

[758] K. N. Campbell, J. F. Ackerman, and B. K. Campbell, *J. Amer. Chem. Soc.*, **71**, 2906 (1949).

[759] L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 361 (1959).

[760] R. Q. Brewster and F. B. Dains, *J. Amer. Chem. Soc.*, **58**, 1364 (1936).

Although thiocyanogen does not react with benzene or naphthalene, it does react with more highly condensed aromatic compounds such as anthracene benzopyrene, etc.[761] The substance may be added to a solution of thiocyanogen (for its preparation see page 104), but it is simpler to generate the thiocyanogen *in situ*. The $(SCN)_2$ is produced in the reaction mixture from alkali thiocyanate and bromine or chlorine or from $Cu(SCN)_2$. Suitable solvents for work with bromine or chlorine are acetic acid, methanol, and methyl acetate, the last two saturated with NaBr or NaCl.

6-Isopropyl-3-methyl-4-thiocyanatophenol:[13] Thymol (15 g) and $NaSCN \cdot 2H_2O$ (35 g) are dissolved in methanol (150 ml) saturated with NaBr. Bromine (20 g) in methanol (30 ml) saturated with NaBr is added to this solution at room temperature with stirring. After 30 min a six- to eight-fold amount of water is added, whereupon the product separates as an oil. This crystallizes in 2 h at 0°, is dried on porous plate, and after recrystallization with charcoal from light petroleum has m.p. 105° (yield 95%).

A similar reaction in methanol at 5° gives a 97% yield of *p*-thiocyanatoaniline.[12]

The preparation of *N,N*-dimethyl-*p*-thiocyanatoaniline, described in detail in *Organic Syntheses*,[762] exemplifies the use of ammonium thiocyanate in glacial acetic acid.

***p*-Thiocyanatoaniline:**[14] Ammonium thiocyanate (11 g) and copper sulfate (12 g) are ground together, and the black viscous mixture is added to a stirred solution of aniline (2.3 g) in 40% sulfuric acid (50 ml) at about 50°. After 10 min the temperature is raised to 75° and held there until the black $Cu(SCN)_2$ is converted into colorless CuSCN. Then the mixture is filtered and the residue is leached with hot water. Neutralizing the united filtrates with Na_2CO_3 affords *p*-thiocyanatoaniline (2.9 g) which, after recrystallization from water, has m.p. 57°.

Alternatively, $Cu(SCN)_2$ may be first prepared by precipitation from copper sulfate solution with an equivalent amount of NaSCN, filtration, and washing with alcohol and ether. The reaction is then run in glacial acetic acid, ethyl acetate, or methanol.

Finally, thiocyanogen may be prepared in the presence of the substance that is to react with it by electrolysis of a solution of an alkali or ammonium thiocyanate in aqueous-ethanolic hydrochloric acid,[763] but this process has no preparative advantage over those described above.

A more active agent for replacement of H by SCN is thiocyanogen chloride (ClSCN), which can be prepared from lead thiocyanate and chlorine in anhydrous acetic acid.[764]

$$Pb(SCN)_2 + 2Cl_2 \longrightarrow PbCl_2 + 2ClSCN$$

$$ArH + ClSCN \longrightarrow ArSCN + HCl$$

It can be used for reaction with aryl ethers and acylated aromatic amines.[764] Various alkylated aromatic compounds can be substituted in the ring by ClSCN in the dark, but in the side chain under UV-irradiation.[765]

For introduction of SCN into aromatic compounds by way of diazonium compounds see page 269.

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[761] J. L. Wood and L. F. Fieser, *J. Amer. Chem. Soc.*, **63**, 2323 (1941).

[762] R. Q. Brewster and W. Schroeder, *Org. Syn.*, Coll. Vol. II, 574 (1943).

[763] J. L. Wood, *Org. Reactions*, 3, 257 (1946).

[764] R. G. R. Bacon and R. G. Guy, *J. Chem. Soc.*, **1960**, 318.

[765] R. G. R. Bacon and R. G. Guy, *J. Chem. Soc.*, **1961**, 2428, 2436, 2447.

II. Replacement of halogen by another halogen or by thiocyanate

1. Replacement of halogen by fluorine*

The particular importance of halogen exchange reactions lies in preparation of aliphatic fluoro and iodo compounds.

In replacement by fluorine, Br is more easily removed than Cl, and I than Br. Any halogen is most easily exchanged when it is part of a carbonyl or sulfonyl halide or in α-position to a carbonyl or carboxyl group or to a C=C bond (allyl position), and less easily from saturated halides of type $RR'CX_2$ or RCX_3. Metal halides must be added to aid conversion of CHX or CH_2X into CHF or CH_2F. Halogen–fluorine exchange is impossible for most vinyl halides, and for aromatic compounds it is possible only when an *o*- or *p*-NO_2 substituent is present. Fluorine on a nearest-neighbor carbon atom makes replacement more difficult.

Industrially reactions with anhydrous HF (see page 119) are favored, but for laboratory work on a smaller scale the reactions with metal fluorides that can be carried out in glass apparatus are preferred, notably those with SbF_3 and mixed antimony fluoride halides SbF_3X_2, which are usually formed *in situ* from 1 mole of SbF_3 and 1 mole of Cl_2 or Br_2. It is usually necessary to exclude water from the reaction mixtures. Replacing a Br or Cl atom by F lowers the boiling point by about 70° or 40°, respectively, so the organic fluoride formed in an exchange reaction can be distilled out through a column.

HF is used only with particularly reactive halides, *i.e.*, with acyl halides or allyl halides. Benzotrichloride between 0° and 140° has all its three Cl replaced by F.[767–771]

Benzotrifluoride:[767] A slow stream of hydrogen fluoride (200 g) is introduced in 72 h into benzotrichloride (500 g) which is stirred at 0° in a copper flask fitted with a copper gas inlet tube that reaches to the bottom, a gas outlet tube, and a copper stirrer. Initially only HCl is evolved, but this includes HF and benzotrifluoride in increasing amounts as reaction proceeds; they are condensed out in a copper receiver cooled in ice-salt. The product in the flask and the condensate in the receiver are united and warmed to room temperature, then shaken with sodium fluoride to bind the HF. Filtration and distillation of the filtrate gives benzotrifluoride (300 g), b.p. 102.3°. Higher-boiling distillate contains partially chlorinated benzotrichloride and can be used in a new batch.

For preparation of benzotrifluoride in about the same yield by means of BF_3 see Pouterman *et al.*[768]

Compounds $RR'CX_2$ and RCX_3 react with HF if SbF_3 and $SbCl_5$ are added; the catalytically active Sb(v) mixed halides are continuously regenerated by the HF, since the $SbCl_3$ formed reacts with HF to give SbF_3 and HCl.

Dichlorodifluoromethane, b.p. −30°, is prepared industrially by passing HF (b.p. 19.4°) and CCl_4 (b.p. 76°) into a vessel containing SbF_3 and a small amount of a Sb(v) halide. HCl

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* For reviews see references [1b,4,15,140d,176,and766]

[766] G. Schiemann, "Die organischen Fluorverbindungen und ihre Bedeutung für die Technik," Verlag D. Steinkopff, Darmstadt, 1951; J. H. Simons, "Fluorine Chemistry," Academic Press Inc., New York, 1950, Vol. 1; C. Slesser and St. R. Schram, "Preparations, Properties and Technology of Fluorine and Organic Fluorine Compounds," McGraw-Hill Book Co., New York, 1951.

[767] J. H. Simons and L. J. Lewis, *J. Amer. Chem. Soc.*, **60**, 492 (1938).

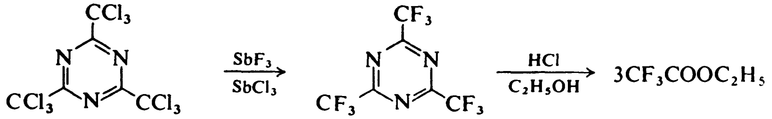
[768] E. Pouterman and A. Giradet, *Helv. Chim. Acta*, **30**, 107 (1947).

and CCl_2F_2 are allowed to distil off continuously through a column, the HF, CCl_3F (b.p. 25°), and CCl_4 being retained.[772] For laboratory processes with $SbCl_5$ and HF see Hudlicky[773] and for those with 10 : 1 SbF_3–$SbCl_5$ see Henne.[15]

The Swarts reaction is an old but still important method of preparing fluorides: a halide is treated with 0.35 mole of SbF_3 per atom of exchangeable halogen. The activity of SbF_3 — not a particularly active catalyst alone — is increased by addition of 2–5% of $SbCl_5$, about 1% of Cl_2, or about 5% of Br_2.[15,774] The halogen exchange occurs stepwise and is favored by successive additions of $SbCl_5$, Cl_2, or Br_2; a complex $SbF_3Cl_2 \cdot 2HF$, obtained from 1 mole of $SbCl_5$ and 5 moles of HF in an autoclave at 150°, is especially effective.[775] Halogen exchange between compounds RR′CHX and SbF_3 or SbF_3X_2 is rarely possible (cf. the lack of reaction with HF).

SbF_3, b.p. 376°, is obtained by dissolution of Sb_2O_3 in an excess of aqueous HF, evaporation to dryness, and distillation in a copper apparatus.[37,776]

Preparation of **ethyl trifluoroacetate** and **trifluoroacetic acid** by way of 1,3,5-tris(trifluoromethyl)-*s*-triazine exemplifies the procedure used with mixed Sb(v) fluoride halides:[4k,777]



Trichloroacetonitrile is cyclized to 1,3,5-tris(trichloromethyl)-*s*-triazine by saturation with dry HBr in the presence of 0.01 mole of $AlBr_3$ or $AlCl_3$. The product (500 g) is added during 4 h, in increasingly large portions, to a hot stirred mixture of SbF_3 (800 g) and $SbCl_3$ (105 g) into which chlorine (100 g) had previously been passed at 150°. The apparatus is fitted with a column and reflux condenser. The mixture is kept just boiling. 30 Min[4k] or 2 hours[777] after the addition is complete, a start is made with removing two fractions at a reflux ratio of 10 : 1, namely, one of b.p. 98–105° (43 g) and a second of b.p. 105–125° (153 g). The second fraction is fluorinated again with a Cl_2-saturated mixture of SbF_3 (500 g) and $SbCl_3$ (105 g); higher-boiling fractions from subsequent distillations are also refluorinated. In this way a total yield of about 49% (160 g) of tris(trifluoromethyl)triazine, b.p. 98–100°, is obtained. According to Norton[777] the yield is 90%.

Heating this triazine with aqueous-ethanolic HCl affords ethyl trifluoroacetate which is mostly collected as an azeotrope, b.p. 52.5–56°, with water; this can be dehydrated by concentrated H_2SO_4 or hydrolysed to sodium trifluoroacetate by sodium hydroxide solution. This salt is powdered and added to concentrated H_2SO_4, and anhydrous trifluoroacetic acid, b.p. 72–74°, is distilled off.

Trifluoroacetic acid and water form an azeotrope, b.p. 105.5°, containing 79.4% of the acid.

Trifluoroacetic acid is best prepared in the laboratory by oxidizing *m*-aminobenzotrifluoride with dichromate and sulfuric acid, as described by

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[769] K. Wiechert, *Angew. Chem.*, **56**, 333 (1943).

[770] J. H. Brown, C. W. Suckling, and W. B. Whalley, *J. Chem. Soc.*, **1949**, 95.

[771] F. Smith and co-workers, *J. Appl. Chem.* (*London*), **2**, 97, 127 (1952).

[772] U.S. Pat. 2,007,208, 1,930,129, 1,833,847; *Chem. Abstr.*, **29**, 5459 (1935); **28**, 179 (1934); **26**, 1047 (1932).

[773] L. Yarkovsky and M. Hudlicky, *Chem. Listy*, **51**, 625 (1957).

[774] S. Swarts, *Bull. Cl. Sci., Acad. Roy. Belg.*, [iii], **24**, 474 (1892).

[775] W. B. Whalley, *J. Soc. Chem. Ind.*, **66**, 427 (1947).

[776] O. Ruff, "Die Chemie des Fluors," Springer Verlag, Berlin 1920.

[777] T. R. Norton, *J. Amer. Chem. Soc.*, **72**, 3527 (1950).

Swarts[778] in 1922; this amine is prepared by nitrating benzotrifluoride and reducing the nitro compound in methanol catalytically with Raney nickel.[779,780] The yield of trifluoroacetic acid amounts to 90–95% if suitable technique is used — apparatus is described in detail by Wächter.[781]

Trifluoroacetic acid can also be obtained by way of 2,3-dichlorohexafluoro-2-butene which is oxidized by permanganate:[782]

$$CCl_2{=}CCl{-}CCl{=}CCl_2 \longrightarrow CCl_3{-}CCl{=}CCl{-}CCl_3 \longrightarrow$$

$$CF_3{-}CCl{=}CCl{-}CF_3 \xrightarrow[KOH]{KMnO_4} 2CF_3COOH$$

Another method of obtaining the acid industrially is to electrolyse a 4% solution of acetic anhydride in anhydrous HF and to trap the CF_3COF evolved by means of water.[783]

Halogen exchange by means of metal halides (AgF, HgF, HgFX, HgF_2, KF) can be effected even when the methods described above fail, and especially with alkyl halides.

Silver fluoride (AgF) is obtained from silver carbonate[776] or silver oxide[784] in aqueous HF; the solution is evaporated and the residue is well dried. It is not easy to obtain AgF anhydrous; further, two moles must be used per mole of exchangeable halogen (X) since the AgX formed produces double salts AgF.[785] AgF is used less often in modern work as KF is almost always equally effective. AgF has the advantage that it reacts under mild conditions.

For example, 21-fluoro steroids have been obtained[786] by adding a slight excess of a 50% aqueous solution of AgF to a solution of the 21-iodo steroid in moist acetonitrile at 30–40°.

3β-Fluoro steroids are prepared in 10 min at room temperature by treating 3β-iodo steroids with a suspension of dry AgF in 1 : 1 acetonitrile–xylene.[787]

AgF in anhydrous acetonitrile at room temperature replaces the bromine of acetobromo sugars by fluorine.[788–790]

The reaction can be carried out with dry HF, a hydrocarbon, or ether as solvent, or without a solvent.

Silver difluoride, AgF_2 (prepared by passing fluorine over a silver halide AgX at 150–200° [4c]) and CoF_3 (prepared from $CoCl_2$, CoF_2, or Co_2O_3 and F_2 at 250–300° [4d,791]) replace both halogen and hydrogen in halogenated hydrocarbons by fluorine.[792] Both compounds are well suited to fluorination

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[778] F. Swarts, *Bull. Cl. Sci., Acad. Roy. Belg.*, **8**, 343 (1922).

[779] F. Weygand and E. Rauch, *Chem. Ber.*, **87**, 213 (1954).

[780] O. T. Schmidt and W. Staab, *Chem. Ber.*, **87**, 390 (1954).

[781] R. Wächter, *Angew. Chem.*, **67**, 305 (1955).

[782] A. L. Henne and P. Trott, *J. Amer. Chem. Soc.*, **69**, 1820 (1947).

[783] E. A. Kauck and A. R. Diesslin, *Ind. Eng. Chem.*, **43**, 2332 (1951).

[784] H. J. Emeléus and H. G. Heal, *J. Chem. Soc.*, **1946**, 1126.

[785] F. Swarts, *Bull. Cl. Sci., Acad. Roy. Belg.*, [v], **7**, 438 (1921).

[786] P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Amer. Chem. Soc.*, **78**, 2658 (1956).

[787] T. N. Jacobsen and E. V. Jensen, *Chem. and Ind. (London)*, **1957**, 172.

[788] B. Helferich and R. Gootz, *Ber. Deut. Chem. Ges.*, **62**, 2505 (1929).

[789] F. Micheel, A. Klemer, and G. Baum, *Chem. Ber.*, **88**, 475 (1955).

[790] F. Micheel, Chem. Ber., **90**, 1612 (1957).

[791] H. F. Priest, *Inorg. Syn.*, **3**, 175 (1950); R. D. Fowler and co-workers, *Ind. Eng. Chem.*, **93**, 343 (1947); E. T. McBee, *Ind. Eng. Chem.*, **39**, 310 (1947).

[792] E. T. McBee and co-workers, *Ind. Eng. Chem.*, **39**, 310 (1947).

of hydrocarbons since per mole of HF formed they liberate only half as much heat of reaction as does elemental fluorine.[4h,793,794]

Fluorinations with AgF_2 or CoF_3 are carried out stepwise in successive four-cornered reaction tubes in which thin layers of the catalyst are spread at successively higher temperatures. The AgF_2 or CoF_3 is prepared in the same apparatus and is also regenerated there by F_2 after the fluorination.

Mercury fluoride (HgF) is more effective than AgF for preparation of alkyl fluorides from alkyl iodides or bromides; addition of iodine helps the reaction.[795] HgF is less effective for alkyl chlorides, and it is not suitable for use with compounds $CRX_2CR'X_2$ since it removes halogen to give halogenated olefins and mercury(II) salts.

Mercury(II) chloride fluoride or fluoride iodide is more effective than HgF; they are prepared by adding the equivalent amount of halogen to HgF.[795]

A particularly efficient reagent for halogen exchange is mercury difluoride, HgF_2, which exchanges both its F atoms for Cl, Br, or I. It reacts with iodides so rapidly that it is advisable to dilute them with a hydrocarbon, fluorinated hydrocarbon, $CHCl_3$, or CH_2Cl_2; ethers and ketones are not suitable diluents. Up to three Br atoms or two Cl atoms on one carbon atom be replaced by means of HgF_2.[796] However, isolation of HgF_2 in bulk is harder than for AgF, HgF, or KF.

HgF_2 is obtained by reaction of HgF and Cl_2 and subsequent sublimation away of the $HgCl_2$ also produced,[776] or by passing F_2 over $HgCl_2$ spread in a copper tube.[796] It is produced, more simply, as intermediate in the reaction of HgO and HF[797-799] or of $HgCl_2$ and HF,[800] but low temperatures and metal apparatus are required.

HF (10–12 moles) is condensed with Dry Ice-cooling on to HgO (1 mole) in a steel autoclave, then the halogen compound (2X per mole of HgO; X = exchangeable halogen), also cooled in Dry Ice, is added. The autoclave is closed and shaken for some hours while being allowed to warm to room temperature.

Monel metal autoclaves are sometimes used,[799] or nickel-plated autoclaves at 90–110°. At the end of the reaction the volatile products are passed through sufficient 6N-NaOH to trap unchanged HF and then through receivers cooled in Dry Ice so as to collect low-boiling products that were not condensed in the alkali. A drying tower may be inserted between the wash-bottle and the receivers. Products condensed in the alkaline wash-liquor are distilled over in steam.

Organic fluorine compounds can sometimes be obtained without recourse to F_2, HF, or metal apparatus, namely, when fluorine can be substituted for a tosyloxy group, $p\text{-}CH_3C_6H_4SO_2O$ (see page 229) or halogen by means of potassium fluoride; this salt (KF) crystallizes with 2 or 4 molecules of H_2O and, apart from a few exceptional cases, must be completely dehydrated before use.

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[793] E. T. McBee and L. D. Bechtol, *Ind. Eng. Chem.*, **39**, 380 (1947).

[794] R. D. Fowler and co-workers, *Ind. Eng. Chem.*, **39**, 292 (1947).

[795] A. L. Henne and M. W. Renoll. *J. Amer. Chem. Soc.*, **60**, 1060 (1938).

[796] A. L. Henne and T. Midgley Jr., *J. Amer. Chem. Soc.*, **58**, 884 (1936).

[797] A. L. Henne, *J. Amer. Chem. Soc.*, **60**, 1569 (1938).

[798] A. L. Henne and J. V. Flanagan, *J. Amer. Chem. Soc.*, **65**, 2362 (1943).

[799] E. T. McBee, H. B. Hass, R. M. Thomas, W. G. Toland Jr., and A. Truchan, *J. Amer. Chem. Soc.*, **69**, 944 (1947).

[800] F. E. Ray and C. E. Albertson, *J. Amer. Chem. Soc.*, **70**, 1954 (1948).

The potassium fluoride is heated for 24 h at 125°, then ground very fine and dried for a further 24 h in a vacuum drying oven at 150°. Larger amounts are dehydrated azeotropically with benzene; after removal of the benzene–water mixture by distillation, a higher-boiling solvent (see below) is added and the residual benzene is distilled off.

Sulfonyl fluorides are readily obtained from sulfonyl chlorides and KF or KHF_2, even in an aqueous medium.[801–804] Carboxylic acid fluorides are formed when the acid chlorides are heated with dry KF and can be removed continuously from the reaction mixture by distillation through a column; formyl and acetyl fluorides are thus obtained when the acid is heated with benzoyl chloride and KF.[805,806] Xylene or acetamide may be used as diluent. Further, α-chloro and α-bromo fatty esters, nitriles, and amides react with KF at temperatures around 100–150°.

Ethyl fluoroacetate:[31,807] A mixture of acetamide (8 moles) and ethyl chloroacetate (5.9 moles) is heated in a three-necked 2-l flask placed in an oil-bath at 110°. The flask is fitted with a gas-tight stirrer and a column carrying a dephlegmator. Finely powdered, dry KF (8.2 moles) is added in portions with vigorous stirring and the oil-bath temperature is then raised to 140°. After about 30 min the crude product begins to distil; a reflux ratio of 10:1 is used. This gives, first, material boiling at 76–115.5° (245 g) and then material boiling at 115.5–117.5° (210 g). Redistillation of both fractions provides 52% of ethyl fluoroacetate, b.p. 117–118°.

Alkyl halides RCH_2X are converted into alkyl fluorides by KF in ethylene glycol or, better, diethylene glycol if water is excluded and stirring is vigorous, but at least 2 moles of KF must be used per mole of X. The lower-boiling 1-fluoro- or ω,ω'-difluoro-alkanes are continuously removed from the reaction mixture through a column at atmospheric or reduced pressure. In this way ω,ω'-difluoroalkanes are obtained from ω,ω'-dichloroalkanes (2.5 moles of KF, ethylene glycol, 150–185°),[808,809] alkyl fluorides from alkyl halides (ethylene glycol, 180°),[810,811] and the corresponding ω-fluoro compounds from ω-chloro or ω-bromo aliphatic acid esters or alcohols (diethylene glycol, 120–130°).[812] The procedure is described in detail in *Organic Syntheses*[813] for the preparation of 1-fluorohexane from 1-bromohexane.

2-Fluoroethanol from ethylene chlorohydrin:[814] Ethylene chlorohydrin (322 g) is dropped during 3 h into a mixture of dry, powdered KF (350 g), ethylene glycol (320 g), and diethylene glycol (130 g) stirred at 170–180°, the 2-fluoroethanol (b.p. 97–104°) being distilled off continuously through a 30-cm column. A slow stream of air is subsequently drawn through the apparatus to complete removal of the fluoroethanol. The crude product (152.5 g) is set aside

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[801] W. T. Truce and F. D. Hoerger, *J. Amer. Chem. Soc.*, **76**, 3230 (1954).

[802] W. Davies and J. H. Dick, *J. Chem. Soc.*, **1931**, 2104; **1932**, 483.

[803] J. E. Millington, G. M. Brown, and F. L. M. Pattison, *J. Amer. Chem. Soc.*, **78**, 3846 (1956).

[804] T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, **1956**, 173.

[805] A. N. Nesmejanow and E. I. Kahn, *Ber. Deut. Chem. Ges.*, **67**, 370 (1934).

[806] A. I. Mashentsev, *Zh. Obshch. Khim.*, **20**, 854 (1947); *Chem. Abstr.*, **42**, 5418 (1948).

[807] E. D. Bergmann and I. Blank, *J. Chem. Soc.*, **1953**, 3786.

[808] F. W. Hoffmann, *J. Org. Chem.*, **14**, 105 (1949).

[809] F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 748 (1956).

[810] H. Kitano and K. Fukui, *J. Chem. Soc., Japan, Ind. Chem. Sect.*, **58**, 353 (1955); *Chem. Abstr.*, **50**, 3995 (1956).

[811] F. L. M. Pattison and J. J. Norman, *J. Amer. Chem. Soc.*, **79**, 2311 (1957).

[812] F. L. M. Pattison and co-workers, *J. Org. Chem.*, **21**, 739 (1956).

[813] A. I. Vogel, J. Leicester, and W. A. T. Macey, *Org. Syn.*, **36**, 40 (1956).

[814] F. W. Hoffmann, *J. Amer. Chem. Soc.*, **70**, 2596 (1948).

over NaF (10 g) to remove traces of HF and is then redistilled, giving a 42.5% yield (109 g). For complete purification (removal of crotonaldehyde) see Hoffmann.[815]

2-Fluoroethanol may also be obtained from ethylene chlorohydrin and KF in glycerol at 50–60°[816] or without a solvent in an autoclave at 130–135°.[817]

Further, KF can be used for halogen (X) exchange in aromatic compounds, but only if the X is rendered very mobile by an *o*- or *p*-NO_2 substituent. The rate of reaction and the amounts of by-product depend greatly on the solvent. Glycols cannot be used in such reactions, which must be effected in nitrobenzene at 190–205°; nevertheless, for *o*- and *p*-chloronitrobenzene and for 1-chloro-2,4-dinitrobenzene the exchange occurs in dimethylformamide or dimethyl sulfoxide as low as ca. 100°.[818]

1-Fluoro-2,4-dinitrobenzene: 1-Chloro-2,4-dinitrobenzene (25.5 g) and dry KF (14.5 g) are allowed to react in dimethylformamide (25.5 g) for 30 min at 140–150° or for 13 h at 95–100°. The mixture is then diluted with water, and the resulting oil is washed well with water, dried, and distilled in a vacuum, giving 77% of 1-fluoro-2,4-dinitrobenzene, b.p. 122–124°/1 mm, 156–158°/12 mm.

Alternatively, a mixture of 1-chloro-2,4-dinitrobenzene and dry KF is heated for 7 h at 180–200°, then cooled and taken up in hot, dry benzene. The benzene is removed and the 1-fluoro-2,4-dinitrobenzene is distilled in a vacuum and recrystallized from methanol. This gives a 92% yield of material having m.p. 27°.[819]

For a preparation by nitration of fluorobenzene see Hudlicky[4b] and Zahn and Würz.[820]

LiF, NaF, and NH_4F are much less useful in these cases, but KHF_2 sometimes gives good yields, *e.g.*, in the preparation of acid fluorides by heating C_2—C_6 acids with dry KHF_2 and benzoyl chloride at 100°.[821]

2. Replacement of halogen by iodine, bromine, or chlorine

Iodine is most easily introduced in place of another halogen in an organic halide RX by allowing the latter to react with an inorganic iodide, especially NaI or, less often, KI or CaI_2.

$$RX + I^- \rightleftarrows RI + X^- \quad (X = Cl \text{ or } Br) \tag{a}$$

The rate at which the equilibrium (a) is established depends greatly on the solvent; it is particularly high in acetone, which has the further advantage that it dissolves NaI very well (1.29 mole/l) but NaBr and particularly NaCl (5.5×10^{-6} mole/l) only very slightly; the solubility of NaI in dry acetone at room temperature is about 20 times that of KI. α-Halo carbonyl compounds, and allyl and benzyl halides are particularly reactive, bromine being more easily replaced than chlorine. Primary alkyl halides react more readily than secondary or tertiary ones.[822,823]

Substitution of I for X in aromatic compounds by means of NaI is possible only when the X is activated by electron-attracting substituents such as *o*-

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[815] F. W. Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).

[816] G. Olah and A. Pavlath, *Acta Chim. Acad. Sci. Hung.*, **3**, 199 (1953).

[817] B. C. Saunders, G. J. Stacey, and I. G. E. Wilding, *J. Chem. Soc.*, **1949**, 773.

[818] G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, **78**, 6034 (1956).

[819] N. N. Vorozhtsov Jr. and G. G. Yakobsson, *Zh. Obshch. Khim.*, **27**, 1672 (1957); *Chem. Abstr.*, **52**, 2777 (1958).

[820] H. Zahn and A. Würz, *Angew. Chem.*, **63**, 147 (1951).

[821] G. Olah, S. Kuhn, and S. Beke, *Chem. Ber.*, **89**, 862 (1956).

[822] H. Finkelstein, *Ber. Deut. Chem. Ges.*, **43**, 1528 (1910).

[823] J. B. Conant and R. E. Hussey, *J. Amer. Chem. Soc.*, **47**, 476 (1925).

and/or p-NO_2: boiling 1 mole of 1-chloro-2,4-dinitrobenzene with 5 moles of NaI in dimethylformamide provides about 70% of 1-iodo-2,4-dinitrobenzene.[824] Other simple methods for halogen–iodine exchange have been worked out recently for the remaining aromatic compounds (see page 212).

Reaction of RX with NaI is normally very smooth but side reactions may be expected in some cases. Particularly when the iodine is very mobile, the HI produced may act as reducing agent (b), so that it is advisable to remove the iodine by thiosulfate or dilute sodium hydroxide solution during working up instead of by hydrogen sulfite.

$$RI + HI \longrightarrow RH + I_2 \qquad (b)$$

α,β-Dihalides give olefins (c), a reaction that is

$$RCHXCHXR' + 2I^- \longrightarrow RCH{=}CHR' + 2X^- + I_2 \qquad (c)$$

sometimes desired, *e.g.*, for introducing C=C bonds into steroids.[825]

The conditions used for treatment of RX with NaI should be adjusted to the reactivity of the RX. 1–1.25 moles of dry NaI are used per mole of RX, or more if the RX is valuable or unreactive, and usually about six times as much dry acetone as NaI.

The mixture is stirred at room temperature or at the boiling point until no more NaBr or NaCl separates. After filtration the solvent is removed, and the residue is treated with ether and freed from iodine by thiosulfate solution.

If the RX is very unreactive a higher-boiling solvent such as ethyl methyl ketone[826,827] or acetylacetone may be used. If a compound RX is to be treated with an amine or a phenol, it may be advantageous to convert a less reactive RX into RI, for which purpose a smaller amount of NaI or KI is added to the reaction mixture.

Halogen exchange by means of NaI or KI can also be effected in methanol, ethanol, or water.

Iodoacetic acid, for instance, is obtained by warming chloroacetic acid (1 mole) with KI (1 mole) in concentrated aqueous solution at 50° for 2 h, decolorization with sulfur dioxide, extraction with ether, drying of the extract with $CaCl_2$, evaporation, and recrystallization from a little water or from light petroleum, giving an acid of m.p. 82°.[828]

Examples of reactions in methanol or ethanol are the preparation of 2-iodoheptane from 2-bromoheptane (NaI, 6 hours' boiling)[829] and of dihydro-α-iodochalmoogric acid from the corresponding bromo compound (KI, 12 hours' boiling).[830]

Replacement of Cl or I or Br is preparatively much less important than the halogen exchange reactions discussed above. In principle the reactions occur similarly, although not under such mild conditions; iodine is more easily replaced than chlorine. Lithium bromide in boiling methanol or acetone, sodium bromide, in boiling methanol or ethanol, or calcium bromide can be used to substitute bromine for a halogen next to a C=C or C≡C group. Anhydrous $AlBr_3$ is particularly reactive, replacing, for instance, one Cl of CCl_4 by Br.

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[824] J. F. Bunnett and R. M. Conner, *J. Org. Chem.*, **23**, 305 (1958); *Org. Syn.*, **40**, 34 (1960).

[825] H. H. Inhoffen, *Ber. Deut. Chem. Ges.*, **69**, 1134 (1936).

[826] A. H. Ford-Moore, *Org. Syn.*, **30**, 10 (1950).

[827] E. Klingsberg, *J. Amer. Chem. Soc.*, **72**, 1031 (1950).

[828] E. Abderhalden and M. Guggenheim, *Ber. Deut. Chem. Ges.*, **41**, 2853 (1908).

[829] M. Schirm and H. Besendorf, *Arch. Pharm.*, **280**, 64 (1942).

[830] Ng. Ph. Buu-Hoï and P. Cagniant, *Ber. Deut. Chem. Ges.*, **75**, 1181 (1942).

Bromotrichloromethane: Bromotrichloromethane can be prepared without great demands on apparatus by allowing $AlBr_3$ (260 g) and CCl_4 (350 ml) to react for 3 days at room temperature.[831]

Considerably better yields of $CBrCl_3$ can be achieved by heating $AlBr_3$ for a relatively short time with a large excess of CCl_4 at the boiling point.[832] Anhydrous $AlBr_3$ (168.5 g) and dry CCl_4 (940 g) are heated under reflux for 45 min, then cooled, filtered, and shaken with 5% potassium carbonate solution (170 ml) and then with water (2 × 170 ml). The organic phase is dried over $CaCl_2$ and fractionated through a Vigreux column, giving CCl_4 (480 g) and then at 102–106° $CBrCl_3$ (193 g, 51.4%), n_D^{20} 1.5063.

$CBrCl_3$ may also be obtained by vapor-phase reaction of $CHCl_3$ with bromine at 420 to 450°.[833]

Tetrabromomethane: If $AlBr_3$ (300 g) is dissolved in ethyl bromide (400 g) with cooling and added during 30 min to a mixture of CCl_4 (130 g) and ethyl bromide (300 g) at −10° to 0°, then set aside for a further 30 min, the main product is tetrabromomethane.[834]

Aluminum bromide: $AlBr_3$ is obtained in excellent yield by dropping bromine (250 g) on to a mixture of aluminum turnings and Raschig rings. Some $AlBr_3$ may be added as catalyst at the beginning of the reaction. If a 1-l flask four-fifths full is used, then during the addition, which requires about 2 h, the $AlBr_3$ distils off owing to the strongly exothermic reaction. After the addition, the residue is heated in an air-bath, further $AlBr_3$ distilling. The product has b.p. 255° and m.p. 94.9°.[835]

C–Cl and C–Br bonds can also be created by the action of chlorine or bromine on organic halogen compounds. For instance, even at −78° 2-chloro- and 2-bromo-octane are formed from 2-iodooctane and chlorine or bromine, respectively, in light petroleum.[836] Such reactions are preparatively unimportant but they play a part in, usually undesirable, side reactions: Side-chain chlorination of *o*-, *m*-, and *p*-bromotoluene, for instance, gives mixtures of ring-halogenated benzyl halides in which chlorine and bromine occur both in the ring and in the side chain.[837] Leading chlorine into bromobenzene for 1 hour under illumination by a 200-W lamp gives 81% of chlorobenzene; and ^{80}Br can be replaced also by ^{82}Br.[838] In the presence of $FeCl_3$ or $AlCl_3$ bromobenzene is chlorinated to *o*- and *p*-bromochlorobenzene.[839] CuCl containing a little $CuCl_2$ smoothly replaces bromine bound to an aromatic ring, particularly well in 2-picoline or dimethylformamide.[840] Chlorine and bromine, however, do not usually replace iodine bound to an aromatic ring.

Alkyl halides R′X may also be used instead of an inorganic halide or elemental halogen to effect halogen exchange:

$$RCl + R'X \overset{AlCl_3}{\rightleftharpoons} RX + R'Cl \quad (X = Br \text{ or } I) \tag{d}$$

Anhydrous $AlCl_3$ (0.02–0.05 mole) catalyses the equilibration (d). When R′ in R′X is CH_3 or C_2H_5 and about 5% excess of this is used, then even

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[831] H. G. Vesper and G. K. Rollefson, *J. Amer. Chem. Soc.*, **56**, 1456.(1934).

[832] G. Lehmann and B. Lücke, *J. Prakt. Chem.*, [iv], **22**, 230 (1963).

[833] L. I. Sacharkin, "Synthesen organischer Verbindungen," VEB Verlag Technik, Berlin, Porta-Verlag, Munich, 1956, Vol. 2, p. 21.

[834] H. S. Nutting and P. S. Petrie, U.S. Pat. 2,120,675; *Chem. Abstr.*, **32**, 5851 (1938).

[835] V. Koutnik and J. Benes, *Chem. Prum.*, **8** (**33**), 187 (1958); *Chem. Zentralbl.*, **1958** 12911.

[836] F. M. Beringer and H. S. Schultz, *J. Amer. Chem. Soc.*, **77**, 5533 (1955).

[837] F. Asinger, *Monatsh. Chem.*, **64**, 153 (1934).

[838] B. Miller and C. Walling, *J. Amer. Chem. Soc.*, **79**, 4189 (1957).

[839] M. A. F. Holleman and T. van der Linden, *Rec. Trav.*, **30**, 253 (1911).

[840] W. B. Hardy and R. B. Fortenbaugh, *J. Amer. Chem. Soc.*, **80**, 1716 (1958).

at 30–40° continuous distillation of the readily volatile CH_3Cl or C_2H_5Cl through a column shifts the equilibrium (d) to the right. For example, tetraiodomethane is obtained in this way from CCl_4 and CHI_3,[841] iodoform from $CHCl_3$ and C_2H_5I[842] or HCI_3,[841] and bromoform ($CHBr_3$) from $CHCl_3$ and C_2H_5Br,[841] all in very good yield. Reaction of two alkanes each containing several halogen atoms under catalysis by $AlCl_3$, *e.g.*, reactions e)[843] and (f),[844] gives mixed bromochloroalkanes; the original papers should be consulted for details of apparatus.

$$CHBr_3 + CHCl_3 \xrightleftharpoons{AlCl_3} CHCl_2Br + CHClBr_2 \qquad (e)$$

$$BrCH_2CH_2Br + ClCH_2CH_2Cl \xrightleftharpoons{AlCl_3} 2ClCH_2CH_2Br \qquad (f)$$

A different halogen can be introduced into an organic halide containing relatively tightly bonded halogen by inserting an organometallic compound — usually a Grignard compound — as an intermediate stage (g). Such reactions

$$2RX + 2Mg \longrightarrow 2RMgX \xrightarrow{2I_2} 2RI + MgX_2 + MgI_2 \qquad (g)$$

are important for the preparation of iodinated aromatic and heterocyclic compounds from chloro or bromo compounds.

The simplest technique is to drop a solution of iodine (*ca.* 0.65 mole, *i.e.*, substantially less than the calculated amount) in dry ether into an ethereal Grignard solution prepared from the aryl bromide (*ca.* 1 mole) and magnesium. When the iodine color has disappeared and subsequent reaction is ended, the mixture is treated with ice-water and dilute hydrochloric acid. The ethereal layer contains unchanged aryl bromide and aromatic hydrocarbon as well as aryl iodide and is worked up by any suitable method.[845]

The Grignard compound may be treated with an organic halide (reaction h) instead of with the elemental halogen,

$$RMgX + R'I \longrightarrow RI + R'MgX \qquad (h)$$

e.g., with cyanogen bromide or iodide[846] or iodoacetonitrile.[847]

The corresponding reactions of diiodoacetylene are very fast even at 0° and give 75–95% yields of alkyl and aryl iodides.[436] As the di-Grignard compounds from acetylene are sparingly soluble in ether, the equilibrium

$$2RMgX + IC{\equiv}CI \rightleftharpoons XMgC{\equiv}CMgX + 2RI \qquad (i)$$

is shifted completely to the right. Working up is very simple since acetylene is evolved as gas on hydrolysis by H_2SO_4; a disadantage is the tendency of dry diodoacetylene to explode[437] (for its preparation see page 160).

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[841] H. Soroos and J. B. Hinkamp, *J. Amer. Chem. Soc.*, **67**, 1642 (1945).

[842] J. W. Walker, *J. Chem. Soc.*, **85**, 1082 (1904).

[843] M. S. Kharasch, B. M. Kuderna, and W. Urry, *J. Org. Chem.*, **13**, 895 (1948).

[844] G. Calingaert and co-workers, *J. Amer. Chem. Soc.*, **62**, 1545 (1940).

[845] R. L. Datta and H. K. Mitter, *J. Amer. Chem. Soc.*, **41**, 287 (1919).

[846] V. Grignard and co-workers, *Ann. Chim.*, [ix], **4**, 28 (1915).

[847] J. von Braun, H. Deutsch, and A. Schmatloch, *Ber. Deut. Chem. Ges.*, **45**, 1246 (1912).

Iodobenzene from chloro- or bromobenzene:[436] Diiodoacetylene (0.1 mole) in ether (50 ml) is dropped into an ethereal Grignard solution from chloro- or bromo-benzene (0.2 moles) with ice-cooling (clouding). The mixture is set aside for 15 min at room temperature and the top layer is decanted from the bottom syrupy layer deposited from the cloud, or the whole is decomposed directly by dilute H_2SO_4. The dried ethereal solution affords a 95% or 97%, respectively, yield of iodobenzene, b.p. 188°/760 mm.

The ethereal Grignard solution obtained from indole and C_2H_5MgBr similarly affords an 83% yield of 3-iodoindole.

3. Replacement of halogen by thiocyanate

The classical, generally applicable method of preparing aliphatic thiocyanates (a) is to treat a halide with an alkali thiocyanate or ammonium thiocyanate:

$$\underset{(b)}{RNCS} \longleftarrow RX \longrightarrow \underset{(a)}{RSCN}$$

General procedure: An alkyl bromide (1 mole) is dropped into a stirred, boiling mixture of finely powdered KSCN (1.5 moles) and ethanol (340 ml; about one-third of the KSCN dissolves), and the mixture is kept at the b.p. for 2 h. Then part of the solvent is distilled off, the remaining mixture is diluted with water, the thiocyanate is extracted in ether, and the ethereal solution is dried over $CaCl_2$ or Na_2SO_4 and worked up by vacuum-distillation. Yields for pentyl to tridecyl thiocyanate are about 80–90%.[850]

Alternatively ethanolic halide solutions, *e.g.*, $Cl(CH_2)_nOH$,[851] and concentrated aqueous KSCN are mixed, boiled for some hours, diluted with water, and extracted with $CHCl_3$. Dioxan may also be used as solvent. Thiocyanatohydrin derivatives $RO(CH_2)_nSCN$ are of value as insecticides.[852]

NaSCN in acetone can also be used, as in other halogen exchange reactions. For the preparation of *cis*-9-octadecenyl thiocyanate[853] the bromide (54 g) and $NaSCN \cdot 2H_2O$ (75 g) in acetone (500 ml) are allowed to react in an autoclave at 80° for 20 hours.

Lower alkyl thiocyanates are very simply obtained by gradually adding the dialkyl sulfate (1 mole) to KSCN (1 mole) in water (50 ml) with shaking and, if necessary, cooling.[854]

The more mobile the halogen to be replaced from RX, the more easily are isothiocyanates (mustard oils) (b) formed. Isothiocyanates have lower boiling points than thiocyanates, are more stable, and can be obtained by heating thiocyanates; addition of $ZnCl_2$ accelerates the rearrangement.[855] Mixtures of thiocyanates and isothiocyanates are often obtained in the main reaction. Halides with readily removable halogen give isothiocyanates directly if higher temperatures (120–130°) are involved in working up or in the reaction.

Chloromethyl methyl or ethyl ether, for instance, and KSCN in light petroleum form methoxymethyl or ethoxymethyl isothiocyanate, respectively,[856] and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl isothiocyanate is obtained from α-acetobromoglucose and AgSCN in toluene.[857]

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[850] P. Allen Jr., *J. Amer. Chem. Soc.*, **57**, 198 (1935).

[851] H. D. Vogelsang, T. Wagner-Jauregg, and R. Rebling, *Ann. Chem.*, **569**, 190 (1950).

[852] T. Wagner-Jauregg, *Ann. Chem.*, **561**, 94 (1949).

[853] T. Wagner-Jauregg and co-workers, *J. Prakt. Chem.*, **155**, 216 (1940).

[854] P. Walden, *Ber. Deut. Chem. Ges.*, **40**, 3215 (1907).

[855] E. Schmidt and co-workers, *Ann. Chem.*, **568**, 193 (1950).

[856] E. Schmidt and W. Striewsky, *Ber. Deut. Chem. Ges.*, **73**, 286 (1940).

[857] F. P. van de Kamp and F. Micheel, *Chem. Ber.*, **89**, 133 (1956).

III. Replacement of OH, OR, or =O by halogen

1. Replacement of alcoholic OH by halogen

a. Replacement of alcoholic OH by fluorine

Direct substitution of F for OH by means of HF has no preparative importance. All the methods of preparing alkyl fluorides from alcohols proceed in principle by way of esters: the alcohol is converted into the alkyl chloride, bromide, iodide, or *p*-toluenesulfonate, and then the halogen atom (see page 204) or the tosyloxy group (see page 229) is replaced by fluorine.

Alkyl and cycloalkyl fluoroformates decompose even at about 50° in presence of boron trifluoride dietherate, the reaction being represented by equation (a):[858]

$$\mathrm{FCOOR} \xrightarrow[\mathrm{BF_3}]{} \mathrm{RF} + \mathrm{CO_2} \qquad \text{(a)}$$

Fluoroformic esters are obtained either from the corresponding chloroformates and thallium fluoride by halogen exchange[859] or, if the expensive TlF is not available, from carbonyl bromide fluoride and alcohols which give only

$$\mathrm{ClCOOR} + \mathrm{TlF} \longrightarrow \mathrm{FCOOR} \longleftarrow \mathrm{OCFBr} + \mathrm{ROH}$$

the fluoroformates. Details, and the preparation of OCFBr from BrF_3 and CO, are described by Olah and Kuhn.[860]

b. Replacement of alcoholic OH by chlorine, bromine or iodine by means of hydrogen halides or acid halides

i. Replacement of alcoholic OH by halogen by means of hydrogen halides

The easiest method of replacing alcoholic OH by Cl, Br, or I is according to the reaction:

$$\mathrm{ROH} + \mathrm{HX} \longrightarrow \mathrm{RX} + \mathrm{H_2O}$$

in which the ease of reaction increases in the order HX = HCl, HBr, HI. Tertiary react better than secondary alcohols with HX, and secondary better than primary ones.[861,862] The purer an alcohol the less it is attacked by dry HCl (at 20° and 30–40 atm).[863] The more easily an alkyl halide is formed, the more easily does it tend to lose HX; thus primary *n*-alkyl halides are the most stable; however, primary branched-chain halides readily lose HX when heated.

Since the reaction is not quantitative it almost always gives a mixture of the chloride and the alcohol, which are not completely separable by fractionation since they form azeotropic mixtures. The alcohols are removed from the crude products by shaking with concentrated H_2SO_4 or, better, concentrated HCl.

The primary step in reaction of an alcohol with HX is formation of an oxonium complex ROH_2^+, so that electron-attracting substituents (halogen,

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[858] S. Nakaniski, T. C. Myers, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 5033 (1955).

[859] S. Nakaniski, T. C. Myers, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 3099 (1955).

[860] G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **21**, 1319 (1956).

[861] G. M. Bennett and F. M. Reynolds, *J. Chem. Soc.*, **1935**, 131.

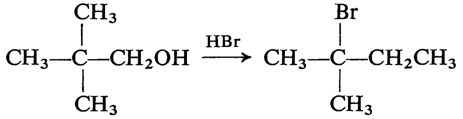
[862] R. B. Bradbury, *J. Amer. Chem. Soc.*, **74**, 2709 (1952).

[863] H. W. Schlubach, H. Elsner, and H. Knoop, *Angew. Chem.*, **47**, 131 (1934).

NO_2, CN, COOAlkyl, etc.) hinder exchange. This effect decreases with increasing distance of the substituent from the OH group; thus, for example, one OH group of α,β-glycols is easily replaced by bromine, which then makes replacement of the second OH group difficult.

HX, SOX_2, and phosphorus halides cause Walden inversion of optically active alcohols that have the OH group at a center of chirality. The inversion may be more or less complete according to the reaction conditions, so that the rotation of the halide obtained is liable to vary from one occasion to the next. For the steric course of replacement of OH by Br in steroids see Fieser.[55e]

Rearrangement of the carbon chain occurs easily when halogen (X) is substituted for OH in much-branched primary alcohols or secondary alcohols having a tertiary H atom in the α-position: tertiary halides are formed preferentially, *e.g.*, *tert*-pentyl bromide is the main product from neopentyl alcohol:



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH_2OH \xrightarrow{HBr} CH_3-\overset{\displaystyle Br}{\underset{\displaystyle CH_3}{C}}-CH_2CH_3$$

Studies of the substitution of Cl for OH in alcohols of the type $RR'CHCH_2OH$ ($R = R' = C_2H_5$)[864] have shown that at least seven isomeric alkyl chlorides are formed on rearrangement of the carbon skeleton by concentrated HCl and $ZnCl_2$ (see page 217), whereas reaction with $SOCl_2$ and pyridine gives 82% or $(C_2H_5)_2CHCH_2Cl$ without rearrangement (see page 222).

Mixtures of isomeric alkyl chlorides are also obtained from straight-chain alcohols on treatment with concentrated HCl and $ZnCl_2$, owing to intermediate formation of olefins and subsequent addition of HCl; *n*-pentyl alcohol, for instance, with concentrated HCl and $ZnCl_2$ gives 57% of *n*-pentyl chloride together with 10% of a mixture of 2- and 3-chloropentane; but treatment with $SOCl_2$ and pyridine gives 80% of *n*-pentyl chloride.[865]

It is also impossible to obtain pure secondary alkyl bromides from alcohols by means of HBr or PBr_3 when formation of isomeric secondary bromides is possible; with these reagents 1-pentanol gives 1-bromopentane, but both 2- and 3-pentanol always give mixtures of 2- and 3-bromopentane under these conditions.[866] A secondary alcoholic OH group can be replaced by halogen without rearrangement by the *p*-toluenesulfonate method[866–868] (see page 229).

Isobutyl halides and other isobutyl compounds rearrange readily to *tert*-butyl compounds; for the older literature see Whitmore and Lux.[869] However, PBr_3 (see page 223) converts isobutyl alcohol into isobutyl bromide in good yield with less than 1% of *tert*-butyl bromide.[869]

The tertiary butyl bromide can be removed by stirring the almost pure isobutyl bromide (1 kg) for 5 h with distilled water (300 ml) and washing the bromide layer with further distilled

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[864] F. C. Whitmore and F. A. Karnatz, *J. Amer. Chem. Soc.*, **60**, 2533 (1938).

[865] F. C. Whitmore, F. A. Karnatz, and A. H. Popkin, *J. Amer. Chem. Soc.*, **60**, 2540 (1938).

[866] H. Pines, A. Rudin, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **74**, 4063 (1952).

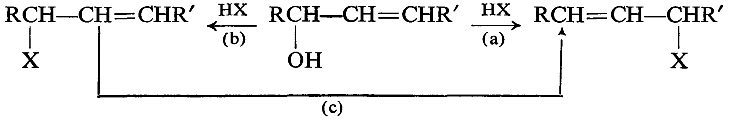
[867] H. Phillips, *J. Chem. Soc.*, **1925**, 2552.

[868] A. J. H. Houssa, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, **1929**, 1700.

[869] F. C. Whitmore and A. R. Lux, *J. Amer. Chem. Soc.*, **54**, 3448 (1932).

water, drying it over K_2CO_3, and distilling it through a column at 135 mm Hg (b.p. 41.8 to 42.5°/135 mm). Cold distilled water hydrolyses only the *tert*-butyl bromide, and the amount of this in the original mixture can be determined by Volhard titration of the aqueous layers.[870] The secondary halides, which are relatively stable to cold water, are, however, unlike unbranched primary halides, cleaved with loss of HX when shaken with alkali carbonate solution, and again this reaction can be used for their approximate determination. Gas chromatography is now available for exact analysis.[871]

When an OH group in an allylic position is replaced by X, the possibility of an allylic rearrangement (a) must not be overlooked. It depends on the reaction medium and on the natures of R and R′ whether reaction (a) or (b) predominates.



$$\underset{\textstyle X}{RCH}—CH{=}CHR' \xleftarrow[(b)]{HX} \underset{\textstyle OH}{RCH}—CH{=}CHR' \xrightarrow[(a)]{HX} RCH{=}CH—\underset{\textstyle X}{CHR'}$$

(c)

Allylic rearrangement of the halide products is also possible and further rearrangements may occur in subsequent reactions, so that prediction of the structure of the ultimate products becomes complicated. Allyl chlorides are more stable than the corresponding bromides. Primary and secondary allyl chlorides show little tendency to isomerize during the usual operations of purification. Allyl halides are considerably more reactive than other alkyl halides, the iodides being particularly reactive and unstable. For further information about the reaction mechanism and numerous references see deWolfe and Young;[872] it must suffice here to mention that the allylic rearrangement can be rendered complete or entirely avoided by maintaining specific conditions. For instance, in the following reactions allylic rearrangement can be achieved to the extent of 100% by using $SOCl_2$ in dilute ethereal solution.[873] The last of these reactions is particularly noteworthy since in general maximum conjugation is retained in exchange reactions.[199,874]

$$CH_3—CH{=}CH—CH_2OH \longrightarrow CH_3—CHCl—CH{=}CH_2$$

$$CH_3—CHOH—CH{=}CH_2 \longrightarrow CH_3—CH{=}CH—CH_2Cl$$

$$C_6H_5—CH{=}CH—CH_2OH \longrightarrow C_6H_5—CHCl—CH{=}CH_2$$

If R, or R and R′, in allyl alcohols of type $RCHOH—CH{=}CHR'$ denote $C{=}C$ or $C{\equiv}C$ groups in suitable positions, the longest chain of conjugation is formed with complete allylic rearrangement.[875-877]

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[870] A. Michael and H. Leupold, *Ann. Chem.*, **379**, 263 (1911).

[871] R. Kaiser, "Gas-Chromatographie," Akademische Verlagsgesellschaft Geest & Portig K.-G., Leipzig, 2nd ed., 1962.

[872] R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 801 (1956).

[873] F. F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *J. Amer. Chem. Soc.*, **77**, 4182 (1955).

[874] L. Claisen and E. Tietze, *Ber. Deut. Chem. Ges.*, **58**, 279 (1925).

[875] A. Roedig and H.-J. Becker, *Chem. Ber.*, **89**, 1726 (1956).

[876] C. Prevost and F. Bidon, *Bull. Soc. Chim. France*, **1955**, 1408.

[877] I. M. Heilbron and co-workers, *J. Chem. Soc.*, **1945**, 77.

Either 2-buten-1-ol or 3-buten-2-ol gives mixtures of 1-bromo-2-butene (b.p. 107°) and 3-bromo-1-butene (b.p. 86.5°). The two bromides rearrange slowly at room temperature or rapidly at 100°, giving an equilibrium mixture containing 86% of the former and 14% of

$$\begin{array}{c} CH_3\text{—}CH{=}CH\text{—}CH_2OH \\ \text{or} \\ CH_3\text{—}CHOH\text{—}CH{=}CH_2 \end{array} \xrightarrow[PBr_3]{HBr\ \text{or}} \begin{array}{ll} CH_3\text{—}CH{=}CH\text{—}CH_2Br & 86\% \\ & \\ CH_3\text{—}CHBr\text{—}CH{=}CH_2 & 14\% \end{array}$$

the latter. Subjecting this mixture to slow fractional distillation at atmospheric pressure affords the lower-boiling 3-bromo-1-butene since this is continuously generated by adjustment of the equilibrium.[878]

3-Buten-2-ol reacts with 37% HCl at room temperature (13 h) to give a 95% yield of a mixture containing 35% of 3-chloro-1-butene (the unrearranged product; b.p. 63.7°/748 mm) and 65% of 1-chloro-2-butene (b.p. 84.2°/748 mm); the former rearranges to the latter in 78% yield in concentrated HCl containing $FeCl_3$ at 64°.[879]

Side reactions may occur, as well as the above-mentioned rearrangements in the preparation of iodides from alcohols. The more mobile the I of RI the more easily the reduction $RI + HI \rightarrow RH + I_2$ occurs. This side reaction can be avoided by converting the alcohol into the chloride, bromide, or *p*-toluenesulfonate and replacing the halogen or tosyloxy group by iodine.

α,β-Diiodides resulting from glycols at once liberate iodine, so that unsaturated compounds are obtained, and these may undergo further reactions. For

$$CH_2OH\text{—}CHOH\text{—}CH_2OH \longrightarrow CH_2I\text{—}CHI\text{—}CH_2OH \xrightarrow[+HI]{-I_2} CH_2{=}CH\text{—}CH_2I \xrightarrow{+HI}$$

$$CH_3\text{—}CHI\text{—}CH_2I \xrightarrow{-I_2} CH_3\text{—}CH{=}CH_2 \xrightarrow{+HI} CH_3\text{—}CHI\text{—}CH_3$$

instance, an excess of glycerol with HI gives allyl iodide, but isopropyl iodide is obtained when an excess of HI is used. For the mechanism see Bradbury.[862]

Substitution of Cl for alcoholic OH by means of HCl: Saturated primary alcohols do not react well with concentrated HCl alone when heated in an open vessel; however, benzyl, cinnamyl, and allyl alcohol give the corresponding chlorides in good yield, reacting with concentrated HCl even at room temperature.[880,881] Reaction with $ZnCl_2$ and concentrated HCl is generally applicable.[882,883]

General procedure: Zinc chloride (2 moles) is dissolved in concentrated HCl (2 moles of HCl) with cooling, the alcohol (1 mole) is added, and the whole is boiled under reflux for 3–4 h (9 h if 5 moles of alcohol are used). After cooling, the upper layer is separated and boiled with an equal volume of concentrated H_2SO_4 for 30 min under reflux, then the chloride is distilled off, washed with water, dried over $CaCl_2$, and redistilled.

Sensitive chlorides, such as chlorocyclopentane,[884] are heated on a steam-bath for 1 h, the upper layer being then separated, washed successively with water, sodium hydrogen carbonate solution, water, and saturated $CaCl_2$ solution, dried over $CaCl_2$, and distilled. Lower-boiling alkyl chlorides are better removed continuously from the reaction mixture (reaction for about 1 h) through an upright condenser that serves as fractionating column;

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[878] W. G. Young and co-workers, *J. Amer. Chem. Soc.*, **57**, 2013 (1935); **58**, 104 (1936); **59**, 2051 (1937); **60**, 847 (1938).

[879] L. F. Hatch and S. S. Nesbit, *J. Amer. Chem. Soc.*, **72**, 728 (1950).

[880] J. F. Norris, *J. Amer. Chem. Soc.*, **38**, 1071 (1916).

[881] R. McCullough and F. Cortese, *J. Amer. Chem. Soc.*, **51**, 225 (1929).

[882] J. F. Norris and H. B. Taylor, *J. Amer. Chem. Soc.*, **46**, 753 (1924).

[883] J. F. Norris and H. B. Taylor, *Org. Syn.*, **5**, 27 (1925).

[884] M. T. Rogers and J. T. Roberts, *J. Amer. Chem. Soc.*, **68**, 843 (1946).

cooling water should be supplied so that a thermometer at the top of the condenser registers at most 2° above the boiling point of the chloride; 70–72% of propyl and 76–77% of butyl chloride are thus obtained.[885]

$CaCl_2$ may replace the $ZnCl_2$, *e.g*, in the preparation of cyclohexyl chloride.[886] For preparation of this chloride by saturating a solution of cyclohexanol in 1.5 times the amount of concentrated HCl (*d* 1.19) with HCl and 2 hours boiling under reflux see Mayes and Turner.[887]

Boiling with concentrated HCl or passing in dry HCl is usually used for substituting Cl for OH of polyhydric alcohols. Procedures in which free OH groups are retained are particularly interesting.

To obtain **3-chloro-1-propanol,** $CH_2ClCH_2CH_2OH$, a very fast stream of HCl may be passed into 25–30 ml of trimethylene glycol, $CH_2OHCH_2CH_2OH$, at 150–170°; a mixture of $CH_2ClCH_2 \cdot CH_2OH$, water, HCl, and unchanged diol distils over, and more diol is added continuously to make up the loss, if possible 2–3 ml/min. For details see *Organic Syntheses*.[888]

The following procedure is better:[889] The glycol (250 g) is shaken with S_2Cl_2 (450 g), the mixture becoming warm, SO_2 being rapidly evolved, and sulfur deposited. This reaction continues for 1 h without heating, whereafter the mixture is heated for a further 6 h on the water-bath and then for 30 min, over a free flame. When no more SO_2 is evolved, the mixture is allowed to cool, then extracted with ether. The sulfur is washed with ether, and the united ethereal layers are shaken with sodium carbonate solution to remove SO_2, dried over Na_2SO_4, and freed from ether. The residue is fractionated and the fraction of b.p. 140–180° is redistilled, giving 60% (160 g) of 3-chloro-1-propanol, b.p. 160–164°/760 mm, 60–64°/10 mm (cf. Gough and King[890]).

ω-Chloro alcohols, $Cl(CH_2)_nOH$ with $n = 5$–10 or 18, are obtained from the α,ω-diols as follows:[812] The diol and concentrated HCl (about 5 moles of HCl per mole of OH), diluted with about one-sixth of their weight of water, are heated with addition of toluene or light petroleum (b.p. 100–120°) which continuously extracts the ω-chloro alcohol and some α,ω-dichloroalkane. The reaction is carried out in a Kutscher–Steudel liquid–liquid extraction apparatus or a simple special apparatus.[891] The volume of HCl must be manipulated to minimize the amount of extractant phase lying above the aqueous acid reactant phase, so that the ω-chloro alcohol formed may be removed from the reaction zone as fast as possible.

ω-Bromo alcohols are obtained analogously: for instance, heating 1,6-hexanediol (1 mole) with 48% HBr (1.2 moles) for 18 h at 80° (extractant: light petroleum) (b.p. 90–100°) gives about 80% of 6-bromo-1-hexanol.[892]

Either one or both of the primary OH groups of glycerol can be replaced selectively by Cl when a carboxylic acid is added as catalyst.

3-Chloro-1,2-propanediol (glycerol α-monochlorohydrin) is obtained by passing HCl into a mixture of 90% glycerol (500 g) and glacial acetic acid (10 g) at 105–110° until a weight increase of 190 g is achieved.[893] According to Smith,[894] HCl should be led into thoroughly dehydrated glycerol containing 2% of succinic acid for 8 h without heating, the heat of reaction alone causing the temperature to rise to 60–70°. On distillation in a vacuum, mainly water passes over up to b.p. 114°/14 mm, then between 114° and 120° 66% (360 g) of 3-chloro-1,2-propanediol (b.p. 113.5°/10.5 mm).

1,3-Dichloro-2-propanol (glycerol α,γ-dichlorohydrin) is obtained similarly, except that for the above batch 440 g of HCl are introduced. For working up see *Organic Syntheses*.[895]

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[885] A. M. Whaley and J. E. Copenhaver, *J. Amer. Chem. Soc.*, **60**, 2497 (1938).

[886] A. I. Vogel, *J. Chem. Soc.*, **1948**, 1811.

[887] H. A. Mayes and E. E. Turner, *J. Chem. Soc.*, **1929**, 502.

[888] C. S. Marvel and H. O. Calvery, *Org. Syn.*, **8**, 112 (1928); Coll. Vol. I, 533 (1941).

[889] C. G. Derick and D. W. Bissel, *J. Amer. Chem. Soc.*, **38**, 2481 (1916).

[890] G. A. C. Gough and H. King, *J. Chem. Soc.*, **1928**, 2439.

[891] K. N. Campbell and A. H. Sommers, *Org. Syn.*, Coll. Vol. III, 446 (1955).

[892] E. F. Degering and L. G. Boatright, *J. Amer. Chem. Soc.*, **72**, 5138 (1950).

[893] J. B. Conant and O. R. Quayle, *Org. Syn.*, **2**, 33 (1922).

[894] L. Smith, *Z. Phys. Chem.*, **94**, 701 (1920).

[895] J. B. Conant and O. R. Quayle, *Org. Syn.*, **2**, 29 (1922).

Tertiary hydroxyl is particularly easily replaced.

tert-Butyl chloride is obtained by shaking *tert*-butyl alcohol (1 mole) or its azeotrope with water (*ca.* 88% of alcohol) with concentrated HCl (3 moles) for some minutes. The two layers are allowed to separate (*ca.* 15 min) and the chloride is washed with water, shaken with 5% $NaHCO_3$ solution, dried over $CaCl_2$, and distilled; it has b.p. 50–52°.[896]

Substitution of Br for alcoholic OH by means of HBr: In principle, alcohols are allowed to react with 48% aqueous HBr, with dry HBr, or with aqueous HBr containing concentrated H_2SO_4. The last of these procedures is the most convenient, but it has the disadvantage that alkyl bromides prepared in that way tend to lose HBr on storage; with HBr the resulting olefins form polymers that may discolor the product.[881]

In the simplest case a mixture of 1 mole of alcohol with 4 moles of 48% HBr is distilled very slowly (1–2 drops per second) and the crude bromide in the distillate is separated. From C_5 the yields are bad. The lowest-boiling alkyl bromides are collected under ice-water.

2-Bromoethylamine hydrobromides, $BrCH_2CH_2NR_2 \cdot HBr$ (R = Alkyl or H), are obtained by adding about 3 molar equivalents of ice-cold 48% HBr dropwise to the ice-cold amino alcohol and then distilling off considerable volumes several times through a column placed on top of the reaction flask. During the intervals the mixture is boiled under reflux. This very simple process, which gives excellent yields, is described in detail in *Organic Syntheses*.[897]

3-Hydroxypropionitrile (obtained from ethylene chlorohydrin) is converted by boiling 40% HBr directly into 3-bromopropionic acid.[898]

The best method of preparing **higher alkyl bromides** (from C_6) is to treat the alcohols with dry HBr:[899–901]

Dry HBr (1.5 moles) is led into an alcohol (1 mole) at 100°, through a glass frit or through a tube reaching to the bottom of the flask and blown at the end into a bulb that is pierced by several holes. 1 mole of HBr is required for the exchange and about 0.5 mole to saturate the water formed. For absorption of the HBr evolved, a weighed wash-bottle whose long tube dips into water is attached to the top of the reflux condenser. Completion of the reaction is recognized by warming of the water and appreciable increase in weight due to evolution of unused HBr. The temperature of the reaction mixture amounts to 100–120° while HBr is being led into it. Since the reaction is exothermic the mixture must be finally heated. After cooling, the crude bromide is separated from the aqueous hydrobromic acid formed. The process is described in detail in *Organic Syntheses*[902] for the case of dodecyl bromide. Yields are usually around 90%, but for cyclohexyl bromide about 70%.

α,ω-Dibromoalkanes, $Br(CH_2)_nBr$, are obtained analogously:

Hydrogen bromide is led rapidly into a glycol, $HO(CH_2)_nOH$, at 100° to saturation and then slowly for a further 6 h at 135°. After cooling, the lower aqueous phase is separated; benzene, light petroleum, or ether may be added as diluent to improve separation. The crude dibromide is washed with an equal volume of warm water, then in small portions with 10%

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[896] J. F. Norris and A. W. Olmsted, *Org. Syn.*, **8**, 50 (1928).

[897] F. Cortese, *Org. Syn.*, Coll. Vol. II, 91 (1943).

[898] E. C. Kendall and B. McKenzie, *Org. Syn.*, Coll. Vol. I, 131 (1956); W. Voigtländer, *Chem. Tech.*, **12**, 1343 (1960).

[899] J. R. Ruhoff, R. E. Burnett, and E. E. Reid, *J. Amer. Chem. Soc.*, **56**, 2784 (1934).

[900] L. I. Smith and co-workers, *J. Org. Chem.*, **4**, 336 (1939).

[901] A. I. Vogel, *J. Chem. Soc.*, **1943**, 636.

[902] E. E. Reid, J. R. Ruhoff, and R. E. Burnett, *Org. Syn.*, Coll. Vol. II, 246 (1943).

sodium carbonate solution until all the HBr is removed, and then again with warm water. It is finally fractionated in a vacuum. Yields are around 75% for $n = 3$[903] or 8[904] and around 90% for $n = 6$, 9, or 10.[903]

Phenethyl bromide, b.p. 99°/15 mm, is obtained similarly in 92% yield.[905]

Glycols $HO(CH_2)_nOH$ lose water both inter- and intramolecularly when treated with dry HBr at 80–200°, so that bis(bromoalkyl) ethers, $Br(CH_2)_nO(CH_2)_nBr$ are obtained as by-products and also cyclic ethers when favored ring systems can be formed.[906] A notable case of cyclic ether formation is that of tetrahydrofuran from 1,4-butanediol; for the reverse reaction see page 237.

The reaction of alcohols with 48% HBr and concentrated H_2SO_4[907] is generally applicable, but the added H_2SO_4 favors the formation of ethers and olefins, the latter particularly from secondary and tertiary alcohols. The amount of these undesirable side reactions can be diminished by deviation from the general procedure for preparation of *n*-alkyl bromides (see below).

***n*-Alkyl bromides:**[148b,901,908] The alcohol (1–1.6-moles) is added to a mixture of 48% HBr (2 moles) and concentrated H_2SO_4 (1 moles), then more concentrated H_2SO_4 (0.8 to 1.6 moles) is added with stirring. The whole is boiled for 3–4 h under reflux, preferably with stirring.

Gentle warming during dropwise addition of concentrated H_2SO_4 (1.5 moles) and condensing the distillate by an efficient downward condenser whose end dips below the surface of an ice–water mixture in the receiver affords **ethyl bromide,** b.p. 39°. Allyl bromide, b.p. 69–72°, is obtained similarly. Boiling the reaction mixture under reflux greatly reduces the yields.

Not too high-boiling alkyl bromides (up to C_6) are distilled directly from the reaction mixture, distillation being continued until no more water-insoluble material passes over (about 1 h). The crude bromide, which contains alcohol, ether, etc., is separated from the aqueous phase of the distillate; or the reaction mixture can be distilled in steam, a procedure that has proved valuable for isolation of *n*-butyl and *n*-decyl bromide.[908]

Reaction mixtures containing higher alkyl bromides are first filtered through glass wool or kieselguhr, and then diluted with water. The crude bromide is separated in a separatory funnel.

Purification of the crude alkyl bromides: The crude bromides can be shaken with about one-third of their volume of concentrated H_2SO_4, which dissolves out the impurities. Alcohols are partly converted into alkyl hydrogen sulfates, which are sparingly soluble in concentrated H_2SO_4 but dissolve well in aqueous-methanolic ammonia. After separation from the H_2SO_4, lower alkyl bromides (up to C_9) are washed with water and sodium carbonate solution. After treatment with concentrated H_2SO_4 and separation therefrom, decyl and higher bromides are mixed with an equal volume of 50% aqueous methanol, then aqueous ammonia is added with shaking until phenolphthalein becomes pink; the bromide is then separated, washed again with an equal volume of 50% methanol, separated, and dried over $CaCl_2$. This procedure, however, causes losses for C_6—C_9-alkyl bromides, and for them as little methanol as possible is used — only enough just to prevent formation of an emulsion between the alkyl bromide and the ammoniacal wash-water. Addition of a little $CaCl_2$ has been recommended[901] to prevent formation of emulsions. The following method of working up is preferable: the crude bromide is shaken twice with an equal volume of concentrated HCl ($d = 1.19$) (which extracts ethers and alcohols), then successively with water, sodium hydrogen carbonate solution, and again water; it is then dried over $CaCl_2$. Boiling points and other physical properties of numerous alkyl chlorides, bromides, and iodides have been recorded by Vogel.[901]

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[903] W. L. McEwen, *Org. Syn.*, Coll. Vol. III, 227 (1955); **20**, 24 (1943).

[904] R. Adams and N. Kornblum, *J. Amer. Chem. Soc.*, **63**, 199 (1941).

[905] F. C. Whitmore and co-workers, *J. Amer. Chem. Soc.*, **67**, 2059 (1945).

[906] A. Müller and W. Vanc, *Chem. Ber.*, **77–79**, 669 (1944–46).

[907] O. Kamm and C. S. Marvel, *J. Amer. Chem. Soc.*, **42**, 229 (1920).

[908] F. C. Whitmore, L. H. Sutherland, and J. N. Cosby, *J. Amer. Chem. Soc.*, **64**, 1361 (1942).

Alcohols from which water is readily split off are treated with concentrated H_2SO_4 and 48% HBr under milder conditions.

***tert*-Butyl bromide:** *tert*-Butyl alcohol (1.6 moles) is added dropwise with stirring to a cooled mixture of 48% HBr (3.2 moles) and concentrated H_2SO_4 (100 ml) at 20°. The crude bromide is separated after 30 min, washed twice with water, and dried with $CaCl_2$ and a little CaO, thus yielding 85% of *tert*-butyl bromide together with a little isobutene.[909]

Although 1,3-propanediol gives about 90% of 1,3-dibromopropane[148b] by the standard procedure with H_2SO_4 (see above), large amounts of dark brown resin are obtained from 1,4-butanediol by this process.

However, the following modification affords 83% of **1,4-dibromobutane,** b.p. 78°/10mm:[910] 1,4-Butanediol (27 g) is dropped into an ice-cold mixture of 48% HBr (138 g) and concentrated H_2SO_4 (117 g). The mixture is left for 24 h at room temperature, then heated for 3 h on a steam bath. After cooling, the crude bromide is separated in a separatory funnel.

Instead of being pre-formed, the 48% HBr may be prepared *in situ* from an alkali bromide and sulfuric acid or from bromine and SO_2. The former alternative is suitable only for C_1—C_4 alkyl bromides and for 1,3-dibromopropane;[148b] it is described in *Organic Syntheses*[148b] for *n*-butyl bromide and by Gattermann and Wieland[330] for ethyl bromide. For larger batches the HBr–H_2SO_4 mixture obtained from bromine and SO_2 (see page 121) can be used directly.[148b]

***n*-Butyl bromide:** SO_2 is led into an ice-cooled mixture of bromine (1200 g) and crushed ice (1300 g) until the red color just disappears. The product is equivalent to a mixture of 15 moles of 48% HBr and 7.5 moles of concentrated H_2SO_4. 1-Butanol (12 moles) is added, followed by more concentrated sulfuric acid (600 g) portionwise with stirring. The mixture is boiled under reflux for 3 h and then distilled (ca. 1 h). Working up is described above. The yield is 95%, and the b.p. is 101–104°.

HI can be used for replacement of alcoholic OH by I, as follows:[901,911]

General procedure: Alkyl iodides are obtained by slow distillation (1–2 drops/sec) of an alcohol (0.5 mole) and constant-boiling HI ($d = 1.7$; 1.5–2 moles). About half of the reaction mixture is distilled off, which requires 4–6 h for C_1—C_4 and 7–9 h for C_5—C_8 iodides. The crude iodide is separated from the distillate, the aqueous residue is returned to the reaction mixture, and distillation is resumed for some time. The crude iodide is washed successively with an equal volume of concentrated HCl, water, 5% sodium carbonate solution, and water, dried over $CaCl_2$, and distilled.

Heat or light causes alkyl iodides to lose iodine; this can be removed by shaking with silver powder.

Benzyl alcohol reacts rapidly and almost quantitatively with HI ($d = 1.7$) even at room temperature.[912]

If allyl alcohol (1 volume) and HI ($d = 1.7$; 6 volumes) are mixed and left at room temperature for 5 days, then separation of the crude product, washing with dilute sodium hydroxide solution and water, drying over $CaCl_2$, and distillation in a stream of nitrogen give **allyl iodide,** b.p. 101°, in 75–80% yield.[881]

α,ω-Diiodoalkanes, $I(CH_2)_nI$ where $n = 8$ or 12, are formed in about 80% yield when the diols are stirred under reflux for 6 h with a 100% excess of HI ($d = 1.94$). Cooling and dilution with water give a heavy oil which is extracted with ether, washed with water and solutions of sodium hydrogen carbonate and sodium hydrogen sulfite, dried over Na_2SO_4, recovered, and distilled in a vacuum.[913]

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[909] D. Bryce-Smith and K. E. Howlett, *J. Chem. Soc.*, **1951,** 1141.

[910] C. D. Nenitzescu and I. Necsoiu, *J. Amer. Chem. Soc.*, **72,** 3483 (1950).

[911] J. F. Norris, *Amer. Chem. J.*, **38,** 639 (1907).

[912] G. H. Daub and R. N. Castle, *J. Org. Chem.*, **19,** 1573 (1954).

[913] E. P. Taylor, *J. Chem. Soc.*, **1952,** 144.

HI may also be produced in the reaction mixture from KI and 95% phosphoric acid. This procedure gives very good yields of iodides from primary, secondary, tertiary, and polyhydric alcohols:[196]

$$\mathrm{ROH + KI + H_3PO_4 \longrightarrow RI + KH_2PO_4 + H_2O}$$

85% phosphoric acid (135 ml) and phosphorus pentoxide (65 g) are mixed and cooled, then finely powdered KI (2 moles) and last the alcohol (1 mole) are added. The mixture is heated for 3–5 h with stirring at 100–120°, then cooled, the iodide is taken up in ether, and the etheral solution is washed with thiosulfate solution and water.

Organic Syntheses[914] gives detailed directions for preparation of 1,6-diiodohexane; for the preparation and purification of octadecyl iodide see Wood.[915]

ii, Replacement of alcoholic OH by halogen by means of acid halides

Substitution of halogen for alcoholic OH can be effected, not only by using hydrogen halides, but also by means of acid halides, of which the phosphorus trihalides (PX_3) PBr_3 and PI_3 are most important for replacement of OH by Br or I, and thionyl chloride ($SOCl_2$) for replacement by Cl. PBr_3 causes less olefin formation than does HBr or $HBr–H_2SO_4$ and is thus particularly suitable for exchange reactions of secondary and tertiary alcohols. PBr_3 is introduced into a reaction mixture as such or is prepared *in situ* from red phosphorus and bromine; PI_3 is almost always produced *in situ* from red phosphorus activated by the yellow allotrope. The reaction does not occur directly in accord with the overall equation (a):

$$\mathrm{3ROH + PX_3 \longrightarrow 3RX + HPO(OH)_2} \tag{a}$$

the halogen of PX_3 is replaced stepwise by OR, and the resulting phosphorous ester is cleaved by the hydrogen halide (HX) formed (b):

$$\mathrm{3ROH + PX_3 \longrightarrow P(OR)_3 + 3HX \longrightarrow 3RX + HPO(OH)_2} \tag{b}$$

For the mechanism of substitution of halogen for OH by means of phosphorus halides see Gerrard *et al.*[916]

The fission of the phosphorous esters by hydrogen halides, which provides the alkylating action, is hindered if the HX is bound by working in ether or by adding pyridine; it is favored by an excess of the alcohol (which dissolves HX), by heating after the primary addition, and by longer reaction times. However, binding of most of the HX by ether or pyridine is often desirable in cases of sensitive alcohols.

Reaction between alcohols and thionyl chloride or bromide occurs by way of sulforous ester halides (halosulfinates) (c):

$$\mathrm{ROH + SOX_2 \longrightarrow HX + ROS(O)X \longrightarrow RX + SO_2 + HX} \tag{c}$$

For information on the mechanism the original literature[917] should be consulted. The preparation of chlorides by $SOCl_2$ with addition of pyridine[918] or

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[914] H. Stone and H. Shechter, *Org. Syn.*, **31**, 31 (1951).

[915] G. W. Wood, *J. Chem. Soc.*, **1953**, 3327.

[916] W. Gerrard and co-workers, *J. Chem. Soc.*, **1940**, 1464; **1944**, 85; **1945**, 106, 848; **1946**, 741; **1949**, 2309; **1952**, 914; **1953**, 1920, 2069; **1955**, 277.

[917] A. Stähler and E. Schirm, *Ber. Deut. Chem. Ges.*, **44**, 319 (1911); E. D. Hughes, C. K. Ingold, and co-workers, *J. Chem. Soc.*, **1937**, 1196; E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.*, **74**, 308 (1952).

[918] G. Darzens, *C. R. Hebd. Séances Acad. Sci.*, **152**, 1314 (1911).

other tertiary amine [919–921] is an important reaction; it does not lead to isomerization[922] and has been applied with success to hydroxy compounds containing groups that are sensitive to HCl; so alkoxy-[920] and alkoxyaryl-alkanols,[921] tetrahydrofurfuryl alcohol,[923] and alkynols[435,924–926] have all given the corresponding chlorides in good yield by this method.

Dichloromethyl methyl ether, CH_3OCHCl_2, which can be regarded as the ester dichloride of orthoformic acid, does not give homogeneous products from alcohols and is thus, in general, unsuitable for preparation of alkyl chlorides.[927]

The general technique for replacing alcoholic OH by Br by means of PBr_3 is illustrated by the following example:

Isobutyl bromide, $(CH_3)_2CHCH_2Br$:[928] Freshly distilled PBr_3 (2.56 moles, 244 ml) is added to dry isobutyl alcohol (7 moles) at −10°, with exclusion of water, with stirring and cooling in ice-salt, and at such a rate that the temperature remains below 0° (ca. 4 h). After removal of the cooling bath the mixture is stirred until it reaches room temperature and is then set aside overnight. A 30-cm column is then placed on the reaction vessel and the crude bromide is distilled off at ca. 50°/200 mm. The distillate is cooled to 0° and washed with concentrated H_2SO_4 (3 × 50 ml) at 0° and then shaken with dry K_2CO_3 until the odor of HBr has disappeared. It is distilled either through a 1-m column at atmospheric pressure (b.p. 91–93°) or at 135 mm through a column with a reflux ratio of 5 : 1 (b.p. 41–43°/135 mm), the yield being 55–60%.

Similarly are obtained 80% of *sec*-butyl bromide, $CH_3—CHBr—C_2H_5$, 95% of *n*-propyl bromide, and 68% of isopropyl bromide. Cyclopentyl bromide is also accessible by this route.[884]

PBr_3, b.p. 171–173°, is obtained by adding bromine to a stirred suspension of red phosphorus in CCl_4. An efficient fractionating column must be used when distilling the PBr_3 produced.[928,929]

The conditions for treatment of alcohols with PBr_3, and the working up, may be widely varied:

The alcohol may be diluted with benzene, light petroleum, ether, or CCl_4. Although it is not generally necessary, pyridine may be added to unsaturated alcohols or to alcohols containing ether linkages since these can undergo side reactions with the HBr formed.

Tetrahydrofurfuryl bromide, for instance, is obtained by dropping tetrahydrofurfuryl alcohol (1 mole) and dry pyridine (5 g) into PBr_3 (0.36 mole), dry pyridine (15 g), and dry benzene (50 ml) at −5° (ice-salt cooling) and allowing reaction to proceed for 24–48 h at room temperature.[930]

According to a procedure detailed in *Organic Syntheses*,[931] 2-ethoxyethyl bromide is obtained from 2-ethoxyethyl alcohol and PBr_3 without addition of pyridine, the temperature being raised gradually to the boiling point, but appreciable amounts of ethyl bromide are also formed.

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[919] A. Cohen, *J. Chem. Soc.*, **1935**, 429.

[920] D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, **1950**, 406.

[921] H. Rapoport and J. E. Campion, *J. Amer. Chem. Soc.*, **73**, 2239 (1951).

[922] J. Cason and J. S. Correia, *J. Org. Chem.*, **26**, 3645 (1961).

[923] L. A. Brooks and H. R. Snyder, *Org. Syn.*, **25**, 84 (1945); Coll. Vol. III, 698 (1955).

[924] M. S. Newman and J. H. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1292 (1949).

[925] M. G. Ettlinger and J. E. Hodgkins, *J. Amer. Chem. Soc.*, **77**, 1835 (1955).

[926] J. Colonge and G. Poilane, *Bull. Soc. Chim. France*, [v], **1955**, 499.

[927] A. Rieche and H. Gross, *Chem. Ber.*, **92**, 83 (1959).

[928] C. R. Noller and R. Dinsmore, *Org. Syn.*, Coll. Vol. II, 358 (1943).

[929] J. F. Gay and R. N. Maxson, *Inorg. Syn.*, **2**, 147 (1946).

[930] L. H. Smith, *Org. Syn.*, **23**, 88 (1943); Coll. Vol. III, 793 (1955).

[931] G. C. Harrison and H. Diehl, *Org. Syn.*, **23**, 32 (1943); Coll. Vol. III, 370 (1955).

Propargyl bromide, b.p. 84°, is obtained in 59% yield as follows:[435] PBr_3 (378 g) containing a little (2 ml) pyridine is dropped, with stirring, into a mixture of anhydrous propargyl alcohol (224 g) and anhydrous pyridine (48 g) at 0°, then the mixture is heated for an hour on a water-bath. The propargyl bromide is distilled off onto dry K_2CO_3 and after some time is redistilled therefrom.

Walden inversion usually occurs when an optically active alcohol is treated with PBr_3. To afford the bromide with as great optical purity as possible the alcohol should be present in continuous excess; for instance, only 0.2 mole of PBr_3 per mole of ROH should be added, slowly, at a low temperature (cooling in Dry Ice).[932,933]

Very mild conditions are also recommended for replacement of secondary or tertiary OH groups by Br when PBr_3 is used. If PBr_3 is added at not more than $-15°$, the temperature allowed to rise to 20° during 2 days, and the mixture left at room temperature for complete reaction, then 2,4-dibromo-2-methylpentane and 2,4-dibromo-3-methylhexane are produced in 90% yield from the corresponding alcohols.[934]

In other cases warming is required to complete reaction. In this process, as well as when distilling the crude bromide from the reaction mixture, the temperature must be raised slowly so as to avoid formation of phosphorus hydrides which may inflame spontaneously. In the preparation of pentaerythritol tetrabromide, $C(CH_2Br)_4$, from pentaerythritol and PBr_3 as described in *Organic Syntheses*[935] the reaction is completed by heating in an oil-bath at 170–180° for 20 h.

As a variation from the general procedure the reaction mixture may be poured into ice-water, and the crude bromide separated, extracted with light petroleum or ether, washed with water or 5% sodium carbonate solution, and dried over $CaCl_2$. It may also be possible, *e.g.*, with cyclopentyl bromide,[936] to add water after completion of the reaction and to distil out the bromide in steam.

Further, it is possible to produce the PBr_3 in the reaction mixture from red phosphorus and bromine, but care must be taken to avoid the bromine coming into contact with dry red phosphorus. The alcohol is first mixed thoroughly with red phosphorus (1 mole), then bromine (about 2 moles) is added with vigorous stirring at such a rate that the temperature amounts to 80–100°. This technique is described in *Organic Syntheses*[937] for the preparation of 1,3-dibromo-2-propanol from glycerol.

When the OH group of 3-pentanol is replaced by Br in the one-stage process partial rearrangement is always to be expected,[922] but there is no isomerization when 2-butanol reacts with PBr_3.[938] The best method of product analysis is gas chromatography on polypropylene glycol; the pure secondary bromides are afforded by degradation of the silver salts of the corresponding carboxylic

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[932] H. Brauns, *Rec. Trav. Chim.*, **65**, 799 (1946).

[933] A. Streitwieser Jr., *J. Amer. Chem. Soc.*, **75**, 5014 (1953).

[934] J. D. Bartleson and co-workers, *J. Amer. Chem. Soc.*, **68**, 2516 (1946).

[935] H. B. Schurink, *Org. Syn.*, Coll. Vol. II, 476 (1943).

[936] C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, **48**, 1084 (1926).

[937] G. Braun, *Org. Syn.*, Coll. Vol. II, 308 (1943).

[938] A. T. Shulgin, *J. Amer. Chem. Soc.*, **77**, 2338 (1955); P. S. Skell, R. G. Allen, and G. H. Helmkamp, *J. Amer. Chem. Soc.*, **82**, 410 (1960).

acids by bromine[939] or by treatment of the corresponding *p*-toluenesulfonates with NaBr in dimethylformamide or dimethyl sulfoxide.[922]

Although PBr_3 is usually pre-formed when used to replace an alcoholic OH group by Br, PI_3 is usually produced in the reaction mixture from phosphorus and iodine.

The normal technique for substituting I for alcoholic OH by means of phosphorus and iodine is as follows: 1.5 moles of iodine and 1–1.2 moles of phosphorus are used per 3 moles of dry alcohol. The exothermic reaction is usually achieved when red phosphorus is used that has been repeatedly boiled out with water (until acid-free) and then dried at 100°; adding about 50% of its weight of yellow phosphorus accelerates the reaction, but yellow phosphorus must not be permitted to come into direct contact with iodine. When yellow phosphorus is added, a special apparatus described below is used and care must be taken that during the working up any residual phosphorus is always covered by the reaction mixture or by water to avoid contact with air.

The alcohol is first thoroughly mixed with red phosphorus, and finely powdered iodine is added in small portions, with stirring and, when necessary, occasional cooling. The reaction is allowed to proceed for some hours at room temperature and finally for 2 h at the boiling point. The preparation of ethyl iodide[33b] may be cited as example. Volatile iodides are distilled directly out of the reaction mixture; mixtures containing high-boiling iodides are poured into ice-water and filtered from unchanged phosphorus, then the iodide is extracted with ether, shaken with thiosulfate solution, 5% sodium carbonate solution, and water, dried over $CaCl_2$, freed from ether, and distilled in a vacuum.

Secondary and tertiary alcohols are allowed to react for about 8 hours at 0–5° and then further at room temperature, but for preparation of primary iodides the mixtures must be heated finally for several hours at temperatures above 100°, as detailed in *Organic Syntheses*[940] for the preparation of hexadecyl iodide from cetyl alcohol.

When yellow phosphorus is added and for larger batches the alcohol–phosphorus mixture is treated with a solution of iodine in the same alcohol until iodine is no longer consumed.

A vessel (*e.g.*, a dropping funnel), fitted with a three-way tap, is sealed to a not too narrow, descending glass tube that is attached to a reaction flask. A reflux condenser is placed above the iodine container. The reaction flask, which contains the alcohol and phosphorus, is heated; alcohol vapor passes through the glass tube into the condenser and falls back on to the iodine which it gradually dissolves out of its container. A layer of glass wool is placed under the iodine to prevent blockage of the three-way tap. The rate of reaction can be controlled by adjusting the tap. This apparatus, described by Vogel,[886,941] operates well also for experiments with red phosphorus only. When the iodine in the container has all been consumed, volatile iodides can be distilled into that container after the tap has been closed. Similar apparatus has been described previously.[942,943]

Thionyl chloride ($SOCl_2$) is a completely general reagent for replacing an OH group in alcohols or hydroxy carboxylic esters by chlorine. It is of especial value when replacement of OH by means of HCl, leads to undesirable side reactions (isomerization, addition of HCl, or fission of ethers); in such cases one of the various modifications of Darzens' procedure[918] can be used, according to which 2–3 moles of $SOCl_2$ are dropped into 2 moles of the alcohol

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[939] J. Cason and R. H. Mills, *J. Amer. Chem. Soc.*, **73**, 1354 (1951).

[940] W. W. Hartman, J. R. Byers, and J. B. Dickey, *Org. Syn.*, Coll. Vol. II, 311 (1943).

[941] A. I. Vogel, Brit. Pat. 565,452 (1944); *Chem. Abstr.*, **40**, 5066 (1946).

[942] R. Adams and V. Voorhees, *J. Amer. Chem. Soc.*, **41**, 797 (1919).

[943] H. S. King, *Org. Syn.*, Coll. Vol. II, 399 (1943).

and 2–3 moles of pyridine cooled in ice or ice–salt; 1–1.1 moles of pyridine and 1.1 moles of $SOCl_2$ are usually used per mole of alkynol or alkoxyalkanol, or 1.3–1.4 moles of $SOCl_2$ for alkanols that are in danger of isomerization by HCl. A larger excess of $SOCl_2$ (2 moles of $SOCl_2$ per mole of OH) is sometimes recommended for *n*-alkyl chlorides, and even 4 moles of $SOCl_2$ — without pyridine — for higher alkyl chlorides such as undecyl and dodecyl chloride.[901] The alcohols may be diluted with benzene,[944] $CHCl_3$,[921] or ether;[435,924,925] and for alkoxyalkanols dimethylaniline[919-921] or quinoline[920] may replace pyridine. The $SOCl_2$ used should be purified (see below) or freshly distilled.

1-Chloropentane:[865] $SOCl_2$ (6.5 moles) is dropped into a mixture of 1-pentanol (5 moles) and dry pyridine (5 moles) at −10°. The mixture is warmed to 104° during 6 h and kept at 104° for 90 min. Evolution of SO_2 begins at about 70°. The crude product is cooled, washed with dilute HCl, dried over K_2CO_3, and distilled, giving an 80% yield of material boiling at 106–106.5°/741 mm.

1-Chloro-2-heptyne:[924] When a solution of the alkynol (1 mole) and dry pyridine (1 mole) in dry ether (100 ml) is dropped into a stirred solution of $SOCl_2$ (1.1 moles) in dry ether (100 ml) the exothermic reaction keeps the mixture at the boiling point. When the reaction ceases, ether is distilled off until the internal temperature reaches 80° (about 150 ml), then further $SOCl_2$ (13 g) is added and the whole is boiled and stirred for a further hour. Cold water (500 ml) is added and the ethereal layer is separated, washed with sodium carbonate solution, dried over $CaCl_2$, and evaporated. The chloroheptyne (77% yield), when rapidly distilled in a vacuum, has b.p. 73°/24 mm.

2-Ethoxyethyl chloride (2-chloroethyl ethyl ether):[920] A mixture of a dry base (1 mole) and 2-ethoxyethanol (1 mole) is cooled to −20° and $SOCl_2$ (1.1 mole) is added, with stirring, at such a rate that the temperature does not exceed 0°. The mixture is allowed to come to room temperature and then kept at 100° for 2 h. The product is cooled and treated with dilute HCl, and the ethoxyethyl chloride is taken up in ether, washed with dilute NaOH solution and with water, and dried over Na_2SO_4. Yields are 61% (with dimethylaniline), 80% (with pyridine), and 84% (with quinoline).

2-Chloro-2-phenylacetic acid:[945] Ethyl mandelate (0.75 mole; from mandelic acid and ethanol–HCl) is dissolved in $SOCl_2$ (0.82 mole), and the solution is set aside at room temperature for 16 h, heated on a water-bath for 30 min, and poured into ice-water. The ethyl 2-chloro-2-phenylacetate formed (81–85% yield) is extracted with ether and, after isolation, is hydrolysed by a boiling mixture of glacial acetic acid and concentrated hydrochloric acid.

Methyl 2-chloro-2-phenylacetate is obtained in poorer yield by adding $POCl_3$ (11.5 g) portionwise to methyl mandelate (12.5 g) and pyridine (12 g) cooled in ice–salt, and further reaction for 1 h in the cooling mixture and for 12 h at room temperature.[946]

α-Chlorodeoxybenzoin, $C_6H_5CHClCOC_6H_5$: The preparation from benzoin (0.47 mole), pyridine (0.63 mole), and $SOCl_2$ (0.63 mole) is detailed in *Organic Syntheses*.[947]

Purification of thionyl chloride: A method often used is to boil technical $SOCl_2$ with about 10% of linseed oil and then to distil it through a column. Distillation with quinoline has also been recommended[948] for removal of impurities such as SO_3 and H_2SO_4, but a warning has been given[949] against using dimethylaniline. For instance, 50 g of $SOCl_2$ may be distilled from 10 ml of quinoline and then from 20 ml of linseed oil.[950] The following simple process is very useful:[951] Crude $SOCl_2$ (900 ml) and flowers of sulfur (25 g) are boiled together under reflux for 4.5 h; rapid distillation through a column then gives 94% of a colored product (sulfur monochloride, b.p. 135.6°, remains in the flask); this product is then redistilled through a column in such a way that it gives a colored forerun (sulfur dichloride, b.p. 69°; etc.) in 12 h and then almost colorless $SOCl_2$ (88%), b.p. 78.8°, in about 2 h.

Disulfur dichloride may be removed by distillation from red phosphorus.[1h]

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[944] C. Barkovsky, *Ann. Chim.*, **19**, 487 (1944).

[945] E. L. Eliel, M. T. Fisk, and T. Prosser, *Org. Syn.*, **36**, 3 (1956).

[946] T. Wagner-Jauregg, *Helv. Chim. Acta*, **12**, 63 (1929).

[947] A. M. Ward, *Org. Syn.*, Coll. Vol. II, 159 (1943).

[948] H. Meyer and K. Schlegel, *Monatsh. Chem.*, **34**, 569 (1913).

[949] E. Besthorn, *Ber. Deut. Chem. Ges.*, **42**, 2697 (1909).

[950] E. L. Martin and L. F. Fieser, *Org. Syn.*, Coll. Vol. II, 569 (1943).

[951] D. L. Cottle, *J. Amer. Chem. Soc.*, **68**, 1380 (1946).

$SOCl_2$ can also be used to replace OH of amino alkanols by Cl in good yield, best after dilution with $CHCl_3$ or benzene. The amino alcohols themselves may be treated with $SOCl_2$ but it is better to use their hydrochlorides.

For the preparation of bis-(2-chloroethylamine) hydrochloride,[952] for example, crude diethanolamine hydrochloride (2 moles) is allowed to react with $SOCl_2$ (5.33 moles, 388 ml) and benzene (400 ml) at about 30°.

Valuable alcohols can also be converted into the corresponding bromides by $SOBr_2$ and pyridine. Admittedly, $SOBr_2$ is not readily obtainable.

$SOBr_2$, b.p. 60°/40 mm, 45°/22 mm, is obtained by the action of either dry HBr at 0° [58,953] or of KBr[954] on liquid SO_2. It decomposes slowly at room temperature and more rapidly at 100°.

$$4SOBr_2 \longrightarrow 2SO_2 + S_2Br_2 + 3Br_2$$

$SOBr_2$ (1.3 moles) is dropped, with stirring, into a mixture of an alcohol (1 mole) and pyridine (1.1 moles) at $-10°$ to 0°, then the mixture is allowed to come slowly to room temperature and finally heated until reaction ceases. Thus are obtained, for example, about 40% of **2-, 3-,** and **4-bromooctane.**[955]

A rapid method of preparing alkyl chlorides from alcohols on a laboratory scale consists in reaction with benzoyl chloride in the presence of dimethylformamide. During the exothermic reaction lower alkyl chlorides distil off spontaneously and can be purified by subsequent fractionation.

Methyl chloride:[956] Methanol (32 g, 40.5 ml) is added during 30 min to a stirred mixture of benzoyl chloride (140.6 g), dimethylformamide (18 g) and pyridine (1 g) at 20–25°. Methyl chloride (17.8 l, 81%) is evolved in a steady stream.

c. Replacement of alcoholic OH by halogen by means of triphenyl phosphite and organic halides or halogen

In a process (a) introduced by Landauer and Rydon[957] alkyl halides are produced by heating equimolar amounts of triphenylphosphite, an alcohol, and a substance R'X where X = Cl, Br, or I; R' may be arylalkyl, alkyl, H, X (*e.g.*, Br_2) and Li, Na, or NH_4;

$$(C_6H_5)_3P + ROH + R'X \longrightarrow RX + R'PO(OC_6H_5)_2 + C_6H_5OH \qquad (a)$$

If R' = arylalkyl or alkyl, then R'X must be more reactive than RX unless RX can be removed continuously from the reaction mixture. The triphenyl phosphite method gives first a quasi-phosphonium compound (A), which is then transesterified (b):

$$\underset{(A)}{(C_6H_5O)_3PR'X} + ROH \longrightarrow (C_6H_5O)_2(RO)PR'X + C_6H_5OH \qquad (b)$$

$$(C_6H_5O)_2(RO)PR'X \longrightarrow (C_6H_5O)_2P(\text{—}O)R' + RX \qquad (c)$$

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[952] K. Ward Jr., *J. Amer. Chem. Soc.*, **57**, 914 (1935).

[953] H. Hibbert and J. C. Pullmann, *Inorg. Syn.*, **1**, 113 (1939).

[954] M. J. Frazer and W. Gerrard, *Chem. & Ind.* (*London*), **1954**, 280; *Angew. Chem.*, **67**, 42 (1955).

[955] F. Asinger, G. Geiseler, and M. Hoppe, *Chem. Ber.*, **90**, 117 (1957).

[956] R. Ohme, personal communication.

[957] S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, **1953**, 2224.

Formation of the desired alkyl halide then follows, this being analogous to the second stage of the Arbusov reaction (d):

$$(RO)_3P + R'X \xrightarrow[\text{stage}]{\text{1st}} (RO)_3PR'X \xrightarrow[\text{stage}]{\text{2nd}} (RO)_2P(\rightarrow O)R' + RX \qquad (d)$$

The reaction is particularly advantageous for preparation of alkyl bromides and iodides from sterically hindered or unsaturated alcohols. For preparative purpose it is especially useful when R'X is benzyl bromide, methyl iodide, bromine (Br_2), or iodine (I_2), but use of benzyl chloride and chlorine (Cl_2) is also significant; R' can usefully be H only when R'X is HCl. When the alcohol is sensitive to heat, the quasi-phosphonium compound should be prepared first and then allowed to react with the alcohol. Also, for use with unsaturated alcohols in cases when R'X is Cl_2, Br_2, or I_2 the crude $(C_6H_5O)_3PX_2$ should be prepared as a separate stage. In general, however, the three reactants can be allowed to react together, as in (a).

Methyltriphenoxyphosphonium iodide:[957] Triphenyl phosphite (31 g) and methyl iodide (21 g) are heated for 36 h under reflux (exclusion of water!); the temperature of the boiling mixture rises from 70° to 115°. Addition of dry ether after cooling gives yellowish-brown needles; these are repeatedly washed with dry ether and dried over phosphorus pentoxide (42 g, 94%). For the following reactions, which must be carried out with careful exclusion of water, it is best to use a crude product that has been stored under dry ether. The iodide can, however, be purified by rapid dissolution in dry acetone and precipitation by dry ether, then having m.p. 146°.

General procedure for preparation of **alkyl iodides** from $(C_6H_5O)_3PCH_3I$:[957] The appropriate alcohol (1 mole) is added cautiously to the crude iodide (1 mole); cooling is necessary for reactive alcohols. The method of working up is suited to the properties of the alkyl iodide: (a) if the iodide boils lower than the phenol it can be distilled out directly in a vacuum; (b) the phenol and alkyl iodide are distilled off together, the distillate is diluted with ether, and the phenol is extracted with dilute, ice-cold NaOH solution; (c) the reaction mixture is diluted with ether, the phenol is washed out with ice-cold, dilute NaOH solution, and water, and the ethereal solution is dried and distilled.

Direct preparation of an alkyl iodide by reaction (a): **neopentyl iodide,** $(CH_3)_3CCH_2I$:[957,958] Methyl iodide (1.4 moles), triphenyl phosphite (1 mole), and neopentyl alcohol (1 mole) are heated in a bath for 24 h, whereby, owing to continuing consumption of methyl iodide, the internal temperature rises from 75° to 130°. The crude iodide and the phenol are distilled off in a vacuum and the distillate is washed with ice-cold, dilute NaOH solution, and water until free from phenol. The product contains about 6% of *tert*-pentyl iodide,[958] to remove which it is shaken for 5 h with three times its volume of water which is then discarded. The organic layer is next shaken with its own volume of 0.1N-aqueous $AgNO_3$, washed with water, dried, and fractionated. This gives a 53–57% yield of iodide of b.p. 71°/100 mm.

For numerous other examples see Rydon and his co-workers.[957,959]

Preparation of $(C_6H_5O)_3PX_2$ and its direct reaction with alcohols:[960] Triphenyl phosphite, b.p. 209–210°/1 mm, is prepared by warming PCl_3 (1 mole) with phenol (3 moles) until no more HCl is evolved and distilling the product in a vacuum.[961] Halogen (X_2) is then added with careful exclusion of moisture, stirring, and cooling. The alcohol (1 mole) is dropped into the crude $(C_6H_5O)_3PX_2$ thus formed, with stirring at room temperature, and cooling if necessary. The alkyl halide is then usually separated by vacuum distillation. Yields are 60 to 98% for saturated alcohols, 75% for allyl bromide.

Direct reaction of triphenyl phosphite, alcohol, and halogen (X_2):[960] The halogen (X_2) is added gradually to an equimolar mixture of triphenyl phosphite and an alcohol at 0°. After reaction for some time at room temperature, the alkyl halide is isolated, *e.g.*, by direct

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[958] N. Kornblum and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6653 (1955).

[959] A. Campbell and H. N. Rydon, *J. Chem. Soc.*, **1953**, 3004.

[960] D. G. Coe, S. R. Landauer, and H. N. Rydon, *J. Chem. Soc.*, **1954**, 2281.

[961] H. B. Gottlieb, *J. Amer. Chem. Soc.*, **54**, 749 (1932).

distillation under reduced pressure. For saturated alkyl halides yields amount to 62–92%; this method cannot be used with unsaturated alcohols.

d. Replacement of alcoholic OH by halogen by way of *p*-toluenesulfonates

In some of the above-mentioned methods for replacement of alcoholic OH by halogen the alcohol was converted into an intermediate sulfinate or phosphite which was then subjected to alkylating cleavage, isolation of the intermediate being usually unnecessary. In the *p*-toluenesulfonate procedure, however, the toluenesulfonic ester of the alcohol is first isolated and then treated with an alkali or alkaline-earth halide MX. This reaction has particular significance for preparation of alkyl fluorides and iododeoxy sugars, and for OH–halogen exchange of compounds that can undergo rearrangement of the carbon skeleton (Wagner–Meerwein rearrangement) or allylic rearrangement.

$$p\text{-}CH_3C_6H_4SO_2Cl + HOR \longrightarrow p\text{-}CH_3C_6H_4SO_2OR + HCl$$

$$p\text{-}CH_3C_6H_4SO_2OR + MX \longrightarrow p\text{-}CH_3C_6H_4SO_2OM + RX$$

Preparation of *p*-toluenesulfonic esters:[962] *p*-Toluenesulfonyl chloride (1.1 moles per mole of alcohol) is added to the alcohol (10 g) in dry pyridine (100 ml), cooled to −5° in an ice–salt bath. The mixture is shaken in an ice-bath until the sulfonyl chloride is dissolved, and then at 0° for a further 2 h. It is then treated with portions (1, 1, 1, 2, and 5 ml) of water at not more than 5°, each addition being spread over 5 min. Then a further 100 ml of water are added. If the toluenesulfonate crystallizes, it is filtered off; if not, it is extracted with $CHCl_3$ or ether. The extracts are washed with ice-cold, dilute H_2SO_4, water, and $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvent the crude ester is often treated directly with the salt MX.

p-Toluenesulfonates of lower alcohols, which often react rapidly with pyridine at 0°, are prepared at lower temperatures.[963]

The following method of converting *p*-toluenesulfonates into alkyl fluorides is suitable for preparation of primary, secondary, and halogen-substituted alkyl fluorides.[963]

Alkyl fluorides by way of *p*-toluenesulfonates:[963] The *p*-toluenesulfonate (1 mole) is heated, with stirring, with KF (5 moles) in diethylene glycol (b.p. 245°), usually under reduced pressure (20–500 mm); the alkyl fluoride, most of which is evolved in the first 2 h, is trapped in suitable cold receivers. The weight of diethylene glycol used is the same as that of the KF. Temperatures used are 70–240°, with reaction times of 3–9 h. Cyclohexyl *p*-toluenesulfonate gives cyclohexene; phenyl *p*-toluenesulfonate does not react.

Alkyl fluorides can be obtained similarly from benzene-[964] or methane-sulfonic esters.[965]

For replacement of alcoholic OH by Br it is advisable to use the *p*-toluenesulfonate method when other methods lead to isomerization. Secondary alcohols do not suffer rearrangement of the carbon skeleton when Br is substituted for their OH group by the *p*-toluenesulfonate method;[867] this is the only way to obtain pure 2- or 3-bromopentane.[866] [1-^{14}C]Allylalcohol yields only [1-^{14}C]allyl bromide by the toluenesulfonate method,[966] *i.e.*, there is no allylic rearrangement.

Although $SOCl_2$–pyridine or PBr_3 converts α,β-acetylenic alcohols in dry ether into the corresponding halides in good yield,[924] satisfactory yields of

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[962] R. S. Tipson, *J. Org. Chem.*, **9**, 238 (1944).

[963] W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.*, **77**, 4899 (1955).

[964] V. V. Razumovskii and A. E. Fridenberg, *Zh. Obshch. Khim.*, **19**, 92 (1949); *Chem. Abstr.*, **43**, 6154 (1949).

[965] F. I. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956).

[966] R. F. Nystrom and J. C. Leak, *J. Amer. Chem. Soc.*, **75**, 3039 (1953).

the chloride, bromide, or iodide are obtained from β,γ- or γ,δ-acetylenic alcohols only when the *p*-toluenesulfonate is treated with LiCl in 2-ethoxyethanol, with dry $CaBr_2$ in 2-(2-ethoxyethoxy)ethanol, or with NaI in acetone; the first two of these reactions are exothermic; the products are distilled off continuously, sometimes under somewhat reduced pressure.[967]

$CaCl_2$ or LiCl in acetone[968] or LiBr in acetone can also be used to replace the tosyloxy group by Cl or Br. Anhydrous $CaBr_2$ (prepared from $CaCO_3 + 2HBr$ and dried finally at 600° for 2 h) is soluble in absolute ethanol and converts 2-butynylene bis-(*p*-toluenesulfonate) therein into 1,4-dibromo-2-butyne in 90% yield.[969]

Pentaerythritol tetrabromide, 1,3-dibromo-2,2-bis(bromomethyl)propane, $C(CH_2Br)_4$:[970] According to a detailed description in *Organic Syntheses*, stirring the benzenesulfonate from about 1 mole of pentaerythritol with 5.8 moles of NaBr in 1 l of diethylene glycol at 140–150° for about 12 h gives the tetrabromide in a yield amounting to 68–78% after recrystallization from acetone. The *p*-toluenesulfonate may be similarly treated with NaBr (20% excess) in diethylene glycol.[971]

Particularly good yields in the replacement of a tosyloxy group by Br by means of NaBr are obtained by working in dimethylformamide or dimethyl sulfoxide.

3-Bromopentane:[922] NaBr (5.1 g, 0.05 mole) is dissolved by shaking in dimethylformamide (100 ml) that has been purified by shaking with KOH and then with CaO and distilled (b.p. 151.0–151.3°). 1-Ethylpropyl *p*-toluenesulfonate (12 g, 0.05 mole; crude product; see page 229) is added and the mixture is set aside for 85 h with exclusion of moisture, then diluted with water (500 ml) and extracted with ether (2 × 100 ml). When dried over K_2CO_3 and fractionally distilled, the ethereal extracts give chromatographically pure 3-bromopentane (4.8 g, 63%), b.p. 117.8–118.8°, n_D^{20} 1.4448.

1-Ethylpropyl *p*-toluenesulfonate (9.7 g, 0.04 mole) is added to a mixture of dimethyl sulfoxide (65 ml) and NaBr (0.05 mole; not all dissolves) and the whole is shaken for 90 h. (In the original paper[922] it is recommended that commercial dimethyl sulfoxide be left in a refrigerator until a quarter of it has crystallized and that the supernatant liquid be decanted; for dimethyl sulfoxide of good quality 3-hours' heating with calcium hydride, followed by distillation at 18 mm, is advised;[972,973] for further literature on the purification of dimethyl sulfoxide see Martin *et al.*[974]). The mixture is filtered, the filtrate is washed with ether (3 × 40 ml), and the ether extracts are washed with ice-cold 10% sulfuric acid (3 × 30 ml), dried over K_2CO_3, and fractionally distilled, giving pure 3-bromopentane (4.9 g).

2-Bromopentane (73%) and 2- (52%) and 3-bromooctane (50%) are obtained similarly.

The *p*-toluenesulfonate is used for replacement of alcoholic OH by iodine as for halogen exchange, usually with NaI in acetone, the reactivity of the toluenesulfonate corresponding approximately to that of the chloride.[975] *p*-Toluenesulfonates of primary alcohols usually react more readily than those of secondary alcohols.

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[967] G. Eglington and M. C. Whiting, *J. Chem. Soc.*, **1950**, 3650.

[968] P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.*, **71**, 3209 (1949).

[969] W. J. Gensler and A. P. Mahadevan, *J. Amer. Chem. Soc.*, **78**, 168 (1956).

[970] H. L. Herzog, *Org. Syn.*, **31**, 82 (1951).

[971] E. R. Buchman, D. H. Deutsch, and G. I. Fujimoto, *J. Amer. Chem. Soc.*, **75**, 6228 (1953).

[972] J. J. Bloomfield, *J. Org. Chem.*, **27**, 2742 (1962).

[973] C. C. Price and D. D. Carmelite, *J. Amer. Chem. Soc.*, **88**, 4039 (1966).

[974] D. Martin, A. Weise, and H.-J. Niclas, *Angew. Chem. Int. Ed Engl.*, **6**, 318 (1967).

[975] R. S. Tipson, M. A. Clapp, and L. H. Cretcher, *J. Org. Chem.*, **12**, 133 (1947).

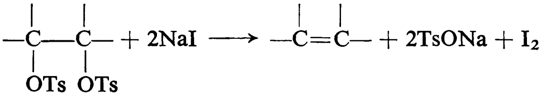
This reaction is often used for determination of structure in the sugar series ("Oldham–Rutherford rule" [976]). It was observed that, when treated with NaI in acetone for 2 hours in a bomb-tube at 100°, completely tosylated methyl β-D-glucoside undergoes exchange only at C-6, and that no exchange occurs with sugars having tosyloxy groups on C-2, C-3, C-4, or C-5; thence it was concluded that under the stated conditions tosylated primary OH is replaced by I whereas tosylated secondary OH is not so replaced. However, there are numerous exceptions to this rule. Thus there are 1,6-ditosylated sugar alcohols in which both primary tosyloxy groups can be replaced by I if, but only if, the standard reaction time is extended to 5 hours,[977] whilst there are others in which only one of two primary tosyloxy groups is replaced by I in 2 hours at 100° [978,979] although in the latter case the double replacement may be effected in good yield by reaction in acetic anhydride.

1,6-Dideoxy-1,6-diiodo-2,4:3,5-bismethylene-D-sorbitol:[979] A mixture of 2,4:3,5-bismethylene-D-sorbitol bis-(*p*-toluenesulfonate) (4.0 g), NaI (3.4 g), and acetic anhydride (40 ml) is boiled under reflux for 2 h and then decomposed with ice-water. The diiodide gradually crystallizes, in 91% yield; after recrystallization from alcohol it melts at 151–152°.

On the other hand, the action of NaI in acetone at 100° may also substitute I in place of tosylated secondary OH groups in some sugar alcohols[980] and in other alcohols, *e.g.*, 3-pentanol,[975] 2-propanol, and 1,3-butanediol;[981] in the last two cases it suffices to use concentrated aqueous KI.

The reactivity of a *p*-toluenesulfonate depends greatly on steric factors. The monoester of *trans*-1,2-cyclohexanediol reacts appreciably faster than the *cis*-compound with NaI or LiCl.[982] Tosylated OH groups directly attached to a multiply substituted ring are especially reactive. For further details and a critical appreciation of results to date see Matheson and Angyal.[783]

Neighboring tosyloxy groups, particularly if terminal, are not replaced by iodine but afford unsaturated compounds and iodine. For numerous references to earlier observations and for the mechanism of this reaction see Forster and Overend.[984]



$$-\underset{\mathrm{OTs}}{\overset{|}{\underset{|}{C}}}-\underset{\mathrm{OTs}}{\overset{|}{\underset{|}{C}}}- + 2\mathrm{NaI} \longrightarrow -\overset{|}{C}=\overset{|}{C}- + 2\mathrm{TsONa} + \mathrm{I_2}$$

$$\mathrm{Ts} = p\text{—}\mathrm{CH_3C_6H_4SO_2}\text{—}$$

For the preparation of iodo steroids by way of the *p*-toluenesulfonates and methanesulfonates (CH_3SO_2OR) see, *inter al.*, Borrevang[985] and Tannhauser *et al.*[786]

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[976] J. W. H. Oldham and J. K. Rutherford, *J. Amer. Chem. Soc.*, **54**, 306 (1932).

[977] L. Vargha and T. Puskas, *Ber. Deut. Chem. Ges.*, **76**, 861 (1943).

[978] A. T. Ness, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, **66**, 1901 (1944).

[979] R. M. Hann, J. K. Wolfe, and C. S. Hudson, *J. Amer. Chem. Soc.*, **66**, 1900 (1944).

[980] R. C. Hockett and co-workers, *J. Amer. Chem. Soc.*, **68**, 927 (1946).

[981] F. Drahowzal and D. Klamann, *Monatsh. Chem.*, **82**, 970 (1951).

[982] M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, **1949**, 315.

[983] N. K. Matheson and S. J. Angyal, *J. Chem. Soc.*, **1952**, 1133.

[984] A. B. Foster and W. G. Overend, *J. Chem. Soc.*, **1951**, 3452.

[985] P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955).

General procedure for conversion of *p*-toluenesulfonates into iodides: The ester (1 mole) and dry NaI (1.2 moles) are heated in dry acetone at 100° for 2–5 h in a pressure flask or a bomb-tube. Reactive *p*-toluenesulfonates also react in ethyl methyl ketone, acetonylacetone, or diethylene glycol; those of lower primary alcohols react even at room temperature. Occurrence of reaction is recognized by precipitation of sodium *p*-toluenesulfonate; this is eventually filtered off and washed with acetone. After removal of the solvent, water is added and the iodide is taken up in ether and washed therein with thiosulfate solution and with water.

Lower alkyl iodides are obtained by treating the *p*-toluenesulfonates with concentrated aqueous potassium iodide (0.2 mole of KI in 10 ml of water) and are distilled off through a column continuously during the reaction. The aryl ester does not react with NaI in acetone. Although neopentyl iodide can be obtained from the *p*-toluenesulfonate and NaI,[986] it is recommended[987] that neopentyl bromide (86% yield) and chloride (60% yield) should be prepared by way of triethylneopentyloxysilane:

$$(CH_3)_3C—CH_2OH + ClSi(C_2H_5)_3 \xrightarrow[\text{Benzene}]{\text{Quinoline}} (CH_3)_3C—CH_2OSi(C_2H_5)_3$$

$$\xrightarrow[(SOCl_2)]{PBr_3} (Cl)BrSi(C_2H_5)_3 + (CH_3)_3—CH_2Br(Cl)$$

2. Replacement of OH by halogen in hemiacetals: Henry synthesis of α-halo ethers

The method most often used for preparation of alkyl 1-haloalkyl ethers (cf. also page 169) is the Henry reaction (a): dry HCl is led into a well cooled equimolar mixture of

$$R'CHO + ROH + HCl \rightleftarrows R'CHClOR + H_2O \quad \ldots \text{(a)}$$

an aldehyde and an alcohol. This synthesis can be considered formally as substitution of halogen for OH in a hemiacetal. Experiments with [^{18}O]acetaldehyde make this reaction mechanism very probable, as the oxygen of the aldehyde is split off whilst the C–O bond of the alcohol remains intact (b):[988]

$$CH_3CH(OC_2H_5)^{18}OH \xrightarrow{HCl} CH_3OH(OC_2H_5)Cl + H_2{}^{18}O \quad \ldots \text{(b)}$$

The principal by-products formed, particularly when cooling is insufficient, are acetals (which are sometimes difficult to separate) and maybe dark tars that result from loss of HCl and polymerization. The HCl should be led in slowly so as to avoid a mixing of the two liquid layers formed which leads to discolored products. If the two phases have approximately the same density, mixing and formation of emulsions can be prevented by adding water-binding salts.

Good yields are also obtained when aldehyde–alcohol mixtures are treated with thionyl chloride instead of with HCl.[989]

Ethyl α-chlorophenethyl ether, $C_6H_5CH_2CHClOC_2H_5$:[990] Dry HCl (11.5 g) is led rapidly, with stirring, into an ice-cold mixture of phenylacetaldehyde (32.5 g), ethanol (12.5 g), and anhydrous Na_2SO_4 (30 g). The liquid product is decanted, $CaCl_2$ (16 g) is added and the mixture is kept at 20 mm for 45 min for removal of HCl. The yield of crude product is 94%.

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[986] F. G. Bordwell, B. M. Pitt, and M. Knell, *J. Amer. Chem. Soc.*, **73**, 5004 (1951).

[987] L. H. Sommer, H. D. Blankman, and P. C. Miller, *J. Amer. Chem. Soc.*, **76**, 803 (1954).

[988] H. Krauch and F. Vester, *Naturwissenschaften*, **44**, 491 (1957).

[989] Ger. Pat. 880,285; *Chem. Abstr.*, **52**, 11110 (1958).

[990] C. D. Hurd and H. L. Wehrmeister, *J. Amer. Chem. Soc.*, **71**, 4007 (1949).

The Henry synthesis gives better yields of purer products if one starts, not from the monomer, but from the polymeric aldehyde, this being produced by passing in HCl for a short time with ice–salt cooling before the main reaction is carried out.[991]

1-Chloropropyl propyl ether:[991] Propionaldehyde is cooled in an ice–salt mixture to about −10°, then a rapid stream of HCl is led in for about 30 sec. After renewed cooling, 1-propanol (60 g) is added and the liquid is saturated with HCl whilst being stirred and cooled. The resulting upper phase (114 g) is separated, dried over $CaCl_2$, and fractionated. The product (85 g, 62%) has b.p. 71–73°/100 mm.

If paraformaldehyde (30 g) and an alcohol (1 mole) are allowed to react with HBr (1 mole), addition of $CaCl_2$ (1 mole) leads to increased yields of alkyl bromomethyl ethers.[992]

The following, *inter alia*, can also be obtained by the Henry synthesis: chloromethyl methyl ether from formaldehyde,[518,993] paraformaldehyde,[994] or *s*-trioxan;[995] 1-chloroethyl ethyl ether from paraldehyde;[531,996] and similarly 1-bromo-[992,997] and 1-iodo-alkyl ethers.[993]

If unsaturated aldehydes are used, there is simultaneous addition of hydrogen halide; for instance, 1,2-dichloropropyl methyl ether is obtained from acrolein, methanol, and HCl.[998,999]

Allowing hydrogen halides to react with aliphatic aldehydes under the above conditions but in absence of an alcohol leads to bis-(α-haloalkyl) ethers (c); for example, bis-(1-chloroethyl) ether[1000,1001] and bis(halomethyl) ethers[1002] are thus obtained.

$$2R'CHO + 2HCl \longrightarrow (R'CHCl)_2O + H_2O \quad \ldots \text{(c)}$$

According to *Organic Syntheses*,[1003] bis(chloromethyl) ether can be obtained, not only from formaldehyde and HCl, but also by dropping chlorosulfuric acid (452 ml, 6.9 moles) into a mixture of concentrated HCl (168 ml) and paraformaldehyde (about 8 moles of CH_2O) in about 5.5 h at less than 10° (cooling!).

Bis(bromomethyl) ether is obtained from paraformaldehyde, concentrated H_2SO_4, and NaBr.[1004] If paraldehyde (70 g) is treated with bromine (320 g) at −5° to −10° and the temperature is then allowed to rise slowly to 15° and in a further 15 min to 20°, subsequently pouring the mixture on ice and

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[991] H. Böhme and H. Bentler, *Chem. Ber.*, **89**, 1486 (1956).

[992] H. W. Lucien and C. T. Mason, *J. Amer. Chem. Soc.*, **71**, 258 (1949).

[993] L. Henry, *Ber. Deut. Chem. Ges.*, **26 R**, **933** (1893); *Bull. Acad. Roy. Belg.*, [iii], **25**, 439 (1893).

[994] E. Wedekind, *Ber. Deut. Chem. Ges.*, **36**, 1384 (1903).

[995] J. F. Walker and A. F. Chadwick, *Ind. Eng. Chem.*, **39**, 974 (1947).

[996] D. Gauthier, *Ann. Chim.*, [viii], **16**, 289 (1909); *C. R. Hebd. Séances Acad. Sci.*, **143**, 831 (1906).

[997] C. M. Blair and H. R. Henze, *J. Amer. Chem. Soc.*, **54**, 399 (1932).

[998] W. Duliere, *Bull. Soc. Chim. France*, [iv], **33**, 1647 (1923).

[999] R. Voet, *Bull. Soc. Chim. France*, [iv], **41**, 1308 (1927).

[1000] A. Geuther and R. Cartmell, *Ann. Chem.*, **112**, 1 (1859).

[1001] A. Geuther and H. Laatsch, *Ann. Chem.*, **218**, 13 (1883).

[1002] W. Tishchenko, *Ber. Deut. Chem. Ges.*, **16**, 2286 (1883); **20 R**, 701 (1887).

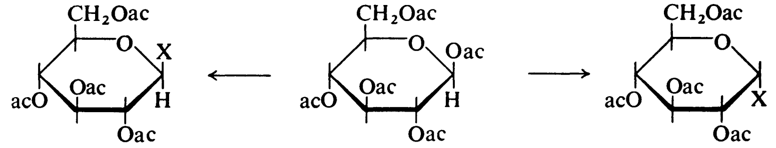
[1003] S. R. Buc, *Org. Syn.*, **36**, 1 (1956).

[1004] H. Stephen, W. F. Short, and G. Gladding, *J. Chem. Soc.*, **135**, 510 (1920).

neutralization with sodium carbonate solution, affords bis-(1,2-dibromoethyl) ether.[1005] In these cases the necessary hydrogen halide is produced during the reaction.

3. Replacement of acyloxy groups by halogen (halo sugars)

The OH groups of hemiacetals, alcohols, and aliphatic hydroxy carboxylic acids can usually be replaced by halogen under mild conditions. This reaction is most important in sugar chemistry, particularly for preparation of the very reactive acetohalogeno sugars that are required for the synthesis of many glycosides and glycosylamines.[1006] A glycosidic acyloxy group is very easily replaced while the other acyloxy groups remain intact. Most procedures give the more stable α-halo product independently of whether an acylated α- or β-sugar forms the starting material. Acetochloro sugars are obtained by treating an acylated sugar with acetyl chloride and $ZnCl_2$,[1007] with PCl_5 and $AlCl_3$,[1008] with $AlCl_3$ alone,[1009] with $TiCl_4$ in alcohol-free anhydrous $CHCl_3$,[1010] or with 1,1-dichloromethyl methyl ether.[1011]



Acetohalo-β-D-glucose Pentaacetyl-β-D-glucose Acetohalo-α-D-glucose

ac = CH_3CO or C_6H_5CO.

A particularly simple process, giving the β-product, is treatment of a solution or suspension of a sugar acetate with dry HCl.

Acetochloro-β-D-glucose:[1012] HCl (50 g) is led during 40 min into a stirred mixture of penta-*O*-acetyl-β-D-glucose (20 g) and dry ether (250 ml) at 5°, whereupon most of the pentaacetylglucose dissolves. The mixture is kept for 2 days in a closed flask at 0°, whereafter the resulting clear solution is concentrated in a vacuum. A total of 65% of crude product is thus obtained and after recrystallization from dry ether has m.p. 98–99°, $[\alpha]_D^{20}$ −12°.

Acetochloro-β-D-glucose can also be obtained by passing dry HCl into a mixture of PCl_3 (100 ml) and penta-*O*-acetyl-β-D-glucose (10 g) at 90–100° for 5 h, and an analogous process gives β-acetochlorogalactose.[1013]

In contrast to other methods,[1007,1008,1010,1011] there is no conversion into the α-form under the conditions described in the preceding example. In earlier

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[1005] H. Hibbert, S. Z. Perry, and K. A. Taylor, *J. Amer. Chem. Soc.*, **51**, 1553 (1929).

[1006] L. J. Haynes and F. H. Newth, *Advan. Carbohyd. Chem.*, **10**, 207 (1955).

[1007] D. H. Brauns, *J. Amer. Chem. Soc.*, **46**, 1484 (1924); **47**, 1280 (1925).

[1008] F. von Arlt, *Monatsh. Chem.*, **22**, 144 (1901); Z. H. Skraup and R. Kremann, *Monatsh. Chem.*, **22**, 375 (1901); E. M. Montgomery and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 247 (1942).

[1009] W. Korytnik and J. A. Mills, *J. Chem. Soc.*, **1959**, 636.

[1010] E. Pacsu, *Ber. Deut. Chem. Ges.*, **61**, 1508 (1928).

[1011] H. Gross and I. Farkas, *Chem. Ber.*, **93**, 95 (1960).

[1012] J. J. Fox and I. Goodman, *J. Amer. Chem. Soc.*, **73**, 3257 (1951).

[1013] J. de Pascual Resesa and F. Garrido Espinosa, *An. Real Soc. Españ. Fis. Quím.*, B Ser. **52**, 347 (1956).

work the less stable acetochloro-β-D-glucose was prepared from acetobromo-α-D-glucose by halogen exchange with freshly precipitated AgCl or by the action of liquid HCl on penta-*O*-acetyl-α-D-glucose in a bomb tube.[1014]

Benzochloro-α-D-glucose is obtained in 77% yield by reaction of penta-*O*-benzoyl-β-D-glucose with 1 mole of $TiCl_4$ in $CHCl_3$ for 4 h at 60°.[1015]

The preparation of acetobromo-α-D-glucose from the penta-*O*-acetyl-β-D-glucose obtained from D-glucose by means of acetic anhydride and sodium acetate[331,1016] is well known, but the method described in detail in *Organic Syntheses*[1017] is simpler.

Acetobromo-α-D-glucose: D-Glucose monohydrate (0.33 mole) is first acetylated with acetic anhydride (280 ml) containing 3 drops of concentrated H_2SO_4, then 200 ml of an acetic acid–anhydride mixture is distilled off, fresh acetic anhydride (60 ml) is added, and HBr (140–160 g) is led in with cooling in ice. The mixture is kept overnight, then HBr, acetic acid, and acetic anhydride are distilled off from a bath at not more than 60° under diminished pressure and finally in an oil-pump vacuum (less than 5 mm) and the residue is recrystallized from diisopropyl ether.

Sugar acetates are usually allowed to react for 12–24 h at 0–20° with glacial acetic acid saturated with HBr at 0°, then ice-water is added and the product is extracted in $CHCl_3$. In another quite generally applicable procedure the sugar acetates are prepared by means of acetic anhydride containing about 0.5 vol.-% of 70% perchloric acid, and the HBr needed for the exchange reaction is produced in the resulting solution by adding, with cooling, red phosphorus, bromine, and 90% of the calculated amount of water; the product is usually worked up by dilution with ice and water and extraction with chloroform.[1018,1019] The reaction mixture can also be used directly for further preparations, *e.g.*, of tri-*O*-acetyl-D-glucal.[1020] A procedure starting from, *e.g.*, D-glucose or penta-*O*-acetyl-β-D-glucose that can be recommended when dry HBr is not available is illustrated by the following synthesis.

Acetobromo-α-D-glucose:[1021] A cooled suspension of red phosphorus (30 g) in glacial acetic acid (300 ml) is treated dropwise with bromine (180 g) and then filtered through glass wool or a glass frit. Glucose (10 g) is added to the resulting solution (100 ml thereof) with shaking, whilst the temperature is kept at 40° or less. The mixture is set aside at room temperature for 2 h, then diluted with $CHCl_3$ (100 ml) and poured into a stirred mixture (200 ml) of ice and water. The $CHCl_3$ layer is separated and the aqueous solution is extracted with $CHCl_3$. The combined $CHCl_3$ solutions are washed with water and with aqueous $NaHCO_3$, dried over $CaCl_2$, and freed from $CHCl_3$ in a vacuum. The residue is dissolved in the minimum amount of ether, from which acetobromo-α-D-glucose, m.p. 87–89°, crystallizes in 66% yield on strong cooling.

An 84% yield is obtained if 216 g of penta-*O*-acetyl-β-D-glucose and the whole of the reagent described above are kept for 24 h at room temperature, then diluted with $CHCl_3$ (300 ml) poured into a mixture (800 ml) of ice and water, and worked up as above.

[1014] H. H. Schlubach, P. Stadler, and I. Wolf, *Ber. Deut. Chem. Ges.*, **61**, 287 (1928).

[1015] R. K. Ness, H. G. Fletcher, and C. S. Hudson, *J. Amer. Chem. Soc.*, **72**, 2200 (1950); 73, 296 (1951).

[1016] E. Fischer, *Ber. Deut. Chem. Ges.*, **49**, 584 (1916).

[1017] C. E. Redemann and C. Niemann, *Org. Syn.*, **22**, 1 (1942); Coll. Vol. III, 11 (1955).

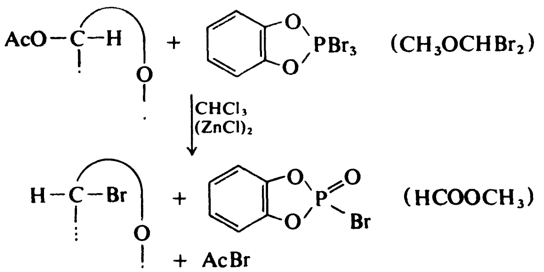
[1018] M. Barczai-Martos and F. Körösy, *Nature*, **165**, 369 (1950).

[1019] B. Helferich and co-workers, *Chem. Ber.*, **86**, 873 (1953); **87**, 1489 (1954).

[1020] B. Helferich, E. N. Mulcahy, and H. Ziegler, *Chem. Ber.*, **87**, 234 (1954).

[1021] P. G. Scheurer and F. Smith, *J. Amer. Chem. Soc.*, **76**, 3224 (1954).

Acetyl derivatives of pentoses, hexoses, and disaccharides are converted into α-acetobromo sugars rapidly and simply on treatment with dibromomethyl methyl ether or with 2,2,2-tribromo-1,3,2-benzodioxophosph(v)ole (for preparation see Gross and Karsch[1022]) in $CHCl_3$ containing a little $ZnCl_2$.[1023] This method is particularly valuable for preparation of acetobromorhamnose.



In principle, acetylated amino sugars can be treated with HX in the same way as the usual acylated sugars, but the acetylated 1-halo-amino sugars readily rearrange. In presence of water the 3,4,6,*N*-tetraacetyl-1-α-bromo-D-glucosamine obtained from penta-*O*-acetyl-α- or -β-D-glucosamine by HBr in glacial acetic acid passes very readily into 1,3,4,6-tetra-*O*-acetyl-α-D-glucosamine hydrobromide.[1024] 3,4,6,*N*-Tetraacetyl-1-α-chloro-D-glucosamine, formed in good yield from *N*-acetyl-D-glucosamine and acetyl chloride, is more stable but rearranges, particularly in the presence of acid, in the same way as the bromo sugar.[1025] However, 3,4,6,*N*-tetraacetyl-1-α-fluoro-D-glucosamine which is obtained, like the usual acetofluoro sugars, from penta-*O*-acetyl-α- or -β-D-glucosamine and liquid HF[1026] is a very stable compound and can even be deacetylated by Zemplen's method.[1027]

Acetoiodo sugars may be obtained by reaction with HI in glacial acetic acid[1028] or from the bromo analogs by halogen exchange with NaI in acetone at room temperature.[1029]

Replacement of acyloxy groups by halogen is used, not only in sugar chemistry, but also for the preparation of dibromides from the acetates of vicinal diols.[1030,1031]

Similarly, γ-bromobutyrolactone, an intramolecularly acylated hydroxy carboxylic acid, is converted by saturation with dry HBr into 4-bromobutyric acid, which yields its methyl ester in 85–90% yield when boiled for several hours with methanol (3 moles), CH_2Cl_2 (300 ml), and concentrated H_2SO_4

[1022] H. Gross and U. Karsch, *J. Prakt. Chem.*, [iv], **29**, 315 (1965).
[1023] I. Farkas, M. Menyhárt, R. Bognár, and H. Gross, *Chem. Ber.*, **98**, 1419 (1965).
[1024] F. Micheel and H. Petersen, *Chem. Ber.*, **92**, 302 (1959).
[1025] F. Micheel, F.-P. van de Kamp, and H. Petersen, *Chem. Ber.*, **90**, 524 (1957).
[1026] D. H. Brauns, *J. Amer. Chem. Soc.*, **45**, 833 (1923).
[1027] F. Micheel and H. Wulff, *Chem. Ber.*, **89**, 1526 (1956).
[1028] E. Fischer and H. Fischer, *Ber. Deut. Chem. Ges.*, **43**, 2535 (1910).
[1029] B. Helferich and R. Gootz, *Ber. Deut. Chem. Ges.*, **62**, 2791 (1929).
[1030] H. J. Lucas, M. J. Schlatter, and R. C. Jones, *J. Amer. Chem. Soc.*, **63**, 22 (1941).
[1031] W. G. Young, Z. Jasaitis, and L. Levanas, *J. Amer. Chem. Soc.*, **59**, 403 (1937).

(3 ml)[1032] (Clinton and Laskowski's method of esterification[1033]). The corresponding ethyl ester is obtained particularly simply by boiling 0.5 mole of γ-butyrolactone for 4 hours with a solution of 1 mole of HBr in 500 ml of absolute ethanol.[1034]

The mixed anhydride of formic and acetic acid with anhydrous hydrogen fluoride in a quartz flask afford formyl fluoride (b.p. −29°) in 61% yield:[1035]

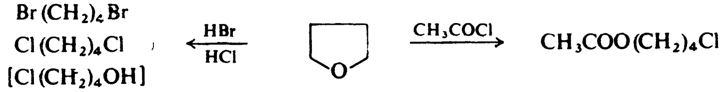
$$2HCO{-}O{-}COCH_3 + 2HF \longrightarrow HCOF + CH_3COF + HCOOH + CH_3COOH$$

Not only the compounds $ROC(=O)R'$, but also esters $ROSO_2OR$ can be converted into halides RX, the other product in this case being $HOSO_2OR$.

This procedure is of practical importance for the preparation of methyl iodide which distils off continuously (b.p. 41–43°) when dimethyl sulfate (630 g) is dropped into a stirred mixture of KI (800 g), $CaCO_3$ (60 g), and water (430 ml) at 60–65°; for details see Gattermann[33b] and Hartman.[1036]

4. Replacement of C–O bonds by C–halogen bonds on fission of ethers or acetals

The fission of ethers by hydrogen halides (HX), acid halides, POX_3 and PX_5, or AlX_3 is important preparatively for liberation of OH groups, but it also provides a means of obtaining halogen compounds from cyclic or alkyl aryl ethers; it is the alkyl halide that is formed in the last case. Of the hydrogen halides HI is particularly reactive in this respect, HBr less so, and HCl still less. For the theory and rich literature of ether fission see Burwell.[1037] The methods for preparation of ω-haloalkanols or α,ω-dihaloalkanes by fission of cyclic ethers are shown in the following experimental examples.



4-Chlorobutyl acetate and **4-chloro-1-butanol:** Acetyl chloride (65 g), tetrahydrofuran (50 g; b.p. 66°), and $ZnCl_2$ (0.01 g) are boiled for 90 min under reflux with exclusion of moisture, whereafter distillation gives 76% of 4-chlorobutyl acetate, b.p. 78–79°/15 mm, 90–91°/20 mm. Yields are considerably less if no $ZnCl_2$ or more $ZnCl_2$ or $AlCl_3$ is added.[1038] Transesterification with methanol and a little concentrated HCl or p-toluenesulfonic acid gives 80% of 4-chloro-1-butanol, b.p. 64–65°/3 mm; in this reaction a temperature of 40°, finally 50°, should not be exceeded, otherwise tetrahydrofuran is re-formed.

5-Chloropentyl acetate is similarly obtained in 85% yield from tetrahydropyran,[1039,1040] and 4-chloro-1-methylpentyl acetate in 77% yield from tetrahydro-2,5-dimethylfuran;[1038] yields are said to be still higher if 2.2 g of $ZnCl_2$ per mole of cyclic ether is used.[206]

4-Chloro-1-butanol is obtained more simply by leading HCl into boiling tetrahydrofuran until the temperature of the boiling mixture reaches 103.5–105.5° (*ca.* 5 h). The product is

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[1032] J. F. Tinker, *J. Org. Chem.*, **16**, 1418 (1951).
[1033] R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).
[1034] W. A. Reckhow and D. S. Tarbell, *J. Amer. Chem. Soc.*, **74**, 4961 (1952).
[1035] G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **82**, 2380 (1960).
[1036] W. W. Hartman, *Org. Syn.*, Coll. Vol. II, 404 (1943).
[1037] R. L. Burwell Jr., *Chem. Rev.*, **54**, 615 (1954).
[1038] J. B. Cloke and P. J. Pilgrim, *J. Amer. Chem. Soc.*, **61**, 2667 (1939).
[1039] M. E. Synerholm, *J. Amer. Chem. Soc.*, **69**, 2581 (1947).
[1040] D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, **1950**, 176.

isolated in 54–57% yield by distillation in a vacuum, best at 15 mm, much HCl being at first evolved.[1041,1042] If anhydrous $ZnCl_2$ is added during this reaction in small portions (altogether 50% of the total weight), then a 59% yield of 1,4-dichlorobutane is formed.[1043]

Tetrahydrofuran (1 mole), $POCl_3$ (0.33 mole), and concentrated H_2SO_4 (10 ml) at 80 to 100° give 70% of bis-(4-chlorobutyl) ether in an exothermic reaction.[1044]

1,4-Dibromobutane (tetramethylene dibromide): This dibromide can be prepared by passing HBr into boiling tetrahydrofuran until the boiling point reaches 150° [1045] or by adding tetrahydrofuran (1 mole) to a cold mixture of 50% aqueous HBr (6 moles) and concentrated H_2SO_4 (50 ml), boiling for 3 h under reflux, and working up by steam-distillation.[1046] The following method[1047] is very simple: Tetrahydrofuran (2 moles) is added to a rapidly stirred solution of NaBr (500 g) in water (600 ml), and then concentrated H_2SO_4 (750 ml) at such a rate that the temperature is maintained at 70–72°. The mixture is warmed for 8 h on the steam-bath and then decanted from the salt, the organic layer is separated, and the aqueous solution and the salts are washed with benzene (500 ml). The organic layer is united with the benzene extract, washed with sodium carbonate solution and sodium hydrogen sulfite solution, dried over $CaCl_2$, and distilled, giving the dibromide, b.p. 194–196°/760 mm, 81°/15 mm, in 86% yield.

1-Bromo-4-chlorobutane: This compound is best obtained by treating crude $Cl(CH_2)_4OH$ (prepared by passing HCl into tetrahydrofuran) with PBr_3[1048] or with red phosphorus and bromine.[1047] Alternatively, in a direct process, concentrated H_2SO_4 (400 ml) may be added to a mixture of NaBr (1.2 moles), NaCl (1.3 moles), water (400 ml), and tetrahydrofuran (1 mole) with stirring, in such a way that the temperature does not exceed 70°; thus are obtained 44% of 1-chloro-4-bromobutane and 10% of 1,4-dibromobutane; for working up see the original paper.[1047]

1,5-Dibromopentane (pentamethylene dibromide) is prepared by boiling a mixture of 48% HBr (1.5 moles), concentrated H_2SO_4 (74 g), and tetrahydropyran (0.25 mole) for 3 h; deteails are given in *Organic Syntheses*.[1049]

Ether fission by hydrogen iodide is usually used for liberation of phenolic hydroxyl groups or for analytical purposes (Zeisel methoxyl determination). It is less suitable for preparation of iodides since HI is easily split off from the iodides at the high reaction temperatures maintained for the necessary long times; moreover, HI is a reducing agent. These side reactions can be avoided by working with KI and 95% phosphoric acid (cf. pages 128 and 222), a procedure that has proved its value for aliphatic, cyclic, and alkyl aryl ethers.[196]

$$ROR + 2KI + 2H_3PO_4 \longrightarrow 2RI + 2KH_2PO_4 + H_2O$$

1,4-Diiodobutane (tetramethylene diiodide):[1050] 85% phosphoric acid (135 ml, 2 moles) is added with slow stirring to phosphorus pentoxide (65 g) in a 1-litre three-necked flask. The mixture is allowed to cool to room temperature, then KI (2 moles) is added, followed by tetrahydrofuran (0.5 mole). The whole is stirred and heated under reflux for 3 h, then cooled to room temperature and treated with water (150 ml) and ether (250 ml). The ethereal layer is washed with thiosulfate solution and saturated salt solution, dried over Na_2SO_4, and evaporated. Distillation in a vacuum then gives the diiodide, b.p. 108–110°/10 mm, in 92–96% yield.

Dibutyl ether gives analogously 81% of butyl iodide, and diisopropyl ether gives 90% of isopropyl iodide.

[1041] D. Starr and R. M. Hixon, *J. Amer. Chem. Soc.*, **56**, 1596 (1934).

[1042] D. Starr and R. M. Hixon, *Org. Syn.*, Coll. Vol. II, 571 (1943).

[1043] S. Fried and R. D. Kleene, *J. Amer. Chem. Soc.*, **63**, 2691 (1941).

[1044] K. Alexander and L. E. Schniepp, *J. Amer. Chem. Soc.*, **70**, 1840 (1948).

[1045] S. Fried and R. D. Kleene, *J. Amer. Chem. Soc.*, **62**, 3258 (1940).

[1046] C. L. Wilson, *J. Chem. Soc.*, **1945**, 48.

[1047] A. Kaluszyner, *J. Org. Chem.*, **22**, 834 (1957).

[1048] M. S. Newman and J. H. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1294 (1949); D. A. Shirley, "Organic Intermediates," J. Wiley and Sons, New York, 1951.

[1049] D. W. Andrus, *Org. Syn.*, 23, **67** (1943); Coll. Vol. III, 692 (1955).

[1050] H. Stone and H. Shechter, *Org. Syn.*, **30**, 33 (1950).

Von Braun[1051] prepared long-chain α,ω-dihaloalkanes from the corresponding bisphenyl ethers, which are accessible from aryl ω-haloalkyl ethers by a Wurtz synthesis (a).

$$2X(CH_2)_nX \xrightarrow{2ArONa} 2X(CH_2)_nOAr \xrightarrow[\text{(ether, b.p.)}]{Na} ArO(CH_2)_{2n}OAr$$

$$ArO(CH_2)_{2n}OAr \xrightarrow[56.7\%\ HI]{48\%\ HBr} X(CH_2)_{2n}X + 2ArOH \quad \ldots \text{(a)}$$

$$X = Br \text{ or } I$$

The α,ω-diphenoxyal kanes may also be prepared by other methods, *e.g.*, according to scheme (b).[1052]

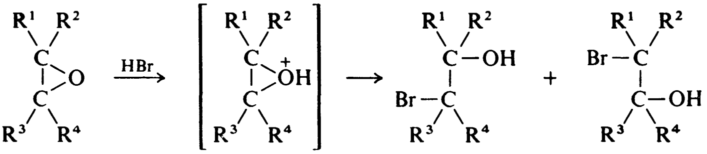
$$\begin{tikzcd} ArO(CH_2)_nX + NaC{\equiv}CH \arrow[r] & ArO(CH_2)_nC{\equiv}CH \arrow[d, "ArO(CH_2)_mX"', "\substack{NaNH_2 \\ Ether}"] \\ ArO(CH_2)_{n+m+2}OAr & ArO(CH_2)_nC{\equiv}C(CH_2)_mOAr \arrow[l, "H_2"'] \end{tikzcd} \quad \ldots \text{(b)}$$

Ethers can be cleaved by 48% aqueous HBr in 48 hours under reflux or at 100–180° in a bomb tube or by three times the theoretical amount of constant-boiling aqueous HI. The ease of fission decreases as the chain length increases. The basicity of phenyl ethers is responsible for the primary step of ether fission, namely, addition of H^+ to the ether oxygen atom, and this basicity is decreased by mesomerism; mesomerism must thus be removed, *e.g.*, by hydrogenation for diphenyl ethers;[1053] on the other hand, *o*- and *p*-methoxy groups, as when Ar = o-$CH_3OC_6H_4$ (guaiacol instead of phenol) or p-$CH_3OC_6H_4$ (hydroquinone monomethyl ether),[1052,1054] increases the basicity and thus leads to easier cleavage.

When Ar = p-$CH_3OC_6H_4$ yields of α,ω-diiodides are very good up to $n = 40$. If the cleavage is carried out by boiling in open vessels, the solid material is filtered off after some hours and heated again with fresh hydriodic acid. The crude diiodides are washed with water, dried, and freed from humin-like decomposition products of hydroquinone by extraction in a Soxhlet with light petroleum.

Epoxides are particularly easily cleaved, giving halohydrins even when treated with 48% HBr under ice-cooling or in an exothermic reaction with concentrated aqueous HI. In an alkaline medium the halohydrins readily regenerate the epoxides.

The steric relations of fission of epoxides, which involves a Walden inversion, are of especial interest. When $R^2 = R^4 = H$ (*cis*-epoxide) and $R^1 = R^3$, a *threo*-halohydrin (±-mixture) is obtained; when $R^1 = R^4 = H$ (*trans*-epoxide) and $R^2 = R^3$, an *erythro*-halohydrin is formed. This behavior has



[1051] J. von Braun, *Ber. Deut. Chem. Ges.*, **42**, 4541 (1909).

[1052] A. W. Nineham, *J. Chem. Soc.*, **1953**, 2601.

[1053] J. von Braun and co-workers, *Ber. Deut. Chem. Ges.*, **70**, 973, 1598 (1937).

[1054] K. Ziegler, H. Weber, and H. G. Gellert, *Ber. Deut. Chem. Ges.*, **75**, 1715 (1942).

been studied for 2,3-epoxybutane.[290] If $R^1 \neq R^3$ or $R^2 \neq R^3$, then structural isomerism also results, as has been demonstrated for 2,3-epoxypentane.[1030]

Experimentally, epoxide cleavage is easy: the epoxide, or a solution thereof in light petroleum or $CHCl_3$, is added gradually, with stirring and cooling in ice, to 48% HBr or 55%HI; after the reaction, the mixture is neutralized cautiously with alkali carbonate, and the halohydrin is taken up in ether. Most halohydrins are too unstable to be distilled. An example will be found in *Organic Syntheses*,[1055] namely, the preparation of 2-bromoethanol in 87 to 92% yield by passing ethylene oxide (3 moles) into at least 46% HBr (4.25 moles) with cooling by ice–salt.

Addition of HF to epoxides affords fluoro alcohols, *e.g.*, 2-fluoroethanol from ethylene oxide and HF in ether.[1056]

A generally applicable process for the preparation of α-halo ethers is the treatment of acetals or hemiacetals with an acid halide (PCl_3, PCl_5, PBr_3, PBr_5, $ClSO_3H$, $SOCl_2$, CH_3COCl, C_6H_5COCl) [cf. (a)] (cf. pages 169 and 232).

$$R'CH(OR'')OR \xrightarrow{PCl_5} R'CHClOR + POCl_3 + R''Cl$$

For instance, 1-chloroethyl ethyl ether is obtained from acetaldehyde diethyl acetal and PCl_5,[1057] α-chlorobenzyl methyl ether from benzaldehyde dimethyl acetal, acetyl chloride and $SOCl_2$[1058] and 1-bromoalkyl ethers from the corresponding acetals.[1059] 1-Bromoalkyl ethers can also be prepared from 1-chloroalkyl ethers into which HBr is passed at about 20°; 1-iodoalkyl ethers are obtained from the 1-chloro analogs by use of NaI in acetone.

5. Replacement of OH by halogen in phenols or heterocycles

PX_5 and POX_3 ($X = Cl$ or Br) is occasionally used for replacement of phenolic OH by halogen, and more often for OH in heterocycles.

The equilibrium $PBr_5 \rightleftarrows PBr_3 + Br_2$ is shifted so far to the right at temperatures above 100° that when PBr_5 is used substitution by bromine and sometimes dehydrogenation are to be expected as side reactions.

The reaction has special preparative importance for chlorine-substituted heterocycles. The hydrochloride of the corresponding hydroxy-N-heterocycle is usually heated under reflux for several hours with an excess of $POCl_3$, then the excess of $POCl_3$ is distilled off, the residue is decomposed with ice and made alkaline, and the chloro heterocycle is extracted in ether. In this way, 2-chloro-,[1060] 2-chloro-4-methyl-,[1061] 2-chloro-4,6-dimethyl-,[1062] and 4,6-dichloro-2-methyl-pyrimidine,[1063] and 2-chloro-4-methylquinoline,[1064] *inter alia*, have been prepared.

[1055] F. K. Thayer, C. S. Marvel, and G. S. Hiers, *Org. Syn.*, **6**, 12 (1926).

[1056] O. V. Kildicheva and I. P. Petrov, *Zh. Obshch. Khim.*, **19**, 95 (1950).

[1057] A. Geuther and A. Bachmann, *Ann. Chem.*, **218**, 39 (1883).

[1058] F. Straus and H. Heinze, *Ann. Chem.*, **493**, 191 (1932).

[1059] A. Kliegl and K. Haas, *Ber. Deut. Chem. Ges.*, **42**, 2581 (1909).

[1060] J. W. Copenhaver and R. F. Kleinschmidt, Brit. Pat. 663,302; *Chem. Abstr.*, **46**, 10212 (1952).

[1061] T. Matsukawa and B. Ohta, *J. Pharm. Soc., Japan*, **69**, 489 (1949); *Chem. Abstr.*, **44**, 3456 (1950).

[1062] T. Matsukawa and B. Ohta, *J. Pharm. Soc. Japan*, **69**, 491 (1949); *Chem. Abstr.*, **44**, 3456 (1950).

[1063] J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J. Chem. Soc.*, **1943**, 383.

[1064] S. E. Krahler and A. Burger, *J. Amer. Chem. Soc.*, **63**, 2367 (1941).

The reaction may also be carried out in the presence of a tertiary amine. 2,6,8-Trichloropurine is obtained from 2,6-dichloro-8-hydroxypurine by means of $POCl_3$ and dimethylaniline,[1065] and the preparation of 3-chloroindazole from 0.2 mole of dry indazolone, 0.2 mole of dry pyridine, and 0.3 mole of $POCl_3$ is detailed in *Organic Syntheses*.[1066]

The $POCl_3$ may be replaced by PCl_5 or a mixture of the two.[1062,1067] For instance, 1,4-dichlorophthalazine is formed when phthalodihydrazide (32 g) is heated with PCl_5 (100 g) for 4 hours at 150°.[1068]

3,6-Dichloropyridazine:[1069,1070] 3,6-Pyridazinediol (25 g; from hydrazine dihydrochloride and maleic anhydride[1069]) is boiled in $POCl_3$ (300 ml) for 5 h under reflux. The excess of $POCl_3$ is distilled off in a vacuum and the residue is cooled, poured on ice, and made weakly alkaline to litmus with ammonia. The precipitated product is dried in a vacuum and the filtrate therefrom is extracted with $CHCl_3$. A further amount of crude product is obtained from the dried $CHCl_3$ extract, the total yield being 87%. Purification by vacuum-distillation (b.p. 89–91°/1.2 mm) or by recrystallization from hexane gives a product of m.p. 69–70°.

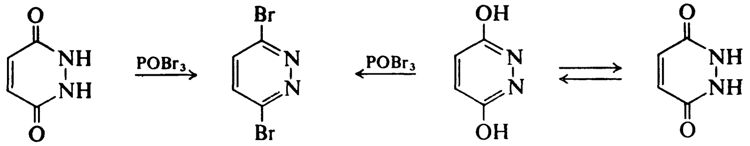
2-Chloropyrimidine:[1061] 2-Pyrimidinol hydrochloride (5.3 g), PCl_5 (15 g), and $POCl_3$ (4 ml) are heated for 45 min at 140–150°. Part of the $POCl_3$ is removed and the residual solution is poured on ice and made alkaline with NaOH. NaCl is added and the 2-chloropyrimidine is extracted in ether. Removal of the ether and recrystallization from light petroeum give the product, m.p. 65°, in 93% yield.

It is particularly easy to replace the OH of picric acid by Cl, although this compound reacts with $POCl_3$ only when present as pyridine picrate.

Picryl chloride:[1071] Pyridine (7.9) is added to a hot solution of picric acid (22.9 g) in 95% alcohol (200 ml); on cooling, pyridine picrate (30.1 g, 98%), m.p. 166°, separates. Dry pyridine picrate (1 mole), $POCl_3$ (0.67 mole), and benzene (250 ml) are boiled under reflux for 15 min; the benzene layer and the oil that separates are washed separately with hot water; after removal of the benzene, the benzene layer affords 73% and the oil 25% of picryl chloride, m.p. 79–81°.

4-Hydroxypyridine [4(1*H*)-pyridone] and PCl_5–$POCl_3$ give 75% of 4-chloropyridine, but heating with PBr_5 at 110° gives only 47% of 4-bromopyridine, 3,4,5-tribromopyridine being a by-product.[1067]

General directions for **substitution of Br for OH in heterocycles** by means of PBr_5 or $POBr_3$: The hydroxy compound (1 mole) is mixed with PBr_5 (1.05 mole) and heated at 100° for 6–8 h with exclusion of water. The mixture is decomposed with ice and made alkaline with Na_2CO_3 or NaOH solution; it is worked up by distillation in steam or extraction with a suitable solvent. See, for example, the preparation of 3-bromo-6-methylpyridazine.[1072]



3,4-Dibromopyridazine

[1065] J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, **1946**, 833.

[1066] E. F. M. Stephenson, *Org. Syn.*, **29**, 54 (1949).

[1067] J. P. Wibaut and F. W. Broekman, *Rec. Trav. Chim.*, **58**, 885 (1939).

[1068] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, **1937**, 16.

[1069] R. H. Mizzoni and P. E. Spoerri, *J. Amer. Chem. Soc.*, **73**, 1874 (1951).

[1070] E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **76**, 3226 (1954).

[1071] R. Boyer, E. V. Spencer, and G. F. Wright, *Can. J. Res.*, **24 B**, 200 (1946).

[1072] C. Grundmann, *Chem. Ber.*, **81**, 7 (1948).

The hydroxy compound (1 mole) is heated with $POBr_3$ (at least 1 mole) for several hours at 120–150°, sometimes with addition of toluene or xylene, then cooled and decomposed with ice. See, for example, the preparation of 2,4,6-tribromopyrimidine from barbituric acid,[1073] or of 3,6-dibromopyridazine from 3,6-pyridazinediol (maleohydrazide).[1070]

In certain circumstances $POBr_3$ has also a dehydrogenating action; for instance, hexahydro-3,6-pyridazinedione and $POBr_3$ at 70–80° give 3,6-dibromopyridazine,[1074] the yield of which is increased on addition of bromine.

Phosphorus pentabromide (PBr_5) suitable for preparative purposes is obtained by dropping PBr_3 (1 mole) into a solution of Br_2 (1 mole) in about ten times its volume of light petroleum (b.p. 30–60°) with rapid stirring, cooling, and exclusion of water.[1075]

PBr_5 can also be prepared in $CHCl_3$, as follows:[1076] A solution of bromine (160 g) in chloroform (300 ml) is dropped into a rapidly stirred solution of PBr_3 (270 g) in chloroform (300 ml). The supernatant solution is then decanted and the yellow crystals of PBr_5 are collected on a glass filter, washed with chloroform, and at once placed in a vacuum-desiccator. The yield is 420 g (98%), and the m.p. 75–77° (dec.).

Phosphoryl tribromide ($POBr_3$), m.p. 56°, b.p. 193°, is prepared by one of the following reactions:[1072,1077]

$$3PBr_5 + P_2O_5 \xrightarrow{100°} 5POBr_3$$

$$PBr_5 + HCOOH \longrightarrow POBr_3 + 2HBr + CO$$

The triphenyl phosphite method (see page 227) is also suitable for substitution of Cl, Br, or I for OH in phenols or heterocycles. For details see Coe *et al.*[1078]

$$(ArO)_3PX_2 + Ar'OH \longrightarrow Ar'X + (ArO)_3PO + HX$$

6. Replacement of OH by halogen in the carboxyl group: carbonyl halides

a. Replacement of OH in the COOH group by fluorine

Carboxylic acid fluorides are not of particular preparative importance since the reactions that can be carried out with them proceed analogously with the cheaper carboxylic acid chlorides. These fluorides are very stable, even towards hydrolysis. Formyl fluoride can be kept at room temperature for several hours before it decomposes into CO and HF. The preparation of carboxylic acid fluorides from the corresponding chlorides and KF was mentioned on page 204. If butyric anhydride is heated gradually to 180° with KHF_2, butyryl fluoride, b.p. 67°/767 mm, distils off, and benzoyl fluoride, b.p. 155–156°, can be obtained analogously from benzoic anhydride at 190–240°. KF can also be used in place of KHF_2. Yields are around 80–90%.[1079]

This procedure requires that the acid anhydrides be prepared as a preliminary, but merely heating lower fatty acids, or mono- or tri-chloroacetic acid, with benzoyl fluoride gives the corresponding acid fluorides provided that these are distilled off continuously so that they are removed from the equilibrium mixture[1080] (cf. page 247).

$$RCOOH + C_6H_5COF \rightleftarrows RCOF + C_6H_5COOH$$

[1073] D. R. V. Golding and A. E. Senear, *J. Org. Chem.*, **12**, 293 (1947).

[1074] C. Pedrali and A. Mantegani, *J. Org. Chem.*, **23**, 778 (1958).

[1075] C. E. Kaslow and M. M. Marsh, *J. Org. Chem.*, **12**, 456 (1947).

[1076] J. Cason and S. Correia, *J. Org. Chem.*, **26**, 3648 (1961).

[1077] H. S. Booth and C. G. Seegmiller, *Inorg. Syn.*, **2**, 151 (1946).

[1078] D. G. Coe, H. N. Rydon, and B. L. Tonge, *J. Chem. Soc.*, **1957**, 323.

[1079] A. J. Mechentsev, *Zh. Obshch. Khim.*, **15**, 915 (1945); *Chem. Abstr.*, **40**, 6443 (1946).

[1080] A. J. Mechentsev, *Zh. Obshch. Khim.*, **16**, 203 (1946); *Chem. Abstr.*, **41**, 706 (1947).

This reaction can be combined with halogen exchange by heating together a carboxylic acid, benzoyl chloride and KF[805] or dry KHF_2.[821]

b. Replacement of OH in the COOH group by chlorine, bromine, or iodine, by means of inorganic acid halides

There are several very practical methods for preparation of the other carboxylic acid halides from the acids. Carboxylic acid chlorides are much the most important of these halides, so that their preparation must be described in greatest detail. In principle, the OH of a carboxyl group is replaced by the chlorine of an acid chloride. In most cases only part of the chlorine presented as inorganic or organic acid chloride is available for the exchange reaction, the remainder being lost as HCl. The most important inorganic acid chlorides for this reaction are PCl_5, PCl_3, and $SOCl_2$; $POCl_3$ reacts only with the salts of carboxylic acids (d). Isobutyryl chloride is also obtained in 85% yield from isobutyric acid and $SiCl_4$ at 50°.[1081]

$$\mathrm{RCOOH + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl} \quad \ldots \text{(a)}$$

$$\mathrm{3RCOOH + 2PCl_3 \longrightarrow 3RCOCl + P_2O_3 + 3HCl} \quad \ldots \text{(b)}$$

$$\mathrm{RCOOH + SOCl_2 \longrightarrow RCOCl + SO_2 + HCl} \quad \ldots \text{(c)}$$

$$\mathrm{2RCOONa + POCl_3 \longrightarrow 2RCOCl + NaPO_3 + NaCl} \quad \ldots \text{(d)}$$

Phosphorus pentachloride is a very vigorous reagent; it is generally applicable if the resulting carboxylic acid boils lower or higher than phosphoryl trichloride (b.p. 105.4°/760 mm, 45°/85 mm). Since reaction (a) is usually highly exothermic, the mixture must be diluted, *e.g.*, with benzene, light petroleum, $CHCl_3$, or CS_2.

Preparation of acid chlorides by PCl_5: A carboxylic acid (1 mole) and PCl_5 (1.05 moles) are heated in dry benzene at 80° until evolution of HCl stops (3–4 h). Then the benzene and $POCl_3$ are distilled off, after which, if desired, toluene may be added and the residual $POCl_3$ driven off with this in a second distillation. Many carboxylic acid chlorides are sparingly soluble in light petroleum, in which $POCl_3$ dissolves, so that $POCl_3$ and the acid chloride can be separated by dilution of the mixture with this solvent.[1082] If the carboxylic acid and PCl_5 are allowed to react in boiling light petroleum, then sometimes the carboxylic acid chloride produced will crystallize out.

In many cases milder conditions suffice: The carboxylic acid (1 mole) and PCl_5 (1–1.1 moles) are merely mixed, if necessary with cooling in ice, and, if necessary they are warmed gently, with exclusion of water, on a water-bath until reaction sets in (evolution of HCl). The reaction is completed by further gentle warming (about 30 min) or allowed to run for several hours at room temperature. If the carboxylic acid boils higher than $POCl_3$, the latter is distilled off, usually in a vacuum, and the crude carboxylic acid chloride is purified by vacuum-distillation; see, for instance, the preparation of *p*-nitrobenzoyl chloride[1083] and itaconoyl dichloride, $CH_2{=}C(COCl)CH_2COCl$.[1084] If the carboxylic acid chloride boils lower than $POCl_3$, it is distilled out of the mixture through a column; see, for instance, the preparation of oxalyl chloride.[1085]

[1081] I. N. Nazarov and I. L. Kotlyarevskii, *Zh. Obshch. Khim.*, **20**, 1441 (1950); *Chem. Abstr.*, **45**, 1964 (1951).

[1082] H. Staudinger, *Ber. Deut. Chem. Ges.*, **41**, 356 (1908).

[1083] R. Adams and R. L. Jenkins, *Org. Syn.*, **3**, 75 (1923).

[1084] H. Feuer and S. M. Pier, *Org. Syn.*, **33**, 41 (1953).

[1085] O. Wallach, *Ber. Deut. Chem. Ges.*, **8**, 300 (1875).

$POCl_3$ can also be used as solvent in the reaction of PCl_5, as in the preparation of betaine chloride, $Cl^{-+}N(CH_3)_3CH_2COCl$, from betaine hydrochloride.[1086]

The yield of carboxylic acid chloride depends on the quality of the PCl_5; it has been recommended that the PCl_3 and $POCl_3$ contained in it should be removed by warming in a vacuum[1087] or, better, that the PCl_5 should be previously isolated.

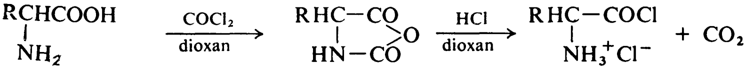
Phosphorus pentachloride (PCl_5):[1083] Dry Cl_2 is led over the surface of liquid PCl_3 until the increase of weight amounts to about 50%. There should be only occasional stirring, as otherwise the inlet tube becomes blocked with PCl_5. At the end of the reaction the product is solid.

Phosphoryl trichloride that is recovered from preparation of carboxylic acid chlorides by reaction (a) may decompose explosively when kept.[1088]

Amino carboxylic acids or their hydrochlorides, when treated with PCl_5 in acetyl chloride[1089] or, better, in CCl_4 (which dissolves PCl_5)[1090] give the amino acid chloride hydrochlorides. Since these salts are very sensitive to moisture, the reaction must be carried out in a closed apparatus and the product must be collected on a protected frit and finally washed with a suitable solvent (light petroleum or CCl_4) and sucked dry.

Aminoacetyl chloride hydrochloride (glycine chloride hydrochloride):[1090] PCl_5 (15 g) is added to a suspension of glycine (5 g) in CCl_4 (200 ml). The vessel is tightly closed and shaken vigorously at room temperature for 10 h. The product is then filtered on a frit with exclusion of water and washed three times with dry CCl_4, three times with light petroleum, and once with ether. Alanyl chloride hydrochloride is prepared analogously. Yields are about 90%, or 75–80% after recrystallization from acetyl chloride.

Analytically pure amino carboxylic acid chloride hydrochlorides are obtained directly if carefully dried HCl ($CaCl_2$ tower, 2 wash-bottles containing concentrated H_2SO_4, P_2O_5 on glass wool) is led at 20° into a clear solution of an *N*-carboxy amino acid anhydride in dioxan until crystallization begins.[1091] These anhydride solutions are obtained by passing dry phosgene (washed with concentrated H_2SO_4) into a vigorously stirred solution of the amino acid in dioxan at 40–50° to complete or nearly complete dissolution, removal of the excess of $COCl_2$ in a stream of dry air, and filtration with exclusion of moisture (cf. page 249).



The last reaction illustrates how useful it can be to convert an acid first into its anhydride and then into its chloride. Most carboxylic anhydrides are relatively stable to inorganic acid chlorides; cyclic anhydrides are even formed preferentially if a dicarboxylic acid such as maleic, tartaric, or phthalic acid is treated with an inorganic acid chloride such as $SOCl_2$ under the usual conditions;[1092] however, phthalic anhydride is converted by PCl_5 at higher temperatures into phthaloyl dichloride (A).

[1086] P. A. Plattner and M. Geiger, *Helv. Chim. Acta*, **28**, 1362 (1945).

[1087] E. Ott, *Org. Syn.*, Coll. Vol. II, 528 (1943).

[1088] *Chemiker-Ztg.*, **86**, 490 (1962); *Chem. Eng. News*, **40**, Jan. 15th, 55 (1962).

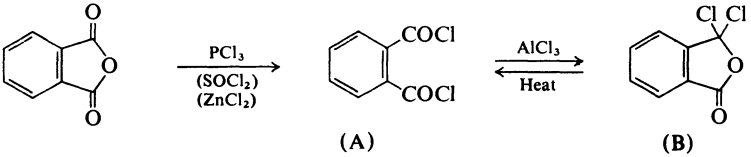
[1089] E. Fischer, *Ber. Deut. Chem. Ges.*, **38**, 606, 2914 (1905); **39**, 544 (1906).

[1090] S. Levine, *J. Amer. Chem. Soc.*, **76**, 1382 (1954).

[1091] M. Brenner and I. Photaki, *Helv. Chim. Acta*, **39**, 1525 (1956).

[1092] H. Meyer, *Monatsh. Chem.*, **22**, 437 (1901).

This reaction probably proceeds by way of 3,3-dichlorophthalide (B), which rearranges to the acid chloride (A) on distillation at atmospheric pressure. On the other hand, (A) is rearranged to (B) by $AlCl_3$.[1039]



At higher temperatures $SOCl_2$ containing $ZnCl_2$ also converts cyclic anhydrides into the diacid dichlorides.

Phthaloyl dichloride from phthalic anhydride and PCl_5:[1039] Phthalic anhydride (1 mole sublimed) and pure PCl_5 (1.06 moles) are heated in a 500-ml round-bottomed flask fitted with a reflux condenser and a $CaCl_2$ tube and placed in an oil-bath at 150°. After 12 h the reflux condenser is replaced by a downward water-condenser and the bath-temperature is raised gradually to 250°. Most of the $POCl_3$ formed distils off. The residual crude dichloride, when distilled, has b.p. 131–133°/9–10 mm, the yield being 92%. The product contains a little phthalic anhydride.

Phthaloyl chloride from phthalic anhydride and $SOCl_2$:[1093] Phthalic anhydride (300 g) and anhydrous $ZnCl_2$ (1.5 g) are heated to 220° in a three-necked flask fitted with a reflux condenser and stirrer. Then $SOCl_2$ (241 g) is allowed to run into the stirred mixture at such a rate that the temperature does not fall below 220°, after which the whole is distilled at greatly reduced pressure. At 119–122°/4.5 mm this gives 380 g of distillate, from which, on cooling, 22 g of phthalic anhydride crystallizes. Filtration from this gave phthaloyl dichloride that was shown by a Cl determination to be 94% pure, which suffices for many purposes.

Succinic anhydride (20 g), anhydrous $ZnCl_2$ (1 g), and $SOCl_2$ (34 g), reacting at 120° during 10 h, give analogously a 74% yield of **succinyl dichloride.**[1094]

Phosphorus trichloride (PCl_3), b.p. 74.5°, is used particularly for preparation of volatile carboxylic acid chlorides (reaction b). Usually about 1.1 moles of the carboxylic acid is allowed to react with 0.5 mole of PCl_3 at room temperature or with slight warming until evolution of HCl ceases and then the acid chloride is distilled off; see, for instance, the preparation of acetyl chloride from glacial acetic acid and PCl_3.[33b] The carboxylic acid chloride can also be taken up in a solvent (benzene, light petroleum, or CS_2) at the end of the reaction and used directly for further reactions:

Phenylacetyl chloride:[1095] Phenylacetic acid (0.5 mole) and PCl_3 (0.25 mole) are heated on a steam-bath for an hour. Dry benzene (400 ml) is added to the warm mixture and the benzene solution of phenylacetyl chloride is decanted from the deposited phosphorous acid. If this solution is added to anhydrous $AlCl_3$, a Friedel–Crafts reaction results, giving an 82% yield of deoxybenzoin.

Thionyl chloride ($SOCl_2$), b.p. 78.8°, is the inorganic acid chloride most used for preparation of carboxylic acid chlorides.[1096] It has the advantage that only gaseous products are formed alongside the organic acid chloride (reaction c) and that the excess of $SOCl_2$ is easily removed; the purification of $SOCl_2$ has been described on page 226. Some impurities present in technical $SOCl_2$, such as SO_3 and H_2SO_4, may influence the course of its reactions.[1097]

[1093] L. P. Kyrides, *J. Amer. Chem. Soc.*, **50**, 206 (1937).

[1094] P. Ruggli and A. Maeder, *Helv. Chim. Acta*, **26**, 1476 (1943).

[1095] C. F. H. Allen and W. E. Barker, *Org. Syn.*, Coll. Vol. II, 156 (1943).

[1096] H. Meyer, *Monatsh. Chem.*, **22**, 109, 415 (1901).

[1097] H. Meyer and R. Turnau, *Ber. Deut. Chem. Ges.*, **42**, 1163 (1909).

On distillation of phenylpropiolyl chloride, b.p. 105–107°/11 mm, that has been prepared by use of technical $SOCl_2$, **explosive decomposition** twice resulted; but distillation of phenylpropiolyl chloride and of cinnamoyl chloride, b.p. 136°/11 mm, was uneventful when the $SOCl_2$ used had been freed from high-boiling impurities by a single fractional distillation.[1098] Pure $SOCl_2$ can be used also for the preparation of carboxylic acid chlorides containing C=C groupings.

The carbonyl groups of CHO, CO, or COOR groups present in keto, formyl, or alkoxycarbonyl carboxylic acids are not attacked by boiling $SOCl_2$, in contrast to their behavior towards PCl_5. Alkoxy groups are relatively stable to PCl_5 and $SOCl_2$, but both these reagents react with alcoholic OH groups and usually with phenolic OH groups.[1099] With hydroxy carboxylic acids it is best to mask the OH groups before converting the COOH into COCl, *e.g.*, by acetylation; this is illustrated by the preparation of acetylmandeloyl chloride.[1100]

Hydroxy carboxylic acids having suitable further substituents can also be treated directly with $SOCl_2$ under mild conditions. Thus 2,3,5,6-tetrabromo-4-hydroxybenzoic acid and $SOCl_2$ at 50° afford the acid chloride in almost quantitative yield; but at higher temperatures condensation occurs giving products of higher molecular weight.[611]

Pyridine catalyses the reaction of carboxylic acids with $SOCl_2$, addition of 1 mole of pyridine per mole of $SOCl_2$ permitting preparation of sensitive acid chlorides under mild conditions.[1101–1103] Adding dimethylformamide also assists the preparation of acid chlorides by $SOCl_2$;[1104] since this reaction proceeds by way of formamidoyl chloride it is reported on page 250.

$SOCl_2$ also reacts with alkali salts of carboxylic acids.

Preparation of carboxylic acid chlorides by $SOCl_2$: A carboxylic acid is dropped, with stirring, into $SOCl_2$ (about 1.2 moles per mole), the flask being cooled in running water when necessary. A larger excess of $SOCl_2$ may be used but this does not increase the yields. If the acid is solid, the $SOCl_2$ is poured or dropped onto it. An efficient reflux condenser must be used. The mixture is warmed on a water-bath to 50–80° until evolution of SO_2 and HCl ceases, the excess of $SOCl_2$ is distilled off, usually at water-pump vacuum, and the crude acid chloride is fractionated. See, for example, the preparation of benzoyl chloride,[33g] butyryl chloride,[1105] and isobutyryl chloride.[1106] Yields are usually around 90%.

In many cases the crude acid chloride can be used for further reactions. For instance, a mixture of adipic acid (1 mole) and $SOCl_2$ (3 moles) is warmed at 50–60° until evolution of HCl and SO_2 ceases (4 h) and the excess of $SOCl_2$ is distilled off in a vacuum; the resulting crude **adipoyl chloride** can be used for preparation of 1,6-diphenyl-1,6-hexanedione.[1107]

Warming 4-phenylbutyric acid (0.2 mole) and pure $SOCl_2$ (0.27 mole) cautiously together, allowing them to react for 30 min without heating and then for 10 min on a water bath, and removing the excess of $SOCl_2$ at a water-pump vacuum give crude **4-phenylbutyryl chloride,** which can be dissolved in CS_2 and treated with $AlCl_3$ for ring closure to 1-tetralone.[950]

Dicarboxylic ester chlorides:[1108] Methyl hydrogen succinate (2 moles) and $SOCl_2$ (2.4 moles) are warmed at 40° for 1 h, left overnight at room temperature, heated for a

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[1098] K. von Auwers and E. Risse, *Ber. Deut. Chem. Ges.*, **64**, 2220 (1931).

[1099] H. Meyer, *Monatsh. Chem.*, **22**, 429 (1901).

[1100] K. Thayer, *Org. Syn.*, **4**, 1 (1925).

[1101] P. Carré and D. Libermann, *C. R. Hebd. Séances Acad. Sci.*, **199**, 1422 (1934).

[1102] W. R. Brown, *J. Chem. Soc.*, **1945**, 601.

[1103] J. P. E. Human and J. A. Mills, *Nature*, **158**, 877 (1956).

[1104] H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

[1105] B. Helferich and W. Schaefer, *Org. Syn.*, **9**, 32 (1929).

[1106] R. E. Kent and S. M. McElvain, *Org. Syn.*, Coll. Vol. III, 490 (1955).

[1107] R. C. Fuson and J. T. Walker, *Org. Syn.*, Coll. Vol. II, 169 (1943).

[1108] J. Cason, *Org. Syn.*, Coll. Vol. III, 170 (1955).

further 2 h at 40°, freed from the excess of $SOCl_2$ in a vacuum, and distilled, affording **methyl-3-(chloroformyl)propionate,** b.p. 92–93°/18 mm, in 90–93% yield. Heating to too high a temperature leads to formation of succinic anhydride by loss of methyl chloride.

The ester chlorides of glutaric, adipic, and sebacic acid may be obtained analogously; they should be distilled at 4 mm or at least as fast as possible.

The **methyl ester chloride of oxalic acid:** Potassium ethyl oxalate (50 g) is covered with dry ether, and $SOCl_2$ (80 g) is dropped in with ice-cooling. The cooling bath is then removed and the mixture left at room temperature until reaction starts, then finally heated for 15 h under reflux on a water-bath. The precipitated KCl is filtered off and washed with ether, and the liquids are fractionated. The fraction distilling at 125–138° consists mainly of the ester chloride and can be used directly for Friedel–Crafts reactions. Yields are up to 70%. A further amount of the ester chloride can be obtained by re-treating the foreruns with $SOCl_2$.

Preparation of carboxylic acid chlorides by $SOCl_2$ and pyridine:[1101–1103] The carboxylic acid (1 mole) is dissolved in ten times its volume of a dry solvent (preferably ether; or benzene, $CHCl_3$, or CCl_4) containing dry pyridine (1 mole), and exactly 1 mole of pure $SOCl_2$ is dropped in with stirring at about 0°. Pyridine hydrochloride separates (except from $CHCl_3$). The mixture is left for an hour at 15–20° for completion of reaction. Sensitive carboxylic acid chlorides are used at once in this solution, *e.g.*, by addition to a mixture of an alcohol or amine with 1 mole of pyridine.

Carboxylic acid bromides are preparatively much less important than the chlorides. They can be obtained from the acids by using PBr_3 or red phosphorus and bromine, or from the acid chlorides and dry HBr.

Acetyl bromide: Bromine (400 g) is allowed to drop slowly onto a mixture of glacial acetic acid (150 g) and red phosphorus (10 g), the mixture is boiled under reflux for an hour, and the acetyl bromide formed is distilled off (b.p. 76°). Acetyl bromide may also be prepared by passing dry HBr (3 moles) into acetyl chloride at room temperature and then distilling the solution.[1109]

Carboxylic acid iodides are obtained from the acid anhydrides by use of PI_3 or of red phosphorus and iodine, or from the carboxylic acid chlorides and dry HI[1109] or CaI_2.[1110]

c. Replacement of OH in the COOH group by chlorine or bromine by means of organic acid halides

Organic acid halides, particularly the chlorides, can also be used to substitute halogen for OH in the carboxylic acid group provided that either the equilibrium (a) is shifted to the right by continuously distilling off the RCOCl formed or the primary exchange reaction is followed by secondary reactions that involve removal of HCl, as in (b)—(f).

$$RCOOH + R'COCl \rightleftharpoons RCOCl + R'COOH \qquad \ldots (a)$$

$$RCOOH + o\text{-}C_6H_4(COCl)_2 \longrightarrow RCOCl + o\text{-}C_6H_4(CO)_2O + HCl \qquad \ldots (b)$$

$$RCOOH + ClCOCOCl \longrightarrow RCOCl + CO + CO_2 + HCl \qquad \ldots (c)$$

$$RCOOH + ClCOCl \longrightarrow RCOCl + CO_2 + HCl \qquad \ldots (d)$$

$$RCOOH + C_6H_5CCl_3 \longrightarrow RCOCl + C_6H_5COCl + HCl \qquad \ldots (e)$$

$$RCOOH + Cl_2CHOCH_3 \longrightarrow RCOCl + HCOOCH_3 + HCl \qquad \ldots (f)$$

[1109] H. Staudinger and F. Anthes, *Ber. Deut. Chem. Ges.*, **46**, 1431 (1913).

[1110] H. Spindler, *Ann. Chem.*, **231**, 272 (1885).

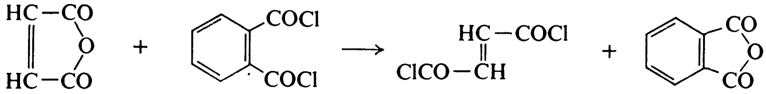
Reaction (a) is used for preparation of volatile carboxylic acids from 1 mole of the corresponding acid and 1.5–2 moles of benzoyl chloride.[1111,1112]

Acryloyl chloride:[1113] A mixture of acrylic acid (3 moles) and benzoyl chloride (6 moles) containing hydroquinone (0.5 g) is distilled at a moderate speed through a 25-cm column, and the portions boiling up to 85° (mostly at 60–70°) are collected in a receiver containing hydroquinone (0.5 g) and cooled in ice. The distillate (215–225 g) is redistilled through the same column, the fraction of b.p. 72–74°/740 mm being collected. The yield is 185–195 g. Yields obtained by using inorganic acid chlorides are not so good. The benzoic acid can be recovered by boiling the distillation residue with water and some H_2SO_4 for 2 h (ca. 90% recovery).

Crotonyl chloride and trichloroacetyl chloride can be obtained similarly.[1111]

In accord with reaction (a), distilling potassium [1-^{14}C]acetate, benzoic acid, and benzoyl bromide gives 75–90% of [1-^{14}C]acetyl bromide.[1114]

If 1 mole of a carboxylic acid is dropped into about 1.1 moles of phthaloyl chloride at about 130–140°, then the carboxylic acid chloride formed in reaction (b), if of suitable boiling point, can be continuously distilled off through a column in about 90% yield.[1093] Acid anhydrides can also be converted into acid chlorides by phthaloyl chloride if $ZnCl_2$ is added:



Fumaroyl chloride:[1115] Maleic anhydride (98 g), *ca.* 94% phthaloyl chloride (230 g), and anhydrous $ZnCl_2$ (2 g) are placed in a flask fitted with a thermometer reaching almost to the bottom and with a 30-cm column which has a heating mantle and is attached to a descending condenser. The mixture is heated for 2 h in an oil-bath so that the internal temperature of the mixture is 130–135° (not higher!) and then allowed to cool to 90–95°, whereafter the crude fumaroyl dichloride is distilled off as fast as possible (b.p. 60–85°/14 mm). Slow fractionation of the distillate gives a 82–95% yield of chloride, b.p. 62–64°/13 mm. This is best stored in a sealed vessel.

Oxalyl chloride (reaction c) is more reactive than phthaloyl chloride and its use enables the chlorides to be obtained from sensitive carboxylic acids[1116] or their Na salts in benzene[1117] at ambient temperature or below. Some of the nitro derivatives of benzoic acid afford only the mixed anhydrides when 2 moles of the acid are heated with 1 mole of oxalyl chloride.[1118] To obtain the free acid chloride, and not its hydrochloride, from basic carboxylic acids an alkali salt of this acid may be treated with oxalyl chloride.

Nicotinoyl chloride:[1119] Oxalyl chloride (12.5 g) in dry benzene (25 ml) is dropped into a suspension of dry, powdered potassium nicotinate (16.1 g) in dry benzene (75 ml), stirred and cooled in an ice-bath. After 15–20 minutes' further stirring, the unmelted ice is removed from the bath, which is allowed to come to room temperature and then heated to the b.p. within 30 min. After cooling, the mixture is filtered from KCl, freed from solvent at water-

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[1111] H. C. Brown, *J. Amer. Chem. Soc.*, **60**, 1325 (1938).

[1112] J. Forrest, D. A. Liddel, and S. H. Tucker, *J. Chem. Soc.*, **1946**, 454.

[1113] G. H. Stempel Jr., R. P. Cross, and R. P. Mariella, *J. Amer. Chem. Soc.*, **72**, 2299 (1950).

[1114] H. S. Anker, *J. Biol. Chem.*, **176**, 1333 (1948).

[1115] L. P. Kyrides, *Org. Syn.*, **20**, 51 (1946); Coll. Vol. III, 422 (1955).

[1116] J. Heer and K. Miescher, *Helv. Chim. Acta*, **29**, 1071, 1895 (1946).

[1117] A. L. Wilds and C. H. Shunk, *J. Amer. Chem. Soc.*, **70**, 2427 (1948).

[1118] R. Adams and L. H. Ulich, *J. Amer. Chem. Soc.*, **42**, 599 (1920).

[1119] H. N. Wingfield Jr., W. R. Harlan, and H. R. Hammer, *J. Amer. Chem. Soc.*, **75**, 4364 (1953).

pump vacuum, and distilled, giving at least an 85% yield. The sodium salt gives a poorer yield.

Acid bromides can be obtained analogously from carboxylic acids or their Na salts by means of oxalyl bromide.[1118]

Oxalyl bromide, b.p. 102–103°/720 mm, is obtained in 85% yield by passing HBr [8 moles per mole of $(COCl)_2$] into pure oxalyl chloride (100 g) for about 12 h and, after a further 6 h, fractionating the mixture. Discoloration due to bromine is removed by shaking with mercury.[1109]

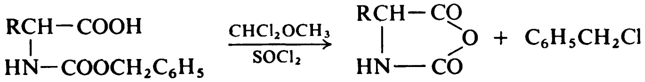
Aliphatic acid chlorides can also be prepared from the acid by reaction with phosgene (d). Yields are increased by fine subdivision and by rapid passage of the $COCl_2$ through the reaction vessel which consists of a cylinder into which a glass frit is sealed and which is heated in a H_2SO_4 bath. The most favorable temperatures are between 140° and 160°, and yields are 70–90%.[1120]

Benzotrichloride and dichloromethyl methyl ether (for preparation see pages 170 and 252) can be considered as chlorides of orthobenzoic acid and of the monomethyl ester of orthoformic acid, respectively, and react with carboxylic acids according to (e) and (f); small amounts of $ZnCl_2$ are usually added. Carboxylic acid anhydrides react analogously to the chlorides, but produce no HCl. Since the reaction with benzotrichloride always gives benzoyl chloride alongside the other chloride RCOCl, reaction (e) can be used only when the latter product boils sufficiently lower or higher than C_6H_5COCl. As examples, fluoroacetyl chloride has been prepared from fluoroacetic acid by means of benzotrichloride,[1121] and phthaloyl chloride from phthalic anhydride.[1093]

The reactions with benzotrichloride usually require temperatures above 100°, but dichloromethyl methyl ether reacts with carboxylic acids even in the cold. Good yields are obtained when 0.01–0.1 mole-% of $ZnCl_2$ is added to the reaction mixture, which is then heated for a short time at 70–100°. When the sodium salt of the carboxylic acid forms the starting material, heating should be for 2 hours at 90–100°.

Carboxylic acid chlorides from the acid and dichloromethyl methyl ether, $CHCl_2OCH_3$:[927] The acid (1 mole) and $ZnCl_2$ (*ca.* 0.01 mole) is treated with $CHCl_2OCH_3$ (1.25 moles) in a rapid sequence of drops and, when evolution of HCl ceases, the mixture is warmed for about 1 h at 70–100°. The methyl formate (b.p. 30–32°) and any excess of $CHCl_2OCH_3$ (b.p. 84–86.5°) are distilled off and the residue is fractionated.

When tosylamino or phthaloylamino carboxylic acids are warmed for a short time at 80–85° with an excess of $CHCl_2OCH_3$, the corresponding acid chlorides are formed in good yield. However, the acid chlorides formed as primary product from α-(benzyloxycarbonylamino) acids and $SOCl_2$ or an excess of $CHCl_2OCH_3$ split off benzyl chloride smoothly, giving *N*-(carboxyamino) acid anhydrides[1122] which are important intermediates in peptide synthesis.



[1120] J. Prat and A. Etienne, *Bull. Soc. Chim. France*, [v], **11**, 30 (1944).

[1121] E. Gryszkiewicz-Trochimowski, A. Sporzynski, and J. Wnuk, *Rec. Trav. Chim.*, **66**, 419 (1947).

[1122] K. Poduska and H. Gross, *Chem. Ber.*, **94**, 527 (1961).

Chloromethyl dichloromethyl ether, $CH_2ClOCHCl_2$, reacts similarly to dichloromethyl methyl ether.[1123]

A very reactive agent for the preparation of acid chlorides is provided by (dichloromethyl)dimethylamine, $(CHCl_2)N(CH_3)_2$, which, analogously to dichloromethyl methyl ether, is to be regarded as the dichloride dimethylamide of orthoformic acid and is formulated as a salt (A).[1104]

$$[(CH_3)_2\overset{+}{N}{=}CHCl]Cl^- \underset{(A)}{\longleftrightarrow} [(CH_3)_2N{-}\overset{+}{C}HCl]Cl^-$$

It is formed on treatment of dimethylformamide with $SOCl_2$, PCl_5, PCl_3, oxalyl chloride, or phosgene and affords the acid chlorides from carboxylic or suflonic acids [reaction (g)].

$$RCOOH + [(CH_3)_2\overset{+}{N}{=}CHCl]Cl^- \longrightarrow RCOCl + (CH_3)_2NCHO + HCl \quad \ldots\ (g)$$

The Cl in the cation of the salt (A) may be replaced by OSOCl or the residue from one of the chlorinating agents mentioned above. Formation of the acid chloride by $SOCl_2$ is activated by even catalytic amounts of dimethylformamide (1/20 mole per mole of carboxylic acid) since, according to (g), dimethylformamide is continuously re-formed. Carboxylic acids can be converted into their chlorides by $SOCl_2$–dimethylformamide even when they react poorly with $SOCl_2$ alone.

For example, heating *p*-nitrobenzoic acid (50.1 g), chlorobenzene (160 ml), dimethylformamide (2.4 ml), and $SOCl_2$ (22.4 ml) for 0.5 h at 90–95° gives ***p*-nitrobenzoyl chloride** in about 90% yield.[1104]

Sulfonyl chlorides can also be obtained by means of $SOCl_2$–dimethylformamide, from sulfonic acids or their Na salts.

Imidoyl chlorides and carboxylic acids in neutral medium also afford acid chlorides from the corresponding carboxylic acids.[1124] Imidoyl chlorides are obtained by treating carboxamides with PCl_5 in benzene or $CHCl_3$.[1124–1126]

$$RCCl{=}NR' + R''COOH \longrightarrow RCONHR' + R''COCl$$

The imidoyl chloride and the carboxylic acid are boiled for about 30 min in ether or benzene and the solution is then worked up by, *e.g.*, distillation.

Finally, phosphorus acid chlorides or bromides containing organic groups can be used for replacing the OH of carboxylic acids by Cl or Br. Carboxylic acids or their anhydrides afford the acid chlorides or bromides when heated for 30–60 minutes at 100° with 2,2,2-trichloro-[1127] or 2,2,2-tribromo-1,3,2-benzodioxaphosph(v)ole (pyrocatechylphosphorus trihalides),[1022,1128] yields being good. This method has the advantages that these trihalides have

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[1123] A. Rieche, H. Gross, and E. Höft, *Angew. Chem.*, **70**, 602 (1958).

[1124] F. Cramer and K. Baer, *Chem. Ber.*, **93**, 1232 (1960).

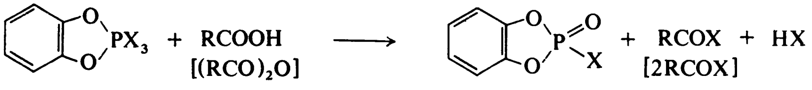
[1125] O. Wallach, *Ann. Chem.*, **184**, 1 (1877); **214**, 193 (1882).

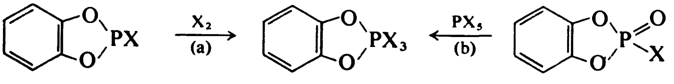
[1126] J. von Braun, F. Jostes, and W. Münch, *Ann. Chem.*, **453**, 125 (1927).

[1127] H. Gross and J. Gloede, *Chem. Ber.*, **96**, 1387 (1963).

[1128] J. Gloede and H. Gross, *Chem. Ber.*, **100**, 1770 (1967).

no oxidizing action, unlike the phosphorus pentahalides PX_5 that can be used for the same purpose but dissociate into PX_3 and X_2, and further that they





are readily soluble in organic solvents such as ether, chloroform, and benzene. The carboxylic acid halides are distilled off from the *P*-oxide monohalides formed as by-products (X = Cl, b.p. 120–122°/13 mm; X = Br, b.p. 133 to 134°/12 mm), or, if necessary, the latter are separated by hydrolysis. The trihalides may be prepared (a) from the monohalides and chlorine[1127] or bromine[1022] or (b) from the oxyhalides by PX_5.

2,2,2-Trichloro-1,3,2-benzodioxaphosph(v)ole:[1127] (a) Chlorine is led into a stirred and ice-cooled solution of 2-chloro-1,3,2-benzodioxaphosphole (15 g) in dry CCl_4 (40 ml) until chlorine can be recognized in the condenser by its color. Vacuum-distillation then gives a 94% yield (19.8 g) of the trichloride, m.p. 61–62°, b.p. 132–135°/13 mm.

(b) PCl_5 (20 g) is added to recovered 2-chloro-1,3,2-benzodioxaphosphole 2-oxide (15 g) in benzene (60 ml). Boiling for 90 min under reflux and subsequent distillation in a vacuum gives an 88% yield (17 g) of the trichloride.

Carboxylic acid chlorides from carboxylic acids and 2,2,2-trichloro-1,3,2-benzodioxaphosph(v)ole:[1127] A mixture of the acid (0.02 mole) and the trichloride (0.02 mole) is heated and the acid chloride is then separated by distillation. Yields are: acetyl chloride 67% (after 30 min at 100°; b.p. 50–51°); benzoyl chloride 81% (after 60 min at 100°; b.p. 82–85°/11 mm); chloroacetyl chloride 77% (after 30 min at 150°; b.p. 105–108°). In other cases the reaction mixture can be diluted with ether, poured on ice, and well shaken therewith; the aqueous phase should be extracted again with ether, the organic phases then being washed with sodium hydrogen carbonate solution and with water and dried over Na_2SO_4, the ether removed, and the residue distilled.

Carboxylic acid bromides can also be obtained from the acids or anhydrides and dibromotriphenylphosphorane in boiling chlorobenzene. A suspension of the reagent is first made from equimolar amounts of triphenylphosphine and bromine in dry chlorobenzene at 0–5°.[1129]

$$\mathrm{RCOOH + (C_6H_5)_3PBr_2 \longrightarrow RCOBr + (C_6H_5)_3PO + HBr}$$

7. Conversion of $\rangle C{=}O$ into $\rangle CCl_2$ or $\rangle CBr_2$

Methods for preparation of dichlorides from aldehydes or ketones do not differ in principle from those for acid chlorides. The reaction is exemplified by the preparation of **benzylidene dichloride** from benzaldehyde, this product being difficult to obtain pure by direct chlorination of toluene.

Heating benzaldehyde (1 mole) with oxalyl chloride (1.5 moles) in a bomb tube for 2 h at 130–140° gives almost the theoretical amount of benzylidene dichloride.[1130] Alternatively,

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[1129] H.-J. Bestmann and L. Mott, *Ann. Chem.*, **693**, 132 (1966).

[1130] H. Staudinger, *Ber. Deut. Chem. Ges.*, **42**, 3976 (1909).

$SOCl_2$ is added gradually, with cooling, to benzaldehyde;[1131] when evolution of SO_2 ceases, the solution is shaken with water, and the oil that separates is taken up in ether and shaken with sodium bisulfite solution to remove unchanged benzaldehyde; after filtration, the ether is distilled off; distillation of the residue affords pure benzylidene dichloride in good yield.

Conversion of $\rangle C{=}O$ into $\rangle CCl_2$ is often carried out by means of PCl_5. Dropping an aliphatic ketone or aldehyde onto a slight excess of finely powdered PCl_5 at 0° replaces the carbonyl-oxygen atom by 2Cl, but loss of HCl leads to monochloroethylenes as by-products and these become the main products from aryl methyl ketones.[1132]

$$RCOCH_2R' + PCl_5 \longrightarrow RCCl_2CH_2R' + POCl_3$$

$$RCOCH_2R' + PCl_5 \longrightarrow RCCl{=}CHR' + HCl + POCl_3$$

Both of these products can be used as starting materials for synthesis of acetylenes.

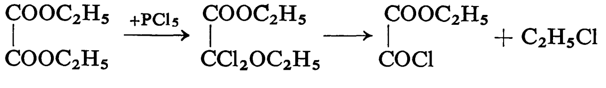
PBr_5 can be used only with very reactive compounds. The $\rangle C{=}O$ of acetaldehyde can be replaced by $\rangle CBr_2$ by means of PCl_3Br_2, which is produced in the reaction flask by adding Br_2 to PCl_3 with cooling.[223] The $\rangle C{=}O$ of alkyl formates can be converted into $\rangle CBr_2$ by 2,2,2-tribromo-1,3,2-benzodioxaphosph(v)ole (see page 251), a method that renders dibromomethyl methyl ether and butyl dibromomethyl ether accessible.[1022] Even HBr converts benzaldehyde into benzylidene dibromide.[1133]

The C=O of alkoxycarbonyl groups are rarely attacked by PCl_5, but the exceptions in which attack does occur are preparatively important. Alkyl formates and PCl_5 give good yields of alkyl dichloromethyl ethers,[1134,1135] which can be separated from $POCl_3$ by fractional distillation.

Dichloromethyl methyl ether:[1136] PCl_5 (832 g, 4.0 moles) and $POCl_3$ (250 ml) are stirred together in a 2-l three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. Methyl formate (272 ml, 4.4 moles) is dropped in within 105 min, with cooling in ice-water such that the inner temperature is kept at 10–20°. After the addition, stirring is continued at an inner temperature of not more than 30° until all the PCl_5 has dissolved (ca. 1 h). Then the stirrer is removed, the reflux condenser is replaced by a descending condenser, and the whole mixture is distilled at 80–120 mm (bath at 50–60°) into a receiver cooled to −10° to −15°. The distillate is redistilled through a column, 90 cm in length and 30 mm in diameter, fitted with an evacuated mantle and filled with Raschig rings (5 × 5 mm), giving a reflux ratio of 1 : 10. The 80–100° fraction is fractionated once more in the same way, whereupon dichloromethyl methyl ether, n_D^{20} 1.4303, passes over between 83° and 85.5° in 77–79.5% yield (353–363 g).

$$HCOOR + PCl_5 \longrightarrow CHCl_2OR + POCl_3$$

Ethyl (chloroformyl)formate (oxalic acid monoethyl ester chloride), b.p. 130–132° (cf. page 247), can be obtained by way of ethyl dichlorodiethoxyacetate which splits off ethyl chloride, sometimes spontaneously and always in the presence of a little metallic platinum.[1137,1138]



$$\begin{matrix} COOC_2H_5 \\ | \\ COOC_2H_5 \end{matrix} \xrightarrow{+PCl_5} \begin{matrix} COOC_2H_5 \\ | \\ CCl_2OC_2H_5 \end{matrix} \longrightarrow \begin{matrix} COOC_2H_5 \\ | \\ COCl \end{matrix} + C_2H_5Cl$$

[1131] F. Loth and A. Michaelis, *Ber. Deut. Chem. Ges.*, **27**, 2548 (1894).

[1132] T. L. Jacobs, *Org. Reactions*, **5**, 20 (1949).

[1133] D. Vorländer, *Ann. Chem.*, **341**, 22 (1905).

[1134] H. Fischer and A. Schwarz, *Ann. Chem.*, **512**, 240 (1934).

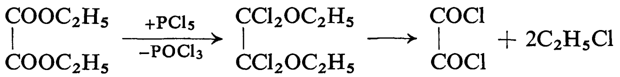
[1135] A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, **93**, 93 (1960).

[1136] H. Gross, A. Rieche, E. Höft, and E. Beyer, *Org. Syn.*, **47**, 47 (1967).

[1137] R. Scholl and W. Egerer, *Ann. Chem.*, **397**, 326 (1913).

[1138] L. Bert and R. Barré, *Bull. Soc. Chim. France* [iv], **37**, 1041 (1945); **41**, 47, 1165 (1927).

To obtain good yields of the ester chloride it is important to use an excess of the oxalic ester so as to avoid conversion of both C=O groups into CCl_2 and the reactions that follow therefrom; also the temperature must be kept as low as possible and the $POCl_3$ formed must be separated before the dichloro ethoxy ester can decompose:[1139]



$$\begin{matrix} COOC_2H_5 \\ | \\ COOC_2H_5 \end{matrix} \xrightarrow[-POCl_3]{+PCl_5} \begin{matrix} CCl_2OC_2H_5 \\ | \\ CCl_2OC_2H_5 \end{matrix} \longrightarrow \begin{matrix} COCl \\ | \\ COCl \end{matrix} + 2C_2H_5Cl$$

A mixture of PCl_5 (2 kg; powdered immediately before use) and diethyl oxalate (1.8 kg) is heated at 95–100° for 4 days with exclusion of moisture. The reaction time can be shortened by shaking. $POCl_3$ (b.p. 27°/18 mm) is then distilled off in a vacuum, and the residue is heated with palladium black (0.5 g) at 95–98°, until no more ethyl chloride is split off (2 h), and it is worked up by vacuum-distillation. The ester chloride (1150 g) has b.p. 39.7°/18 mm.

IV. Replacement of C–N bonds by C–halogen bonds

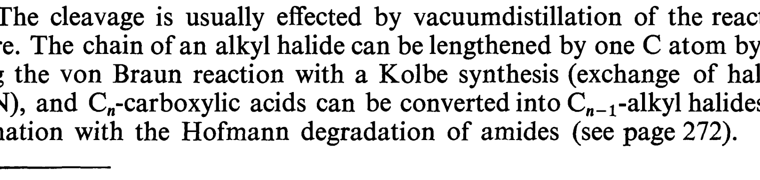
1. Replacement of C-N bonds by C-halogen bonds in aliphatic compounds

a. Replacement of C-N bonds by C-halogen bonds in aliphatic amines by means of PCl_5 or PBr_5

Imidoyl chlorides are decomposed by heat into nitriles and alkyl chlorides.[1140] This is the basis of the von Braun reaction,[1141] in which alkylamines, phenylalkylamines, α,ω-diamines, or secondary cyclic amines are first benzoylated, next the benzoyl compounds are converted into (a) α-chlorobenzylidene amines or (b) α,α-dichlorobenzyl amines, and finally these products are cleaved thermally.

$$RNH_2 \xrightarrow{+C_6H_5COCl} RNH{-}COC_6H_5 \xrightarrow[-POX_3 \atop -HX]{+PX_5} RN{=}CX{-}C_6H_5 \qquad (a)$$

$$\longrightarrow RX + C_6H_5CN$$



(b)

X = Cl or Br

The cleavage is usually effected by vacuumdistillation of the reaction mixture. The chain of an alkyl halide can be lengthened by one C atom by combining the von Braun reaction with a Kolbe synthesis (exchange of halogen for CN), and C_n-carboxylic acids can be converted into C_{n-1}-alkyl halides by combination with the Hofmann degradation of amides (see page 272).

[1139] K. Kindler, W. Metzendorf, and Dschi-yin-Kwok, *Ber. Deut. Chem. Ges.*, **76**, 311 (1943).

[1140] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **33**, 611 (1900).

[1141] J. von Braun and co-workers, *Ber. Deut. Chem. Ges.*, **37**, 2915, 3210 (1904); **38**, 2336 (1905); **39**, 2018 (1906); **43**, 2837 (1910); **55**, 3526 (1922).

General procedure for the von Braun reaction with PX_5:[1142] The amine (1 mole) is first benzoylated with benzoyl chloride in the presence of sodium hydroxide solution. The dry benzoyl derivative is warmed carefully with PCl_5 or PBr_5, with exclusion of water, until a homogeneous melt or solution results. The PX_5 may be produced in the reaction mixture by adding to the benzoyl derivative, first, PBr_3 (*ca.* 1.02 moles) and then Br_2 (1.01 moles) with stirring and cooling.[1143–1145] Alternatively, for preparation of bromides, the PBr_5 may be replaced by PCl_3Br_2; for this variation, before the amine is added, bromine (1 mole) is added slowly to PCl_3 and this mixture is shaken with cooling in ice.[1146]

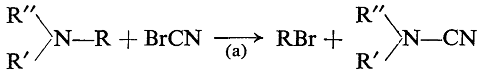
The product can be worked up in many different ways. $POCl_3$ (b.p. 105.4°) is usually distilled off from the reaction mixture at atmospheric pressure; a fractionating column is used if the organic chloride produced has a low boiling point, but this case rarely arises since the von Braun reaction is generally used for preparation of relatively high-boiling halides. $POBr_3$ (b.p. 193°) usually distils together with the organic bromide and benzonitrile (b.p. 191°) at water-pump vacuum (external temperature 70–120°). For preparation of high-boiling bromides most of the $POBr_3$ is distilled off at water-pump vacuum and the imidoyl bromide is then decomposed at oil-pump vacuum.[1147]

POX_3 is removed from the distillate by treatment with ice-water. However, it is generally impossible to separate benzonitrile from the organic halide by distillation; it can be hydrolysed to benzoic acid by boiling the mixture for several hours with concentrated HCl or 48% HBr; the halide is then isolated by extraction in ether or steam-distillation and freed completely from benzoic acid by treatment with sodium hydroxide solution. Benzonitrile can also be separated from the organic halide by adding absolute ethanol (1 mole per mole of benzoyl amine used) to the dry mixture and passing in dry HCl; after 2–5 days ether is added, precipitating the ether-insoluble ethyl benzimidoate hydrochloride; this is filtered off and the ethereal solution of the organic halide is washed with water and worked up by distillation.

As examples for the conversion of secondary cyclic amines into α,ω-diamines may be cited the preparation of 1,5-dibromopentane from 1-benzoylpiperidine[1148] and of 1,5-dibromo-3-methylpentane from 1-benzoyl-4-methylpiperidine.[1143]

b. Replacement of C–N bonds by C–Br bonds in aliphatic amines by means of cyanogen bromide

The von Braun degradation of tertiary cyclic amines by cyanogen bromide[1149,1150] is less important as a preparative reaction than the treatment of benzoyl amines with PX_5, but it plays a role in the determination of the structure of alkaloids (see, *e.g.*, Bartlett *et al.*[1151]).



$$\begin{matrix}R'' \\ R'\end{matrix}\!\!>\!N{-}R + BrCN \xrightarrow[(a)]{} RBr + \begin{matrix}R'' \\ R'\end{matrix}\!\!>\!N{-}CN$$

The effect of cyanogen bromide on acyclic tertiary amines is to remove the smallest *n*-alkyl group (up to *n*-hexyl) as alkyl bromide in reaction (a). This reaction usually leads to the alkyl bromide that most readily exchanges its bromine; thus, when R is allyl or benzyl it readily appears as the bromide RBr, but when R is phenyl this is not so. The quaternary ammonium bromide is obtained as by-product, by reaction of the RBr with the tertiary amine used,

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[1142] J. von Braun and W. Sobecki, *Ber. Deut. Chem. Ges.*, **44**, 1464, 2867 (1911).

[1143] N. J. Leonard and Z. W. Wicks, *J. Amer. Chem. Soc.*, **68**, 2402 (1946).

[1144] J. A. Arvin and R. Adams, *J. Amer. Chem. Soc.*, **50**, 1983 (1928).

[1145] N. J. Leonard and E. W. Nommensen, *J. Amer. Chem. Soc.*, **71**, 2809 (1949).

[1146] J. von Braun and G. Irmisch, *Ber. Deut. Chem. Ges.*, **65**, 880 (1932).

[1147] W. John and H. Pini, *Z. Physiol. Chem.*, **273**, 225 (1942).

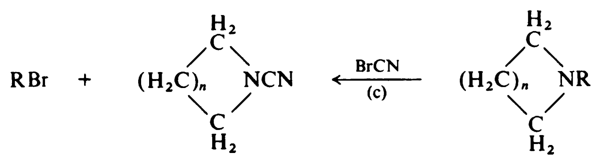
[1148] J. von Braun, *Org. Syn.*, **9**, 70 (1929).

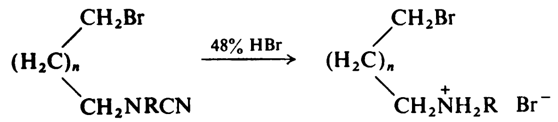
[1149] J. von Braun, *Ber. Deut. Chem. Ges.*, **33**, 1438 (1900); **40**, 3914 (1907); **42**, 2219 (1909).

[1150] H. A. Hageman, *Org. Reactions*, **7**, 198 (1953).

[1151] M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.*, **80**, 126 (1958).

wherefore an excess of BrCN should be present throughout the reaction. Only small batches should be used because of the toxicity (fume cupboard) and volatility of BrCN (b.p. 62°). The preparation of cyanogen bromide from NaCN and bromine is detailed in *Organic Syntheses.*[1152]





The reaction of tertiary cyclic amines with cyanogen bromide involves either ring fission (b) or dealkylation and retention of the ring (c). 1-Butylpyrrolidine and BrCN in benzene give *N*-(4-bromobutyl)-*N*-butylcyanamide quantitatively by reaction (b).[1153] On reaction of BrCN with 1-ethylpyrrolidine reaction (b) occurs to the extent of 94%, but reaction (c) intervenes to the extent of 66% with 1-ethylpiperidine.[1154] A good yield of bromoacetonitrile is obtained from piperidinoacetonitrile ($n = 3$, $R = CH_2CN$)[1155] and BrCN in reaction (c).[1156] If R is benzyl there is no fission of a five- or of a six-membered ring.[1157]

General procedure (cf. Hagemann[1150]): A solution of the amine in dry ether, $CHCl_3$, or benzene is added gradually to the BrCN solution (fume cupboard!). The reaction is exothermic. The mixture of amine and BrCN (1–1.1 moles per moles of amine) may also be warmed on a water-bath. By-products, mostly precipitated when a solvent is used, may contain the hydrobromide of the tertiary amine as well as the quaternary ammonium bromide (see above), the requisite HBr being liberated by olefin formation. When no solvent is used, the reaction mixture is extracted with ether. The unused amine and the salts are removed by shaking the solution of *N*-substituted ω-(bromoalkyl)cyanamide with dilute aqueous acid.

The *N*-substituted ω-(bromoalkyl)cyanamide may be isolated by vacuum-distillation, or the crude product may be used for further reactions; for instance, the Br may be replaced by $N(Alkyl)_2$,[1153] or the CN may be split off by boiling 48% HBr. An example of the last-mentioned reaction is the preparation of *N*-(5-bromopentyl)aniline hydrobromide by boiling for 48 h a mixture of 48% HBr and the $Br(CH_2)_4CH_2$–$N(C_6H_5)$–CN obtained from 1-phenylpiperidine and BrCN.[1158]

In other cases the desired product may be the substituted cyanamide formed by dealkylation; see, for instance, the preparation of *N*-methyl-*N*-(1-naphthyl)cyanamide from *N,N*-dimethyl-1-naphthylamine and BrCN described in *Organic Syntheses.*[1159]

[1152] W. W. Hartman and E. E. Dreger, *Org. Syn.*, Coll. Vol. II, 150 (1943).
[1153] R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 626 (1949).
[1154] J. von Braun, *Ber. Deut. Chem. Ges.*, **44**, 1252 (1911).
[1155] E. Knoevenagel, *Ber. Deut. Chem. Ges.*, **37**, 4082 (1904).
[1156] J. von Braun, *Ber. Deut. Chem. Ges.*, **41**, 2113 (1908).
[1157] J. von Braun, *Ber. Deut. Chem. Ges.*, **49**, 2629 (1916); **50**, 45 (1917).
[1158] H. J. Nitzschke and G. Faerber, *Chem. Ber.*, **87**, 1637 (1954).
[1159] W. J. Cressman, *Org. Syn.*, Coll. Vol. III, 608 (1955).

c. Replacement of NH_2 in aliphatic compounds by halogen by means of a nitrosyl halide

Reaction of aliphatic amines[1160] or amino carboxylic acids[1161] with nitrosyl halides (NOX) leads to halides, and not, as in the analogous reaction of aromatic amines, to diazonium halides.

$$RNH_2 + NOX \longrightarrow RX + N_2 + H_2O$$

Nitrosyl chloride (NOCl) or bromide (NOBr) is produced in the reaction mixture by slowly adding sodium nitrite to a solution of the amino carboxylic acid in hydrochloric or hydrobromic acid or in 2.5N-sulfuric acid containing KBr (at 0°).[1162,1163] If bromine is dropped into a cooled solution of an amino acid or its ester in 10–20% aqueous HBr and then nitric oxide is passed in below 0°, then NOBr is formed as an intermediate:[1164]

$$2NO + Br_2 \rightleftarrows 2NOBr$$

The reaction of α-amino carboxylic acids with NOX usually occurs without inversion of configuration at the α-carbon atom.[1165] The sign of rotation may, however, change; for example, (*S*)-2-chloro- or (*S*)-2-bromo-propionic acid is formed from dextrorotatory L(*S*)-alanine . NOX can be used to obtain optically active α-halo aliphatic acids from optically active α-amino acids.

(*R*)- or (*S*)-2-Chloropropionic acid and (*R*)- or (*S*)-2-bromopropionic acid:[1166] Newly powdered $NaNO_2$ (0.32 mole) is added in about 2.5 h to a rapidly stirred solution of optically pure D- or L-alanine (0.2mole) in 6N-HCl or 6N-HBr (250ml) at 0–5°. Stirring is continued for a further 4 h at 0°. Ether-extraction, drying over $CaCl_2$, and fractional distillation then afford 32% of the theoretical amount of (*R*)- or (*S*)-2-chloropropionic acid, b.p. 77°/10 mm, or 60–65% of (*R*)- or (*S*)-bromopropionic acid, b.p. 78°/4 mm, respectively.

d. Halo ketones from diazo ketones

Monohalo or dihalo alkanes, carboxylic acids, or ketones are obtained on treating diazoalkanes,[1167] diazocarboxylic esters,[1168] or diazo ketones with hydrogen halides or halogens. The reaction usually occurs at room temperature or below. However, preparative importance attaches only to the formation of the halo ketones; from diazo ketones they are obtained free from isomers (cf. page 189).

$$RCHN_2 + HX \longrightarrow RCH_2X + N_2 \qquad (X = F, Cl, \text{or } Br)$$

$$RCHN_2 + X_2 \longrightarrow RCHX_2 + N_2 \qquad (X = Cl, Br, \text{or } I)$$

[1160] W. Solonina, *J. Russ. Phys.-chem. Ges.*, **30**, 431 (1898).

[1161] P. Walden, *Ber. Deut. Chem. Soc.*, **28**, 2766 (1895); **29**, 133 (1896).

[1162] K. Pfister and co-workers, *J. Amer. Chem. Soc.*, **71**, 1096 (1949).

[1163] V. I. Maimind, K. M. Ermalaev, and M. M. Shemyakin, *Zh. Obshch. Khim.*, **26**, 2313 (1956); *Chem. Abstr.*, **51**, 4944 (1957).

[1164] E. Fischer and co-workers, *Ber. Deut. Chem. Ges.*, **39**, 2929 (1906); **40**, 489, 1054 (1907); **41**, 890 (1908).

[1165] K. Freudenberg, W. Kuhn, and I. Bumann, *Ber. Deut. Chem. Ges.*, **63**, 2382 (1930); W. A. Cowdrey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, **1937**, 1243; A. Neuberger, *Advan. Protein Chem.*, **4**, 197 (1948).

[1166] S.-C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *J. Amer. Chem. Soc.*, **76**, 6054 (1954).

[1167] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **27**, 1889 (1894).

[1168] T. Curtius, *J. Prakt. Chem.*, [ii], **38**, 430 (1888).

Monohalo ketones may be prepared by starting from pure diazo ketones; an ethereal or benzene solution or suspension of a carboxylic acid chloride (1 mole) is added during 1–2 h to a stirred solution of diazomethane (3 moles) at 0–5°, reaction is allowed to proceed at 20–25°, the solvent is removed in a vacuum, and the product is recrystallized;[1169] α-chloro ketones may be formed as by-products during preparation of the diazo ketone, particularly if an insufficient excess of diazomethane is used; hydrogen halide is often added directly to the ethereal solution of acid chloride and diazomethane;[1170,1171] if then, for example, HBr is used, the resulting α-bromo ketone will contain

$$\mathrm{RCOCl + CH_2N_2 \longrightarrow RCOCHN_2 + HCl}$$

α-chloro ketone as impurity. If a pure bromo ketone is required, the acid bromide can be treated with diazomethane, dry HBr being led into the ethereal solution at 0°.[1172]

Fluoro ketones, *e.g.*, ω-fluoroacetophenone,[1173] are obtained from diazo ketones by means of anhydrous hydrogen fluoride in ether,[1174,1175] chloro ketones by means of dry HCl in ether or methylene chloride,[1176] or by means of concentrated HCl with dioxan[1177] or aqueous acetone.[1178] As examples may be cited the preparation of benzyl chloromethyl ketone from phenylacetyl chloride as described in detail in *Organic Syntheses*,[1179] and the preparation of pure chloroacetone from acetyl chloride.[663] Dry or 42–48% HBr in ether, dioxan, or even light petroleum is used for the preparation of bromo ketones; glacial acetic acid, whose use as solvent has also been described,[1180,1181] is less suitable as with diazo ketones it may lead to acetylated ketols, $\mathrm{RCHCH_2OCOCH_3}$.[1182] Diazo ketones and HI give methyl ketones and iodine.[1183] The reactions with hydrogen halides usually occur at 0–20°.

3-Bromo-1,1-diphenylacetone:[1170,1183] A solution of diphenylacetyl chloride (0.057 mole) in dry ether (100 ml) is dropped into a stirred, ice-cold ethereal solution of diazomethane (from 20 g of methylnitrosourea). The mixture is left for 30 min at 0° and then for 1 h at room temperature, after which the excess of diazomethane and the ether are distilled off and the residue is dissolved in dry ether (100 ml). Into this solution is dropped a mixture of 48% HBr (14 ml) and ether (14 ml), if desired with ice-cooling. When the evolution of N_2 stops, the solution is concentrated. The bromo ketone crystallizes and, when recrystallized from methanol or 2-propanol, has m.p. 66–67°.

[1169] W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 48 (1942).

[1170] R. E. Lutz and J. W. Wilson, *J. Org. Chem.*, **12**, 769 (1947).

[1171] J. W. Wilson, R. E. Lutz, and R. H. Jordan, *J. Org. Chem.*, **12**, 778 (1947).

[1172] J. R. Catch and co-workers, *J. Chem. Soc.*, **1948**, 278.

[1173] I. L. Knunyants, Ya. M. Kissel, and E. G. Bykhovskaya, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1956**, 377; *Chem. Abstr.*, **50**, 15454 (1956).

[1174] R. R. Fraser, J. E. Millington, and F. L. M. Pattison, *J. Amer. Chem. Soc.*, **79**, 1959 (1957).

[1175] G. Oláh and S. Kuhn, *Chem. Ber.*, **89**, 864 (1956).

[1176] R. B. Turner, J. Mills, and A. C. Cope, *J. Amer. Chem. Soc.*, **68**, 2220 (1946).

[1177] R. B. Wagner and J. M. Tome, *J. Amer. Chem. Soc.*, **72**, 3477 (1950).

[1178] P. Ruggli and K. Knecht, *Helv. Chim. Acta*, **27**, 1108 (1904).

[1179] W. D. McPhee and E. Klingsberg, *Org. Syn.*, Coll. Vol. III, 119 (1955).

[1180] K. Balenović, D. Cerar, and L. Filipović, *J. Org. Chem.*, **18**, 868 (1953).

[1181] H. Schlenk, B. G. Lamp, and B. W. De Haas, *J. Amer. Chem. Soc.*, **74**, 2552 (1952).

[1182] J. F. Lane and R. L. Feller, *J. Amer. Chem. Soc.*, **73**, 4231 (1951).

[1183] W. G. Dauben, C. F. Hiskey, and M. A. Muhs, *J. Amer. Chem. Soc.*, **74**, 2083 (1952).

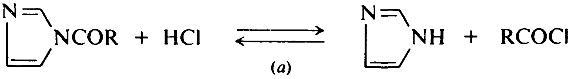
1,12-Dibromo-2,11-dodecanedione:[1171] A solution of sebacoyl dichloride (0.243 mole) in dry ether (75 ml) is dropped during 3 h into one of diazomethane (1.43 moles) in ether (2 l) at 5–10°. The diazo ketone that separates as a solid is not isolated. The mixture is kept overnight and then treated dropwise with stirring with a mixture of 42% HBr (235 g) and ether (200 ml) at 18°, set aside for 8–10 h (cessation of evolution of N_2), and cooled to 0°. The dibromo ketone (yield 87%; m.p. 97–98°) is then filtered off and after repeated recrystallization from ethanol has m.p. 102–103°.

Examples of the application of this reaction to sugar derivatives are given by Wolfrom and Brown.[1184]

α,α-Dichloro and α,α-dibromo ketones are obtained, for example, by the action of chlorine or bromine, respectively, on solutions of the diazo ketones in CCl_4;[1185] and α,α-diiodo ketones are obtained from diazo ketones and iodine in $CHCl_3$.[1186,1187]

e. Carboxylic acid chlorides from N-acylimidazoles

N-Acylimidazoles can acylate hydrogen chloride if the equilibrium (*a*) is shifted to the right by passing 2 moles of dry HCl into a solution of 1 mole of the *N*-acylimidazole in chloroform. In many cases the RCOCl is formed quantitatively in a few minutes at room temperature; imidazole hydrochloride, which is difficulty soluble in chloroform separates.[1188] The procedure is suitable for synthesis of the chlorides of hindered *o,o'*-disubstituted aromatic carboxylic acids. When HCl is passed into a solution of 1-formylimidazole in $CHCl_3$ at −60°, a solution of formyl chloride results, this being stable at that temperature.[1189]



2. Replacement of C–N bonds by C–halogen bonds in aromatic compounds and heterocycles

Replacement of aromatic amino groups by halogen or thiocyanogen by way of diazonium compounds is a most important preparative method for introducing F, Cl, Br, I, or SCN at defined sites or at sites where direct replacement of hydrogen by halogen is difficult or impossible, *e.g.*, *meta*-halogenation when *ortho-para*-directing substituents are already present or the preparation of halo aldehydes. The available methods are classified into three types: treatment of diazonium salt solutions with hydrohalogen acids in the presence of copper(I) halides (Sandmeyer reaction[1190]) or without a catalyst (principally replacement of $-N_2^+X^-$ by I); cleavage of diazonium perbromides; and thermal decomposition of diazonium compounds (Schwechten and Schiemann reactions).

[1184] M. L. Wolfrom and R. L. Brown, *J. Amer. Chem. Soc.*, **65**, 1516 (1943).

[1185] A. Roedig and H. Lunk, *Chem. Ber.*, **87**, 975 (1954).

[1186] L. Wolff, *Ann. Chem.*, **325**, 143 (1902); **394**, 40 (1912).

[1187] F. Arndt, B. Eistert, and W. Partale, *Ber. Deut. Chem. Ges.*, **60**, 1369 (1927).

[1188] H. A. Staab, K. Wendel, and A. P. Datta, *Ann. Chem.*, **694**, 78 (1966).

[1189] H. A. Staab and A. P. Datta, *Angew. Chem. Intern. Ed., Engl.*, **3**, 132 (1964).

[1190] T. Sandmeyer, *Ber. Deut. Chem. Ges.*, **17**, 1633, 2650 (1884).

a. Replacement of NH_2 in aromatic compounds and heterocycles by Cl or Br (Sandmeyer reaction)

$$[ArN_2]^+Cl^- + CuCl \rightleftarrows ArN_2CuCl \qquad \text{... (a)}$$

$$ArN_2CuCl_2 \longrightarrow Ar^{\bullet} + CuCl_2 + N_2 \qquad \text{... (b)}$$

$$Ar^{\bullet} + CuCl_2 \longrightarrow ArCl + CuCl_2 \qquad \text{... (c)}$$

The Sandmeyer reaction probably involves radical-like intermediate stages[1191,1192] or free radicals;[240] see Pfeil *et al.*[1192,240] for details of the primary step. The role of the copper ion as redox catalyst is decisive. Increasing the concentration of halogen ions decreases the rate of the Sandmeyer reaction since, for example, the catalytically active copper(I) chloride and Cl^- form a complex ion $[CuCl_3]^{2-}$.[1192] However, increasing the halogen ion concentration hinders the side reactions (d) and (e) still more strongly,[1192] so that the yield of aryl halide is increased in spite of the slower reaction.

In aqueous solution, instead of undergoing reaction (c), the aryl radicals can dimerize to give biaryls (d) or react with diazonium ions to give azo compounds (e), copper(I) chloride

$$2[ArN_2]^+Cl^- + 2CuCl \longrightarrow Ar\text{—}Ar + 2N_2 + 2CuCl_2 \qquad \text{... (d)}$$

$$2[ArN_2]^+Cl^- + 2CuCl \longrightarrow ArN{=}NAr + N_2 + 2CuCl_2 \qquad \text{... (e)}$$

being consumed in both cases. Dilution with water and decrease in the Cl^- concentration favors these side reactions. The Cl^- concentration can be decreased by, for instance, allowing the solution of copper(I) halide in hydrochloric acid to flow into the diazonium salt solution, contrary to the usual method of working.

The copper(I) chloride concentration can also be decreased by complex formation with $CuCl_2$ and HCl. In the presence of $CuCl_2$ the side reactions (d) and (e) are suppressed to such an extent that only very little copper(I) chloride is required (0.01 mole per mole of diazonium compound instead of the usual 0.1–0.2 mole). The catalytic activity of $CuCl_2$ alone[1193] is explained by the fact that part of this salt is reduced in an intermediate stage.[1191]

If high yields of aryl halides are desired in a reaction of diazonium salts with HCl it is essential to suppress the side reactions (d) and (e) by adding complex-forming agents (HCl or $CuCl_2$), even though the rate of the reaction

$$[ArN_2]^+Cl^- + H_2O \longrightarrow ArOH + N_2 + HCl \qquad \text{... (f)}$$

is thereby reduced. The rate can, it is true, be increased by using a higher temperature, but this leads to greater formation of phenol (f); the latter is the main reaction of diazonium chlorides or bromides in the absence of added copper halide.

In special cases diazotized amines can be converted into chloro compounds by HCl alone; for instance, diazotizing 2-aminopyrimidine in concentrated HCl at $-15°$ to $-10°$ and stirring the acid solution for 1 hour at $-10°$ to $-5°$ gives about 27% of 2-chloropyrimidine (for details see *Organic Syntheses*[1194]).

[1191] E. Pfeil and O. Velten, *Ann. Chem.*, **562**, 163 (1949); **565**, 183 (1949).

[1192] E. Pfeil, *Angew. Chem.*, **65**, 155 (1953).

[1193] H. Hodgson, *J. Chem. Soc.*, **1944**, 18; **1946**, 745.

[1194] I. C. Kogan, R. Minin, and C. G. Overberger, *Org. Syn.*, **35**, 34 (1955).

As a further variant, copper powder may replace copper(I) halides as catalyst.[1195,1196]

For reviews of the mechanism of the Sandmeyer reaction see Cowdrey and Davies[1197] and Hodgson.[1198]

Since nitro groups in the *ortho*- or *para*-position to a diazonium group undergo nucleophilic exchange reactions relatively easily, they may be replaced by Cl^- or Br^- in a Sandmeyer reaction.[1199]

The technique used in the Sandmeyer reaction is illustrated in the following set of examples.

***m*-Chlorobenzaldehyde:**[1200] First, $SnCl_2 \cdot 2H_2O$ (2 moles) is dissolved in concentrated HCl (600 ml) in a 3-l beaker. The solution is cooled to 5° and *m*-nitrobenzaldehyde (0.66mole) is added all at once with vigorous stirring and cooling in ice (temperature rise to about 100°!). The resulting red solution of *m*-aminobenzaldehyde is cooled in ice–salt to 2° and to the resulting slurry is dropped in a solution of $NaNO_2$ during 90 min, with vigorous stirring (temperature 0–5°), through a dropping funnel whose tip dips into the reaction mixture; addition is stopped when the solution gives a positive starch–iodide reaction for free HNO_2 (about 5 ml remain out of a solution of 0.67 mole of $NaNO_2$ in 150 ml of water).

The diazonium chloride solution is added with shaking to a copper(I) chloride solution at 75°; the mixture is then treated with concentrated HCl (840 ml), set aside overnight and worked up by distillation in steam. *m*-Chlorobenzaldehyde, which passes over with the first 1.5 l of distillate, is extracted in ether (2 × 150 ml), being obtained in 75–79% yield with b.p. 84–86°/8 mm, 107–109°/26 mm.

m-Bromobenzaldehyde is obtained analogously[1201] when $SnBr_2$–HBr is used for the reduction and the diazonium bromide solution is added to a hot suspension of copper(I) bromide and then treated with 48% HBr.

Preparation of **copper(I) chloride solution:**[1200] $CuSO_4 \cdot 5H_2O$ (0.75 mole) and NaCl (161 g) are dissolved in hot water (600 ml) in a 5-l flask, and a solution of $Na_2S_2O_5$ (41 g) and NaOH (27 g) in water (300 ml) is added.

A **solution of copper(I) chloride** (5 moles) **in hydrochloric acid** is prepared as follows, for use in, *e.g.*, the preparation of *p*-or *o*-chlorotoluene (cf. Heller[1202]) as described in *Organic Syntheses*:[1203] A solution of sodium hydrogen sulfite (265 g) and NaOH (175 g) in water (2 l) is added in 5–10 min to a stirred solution of $CuSO_4 \cdot 5H_2O$ (5 moles) and NaCl (5.6moles) in hot water (4 l). The mixture is left to cool and the liquid is decanted. Copper(I) chloride is obtained as a white powder but becomes dark on exposure to air. The crude copper(I)chloride is dissolved in 28% HCl (*d* 1.14; 2 kg).

Copper(I) chloride from $CuCl_2$ and Cu: $CuSO_4$ (250 g), NaCl (120 g), water (500 ml), concentrated HCl (1000 g), and copper (130 g) are heated until decolorized. The solution is made up to 2036 g with concentrated HCl, then containing about 10% of copper(I) chloride, and after decantation from solid material can be stored if protected from the air. If crystalline copper(I) chloride is wanted, the solution is filtered or decanted, treated with water, and left to cool. Samples that have become partially oxidized during storage can be dissolved in warm hydrochloric acid containing NH_4Cl and heated with copper or sodium sulfite until decolorized.

In the preparation of the above and other aromatic chlorides and bromides copper(I) chloride may be replaced by **copper powder** prepared, according to Gattermann,[1195] as follows: zinc dust is added through a fine sieve to aqueous copper sulfate solution (saturated in the cold) with stirring and the mixture is finally warmed to about 80°; it should become

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[1195] L. Gattermann, *Ber. Deut. Chem. Ges.*, **23**, 1218 (1890); **25**, 1086 (1892).

[1196] W. A. Waters, *J. Chem. Soc.*, **1942**, 266.

[1197] W. A. Cowdrey and D. S. Davies, *Quart. Rev.* (*London*), **6**, 358 (1952).

[1198] H. H. Hodgson, *Chem. Rev.*, **40**, 251 (1947).

[1199] R. Huisgen, *Angew. Chem.*, **67**, 439 (1955).

[1200] J. S. Buck and W. S. Ide, *Org. Syn.*, Coll. Vol. II, 130 (1943).

[1201] F. T. Tyson, *Org. Syn.*, Coll. Vol. II, 132 (1943).

[1202] G. Heller, *Angew. Chem.*, **23**, 392 (1910).

[1203] C. S. Marvel and S. M. McElvain, *Org. Syn.*, **3**, 33 (1923).

pale blue; the finely divided copper powder is separated from the zinc sulfate solution by decantation, washed several times with cold water, freed from residual zinc by very dilute hydrochloric acid, and washed until acid-free. This very reactive **Gattermann copper** is brought into reaction at once or stored as wet paste.

The preparation of *o*-bromotoluene from diazotized *o*-toluidine and copper powder is described in detail in *Organic Syntheses.*[1204]

o-Bromochlorobenzene:[1205] A solution of $NaNO_2$ (1 mole) in water (125 ml) is added, rapidly, with stirring and cooling in ice, to a mixture of *o*-chloroaniline (1 mole) and 48% HBr (300 ml, 2.5 moles) at 0°; small pieces of ice are also added so as to maintain the temperature below 10°. The solution must be kept distinctly acid to Congo Blue during the diazotization. The last few ml of $NaNO_2$ solution are added slowly, being stopped when the solution changes starch–iodide paper to blue.

In a flask fitted with a descending condenser, dropping funnel, and steam-inlet (at first shut off) copper(I) bromide (0.55 mole) and 48% HBr (80 ml) are heated to the boiling point. Then, whilst heating is maintained, the diazonium salt solution (removed in portions from the cold bath) is run in during about 30 min, during which a large part of the *o*-bromochlorobenzene distils. After this addition a powerful stream of steam is blown through the solution until 1–1.5 l of distillate has been collected. The organic layer is separated and washed successively with concentrated H_2SO_4 (*ca.* 4 × 10 ml; until the acid is only weakly colored), water, 5% NaOH solution, and water, dried over $CaCl_2$ (3 g), and distilled. The product (89–95% yield) has b.p. 199–201°/742 mm.

m-Bromochlorobenzene, *m*-dibromobenzene, and *o*-bromoanisole are obtained analogously in about 90% yields. In the last case the treatment with H_2SO_4 is omitted.

o-Bromonitrobenzene is also obtained analogously:[1206] *o*-Nitroaniline is diazotized slowly below 10° as a suspension in 48% HBr (400 ml). The amount of 48% HBr used in the exchange reaction is increased (from 80 to 120 ml). The product distilling in steam solidifies and has m.p. 41–42.5°.

Preparation of copper(I) bromide:[1205] Sodium sulfite (1.2 moles) is added in 10 min to a stirred solution of $CuSO_4 \cdot 5H_2O$ (2.4 moles) and NaBr (3.4 moles) in warm water (2 l); occasionally more sulfite must be added to remove the blue color. The mixture is then cooled and the copper(I) bromide (320 g, 93%) is filtered off with good suction and dried overnight in the air.

A solution of copper(I) bromide in hydrobromic acid suitable for use in the preparation of *o*-bromoanisole (from about 4 moles of diazotized *o*-anisidine) is obtained very simply by treating a solution of $CuSO_4 \cdot 5H_2O$ (260 g) and NaBr (625 g) in water (500 ml) with concentrated H_2SO_4 (120 g) and boiling the mixture for 4 h with copper powder or turnings (80 g).[1207]

The same procedure is used for the preparation of *p*-bromotoluene from *p*-toluidine as detailed in *Organic Syntheses,*[1208] except that the copper(I) bromide solution is prepared in 8 times as much water.

In the last-mentioned two cases the diazonium salt solution is prepared in dilute sulfuric acid and steam is passed in during its addition.

Aryl halides from weakly basic aromatic amines: Very weakly basic amines must be diazotized in concentrated acid, *e.g.*, concentrated H_2SO_4. However, with $NaNO_2$ this H_2SO_4 forms nitrosylsulfuric acid, from which the nitrous acid must be generated during the diazotization by adding glacial acetic acid,[1209,1210] or phosphoric acid.[1211,1212] Diazotization can be effected in a mixture of 84% phosphoric acid and nitric acid (*d* 1.4) with aqueous $NaNO_2$

[1204] L. A. Bigelow, *Org. Syn.*, **9**, 22 (1929); Coll. Vol. I, 135 (1956).

[1205] J. L. Hartwell, *Org. Syn.*, **24**, 22 (1944); Coll. Vol. III, 185 (1955).

[1206] R. B. Carlin and G. W. Larson, *J. Amer. Chem. Soc.*, **79**, 939 (1957).

[1207] E. Hardegger, D. Redlich, and A. Gal, *Helv. Chim. Acta*, **28**, 631 (1945).

[1208] L. A. Bigelow, *Org. Syn.*, **5**, 21 (1925).

[1209] H. H. Hodgson and J. Walker, *J. Chem. Soc.*, **1933**, 1620; **1935**, 530.

[1210] A. H. Stepan and C. S. Hamilton, *J. Amer. Chem. Soc.*, **71**, 2438 (1949).

[1211] H. A. J. Schoutissen, *J. Amer. Chem. Soc.*, **55**, 4531 (1933).

[1212] L. H. Welsh, *J. Amer. Chem. Soc.*, **63**, 3276 (1941).

at −8° to −12°, decomposition then being by concentrated HCl or 48% HBr in the cold in presence of Gattermann copper or copper bromide; in this way are obtained, *e.g.*, 2-chloro- and 2-bromo-4-methoxybenzothiazole,[1213] ethyl 2-bromothiazole-4-carboxylate,[1214] and 2-bromothiazole.[1215,1216]

***p*-Dichlorobenzene from *p*-phenylenediamine:**[1217] A solution of $NaNO_2$ (3 g) in concentrated H_2SO_4 (30 ml) is dropped into a vigorously stirred solution of *p*-phenylenediamine hydrochloride (3.62 g) in phosphoric acid (*d* 1.7; 70 ml) at −5° (ice–salt cooling). After 30 min finely powdered urea (2 g) is added. The diazonium solution is dropped with vigorous stirring into an ice-cooled solution of copper(I) chloride obtained by refluxing a mixture of $CuSO_4 \cdot 5H_2O$(10.8 g), NaCl (5.4 g), water (45 ml), concentrated HCl (*d* 1.19; 150 ml), and copper (30 g). *p*-Dichlorobenzene, m. p. 53°, is isolated in about 70% yield by distillation in steam.

If the above diazonium salt solution is poured into a concentrated solution of KI (8 g) containing some pieces of ice, left overnight, then diluted with water, and the precipitate is washed with water and thiosulfate solution, ***p*-diiodobenzene** is obtained in almost quantitative yield.

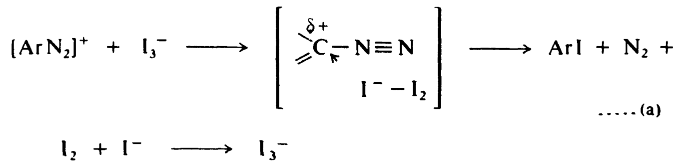
Interaction of nitroso compounds with hydroxylamine salts in the presence of copper(I) chloride or bromide and concentrated HCl or HBr, respectively, affords aryl halides by way of diazonium compounds.[1218] This method is

$$ArNO + NH_2OH{\cdot}HX \longrightarrow 2H_2O + [ArN_2]^+X^- \longrightarrow ArX + N_2$$

suitable for the preparation of *p*-chloro- and *p*-bromo-phenols.

b. Replacement of NH_2 in aromatic compounds by iodine

The preparation of *p*-diiodobenzene given as an example above showed that iodine can be very easily substituted for a diazonium group by means of hydriodic acid without addition of a copper(I) salt. A little urea is added to the diazotized solution (to remove residual HNO_2), which is usually prepared in hydrochloric or sulfuric acid, followed by a cold iodide solution (1–2 moles of alkali iodide per mole of diazotized amine); or the solution of the diazonium salt in mineral acid is added to a cold iodide solution. Evolution of nitrogen ceases after storage for several hours or, if necessary, subsequent warming on a wather-bath. Phenols can be expected as by-products and may be removed by basification before isolation of the aryl iodide; the latter is obtained then by distillation in steam, extraction in ether, $CHCl_3$, benzene, or toluene, or filtration. Biaryls and azo compounds are not formed, because the mechanism



[1213] H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, **25**, 515 (1942).
[1214] H. Erlenmeyer and C. J. Morel, *Helv. Chim. Acta*, **25**, 1073 (1942).
[1215] K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22 A**, 362 (1945).
[1216] G. Klein and B. Prijs, *Helv. Chim. Acta*, **37**, 2064 (1954).
[1217] H. A. J. Schoutissen, *J. Amer. Chem. Soc.*, **55**, 4537 (1933).
[1218] H. H. Hodgson and W. H. H. Norris, *J. Chem. Soc.*, **1949**, Suppl. 181.

of this reaction (a) is different from that of the Sandmeyer reaction.[1198] Yields are sometimes increased on addition of iodine.[1218,1219]

The usual experimental procedure is exemplified in the preparation of iodobenzene from aniline detailed in *Organic Syntheses*.[1221]

Acid-sensitive diazotized amines are treated with acidified iodide solution in the presence of a water-immiscible solvent, *e.g.*, $CHCl_3$, which removes the aryl iodide as it is formed.[1220,1222]

Diazonium salt solutions that have been obtained from weakly basic amines in concentrated H_2SO_4 with nitrosylsulfuric acid and 85% phosphoric acid give good yields of the derived aryl iodides when treated with cold aqueous KI; for example, the preparation of 1,2,3-triiodo-5-nitrobenzene from 2,6-diiodo-4-nitroaniline is described in detail in *Organic Syntheses*;[1223] and *m*-iodonitrobenzene, 1,2-diiodo-4-nitrobenzene, 1,4-diiodo-2-nitrobenzene, and 1,2,4-triiodo-3-nitrobenzene have been obtained analogously.[1224]

Amino carboxylic acids can be diazotized "directly" in (i) dilute or (ii) concentrated H_2SO_4, or (iii) "indirectly" by dissolving their alkali salts and $NaNO_2$ in water and pouring this solution into concentrated HCl. Treatment of such diazonium salt solutions, in the cold, with aqueous KI has afforded, for example, 2- and 3-iodo-*p*-toluic acid[1225] (method i), 2,3,5-triiodobenzoic acid[1226,1227] (method ii), and 2-iodo-6-nitrobenzoic acid[1228] (method iii). Acids having NH_2 groups at one or both of the *o*-positions to the COOH give only the corresponding hydroxy acids when diazotized in dilute sulfuric acid and treated with KI.[1229]

Addition of copper is sometimes recommended: for instance, adding 1.2 moles of KI and 1 g of copper bronze to a diazonium solution from 1 mole of *p*-aminophenol in dilute sulfuric acid give 69–72% of *p*-iodophenol.[1230] The technique for addition of iodine is illustrated in the following example.

o-Iodonitrobenzene:[1219] Water (1 l) is poured over *o*-nitroaniline (100 g), then concentrated H_2SO_4 (600 g) is added; the resulting clear solution is cooled to 5° and diazotized with the appropriate amount of $NaNO_2$, during which the temperature should not rise above 10°. The diazonium salt solution is added in portions to a solution of KI (200 g) and iodine (200 g) in water (200 ml). When evolution of N_2 ceases, the mixture is warmed for some time on a water-bath and shaken while still warm with sulfiite solution; on cooling, *o*-iodonitrobenzene, m.p. 54°, crystallizes in quantitative yield.

m- and *p*-Iodonitrobenzene are obtained analogously.

c. Replacement of NH_2 in aromatic compounds and heterocycles by Br by means of diazonium perbromides

Diazonium bromides and bromine in hydrobromic acid give diazonium perbromides that are sparingly soluble in water. In the presence of water or when

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[1219] A. Baeyer, *Ber. Deut. Chem. Ges.*, **38**, 2760 (1905).

[1220] B. A. Hems and co-workers, *J. Chem. Soc.*, **1949**, 3432.

[1221] H. J. Lucas and E. R. Kennedy, *Org. Syn.*, Coll. Vol. II, 351 (1943).

[1222] K. Freudenberg and M. Reichert, *Chem. Ber.*, **87**, 1837 (1954).

[1223] R. B. Sandin and T. L. Cairns, *Org. Syn.*, Coll. Vol. II, 604 (1943).

[1224] H. Cassebaum, *Arch. Pharm.*, **292**, 571 (1959).

[1225] E. Kloeppel, *Ber. Deut. Chem. Ges.*, **26**, 1733 (1893).

[1226] C. J. Klemme and J. H. Hunter, *J. Org. Chem.*, **5**, 509 (1940).

[1227] S. C. J. Olivier and W. P. Combé, *Rec. Trav. Chim.*, **69**, 25 (1950).

[1228] B. R. Baker and co-workers, *J. Org. Chem.*, **17**, 164 (1952).

[1229] H. Abbes, *Ber. Deut. Chem. Ges.*, **26**, 2955 (1893).

[1230] F. B. Dains and F. Eberly, *Org. Syn.*, Coll. Vol. II, 355 (1943).

heated in ethanol or acetic acid these perbromides decompose according to reaction (a) [compare reaction (a) of the preceding section]. The reaction is

$$[RN_2]^+Br^- + Br_2 \longrightarrow [RN_2]^+Br_3^- \longrightarrow RBr + N_2 + Br_2 \quad \dots \text{(a)}$$

preparatively important for preparation of bromine-substituted heterocycles from amino heterocycles (the Craig reaction).

2-Bromopyridine:[1231,1232] 2-Aminopyridine (150 g, 1.59 moles) is added during 10 min to 48% HBr (790 ml, 7 moles) (Craig used 63% HBr) cooled in ice–salt to 10–20°. Bromine (120 ml) is dropped in during 30 min with vigorous stirring at not more than 0°, whereupon the mixture becomes stiff with separated orange-yellow perbromide; more bromine (120 ml; a total of 4.7 moles) is added during 15 min. Then the mixture is poured during 4 h into a solution of $NaNO_2$ (4 moles) in water (400 ml), the temperature being carefully kept at 0° or below. Nitrogen begins to be evolved when most of the $NaNO_2$ has been added. The mixture is stirred for a further 30 min, then treated with NaOH (15 moles) in water (600 ml) at such a rate that the temperature does not exceed 20–25° and extracted with ether (4 × 250 ml). The ethereal extracts are dried over KOH (100 g) and worked up by distillation giving an 86–92% yield of material of b.p. 74–75°/13 mm. It is important that the stirrer be efficient, moving also the thick mixture near the walls of the vessel.

2-Iodopyridine cannot be obtained by this method.

The following have also been prepared from the corresponding amino compounds by Craig's method in the yields stated: 2-bromo-3- (87%) and -5-methylpyridine (80%);[1233] 2-bromo-6-methylpyridine (79%);[1234] 4-bromopyridine, stable only as its hydrochloride (85–95%);[1235] methyl 2-bromo-3-pyrazinecarboxylate (43%);[1236] 1-bromo-5,6,7,8-tetrahydroisoquinoline (77.5%);[1237] and 2-bromo-4-chlorobenzothiazole (72%).[1238] The reaction conditions are occasionally varied; for instance, in the last-mentioned case stirring in the cooling bath after addition of the nitrite is for 2 h instead of for 30 min.

d. Replacement of NH_2 in aromatic compounds by Cl or Br (Schwechten reaction)

The Sandmeyer procedure and its Gattermann variant (see page 259) often give poor yields when applied to diphenylamines, naphthylamines, or phenanthrenamines, but good results can be obtained by the method worked out by Schwechten[1239] as a variant of the Schiemann reaction (thermal decomposition of diazonium fluoroborates, see below).

$$[ArN_2]^+X^- + HgX_2 \longrightarrow [ArN_2]^+HgX_3^- \longrightarrow ArX + N_2 + HgX_2 \quad \dots \text{(a)}$$

$$2[ArN_2]^+X^- + HgX_2 \longrightarrow [ArN_2]_2^{2+}HgX_4^{2-} \longrightarrow 2ArX + 2N_2 + HgX_2 \quad \dots \text{(b)}$$

$$X = Cl \text{ or } Br$$

Adding aqueous solutions of equal amounts of $HgCl_2$ and KCl or of $HgBr_2$ [or $Hg(NO_3)_2$] and KBr to solutions of the diazotized amine precipitates complex salts according to reaction (a) or (b) above. These salts are washed with acetone or with methanol and ether or simply dried in the air, then mixed with twice the weight of KCl, NH_4Cl, or KBr and

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[1231] L. C. Craig, *J. Amer. Chem. Soc.*, **56**, 231 (1934).

[1232] C. F. H. Allen and J. R. Thirtle, *Org. Syn.*, **26**, 16 (1946); Coll. Vol. III, 136 (1955).

[1233] H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **14**, 512 (1949).

[1234] R. Adams and S. Miyano, *J. Amer. Chem. Soc.*, **76**, 3170 (1954).

[1235] A. Murray Tert. and W. H. Langham, *J. Amer. Chem. Soc.*, **74**, 6289 (1952).

[1236] R. C. Ellingson and R. L. Henry, *J. Amer. Chem. Soc.*, **71**, 2798 (1949).

[1237] R. Grewe, A. Mondon, and E. Nolte, *Ann. Chem.*, **564**, 180 (1949).

[1238] R. C. Elderfield and F. W. Short, *J. Org. Chem.*, **18**, 1099 (1953).

[1239] H.-W. Schwechten, *Ber. Deut. Chem. Ges.*, **65**, 1605 (1932).

decomposed thermally. 2,2′- and 4,4′-Dichlorobiphenyl and 2,2′-dibromobiphenyl are obtained in about 80% yield by reaction (a),[1239] and 2-bromonaphthalene in 60% yield by reaction (b).[1239,1240]

The decomposition may be effected by cautious warming in a round-bottomed flask under an air-condenser, in a wide hard-glass tube, or even in an evaporating dish. The last of these techniques was used for preparation of 1-, 2-, and 3-chlorophenanthrene, and for the corresponding bromo compounds,[1241] the amines having been diazotized at 0° by nitrosylsulfuric acid (prepared from $NaNO_2$ and a 2 : 1 mixture of concentrated H_2SO_4 and water) to which pyridine solutions of the bases were added.

e. Replacement of NH_2 in aromatic or heterocyclic compounds by fluorine (Schiemann reaction)

The process most widely used for introducing fluorine into an aromatic nucleus is thermal decomposition of diazonium fluoroborates (Schiemann reaction);[1c,1242–1244] these salts are usually very stable, even towards deflagration. They are precipitated (i) on addition of hydrogen tetrafluoroborate or $NaBF_4$ to a diazonium solution obtained as usual from the amine in hydrochloric acid or (ii) on diazotization of the amine in HBF_4 solution by aqueous

$$\mathrm{ArNH_2{\cdot}HX + HNO_2 + BF_4^-} \longrightarrow \mathrm{2H_2O + X^- + [ArN_2]^+BF_4^-}$$
$$\longrightarrow \mathrm{ArF + N_2 + BF_3}$$

$NaNO_2$. The volume of solutions containing BF_4^- must be kept as small as possible and contain less than 1 mole of H^+ per liter, since many diazonium fluoroborates are somewhat soluble in cold water and the solubility is greater in strongly acid media. Diazonium fluoroborates from phenols an dcarboxylic acids are readily soluble in water; however, nuclear-fluorinated carboxylic acids can be obtained by applying the Schiemann reaction to their esters (see page 267). Since the product of diazotization by procedure (ii) is at once precipitated as fluoroborate, side reactions, *e.g.*, formation of phenols, are minimal, but disadvantages are the continuous thickening of the reaction mixtures and the working in excess of the aggressive HBF_4. Diazonium fluoroborates obtained by either of methods (i) and (ii) are kept at 0° or below for at least 30 min, filtered off with good suction, washed with cold HBF_4 or $NaBF_4$ solution, alcohol, and ether, and dried carefully in filter paper placed on a wire net in a fume cupboard; decomposition of moist fluoroborates gives poor yields.

Yields are better the lower the decomposition temperature — the beginning of thermal decomposition can be recognized by evolution of white BF_3 fumes. The decomposition is carried out in glass flasks that should be about half-filled, or in wide hard-glass tubes leading to a cooled receiver fitted with a reflux condenser; for work with volatile fluoro compounds this condenser should be attached at the top to a second cooled receiver. BF_3 can be trapped in receivers containing water, sodium hydroxide solution, or a suspension of NaF in water (giving $NaBF_4$), but blockages must be watched for. The dry

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[1240] M. S. Newman and P. H. Wise, *J. Amer. Chem. Soc.*, **63**, 2847 (1941).

[1241] W. E. Bachmann and C. H. Boatner, *J. Amer. Chem. Soc.*, **58**, 2194 (1936).

[1242] G. Balz and G. Schiemann, *Ber. Deut. Chem. Ges.*, **60**, 1186 (1927).

[1243] G. Schiemann, *J. Prakt. Chem.*, [ii], **140**, 97 (1934).

[1244] A. Roe, *Org. Reactions*, **5**, 193 (1949).

salt is heated from outside near the surface, decomposition then usually proceding spontaneously. Compounds containing NO_2 groups often decompose very violently; they are therefore usually mixed with three to five times their weight of sand, $BaSO_4$, or NaF and decomposed only in 5—25-g batches.

When a diazonium fluoroborate gives only a poor yield of the corresponding fluorinated aromatic compound on thermal decomposition in the dry state, it may be added in portions to an anhydrous hydrocarbon that is heated a few degrees above the decomposition temperature of the fluoroborate; *m*- and *o*-fluoropropiophenone, for instance, have been obtained in this way in boiling toluene or heptane;[1245] the procedure has also been applied, in particular, to decomposition of heterocyclic diazonium fluoroborates, *e.g.*, for the preparation of 3-fluoropyridine,[1246] 3-fluoroquinoline,[1247] and 4-fluoroisoquinoline.[1248]

Diazonium fluoroborates from some heterocyclic amines are so unstable that they cannot be obtained dry and these are decomposed, whilst still moist with ether, in light petroleum or xylene. Indeed all isolated diazonium fluoroborates should be treated as potentially unstable until their stability has been determined on small samples; for instance, an **explosion** has been reported[1250] with 3-pyridinediazonium fluoroborate[1249] that was still moist with solvent; diazonium fluoroborates from α- and γ-amino N-heterocycles usually decompose at or below 20°, so the amines are diazotized in tetrafluoroboric acid and decomposition is induced by warming the diazotization solution.[1246,1247]

The Schiemann reaction (thermal decomposition of dry diazonium fluoroborates) has recently been supplemented by other methods for replacement of NH_2 in aromatic compounds by fluorine; such methods resemble the Sandmeyer reaction or its Gattermann variants. For example, the diazonium fluoroborate may be converted into the aromatic fluoro compound even at room temperature if its solution in acetone, aqueous acetone, or water is stirred with Gattermann copper or, better, copper(I) chloride.[1251] This technique can be used with advantage for water-soluble diazonium fluoroborates, *e.g.*, for the prepation of *p*-fluorophenol,[1251] or *p*- or *m*-fluoroacetanilide,[1252] and when otherwise only small batches can be decomposed because of the violence of the reaction (NO_2 compounds); it gives good yields from unsubstituted aromatic amines or amines containing only alkyl groups or halogen atoms; however, undesirable side reactions (deamination, introduction of Cl by CuCl) may be observed.[1253,1254]

Fluorobenzene:[1242,1255] Water (1350 ml) and hydrochloric acid (1650 ml; *d* 1.19) are mixed in a 40-l pot or in a glass jar (30 × 30 cm) and stirred vigorously whilst cooling in

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[1245] B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 449 (1946).
[1246] A. Roe and G. F. Hawkins, *J. Amer. Chem. Soc.*, **69**, 2443 (1947).
[1247] A. Roe and G. F. Hawkins, *J. Amer. Chem. Soc.*, **71**, 1785 (1949).
[1248] A. Roe and C. E. Teague Jr., *J. Amer. Chem. Soc.*, **73**, 687 (1951).
[1249] T. Talik and S. Talik, *Rocz. Chem.*, **38**, 777 (1964); *Chem. Abstr.*, **61**, 10653 (1964).
[1250] *Chem. Eng. News*, **45**, Oct. 16, **44** (1967).
[1251] E. D. Bergmann, S. Berkovic, and R. Ikan, *J. Amer. Chem. Soc.*, **78**, 6037 (1956).
[1252] E. D. Bergmann and M. Bentov, *J. Org. Chem.*, **19**, 1594 (1954).
[1253] I. K. Barben and H. Suschitzky, *Chem. & Ind. (London)*, **1957**, 1039.
[1254] E. C. Fisher and M. M. Joullié, *J. Org. Chem.*, **23**, 1944 (1958).
[1255] D. T. Flood, *Org. Syn.*, Coll. Vol. II, 295 (1943).

ice–salt. Then a solution of $NaNO_2$ (1200 g) in water (1500 ml) is prepared, and one-third of the total (2075 g) aniline hydrochloride is added to the hydrochloric acid at 5°. Sodium nitrite solution is added to this solution so that the temperature does not rise above 7°. Further portions of aniline hydrochloride are added, ensuring that solid is always present. All the aniline hydrochloride should have been added by the time that half the $NaNO_2$ has been added. Complete diazotization requires about all the nitrite (test with starch–iodide paper!). Meanwhile a solution of HBF_4 is prepared by portionwise mixing, with stirring, of boric acid (1000 g, 16.2 moles) and 60% HF (2150 g, 65 moles) in copper, lead, or polyvinyl chloride vessels, the temperature not being allowed to exceed 25° (cooling in ice–water); this solution is then cooled to 0° and allowed to flow into the diazonium solution, cooled to below 0°, at such a rate that the temperature does not exceed 10°. The thick mass is well stirred by a slowly rotating metal or wooden stirrer with large wings and an acid-fast coating or a rubber covering. When all the HBF_4 has been added (20–30 min), the solids are filtered off and washed successively with ice-water (about 800 ml), methanol or ethanol (about 800 ml), and ether (900 ml), the mass being sucked as dry as possible on each occasion. The diazonium fluoroborate is spread in a thin layer and left in the air to dry, then placed in a 12-l flask or divided between two 5-l flasks. The reaction flask is connected by wide tubes to a wide condenser and thence to a series of three Erlenmeyer flasks standing in a freezing bath and acting as receivers. The exit gases are led directly to a fume cupboard or first through ice-water or sodium hydroxide solution. When the diazonium fluoroborate is warmed externally by a free flame at a position near its surface, decomposition soon sets in; this reaction is allowed to proceed as long as it continues quietly; if it becomes too violent ice-cooling is applied, if it slackens heating is repeated, until finally no more BF_3 vapor is evolved on substantial heating.

The distillate collected in the receivers is separated from the phenol that has crystallized out. It is then washed several times with 10% sodium hydroxide solution (until the washings are almost colorless) and last with water; the density of fluorobenzene is 1.025, so the last portion of sodium hydroxide solution must be very carefully separated, lest a dilute sodium hydroxide solution be obtained of almost this density, making separation from fluorobenzene very difficult. Drying over $CaCl_2$ and fractionation through a column give a 50–56% yield (780–870 g) of fluorobenzene, b.p. 84–85°.

Directions for work on a smaller, laboratory scale, involving use of $NaBF_4$ and decomposition in a hard-glass tube and giving a 64% yield of fluorobenzene are provided by Hudlicky.[4j]

A solution of **sodium fluoroborate** (about 5.38 moles) is obtained by adding NaF (900 g) to a mixture of boric acid (333 g) and concentrated HCl (1338 ml) with stirring and cooling, followed after 2 h by filtration.[1256]

***p*-Fluorobenzoic acid:**[1257] Ethyl *p*-aminobenzoate (165 g) is warmed, with shaking, on a water-bath with hydrochloric acid (*d* 1.19; 204 ml) and water (300 ml), this giving a colorless paste of the hydrochloride. The mixture is cooled in ice–salt to 0°, and a solution of $NaNO_2$ (72.6 g, = 1 mole of 95% $NaNO_2$) in a little water is allowed to run in slowly with stirring until the starch–iodide reaction remains weakly positive for 10 min; the temperature should not exceed 7°.

Meanwhile a solution of HBF_4 is prepared. Boric acid (68 g, 1.1 moles) is dissolved in 60% HF (133 g) in a paraffin-coated beaker or a lead jar, with ice-cooling to keep the temperature below 25° (so that the paraffin wax does not melt); alternatively, commercial 40% HF (200 g) may be used. The ice-cold solution is allowed to run into the diazonium solution fairly fast, although the temperature should remain below 10°. After this addition the mixture is stirred for a further 20–30 min and the diazonium fluoroborate that has separated as a thick paste is filtered off, washed successively with cold water (300 ml), methanol (300 ml), and ether (200 ml), with good suction in each case, and then dried in a vacuum over concentrated H_2SO_4. This affords a 75–78% yield (198–205 g) of p-$C_2H_5O_2C$–C_6H_4–N_2BF_4, dec. 93–94°.

Thermal decomposition of the fluoroborate involves losses due to resinification unless the salt is completely dry. 85 g portions of the fluoroborate are placed in a 2-l flask which is connected by a bent glass wide tube to a 1-l flask, and the uncondensed vapors of BF_3 are led over water; the unabsorbed gas is fed into an efficient fume cupboard. The diazonium fluoroborate is heated from above with a luminous Bunsen flame until white fumes of BF_3

[1256] A. Roe, *Org. Reactions*, **5**, 203 (1949).

[1257] G. Schiemann and W. Winkelmüller, *Org. Syn.*, Coll. Vol. II, 299 (1943).

appear, then decomposition is allowed to proceed spontaneously. If the reaction slackens it is hastened again by temporary heating, until finally on substantial heating the solid mass is completely liquified. Most of the ethyl p-fluorobenzoate, b.p. 105–106°/25 mm, remains in the reaction vessel but a small part of it is carried into the receiver. It is taken up in ether, filtered, and freed from ether.

The crude ester is hydrolysed by one hour's boiling under reflux with a solution of KOH (56 g) in 95% ethanol (80 ml). The mixture is then filtered and acidified to Congo Red paper with concentrated HCl. The precipitated *p*-fluorobenzoic acid is filtered off and dried. For purification it is dissolved in a hot solution of K_2CO_3 (40 g) in water (400 ml), decolorized by charcoal, filtered hot, and reprecipitated by hydrochloric acid. The yield is 63–69% (38 to 40 g) calculated on ethyl *p*-aminobenzoate; the m.p. is 186°.

***p*-Fluorophenol:**[1251] Solutions of *p*-aminophenol (10.9 g) in 56% tetrafluoroboric acid (50 ml) and of $NaNO_2$ (6.9 g) in water (50 ml) are added portionwise and simultaneously, with good stirring, to 56% tetrafluoroboric acid (200 ml) that is cooled in ice–salt to −6°, additions being adjusted so that the mixture contains an excess of nitrite throughout. Copper(I) chloride (5 g) is then added to the clear solution and the whole is stirred at 80–90° for 2 h. On cooling, 71% of p-fluorophenol, m.p. 46°, is obtained.

(p-Fluorophenyl)acetic acid is obtained similarly, in 87% yield.

2-Fluoro-3-methylpyridine:[1258] $NaNO_2$ (51 g, 0.74 mole) is added to a solution of 3-methyl-2-pyridinamine (80 g, 0.74 mole) in 40% HBF_4 (310 g) stirred in an ice-cooled 1.5-l beaker. After the addition, the mixture is stirred for a further 30 min in the ice-bath, then warmed to 45° to complete the decomposition, and next neutralized with Na_2CO_3 and distilled in steam. The yellow oil that separates in the distillate is separated, the residual distillate is extracted with ether, the oil is added to the extract, and the resulting solution is dried over Na_2SO_4. The ether is distilled off and the residue is distilled, giving a 48% yield (39.5 g) of product, b.p. 150.5–151°.

5-Methyl-2-pyridinamine affords 46% of **2-fluoro-5-methylpyridine,** b.p. 155–156°, analogously.

Many aromatic amines can be successfully converted into the corresponding aromatic fluoro compounds by diazotizing them with dry $NaNO_2$ (1.2 moles) in anhydrous HF (20 moles per mole of amine) at 0° and then removing nitrogen by gently warming the resulting solution.[1259] In contrast to the

$$ArNH_2 + 2HF + NaNO_2 \longrightarrow [ArN_2]^+F^- + NaF + 2H_2O$$
$$[ArN_2]^+F^- \longrightarrow ArF + N_2$$

procedures discussed above, this method requires use of Monel metal, copper, or stainless steel vessels. Since this method is suitable also for large batches it has particular industrial importance.

f. Replacement of NO_2 in heterocycles by halogen

Very mobile nitro groups can be replaced directly by chlorine or bromine, a reaction that has preparative importance for bromo- and chloro-pyridine and -quinoline derivatives. 5-Ethoxy-2-nitropyridine gives 2-bromo-5-ethoxypyridine when heated with HBr in glacial acetic acid in a sealed tube for 3 hours at 130°,[1260] and 2-bromo-3-ethoxypyridine is obtained from the corresponding nitro compound and boiling 48% HBr.[1261] It is particularly easy to introduce Cl or Br in place of a 4-nitro group in pyridine 1-oxide or quino-

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[1258] J. T. Minor, G. F. Hawkins, C. A. VanderWerf, and A. Roe, *J. Amer. Chem. Soc.*, **71**, 1125 (1949).

[1259] R. L. Ferm and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **72**, 4809 (1950).

[1260] E. Koenigs, H. C. Gerdes, and A. Sirot, *Ber. Deut. Chem. Ges.*, **61**, 1027 (1928).

[1261] H. J. Den Hertog and co-workers, *Rec. Trav. Chim.*, **68**, 283 (1949).

line 1-oxide,[1262,1263] the best method of obtaining 4-chloro and 4-bromopyridine 1-oxide being to treat the 4-nitro oxide with acetyl chloride or bromide, respectively, at 50° or with $POCl_3$ at 70°.

4-Chloropyridine 1-oxide:[1263] 4-Nitropyridine 1-oxide (8 g) is introduced in small portions into acetyl chloride (40 ml) in a flask under a reflux condenser, a vigorous reaction occurring after brief warming. Finally, warming for 30 min at *ca.* 50° affords a crystalline mass. This is decomposed cautiously with ice-water, and the mixture is made alkaline with Na_2CO_3 and extracted with chloroform. The extract is dried over Na_2CO_3 and on evaporation gives a product which crystallizes from acetone in colorless needles (4.0 g, 55%), m.p. 169.5° (dec.).

g. Replacement of NH_2 in aromatic compounds by SCN

For introduction of SCN into aromatic compounds the Sandmeyer reaction or its Gattermann variant is much more widely applicable than direct replacement of H by SCN (see page 202). An aqueous thiocyanate solution and CuSCN are added to a diazonium salt solution prepared in the usual way, or the addition is made gradually in the reverse direction — the diazonium salt to an aqueous solution of $K_3[Cu(SCN)_4]$; copper powder can also be used.[1264–1266] Reaction, with evolution of nitrogen, often occurs at room temperature or on gentle warming. Aryl isothiocyanates (aryl mustard oils) may be formed as well as the aryl thiocyanates.[1267]

$$[ArN_2]^+X^- + SCN^- \xrightarrow[\text{or Cu}]{\text{CuSCN}} ArSCN + N_2 + X^-$$

5-Thiocyanatosalicylic acid:[1268] 5-Aminosalicylic acid (7.65 g) is dissolved in water (600ml) and concentrated HCl (14.5 ml) and diazotized in the usual way with $NaNO_2$ (3.8 g). The greyish-blue diazonium salt is pressed as dry as possible and added in portions to a solution of CuSCN (6.1 g) and KSCN (30 g) in water (17 ml) at 65°. Nitrogen is evolved and the solution becomes pale brown. On cooling, 5-thiocyanatosalicylic acid separates and for purification is dissolved in dilute sodium carbonate solution, reprecipitated by hydrochloric acid, and recrystallized from benzene (yield 73%, m.p. 167–168°).

V. Replacement of C–S bonds by C–halogen bonds

SO_3H groups in aromatic compounds can in some cases be replaced very nicely by Cl or Br — particularly easily when an OH or NH_2 group is present in the *ortho-* or *para*-position thereto.[1269] In these reactions, however, there may also be replacement of H by halogen; for instance, 2,4,6-tribromoaniline is obtained quantitatively when sulfanilic acid reacts with a bromide–bromate solution in an acid medium at room temperature[460] (cf. page 163). Nevertheless the reaction can be used preparatively if another, electrophilic substituent is

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[1262] E. Ochiai, *J. Org. Chem.*, **18**, 549 (1953).

[1263] K. Thomas and D. Jerchel, *Angew. Chem.*, **70**, 735 (1958).

[1264] L. Gattermann and W. Hausknecht, *Ber. Deut. Chem. Ges.*, **23**, 738 (1890).

[1265] G. Thurnauer, *Ber. Deut. Chem. Ges.*, **23**, 769 (1890).

[1266] A. Hantzsch and B. Hirsch, *Ber. Deut. Chem. Ges.*, **29**, 947 (1896).

[1267] J. W. Dienske, *Rec. Trav. Chim.*, **50**, 407 (1931).

[1268] H. P. Kaufmann and E. Rossbach, *Ber. Deut. Chem. Ges.*, **58**, 1559 (1925).

[1269] R. L. Datta and J. C. Bhoumik, *J. Amer. Chem. Soc.*, **43**, 303 (1921).

present that hinders substitution by halogen, *e.g.*, NO_2 or a second SO_3H group; for example, 2,4-dibromo-6-nitrophenol and 2-bromo-6-nitrophenol-4-sulfonic acid have been prepared from 6-nitrophenol-2,4-disulfonic acid by bromine water at 0–15° [1270] and chlorinated nitronaphthalenes from nitronaphthalenesulfonic acids by $NaClO_3$ in hydrochloric acid at 90–95°.[1271]

1- and 2-Chloro- and 1,5-, 1,6-, 1,7-, and 1,8-dichloroanthraquinone have been obtained from the corresponding sulfonic acids by means of $NaClO_3$ or Cl_2 in hydrochloric acid at 100°, and the corresponding bromoanthraquinones by means of bromine and a little water under pressure at 190–240°.[1272–1274] In the case of 1,2,3,4,5,6,7,8-octahydro-9-anthracenesulfonic acid, where introduction of additional halogen into the aromatic ring is impossible, the SO_3H group is smoothly replaced by Br or I by means of bromide–bromate or iodide–iodate, respectively, in N-HCl at about 35°.[1275] Further, the SO_2Cl group of arenesulfonyl chlorides can be replaced by Cl, *e.g.*, by heating with PCl_5 in a sealed tube at about 220° or in trichlorobenzene or with $SOCl_2$ at about 220°.[1273,1276]

Aliphatic and aryl sulfonyl chlorides can be cleaved thermally to the alkyl or aryl chlorides and SO_2, although there are usually side reactions that often

$$RSO_2Cl \longrightarrow RCl + SO_2$$

make it impossible to use this method for preparation of aromatic chlorides; literature references and quantitative experiments are reported by Rieche and Naumann.[1277] Nevertheless, good yields are obtained on cleavage of aliphatic sulfonyl chlorides, *e.g.*, of dodecanesulfonyl chloride to dodecyl chloride and SO_2 in boiling xylene,[1278] and fission of toluene-α-sulfonyl chloride is also moderately successful.[1279]

Removal of SO_2 from aryloxymethanesulfonyl chlorides occurs particularly easily. Whereas toluene-α-sulfonyl chloride, $C_6H_5CH_2SO_3H$, and PCl_5 give benzyl chloride only at 100°,[1280] and the sodium salt and PBr_5 give benzyl bromide only at 90°,[1281] yet simply rubbing the dry sodium salt of an aryloxymethanesulfonic acid (1 mole) with PCl_5 or PBr_5 (2 moles) in a mortar

$$ArOCH_2SO_3Na + PCl_5 \longrightarrow ArOCH_2Cl + SO_2 + NaCl + POCl_3$$

gives 80–90% yields of the otherwise inaccessible aryl chloromethyl or bromomethyl ethers.[1282]

Replacement of C–S by C–halogen bonds is also used in the preparation of chlorinated heterocycles. If chlorine is led into an ice-cooled, aqueous suspen-

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[1270] E. Sakellarios, *Ber. Deut. Chem. Ges.*, **55**, 2846 (1922).

[1271] P. Friedländer, S. Karamessinis, and O. Schenk, *Ber. Deut. Chem. Ges.*, **55**, 45 (1922).

[1272] Ger. Pat. 205,195; *Friedländer*, **9**, 673 (1908–1910).

[1273] H. E. Fierz-David, A. Krebser, and W. Anderau, *Helv. Chim. Acta*, **10**, 197 (1927).

[1274] A. A. Goldberg, *J. Chem. Soc.*, **1932**, 77.

[1275] C. Schroeter, *Ber. Deut. Chem. Ges.*, **60**, 2042 (1927).

[1276] E. Nölting, *Ber. Deut. Chem. Ges.*, **8**, 1091 (1875).

[1277] A. Rieche and E. Naumann, *J. Prakt. Chem.* [iv], **9**, 108 (1959).

[1278] F. Asinger, *Ber. Deut. Chem. Ges.*, **77–79**, 193 (1944–1946).

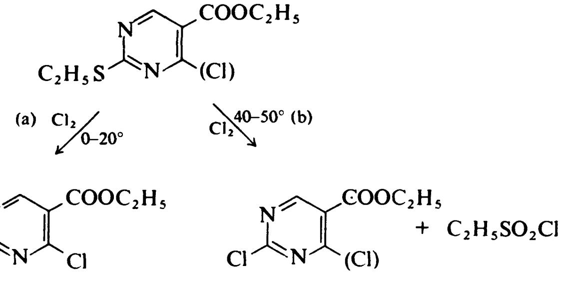
[1279] H. Limpricht and H. von Pechmann, *Ber. Deut. Chem. Ges.*, **6**, 534 (1873).

[1280] T. B. Johnson and J. A. Ambler, *J. Amer. Chem. Soc.*, **36**, 381 (1914).

[1281] W. H. Hunter and B. E. Sorenson, *J. Amer. Chem. Soc.*, **54**, 3365 (1932).

[1282] H. J. Barber and co-workers, *J. Appl. Chem. (London)*, **3**, 266 (1953).

sion of an (ethylthio)pyrimidine, the sulfone is usually obtained (reaction a), but in many cases ethanesulfonyl chloride and a chlorinated heterocycle are

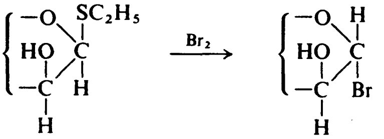


formed (reaction b), the proportion of the latter reaction increasing appreciably at slightly higher temperatures; examples are the preparation of 2-chloropyrimidine and ethyl 2,4-dichloro-5-pyrimidinecarboxylate.[1283,1284] For the mechanism of the reaction see Kwart and Body.[1285]

SH groups can also be replaced by chlorine.

2-Chlorobenzothiazole:[1286] S_2Cl_2 (1.1 moles) is added in small portions to 2-mercaptobenzothiazole in a 3-l flask fitted with a stirrer and an air-condenser. When the exothermic reaction ceases, the mixture is heated cautiously until foaming ceases, then boiled under reflux for 90 min, and set aside overnight. The black product is distilled, the fraction boiling at 150–170°/55–65 mm being collected. It is washed with 10% sodium carbonate solution and water, dried over Na_2SO_4, and redistilled (b.p. 158–162°/50 mm; yield 72%).

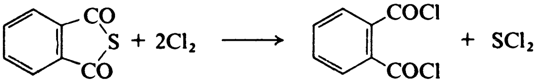
Little preparative importance attaches to conversion of organic sulfides into chloro compounds: The fission of compounds R–S–R′ by chlorine, bromine, cyanogen bromide, and methyl iodide, with replacement of C–S by C–halogen bonds has been reviewed by Tarbell and Harnish.[1287] The action of 1 mole of bromine on thioacetals in an anhydrous medium (ether) at room temperature affords bromo hemiacetals (α-bromo sulfides) and a sulfenyl bromide, and bromo sugars analogously from ethyl thioglycosides.



Thus bromine that has been distilled over H_2SO_4 converts ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-thioglucoside in dry ether at 20° into acetobromo-α-D-glucose, and ethyl 2,3,4,6-tetra-*O*-acetyl-α-D-thioglucoside into the otherwise inaccessible acetobromo-β-D-glucose.[1288]

[1283] J. M. Sprague and T. B. Johnson, *J. Amer. Chem. Soc.*, **57**, 2252 (1935).
[1284] E. Ballard and T. B. Johnson, *J. Amer. Chem. Soc.*, **64**, 797 (1942).
[1285] H. Kwart and R. W. Body, *J. Org. Chem.*, **30**, 1188 (1965).
[1286] W. Scott and G. W. Watt, *J. Org. Chem.*, **2**, 149 (1937).
[1287] D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).
[1288] F. Weygand, H. Ziemann, and H. J. Bestmann, *Chem. Ber.*, **91**, 2534 (1958).

Dicarboxylic acid dichlorides can be obtained in very good yield from cyclic dicarboxylic thioanhydrides, which is useful when the latter are readily accessible.



Phthalic thioanhydride, for example, is readily obtained from phthalic anhydride and Na_2S,[1289] and when Cl_2 is led through this material molten at 245° until SCl_2 is no longer formed, phthaloyl chloride is obtained in almost quantitative yield.[1290]

VI. Replacement of C–C bonds by C–halogen bonds

The fission of C–C bonds with formation of organic halogen compounds is discussed in other Sections, and here only references to these Sections will be given. The spontaneous loss of CO_2 or CO on bromination of aromatic *o*- and *p*-hydroxy and -amino acids is mentioned on page 163. The haloform reaction is described in the Chapter on fission of C–C bonds, pages 1042 and 1049, as well as in the present Chapter, page 1005. In the Chapter on the fission of C–C bonds (page 197) is also to be found the reaction of dry silver salts of carboxylic acids with halogen compounds in the molar ratio 1 : 1 (the Hunsdiecker reaction), which is of interest for the preparation of alkyl halides and ω-halo carboxylic esters.

[1289] A. Reissert and H. Holle, *Ber. Deut. Chem. Ges.*, **44**, 3029 (1911).

[1290] E. Ott, A. Langenohl, and W. Zerweck, *Ber. Deut. Chem. Ges.*, **70**, 2360 (1937).

CHAPTER 4

Formation of Carbon-Oxygen Bonds

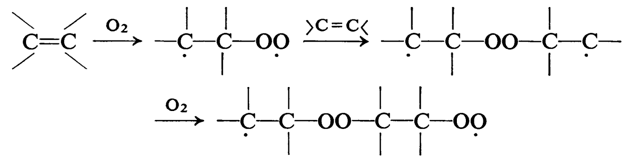
Compiled by
M. Schulz and H. Seeboth

4.1. Formation of the carbon-oxygen bond by addition

I. Addition of oxygen to ethylenic bonds

1. Molecular oxygen

Molecular oxygen can add to the double bonds of olefins such as styrene, 1,1-diphenylethylene, dimethyl- and diethyl-ketene, vinyl acetate, cyclopentadiene and cyclohexadiene with formation of polymeric peroxy compounds. The course of the reaction corresponds to that of a mixed polymerization:[1r,2,3,4b,d]



Most of the mixed polymerisates with oxygen are extremely explosive; special protective measures are required when working with them, and these are collected in the Section on "Formation of peroxides by autoxidation."

According to Staudinger[5] **1,1-diphenylethylene peroxide** is obtained as follows: 10 g of 1,1-diphenylethylene are placed in a small vessel fitted with an interior cooler and are irradiated by a 500-candle-power metal-filament lamp while oxygen is passed through. After 3 days, addition of light petroleum precipitates 0.5–1 g of colorless, amorphous diphenylethylene peroxide. After being washed with ether it decomposes at 131–132°C.

In contrast to this formation of polymeric peroxides from olefins and oxygen, "photosensitized autoxidation" of dienes leads to cyclic monomeric

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[1] Houben–Weyl, "Methoden der organischen Chemie," 4th Ed., Georg Thieme Verlag, Stuttgart, (a) Vol. 3 (1923), p. 77, Vol. 6, Part 3 (1965), pp. (b) 4, (c) 21, (d) 203, (e) 308, (f) 325, (g) 362, (h) 374, (i) 523, (j) Vol. 6, Part 4 (1966), (k) p. 1, Vol. 7, Part 1 (1954), pp. (l) 149, (m) 162, (n) 173, (o) 177, (p) 188, (q) 417, Vol. 8 (1952), pp. (r) 1, (s) 476, (t) 516, Vol. 8, Part 3 (1952), (u) p. 558, Vol. 11, Part 2 (1958), (v) p. 133.

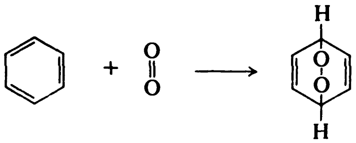
[2] W. Kern and H. Willersinn, *Angew. Chem.*, **67**, 573 (1955).

[3] A. A. Miller and F. R. Mayo, *J. Amer. Chem. Soc.*, **78**, 1017 (1956).

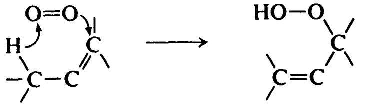
[4] (a) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, (b) p. 85; (c) E. G. E. Hawkins, "Organic Peroxides, Their Formation and Reactions," E. and F. F. Spon Ltd., London, 1961, (d) p. 370.

[5] H. Staudinger, *Ber. Deut. Chem. Ges.*, **58**, 1075 (1925).

peroxides. The reaction proceeds analogously to a diene synthesis with O_2 as philodiene:[6,7]

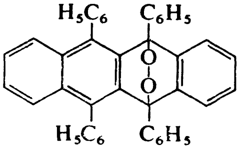


According to McKeown and Waters,[8] and also Foote and Wexler,[9] this dienophile oxygen is excited singlet oxygen ($^1\Delta_g$). Singlet oxygen reacts with a variety of olefins by addition to the allylic double bond, with intramolecular hydrogen transfer, leading to allyl hydroperoxides:[10-12]



Epidioxides (sometimes called endoperoxides) can be prepared from acenes, from suitable steroids, and from dienes of low molecular weight (*e.g.*, cyclohexadiene).[13] Irradiation is essential for initiation of reaction, and sensitizers must sometimes be added.

Autoxidation of acenes has been studied in particular by Dufraisse and his co-workers.[14] Irradiation without addition of a sensitizer converts them in solution (*e.g.*, in CS_2) rapidly into the corresponding peroxide; an example is rubrene peroxide (5,12-epidioxy-5,12-dihydrorubrene):



Peroxides of the steroid series were discovered by Windaus and Brunken[15] for the case of ergosterol. Later studies have shown that it has the structure

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[6] K. Adler and M. Schumacher, in "Fortschritte der Chemie organischen Naturstoffe," Springer-Verlag, Vienna, 1953, Vol. 10, pp. 96ff.

[7] K. Gollnick and G. O. Schenck, "Oxygen as a dienophile in 1,4-Cycloaddition Reactions," Academic Press Inc., New York, 1967.

[8] E. McKeown and W. A. Waters, *J. Chem. Soc.*, **1966**, **B**, 1040.

[9] C. S. Foote and S. Wexler, *J. Amer. Chem. Soc.*, **86**, 3879, 3880 (1964).

[10] G. O. Schenck, H. Eggert, and W. Denk, *Ann. Chem.*, **584**, 177 (1953).

[11] C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Letters*, **1965**, 4111.

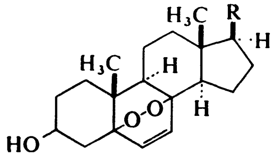
[12] A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965).

[13] A. Schönberg, "Präparative Organische Photochemie," Springer-Verlag, Berlin, Göttingen, Heidelberg, 1958, pp. 47ff.

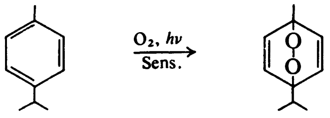
[14] C. Dufraisse, *Bull. Soc. Chim. France*, [v], **6**, 422 (1939); C. Dufraisse and L. Velluz, *Bull. Soc. Chim. France*, [v], **5**, 1073 (1938).

[15] A. Windaus and J. Brunken, *Ann. Chem.*, **460**, 225 (1928).

of an epidioxide:[16]



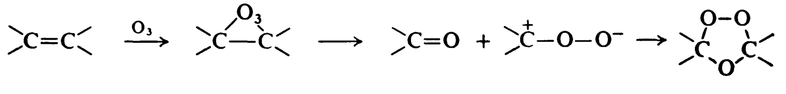
Particular importance attaches to photosensitized autoxidation which, owing to the work of Schenck and his collaborators[7,17] has achieved general application. A naturally occurring peroxide was first synthesized by Schenck and Ziegler, namely, ascaridole by photosensitized autoxidation of α-terpinene:[18]



Ergosterol peroxide (5,8-epidioxy-6-ergosten-3β-ol):[15] A solution of ergosterol (4 g) in 95% alcohol (1200 ml) is warmed to 60°, treated with a little eosin (6 mg), and irradiated in a large beaker as follows: Into the vessel containing this solution dips a narrower beaker inside which burns a 200-W lamp (Osram-Nitra) under water; this inner beaker is fitted for inflow and outflow of water. A slow stream of oxygen is led through the ergosterol solution, until, after about 3 hours, addition of alcoholic digitonin to a portion no longer causes a precipitate, *i.e.*, until all the ergosterol has been consumed. Most of the alcohol is then evaporated in a vacuum; the crystals separating from the residue are isolated and recrystallized from alcohol or acetone to constant m.p. 178°. The yield is 70%.

2. Ozone

In the cleavage of olefins by ozone the first product is an unstable „primary ozonide," as was proved experimentally by Criegee and Schroder[19] for ionization of *trans*-di-*tert*-butylethylene (*trans*-2,2,5,5-tetramethyl-3-hexene) in pentane at −75°. The primary ozonide decomposes exothermally to an aldehyde or ketone and a peroxidic zwitterion. It is only by reunion of the two fragments that the ozonides are formed (see various reviews[20,21]):



Ozonides and their fission are treated in Part C, "Cleavage of carbon–carbon bonds."

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[16] W. Bergmann, F. Hirschmann, and E. L. Skau, *J. Org. Chem.*, **4**, 29 (1939).

[17] G. O. Schenck, *Angew. Chem.*, **64**, 12 (1952); **69**, 579 (1957).

[18] G. O. Schenck and K. Ziegler, *Naturwissenschaften*, **32**, 157 (1944).

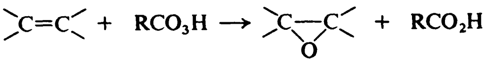
[19] R. Criegee and G. Schröder, *Chem. Ber.*, **93**, 689 (1960).

[20] P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

[21] M. Schulz and K. Kirschke, *Advan. Heterocyclic Chem.*, ed A.R. Katritzky and A. J. Boltón, **8**, 187 (1966).

3. Epoxides from ethylenic derivatives

The oxidation of unsaturated compounds by organic peroxy acids in anhydrous solvents such as chloroform, ether, dioxan, benzene, or acetone proceeds with formation of 1,2-epoxides according to the equation:



The following peroxy acids have achieved particular importance for epoxidations: peroxybenzoic, monoperoxyphthalic, peroxyacetic, and trifluoroperoxyacetic acid.

Owing to the sensitivity of the alkene peroxides good yields are obtained only by working at as low reaction temperatures as possible[22] and excluding strong acids.[23]

Inert solvents are required when using peroxybenzoic or monoperoxyphthalic acid; epoxidation by peroxyacetic acid can be carried out in acetic acid as solvent if strong mineral acids (which are often used as catalyst for formation of the peroxy acid) are absent and the reaction temperature is below 30°.

The epoxides that are the first products of oxidation by peroxyacetic, trifluoroperoxyacetic, or, particularly, peroxyformic acid are readily converted into α-glycol derivatives.

The rate of reaction of olefins with peroxy acids depends on the number and nature of the substituents attached to the doubly bonded atoms.[24] Alkyl and, particularly, alkoxy groups attached to C=C increase the rate of reaction. 2,3-Dimethyl-2-butene is oxidized very rapidly; reaction of ethyl vinyl ether[25] with peroxybenzoic acid is complete within a few minutes and is strongly exothermic, the product being 2,5-diethoxy-1,4-dioxan. Phenyl groups usually behave like alkyl groups in such reactions. Olefins in which the double bond is conjugated to a carboxyl, alkoxycarbonyl, or carbonyl group are converted into epoxides by trifluoroperoxyacetic acid[26] or by peroxyacetic acid in ethyl acetate[27] but are hardly attacked by other peroxy acids; examples are cinnamic, maleic, fumaric, and 2-butenoic acids, and their esters.

These rules apply in principle also to compounds containing several C=C double bonds (isoprene, geraniol, citral, etc.). Epoxidation by organic peroxy acids has been reviewed by Swern.[28]

Peroxybenzoic acid (often called simply **perbenzoic acid**) is the commonest reagent for preparation of epoxides. It is best obtained directly from benzoyl chloride and sodium peroxide[29] or by cleavage of dibenzoyl peroxide with sodium alkoxide:[30]

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[22] T. W. Findley, D. Swern, and J. T. Scanlan. *J. Amer. Chem. Soc.*, **67**, 412 (1945).

[23] D. Swern, G. N. Billen, T. W. Findley, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **67**, 1786 (1945).

[24] D. Swern, *J. Amer. Chem. Soc.*, **69**, 1692 (1947).

[25] M. Bergmann and A. Mikeley, *Ber. Deut. Chem. Ges.*, **54**, 2150 (1921); **62**, 2298 (1929).

[26] W. D. Emmons and A. S. Pagano, *J. Amer. Chem. Soc.*, **77**, 89 (1955).

[27] D. L. MacPeek, P. S. Starcher, and B. Phillips, *J. Amer. Chem. Soc.*, **81**, 680 (1959).

[28] D. Swern, *Org. Reactions*, **7**, 378 (1953).

[29] J. R. Moyer and N. C. Manley, *J. Org. Chem.*, **29**, 2099 (1964).

[30] J. D'Ans, J. Mattner, and W. Busse, *Angew. Chem.*, **65**, 57 (1953).

A solution of dibenzoyl peroxide* (10 g) in toluene (20 ml) is cooled, with stirring, to −5° and then treated during 5 min with a pre-cooled (−2°) solution of sodium (2 g) in 96% ethanol (50 ml). Sodium peroxybenzoate separates at once. To this mixture is added ice-water, in which the sodium peroxybenzoate dissolves. The aqueous peroxybenzoate solution is separated from the toluene in a separatory funnel and washed twice with ether which removes residual toluene and ethyl benzoate. This purified aqueous solution is cooled and treated with a mixture of concentrated sulfuric acid (5 g) and ice-water (60 g), and the peroxybenzoic acid liberated is shaken into chloroform (60 ml in two portions). The chloroform extracts are united and dried over sodium sulfate; they may then be used for oxidations. For preparation of crystalline peroxybenzoic acid the chloroform is evaporated in a stream of dry air at ca. 30 mm and 25–30°. The content of active oxygen is determined by iodometric titration.

Epoxides are usually prepared from olefins and peroxy acids (especially peroxybenzoic acid) according to the following general procedure: The olefin is dissolved in chloroform, cooled, and treated with a slight excess of peroxy acid in cold chloroform. The reaction mixture is set aside at 0°, or for less reactive olefins at room temperature. The course of the reaction is followed by titration of small samples; when the reaction is ended, unchanged peroxy acid and the carboxylic acid formed are carefully extracted, and the chloroform solution is worked up.

The danger associated with organic peroxy compounds makes it essential to maintain the safety precautions described in the Section on "Hydroperoxides and peroxides by autoxidation." The behavior of an untested olefin on oxidation must be tested on a small sample before larger amounts are brought into reaction. Reaction mixtures must be worked up only after destruction or extraction of the excess of peroxy acid by alkali hydroxide solutions (danger of explosion!).

The preparation of **styrene oxide (phenyloxirane)** may be described as an example:[33] Styrene (30 g, 0.29 mole) is added to a solution of peroxybenzoic acid (42 g, 0.30 mole) in chloroform (500 ml), and the mixture is set aside at 0° for 24 h, being repeatedly shaken during the first few hours. Completion of the oxidation can be determined by titration of an aliquot part of the chloroform solution. Then the benzoic acid formed and the small excess of peroxybenzoic acid are removed by repeated extraction with 10% sodium hydroxide solution, and the organic phase is washed with water until free from alkali and then dried over sodium sulfate. Fractional distillation affords styrene oxide (24–26 g, 70–75%) as a colorless liquid, b.p. 101°/40 mm.

Benzaldehyde reacts readily with molecular oxygen with formation of peroxybenzoic acid (see the Section "Autoxidation"). This tendency of benzaldehyde to autoxidation has been utilized in an epoxidation procedure that avoids the preparation of pure peroxy acid.[34] It is only necessary to treat an olefin–benzaldehyde mixture with oxygen or air to obtain the epoxides in good yield. Yields of epoxide are, however, poor if an aliphatic aldehyde is used.[35]

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* Heat must never be used when recrystallizing dibenzoyl peroxide. The best method is that given by Nozaki and Bartlett,[31] in which the peroxide is dissolved in chloroform at room temperature, addition of cold methanol then precipitating the peroxide in beautiful crystals. Recrystallization from hot chloroform is dangerous! See also Rieche and Schulz.[32]

[31] K. Nozaki and P. D. Bartlett, *J. Amer. Chem. Soc.*, **68**, 1686 (1946).

[32] A. Rieche and M. Schulz, *Chem. Technol.*, **11**, 264 (1959).

[33] H. Hibbert and P. Burt, *Org. Syn.*, **8**, 102 (1928).

[34] D. Swern, T. W. Findley, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **66**, 1925 (1944).

[35] D. Swern and T. W. Findley, *J. Amer. Chem. Soc.*, **72**, 4315 (1950); T. W. Findley and D. Swern, U.S. Pat. 2,567,930; *Chem. Abstr.*, **46**, 3560 (1952).

Monoperoxyphthalic acid can be used for preparation of epoxides in the same way as peroxybenzoic acid. In general, good yields are obtained under almost the same conditions as with peroxybenzoic acid, but monoperoxyphthalic acid has the advantage that it is more stable. Because of this stability monoperoxyphthalic acid is particularly suited for epoxidation of less reactive olefins; when reaction is effected in chloroform solution the phthalic acid produced is readily separated because it is insoluble in this solvent.

Monoperoxyphthalic acid is advantageously prepared from phthalic anhydride and alkaline hydrogen peroxide solution in a method due to Böhme[36] or by a modification thereof due to Payne:[37]

A solution of sodium carbonate (62 g, 0.50 mole) in water (250 ml) is placed in a 1-l flask fitted with a stirrer and thermometer and cooled in ice-salt to 5°C, whereupon 30% hydrogen peroxide (70 g, 0.6 mole) is added in one portion. This mixture is cooled to 0° and treated with finely powdered and sieved phthalic anhydride (75 g, ca. 0.5 mole), then stirred rapidly at $-5°$ to 0° for 30 min or until almost all the anhydride has dissolved. Next the solution is treated in a separatory funnel with ether (350 ml) and shaken with a cold solution of concentrated sulfuric acid (30 ml) in water (150 ml), then extracted three times with ether (150 ml portions). The ether extracts are united, washed with 40% ammonium sulfate solution (200 ml), and dried overnight in the ice-chest over anhydrous magnesium sulfate (50 g). The content of peroxyphthalic acid is determined by titration. The yield is 78% (calculated on phthalic anhydride).

For the preparation of crystalline monoperoxyphthalic acid see Böhme.[38]

Epoxidation by monoperoxyphthalic acid has achieved particular importance in the chemistry of natural products.[28,39]

Peroxyacetic acid has importance alongside that of the acids discussed above, this time because it is conveniently prepared. It is almost always used in acetic acid solution, for in pure or concentrated form peroxyacetic acid is highly explosive. Acetic acid solutions of peroxyacetic acid are obtained by mixing acetic acid or acetic anhydride with 25–90% hydrogen peroxide and then adding a little concentrated sulfuric acid as catalyst (armoured cupboard, danger of explosion). 10–40% solutions are obtained according to the concentration of the hydrogen peroxide used.

According to Findley, Swern, and Scanlan,[22] work with peroxyacetic acid solutions is best carried out at reaction temperatures of 20–25° with reaction times as short as possible; strong mineral acids (H_2SO_4) must not be present in the reaction mixture, for which reason it is recommended that sodium acetate be added as buffer.

1,2-Epoxydodecane (decyloxirane):[40] A mixture of 1-dodecene (50.5 g, 0.3 mole) and about 0.9m-peroxyacetic acid solution (408 g, 0.36 mole) is stirred for 24 h at 20–25°. 80–85% of the peroxy acid is consumed during this process. After the stated time the solution is poured into cold water and the whole is extracted with ether. This extract is washed with water and then freed from solvent. On fractional distillation of the residue, 1,2-epoxydodecane (29 g, 52%), b.p. 97–98°/3.5 mm, n_D^{20} 1.4356, is obtained.

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[36] H. Böhme, *Org. Syn.*, **20**, 70 (1940).

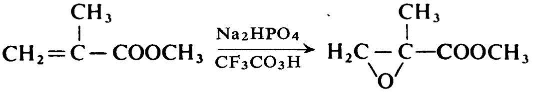
[37] G. B. Payne, *J. Org. Chem.*, **24**, 1354 (1959); cf. *Org. Syn.*, **42**, 77 (1962).

[38] H. Böhme, *Org. Syn.*, Coll. Vol. III, 619 (1955).

[39] A. Bowers, E. Denot, R. Urquiza, and L. M. Sanchez-Hidalgo, *Tetrahedron*, **8**, 116 (1960); P. Karrer, "Fortschritte der Chemie organischer Naturstoffe," Springer-Verlag, Vienna, 1948, Vol. 5, p. 1.

[40] D. Swern, G. N. Billen, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **68**, 1504 (1946).

According to Emmons and Pagano[26] trifluoroperoxyacetic acid is an effective epoxidizing reagent. It is prepared from trifluoroacetic anhydride and hydrogen peroxide in methylene dichloride. Reaction with olefins is usually effected in that solvent in the presence of sodium carbonate, sodium hydrogen carbonate, or disodium hydrogen phosphate. In the presence of this phosphate even negatively substituted olefins such as ethyl methacrylate and crotonate are converted into their epoxides in 84% and 73% yield, respectively.



$$CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}{-}COOCH_3 \xrightarrow[CF_3CO_3H]{Na_2HPO_4} \underset{\diagdown O \diagup}{H_2C{-}\overset{\displaystyle CH_3}{\overset{|}{C}}}{-}COOCH_3$$

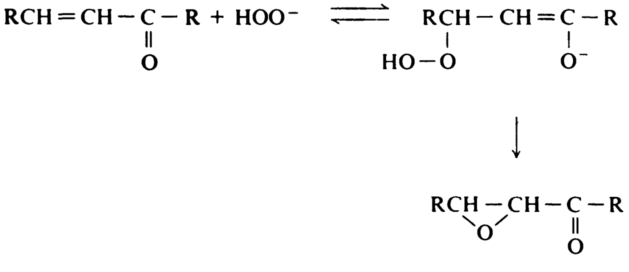
Methyl α-methylglycidate:[26] A solution of trifluoroperoxyacetic acid, prepared from 90% hydrogen peroxide (7.0 ml, 0.25 mole), trifluoroacetic anhydride (42.3 ml, 0.3 mole), and methylene dichloride (50 ml), is added within 20 min, with vigorous stirring, to a boiling mixture of methyl methacrylate (20 g, 0.2 mole), methylene dichloride (200 ml), and disodium hydrogen phosphate (113 g, 0.8 mole). When the exothermic reaction ceases, the mixture is heated for a further 30 min, then poured into water and extracted with methylene dichloride. Working up by distillation gives methyl α-methylglycidate (19.4 g, 84%), b.p. 62–65°/32 mm.

Reaction of α,β-unsaturated ketones with peroxy acids does not usually lead to peroxides; instead, rearrangements follow attack of the peroxy acid on the carbon group.[41,42]

However, as Weitz and Scheffer found,[43] α,β-unsaturated ketones give epoxy ketones in reaction with hydrogen peroxide in alkaline solution.

As an example of this, the preparation of **2-benzoyl-3-phenyloxirane (benzylideneacetophenone oxide)** will be described: A solution of benzylideneacteophenone (2.08 g, 10 mmoles) in methanol (25 ml) is treated with 15% hydrogen peroxide (3 ml, ca. 12 mmoles) and 2N sodium hydroxide solution (2.5 ml), with cooling to keep the temperature at not more than 30°. After a short time the solution suddenly sets to a crystal paste. Suction and washing with a little methanol give colorless crystals (1.8 g); if treated with water the mother-liquor provides a further 0.2 g. Total yield, 89%; m.p. 90°C.

This reaction is considered as nucleophilic addition of HOO⁻ to the β-carbon atom, followed by heterolysis of the O–O bond:[44,45]



$$RCH{=}CH{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R + HOO^- \rightleftharpoons \underset{\displaystyle HO{-}O}{\underset{|}{RCH}}{-}CH{=}\underset{\displaystyle O^-}{\underset{|}{C}}{-}R$$

$$\downarrow$$

$$\underset{\diagdown O \diagup}{RCH{-}CH}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R$$

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[41] H. M. Walton, *J. Org. Chem.*, **22**, 1161 (1957).

[42] G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 284 (1959).

[43] E. Weitz and A. Scheffer, *Ber. Deut. Chem. Ges.*, **54**, 2327 (1921).

[44] C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, **1949**, 665.

[45] S. Patai and Z. Rappoport in "The Chemistry of Alkenes," Interscience Publ. Inc., London, 1964, p. 512.

Other epoxidations by alkaline hydrogen peroxide have also been reported, *e.g.*, in preparation of isophorone oxide (2,3-epoxy-3,5,5-trimethylcyclohexanone)[46] and mesityl oxide epoxide[47] (cf. Winstein and Henderson[48] and Payne[49]).

Oxidation of unsaturated ketones such as mesityl oxide, methyl vinyl ketone, isopropenyl methyl ketone, chalcone, and 2-cyclohexenone to the corresponding epoxides can also be effected by *tert*-butyl hydroperoxide in the presence of Triton B;[50] and similar conditions have been used for epoxidation of α,β-unsaturated aldehydes.[51]

α,β-Unsaturated nitriles containing an α-branch form epoxy amides when treated with hydrogen peroxide in the presence of sodium carbonate and aqueous acetone;[52] for instance, 2,3-diphenylacrylonitrile gives the derived α,β-diphenylglycidamide.[53]

Chromic oxide in glacial acetic acid converts tetraarylethylenes into their epoxides;[54,55] and various steroids are oxidized at positions 5,6 to epoxides by potassium permanganate in glacial acetic acid.[56]

II. Addition of water to ethylenic bonds

Electrophilic addition of water to olefins, yielding alcohols, occurs readily under catalysis by acids, sulfuric acid being that generally used:

$$\mathrm{RCH{=}CHR'} + \mathrm{H_2O} \longrightarrow \mathrm{RCH_2{-}CHR'{-}OH}$$

Addition of water follows Markovnikov's rule in principle, but mixtures are formed rather than the single homogeneous adduct expected according to the rule.[57] Some olefins are hydrated in the presence of dilute sulfuric acid (isobutene), but others require concentrated acids (propene, 1- and 2-butene). Negative substituents on the doubly bonded atoms reduce the reactivity (as for cinnamic acid and dichloroethylene), whereas alkyl groups increase it. In all cases reaction should be at as low a temperature as possible when sulfuric acid is used. Too great a concentration of sulfuric acid often causes polymeri-

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[46] R. I. Wasson and H. O. House, *Org. Syn.*, **37**, 58 (1957).

[47] G. B. Payne, *J. Org. Chem.*, **23**, 310 (1958).

[48] S. Winstein and R. B. Henderson in R. C. Elderfield, "Heterocyclic Compounds," J. Wiley and Sons, New York, 1950, Vol. 1, p. 7.

[49] G. B. Payne, *J. Org. Chem.*, **24**, 2048 (1959).

[50] N. C. Yang and R. A. Finnigan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958).

[51] G. B. Payne, *J. Org. Chem.*, **25**, 275 (1960); *J. Amer. Chem. Soc.*, **81**, 4901 (1959).

[52] G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961); G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, **26**, 659 (1961); G. B. Payne, *J. Org. Chem.*, **26**, 663, 668 (1961); *Tetrahedron*, **18**, 763 (1962); Y. Ogata and Y. Sawaki, *Tetrahedron*, **20**, 2065 (1964).

[53] I. V. Murray and I. B. Cloke, *J. Amer. Chem. Soc.*, **56**, 2749 (1934).

[54] W. Bockemüller and R. Janssen, *Ann. Chem.*, **542**, 166 (1939).

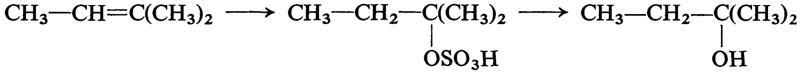
[55] W. A. Mosher, F. W. Steffgen, and P. T. Lansbury, *J. Org. Chem.*, **26**, 670 (1961).

[56] M. Ehrenstein and M. T. Decker, *J. Org. Chem.*, **5**, 544 (1940).

[57] Cf. S. Ehrenson, S. Seltzer, and R. Diffenbach, *J. Amer. Chem. Soc.*, **87**, 563(1965).

zation; this may be avoided by replacing the sulfuric acid by an organic acid, *e.g.*, a 5–10% aqueous solution of oxalic acid.[1a]

The preparation of ***tert*-pentyl alcohol** from 2-methyl-2-butene will be described as an example:[58]



$$CH_3{-}CH{=}C(CH_3)_2 \longrightarrow CH_3{-}CH_2{-}\underset{OSO_3H}{\underset{|}{C}}(CH_3)_2 \longrightarrow CH_3{-}CH_2{-}\underset{OH}{\underset{|}{C}}(CH_3)_2$$

A mixture of ice (500 g) and concentrated sulfuric acid (500 g) is cooled to 0° and 2-methyl-2-butene (500 ml) is added to it with vigorous stirring. The mixture is stirred for a further hour, then the aqueous layer is separated from the unchanged olefin, poured on ice (ca. 2 kg), neutralized cautiously with a concentrated solution of sodium hydroxide (720 g), and distilled until addition of potassium carbonate to a portion of the distillate no longer separates pentyl alcohol. Addition of potassium carbonate to the distillate causes separation of the *tert*-pentyl alcohol, which is dried with the same reagent and distilled, affording ca. 90% of the pure alcohol, b.p. 103°.

Reviews of the hydration of olefins are given by Asinger[59] and Seka,[60] and of the use of boron trifluoride for that purpose by Topchiev *et al.*[61]

When in the α,β-position to a carbonyl group (or to a group analogous to carbonyl), a C=C double bond reacts with nucleophilic reagents;[62] catalysis may be either by base or by acid.

α,β-Unsaturated acids add water readily, giving hydroxy acids. For instance, a solution of 3-nitroacrylic acid in 70% formic acid gives an 83% yield of 2-hydroxy-3-nitropropionic acid when heated for 3 hours at 85–100°C:[63]

$$O_2N{-}CH{=}CH{-}COOH \xrightarrow{H_2O} O_2N{-}CH_2{-}CH(OH){-}COOH$$

3-Hydroxypropionic acid (hydracrylic acid) is formed when acrylic acid is heated with sodium hydroxide solution.[64] Fumaric and maleic acid add water even in absence of a catalyst at temperatures between 150° and 200°; in the presence of alkali hydroxide solution addition of water occurs on longer heating at 100°;[65] addition of water to maleic acid can also be effected in the presence of acids (CO_2, H_2SO_4) or heavy metal salts (Hg, Cd, Zn, or Cu) at elevated temperatures.[60]

3-Hydroxybutyric acid can be obtained by hydration of crotonic acid with aqueous sulfuric acid.[66]

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[58] R. Adams, O. Kamm, and C. S. Marvel, *J. Amer. Chem. Soc.*, **40**, 1955 (1918).

[59] F. Asinger, "Chemie und Technologie der Monoolefine," Akademie-Verlag, Berlin, 1957, p. 540.

[60] R. Seka in G. M. Schwab, "Handbuch der Katalyse," Springer-Verlag, Vienna, 1943, Vol. 7, Part 2, p. 37.

[61] A. V. Topchiev, S. V. Zavgorodnii, and Ya. M. Paushkin, "Boron Fluoride and its Compounds as Catalyst in Organic Chemistry," Pergamon Press, London, 1959, p. 205.

[62] S. Patai and Z. Rappoport, "Nucleophilic Attacks on Carbon–Carbon Double Bonds," in S. Patai, "The Chemistry of Alkenes," Interscience Publ., London, 1964, p. 469.

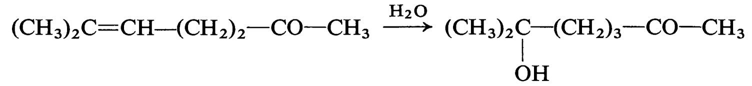
[63] H. Shechter, F. Conrad, A. L. Daulton, and R. B. Kaplan, *J. Amer. Chem. Soc.*, **74**, 3052 (1952).

[64] E. Erlenmeyer, *Ann. Chem.*, **191**, 281 (1878).

[65] F. Lloyd, *Ann. Chem.*, **192**, 80 (1878); H. J. van't Hoff, *Ber. Deut. Chem. Ges.*, **18**, 2713 (1885).

[66] D. Pressman and H. J. Lucas, *J. Amer. Chem. Soc.*, **61**, 2276 (1939).

6-Methyl-5-hepten-2-one in 35% sulfuric acid adds water at room temperature, forming **6-hydroxy-6-methyl-2-heptanone:**[67]

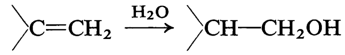


$$(CH_3)_2C{=}CH{-}(CH_2)_2{-}CO{-}CH_3 \xrightarrow{H_2O} (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}{-}(CH_2)_3{-}CO{-}CH_3$$

A mixture of 6-methyl-5-hepten-2-one and 35% sulfuric acid is shaken under nitrogen for 9 h at room temperature, then kept in a refrigerator overnight, diluted with ice-water, and carefully neutralized with aqueous sodium hydroxide below 5°C. Exhaustive extraction with ether and working up by distillation gives an 85% yield of the tertiary alcohol, b.p. 100 to 102°/7 mm.

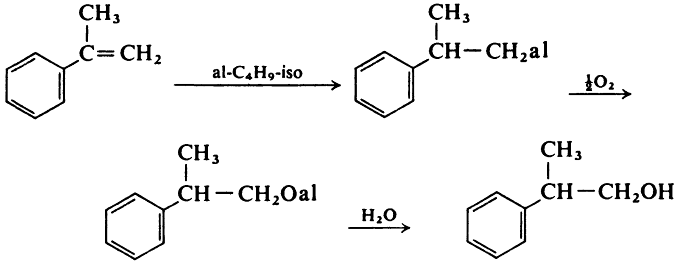
Methallyl alcohol, $CH_2{=}C(CH_3){-}CH_2OH$, is hydrated by a mixture of 25% sulfuric acid and isobutyraldehyde with formation of a cyclic acetal of 2-methyl-1,2-propane-diol; hydrolysis of the acetal by dilute mineral acid gives a 94% yield of the glycol.[68]

Ziegler and his colleagues[69] developed a method of converting an olefin containing a terminal $=CH_2$ group into the primary alcohol:



$$\rangle C{=}CH_2 \xrightarrow{H_2O} \rangle CH{-}CH_2OH$$

First they treat such an olefin with an organoaluminum compound, obtaining the primary alkylaluminum; then oxidation with air or oxygen leads to an aluminum alkoxide which on hydrolysis gives the primary alcohol, *e.g.*:



Preparation of β-methylphenethyl alcohol: Triisobutylaluminum (125 g, 0.63 mole) and α-methylstyrene (354 g, 3.0 moles) give a forerun (19 g) and then 78% (200 g) (calculated on aluminum) of **β-methylphenethyl alcohol,** b.p. 107.5–108°/15 mm.

A reaction known as hydroboration is of especial preparative importance for the conversion of olefins into alcohols.[70–73] This consists in treating simple olefins such as ethylene, 1- or 2-pentene, cyclohexene, or styrene with sodium tetrahydridoborate in the presence of aluminum chloride at 25°, wherepon

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[67] J. Meinwald, *J. Amer. Chem. Soc.*, **77**, 1617 (1955).

[68] G. Hearne, M. Tamele, and W. Converse, *Ind. Eng. Chem.*, **33**, 806 (1941).

[69] K. Ziegler, F. Krupp, and K. Zosel, *Ann. Chem.*, **629**, 241 (1960).

[70] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **78**, 5694 (1956).

[71] H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1136, 1137 (1957).

[72] H. C. Brown, "Organoboranes," in H. Zeiss, "Organometallic Chemistry," Reinhold Publ. Corp., New York, 1960, p. 166.

[73] H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, 1962.

trialkylboranes are formed in 90% yields. These are readily oxidized by alkaline hydrogen peroxide to the corresponding boric esters, which can be hydrolysed to the alcohols. The individual stages need not be isolated. The adduct pyridine · borane, $C_5H_5N \cdot BH_3$,[74] may also be used for this reaction. This method of hydration has been used for preparation of numerous primary alcohols, and also in the steroid series.[75,76] From a formal point of view hydroboration involves addition of water to an olefinic double bond, wherein the direction and steric course of reaction are the reverse of those in acid-catalysed hydration of olefins.

Preparation of **2,2-diphenylethanol:**[70]

$$3(C_6H_5)_2C{=}CH_2 \longrightarrow [(C_6H_5)_2CH{-}CH_2]_3B \longrightarrow$$
$$[(C_6H_5)_2CH{-}CH_2{-}O]_3B \longrightarrow 3(C_6H_5)_2CH{-}CH_2OH$$

1,1-Diphenylethylene is added slowly, with stirring, to a solution of sodium tetrahydridoborate and aluminum chloride in diethylene glycol dimethyl ether (diglyme). The mixture is kept under nitrogen for 3 h at room temperature, then warmed for 1 h on a water-bath. About half of the solvent is distilled off in a vacuum below 40°, and the remainder is washed out with dilute hydrochloric acid and water. The residue is treated with ethanolic sodium hydroxide, and a 20% excess of 30% hydrogen peroxide is dropped in at such a rate that the mixture just boils under reflux. The organic material is taken up in ether and worked up by distillation, affording 87% (86.4 g) of 2,2-diphenylethanol, b.p. 192–194°/20 mm.

Experiments with cycloalkenes have shown that hydration of a double bond by addition of borane involves *cis*-addition to the double bond; thus 85% of *trans*-2-methylcyclopentanol is formed from 1-methylcyclopentene.[77]

III. Addition of water to acetylenic bonds

Addition of water to acetylenes occurs in acid media, particularly in the presence of mercury compounds. Acetylene itself gives acetaldehyde:[78]

$$HC{\equiv}CH + H_2O \longrightarrow CH_3{-}CHO$$

Addition of water to acetylenes with terminal triple bonds affords ketones exclusively — trifluoromethylacetylene is an exception.[79]

$$RC{\equiv}CH + H_2O \longrightarrow R{-}CO{-}CH_3$$

Hydration of mono- and di-substituted acetylenes can in many cases be effected by acid alone, particularly readily by sulfuric acid; thus (*p*-bromophenyl)propiolic acid in concentrated sulfuric acid gives (*p*-bromobenzoyl)acetic acid quantitatively:[80]

$$p\text{-}BrC_6H_4{-}C{\equiv}C{-}COOH \xrightarrow{H_2O} p\text{-}BrC_6H_4{-}CO{-}CH_2{-}COOH$$

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[74] M. F. Hawthorne, *J. Org. Chem.*, **23**, 1788 (1958).

[75] S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959); R. Pappo, *J. Amer. Chem. Soc.*, **81**, 1010 (1959).

[76] F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961).

[77] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 247 (1959); **82**, 3222 (1960); **83**, 124 (1961).

[78] Gattermann–Wieland, "Die Praxis des organischen Chemikers," Walter de Gruyter & Co., Berlin, 1953, pp. (a) 183, (b) 198, (c) 200, (d) 208, (e) 358.

[79] R. N. Haszeldine and K. Leedham, *J. Chem. Soc.*, **1952**, 3483; R. N. Haszeldine, *J. Chem. Soc.*, **1952**, 3490.

[80] M. Reierm and E. Tobin, *J. Amer. Chem. Soc.*, **63**, 2490 (1941).

4,4′-Dimethyltolane[81] and phenylacetylene[82] are hydrated in glacial acetic acid containing appropriate amounts of dilute sulfuric acid.

However, hydration of alkynes by acid alone is less important than addition of water under the influence of mercury salts. For this purpose solutions of mercury(II) sulfate in sulfuric acid or of mercury(II) acetate in acetic acid are generally used. When the products are water-soluble, the hydration can be effected with aqueous catalyst solutions; for water-insoluble acetylenes it is advisable to add solvents such as 70% methanol, 70% acetone, or acetic acid.[83]

2-Hexanone from 1-hexyne: A mixture of 1 g of mercury(II) sulfate, 1 g of concentrated sulfuric acid, and 150 g of 70% methanol (or 150 g of 70% acetone or 50 g of 60% acetic acid) is warmed to 60° in a 500-ml three-necked flask fitted with a stirrer, dropping funnel, and reflux condenser. 1-Hexyne (41.0 g, 0.5 mole) is dropped in, with stirring, within 1 h. The mixture is stirred for a further 3 h at the temperature stated, then cooled, and worked up. The methanol (or acetone) is distilled off and the 2-hexanone is salted out from the residue by solid sodium chloride. The ketone layer is separated, washed, neutralized, dried over calcium chloride, and distilled, giving 78.8% of 2-hexanone, b.p. 120°. When acetic acid has been used as solvent, it is neutralized with sodium carbonate solution before working up as above.

The mixture of mercury oxide, boron trifluoride-ether, and trifluoroacetic acid is a particularly effective catalyst for hydration of alkynes;[84] mixtures of mercury oxide and boron trifluoride[88] and of mercury oxide with sulfuric acid[86] have also been used. Addition to acid-sensitive acetylenes is carried out under neutral conditions by means of mercuriacetamide or mercuri-*p*-toluenesulfonamide.[87] Acid exchange resins loaded with mercury ions can also be used for addition of water to alkynes.[88]

Disubstituted acetylenes may add water in two directions:

$$\underset{\text{(II)}}{RCH_2COR'} \xleftarrow{H_2O} RC{\equiv}CR' \xrightarrow{H_2O} \underset{\text{(I)}}{RCOCH_2R'}$$

The substituents R and R′ control the course of the reaction: the oxygen is introduced on to that triply bonded carbon atom that is furthest removed from the more electronegative group; if there is no difference in polarity between the substituents R and R′, then mixtures of ketones I and II are formed. For instance, addition of water to 2-heptyne in methanol by the method of Thomas, Campbell, and Hennion[83] leads to 2- and 3-heptanone in approximately equal amounts.[89]

α-Acetylenic carboxylic acids add water to give the corresponding β-keto acids:

$$RC{\equiv}C{-}COOH \xrightarrow{H_2O} RCO{-}CH_2{-}COOH$$

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[81] W. P. Buttenberg, *Ann. Chem.*, **279**, 335 (1894).

[82] J. U. Nef, *Ann. Chem.*, **308**, 294 (1899).

[83] R. J. Thomas, K. N. Campbell, and G. F. Hennion, *J. Amer. Chem. Soc.*, **60**, 718 (1938).

[84] J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, **1951**, 2652.

[85] N. A. Dobson and R. A. Raphael, *J. Chem. Soc.*, **1955**, 3558.

[86] G. W. Stacy and R. A. Miculec, *Org. Syn.*, **35**, 1 (1955).

[87] M. W. Goldberg and R. Aeschbacher, *Helv. Chim. Acta*, **22**, 1185 (1939); M. W. Goldberg, R. Aeschbacher, and E. Hardegger, *Helv. Chim. Acta*, **26**, 680 (1943).

[88] (a) M. S. Newman, *J. Amer. Chem. Soc.*, **75**, 4740 (1953); (b) J. D. Billimoria and N. F. Maclagan, *J. Chem. Soc.*, **1954**, 3257.

[89] G. F. Hennion and C. J. Pillar, *J. Amer. Chem. Soc.*, **72**, 5317 (1950).

According to Moureu and Delange[90] this reaction occurs on boiling the acid in alcoholic potassium hydroxide; in aqueous alkali hydroxide solutions decarboxylation occurs simultaneously, giving the corresponding methyl ketones.

α-Acetylenic nitriles and amides were converted by Moureu and Lazennec[91] into the corresponding keto nitriles and keto amides by boiling their alcoholic solutions with amines.

Alkynyl ketones add water, forming β-diketones:

$$\mathrm{RCO{-}C{\equiv}CR'} \xrightarrow{\mathrm{H_2O}} \mathrm{RCO{-}CH_2{-}COR'}$$

Nef[92] obtained dibenzoylmethane by the action of concentrated sulfuric acid on benzoylphenylacetylene, and numerous other β-diketones have been synthesized by this method.[93] Benzoylacetylene is unaffected by concentrated sulfuric acid at 20° and decomposes therein at higher temperatures; in dilute sulfuric acid containing mercury sulfate at 80–100° it affords **1-phenyl-1,2-propanedione:**[94]

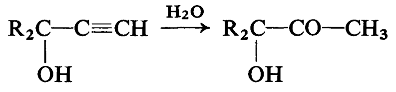
$$\mathrm{C_6H_5{-}CO{-}C{\equiv}CH} \xrightarrow{\mathrm{H_2O}} \mathrm{C_6H_5{-}CO{-}CO{-}CH_3}$$

2N-Sulfuric acid (50 ml) containing mercury(II) sulfate (0.25 g) is added to a solution of benzoylacetylene (6.5 g) in ethanol (100 ml). The mixture is stirred on a boiling water-bath for 6 h during which further mercury sulfate (0.25 g) in 2N-sulfuric acid is gradually added. Isolation by means of ether gives 1-phenyl-1,2-propanedione (4.1 g) as a yellow oil, b.p. 88°/17 mm, n_D^{17} 1.5350.

Alkoxyacetylenes add water at room temperature in presence of hydrochloric acid and mercury(II) acetate, yielding esters. 1-Phenoxy-1-hexyne (4.96 g) thus give phenyl hexanoate (2.8 g).[95]

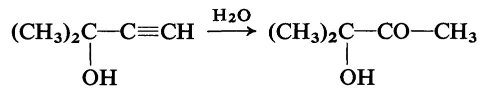
$$\mathrm{C_4H_9{-}C{\equiv}C{-}OC_6H_5} \xrightarrow{\mathrm{H_2O}} \mathrm{C_4H_9{-}CH_2{-}COOC_6H_5}$$

Hydration of alkynols leads to hydroxy ketones:



$$\mathrm{R_2\underset{\displaystyle OH}{\underset{|}{C}}{-}C{\equiv}CH} \xrightarrow{\mathrm{H_2O}} \mathrm{R_2\underset{\displaystyle OH}{\underset{|}{C}}{-}CO{-}CH_3}$$

3-Hydroxy-3-methyl-2-butanone is formed in good yield from 2-methyl-3-butyn-2-ol and mercury sulfate in an excess of dilute sulfuric acid.[96]



$$\mathrm{(CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}{-}C{\equiv}CH} \xrightarrow{\mathrm{H_2O}} \mathrm{(CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}{-}CO{-}CH_3}$$

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[90] C. Moureu and R. Delange, *C. R. Hebd. Séances Acad. Sci.*, **136**, 753 (1903).

[91] C. Moureu and J. Lazennec, *C. R. Hebd. Séances Acad. Sci.*, **143**, 553 (1906); **144**, 491 (1907); **144**, 806 (1907); *Bull. Soc. Chim. France*, [iv], **1**, 1062 (1907); [iii], **35**, 1179 (1906).

[92] J. U. Nef, *Ann. Chem.*, **308**, 277 (1899).

[93] M. Yvon, *C. R. Hebd. Séances Acad. Sci.*, **180**, 748 (1925); C. Moureu and R. Delange, *Bull. Soc. Chim. France*, **25**, 306 (1901); *Ann. Chim. (Paris)*, **2**, 277 (1914); R. C. Fuson, G. E. Ullyot, and J. L. Hickson, *J. Amer. Chem. Soc.*, **61**, 410 (1939); R. A. Morton, A. Hassan, and T. C. Calloway, *J. Chem. Soc.*, **1934**, 899.

[94] K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, **1946**, 945.

[95] T. L. Jacobs, R. Cramer, and F. T. Weiss, *J. Amer. Chem. Soc.*, **62**, 1849 (1940).

[96] H. Scheibler and A. Fischer, *Ber. Deut. Chem. Ges.*, **55**, 2903 (1922).

If mercury chloride is added to an aqueous solution of the 2-methyl-3-butyn-2-ol a white mercury derivative is precipitated, and if this is boiled with hydrochloric acid it gives the same 3-hydroxy-3-methyl-2-butanone as mentioned above.[97] With mercury acetate in glacial acetic acid at 75–95° the alkynol gives a 98.5% yield of the acetoxy ketone.[98]

1-Ethynylcyclohexanol is hydrated to 1-hydroxycyclohexyl methyl ketone by use of an ion-exchange resin treated with 1% mercury sulfate solution;[88] **hydroxyacetone** has been synthesized analogously from propargyl alcohol:[88a]

Dowex 50 ion-exchange resin is treated with a solution of mercury sulfate in dilute sulfuric acid, then carefully washed and dried. This resin (2 g) is added, with stirring, to a solution of propargyl alcohol (10.4 g, 0.2 mole) in water (100 ml); the temperature rises to 55° within 13 min. The mixture is stirred for 25 min at 50° and subsequently at 40°. After 100 min the resin is filtered off and washed with water (20 ml). An aliquot part (12 ml) of the solution is treated with phenylhydrazine, giving hydroxyacetone phenylhydrazone (2.85 g, 87%), m.p. 99–101°C.

Tertiary alkynols give α,β-unsaturated ketones when heated in 85% formic acid.[99,100]

Ruzicka and Meldahl[101] describe the addition of water to ethynyl alcohols of the steroid series in glacial acetic acid containing a little acetic anhydride, the catalysts being mercuric oxide and boron trifluoride. Addition is accompanied by rearrangement and ring expansion; 17β-ethynyl-5-androstene-3,17-diol provides an example. Mondon[102] added water to a tertiary acetylenic glycol under extremely mild conditions, namely by an ice-cold solution of mercury sulfate in 85% formic acid, achieving a quantitative yield.

For some further hydrations see Kupin and Petrov.[103]

IV. Addition of hydroxyl groups to ethylenic bonds

1. Hydroxylation by organic peroxy acids

The action of organic peroxy acids on olefins gives epoxides (see preceding Section) or α-glycols, formation of the latter being favored by higher temperatures, longer reaction times, and presence of strong acids. Under these conditions the epoxides first formed are unstable and are hydrolysed to the α-glycols

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[97] K. Hess and H. Munderloh, *Ber. Deut. Chem. Ges.*, **51**, 377 (1918).

[98] E. M. McMahon, J. N. Roper Jr., W. P. Utermohlen Jr., R. H. Hasek, R. C. Harries, and J. H. Brant, *J. Amer. Chem. Soc.*, **70**, 2971 (1948).

[99] H. Rupe, W. Messner, and E. Kambli, *Helv. Chim. Acta*, **11**, 449 (1928); F. G. Fischer and K. Löwenberg, *Ann. Chem.*, **475**, 203 (1929); J. D. Chanley, *J. Amer. Chem. Soc.*, **70**, 246 (1948).

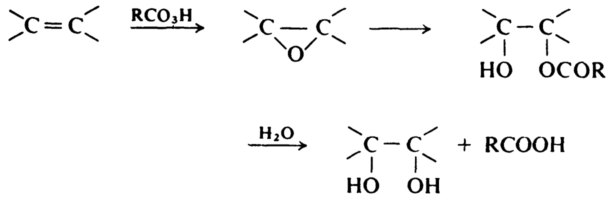
[100] G. F. Hennion, R. B. Davis, and D. E. Maloney, *J. Amer. Chem. Soc.*, **71**, 2813 (1949).

[101] L. Ruzicka and H. F. Meldahl, *Nature*, **142**, 399 (1938).

[102] A. Mondon, *Ann. Chem.*, **585**, 43 (1954).

[103] B. S. Kupin and A. A. Petrov, *Zh. Obshch. Khim.*, **31**, 2858 (1961); *Chem. Abstr.*, **57**, 2125 (1962).

by way of a hydroxy ester:[28]



Hydrolysis of the epoxide occurs by *trans*-ring fission; *e.g.*, *trans*-1,2-cyclohexanediol is formed from 1,2-epoxycyclohexane.[104]

The usual reagents for such oxidation of olefins are peroxyacetic and peroxyformic acid. Because of the inherent danger these peracids are not prepared in the pure state but are used in dilute solution.

According to Swern *et al.*[23] the olefin is treated with an almost stoichiometric amount of 25–30% hydrogen peroxide in glacial acetic acid containing a small amount of concentrated sulfuric acid. This method gives good yields of α-glycols when the reaction temperature is about 40° and the reaction time a few hours.

***trans*-1,2-Cyclohexanediol:**[105] A mixture of glacial acetic acid (43.9 g), 30% hydrogen peroxide (43.9 g), and concentrated sulfuric acid (4.5 g) is added, with good stirring and initial cooling, to cyclohexene (28.9 g) at such a rate that the temperature remains between 20° and 25°. The mixture, which is still turbid, is then heated at 45° for 2–3 h — until it becomes completely clear — then neutralized with sodium hydroxide solution and extracted exhaustively with ether. Evaporation of the ether leaves crystalline *trans*-1,2-cyclohexanediol (31.2 g, 75%) which, after recrystallization from ethyl acetate has m.p. 103–104° (yield, 22 g, 53%).

Peroxyformic acid is particularly valuable as hydroxylating agent. It is prepared by mixing a slight excess of 30% hydrogen peroxide with 98–100% formic acid. N.B.: Pure peroxyformic acid is highly explosive. Oxidation of olefins by this peroxy acid occurs at about 40° and is rapidly completed; any hydroxy ester formed can be hydrolysed by dilute sodium hydroxide solution or even by heating with water; the products are α-glycols.

***trans*-1,2-Cyclohexanediol:**[106] Cyclohexene (8.0 g, 0.097 mole) is added to a mixture of 98–100% formic acid (105 g) and 30% hydrogen peroxide (13 g, 0.115 mole). After the mixture has been shaken for a short time, much heat is evolved and at 65–70° the suspension changes to a homogeneous liquid. This solution is then heated at 65–70° on a water-bath for 2 h, after which the excess of formic acid is removed in a vacuum. The residue is heated with 20% sodium hydroxide solution on the water-bath for 45 min, then cooled and neutralized with hydrochloric acid. Evaporation in a vacuum leaves a residue, which is distilled. The fraction boiling at 128–132°/15 mm is collected (10.25 g); it soon begins to crystallize. Recrystallization from acetone gives *trans*-1,2-cyclohexanediol (7.9 g, 70%), m.p. 102–103°.

According to Greenspan,[107] olefins can be hydroxylated in very high yield by a mixture of acetic acid and 90% hydrogen peroxide. A mixture of con-

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[104] S. Winstein, *J. Amer. Chem. Soc.*, **64**, 2792 (1942).

[105] H. Meerwein and co-workers, Ger. Pat. 574,838; *Chem. Abstr.*, **27**, 4540 (1933).

[106] A. Roebuck and H. Adkins, *Org. Syn.*, **28**, 35 (1948).

[107] F. P. Greenspan, *J. Amer. Chem. Soc.*, **68**, 907 (1946); *Ind. Eng. Chem.*, **39**, 847 (1947).

centrated formic acid and 90% hydrogen peroxide is also very effective and has been used particularly for hydroxylation of α,β-unsaturated acids.[108]

Trifluoroperoxyacetic acid is also an efficient reagent for oxidation of olefins to α-glycols (preparation: see the Section on Epoxides);[109] in this reaction the α-glycols are first formed as monoesters with trifluoroacetic acid and are obtained therefrom by treatment with methanol. Excellent yields of α-glycols are obtained by adding triethylammonium trifluoroacetate to the reaction mixture.

Preparation of **2,3-pentanediol** from 2-pentene: Trifluoroacetic anhydride (37.2 ml, 0.264 mole) is added with stirring to a cooled suspension of 90% hydrogen peroxide (6.0 ml, 0.22 mole) in methylene dichloride (50 ml). The resulting solution is stirred in the cold for a further 10 min, then transferred to a dropping funnel fitted for pressure equalization. The mixture is dropped within 30 min into a solution of 2-pentene (14.0 g, 0.2 mole) and triethylammonium trifluoroacetate (21.4 g, 0.1 mole) in methylene dichloride (50 ml), whereupon vigorous ebullition sets in. After this addition the whole is stirred for a further 15 min, then the volatile constituents are removed in a vacuum; the colorless residue has b.p. 38 to 60°/2 mm and affords a hydroxyalkyl trifluoroacetate (50.5 g). This ester is boiled for 2 h with 3% methanolic hydrochloric acid (300 ml), then freed from solvent in a vacuum. On distillation, 74% (15.1 g) of colorless 2,3-pentanediol, b.p. 58–59°/0.5 mm, n_D^{20} 1.4412, is obtained.

2. Hydroxylation by potassium permanganate

Olefins can be easily oxidized to *cis*-1,2-glycols by dilute potassium permanganate solutions.[110] This reaction has been used for hydroxylation of numerous unsaturated compounds of the most diverse types.[111]

It is very important to choose the reaction conditions so as to avoid further oxidation of the glycols formed; if, for instance, the permanganate is added too rapidly to a neutral solution of olefin, the main product is an acyloin RCH(OH)—COR′.[112] Hydroxylation is usually effected in the cold with neutral or alkaline potassium permanganate solution; water, acetone, alcohols, methylcyclohexane, and mixtures of alcohol and water can serve as solvent. Magnesium sulfate is often added for reactions in a neutral medium.[113]

Oxidation of olefins in alkaline solution (pH < 12) in mixed solvents (*tert*-butyl alcohol/water) gives higher yields of purer glycols and proceeds more readily than does reaction in neutral solution.[114,115]

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[108] J. English Jr. and J. D. Gregory, *J. Amer. Chem. Soc.*, **69**, 2120 (1947).

[109] W. D. Emmons, A. S. Pagano, and J. P. Freeman, *J. Amer. Chem. Soc.*, **76**, 3472 (1954).

[110] G. Wagner, *Ber. Deut. Chem. Ges.*, **21**, 1230, 3343, 3347 (1888); **23**, 2307 (1890); **27**, 1636 (1894); J. Boeseken, *Rec. Trav. Chim.*, **47**, 683, 839 (1928).

[111] Steroids: *e.g.*, A. Windaus, *Ber. Deut. Chem. Ges.*, **40**, 257 (1907); R. Tull, R. E. Jones, S. A. Robinson, and M. Tishler, *J. Amer. Chem. Soc.*, **77**, 196 (1955); M. Fieser, A. Quilico, A. Nickon, W. E. Rosen, E. J. Tarlton, and L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4066 (1953). Carbohydrates: *e.g.*, R. A. Raphael and C. M. Roxburgh, *J. Chem. Soc.*, **1955**, 3405. *cis*-Dimethylcyclohexene: H. Meerwein, *Ann. Chem.*, **542**, 123 (1939).

[112] G. King, *J. Chem. Soc.*, **1936**, 1788.

[113] F. Straus and A. Rohrbacher, *Ber. Deut. Chem. Ges.*, **54**, 69 (1921).

[114] K. B. Wiberg and K. A. Saegebarth, *J. Amer. Chem. Soc.*, **79**, 2822 (1957).

[115] A. Lapworth and E. N. Mothram, *J. Chem. Soc.*, **127**, 1628 (1925).

Preparation of ***erythro*-9,10-dihydroxystearic acid** from oleic acid:[114] A solution obtained by heating a mixture of oleic acid (1.00 g, 3.5 mmoles), sodium hydroxide (1.0 g, 25 mmoles), and water (100 ml) is cooled and diluted with ice-water (800 ml) and crushed ice (100 g). To this cold solution is added, as fast as possible and with vigorous stirring, a solution of potassium permanganate (0.80 g, 5.1 mmoles) in water (80 ml). After 5 min the mixture is decolorized by SO_2, concentrated hydrochloric acid (30 ml) is added, and the whole is cooled for 1 h in ice. The precipitate is then filtered off and dried in a drying pistol at room temperature, affording crude *erythro*-9,10-dihydroxystearic acid (1.05 g, 94%). Recrystallization from 95% ethanol gives a pure product (0.90 g, 81%), m.p. 130–131°C.

If more potassium permanganate (1.10 g, 7 mmoles) in water (110 ml) is used and decolorization is effected after reaction for 1 min, the yield of crude diol is 98% (1.10 g) and of pure product 79% (0.88 g).

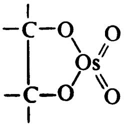
According to Rigby[117] olefins can be oxidized to *cis*-α-glycols also by alkaline potassium manganate.

For hydroxylation of unsaturated aldehydes it is preferable to use the corresponding acetals: glyceraldehyde diethyl acetal is obtained from acrolein diethyl acetal by means of permanganate in aqueous solution.[116]

3. Hydroxylation by osmium tetroxide

Olefins can be oxidized stereospecifically to *cis*-α-glycols by aqueous potassium chlorate solutions[118] or, better, silver chlorate solutions[119] if a little osmium tetroxide is added (Hofmann). The method is suitable mainly for conversion of water-soluble olefins into glycols and cannot be used for water-insoluble olefins.[120,121]

Osmic esters of type (I) are intermediates in Hofmann oxidation of olefins and they have been isolated by Criegee.[122] They are cleaved to glycols by boiling aqueous chlorate solutions, so that osmium tetroxide is regenerated and can add to further molecules of olefin. For the mechanism of the reaction see Criegee[120] and Milas.[121]



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There is a preparative advantage in hydrolysing the osmic ester by aqueous-alcoholic sodium sulfite solution, for then the osmium is precipitated as sparingly soluble sulfite complex.

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[116] E. J. Witzemann and co-workers, *Org. Syn.*, Coll. Vol. II, 307 (1943).

[117] W. Rigby, *J. Chem. Soc.*, **1956**, 2452.

[118] K. A, Hofmann, *Ber. Deut. Chem. Ges.*, **45**, 3329 (1912); K. A. Hofmann, O. Ehrhart, and O. Schneider, *Ber. Deut. Chem. Ges.*, **46**, 1657 (1913).

[119] G. Braun, *J. Amer. Chem. Soc.*, **51**, 228 (1929).

[120] R. Criegee in G. M. Schwab, "Handbuch der Katalyse," Springer-Verlag, Vienna, 1943, Vol. 7, Part 1, p. 597.

[121] N. A. Milas in "The Chemistry of Petroleum Hydrocarbons," Reinhold Publ. Corp., New York, 1955 2, pp. (a) 419, (b) 431.

[122] R. Criegee, *Ann. Chem.*, **522**, 75 (1936).

According to Criegee and his colleagues the osmium tetroxide method of hydroxylation can be adapted also for application to water-insoluble olefins.[122,123] Osmic esters (I) form stable adducts with 2 moles of pyridine and these crystallize well. They can be prepared directly from the three components olefin, osmium tetroxide, and pyridine in some suitable solvent (chloroform, ethyl acetate, benzene, carbon tetrachloride). The pyridine–olefin–osmium tetroxide adducts are readily hydrolysed in good yield to the *cis*-α-glycols, this being effected by reductive fission (boiling with aqueous-alcoholic sodium sulfite solution or with formaldehyde in dilute alkali hydroxide solution[124]) or by alkaline transesterification with mannitol in dilute alkali hydroxide.[123]

Preparatively the last method is carried out by shaking the powdered solid pyridine compound with an aqueous-alcoholic solution of mannitol (2 moles of KOH and 2 moles of mannitol per atom of osmium) until there is complete dissolution; or the pyridine compound is first dissolved in methylene dichloride (or chloroform) and then shaken with the alkaline mannitol solution until the methylene chloride solution is completely decolorized. Yields of diol are usually excellent. Since warming is not involved, side reactions rarely occur. The method is particularly important in the steroid field.[125]

Badger[126] has treated numerous polycyclic aromatic compounds with osmium tetroxide and has studied the kinetics of the reaction.

***cis*-1,2-Heptanediol:**[123] Cycloheptene (1.92 g), osmium tetroxide (5.10 g), and pyridine (3.5 ml) are mixed in dry ether (100 ml) at 0°, the whole setting to a brown crystal paste almost immediately. After 0.5 h the crystals are filtered off under suction and washed with ether; this gives a pale brown, readily electrified crystal powder (10.01 g, 98.5%), which is recrystallized from methylene dichloride/light petroleum.

This adduct (9.5 g) is shaken with mannitol (10 g) in aqueous potassium hydroxide solution (100 ml), all the material rapidly dissolving. The whole is extracted with methylene dichloride for 12 h, the solvent is removed from the extract, and the residue is distilled in a high vacuum. Pure *cis*-1,2-cycloheptanediol distils at 90–100° (bath)/0.1 mm in almost theoretical yield; it solidifies and then has m.p. 48°.

4. Hydroxylation by iodine–silver benzoate (Prèvost reagent)

According to Prèvost and his collaborators olefins are converted by a solution of the complex compound $[(C_6H_5COO)_2Ag]I$ (obtained from silver benzoate and iodine in benzene) stereospecifically into *trans*-1,2-benzoates, whence the *trans*-1,2-glycols are easily prepared.

This reaction has been reviewed by Milas.[121b]

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[123] R. Criegee, B. Marchand, and H. Wannowius, *Ann. Chem.*, **550**, 99 (1942).

[124] E. R. H. Jones and R. J. Meakins, *J. Chem. Soc.*, **1940**, 456; H. Reich, M. Sutter and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

[125] A. Butenandt, *Z. Naturforsch.*, **1**, 222 (1946); J. W. Cook, J. Jack, J. D. Loudon, G. L. Buchanan, and J. McMillan, *J. Chem. Soc.*, **1951**, 1397; L. H. Sarrett, *J. Amer. Chem. Soc.*, **71**, 1169 (1949); R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952); R. Hirschmann, C. S. Snoddy Jr., C. F. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954); W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, **78**, 1909 (1956); K. Biemann, G. Büchi, and B. H. Walker, *J. Amer. Chem. Soc.*, **79**, 5558 (1957).

[126] G. M. Badger, *J. Chem. Soc.*, **1949**, 456; **1950**, 1809; G. M. Badger and K. R. Lynn, *J. Chem. Soc.*, **1950**, 1726.

1,2-Hexadecanediol:[127] Iodine (10.6 g) in benzene (100 ml) is added with shaking to a suspension of silver benzoate (26.5 g) in benzene (150 ml). This product is treated slowly, with shaking, with a solution of 1-hexadecene (10.5 g) in benzene (50 ml), after which the whole is boiled under reflux for 1 h, then cooled and filtered. The solvent is distilled off from the filtrate and the residue of 1,2-hexadecanediyl dibenzoate is hydrolysed by potassium hydroxide (12 g) in boiling ethanol (75 ml) and water (25 ml) for 3 h. The hydrolysate is poured into hot water (500 ml) and, after cooling, the product that separates is filtered off. It is recrystallized from methanol, then from light petroleum (b.p. 60–70°), and again from methanol, giving 1,2-hexadecanediol (4 g, 33%), m.p. 73.1–73.6°.

5. Woodward *cis*-hydroxylation

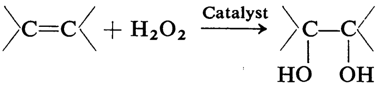
Woodward and Brutcher Jr.[128] described the conversion of olefins into *cis*-α-glycols by iodine and silver acetate in aqueous acetic acid. The reaction gives *cis*-β-hydroxy α-acetates in one operation, and thence hydrolysis affords the *cis*-α-glycols. Applications in steroid chemistry[129] and elsewhere have given the method general importance[130–132] for *cis*-hydroxylation.

Woodward *cis*-hydroxylation is based on the work of Winstein and his co-workers on the neighboring group effect in organic chemistry; for a review see Lwowski.[133]

***cis*-1,2-Cyclohexanediol:**[132] Freshly distilled cyclohexene (b.p. 83–85°; 3.42 g, 0.042 mole) is added to a suspension of silver acetate (16 g, 0.096 mole) in glacial acetic acid (150 ml) placed in a three-necked flask fitted with a reflux condenser, thermometer, and stirrer. Powdered iodine (11.7 g, 0.046 mole) is added with vigorous stirring during 30 min, then water (6.67 g) is added, and the whole is heated with stirring at 90–95° for 3 h, then cooled and filtered. The solid material is washed with hot benzene and ethyl acetate, the filtrates are united and the solvents are removed at water-pump vacuum. The residual yellow oil is taken up in methanol and filtered; the filtrate is neutralized with a little alcoholic potassium hydroxide and then boiled for 1.5 h with a solution of potassium hydroxide (3.5 g) in methanol (20 ml). The methanol is then removed in a vacuum and the residue is dissolved in hot ether (500 ml) and filtered. Removal of the solvent then gives 81% (3.92 g) of crude product. This is recrystallized from carbon tetrachloride, giving pure *cis*-1,2-cyclohexanediol, m.p. 97–98° (3.2 g, 66%).

6. Hydroxylation by hydrogen peroxide and inorganic catalysts

Direct addition of hydrogen peroxide to double bonds of olefins in accord with the reaction:



$$>C=C< + H_2O_2 \xrightarrow{\text{Catalyst}} >\underset{\text{HO}}{\underset{|}{C}}-\underset{\text{OH}}{\underset{|}{C}}<$$

usually occurs in organic solvents in the presence of catalytic amounts of metal oxides such as OsO_4, V_2O_5, WO_3, MoO_3, CrO_3, or SeO_2.[134] According to

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[127] C. Niemann and C. D. Wagner, *J. Org. Chem.* **7**, 227 (1942).

[128] R. B. Woodward and F. V. Brutcher Jr., *J. Amer. Chem. Soc.*, **80**, 209 (1958).

[129] W. S. Knowles and Q. E. Thompson, *J. Amer. Chem. Soc.*, **79**, 3212 (1957); L. B. Barkley, W. S. Knowles, and Q. E. Thompson, *J. Amer. Chem. Soc.*, **78**, 4111 (1956).

[130] D. Ginsburg, *J. Amer. Chem. Soc.*, **75**, 5746 (1953).

[131] F. D. Gunstone and L. J. Morris, *J. Chem. Soc.*, **1957**, 487.

[132] F. V. Brutcher Jr. and G. Evans, *J. Org. Chem.*, **23**, 618 (1958).

[133] W. Lwowski, *Angew. Chem.*, **70**, 490 (1958).

[134] N. A. Milas, *J. Amer. Chem. Soc.*, **59**, 2342 (1937).

Treibs[135,136] those metal oxides are suitable that are readily converted by hydrogen peroxide into inorganic peracids. Detailed studies of the catalysts named above have been instituted by Mugdan and Young.[137]

Hydroxylation of olefins by hydrogen peroxide in the presence of osmium tetroxide leads to *cis*-glycols because a cyclic osmic ester is formed as intermediate and the *cis*-glycol is formed by hydrolysis of that intermediate. Other catalysts afford *trans*-hydroxylation, which occurs by way of an intermediate epoxide.[138]

Oxidation of olefins by hydrogen peroxide and catalytic amounts of osmium tetroxide is effected in anhydrous *tert*-butyl alcohol (Milas reagent[139]), ether,[122] aqueous methanol,[140] or acetone.[141] Also, *tert*-butyl hydroxyperoxide may be used in place of hydrogen peroxide.[142]

Hydroxylation of polyolefins by Milas reagent can be so arranged that only one double bond is affected: *e.g.*, cyclopentadiene gives a mixture of 3-cyclopentene-1,2-diol and 4-cyclopentene-1,3-diol.[139,143] Another application of this method was the selective oxidation of β-carotene to vitamin-A aldehyde.[144]

Vanadium(v) oxide and hydrogen peroxide are used in anhydrous *tert*-butyl alcohol, dilute methanol, or acetone solution. Experiments by Treibs and his collaborators[135,136] showed that these reactions are unspecific since oxidation occurs at the allylic position as well as the desired hydroxylations.

Mugdan and Young recommend tungsten(vi) oxide as catalyst for hydroxylation by hydrogen peroxide,[137] best in aqueous or acetic acid solution between 50° and 70°. The reaction gives *trans*-α-glycols stereospecifically. The method also has technical importance and yields are usually good. Molybdenum oxide and selenium dioxide[145] can also be used as catalysts for such reactions but offer no significant advantage over osmium tetroxide and tungsten oxide.

V. Addition of carboxylic acids and alcohols to olefins and acetylenes

The present Section is devoted to showing, by some examples, the value of those additions that lead to ethers, esters, ketals, and acid anhydrides.

The ease of addition of organic carboxylic acids to a carbon–carbon double bond increases with activation of the latter by neighboring substituents and with the acidity of the acid. Esters of tertiary alcohols are formed with particular

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[135] W. Treibs, *Ber. Deut. Chem. Ges.*, **72**, 1194 (1939).

[136] W. Treibs, G. Franke, G. Leichsenring, and H. Röder, *Chem. Ber.*, **86**, 616 (1953).

[137] M. Mugdan and D. P. Young, *J. Chem. Soc.*, **1949**, 2988.

[138] G. B. Payne and C. W. Smith, *J. Org. Chem.*, **22**, 1682 (1957).

[139] N. A. Milas and S. Sussman, *J. Amer. Chem. Soc.*, **58**, 1302 (1936); **59**, 2345 (1937); N. A. Milas, S. Sussman, and H. S. Mason, *J. Amer. Chem. Soc.*, **61**, 1844 (1939); N. A. Milas and L. C. Maloney, *J. Amer. Chem. Soc.*, **62**, 1841 (1940); R. C. Hockett, A. C. Sapp, and S. R. Millmann, *J. Amer. Chem. Soc.*, **63**, 2051 (1941); C. D. Hurd and C. D. Kelso, *J. Amer. Chem. Soc.*, **70**, 1484 (1948).

[140] N. Clauson-Kaas and J. Fakstrop, *Acta Chem. Scand.*, **1**, 216 (1947).

[141] J. W. Cook and R. Schoental, *J. Chem. Soc.*, **1950**, 47.

[142] T. L. Gresham and T. R. Steadman, *J. Amer. Chem. Soc.*, **71**, 737 (1949).

[143] L. N. Owen and P. N. Smith, *J. Chem. Soc.*, **1952**, 4035.

[144] N. L. Wendler, C. Rosenblum, and M. Tishler, *J. Amer. Chem. Soc.*, **72**, 234 (1950); G. C. L. Goss and W. D. McFarlane, *Science*, **106**, 375 (1947).

[145] P. Seguin, *C. R. Hebd. Séances Acad Sci.*, **216**, 667 (1943).

ease:

$$(CH_3)_2{=}CH_2 + RCOOH \rightleftarrows (CH_3)_3O{-}COR$$

The reaction is reversible and is catalysed by strong acids; 95% sulfuric acid, organic sulfonic acids and $ZnCl_2$[146] or boron trifluoride[147–149] are especially effective. However, if more than 10% of boron trifluoride is used, polymerization intervenes seriously. For good yields of esters the reaction temperature must be kept as low as possible. The preparation of ***tert*-butyl *o*-benzoylbenzoate** will be detailed as an example:[150]

A solution of *o*-benzoylbenzoic acid (10.0 g) in ether (70 ml) containing 1 ml of concentrated sulfuric acid is mixed with liquid isobutene (100 g) in a 500-ml pressure flask. The flask is closed, kept overnight at room temperature, cooled in ice–salt, and then opened. The contents are poured into a cold solution of sodium hydroxide (40 g) in ice-water (500 ml). The organic phase is separated and dried over potassium carbonate. Evaporation affords the almost pure ester, m.p. 66–70° (8.81 g, 70%).

Acid-catalysed addition of alcohols to olefins leads to ethers. It is catalysed by concentrated sulfuric acid,[151] hydrochloric acid, acid salts, or aluminum chloride; and hydrogen tetrafluoroborate and perchloric acid have also proved valuable,[152,153] as has boron trifluoride.[154] Addition of trisubstituted ethylenes such as isobutene and isopentene to alcohols is particularly easy; it yields *tert*-alkyl ethers.[151] Disubstituted ethylenes react less easily, requiring higher temperatures and giving poorer yields. Cycloalkenes react only if there is a substituent attached to one of the doubly bonded atoms.[155] Primary alcohols add more easily than do secondary ones, and tertiary alcohols rarely add at all.

Reaction of phenols and olefins may lead to ether formation and to nuclear alkylation; catalysts are mineral acids, sulfonic acids, or boron trifluoride. Ethers are formed at lower temperatures, *C*-alkylation occurs by rearrangement at higher temperatures.[156,157]

Addition of alcohols to camphene occurs with rearrangement to the isobornyl ether (see Meerwein and Gérard[158]).

In the presence of alkaline catalysts alcohols can undergo nucleophilic addition to the C=C double bond of α,β-unsaturated carbonyl compounds, nitriles, sulfones, or sulfoxides. Similarly the doubly bonded carbon atoms in polyfluoroethylenes are susceptible to nucleophilic attack by alcohols in the

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[146] H. Meerwein, *Ann. Chem.*, **455**, 227 (1927); J. Kondakoff, *Ber. Deut. Chem. Ges.*, **26**, ref. 1012 (1893); **25**, ref. 864 (1892); *J. Prakt. Chem.*, [ii], **48**, 467 (1893).

[147] H. Meerwein, *Ber. Deut. Chem. Ges.*, **66**, 411 (1933); *J. Prakt. Chem.*, [ii], **141**, 126 (1934).

[148] T. B. Dorris, F. J. Sowa, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 2689 (1934).

[149] H. L. Wundersly and F. J. Sowa, *J. Amer. Chem. Soc.*, **59**, 1010 (1937).

[150] W. S. Johnson, A. L. McCloskey, and D. A. Dunnigan, *J. Amer. Chem. Soc.*, **72**, 514 (1950).

[151] T. W. Evans and K. R. Edlund, *Ind. Eng. Chem.*, **28**, 1186 (1936).

[152] R. D. Morin and A. E. Beavse, *Ind. Eng. Chem.*, **43**, 1596 (1951).

[153] K. Ziegler and H. Dislich, *Chem. Ber.*, **90**, 1108 (1957).

[154] H. Meerwein, *Ber. Deut. Chem. Ges.*, **66**, 411 (1933); *J. Prakt. Chem.*, [ii], **141**, 126 (1934).

[155] W. Hückel and co-workers, *Ann. Chem.*, **645**, 117, 131 (1961).

[156] J. B. Niederl and S. Natelson, *J. Amer. Chem. Soc.*, **53**, 272, 1928 (1931).

[157] F. J. Sowa, H. D. Hinton, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **54**, 2019, 3694 (1932).

[158] H. Meerwein and J. Gérard, *Ann. Chem.*, **435**, 174 (1924).

presence of bases, yielding fluoro ethers.[159,160] The alkaline catalyst may be an alkali alkoxide or hydroxide or a quaternary ammonium hydroxide.

3-Methoxybutyraldehyde:[1c] A mixture of crotonaldehyde (25 g) and anhydrous methanol (50 ml) is cooled to −10°; it usually reacts acid and is then neutralized with a few drops of potassium methoxide solution; next, 10% potassium methoxide solution (1 ml) is added, whereupon the temperature rises to 40° and the odor of crotonaldehyde disappears. The solution is cooled, made just acid with acetic acid, and extracted with much ether. The ethereal solution is dried over K_2CO_3, then the ether is distilled off and the residue is fractionated, giving 3-methoxybutyraldehyde, b.p. 128°/760 mm, in 50% yield.

Dimethyl methoxysuccinate is obtained from dimethyl maleate or fumarate and sodium methoxide.[161]

Rehberg and his co-workers[162] report that primary and secondary, but not tertiary, alcohols add readily to the double bond of acrylic ester under anhydrous conditions and in the presence of weak alkalis, affording 3-alkoxypropionates in good yields. Phenols are also added.[163]

α,β-Unsaturated acyclic aldehydes react readily with lower alcohols, giving β-alkoxy acetals and β-alkoxy aldehydes; this reaction is catalysed both by hydrogen and by hydroxyl ions. Addition of higher alcohols is more difficult. Acrolein, for instance,[164] gives the 3-alkoxypropionaldehyde dialkyl acetal as well as the β-alkoxypropionaldehyde when heated in an alcohol containing hydrochloric or toluenesulfonic acid; using an excess of the alcohol increases the yield of the acetal. Catalysts that react acid can readily resinify acrolein and crotonaldehyde.

3-Methoxypropionaldehyde:[165] A mixture of 93.5% acrolein (600 g, 10 moles), methanol (1300 g, 40 moles), and concentrated sulfuric acid (3 g) is boiled for 6 h under reflux. When boiling begins, the temperature of the mixture is about 60° but it rises to 75–76° during 5 hours' boiling. Powdered, anhydrous barium hydroxide (6 g, or an equivalent amount of hydrated barium hydroxide) is stirred into the mixture to ensure neutralization and complete removal of sulfate ions, after which stirring is continued for 4 h at room temperature. Next, powdered anhydrous oxalic acid (1.8 g) is added and the mixture is again stirred for 2 h. A sample is titrated to ensure that 0.04% of free oxalic acid is present. After about 2 h, the 3-methoxypropionaldehyde dimethyl acetal formed as by-product has been hydrolysed, and the mixture is then filtered and fractionated through a column. 3-Methoxypropionaldehyde has b.p. 121°/760 mm and forms an azeotrope, b.p. 92°/760 mm, with water.

The double bond of vinyl ketones is particularly reactive and adds alcohols to give β-alkoxy ketones, either alkali or acid acting as catalyst. Addition of inhibitors (*e.g.*, hydroquinone) reduces the amount of side reactions. This addition will be illustrated by the preparation of 4-methoxy-2-butanone from methyl vinyl ketone:

$$CH_3{-}CO{-}CH{=}CH_2 + CH_3OH \longrightarrow CH_3{-}CO{-}CH_2{-}CH_2{-}OCH_3$$

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[159] J. D. Park and co-workers, *J. Amer. Chem. Soc.*, **73**, 861, 1329, 3242 (1951); **74**, 4104 (1952); **78**, 1685 (1956).

[160] D. C. England and co-workers, *J. Amer. Chem. Soc.*, **82**, 5116 (1960).

[161] T. Purdie, *J. Chem. Soc.*, **47**, 859 (1885); T. Purdie and W. Marshall, *J. Chem. Soc.*, **59**, 469 (1891); Beilstein, "Handbuch der Organischen Chemie," Vol. 3, p. 437.

[162] C. E. Rehberg, M. B. Dixon, and C. H. Fisher, *J. Amer. Chem. Soc.*, **68**, 544 (1946); **69**, 2970 (1947); C. E. Rehberg and M. B. Dixon, *J. Amer. Chem. Soc.*, **72**, 2205 (1950).

[163] R. H. Hall and E. S. Stern, *J. Chem. Soc.*, **1949**, 2035.

[164] L. Claisen, *Ber. Deut. Chem. Ges.*, **31**, 1014 (1898).

[165] H. Schulz and H. Wagner, *Angew. Chem.*, **62**, 115 (1950).

(*a*) In the presence of sodium methoxide:[166] Methyl vinyl ketone (231 g, 3.3. moles) is stirred during 2 h into a mixture of anhydrous methanol (368 g, 11.5 moles) and sodium methoxide (4.5 g) at 10–15°. The whole is stirred with ice-cooling for a further 3 h, then neutralized with hydrochloric acid to pH 7, left at 5° overnight, and worked up by distillation. This gives a 73% yield (246 g) of **4-methoxy-2-butanone**, b.p. 137–140°/760 mm, 64–66°/50 mm, n_D^{20} 1.4050.

(*b*) In the presence of mercury oxide and boron trifluoride:[167] Red mercuric oxide (1–2 g), boron trifluoride-ether (1 ml), and anhydrous methanol (2 ml) are placed in a 1-l three-necked flask; when the heat evolution has subsided, a further 26 g of methanol are added and then a mixture of methyl vinyl ketone (65 g, 1.08 mole) and methanol (48 g, 1.05 mole) is dropped in with stirring. The whole is heated on the water-bath under reflux for 1 h, left overnight, neutralized with anhydrous potassium carbonate, and worked up by distillation. Yield, 61%. B.p. 137–138°/745 mm.

Dufraisse and Gerald[168] studied the addition of alcohols to unsaturated ketones having halogen attached to one of the doubly bonded atoms. In accord with the equation:

$$C_6H_5—CO—CBr{=}CHC_6H_5 + ROH \xrightarrow{OH^-} C_6H_5—CO—CHBr—CH(C_6H_5)—OH$$

α-bromobenzylideneacetophenone adds methanol, ethanol, and straight-chain or branched propanols and butanols in the presence of a little alkoxide in cold, anhydrous alcoholic solution. In an alkaline medium at higher temperatures the adducts split off hydrogen bromide, to give enol ethers of type $C_6H_5—CO—CH{=}CR(OR')$.

Acrylonitrile combines with primary or secondary alcohols or with phenols under the influence of a basic catalyst, giving 3-alkoxypropionitriles[169] or 3-phenoxypropionitrile,[170] respectively.

3-Butoxypropionitrile:[172] 1-Butanol (148 g, 2 moles) is treated with aqueous 40% benzyltrimethylammonium hydroxide (Triton B) (2 g), with stirring under reflux. Acrylonitrile (106 g, 2 moles) is added at such a rate that the temperature does not rise above 45°, whereafter the mixture is stirred for a further hour, then acidified with acetic acid and fractionated in a vacuum, giving the aldehyde (219 g, 86%), b.p. 98°/20 mm.

α,β-Unsaturated nitro compounds, such as α-nitrostilbene[172] and 3,4-dinitro-3-hexene,[173] add alcohols in the presence of bases. 2-Nitroacrylic acid and methanol give 2-methoxy-3-nitropropionic acid without requiring addition of a catalyst.[63]

Alcohols and phenols[174] are added readily to vinyl ethers in the presence of catalytic amounts of mineral acid or cation-exchange resin.[175] This gives sym-

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[166] R. C. Elderfield, B. M. Pitt, and I. Wempen, *J. Amer. Chem. Soc.*, **72**, 1334 (1950).

[167] D. P. Kilian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **58**, 892 (1936).

[168] C. Dufraisse and P. Gerald, *C. R. Hebd. Séances Acad. Sci.*, **173**, 985 (1921); **174**, 1631 (1922); *Bull. Soc. Chim. France*, [iv], **31**, 1292 (1922).

[169] C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 437 (1943); R. V. Christian Jr. and R. M. Hixon, *J. Amer. Chem. Soc.*, **70**, 1333 (1948).

[170] A. H. Cook and K. J. Reed, J. *Chem. Soc.*, **1945**, 920.

[171] W. P. Utermohlen Jr., *J. Amer. Chem. Soc.*, **67**, 1505 (1945).

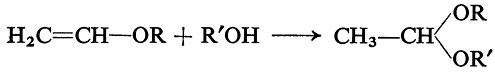
[172] A. Dornow and F. Boberg, *Chem. Ber.*, **83**, 261 (1950).

[173] L. B. Clapp, J. F. Brown Jr., and L. Zeftel, *J. Org. Chem.*, **15**, 1043 (1950).

[174] W. Reppe, *Ann. Chem.*, **601**, 81 (1934).

[175] P. Mastagli and P. Lambert, *C. R. Hebd. Séances Acad. Sci.*, **245**, 354 (1957).

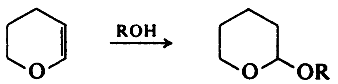
metrical or unsymmetrical acetals according to the nature of the alcohol added:



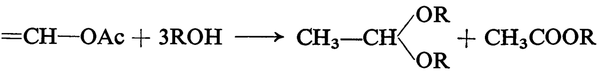
$$H_2C{=}CH{-}OR + R'OH \longrightarrow CH_3{-}CH\begin{matrix}/OR\\ \backslash OR'\end{matrix}$$

When warmed, vinyl ethers react with higher alcohols in the presence of hydrochloric acid but with rearrangement to give symmetrical acetals only.[176] Cyclic acetals are formed from ethylene glycol and vinyl ethers at 140–180°.[177]

Dihydropyran is important as a hydroxyl-protecting group that is readily removed; in the presence of acid it reacts readily with a hydroxylic compound, giving the 2-alkoxytetrahydropyran:[178]



Enol esters, *e.g.*, vinyl acetate, react with alcohols in the presence of acid catalysts, to give acetals:[179]



$$H_2C{=}CH{-}OAc + 3ROH \longrightarrow CH_3{-}CH\begin{matrix}/OR\\ \backslash OR\end{matrix} + CH_3COOR$$

A mixture of mercury(II) oxide or acetate with boron trifluoride–ether is a suitable catalyst.

Addition of carboxylic acids to ketene leads to acid anhydrides. Ketene and glacial acetic acid thus yield acetic anhydride according to the general equation:

$$CH_2{=}CO + HOOCR \longrightarrow CH_3{-}CO{-}O{-}CO{-}R$$

Other carboxylic acids give mixed anhydrides in this reaction,[180-182] but these readily disproportionate to the pair of symmetrical anhydrides. This provides a method of obtaining good yields of acid anhydrides that are difficultly accessible by other routes. In *Org. Syn.* Williams and Krynitzky[183] describe the preparation of hexanoic anhydride from the acid and ketene.

No solvent is needed for acylation of a carboxylic acid when that acid is a liquid; solid acids are dissolved in ether,[180] acetone,[184] or benzene.[185] Various reaction temperatures have been quoted, from ice-cooling[183] to 20° [184] and 90°.[185] Quadbeck[186] has reviewed "Ketene in preparative organic chemistry."

Lower alicylic alcohols are acetylated smoothly by ketene at room temperature:

$$ROH + CH_2{=}CO \longrightarrow RO{-}COCO_3$$

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[176] M. G. Voronkov, *Doklady Akad. Nauk. S.S.S.R.*, **63**, 539 (1948); *Chem. Abstr.*, **43**, 5365 (1949).

[177] A. Sieb, Ger. Pat. 855,864; *Chem. Abstr.*, **52**, 9197 (1958).

[178] Cf. W. E. Parham and E. L. Anderson, *J. Amer. Chem. Soc.*, **70**, 4187 (1948).

[179] D. H. Hirsch, R. I. Hoaglin, and D. G. Kubler, *J. Org. Chem.*, **23**, 1083 (1958).

[180] C. D. Hurd and M. F. Dull, *J. Amer. Chem. Soc.*, **54**, 3427 (1932).

[181] A. R. Emery and V. Gold, *J. Chem. Soc.*, **1950**, 1443.

[182] A. B. Boese Jr., *Ind. Eng. Chem.*, **32**, 16 (1940).

[183] J. W. Williams and J. A. Krynitzky, *Org. Syn.*, **21**, 13 (1941).

[184] A. H. Gleason, U.S. Pat. 2,178,752; *Chem. Abstr.*, **33**, 1336 (1939).

[185] G. De W. Graves, U.S. Pat. 2,135,709; *Chem. Abstr.*, **32**, 1347 (1938).

[186] G. Quadbeck, *Angew. Chem.*, **68**, 361 (1956).

With higher alcohols, and with *tert*-butyl alcohol, the reaction can be effected by acid catalysts[187] and occasionally by basic ones.[182,188]

The acetylation of monohydric alcohols is, in general, not hindered by the presence of other functional groups in the molecule, but polyhydric alcohols do not react satisfactorily, even in the presence of catalysts.[189] It seems that accumulation of OH groups in a molecule reduces the reactivity towards ketene.

Reaction of phenols with ketene occurs only in the presence of catalysts; it almost always gives good yields in the presence of sulfuric or *p*-toluenesulfonic acid or other acid catalysts;[187,190,191] only hydroquinone[192] and resorcinol[191] among the polyphenols react well; even in the presence of sulfuric acid phloroglucinol reacts only slowly and gives poor yields.

***tert*-Butyl acetate:**[187] *tert*-Butyl alcohol (74 g) is treated with concentrated sulfuric acid (0.5 ml) and heated to 60°, at which temperature ketene is led in for 1.5 h. The pale brown product is washed with 2N-sodium hydroxide (10 ml) and then with water (20 ml), both aqueous solutions are extracted with ether, and the two ether extracts are added to the crude ester. The product is then dried over K_2CO_3 and distilled at atmospheric pressure. After a short forerun *tert*-butyl acetate (83 g), b.p. 94–96°/750 mm, passes over.

Whereas olefins react with nucleophiles only when polarized by an electron-attracting group, the acetylene bond is susceptible to nucleophilic attack without such stimulus.[193,194] In the presence of alkaline catalysts alcohols and acetylenes under pressure give vinyl ethers (vinylation):[195]

$$CH{\equiv}CH + HOR \longrightarrow CH_2{\equiv}CHOR$$

Addition of alcohols to diacetylene is substantially easier; methanol affords 3-butyn-1-enyl methyl ether.[193] Tri- and tetra-acetylenic compounds react still more rapidly.[196]

In the presence of an acid catalyst such as boron trifluoride or mixtures of mercury oxide and boron trifluoride two molecules of alcohol are added, the products being acetals:[197–200]

$$CH{\equiv}CH + 2ROH \longrightarrow CH_3{-}CH(OR)_2$$

For a review see Kästner.[201]

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[187] C. D. Hurd and A. S. Roe, *J. Amer. Chem. Soc.*, **61**, 3355 (1939).

[188] F. Chick and N. T. M. Wilsmore, *J. Chem. Soc.*, **93**, 946 (1908); **97**, 1978 (1910).

[189] C. D. Hurd, S. M. Cantor, and A. S. Roe, *J. Amer. Chem. Soc.*, **61**, 426 (1939).

[190] G. De W. Graves, U.S. Pat. 2,007,968; *Chem. Abstr.*, **29**, 5857 (1935).

[191] R. Nodzu and T. Ishoshima, *Bull. Inst. Chem. Res., Kyoto Univ.*, **32**, 139 (1954).

[192] F. O. Rice, J. Greenberg, C. E. Waters, and R. E. Vollrath, *J. Amer. Chem. Soc.*, **56**, 1760 (1934).

[193] R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths, London, 1955.

[194] F. Bohlmann, *Angew. Chem.*, **69**, 82 (1957).

[195] W. Reppe, "Chemie und Technik der Acetylen-Druck-Reaktionen," Verlag Chemie, Weinheim/Bergstraße, 1952.

[196] F. Bohlmann and H. G. Viehe, *Chem. Ber.*, **88**, 1017 (1955).

[197] J. A. Nieuwland, R. V. Vogt, and W. L. Foohey, *J. Amer. Chem. Soc.*, **52**, 1018 (1930).

[198] H. D. Hinton and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **52**, 2892 (1930).

[199] H. Bowlus and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **53**, 3835 (1931).

[200] L. A. O'Leary and H. H. Wenzke, *J. Amer. Chem. Soc.*, **55**, 2117 (1933).

[201] D. Kästner in "Neuere Methoden der präparativen organischen Chemie," ed. W. Foerst, 2nd ed, Verlag Chemie, Berlin, 1944, p. 419.

Acetaldehyde diisopentyl acetal: Acetylene (29.5 g) is led into isopentyl alcohol (200 g) containing a 63% solution (10 g) of boron trifluoride in methanol and also some (1 g) mercury(II) oxide. When reaction is over, the solution is washed with a little water and sodium carbonate solution and extracted with ether. The ethereal solution is dried over K_2CO_3 and fractionated.

For acid-sensitive acetals, and particularly for ketals, it is preparatively important to neutralise the reaction mixture carefully with anhydrous sodium carbonate before treating it with water.

Acetylene reacts with polyhydric alcohols, and α-hydroxy acids and their derivatives.[197] In these reactions 1,2-, 1,3-, and 1,4-diols give cyclic glycols preferentially.[197,201,202]

Substituted acetylenes afford ketals.[203,204] Reaction of butylacetylene (1-hexyne) with methanol gives 2-hexanone dimethyl acetal in 70% yield:

$$C_4H_9{-}C{\equiv}CH + 2CH_3OH \longrightarrow C_4H_9{-}C(OCH_3)_2{-}CH_3$$

For this reaction the catalyst may be boron trifluoride-ether and mercury oxide. However, boron trifluoride and mercury oxide can be used as catalyst in such cases only with methanol — other monohydric alcohols are converted into polymeric products thereby in an obscure reaction. Nevertheless, if a little trichloroacetic acid is added to these catalyst mixtures even the higher alcohols react normally.[205]

Acetylenes in which the triple bond is conjugated to an olefinic double bond add three molecules of an alcohol in the presence of mercury oxide and boron trifluoride alcoholate. For example, vinylacetylene (butenyne) and methanol give **2,2,4-trimethoxybutane:**[167,206]

$$CH_2{=}CH{-}C{\equiv}CH + 3CH_3OH \longrightarrow CH_3O{-}CH_2{-}CH_2{-}C(OCH_3)_2{-}CH_3$$

Methanol (480 g, 15 moles) is added to a catalyst mixture containing red mercury oxide (15 g), boron trifluoride-ether (4.5 ml), trichloroacetic acid (2 g), and methanol (10 ml). The whole is then placed in a 3-l three-necked flask fitted with an extremely efficient condenser. Vinylacetylene (312 g, 6 moles) is led in during 3 h with stirring and cooling in tap-water. The water-bath temperature is then raised to 50° and stirring is continued for a further 1 h, after which potassium carbonate (10 g, anhydrous) is added and stirring again continued for 15 min. The liquid phase is separated and worked up by distillation. 2,2,4-Trimethoxybutane, b.p. 63–65°/25 mm, n_D^{26} 1.4082, is obtained in 65% yield calculated on methanol (487 g).

Acetylenes whose triple bond is conjugated to a carboxyl or a phenyl group add primary alcohols in the presence of sodium alkoxide;[207-210] thus at 135° phenylacetylene gives β-alkoxystyrene:

$$C_6H_5{-}C{\equiv}CH + ROH \longrightarrow C_6H_5{-}CH{=}CHOR$$

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[202] H. S. Hill and H. Hibbert, *J. Amer. Chem. Soc.*, **50**, 2246 (1928).

[203] G. F. Hennion, D. B. Killian, T. H. Vaughn, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 1130 (1934).

[204] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.*. **56**, 1384 (1934).

[205] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **58**, 80 (1936).

[206] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 1786 (1934).

[207] J. U. Nef, *Ann. Chem.*, **308**, 270 (1899).

[208] C. Moureu, *C. R. Hebd. Séances Acad. Sci.*, **138**, 286 (1904); *Bull. Soc. Chim. France*, [iii], **31**, 527 (1904).

[209] K. Auwers, *Ber. Deut. Chem. Ges.*, **44**, 3514 (1911).

[210] K. Auwers and B. Ottens, *Ber. Deut. Chem. Ges.*, **58**, 2067 (1925).

VI. Oxonium salts

Tertiary oxonium salts[1f] and pyrylium salts[211] have especial importance in preparative organic chemistry; the former are the strongest known alkylating agents. Alkylation is effected at relatively low temperatures; moisture is excluded. The ether from which the trialkyloxonium salt may be derived is formed alongside the alkylation product. In principle, any organic oxygen, nitrogen, sulfur, or phosphorus compound that can add a proton can be alkylated by oxonium compounds; such reactants include alcohols, ethers, carbonyl compounds, amines, nitriles, sulfides, sulfoxides, phosphines, *e.g.*:

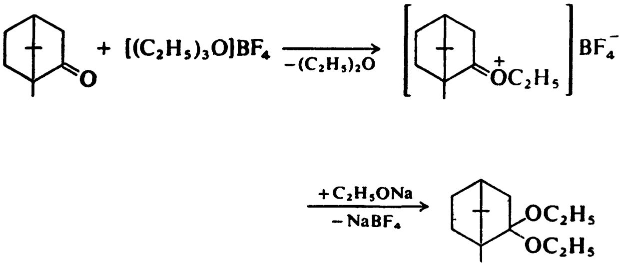
$$(C_2H_5)_2S{=}O + [(C_2H_5)_3O]BF_4 \longrightarrow [(C_2H_5)_2S{-}OC_2H_5]BF_4 + (C_2H_5)_2O$$

However, when ethers of alcohols are to be prepared the trialkyloxonium salt method will be used only when other, more usual, methods fail.

As an example, alkylation of α-chlorohydrin to β-halo ethers cannot be carried out by the usual methods. It is effected, however, in excellent yield by means of trialkyloxonium salts:[212]

$$R{-}CHCl{-}CH_2OH + [R'_3O]BF_4 \longrightarrow R{-}CHCl{-}CH_2OR' + HBF_4 + R'_2O$$

The action of trialkyloxonium salts on aliphatic ethers leads to exchange of alkyl groups. Sulfoxides,[212] nitriles,[213] and disulfides[214] can be alkylated smoothly by oxonium salts. Saturated aldehydes and ketones can be alkylated only if, like pinacolin and camphor, they contain a tertiary alkyl group neighboring the carbonyl group. Then for instance, the carboxonium salts obtained can be readily converted by alkali alkoxides into acetals and orthoesters which are difficult to obtain in other ways.



Camphor diethyl acetal, obtained in only 25–30% yield from camphor and orthoformic ester,[215] is obtained in 87% yield from *O*-ethylcamphor oxonium fluoroborate and sodium ethoxide.[1g]

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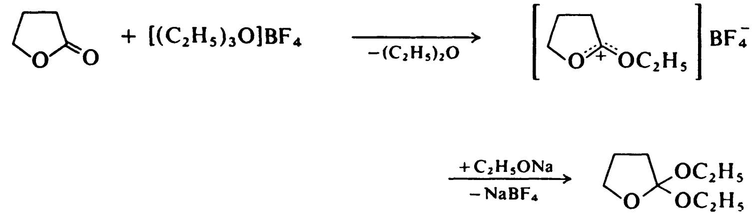
[211] K. Dimroth, *Angew. Chem.*, **72**, 331 (1960); A. T. Balaban and C. D. Nenitzescu, *Ann. Cem.*, **625**, 80 (1959).

[212] H. Meerwein and co-workers, *Ann. Chem.*, **566**, 161 (1950).

[213] S. Hünig, L. Geldern, and E. Lücke, *Angew. Chem. Int. Ed., Engl.*, **2**, 327 (1963).

[214] D. J. Pettitt and G. K. Hehnkamp, *J. Org. Chem.*, **28**, 2932 (1963).

[215] M. Bredt-Sarelsberg and C. Rumscheidt, *J. Prakt. Chem.*, [ii], **115**, 238 (1927).



2,2-Diethoxytetrahydrofuran:[1g] A solution of *O*-ethylbutyrolactonium fluoroborate (101 g) in dry dichloromethane (70 ml) is dropped into a stirred solution of sodium (13 .9 g) in anhydrous ethanol (250 ml) with ice-water cooling. Reaction occurs with instantaneous precipitation of sodium fluoroborate. Stirring is continued for an hour after addition of the oxonium salt, then the solution is treated with 3–4 times the amount of dilute sodium hydrogen carbonate solution and extracted with ether. The ethereal layer is separated, dried over K_2CO_3, and evaporated. Distillation of the residue gives 2,2-diethoxytetrahydrofuran, b.p. 60–61.5°/10 mm (68.4 g, 85.4%).

2-Ethoxy-1-oxa-1-cyclopentenium fluoroborate (*O*-ethylbutyrolactonium fluoroborate; 2-ethoxy-1-oxolenium fluoroborate):[216] Triethyloxonium fluoroborate (95 g, 0.5 mole) is added to dry butyrolactone (43 g, 0.5 mole). The salt dissolves to a clear solution, which, however, soon discolors and separates into two layers. After 3 days the lower layer is separated off; it crystallizes in a freezing mixture and is then filtered off with cooling and exclusion of moisture. This gives 87% (88 g) of crude product that is pure enough for further reaction. Recrystallization can be effected from *p*-tolunitrile below 50°; the m.p. is then 42°.

The stability of the oxonium salts is greater the smaller the polarizability of the anion; thus for their preparation perchloric acid and halo acids such as $H[SbCl]_6$, $H[FeCl_4]$, and $H[BF_4]$ are preferred.

Several methods are available for the preparation of acyclic and cyclic tertiary oxonium salts.[1] The action of metal or non-metal halide ether complexes on epoxides is generally applicable. For eaxample, **triethyloxonium fluoroborate** can be prepared as follows:[217]

Epichlorohydrin (140 g) is added, with stirring and exclusion of moisture, to a solution of boron trifluoride-ether (285 g, 2 moles) in ether (500 ml) at such a rate that the ether remains boiling vigorously. The oily product that separates at first solidifies towards the end of the addition of the epichlorohydrin. Stirring is continued for a further 2 h, the mixture is left overnight, then the triethyloxonium fluoroborate is filtered off, washed thoroughly with ether, and dried in a vacuum. The yield is 269 g. The material is stable almost indefinitely under ether.

Trialkyloxonium fluoroborates can be conveniently prepared from the ether, alkyl halide, and silver fluoroborate.

Triethyloxonium fluoroborate:[218] Diethyl ether (10 ml) is treated with a 1,2-dichloroethane solution (50 ml) of silver fluoroborate containing 108 mg of Ag^+ per 1 ml. Ethyl bromide (10 ml) is added, and the mixture is set aside for several hours, then filtered from silver bromide and washed with a little 1,2-dichloroethane. Triethyloxonium fluoroborate, m.p. 90–91° (8.5 g, 89.5%), is precipitated by ether.

Triaryloxonium salts are very stable even when the anion is simple. Triphenyloxonium fluoroborate is conveniently prepared from diphenyl ether and

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[216] H. Meerwein and co-workers, *Chem. Ber.*, **89**, 2060 (1956).

[217] H. Meerwein and co-workers, *J. Prakt. Chem.*, [ii], **154**, 83 (1939); *Org. Syn.*, **46**, 113 (1966).

[218] H. Meerwein, V. Hederich, and K. Wunderlich, *Arch. Pharm.*, **291**, 552 (1958).

benzenediazonium fluoroborate.[219] Trimethyloxonium 2,4,6-trinitrobenzenesulfonate, which is also stable, can be obtained from dimethyl ether, diazomethane, and 2,4,6-trinitrobenzenesulfonic acid.[212]

Phosphoric, or, better, thiophosphoric, esters alkylate ethers smoothly to tertiary oxonium salts in the presence of antimony pentachloride.[213]

Triethyloxonium hexachloroantimonate: Antimony pentachloride (17.94 g, 7.70 ml, 0.06 mole) is dropped into a solution of triethyl thionophosphate (5.95 g, 0.03 mole) in anhydrous ether (50 ml) under a stream of nitrogen and with cooling in ice–salt. The mixture becomes first yellow and then turbid. Subsequently a yellow precipitate begins to separate which becomes paler as the reaction proceeds. When all the antimony pentachloride has been added the mixture is allowed to warm to room temperature but the nitrogen stream is maintained and occasional shaking applied. After some hours the precipitate is filtered through a fritted filter that can be closed, stirred three times with ether on that filter, sucked dry and finally dried in a vacuum. The white substance (12.5–13 g, 95–99%) is pure enough for use as alkylating agent; it has a sharp decomposition point between 125° and 139°.

4.2. Formation of the carbon–oxygen bond by replacement with formation of hydroxyl or carbonyl groups

I. Replacement of hydrogen by oxygen

Replacement of hydrogen by oxygen in organic compounds can be effected by very varied oxidizing agents. Reaction conditions must, however, be strictly observed to avoid oxidative destruction of the molecule.

Among the most usual oxidizing agents, potassium permanganate, chromium(VI) oxide, and nitric acid have little specificity. However, lead tetraacetate and selenium dioxide have specific effects. Other oxidizing agents used are hydrogen peroxide and its derivatives, dinitrogen tetroxide, manganese dioxide, ruthenium tetroxide,[214] and potassium ferricyanide.[215]

Oxidations that are carried out with atmospheric oxygen usually lead to peroxy compounds. The attack by oxygen is generally highly selective and is strongly influenced by activating groups. Autoxidations are very sensitive to added substances (inhibitors or initiators).

In certain condensation reactions hydrogen may be replaced by oxygen, with interchange of the oxidation states of the carbon atoms that are to be bonded to one another. In such cases it is particularly nitroso compounds and derivatives of nitrous acid that serve as oxidant; with active methylene groups they form Schiff bases or oximes, which afford the oxo compound on hydrolysis.

Dehydrogenation of compounds containing hydroxyl groups is also to be regarded as an oxidation. As part of the dehydrogenation a C–O single bond is converted into a C=O double bond, *e.g.*, in the dehydrogenation of alcohols, aldehyde hydrates, and polyhydric phenols.

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[219] A. N. Nesmeyanov and T. P. Tolstaya, *Doklady Akad. Nauk S.S.S.R.*, **117**, 626 (1957); *Chem. Abstr.*, **52**, 9005 (1958).

[212] G. K. Helmkampf and D. J. Pettitt, *Org. Syn.*, **46**, 122 (1966).

[213] G. Hilgetag and H. Teichmann, *Chem. Ber.*, **96**, 1446 (1963).

[214] L. M. Berkowitz and P. N. Rylander, *J. Amer. Chem. Soc.*, **80**, 6682 (1958).

[215] B. S. Thyagarajan, *Chem. Rev.*, **58**, 439 (1958).

1. Replacement of hydrogen by the hydroxyl group

In broad terms it is only in special cases that the oxidation of hydrocarbons to primary or secondary alcohols is of practical importance. One such case is oxidation of toluene and its derivatives to the corresponding benzyl alcohols, by *e.g.*, manganese dioxide, lead dioxide, lead tetraacetate, or Caro's acid. It is advantageous to use lead tetraacetate in glacial acetic acid solution since then the alcohol formed is protected by esterification against further oxidation.

Preparation of benzyl acetate from toluene:[216] Lead tetraacetate (120 g) and toluene (40 g) are boiled for 4 h in glacial acetic acid (200 ml; previously distilled from potassium permanganate). Then most of the acetic acid is distilled off and the residue is treated with water and extracted with ether. The extract is washed with sodium hydrogen carbonate solution and dried; then distillation in a vacuum affords the crude benzyl acetate (7.5 g).

For the preparation of **lead tetraacetate,** pure red lead (200 g) is stirred in very small portions into glacial acetic acid (1 l) at 80° without allowing the temperature to rise any higher. Then the solution is filtered if necessary; on cooling, it affords lead tetraacetate in colorless needles, which are filtered off, washed with a little glacial acetic acid, and dried in a desiccator.

For the preparation of larger amounts see Criegee[217] and Mendel.[218]

In the aliphatic series there are many cases where a CH_3 group that has an oxygen-substituted carbon as nearest neighbor can be oxidized by lead tetraacetate to a CH_2OH group: from acetone, both mono- and di-hydroxyacetone can be isolated as their acetates; acetic anhydride gives glycolic anhydride diacetate; acetophenone gives ω-acetoxyacetophenone.[219]

Secondary alcohols may be formed by the same oxidizing agents; *e.g.*, diphenylmethane and lead tetraacetate give benzhydryl acetate, the oxidation occurring somewhat more readily than that of toluene. Malonic ester gives acetoxymalonic ester, and acetoacetic ester gives α-acetoxyacetoacetic ester, both products being difficultly accessible by other routes.

As further examples may be cited the conversion of acenaphthene into 1-acenaphthenol by Marquis[220] using lead dioxide in glacial acetic acid and by Casow[221] using red lead in the same solvent.

Comprehensive studies of oxidation by lead tetraacetate alone[222] and with periodic acid[223] have been published by Criegee.

The CH_2 group next to the carbonyl group of a ketone is not attacked by Caro's acid; instead, in analogy to biological oxidation of fatty acids, a hydroxyl group is introduced at the β-position to the carbonyl group. For example, 2-pentanone affords 4-hydroxy-2-pentanone; but, as an ecxeption to this rule, 3-pentanone (diethyl ketone) affords 2-hydroxy-3-pentanone.

Selenium dioxide is a specific reagent for introducing a hydroxyl group into a methylene group adjacent to a double bond, though this method of preparing

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[216] O. Dimroth and R. Schweizer, *Ber. Deut. Chem. Ges.*, **56**, 1384 (1923).

[217] R. Criegee, *Ann. Chem.*, **481**, 283 (1930).

[218] H. Mendel, *Rec. Trav. Chim.*, **59**, 720 (1940).

[219] O. Dimroth and R. Schweizer, *Ber. Deut. Chem. Ges.*, **56**, 1375 (1923).

[220] R. Marquis, *C. R. Hebd. Séances Acad. Sci.*, **182**, 1227 (1926).

[221] J. Casow, *Org. Syn.*, **21**, 1 (1941).

[222] R. Criegee, *Angew. Chem.*, **70**, 173 (1958).

[223] R. Criegee in "Neuere Methoden der präparativen organischen Chemie," 3rd ed, Verlag Chemie, Weinheim, 1949, p. 21.

unsaturated alcohols seems to be limited, in the aliphatic series, to olefins with more than five carbon atoms. As an example, 3-methyl-2-pentene gives 3-methyl-3-penten-2-ol:[224]

$$CH_3—CH{=}C(CH_3)—CH_2—CH_3 \xrightarrow{SeO_2} CH_3—CH{=}C(CH_3)—CH(OH)—CH_3$$

The reactions of alicyclic olefins with SeO_2 have been extensively investigated. Heating cyclopentene with SeO_2 in acetic anhydride (acylating oxidation) oxidizes it to much **monoacetoxy-** and a little **diacetoxy-cyclopentene**; but in a bomb tube at 90–100° much diacetate and little monoacetate are obtained.[225] Thus the second methylene group next to the double bond is more or less attacked according to the reaction conditions.

A solution of cyclopentene (50 g) in acetic anhydride (50 ml) is heated with SeO_2 (50g) on the water-bath so long as boiling is observed (6–8 h). The mixture is then heated for a further 3 h at 100°. The brownish-red mass is distilled, first at atmospheric pressure into a well-cooled receiver, and then at 12 mm. The fraction distilling at atmospheric pressure and a bath-temperature of about 80–130° contains the monoacetate together with glacial acetic acid and acetic anhydride. Purification by repeated fractionation gives the monoacetate of b.p. 154–155°/760 mm. The fraction distilling at 120–130°/15 mm contains the diacetate (4–5 g after repeated distillation).

SeO_2 is also used in the steroid series for replacing an allylic hydrogen atom by a hydroxyl group.[226]

In branched-chain fatty acids the hydrogen on a tertiary carbon atom can be replaced by hydroxyl by means of alkaline permanganate solution: *e.g.*, 2-hydroxy-2-methylpropionic acid, $HO—C(CH_3)_2—CO_2H$, is obtained from isobutyric acid, and 4-methyl-γ-valerolactone is obtained from 4-methylvaleric acid.[227]

Preparation of tertiary alcohols from the corresponding hydrocarbons can be realized in some cases also by use of hydrogen peroxide or its derivatives. *E.g.*, 10-hydroxy-10-methyl-9-anthrone is obtained from 10-methyl-9-anthrone by means of alkaline hydrogen peroxide solution.[228]

Triphenylmethane derivatives can be converted into triphenylmethanol derivatives by various oxidizing agents. Triphenylmethane itself with nitric acid or with chromic acid in glacial acetic acid gives triphenylmethanol, and with lead tetraacetate gives triphenylmethyl acetate. The principal importance of this reaction lies in the technical synthesis of triphenylmethane dyes from their leuco bases, for which purpose very varied oxidants such as arsenic acid, nitrobenzene, nitrous acid, and nitrosylsulfuric acid are used.

Leuco compounds that have been isolated in substance are best oxidized by manganese dioxide or lead dioxide in hydrochloric acid, yielding dye salts

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[224] A. Guillmonat, *C. R. Hebd. Séances Acad. Sci.*, **201**. 904 (1935).

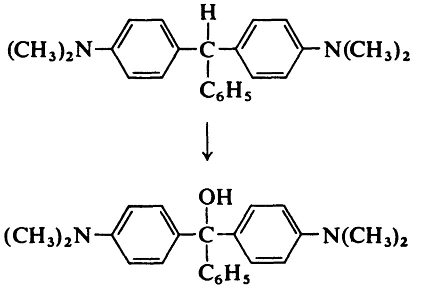
[225] E. Dane, J. Schmitt, and C. Rautenstrauch, *Ann. Chem.*, **532**, 29 (1937).

[226] B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Org. Chem.*, **28**, 3474 (1963).

[227] R. Meyer, *Ann. Chem.*, **219**, 240 (1883).

[228] H. Heymann and L. Trowbridge, *J. Amer. Chem. Soc.*, **72**, 85 (1950).

from which the alcohols are liberated by alkali:



Leuco-malachite green (3.3 g) is dissolved in hot N-hydrochloric acid (40 ml), which is then diluted with water (300 ml), cooled, and treated with a suspension of lead dioxide (2.4 g) in water (20 ml) gradually, within 5 min, with vigorous shaking. The mixture is shaken for a further 5 min on the water-bath, then treated with a clear solution of zinc chloride (4 g). The zinc chloride double salt of the dye salt is then salted out by addition of saturated sodium chloride solution, collected, dissolved again in hot water, and again salted out (yield ca. 3 g).

According to Villiger and Kopechni[229] very dilute sodium hydroxide or carbonate solution is dropped gradually, with stirring, into a dilute aqueous solution of the dye salt. The precipitated carbinol base is collected; from light petroleum it forms crystalline flakes of m.p. 120–122°, and from ether cubes of m.p. 109–110°.

Hydrogen attached to an aromatic ring can be replaced by hydroxyl in numerous special cases and this reaction is often of preparative importance. A classical example of direct introduction of a hydroxyl group is the formation of alizarin from anthraquinone-2-sulfonic acid in an alkali melt containing the calculated amount of $NaClO_3$ or $NaNO_3$; here, not only is the sulfo group replaced by OH (cf. page 353), but also a second OH group is introduced at position 1. The same method has preparative value also in some other cases, *e.g.*, formation of 2-quinolinol (carbostyril) from quinoline.[300]

The basic copper salts of benzoic acid and the three toluic acids decompose in nitrobenzene at 200–220° (16 min), the OH group being introduced into the ring next to the carboxyl group, thus giving salicylic and methylsalicylic acids.[301]

A generally applicable reaction is that due to Elbs[302] in which phenols are oxidized to dihydric phenols by 1 mole of peroxydisulfuric acid in an alkaline medium. The second hydroxyl group enters the *para*-position to the first. A *para*-substituted monohydric phenol gives good yields of *ortho*-oxidation products on oxidation with 3 moles of $H_2S_2O_8$.

3,5-Dihydroxy-2-methoxyacetophenone from 2-hydroxy-6-methoxyacetophenone:[303] 2-Hydroxy-6-methoxyacetophenone (16 g) is dissolved in 10% sodium hydroxide solution (200 ml) and cooled to 15°, at which temperature a solution of potassium persulfate (26 g) in water (500 ml) is dropped in during 4 h. The mixture is set aside at room temperature for

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[229] V. Villiger and E. Kopechni, *Ber. Deut. Chem. Ges.*, **45**, 2916 (1912).

[300] A. E. Chitchibabin, *Ber. Deut. Chem. Ges.*, **56**, 1883 (1923).

[301] W. W. Kaeding and A. T. Schulgin, *J. Org. Chem.*, **27**, 3551 (1962).

[302] K. Elbs, *J. Prakt. Chem.*, [ii], **48**, 179 (1893).

[303] K. Wallenfels, *Ber. Deut. Chem. Ges.*, **75**, 790 (1942).

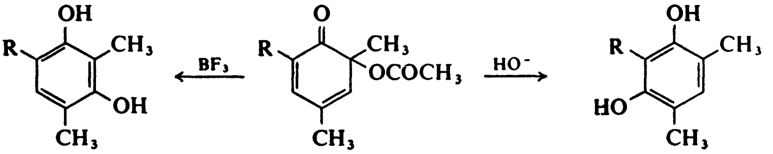
24 h, then made acid to Congo Red with concentrated hydrochloric acid, which precipitates unchanged starting material. More concentrated hydrochloric acid (150 ml) is added and the whole is heated on the steam-bath for 1 h, after which the hot solution is treated with charcoal and filtered. When the filtrate is cooled to 0° 3,5-dihydroxy-2-methoxyacetophenone (3.5 g) separates; it forms pale yellow prisms, m.p. 90°, from methanol. Extraction of the mother-liquors with ether yields a further 1.5 g.

By the same procedure 2-nitrohydroquinone is obtained in 30% yield from *o*-nitrophenol.[304] Protocatechuic acid is obtained in 50% yield from *p*-hydroxybenzoic acid.[305]

Behrman and Pitt[306] have applied the Elbs peroxydisulfate oxidation to the pyridine series, obtaining, for instance, 2,5-pyridinediol in 42% yield from 2-pyridinol.

Bacon[307] and Sethna[308] have reviewed the Elbs persulfate reaction.

Discovery of the dienone–phenol rearrangement of quinol acetates has made possible the synthesis of dihydric phenols that were difficult of access by other routes. The starting materials are obtained from phenols and lead tetraacetate, and with acetic anhydride and sulfuric acid (Thiele acetylation) or with boron trifluoride in ether they give, respectively, di- and mono-acetyl derivatives of resorcinol or hydroquinone.[309] When treated with 1N-sodium hydroxide, *o*-quinol acetates of type **(1)** undergo nucleophilic addition of an OH^- ion, giving resorcinol derivatives **(2)**.[310] Occurrence of the reaction is considered due to the substituents, which reduce the electron density at the site of reaction (C-5 of the quinol acetates). The isomeric resorcinol derivatives **(3)**[310] are obtained as their acetyl derivatives by a dienone–phenol rearrangement catalysed by boron trifluoride.



(3) (1) (2)

R = CN (2, 85%), $CONH_2$ (3, 36%), $COCH_3$ (2, 74%; 3, 60%), $COOC_2H_5$ (2, 70%; 3, 73%), or CHO (2, 42%; 3, 75%)

A mixture of trifluoroperoxyacetic acid and boron trifluoride has proved an excellent reagent for electrophilic hydroxylation of aromatic compounds; *e.g.*, its use leads to an 88% yield of mesitol from mesitylene below 7°.[311]

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[304] M. J. Astle and St. P. Stephenson, *J. Amer. Chem. Soc.*, **65**, 2402 (1943).

[305] K. B. Rao and N. V. S. Rao, *J. Sci. Ind. Res.* (*New Delhi*), **B**, **14**, 130 (1955).

[306] E. J. Behrman and B. M. Pitt, *J. Amer. Chem. Soc.*, **80**, 3717 (1958).

[307] R. G. R. Bacon, *Sci. Proc. Roy. Dublin Soc.*, **27**, 177 (1956).

[308] S. M. Sethna, *Chem. Rev.*, **49**, 91 (1951).

[309] F. Wessely and W. Metlesics, *Monatsh. Chem.*, **85**, 637 (1954); F. W. Wessely, E. Zbiral, and H. Sturm, *Chem. Ber.*, **93**, 2840 (1960).

[310] E. Zbiral, F. W. Wessely, and H. Sturm, *Monatsh. Chem.*, **93**, 15 (1963).

[311] C. A. Buehler and H. Hart, *J. Amer. Chem. Soc.*, **85**, 2177 (1963).

2. Formation of peroxides by autoxidation[1r,4a,b,312–314]

Many organic compounds of the most varied types undergo autoxidation, that is, they are subject to change under the influence of atmospheric oxygen. This reaction often leads to peroxides, which are compounds containing a —OO— group.

Replacement of hydrogen by oxygen gives only alkyl hydroperoxides ROOH, peroxy acids R—CO—OOH, and dialkyl peroxides ROOR (cf. p. 273).

a. Dangers in work with peroxides

Peroxide explosions are usually caused by heat, shock, impact, or catalysts, but the possibility of spontaneous explosions must not be left out of account, even with peroxides that are normally considered to be harmless. Among the most important protective measures in work with these substances is to wear protective glasses: many organic peroxides (*tert*-butyl hydroperoxide, cumyl hydroperoxide, cyclohexanone peroxide, 2-butanone peroxide, diacetyl peroxide) cause serious injury on entry into the eye.[315] If such an accident happens, the eye should be bathed at once with water or, better, 2% sodium hydrogen carbonate solution; oily media must *not* be used.

Utmost precautions are necessary during the preparation of work with, and storage of large amounts of peroxides. The use of protective curtains of safety glass, and of movable protective fencing of fine-meshed wire, has proved useful; also the wearing of leather gloves. Flasks containing peroxides should be moved in little baskets made of fine-meshed wire, even in the laboratory. Peroxides must be kept in a cold cupboard; vessels containing peroxide must not be left merely lying about. Use of thick-walled glass vessels with ground stoppers is dangerous. Explosive peroxides must not be pressed on porcelain with metal or glass spatulas: drying should be on filter-paper, horn spatulas being used.

Liquid peroxides should be distilled only in a vacuum, the temperature of the water-bath never exceeding 70–80°. Residues from such distillations must be carefully diluted with a solvent at once and destroyed.

Melting points of highly explosive peroxides should not be determined in a sulfuric acid bath: metal blocks or micro-m.p. apparatus may be used.

b. Formation of hydroperoxides

On autoxidation, compounds containing activated C–H bonds (olefins, ethers, alcohols, aldehydes, ketones, and hydrocarbons) always afford in the

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[312] R. Criegee in "Fortschritte Chemische Forschung," Springer-Verlag, Berlin, 1949/50, Vol. 1, p. 508.

[313] A. Rieche, E. Schmitz, and M. Schulz, *Z. Chem.*, **3**, 443 (1963).

[314] G. Scott, "Atmospheric Oxidation and Antioxidants," Elsevier Publ. Co., Amsterdam, 1965.

[315] H. J. Küchle, *Zentralbl. Arbeitsmed. Arbeitsschutz*, **8**, 25 (1958).

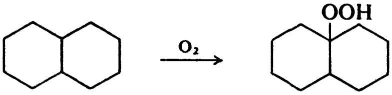
first place the hydroperoxide ROOH (Rieche).[316] This involves a radical chain reaction:

$$R^{\cdot} + O_2 \longrightarrow ROO^{\cdot} \xrightarrow{RH} ROOH + R^{\cdot} \longrightarrow \text{Chain}$$

Before its oxidation the starting material should be cleaned so as to remove all autoxidation-inhibitors. Crystalline organic compounds are dissolved in benzene, chloroform, ethyl acetate, carbon disulfide, or chlorobenzene, liquid compounds can be autoxidized neat or after dilution. Treatment with oxygen is best carried out in a shaking machine with cylinder oxygen or by passing a finely divided oxygen or air stream into the material. In the latter case loss of volatile material can be reduced by placing a Raschig column at the end of the train. Readily autoxidizable, involatile materials often give hydroperoxides or dialkyl peroxides when merely exposed to the air in crystallizing dishes.

Irradiation with ultraviolet light accelerates the uptake of oxygen and is usually essential. Addition of catalytic amounts of heavy-metal salts or other peroxides shortens the induction period and thus the total time for autoxidation. However, traces of heavy metals also lead to more decomposition of the hydroperoxides formed and thus make working up more difficult. It is usually advisable to cease an autoxidation when the peroxide content reaches 5–10%.

Autoxidation of hydrocarbons:[317,318] Saturated hydrocarbons react relatively sluggishly with oxygen. For their autoxidation temperatures of 100–110° are required, also almost always catalysts must be added. Unbranched hydrocarbons give all the possible hydroperoxides in statistical proportions, since the various hydrocarbon groups have almost the same reactivity to oxygen. However, hydrogen on tertiary carbon atoms is preferentially replaced: Criegee[319] thus obtained decahydro-4a-naphthyl hydroperoxide from decalin:



Gas-phase autoxidation of branched-chain hydrocarbons, *e.g.*, isobutane, can be markedly accelerated by addition of hydrogen bromide (HBr-induced autoxidation).[320] This variant of the normal autoxidation, where the added HBr provides the free radical, opened up the technical production of *tert*-butyl hydroperoxide and di-*tert*-butyl peroxide.

For the synthesis of definite hydroperoxides from hydrocarbons it is preferable to choose methods other than direct autoxidation, namely, either

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[316] A. Rieche, *Angew. Chem.*, **50**, 520 (1937); "Die Bedeutung der organischen Peroxyde für die chemische Wissenschaft und Technik," F. Enke, Stuttgart, 1936; *Angew. Chem.*, **51**, 707 (1938).

[317] H. Hock and H. Kropf, *Angew. Chem.*, **69**, 313 (1957).

[318] W. Langenbeck and W. Pritzkow, (a) *Chem. Techn.*, **2**, 116 (1950); **4**, 391 (1952); (b) *Fette und Seifen, Anstrichm.*, **55**, 435, 506 (1953); (c) W. Pritzkow and K. A. Müller, *Ann. Chem.*, **597**, 167 (1955).

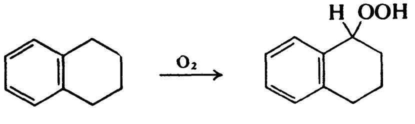
[319] R. Criegee, *Ber. Deut. Chem. Ges.*, **77**, 22 (1944).

[320] E. R. Bell, F. H. Dickey, J. H. Raleigh, F. F. Rust, and W. E. Vaughn, *Ind. Eng. Chem.*, **41**, 2597 (1949); B. Barnett, E. R. Bell, F. H. Dickey, F. F. Rust, and W. E. Vaughn, *Ind. Eng. Chem.*, **41**, 2612 (1949).

autoxidation of the appropriate Grignard compound[321] or perhydrolysis of alcohols,[322] dialkyl sulfates,[323] or methanesulfonates.[324]

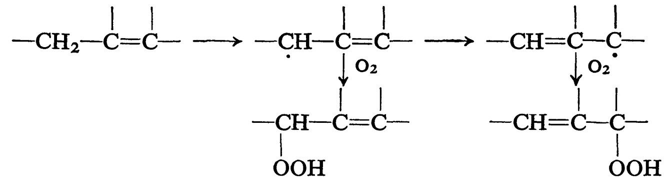
If there is a CH_2 or a CH group in α-position to an aromatic system, it is attacked preferentially by oxygen with formation of a "substituted benzyl hydroperoxide,"[317] examples being tetralin, indane, fluorene, cumene, *p*-xylene, and ethylbenzene. Temperatures required for autoxidation of such compounds are lower than for alkanes.

The hydroperoxides formed can be isolated by distilling off the solvent and the excess of starting material in a vacuum, sometimes in a high vacuum. The hydroperoxides crystallize either spontaneously or after long storage in a refrigerator. Low-boiling hydroperoxides can usually be purified by distillation in a high vacuum. Hydroperoxides that have acid properties can be extracted in cold sodium hydroxide solution after dilution of the autoxidation mixture with ether or light petroleum; the alkaline extract must be neutralized carefully, whereafter the hydroperoxide can be shaken into ether.



For autoxidation to give **1,2,3,4-tetrahydro-1-naphthyl hydroperoxide**[325] a vigorous, finely divided stream of air is led slowly through technical tetralin (1 l) at about 75° for 50–60 h; after some time the liquid becomes yellow. Loss of material is limited by use of a very efficient condenser. After the stated time about four-fifths of the total volume of unchanged tetralin is distilled off at 1–2 mm (bath temperature 75°). The distillation residue crystallises when set aside for a long time, more rapidly if cooled to 0°. The crystalline peroxide is filtered off and dried cautiously; it amounts to 15–17% of the crude autoxidation mixture and melts at ca. 52°; for purification it is crystallized several times from much light petroleum, then forming needles, of m.p. 56°, that are colorless and almost free from odor.

Autoxidation of olefins: Olefins react with oxygen at the α-position to the double bond. This can yield, not merely the hydroperoxide with the double bond in the original position, but also isomeric hydroperoxides resulting from migration of the double bond. According to Farmer and his co-workers the cause of this is mesomerism of the α,β-unsaturated radical first formed (α-methylene mechanism):



$$\begin{tikzcd}[column sep=small] -CH_2-C{=}C- \arrow[r] & -\dot{C}H-C{=}C- \arrow[r] \arrow[d, "O_2"] & -CH{=}C-\dot{C}- \arrow[d, "O_2"] \\ & -\underset{OOH}{CH}-C{=}C- & -CH{=}C-\underset{OOH}{C}- \end{tikzcd}$$

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[321] C. Walling and S. A. Buckler, *J. Amer. Chem. Soc.*, **77**, 6032 (1955).

[322] N. A. Milas and A. Harris, *J. Amer. Chem. Soc.*, **60**, 2434 (1938); N. A. Milas and D. Surgenor, *J. Amer. Chem. Soc.*, **68**, 205, 643 (1946); N. A. Milas and L. H. Perry, *J. Amer. Chem. Soc.*, **68**, 1938 (1946); R. Criegee and H. Dietrich, *Ann. Chem.*, **560**, 135 (1948).

[323] A. von Bayer and V. Villiger, *Ber. Deut. Chem. Ges.*, **27**, 1510 (1894); **34**, 738 (1901); A. Rieche and F. Hitz, *Ber. Deut. Chem. Ges.*, **62**, 2458 (1929); E. J. Harris, *Proc. Roy. Soc.* (*London*), *Ser. A*, **173**, 132 (1939); W. Eggersglüss, Monographie zur Angewandten Chemie und Chemie-Ing. Techn. No. 61, Verlag Chemie, Weinheim, 1951.

[324] H. R. Williams and H. S. Mosher, *J. Amer. Chem. Soc.*, **76**, 2984, 2987, 3495 (1954)

[325] H. Hock and W. Susemihl, *Ber. Deut. Chem. Ges.*, **66**, 61 (1933).

Cyclic olefins, *e.g.*, cyclohexene,[326] are attacked by oxygen more easily than are aliphatic olefins. Combined action of bromine and oxygen, or of hydrogen bromide and oxygen, on olefins in benzene solution affords 2-bromoalkyl hydroperoxides.[327]

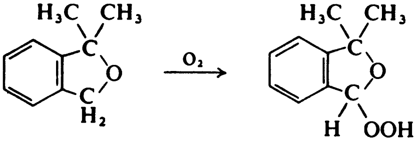
Autoxidation of ethers is very important since the peroxides formed are often the cause of violent explosions; for details see Rieche's review.[328] Peroxide-containing ethers, particularly diethyl ether, tetrahydrofuran, diisopropyl ether, and dioxan are sources of great danger since violent explosions can result on distillation. Moreover, petrol, light petroleum, decalin, xylene, cumene, and tetralin may all also contain peroxides.

Hydroperoxides may be removed from solvents by shaking them with solid potassium hydroxide[329] and then distilling them from potassium hydroxide (tetrahydrofuran containing much peroxide can undergo a vigorous reaction at this stage). Small amounts of peroxide are removed by pressing sodium wire into the solvent.

Hydroperoxides are converted into alcohols by reducing agents such as hydrogen sulfite, copper–zinc alloys,[330] or lithium tetrahydridoaluminate. Oxidizing agents such as $KMnO_4$[331] and PbO_2[332] also destroy peroxides. Prolonged action of a solution of iron(II) sulfate in 50% sulfuric acid destroys also aldehyde and ketone peroxides. Light petroleum and petrol are easily freed from peroxides by filtration through an alumina column.

Crystalline ether hydroperoxides can be isolated after autoxidation of cyclic benzyl ethers such as isochroman[333] and phthalan.[334]

Formation of **1,1-dimethylphthalan 3-hydroperoxide** by autoxidation:[334]



1,1-Dimethylphthalan (100 g) is shaken at room temperature while being irradiated with ultraviolet light. Autoxidation is stopped at a peroxide content of 40%. Then an equal volume of ether, and after that an equal volume of light petroleum, are added and the whole is shaken with 5% sodium hydrogen carbonate solution (25 ml), followed by water (10 ml). Then the hydroperoxide is extracted with ice-cold 2N-sodium hydroxide solution (30 ml, followed by three 25-ml portions). The pale yellow alkaline extracts are united and shaken with cold ether (10 ml) to remove ether-soluble substances. The alkaline solution is then strongly cooled and treated dropwise, with continuous stirring, with 2N-sulfuric acid, which precipitates 1,1-dimethylphthalan 3-hydroperoxide as an oil. The acid is added until a permanent emulsion is formed (pH about 9), then the mixture is extracted exhaustively with ether, the ether extracts are shaken first with 2N-sodium hydrogen carbonate and then with water and dried overnight with sodium sulfate, and the solvent is finally removed. The viscous residue, which forms a crystal paste when rubbed with light petroleum, affords the hydroperoxide, m.p. 63–64°, when recrystallized from ether/light petroleum.

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[326] R. Criegee, H. Pilz, and H. Flygare, *Ber. Deut. Chem. Ges.*, **72**, 1799 (1939).

[327] A. Rieche, M. Schulz, and K. Kirschke, *Chem. Ber.*, **99**, 3244 (1966).

[328] A. Rieche, *Angew. Chem.*, **70**, 251 (1958).

[329] W. Lepper, *Chemiker-Ztg.*, **66**, 314 (1942).

[330] H. Fierz-David, *Chimia*, **1**, 246 (1948).

[331] A. Harmse, *Pharm. Weekbl.*, **78**, 1085 (1941).

[332] F. R. Fischer and R. A. Baxter, *Mines Mag.*, **1940**, 447.

[333] A. Rieche and E. Schmitz, *Chem. Ber.*, **90**, 1082 (1957).

[334] A. Rieche and M. Schulz, *Ann. Chem.*, **653**, 32 (1962).

Acetals are also readily autoxidized; and crystalline acetal hydroperoxides can be isolated in the case of benzaldehyde ethylene acetal and its derivatives.[335] Autoxidation of ketones leads to aldehydes and acids by way of the usually unstable ketone hydroperoxides.[336,337] In the steroid series oxygen and potassium *tert*-butoxide in *tert*-butyl alcohol give 17-hydroperoxides,[337] which can be degraded to the 17-keto steroids;[338] in this way androstenolone is obtained from pregnenolone by way of the corresponding hydroperoxide (cf. Sucrow[339]):

$$\mathrm{R{-}CO{-}CH_2R} \xrightarrow{O_2} \mathrm{R{-}CO{-}CH(OOH){-}R} \longrightarrow \mathrm{RCHO + HOOCR}$$

Autoxidation of aldehydes leads to peracids:[340]

$$\mathrm{RCHO + O_2 \longrightarrow RCO{-}OOH}$$

For example, peroxybenzoic acid is obtained by autoxidation of benzaldehyde;[341] autoxidation of benzaldehyde in the presence of acetic anhydride leads to acetyl benzoyl peroxide, $C_6H_5CO{-}OO{-}COCH_3$.[342]

c. Formation of dialkyl peroxides

Dialkyl peroxides ROOR are often obtained as the principal product or as by-product of autoxidation of organic compounds, but almost always as a result of secondary reactions of alkyl hydroperoxides. Direct union of relatively long-lived radicals with oxygen is of minor importance and occurs only in exceptional cases, *e.g.*, in the formation of bis(triphenylmethyl) peroxide from triphenylmethyl:[343]

$$\mathrm{R\cdot + O_2 \longrightarrow ROO\cdot \xrightarrow{R\cdot} ROOR}$$

In most cases dialkyl peroxides arise from the alkyl hydroperoxides formed as primary products; this is so in autoxidation of isochroman,[333] phthalan,[334] 2-methyl-1,3-dioxolane,[344] and tetrahydroacenaphthacene.[345] Formation of dialkyl peroxides from alkyl hydroperoxides can occur under the influence of acids, and in this "ionic dimerization"[333,334] hydrogen peroxide is also formed:

$$\mathrm{2ROOH \xrightarrow{H^+} ROOR + H_2O_2}$$

An alternative method of obtaining dialkyl peroxides is a radical reaction under the influence of heavy-metal catalysts.[346,347]

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[335] A. Rieche, E. Schmitz, and E. Beyer, *Chem. Ber.*, **91**, 1935 (1958).

[336] D. B. Sharp, L. W. Patton, and S. E. Whitcomb, *J. Amer. Chem. Soc.*, **73**, 5600 (1951)

[337] E. J. Bailey, J. Elks, and D. H. R. Barton, *Proc., Chem. Soc.*, **1960**, 214; E. J. Bailey D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, **1962**, 1578.

[338] J. B. Siddol, G. V. Baddeley, and J. A. Edwards, *Chem. & Ind.* (*London*), **1966**, 25.

[339] W. Sucrow, *Chem. Ber.*, **100**, 259 (1967).

[340] G. Wittig, *Ann. Chem.*, **558**, 201 (1947).

[341] W. P. Jorissen, P. A. A. van der Beck, *Rec. Trav. Chim.*, **45**, 245 (1926); P. A. A. van der Beck, *Rec. Trav. Chim.*, **47**, 286 (1928).

[342] J. U. Nef, *Ann. Chem.*, **298**, 280 (1897); see A. von Bayer and V. Villiger, *Ber. Deut. Chem. Ges.*, **33**, 1569 (1900).

[343] K. Ziegler, *Angew. Chem.*, **61**, 168 (1949).

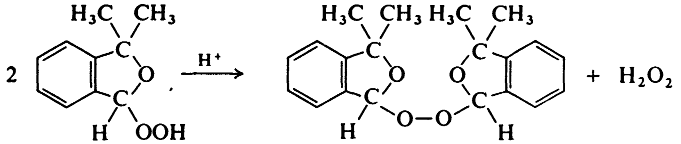
[344] R. Criegee and M. Lederer, Diplomarbeit Lederer, Karlsruhe, 1950.

[345] W. Treibs and J. Thörmer, *Chem. Ber.*, **90**, 94 (1957).

[346] W. Treibs and G. Pellmann, *Chem. Ber.*, **87**, 1201 (1954).

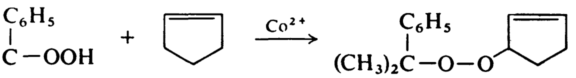
[347] M. S. Kharasch and A. Fono, *J. Org. Chem.*, **23**, 324 (1958).

As an example of ionic dimerization the preparation of **bis-(1,1-dimethylphthalan) 3,3′-peroxide** from 1,1-dimethylphthalan 3-hydroperoxide is described:[334]



1,1-Dimethylphthalan 3-hydroperoxide (500 mg) is dissolved in cold 2N-sodium hydroxide (10 ml) and treated first with methanol (5 ml) and then with 2N-sulfuric acid (20 ml). An oil separates; it crystallizes in the refrigerator (yield, 390 mg, 86%). Recrystallization from benzene/light petroleum gives the peroxide, m.p. 114–115°.

An example of the radical mechanism is provided by the preparation of **7-cumyl 3-cyclopentenyl peroxide** from cumyl hydroperoxide and cyclopentene:[346]



In a 250-ml three-necked flask into which a stream of nitrogen is passing, a mixture of cumyl hydroperoxide (20 g) and cyclopentene (70 g) is treated dropwise with an 18% solution (2 ml) of cobalt(II) stearate (corresponding to 30 mg of Co) in benzene. The temperature is thereby raised to 40°. The mixture is then warmed for 5 h in a thermostat at 45° still under nitrogen, and the residue is fractionated at 2 mm under nitrogen; this gives two main fractions, (*a*) b.p. 63–68°, α,α-dimethylbenzyl alcohol, and (*b*) b.p. 112–113°, cumyl cyclopentenyl peroxide, d_4^{20} 1.0195, n_D^{20} 1.5196.

3. Replacement of hydrogen by carbonyl–oxygen

a. Preparation of aldehydes and ketones

In order to avoid over-oxidation during conversion of methyl and methylene groups into carbonyl groups it is advisable to use mild oxidizing agents such as manganese(IV) compounds, chromyl chloride, nitro or nitroso compounds, or selenium dioxide. Powerful oxidizing agents can be used only if specific reaction conditions are most exactly observed and when the oxidation product is very inert.

α-Methylene groups of ketones can be oxidized particularly easily by way of the derived hydroxyimino ketones, thus:

$$\text{R—CO—CH}_2\text{R}' \xrightarrow{\text{HONO}} \text{R—CO—}\underset{\underset{\text{NOH}}{\|}}{\text{C}}\text{—R}' \longrightarrow \text{R—CO—CO—R}'$$

Thus biacetyl is obtained by treating 2-butanone with isopentyl nitrite and hydrolysing the resultant diketone monoxime (without isolating it) with sulfuric acid.[348] The intermediate need also not be isolated when malonic ester is converted into mesoxalic ester by nitrous gases.[349]

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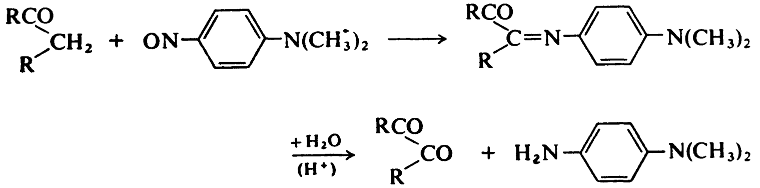
[348] O. Diels and E. Stephan, *Ber. Deut. Chem. Ges.*, **40**, 4337 (1907).

[349] A. W. Dox, *Org. Syn.*, **4**, 27 (1925).

The nitrosation of substituted ethylbenzenes was carried out by Kövendi and Kirez[350] with ethyl or methyl nitrite; the resulting benzophenone oxime was hydrolysed by boiling for 3–4 h with 20% hydrochloric acid; and the acetophenone produced was extracted with benzene.

Sachs[351] devized a generally applicable method in which activated methylene groups are condensed with *N*,*N*-dimethyl-*p*-nitrosoaniline and the resulting Schiff bases are cleaved by dilute mineral acid:



Mehr and his collaborators used this method to convert 4′-substituted tetraphenylcyclopentadienes into the corresponding **tetraphenylcyclopentadienones:**[352]

The diene is dissolved in benzene/methanol (3 : 1 or 3 : 4), treated with 3 molar equivalents of *N*,*N*-dimethyl-*p*-nitrosoaniline, and heated to the b.p. Then a few drops of methanolic 10% sodium methoxide solution are added and the mixture is kept for 5–10 min just below the boiling point, next treated with concentrated hydrochloric acid and boiled for 5–10 min. The tetraphenylcyclopentadiene is extracted with benzene.

Anil formation can also be effected in alcoholic solution in the presence of catalytic amounts of sodium carbonate or piperidine; the Schiff bases (usually deeply colored) are then precipitated and can be hydrolysed by acid in the usual way.

Reactive methylene groups can also be caused to react with *N*,*N*-dimethyl-*p*-nitrosoaniline, whereby aldehydes are finally obtained.[353] In this way 4,6-dinitroisophthalaldehyde can be prepared from 4,6-dinitro-*m*-xylene. Ethyl nitrite has also proved very useful for such reactions.

Another excellent reagent for oxidation of reactive methylene and methyl groups is selenium dioxide, which was introduced by Riley.[1f,355] Methyl ketones and Schiff bases derived from them react particularly readily with this dioxide. The same is true for methylene groups that adjoin a carbonyl group, so that compounds such as glyoxal and phenylglyoxal have become readily accessible from the corresponding monoaldehydes by oxidation with SeO_2; mesoxalic esters (mentioned above) can also be obtained by this method in good yield. The quality of the SeO_2 is important for its oxidizing properties; dioxan, glacial acetic acid, ethanol, butanol, toluene, and water have been mentioned as solvents. Cycloheptanone, for example, gives the 1,2-diketone in 90% yield.[354] **Phenylglyoxal** can be obtained both from phenylacetaldehyde and from acetophenone.[1f,355]

Selenium dioxide (112 g, 1 mole) is added, with stirring, to a mixture of dioxan (500 ml) and water (20 ml) at 60°. When dissolution is complete, acetophenone (120 g, 1 mole) is

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[350] A. Kövendi and M. Kirez, *Chem. Ber.*, **97**, 1902 (1964).

[351] F. Sachs and P. Ehrlich, *Ber. Deut. Chem. Ges.*, **32**, 2341 (1899).

[352] L. Mehr and co-workers, *J. Amer. Chem. Soc.*, **77**, 989 (1955).

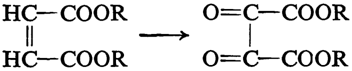
[353] P. Rüggli and P. Hindermann, *Helv. Chim. Acta*, **20**, 279 (1937).

[354] R. W. V. Harr and co-workers, *J. Org. Chem.*, **14**, 836 (1949).

[355] H. L. Riley and co-workers, *J. Chem. Soc.*, **1932**, 1875.

added all at once and the whole is heated for about 3 h with stirring under reflux. After cooling, the selenium that has separated is filtered off. It is advisable then to distill the dioxan off cautiously on the water-bath under diminished pressure. Phenylglyoxal tends very readily to polymerize but may be purified either by fractional distillation (b.p. 96°/22 mm) or by recrystallization of its hydrate from diethyl ether. The yield amounts to ca. 70%. The hydrate is obtained by recrystallization from a little water.

The synthesis of 2-naphthaldehyde from 2-methylnaphthalene by means of SeO_2 (66% yield) illustrates the ability of methyl groups attached to an aromatic system to react with this oxide.[356] The methyl groups of toluidines whose amino groups are protected by phthaloylation, and of cresols whose hydroxyl groups are protected by benzenesulfonylation, are oxidized by selenium dioxide to aldehyde or carboxyl groups in various proportions.[357] Similarly, Badger converted fluorene into fluorenone by SeO_2 in an aqueous medium at 230–240°;[358] and treatment of maleic ester with SeO_2 affords dioxosuccinic ester:[359]



$$\begin{array}{c} \mathrm{HC{-}COOR} \\ \| \\ \mathrm{HC{-}COOR} \end{array} \longrightarrow \begin{array}{c} \mathrm{O{=}C{-}COOR} \\ | \\ \mathrm{O{=}C{-}COOR} \end{array}$$

For reviews of selenium dioxide oxidations see ref. [360].

A reminder that, to avoid unpleasant explosions, care must be taken when working up selenium formed from SeO_2!

Weygand and his colleagues[361] have shown that in oxidations by $KMnO_4$ the medium can conveniently be maintained neutral by adding salts that act as buffers, *e.g.*, magnesium salts; the alkali formed in the reaction can also be bound by addition of acetic anhydride. However, if neutrality is maintained, non-aqueous solvents such as acetone are stable, so that water-insoluble substances can thus be oxidized in a homogeneous system.

The following are examples of oxidation by neutral permanganate:

***p*-Diacetylbenzene** from 4-ethylacetophenone: Magnesium nitrate hexahydrate (30 g) is dissolved in water (250 ml), and 4-ethylacetophenone (15 g) is added. The mixture is warmed to 50° and powdered potassium permanganate (16 g) is added in small portions with rapid stirring. The temperature rises to 70°. Oxidation is complete in 2 h, the mixture is then allowed to cool and the manganese dioxide formed is filtered off and washed with ether. The aqueous filtrate is also shaken with ether. The combined ether extracts are dried over calcium chloride, filtered, and evaporated, whereupon *p*-diacetylbenzene separates (13.8 g, 84%; m.p. 114°).

1-Tetralone from tetralin in acetone as solvent: Tetralin (38 g) is dissolved in acetone (500 ml) in a three-necked flask fitted with a stirrer and reflux condenser, and the solution is then heated to the b.p. Then a powdered, intimate mixture of potassium permanganate (66 g) and calcium nitrate tetrahydrate (49 g) is added gradually, with stirring, through the third neck of the flask. The permanganate is all consumed in 10 h, after which the mixture is filtered and the acetone distilled off at atmospheric pressure. The residual oil is fractionated in a vacuum: tetralin (20.5 g) is recovered at 95–99°/19 mm; at 134–137°/19 mm pale yellow 1-tetralone (14.5 g) distils; it can be purified through its semicarbazone. The yield amounts to 65% based on the tetralin consumed.

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[356] W. M. Rodionow, "Synthese organischer Verbindungen," VEB Verlag Technik, Berlin, and Porta-Verlag, Munich, 1956, Vol. 2, p. 114.

[357] G. Zemplén and L. Kisfaludy, *Chem. Ber.*, **93**, 1125 (1960).

[358] G. M. Badger, *J. Chem. Soc.*, **1941**, 535.

[359] S. Ashin, L. de V. Moulds, and H. L. Riley, *J. Chem. Soc.*, **1935**, 902.

[360] G. Stein, "Neuere Methoden der präparativen organischen Chemie," 3rd ed, Verlag Chemie, Weinheim, 1949, Vol. 1, p. 1; N. Rabjohn, *Org. Reactions*, **5**, 331 (1949); G. R. Waitkins and C. W. Clark, *Chem. Rev.*, **36**, 235 (1945).

[361] See W. Winkler, *Chem. Ber.*, **81**, 256 (1948).

A further method of converting cycloalkenes and cycloalkanes into ketones in organic solvents was opened up by Treibs and his co-workers.[136,362] Their oxidant is hydrogen peroxide with peroxyvanadic acid as catalyst. The attack on cycloalkenes is at the position next to the double bond, and on tetralins at the α-position to the aromatic ring. Acetone is usually used as solvent. The end of the reaction is recognized by a color change from reddish-yellow to reddish-brown or green. This method affords good yields of, *e.g.*, cyclohexenone from cyclohexene and of 1-tetralone from tetralin.

Methyl groups attached to an aromatic ring can be converted into aldehyde groups by a mixture of manganese dioxide and moderately concentrated sulfuric acid.[363] The process is recommended particularly for oxidation of compounds that dissolve in 90–95% sulfuric acid. However, provided that sulfonation does not intervene, oleum or a mixture of sulfuric and acetic acid may be used. Almost all toluene derivatives can thus be converted into aldehydes; *e.g.*, *o*-toluenesulfonic acid and 2,4-toluenedisulfonic acid give 80% yields of the corresponding aldehydes by this method.[364]

For oxidation of toluene derivatives, the manganese dioxide may be replaced by chromic acid in acetic anhydride or sulfuric acid; the resulting aldehydes are isolated as their diacylates, which are stable against further oxidation. The fact that *o*-nitrotoluene is not attacked by manganese dioxide in an acid medium but is oxidized to *o*-nitrobenzaldehyde by chromic acid shows the latter method to be more generally applicable than the former. This reaction will be described in detail as an example:[365]

o-Nitrobenzaldehyde diacetate (2-nitrobenzylidene diacetate): *o*-Nitrotoluene (50 g) is dissolved in glacial acetic acid (570 ml) and acetic anhydride (565 ml), and the mixture is treated cautiously with concentrated sulfuric acid (85 ml). To this mixture at 5–10° CrO_3 (100 g) is stirred in gradually during 2 h, after which stirring is continued for a further 3 h. The solution is then poured on crushed ice, diluted to 6 l with water, and stirred until the precipitated oil has compacted. The solid product is collected, washed with water, and stirred with 2% sodium carbonate solution; it is then dried, stirred with light petroleum (b.p. 60–70°; 150 ml) at the b.p., and, after cooling, collected. The yield is 23–24% (21–22 g), and the m.p. is 87–88°.

A second fraction is obtained if the acid mother-liquors are extracted with chloroform. The extract is washed with sodium hydrogen carbonate solution, then dried over Na_2SO_4 and evaporated. The resulting brown syrup crystallizes when treated with heptane and kept at 0°.

o-Nitrobenzaldehyde: A mixture of the above diacetate (51.6 g), concentrated hydrochloric acid (272 ml), water (450 ml), and ethanol (80 ml) is heated with stirring for 1 h under reflux. If, on cooling to 0°, the aldehyde separates as an oil, about twice the volume of water is added and the mixture is kept for a long time in the cold. The crude product is filtered off, washed with water, and purified by rapid distillation in steam (yield, 23.7 g, 74%). The m.p. is 44–45°.

Chromic acid is also more suitable than SeO_2 or MnO_2 for preparation of brominated benzaldehydes from the corresponding substituted toluenes.[366]

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[362] W. Treibs and co-workers, *Angew. Chem.*, **52**, 698 (1939).

[363] A. Boner, *Chemiker-Ztg.*, **24**, 446 (1900).

[364] Friedländer, 7, 108 (1902–1904).

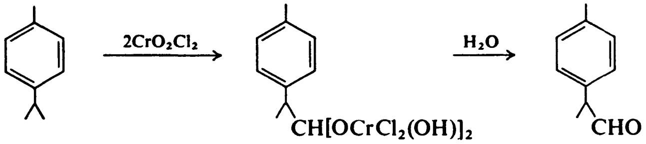
[365] S. M. Tsang and co-workers, *Org. Syn.*, **24**, 75 (1944); A. F. Walton and co-workers, *J. Amer. Chem. Soc.*, **67**, 1501 (1945).

[366] B. M. Bogolovskiĭ and T. I. Yakovenko, *Zh. Obshch. Khim.*, **24**, 1043 (1954); *Chem. Abstr.*, **49**, 9552 (1955).

Ketones can also be successfully obtained by oxidation of hydrocarbons with chromic acid. Thus treating acenaphthene in boiling glacial acetic acid with sodium dichromate gives 1,2-acenaphthenequinone;[367] and Fieser has converted cholesterol into 4-cholestene-3,6-dione by treatment with sodium dichromate in glacial acetic acid and benzene at 0° for 40–48 h.[368] Waters[369] has described the mechanism of oxidations by chromium and manganese compounds, and Ladbury and Cullis[370] have reviewed the kinetics and mechanism of oxidation by permanganate.

The Étard method of converting methyl into aldehyde groups by means of chromyl chloride is of value when xylene, mesitylene, and other polymethyl compounds are to be transformed into monoaldehydes; this synthesis affords satisfactory yields of the three isomeric tolualdehydes from their corresponding xylenes.[371]

p-Cymene and chromyl chloride do not give *p*-isopropylbenzaldehyde but instead 2-(*p*-tolyl)propionaldehyde:[372]



(I)

Chromyl chloride (2 moles) in ether is dropped during 3 h into a stirred, ice-cold ethereal solution of *p*-cymene (1 mole); the mixture is then warmed at 35° for 30 min. The precipitate [the complex (I)] is filtered off, washed with ether, and decomposed with ice-water. The mixture is neutralized with sodium hydroxide solution and the **2-(*p*-tolyl)propionaldehyde** is extracted with ether (yield 85%). It has b.p. 110–111°/15 mm.

Several aromatic alkyl-substituted compounds can be converted into ketones in the gas phase by means of air in the presence of chromium(VI) oxide:

$$ArCH_2—CH_3 \xrightarrow[CrO_3]{O_2} Ar—CO—CH_3$$

Passing air through a suspension of *m*-diethylbenzene, CrO_3 (1%), and $CaCO_3$ (4%) at 130° for a period of 40 h gives a 50% yield of 3-ethylacetophenone.[373] Alkyl-substituted aromatic carboxylic esters, acetophenones, and halobenzenes similarly give the corresponding keto esters, diketones, and halo ketones, respectively.[374]

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[367] C. S. Maxwell and C. F. H. Allen, *Org. Syn.*, **24**, 1 (1944).

[368] L. F. Fieser, *Org. Syn.*, **35**, 36 (1955).

[369] W. A. Waters, *Quart. Rev.*, **12**, 277 (1958).

[370] J. W. Ladbury and C. F. Cullis, *Chem. Rev.*, **58**, 403 (1958).

[371] H. D. Law and F. M. Perkin, *J. Chem. Soc.*, **91**, 258 (1907).

[372] W. Strubell, *J. Prakt. Chem.*, [iv] **10**, 349 (1960).

[373] D. T. Mowry, *J. Amer. Chem. Soc.*, **67**, 1050 (1945).

[374] W. S. Emerson and co-workers, *J. Amer. Chem. Soc.*, (a) **68**, 674, 1666 (1946); (b) **69**, 1905 (1947); (c) **70**, 1180 (1948).

The action of $PdCl_2$ on olefins in aqueous solution provides a process for the synthesis of ketones that is used both in the laboratory and in industry.[375] In accord with the equation:

$$R{-}CH{=}CH_2 + PdCl_2 + H_2O \longrightarrow R{-}CO{-}CH_3 + Pd + 2HCl$$

1-alkenes undergo nucleophilic attack by the reagent at the alkylated carbon atom of the ethylenic group, so that methyl ketones are obtained, and yields are usually in excess of 90%.

Reaction temperatures are between 20° and 70°. Within a homologous series the rate of reaction decreases with increasing chain length: for instance, the conversion of propene into acetone is 90% in 5 min, but of 1-decene is only 34% after 60 min; in this respect the solubility of the alkene in the aqueous $PdCl_2$ plays a role. 2-Alkenes also react to give methyl ketones, but more slowly than the corresponding 1-alkenes.

Acetaldehyde is obtained from ethylene in excellent yield, and this is the most attractive method of industrial synthesis since the metallic palladium formed in the reaction can be regenerated by atmospheric oxygen.

b. Preparation of quinones

It is often possible to convert aromatic hydrocarbons directly into quinones. According to a German patent[376] *p*-benzoquinone is obtainable in 50–55% yield by heating benzene with moist lead dioxide in 100% sulfuric acid at 56° for 5 min, then pouring the mass on ice and extracting the quinone with chloroform; this quinone can also be prepared by electrolytic oxidation of benzene, in 65% yield.[377]

Graebe and Liebermann[378] converted anthracene into anthraquinone by oxidation with chromic acid in glacial acetic acid, although it is preferable[379] to use sodium chlorate and vanadium pentoxide as catalysts. However, **anthraquinone** can also be prepared in good yield by use of potassium permanganate:

According to directions by Weygand, anthracene (2.5 g) is dissolved in warm acetic anhydride (125 ml), treated gradually and cautiously at 80–90° with finely powdered potassium permanganate (10 g). Oxidation is complete in 3–4 h. The mixture is cooled in ice and filtered through a glass frit which retains the anthraquinone and potassium acetate whilst the manganese dioxide passes in colloidal form through the filter. The material on the filter is washed with acetic anhydride, and the sodium acetate is leached out with water. The residue consists of anthraquinone (2.2 g, 78%).

When melted with oxidizing agents such as nitrates, permanganates, or chlorates, anthracene gives anthraquinone, in some cases in theoretical yield.[380]

9,10-Phenanthraquinone is obtained in 80% yield by treating phenanthrene with chromic–sulfuric acid,[381] and 2,3-dimethylnaphthalene gives 2,3-di-

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[375] J. Schmidt and co-workers, *Angew. Chem.*, **71**, 176 (1959); W. Hafner and co-workers, *Chem. Ber.*, **95**, 1575 (1962).

[376] Ger. Pat. 533,128; *Chem. Abstr.*, **26**, 480 (1932).

[377] A. Seyewetz and G. Miodon, *Bull. Soc. Chim. France*, [iv], **33**, 449 (1923).

[378] C. Graebe and C. Liebermann, *Ann. Chem. Pharm.*, **7**, 284 (1870).

[379] H. W. Underwood Jr. and W. L. Walsh, *Org. Syn.*, Coll. Vol. 2, 554 (1943).

[380] J. Sielisch, Ger. Pat. 568,784; *Chem. Abstr.*, **27**, 2698 (1933).

[381] R. P. Linstead and P. Levine, *J. Amer. Chem. Soc.*, **64**, 2023 (1942).

methyl-1,4-naphthaquinone when treated with chromic–acetic acid.[382] The original literature[383] should be consulted for details of catalytic oxidation of naphthalene to 1,4-naphthaquinone in the gas phase.

Teuber and his co-workers have found that monohydric phenols and naphthols can be converted into quinones by potassium nitrosodisulfonate.[384] When the *para*-position is unoccupied, use of 2 moles of $NO(SO_3K)_2$ per mole usually gives *p*-quinones: phenol gives *p*-benzoquinone, and 1-naphthol gives 1,4-naphthaquinone. 5-Hydroxy-1,4-naphthaquinone is accessible equally from 1,5- and 1,8-naphthalenediol. Phenols with occupied *para*- but free *ortho*-positions are oxidized to *o*-quinones: thus 4,5-dimethyl-1,2-benzoquinone is obtained from 3,4-dimethylphenol, and 4-methyl-1,2-benzoquinone from *p*-cresol. The yields are 70–80% and the experimental conditions are extremely favorable: reaction is effected in water at 5–25°, and reaction times vary from case to case from 10 min to 3–4 hours. The authors found this oxidant to be stable for months in the dry state and to be easily prepared.

4. Replacement of hydrogen by carboxyl–oxygen

Aromatic and heterocyclic mono- and poly-carboxylic acids are important intermediates, wherefore many methods of synthesizing them have been developed. One of the most attractive is their preparation from methyl compounds by oxidizing agents, in particular potassium permanganate and chromic acid; however, oxygen, nitric acid, sulfur and its derivatives are also often good reagents for conversion of methyl into carboxyl groups. When long-chain or branched-chain alkyl-aromatic compounds are oxidized the side-chain is usually oxidized away so that acids are obtained in which the carboxyl group is attached directly to a ring. Polycyclic aromatic compounds are particularly easily oxidized in the ring by chromic acid or permanganate (see preceding Section), and in such cases it is problematical whether selective oxidation of the methyl group is possible and, if it is, specific reaction conditions must be strictly observed.

In some cases nitric acid is recommended as oxidant — provided that nitration does not occur. In the aromatic series it is often possible to oxidize one of several methyl groups while the others remain intact. Boiling *o*- or *p*-xylene in a mixture of 1 volume of concentrated nitric acid (*d* 1.4) with 2–4 volumes of water gives the respective toluic acid;[385] but a greater concentration of acid (2 volumes of concentrated nitric acid to 3 volumes of water) is required to oxidize *m*-xylene to *m*-toluic acid.[386] Mellitic acid is formed in 35% yield on treatment of hexamethylbenzene with fuming nitric acid.[387]

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[382] L. I. Smith and I. M. Webster, *J. Amer. Chem. Soc.*, **59**, 664 (1937).

[383] H. E. Fierz-David, L. Blangey, and W. von Krannichfeldt, *Helv. Chim. Acta*, **30**, 247 (1947).

[384] H.-J. Teuber and co-workers, *Chem. Ber.*, **85**, 95 (1952); **86**, 1036 (1953); **87**, 1236, 1251 (1954); **88**, 802 (1955).

[385] H. E. Zaug and R. T. Rapala, *Org. Syn.*, **27**, 84 (1947).

[386] A. Reuter, *Ber. Deut. Chem. Ges.*, **17**, 2028 (1884).

[387] J. P. Wibaut and co-workers, *Rec. Trav. Chim.*, **60**, 743 (1941); M. Chaigneau, *C. R. Hebd. Séances Acad. Sci.*, **233**, 657 (1951).

OH^- ions are formed during oxidations by $KMnO_4$ in a neutral medium:

$$2KMnO_4 + 3H_2SO_4 \longrightarrow 2MnO_2 + 2KOH + 3O$$

and it is advisable to buffer them by addition of magnesium sulfate. The oxidizing power of the MnO_2 is also used if reaction is effected in acid solution:

$$2KMnO_4 + 3H_2SO_4 \longrightarrow K_2SO_4 + 2MnSO_4 + 5O$$

Most permanganate oxidations are carried out in a neutral medium. *o*-Xylene is converted by potassium permanganate into *o*-phthalic acid under all conditions and *o*-toluic acid cannot be isolated.[388] The toluic acids are easily converted into the corresponding phthalic acids by alkaline permanganate.[389]

Preparation of **o-chlorobenzoic acid** from *o*-chlorotoluene:[390] *o*-Chlorotoluene (200 g), water (7 l), and potassium permanganate (600 g) are heated, with stirring, slowly to the b.p. in a 12-l flask under a reflux condenser. The reaction must be controlled at first so that it does not become too violent. When the permanganate color has disappeared (3–4 h), some unchanged *o*-chlorotoluene (25–30 g) is distilled off in steam with continued stirring. The residue is filtered while hot; the manganese dioxide is washed with two 500-ml portions of hot water; the total filtrate is evaporated in a vacuum to 3.5 l; it is then decolorized (when necessary) with charcoal, filtered, and, whilst continuously shaken, is acidified with hydrochloric acid (*d* 1.19; 250 ml). After cooling, the precipitate is filtered off, washed with water, and dried. It consists of almost pure *o*-chlorobenzoic acid (163–167 g, 74–78%), m.p. 137 to 138°. For purification it is recrystallized from toluene (600 ml), giving after one crystallization 135–140 g, of m.p. 139–140°.

Isonicotinic and picolinic acid are similarly obtained from 4- and 2-picoline, respectively, by oxidation with permanganate,[391] yields being 50–60% and 50% (as hydrochloride), respectively.

4-Picoline is also efficiently oxidized to isonicotinic acid by the black manganese dioxide that is formed in some permanganate oxidations of organic substances.[392]

Chromic acid is mostly used in concentrated acetic acid, or in sulfuric acid solution of any desired concentration. A chromic acid mixture that is often used consists of 40 parts of K_2CrO_4 or Na_2CrO_4, 55 parts of concentrated sulfuric acid, and twice that volume of water. This mixture converts *m*- and *p*-xylene into the corresponding phthalic acids but destroys *o*-xylene.

Preparation of ***p*-nitrobenzoic acid** from *p*-nitrotoluene:[393] Sodium bichromate (680 g) is stirred with water (1500 ml) and *p*-nitrotoluene (230 g) while concentrated sulfuric acid (1700 ml) is run into it. This melts the nitrotoluene, and reaction soon becomes vigorous; the last half of the acid must therefore be added carefully in portions. The mixture is finally boiled for 0.5 h, diluted with water (2 l), and filtered through a cloth. The crude solid product is washed with water (ca. 1 l), then digested with 5% sulfuric acid (1 l) on the water-bath, and again filtered off. This material is dissolved in 5% sodium hydroxide solution and filtered into an excess of dilute sulfuric acid, giving the pale yellow crude acid (230–240 g, 82–86%). When purified by crystallization from benzene it has m.p. 238°.

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[388] A. Claus and E. Pieszek, *Ber. Deut. Chem. Ges.*, **19**, 3083 (1886).

[389] W. Weith, *Ber. Deut. Chem. Ges.*, **7**, 1058 (1874).

[390] O. Emmerling, *Ber. Deut. Chem. Ges.*, **8**, 880 (1875); H. T. Clarke and E. R. Taylor, *Org. Syn.*, Coll. Vol. 2, 135 (1943).

[391] R. L. Malan and P. M. Dean, *J. Amer. Chem. Soc.*, **69**, 1797 (1947); A. W. Singer and S. M. McElvain, *Org. Syn.*, Coll. Vol. 3, 740 (1955).

[392] A. M. Tyatji, *Chem. Ber.*, **92**, 2677 (1959).

[393] O. Kamm and A. O. Matthews, *Org. Syn.*, **2**, 53 (1922).

Friedman, Fishel, and Shechter[394] have provided a large number of examples showing that aqueous dichromate solution at elevated temperatures and under pressure is an excellent reagent for oxidation of alkylated aromatic compounds. The particular value of the method is for converting methyl and polymethyl derivatives of polycyclic aromatic compounds into mono- and poly-carboxylic acids. For instance, 1-methylnaphthalene with a 42% excess of aqueous sodium dichromate solution in an autoclave at 240–250° gives 95% of 1-naphthoic acid in 18 h; 2-methylnaphthalene with a 55% excess gives a 93% yield of 2-naphthoic acid; the methyl group in fluoro-, bromo-, chloro-, nitro-, and methoxy-toluene as well as in xylenes and heterocycles can usually be oxidized smoothly to a carboxyl group. An excess of $Na_2Cr_2O_7$ acts as a buffer and favors smooth reaction. With 1.5 moles of $Na_2Cr_2O_7$ the reaction occurs in accord with the equation:

$$ArCH_3 + 1.5Na_2Cr_2O_7 \longrightarrow ArCOONa + Na_2CrO_4 + Cr_2O_3 + 1.5H_2O$$

Reitsema and Allphin[395] found that chromic acid oxidation of ethyl-, propyl-, isopropyl-, and butyl-benzene under certain conditions led to formation of ω-phenylalkanoic acids. For example, heating a mixture of ethylbenzene (0.025 mole) with $Na_2Cr_2O_7 \cdot 2H_2O$ (0.05 mole) in water (100 ml) in an autoclave (300-ml capacity) for 1 h at 275° is said to give 96% of phenylacetic acid (after allowance for 8% of recovered hydrocarbon); however, raising the temperature to 300° leads to formation of 55% of benzoic acid and 12% of phenylacetic acid.

Oxidation of methyl groups attached to aromatic rings by oxygen usually requires energetic conditions and addition of acatalyst. In general, oxygen converts polymethylbenzenes in presence of a metal ion only into monocarboxylic acids. At 180–200° with an initial oxygen pressure of 30–50 atm (measured at 20°) and in presence of 0.5–2.0% of hydrogen bromide, water-soluble methylated aromatic compounds such as toluic acids, *p*-toluenesulfonic acid, 4-picoline, and *p*-nitrotoluene give very good yields of the corresponding di- or monocarboxylic acids in 2–5 hours.[396] However, even the alkyl groups of toluene, ethylbenzene, and cumene can be converted into carboxyl groups in the presence of V_2O_5 or ammonium vanadate; 54% of *p*-bromobenzoic acid is obtained from *p*-bromotoluene, and 40% or 59% of benzoic acid from ethylbenzene or cymene, respectively.

In the presence of cobalt acetate bromide, oxygen will convert methyl into carboxyl groups even at atmospheric pressure. If oxygen is led into a solution of *o*-bromotoluene in acetic acid containing cobalt acetate and HBr at 90°, 91% of *o*-bromobenzoic acid is formed after reaction for 2 hours.[397]

Sulfur, and derivatives of sulfur in a low oxidation state, can also be applied for oxidation of methylated aromatic compounds. Thus, under the conditions of a modified Willgerodt reaction, dimethylnaphthalenes can be converted into methylnaphthoic acids (ca. 40%) and naphthalenedicarboxylic acids (ca. 60%) (molar ratios of Hydrocarbon : S : NH_3 : H_2O = 1 : 7 : 5.6 : 65;

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[394] L. Friedman, D. L. Fishel, and H. Shechter, *J. Org. Chem.*, **30**, 1453 (1965).

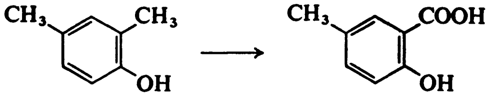
[395] R. H. Reitsema and N. L. Allphin, *J. Org. Chem.*, **27**, 27 (1962).

[396] J. E. McIntyre and D. A. S. Ravens, *J. Chem. Soc.*, **1961**, 4082.

[397] A. S. Hay and H. S. Blanchard, *Can. J. Chem.*, **43**, 1306 (1965).

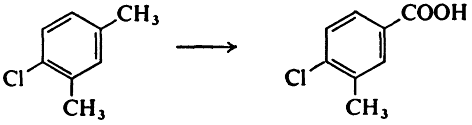
275°; 1 h).[398] The procedure is said to have also industrial importance. Heating *m*-xylene for 1 h at 325°/ca. 20 atm with aqueous ammonium hydrogen sulfate solution containing sulfur gives 89% of isophthalic acid.[399]

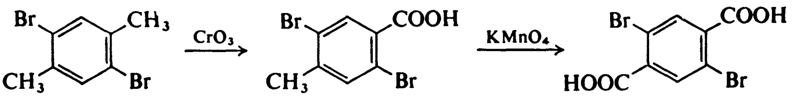
In certain cases side chains of aromatic compounds can be oxidized in an oxidizing alkali melt — the substance is heated at 200–300° with 3–4 parts of solid sodium hydroxide or potassium hydroxide to which a little water is added. This process has been recommended specifically for homologous phenols since the experiment can be made with the free phenol. An example is the conversion of 2,4-xylenol into 2-hydroxy-5-methylbenzoic acid, which shows also that the alkyl group next to the hydroxyl group is preferentially oxidized.[400]



The regularities attaching to the various oxidation reactions, and their mechanisms, have not yet been fully clarified. In general, the formation of a second carboxyl group on side-chain oxidation of dialkyl aromatic compounds is favored by alkalinity and disfavored by acidity of the medium. Beyond this, the following paragraphs give some indications of the influence of substituents.

Nuclear halogen often makes oxidation more difficult: it protects alkyl groups against attack. Thus oxidation of 4-chloro-*m*-xylene and 2,5-dibromo-*p*-xylene by chromic acid proceeds only as far as 4-chloro-*m*-toluic and 2,5-dibromo-*p*-toluic acid, respectively;[401] the latter requires alkaline permanganate for conversion into the dibromoterephthalic acid.[402]





Sulfo and nitro substituents also often make it harder to degrade the side chain. For the preparation of nitrobenzoic acids from nitrotoluenes a dichromate–sulfuric acid mixture is superior to chromic acid alone in glacial acetic acid; trinitrotoluene is converted into trinitrobenzoic acid by the former but is not attacked by the latter reagent. *o*-Toluenesulfonamide (obtained from the acid by way of the chloride) is oxidized by alkaline permanganate solution

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[398] D. Klamann and O. Krämer, *Erdöl und Kohle*, **15**, 263, 438 (1962).

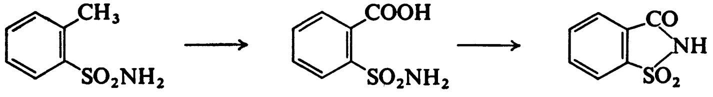
[399] W. G. Toland, *J. Amer. Chem. Soc.*, **82**, 1911 (1960).

[400] O. Jacobsen, *Ber. Deut. Chem. Ges.*, **11**, 376, 570 (1878).

[401] O. Jacobsen, *Ber. Deut. Chem. Ges.*, **18**, 1761 (1885).

[402] B. Schultz, *Ber. Deut. Chem. Ges.*, **18**, 1762 (1885).

at 60° to saccharin:



If nitro and sulfo groups are both present in the nucleus, persulfate is sometimes the best side-chain oxidant.[403]

When groups such as hydroxyl or amino that are sensitive to oxidation are present as well as an alkyl group, then oxidation of the latter is seldom a smooth reaction. Amino groups can be acetylated, so that, for example, *p*-(acetylamino)benzoic acid is obtained from *N*-acetyl-*p*-toluidine by permanganate;[404] anthranilic acid can be derived similarly from *N*-acetyl-*o*-toluidine. In such cases it is best to keep the reaction mixture neutral by adding magnesium sulfate.

Homologs of pyridine, quinoline, thiophen, and various other heterocycles can be oxidized to carboxylic acids generally without destruction of the hetero ring; in the pyrrole series, however, this cannot be done directly but requires intervention of an intermediate (see Fischer *et al.*[405]). More circuitous routes are also sometimes preferable in the quinoline series; for instance, in their total synthesis of hydroquinine Rabe *et al.*[406] obtained the 4-carboxylic acid from 6-methoxy-4-methylquinoline by oxidizing the 4-styryl derivative (obtained by reaction with benzaldehyde) instead of oxidizing the methyl compound directly. Alkyl groups at positions 2 and 4 of pyridine are more easily oxidized than those at position 3.

Preparation of **phenylglyoxalic acid** from acetophenone:[407] A solution of potassium permanganate (32 g) and potassium hydroxide (12 g) in water (200 ml) is warmed to 70° and added in 5–6 portions to acetophenone (12 g) in water (200 ml); with stirring; decoloration should be allowed to occur between successive additions; the whole oxidation requires barely 30 min. Working up by filtration, acidification, extraction with ether, etc., gives phenylglyoxalic acid (more than 7 g). 4-Methylacetophenone gives as much as 70% of *p*-toluylglyoxalic acid.

Finally, the preparation of dimethylmalonic acid by heating trimethylacetic acid with alkaline permanganate solution is worth mention.[408]

5. Dehydrogenation of alcohols to carbonyl compounds

a. Aldehydes

The ready availability of primary aliphatic alcohols makes their oxidation to aldehydes of considerable practical importance. The most significant method of dehydrogenation is the catalytic removal of hydrogen at elevated temperatures

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[403] Ger. Pat. 80,165; Friedländer, **4**, 146.

[404] I. Meisenheimer and co-workers, *Ann. Chem.*, **423**, 86 (1921).

[405] Cf. H. Fischer and co-workers, *Ann. Chem.*, **461**, 244 (1928).

[406] P. Rabe and co-workers, *Ber. Deut. Chem. Ges.*, **64**, 2493 (1931).

[407] A. Claus and W. Neukranz, *J. Prakt. Chem.*, [ii], **44**, 77 (1891).

[408] P. D. Bartlett, G. L. Fraser, and R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 498 (1941).

in either the presence or absence of hydrogen-acceptors. Nevertheless, for the preparation of carbonyl compounds the classical oxidants chromic acid, manganese dioxide, and nitric acid still receive manifold applications.

Chromic acid dehydrogenates primary alcohols between 0° and 100°; yields of aldehyde lie between 40% and 60%, by-products being mainly carboxylic acids and their esters. A proven oxidation mixture consists of 1 mole of dichromate, 2.5 moles of sulfuric acid, and 300 g of water (Beckmann mixture), into which the alcohol is dropped; CO_2 or N_2 is led through the mixture so as to prevent the aldehyde's being further oxidized; and, if possible, cooling is arranged so that only the alcohol is condensed. The aldehyde that distils off is best collected in cooled receivers. It is best to use an excess of chromic acid calculated according to the equation:

$$3RCH_2OH + 2CrO_3 + 3H_2SO_4 \longrightarrow 3RCHO + Cr_2(SO_4)_3 + 6H_2O$$

Isobutyraldehyde is obtained as follows:[409] Isobutyl alcohol (100 g) and water (750 ml) are heated to 70–80° in a flask fitted with a dropping funnel and a descending condenser while carbon dioxide is led through and a solution of potassium dichromate (135 g) in water (675 ml) and concentrated sulfuric acid (50 g) is dropped in. The aldehyde is separated from the distillate as bisulfite compound by adding sodium hydrogen sulfite; this compound is collected and reconverted into aldehyde by admixture with an excess of sodium carbonate solution and distillation. The pure aldehyde boils at 61°.

Details for the preparation of propionaldehyde and propargylaldehyde from the corresponding alcohols will be found in *Organic Syntheses*.[410]

N.B.: Propargylaldehyde attacks the mucous membranes of the eyes and nose. It can also be prepared by oxidation of propargyl alcohol with active manganese dioxide.[10]

An interesting variation of the chromic acid oxidation of alcohols to aldehydes was discovered by Oppenauer and Oberrauch.[411] When dissolved in *tert*-butyl alcohol and an organic solvent, alcohols are dehydrogenated to aldehydes by *tert*-butyl chromate in 90% yield. Experimental details are given in Houben-Weyl's reference work.[1n]

Benzaldehydes can be prepared in good yield from benzyl alcohols by means of various oxidants, including dinitrogen tetroxide (for its preparation see Park and Partington[412]) in chloroform or carbon tetrachloride,[413] concentrated nitric acid,[414a] aqueous hypochlorite,[414b] or cerium(IV) ammonium nitrate in 50% acetic acid.[415]

m-Nitrobenzenesulfonic acid is often suitable as dehydrogenating agent, particularly for oxidation of water-soluble hydroxybenzyl alcohols.[416]

For dehydrogenation of valuable alcohols it is often advantageous to use the Meerwein–Ponndorf–Verley–Oppenhauer reaction (cf. page 329). The

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[409] A. Lipp, *Ann. Chem.*, **205**, 2 (1880); cf. A. Pfeiffer, *Ber. Deut. Chem. Ges.*, **5**, 699 (1872).

[410] C. D. Hurd and R. N. Meinert, *Org. Syn.*, Coll. Vol. II, 541 (1943); I. C. Sauer, *Org. Syn.*, **36**, 66 (1956).

[411] R. V. Oppenauer and H. Oberrauch, *An. Asoc. Quim. Argent.*, **37**, 246 (1949).

[412] J. R. Park and J. R. Partington, *J. Chem. Soc.*, **125**, 74 (1924).

[413] B. O. Field and J. Grundy, *J. Chem. Soc.*, **1955**, 1110.

[414] (a) B. Helferich, R. Streeck, and E. Günther, *J. Prakt. Chem.*, [ii], **151**, 251 (1948); (b) C. Y. Meyers, *J. Org. Chem.*, **26**, 1046 (1961).

[415] W. S. Trahanovsky and L. B. Young, *J. Chem. Soc.*, **1965**, 5777.

[416] F. Hanns, *J. Prakt. Chem.*, [ii], **158**, 254 (1941).

following equilibria are set up when aldehydes or ketones react with alkoxides of primary alcohols:

$$RCH_2Oal + R'CHO \rightleftarrows RCHO + R'CH_2Oal$$

or

$$RCH_2Oal + R'COR'' \rightleftarrows RCHO + R'R''CHOal$$

$$(al = 1/3\ Al)$$

This method has proved of special value in preparation of terpene aldehydes. To shift the equilibrium to the side of the desired carbonyl compound (Oppenhauer), the concentration of the hydrogen-acceptor may be raised or its boiling point may be such that the aldehyde formed distils out of the mixture.

When α,β-unsaturated alcohols, which react at relatively low temperatures, are used it is advisable to use a high concentration of hydrogen-acceptor. Cinnamaldehyde has proved particularly valuable as hydrogen-acceptor in the preparation of aliphatic aldehydes, and anisaldehyde in preparation of alicyclic aldehydes. The alcohol to be oxidized is first converted into alkoxide by the calculated amount of aluminum triisopropoxide and is then brought into redox equilibrium with 120 – 200% of the higher-boiling aldehyde.

Djerassi has reviewed this reaction,[417] and a critical evaluation of it has been provided by Lauchenauer and Schinz.[1p], [418] The latter authors give the following prescription for preparation of **α-cyclocitral** from α-cyclogeraniol:

α-Cyclogeraniol (3.75 g) is placed in a three-necked flask fitted with a capillary tube, a dropping funnel, and a column 10 cm in length, it is then treated at 70–100° (bath)/12 mm with the theoretical amount (1.66 g) of aluminum triisopropoxide. Conversion is complete in about 45 min. Then 155% (5.1 g) of *p*-anisaldehyde is added all at once and the mixture is heated further at 12 mm so that the aldehyde slowly distils out of it. The fractions obtained are purified by repeated distillation. The yield is 66%, and the b.p. 75°/12 mm.

A further method for preparation of aldehydes consists of the action of *N*-bromosuccinimide (see page 329) on primary alcohols, which proceeds smoothly when the components are boiled for a short time in an organic solvent. Blair *et al.* have converted 4,5-dimethoxy-1,2-benzenedimethanol into 4,5-dimethoxyphthaldialdehyde.[419] Filler[420] has reviewed the oxidation of primary and secondary alcohols by *N*-halo imides (cf. page 330).

Active manganese dioxide gives high yields of aldehydes and ketones by oxidation, not only of allylic alcohols such as primary and secondary benzyl alcohols (see page 328), but also of saturated primary and secondary alcohols provided that pure solvents and sufficient of the reagent are used.[421] The nature of the solvent has a considerable effect. Butanal is formed in 70% yield when a solution of 1-butanol in benzene is passed through a column filled with MnO_2; if the components are stirred together the aldehyde formed is rapidly further oxidized.

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[417] C. Djerassi, *Org. Reactions*, **6**, 207 (1951).

[418] A. Lauchenauer and H. Schinz, *Helv. Chim. Acta*, **32**, 1265 (1949).

[419] J. Blair, W. R. Logan, and G. T. Newbold, *J. Chem. Soc.*, **1956**, 2443.

[420] R. Filler, *Chem. Rev.*, **63**, 21 (1963).

[421] I. T. Harrison, *Proc. Chem. Soc.*, **1964**, 110.

Imidazole-2-carbaldehyde is obtained in 70% yield from imidazole-2-methanol and the six-fold amount of activated manganese dioxide-B in anhydrous ether, acetone, or CCl_4 at 20°.[422]

Oxidation of organic compounds by active MnO_2 has been reviewed by Korshunov *et al.*[423]

Primary and secondary alcohols are converted into carbonyl compounds in good yield by lead tetraacetate in pyridine.[424] The reaction requires 10 – 20 hours at 20° and proceeds no further than the aldehyde or ketone stage; about 5% of acetate is formed as by-product, and 5–20% of the alcohol remains unchanged.

General procedure: The alcohol (0.02 mole), dissolved in pyridine (100 ml), is stirred at room temperature whilst being treated with an equivalent amount of powdered lead tetraacetate. The solution at once becomes deep red; after about 30 min it becomes homogeneous; it is stirred until, after several hours, it has become pale yellow, signalling that all the lead tetraacetate has been reduced. The lead(II) acetate formed is precipitated on cooling and is filtered off. The filtrate is worked up according to the physical properties of the aldehyde formed. Thus are obtained, for instance (yields in parentheses) butanal (70%), benzaldehyde (80%), furaldehyde (70%), benzophenone (80%), and 2,5-hexanedione (89%).

A new selective method of oxidizing alcohols was found by Pfitzner and Moffat.[425] Treating primary or secondary alcohols with 2–5 moles of dicyclohexycarbodiimide (or related compounds such as diisopropylcarbodiimide) in anhydrous dimethyl sulfoxide containing 0.1–2 moles of H_3PO_4 leads to aldehydes or ketones. The phosphoric acid can be replaced by pyridinium phosphite, cyanoacetate, hydrochloride, sulfate, or even phosphate; the dimethyl sulfoxide may be diluted with 9 times its volume of an inert solvent. The reaction is carried out at 20° and sometimes gives superlative yields; it is recommended particularly for steroid chemistry: testosterone gives, *e.g.*, 92% of 4-androstene-3,17-dione by this method.

If a stream of air is passed through the solution the above oxidation occurs even in absence of the carbodiimide.[426]

Heyns and Blazejewicz[427] studied the oxidation of alcohols, in water or organic solvents, by oxygen at platinum catalysts under mild conditions. Primary alcohols gave aldehydes or carboxylic acids according to the reaction conditions; secondary alcohols gave ketones. This method is especially suitable for preparation of long-chain aldehydes; double bonds are not attacked.

The reaction is preferably carried out in a Theilacker hydrogenation apparatus arranged for heating, with water, aqueous acetone, petrol, or heptene as solvent. Only the lower primary alcohols, isopropyl alcohol, and 1,2-ethanediol can be thus oxidized in water; conditions are: Pt–charcoal catalyst (10% of Pt), 10–30 h, 20° to 100°, 2.5 mmole in 25 ml of solvent with 0.3 g of catalyst. The reaction is strongly pH-dependent.

In organic solvents the Adams–Shriner pure platinum dioxide[428] is more active than Pt–charcoal. With this catalyst the reaction must be effected in

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[422] H. Schubert and W.-D. Rudorf, *Angew. Chem.*, **78**, 715 (1966).

[423] S. P. Korshunov and L. I. Vereshchagin, *Usp. Khim.*, **35**, 2255 (1966); *Chem. Abstr.*, **66**, 54,653 (1967).

[424] R. E. Partch, *Tetrahedron Letters*, **1964**, 3071.

[425] K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, **85**, 3027 (1963).

[426] V. J. Traynelis and W. H. Hergenrother, *J. Amer. Chem. Soc.*, **86**, 298 (1964).

[427] K. Heyns and L. Blazejewicz, *Tetrahedron*, **9**, 67 (1960).

[428] R. Adams and R. L. Shriner, *J. Amer. Chem. Soc.*, **46**, 1683 (1924).

dilute solutions, so that the water formed by the oxidation can be taken up by the solvent. Dodecyl alcohol in heptane is oxidized to dodecanal in 15 min; if the reaction is continued for 2 hours dodecanoic acid is formed quantitatively.

Catalytic dehydrogenation of alcohols is best effected in the vapor phase since the equilibrium:

$$RCH_2OH \longrightarrow RCHO + H_2$$

is shifted strongly to the right at elevated temperatures. Dehydrogenation of unsaturated alcohols requires the presence of a hydrogen acceptor, because otherwise the aldehyde formed can be re-hydrogenated; in such cases air is passed through the apparatus during the dehydrogenation; but no hydrogen-acceptor is necessary with saturated alcohols. It is often advisable to conduct the dehydrogenation of unsaturated or higher-boiling alcohols under reduced pressure. Reaction temperatures are between 300° and 400°. Yields of over 80% can be obtained in the dehydrogenation of saturated aliphatic alcohols containing up to nine carbon atoms. The best catalysts are copper, silver, and zinc compounds (for their preparation see Houben–Weyl's reference book[1m].

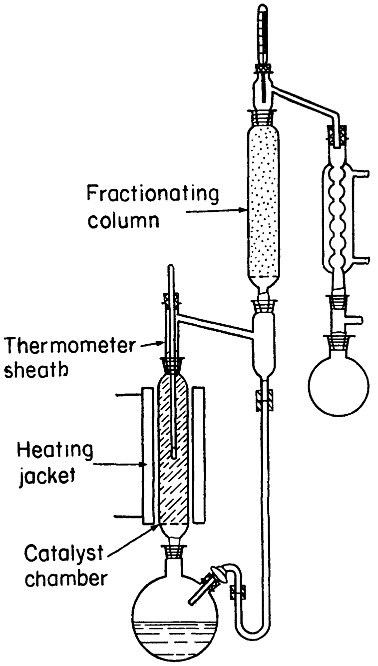

Figure 4. Apparatus for catalytic dehydrogenation.

A dehydrogenation apparatus is illustrated in Figure 4. It is suitable for use in the laboratory with high-boiling alcohols and for work in a vacuum. It consists of a boiling flask from which the alcohol vapors pass to the catalyst space, where a thermometer is used to monitor the temperature. Above this is a fractionating apparatus, in which the aldehyde product is separated from unchanged alcohol; the latter is returned to the boiling flask, and the former passes to a condenser and thence to a receiver; the hydrogen escapes. Detailed dimensions are suited to the conditions. For instance, if the catalyst tube is 1 m long its diameter is 25–30 mm. The copper catalyst may be prepared, *e.g.*, from a small roll of copper-wire net filled with a copper oxide paste to which 1% of silver oxide has been added. This catalyst is placed in position in the apparatus, dried in a stream of hydrogen while the temperature is raised slowly, and the oxide is then reduced, also slowly, at 300°, the time required being 8–10 h. It is then allowed to cool without exposure to the air. Atmospheric pressure can be used if the boiling point of the aldehyde does not exceed 200°; if it does, diminished pressure must be used. The catalyst space must be heated to a temperature slightly higher than the boiling point of the aldehyde product.

Geraniol is converted into α- and β-citral at atmospheric pressure; phenethyl alcohol gives phenylacetaldehyde; cinnamaldehyde is obtained from cinnamyl alcohol in good yield by use of a silver catalyst at 200°/20 mm.[429] Bremner *et al.*[430] describe a laboratory method for oxidation of tetrahydrofurfuryl alcohol by air on silver wool.

The following is a generally applicable procedure, applied here to the conversion of 1-nonanol into **nonanal**:[431]

The success of the operation depends on careful preparation of the dehydrogenating catalyst. An aqueous solution of pure copper nitrate is treated with the calculated amount of pure sodium hydroxide solution, and the precipitated copper(II) hydroxide is washed by decantation with lukewarm water until completely neutral. The excess of water is then sucked off on a filter without allowing the hydroxide to become dry. This material may be stored as a paste in closed vessels. The copper hydroxide paste is spread in a thin layer on pieces of copper gauze 10 × 5 cm, which are then formed into a roll 10 cm long and placed in a copper tube 80 cm long into which thirty such rolls can be packed. The copper gauze should not have too fine a mesh, otherwise the catalytic effect is less. For reduction of the copper hydroxide the whole system is first washed through with hydrogen that has been washed with permanganate and dried by sulfuric acid. The catalyst tube is then heated electrically to 300°, whereby the hydroxide is converted into spongy metallic copper; this reduction requires 8 h; the product is allowed to cool in a stream of hydrogen unless it is to be used immediately. If the material is to be kept overnight a constant slow stream of hydrogen is led through the apparatus. Before the dehydrogenation is begun the temperature is raised again to 300° for 0.5 h and the whole is washed through with hydrogen. Then 1-nonanol is brought into the boiling flask, the hydrogen stream is throttled back, the apparatus is evacuated to 3 to 5 mm, the temperature in the catalyst space is adjusted to 240°, and the alcohol is brought to the boiling point. The receiver is arranged for collection of various fractions in a vacuum; so, if the rate of distillation becomes temporarily too fast so that unchanged nonanol passes over (recognized by a rise in temperature at the column head), then that portion of the distillate is collected separately.

When the operation is finished, the apparatus is filled with hydrogen and allowed to cool without entry of air; the catalyst then retains its activity. The yield of nonanal amounts to 90%, the b.p. being 78°/3 mm.

More than monohydric alcohols can be only incompletely dehydrogenated, and carbohydrate alcohols do not survive attempted dehydrogenation.

High-boiling alcohols are sometimes better dehydrogenated in the liquid phase in presence of a hydrogen-acceptor such as copper and nitrobenzene or *m*-dinitrobenzene. The preparation of *o*-chlorobenzaldehyde in 86% yield from 2-chlorobenzyl alcohol at 205–210° may be cited as example.[432]

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[429] C. Moureu and G. Mignonac, *C. R. Hebd. Séances Acad. Sci.*, **171**, 652 (1920)

[430] I. G. M. Bremner and co-workers, *J. Chem. Soc.*, **1949**, Suppl., 25.

[431] A. Lewisohn, *Perfum. Essent. Oil Rec.*, **15**, 13 (1924).

[432] F. Zetsche and P. Zala, *Helv. Chim. Acta*, **9**, 288 (1926).

b. Ketones

Dehydrogenation of secondary alcohols to ketones is carried out analogously to the aldehyde syntheses described above; the same oxidants and procedures are used. The reactions are in general smoother, since the ketones formed are appreciably more stable than the aldehydes towards an excess of oxidant.

Chromic–sulfuric acid is used in aqueous or acetic acid solution between 20° and 40°, rarely at higher temperatures (50–80°); vigorous stirring is necessary with sparingly soluble alcohols. Yields of ketone lie between 60% and 80%. The preparation of **menthone** from menthol[433] provides a simple example.

Recrystallized menthol (45 g) is added to a solution of potassium dichromate (60 g, 1 equivalent) in concentrated sulfuric acid (50 g) and water (300 ml) at 30°; the mixture is stirred, heat being evolved as the reaction proceeds. A dark brown mass is formed which liquifies above 53°; if within 30 min the temperature does not reach 55°, or exceeds 55°, the mixture is respectively warmed or cooled. After cooling, the oily layer is taken up in ether, washed with 5% sodium carbonate solution, dried, and evaporated. Distillation in a vacuum affords menthone (83–85%) at 98–100°/18 mm.

Working in acetic acid has two disadvantages, namely, that under these conditions acid-sensitive compounds such as ketals may not be oxidized, and that activated methylene groups next to double bonds are often thus converted into keto groups. Both disadvantages are overcome by using as solvent dimethylformamide containing a few drops of concentrated sulfuric acid,[434] a method that is recommended particularly for oxidation of OH groups in the steroid series.

Acetylenic alcohols can be converted into ketones in good yield and without side reactions by means of chromic–sulfuric acid in acetone; for example, 3-pentyn-2-ol gives 3-pentyn-2-one smoothly at 5–10°.[435] Mild oxidation of various steroids and terpenes has been achieved by this procedure.[436]

A simple and convenient method of obtaining very pure ketones from secondary alcohols has been described by Brown and Garg.[437]

According to them, the theoretical amount of CrO_3 is added within 15 min to a vigorously stirred solution of the alcohol in ether at 25–30°. After 2 h the ethereal layer is separated and the ketone is isolated. Yields lie between 85% and 97%, an example being conversion of menthol into menthone.

Potassium permanganate may replace the dichromate but generally this has no advantage. 2,2,4,4-Tetramethyl-3-pentanol can be oxidized to the ketone by concentrated nitric acid.[438]

According to Grundy the best yields of alkyl aryl ketones from secondary alcohols are obtained by means of dinitrogen tetroxide[439] (cf. page 322): the alcohol is dissolved in cold, dry chloroform, an excess of dinitrogen tetroxide is added, then after a rather long reaction time at room temperature the solution is washed with sodium carbonate solution and water, the solvent is removed together with the nitrogen oxides, and the ketone is purified by distillation.

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[433] E. Beckmann, *Ann. Chem.*, **250**, 325 (1889).

[434] G. Snatzke, *Chem. Ber.*, **94**, 729 (1961).

[435] Cf. E. A. Braude and co-workers, *J. Chem. Soc.*, **1940**, 612.

[436] K. Bowden and co-workers, *J. Chem. Soc.*, **1946**, 39.

[437] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

[438] P. D. Bartlett and A. Schneider, *J. Amer. Chem. Soc.*, **67**, 143 (1945).

[439] J. Grundy, *J. Chem. Soc.*, **1957**, 5087.

By earlier procedures benzoins were converted into diketones by nitric acid, but this dehydrogenation is better effected by means of copper compounds. For instance, benzoin itself gives 86% of benzil on treatment with copper sulfate in pyridine.[440] **Cholestenone** has been prepared as follows by Diels and Abderhalden:[441]

Cholesterol (100 g) is heated to 300°; copper oxide, not too finely powdered (20 g), is added in portions and the bath temperature is kept at 300–310° for 15 min. The mixture is left to cool completely and then dissolved in warm methanol (1 l), filtered, and stirred at 0° whilst seeding with crystalline cholestenone. When no more crystals separate, the methanol is allowed to evaporate in a vacuum above sulfuric acid; this gives 60 g of cholestenone.

Highly recommended is oxidation by means of catalytic amounts of copper acetate, which is continuously regenerated in the presence of ammonium nitrate. The nitrate then passes into ammonium nitrite, which slowly decomposes into nitrogen and water.[442] Numerous substituted benzoins have been converted in diketones in this way, *e.g.*, 2-hydroxycyclodecanone into 1,2-cyclodecanedione.[443] Barakat and his co-workers[444] have established that benzoins are converted into benzils by treatment with precipitated manganese dioxide, and they and Korshunov *et al.*[423] have given further details for the action of MnO_2 on readily oxidizable organic compounds in water or organic solvents. The oxidation of primary and secondary alcohols by MnO_2 can be controlled by distilling off and measuring the amount of water formed, and this process can be adapted for preparative purposes.[445] β-Substituted benzyl alcohols react particularly rapidly. The reaction probably proceeds by way of radicals.

Ethylenic and acetylenic alcohols can be converted into ketones or aldehydes by a mild reaction at room temperature, which consists of shaking them in an inert solvent such as petrol, chloroform, benzene, or acetone with a synthetic $MnO_2 \cdot H_2O$.[446] The reaction is highly recommended for oxidation of hydroxyl groups in sensitive compounds; 1-phenyl-2-propyn-1-one is thus obtained in 67.6% yield from 1-phenyl-2-propyn-1-ol.[447]

When 5α-androstan-17β-ol (100 mg) is stirred with active MnO_2 (2 g) in hexane or acetonitrile (20 ml) for 20 h, 99% pure 5α-androstan-17-one is obtained.[420]

Applications of this process, reaction conditions, and preparation of the active MnO_2 have been summarized by Evans[448] (for oxidation of primary alcohols see above).

In some cases secondary alcohols can be converted into keto compounds by lead tetraacetate, *e.g.*, α-hydroxy carboxylic esters into α-keto carboxylic esters;[449] this reaction with lead tetraacetate is advantageously effected in

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[440] H. T. Clarke and E. E. Dreger, *Org. Syn.*, **6**, 6 (1926).

[441] O. Diels and co-workers, *Ann. Chem.*, **459**, 21 (1927).

[442] M. Weiss and M. Appel, *J. Amer. Chem. Soc.*, **70**, 3666 (1948).

[443] A. T. Blomquist and A. Goldstein, *Org. Syn.*, **36**, 77 (1956).

[444] M. Z. Barakat and co-workers, *J. Chem. Soc.*, **1956**, 4685.

[445] E. F. Pratt and J. F. van de Castle, *J. Org. Chem.*, **26**, 2973 (1961).

[446] J. Attenburrow and co-workers, *J. Chem. Soc.*, **1952**, 1094.

[447] I. Iwai, Y. Okajima, and T. Konotsune, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **78**, 505 (1958); *Chem. Abstr.*, **52**, 17200 (1958).

[448] R. M. Evans, *Quart. Rev.*, **13**, 61 (1959).

[449] V. Prelog and H. L. Meier, *Helv. Chim. Acta*, **36**, 322 (1953).

pyridine[450] (see page 324). γ-Keto acids are relatively simply accessible by oxidation of γ-lactones by bromine in presence of $Mg(OH)_2$.[417]

A mild method, much favored in the steroid series, for preparation of ketones is the Oppenauer dehydrogenation of secondary alcohols under catalysis by metal alkoxides (see page 322):

$$\mathrm{R^1R^2CHOAl + R^3R^4C{=}O \rightleftharpoons R^1R^2C{=}O + R^3R^4CHOAl}$$

This has been reviewed by several authors.[417, 452] The hydrogen acceptor is used in great excess (40–80-fold) in order to shift the equilibrium towards the desired carbonyl compound. Acetone, 2-butanone, and cyclohexanone have proved their utility as hydrogen-acceptors and can be recovered from the reaction mixture after the reaction, together with any condensation products, usually quite readily by steam-distillation. Benzil is a very useful hydrogen-acceptor for ketones that must be distilled out of the reaction mixture below 100°. Benzoquinone and fluorenone[453] are occasionally recommended as hydrogen-acceptors.

The reaction time and concentrations used depend on the reactants. Reaction is usually effected at 60°. Formation of condensation products from the ketones is largely repressed by working in inert solvents such as benzene, dioxan, and toluene. Aluminum isobutoxide, as well as the isopropoxide, has proved its value as metal alkoxide; usually it is added to the reaction mixture in the proportion of 0.5 mole per mole of alcohol. Compounds containing nitrogen and halogen can also be oxidized by the Oppenauer method. Dehydrogenation of cholesterol to **cholestenone** will be described as an example:[454]

A solution of cholesterol (10 g) in hot acetone (120 g) is treated with a solution of crystalline aluminum *tert*-butoxide (12 g) in benzene (300 ml), and the whole is boiled under reflux for 10 h. The mixture is then thoroughly extracted with dilute sulfuric acid for removal of the aluminum, and the benzene layer is washed, dried, and evaporated, giving ketone of m.p. 79–80° (8.9 g).

Recommended reagents for mild dehydrogenation of primary and secondary alcohols are *N*-bromoacetamide[455] and *N*-bromosuccinimide,[456] also the *N*-halo imides *N*-bromophthalimide, *N*-chlorosuccinimide, isocyanuric bromide and chloride, and *N*-bromohexanolactam. These differ in oxidizing activity: under comparable conditions *N*-chlorosuccinimide and isocyanuric chloride have greater efficiency than isocyanuric bromide but less than *N*-bromoacetamide. Because of the mildness of the conditions required they find particular use in stereoselective oxidation of steroid alcohols.[455]

11α-Hydroxy-5β-pregnane-3,20-dione:[457] 3α,11α-Dihydroxy-5β-pregnan-20-one (0.002 mole) in aqueous acetone was treated with *N*-bromoacetamide (0.015 mole), kept in

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[450] R. E. Partch, *Tetrahedron Letters*, **1964**, 3071.

[451] R. R. Russel and C. A. Vandewerf, *J. Amer. Chem. Soc.*, **69**, 12 (1947).

[452] T. Bersin, in "Neuere Methoden der präparativen Chemie," 3rd ed, Verlag Chemie, Weinheim, 1949, p. 137.

[453] E. W. Warnhoff and P. Reynolds-Warnhoff, *J. Org. Chem.*, **28**, 1431 (1963).

[454] T. Bersin, in "Neuere Methoden der präparativen organischen Chemie," 3rd ed, Verlag Chemie, Weinheim, 1949, p. 147; cf. R. V. Oppenauer, *Org. Syn.*, **21**, 18 (1941).

[455] M. D. Soffer and M. A. Jevnik, *J. Amer. Chem. Soc.*, **77**, 1005 (1955); E. P. Oliveto and co-workers, *J. Amer. Chem. Soc.*, **78**, 1414 (1956).

[456] L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 354 (1959).

[457] E. P. Oliveto, H. L. Herzog, and E. B. Hershberg, *J. Amer. Chem. Soc.*, **75**, 1505 (1953).

the dark for 3 h between 5° and 10°, and then poured into 5% sodium sulfite solution. Extraction with methylene chloride, drying and evaporation of the extract, and crystallization of the residue gave the dione.

Dehydrogenation by *N*-halo imides has been reviewed by Filler.[420] Mild dehydrogenation of various alcohols can be achieved, not merely by *N*h-alo imides, but also by diethyl azodicarboxylate $C_2H_5O_2CN{:}NCO_2C_2H_5$ [458] and 4-phenyl-1,2,4-triazole-3,5-dione;[459] equivalent amounts of the triazole and alcohol are used in benzene at room temperature, reaction being complete within a few hours and yields being good; examples are 90% of benzophenone from benzhydrol, and 84% of cyclohexanone from cyclohexanol.

Heyns *et al.*[427] have worked out a method for oxidation of cyclic alcohols to ketones (*e.g.*, cyclohexanol to cyclohexanone) by means of oxygen in the presence of platinum (see page 324); with bicyclic systems composed of two fused five-membered rings, only *endo*-hydroxyl groups are attacked.[460]

Polyols of six-membered ring systems, including those of the cyclitol and pentopyranoside series, are oxidized only at axial hydroxyl groups, reaction ceasing at the monoketone stage even if other axial hydroxyl groups are present.[461] For example, benzyl β-D-arabopyranoside gives 29% of benzyl β-D-*threo*-pentopyran-4-uloside (as monohydrate).

Among other details given[427] are the conditions under which this reaction converts primary alcohols into (a) aldehydes or (b) carboxylic acids, and secondary alcohols into ketones, with special recommendation of the process for preparation of long-chain aldehydes from the corresponding alcohols.

For catalytic dehydrogenation of secondary alcohols in the vapor phase the same catalysts are successful as for primary alcohols, but here the reaction is even easier because ketones form fewer by-products. Hurd, Greengard, and Roe[462] obtained 60% of cyclohexanone from cyclohexanol by using Adkin's copper chromite catalyst. Also secondary alcohols can be dehydrogenated in the liquid phase, for which, *e.g.*, Raney nickel was used as catalyst; in such cases it is useful to add a hydrogen acceptor such as cyclohexanone, reaction being effected by short heating of the alcohol, solvent, catalyst, and hydrogen acceptor.[463]

Phenols can be oxidized to quinones by a variety of oxidants: for instance, hydroquinone is converted into *p*-benzoquinone by chromic–sulfuric acid[464] or by sodium chlorate in the presence of V_2O_5,[465] yields exceeding 90% in both cases. Substituted hydroquinones have been oxidized to quinones by iron(III) salts[466] and by Ag_2O.[467, 468] The reaction is effected in media such

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[458] F. Yoneda, K. Suzuki, and Y. Nitta, *J. Amer. Chem. Soc.*, **88**, 2328 (1966).

[459] R. C. Cookson, I. D. R. Stevens, and C. T. Watts, *Chem. Commun.*, **1966**, 744.

[460] K. Heyns, W.-P. Trautwein, and H. Paulsen, *Chem. Ber.*, **96**, 3195 (1963).

[461] K. Heyns, J. Lenz, and H. Paulsen, *Chem. Ber.*, **95**, 2964 (1962).

[462] C. D. Hurd, H. Greengard, and A. S. Roe, *J. Amer. Chem. Soc.*, **61**, 3359 (1939).

[463] E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, **13**, 455 (1948); cf. Brit. Pat. 767,093 (*Chem. Abstr.*, **51**, 13928 (1957); *J. Appl. Chem. (London)*, **8**, 615 (1958).

[464] E. B. Vliet, *Org. Syn.*, **2**, 85 (1922).

[465] H. W. Underwood and W. L. Walsh, *Org. Syn.*, Coll. Vol. II, 553 (1943).

[466] L. I. Smith and P. F. Wiley, *J. Amer. Chem. Soc.*, **68**, 889 (1946).

[467] J. W. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, **1956**, 3820.

[468] M. F. Ansell and co-workers, *J. Chem. Soc.*, **1963**, 3028.

as alcohol or acetic acid. Iron(III) salts are preferred for oxidation of *p*-aminophenols, yields exceeding 60%.

Dehydrogenation of pyrocatechol by silver oxide gives *o*-benzoquinone.[469] For preparation of amino-*o*-benzoquinones see Horner and Lang.[470] Hydroquinones are also dehydrogenated with success by lead tetraacetate.[222] Further, 2,3-dichloro-5,6-dicyano-1,2-benzoquinone is obtained from the hydroquinone in 83% yield when a solution of the latter in 5% ethanolic hydrogen chloride is shaken with a mixture of PbO_2 and benzene.[471]

Singly or doubly substituted *p*-benzoquinones can also be prepared by oxidizing the hydroquinone with concentrated nitric acid in ether at −20° to 0°, yields by this process being higher than 80%.[468]

2-Methyl-1,4-naphthoquinone was obtained in 93% yield from 2-methyl-1,2-naphthalenediol by oxidation with NaOBr in aqueous-alcoholic sulfuric acid at room temperature.[472]

The various methods of preparing benzoquinones by oxidation have been reviewed by Cason.[473]

c. Oxidation of polyhydric alcohols

Fenton and Jackson[474] devised a method whereby 1,2-glycols are converted into α-hydroxy aldehydes by 3–6% hydrogen peroxide and iron(II) salts at room temperature. Simple primary and secondary alcohols are not attacked under these conditions. The process gives only moderate yields.

For the preparation of **mannose**, mannitol (50 g) was dissolved in a little water and treated with ferrous sulfate (12.5 g) in aqueous solution and then with 5–6% hydrogen peroxide (150 ml). At the end of the reaction the mixture was treated with an excess of freshly precipitated barium carbonate, filtered, much concentrated at 50°/30 mm, and finally evaporated to a syrup in a vacuum. The syrup was treated with 10 times its volume of anhydrous ethanol, then filtered, and an excess of ether was added. The resulting colorless flocks collected to form a pale yellow syrup, which partly crystallized when rubbed with alcohol and ether. The yield was not given; the identity of the product with mannose was proved by conversion into the phenylhydrazone.

The literature of this method has been reviewed by Criegee.[475]

Fischer and Hirschberger[476] prepared mannose by oxidation of mannitol with nitric acid.

6. Oxidation of alcohols and aldehydes to carboxylic acids

Almost all the oxidants and processes described in the preceding Sections can be applied also to conversion of alcohols and aldehydes into carboxylic acids. When acidic reagents are used with alcohols, esters are formed as by-

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[469] R. Wilstätter and A. Pfannenstiel, *Ber. Deut. Chem. Ges.*, **37**, 4744 (1904).

[470] L. Horner and H. Lang, *Chem. Ber.*, **89**, 2768 (1956).

[471] P. W. D. Mitchel, *Can. J. Chem.*, **41**, 550 (1963).

[472] V. A. Zagorevskiĭ and D. A. Zykov, *Zh. Priklad. Khim.*, **32**, 2815 (1959); *Chem. Abstr.*, **54**, 9818 (1960).

[473] J. Cason, *Org. Reactions*, **4**, 305 (1948).

[474] H. J. H. Fenton and H. Jackson, *J. Chem. Soc.*, **75**, 1 (1899).

[475] R. Criegee, "Handbuch der Katalyse," Springer-Verlag, Vienna, 1943, Vol. 7, Part 1, p. 590.

[476] E. Fischer and J. Hirshberger, *Ber. Deut. Chem. Ges.*, **22**, 365 (1889).

products so that occasionally oxidation by alkaline permanganate is to be preferred; this reaction must be carried out at room temperature, with stirring and cooling; yields are never quantitative. Fournier,[477] for instance, described the oxidation of 1-propanol to propionic acid.

10-Fluoro-1-decanol is converted by chromium(VI) oxide in glacial acetic acid into the corresponding fluoro carboxylic acid in 93% yield.[478]

2-Furoic acid has been prepared as follows, in a modification of an older process:[479]

2-Furaldehyde (19 g) is dissolved in pyridine (50 ml) and cooled in ice–salt. A solution of potassium permanganate (21 g) in pyridine (280 ml) and water (120 ml) is then added with rapid stirring, at such a rate that the temperature does not rise above −3°. The mixture is stirred for 30 min after the addition, then filtered from the manganese dioxide formed, and the latter is washed with a little pyridine. The solvent is distilled off from the filtrate in a vacuum, and the dry residue is acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the ether affords 2-furoic acid (19 g, 86%) as yellowish crystals.

2-Furaldehyde is oxidized to the acid also by oxygen in the presence of a Cu_2–Ag_2O catalyst in an alkaline medium, the yield being 86–90%.[480]

Preparation of carboxylic acids from primary alcohols in the presence of dehydrogenating catalysts at 120–150° is described by Russian authors.[481]

Aldehydes can usually be converted into carboxylic acids by hydrogen peroxide;[482] for instance, 2-furoic acid is obtained in 73% yield by keeping 2-furaldehyde (96 g) for 12 h in a mixture of 30% hydrogen peroxide (170 ml) and pyridine (50 ml), the temperature being kept at 60–70° for the first 2–3 h.[483] Peroxy acids can also be used to advantage for this oxidation.[484]

A reagent much to be recommended for converting aldehydes into acids is silver oxide. It is readily accessible, does not attack other oxidizable groups, and gives very pure acids. Asinger thus obtained **heptanoic acid** from heptanal and palmitic acid in 97.5% yield from hexadecanal.[485]

Heptanal (114 g) is added during 1 h with good stirring to a suspension of silver oxide (300 g) in 10% sodium hydroxide solution (500 ml) at 95°. After 6 hours' stirring at that temperature, the mixture is treated dropwise at 70° with concentrated nitric acid (600 g; d_4^{20} 1.40) and allowed to cool whilst stirring for 1 h. The heptanoic acid is taken up in pentane and can be separated from non-hydrolysable material as described by Spitz and Hönig.[486]

Smith and Holm[487] have reported the preparation of an unsaturated acid from an unsaturated aldehyde by use of hydrogen peroxide in the presence of selenium dioxide. 3-Chloropropionaldehyde is converted into 3-chloro-

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[477] H. Fournier. *C. R. Hebd. Séances Acad. Sci.*, **144**, 333 (1907).

[478] F. L. M. Pattison, I. B. Stothers, and R. G. Woolford, *J. Amer. Chem. Soc.*, **78**, 2256 (1956).

[479] J. Volhard, *Ann. Chem.*, **261**, 380 (1891).

[480] R. J. Harrison and M. Moyle, *Org. Syn.*, **36**, 36.

[481] V. I. Lyubomilov, A. I. Kutzenko, and R. A. Abramova, *Zh. Obshch. Khim.*, **27**, 2054 (1957); *Chem. Abstr.*, **52**, 6194 (1955).

[482] A. Dombrowsky, *Monatsh. Chem.*, **86**, 325 (1955).

[483] S. P. Korshunov and L. I. Vereshchagin, *Zh. Priklad. Khim.*, **36**, 1157 (1963); *Chem. Abstr.*, **59**, 9942 (1963).

[484] A. von Wacek and A. von Bézard, *Ber. Deut. Chem. Ges.*, **74**, 857 (1941).

[485] F. Asinger, *Ber. Deut. Chem. Ges.*, **75**, 658 (1942).

[486] Cf. H. P. Kaufmann, *Fette und Seifen*, **43**, 218 (1936).

[487] C. W. Smith and R. T. Holm, *J. Org. Chem.*, **22**, 746 (1957).

propionic acid in 81% yield by means of nitric acid.[488] The oxidation of aldehydes to acids in the gas phase has been studied by Foster and Keyes[489] using a platinum–silica gel catalyst.

Special methods are customary for oxidation of the aldehyde group in the sugar series, different methods being used for analytical and preparative purposes. Aldoses are advantageously converted into aldonic acids by an electrochemical method first described by Isbell and Frush.[490] Kiliani[491] later took up the Isbell process and re-worked it; he showed it to be exceedingly useful for pentoses as well as for hexoses. Here we reproduce Kiliani's directions for the preparation of D-**mannonic acid** from D-mannose.[491, 492]

A solution of D-mannose (100 g) in water (2 l) was treated with calcium bromide (17.7 g) and calcium carbonate (55 g) and electrolysed, with stirring, in a suitable cylinder. Carbon electrodes, of 12 mm diameter, were placed about 8 cm apart; the current density was 0.5 to 0.7 amp. After 50–55 hours the reducing power of the solution was negligible, so the solution was filtered, evaporated as far as possible, and left to solidify. The gelatinous mass was powdered and dried. The original papers should be consulted for preparation of crystalline calcium mannonate. To obtain the lactone of D-mannonic acid one part of the calcium salt is dissolved in 3 parts of water on the water-bath, an excess of oxalic acid is slowly added, the precipitated calcium oxalate is filtered off, and the filtrate is concentrated until its weight equals that of the calcium salt used; this material is then left to crystallize.

Aldoses can be converted into aldonic acids also by bromine in an aqueous medium.[493]

Use of oxygen in the presence of platinum-containing catalysts has achieved preparative importance through the investigations of Heyns and his co-workers. This method also can be applied to the preparation of aldonic acids from aldoses.[494] Pentoses are oxidized appreciably faster than hexoses; *e.g.*, under conditions where pentoses require only 45 min at 22°, D-glucose requires 5 hours. In the presence of platinum, oxygen attacks primary rather than secondary alcohol groups, whence an effective synthesis of uronic acids has been developed; the reducing group must, of course, be blocked, *e.g.*, by glycosidization.[495] A paper by Maurer and Drefahl[496] should be consulted for oxidation of terminal primary alcohol groups of carbohydrates by dinitrogen tetroxide.

α-Keto alcohols are very readily oxidized. The process still used today is that of Breuer and Zinke;[497] in this, the only useful process, copper(II) compounds are allowed to act on the alcohols in an aqueous medium: *e.g.*, treating dihydroxyacetone with copper(II) acetate in excess gives 87% of mesoxalic acid.[498]

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[488] C. Moureu and R. Chaud, *Org. Syn.*, **8**, 54 (1928).

[489] H. D. Foster and D. B. Keyes, *Ind. Eng. Chem.*, **29**, 1254 (1937).

[490] H. S. Isbell and H. L. Frush, *Bur. Stand. J. Res.*, **6**, 1145 (1931).

[491] H. Kiliani, *Ber. Deut. Chem. Ges.*, **66**, 117 (1933).

[492] Cf. K. Bernhauer and K. Irrgang, *Biochem. Z.*, **249**, 216 (1932).

[493] W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, **1949**, 1358.

[494] K. Heyns and co-workers, *Ann. Chem.*, **558**, 187, 192 (1947).

[495] K. Heyns and H. Paulsen, *Angew. Chem.*, **69**, 603 (1957).

[496] K. Maurer and G. Drefahl, *Ber. Deut. Chem. Ges.*, **80**, 94 (1947).

[497] A. Breuer and T. Zinke, *Ber. Deut. Chem. Ges.*, **16**, 636 (1880); *Ann. Chem.*, **216**, 313 (1883).

[498] W. E. Evans Jr., C. J. Carr, and J. C. Krantz Jr., *J. Amer. Chem. Soc.*, **60**, 1628 (1938).

7. Cannizzaro and Tishchenko reactions

Aldehydes that have no hydrogen on the α-carbon atom are converted by aqueous or alcoholic alkali into the corresponding alcohols and carboxylic acids:

$$2RCHO + H_2O \xrightarrow{HO^-} RCOOH + RCH_2OH$$

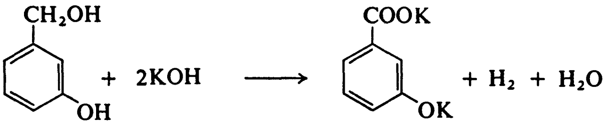
In general it is aldehydes of aromatic hydrocarbons and of heterocycles that can be subjected to this reaction, named after its discoverer the Cannizzaro reaction; but there a similar oxidation–reduction, brought about by an enzyme, plays an important part in biological events in the cell. In the laboratory the Cannizzaro reaction serves for preparation of both acids and alcohols, each normally in 50% yield. As example, the preparation of **2-furoic acid and furfuryl alcohol** from 2-furaldehyde is here recorded.[499]

Technical 2-furaldehyde (1 kg) in a 4-l vessel is cooled to 5–8° whilst being stirred and a solution of sodium hydroxide (275 g) in water (350 ml) is allowed to run in from a separatory funnel at a rate such that the temperature of the mixture does not exceed 20°. The whole is then stirred for a further hour, then sufficient water is added to dissolve the crystals of sodium furoate, and the solution is perfused with ether (1500–2000 ml) which removes most of the furfuryl alcohol.

The residual alkaline solution is acidified to Congo Red with 40% sulfuric acid (about 400 ml being needed). On cooling, a discolored mixture of 2-furoic acid and sodium hydrogen sulfate separates; this is filtered off, dissolved in boiling water (2300 ml), treated with animal charcoal (60 g) for ca. 45 min at the b.p., filtered, and cooled to below 16°. This gives 60 to 63% of 2-furoic acid that is pure enough for many further reactions. For purification it is sublimed in small amounts, best at ca. 2 mm, but for large amounts is distilled under reduced pressure; the m.p. is 133–134°.

Furfuryl alcohol is obtained from the ethereal extract by distilling it, first at atmospheric pressure until the temperature of the boiling liquid is 95°, then fractionally in a vacuum. This gives 61–63% (310–325 g) of furfuryl alcohol, b.p. 75–77°/15 mm. If this alcohol is to be stored it is stabilized with 1% of urea.

Nitro- and halo-benzoic acids are obtained from the corresponding aldehydes in 84–90% yield.[500] In a KOH melt at 190° *m*-hydroxybenzaldehyde gives *m*-hydroxybenzoic acid almost quantitatively since the intermediate benzyl alcohol reacts with the potassium hydroxide according to the equation:



When two different aldehydes are together treated with concentrated alkali this constitutes a crossed Cannizzaro reaction; it is much to be recommended for the preparation of primary alcohols by using formaldehyde as one of the reactants; formaldehyde is preferentially oxidized to the acid, and the higher aldehyde is thus preferentially reduced to the alcohol:

$$RCHO + CH_2O + HO^- \longrightarrow RCH_2OH + HCOO^-$$

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[499] W. C. Wilson, *Org. Syn.*, **6**, 44 (1926).

[500] G. Lock, *Ber. Deut. Chem. Ges.*, **63**, 855 (1930).

In this way alcohols can be obtained in excellent yield, rapidly, and without unusual apparatus or special reagents. A generally applicable and thoroughly worked out preparation of 4-methylbenzyl alcohol from *p*-tolualdehyde has been reported by Davidson and Weiss.[501] Similarly, warming 2-furaldehyde with an excess of formaldehyde and sodium hydroxide at 30° gives an excellent yield of furfuryl alcohol, which can be isolated by extraction with carbon tetrachloride.[502] Crossed Cannizzaro reactions of mono-, di-, and tri-substituted benzaldehydes with formaldehyde have been described by Misra and Srivastava.[503]

Preparative importance attaches to the crossed Cannizzaro reaction of formaldehyde with aldehydes that contain hydrogen on the α-carbon atom. These hydrogen atoms are replaced by hydroxymethyl groups, and the aldehyde groups are reduced to alcohols by the excess of formaldehyde. Aldehydes containing two α-hydrogen atoms give tris(hydroxymethyl)alkanes:[504]

$$RCH_2CHO + 2CH_2O \xrightarrow{HO^-} RC(CH_2OH)_2CHO$$

$$RC(CH_2OH)_2CHO + CH_2O \xrightarrow{HO^-} RC(CH_2OH)_3 + HCOO^-$$

Pentaerythritol, $C(CH_2OH)_4$, has been obtained from acetaldehyde in this way.[505]

The Cannizzaro reaction can be carried out with almost all disubstituted benzaldehydes. However, if both *ortho*-positions are occupied by negative substituents, as in 2,6-dinitrobenzaldehyde, the carbonyl group is eliminated.

The best yields in the Cannizzaro reaction are obtained by using 50% KOH or NaOH solution. However, only 15–35% concentrations of alkali may be used with nitrobenzaldehydes. Sparingly soluble aldehydes can be treated in 25% alcoholic potassium hydroxide. Thorough shaking is necessary when working with aqueous media. The crossed Cannizzaro reaction is carried out in methanolic solution. Some cooling must be applied if heat is evolved in the reaction; mild warming is permissible for sluggish reactions; 45° is often a favorable reaction temperature.

The Cannizzaro reaction has been reviewed by Geissman,[506] and studies of its reaction mechanism have been published by Kharasch and Snyder.[507]

Alkoxides can cause dimerization of aldehydes. Thus, according to observations by Tishchenko,[508] the catalytic action of aluminum or magnesium alkoxides provides a method of preparing esters whose alcoholic and acidic components have the same number of carbon atoms; the general scheme, according to a reaction:

$$2RCHO \longrightarrow RCOOCH_2R$$

can be exploited for preparative purposes. Esters of this type occur in Nature, *e.g.*, spermaceti, which is palmityl palmitate. This procedure is useful when

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[501] D. Davidson and M. Weiss, *Org. Syn.*, Coll. Vlo. II, 590 (1943).

[502] J. Issoire, Mém. Poudres, **42**, 333 (1960).

[503] G. S. Misra and S. B. Srivastava, *J. Indian Chem. Soc.*, **32**, 201 (1955); *J. Prakt. Chem.*, [iv], **6**, 170 (1958).

[504] M. G. Dupont, R. Dulou, and A. Duplessis-Kergomard, *Bull. Soc., Chim. France*, **1949**, 314.

[505] H. T. Clarke and R. Phillips, *Org. Syn.*, **4**, 53 (1925).

[506] T. A. Geissman, *Org. Reactions*, **2**, 94 (1944).

[507] M. S. Kharasch and H. Snyder, *J. Org. Chem.*, **14**, 819 (1949).

[508] V. Tishchenko, *J. Russ. Phys.-Chem. Ges.*, **38**, 355, 482 (1906).

the aldehyde in question is more accessible than the alcohol and the acid, as in the case of 2-furaldehyde. It requires very pure starting materials but can be effective also with aldehydes having an α-hydrogen atom.

Sodium alkoxides can be used with aromatic aldehydes, as was already discovered by Claisen.[509] For instance, benzyl benzoate is obtained in 90–93% yield from benzaldehyde in the presence of sodium benzyl oxide.[1n,510] However, aliphatic aldehydes undergo the aldol condensation under the influence of sodium alkoxides.

Child and Adkins[511] undertook intensive studies to elucidate the best reaction conditions. Catalytic amounts of alkoxide suffice, in contrast to the requirement of the Cannizzaro reaction for at least 1 equivalent of alkali. Under these conditions aliphatic aldehydes containing 2–8 carbon atoms give 69–100% yields of the corresponding esters. Dimerization of aldehydes under the influence of aluminum alkoxides is usually accompanied by formation of about 30% of by-products. Zinc alkoxides or halogen-containing aluminum alkoxides appear to be the best catalysts for the dimerization; they even induce conversion of acetaldehyde into ethyl acetate.[1n] A crossed Tishchenko reaction can be effected by magnesium alkoxides or by the complex $Mg[Al(OC_2H_5)_4]_2$;[512] here the aldol that is first formed reacts with the aldehyde to give an ester of a 1,3-diol:

$$RCH_2—CH(OH)—CHR—CH_2OCO—CH_2R$$

II. Replacement of halogen by oxygen

Halogen attached to an aliphatic chain is readily replaced by oxygen and this leads to alcohols, aldehydes or ketones, or carboxylic acids. The reactivity usually decreases in the order RI > RBr > RCl; replacement of fluorine by oxygen so far plays an insignificant part in preparative organic chemistry. Nucleophilic replacement of halogen by an OH group is usually accompanied by loss of hydrogen halide; it occurs either by an S_N2 mechanism (*e.g.*, CH_3Br) or by an S_N1 mechanism (*e.g.*, tertiary butyl bromide). When the hydrolysis is a reaction of the second order, the reactivity decreases in the order $R_2CHX > RCH_2X > CH_3X$.

The rate-determining step of S_N1 reactions is formation of a carbonium ion; this is independent of the hydroxyl ion concentration and is faster the higher the polarity of the solvent. In general, the allylic halogen of allyl halides, benzyl halides, and α-halo carbonyl compounds can be hydrolysed under mild conditions, since in these cases the carbonium ion formed is stabilized by mesomerism. In contrast, the reaction of vinyl halides or halobenzene derivatives is very sluggish owing to occurrence of a certain amount of overlap between a *p*-orbital of the halogen and the π-orbital of the neighboring carbon atom; thus preparation of aromatic hydroxy compounds from aryl halides requires energetic conditions and is usually restricted to industrial processes.

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[509] L. Claisen, *Ber. Deut. Chem. Ges.*, **20**, 646 (1887).

[510] O. Kamm and F. W. Kamm, *Org. Syn.*, **2**, 5 (1922).

[511] W. C. Child and H. Adkins, *J. Amer. Chem. Soc.*, **47**, 798 (1925).

[512] F. J. Villani and F. F. Nord, *J. Amer. Chem. Soc.*, **69**, 2605 (1947).

1. Replacement of halogen by the hydroxyl group

Hydrolysis of alkyl halides is carried out in practice by boiling them with aqueous alkali, with a suspension of alkaline-earth carbonates, or with a suspension of lead(II) oxide. A two-stage process is often used, in which the halide is converted by treatment with an alkali acetate into the ester which is then hydrolysed. This route is particularly useful for synthesis of 1,2-diols because hydrolysis of 1,2-dihalides usually gives poor yields owing to formation of by-products.

3-Chloro-1-cyclopentene is converted into 2-cyclopenten-1-ol by ice-cold sodium hydrogen carbonate solution.[513] If 1,3-dichloro-2-butene is treated with 4.2% sodium carbonate solution for 2 hours, the halogen attached to doubly bonded carbon is unaffected and 3-chloro-2-buten-1-ol is obtained in 63% yield.[514] Silver nitrate has also been used successfully for hydrolysis of alkyl halides.[515] In a few special cases hydrolysis of alkyl halides has been effected in an acidic medium; *e.g.*, 4-nitrotriphenylmethyl chloride affords 4-nitrotriphenylmethyl alcohol in glacial acetic acid containing perchloric acid;[516] also 4-chlorocarbostyril has been obtained by boiling 2,4-dichloroquinoline for 2 hours with 6N-hydrochloric acid and dioxan.[517] McCloskey and Coleman[518] have described the conversion of acetobromoglucose into β-D-glucose 2,3,4,6-tetraacetate by silver carbonate. As mentioned above, benzyl halides are particularly readily hydrolysed: according to Lauth and Grimaux it suffices to boil benzyl chloride with three times its weight of freshly precipitated lead dioxide and ten times its weight of water for 2 hours;[519] and Meunier boiled equimolar amounts of benzyl chloride and potassium carbonate in 8–10 parts of water until after several hours the oil swam on the surface, but he did not give the yield of benzyl alcohol.[520]

Hydrolysis of α-halo carbonyl compounds must be effected very cautiously since the resulting α-hydroxy carbonyl compounds are sensitive to alkali. An aqueous suspension of barium carbonate has been used for preparation of 2-hydroxy-3-phenylpropionaldehyde.[521] The preparation of α-hydroxy carboxylic acids is important; Witzemann[522] has given details for preparation of glycolic acid, and Bischoff and Walden[523] recorded that of **2-hydroxybutyric acid:**

2-Bromobutyric acid (100 g) was boiled for 5–6 h with an equivalent amount (83 g) of potassium carbonate in water (500 ml). The solution was then evaporated, the residue was treated with the calculated amount of hydrochloric acid, and the viscous solution was filtered from the precipitated mixture of potassium chloride and bromide and extracted with ether. Drying of the extract over sodium sulfate, removal of the ether, and several fractionations in a vacuum gave 2-hydroxybutyric acid, m.p. 42°, b.p. 140°/12 mm. The yields were not stated.

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[513] K. Alder and F. H. Flock, *Chem. Ber.*, **89**, 1735 (1956).

[514] L. F. Hatch and V. Chiola, *J. Amer. Chem. Soc.*, **73**, 361 (1951).

[515] H. Gilman, C. G. Brannen, and R. K. Ingham, *J. Amer. Chem. Soc.*, **78**, 1690 (1956).

[516] P. D. Bartlett and J. D. Cotmman Jr., *J. Amer. Chem. Soc.*, **72**, 3098 (1950).

[517] R. J. Rowlett Jr. and R. E. Lutz, *J. Amer. Chem. Soc.*, **68**, 1290 (1946).

[518] C. M. McCloskey and G. H. Coleman, *Org. Syn.*, Coll. Vol. III, 434 (1955).

[519] C. Lauth and E. Grimaux, *Ann. Chem.*, **143**, 81 (1867).

[520] J. Meunier, *Bull. Soc., Chim. France*, [ii], **38**, 159 (1882).

[521] S. Danilow and E. Venus-Danilowa, *Ber. Deut. Chem. Ges.*, **63**, 2769 (1930).

[522] E. J. Witzemann, *J. Amer. Chem. Soc.*, **39**, 109 (1917).

[523] C. Bischoff and P. Walden, *Ann. Chem.*, **279**, 102 (1894).

Loss of hydrogen halide may occur as a side reaction to hydrolysis of aliphatic halides, but this can often be prevented by working with freshly precipitated silver oxide, which reacts even in the cold. Olefin formation can, however, be avoided with certainty by hydrolysing the olefin by way of the acetate.

If hydrolysis of a halide is difficult or if hydrogen halide is removed, a route proposed by Bouveault[524] may be useful; this involves treating the Grignard compound of the halide in ethereal solution with oxygen and decomposing the product with water and is particularly valuable in the aromatic series. Yields by this method are generally poor but can often be improved by adding an aliphatic organometallic compound.[525]

It is difficult to replace aromatically bound halogen by a hydroxyl group. Hydrolysis of halobenzenes has been effected under pressure in the presence of alkali or after addition of catalytically active substances.[526] There are numerous patents describing, *e.g.*, the conversion of chlorobenzene into phenol;[527] and phenols have been obtained from bromobenzene derivatives in an autoclave in the presence of copper catalysts.[528] Hydrolysis of halobenzene derivatives is easier if they contain electron-attracting substituents in the *ortho*- or *para*-position to the halogen.

For the preparation of **5-chloro-1-naphthol,**[529] 1,5-dichloronaphthalene (10g), sodium hydroxide (6 g), copper powder (0.2 g), and methanol (45 ml) are heated for 6 h in an autoclave at 195–200°. The mixture is then filtered, the methanol is distilled off, and any 1-chloro-5-methoxynaphthalene formed is distilled off in steam. Acidification of the alkaline solution finally affords 73–86% of 5-chloro-1-naphthol.

6-Chloro-2-naphthol is obtained analogously in 66–74% yield from 2,6-dichloronaphthalene.

2. Replacement of halogen by carbonyl-oxygen

gem-Dihalides can be converted into aldehydes or ketones by acidic or alkaline reagents. Hydrolysis is often smooth in an aqueous medium containing iron(III) chloride. Hydrolysis of purely aliphatic dihalides needs more energetic conditions than that of benzylidene halides.

Benzylidene chloride obtained by chlorination of toluene is converted into benzaldehyde by dissolving iron(II) benzoate in the chloride, covering the solution with a layer of water, and heating the mixture at 90–95° until evolution of hydrogen chloride ceases. Saturation with slaked lime and distillation in steam affords the aldehyde.[530]

4-Chlorobenzylidene chloride is hydrolysed by concentrated sulfuric acid in 5 hours at room temperature,[531] and 4-chloro-3,3,4-trifluoro-1-phenyl-cyclobutene gives 3-phenyl-3-cyclobutene-1,2-dione (75% yield) when treated with

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[524] M. L. Bouveault, *Bull. Soc. Chim. France*, [iii], **29**, 1053 (1903).

[525] C. D. Hurd and K. L. Kreuz, *J. Amer. Chem. Soc.*, **72**, 5543 (1950).

[526] Ger. Pat. 539,176, 588,649; *Chem. Abstr.*, **26**, 2989 (1932); **28**, 2020 (1934); W. Mathes, *Angew. Chem.*, **52**, 591 (1939).

[527] G. S. Sanshaw, *Chem. Age*, **45**, 61 (1941); E. Hausmann, *Erdöl und Kohle*, **7**, 496 (1954).

[528] I. Lowenthal and J. M. Pepper, *J. Amer. Chem. Soc.*, **72**, 3292 (1950).

[529] N. N. Vorozhtsov Jr. and V. N. Lisitsyn, *Zh. Obshch. Khim.*, **30**, 2816 (1960); *Chem. Abstr.*, **55**, 16497 (1961).

[530] P. Schultze, Ger. Pat. 81,927; *Friedlander*, **4**, 144 (1894–97).

[531] M. L. McEwen, *Org. Syn.*, Coll. Vol. II, 133 (1943).

92% sulfuric acid at 100°.[532] For the preparation of 1-methyl-2-pyridone (80% yield) a mixture of 2-iodo-1-methylpyridinium iodide and 6N-hydrochloric acid was heated under reflux for 24 hours and then neutralized with solid sodium carbonate.[533] 4-Bromobenzylidene bromide is hydrolysed when heated with an aqueous hot slurry of calcium carbonate for 15 hours, the resulting *p*-bromobenzaldehyde being isolated by distillation in steam;[534] and *o*-fluorobenzaldehyde has been obtained by hydrolysis of 2-fluorobenzylidene bromide with potassium carbonate.[535] Wittig and Vidal[536] converted 9,9-dibromofluorene into fluorenone by means of sodium acetate in 60% acetic acid. Treatment with an equimolar amount of anhydrous oxalic acid at 110–130° has been recommended for some conversions of *gem*-dihalides into carbonyl compounds, as then all the by-products are gaseous; for example, 2-(dichloromethyl)benzamidazole and powdered oxalic acid give benzimidazole-2-carbaldehyde in 80% yield.[537] Phthalaldehyde and 2,3-naphthalenedicarbaldehyde can be obtained by heating $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene and 2,3-bis(dibromomethyl)naphthalene, respectively, in aqueous-alcoholic potassium oxalate for 40 hours.[535]

It is not always necessary to start with *gem*-dihalides for the synthesis of aldehydes or ketones. There is a process by which carbonyl compounds can be obtained from monohalides, sometimes in excellent yield: for instance, when 3-chlorocyclopentene is stirred vigorously with aqueous sodium dichromate solution at 0°, a chromium complex of 2-cyclopenten-1-one is formed, and this is decomposed to give a 60–68% yield of the ketone if 50% sulfuric acid is dropped in carefully with cooling;[513] and 1,2-cyclopentanedione can be obtained in 80% yield by dropwise addition of aqueous iron(III) chloride solution to 2-chlorocyclopentanone in water with rapid stirring at 100°.[539]

A process due to Sommelet[540] is generally applicable: (halomethyl)aryl compounds react with hexamethylenetetramine in alcohol or chloroform to yield quaternary ammonium salts, which decompose to aldehydes, formaldehyde, methylamine, and ammonia when boiled with water or dilute acid; it is usually unnecessary to isolate the intermediate compound if the whole process is carried out in 1 : 1 acetic acid–water.

o-Tolualdehyde: α-Bromo-*o*-xylene (60 g) is mixed with ethanol (250 ml); hexamethylenetetramine (48 g = a slight excess) and water (50 ml) are added, the amine dissolving on shaking and warming. The odor of the bromide disappears in 5 min. Then more water (200 ml) is added and the whole is boiled under reflux for 2 h and then steam-distilled. When about 1.5 l of distillate has collected and the distillate, although still turbid, no longer smells of aldehyde, the distillate is extracted with ether, and the extract is washed with water, dried, and fractionated. This affords a 70% yield (27 g) of *o*-tolualdehyde, b.p. 86–88°/19 mm.

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[532] E. J. Smutny and I. D. Roberts, *J. Amer. Chem. Soc.*, **77**, 3420 (1955).

[533] H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, **16**, 1151 (1951).

[534] G. H. Coleman and G. E. Honeywell, *Org. Syn.*, Coll. Vol. II, 89 (1943).

[535] W. W. Korschak and G. S. Kolesnikow, "Synthese organischer Verbindungen," Vol. 2, 1956, VEB Verlag, Berlin, and Porta Verlag, Munich, p. 136.

[536] G. Wittig and F. Vidal, *Chem. Ber.*, **81**, 370 (1948).

[537] H. Baganz, *Angew. Chem.*, **68**, 151 (1956).

[538] A. C. Cope and S. W. Fenton, *J. Amer. Chem. Soc.*, **73**, 1672 (1951); W. Ried and H. Bodem, *Chem. Ber.*, **89**, 711 (1956).

[539] H. H. Inhoffen and H. Kramer, *Chem. Ber.*, **87**, 493 (1954).

[540] W. Sommelet, *C. R. Hebd. Séances Acad. Sci.*, **157**, 852 (1913).

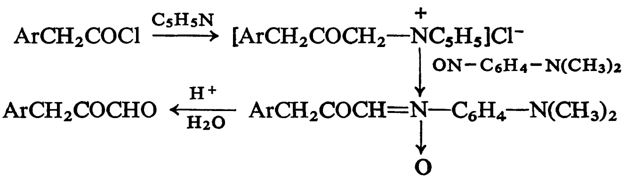
1-Naphthaldehyde:[541] 1-(Chloromethyl)naphthalene (106 g), hexamethylenetetramine (106 g), glacial acetic acid (250 ml), and water (250 ml) are boiled under reflux for 2 h. The mixture becomes homogeneous in 15 min and then an oil begins to separate. Next, concentrated hydrochloric acid (200 ml) is added and the whole is heated for a further 15 min, then cooled and extracted with ether. The ethereal layer is washed several times with water, then with sodium carbonate solution and again with water, and dried over sodium sulfate. After removal of the ether, the aldehyde distils at 105–107°/0.2 mm or 160–162°/18 mm, solidifying at 0–2.5°. The yield is 70–77 g, 75–82%. N.B.: 1-(Chloromethyl)naphthalene and 1-naphthaldehyde attack the skin and eyes.

The preparation of 2-thiophenecarbaldehyde from the corresponding chloromethyl compound,[542] and of 4-stilbenecarbaldehyde from 4-methylstilbene by way of 4-(bromomethyl)stilbene,[543] may also be noted. *m*- and *p*-Dialdehydes, but not *o*-dialdehydes, can also be obtained by the Sommelet reaction.

Aliphatic aldehydes can only rarely be prepared in this way as they at once react further. However, they can often be prepared by isolating the quaternary compound of the alkyl halide with hexamethylenetetramine, adding it slowly to 50% acetic acid, and immediately removing the aldehyde in a current of steam.

Angyal has reviewed the Sommelet reaction in *Organic Reactions.*[544]

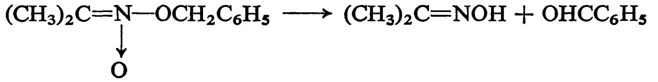
It was found by Kröhnke that compounds of the types $ArCH{=}CHCH_2Cl$, $ArCOCH_2Cl$, and $ArCH_2Cl$, that contain particularly reactive halogen, form pyridinium salts whose reaction with *N*,*N*-dimethyl-*p*-nitrosoaniline gives nitrones from which aldehydes are formed smoothly on hydrolysis by acids:



$$\begin{tikzcd} ArCH_2COCl \arrow[r, "C_5H_5N"] & {[ArCH_2COCH_2{-}\overset{+}{N}C_5H_5]Cl^-} \arrow[d, "ON{-}C_6H_4{-}N(CH_3)_2"] \\ ArCH_2COCHO & ArCH_2COCH{=}\underset{\downarrow \atop O}{N}{-}C_6H_4{-}N(CH_3)_2 \arrow[l, "H^+", "H_2O"'] \end{tikzcd}$$

All these reactions can be effected conveniently under mild conditions and at low temperatures. Thus the procedure is especially advantageous for the preparation of α,β-unsaturated aldehydes and substituted glyoxals. A review of the reaction has been published by Kröhnke, where he gives also experimental details.[545] The Kröhnke process also enabled Ried and Bender[546] to succed in the first synthesis of a heterocyclic dialdehyde (2,3-thionaphthenedicarbaldehyde).

A general procedure for conversion of substituted benzyl halides into aldehydes consists in their reaction with the sodium salts of aliphatic nitro compounds, particularly those of 2-nitropropane and nitrocyclohexane which afford unstable ester-like intermediates with benzyl halides; the intermediates decompose to oxime and aldehyde:



$$(CH_3)_2C{=}\underset{\downarrow \atop O}{N}{-}OCH_2C_6H_5 \longrightarrow (CH_3)_2C{=}NOH + OHCC_6H_5$$

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[541] S. J. Angyal, J. R. Tetaz, and J. G. Wilson, *Org. Syn.*, **30**, 67 (1950).

[542] K. B. Wiberg, *Org. Syn.*, **29**, 87 (1949).

[543] G. Drefahl and W. Hartrodt, *J. Prakt. Chem.*, [iv], **4**, 127 (1956).

[544] S. J. Angyal, *Org. Reactions*, **8**, 197 (1954).

[545] F. Kröhnke, *Angew. Chem.*, **65**, 613 (1953).

[546] W. Ried and H. Bender, *Chem. Ber.*, **89**, 1574 (1956).

For example, *o*-tolualdehyde is obtained in about 70% yield from α-bromo-*o*-xylene by this method.[547]

Kornblum and Frazier[548] describe a one-stage synthesis of α-keto aldehydes and α,β-diketones from α-halo ketones by way of nitrate esters, which may be exemplified by the case of ***p*-(bromophenyl)glyoxal**:

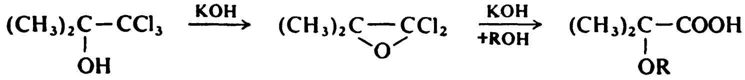
4,ω-Dibromoacetophenone (5.5 g) is dissolved in acetonitrile (20 ml), and silver nitrate (4.25 g) in acetonitrile (20 ml) is added. The mixture is stirred at 20° for 24 h, and filtered from silver bromide, which is washed with ether. The filtrate is evaporated at 30 mm and the residue is taken up in ether, washed with water, dried, and freed from solvent. The crude nitrate ester is dissolved in dimethyl sulfoxide (100 ml) and treated, with stirring, with a suspension of sodium acetate trihydrate (0.27 g) in dimethyl sulfoxide (40 ml).

This mixture is kept for 25 min at 20–25°, then poured into ice-water (400 ml). The mixture is saturated with sodium chloride and again extracted with ether. The ethereal solution is washed with water and sodium hydrogen carbonate solution, dried with magnesium sulfate, and freed from solvent at 30°/30 mm. This gives *p*-bromophenylglyoxal (4.19 g, 92%), which, when recrystallized from acetone, has m.p. 125–126°.

3. Replacement of halogen by carboxyl-oxygen

The halogen of trihalides may be replaced analogously to that of mono- and *gem*-di-halides, no new considerations being involved. The usual reagents are slaked lime at 50°, alcoholic alkali hydroxides, acids, or iron(III) chloride in aqueous solution. Some trichloromethyl compounds are converted into carboxylic acids in excellent yield by heating them in chloroform in the presence of anhydrous iron(III) chloride whilst the appropriate amount of water is dropped in.[549]

Such processes have, however, little preparative importance since the starting materials are mostly difficult of access. In a few cases (chloral, 1,1,1-trihalo-acetone) fission of a C–C bond occurs alongside the hydrolysis. Weizmann *et al.*[550] report an interesting synthesis of 2-alkoxy-2-methylpropionic acids: they obtained these acids by treating acetone with chloroform and hydrolysing the condensation product with alkali in the presence of an alcohol; the hydrolysis presumably proceeds by way of an epoxide:



$$(CH_3)_2C(OH)-CCl_3 \xrightarrow{KOH} (CH_3)_2C\underset{O}{—}CCl_2 \xrightarrow[+ROH]{KOH} (CH_3)_2C(OR)-COOH$$

Interaction of 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)ethane (DDT) and alkali gives, according to the conditions, either bis-(*p*-chlorophenyl)acetic acid or 2,2-dichloro-1,1-bis-(*p*-chlorophenyl)ethylene.[551]

p-Bromobenzotrichloride is hydrolysed when heated to between 30° and 50° with 85% sulfuric acid for 5 h. ***p*-Bromobenzoic acid** is then isolated in 95% yield by pouring the mixture on crushed ice.

Benzotrifluoride is hydrolysed in 94% yield to **benzoic acid** when heated in 100% sulfuric acid until the benzotrifluoride layer disappears.[552]

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[547] H. B. Hass and M. L. Bender, *Org. Syn.*, **30**, 99 (1950).

[548] N. Kornblum and H. W. Frazier, *J. Amer. Chem. Soc.*, **88**, 865 (1966).

[549] M. E. Hill, *J. Org. Chem.*, **25**, 1115 (1960).

[550] C. Weizmann, M. Sulzbacher, and E. Bergmann, *J. Amer. Chem. Soc.*, **70**, 1153 (1948).

[551] O. Grummit, A. Buck, and R. Egan, *Org. Syn.*, **26**, 21 (1946).

[552] G. M. LeFave, *J. Amer. Chem. Soc.*, **71**, 4148 (1949).

Carboxylic acids are rarely prepared in practice from carbonyl chlorides. This hydrolysis occurs when the acid halide is dropped with vigorous stirring into ice-cold water or ice-cold sodium carbonate solution; alcoholic potassium hydroxide is required only in exceptional cases. Aromatic acid halides are more stable than their aliphatic counterparts.

III. Replacement of nitrogen by oxygen

1. Replacement of the amino group by the hydroxyl group

In the aliphatic series replacement of an amino by a hydroxyl group is effected by means of nitrous acid, although the reaction does not occur homogeneously according to the equation:

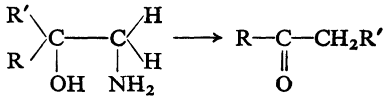
$$RCH_2NH_2 + ONOH \longrightarrow N_2 + H_2O + RCH_2OH$$

in fact, deamination of *n*-alkylamines affords mixtures of primary and secondary alcohols, olefins, and esters (*e.g.*, alkyl chlorides if the reaction is carried out in hydrochloric acid); but the principal products are the primary alcohols (30–50%) and the olefins (25–35%). Formation of esters can be avoided by carrying out the reaction in phosphoric or perchloric acid. Usually the amine is dissolved in the calculated amount of 10–15% acetic acid, the equivalent amount of saturated sodium nitrite solution is added in one portion to that solution, and the whole is heated for some hours at 80–90°.

For conversion of L-asparagine into L-malic acid, Walden[553] dissolved the amino acid in dilute nitric acid and heated the solution, with continuous shaking, with nitrous oxide in a warm water-bath until evolution of nitrogen was no longer evident (7 h). The action of nitrous acid on α-amino acids gives α-hydroxy acids without inversion at the asymmetric center.

Treating cyclic amines with nitrous acid gives secondary alcohols and cycloalkenes. Deamination of alkylcycloalkylamines is stereospecific in most cases: the equatorial amines give cycloalkanols with equatorial hydroxyl groups; when the amino group is axial the cyclohexene is the main product, being accompanied by a small amount of the hydroxy compound of inverted configuration.[554]

Whereas 1,3- and 1,4-amino alcohols are generally converted by nitrous acid into dihydric alcohols, the reaction of 1,2-amino alcohols is usually accompanied by rearrangement to ketones, *e.g.*:



A detailed and clear account of the behavior of amines with nitrous acid is given by Freytag *et al.*[1v]

Aliphatic amines are usually less accessible than the related hydroxy compounds, wherefore conversion of aliphatic primary amines into alcohols is of

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[553] P. Walden, *Ber. Deut. Chem. Ges.*, **28**, 2771 (1895).

[554] A. K. Bose, *Experientia*, **9**, 256 (1953).

less preparative importance than that of primary aromatic amines into aromatic hydroxy compounds.

Primary aromatic amines can be converted into the corresponding hydroxy compounds in various ways. In some cases this can be done by use of dilute acid or alkali under specific conditions, but that method is used mainly in industry and is rarely suitable for laboratory practice. 4-Amino-2,7- and -2,6-naphthalenedisulfonic acid and 8-amino-1,6-naphthalenedisulfonic acid are converted quantitatively into the corresponding hydroxynaphthalenedisulfonic acids when their acid salts are heated in water at 180°;[555] and 2-methoxy-4-nitroaniline affords 4-nitroguaiacol in 86% yield when boiled for 30 hours with aqueous sodium hydroxide.[556]

A generally applicable procedure for conversion of aromatic amines into phenols or naphthols consists of "boiling" aromatic diazonium compounds (for their preparation see page 581). This method will be illustrated here by some examples.

$$\mathrm{ArN_2^+HSO_4^-} + \mathrm{H_2O} \longrightarrow \mathrm{ArOH} + \mathrm{H_2SO_4} + \mathrm{N_2}$$

Side reactions that occur in this process with diazonium halides and nitrates prevent the diazotization being effected in nitric or hydrochloric acid solution; it is necessary to do this in sulfuric acid solution, and the sparing solubility of the sulfates of aromatic amines necessitates certain departures from the usual diazotization procedures.

Preparation of ***m*-nitrophenol** from *m*-nitroaniline:[557] A cold mixture of water (450 ml and concentrated sulfuric acid (330 ml) is poured, with stirring, over finely powdered *m*-nitroaniline (210 g), and ice (800 g) is added. When the mixture has become homogeneous, a solution of sodium nitrite (105 g) in water (250 ml) is run in during 8–10 min from a dropping funnel until the starch–iodine reaction remains positive. The temperature is kept between 0° and 5° and the mixture is stirred for a further 5–10 min. Then the *m*-nitrobenzenediazonium sulfate is allowed to settle, the supernatant liquid is poured off and the solid washed, if necessary, with water by decantation in order to purify the salt; filtration is necessary only when gross impurity is present.

Meanwhile a mixture of water (750 ml) and concentrated sulfuric acid (1 l) has been brought to boil in a large (5-l) flask, and to this the liquid decanted from the diazonium salt is run in from a dropping funnel at such a rate that the mixture remains in lively ebullition for 50 min. Then the solid diazonium salt is added in small portions, care being taken to avoid losses due to foaming. After these additions the mixture is boiled for a few minutes and then poured into a large beaker that is cooled in running water; there it is vigorously stirred while cooling, so that the dark oily *m*-nitrophenol that separates solidifies in as finely divided a state as possible, rather than in large lumps. When cold, the solid is filtered off, sucked as dry as possible, and washed with ice-water (450 ml in all). The crude product (170–180 g, 81–86%) is dried in the air, and is purified by distillation in a vacuum (b.p. 160–165°/12 mm) or by recrystallization from benzene.

This procedure can be used also for other, relatively stable nitro diazonium compounds. However, when the diazonium compounds are unstable, their separation in the solid state is to be avoided. The following directions for preparation of ***m*-chlorophenol** are given by Holleman and Rinkes:[558]

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[555] A. Rieche and H. Seeboth, *Ann. Chem.*, **638**, 102 (1960).

[556] N. L. Drake, H. C. Harris, and C. B. Jäger, *J. Amer. Chem. Soc.*, **70**, 170 (1948).

[557] R. H. F. Manske, *Org. Syn.*, **8**, 80 (1928).

[558] A. F. Holleman and I. J. Rinkes, *Rec. Trav. Chim.*, **30**, 81 (1911).

The diazonium sulfate solution obtained in the usual way from *m*-chloroaniline is dropped slowly into a mixture of concentrated sulfuric acid (2 parts) and water (1 part) at 140°. Distillation in steam, extraction with ether, drying, and distillation in a vacuum give the phenol (67%), b.p. 214°.

A generally applicable procedure given by Ungnade and Orwoll was illustrated for the conversion of 2-bromo-*p*-toluidine (NH_2 = 1) into **2-bromo-*p*-cresol** (OH = 1):[559]

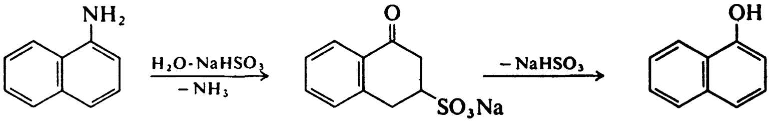
An aqueous solution of sodium nitrite was added, with stirring, during 15 min, under the surface of a solution of the amine in sulfuric acid at 0–5°. The mixture was stirred for a further 5 min and then treated with, successively, water, urea, and ice. The resulting mixture was added in portions to a solution of sodium sulfate (150 g) and sulfuric acid (200 g) in water (100 g) at 130–135°. The yield amounts to 80–92%.

An analogous conversion of *m*-aminobenzaldehyde into *m*-hydroxybenzaldehyde has also been described.[560]

Brockmann and Dorlars[561] converted diazonium halides into phenols in the presence of phosphoric acid. Treating diazonium fluoroborates with glacial acetic acid gives phenol esters, which can be deacylated in the usual way.[562] Diazonium trifluoroacetates are relatively stable and can be converted by warming into phenols in good yield.[563]

In many cases amino groups attached to pseudoaromatic heterocyclic systems can also be replaced by hydroxy groups by way of the diazonium compounds. *E.g.*, xanthine was obtained from guanine in this way.[564]

The amino group of α- and β-naphthylamines can usually be replaced by hydroxyl groups by reaction with sodium hydrogen sulfate (the Bucherer reaction) (see also page 530):



The naphthylamine is treated with a four- to eight-fold excess of sodium hydrogen sulfite in an aqueous medium at 90–150° for 6–30 hours, the time required varying from case to case: this affords the 1,2,3,4-tetrahydro-4-oxo-2-naphthalenesulfonic acid which is stable in an acid or neutral medium but decomposes in alkali to sulfite and the naphthol;[565] yields are almost quantitative. Moreover, 5-quinolinamine has been converted into 5-quinolinol by this route.[566] The reaction fails, however, if there is a sulfo group in the *meta*-position to the amino group.

The mechanism of the Bucherer reaction has been clarified by Rieche and Seeboth;[565] its preparative details, selectivity, and applicability have been reviewed by Drake[567] and Seeboth.[568]

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[559] H. E. Ungnade and E. F. Orwoll, *Org. Syn.*, **23**, 11 (1943).

[560] R. N. Icke and co-workers, *Org. Syn.*, **29**, 63 (1949).

[561] H. Brockmann and A. Dorlars, *Chem. Ber.*, **85**, 1180 (1952).

[562] L. E. Smith and H. L. Haller, *J. Amer. Chem. Soc.*, **61**, 143 (1939).

[563] M. R. Pettit, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, **1953**, 3081.

[564] F. Korte and H. Barkemeyer, *Chem. Ber.*, **89**, 2404 (1956).

[565] A. Rieche and H. Seeboth, *Ann. Chem.*, **638**, 57, 66 (1960).

[566] E. B. Hartshorn and S. L. Baird Jr., *J. Amer. Chem. Soc.*, **68**, 1562 (1946).

[567] N. L. Drake, *Org. Reactions*, **1**, 105 (1942).

[568] H. Seeboth, *Angew. Chem., Int. Ed., Engl.*, **6**, 307 (1967).

Carboxamides, like esters, are hydrolysed by boiling strong acids or alkalis (cf. the hydrolysis of nitriles, page 351). The rate of reaction is decreased by the presence of bulky groups; at moderate concentrations it is proportional to the product of the amide and hydroxyl or hydrogen ion concentrations. Base hydrolysis is accelerated, as is hydrolysis of esters, by electron-attracting groups. In concentrated acidic solution the rate of hydrolysis passes through a maximum; the H^+ concentration corresponding to this maximum differs for different amides.[569]

A mixture of glacial acetic acid and hydrochloric acid has been recommended for insoluble amides. Benzoylglycyl-DL-leucine was obtained in 68% yield when benzoylglycyl-DL-leucine amide was treated with N-sodium hydroxide solution at 100° for 30 min.[570]

Hydrolysis of amides can often be accelerated by addition of metal ions, especially those of the Fourth Group or Ce^{3+} or Ce^{4+};[571] it is fastest in the weakly alkaline region. This has been studied particularly in the dipeptide field.

Amides that are difficult to hydrolyse can be converted into carboxylic acids by Bouveault's method,[572] namely, treatment with nitrous acid, yields being good.

Conversion of triphenylacetamide into **triphenylacetic acid**:[573] The amide is finely powdered (0.2 g) and dissolved in concentrated sulfuric acid (2 g) by gentle warming. The solution is cooled in ice and treated quite slowly with sodium nitrite (0.2 g) in water (1 ml), then warmed gradually in a water-bath. Lively evolution of nitrogen begins at 60–70°; it is complete at 80–90°. Heating in the boiling water-bath is continued for a few minutes but not longer. After cooling, the triphenylacetic acid is precipitated by ice-water and recrystallized from glacial acetic acid; it has decomp. pt. 255°.

In connexion with this method see also Sudborough[574] and Meyer and Molz.[575]

The above process cannot be used in cases where the nitrous acid has a nitrosating action.

Dinitrogen trioxide, N_2O_3, can be recommended for conversion of some amides into the acids. For example, 2,2-dibutylhexanoic acid is obtained in 80% yield by passing N_2O_3 into an ice-cold solution of the amide in glacial acetic acid, leaving the mixture overnight and then heating it for 2 hours on a water-bath.[576] Grewe and Rockstroh[577] reported the conversion of a glucosecarboxamide into the corresponding carboxylic acid by liquid N_2O_3.

Sterically hindered carboxamides and sulfonamides can be deaminated in high yields by $NO[BF_4]$.[578] For this reaction the nitrosyl tetrafluoroborate is dissolved in acetonitrile, treated, with stirring, with a solution of the amide in acetonitrile, and warmed until evolution of nitrogen stops.

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[569] R. H. Krieble and K. H. Holst, *J. Amer. Chem. Soc.*, **60**, 2976 (1938).

[570] T. Wieland and H. Fritz, *Chem. Ber.*, **86**, 1198 (1953).

[571] E. Bamann, H. Munstermann, and H. Trapmann, *Naturwissenschaften*, **48**, 599 (1961).

[572] M. L. Bouveault, *Bull. Soc. Chim. France*, [iii], **9**, 368 (1893).

[573] G. Heyl and V. Meyer, *Ber. Deut. Chem. Ges.*, **28**, 2783 (1895).

[574] J. J. Sudborough, *Ber. Deut. Chem. Ges.*, **28**, ref. 917 (1895).

[575] V. Meyer and W. Molz, *Ber. Deut. Chem. Ges.*, **30**, 1279 (1897).

[576] N. Sperber, D. Papa, and E. Schwenk, *J. Amer. Chem. Soc.*, **70**, 3093 (1948).

[577] R. Grewe and G. Rockstroh, *Chem. Ber.*, **86**, 546 (1953).

[578] G. A. Olah and J. A. Olah, *J. Org. Chem.*, **30**, 2386 (1965).

Carbohydrazides can be converted into carboxylic acids by *N*-bromosuccinimide.[579]

2. Replacement of nitrogen by carbonyl-oxygen

Oxygen can be substituted for the nitrogen of the functional groups of nitriles, primary and secondary aliphatic nitro compounds, and often of aliphatic amines, a number of very usable methods having been worked out, of which many are generally applicable.

It is preparatively important that aldehydes and ketones can be regenerated by hydrolytic processes from their nitrogenous condensation products such as oximes, phenylhydrazones, semicarbazones, and Schiff bases.

Reaction of nitriles with dry hydrogen chloride in anhydrous ether or in an ether–chloroform mixture affords imidoyl chlorides which are reduced by stannous chloride to products that afford aldehydes on hydrolysis. The method seems to be generally applicable only to aromatic and heterocyclic aldehydes; the activity of the stannous chloride used for the reduction seems to be the most important factor in the reaction.[580] 2-Naphthaldehyde has been synthesized[580] in 95% yield by this method, and 4-methyl-5-thiazolecarbaldehyde in 40% yield.[581]

A similar conversion of nitriles into aldehydes has been reported by Henle.[582] He used sodamide in place of stannous chloride and added phenylhydrazine to the mixture; this led to phenylhydrazones that were cleaved to the aldehydes in the usual way.

A simple method of preparing aldehydes is to trap the aldehydes formed as intermediates in the catalytic hydrogenation of nitriles, for which purpose semicarbazide is eminently suitable. The method has been used with particular success with derivatives of benzyl cyanide;[583] the resulting phenylacetaldehyde semicarbazones were cleaved by formadehyde solution.

Reduction by a hydridoaluminate is generally applicable. For instance, 3-pyridinecarbaldehyde was obtained in 83% yield by the action of sodium triethoxyhydridoaluminate on 3-pyridinecarbonitrile in tetrahydrofuran for 1–2 hours.[584] The lithium salt in ether at 0° seems to be even more effective, giving aliphatic aldehydes in 70–80% yield and aromatic aldehydes in 80–90% yield.[585] Sodium tetrahydridoaluminate can also be used to prepare aromatic aldehydes from the corresponding nitriles; reaction in tetrahydrofuran for 2–3 hours at 0° gives 65–85% yields; but yields of aliphatic aldehydes are only 15–20% by this method.[586]

Reduction of nitriles to aldehydes by elemental hydrogen, through the aldimine, is of special preparative value. The pH of the medium must be chosen

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[579] E. R. Blout, *J. Org. Chem.*, **30**, 315 (1965); B. Bator and co-workers, *Roczniki Chem.*, **40**, 761 (1966)

[580] W. Williams, *Org. Syn.*, **23**, 63 (1943).

[581] C. R. Harington and R. C. G. Moggridge, *J. Chem. Soc.*, **1939**, 445.

[582] F. Henle, *Ber. Deut. Chem. Ges.*, **35**, 3039 (1902); **38**, 1362 (1905).

[583] H. Plieninger and G. Werst, *Angew. Chem.*, **67**, 156 (1955).

[584] G. Hesse and R. Schrödel, *Angew. Chem.*, **68**, 438 (1956).

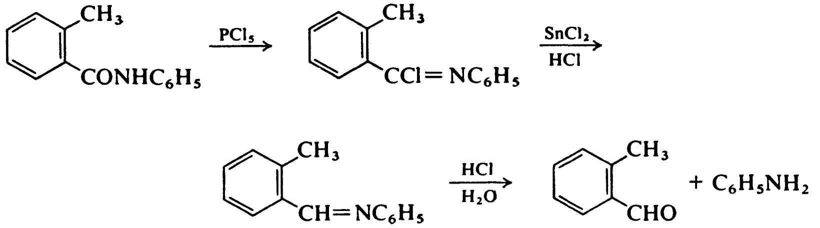
[585] H. C. Brown, C. J. Shoaf, and C. P. Garg, *Tetrahedron Letters*, **1959**, No. 3, p. 9.

[586] L. I. Zakharkin, D. N. Maslin, and L. V. Gavrilenko, *Izvest. Akad. Nauk S.S.S.R., Ser. Khim.*, **1964**, 1511.

to provide the most favorable conditions for hydrolysis of the aldimine. In acid solution (pH 2–5) zinc, chromium, or iron is used, in strongly basic solutions aluminum or Raney, Wood, Devarda, or Arndt alloy. For example, sulfuric acid is added gradually to the nitrile and zinc in water. For a variety of nitriles yields vary from 30–90%.[587]

***p*-Chlorobenzaldehyde** is obtained from *p*-chlorobenzonitrile in 80% yield by adding Raney nickel alloy, with stirring, during 2 h to a warm (40–45°) solution of the nitrile in an acetic acid–water mixture that is kept acid to litmus.[588] The yield becomes quantitative if the nitrile is heated under reflux with Raney nickel in 75% formic acid.[589]

Methods for converting carboxanilides into aldehydes are similar to those used for nitriles. For the preparation of *o*-tolualdehyde, Williams *et al.*[590] treated *o*-toluanilide with phosphorus pentachloride, obtaining an imidoyl chloride which they reduced with an ethereal solution of stannous chloride saturated with hydrogen chloride; subsequent steam-distillation split the reduced product into aldehyde and aniline. β-Ionylideneacetaldehyde was obtained analogously by Kuhn and Morris,[591] who used an ethereal suspension of $CrCl_2$ in place of $SnCl_2$.



N-Methyl carboxanilides can often be converted into aldehydes in good yield by lithium aluminum hydride; the reduction is best carried out in tetrahydrofuran, usually at 0°.[592]

A modification of the Sommelet reaction (see page 339) is to convert primary and secondary benzylamines into aldehydes by means of formaldehyde and hexamethylenetetramine. For instance, Greymore and Davies obtained benzaldehyde from benzylamine hydrochloride by this route;[593] and 2-fluorenecarbaldehyde has been similarly prepared in 70% yield from 2-(aminomethyl)-fluorene hydrochloride.[594] Papers by Snyder *et al.*[595] and by M. M. Robison and B. L. Robison[596] should be consulted for the reaction of tertiary amines with hexamethylenetetramine. Benzaldehydes can be synthesized by treating benzylamines with sodium nitrite and trifluoroacetic acid (molar ratio 1 : 2 : 3)

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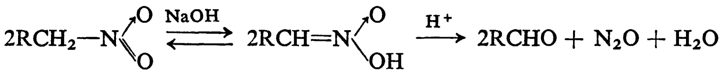
[587] A. Gaiffe and R. Palland, *C. R. Hebd. Séances Acad. Sci.*, **254**, 3099 (1962).
[588] O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, **1962**, 3961.
[589] T. van Es and B. Staksun, *J. Chem. Soc.*, **1965**, 5775.
[590] W. Williams, C. H. Witten, and J. A. Krynitsky, *Org. Syn.*, **26**, 97 (1946).
[591] R. Kuhn and C. Morris, *Ber. Deut. Chem. Ges.*, **70**, 857 (1937).
[592] F. Weygand and co-workers, *Angew. Chem.*, **65**, 525 (1953).
[593] J. Greymore and D. R. Davies, *J. Chem. Soc.*, **1945**, 293.
[594] S. J. Angyal, G. B. Barlin, and P. C. Wailes, *J. Chem. Soc.*, **1951**, 3512.
[595] H. R. Snyder, S. Swaminathan, and H. J. Sims, *J. Amer. Chem. Soc.*, **74**, 5110 (1952).
[596] M. M. Robison and B. L. Robison, *J. Amer. Chem. Soc.*, **77**, 457 (1955).

in dimethyl sulfoxide;[597] benzaldehyde itself is thus obtained in 82% yield from benzylamine at 100° in 2 hours.

Oxidation of primary aliphatic amines by sodium peroxysulfate in an alkaline medium containing catalytic amounts of silver nitrate affords Schiff bases, which are hydrolysed by boiling 2N-hydrochloric acid in 10 min to the initial amine and the aldehyde;[598] the yields of aldehyde are between 15% and 95%.

Another method of converting primary aliphatic amines into aldehydes appears to be by the action of atmospheric oxygen in the presence of copper powder,[599] but this reaction has been little studied.

Conversion of aliphatic nitro compounds into ketones is known as the Nef reaction; it proceeds through the *aci*-form of the nitro compound:



$$2RCH_2{-}N{\lesssim}^{O}_{O} \xrightleftharpoons{NaOH} 2RCH{=}N{\lesssim}^{O}_{OH} \xrightarrow{H^+} 2RCHO + N_2O + H_2O$$

For instance, 3-(1-nitroethyl)cyclohexanone is dissolved in dilute sodium hydroxide solution, 30% sulfuric acid is added with stirring at 0°, and the mixture is warmed slowly, first to room temperature, then to 55°, thus giving 3-acetylcyclohexanone.[600] Johnson and Degering[601] established exact conditions for converting primary and secondary aliphatic nitro compounds by way of the sodium salts of their *aci*-forms into aldehydes and ketones, respectively. Noland[602] has reviewed the applications and technique of the Nef reaction. Disadvantages of the Nef reaction are that it is not applicable when acid-sensitive groups are present and that in the acidic hydrolysis medium there is a strong tendency for the nitronic acids to isomerize to nitro compounds. Other molecular rearrangements can also occur.

A better method of converting mononitro into carbonyl compounds was found by Shechter and Williams.[603] Salts of nitronic acids give aldehydes or ketones when treated with the stoichiometric amount of neutral permanganate, in accord with the reaction:

$$3R_2C{=}NOOK + 2KMnO_4 + H_2O \longrightarrow 2R_2CO + 2MnO_2 + 3KNO_2 + 2KOH$$

Yields are 68–84% from salts of primary nitro compounds, and 66–96% from those of secondary nitro compounds. The method can be used with relatively complex nitro compounds. Primary nitro compounds can also be oxidized to carboxylic acids by an excess of permanganate; however, to obtain high yields it is advisable to begin the oxidation with only 70–90% of the requisite permanganate and to separate the resulting aldehyde before completing the oxidation.

General procedure: 2M-Magnesium sulfate solution (15–25 ml) is added to the nitro compound (0.001–0.006 mole) in 0.1N-potassium hydroxide (0.010–0.015 mole), and the volume is made up (to ca. 0.5 l) with water. The calculated amount of aqueous potassium permanganate

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[597] K. H. Scheit and W. Kampe, *Angew. Chem. Int. Ed., Engl.*, **4**, 787 (1965).

[598] R. G. R. Bacon and D. Stewart, *J. Chem. Soc.*, C, **1966**, 1384.

[599] Z. I. Shuikina, *J. Gen. Chem. (U.S.S.R.)*, **7**, 983 (1937); *Chem. Abstr.*, **31**, 5332 (1937).

[600] A. McCoubrey, *J. Chem. Soc.*, **1951**, 2933.

[601] K. Johnson and E. F. Degering, *J. Org. Chem.*, **8**, 10 (1943).

[602] W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

[603] H. Shechter and F. T. Williams, *J. Org. Chem.*, **27**, 3699 (1962).

solution (3-7% excess for secondary nitro compounds) is then dropped in at 0-5° with rapid stirring. The resulting aldehyde is separated by distillation in steam and may be identified as its 2,4-dinitrophenylhydrazone).

Oximes and hydrazones are often used for purification and separation of aldehydes and ketones, so that regeneration of the latter is an important reaction. Ketone derivatives are the most easily cleaved, aromatic aldehydes somewhat less easily, and aliphatic aldehyde derivatives require the most energetic conditions. Oximes are cleaved more easily than hydrazones. Cleavage of simple oximes and hydrazones is a smooth reaction, but that of hydroxyimino ketones is occasionally difficult. It is best to work in hydrochloric or dilute sulfuric acid, sometimes adding a little alcohol to increase the solubility. Oxalic, phthalic, or acetic acid is used to advantage with readily cleaved carbonyl derivatives. Tiemann[604] described a very generally useful method, in which the oxime or semicarbazone of a volatile aldehyde was distilled in steam in presence of phthalic anhydride, yields being almost quantitative.

Conversion of the monooxime of methyl phenyl diketone into the diketone by means of aqueous sulfuric acid is an example of acid hydrolysis.[605] *p*-Benzoquinone oxime was hydrolysed in good yield in aqueous copper(II) chloride solution.[606] 2,4-Dinitrophenylhydrazones can be very smoothly split by 80% or more concentrated formic acid containing copper carbonate[607] or by a solution of levulic acid (9 volumes) and N-hydrochloric acid (1 volume),[608] if necessary with an auxiliary solvent; the latter method has also proved its value for hydrolysis of oximes. A method of purifying steam-volatile ketones by way of their 2,4-dinitrophenylhydrazones has been recorded by Harrison and Eisenbraun.[609] Lederer and Nachmias[610] recommend 0.5-2.0N-hydrochloric acid for cleavage of Girard derivatives, this requiring 12-16 hours at room temperature.

When benzoin phenylhydrazone is heated for 2 hours in glacial acetic acid, a 77% yield of benzil is obtained,[611] the phenylhydrazine formed acting as dehydrogenating agent on the secondary hydroxyl group. Oximes can be cleaved in a very mild reaction by nitrous acid or isopentyl nitrite in the cold, these methods being especially indicated for isolation of sensitive aldehydes; for instance, Mannich and Budde prepared **succindialdehyde** as follows:[612]

The dioxime (30 g) of succindialdehyde is suspended in dioxan (40 ml), cooled in ice, and treated in about 40 min with ethyl nitrite at such a rate that the temperature remains between 5° and 15°; addition is stopped when a fresh portion causes no rise in temperature. The mixture is set aside overnight, then fractionated in a stream of carbon dioxide. This gives a forerun of dioxan and then at 67°/13 mm the monomeric dialdehyde (13-14 g; ca. 60%). This monomer can be kept for some time in absence of moisture, but slowly passes into a glassy polymer from which it can be regenerated by distillation.

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[604] F. Tiemann, *Ber. Deut. Chem. Ges.*, **33**, 3721 (1900).
[605] W. W. Hartmann and L. J. Roll, *Org. Syn.*, **23**, 1 (1943).
[606] W. T. Sumerford and D. N. Dalton, *J. Amer. Chem. Soc.*, **66**, 1330 (1944).
[607] R. Robinson, *Nature* (*London*), **173**, 541 (1954).
[608] C. H. De Puy and B. W. Ponder, *J. Amer. Chem. Soc.*, **81**, 4629 (1959).
[609] H. R. Harrison and E. J. Eisenbraun, *J. Org. Chem.*, **31**, 1294 (1966).
[610] E. Lederer and G. Nachmias, *Bull. Soc. Chim. France*, **1949**, 400.
[611] W. Theilacker and P. Tröster, *Ann. Chem.*, **572**, 144 (1951).
[612] C. Mannich and H. Budde, *Arch. Pharm.*, **270**, 283 (1932).

Glutardialdehyde has been obtained from its dioxime by the action of sodium nitrite in hydrochloric acid at −10° to −5°, the yield being 85–95%.[613]

The above method is also applicable to semicarbazones.[614]

With sensitive aldehydes, especially in the carbohydrate series, a process proves advantageous in which the desired carbonyl compound is "dispossessed" from its derivative by another carbonyl compound:

$$\mathrm{RCH{=}NR' + R''CHO \longrightarrow R''CH{=}NR' + RCHO}$$

Benzaldehyde, 2,4-dinitrobenzaldehyde, formaldehyde, and pyruvic acid are used as "dispossessing" agents. Use of formaldehyde can lead to undesirable side reactions; only benzaldehyde is used in carbohydrate chemistry. The following description by Fischer[615] illustrates the cleavage by means of benzaldehyde:

Galaheptose phenylhydrazone (10 g) is dissolved in hot water (400 ml) and shaken with pure benzaldehyde (5 ml). When separation of the oily product is almost complete and the liquid is clear, a further amount (6 g) of phenylhydrazone is dissolved in the reaction solution, benzaldehyde (2.5 ml) is again added, and the whole is shaken. This cycle is repeated yet again. Finally the mixture is heated for 15 min on the water-bath, cooled, filtered from benzaldehyde phenylhydrazone, extracted with ether (to remove the excess of benzaldehyde and the benzoic acid), decolorized with animal charcoal, filtered again and evaporated to dryness in a vacuum, whereupon **galaheptose** remains as a syrupy residue.

3,5-Methylene-D-xylose was prepared by Schmidt and Nieswandt analogously.[616]

Osazones can be cleaved in the same way. According to Fischer and Armstrong[617] maltose phenylosazone (20 g) is dissolved in boiling water (1600 ml) and pure benzaldehyde (16 g) is added with vigorous stirring. If the benzaldehyde is kept well distributed the reaction requires about 20 min. After cooling, filtration gives benzaldehyde phenylhydrazone in almost theoretical yield, and the maltose is worked up as described above.

In the steroid series it is preferred to liberate carbonyl compounds from their semicarbazones by pyruvic acid.[618] This cleavage is also efficiently effected by means of an acid ion-exchanger in an aqueous-organic solvent.[619]

The semicarbazone (1 part) and a strongly acidic cation-exchanger in the H^+ form (3 parts) are rapidly stirred in 90–95% alcohol boiling under reflux for 5–6 h. The filtrate is evaporated in a vacuum and the residual carbonyl compound is recrystallized.

Hydrolysis of a Schiff base to carbonyl compound and amine occurs analogously to that of oximes and hydrazones. It is dependent on the basicity of the amine and the reactivity of the aldehyde into which the azomethine is cleaved. Hydrolysis can be achieved in relatively mild conditions, *e.g.*, by short warming in dilute mineral acid, occasionally in dilute alcohol or acetic acid. The condensation products of amines and aldoses are decomposed by even traces of acid; Schiff bases are generally resistant to alkali. As in oximes and hydrazones, the aldehyde residue of Schiff bases can be replaced by another aldehyde residue; there is a preference for formaldehyde in this case.[620]

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[613] A. C. Cope and co-workers, *J. Amer. Chem. Soc.*, **73**, 3416 (1951).

[614] E. P. Oliveto and co-workers, *J. Amer. Chem. Soc.*, **78**, 1736 (1956).

[615] E. Fischer, *Ann. Chem.*, **288**, 145 (1895).

[616] O. T. Schmidt and G. Nieswandt, *Chem. Ber.*, **82**, 5 (1949).

[617] E. Fischer and E. F. Armstrong, *Ber. Deut. Chem. Ges.*, **35**, 2142 (1902).

[618] D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Amer. Chem. Soc.*, **79**, 454 (1957).

[619] F. Hodosan and co-workers, *Z. Chem.*, **2**, 151 (1962).

[620] R. Adams and G. H. Coleman, *Org. Syn.*, **2**, 17 (1922).

3. Replacement of nitrogen by carboxyl-oxygen

Since nitriles are usually conveniently accessible their conversion into carboxylic acids is important for aliphatic, aromatic hydrocarbon and heterocyclic chemistry. Hydrolysis of the nitrile group requires energetic conditions, such as treatment with strong acid or alkali. The individual case will decide whether acid or alkali is used. Where possible, acid hydrolysis is preferable, especially by concentrated hydrochloric acid, and, to increase the solubility of the nitrile, this is often carried out in presence of acetic acid. For the same reason alkaline hydrolysis is effected in presence of alcohol or pyridine, sometimes under pressure. Primary cyanides are hydrolysed more easily than secondary or tertiary ones, and aliphatic more easily than aromatic. The last traces of the nitrile and of the amide formed as intermediate are not always easy to remove. In some cases hydrolysis is stopped at the amide stage and completed by a different process, *e.g.*, by means of nitrous acid (see page 345).[621]

For conversion of aliphatic dinitriles into dicarboxylic acids it is best to use concentrated hydrochloric acid, *e.g.*, for the preparation of glutaric acid from the dinitrile.[622] Aromatic nitriles such as *o*-tolunitrile are hydrolysed by ca. 75% sulfuric acid.

o-Toluic acid:[623] 75% sulfuric acid (*d* 1.67; 3 kg) is heated to 150° and stirred while *o*-tolunitrile (1 kg) is introduced during 2 h down the reflux condenser. The mixture is next stirred for a further 2 h at 150–160° and for yet another hour at 190°. Working up is by precipitation with water, conversion into the sodium salt (and removal of the toluamide by filtration at this stage), acidification, and recrystallization from benzene. The yield is 930 to 1030 g (80–89%), and the m.p. is 102–103°.

Nitriles that are hard to hydrolyse, such as *ortho*-disubstituted benzonitriles, are effectively converted into carboxylic acids in 100% phosphoric acid,[624] although polyphosphoric acid converts simpler aromatic and aliphatic nitriles only to the amide stage, giving these in good yield in 1 hour at 110°.[625]

Dilute sulfuric acid is used for hydrolysis of phenylacetonitrile (benzyl cyanide) to **phenylacetic acid**:[626]

The nitrile (700 g), concentrated sulfuric acid (840 ml), and water (1150 ml) are heated, with stirring, for 3 h. The yield is 77.5% (630 g) of phenylacetic acid.

If **phenylacetic acid** is desired free from foreign odor, it seems advantageous to use a process due to Mann,[627] in which benzyl cyanide is hydrolysed by alkali instead of by acid:

Benzyl cyanide is heated with potassium hydroxide in aqueous-ethanolic solution until no further evolution of ammonia can be detected, then the alcohol is distilled off and the aqueous solution is cooled, extracted with ether (to remove unchanged benzyl cyanide as well as phenylacetamide), acidified, and worked up as usual.

Phenylacetic acid is best purified by distillation and then has m.p. 76.5°.

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[621] S. Sarel and M. S. Newman, *J. Amer. Chem. Soc.*, **78**, 5418 (1956).

[622] C. S. Marvel and W. F. Tuley, *Org. Syn.*, **5**, 69 (1925).

[623] H. T. Clarke and E. R. Taylor, *Org. Syn.*, Coll. Vol. II, 588 (1943).

[624] G. Berger and S. C. J. Olivier, *Rec. Trav. Chim.*, **46**, 600 (1927).

[625] H. R. Snyder and C. T. Elston, *J. Amer. Chem. Soc.*, **76**, 3039 (1954).

[626] R. Adams and A. F. Thal, *Org. Syn.*, **2**, 63 (1922).

[627] W. Mann, *Ber. Deut. Chem. Ges.*, **14**, 1645 (1881).

It is best to use alkali for hydrolysis of aliphatic nitriles. **Heptadecanoic acid (margaric acid)** is prepared from heptadecanonitrile as follows:[628]

The nitrile (30 g) and potassium hydroxide (10 g) are boiled in ethanol (60 ml) and water (15 ml) until no more ammonia can be detected (31 h). The soap remaining on removal of the alcohol by distillation is split by hydrochloric acid, and the precipitated heptadecanoic acid is washed well with water and dried by gentle heat. After the acid has been twice recrystallized from light petroleum the m.p. is 61.2°. The yield is 78.5%.

The preparation of malonic acid by alkaline hydrolysis of cyanoacetic acid is described in *Organic Syntheses*,[629] as also is the conversion of acyl cyanides into α-keto acids by storage for several days in cold concentrated hydrochloric acid.[630]

Cyanohydrins in concentrated hydrochloric acid yield α-hydroxy carboxylic acids, whereas on alkaline hydrolysis a large part of the cyanohydrin is cleaved to the starting materials. Directions for synthesis of mandelic acid from mandelonitrile are given in *Organic Syntheses.*[631]

Amino cyanides are obtained by the action of ammonia and hydrocyanic acid, or of ammonium chloride and sodium cyanide, on aldehydes, or alternatively from cyanohydrins and ammonia. They are best hydrolysed by concentrated hydrochloric acid, the resulting amino acids being then obtained as hydrochlorides, whence the free amino acids can be liberated by means of lead monoxide, ammonia, or pyridine. For a critical consideration of the hydrolysis of amino cyanides see Cocker and Lapworth.[632] The synthesis of DL-alanine has been detailed twice.[78c, 633] That of racemic α-amino-α-phenylpropionic acid from acetophenone, sodium cyanide, and ammonium chloride by way of the amino cyanide was worked out by Steiger.[634] β-Alanine is obtained in 85–90% yield when 3-aminopropionitrile is added to aqueous barium hydroxide at 90–95° during 40 min and kept at that temperature for a further 40 min.[635]

As mentioned above, it is sometimes preferable to use a circuitous route for hydrolysis of nitriles. Pfeiffer and Matton[636] led hydrogen chloride into a hot methanolic solution of a stilbenecarbonitrile and observed that the nitrile group passed into a methoxycarbonyl one. Thus a nitrile group can be converted into an ester group in one operation, by boiling alcoholic hydrochloric or sulfuric acid; when hydrogen chloride is used, the imidoyl chloride is formed as intermediate[637] but is hydrolysed by water to the carboxylic ester and ammonium chloride. Drefahl *et al.*[638] obtained methyl 4′-amino-4-stilbenecarboxylate hydrochloride by boiling 4′-(acetylamino)-4-stilbenecarbo-

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[628] R. L. Shriner, J. M. Fulton, and D. Burks Jr., *J. Amer. Chem. Soc.*, **55**, 1496 (1933).

[629] N. Weiner, *Org. Syn.*, Coll. Vol. II, 376 (1943).

[630] T. S. Oakwood and C. A. Weisgerber, *Org. Syn.*, **24**, 14, 16 (1944).

[631] B. B. Corson and co-workers, *Org. Syn.*, **6**, 58 (1926); cf. ref. 78b.

[632] W. Cocker and A. Lapworth, *J. Chem. Soc.*, **1931**, 1391.

[633] E. C. Kendall and B. F. McKenzie, *Org. Syn.*, **9**, 4 (1929).

[634] R. E. Steiger, *Org. Syn.*, **24**, 9 (1944).

[635] J. H. Ford, *Org. Syn.*, **27**, 1 (1947).

[636] P. Pfeiffer and K. Matton, *Ber. Deut. Chem. Ges.*, **44**, 1115 (1911).

[637] A. Pinner, "Die Iminoäther und ihre Derivate," Verlag Robert Oppenheim (Gustav Schmidt), Berlin, 1892.

[638] G. Drefahl, H. Seeboth, and W. Degen, *J. Prakt. Chem.*, [iv], **4**, 104 (1956).

nitrile for 2 hours in methanol saturated with hydrogen chloride. Spiegel[639] showed that it is advisable to use up to 10 moles of the alcohol and 1 mole of sulfuric acid per mole of nitrile and that heating on the water-bath does not always give satisfactory results, whereas yields are theoretical from a reaction in a sealed tube.

A simple method of converting nitriles into amides is by the action of 3–30% hydrogen peroxide in an alkaline medium at temperatures around 50°.[640] Nicotinamide has thus been obtained from 3-pyridinecarbonitrile,[641] which is difficult to hydrolyse in other ways. Aliphatic dinitriles such as succinonitrile to suberonitrile, and aromatic dinitriles such as terephthalonitrile, isophthalonitrile, and · 2,6-pyridinedicarbonitrile, are hydrolysed as far as the cyano amide by means of a strongly basic ion-exchange resin on a polystyrene base at 60–95°.[642]

2,3-Diphenyltartaronitrile gives the diamide in 82% yield when treated with a large excess of hydrogen bromide in glacial acetic acid at 20°.[643] Passing HCl (8 g) into a solution of 2,3-dichloropropionitrile (6.2 g) in water (0.9 g) and ether (20 ml) gives a 93% yield of the amide.[644] Other amides are obtained similarly in good yields.

Manganese dioxide in organic solvents is an excellent reagent for converting nitriles into amides under neutral conditions; for instance, *trans*-3-bromo-4-methoxycinnamonitrile gives a 90% yield of the amide when stirred with 3–10 parts of MnO_2 in methylene chloride for 18 h at 20°.[645]

IV. Replacement of the sulfo group by the hydroxyl group

Substitution of a hydroxyl for a sulfo group is one of the most important methods for the preparation of phenols. Subjecting sulfonic acids to an alkali melt is the commonest means of putting this into practice, but it does not always proceed according to the simple scheme:

$$RSO_3K + KOH \longrightarrow K_2SO_3 + ROH$$

It is well known that the normal exchange reaction is often accompanied by oxidation, the classical example of which is the conversion of anthraquinone-2-sulfonic acid into alizarin.

In spite of their similarity potassium hydroxide and sodium hydroxide differ in their effects. Potassium benzenesulfonate and potassium hydroxide give an almost quantitative yield of phenol, but only a partial yield is obtained in sodium hydroxide. This relationship is, however, reversed when one tries to convert benzenetrisulfonic acid into phloroglucinol: with potassium hydroxide

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[639] L. Spiegel, *Ber. Deut. Chem. Ges.*, **51**, 296 (1918).

[640] C. R. Noller, *Org. Syn.*, Coll. Vol. II, 586 (1943).

[641] A. Georg and P. Bachmann, *Helv. Chim. Acta*, **26**, 358 (1943).

[642] C. Berther, *Chem. Ber.*, **92**, 2616 (1959).

[643] F. Michel, R. Austrup, and A. Striebeck, *Chem. Ber.*, **94**, 132 (1961).

[644] E. N. Zil'berman, S. B. Meĭman, and A. E. Kulikova, *Zh. Priklad. Khim.*, **33**, 2375 (1960); *Chem. Abstr.*, **55**, 11296 (1961).

[645] M. J. Cook, E. J. Forbes, and G. M. Khan, *Chem. Commun.*, **1966**, 221.

only two sulfo groups are replaced, but with sodium hydroxide the third may also be replaced, although with poorer yield.[646]

If the reaction temperature and the concentration are chosen suitably it is often possible to remove successive sulfo groups separately by means of potassium or sodium hydroxide. For example, according to the concentration of alkali used, *m*-hydroxybenzenesulfonic acid[647] or resorcinol[648] is obtained from *m*-benzenedisulfonic acid. The reaction is carried out by adding the sulfonate in portions to a molten mixture of KOH or NaOH and a little water in a silver, nickel, copper, or iron crucuible at a temperature between 200° and 300°. Carefully defined conditions for preparation of *β*-naphthol are given in the Gattermann–Wieland book;[78d] also for *p*-cresol in *Organic Syntheses*.[649] Fürst and Dietz[650] have obtained 3-pyridinol in about 80% yield from 3-pyridinesulfonic acid.

The conversion of 1,8-naphthalenesultone into **1,8-naphthalenediol**[651] will serve as example: Potassium hydroxide (60 g), water (20 ml), and 1,8-naphthalenesultone (14 g) are melted together in a silver crucible, then heated with stirring to 200–300° for 15–20 min during which the crucible is covered. The dark product is allowed to cool, decomposed with 13% hydrochloric acid (300 ml), treated with concentrated hydrochloric acid until bubbling ceases, and then heated with water (1 l), in which everything dissolves except a small amount of tar. When the filtrate cools, crude 1,8-naphthalenediol (6 g) crystallizes, and a further amount (2 g) is obtained by ether-extraction of the mother liquor. After recrystallization from water containing sulfur dioxide, the product has m.p. 140°.

1,3-Naphthalenediol is obtained in 67% yield when sodium 3-hydroxy-1-naphthalenesulfonate (6.3 g) is heated with KOH (13.4 g) and water (3 ml) at 190–200°.[652] Only 5% of the diol is obtained if the mixture is fused at 250–260°.

Melting each of the three isomeric potassium toluenesulfonates (50 mmoles of dry salt) with KOH (350 mmoles) at 300° for 60–70 min gives 35–45 mmoles of crude cresol.[653] It was not possible to establish isomerization of the sulfonates, and, if this is so, the reaction proceeds by an addition–elimination and not by an aryne mechanism.

A method for replacing thiol by hydroxyl groups consists of treating them with chloroacetic acid, which converts them into sulfide groups; these products are hydrolysed to the hydroxy compound and mercaptoacetic acid, partly already in hot water but completely only under the action of hot concentrated hydrochloric acid:

$$\mathrm{RSH + ClCH_2COOH \xrightarrow{HCl} RSCH_2COOH \xrightarrow{H_2O} ROH + HSCH_2COOH}$$

4-Amino-2-pyrimidinol (cytosine) can be obtained in this way from 4-amino-2-pyrimidinethiol.[654]

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[646] L. Barth and J. Schreder, *Ber. Deut. Chem. Ges.*, **12**, 422 (1879).

[647] F. Willson and K. H. Meyer, *Ber. Deut. Chem. Ges.*, **47**, 3162 (1914).

[648] H. E. Fierz-David and G. Stamm, *Helv. Chim. Acta*, **25**, 368 (1942).

[649] W. W. Hartman, *Org. Syn.*, **3**, 37 (1923).

[650] H. Fürst and H. J. Dietz, *J. Prakt. Chem.*, [iv], **4**, 154 (1956).

[651] H. Erdmann, *Ann. Chem.*, **247**, 356 (1888).

[652] V. V. Kozlov, N. I. Zil'berman, D. I. Brozovskii, L. M. Demkova, and T. D. Sistaeva, *Zh. Priklad. Khim.*, **35**, 880 (1962); *Chem. Abstr.*, **57**, 5855 (1962).

[653] W. Pritzkow *et al.*, *Z. Chem.*, **5**, 300 (1965).

[654] G. H. Hitchings and P. B. Russel, *J. Chem. Soc.*, **1949**, 2454.

4.3. Formation of the carbon–oxygen bond by replacement with formation of additional carbon–oxygen bonds

I. Ethers

1. Ether formation by replacement of oxygen by oxygen

a. Removal of water from two molecules of alcohol

Ethers are formed by loss of water between two molecules of alcohol in the presence of a catalyst:

$$\mathrm{ROH + HOR \longrightarrow ROR + H_2O}$$

The reaction requires a dehydrating catalyst, which, for reactions in the liquid phase, is an acid substance; this is usually a concentrated mineral acid, but may also be an organic sulfonic acid, acid salt, or halogen compound such as boron trifluoride, zinc chloride, or aluminum chloride. For etherification in the gaseous phase the alcohol vapor is passed over a solid catalyst such as Al_2O_3, TiO_2, or dehydrated alum.[656]

Some alcohols, *e.g.*, triphenylmethanol and benzhydrol, are etherified even on recrystallization from methanol or ethanol if a trace of acid is carried over from the synthesis; fluorenol is particularly easily transformed into an ether. Ethers of lower alcohols can be prepared by heating a mixture of the alcohol and sulfuric acid, but in this procedure the experimental conditions, in particular the temperature, must be rigidly controlled as otherwise the olefin is very easily formed; only alcohols with a chain length of one to three carbon atoms give ethers in good yield by this robust method; olefins are the main products from higher alcohols under these conditions.[657–659] Vogel[657] was able, however, to etherify higher alcohols (up to C_8) by a modified procedure in which specific reaction temperatures must be exactly maintained and the theoretical amount of water removed in a continuous process.

Unsymmetrical ethers can be prepared by dehydration of aliphatic alcohols only when one reactant is a tertiary alcohol;[660] sulfuric acid is often the condensing agent in such cases.

For the preparation of ***tert*-butyl ethyl ether**,[661] *tert*-butyl alcohol (1 mole) is added gradually to a boiling mixture of ethanol (2 moles) and twice that amount of 15% sulfuric acid, and the azeotropic ether–water mixture is removed by continuous distillation. This gives a 95% yield.

In the preparation of ***tert*-butyl isopropyl ether**,[660] replacing the 15% sulfuric acid by an aqueous solution of sodium hydrogen sulfate increases the yield considerably.

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[655] "The Chemistry of the Ether Linkage," ed. S. Patai, Interscience Publishers, London, 1967.

[656] Cf. F. Klages in G. M. Schwab, "Handbuch der Katalyse," Springer-Verlag, Vienna, 1943, Vol. 7, Part 2, p. 292.

[657] A. I. Vogel, *J. Chem. Soc.*, **1948**, 616.

[658] L. M. Norton and C. O. Prescott, *Amer. Chem. J.*, **6**, 245 (1884).

[659] G. Schroeter and W. Sondag, *Ber. Deut. Chem. Ges.*, **41**, 1921 (1908).

[660] J. F. Norris and G. W. Rigby, *J. Amer. Chem. Soc.*, **54**, 2088 (1932).

[661] I. N. Hultman, A. W. Davis, and H. T. Clarke, *J. Amer. Chem. Soc.*, **43**, 366 (1921).

Isopentyl triphenylmethylether[662] is formed in 88% yield when triphenylmethanol is dissolved in 100% sulfuric acid (from 96% acid and SO_3), this mixture being treated at −10° with isopentyl alcohol, poured into ice-water, and then worked up.

Benzhydryl 2-chloroethyl ether[663] is obtained analogously by warming a mixture of ethylene chlorohydrin, concentrated sulfuric acid, and benzhydrol in benzene on a water-bath.

Undesirable side reactions often occur when concentrated sulfuric acid is used. For sensitive substances it is thus advisable to use an organic sulfonic acid such as *p*-toluenesulfonic acid as etherification catalyst.[664] For example, ethers of cyclic enols[665, 666] can be obtained by boiling the reactants with a little *p*-toluenesulfonic acid in benzene while removing the resulting water in a continuous water-separator.

This method has been described for the preparation of **dihydroresorcinol monoethyl ether**:[666] Dihydroresorcinol (215 g) and 96% ethanol (300 ml) in benzene (1500 ml) containg *p*-toluenesulfonic acid (7 g) give a 90% yield of the enol ether when the mixture is boiled under a water-separator until reaction ceases.

Long-chain symmetrical ethers can also be prepared from the alcohols by using *p*-toluenesulfonic acid;[667] boiling 2,2′-thiodiethanol (thiodiglycol) with isopentyl alcohol and *p*-toluenesulfonic acid under reflux for 4 hours gives an 83% yield of the diisopentyl ether:[668]

$$S(CH_2CH_2OH)_2 + 2\text{iso-}C_5H_{11}OH \longrightarrow S(CH_2CH_2OC_5H_{11}\text{-i})_2$$

Etherification by means of concentrated hydrochloric acid may be illustrated by the preparation of **di-(2-cyclopentenyl)ether**[669] from 2-cyclopenten-1-ol:

Concentrated hydrochloric acid (10 ml) is dissolved in 2-cyclopenten-1-ol (420 g). An aqueous layer separates during a few hours. This is removed and the oily product is distilled in a vacuum from a little sodium hydrogen carbonate. A small forerun consists of water and unchanged cyclopentenol (b.p. 48°/11 mm). The ether, forming the main product, distils at 81°/11 mm as a colorless liquid in almost quantitative yield.

Warming a mixture of 1-butanol, concentrated hydrochloric acid, and *N*-(hydroxymethyl)-*N*′-phenylurea at 50° affords an 86% yield of the butoxymethyl derivative:[670]

$$C_6H_5NHCONHCH_2OH + C_4H_9OH \longrightarrow C_6H_5NHCONHCH_2OC_4H_9 + H_2O$$

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[662] H. A. Smith and R. J. Smith, *J. Amer. Chem. Soc.*, **70**, 2400 (1949).

[663] S. Sugasawa and K. Fujiwara, *Org. Syn.*, **33**, 11 (1953).

[664] F. Krafft, *Ber. Deut. Chem. Ges.*, **26**, 2829 (1893).

[665] R. L. Frank and H. K. Hall Jr., *J. Amer. Chem. Soc.*, **72**, 1645 (1950).

[666] R. Grewe, E. Nolte, and R. H. Rotzoll, *Chem. Ber.*, **89**, 600 (1956).

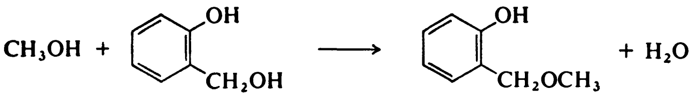
[667] R. Perron and C. Paquot, *C. R. Hebd. Séances Acad. Sci.*, **228**, 584 (1949); *Bull. Soc. Chim. France*, **1949**, 333.

[668] F. Richter, F. B. Augustine, E. Koft Jr., and E. E. Reid, *J. Amer. Chem. Soc.*, **74**, 4076 (1952).

[669] K. Alder and F. H. Flock, *Chem. Ber.*, **89**, 1732 (1956).

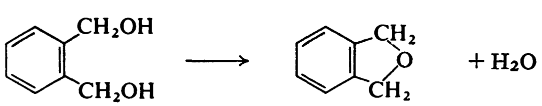
[670] S. Zigeuner, K. Voglar, and R. Pitter, *Monatsh. Chem.*, **85**, 1196 (1954).

Benzyl alcohols are readily etherified,[671] best by azeotropic distillation with benzene as carrier;[672] saligenin has been converted into 2-hydroxybenzyl methyl ether by heating it with methanol in a bomb tube at 150°:[673]



Five- and six-membered cyclic ethers are readily formed by loss of water from appropriate diols.[11,k] As examples of reactions in the liquid phase, cyclization of α,δ-alkanediols to tetrahydrofurans and of α,ε-alkanediols to tetrahydropyrans generally occurs when they are warmed in the presence of an inorganic or organic acid. These reactions can also be induced by warming the diols in dimethyl sulfoxide.[674]

Heating phthalyl alcohol (*o*-phenylenedimethanol) with a small amount of *p*-toluenesulfonic acid gives the cyclic benzyl ether (phthalan)[675] in about 60% yield:



The product is easily resinified by acid, so that it must be removed from the reaction mixture by distillation under nitrogen as soon as it is formed.

Phosphoric acid is the dehydrating agent of choice for preparation of furan derivatives from α,δ-diols.

Catalytic etherification in the gas phase can be exemplified by the preparation of **phthalan** from phthalyl alcohol:[676]

Molten phthalyl alcohol (276 g) is dehydrated by passing its vapor through a column filled with activated alumina and heated at 300°; after distillation of the product in steam in the presence of 10% aqueous sodium hydroxide, phthalan is isolated in 89% yield (214 g).

Jones and Taylor[677] report details of the chemistry of furans and pyrans.

A simple synthesis of oxetane (trimethylene oxide)[678] is to introduce a solution of 1,3-propanediol in concentrated sulfuric acid into a hot concentrated solution of sodium hydroxide, distilling off the cyclic ether produced.

Preparation of alkyl aryl ethers by loss of water between a phenol and an alcohol is generally of little importance. It may, however, be noted that phloroglucinol can be converted into di- or tri-alkyl ethers by means of hydrochloric acid;[679] also some naphthols, anthracenols, and phenanthrols,[680] *e.g.*, α- and

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[671] J. Meisenheimer, *Ber. Deut. Chem. Ges.*, **41**, 1421 (1908).

[672] E. F. Pratt and P. W. Erickson, *J. Amer. Chem. Soc.*, **78**, 76 (1956).

[673] J. de Jonge and B. H. Bibo, *Rec. Trav. Chim.*, **74**, 1448 (1955).

[674] B. T. Gilli and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963); V. J. Traynelis, E. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).

[675] A. J. Weinheimer, S. W. Kantor, and C. R. Hauser, *J. Org. Chem.*, **18**, 801 (1953).

[676] J. Entel, C. H. Ruof, and H. C. Howard, *J. Amer. Chem. Soc.*, **74**, 441 (1952).

[677] D. G. Jones and A. W. C. Taylor, *Quart. Rev.*, **4**, 195 (1956).

[678] L. F. Schmoyer and L. C. Case, *Nature (London)*, **183**, 389 (1959).

[679] W. Will and K. Albrecht, *Ber. Deut. Chem. Ges.*, **17**, 2107 (1884); W. Will, *Ber. Deut. Chem. Ges.*, **21**, 603 (1888); J. Herzig and H. Kaserer, *Monatsh. Chem.*, **21**, 875 (1900); K. Freudenberg, *Ber. Deut. Chem. Ges.*, **53**, 1425 (1920).

[680] F. R. Japp and A. Findlay, *J. Chem. Soc.*, **71**, 1122 (1897); L. Gattermann, *Ann. Chem.*, **244**, 72 (1888).

β-naphthol, 1,5-anthracenediol, and 1- and 2-anthracenol,[681] can be etherified by alcohols in the presence of hydrochloric or sulfuric acid.

Methyl α-naphthyl ether:[682] α-Naphthol (25 g) is heated with anhydrous methanol (25 g) and concentrated sulfuric acid (10 g) in an oil-bath at 125° for 4 h under reflux. It is advisable to carry out this reaction under the pressure of a small column of mercury. The product is poured into water, and the oily layer is washed with dilute alkali to remove unchanged naphthol and is then fractionated (b.p. 258°). The yield is almost quantitative.

β-Naphthol is still more easily etherified.

b. Alkylation by dialkyl sulfates

Alcohols and phenols can be alkylated by use of alkyl sulfates (contrast the use of alkyl halides in many other cases). Particular importance attaches to the preparation of methyl ethers by means of dimethyl sulfate.[683]

Phenols are generally etherified by Ullmann's method,[684–686] reaction occurring in two stages:

$$\mathrm{ROH} + (\mathrm{CH_3})_2\mathrm{SO_4} \longrightarrow \mathrm{ROCH_3} + \mathrm{CH_3SO_4H}$$

$$\mathrm{ROH} + \mathrm{CH_3SO_4H} \longrightarrow \mathrm{ROCH_3} + \mathrm{H_2SO_4}$$

The first stage occurs readily, on gentle warming; it is often possible to use the second alkyl group of the alkylating agent to etherify a second molecule of the hydroxy compound, but higher temperatures are usually required for this. The methylation is usually conducted by adding the calculated amount of dimethyl sulfate gradually to an alkaline solution of the phenol.

Anisole:[687] Phenol (235 g) and sodium hydroxide (100 g) are dissolved in water (1 l) in a 5-l flask fitted with a stirrer, reflux condenser, and dropping funnel. The mixture is cooled with stirring to slightly below 10° and dimethyl sulfate (315 g) is run into the stirred mixture from the dropping funnel during 1 h. The whole is heated for 30 min on a water-bath. Next a second solution of phenol (235 g) and sodium hydroxide (100 g) in water (1 l) is added, this time during 15 min, and that mixture is heated at the b.p. over a free flame for 15 h. Working up is by separating the two layers, extracting the aqueous solution with benzene (200 ml), drying, and two distillations. This gives 72–75% of anisole (388–405 g), b.p. 153–154°/748 mm.

N.B.: Dimethyl sulfate is highly poisonous. Work with it should always be in a fume cupboard, and all glass vessels should be rinsed with methanolic ammonia after use.

For etherification of alkali-sensitive substances such as polyphenols it is advisable to treat the derived acetate with dimethyl sulfate and alkali (if necessary, with addition of acetone), which achieves simultaneous hydrolysis

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[681] B. Lampe, *Ber. Deut. Chem. Ges.*, **42**, 1416 (1909); cf. C. Liebermann and A. Hagen, *Ber. Deut. Chem. Ges.*, **15**, 1427 (1882); H. Dienel, *Ber. Deut. Chem. Ges.*, **38**, 2864 (1905).

[682] O. N. Witt and F. Schneider, *Ber. Deut. Chem. Ges.*, **34**, 3173 (1901).

[683] C. Cerchez. *Bull. Soc. Chim. France*, **43**, 762 (1928).

[684] F. Ullmann and P. Wenner, *Ber. Deut. Chem. Ges.*, **33**, 2476 (1900); *Ann. Chem.*, **327**, 114 (1903).

[685] D. M. Musser and H. Adkins, *J. Amer. Chem. Soc.*, **60**, 667 (1938).

[686] W. H. Perkin Jr. and C. Weizmann, *J. Chem. Soc.*, **89**, 1649 (1906).

[687] G. S. Hiers and F. D. Hager, *Org. Syn.*, Coll. Vol. I, 58 (1941).

and methylation.[688] In some cases it has proved advantageous to replace the sodium hydroxide by sodium carbonate or sodium hydrogen carbonate.[689]

Alkali-sensitive compounds can be methylated by adding the alkali solution to the stirred mixture of dimethyl sulfate and the substance to be alkylated, taking care that each portion is rapidly consumed.[690] Another procedure for alkylation of alkali-sensitive compounds is to add the dimethyl sulfate and *ca.* 30% sodium hydroxide solution from two separate dropping funnels to a vigorously stirred solution of the hydroxy compound in water, in such a way that the mixture never becomes acid or strongly alkaline.

Alcohols are appreciably harder than phenols to alkylate with dialkyl sulfates. Here an essential point for success is complete exclusion of water.[691] Alkylation of alcohols is relatively smooth only if they contain activated hydroxyl groups, as in allyl alcohol, benzyl alcohol,[692] acetylenic alcohols,[693] cyanohydrins, trifluoroethanol,[694] mandelic acid,[695] 2-chloroethanol,[696] or 2-alkoxyethanols.[697]

Methylation of carbohydrates by dimethyl sulfate and alkali has been much used for preparative purposes. According to Haworth and Leitch[698] monosaccharides can be methylated as follows:

α-D-Glucose (37 g) is dissolved in water (10 ml), treated with dimethyl sulfate (about 30 g, (2 ml), and warmed in a water-bath to 35°. The mixture is vigorously stirred while part 238 ml) of a solution of sodium hydroxide (109 g) in water (190 ml) is slowly dropped in. The temperature is next raised to 40° and gradually during 3 h to 60°, whereafter the remainder of the sodium hydroxide solution and dimethyl sulfate (total 143 g, 109 ml) are run in slowly from two dropping funnels in approximately equal amounts with continued stirring. Finally the temperature is raised to 100° and stirring continued for a further 30 min. After cooling, the product is extracted in chloroform, dried, and fractionated. After removal of the chloroform, almost all the residue distils at 108–110°/0.23 mm; it at once solidifies when seeded with **β-pentamethylglucose.** The m.p. is 39–41°, and $[\alpha]_D$ is $-13.3°$.

Complete methylation of sucrose by dimethyl sulfate in ethereal solution has been described by Bredereck *et al.*[699]

c. Alkylation by *p*-toluenesulfonic esters

Like dimethyl sulfate, aromatic sulfonic esters are powerful alkylating agents. Aqueous or anhydrous alkali can be used for alkylation of phenols

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[688] K. Freudenberg, *Ann. Chem.*, **433**, 230 (1923); W. W. Haworth and H. Machemer, *J. Chem. Soc.*, **1932**, 2270.

[689] Ger. Pat. 122,851; cf. H. Meyer, *Monatsh. Chem.*, **24**, 837 (1903); G. Wolf, *J. Amer. Chem. Soc.*, **75**, 2673 (1953); G. W. Gray, J. B. Hartley, and A. Ibbotson, *J. Chem. Soc.*, **1955**, 2686; F. Faltis, G. Wagner, and E. Adler, *Ber. Deut. Chem. Ges.*, **77**, 686 (1944); see also H. Shapiro and K. A. Smith, *J. Chem. Soc.*, **1946**, 143.

[690] H. Decker and O. Koch, *Ber. Deut. Chem. Ges.*, **40**, 4794 (1907); cf. K. Freudenberg, *Ber. Deut. Chem. Ges.*, **53**, 1424 (1920).

[691] E. M. Marks, *J. Amer. Chem. Soc.*, **59**, 946 (1937).

[692] R. Pschorr and F. Dickhäuser, *Ber. Deut. Chem. Ges.*, **44**, 2639 (1911).

[693] W. Reppe and co-workers, *Ann. Chem.*, **596**, 74, 77 (1955).

[694] A. L. Henne and M. A. Smook, *J. Amer. Chem. Soc.*, **72**, 4378 (1950).

[695] W. Reeve and J. Cchristoffel, *J. Amer. Chem. Soc.*, **72**, 1482 (1950).

[696] L. C. Swallen and C. E. Boord, *J. Amer. Chem. Soc.*, **52**, 653 (1930).

[697] R. K. Summerbell and B. A. Neslon, *J. Amer. Chem. Soc.*, **77**, 5444 (1955).

[698] W. N. Haworth and G. C. Leitch, *J. Chem. Soc.*, **113**, 194 (1918).

[699] H. Bredereck, G. Hagelloch, and E. Hambsch, *Chem. Ber.*, **87**, 35 (1954).

with arenesulfonic esters.[700] Smooth alkylation is often achieved by bringing a sulfonic ester into reaction with the dry alkali phenoxide in solution in acetone or, in a method due to Claisen and Eisleb,[701] with a mixture of the phenol, acetone, and anhydrous potassium carbonate. According to Drahowzal and Klamann[702] phenols can be alkylated by *p*-toluenesulfonic esters in aqueous alkali, good yields being achieved by this method with esters of primary mono- or di-hydric alcohols; sulfonic esters of secondary or cyclalkane alcohols do not react so well.

Phenetole:[703] Phenol (19 g, 0.2 mole) is dissolved in 3N-sodium hydroxide solution (0.2 mole of NaOH), treated with ethyl *p*-toluenesulfonate (40 g), and heated and stirred under reflux on a boiling water-bath. Further 6N-sodium hydroxide solution (10 ml) was added and the whole heated for a further 30 min. After cooling, the upper, organic, layer was taken up in ether, washed with dilute sodium hydroxide solution, dried, and evaporated. The residue, distilled in a vacuum, gave the ethyl ether (19.2 g, 78.7%), n_D^{20} 1.5075.

It is not always necessary to isolate the sulfonic ester: the same ethers can be obtained by using *p*-toluenesulfonyl chloride,[703, 704] an alcohol, and a phenol. However, after reaction of the sulfonyl chloride with the alcohol it is necessary to adjust the alkali concentration to that required for alkylation before the phenol is added.

Nerolin:[703] *p*-Toluenesulfonyl chloride (47.5 g, 0.25 mole) and ethanol (20 g, 0.45 mole) are treated at 15° with 25% sodium hydroxide solution (40 ml) and stirred for 3 h at 15°. Then β-naphthol (29 g, 0.2 mole), sodium hydroxide (8 g, 0.2 mole), and water (10 ml) are added, bringing the sodium hydroxide concentration to about 4N. This mixture is heated for 30 min on a boiling water-bath, treated with 6N-sodium hydroxide solution (10 ml), and again heated for 30 min. A mass of crystals separates on cooling; this is filtered off, washed with dilute sodium hydroxide solution and with water, and dried. It constitutes ethyl β-naphthyl ether (nerolin), m.p. 36°, in a yield of 96% calculated on β-naphthol (*i.e.*, 33.0 g).

Aliphatic alcohols can also be converted into their ethers by *p*-toluenesulfonic esters. For this purpose, either the anhydrous alcohol is treated with the amount of sodium necessary for formation of the alkoxide or the corresponding amount of alkali hydroxide is dissolved in an excess of the alcohol, and the resulting mixture is brought into reaction with the *p*-toluenesulfonic ester. Yields are about 70–80% by both methods. When the costly higher aliphatic alcohols are in question the sodium alkoxide is prepared in benzene, and that mixture is treated at the boiling point with the sulfonic ester.

***n*-Butyl ethyl ether:**[703] Sodium (5 g, 0.22 mole) is dissolved in anhydrous ethanol (50 ml), and *n*-butyl *p*-toluenesulfonate (46 g, 0.2 mole) is added gradually. The mixture is then stirred and slowly warmed. Reaction begins spontaneously. When the exothermic reaction has ceased the mixture is boiled under reflux for 30 min, then cooled, treated with 10% sodium chloride solution and shaken. The ether that separates is removed, washed several times with sodium chloride solution, dried over sodium sulfate, and distilled, giving *n*-butyl ethyl ether, b.p. 90–91°, in 77.5% yield (15.8 g).

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[700] Z. Foldi, *Ber. Deut. Chem. Ges.*, **53**, 1839 (1920).

[701] L. Claisen and O. Eisleb, *Ann. Chem.*, **401**, 29 (1913).

[702] F. Drahowzal and D. Klamann, *Monatsh. Chem.*, **82**, 588 (1951).

[703] F. Drahowzal and D. Klamann, *Monatsh. Chem.*, **82**, 594 (1951).

[704] J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, **1951**, 2467; see also P. Shorigin and J. Kakaroff-Semljanski, *Ber. Deut. Chem. Ges.*, **65**, 1293 (1932).

2. Ether formation by replacement of halogen by oxygen: alkylation by halogen compounds

The classical Williamson ether synthesis is by reaction of alkyl halides with alkali alkoxides or phenoxides:

$$\mathrm{RONa} + \mathrm{R'X} \longrightarrow \mathrm{ROR'} + \mathrm{NaX}$$

It provides both unsymmetrical and symmetrical ethers by a simple and clear metathesis.

Alkyl iodides are used as the halide, when possible, as they react more readily than the bromides; chlorides are mostly still less reactive. However, the lower reactivity of alkyl chlorides and bromides can be overcome by adding a little sodium iodide to the reaction mixture (0.1–0.2 equivalent, warming).[705] Further, the halogen atoms of benzyl chloride,[374b, 706] furfuryl chloride,[707] allylic chlorides,[708–711] and epichlorohydrin[712] are easily replaced by alkoxyl groups. Unusually activated halogen compounds such as di- and tri-phenylmethyl halides,[713] and 2- and 4-nitrobenzyl chloride, react with alcohols to give ethers even when merely set aside or when warmed for a short time. The reaction of triphenylmethyl chloride with primary alcohols—secondary alcohols react appreciably more slowly—has special importance in carbohydrate chemistry (for a review see Helferich[714]).

When sodium alkoxides react with secondary or tertiary alkyl halides, loss of hydrogen halide can easily lead to formation of olefins alongside that of the ethers. The amount of this side reaction can be reduced by suitable choice of reactants: it is preferable to introduce the secondary or tertiary component as the alkoxide. Also olefin formation can be largely prevented by use of magnesium alkoxides.[715]

Alkoxides are prepared by the usual method, from the alkali metal and the appropriate alcohol. With complex alcohols, *e.g.*, partially substituted sugars, solvents such as anhydrous ether,[716] dioxan,[717] and liquid ammonia[718] are used. Alcohols that react sluggishly with sodium can often be converted into alkoxides by potassium or the liquid 2:1 potassium–

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[705] A. Wohl, *Ber. Deut. Chem. Ges.*, **39**, 1951 (1906).

[706] W. J. Monacelli and G. F. Hennion, *J. Amer. Chem. Soc.*, **63**, 1722 (1941).

[707] W. R. Kirner, *J. Amer. Chem. Soc.*, **50**, 1955 (1928).

[708] M. Conrad and C. Brückner, *Z. Phys. Chem.*, **4**, 631 (1889).

[709] W. T. Olson, H. F. Hipsher, C. M. Buess, I. A. Goodman, I. Hart, J. H. Lanneck Jr., and L. C. Gibbons, *J. Amer. Chem. Soc.*, **69**, 2451 (1947).

[710] M. Tamele, C. J. Ott, K. E. Marple, and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

[711] Cf. D. S. Tarbell, *Org. Reactions*, **2**, 22, 26 (1944).

[712] M. J. Böeseken, *Rec. Trav. Chim.*, **34**, 102 (1915).

[713] M. M. C. Friedel and J. M. Crafts, *Ann. Chim. (Paris)* [vi], **1**, 502 (1884).

[714] B. Helferich, *Advan. Carbohyd. Chem.*, **3**, 79 (1948).

[715] O. Diels and P. Blumberg, *Ber. Deut. Chem. Ges.*, **44**, 2847 (1911).

[716] A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946); K. Freudenberg and R. M. Hixon, *Ber. Deut. Chem. Ges.*, **56**, 2119 (1923).

[717] K. Freudenberg, K. Friedrich, and I. Bumann, *Ann. Chem.*, **494**, 57 (1932).

[718] K. Freudenberg and H. Boppel, *Ber. Deut. Chem. Ges.*, **71**, 2505 (1938); B. C. Hendricks and R. E. Rundle, *J. Amer. Chem. Soc.*, **60**, 2563 (1938); M. L. Wolfrom, W. W. Binkley, W. L. Shilling, and H. W. Hilton, *J. Amer. Chem. Soc.*, **73**, 3553 (1951).

sodium alloy.[719] Sodium alkoxides may also be prepared by means of sodamide in either an organic solvent[720] or in liquid ammonia.[721]

Moreover, alkoxides are often formed merely by adding alcoholic potassium hydroxide[722] or a suspension of alkali hydroxide[723] or alkali carbonate[701] to the alcohol.

The ether synthesis is effected either by heating a suspension of the alkoxide in the halide or by heating the alkoxide solution and the halide in a solvent, *e.g.*, in the alcohol being etherified. The following examples show applications of the Williamson synthesis.

For preparation of **ethyl isobutyl ether,**[724] sodium (9 g) is dissolved in pure isobutyl alcohol, and the excess of alcohol is distilled off in a stream of hydrogen at 180°. The residual sodium isobutoxide is rapidly powdered and then heated in a closed tube at 75° with ethyl iodide (60 g) until all the iodide has reacted (about 7 days). Isobutene escapes when the tube is opened. The ethyl isobutyl ether formed is distilled from the tube, washed with water, dried, and finally distilled over sodium (b.p. 79–80°). The yield is good.

It is not necessary to isolate the alkoxide in preparing 2-alkoxyethanols[725] from ethylene glycol and alkyl halides, α,α'-ethers from glycerol α,α'-dichloride,[726] or monoethers from 1,3-propanediol.[727] Ethylene glycol diethers, $ROCH_2CH_2OR'$, are best obtained by adding an alkyl halide to a solution of sodium in an excess of the monoether, $ROCH_2CH_2OH$.

Ethylene glycol dimethyl ether (1,2-dimethoxyethane):[728] Ethylene glycol monomethyl ether (2-methoxyethanol) (1830 g, 24 moles) is placed in a three-necked 3-l flask fitted with a reflux condenser and a stirrer, and sodium (138 g, 6.0 moles) is added in portions with stirring. When all the sodium has dissolved, methyl chloride is led in slowly, the temperature being maintained at 60°. After about 3 h, the mixture is cooled and the liquid is filtered from the sodium chloride that has separated. Distillation affords 422 g of ethylene glycol dimethyl ether (78%, calculated on sodium), b.p. 83.5–84.0°, n_D^{20} 1.3813.

Halo ethers of type $RO(CH_2)_nHal$ are formed on addition of an alcoholic solution of a sodium alkoxide to the corresponding dihalide in anhydrous ether; *e.g.*, 6-bromohexyl methyl ether is obtained in 80% yield from 1,6-dibromohexane and the theoretical amount of sodium methoxide in methanol.[729]

α,β-Dichloro aldehydes react readily below 15° with dilute sodium alkoxide solutions to give dialkoxy aldehydes in good yield.[730] Ethyl 3-bromopropionate and an excess of sodium in anhydrous ethanol afford ethyl 3-ethoxypropionate in 88% yield.[731] The preparation of alkoxy acids such as methoxyacetic acid

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[719] A. Baeyer, *Ber. Deut. Chem. Ges.*, **26**, 826, 2520 (1893).

[720] J. B. Wright, H. G. Kolloff, and J. H. Hunter, *J. Amer. Chem. Soc.*, **70**, 3098 (1948); R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France, Mém.*, [v], **14**, 341 (1947).

[721] C. L. Stevens and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **80**, 4072 (1958).

[722] J. U. Nef, *Ann. Chem.*, **318**, 7 (1901).

[723] U.S. Pat. 1,459,177; *Chem. Abstr.*, **17**, 2886 (1923).

[724] W. Lippert, *Ann. Chem.*, **276**, 160 (1893).

[725] F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, **1950**, 462.

[726] H. R. Henze and B. G. Rogers, *J. Amer. Chem. Soc.*, **61**, 433 (1939); **62**, 1758 (1940).

[727] L. I. Smith and J. A. Sprung, *J. Amer. Chem. Soc.*, **65**, 1276 (1943); G. M. Bennett and A. L. Hock, *J. Chem. Soc.*, **1927**, 472.

[728] J. V. Capinjola, *J. Amer. Chem. Soc.*, **67**, 1615 (1945).

[729] P. Baudart, *Bull. Soc. Chim. France*, [v], **11**, 336 (1944); see also N. L. Drake and co-workers, *J. Amer. Chem. Soc.*, **68**, 1537 (1946).

[730] L. Lichtenberger and M. Naftali, *Bull. Soc. Chim. France*, [v], **4**, 325 (1937).

[731] M. Swaminathan, *J. Indian Chem. Soc.*, **23**, 388 (1946).

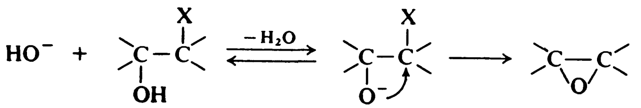
is described by Leffler and Calkins.[732] Ethoxyacetaldehyde diethyl acetal[733] is obtained by heating bromoacetaldehyde diethyl acetal and sodium ethoxide on a water-bath for 24 h. Further, aliphatic amino ethers can be synthesized by this method.

Tris-(2-ethoxyethyl)amine:[734] A solution of potassium hydroxide (6.24 g, 0.11 mole) in 95% ethanol (25 ml) is heated with tris-(2-chloroethyl)ammonium chloride for 3 h under reflux. The precipitated sodum chloride is filtered off, the alcoholic solution is evaporated at 10 mm, and the residue is dissolved in water. The solution is extracted with ether, and the extract is dried over magnesium sulfate and distilled, giving tris-(2-ethoxyethyl)amine, $(ROCH_2CH_2)_3N$ (2.80 g, 66%), b.p. 134–137°/12 mm (hydrochloride, m.p. 193–195°).

The Williamson ether synthesis can also be applied to heterocyclic compounds. 2-Chloro-4-quinolinamine and a solution of sodium in anhydrous 1-butanol, when heated for 24 h in a bomb-tube at 150°, give an 88% yield of 2-butoxy-4-quinolinamine.[735] 2-Chlorobenzothiazole is converted into 2-ethoxybenzothiazole by a solution of an equivalent amount of sodium in ethanol at 0°;[736] and ethyl 2-chloro-3-quinoxalinecarboxylate similarly gives ethyl 2-ethoxy-3-quinoxalinecarboxylate.[737]

It is possible to effect only partial replacement of the bromine of 2,4,6-tribromopyrimidine by alkoxyl: when a solution of two equivalents of sodium in anhydrous ethanol is used in benzene as solvent and room temperature is not exceeded, then the product is 4-bromo-2,6-diethoxypyrimidine (89% yield).[738] If the excess of ethanol is removed from a solution of sodium in ethanol and xylene by distillation and the residue is heated with 4-chloro-6-methoxy-2-pyrimidinamine for 2 hours under reflux, 4-ethoxy-6-methoxy-2-pyrimidinamine is formed;[739] but if more ethanol is present the methoxyl group is also replaced by ethoxyl and the product is 4,6-diethoxy-2-pyrimidinamine.

Treatment of α-chloro alcohols (chlorohydrins) with a base leads to epoxides (oxiranes).[1h] Epoxide formation is appreciably favored by alkyl substituents; thus, tetramethylethylene chlorohydrin (3-chloro-2,3-dimethyl-2-butanol) reacts 1000 times faster than ethylene chlorohydrin.[740, 741] The ease of ejection of the halogen X decreases in the order I > Br > Cl > F. The base used is normally an alkali or alkaline-earth hydroxide,[742] but occasionally an organic



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[732] M. T. Leffler and A. E. Calkins, *Org. Syn.*, **23**, 52 (1943); R. C. Fuson and B. H. Wojcik, *Org. Syn.*, Coll. Vol. II, 260 (1943).

[733] E. Späth, *Monatsh. Chem.*, **36**, 5 (1915).

[734] H. H. Richmond and G. F. Wright, *J. Amer. Chem. Soc.*, **67**, 2272 (1945).

[735] J. Büchi, H. Hurni, and R. Lieberherr, *Helv. Chim. Acta*, **32**, 1806 (1949).

[736] H. Gilman, K. E. Lentz, and J. A. Beel, *J. Amer. Chem. Soc.*, **74**, 1081 (1952).

[737] A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, **1945**, 622.

[738] B. W. Langley, *J. Amer. Chem. Soc.*, **78**, 2136 (1956).

[739] F. L. Rose and G. A. P. Tuey, *J. Chem. Soc.*, **1946**, 81.

[740] H. Nilsson and L. Smith, *Z. Phys. Chem.*, **A**, **166**, 136 (1933).

[741] E. N. Barantsevich and T. I. Temnikova, *Reakts. Sposobnost. Org. Soedin, Tartu. Gos. Univ.*, **3**, 81 (1966); *Chem. Abstr.*, **66**, 115200 (1967).

[742] H. T. Clarke and W. W. Hartman, *Org. Syn.*, Coll. Vol. I, 233 (1948).

base[743] or a salt that reacts alkaline (potassium or barium carbonate). The use of other epoxides, and in particular of ethylene oxide, plus a basic catalyst has been recommended for removal of hydrogen halide from halohydrins;[744] ether, benzene, and dioxan are favored as solvents; large batches of water-soluble halohydrins can be brought to reaction in an aqueous medium, but in such cases the residence time of the epoxide in the reaction mixture must be as short as possible (removal of the epoxide by distillation)[745–747] or the alkali hydroxide solution must be added to the halohydrin gradually and at as low a temperature as feasible.[748] Ethanol can also be used as solvent, particularly when the halohydrin is insoluble in water[749] or when use of ethanol leads to easier isolation of the epoxide.[750]

For the preparation of cyclic ethers containing large rings see Houben-Weyl's Handbook.[1h,j]

Phenols can also be converted into ethers by the procedures described above. As example, the preparation of *p*-nitrophenyl ethers recorded by Weygand and Gabler[751] is reproduced below—it can be carried out smoothly if ketones are used that boil higher than cyclopentanone. Other solvents used for such reactions are acetone, ethyl methyl ketone, dioxan,[752] toluene, xylene, and chlorobenzene. Similar methods can be used for etherification of *p*-hydroxybenzaldehyde with higher alcohols.

For the preparation of **heptyl *p*-nitrophenyl ether,** potassium *p*-nitrophenoxide (20 g) was boiled under reflux, with rapid stirring, with heptyl bromide (25 g) and cyclopentanone (60 g). Formation of a thick slurry of potassium bromide began in 30 min and the reaction was complete in 2.5 h. After cooling, the mixture was taken up in ether, shaken with sodium hydroxide solution, and worked up as usual. The ether was formed in 89% yield. Most of the cyclopentanone is recovered.

We exemplify the preparation of a higher alkoxybenzaldehyde by that of ***p*-octyloxybenzaldehyde:** *p*-Hydroxybenzaldehyde (6.1 g, 0.05 mole) and potassium hydroxide (4 g) are dissolved in cyclohexanol (50 ml) and mixed with a solution of octyl iodide (14.4 g, 20% excess) in cyclohexanol (50 ml). The mixture is then stirred vigorously for 4 h in an oil-bath at 120–130°; potassium iodide separates. After cooling, the mixture is taken up in ether, washed with water and with dilute hydrochloric acid, dried over sodium sulfate, freed from ether, and fractionated in a vacuum. The mixed ether distils at 162–163°/4 mm (7.6 g, 65%).

Alkyl aryl ethers can also be obtained by Claisen's method:[701] the phenol is treated with an alkyl bromide in boiling acetone (water-bath) containing potassium carbonate. The alkyl chloride in admixture with potassium iodide may be used instead of the alkyl bromide.[753, 754] The acetone may be replaced

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[743] P. Karrer and E. Rodmann, *Helv. Chim. Acta*, **31**, 1076 (1948).

[744] W. Bradley, J. Forrest, and O. Stephenson, *J. Chem. Soc.*, **1951**, 1589.

[745] H. O. House, *J. Amer. Chem. Soc.*, **77**, 5083 (1955); **78**, 2298 (1956).

[746] R. G. Kadesch, *J. Amer. Chem. Soc.*, **68**, 44 (1946).

[747] C. E. Wilson and H. J. Lucas, *J. Amer. Chem. Soc.*, **58**, 2399 (1936).

[748] E. Abderhalden and E. Eichwald, *Ber. Deut. Chem. Ges.*, **48**, 1854 (1915).

[749] F. Straus and A. Rohrbacher, *Ber. Deut. Chem. Ges.*, **54**, 58 (1921).

[750] N. F. Blau, J. W. Johnson, and C. G. Stucknisch, *J. Amer. Chem. Soc.*, **76**, 5107 (1954).

[751] C. Weygand and R. Gabler, *J. Prakt. Chem.*, [ii], **155**, 334 (1940).

[752] H. L. Yale, E. J. Pribyl, W. Braker, J. Bernstein, and W. A. Lott, *J. Amer. Chem. Soc.*, **72**, 3710 (1950).

[753] L. I. Smith, H. H. Hoehn, and A. G. Whitney, *J. Amer. Chem. Soc.*, **62**, 1863 (1940).

[754] F. Mauthner, *J. Prakt. Chem.*, [ii], **148**, 95 (1937).

by ethyl methyl ketone. If ketones react in the particular circumstances, *e.g.*, with phenolic aldehydes, alcohols may be used as solvent.[701, 755] The synthesis of allyl aryl ethers has been reviewed by Tarbell.[711]

Preparation of **allyl phenyl ether**[756] serves as example of Claisen's method of etherification: A mixture of phenol (188 g), allyl bromide (242 g), finely powdered potassium carbonate (280 g), and acetone (300 ml) is heated on the water-bath under reflux for 8 h. Potassium bromide separates. After cooling, the mixture is treated with water and extracted with ether. The ethereal solution is shaken with 10% sodium hydroxide solution, dried over potassium carbonate, and evaporated. Distillation of the residue in a vacuum gives the ether (230 g, 86%), b.p. 85°/19 mm.

Reaction of benzylic or allylic halides with sodium or potassium salts of phenols in solution leads to almost exclusive *O*-alkylation, whereas reaction in a heterogeneous system leads to almost complete *C*-alkylation.[757] In polar solvents (alcohol, acetone) there is mainly *O*-alkylation, but in apolar solvents (benzene, toluene) *o*-alkylphenols are the main products.[758, 759]

Alkylation of polyhydric phenols such as resorcinol, hydroxyhydroquinone, orcinol, and pyrogallol with an alkyl iodide and alkali gives nuclear alkylation products as well as aryl ethers.[760] In this reaction phloroglucinol gives hexamethyl-1,3,5-cyclohexanetrione; but there is a 65% yield of the *O*-alkylation product 1,3,5-trimethoxybenzene if the mixture is kept acid during the alkylation.[761] Philbrook and Massey[762] report the preparation of picryl ethers from silver picrate and alkyl halides.

Purely aromatic ethers such as diphenyl ether[763] can be prepared from aromatic halogen compounds and aryl oxides by a method due to Ullmann and Sponagel:[764–768] adding a little copper powder or copper salt to the reaction mixture increases the reactivity of the halogen in the aryl halide. Bromides are generally used, but chlorides will react if the aryl group contains also a nitro or a carbonyl group.[769] Addition of solvents or diluents[770] is recommended,[771] especially dimethylformamide.

Diphenyl ether is obtained[764] when a mixture of bromobenzene (15.7 g), phenol (11.8 g) potassium hydroxide (6.2 g), and copper bronze (*ca.* 0.1 g) is heated under reflux in an oil-bath at 210–230° for 2–2.5 h. Steam is then led through the mixture, whereupon unchanged bromobenzene distils first, and then diphenyl ether (12.7 g, 90%), m.p. 28°, b.p. 257°.

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[755] B. Loev and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 6095 (1956).

[756] L. Claisen, *Ann. Chem.*, **418**, 97 (1919).

[757] N. Kornblum and A. P. Lurie, *J. Amer. Chem. Soc.*, **81**, 2705 (1959).

[758] L. Claisen, P. Kremers, F. Roth, and E. Tietze, *Ann. Chem.*, **442**, 210 (1925).

[759] Review of ambidentate nucleophilic compounds: R. Gompper, *Angew. Chem. Intern. Ed., Engl.*, **3**, 500 (1964).

[760] J. Herzig and S. Zeisel, *Monatsh. Chem.*, **10**, 144 (1889); **11**, 291 (1890); J. Herzig and B. Erthal, *Monatsh. Chem.*, **32**, 491 (1911); cf. E. Ott and E. Nauen, *Ber. Deut. Chem. Ges.*, **55**, 924 (1922).

[761] J. Herzig and F. Wenzel, *Monatsh. Chem.*, **27**, 786 (1906).

[762] G. E. Philbrook and D. J. Massey, *J. Amer. Chem. Soc.*, **73**, 3454 (1951).

[763] H. E. Ungnade, *Chem. Rev.*, **38**, 405 (1946).

[764] F. Ullmann and S. Sponagel, *Ber. Deut. Chem. Ges.*, **38**, 2211 (1905).

[765] R. Q. Brewster and T. Groening, *Org. Syn.*, Col. Vol. II, 445 (1943).

[766] H. E. Ungnade and E. F. Orwell, *Org. Syn.*, **26**, 50 (1946).

[767] H. Stetter and G. Duve, *Chem. Ber.*, **87**, 1699 (1954).

[768] W. M. Whaley, L. Starker, and M. Meadow, *J. Org. Chem.*, **18**, 833 (1953).

[769] R. Scholl, O. Böttger, and L. Wanke, *Ber. Deut. Chem. Ges.*, **67**, 603 (1934).

[770] P. E. Fanta, *Chem. Rev.*, **38**, 149 (1946).

[771] N. Kornblum and D. L. Kendall, *J. Amer. Chem. Soc.*, **74**, 5782 (1952).

Ethers can be prepared under mild conditions from aromatic halogen compounds that contain *ortho*- or *para*-nitro groups.[772-775] Alkyl 2,4-dinitrophenyl ethers are obtained from 1-fluoro-2,4-dinitrobenzene and alcohols in the presence of triethylamine,[776] a reaction that can be used for identification of alcohols.

2,4-Dinitrophenyl propyl ether:[776] Triethylamine (3 drops) is added to a solution of 1-fluoro-2,4-dinitrobenzene (0.5 g) in propyl alcohol (0.2 g). After 12 h the mixture is acidified with hydrochloric acid, and the oil that separates is extracted in ether (3 × 20 ml). The ethereal extracts are washed with sodium hydrogen carbonate solution, then dried. After removal of the ether, the residue is recrystallized from aqueous methanol. This product (0.4 g) has m.p. 29°.

N.B.: 1-Fluoro-2,4-dinitrobenzene attacks the skin.

Bis(nitroaryl) ethers are obtained if *o*- or *p*-chloronitrobenzenes are boiled for several hours with the alkali salts of a mononitrophenol in dimethylformamide or dimethyl sulfoxide.[777]

In Purdie and Irvine's method[778] hydroxy compounds are alkylated by alkyl iodides in the presence of silver oxide. This method is of particular significance for methylation of carbohydrates, where, to avoid its oxidation, the reducing group is protected by glycosidation.

The methylation of methyl α-D-glucoside to **methyl tetra-*O*-methyl-α-D-glucoside** will be described:[779] Silver oxide (680 g, 9.5 moles) is added gradually to a mixture of methyl α-D-glucoside (60 g, 1 mole), methanol (200 ml), and methyl iodide (900 g), with initial cooling but later warming on the water-bath. The product is extracted with ether, and the extract is filtered and distilled in a vacuum, giving a product (62.5 g) of b.p. 148–150°/13 mm.

Etherification of a sugar is often incomplete, and methylation must be repeated several times to give the desired methoxyl content. Kuhn *et al.*[780] used methyl iodide and silver oxide in dimethylformamide and the repeated methylations were then unnecessary.

Permethylation of sucrose:[780] Sucrose (10.2 g) is dissolved in warm dimethylformamide (120 ml; b.p. 43–44°/12 mm) and treated at about 20° with methyl iodide (45 ml). Silver oxide (45 g) is then added with vigorous stirring during about 15 min. After addition of part (about 20 g) of the silver oxide the temperature has risen to about 30°, and care must be taken that the temperature is not exceeded during further additions. When the temperature begins to fall spontaneously (about 40 min after the last addition of silver oxide), the flask is closed and shaken mechanically. The solid material is then separated on a centrifuge and washed with dimethylformamide (50 ml) and chloroform (50 ml). The united solutions are treated with water (500 ml) and potassium cyanide (5 g) and extracted 4–5 times with chloroform (100-ml batches). The united chloroform extracts are washed with 3–4 batches of water (each 100 ml) and dried over sodium sulfate. They yield octa-*O*-methylsucrose (11.5 g), b.p. 140–145°/0.001 mm, n_D^{22} 1.4559.

The silver oxide can be replaced by barium hydroxide, which has no oxidizing action. Mixtures of strontium oxide and hydroxide or of barium oxide and

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[772] L. C. Raiford and J. C. Colbert, *J. Amer. Chem. Soc.*, **48**, 2652 (1926).

[773] F. Ullmann, *Ber. Deut. Chem. Ges.*, **29**, 1880 (1896).

[774] C. Willgerodt, *Ber. Deut. Chem. Ges.*, **12**, 762 (1879).

[775] R. W. Bost and F. Nicholson, *J. Amer. Chem. Soc.*, **57**, 2368 (1935).

[776] W. B. Whalley, *J. Chem. Soc.*, **1950**, 2241.

[777] J. J. Randall, C. E. Lewis, and P. M. Slagan, *J. Org. Chem.*, **27**, 4098 (1962).

[778] T. Purdie and J. C. Irvine, *J. Chem. Soc.*, **75**, 157, 485 (1899); **83**, 102 (1903); **79**, 957 (1901).

[779] W. N. Haworth, *J. Chem. Soc.*, **107**, 13 (1915).

[780] R. Kuhn, H. Trischmann, and I. Löw, *Angew. Chem.*, **67**, 32 (1955); cf. R. Kuhn, H. H. Baer, and A. Seeliger, *Ann. Chem.*, **611**, 236 (1958).

hydroxide in dimethylformamide as solvent permit particularly mild methylation.[781]

Triphenylmethyl ethers of sugars are important, as well as the methyl,[782] ethyl, and benzyl ethers.[783] For a comprehensive collection of references see Staněk *et al.*[784]

Carbohydrate ethers can also be obtained from alkyl halides and the sodium derivatives of carbohydrates. The alkali derivatives can be prepared by treating the sugar or a derivative thereof with sodium in liquid ammonia, ether, or dioxan.

This method has been applied to the preparation of **3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucose:**[783] 1,2:5,6-Di-*O*-isopropylidene-α-D-glucose (45 g, 0.17 mole) is dissolved in anhydrous ether (500 ml) in a flask (250 ml) fitted with a drying tube, and is there treated with sodium wire (9 g, 0.39 mole). The mixture is set aside for 16 h, then the unchanged sodium is removed. Next, benzyl bromide (22 ml, 0.18 ml) is dropped in, whilst the ether is being removed. The temperature rises gradually to 70° and is kept at that point for 5 h. The residue is dissolved in light petroleum (b.p. 60–70°) and washed with five portions of water (each 200 ml). The solvent is removed in a vacuum and the residue is distilled in a high vacuum, giving the product, b.p. 146–149°/0.05 mm, in 63–73% yield (38–44 g).

Triphenylmethyl chloride attacks primary hydroxyl groups preferentially, and with the usual sugars etherifies only the hydroxyl group in position 6. As the triphenylmethyl group is easily removed by dilute acid (see page 392) this permits sugar derivatives to be obtained that have a free 6-hydroxyl group: first, the sugar is caused to react with triphenylmethyl chloride, then the remaining hydroxyl groups are, *e.g.*, acetylated, and finally the triphenylmethyl group is removed.[714, 785]

6-*O*-Trityl-α-D-glucose:[786] A cold solution of anhydrous glucose (36 g) in anhydrous pyridine (180 ml) is treated with triphenylmethyl chloride (58 g) and left for one or two days at room temperature. An addition product of triphenylmethanol and hydrogen chloride separates; this is filtered off and the filtrate is treated with water, dropwise at 0°, to incipient turbidity. The mixture is placed in ice for 0.5 h, then poured into ice-water (1.75 l). The pale yellow oil that separates is digested with water several times, allowed to agglomerate, and then dissolved in methanol (200 ml). When the solution is set aside, a little triphenylmethanol first separates and then the tritylglucose crystallizes at 0°. The latter is dried on a porous plate, giving a crude yield of 36% (30 g). For purification it is crystallized from anhydrous ethanol, affording a diethanolate of m.p. 57–58°.

Trityl ethers are also important for the synthesis of mixed glycerides. Glycerol can be made to react with either one or two molecules of triphenylmethyl chloride.

Glycerol 1-trityl ether:[787] Glycerol (8 g) and triphenylmethyl chloride (12 g) are dissolved in pyridine (30 ml), then set aside for 16 h at room temperature and next poured into water without regard to the pyridine hydrochloride that has crystallized. An oil separates and it

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[781] S. R. Kuhn and co-workers, *Angew. Chem.*, **72**, 808 (1960).

[782] E. J. Bourne and S. Peat, *Advan. Carbohyd. Chem.*, **5**, 145 (1950).

[783] C. M. McCloskey, *Advan. Carbohyd. Chem.*, **12**, 137 (1957).

[784] A comprehensive list of references is given by J. Staněk, M. Černý, J. Kocourek, and J. Pacák in "The monosaccharides," Publishing House of the Czechoslovak Academy of Sciences, Prague, 1963, p. 300.

[785] B. Helferich and J. Becker, *Ann. Chem.*, **440**, 1 (1924); B. Helferich, *Angew. Chem.*, **41**, 871 (1928).

[786] B. Helferich, L. Moog, and A. Jünger, *Ber. Deut. Chem. Ges.*, **58**, 875 (1925).

[787] B. Helferich, P. E. Speidel, and W. Toeldte, *Ber. Deut. Chem. Ges.*, **56**, 769 (1923).

is dissolved in ether, washed successively with hydrochloric acid, water, and sodium hydrogen carbonate solution, dried, and evaporated. The oily residue gradually solidifies when kept at 0° and after recrystallization successively from ethanol, benzene, and ethyl acetate affords analytically pure glycerol 1-trityl ether (3 g), m.p. 92–94°.

For the preparation of glycerol ditrityl ether (m.p. 170–171°; presumably the 1,3-diether), glycerol (1 g) is heated with triphenylmethyl chloride (7 g) in pyridine (20 ml) for 30 min on the water-bath. Working up is as described above.

3. Ether formation by replacement of nitrogen by oxygen: alkylation by diazomethane

Diazomethane reacts with phenols under mild conditions in an inert medium such as ether, alcohol, or chloroform and is particularly valuable for quantitative methylation of sensitive or valuable phenols.

$$C_6H_5OH + CH_2N_2 \longrightarrow C_6H_5OCH_3 + N_2$$

N.B.: Diazomethane is extremely **poisonous** and experiments with it should be conducted under a powerful hood. Undiluted gaseous diazomethane is **highly explosive.**

Etherification of aliphatic alcohols is in general a slow reaction, so that many carboxylic acids can be esterified, and many phenols etherified, by means of diazomethane in alcoholic solution.

However, aliphatic alcohols can be alkylated by diazomethane if boron trifluoride etherate,[788] hydrogen tetrafluoroborate,[789] or aluminum chloride[788] is added to the reaction mixture. Further, aliphatic alcohols can be methylated without further ado by diazomethane if hexane or heptane replaces ether as the solvent.[790] Also the hydroxyl groups of hydroxy acids such as tartaric acid and their esters are smoothly methylated by diazomethane in ether;[791, 792] and aliphatic alcohols can be methylated by diazomethane in the presence of sulfur dioxide or sublimed selenium dioxide, this reaction proceeding by way of the unstable alkyl methyl sulfite or selenite, respectively.[793]

II. Esters

1. Replacement of oxygen by oxygen

a. Carboxylic esters from carboxylic acids and alcohols

Alcohols and acids interact with loss of water to give esters:[1c]

$$RCOOH + R'OH \longrightarrow RCOOR' + H_2O$$

This is an equilibrium reaction. So, in accord with the law of mass action, the yield of ester is increased by increasing the concentration of either of the

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[788] E. Müller and W. Rundel, *Angew. Chem.*, **70**, 105 (1958); E. Müller and co-workers, *Ann. Chem.*, **662**, 38 (1963).

[789] M. C. Caserio, J. D. Roberts, M. Neeman, and W. S. Johnson, *J. Amer. Chem. Soc.*, **80**, 2584 (1958); M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).

[790] H. Meerwein, T. Bersin, and W. Burneleit, *Ber. Deut. Chem. Ges.*, **62**, 1006 (1929); cf. H. Meerwein and G. Hinz, *Ann. Chem.*, **484**, 1 (1930).

[791] G. Hesse, F. Exner, and H. Hertel, *Ann. Chem.*, **609**, 60 (1957).

[792] O. T. Schmidt and co-workers, *Ber. Deut. Chem. Ges.*, **74**, 33 (1941).

[793] G. Hesse, *Angew. Chem.*, **70**, 134 (1958).

starting materials; and the same effect is produced by removing the product water or the ester from the reaction mixture. However, such an esterification becomes a practical reaction only if the temperature is raised or if an acid catalyst is added.

The rate of esterification depends on the structures of the acid and the alcohol in question: primary alcohols are esterified faster than secondary or tertiary ones, and the same series primary > secondary > tertiary holds for the carboxylic acids. Difficulties arise in esterification of tertiary alcohols with the usual acid catalysts in that olefins are readily formed under their influence. Also, in the aromatic series steric effects can reduce the rate of esterification, *e.g.*, *ortho*-substituted carboxylic acids react with difficulty.

i, Esterification in absence of special catalysts

Because of its acidity any carboxylic acid must catalyse its own esterification, so that esters can be produced merely by heating together the acid and the alcohol. Indeed, strongly acidic carboxylic acids such as formic, oxalic, and pyruvic acid pass into their esters simply when heated with an alcohol; and this method assumes preparative importance when the instability of the carboxylic acid in presence of mineral acids excludes the use of the latter as catalyst for the esterification.

The yield of ester can be raised appreciably by continuous removal of the water produced. If neither of the reactants boils at a lower temperature than water, the latter can be removed merely by distillation, as in the preparation of triglycerides from glycerol and a relatively involatile higher fatty acid or in the preparation of pentyl pyruvate. According to Simon[794] the latter ester is obtained in 99% yield by heating pyruvic acid and the equivalent amount of pentyl alcohol in a water-pump vacuum, provided that after equilibrium has become established the water formed is slowly distilled off.

Benzyl phenylacetate: Phenylacetic acid (1 mole) and benzyl alcohol (2 moles) are heated in a round-bottomed flask (500 ml) under a descending condenser so that a mixture of benzyl alcohol and water distils over. The upper, aqueous, layer of the distillate is removed and the benzyl alcohol is returned to the flask. After 1–1.5 days the reaction is complete, 1 mole of water having distilled off. The mixture is finally fractionated in a vacuum, yielding benzyl phenylacetate, b.p. 270°/166 mm, in a 95% yield.

Continuous removal of the product water by azeotropic distillation after addition of a carrier such as benzene, toluene, xylene, or a halogenated aliphatic solvent leads to rapid esterification ("azeotropic esterification") and usually also to high yields. The course of the reaction can be followed directly from the amount of water liberated; the apparatus used for this purpose (a water separator) is well known.

Thielepape[795] removed the product water from the azeotropic mixture by allowing the distillate to drop into an extraction thimble filled with calcium carbide before the organic phase was returned to the reaction mixture.

If a relatively involatile acid is to be esterified with a readily volatile alcohol an alcohol–water mixture can be allowed partly to distil away continuously

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[794] L. Simon, *Ber. Deut. Chem. Ges.*, **26**, ref. 769 (1893).

[795] E. Thielepape, *Ber. Deut. Chem. Ges.*, **66**, 1454 (1933).

from the boiling reaction mixture, being then dried over roasted potassium carbonate before being continuously returned to the process; this method was described by Kenyon[796] for the preparation of **diethyl oxalate**:

Aqueous alcohol is distilled from a mixture of anhydrous oxalic acid (180 g) and ethanol (500 ml), through a short column, into a second flask containing roasted potassium carbonate (200 g) under ethanol (250 ml). This second flask is heated just to the boiling point of alcohol and is connected to the reaction flask by a slightly inclined tube so that the vapor of the dehydrated alcohol passes back into the reaction mixture. After 5 hours' heating diethyl oxalate is thus obtained in 80–90% yield.

Formic esters are formed merely by heating the acid with the desired alcohol.[797] Ethyl formate, for instance, is obtained by slowly distilling a mixture of ethanol (35 ml), formic acid (20 ml), and water 50 ml, the ester (b.p. 54°) distilling over in 83.4% yield.

According to Guérin[798] ethyl hydrogen tartrate is formed smoothly on distillation of the acid with anhydrous ethanol; the product crystallizes on addition of water.

Ethyl hydrogen oxalate: According to Anschütz[799] this is obtained as follows. Equal amounts of anhydrous oxalic acid and anhydrous ethanol are heated slowly to 135° and are then allowed to cool, filtered from the excess of oxalic acid, and concentrated in a vacuum until the temperature of the oil-bath reaches at most 140°. Decomposition of the residual dissolved oxalic acid is shown by gradual worsening of the vacuum, and proceeds gradually until it is complete when the vacuum is regenerated. Finally, when the water-pump vacuum is re-established the mixture is distilled and fractionation provides pure ethyl hydrogen oxalate, b.p. 117°/15 mm.

Esterification of glycerol with higher fatty acids occurs with particular ease; no catalyst is needed, but adding zinc dust has been found to accelerate the reaction. This is exemplified by the preparation of **glycerol tridecanoate** from glycerol and tridecanoic acid as described by Verkade *et al.*[800] but modified by Weygand:

Tridecanoic acid (8 g), distilled, anhydrous glycerol (1.1 g), and a pinch of zinc dust under a slow stream of carbon dioxide are heated gradually at 150 mm during 7 h from 130° to 200° (bath temperatures), then the pressure is reduced to 120 mm and the temperature is raised during a further 3 h to 240°. The residue in the flask was taken up, whilst still warm, in ether, filtered from zinc and zinc soap, and, again while warm, neutralized to phenolphthalein with alcoholic potassium hydroxide. This solution was decolorized with animal charcoal, filtered again, treated with twice its volume of ethanol, and left to crystallize at 0°. Next morning the triglyceride was filtered off and washed carefully with ice-cold alcohol; after drying, it had m.p. 43.0°.

ii, Esterification with addition of catalysts

Sulfuric and hydrochloric acid are the usual catalysts for esterification, but phosphoric and arenesulfonic acids, acid salts, and acid cation-exchangers are also used. Mineral acids act not merely as catalysts but also have water-binding properties; so they are generally used in greater than catalytic amounts, usually 5–10%.

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[796] J. Kenyon, *Org. Syn.*, Coll. Vol. I, 258 (1933).

[797] F. Bodroux, *C. R. Hebd. Séances Acad. Sci.*, **160**, 204 (1915); see also M. H. Palomaa, *Ann. Acad. Sci. Fenn.*, *A*, **4**, No. 2, 1 (1913).

[798] Guérin, *Ann. Chim. (Paris)*, **22**, 252 (1837).

[799] R. Anschütz, *Ber. Deut. Chem. Ges.*, **16**, 2413 (1883).

[800] P. E. Verkade, J. van der Lee, and W. Meerburg, *Rec. Trav. Chim.*, **51**, 851 (1932).

When sulfuric acid is used the technique is to heat a mixture of the carboxylic acid with a four- to five-fold amount of the alcohol for 5–7 hours. Pyridine- and quinoline-carboxylic acids[801] require for their esterification appreciably more catalyst acid than usual; but in general too high concentrations of sulfuric acid lead to decomposition.

The customary method of using hydrochloric acid is to saturate an alcoholic solution of the carboxylic acid with gaseous hydrogen chloride, a method that permits mild esterification of sensitive substances at room temperature, or if necessary with cooling. In general, however, the mixture is heated under reflux even when hydrochloric acid is used, the HCl concentration being maintained by occasionally passing in more gaseous hydrogen chloride.

The preparation of **ethyl benzoate** provides an example of a generally applicable technique for acid-catalysed esterification:[802] Benzoic acid (50 g) is boiled under reflux for 3 h with anhydrous ethanol (100 g) containing concentrated sulfuric acid (10 g), then most of the alcohol is distilled off on the water-bath. The residue is treated with five times its amount of water and neutralized with solid sodium carbonate. The oil that separates is removed in ether, and the ethereal solution is dried over potassium carbonate. The ether is distilled off and the residue is fractionated, affording almost 90% (55 g) of ethyl benzoate, b.p. 95°/17 mm.

Use of hydrogen chloride as catalyst (100 g of anhydrous ethanol containing 3% of HCl), boiling for 2 h, and analogous working up gives 76% of the theoretical amount of ethyl benzoate.

Azeotropic esterification, applied to the acid-catalysed reaction, permits a considerable saving in mineral acid. Mineral acids can then be replaced by aliphatic or aromatic sulfonic acids, and decomposition is then reduced. Secondary as well as primary alcohols can be converted into esters by azeotropic esterification, but in general not tertiary alcohols.

Methyl esters of carboxylic acids cannot be prepared by the usual method of azeotropic esterification. In a process for production of methyl esters, Clinton and Laskowski[803] heated a carboxylic acid with methanol for 6–15 h in the presence of methylene dichloride or 1,2-dichloroethane and with sulfuric acid as catalyst, without removing the product water; then they separated the organic phase containing the ester, washed it with sodium hydrogen carbonate solution, and worked it up as usual.

A further method of preparing methyl esters was provided by Lorette and Brown Jr.[804] who used acetone dimethyl acetal as water-binding agent:

$$\mathrm{RCOOH + CH_3OH \xrightarrow{H^+} RCOOCH_3 + H_2O}$$

$$\mathrm{H_2O + (CH_3)_2C(OCH_3)_2 \longrightarrow 2CH_3OH + (CH_3)_2CO}$$

Aliphatic amino esters can be prepared by boiling the amino acid with alcohol and an excess of hydrogen chloride.

Glycine ethyl ester hydrochloride:[805] A mixture of glycine and ethanol is saturated with hydrogen chloride and then boiled for 4 h under reflux. On cooling, the ester hydrochloride crystallizes. The yield may be increased by working up the mother liquor.

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[801] R. Camps, *Arch. Pharm.*, **240**, 346 (1902).

[802] E. Fischer and A. Speier, *Ber. Deut. Chem. Ges.*, **28**, 3252 (1895).

[803] R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

[804] N. B. Lorette and J. H. Brown Jr., *J. Org. Chem.*, **24**, 261 (1959).

[805] T. Curtius and F. Goebel, *J. Prakt. Chem.*, [ii], **37**, 159 (1888).

p-Aminophenylacetic acid hydrochloride[806] is converted into its ethyl ester merely on recrystallization from ethanol.

A method of esterification introduced by Meyer[807] is to dissolve the carboxylic acid in an excess of concentrated sulfuric acid (if necessary with warming) and to treat the solution cautiously with a small excess of the requisite alcohol; when the reaction, which is often violent, ceases—if the mixture does not become warm, it must be heated—the solution is poured on solid sodium carbonate and worked up. This method has been used for esterification of sterically hindered acids and for carboxy derivatives of nitrogenous heterocycles, also for preparation of acetonedicarboxylic esters from citric acid and alcohols.[808]

Anhydrous salts[809] can often be used with advantage in place of the catalysts discussed above, *e.g.*, copper, iron, nickel, zinc, cobalt, or manganese sulfate. Hydroxy acids such as lactic, 2-hydroxybutyric, and hydroxyvaleric acid are smoothly esterified in the presence of anhydrous copper sulfate.[810]

Acid chlorides such as thionyl chloride, acetyl chloride, stearoyl chloride, and chloroformic esters have also proved to be very effective esterification catalysts, being superior to mineral acids for, in particular, heat-sensitive substances.[811] Even acids that react sluggishly, such as 2-phenyl-4-quinolinecarboxylic acid, can be esterified in good yield by using chlorosulfonic acid, of which only small quantities are required (0.01–0.05 equivalent).[812]

Dimethyl sulfite,[813] boron trifluoride,[148, 814, 815] aromatic sulfonyl chlorides,[816] and phosphoryl chloride[817] have also proved their value for catalysing esterifications.

Esterification in the presence of phosphoryl chloride is carried out as follows: The carboxylic acid is dissolved or suspended in three to fives times its weight of the alcohol; then phosphoryl chloride (3–5% calculated on the amount of acid used) is dropped into this solution with stirring and cooling during 20–30 min at such a rate that the temperature does not rise above 30–40°.

The phosphoryl chloride may also be added in larger portions with shaking; the mixture must then be either boiled for 2–3 h or set aside at room temperature for 1–3 days.

For the synthesis of esters that cannot be obtained by the usual methods, Staab[818] recommends the use of 1,1′-carbonyldiimidazole; this process is useful for preparing esters of acid-sensitive alcohols or acids.

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[806] H. Salkowski, *Ber. Deut. Chem. Ges.*, **28**, 1917 (1895); B. Flürsheim, *J. Prakt. Chem.*, [ii], **68**, 347 (1903).

[807] H. Meyer, *Monatsh. Chem.*, **25**, 1202 (1904).

[808] G. Schroeter, *Ber. Deut. Chem. Ges.*, **49**, 2710 (1916).

[809] A. Bogojawlensky and J. Narbutt, *Ber. Deut. Chem. Ges.*, **38**, 3344 (1905).

[810] E. Clemmensen and A. H. C. Heitman, *J. Amer. Chem. Soc.*, **42**, 319 (1909).

[811] K. Freudenberg and W. Jakob, *Ber. Deut. Chem. Ges.*, **74**, 1001 (1941).

[812] J. Erdos, *Angew. Chem.*, **63**, 329 (1951).

[813] J. C. Sheehan and R. C. O'Neill, *J. Amer. Chem. Soc.*, **72**, 4614 (1950).

[814] H. D. Hinton and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **54**, 2017 (1932).

[815] F. J. Sowa and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **58**, 271 (1936); T. B. Dorris and F. J. Sowa, *J. Amer. Chem. Soc.*, **60**, 358 (1938).

[816] J. H. Brewster and C. J. Ciotti Jr., *J. Amer. Chem. Soc.*, **77**, 6214 (1955).

[817] J. Klosa, *Arch. Pharm.*, **289**, 125 (1956).

[818] H. A. Staab, *Angew. Chem.*, **71**, 194 (1959).

The preparation of **phenyl benzoate** is an example of this: 1,1′-Carbonyldiimidazole (3.24 g) is added to benzoic acid (2.44 g) in dry tetrahydrofuran (30 ml) at room temperature. When evolution of carbon dioxide ceases, the mixture is treated with phenol (1.88 g) and heated under reflux for a further hour. Evaporation of the tetrahydrofuran and washing with water leaves pure phenyl benzoate, m.p. 70°, in 85% yield.

Brewster and Ciotti Jr. prepare esters of tertiary alcohols by adding *p*-toluenesulfonyl chloride to the acid and the alcohol in pyridine; an anhydride is formed as intermediate, which reacts at once with the alcohol.

General directions:[816] The carboxylic acid (1 part) is dissolved in pyridine (20–50 parts), a salt often separating. Benzene- or *p*-toluene-sulfonyl chloride (2 equivalents) is then added to the mixture, which is next cooled to 0° and treated with the alcohol or phenol (1 equivalent). The whole is set aside for a further hour and then poured into three or four times its volume of water. The yields of ester are excellent.

Tertiary acetylenic alcohols can also be esterified by that method[819] although they react too slowly for other methods to be successful.

Ammonium salts of carboxylic acids react with alcohols according to the equation:

$$RCOONH_4 + R'OH \rightleftharpoons RCOOR' + NH_3 + H_2O$$

This forms the basis for a method of esterification[820] that is particularly useful for acid-sensitive starting materials; and the need to use anhydrous ammonium salts can be avoided by a modification[821] in which ammonium carbonate, the carboxylic acid, and the alcohol are heated together in water.

b. Carboxylic esters by alkylation with dimethyl sulfate

Dialkyl sulfates can be used in place of alkyl halides for alkylation of carboxylic acids, particular importance attaching to dimethyl sulfate.

Under mild conditions reaction occurs according to equation (1):

$$RCOONa + (CH_3)_2SO_4 \longrightarrow RCOOCH_3 + CH_3OSO_3Na \qquad \dots (1)$$

$$2RCOONa + (CH_3)_2SO_4 \longrightarrow 2RCOOCH_3 + Na_2SO_4 \qquad \dots (2)$$

The dimethyl sulfate can be utilized completely (equation 2) if the mixture is heated in a bomb tube.

N.B.: Dimethyl sulfate is **highly poisonous.** Experiments with it must be conducted under a hood, and glassware must be washed with methanolic ammonia after use.

The reaction is carried out in aqueous solution at room temperature or with gentle warming.[822] The carboxylic acid is dissolved in the calculated amount of alkali hydroxide solution, and the alkylating agent is dropped in with stirring. Subsequent warming (to 60°) usually ensures complete reaction. The excess of dimethyl sulfate can be removed by heating with sodium carbonate solution on a water-bath. If methylation in aqueous solution is impossible it suffices to heat the dry potassium salt of the carboxylic acid with dimethyl sulfate.[823]

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[819] J. Klosa, *Angew. Chem.*, **69**, 135 (1957).

[820] E. M. Filachione, E. J. Costello, and C. H. Fisher, *J. Amer. Chem. Soc.*, **73**, 5265 (1951).

[821] R. R. Ballaro. *Rev. Fac. Cienc. Quim., Univ., Nac. La Plata*, **25**, 31 (1952).

[822] A. Werner and W. Seybold, *Ber. Deut. Chem. Ges.*, **37**, 3658 (1904).

[823] C. Graebe, *Ann. Chem.*, **340**, 246 (1905).

Free carboxylic acids can be advantageously treated with dimethyl sulfate in organic solvents, according to the following **general procedure:**[1b]

An acetone solution of a carboxylic acid and an equivalent amount of dimethyl sulfate is dropped, with stirring, into a boiling mixture of acetone and the equivalent amount of finely powdered potassium carbonate; the mixture is then boiled for several hours with stirring, and the ester is isolated as usual.

c. Carboxylic esters by acylation with acid anhydrides

Acylation of alcohols and phenols by acid anhydrides is often a simpler process than that with acid chlorides:

$$\mathrm{RCO{-}O{-}COR + R'OH \longrightarrow RCOOR' + RCOOH}$$

Adding small amounts of concentrated sulfuric acid,[824–826] perchloric acid,[827] zinc chloride,[828–832] acetyl chloride,[833, 834] alkali acetate,[78e, 835–837] or tertiary base[838] accelerates the reaction considerably.

The reaction is particularly important in carbohydrate chemistry. Micheel[839] has reviewed the subject.

α-D-Glucose pentaacetate:[840] Acetic anhydride (1 l) is treated cautiously with 70% perchloric acid (0.5–1 ml), and glucose (250 ml) is added to this mixture with stirring and cooling in ice. This mixture is set aside for 2 h at room temperature, then poured slowly, with stirring, into ice-water (4 l), giving a white precipitate. The whole is set aside for 10–12 h so that the excess of acetic anhydride may be destroyed. The acetate is then filtered off, suspended in water (5 l), again collected, and dried on filter paper in the air. The yield is 70% (390 g), and the m.p. is 109–110° after crystallization from ethanol.

Wohl and Oesterlin describe the preparation of **tartaric anhydride diacetate:**[841] A mixture of acetic anhydride (120 ml) and concentrated sulfuric acid (3 ml) is poured on finely powdered tartaric acid (100 g), considerable heat being evolved and the tartaric acid dissolving. The mixture is boiled for a short time, then cooled. Tartaric anhydride diacetate crystallizes in almost quantitative yield and is filtered off and washed with benzene. The crude product can be used for preparation of carbon suboxide. For purification it is crystallized from benzene, then having m.p. 135°.

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[824] W. W. Prichard, *Org. Syn.*, **28**, 68 (1948).

[825] A. P. N. Franchimont, *Ber. Deut. Chem. Ges.*, **14**, 1920 (1881).

[826] R. Burns, D. T. Jones, and P. D. Ritchie, *J. Chem. Soc.*, **1935**, 403.

[827] D. Krüger and W. Roman, *Ber. Deut. Chem. Ges.*, **69**, 1830 (1936); cf. ref. 840.

[828] E. Erwig and W. Koenigs, *Ber. Deut. Chem. Ges.*, **22**, 1464, 2207 (1889).

[829] A. P. N. Franchimont, *Ber. Deut. Chem. Ges.*, **12**, 2059 (1879).

[830] C. S. Hudson and J. K. Dale, *J. Amer. Chem. Soc.*, **37**, 1264 (1915).

[831] R. H. Baker and F. G. Bordwell, *Org. Syn.*, **24**, 18 (1944).

[832] W. H. Perkin Jr. and J. L. Simonsen, *J. Chem. Soc.*, **85**, 858 (1905).

[833] F. Adickes, *J. Prakt. Chem.*, [ii], **161**, 275 (1943).

[834] G. R. Clemo and S. B. Graham, *J. Chem. Soc.*, **1930**, 215.

[835] C. Liebermann, *Ber. Deut. Chem. Ges.*, **11**, 1619 (1878).

[836] H. Meyer, *Monatsh. Chem.*, **34**, 651 (1913); W. S. Emerson and co-workers, *J. Amer. Chem. Soc.*, **68**, 1665 (1946).

[837] T. J. Otterbacher, *Org. Syn.*, Coll. Vol. I, 285 (1941).

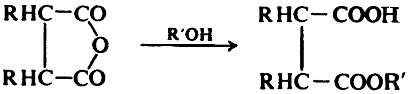
[838] C. Liebermann, *Ann. Chem.*, **331**, 362 (1904).

[839] F. Micheel, "Chemie der Zucker und Polysaccharide," 2nd ed, Akademische Verlagsgesellschaft Geest & Portig K. G., Leipzig, 1956, pp. (a) 75, (b) 120.

[840] S. D. Nicholas and F. Smith, *Nature* (*London*), **161**, 349 (1948).

[841] A. Wohl and C. Oesterlin, *Ber. Deut. Chem. Ges.*, **34**, 1139 (1901).

Cyclic anhydrides are cleaved by alcohols to give acid esters:[842-847]



Use of phthalic anhydride in this way provides a useful method of separating alcohols from mixtures containing them.[843, 847]

d. Carboxylic esters by transesterification

When an ester is heated with a different alcohol, a reaction known as "transesterification" occurs. It is catalysed by acids[848-851] or bases: [852-857]

$$RCOOR' + R''OH \rightleftarrows RCOOR'' + R'OH$$

A large excess of the alcohol R''OH is used so as to shift the equilibrium in the desired direction.

This alcoholysis of carboxylic esters under the influence of alkaline catalysts is important for the preparation of esters of long-chain alcohols with heat-sensitive carboxylic acids, *e.g.*, with β-keto carboxylic acids,[858-864] and of esters of acid-sensitive alcohols[860-863] that cannot be subjected to the usual methods of esterification. For such reactions sodium alkoxides,[853] sodium hydroxide,[854, 855] and potassium carbonate[856] have proved useful as catalysts.

Geranyl anthranilate, which is difficult of access by other methods, can be obtained as follows: One equivalent each of methyl anthranilate and geraniol are heated at 100–120° with 0.05 equivalent of sodium, aluminum, or magnesium alkoxide. Methyl alcohol distils off slowly; the reaction can be accelerated by working in a vacuum. When distillation ceases,

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[842] J. Cason, *Org. Syn.*, **25**, 19 (1945).

[843] E. L. Eliel and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **71**, 2252 (1949).

[844] R. Adams and J. M. Wilkinson Jr., *J. Amer. Chem. Soc.*, **65**, 2207 (1943).

[845] J. W. Brühl, *Ber. Deut. Chem. Ges.*, **26**, 284, 1097 (1893).

[846] E. Blaise and A. Koehler, *C. R. Hebd. Séances Acad. Sci.*, **148**, 489 (1909).

[847] K. Freudenberg, K. Friedrich, and I. Bumann, *Ann. Chem.*, **494**, 56 (1932).

[848] J. C. Sauer, B. E. Hain, and P. W. Boutwell, *Org. Syn.*, **20**, 67, 69 (1940).

[849] C. E. Rehberg and C. H. Fisher, *J. Amer. Chem. Soc.*, **66**, 1203 (1944); C. E. Rehberg, *Org. Syn.*, **26**, 18 (1946).

[850] E. Fischer and M. Bergmann, *Ber. Deut. Chem. Ges.*, **52**, 833 (1919).

[851] R. Baltzly and J. S. Buck, *J. Amer. Chem. Soc.*, **63**, 2022 (1941).

[852] E. E. Reid, *Ind. Eng. Chem.*, **29**, 1344 (1937).

[853] J. Purdie, *Ber. Deut. Chem. Ges.*, **20**, 1555 (1887).

[854] M. Reimer and H. R. Downes, *J. Amer. Chem. Soc.*, **43**, 945 (1921).

[855] R. Kremann, *Monatsh. Chem.*, **26**, 783 (1905); **29**, 23 (1908); see also M. Pfannl, *Monatsh. Chem.*, **31**, 301 (1910).

[856] E. Fischer. *Ber. Deut. Chem. Ges.*, **53**, 1637 (1920).

[857] G. Zemplén and A. Kunz, *Ber. Deut. Chem. Ges.*, **56**, 1705 (1923); G. Zemplén, *Ber. Deut. Chem. Ges.*, **59**, 1258 (1926); G. Zemplén, A. Gerecs, and I. Hadacsy, *Ber. Deut. Chem. Ges.*, **69**, 1827 (1936).

[858] T. Peters, *Ber. Deut. Chem. Ges.*, **20**, 3323 (1887).

[859] M. Conrad and W. Epstein, *Ber. Deut. Chem. Ges.*, **20**, 3057 (1887).

[860] P. Cohn, *Monatsh. Chem.*, **21**, 200 (1900).

[861] A. Lapworth and A. C. O. Hann, *J. Chem. Soc.*, **81**, 1499 (1902).

[862] H. Rupe and E. Lenzinger, *Ann. Chem.*, **395**, 87 (1913).

[863] H. Kägi, *Ann. Chem.*, **420**, 33 (1920).

[864] A. R. Bader, L. O. Cummings, and H. A. Vogel, *J. Amer. Chem. Soc.*, **73**, 4195 (1951).

a little unchanged methyl ester is removed from the residue by washing with 10% sulfuric acid (which does not attack the geranyl ester). Working up then gives the geranyl ester as a golden-yellow oil, b.p. 188°/4 mm.

This method is always successful in replacing one primary alcohol residue by another or by the residue of a secondary alcohol of higher boiling point, but it cannot be used for preparation of esters of tertiary alcohols. Esters of tertiary alcohols can be prepared by Verley's method,[865] namely, mutual transesterification of two carboxylic esters:

$$\mathrm{RCOOCH_3 + HCOOC(CH_3)_2 \rightleftharpoons RCOOC(CH_3)_2 + HCOOCH_3}$$

This reaction is carried out as follows: First the formic ester is prepared of the tertiary alcohol that is to be esterified with a desired carboxylic acid. This is done by heating the tertiary alcohol for several days with the mixed anhydride of formic and acetic acid. This formic ester, isolated as usual, is mixed with an equivalent amount of the methyl ester of the other carboxylic acid, treated with 0.05 equivalent each of the free tertiary alcohol and sodium, and heated at 100–120°. The lowest-boiling component of the equilibrium mixture slowly distils off, namely, methyl formate. The reaction is sometimes quite vigorous and is usually complete in 3–4 h. After the free alkali has been neutralized with acetic acid, the distillation residue is worked up in the usual way.

Transesterification can also be achieved by the action of a free carboxylic acid on an ester:

$$\mathrm{RCOOH + R'COOR'' \rightleftharpoons RCOOR'' + R'COOH}$$

This reaction is useful for preparation of esters of an unstable alcohol, *e.g.*, vinyl esters from vinyl acetate.[866, 867]

Alcoholysis of lactones occurs with ring fission analogously to the cleavage of esters to hydroxy carboxylic esters.[868–870]

e. Orthocarboxylic esters by transesterification

When an orthocarboxylic ester is heated with a primary alcohol, or less well with a secondary alcohol, the alkoxyl groups are exchanged ("transesterification"):[871, 872]

$$\mathrm{HC(OR)_3 + 3R'OH \rightleftharpoons HC(OR')_3 + 3ROH}$$

This can be put to preparative use if the two alcohols in the equilibrium mixture have different boiling points so that the lower-boiling of them can be removed from the mixture by distillation.

The reaction can be used for the preparation of orthocarbonic esters of higher primary alcohols and of 2-alkoxy-1,3-dioxolanes and -dioxanes.[1e, 873] For example, 2-methoxy-1,3-dioxolane is obtained in 70% yield by heating

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[865] A. Verley, *Bull. Soc. Chim. France*, [iv], **41**, 803 (1927).

[866] D. Swern and E. F. Jordan Jr., *Org. Syn.*, **30**, 106 (1950).

[867] H. Lüssi, *Helv. Chim. Acta*, **49**, 1684 (1966).

[868] A. Baeyer and V. Villiger, *Ber. Deut. Chem. Ges.*, **33**, 862 (1900).

[869] E. R. Meincke and S. M. McElvain, *J. Amer. Chem. Soc.*, **57**, 1444 (1935).

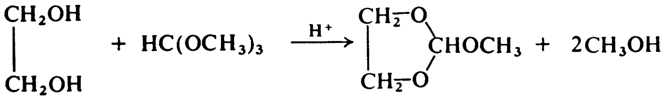
[870] T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory, and W. L. Beears, *J. Amer. Chem. Soc.*, **70**, 1004 (1948).

[871] R. M. Roberts, T. D. Higgins, and P. R. Noyes, *J. Amer. Chem. Soc.*, **77**, 3801 (1955).

[872] E. R. Alexander and H. M. Busch, *J. Amer. Chem. Soc.*, **74**, 554 (1952).

[873] H. Baganz and L. Domaschke, *Chem. Ber.*, **91**, 650 (1958).

trimethyl orthoformate with ethylene glycol in the presence of a few drops of concentrated sulfuric acid while the liberated methanol is being continuously removed:[873]



Triethyl orthoformate is best prepared by the simple process of heating triethyl trithioorthoformate (see page 652) with ethanol in the presence of zinc chloride.[874]

2. Replacement of halogen by oxygen

a. Carboxylic esters by alkylation of salts of carboxylic acids by alkyl halides

The preparation of esters by alkylation of salts of carboxylic acids in accord with the Scheme:

$$\text{RCOOM} + \text{XR}' \longrightarrow \text{RCOOR}' + \text{MX}$$

can be recommended when there is steric hindrance, *e.g.*, for esterification of *o,o'*-disubstituted aromatic carboxylic acids and tertiary carboxylic acids.

It is also useful when monoacyl derivatives are required but several hydroxyl groups or various carboxyl groups might otherwise react. For instance, monoacyl derivatives of ethylene glycol can be obtained conveniently from chlorohydrin in accord with the Scheme:

$$\text{RCOONa} + \text{ClCH}_2\text{CH}_2\text{OH} \longrightarrow \text{RCOOCH}_2\text{CH}_2\text{OH} + \text{NaCl}$$

The technique for alkylating salts of carboxylic acids is simple: The salt is heated with the halide, if necessary in a closed tube or an autoclave. The product is worked up by any suitable process.

For sensitive or valuable carboxylic acids silver salts are usually used; these are readily prepared and sparingly soluble, but lead or alkali salts react similarly.

Brühl[875] observed that alkali salts often do not react smoothly with alkyl halides, but that in such cases addition of a little methanol may be helpful. It is essential that the salt be finely divided: lead or silver salts should be washed with water, alcohol, and ether after their preparation and then dried in a vacuum-desiccator; heat should be avoided during drying.

Iodides react most readily of the halides and are also to be recommended because of their relatively high boiling points. In many cases solvents or diluents are helpful, *e.g.*, xylene, benzene, toluene, light petroleum, chloroform, ether, or acetone.

According to Liebermann and Lindenbaum[876] it is unnecessary to isolate the silver salt: the mixture of acid and alkyl halide may be treated with silver oxide in a diluent.

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[874] W. E. Mochel, C. L. Agre, and W. E. Hanford, *J. Amer. Chem. Soc.*, **70**, 2268 (1948).

[875] J. W. Brühl, *Ber. Deut. Chem. Ges.*, **35**, 3627 (1902).

[876] C. Liebermann and S. Lindenbaum, *Ber. Deut. Chem. Ges.*, **42**, 1397 (1909).

b. Carboxylic esters by acylation of alcohols or phenols by acid chlorides

Treatment of acid chlorides with alcohols or phenols also leads to carboxylic esters:

$$\mathrm{RCOCl + R'OH \longrightarrow RCOOR' + HCl}$$

This reaction is particularly important for characterisation of alcohols and phenols as acyl derivatives. Moreover, aryl esters are thus easily prepared, *e.g.*, those required as starting materials for a Fries rearrangement. The process is used when the usual methods of esterification fail and can also be applied to tertiary alcohols. In the simplest cases hydroxy compounds are acylated for characterization by shaking them with benzoyl chloride or one of its substitution products in 10% sodium hydroxide solution until all the acid chloride is consumed (Schotten–Baumann reaction[877]). Panormow[878] recommends that, to ensure as complete a benzoylation as possible, 20 parts of 20% sodium hydroxide solution should be used for every 6 parts of benzoyl chloride. Skraup[879] believed that, to obtain as complete a reaction as possible, 7 equivalents of 10–30% sodium hydroxide solution and 5 equivalents of acid chloride should be used for each hydroxyl group. When alkali-sensitive substances are to be acylated, dilute sodium hydroxide solution or sodium carbonate or hydrogen carbonate solution may be used. Aliphatic alcohols usually react in the cold, but gentle warming is advisable for phenols.

The Schotten–Baumann method can also be applied with acetyl chloride, but because of the sensitivity of this chloride it is better replaced by some other process, *e.g.*, use of acetic anhydride.

A procedure due to Einhorn,[880] in which the sodium hydroxide solution is replaced by pyridine, is an improvement on the Schotten–Baumann method:

The following technique is usually successful: The substance to be acylated is dissolved in dry pyridine and cooled, and the acid chloride is added gradually; it is sometimes advisable to add chloroform. After several hours the mixture is dropped into cold dilute sulfuric acid or water.

In many cases it is unnecessary to add alkali or pyridine for esterification by acid chlorides:

For preparation of **diphenyl phthalate** Blicke and Weinkauff[881] mixed equivalent amounts of phthaloyl chloride and phenol, set the mixture aside for several hours, then washed the product with alcohol and crystallized it from alcohol. The yield is almost quantitative. The m.p. is 74–76°.

In the preparation of phenyl esters addition of magnesium turnings leads to easier and more complete acylation.[882]

The acid chloride may be replaced by using a mixture of the phenol, carboxylic acid, and a halogen carrier (phosphoryl chloride, phosphorus tri- or penta-

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[877] E. Baumann, *Ber. Deut. Chem. Ges.*, **19**, 3218 (1886).

[878] A. Panormow, *Ber. Deut. Chem. Ges.*, **24**, ref. 971 (1891).

[879] Z. H. Skraup, *Monatsh. Chem.*, **10**, 390 (1891).

[880] A. Einhorn and F. Hollandt, *Ann. Chem.*, **301**, 95 (1898); A. Deninger, *Ber. Deut. Chem. Ges.*, **28**, 1322 (1895); F. Ullmann and G. Nadai, *Ber. Deut. Chem. Ges.*, **41**, 1870 (1908).

[881] F. I. Blicke and O. J. Weinkauff, *J. Amer. Chem. Soc.*, **54**, 331 (1932).

[882] A. Spassow, *Ber. Deut. Chem. Ges.*, **75**, 779 (1942); *Org. Syn.*, **20**, 21 (1940); E. H. Man, F. W. Swamer, and C. R. Hauser, *J. Amer. Chem. Soc.*, **73**, 902 (1951).

chloride, or thionyl chloride),[883] a process that has advantages when the acid chloride is not easy to prepare.

Phenyl hippurate:[884] Finely powdered hippuric acid (10 g) is mixed with phenol (7 g), heated on a water-bath, and treated gradually with phosphoryl chloride (6–8 g). The mixture is heated until all is dissolved, then poured into ice-water and neutralized with sodium carbonate solution. The liquid is decanted from the viscous product which is rubbed with water until fully crystalline. Crystallized from ethanol it has m.p. 104°.

Phenols can also be acylated in the presence of small amounts of sulfuric acid[885] or tin(IV) chloride.[882, 886, 887]

Stoughton[885] prepared **esters of α-naphthol** as follows: α-Naphthol (50–100 g) is treated with a 10% excess of the requisite acid chloride in a flask fitted with a reflux condenser. If reaction is sluggish, one drop of concentrated sulfuric acid is added as catalyst. The mixture is kept for 2 h at room temperature, then warmed for an hour on the water-bath and finally poured into ice-water. The product is taken up in ether, washed with sodium hydrogen carbonate solution, and distilled in a vacuum. Yields amount to 90–95%.

c. Orthocarboxylic esters from halogen compounds

Reaction of chloroform with sodium ethoxide gives triethyl orthoformate:[888]

$$CHCl_3 + 3NaOC_2H_5 \longrightarrow HC(OC_2H_5)_3 + 3NaCl$$

and that of benzotrichloride with sodium methoxide gives trimethyl orthobenzoate analogously.[889]

α,α-Dihalo ethers also give orthocarboxylic esters readily, by reaction with alkali alkoxides;[890] *e.g.*, mixed esters of orthoformic acid are formed on treatment of dichloromethyl methyl ether with various alkoxides,[891] and esters of orthooxalic acid are obtained by heating 1,1,2,2-tetrachloro-1,2-diethoxyethanes with sodium alkoxides in an autoclave:[892]

$$ROCCl_2CCl_2OR + 4NaOR \longrightarrow (RO)_3C{-}C(OR)_3$$

3. Replacement of nitrogen by oxygen

a. Carboxylic esters by alkylation with diazomethane

Whenever other methods of esterification fail for any reason, *e.g.*, because of the sensitivity of the acid, or when small amounts of valuable carboxylic acids are to be esterified, the reaction can be carried out by use of a diazoalkane. Esterification with these reagents occurs in an inert medium, in ether,

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[883] M. Nencki, *J. Prakt. Chem.*, [ii], **25**, 282 (1882); R. Seifert, *J. Prakt. Chem.*, [ii], **31**, 467 (1885).

[884] F. Weiss, *Ber. Deut. Chem. Ges.*, **26**, 1700 (1893).

[885] R. W. Stoughton, *J. Amer. Chem. Soc.*, **57**, 203 (1935).

[886] H. Huber and K. Brunner, *Monatsh. Chem.*, **56**, 325 (1930).

[887] H. Reihlen, Ger. Pat. 463,518; *Chem. Zentrabl.*, I, 2235 (1929).

[888] W. E. Kaufmann and E. E. Dreger, *Org. Syn.*, Coll. Vol. I, 2nd ed, p. 258.

[889] S. M. McElvain and J. T. Venerable, *J. Amer. Chem. Soc.*, **72**, 1664 (1950).

[890] Review: H. Gross and E. Höft, *Z. Chem.*, **4**, 401 (1964).

[891] H. Gross and A. Rieche, *Chem. Ber.*, **94**, 538 (1961).

[892] H. Baganz and K. E. Krüger, *Chem. Ber.*, **91**, 806 (1958).

or in alcohol, is not accompanied by appreciable side reactions, and involves only a convenient technique. It has been reviewed by Eistert.[893] Methyl esters, prepared by means of diazomethane, are usually preferred:

$$\mathrm{RCOOH + CH_2N_2 \longrightarrow RCOOCH_3 + N_2}$$

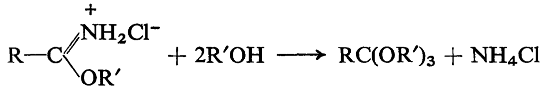
N.B.: Diazomethane is extremely **poisonous** and experiments with it must be carried out under a hood. Undiluted gaseous nitromethane is highly **explosive**, and large amounts of carboxylic acids should not be subjected to this reaction.

For esterifications it is best to prepare an ethereal solution of diazomethane. Such solutions are not stable, decolorizing gradually with evolution of nitrogen. Diazomethane solutions can be dried with potassium hydroxide, but losses must then be allowed for. Alcoholic solutions of diazomethane are less stable than ethereal ones.

For esterification of carboxylic acids it is best to work with ethereal solutions at room temperature. Acids that are sparingly soluble in ether are dissolved in a solvent inert to the diazo compound, and this solution is added gradually to the ethereal diazomethane until evolution of nitrogen ceases. When necessary, the solution is warmed gently; adding a little methanol accelerates the methylation.[894] If the yellow color persists after evolution of nitrogen has stopped it can be assumed that alkylation is complete; if it is not, a further portion of diazomethane can be added. Working up of the reaction mixture requires no special comment; it depends on the nature of the ester; in general, any polyethylene derivatives formed are filtered off and the solvent is evaporated.

b. Orthocarboxylic esters from formamide or carbimidic ester hydrochlorides

Alcoholysis of carbimidic ester hydrochlorides leads to orthocarboxylic esters.[1b, 895] It is essential to use well-dried alcohols and acid-free imidic ester hydrochlorides and completely to exclude moisture.



$$\mathrm{R{-}C\begin{cases}\overset{+}{N}H_2Cl^- \\ OR'\end{cases} + 2R'OH \longrightarrow RC(OR')_3 + NH_4Cl}$$

Carboxamides and sometimes carboxylic esters and carbonitriles are formed as by-products of the alcoholysis.

Orthocarboxylic esters (general procedure):[896] A mixture of a carboximidic ester hydrochloride (0.2 mole) and an alcohol (3 moles) is stirred with careful exclusion of moisture until the salt has dissolved (the reaction vessel is fitted with a reflux condenser and a thermometer). Then anhydrous ether is added in the amount shown in the Table. The ethereal solution is then heated to the b.p. (temperature and duration shown in the Table), after which it is cooled to 0° and filtered from the precipitated ammonium chloride. The filtrate is washed with an equal volume of 10% sodium carbonate solution, then with saturated sodium carbonate solution (50 ml), dried over potassium carbonate, and fractionated at 10–30 mm.

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[893] B. Eistert in W. Foerst, "Neuere Methoden der präparativen organischen Chemie," 2nd ed, Verlag Chemie, Berlin, 1944, pp. 359 et seq.

[894] B. Eistert, F. Arndt, L. Loewe, and A. Ayca, *Chem. Ber.*, **84**, 165 (1951).

[895] R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 181 (1961).

[896] S. M. McElvain and J. W. Nelson, *J. Amer. Chem. Soc.*, **64**, 1827 (1942).

Yields are given in the Table. Preparation of a pure formimidic ester hydrochloride, which is dangerous, can be avoided.[897]

Ethanolysis of carbimidic ester hydrochlorides $RC(OC_2H_5){=}NH_2Cl$

R	Reaction time (hours)	Alcohol : ether (vol/vol)	Temp. (°C)	Yield (%) of $RC(OC_2H_5)_3$
CH_3	6	1 : 1	46	75–78
C_2H_5	9	1 : 2	42	75–78
n-C_3H_7	18	1 : 3	41	60–63
i-C_3H_7	24	1 : 5	39	27–30
n-C_4H_9	12	1 : 3	42	59–61
i-C_4H_9	28	1 : 5	39	21–23
CH_2Cl	6	1 : 0	40	70–73

Trialkyl orthoformates can be prepared by allowing the requisite alcohol and either benzoyl chloride or ethyl chloroformate to react simultaneously with formamide, in a process devised by Ohme and Schmitz:[665e]

$$HCONH_2 + 3ROH + C_6H_5COCl \longrightarrow HC(OR)_3 + C_6H_5COOH + NH_4Cl$$

Triethylorthoformate:[898] Benzoyl chloride (1 mole; 140.5 g) is dropped during 20 min, with stirring and cooling, into a mixture of anhydrous ethanol (180 ml, 3 moles), formamide (45 g, 1 mole), and light petroleum (b.p. 70–80°; 200 ml). The mixture is stirred for 1 h at 30–40°, then allowed to cool, and after 2 h the mixture of benzoic acid and ammonium chloride that has crystallized is filtered off. The filtrate is dropped with stirring and cooling into ice-cold 3N-sodium hydroxide solution (500 ml). The organic phase is separated, washed with a little water, and dried over potassium carbonate. Fractional distillation from a heating bath and through a 70-cm Widmer column gives triethyl orthoformate, b.p. 143–148° (58–64 g, 40–44%). Ethyl benzoate (ca. 20 g) is obtained as distillation residue.

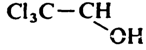
Tripropyl, b.p. 82–86° (58% yield), and tributyl orthoformate, b.p. 122°/12 mm (yield 52.5%), are prepared analogously.

III. Acetals[1d,g, 899, 900]

1. Replacement of oxygen by oxygen

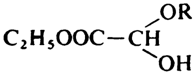
a. Acetals from carbonyl compounds and alcohols

Addition products of alcohols to carbonyl compounds (hemiacetals) can be isolated only in a few cases. They are stable only if the original carbonyl group is markedly electron-deficient, as is the case with chloral from which a series of semiacetals (1) has been isolated.[901] Similarly the semiacetals (2) and (3) of ethyl glyoxalate[902] and cyclopropenone,[903] respectively, have been isolated.



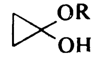
$Cl_3C{-}CH(OR)(OH)$

(1)



$C_2H_5OOC{-}CH(OR)(OH)$

(2)



(3)

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[897] J. G. Erickson, *J. Org. Chem.*, **20**, 1573 (1955).

[898] R. Ohme and E. Schmitz, Ger. Pat. 48,595, 5th May, 1966 (provisional).

[899] F. Klages in G. M. Schwab, "Handbuch der Katalyse," Springer Verlag, Vienna, 1943, Vol. 7, Part 2, p. 305.

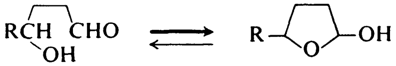
[900] E. Schmitz and I. Eichhorn on p. 309 of ref. 655.

[901] E. Schmitz and I. Eichhorn on p. 311 of ref. 655.

[902] W. Traube, *Ber. Deut. Chem. Ges.*, **40**, 4944 (1907).

[903] P. Lipp, J. Buchkremer, and H. Seeles, *Ann. Chem.*, **499**, 1 (1932).

Semiacetals are also stable if their formation is accompanied by ring closure, as with γ- and δ-hydroxy carbonyl compounds[904] (oxo-cyclo tautomerism of carbohydrates) [see **(4)**/**(5)**].



The reaction of amines with carbonyl compounds, giving *O,N*-semiacetals, is discussed on page 411.

The acid-catalysed formation of acetals from carbonyl compounds is only smooth when the equilibria

$$\text{Aldehyde} + \text{Alcohol} \rightleftarrows \text{Semiacetal} \overset{+\text{ROH}}{\rightleftarrows} \text{Acetal} + \text{Water}$$

lie well to the right or when the product water is removed. Acid catalysts are needed to convert semiacetals into acetals.

The ease of acetal formation depends largely on the structures of the reacting carbonyl compounds and alcohol.[905] Primary alcohols react better than secondary or tertiary ones; the ease of reaction of carbonyl compounds decreases in the order formaldehyde, aliphatic aldehydes, α,β-unsaturated aldehydes, aromatic aldehydes, ketones; acetone gives cyclic ketals very readily with 1,2- and 1,3-diols.

Adams and Adkins[905, 906] studied the value of various catalysts for acetal formation; those that have proved most useful are calcium chloride,[907] iron(III) chloride,[905, 906] zinc chloride, pyridine hydrochloride, and sodium hydrogen sulfate.[1a]

Formaldehyde, the three nitrobenzaldehydes, isophthalaldehyde, and terephthaldehyde are converted into acetals by dimethyl sulfate and alkali, but *o*-phthalaldehyde gives 1,3-dimethoxyphthalan under these conditions.[908]

The preparation of acetaldehyde diethyl acetal in 65% yield by use of calcium chloride and hydrochloric acid as catalysts is described in *Organic Syntheses*.[909]

Methylal (formaldehyde dimethyl acetal) was obtained by Fischer and Giebe[910] as follows: 1% methanolic hydrochloric acid (2.5 parts) is poured over finely powdered paraformaldehyde (1 part), and the mixture is warmed at 100° for 12–15 h. All the solid dissolves and the smell of formaldehyde soon disappears. The mixture is neutralized with sodium hydroxide solution and fractionated through an efficient column. This gives methylal, b.p. 41–42°, in 80% yield.

35–40% commercial formalin solution also affords methylal; the formation (1 part) is treated with 2% methanolic hydrochloric acid (2.5 parts), and then with calcium chloride (1 part) to bind the water; the mixture becomes warm and after about 15 min methylal separates as an oil. After 15 h the mixture is distilled giving 75% of pure methylal.

Processes involving continuous removal of the product water by azeotropic distillation have proved very valuable for preparation of acetals.[911] Only

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[904] B. Helferich and H. Köster, *Ber. Deut. Chem. Ges.*, **56**, 2088 (1923).

[905] W. H. Hartung and H. Adkins, *J. Amer. Chem. Soc.*, **49**, 2517 (1927).

[906] E. W. Adams and H. Adkins, *J. Amer. Chem. Soc.*, **44**, 2749 (1922); **47**, 1358, 1368 (1925); **50**, 178 (1928).

[907] R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **121**, 80 (1922); see also *Org. Syn.*, **1**, 1 (1932).

[908] E. Schmitz, *Chem. Ber.*, **91**, 410 (1958).

[909] H. Adkins and B. H. Nissen, *Org. Syn.*, **3**, 1 (1923).

[910] E. Fischer and G. Giebe, *Ber. Deut. Chem. Ges.*, **30**, 3054 (1897).

[911] E. J. Salmi, *Ber. Deut. Chem. Ges.*, **71**, 1803 (1938).

a relatively small excess of alcohol (20–50%) is then needed; side reactions such as resinification and formation of ethers or olefins (which reduce the yield) are avoided since the amounts of catalyst can be kept small; in general 0.1% of *p*-toluenesulfonic acid suffices; acid ion-exchangers[912] have also been used. The method is, however, unsuitable for preparation of acetals from low-boiling alcohols or carbonyl compounds, such as acetaldehyde dimethyl or diethyl acetal or acetone dialkyl ketals, since in these cases it is difficult to remove the product water by distillation.

Cyclic acetals, from carbonyl compounds and polyhydric alcohols, are formed with particular ease;[913] their synthesis follows in general that of acetals of monohydric alcohols.

Ketone derivatives of tetritols, pentitols, and hexitols have been reviewed by Barker and Bourne.[914]

Isopropylidene derivatives of carbohydrates (acetone sugars)[915b] are obtained from sugars or suitable derivatives by treatment with much acetone in the presence of a catalyst such as an acid, zinc chloride, or anhydrous copper sulfate. It helps further to add a water-binding material such as sodium sulfate.

Glucose and acetone give the diisopropylidene derivative very smoothly.

1,2:5,6-Diisopropylidene-α-D-glucofuranose:[916] Finely powdered, sieved glucose (65 g) is suspendied in pure acetone (1800 ml) and shaken mechanically with concentrated sulfuric acid (55 ml). All except the last *ca.* 5 g dissolve in 4–5 h. The mixture is then filtered and the filtrate is treated with an excess of anhydrous sodium carbonate until the dark solution has become pale yellow. It is then filtered and evaporated to dryness in a vacuum. The residue is taken up in ether, which rejects monoisopropylideneglucose. This ethereal solution is set aside overnight at 0° to complete separation of the isopropylidene derivative, then filtered and treated gradually with light petroleum. A thick crystal paste separates, which is washed with light petroleum and dried, affording thus the diisopropylidene derivative, m.p. 102° (other citations 110–111°), $[\alpha]_D^{20}$ −19° (45–55 g).

Monoisopropylidenglucose, which occurs as by-product in this preparation, was obtained as main product by Fischer[917] by shortening the reaction period for glucose, acetone, and hydrogen chloride.

Fischer also showed that D-mannitol gives a triisopropylidene derivative[918] (for its structure see Wiggins[919]).

An important practical method[920] is the treatment of the carbonyl compound with an orthoformic ester or some other orthoester (tetramethyl or tetraethyl orthocarbonate) in the presence of a small amount of mineral acid:

$$R_2CO + HC(OR')_3 \longrightarrow R_2C(OR')_2 + HCOOR'$$

Inorganic salts may be used as well as the free acids as catalysts. Reaction is fast with iron(III) chloride, somewhat slower with ammonium chloride. The

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[912] A. A. Dolnick and M. Potash, U. S. Pat. 2,566,559; *Chem. Abstr.*, **46**, 2566 (1952); Z. Mastagli and Z. Zafiriadis, *C. R. Hebd. Séances Acad. Sci.*, **236**, 616 (1953); P. Mastagli, P. Zafiriadis, and G. Lagrange, *C. R. Hebd. Séances Acad. Sci.*, **237**, 187 (1953).

[913] Review: M. Senkus, *J. Amer. Chem. Soc.*, **68**, 735 (1946).

[914] S. A. Barker and E. J. Bourne, *Advan. Carbohyd. Chem.*, **7**, 137 (1952).

[915] J. Staněk, M. Černý, J. Kocourek, and J. Pacák, "The Monosaccharides," Publishing House of the Czechoslovak Academy of Sciences, Prague, 1963, pp. (a) 255, (b) 324.

[916] K. Freudenberg and K. Smeyhal, *Ber. Deut. Chem. Ges.*, **59**, 107 (1926).

[917] E. Fischer, *Ber. Deut. Chem. Ges.*, **28**, 2496 (1895).

[918] E. Fischer, *Ber. Deut. Chem. Ges.*, **28**, 1168 (1895).

[919] L. F. Wiggins, *J. Chem. Soc.*, **1946**, 13.

[920] L. Claisen, *Ber. Deut. Chem. Ges.*, **29**, 1005 (1896); **40**, 3903 (1907); **47**, 3171 (1914).

principle of the technique is simple: the carbonyl compound (1 equivalent) is dissolved in the appropriate alcohol (often 2 equivalents), then the orthoester (about 1.2 equivalents) and lastly the catalyst are added. Owing to the sensitivity of acetals to acid, alkaline or neutral conditions must be maintained during working up.

According to Claisen[920] **benzaldehyde diethyl acetal** is obtained as follows: Benzaldehyde (37.5 g) is mixed with ethyl orthoformate (57 g) and ethanol (49 g) and treated with concentrated hydrochloric acid (0.15 ml), whereupon the temperature rises quickly to 48°. The mixture is then boiled on the water-bath for a short time. It is then rapidly cooled, made weakly alkaline with a few drops of alcoholic potassium hydroxide, and fractionated. After the alcohol and ethyl formate have been removed the acetal distils over at 217–223° in 99% yield (63 g).

If finely powdered ammonium chloride (0.75 g) is used in place of hydrochloric acid and the mixture is boiled for 10 min, the yield is again almost quantitative. Potassium hydrogen sulfate (0.3 g) and iron(III) chloride may also be used as catalyst.

Aldehydes containing very reactive double bonds, *e.g.*, acrylaldehyde and crotonaldehyde, give acetals when treated with ethyl orthoformate and ammonium nitrate.[921, 922]

Acrylaldehyde diethyl acetal:[923] A warm solution of ammonium nitrate (1.5 g) in anhydrous ethanol (15 ml) is added to a mixture of stabilized acrylaldehyde (22 g) and ethyl orthoformate (72 g). The whole is boiled for 8–10 min under reflux (becoming deep brown), then filtered and treated with double its volume of ether, shaken with dilute aqueous ammonia for as long as amorphous material separates, then washed with water, dried over potassium carbonate, and fractionated, giving the acetal, b.p. 120–125° (37.5 g, 73%).

Ketones afford acetals in exactly the same way as aldehydes do; yields are in general somewhat lower, but usually about 80%.

Helferich and Hausen[924] have described formation of acetals by means of orthosilicic esters:

An aldehyde or ketone (1 mole) is mixed with the requisite anhydrous alcohol (2–3 moles) and ethyl orthosilicate (1.1 moles); then 10 drops of saturated alcoholic hydrogen chloride are added or a few bubbles of gaseous hydrogen chloride are led in. The whole is then either set aside for some days or is boiled for some time under reflux.

Benzophenone dimethyl acetal crystallizes directly in good yield, but in most cases the reaction mixture is fractionated, if necessary in a vacuum. The acetals thus obtained are, however, not quite free from silicon compounds; to destroy the latter, the distillate is boiled with potassium hydroxide and a little alcohol; or the undistilled liquid is treated as follows: The liquid is poured (if necessary with cooling) into *ca.* 30% potassium hydroxide solution (500 ml per mole of orthoester) and shaken for about 10 min at room temperature or boiled (for, *e.g.*, higher alcohols) for some time under reflux; the alcoholic layer, now containing no silicon compounds is separated, dried over potassium carbonate, and fractionated (yield 70–90%).

Acetal formation by means of dimethyl sulfite[925] requires almost the same conditions as does that with orthoformic esters. This procedure can be applied to cyclic but not to aliphatic ketones.

Cyclohexanone dimethyl acetal: Cyclohexanone (49 g), dimethyl sulfite (60 g), methanol (60 ml), and *ca.* 10% methanolic hydrochloric acid (1 ml) are boiled together on the water-bath under reflux. Vigorous evolution of sulfur dioxide begins after a few minutes, then the solution is heated for 3 h, allowed to cool, made alkaline with a few drops of sodium methoxide,

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[921] J. Klein and E. D. Bergmann, *J. Amer. Chem. Soc.*, **79**, 3452 (1957).

[922] O. Isler, *Helv. Chim. Acta*, **39**, 256 (1956).

[923] H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 516 (1935).

[924] B. Helferich and J. Hausen, *Ber. Deut. Chem. Ges.*, **57**, 795 (1924).

[925] W. Voss, *Ann. Chem.*, **485**, 283 (1931).

and shaken with 40% potassium hydroxide solution (200 ml) to destroy unused dimethyl sulfite. Then dilution with water, extraction with ether, drying of the extract with potassium carbonate, and fractionation give the acetal (57 g, 79%), b.p. 63–65°/22.5 mm.

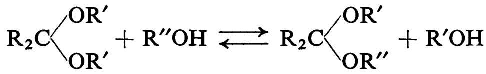
Homologs of dimethyl sulfite can equally be used in that reaction. Acetals containing higher alkyl residues can also be obtained similarly, by treating the aldehyde with dimethyl sulfite in presence of the requisite alcohol.

Benzaldehyde dibutyl acetal: Benzaldehyde (10.5 g) is heated in an oil-bath with dimethyl sulfite (12 g), 1-butanol (27 g), and a few drops of 20% methanolic hydrogen chloride. Evolution of sulfur dioxide begins in a few minutes. The bath-temperature is then raised to 150–160° during 2 h, while a mixture (20 ml) of methanol with a little butanol distils over (temperature at the column head 65–70°). The residue is fractionated in a vacuum and affords benzaldehyde dibutyl acetal (18.5 g, 80%), b.p. 149–150°/14 mm.

The process can also be used for long-chain alcohols such as 1-hexadecanol, and for converting carbohydrates into their glucosides.

b. Acetals by transacetalization

When an acetal is heated with an excess of an alcohol containing an acid catalyst, transacetalization occurs to some extent:



$$R_2C\begin{cases}OR'\\OR'\end{cases} + R''OH \rightleftharpoons R_2C\begin{cases}OR'\\OR''\end{cases} + R'OH$$

This process can be used for preparation of either symmetrical or mixed acetals.[926, 927] The equilibrium can be shifted in the direction of the new alcohol by using a large excess of the alcohol or by distilling off a lower-boiling alcohol or a lower-boiling acetal if such is formed.[928, 929]

Mixed alcohols can be prepared if an excess of the acetal is used. When an ester group is present in the molecule as well as an acetal group, transacetalization can be achieved without transesterification if precise reaction conditions are observed.[930] Secondary alcohols can also be used in transacetalizations.[927]

Transacetalization is particularly suitable for the synthesis of cyclic acetals.[931, 932] It is sometimes an advantage first to prepare the starting acetal and then to perform the transacetalization operation in that reaction mixture.[926, 927, 933, 934]

2. Replacement of halogen by oxygen

The reaction of α-halo ethers with alcohols in the presence of acid-binding substances gives acetals:[890]

$$ROCH_2Cl + R'OH \longrightarrow ROCH_2OR' + HCl$$

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[926] N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

[927] W. L. Howard and N. B. Lorette, *J. Org. Chem.*, **25**, 525 (1960).

[928] H. J. Lucas and M. S. Guthrie, *J. Amer. Chem. Soc.*, **72**, 5491 (1950).

[929] N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 1814 (1960).

[930] E. H. Pryde, D. J. Moore, H. M. Teeter, and J. C. Cowan, *J. Org. Chem.*, **29**, 2083 (1964).

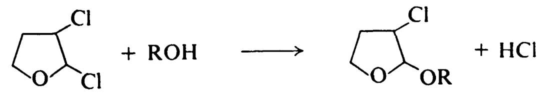
[931] S. M. McElvain and M. J. Curry, *J. Amer. Chem. Soc.*, **70**, 3781 (1948).

[932] C. Piantadosi, C. E. Anderson, E. A. Brecht, and C. L. Yarbro, *J. Amer. Chem. Soc.*, **80**, 6613 (1958).

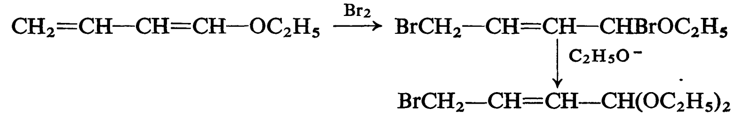
[933] C. A. McKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1995 (1955).

[934] E. Vogel and H. Schinz, *Helv. Chim. Acta*, **33**, 128 (1950).

Such reactions have preparative value when the α-halo ether is easily accessible by halogenation of an ether. For example, 2,3-dichlorodioxan and ethanol yield the cyclic acetal of glyoxal;[935] and cyclic acetals of 2-chloro-4-hydroxybutyraldehyde are formed from 2,3-dichlorotetrahydrofuran and alcohols:[936, 937]



Similarly, 4-bromocrotonaldehyde diethyl acetal is obtained by treatment of 1-butadienyl ethyl ether with bromine and then of the resulting intermediate with sodium ethoxide:[938]

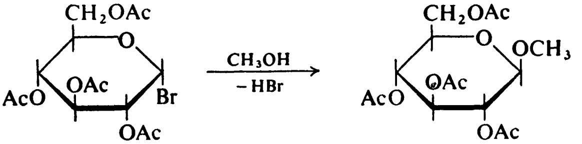


$$\begin{array}{l} CH_2{=}CH{-}CH{=}CH{-}OC_2H_5 \xrightarrow{Br_2} BrCH_2{-}CH{=}CH{-}CHBrOC_2H_5 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \big\downarrow C_2H_5O^- \\ \qquad\qquad\qquad\qquad\qquad\qquad BrCH_2{-}CH{=}CH{-}CH(OC_2H_5)_2 \end{array}$$

Acetals of α-bromo aldehydes are obtainable from α,β-dibromoalkyl acetates by an analogous procedure in which these esters are prepared from enol acetates and bromine and are then converted into acetals by means of alcohols.[939] A simple synthesis of α-keto aldehydes is to treat α-brominated phenacyl phenyl ethers with alkoxides or phenoxides.[940] This method is particularly useful for the preparation of aryl acetals because it avoids the side reactions that can complicate reactions between phenols and aldehydes in an acidic medium.

1-Alkoxy-1,2-alkylene diacetates (acetals or acylals of α-hydroxy aldehydes) can be obtained by reaction of α,β-dibromo ethers with sodium acetate or with silver acetate and acetic anhydride.[941] The analogous reaction of vinyl acetate with bromine, sodium acetate and acetic anhydride gives the "glycolaldehyde triacetate" that can replace glycolaldehyde in syntheses, *e.g.*, of serine (p. 140).

Some of the most important syntheses of glycosides start from glycosyl halides, which are converted into acetylated glycosides, with Walden inversion, by reaction with alcohols or phenols in the presence of acid-binding compounds. For example, methyl tetra-*O*-acetyl-β-D-glucoside is obtained from α-acetobromoglucose by this method (the Koenigs–Knorr reaction):[942]



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[935] J. Boeseken, F. Tellegen, and P. C. Henriquez, *Kon. Ned. Akad. Wetensch., Proc. B*, **34**, 631 (1931); *J. Amer. Chem. Soc.*, **54**, 4461 (1932).

[936] W. Reppe and co-workers, *Ann. Chem.*, **596**, 86, 113 (1955).

[937] H. Normant, *C. R. Hebd. Séances Acad. Sci.*, **226**, 185 (1948).

[938] W. Flaig, *Ann. Chem.*, **568**, 24 (1950).

[939] P. Z. Bedoukian, *J. Amer. Chem. Soc.*, **66**, 651, 1325 (1944).

[940] F. Kröhnke, G. Kröhnke, and H. Bernhardt, *J. Prakt. Chem.*, [iv], **11**, 249 (1960).

[941] H. Gross, K.-P. Hilgetag, J. Gloede, and H. Geipel, *Chem. Ber.*, **98**, 1673 (1965).

[942] W. Koenigs and E. Knorr, *Ber. Deut. Chem. Ges.*, **34**, 965 (1901).

Silver oxide, silver carbonate, mercuric oxide, or zinc oxide is used as acid-binding material;[839a, 915b, 943] when silver carbonate is used it is an advantage to add sodium sulfate, calcium sulfate, or calcium hydride to remove the water formed.

Methyl tetra-*O*-acetyl-*β*-D-glucoside:[942] Acetobromoglucose (8.6 g) is dissolved in anhydrous methanol (126 ml) and shaken at room temperature with dry, powdered silver carbonate (8.5 g). The evolution of carbon dioxide, which is initially rapid, slackens after about an hour, and the mixture is then shaken mechanically for about 6 h in a closed vessel. Insoluble material is then filtered off and washed well with ether, and the filtrate is treated with water and a small amount of barium carbonate, then filtered again and evaporated in an evacuated desiccator over sulfuric acid. The dry residue is shaken with water and repeatedly with ether. The united ethereal solutions are shaken with sodium carbonate solution and water and dried over sodium sulfate. Evaporation of the ether affords a nicely crystalline compound; when this glycoside is recrystallized from methanol and then from light petroleum it has m.p. 104–105°, the yield being 3.75 g.

β-Glycoside acetates can be rearranged to the difficulty accessible *α*-glycosides by titanium(IV) chloride[944] or boron trifluoride.[945]

According to Zemplén[943, 946] the above Koenigs–Knorr process is convenient for preparation of glycosides from acetohalo-*α*-sugars and alcohols or phenols in the presence of mercuric acetate in benzene, *α*- or *β*-glycosides being obtained according to the amounts of alcohol and catalyst used.

Benzyl tetra-*O*-acetyl-*β*-D-glucoside:[947] Acetobromoglucose (10 g), dissolved in benzene (60 ml), is boiled for 2 h under reflux with mercuric acetate (3.8 g) and benzyl alcohol (10.4 g). The mixture is then shaken with water, the benzene is evaporated in a vacuum, and the residual syrup is taken up in a little methanol. Crystallization usually sets in when this mixture is rubbed with water. The crude product, when recrystallized from ether, gives the glucoside, m.p. 95–97° (60–80%).

Aryl glycosides are formed, according to Helferich *et al.*,[948] when phenols and carbohydrate acetates are melted together with an acid catalyst.

Various reviews[949–951] are available for methyl and phenyl glycosides.

IV. Carboxylic anhydrides[1s]

Anhydrides of carboxylic acids are best prepared by the classical method of treating acid chlorides with salts of acids, a method that can be used equally for preparing mixed anhydrides. The salt may be replaced by the free acid if pyridine is added to the reaction mixture. Further, water may be removed directly from carboxylic acids, either by heat in certain cases where aliphatic or aromatic dicarboxylic acids give cyclic anhydrides, or by means of acetic anhydride or acetyl chloride.

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[943] G. Zemplén, *Fortschr. Chem. Org. Naturst.*, **1**, 1 (1938).

[944] E. Pascu, *J. Amer. Chem. Soc.*, **52**, 2563, 2568 (1930).

[945] H. Lindberg, *Acta Chem. Scand.*, **2**, 426, 534 (1948).

[946] G. Zemplén and co-workers, *Ber. Deut. Chem. Ges.*, **63**, 368, 2720 (1930); **64**, 744, 1545, 1852 (1931).

[947] F. Klages and H. Niemann, *Ann. Chem.*, **529**, 201 (1937).

[948] B. Helferich and E. Schmitz-Hillebrecht, *Ber. Deut. Chem. Ges.*, **66**, 378 (1933).

[949] J. Conchie, G. A. Levvy, and C. A. Marsh, *Advan. Carbohyd. Chem.*, **12**, 157 (1957).

[950] W. L. Evans, D. D. Reynolds, and E. A. Talley, *Advan. Carbohyd. Chem.*, **6**, 27 (1951).

[951] R. U. Lemieux, *Advan. Carbohyd. Chem.*, **9**, 1 (1954).

1. Carboxylic anhydrides by direct removal of water

Anhydrides are obtained most easily from aromatic *ortho*-dicarboxylic acids. Further, aliphatic dicarboxylic acids containing four or five carbon atoms in the chain occupy a special position because the formation of fiveor six-membered rings is particularly favorable for removal of water (see Blanc 'srule, page 1005). ω,ω'-Dicarboxylic acids with longer chains readily form polymeric anhydrides at higher temperatures.

Glutaric acid loses water when slowly heated to 230–280°, giving its anhydride, m.p. 56–57°. Maleic anhydride can be obtained in 90% yield if the water liberated is removed by azeotropic distillation with tetrachloroethane.[952] Fumaric acid rearranges when heated, giving maleic anhydride. Adipic acid requires boiling for several hours with acetic anhydride, then giving a polymeric anhydride that becomes converted into cyclopentanone with loss of carbon dioxide (see page 1005).

Formation of anhydrides from dibasic acids is aided by heating with acetyl chloride,[953–959] phosphoryl chloride,[953, 954] thionyl chloride,[965] or acetic anhydride.[960–964]

Succinic anhydride:[966] Succinic acid (100 g) is heated with phosphoryl chloride (65 g) at 100–120° until evolution of hydrochloric acid ceases. This gives succinic anhydride, b.p. 261°, m.p. 120°, in 95% yield (80 g).

Glutaric anhydride:[967] Glutaric acid is heated cautiously to 40° with twice its weight of acetyl chloride. On cessation of the evolution of hydrochloric acid, fractionation in a vacuum and recrystallization from ether give the anhydride, b.p. 150°/10 mm, m.p. 56–57°.

Heating for several hours with two to three times the weight of thionyl chloride gives a 78% yield of the anhydride.[965]

Adipic anhydride: according to Voerman[968] this is obtained by heating adipic acid for 6–7 h with ten times its weight of thionyl chloride on a water-bath.

2. Carboxylic anhydrides by double reaction

Formation of acid anhydrides from acid chlorides and alkali salts of carboxylic acids is carried out by mixing the reactants and distilling off the anhydride formed.

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[952] A. Mason, *J. Chem. Soc.*, **1930**, 701.

[953] L. F. Fieser and E. L. Martin, *Org. Syn.*, Coll. Vol. II, 560 (1943).

[954] J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *J. Amer. Chem. Soc.*, **64**, 1749 (1942).

[955] C. C. Price and A. J. Tomisek, *J. Amer. Chem. Soc.*, **65**, 440 (1943).

[956] B. R. Baker, *J. Amer. Chem. Soc.*, **65**, 1577 (1943).

[957] L. F. Fieser and W. H. Daudt, *J. Amer. Chem. Soc.*, **63**, 784 (1941).

[958] E. C. Kornfeld, R. G. Jones, and T. V. Parke, *J. Amer. Chem. Soc.*, **71**, 158 (1949).

[959] W. E. Bachmann, S. Kushner, and A. C. Stevenson, *J. Amer. Chem. Soc.*, **64**, 977 (1942).

[960] O. Grummitt, R. Egan, and A. Buck, *Org. Syn.*, **29**, 49 (1949).

[961] E. C. Horning and A. F. Finelli, *J. Amer. Chem. Soc.*, **71**, 3205 (1949).

[962] R. C. Roberts and T. B. Johnson, *J. Amer. Chem. Soc.*, **47**, 1399 (1925).

[963] J. C. Roberts and B. Shaw, *J. Chem. Soc.*, **1950**, 2844.

[964] B. H. Nicolet and J. A. Bender, *Org. Syn.*, Coll. Vol. I, 410 (1941).

[965] L. McMaster and F. F. Ahmann, *J. Amer. Chem. Soc.*, **50**, 146 (1928).

[966] J. Volhard, *Ann. Chem.*, **242**, 150 (1887).

[967] D. Mol, *Rec. Trav. Chim.*, **26**, 381 (1907).

[968] G. L. Voerman, *Rec. Trav. Chim.*, **23**, 269 (1904).

Acetic anhydride:[969] Acetyl chloride (5 g) is dropped, with cooling, on powdered, anhydrous sodium acetate (8 g). The mixture is warmed gently, then the anhydride formed is distilled off. To remove traces of acetyl chloride it is distilled over sodium acetate. It has b.p. 136.5°. The yield is 80–90% (5–6 g).

The preparation of pure acid chlorides can be avoided by heating the sodium salts of the carboxylic acids with a halogen carrier such as phosphorus oxychloride, phosphorus pentachloride, or thionyl chloride, as the acid chlorides are then formed as intermediates.[1s]

Further, preparation of the carboxylic acid salts is unnecessary if the free acid is acylated directly with the acid chloride.

Butyric anhydride:[970] Molar quantities of butyric acid and butyryl chloride are heated together on a water-bath for 1 h and then boiled for 7 h in an oil-bath. Butyric anhydride, b.p. 198–199°/765 mm, is obtained on distillation of the resulting mixture.

Acid chlorides and tertiary bases, in particular pyridine, form addition compounds that act as efficient acylating agents even at low temperatures; and acid anhydrides are obtained in good yield by adding, first, pyridine and then a little water to acid chlorides.[971]

Benzoic anhydride: Freshly distilled benzoyl chloride (14 g, 0.1 mole) is dissolved in anhydrous dioxan (40 ml) and then cooled in ice-water whilst anhydrous pyridine (10 ml) is added. Cooling being maintained, water (1 ml) is added, preferably diluted with a little dioxan, after which the mixture is set aside with ice-cooling for 10 min and then poured into a mixture of concentrated hydrochloric acid (75 ml), ice (75 g), and water (75 ml). The crystalline anhydride that separates is filtered off, washed with ice water, dried in a vacuum, and crystallized from ether–light petroleum; it (11 g, 97%) then has m.p. 42–43°.

A mixture of acid chloride and pyridine reacts similarly with free carboxylic acids.

1-Acylimidazoles also give carboxylic anhydrides on reaction with carboxylic acids.[972]

The indirect method of preparing anhydrides by treating free carboxylic acids with acetic anhydride[973] is both valuable and generally applicable: the appropriate acid is boiled under reflux for about 2 hours with five to six times its weight of acetic anhydride, after which it is best to remove the acetic acid produced, with the excess of acetic anhydride, by distillation in a vacuum.

Benzoic anhydride:[974] A mixture of benzoic acid (48.8 g), acetic anhydride (41 g), and anhydrous benzene (200 g) is boiled under reflux for 6 h and then fractionated. Removal of the benzene and acetic acid by distillation yields benzoic anhydride (36.8 g, 81%), b.p. 347 to 348°, m.p. 42°.

It is also possible to treat acid chlorides with acetic anhydride, this giving acetyl chloride and the polymeric anhydride;[975] equally, anhydrides are formed when carboxylic acids react with acid chlorides.[976]

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[969] C. Gerhardt, *Ann. Chim.* (*Paris*), [iii], **37**, 313 (1853).

[970] E. Linnemann, *Ann. Chem.*, **161**, 179 (1872).

[971] H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949).

[972] H. A. Staab, G. Walther, and W. Rohr, *Chem. Ber.*, **95**, 2073 (1962).

[973] W. Autenrieth and G. Thomae, *Ber. Deut. Chem. Ges.*, **57**, 430 (1924).

[974] A. Kaufmann and A. Luterbacher, *Ber. Deut. Chem. Ges.*, **42**, 3484 (1909).

[975] F. Zetsche, C. Flütsch, F. Enderlin, and A. Loosli, *Helv. Chim. Acta*, **9**, 181 (1926).

[976] M. H. Fournier, *Bull. Soc. Chim. France*, [iv], **5**, 920 (1909).

Mixed anhydrides can be obtained by those of the above methods in which acid chlorides are used. Further, formation of anhydrides from carboxylic acids and acetic anhydride involves mixed anhydrides as intermediates, and in some cases these can be isolated, *e.g.*, the mixed formic acetic anhydride.[977] This anhydride can replace the unstable formic anhydride itself, for only the reactive formyl group is transferred in its reactions; this fact has been utilized in the preparation of numerous formic esters, which in turn can be transformed into esters of tertiary alcohols that are otherwise difficult of access (see page 376).

According to Behal,[977] **acetic formic anhydride** is obtained as follows: Anhydrous formic acid (138 g) is treated, under ice-cooling, with acetic anhydride (408 g), then set aside for some time, next heated on a water-bath to 50° and subsequently cooled again. The mixture is next distilled, fractions boiling at 18 mm at 27–31°, 31–32°, and above 32° being collected separately. The middle fraction is treated with light petroleum, which dissolves the acetic acid most easily, the acetic anhydride also moderately well, and the mixed anhydride very sparingly. The portion insoluble in the light petroleum is fractionated again in a vacuum, then giving a middle cut at 29°/17 mm that constitutes an 80% yield of the mixed anhydride.

According to Bryce-Smith,[978] acid anhydrides are formed in good yield when the silver salt of a carboxylic acid is heated with carbon disulfide at 100–150° for 6–20 h; the anhydride is obtained in a very pure state, and the only by-product is the free carboxylic acid.

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[977] A. Behal, *Ann. Chim. Phys.*, [vii], **2**, 417 (1900); cf. *C. R. Hebd. Séances Acad. Sci.*, **128**, 1460 (1899).

[978] D. Bryce-Smith, *Proc. Chem. Soc.*, **1957**, 20.

CHAPTER 5

Cleavage of Carbon–Oxygen Bonds

Compiled by
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The carbon–oxygen bond can be cleaved in the following types of compound:

carboxylic anhydrides
orthoesters, acetals, and hemiacetals
carboxylic esters
ethers

This cleavage occurs the more easily the greater the number of hetero atoms attached to a carbon atom of the C–O–C group: the above types of compound are thus arranged in order of increasing stability.

Special features are that the ester linkage of lactones and lactides are cleaved more easily than those of normal esters and that rings containing oxygen as ring member are the more easily cleaved the greater the number of such oxygen atoms; for instance, paraldehyde is more easily cleaved than dioxan.

I. Cleavage of ether bonds

Cleavage of the ether bond usually requires rather energetic conditions and is often not clear-cut; further, the requisite reagents are not equally well applicable in all cases. Ether fission can be achieved by acid reagents such as AlX_3, H_2SO_4, acid anhydrides, acid chlorides, and hydrogen halides, as well as by bases, organometallic compounds, and alkali metals, in some cases also by hydrogenation.

Hydrogen iodide is the most suitable of the hydrogen halides. When equivalent amounts are used, the products are the alkyl iodide and an alcohol, the group of higher molecular weight usually providing the alcohol and that of lower molecular weight the alkyl iodide.[1] Ethers containing a methyl group and a group of higher molecular weight are cleaved smoothly and relatively rapidly in this way, yielding methyl iodide and an alcohol. This method is

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[1] R. D. Silva, *Ber. Deut. Chem. Ges.*, **8**, 1352 (1875); W. Sippert, *Ann. Chem.*, **276**, 196 (1893).

the basis of the Zeisel determination of methoxyl groups;[2] a sample is boiled under reflux with concentrated aqueous hydriodic acid, and the methyl iodide evolved is caused to react with silver nitrate and determined gravimetrically as silver iodide.

When an excess of hydrogen iodide is used with aliphatic ethers, both portions of the molecule are to be expected as alkyl iodides, but alkyl aryl ethers always give alkyl iodide and the phenol:

$$C_6H_5OR + HI \longrightarrow C_6H_5OH + RI$$

Cleavage of aryl methyl ethers is often used as a method of preparing phenols, the yields of phenol usually being between 72 and 93%; for this purpose the ether is boiled under reflux with aqueous hydriodic or hydrobromic acid, often in admixture with glacial acetic acid.

For the preparation of **pyrocatechol,** guaiacol is boiled with 48% hydrobromic acid for 6–7 h, and the guaiacol distilling over in the steam is isolated in a separator and returned automatically to the reaction vessel.[3]

Boiling *m*-methoxyphenylacetic acid in hydriodic acid for 1.5 h gives a 72% yield of ***m*-hydroxyphenylacetic acid.**[4]

Bis-(*p*-hydroxyphenyl) ether is synthesized as follows:[5] Bis-(*p*-methoxyphenyl) ether (24 g) is boiled for 4 h with 48% aqueous hydrobromic acid (60 ml) and acetic anhydride (30 ml) (previously mixed with caution) and the whole is then poured into warm water (300 ml). On cooling, the bis(hydroxyphenyl) ether crystallizes in colorless leaflets (19.7 g, 93%), m.p. 160–161°. Demethylation by $AlCl_3$ gives much resinous by-products.

Lüttringhaus and von Sääf[5] have briefly reviewed the methods of cleaving aryl ethers.

Ether cleavage by hydrogen iodide is carried out either by means of aqueous hydriodic acid, sometimes in admixture with glacial acetic acid, or by saturating the ether with HI at 0° and then heating it in a sealed tube on a water-bath. There are limitations to the use of hydrogen iodide because of its reducing action, and to avoid this it may be advantageous to use an alkyl iodide and phosphoric acid; when this mixture is used in excess with aliphatic ethers alkyl iodides are obtained,[6] but aryl ethers are not attacked by it.

It is almost always possible to use hydrobromic in place of hydriodic acid, but the reactions are then somewhat slower. Reactive ethers can also be cleaved by hydrochloric acid.

Triphenylmethyl ethers are unstable even to dilute mineral acids: they are cleaved by such acids in acetone or alcoholic solution at room temperature, or by hot 80% acetic acid, yielding triphenylmethanol and an alcohol.[7]

Ethers of tertiary aliphatic ethers give the halides smoothly when treated with hydrogen chloride.[8] Benzyl ethers are also easily cleaved: both benzyl groups of 1,3-dibenzyloxy-2,5-dimethoxybenzene are removed in one hour by hydrochloric acid at 65°, but the methoxyl groups remain unaffected;[9]

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[2] S. Zeisel and R. Fanto, *Z. Anal. Chem.*, **42**, 599 (1903); cf. F. Vieböck and A. Schwappach, *Ber. Deut. Chem. Ges.*, **63**, 2818 (1930); V. A. Klimova and K. S. Zabrodina, *Zh. Anal. Khim.*, **18**, 109 (1963); *Chem. Abstr.*, **59**, 1094 (1963).

[3] H. T. Clarke and E. R. Taylor, *Org. Syn.*, **3**, 28 (1923).

[4] E. C. Kornfeld, *J. Amer. Chem. Soc.*, **70**, 1375 (1948).

[5] A. Lüttringhaus and F. von Sääf, *Angew. Chem.*, **51**, 915 (1938).

[6] H. Stone and H. Shechter, *J. Org. Chem.*, **15**, 491 (1950).

[7] B. Helferich, *Advan. Carbohyd. Chem.*, **3**, 81 (1948).

[8] J. L. E. Eerickson and W. H. Ashton, *J. Amer. Chem. Soc.*, **63**, 1769 (1941).

[9] W. Baker, R. Nodzu, and R. Robinson, *J. Chem. Soc.*, **1929**, 74.

benzyl methyl ethers are cleaved almost quantitatively to benzyl chloride and methyl chloride when vigorously stirred with 2 parts of concentrated hydrochloric acid at 90° for 10 hours whilst gaseous HCl is led through the mixture.[10]

Reactive groups present in a molecule may also have a decisive influence on ether fission: vinyl ethers and enol ethers of 1,3-diketones or of 1,3-dioxo esters are as sensitive to acids as are glycosides; and ethers of ketones, *e.g.* 2-hydroxycyclohexanone, are also surprisingly easily attacked.[11]

Cyclic ethers are relatively readily cleaved, a reaction that is the basis of an elegant procedure for preparing 1,4-dihaloalkanes from tetrahydrofuran and its derivatives. In this reaction HI is more effective than HBr, and HBr more effective than HCl; leading any of these acids, as gas, for several hours through hot tetrahydrofuran containing zinc chloride gives the 1,4-dihalide in 59–75% yield;[12] using HCl similarly without the zinc chloride affords 4-chloro-1-butanol in 65% yield.[13] Reactions analogous to those described for tetrahydrofuran can be carried out also with tetrahydropyran.

Klemenc[14] observed fission when melting aniline hydrochloride with ethers,[13] this method being especially suitable for ethers that afford volatile alkyl halides; the reaction occurs more readily if dry, gaseous hydrogen chloride is passed through the mixture.[15] The aniline hydrochloride may be replaced by pyridine hydrochloride or hydrobromide at temperatures around 200°.

A number of aryl ethers are cleaved by sulfuric acid in good yield.[16]

Anhydrous sulfonic acids such as *p*-toluenesulfonic and methanesulfonic acid are very useful for ether fission according to the equation:[17]

$$\mathrm{ROR} + \mathrm{R'SO_3H} \longrightarrow \mathrm{ROH} + \mathrm{R'SO_2OR}$$

When an excess of the acid is applied, symmetrical alkyl ethers give the corresponding alkyl sulfonate as sole product, since the alcohol formed as intermediate is rapidly esterified; this reaction is thus to be recommended for the preparation of alkyl sulfonates, though it should be noted that the water formed slows down the process; the aryl–oxygen bond of alkyl aryl ethers is not broken, these compounds giving the alkyl sulfonate and the corresponding phenol.

To effect the reaction the ether (0.4–0.8 mole) is heated with the sulfonic acid (0.1–0.3 mole) under reflux at the boiling point of the ether or in a bomb tube for 6–15 h at 120–180°.

In the presence of Lewis acids such as $ZnCl_2$, $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, $SbCl_5$, or BF_3, acid chlorides or anhydrides can convert ethers into esters and alkyl halides. This method is generally restricted to alkyl ethers, since

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[10] E. Rieche and H. Seeboth, *Chem. Techn.*, **10**, 614 (1961).

[11] M. Bergmann and M. Gierth, *Ann. Chem.*, **448**, 65, 69 (1926).

[12] S. Fried and R. D. Kleene, *J. Amer. Chem. Soc.*, **63**, 2691 (1941); D. S. Tarbell and C. Weaver, *J. Amer. Chem. Soc.*, **63**, 2939 (1941).

[13] D. Starr and R. M. Hixon, *Org. Syn.*, Coll. Vol. 2, 571 (1943).

[14] A. Klemenc, *Ber. Deut. Chem. Ges.*, **49**, 1371 (1916).

[15] E. A. Zofin and K. A. Chilovadse, *Khim.-Farm. Prom.*, **1932**, 376; *Chem. Zentralbl.*, **1933**, II, 3118.

[16] O. Diels and F. Bunzl, *Ber. Deut. Chem. Ges.*, **38**, 1491 (1905); G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N.S.W.*, **71**, 103 (1938).

[17] D. Klamann and P. Weyerstahl, *Chem. Ber.*, **98**, 2070 (1965).

aryl ethers then mostly undergo the Friedel–Crafts reaction. Detailed studies of the course of the reaction, together with yields, have been reported by Meerwein and his co-workers for a number of Lewis acids.[18] $ZnCl_2$ and $SnCl_4$ appear to be the best catalysts for this process. For instance, when 0.1 mole of $SnCl_4$ is used per mole of benzoyl chloride, diethyl ether gives, in 4 hours at 110°, an 80% yield of alkyl chloride and a 90% yield of ethyl benzoate.[19] The action of acid chlorides on tetrahydrofuran in the presence of $ZnCl_2$ gives the 4-chlorobutyl esters.[20] Acid bromides or, more readily, acid iodides cleave ethers without the need for a catalyst.[21]

Aliphatic ethers are cleaved by acetic anhydride containing boron trifluoride etherate plus lithium iodide at 20°:[22] the alcoholic parents of the ether are obtained as main products, together with small amounts of olefin; for instance, cyclohexyl acetate and 3β-cholestanyl acetate are formed from alkoxycyclohexanes and 3β-alkoxycholestanes, respectively.

Aluminum halides have preparative importance, particularly for removal of methyl and ethyl groups; it does not attack diaryl ethers. The ether-cleaving action of aluminum chloride was discovered with fission of anisole.[23] A crystalline double compound is formed in the reaction and decomposes to alkyl halide and aluminum phenoxide when warmed.

Anisole (10 g) is heated with aluminum chloride (15 g) for 3 h at 120°, methyl chloride being evolved. The residual phenoxide is decomposed by water, the mixture is acidified, and the phenol is taken up in ether and worked up in the usual way.

Aluminum bromide is superior to the chloride for cleavage of alkyl aryl ethers; it is soluble in indifferent solvents such as benzene, carbon disulfide, and light petroleum. According to Pfeiffer and Haack,[24] the reaction takes place according to the scheme:

$$ROCH_3 + AlBr_3 \longrightarrow ROCH_3{\cdot}AlBr_3 \longrightarrow ROAlBr_2 + CH_3Br$$

$$ROAlBr_2 + H_2O \longrightarrow ROH + AlBr_2OH$$

If the molecule contains carbonyl groups, each adds an additional mole of aluminum chloride.[24] In simple cases it suffices to heat the substance with the requisite amount of aluminum bromide under reflux in thiophene-free benzene.[25]

For the preparation of **p-hydroxybenzoic acid,** p-anisic acid (0.79 g; dried over P_2O_5) is dissolved in warm benzene (35 ml), treated with a solution of $AlBr_3$ (4.9 g) in benzene (30ml), and boiled for 4.5 h under reflux. After cooling, the solution is decomposed with concentrated hydrochloric acid and extracted with ether, the hydroxy acid is removed from the ether by sodium hydroxide solution, liberated from the alkaline solution by acid, taken up again in ether, and recovered on evaporation (0.37 g).

Compounds such as papaverine and piperonaldehyde have been similarly dealkylated.

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[18] H. Meerwein and co-workers, *J. Prakt. Chem.*, [ii], **134**, 51 (1932); **147**, 257 (1937).

[19] L. M. Smorgonskii, *Zh. Obshch. Khim.*, **17**, 416 (1947); *Chem. Abstr.*, **42**, 858 (1948).

[20] M. E. Synerholm, *Org. Syn.*, **29**, 30 (1949).

[21] E. L. Gustus and P. G. Stevens, *J. Amer. Chem. Soc.*, **55**, 378 (1933); N. O. V. Sonntag, *Chem. Rev.*, **52**, 353 (1953).

[22] R. D. Youssefyeh and Y. Mazur, *Tetrahedron Lett.*, **26**, 1287 (1962).

[23] C. Hartmann and L. Gattermann, *Ber. Deut. Chem. Ges.*, **25**, 3531 (1892).

[24] P. Pfeiffer and E. Haack, *Ann. Chem.*, **460**, 156 (1928).

[25] P. Pfeiffer and W. Loewe, *J. Prakt. Chem.*, [ii], **147**, 293 (1936).

Ether fission can also be brought about by MgI_2,[26] BCl_3,[27] $SiCl_4$,[28] or $LiAlH_4$,[29] but these reagents have so far been little used for this purpose. Boron tribromide is an effective dealkylating agent for aryl ethers.[30]

The ether and BBr_3 are mixed in CH_2Cl_2 or pentane at −80° and allowed to warm slowly to 20°, then poured into water. The phenol formed is, if necessary, extracted with ether, and is purified by recrystallization.

Certain arylalkyl ethers, with which cleavage by acid fails or leads to undesired by-products, can be decomposed by alkalis or alkoxides at temperatures above 150°, preferably with addition of ethanol or a higher-boiling alcohol. Veratrole, for instance, can be partially converted into guaiacol by 3 hours' heating with equal parts of potassium hydroxide and ethanol;[31] and *o*-methoxyphenyl phenyl ether is cleaved to *o*-hydroxyphenyl phenyl ether in 91% yield by 10 hours' boiling with sodium hydroxide in diethylene glycol.[32]

As expected, the ease of fission of aryl ethers parallels their ease of formation; ethers of nitrophenols, for example, can be hydrolysed by even gentle warming with alcoholic potassium hydroxide. Polynitrophenyl ethers are often cleaved even by water, ammonia, or primary or secondary amines.[33] Ethers of hydroxy quinones are also decomposed by cold dilute sodium hydroxide solution.[34]

A further method of cleaving C–O–C bonds consists in treating them with organometallic compounds. Grignard compounds can react with ethers according to the equation:

$$\mathrm{PhOR + R'MgX \longrightarrow PhOMgX + R{-}R'}$$

This reaction is occasionally used for fission of alkyl aryl ethers, particularly benzyl ethers. In general, temperatures between 150° and 200° are required,[35] but fission of β,γ-unsaturated phenyl ethers occurs already at 55°.[5]

Other organometallic compounds may be more effective than Grignard compounds. For instance, cholesteryl ethyl, isopropyl, and *tert*-butyl ether are converted into cholesterol, pentane, and olefin by pentylsodium at 10°, thus:[36]

$$\mathrm{Chol{-}O{-}C_2H_5 + C_5H_{11}Na \longrightarrow Chol{-}ONa + C_5H_{12} + C_2H_4}$$

Cholestadiene is formed as by-product by the following reaction:

$$\mathrm{Chol{-}OR + C_5H_{11}Na \longrightarrow Cholestadiene + C_5H_{12} + RONa}$$

If there is no β-hydrogen atom in the alkyl group R, as is the case with cholesteryl methyl or benzyl ether, then cholestadiene is the sole product. According

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[26] V. Grignard and J. Ritz, *Bull. Soc. Chim. France*, [v], **3**, 1181 (1936).

[27] W. Gerrard and M. F. Lappert, *Chem. Rev.*, **58**, 1091 (1958).

[28] R. Schwarz and W. Kuchen, *Chem. Ber.*, **89**, 169 (1956).

[29] P. Karrer and O. Rüttner, *Helv. Chim. Acta*, **33**, 812 (1950); cf. V. Tweedie and M. Cuscurida, *Angew. Chem.*, **66**, 646 (1954).

[30] J. F. W. McOmie and M. L. Watts, *Chem. & Ind. (London)*, **1963**, 1658.

[31] L. Bouveault, *Bull. Soc. Chim. France*, [iii], **19**, 75 (1898).

[32] H. E. Ungnade and K. T. Zilch, *J. Org. Chem.*, **15**, 1109 (1950).

[33] R. J. W. Le Fèvre, S. L. Saunders, and E. E. Turner, *J. Chem. Soc.*, **1927**, 1168.

[34] U. Nef, *J. Prakt. Chem.*, **42**, 168 (1890).

[35] E. Späth, *Monatsh. Chem.*, **35**, 319 (1914).

[36] D. H. Gould, K. H. Schaaf, and W. L. Ruigh, *J. Amer. Chem. Soc.*, **73**, 1263 (1951).

to Letsinger and his co-workers,[37] alkenylsodiums can be used for ether fission, and Löttringhaus and Sääf[5] have used phenyllithium.

Fission of aryl ethers can also be effected by metallic sodium or potassium. For instance, diphenyl ether, which is one of the most resistant ethers, is decomposed by liquid potassium–sodium alloy at room temperature.[38] Weber and Sowa have cleaved 4,4′-disubstituted diphenyl ethers into benzene and phenol derivatives by sodium in liquid ammonia.[39] Diallyl ether is converted by sodium dust at 35° into allylsodium and sodium allyl oxide, which provides a suitable method for preparation of allylsodium.[37a] Anisole, phenetole, benzyl phenyl ether, and diphenyl ether give the phenols in 90% yield, without by-products, when boiled with sodium or potassium in pyridine.[40]

The methods discussed above all require chemically aggressive reagents. Freudenberg and his co-workers,[41] however, found that benzyl ethers can also be cleaved by catalytic hydrogenation; alkyl benzyl ethers can be converted into toluene and an alcohol by hydrogenation under very mild conditions in presence of platinum metals or Raney nickel; reductive cleavage of aryl benzyl ethers is best carried out in presence of palladium–charcoal.

3-Galloylglucose:[42] 3-*O*-(Tri-*O*-galloyl)glucose (10 g) in methanol (250 ml) is hydrogenated at 25° in presence of 2% palladium–charcoal (2 g). Hydrogenation is complete in 3.5 h after absorption of 1260 ml of hydrogenation (theor. 1240 ml). The catalyst is filtered off and washed with ethanol, and the filtrates are evaporated in a vacuum. The residual colorless foam is dissolved in a little water, and the solution is evaporated in a vacuum-desiccator, leaving a colorless brittle residue (5.4 g, 98%).

In this way hydroxyl groups can be protected during synthetic work by conversion into benzyl ether groups and can be regenerated later under mild conditions.

Organic Reactions contains a review of the fission of benzyl ethers, including cyclic benzyl ethers, by hydrogenation.[43] Ring fission of furans has been reviewed by Jones and Taylor.[44] Burwell[45] has written an excellent and detailed report on the cleavage of ethers, in which he discusses also the theoretical problems involved; he concludes with some indications for the fission of sulfides, a subject that is treated also by Tarbell and Harnish.[46]

II. Hydrolysis of carboxylic esters

Hydrolysis of carboxylic esters to a carboxylic acid and an alcohol occurs in an alkaline or an acid medium:

$$\mathrm{RCOOR'} + \mathrm{H_2O} \rightleftarrows \mathrm{RCOOH} + \mathrm{R'OH}$$

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[37] R. L. Letsinger and co-workers, *J. Amer. Chem. Soc.*, (a) **70**, 3342 (1948); (b) **73**, 5708 (1951); **75**, 2649 (1953).

[38] E. Müller and W. Bunge, *Ber. Deut. Chem. Ges.*, **69**, 2171 (1936).

[39] F. C. Weber and F. J. Sowa, *J. Amer. Chem. Soc.*, **60**, 94 (1938).

[40] V. Prey, *Ber. Deut. Chem. Ges.*, **76**, 156 (1943).

[41] K. Freudenberg, W. Dürr, and H. von Hoschstetter, *Ber. Deut. Chem. Ges.*, **61**, 1739 (1928).

[42] O. T. Schmidt and A. Schach, *Ann. Chem.*, **571**, 35 (1951).

[43] W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 263 (1953).

[44] D. G. Jones and A. W. C. Taylor, *Quart. Rev.*, **4**, 199 (1950).

[45] R. L. Burwell Jr., *Chem. Rev.*, **54**, 615 (1954).

[46] D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).

Acid hydrolysis requires only catalytic amounts of an acid; however, for alkaline hydrolysis (saponification) an equimolar amount of alkali is necessary since this is not merely a catalyst but also acts by withdrawing the acid as salt from the equilibrium mixture.[47a, 48]

The rate of hydrolysis of carboxylic esters can be increased by raising the temperature. It is also advantageous to remove the alcohol produced by continuous distillation. Acid hydrolysis is dependent on the hydrogen ion concentration; it is usually considerably slower than alkaline hydrolysis of esters.

The rate of hydrolysis of an ester also depends on the constitutions of the acid and of the alcoholic group, whether in an acid or[49] an alkaline medium.[50] Steric factors have a great effect on the ease of hydrolysis of esters; branching of a carbon chain in the neighborhood of the esterified carboxyl group makes cleavage more difficult; and branching in the alcoholic component has a similar effect. The rate of hydrolysis is also affected by the acidity of the parent acid: the more acidic the acid the faster are its esters hydrolysed by alkali.[51] Esters of primary alcohols are hydrolysed by alkali hydroxides faster than those of secondary alcohols, and the latter faster than esters of tertiary alcohols; however, in an acid medium esters of tertiary alcohols are particularly easily cleaved. Purely aliphatic esters react more easily than aromatic ones. It is thus apparent that the ease of hydrolysis of esters parallels their ease of formation.

Hydrolysis by alkali: The usual reagent is a solution of sodium hydroxide or potassium hydroxide in water or an alcohol (methanol, ethanol, or diethylene-glycol). Milder reagents are solutions of barium or calcium hydroxide. If fission of an ester gives products that are sensitive to strong alkali, it can often be effected with advantage by a solution of sodium carbonate, sodium hydrogen carbonate, or sodium methoxide.[52] For hydrolysis of particularly stable esters, such as *o,o'*-disubstituted aromatic carboxylic esters, it is sometimes necessary to use an alkali melt.

The concentration of the alkali and the temperature to be used depend on the ease of hydrolysis of the ester and on the stability of the products.

Simple straight-chain alkyl esters of lower aliphatic carboxylic acids are usually hydrolysed by boiling them for 0.5–2 hours in 25% sodium hydroxide solution. For water-insoluble esters it is preferable to use alcoholic alkali so as to obtain a homogeneous mixture. For high-boiling esters solutions of potassium hydroxide in diethylene glycol can be used to advantage.[53] The

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[47] Detailed description and reaction mechanismus: H. Henecka in Houben–Weyl, "Methoden der organischen Chemie," 4th ed, Georg Thieme Verlag, Stuttgart, 1952, Vol. 8, pp. (a) 418, (b) 422.

[48] F. Klages in G. M. Schwab, "Handbuch der Katalyse," Springer Verlag, Vienna 1943, Vol. 7, Part 2, p. 325.

[49] K. Kindler, *Ann. Chem.*, **450**, 1 (1926); **452**, 90 (1927); **464**, 278 (1928); C. N. Hinshelwood and co-workers, *J. Chem. Soc.*, **1936**, 1357; **1935**, 1482; **1938**, 1801; G. Davies and D. P. Evans, *J. Chem. Soc.*, **1940**, 339.

[50] H. Olsson and co-workers, *Z. Phys. Chem.*, **102**, 26 (1922); **118**, 99, 107 (1925); **125**, 243 (1927).

[51] H. Olsson, *Z. Phys. Chem.*, **133**, 233 (1928).

[52] L. Claisen, *Ber. Deut. Chem. Ges.*, **38**, 703 (1905).

[53] C. E. Redemann and H. J. Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

excess of alkali hydroxide can be removed at the end of the reaction by passing in carbon dioxide.

Alkaline hydrolysis of esters is used in determination of the "Saponification value" of an ester; this term gives the amount of potassium hydroxide in mg required for hydrolysis of 1 gram of the ester. For experimental details see reference[54].

Some esters are hydrolysed merely on treatment with water, *e.g.*, methyl and ethyl formate,[48] half-esters of 1,2-ethanediol,[55] hydroxy carboxylic acids esterified on the carboxyl group,[56] *O*-acylglycolic esters,[57] and some esters of tropine alkaloids.[58]

Simple α- and β-amino esters should be included among the readily hydrolysed esters; they can often be cleaved by boiling water,[59] but it is usually preferable to use aqueous barium hydroxide.[60, 61] This reagent has the particular preparative advantages that barium salts of many carboxylic acids are sparingly soluble and can thus easily be separated and that the excess of barium hydroxide is readily removable at the end of the reaction by means of carbon dioxide or sulfuric acid.

β-Alanine:[60] Ethyl cyanoacetate (30 g) is converted into β-alanine ethyl ester by catalytic hydrogenation on PtO_2 in glacial acetic acid/sulfuric acid. After removal of the catalyst the solution is concentrated in a vacuum so far as possible, and the residue is poured into water (300 ml), treated with finely powdered barium hydroxide (100 g), and boiled for 3 h. Then, after cooling, the barium is precipitated with dilute sulfuric acid and separated by centrifugation. The solution is concentrated greatly in a vacuum, whereupon the β-alanine rapidly crystallizes (17 g, 72%); recrystallized from aqueous alcohol–ether, it has m.p. 195°.

Esters of strongly acidic acids such as cyanoacetic acid[47b] are hydrolysed by 20% sodium hydroxide solution even in the cold; esters of dicarboxylic acids such as diethyl malonate[62] or 2-methylheptanedioic acid[63] are converted in that way into their acid esters.

Complete hydrolysis of dicarboxylic esters requires prolonged boiling with alcoholic potassium hydroxide. On alkaline hydrolysis of unsaturated carboxylic esters a double bond may migrate,[64] but this does not occur on hydrolysis by hydrochloric acid.

Esters of α-keto acids are best hydrolysed by aqueous alkali hydroxides or by alcoholic potassium carbonate; using alcoholic alkali hydroxides often causes decomposition.[65]

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[54] Organikum, Organisch-Chemisches Grundpraktikum, VEB Deutscher Verlag der Wissenschaften, Berlin, 1962, p. 382.

[55] E. Erlenmeyer, *Ann. Chem.*, **192**, 249 (1878).

[56] L. Schreiner, *Ann. Chem.*, **197**, 7, 12, 15 (1879).

[57] M. Senff, *Ann. Chem.*, **208**, 274 (1881).

[58] S. P. Findley, *J. Amer. Chem. Soc.*, **76**, 2855 (1954).

[59] E. Fischer, *Ber. Deut. Chem. Ges.*, **34**, 445 (1901).

[60] F. Weygand, *Ber. Deut. Chem. Ges.*, **74**, 257 (1941).

[61] T. Kobayashi, *Ann. Chem.*, **536**, 158 (1938).

[62] D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1286 (1944).

[63] L. F. Fieser, M. T. Leffler, and co-workers, *J. Amer. Chem. Soc.*, **70**, 3206 (1948).

[64] B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org., Chem.*, **13**, 123 (1948).

[65] L. Bouveault, *Bull. Soc. Chim. France*, [iii], **15**, 1017 (1896); F. F. Blicke and M. U. Tsao, *J. Amer. Chem. Soc.*, **66**, 1645 (1944); F. F. Blicke and R. F. Feldkamp, *J. Amer. Chem. Soc.*, **66**, 1087 (1944).

Phenylglyoxylic acid:[66] A suspension of methyl glyoxylate (140 g) in 2N sodium hydroxide solution (700 ml) is shaken until most of it has dissolved, then hydrolysis is completed by 0.5 hour's heating on a water-bath. Residual insoluble material is removed by extraction of the cold solution with ether. The aqueous solution is acidified with 5N hydrochloric acid (350 ml) and extracted with ether; working up the extract and recrystallization from CCl_4 give the phenylglyoxylic acid (115.5 g, 90%), b.p. 105°/0.5 mm, m.p. 64.5–65.5°.

For hydrolysis of β-keto esters, particularly of higher β-keto esters, at room temperature it is best to use a mixture of glacial acetic and hydrochloric acid.[67]

Lactones are readily converted into the corresponding hydroxy carboxylic acids by aqueous bases.

Alkaline hydrolysis of carbohydrate acetates presents no difficulty if the reducing group of the carbohydrate is protected by an alkali-resistant substituent. Thus glycosides and isopropylidene derivatives of carbohydrates can be deacetylated by alcoholic alkali, barium hydroxide solution, or liquid[68] or alcoholic[69] ammonia.

Acetates of some carbohydrate derivatives are best hydrolysed by Zemplén's method[70] in which catalytic amounts of methanolic sodium methoxide are used.

Mannitol from hexa-*O*-acetylmannitol:[71] Anhydrous methanol (20 ml) is poured on hexa-*O*-acetylmannitol (8 g), the mixture is warmed on a water-bath, and 0.1N sodium methoxide solution (2 ml) is added. Mannitol begins to separate in 3 min. The mixture is evaporated to dryness under reduced pressure, the residue is dissolved in water (5 ml), and to this hot solution anhydrous alcohol (25 ml) is added. On cooling, the mannitol (2.7 g, 80.5%; m.p. 165°) separates.

Such hydrolyses can also be carried out by keeping the mixture for several days at room temperature or even at 0°; the reactions proceed to completion even if the compound to be deacetylated is sparingly soluble or as good as insoluble. Acetylcellulose was completely hydrolysed by warm methanolic sodium methoxide.[70] 0.1–0.01N-Sodium methoxide is the usual reagent.

Trifluoroacetic esters of carbohydrates are hydrolysed even by water or methanol.[72]

Hydrolysis by acid: Acid hydrolysis is less often used for esters in laboratory practice. It is, however, useful for alkali-sensitive compounds and in cases, such as for tetramethylsuccinic esters,[73] when alkaline hydrolysis is ineffective. To carry out the hydrolysis, the ester is boiled with aqueous mineral acid, but acetone, dioxan, or glacial acetic acid is added if the ester is insoluble in water.

Hydrolysis of an ester can be accelerated by raising the temperature or the hydrogen ion concentration. Dilute sulfuric or hydrochloric acid is usually taken as acid catalyst, but *p*-toluenesulfonic acid is also suitable.

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[66] E. Baer and M. Kates, *J. Amer. Chem. Soc.*, **67**, 1482 (1945).

[67] M. A. Mitz, A. E. Axelrod, and K. Hofmann, *J. Amer. Chem. Soc.*, **72**, 1231 (1950).

[68] E. Fischer and H. Strauss, *Ber. Deut. Chem. Ges.*, **45**, 2467 (1912).

[69] E. Fischer and M. Bergmann, *Ber. Deut. Chem. Ges.*, **50**, 1047 (1917).

[70] G. Zemplén and co-workers, *Ber. Deut. Chem. Ges.*, **56**, 1705 (1923); **59**, 1258 (1926); **69**, 1827 (1936).

[71] G. Zemplén and E. Pacsu, *Ber. Deut. Chem. Ges.*, **62**, 1613 (1929).

[72] E. J. Bourne, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, **1950**, 1367.

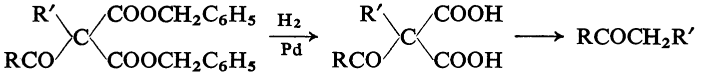
[73] K. von Auwers, *Ann. Chem.*, **292**, 180 (1896).

When concentrated hydrochloric or hydrobromic acid is used, the free carboxylic acid is accompanied by the derived alkyl halide which can be readily removed from the reaction mixture by evaporation,[74] and this method is sometimes used for the preparation of carboxylic acids.

Sensitive carboxylic acids can be prepared from their esters by acid-catalysed transesterification; *e.g.*, acrylic acid can be obtained from its methyl ester by means of formic acid containing sulfuric acid.[75]

Industry uses acid cleavage of esters on a large scale for saponification of fats, favoring certain catalysts such as the rapid-acting Twitchell reagent. Schlutius[76] carried out penetrating experiments on the nature and mode of action of these catalysts.

Hydrogenating ester cleavage: Esters of benzyl alcohol are converted by catalytic hydrogenation (Pd) into carboxylic acid and toluene.[77] This method has preparative importance, *e.g.*, for hydrolysis of acylmalonic esters, $RCO—CR'(COOC_2H_5)_2$, because alkali hydroxides remove the acyl group faster than they hydrolyse the ester. The benzyl groups of analogous benzyl esters are removed on hydrogenation in the presence of palladium–charcoal under mild conditions, and this route is sometimes used for the preparation of ketones:[78]



$$(R')(RCO)C(COOCH_2C_6H_5)_2 \xrightarrow[Pd]{H_2} (R')(RCO)C(COOH)_2 \longrightarrow RCOCH_2R'$$

An important application of hydrogenating ester cleavage is involved in Bergmann's benzyloxycarbonyl method of synthesizing peptides.[79] In this an amino acid is treated with benzyl chloroformate and then coupled with another amino acid molecule; the benzyl group of the resulting benzyl carbamate residue produced is finally removed as toluene, the carbamic acid derivative that results decomposing immediately to carbon dioxide and the desired peptide:

$$C_6H_5CH_2OCO—NHCHRCO—NHCHR'COOH \xrightarrow[Pd]{H_2}$$

$$NH_2CHRCO—NHCHR'COOH + C_6H_5CH_3 + CO_2$$

III. Hydrolysis of acetals, mercaptals, ketals, and orthoesters

Acetals, ketals, and mercaptals are excellently suited for masking of carbonyl groups. The carbonyl group that is masked as acetal is particularly readily regenerated after the compound has undergone the desired reaction.

Hydrolysis of acetals is also important because unsaturated aldehydes are often prepared by way of their acetals and because aldehydes often arise as products of, *e.g.*, Grignard syntheses. In general, acetals are smoothly hydro-

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[74] W. Theilacker and G. Wendtland, *Ann. Chem.*, **570**, 50 (1950).

[75] C. E. Rehbaerg, *Org. Syn.*, **29**, 5 (1949).

[76] E. Schlutius, *J. Prakt. Chem.*, [ii], **142**, 49 (1935).

[77] K. W. Rosenmund, F. Zetzsche, and F. Heise, *Ber. Deut. Chem. Ges.*, **54**, 2038 (1921); W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 272 (1953).

[78] R. E. Bowman, *J. Chem. Soc.*, **1950**, 325.

[79] M. Bergmann and L. Zervas, *Ber. Deut. Chem. Ges.*, **65**, 1192, 1201 (1932).

lysed by dilute mineral acids but are stable to alkali. Their fission is usually carried out by 0.01–3N sulfuric acid; but dilute hydrochloric acid, sodium hydrogen sulfite, and organic acids such as acetic, oxalic, and tartaric acid have also been used. Water-insoluble acetals are decomposed in the presence of organic solvents such as ethanol, glacial acetic acid, or acetone.

Phenylpropiolaldehyde is obtained in 70–81% yield from its diethyl acetal by heating the latter in approximately 12% sulfuric acid on a water-bath for 30 min with occasional shaking.[80]

Glyceraldehyde diethyl acetal is cleaved to glyceraldehyde in 80% yield when shaken with 0.1N sulfuric acid for 7 days at 20°.[81]

Most ketals are hydrolysed instantaneously by very dilute acid. Cyclic acetals and ketals are relatively stable, as are acetals of aldehydes containing basic groups. Hydrolysis of the last-mentioned class may lead to aldol condensation or formation of the Schiff base, so that concentrated acids are used in such cases.

The way to undertake hydrolysis of sensitive acetals was shown by Fischer and Löwenberg for the case of 3-methylcrotonaldehyde diethyl acetal:[82]

The acetal (53 g) is shaken with cold, saturated, aqueous tartaric acid solution (10 ml); the mixture becomes homogeneous and very cold. The whole is added, with shaking, to cold saturated calcium chloride solution (200 ml), whereupon **3-methylcrotonaldehyde** separates as an oil.

Schinz and Schäppi[83] hydrolysed a sensitive acetal by treatment with acetone containing benzenesulfonic acid; this gave the acetone ketal, which is more stable than the acetal.

Stepwise hydrolysis of tri-*O*-isopropylidene-D-mannitol was carried out by Irvine and Patterson as follows:[84]

Tri-*O*-isopropylidene-D-mannitol (30 g) was dissolved in alcohol (450 ml) containing 32% of water and 0.1% of hydrogen chloride. This solution was stirred in a thermostat at 4° for 150 min, then the hydrochloric acid was removed by addition of silver carbonate, and the filtrate was shaken with animal charcoal. On concentration of the filtrate therefrom under reduced pressure unchanged triisopropylidenemannitol separated first; this was filtered off and that filtrate was evaporated to dryness. Triturating the residue with cold acetone left free mannitol as a solid, whereas the mono- and di-isopropylidenemannitol dissolved. Evaporating the acetone in a vacuum gave 50% of the starting material as a mixture of mono- and di-isopropylidene derivatives. To separate them, the mixture was boiled with a large excess of benzene, from which, on cooling, monoisopropylidenemannitol crystallized. The filtrate therefrom was freed from solvent; the residual syrup distilled at 172°/11 mm and crystallized during several weeks to a mass of needles, m.p. 37–39°. This product is 3,4:5,6-di-*O*-isopropylidenemannitol, the so-called α-compound. The isomeric, symmetrical, 1,2:5,6-diisopropylidenemannitol is obtained by partial isopropylidenation of mannitol.[85]

On continued hydrolysis of the α-compound Irvine and Patterson obtained 3,4-mono-*O*-isopropylidenemannitol.[84,86] The isomeric 1,2-isopropylidenemannitol was prepared by a route involving a boric ester.[87]

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[80] C. F. H. Allen and C. O. Edens Jr., *Org. Syn.*, Coll. Vol. 3, 731 (1955).

[81] E. J. Witzemann and co-workers, *Org. Syn.*, Coll. Vol. II, 305 (1943).

[82] F. G. Fischer and K. Löwenberg, *Ann. Chim.*, **494**, 272 (1932).

[83] H. Schinz and G. Schäppi, *Helv. Chim. Acta*, **30**, 1483 (1947).

[84] J. C. Irvine and B. M. Patterson, *J. Chem. Soc.*, **105**, 907 (1914).

[85] E. Fischer and C. Rund, *Ber. Deut. Chem. Ges.*, **49**, 41 (1916); L. von Vargha, *Ber. Deut. Chem. Ges.*, **66**, 1297 (1933).

[86] Cf. A. Müller, *Ber. Deut. Chem. Ges.*, **65**, 1056 (1932).

[87] L. von Vargha, *Ber. Deut. Chem. Ges.*, **66**, 1396 (1933).

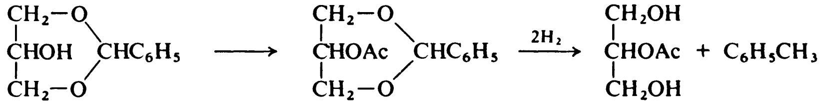
Hydrolysis of 3,5,6-tri-*O*-benzyl-1,2-isopropylidene-D-glucose to 3,5,6-tri-*O*-benzyl-α-D-glucose was effected in 73% yield by means of a mixture of 96% ethanol and 5N sulfuric acid in 4 h at 80°.[88]

For hydrolysis, 4,6-*O*-benzylidene-2-deoxygalactonitrile is heated in 20% acetic acid, and a mixture of acetic acid and benzaldehyde is distilled off whilst 10% acetic acid is slowly dropped into the mixture.[89]

Partial hydrolysis of acetoacetaldehyde bis(dimethyl acetal) to acetoacetaldehyde dimethyl acetal can be achieved in 91% yield by warming the former with an equivalent amount of water for 20–30 min at 50–60°.[90]

Selective hydrolysis of the acetal group of ester acetals may be effected by using acetic acid.[91]

On hydrogenation in presence of a platinum metal, benzaldehyde acetals give toluene and the parent alcohol. This process has been used for preparation of monoesters of polyhydroxy compounds, notably for synthesis of glycerol β-esters:[92]



Methyl *O*-benzylidene-α-D-glucoside is reductively cleaved by hydrogen in the presence of platinum black, giving toluene and methyl α-D-glucoside.[93]

Another mild fission of acetals and ketals that can be recommended for some cases consists in the use of ion-exchange resins.[94]

Yet a further method of cleaving acetals is to treat them with acid anhydrides, such as acetic or benzoic anhydride, in the presence of hydrogen ions;[95] equimolar amounts of acetal and anhydride give the aldehyde and the ester. Oximes, hydrazones, and Schiff bases can be obtained directly on acid hydrolysis of acetals in the presence of, *e.g.*, hydroxylamine, hydrazine, or amines, respectively.

Mercaptals are more stable than acetals towards hydrolysis. They can be cleaved by means of $HgCl_2$ in the presence of $CaCO_3$ or $CdCO_3$ or, better, by means of HgO. This method has become important particularly in carbohydrate chemistry.[96]

5-Deoxy-D-arabinose:[97] 5-Deoxy-D-arabinose (0.01 mole) is stirred for 8 h at 40° with acetone (60 ml), water (6 ml), yellow mercury oxide (6 g), and $HgCl_2$ (6 g). The solids are then filtered off and washed with water, and the filtrates are evaporated at 40° in a vacuum in the presence of mercuric oxide (1 g). The residue is extracted three times with warm water

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[88] F. Weygand and O. Trauth, *Chem. Ber.*, **85**, 60 (1952).

[89] R. Grewe and H. Pochaly, *Chem. Ber.*, **87**, 52 (1954).

[90] W. Franke and co-workers, *Chem. Ber.*, **86**, 793 (1953).

[91] R. Grewe and E. Nolte, *Ann. Chem.*, **575**, 11 (1952).

[92] M. Bergmann and N. M. Carter, *Z. Physiol. Chem.*, **191**, 211 (1930).

[93] K. Freudenberg, H. Toepffer, and C. Andersen, *Ber. Deut. Chem. Ges.*, **61**, 1759 (1928).

[94] W. L. Glen, G. S. Meyers, and G. A. Grant, *J. Chem Soc.*, **1951**, 2570; C. E. Ballou and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **78**, 1660 (1956).

[95] A. Wohl and H. Roth, *Ber. Deut. Chem. Ges.*, **40**, 217 (1907).

[96] E. Sovkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 940 (1945); H. Zinner and co-workers, *Chem. Ber.*, **91**, 1, 48, 427, 1006, 1657 (1958); **92**, 1618, 2893, 3151 (1959); and other references.

[97] H. Zinner, K. Wessely, and H. Kristen, *Chem. Ber.*, **92**, 1623 (1959).

(30-ml portions), and the mercury is precipitated as sulfide from the united filtrates by means of H_2S. The sulfide is filtered off and the hydrochloric acid is removed from the filtrate by use of an anion-exchanger (Wofatit L). Evaporation in a vacuum finally provides the syrupy product in 67% yield (0.9 g).

Drefahl, Seeboth, and Degen dissolved 4′-ureido-4-stilbenecarbaldehyde diethyl mercaptal in aqueous acetone and stirred the solution with $HgCl_2$ and HgO at room temperature. The mercury compounds were filtered off after 1 h. On addition of water, **4′-ureido-4-stilbenecarbaldehyde** crystallized in 89% yield.[98]

Hydrolysis of mercaptals and mercaptols has been reviewed by Tarbell and Harnish.[99]

Orthoesters can be regarded as ketals of carboxylic esters and can be hydrolysed analogously to ketals. This fission has no preparative value since it leads to the normal carboxylic acids which can, without exception, be prepared more conveniently in other ways.

Carboxylic anhydrides are hydrolysed smoothly by water, as described in every elementary textbook of organic chemistry.

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[98] G. Drefahl, H. Seeboth, and W. Degen, *J. Prakt. Chem.*, [iv], **4**, 102 (1956).

[99] D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 67 (1950).

CHAPTER 6

Formation of Carbon-Nitrogen Bonds

Compiled by
G. Lehmann and H. Teichmann

6.1. Formation of the carbon–nitrogen bond by addition

I. Addition of nitrogen compounds to C–C multiple bonds

1. Addition of ammonia and its substitution products

Ammonia and amines add to simple olefins only when catalysed and under energetic conditions. For example, *N*-methylaniline is obtained in 80–90% yield from aniline and ethylene at 300°/200 atm in the presence of sodium.[1] Rather high pressures and catalysts are also necessary for addition of amines to a C–C triple bond;[2–4] however, the reaction often does not stop at simple vinylation but gives the Schiff base instead of the expected isomeric vinylamine.[2–4] Tertiary amines can also be vinylated, as when neurine[2] is obtained in good yield from a 2 : 1 mixture of acetylene and nitrogen at 60–70°/20 atm:[5]

$$(CH_3)_3N + C_2H_2 + H_2O \longrightarrow [(CH_3)_3N{-}CH{=}CH_2]^+OH^-$$

Olefins react appreciably more readily if their double bond is activated by conjugation with another, neighboring multiple bond, as in α,β-unsaturated carboxylic acids, ketones,[6] nitriles,[7] etc.; in the simplest case even activation in a conjugated diene or by a benzene ring suffices. *E.g.*, boiling aniline with styrene under reflux in the presence of small amounts of sodium gives *N*-phenylphenethylamine in 70% yield.[8] According to Engel[9] β-amino acids are obtained by heating α,β-unsaturated carboxylic acids with ammonia in a sealed tube at about 100°. Adamson[10] prepared 3-aminobutyric esters in yields of up to 85% by keeping alcoholic solutions of crotonic esters and a primary or

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[1] R. Stroh, J. Ebersberger, H. Haberland, and W. Hahn, *Angew. Chem.*, **69**, 130 (1957).

[2] W. Reppe and co-workers, *Ann. Chem.*, **601**, 128 (1956).

[3] C. W. Kruse and R. F. Kleinschmidt, *J. Amer. Chem. Soc.*, **83**, 216 (1961).

[4] C. W. Kruse and R. F. Kleinschmidt, *J. Amer. Chem. Soc.*, **83**, 213 (1961).

[5] W. Reppe and co-workers, *Ann. Chem.*, **596**, 10 (1955), describe the technique for working with acetylene and the necessary protective measures.

[6] N. H. Cromwell, *Chem. Rev.*, **38**, 83–137 (1946).

[7] F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Amer. Chem. Soc.*, **66**, 725 (1944).

[8] R. Wegler and G. Pieper, *Chem. Ber.*, **83**, 1 (1950).

[9] R. Engel, *Bull. Soc. Chim. France*, [ii], **50**, 102 (1888).

[10] D. W. Adamson, *J. Chem. Soc.*, **1950**, 886.

secondary amine for 14 days at room temperature. Morpholine adds to acrylic acid derivatives in acetic acid so smoothly that this reaction can be used for quantitative determination of unsaturated compounds of this type.[11] An example of the ready addition to α,β-unsaturated ketones is the preparation of diacetonamine (4-amino-4-methyl-2-pentanone) by stirring mesityl oxide with aqueous ammonia for several hours;[12] the analogous hydroxyamino compound is readily formed in a similar reaction.[13]

Acid amines can be prepared by addition of ammonia or an amine to ketenes; amides of acetoacetic acid are accessible in high yields from diketene in this simple way.[14,15]

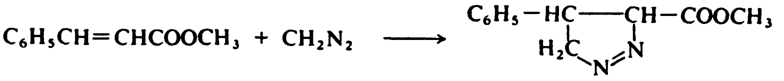
N-Halo amines add more easily than unsubstituted amines, and even to only slightly reactive double bonds; naturally a halogen atom is introduced at the α-position at the same time. *N*-Halo sulfonamides behave analogously, but *N*-halogenated carboxamides react almost exclusively in a quite different manner.

2. Addition of other nitrogen compounds

a. Addition of diazoalkanes and azides

Diazoalkanes and azides add in some cases quite extraordinarily easily, particularly to activated double bonds. Nitrogen is often split off from the primary products, with formation of a C–C bond, sometimes in the cold, more often on heating. In many cases, however, such addition forms the most elegant route to N-heterocycles.

Von Pechmann and Burkard,[16] for example, obtained an almost quantitative yield of methyl 4-phenyl-Δ^1-pyrazoline-3-carboxylate on adding methyl cinnamate to a cooled ethereal solution of diazomethane:



In a similar reaction benzylideneacetophenone affords 3-benzoyl-4-phenylpyrazoline, also almost quantitatively.[17] A large number of pyrazoline derivatives can be obtained in similar reactions of diazomethane or diazoacetic ester.

Pyrazole derivatives can be prepared analogously from alkynes; *e.g.*, reaction of propynal with ethereal diazomethane gives 84% of pyrazole-3-carbaldehyde and that with diazoacetic ester gives 86% of ethyl 5-formyl-pyrazole-3-carboxylate.[18] Further, pyrazole itself is readily accessible from acetylene and diazomethane.[19]

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[11] F. E. Critchfield, G. L. Funk, and J. B. Johnson, *Anal. Chem.*, **28**, 76 (1956).

[12] P. R. Haeseler, *Org. Syn.*, **6**, 28 (1926).

[13] C. Harries and R. Gley, *Ber. Deut. Chem. Ges.*, **31**, 1808 (1898).

[14] C. E. Kaslow and D. J. Cook, *J. Amer. Chem. Soc.*, **67**, 1969 (1945).

[15] J. W. Williams and J. A. Krynitzky, *Org. Syn.*, **21**, 4 (1941).

[16] H. von Pechmann and E. Burkard, *Ber. Deut. Chem. Ges.*, **33**, 3594 (1900).

[17] L. I. Smith and W. B. Pings, *J. Org. Chem.*, **2**, 23 (1938).

[18] R. Hüttel, *Ber. Deut. Chem. Ges.*, **74**, 1680 (1941).

[19] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **31**, 2950 (1898); W. Hückel, J. Datow, and E. Simmersbach, *Z. Phys. Chem.*, *A*, **186**, 159 (1940).

Triazoles are obtained in the same way when hydrogen azide or its esters, in place of diazo compounds, are added to C–C multiple bonds.[18]

b. Addition of nitriles

Addition of hydrogen cyanide or nitriles to olefins in the presence of concentrated sulfuric acid or some other strong acid is a preparatively important method of synthesizing alkylated amides containing secondary or tertiary alkyl groups on the nitrogen atom (the Graf–Ritter reaction): [20–26]

$$RC{\equiv}N + R'_2C{=}CR'_2 + H^+ \longrightarrow [R{-}C{=}\overset{+}{N}{-}CR'_2{-}CHR'_2]$$

$$\xrightarrow[-H^+]{H_2O} RCO{-}NH{-}CR'_2{-}CHR'_2$$

This reaction takes place in glacial acetic acid or in dibutyl ether at room temperature or on moderate warming and gives good yields.

As an example of the ready reaction the preparation of **N-acetyl-α-methylbenzylamine**[20] may be cited:

Styrene (10.4 g) and acetonitrile (6.1 g) are mixed and added to a solution of benzenesulfonic acid (17 g) in glacial acetic acid (50 ml). The whole is set aside for 15 h, then poured on crushed ice (200 g) and neutralized with aqueous ammonia. A viscous oil that separates is extracted three times with ether (100-ml portions). The extracts are united, dried over potassium carbonate, and freed from ether. The residue is distilled (b.p. 175–180°/7 mm). Recrystallization of the distillate from light petroleum gives the product (7 g, 43%), m.p. 72 to 73°.

The formamides resulting from the use of hydrogen cyanide can be particularly easily hydrolysed to the amines, thus providing an elegant method for synthesis of tertiary alkylamines that are otherwise difficult of access.[21] The reaction is capable of very wide generalization and is suitable also for the preparation of other classes of compound such as *N*-acylamino acids,[23] isoquinolines,[24] and oxazolines.[25]

Secondary or tertiary alcohols, or even tertiary carboxylic acids,[27] can be used with equal success in place of the corresponding olefins, and isoxazoles may replace the corresponding α-keto nitriles.[28]

c. Addition of nitrogen oxides and oxychlorides*

Dinitrogen tetroxide adds to olefinic double bonds with formation of dinitro compounds and nitro nitrites; the latter are unstable and are readily oxidized to nitro nitrates or hydrolysed to nitro alcohols; in the presence

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* Cf. p. 141.

[20] J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948).

[21] J. J. Ritter and J. Kalish, *J. Amer. Chem. Soc.*, **70**, 4048 (1948).

[22] F. R. Benson and J. J. Ritter, *J. Amer. Chem. Soc.*, **71**, 4128 (1949).

[23] L. W. Hartzel and J. J. Ritter, *J. Amer. Chem. Soc.*, **71**, 4130 (1949).

[24] J. J. Ritter and F. X. Murphy, *J. Amer. Chem. Soc.*, **74**, 763 (1952); H. Wollweber and R. Hiltmann, *Angew. Chem.*, **72**, 1001 (1960).

[25] R. M. Lusskin and J. J. Ritter, *J. Amer. Chem. Soc.*, **72**, 5577 (1950).

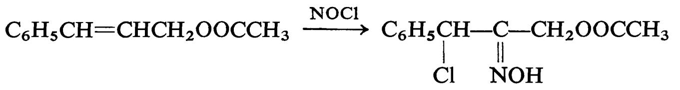
[26] H. Plaut and J. J. Ritter, *J. Amer. Chem. Soc.*, **73**, 4076 (1951); C. L. Parris and R. M. Christenson, *J. Org. Chem.*, **25**, 331 (1960).

[27] W. Haaf, *Chem. Ber.*, **96**, 3359 (1963).

[28] C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963).

of oxygen nitro ketones are also formed.[29] However, in spite of the high yields this reaction is of preparative importance only in special cases because reaction conditions must be adjusted very precisely, very pure reagents are required, and mixtures are usually formed. The same is true for the similar addition of nitryl chloride.

Addition of nitrosyl chloride also does not give single products.[30] However, it seems to be of practical use for esters of unsaturated alcohols: for instance, Pfleger and Landauer[31] obtained 65% of 3-chloro-2-(hydroxyimino)-3-phenylpropyl acetate in this way from cinnamyl acetate:



$$C_6H_5CH{=}CHCH_2OOCCH_3 \xrightarrow{NOCl} C_6H_5\underset{\displaystyle Cl}{\underset{|}{C}}H{-}\underset{\displaystyle NOH}{\underset{\|}{C}}{-}CH_2OOCCH_3$$

2,2,3,3-Tetraalkylaziridines can be prepared in astonishingly high yields from tetraalkylethylenes by addition of NOCl, reduction by $SnCl_2$, and ring closure by alkali.[32]

II. Addition of nitrogen compounds to C–N multiple bonds

1. Addition of hydrogen cyanide derivatives

The reactivity of the C–N triple bond in hydrogen cyanide and its derivatives can be utilized for formation of C–N bonds. In the simplest cases, namely, the reaction of amines to give amidines, the polarization of the C–N bond must be increased. For instance, Short and his co-workers[33] obtained good yields of amidines by heating the corresponding nitriles and amines in the presence of aluminum chloride. Unsubstituted amidines can be prepared in excellent yield by working with liquid ammonia containing ammonium salts under pressure.[34] The addition of alkali-metal amides to nitriles can occasionally be used for the synthesis of amidines;[35] however, this reaction is usually not a smooth one. Amidines are formed considerably more smoothly and in excellent yield by treating aromatic nitriles with magnesium derivatives of secondary amines which can be prepared in the same operation from ethylmagnesium bromide and the amine.[36,37]

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[29] N. Levy and co-workers, *J. Chem. Soc.*, **1946**, 1093, 1096, 1100; **1948**, 52; **1949**, 2627; T. E. Stevens, *J. Amer. Chem. Soc.*, **81**, 3593 (1959); W. K. Seifert, *J. Org. Chem.*, **28**, 125 (1963).

[30] L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951), especially pp. 369–378.

[31] R. Pfleger and F. Landauer, *Ann. Chem.*, **610**, 115 (1957).

[32] G. L. Closs and St. J. Brois, *J. Amer. Chem. Soc.*, **82**, 6068 (1960).

[33] P. Oxley, M. W. Partridge, and W. F. Short, *J. Chem. Soc.*, **1947**, 1110.

[34] F. C. Schaefer and A. P. Krapcho, *J. Org. Chem.*, **27**, 1255 (1962).

[35] G. Newbery and W. Webster, *J. Chem. Soc.*, **1947**, 738; K. Ziegler and H. Ohlinger, *Ann. Chem.*, **495**, 99 (1932).

[36] E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, **70**, 1904 (1948).

[37] E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, **71**, 3992 (1949); **73**, 93 (1951).

The usual procedure[36] is to add a slight excess of a secondary amine to an ethereal solution of ethylmagnesium bromide (50% excess relative to the nitrile) and, when evolution of ethane ceases, to heat the mixture under reflux for about 20 min before adding an ethereal solution of the nitrile; the whole is then boiled under reflux for 2–3 h, then decomposed with ice. In many cases this method is superior to the Pinner synthesis of amidines from imidoyl esters.

Hydroxylamines add appreciably more easily than amines to nitriles; they yield amide oximes,[38] $RC(=NOH)NH_2$.

Benzamide oxime,[39] for example, is obtained merely by warming an aqueous–alcoholic solution of equivalent amounts of hydroxylamine hydrochloride, benzonitrile, and sodium carbonate for several hours at 60–80°.

Amidrazones, $RC(NH_2)=NNH_2$ or $RC(=NH)—NHNH_2$, are formed in good yield by adding sodium hydrazide to nitriles and including hydrolysis in the working up.[40]

For the addition of compounds containing amine groups to cyanic esters see Martin.[41]

N,N'-Disubstituted formamidines are accessible from isocyanides and primary amines.[42]

Adding ammonia derivatives to cyanamide leads to guanidines. Salts of unsubstituted guanidine are obtained by melting dicyanodiamide with ammonium salts, *e.g.*, with ammonium nitrate.[43] Amines react smoothly with cyanamide only if presented as hydrochlorides; the components are boiled in anhydrous ethanol under reflux.[44] This process fails with too feebly basic amines, *e.g.*, with nitroanilines; however, even in such cases almost quantitative yields of guanidines can be obtained by melting the amine with an excess of cyanamide and treating the product with an excess of concentrated hydrochloric acid.[45]

Aminoguanidine can be prepared in high yield by addition of hydrazine to cyanamide; a simple procedure starting from disodium cyanamide and hydrazine sulfate is given by Fantl and Silbermann.[46]

Guanidines are also obtained from carbodiimides (which are isomeric with cyanamides) since these react extremely readily with ammonia or amines. Thus, for instance, *N,N',N''*-triphenylguanidine is formed exothermally when diphenylcarbodiimide is mixed with aniline.[47] The analogous addition of phenylhydrazine to diphenylcarbodiimide, giving *N,N'*-diphenyl-*N''*-(phenylamino)guanidine, forms the first step in the synthesis of nitrone.[48]

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[38] F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962).

[39] F. Tiemann, *Ber. Deut. Chem. Ges.*, **17**, 128 (1884).

[40] T. Kauffmann, S. Spaude, and D. Wolf, *Chem. Ber.*, **17**, 3436 (1964).

[41] D. Martin, *Z. Chem.*, **7**, 123 (1967).

[42] T. L. Davis and W. E. Yelland, *J. Amer. Chem. Soc.*, **59**, 1998 (1937); T. Saegusa and co-workers, *Tetrahedron Lett.*, **1966**, 6121.

[43] T. L. Davis, *Org. Syn.*, **7**, 46 (1927).

[44] A. Kämpf, *Ber. Deut. Chem. Ges.*, **37**, 1681 (1904).

[45] F. Arndt, *Ber. Deut. Chem. Ges.*, **46**, 3522 (1913); F. Arndt and B. Rosenau, *Ber. Deut. Chem. Ges.*, **50**, 1260 (1917).

[46] P. Fantl and H. Silbermann, *Ann. Chem.*, **467**, 279 (1928).

[47] W. Weith, *Ber. Deut. Chem. Ges.*, **7**, 10 (1874).

[48] M. Busch, *Ber. Deut. Chem. Ges.*, **38**, 858 (1905).

The azide ion adds to the triple bond of nitriles with formation of the tetrazole ring. The reaction is often very smooth but usually requires a long reaction period[49] or heating in a bomb tube.[50]

The preparation of **5-(*p*-methoxyphenyl)tetrazole**[49] will be described as an example: *p*-Methoxybenzonitrile (33 g, 0.25 mole), sodium azide (22 g, 0.33 mole), glacial acetic acid (20 g, 0.33 mole), and 1-butanol (100 ml) are boiled under reflux for 4 days, then more sodium azide (5 g), glacial acetic acid (10 g), and butanol (10 ml) are added, and the whole is heated for a further 2 days. Water (300 ml) is next added and the whole is concentrated in a vacuum to 100 ml. The resulting suspension is made alkaline with 10% sodium hydroxide solution, filtered, and extracted twice with benzene (50-ml portions). The aqueous alkaline solution is acidified with dilute hydrochloric acid, and the precipitate formed is washed with cold water and recrystallized twice from 20% 2-propanol, giving the product, m.p. 238–239°, in 81% yield.

Duration of the reaction can be shortened to about 24 h by using dimethylformamide as solvent.[51]

Dicyanodiamide reacts particularly readily with azides, giving 5-aminotetrazoles.[50] The parent compound is obtained analogously in about 80% yield by heating an alcoholic solution of hydrogen azide with anhydrous hydrogen cyanide at 100° for 2–3 days.[52]

Finally this is the place to mention the hydrogen cyanide derivatives that react with themselves to give dimers, trimers, or polymers. In the presence of acidic catalysts[53] cyanogen chloride trimerizes very easily to cyanuric chloride; cyanamide is dimerized smoothly by alkali to dicyanodiamide;[54] and trimerization to melamine is suitable as a preparative method starting from dicyanodiamide and ammonia under pressure.[55]

Nitriles can also trimerize; they yield triazines or aminopyrimidines according to the nature of the nitrile (cf. p. 205).

When, for instance, acetonitrile[56] is heated with an equimolar amount of dry potassium methoxide at 140° for 5 h, it affords 70% of 4-amino-2,6-dimethylpyrimidine ("cyanomethine"), but 85% of 2,4,6-tris(dichloromethyl)-*s*-triazine is obtained from dichloroacetonitrile in the presence of aluminum chloride and hydrogen chloride at room temperature.[57] Benzonitrile trimerizes in an acid catalysed reaction, most simply when its solution in chlorosulfonic acid is kept at 0° for 1–2 days, giving 2,4,6-triphenyl-*s*-triazine (cyaphenin),[58] but 85% of 1,2-dihydro-2,2,4,6-tetraphenyl-*s*-triazine is formed under the influence of a sodium suspension.[59]

Unsymmetrically substituted *s*-triazines have been prepared by "mixed polymerization" of different nitriles[57] and by exchange reactions[60] between

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[49] R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

[50] J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950); W. R. Carpenter, *J. Org. Chem.*, **27**, 2085 (1962).

[51] W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).

[52] O. Dimroth and G. Fester, *Ber. Deut. Chem. Ges.*, **43**, 2219 (1910).

[53] O. Diels, *Ber. Deut. Chem. Ges.*, **32**, 692 (1899).

[54] L. A. Pinck, *Inorg. Syn.*, **3**, 43 (1950).

[55] Swiss. Pat. 189406; *Chem. Abstr.*, **31**, 6678 (1937).

[56] A. R. Ronzio and W. B. Cook, *Org. Syn.*, **24**, 6 (1944).

[57] C. Grundmann, G. Weisse, and S. Seide, *Ann. Chem.*, **577**, 77 (1952).

[58] A. H. Cook and D. G. Jones, *J. Chem. Soc.*, **1941**, 278.

[59] J. J. Ritter and R. D. Anderson, *J. Org. Chem.*, **24**, 208 (1959).

[60] H. Meerwein and co-workers, *Chem. Ber.*, **89**, 217 (1956).

acid chlorides and nitriles.[61] 2-Aminopyridines[62] and 3-aminoisoquinolines[63] can be obtained in good yield by cyclizing dinitriles with hydrogen bromide.

2. Addition of cyanates and thiocyanates

The principle of Wöhler's method provides a method of very wide and varied applicability for the preparation of urea derivatives. Alkali cyanates and isocyanic and isothiocyanic esters on the one hand and ammonia, amines, amides, hydrazines, etc., on the other, undergo the reaction. When an alkali cyanate is used it is usually possible to work in aqueous solution and add the amine as a salt; alternatively, the free amine can be used in dilute acetic acid; room temperature or moderate temperatures usually suffice. A series of examples for the preparation of monoarylureas by this method is to be found in *Organic Syntheses.*[64]

Isocyanic esters and primary amines in indifferent solvents at room temperature give exothermally almost quantitative yields of the corresponding mixed ureas; secondary amines react more slowly, aromatic secondary amines in fact poorly. Water-soluble amines can often be used in aqueous solution since isocyanates react faster with amines than with water.

α-Amino acids can thus be converted into the derived ureido acids by shaking them with 1-naphthyl isocyanate in alkaline solution; insoluble dinaphthylurea — the product of condensation of the excess of isocyanate — is filtered off and the ureido acid is precipitated quantitatively by acidification.[65]

Thioureas are obtained analogously by boiling an amine hydrochloride and an alkali thiocyanate in aqueous solution[66] or an amine and a thioisocyanate in alcohol;[67] aromatic thioisocyanates generally react even in the cold. Further, aqueous ammonia solutions are converted smoothly into monoalkylthioureas by isothiocyanates.[68] Isothiocyanates can be converted directly into symmetrical thioureas by boiling them in aqueous dimethylformamide or dimethyl sulfoxide; the thiocarbamic acids formed as intermediates by partial hydrolysis add to unchanged isothiocyanate with loss of COS.[69]

The following directions have proved valuable for the preparation of **thiosemicarbazide**:[70]

Hydrazine sulfate (72 g) is added gradually with stirring to a solution of 100% hydrazine hydrate (28 ml) in water (80 ml). The pH is adjusted to 3–4 and ammonium thiocyanate (120 g) is added in portions at 40°. Stirring is continued for a further 10 min, then methanol (210 ml) is added. After a further 30-minutes' stirring the precipitated ammonium sulfate is filtered off. Acetone (2–3 ml) is added to the filtrate and the mixture is boiled under reflux for 24 h. After a further 12 h, more acetone (1 ml) is added to make up for losses. Crystals begin to separate even during the boiling. Filtration and washing with methanol affords

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[61] F. Krafft and co-workers, *Ber. Deut. Chem. Ges.*, **22**, 803 (1889); **23**, 2382 (1890); **25**, 2263 (1892).

[62] F. Johnson and co-workers, *J. Org. Chem.*, **27**, 2473 (1962).

[63] F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **27**, 3953 (1962).

[64] F. Kurzer, *Org. Syn.*, **31**, 8 (1951).

[65] C. Neuberg and A. Manasse, *Ber. Deut. Chem. Ges.*, **38**, 2359 (1905).

[66] F. Kurzer, *Org. Syn.*, **31**, 21 (1951).

[67] T. Otterbacher and F. C. Whitmore, *J. Amer. Chem. Soc.*, **51**, 1909 (1929).

[68] M. L. Moore and F. S. Crossley, *Org. Syn.*, **21**, 83 (1941); E. Schmidt, W. Striewsky, M. Seefelder, and F. Hitzler, *Ann. Chem.*, **568**, 192 (1950).

[69] D. Martin and W. Mucke, *Monatsber. DAW Berlin*, **6**, 632 (1964).

[70] Ger. Pat. 1067426; *Chem. Abstr.*, **56**, 8574 (1962).

thiosemicarbazide, m.p. 180–181°, in 89–94% yield (90–95 g) calculated on the hydrazine used.

Preparation of acylureas from amides and isocyanic esters requires more critical conditions but generally gives good yields.

1-Benzoyl-3-phenylurea:[71] A mixture of benzamide (12.1 g) and phenyl isocyanate (11.9 g) is heated slowly to 115°, at which temperature a violent reaction sets in, causing a further rise in temperature to 185°, whereupon heating is stopped. On cooling, the whole rapidly solidifies; recrystallization from dioxan gives the product, m.p. 203–204° (19.8 g, 82%).

Sulfonamides react particularly smoothly with isocyanates or isothiocyanates[72] in aqueous alkaline solution,[73] often in the cold, yielding sulfonylureas which are precipitated on acidification.

There is similar ready reaction of hydrazines with salts or esters of cyanic acid, under conditions similar to those required by amines. Hydrazine itself is in most cases substituted on both nitrogen atoms; alkylhydrazines usually react at the α-nitrogen atom but arylhydrazines at the β-nitrogen atom.[74]

Like cyanic esters, isocyanic esters can dimerize and trimerize. The dimeric uretediones[75,76] are formed under the influence of trialkylphosphine catalysts, but the trimeric isocyanuric esters are formed when potassium acetate[76] or sodium ethoxide[77] is used.

III. Addition of nitrogen compounds to C=O bonds

Addition of nitrogen compounds to carbonyl compounds usually leads to further reaction involving loss of water and formation of a C–N double bond. Since the end result is replacement of oxygen by nitrogen, these reactions are treated in subsection III of section 6.2 of this Chapter (see pages 504 et seq.).

In only realtively few cases are the primary adducts so stable that the customary loss of water does not occur. Such is the case with those aldehydes that also form stable hydrates; chloral, for example, adds a series of amines to give quite stable compounds:[78]

$$CCl_3CHO + NH_2R \longrightarrow CCl_3CH(OH)NHR$$

Benzaldehyde[79] and formaldehyde[80] also form such 1-amino alcohols ("*O,N*-semiacetals"), although these products are unstable. Oxazolidines,[81] which are obtained from α,β-aminoalcohols and carbonyl compounds, may also be regarded as *O,N*-semiacetals on the basis of their chemical behavior.

The adducts of amides to aldehydes are somewhat more stable. *N*-(Hydroxymethyl)phthalimide, which is interesting from both a preparative[82] and an

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[71] P. F. Wiley, *J. Amer. Chem. Soc.*, **71**, 1310 (1949).

[72] F. Kurzer, *Chem. Rev.*, **50**, 7 (1952).

[73] S. Petersen, *Chem. Ber.*, **83**, 551 (1950).

[74] G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949).

[75] L. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 230 (1943).

[76] A. W. Hofmann, *Ber. Deut. Chem. Ges.*, **18**, 764 (1885).

[77] A. Michael, *Ber. Deut. Chem. Ges.*, **38**, 22 (1905).

[78] L. Rügheimer, *Ber. Deut. Chem. Ges.*, **39**, 1653 (1906).

[79] A. Dornow and H. Thies, *Ann. Chem.*, **581**, 224 (1953).

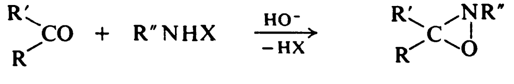
[80] H. Hellmann and G. Opitz, *Chem. Ber.*, **89**, 81 (1956).

[81] E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).

[82] H. Hellmann, *Angew. Chem.*, **69**, 463 (1957); H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie G.m.b.H., Weinheim/Bergstraße, 1960.

analytical[83] point of view, is obtained in more than 90% yield by refluxing phthalimide with aqueous formaldehyde solution for only a short time.[83,84] A series of other *N*-(hydroxymethyl) carboxamides has been prepared by heating amides[85] or *N*-alkylamides[86] with aqueous formaldehyde solution in the presence of alkaline condensing agents such as potassium carbonate, sodium hydroxide, and triethylamine.

N-Chloroalkylamines and alkylaminyl hydrogen sulfates cyclize under base catalysis with ketones, giving oxaziridines, but with aldehydes formation of the amide competes or predominates;[87] 2-methyl-1-oxa-2-azaspiro[2.5]octane, for example, is formed in 81% yield from cyclohexanone and *N*-chloromethylamine.[88]



(X = Cl or OSO_3H)

A number of carbonyl compounds add cyanic acid, giving α-hydroxy isocyanates.[89]

IV. Addition of nitrogen compounds to C=S bonds

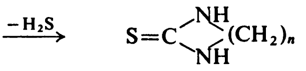
In this connexion only the addition of ammonia and its derivatives to carbon disulfide is of preparative interest; this gives dithiocarbamates which find use as intermediates in manifold syntheses.

Ammonia and aliphatic or carbocyclic[90] amines react highly exothermally with carbon disulfide, forming (substituted) ammonium salts of dithiocarbamic acid or its derivatives:

$$2RNH_2 + CS_2 \longrightarrow [RNHCSS]^-[RNH_3]^+$$

The second amine group in the product from an aliphatic diamine can form salts, and the betaine that forms the primary product cyclizes when heated in hydrochloric acid, forming cyclic thiourea derivatives in good yields:[91,92]

$$NH_2-(CH_2)_n-NH_2 + CS_2 \longrightarrow {}^+NH_3-(CH_2)_n-NH-CSS^-$$



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[83] M. B. Winstead and H. W. Heine, *J. Amer. Chem. Soc.*, **77**, 1913 (1955).

[84] S. R. Buc, *J. Amer. Chem. Soc.*, **69**, 254 (1947).

[85] A. Einhorn, *Ann. Chem.*, **343**, 207 (1905); Ger. Pat. 157355; *Friedländer*, **7**, 616 (1902–1904).

[86] H. Böhme, A. Dick, and G. Driesen, *Chem. Ber.*, **94**, 1879 (1961); S. L. Vail, C. M. Moran, and H. B. Moore, *J. Org. Chem.*, **27**, 2067 (1962).

[87] E. Schmitz, "Dreiringe mit zwei Heteratomen," Springer-Verlag, Berlin–Heidelberg–New York, 1967.

[88] E. Schmitz, R. Ohme, and D. Murawski, *Chem. Ber.*, **98**, 2516 (1965).

[89] F. W. Hoover, H. B. Stevenson, and H. S. Rothrock, *J. Org. Chem.*, **28**, 1825 (1963).

[90] A. Skita and H. Rolfes, *Ber. Deut. Chem. Ges.*, **53**, 1246 (1920).

[91] C. F. H. Allen, C. O. Edens, and J. VanAllan, *Org. Syn.*, Coll. Vol. III, 394 (1955); T. B. Johnson and C. O. Edens, *J. Amer. Chem. Soc.*, **64**, 2707 (1942).

[92] G. E. P. Smith Jr., G. Alliger, E. L. Carr, and K. C. Young, *J. Org. Chem.*, **14**, 935 (1949).

Aromatic amines are too weak to undergo the above reactions; they do add to carbon disulfide but the resulting dithiocarbamic acids cannot form salts; the resulting unstable free acids decompose at once with evolution of hydrogen sulfide and formation of isothiocyanates which add the excess of amine and thus give thioureas as final products;[93,94] a small amount of sulfur catalyses the formation of the thioureas.[95] Treatment of salts of the dithiocarbamic acids obtained in this way with chloroformic esters in chloroform at 0° leads to loss of COS and alcohol and formation of isothiocyanates in high yield.[96]

Aromatic amines, however, react smoothly with carbon disulfide, giving dithiocarbamates, provided that the reactants are used in the molar ratio 1 : 1 and a fairly strong base such as sodium hydroxide or a tertiary amine is added. Buess[97] has described a simple procedure by which he has converted a series of aliphatic, aromatic, and heterocyclic amines, in chloroform containing triethylamine, into dithiocarbamates in consistently high yields.

Further, hydrazines react analogously. Thus phenylhydrazine in ether gives an almost quantitative yield of the salt of β-phenyldithiocarbazinic acid (C_6H_5—NHNH—CSSH) which serves as starting material for the synthesis of dithizone.[98] However, contrary to earlier statements, the azide ion adds with cyclization to thiatriazolethiones.[99]

For the reaction of carbon oxysulfide with ammonia and amines the review by Ferm[100] should be consulted.

6.2. Formation of the carbon–nitrogen bond by exchange

I. Replacement of hydrogen by nitrogen

1. Nitration

a. General; nitrating agents

Replacement of hydrogen by the nitro group is one of the most important reactions in the whole of organic chemistry, particularly in the aromatic series. It is effected not merely by nitric acid itself in various concentrations or in mixtures or solvents, but also by a number of other reagents which, however, are less important than nitric acid; the commonest reagent is the mixture of nitric and sulfuric acid known as nitrating acid.

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[93] L. C. Raiford and G. M. McNulty, *J. Amer. Chem. Soc.*, **56**, 680 (1934).

[94] S. Hünig, H. Lehmann, and G. Grimmer, *Ann. Chem.*, **579**, 77 (1953).

[95] A. Hugershoff, *Ber. Deut. Chem. Ges.*, **32**, 2245 (1899).

[96] J. E. Hodgkins and W. P. Reeves, *J. Org. Chem.*, **29**, 3098 (1964).

[97] C. M. Buess, *J. Amer. Chem. Soc.*, **77**, 6613 (1955).

[98] J. H. Billman and E. S. Cleland, *Org. Syn.*, Coll. Vol. III, 360 (1955).

[99] E. Lieber, E. Oftedahl, and C. H. R. Rao, *J. Org. Chem.*, **28**, 194 (1963).

[100] R. J. Ferm, *Chem. Rev.*, **57**, 630 (1957).

[101] T. Urbanski, "Chemie und Technologie der Explosivstoffe," VEB Deutscher Verlag für Grundstoffindustrie, Leipzig, 1961, Vol. 1; G. A. Olah and St. J. Kuhn in G. A. Olah, "Friedel-Crafts and Related Reactions," Interscience Publ., New York–London–Sydney, 1964, Vol. 3, Part 2, p. 1393.

Dilute nitric acid is used in special cases such as for the very easily nitratable phenols and for aliphatic hydrocarbons. Concentrated nitric acid and nitrating acid are usually quite unsuitable for nitration of phenols, as they lead to decomposition products. Dilute nitric acid is a weak nitrating agent but a strong oxidant, thus providing for constant presence of nitrous acid; the latter, which normally hinders nitration, has a powerful catalytic action on the nitration of phenols and aromatic amines.[102] There are, however, narrow limits to the use of dilute nitric acid, since in general its nitrating action becomes appreciable only at elevated temperatures where oxidizing side reactions become preponderant.

If mercury salts are added, the oxidizing action of dilute nitric acid can be elegantly utilized for simultaneous introduction of hydroxyl and several nitro groups. This "oxynitration", discovered by Wolffenstein and Böters,[103] permits the one-step conversion of, *e.g.*, benzene into picric acid in about 50% yield[104] and of benzoic acid into 3-hydroxy-2,4,6-trinitrobenzoic acid, although in less good yield in the latter case[105] (for the mechanism see Westheimer *et al.*[106]).

The preparation of **2,4-dinitrophenol**[107] serves as example of the procedure: Mercuric oxide (60 g) is dissolved in 70% nitric acid (541 ml) contained in a 1.5-l flask fitted with a stirrer, reflux condenser, and dropping funnel. The solution is diluted wih water to 750 ml, then sodium nitrite (0.1 g) is added. Benzene (50 g) is dropped in at 50° during 200 min and the mixture is stirred for a further 160 min at 50° and then allowed to cool. 12 Hours later the product is filtered off and washed with dilute nitric acid and then with cold water; it has m.p. 112–113°, the yield being 67 g. If the filtrate is worked up, a total of 68% of dinitrophenol is obtained.

Concentrated nitric acid allows nitration to be carried out at lower temperatures and tends to cause less of the undesired oxidation; however, it is being constantly diluted by the water formed, so that attainment of satisfactory yields requires extremely large excesses of the nitrating agent, and this severely limits its utility.

To overcome this difficulty nitration was carried out in the presence of concentrated sulfuric acid, even in the very early experiments. For aromatic compounds the resulting "mixed acid" or "nitrating acid" is the most important nitrating agent. The differing reactivities of the various classes of compound to be nitrated have led to the use of nitrating acids made by mixing nitric acid of the most varied concentration with concentrated sulfuric acid or oleum. In principle, the nitrating mixture should have a lower water content the harder the compound is to nitrate. A series of standard mixed acids is used in industry, *e.g.*, for mononitration of toluene an acid containing, by weight, 35% of nitric acid, 53% of sulfuric acid, and 12% of water, but for introduction of a second nitro group a "water-free" mixture containing 33% of

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[102] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, (a) pp. 269ff., (b) 285ff.

[103] R. Wolffenstein and O. Böters, *Ber. Deut. Chem. Ges.*, **46**, 586 (1913).

[104] E. E. Aristoff and co-workers, *Ind. Eng. Chem.*, **40**, 1281 (1948).

[105] R. Wolffenstein and W. Paar, *Ber. Deut. Chem. Ges.*, **46**, 589 (1913).

[106] F. H. Westheimer, E. Segel, and R. Schramm, *J. Amer. Chem. Soc.*, **69**, 773 (1947).

[107] W. E. Bachman, J. M. Chemerda, N. C. Deno, and E. C. Horning, *J. Org. Chem.*, **13**, 390 (1948).

nitric and 67% of sulfuric acid. For mononitrations the amount of mixed acid is selected so as to provide the stoichiometric amount of nitric acid, but for dinitrations an excess of nitric acid is advisable. It is of the utmost importance to dissipate the heat of reaction rapidly, *i.e.*, there must be continuous good stirring; since all nitrations are exothermic, considerable heat may be evolved at the point where the acid is dropped in and this can lead to explosions if stirring is inefficient or starts too late.

The sulfuric acid in a nitrating mixture not only serves to bind the water, but is also important in maintaining a sufficient concentration of the nitryl cations that are the actual nitrating agent;[102a,108] this contributes to the considerable suppression of oxidative side reactions; and further advantages of sulfuric acid are that it is an excellent solvent and has a high boiling point and a large heat capacity.

On the other hand, mixed acid cannot be used when the compound to be nitrated is attacked by sulfuric acid, *e.g.*, when it is hydrolysed or sulfonated thereby. In such cases solvents are used such as glacial acetic acid, chloroform, carbon tetrachloride, methylene dichloride, benzene, ether, or even such not completely indifferent substances as ethanol or acetone. Acetic anhydride, which is also a powerful dehydrating agent and in admixture with nitric acid comes closest to mixed acid in its action, is itself easily nitrated and thus can be used only at low temperatures; when it is used, the ratio of *ortho*- to *para*-substitution sometimes deviates greatly from that produced by nitrating acid,[109] and the same is true for nitration in glacial acetic acid[110] and the use of acetyl nitrate discussed below. Trifluoroacetic anhydride has been applied successfully to nitration of benzonitrile, whereas half the nitrile is hydrolysed by nitrating acid under the same conditions[111] (cf. Blanksma and Petri[112]).

Attempts have also been made to replace the sulfuric acid in nitrating acid by other mineral acids. Kispersky and Klager had good success in applying a mixture of anhydrous nitric acid and polyphosphoric acid to the nitration of alkylmalonic esters.[113] A mixture of hydrofluoric acid and nitric acid has also been shown[114] to have a powerful nitrating action and to convert, *e.g.*, benzene into nitrobenzene in 83% yield at about 0°.

In many cases a mixture of an alkali nitrate and concentrated sulfuric acid is superior to nitrating acid.

Pyridine, which is barely attacked by nitric acid or nitrating acid, is nitrated in 15–20% yield when potassium nitrate is added in portions to its solution in 18% oleum at 330° (!).[115] 6-Nitroquinoline, which is also indifferent, can be dinitrated by the calculated amount of potassium nitrate in concentrated sulfuric acid in a sealed tube at 130–140°.[116]

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[108] R. J. Gillespie and D. C. Millen, *Quart. Rev.*, **2**, 277 (1948).

[109] O. N. Witt and A. Utermann, *Ber. Deut. Chem. Ges.*, **39**, 3901 (1906).

[110] C. Schwalbe, *Ber. Deut. Chem. Ges.*, **35**, 3301 (1902).

[111] E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, **1952**, 1695.

[112] J. J. Blanksma and E. M. Petri, *Rec. Trav. Chim.*, **66**, 353 (1947).

[113] J. P. Kispersky and K. Klager, *J. Amer. Chem. Soc.*, **77**, 5433 (1955).

[114] J. H. Simons, H. J. Passino, and S. Archer, *J. Amer. Chem. Soc.*, **63**, 608 (1941).

[115] (a) F. Friedl, *Ber. Deut. Chem. Ges.*, **45**, 428 (1912); A. Kirpal and E. Reiter, *Ber. Deut. Chem. Ges.*, **58**, 699 (1925); (b) H. J. Den Hertog Jr. and K. Overhoff, *Rec. Trav. Chim.*, **49**, 552 (1930).

[116] A. Kaufmann and H. Decker. *Ber. Deut. Chem. Ges.*, **39**, 3648 (1906).

Mixtures of sodium nitrite and sulfuric or hydrochloric acid are also occasionally very effective for nitration of a benzene nucleus, in competition with the expected nitrosation, and this is important for nitration of some dialkylanilines (see p. 423).

Mixed anhydrides of nitric acid,[117] such as acetyl and benzoyl nitrate, are excellent nitrating agents for aromatic compounds; they often give quantitative yields of mononitro derivatives and favor *ortho*-substitution quite remarkably (cf., however, Sparks[118]). Unfortunately use of these readily accessible reagents is not without danger; acetyl nitrate, in particular, has caused severe accidents by spontaneous explosion, not merely on heating[119] but also even in the cold.[120]

Nitric esters, especially ethyl nitrate, have been used occasionally for nitration of aromatic compounds[121] in the presence of concentrated sulfuric acid[122] or aluminum chloride.[123,124] However, their use for compounds containing active methylene groups (see below) in the presence of an alkaline condensing agent is more important, a kind of ester condensation occurring.

Nitration of aromatic compounds by tetranitromethane is also effected in an alkaline medium, *e.g.*, in pyridine solution.[125,126] *N,N*-Dimethyl- and *N,N*-diethyl-*p*-toluidine and *p*-cresol, for example, are mononitrated in high yield by this reagent.[127] The reaction occurs smoothly with ice-cooling, but heating in a boiling water-bath causes dealkylation and nitrosation of the tertiary bases.[128] Use of tetranitromethane in acetone solution under the prescribed conditions even permits nitration of aromatic propenyl compounds such as *o*-anethole, isosafrole, and isoeugenol ethers in the *β*-position without affecting the double bond or the aromatic ring, whereas the isomeric allyl compounds do not react.[127,129]

Recently a further method of alkaline nitration has been developed. It involves acetone cyanohydrin nitrate, which is readily obtained from acetone cyanohydrin and fuming nitric acid, and applies to compounds such as arylacetonitriles and malonic and acetoacetic esters that contain active methylene groups.[130]

Dinitrogen pentoxide (the anhydride of nitric acid) has also been utilized for nitrations. It proved a very powerful nitrating agent,[131] as did its complex

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[117] V. Gold, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, **1950**, 2467.

[118] A. K. Sparks, *J. Org. Chem.*, **31**, 2299 (1966).

[119] A. Pictet and E. Khotinsky, *Ber. Deut. Chem. Ges.*, **40**, 1163 (1907).

[120] W. König, *Angew. Chem.*, **67**, 157 (1955).

[121] R. Boschan, R. T. Merrow, and R. W. van Dolah, *Chem. Rev.*, **55**, 498 (1955).

[122] H. Raudnitz, *Ber. Deut. Chem. Ges.*, **60**, 738 (1927).

[123] H. Willstaedt and G. Scheiber, *Ber. Deut. Chem. Ges.*, **67**, 471 (1934).

[124] B. V. Tronov and N. Kh. Sibgatullin, *J. Russ. Phys. Chem. Soc.*, **62**, 2267 (1930); *Chem. Abstr.*, **25**, 3973 (1931).

[125] K. F. Hager, *Ind. Eng. Chem.*, **41**, 2168 (1949) (literature review).

[126] P. Liang, *Org. Syn.*, Coll. Vol. III, 803 (1955).

[127] E. Schmidt and H. Fischer, *Ber. Deut. Chem. Ges.*, **53**, 1529 (1920).

[128] E. Schmidt and H. Fischer, *Ber. Deut. Chem. Ges.*, **53**, 1537 (1920).

[129] E. Schmidt, R. Schumacher, W. Bäjen, and A. Wagner, *Ber. Deut. Chem. Ges.*, **55**, 1751 (1922).

[130] W. D. Emmons and J. P. Freeman, *J. Amer. Chem. Soc.*, **80**, 4391 (1955).

[131] V. Gold, E. D. Hughes, C. K. Ingold, and G. H. Williams, *J. Chem. Soc.*, **1950**, 2452.

$N_2O_5 . BF_3$,[132] and, for example, converts benzene quantitatively into nitrobenzene at 0°.[133]

Dinitrogen tetroxide is less reactive than the pentoxide but more selective. Thus, although benzene is hardly attacked by pure N_2O_4, pyridine is converted by it into 3-nitropyridine in about 10% yield.[134]

Explicit reference must be made to the danger of explosions with mixtures of N_2O_4 and hydrocarbons.

In contrast to the pure substance, N_2O_4 in combination with sulfuric acid[135] or aluminum chloride[136,137] is a very powerful nitrating agent; again this is probably due to the easier formation of nitryl ions, such as undoubtedly occur in the solid complex $N_2O_4 . BF_3$ which has powerful nitrating action.[138]

Nitryl chloride, NO_2Cl, which when used alone has more chlorinating than nitrating effect on aromatic compounds,[139,140] is converted into a strong nitrating agent if dissociation into nitryl ions is promoted by the presence of acid catalysts such as hydrogen fluoride, boron trifluoride, or aluminum chloride.[141] Nitryl fluoride effects nitration even in absence of a catalyst, although yields are poor.[142] Oláh[143-145] prepared nitryl tetrafluoroborate, $[NO_2]^+[BF_4]^-$, from nitryl fluoride and boron trifluoride, and from dinitrogen pentoxide, hydrogen fluoride, and boron trifluoride, and used it to nitrate aromatic compounds, in some cases with cooling in ice–salt, in very high yields.

b. Nitration of aliphatic compounds[146]

The replacement of hydrogen of aliphatic hydrocarbons by a nitro group is of only minor importance in laboratory practice. That this reaction can be effected at all in satisfactory yield was first shown by Konovalov,[147] who worked with 13% nitric acid in a sealed tube at 130–150°.

Methods of practical interest for the direct nitration of aliphatic hydrocarbons have been developed only during recent decades. Hass worked out a process for mononitration of lower aliphatic hydrocarbons in the gas phase by 70% nitric acid at temperatures above 400° and this has been carried out on an industrial scale.[148] It is not really suitable for laboratory use because the nitration is accompanied by fission of carbon–carbon bonds, so that the

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[132] G. B. Bachman and J. L. Dever, *J. Amer. Chem. Soc.*, **80**, 5871 (1958).

[133] L. B. Haines and H. Adkins, *J. Amer. Chem. Soc.*, **47**, 1419 (1925).

[134] P. Shorigin and A. Topchiev, *Ber. Deut. Chem. Ges.*, **69**, 1874 (1936).

[135] L. A. Pinck, *J. Amer. Chem. Soc.*, **49**, 2536 (1927).

[136] A. Schaarschmidt, *Ber. Deut. Chem. Ges.*, **57**, 2065 (1924).

[137] A. Schaarschmidt, H. Balzerkiewicz, and J. Gante, *Ber. Deut. Chem. Ges.*, **58**, 499 (1925).

[138] G. B. Bachmann and C. M. Vogt, *J. Amer. Chem. Soc.*, **80**, 2987 (1958).

[139] F. P. Gintz, D. R. Goddard, and M. J. Collis, *J. Chem. Soc.*, **1958**, 445.

[140] M. J. Collis and D. R. Goddard, *J. Chem. Soc.*, **1958**, 1952.

[141] C. C. Price and C. A. Sears, *J. Amer. Chem. Soc.*, **75**, 3276 (1953).

[142] G. Hetherington and P. L. Robinson, *J. Chem. Soc.*, **1954**, 3512.

[134] G. Oláh and S. Kuhn, *Chem. & Ind. (London)*, **1956**, 98.

[144] G. Oláh, S. Kuhn, and A. Mlinkó, *J. Chem. Soc.*, **1956**, 4257.

[145] G. A. Oláh and S. J. Kuhn, *J. Amer. Chem. Soc.*, **80**, 6541 (1958).

[146] N. Kornblum, *Org. Reactions*, **12**, 101 (1962).

[147] M. Konovalov, *Ber. Deut. Chem. Ges.*, **26**, R. 878 (1893).

[148] F. Asinger, "Chemie und Technologie der Paraffinkohlenwasserstoffe," Akademie-Verlag, Berlin, 1956, pp. 311ff.

product always consists of a mixture of isomeric nitro derivatives of the hydrocarbon used and their fission products. Attempts to extend the Hass procedure to aliphatic ethers, alcohols, ketones, and carboxylic acids have had very unsatisfactory results.[149]

Higher aliphatic hydrocarbons (b.p. from about 200° upwards) can be mononitrated in the liquid phase at atmospheric pressure in a relatively simple laboratory apparatus by using a procedure due to Grundmann[150] in which superheated nitric acid (*d* 1.40) is led through a frit into the hydrocarbon preheated at 140–200°; this gives a statistical mixture of all the possible isomers.[151–153]

For example, in 3 h at 180–190° there are produced from dodecane 40% of **mononitrododecanes**, together with 43% of unchanged material and small amounts of di- and polynitro compounds. There is more dinitration if a longer residence time or a greater excess of nitric acid is used.[150]

For aliphatic hydrocarbons in the medium range (7–12 carbon atoms), which are not satisfactorily amenable to either the Hass or the Grundmann method, Geiseler[154] has described a process of nitration by nitrogen dioxide under pressure, for which the overall reaction is:

$$2RH + 3NO_2 \longrightarrow 2RNO_2 + NO + H_2O$$

This is carried out at 150–200°/ca. 40 atm with a V2A pressure tube as reaction vessel; it is likely to be worthwhile only on continuous operation on a semi-industrial scale.

A nitro group can be introduced into a compound containing an active methylene group by the alkaline condensation with alkyl nitrates mentioned above.

For example, dropping a mixture of benzyl cyanide and methyl or ethyl nitrate into a cooled alkoxide solution leads to an 80% yield of 2-*aci*-nitro-2-phenylacetonitrile, which gives phenylnitromethane on hydrolysis and decarboxylation.[155,156] Ethyl phenylacetate also gives phenylnitromethane analogously and in the same yield.[157] Further examples are described by Wislicenus and Wren.[158] Wieland *et al.*[159] have converted cyclohexane by this method into the potassium salt of 2-*aci*-nitrocyclohexanone in about 40% yield, and cyclopentanone almost quantitatively into the dipotassium salt of 2,5-di-*aci*-nitrocyclopentanone.

Pentyl nitrate in dry tetrahydrofuran with potassium *tert*-butoxide as condensing agent has proved particularly valuable;[160,161] for instance, by this method adipodinitrile at −50° gives 93% of the 2,5-dinitro derivative, which can be worked up to give 1,4-dinitrobutane by hydrolysis and decarboxylation.[161]

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[149] H. B. Hass and D. E. Hudgin, *J. Amer. Chem. Soc.*, **76**, 2692 (1954).

[150] C. Grundmann, *Die Chemie* [*Angew. Chem.*], **56**, 159 (1943).

[151] F. Asinger, *Ber. Deut. Chem. Ges.*, **77**, 73 (1944).

[152] C. Grundmann, *Ber. Deut. Chem. Ges.*, **77**, 82 (1944).

[153] F. Asinger and K. Halcour, *Chem. Ber.*, **94**, 83 (1961).

[154] G. Geiseler, *Angew. Chem.*, **67**, 270 (1955).

[155] W. Wislicenus and A. Endres, *Ber. Deut. Chem. Ges.*, **35**, 1755 (1902).

[156] A. P. Black and F. H. Babers, *Org. Syn.*, Coll. Vol. II, 512 (1943).

[157] W. Wislicenus and R. Grützner, *Ber. Deut. Chem. Ges.*, **42**, 1930 (1909).

[158] W. Wislicenus and H. Wren, *Ber. Deut. Chem. Ges.*, **38**, 502 (1905).

[159] H. Wieland, P. Garbsch, and J. J. Chavan, *Ann. Chem.*, **461**, 295 (1928); cf. ref. 142.

[160] H. Feuer, J. W. Shepherd, and C. Savides, *J. Amer. Chem. Soc.*, **78**, 4364 (1956).

[161] H. Feuer and C. Savides, *J. Amer. Chem. Soc.*, **81**, 5826 (1959).

Compounds such as arylacetonitriles and malonic and acetoacetic esters, containing active methylene groups, can be nitrated by acetone cyanohydrin nitrate.[162]

The compound containing the active methylene group is first converted in tetrahydrofuran solution into its sodium salt by means of sodium hydride, then a two- to three-fold excess of acetone cyanohydrin nitrate is added and the whole is boiled for 2 h under reflux. Substituted acetoacetic and malonic esters thus give good yields of α-nitro carboxylic esters.

By careful work malonic esters can also be nitrated directly with nitric acid; Weisblat and Lyttle[163] used concentrated nitric acid (*d* 1.5) at 15–20° to obtain more than 90% of ethyl nitromalonate; similar work is described by Kispersky and Klager[113] and by Kornblum and Eicher.[164]

Aliphatic geminal dinitro compounds are obtained by oxidative nitration of mononitro compounds with silver nitrate and sodium nitrite in an alkaline medium.[165]

c. Nitration of aromatic and heterocyclic compounds

The ease with which a nitro group can be introduced into an aromatic nucleus is well known to depend greatly on the substituents present. Substitution becomes noticeably easier as benzene is converted into its methyl homologs: whereas for benzene use of mixed acid and elevated temperature (about 50°) is advisable, xylene is nitrated even by concentrated nitric acid at room temperature; it is no longer possible to mononitrate durene with nitric acid, as the reaction at once goes to introduce a second nitro group. In the nitration of polyalkylbenzenes migration of alkyl groups or their replacement by nitro groups is occasionally observed.[166] Higher homologs such as ethylbenzene and cumene are also nitrated in the nucleus by mixed acid, and yields are good. Mononitration of alkylbenzene usually gives a mixture of the three possible isomers, the *meta*-compound being formed in relatively the smallest amount; as the size of the side chain increases, the amount of *para*- and to a smaller extent that of *meta*-substitution increases at the expense of the *ortho*-substitution.[167]

Nitration in the side chain, exclusively at the α-position, occurs, however, on use of hot dilute nitric acid in a sealed tube, but with unsaturated or with longer, branched side chains the oxidizing action of nitric acid becomes evident.

Considerably more energetic conditions, *i.e.*, stronger acid and higher temperature, are necessary for introduction of several nitro groups than for that of one. In such cases also it is evident that the presence of alkyl substituents facilitates substitution; thus trinitrotoluene can be obtained comparatively readily by direct trinitration of the hydrocarbon, whereas to prepare trinitrobenzene in this way would require extreme conditions and this deri-

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[162] W. D. Emmons and J. P. Freeman, *J. Amer. Chem. Soc.*, **77**, 4391 (1955).

[163] D. I. Weisblat and D. A. Lyttle, *J. Amer. Chem. Soc.*, **71**, 3079 (1949).

[164] N. Kornblum and J. H. Eicher, *J. Amer. Chem. Soc.*, **78**, 1494 (1956).

[165] R. B. Kaplan and H. Shechter, *J. Amer. Chem. Soc.*, **83**, 3535 (1961).

[166] D. V. Nightingale, *Chem. Rev.*, **40**, 117 (1947).

[167] K. LeRoi Nelson and H. C. Brown, *J. Amer. Chem. Soc.*, **73**, 5605 (1951).

vative is better obtained in other ways, *e.g.*, by oxydation of trinitrotoluene with chromic acid and subsequent decarboxylation.[168]

It is impossible to introduce more than three nitro groups into one benzene ring: the products would contain at least two nitro groups in the *ortho*-position to one another, and such compounds are very reactive. The two isomeric tetranitrobenzenes should be preparable by oxidation of other nitrogenous groups present in trinitrobenzene derivatives.[169] In di- and tri-nitrations the nitro groups normally enter positions *meta* to one another, in accord with the well-known rules of substitution. However, occasionally, when these rules are overcome by some specific activation by other substituents, *o*-dinitro compounds will result; for instance, about 4% of *m*-nitrotoluene is formed on mononitration of toluene and on further nitration this leads to a mixture of 2,3-, 3,4-, and 3,6-dinitrotoluenes.

Fused aromatic systems can be nitrated under conditions similar to those used for benzene, but it is impossible to generalize about the position of entry of the nitro group. In the presence of concentrated sulfuric acid even at (or slightly above) room temperature naphthalene is nitrated by nitric acid[170,171] or nitrogen dioxide,[135] giving 1-nitronaphthalene in about 90% yield; 2-nitronaphthalene is obtained to a quite minor extent (about 4.5%) by the direct nitration and is synthesized from diazotized 2-naphthylamine by a modified Sandmeyer reaction.[172] Further nitration of the 1-nitro compound with mixed acid leads to a mixture of 1,5- and 1,8-dinitronaphthalene, in which the relative amounts of the two isomers shift in favor of the 1,8-compound as the reaction temperature is lowered.[173] The higher-melting 1,5-compound is the less soluble in pyridine and can be separated thus from the 1,8-compound.

However, mononitration of tetralin, which is substituted only in the aromatic ring, by mixed acid at 0° leads to an 80–90% yield of a mixture of about equal parts of 5- and 6-nitrotetralin.[174] The danger of an explosion during separation of the nitrotetralin mixture by distillation[175] should be carefully noted. Under energetic conditions 5,7- and, surprisingly, 5,6-dinitrotetralin are both obtained.[174]

The behavior of anthracene towards nitrating agents is determined largely by the great reactivity at positions 9 and 10. According to the reaction conditions it gives either oxidation products such as anthraquinone or nitro derivatives thereof, or else, by way of primary adducts, 9-nitro- or 9,10-dinitroanthracene. Directions for the preparation of 9-nitroanthracene are to be found in *Organic Syntheses*.[176]

Fluorene, in solution in glacial acetic acid, is nitrated readily in the 2-position by concentrated nitric acid at 50–65°,[177] but the methylene group reacts

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[168] H. T. Clarke and W. W. Hartman, *Org. Syn.*, **2**, 93 (1922).

[169] W. Borsche, *Ber. Deut. Chem. Ges.*, **56**, 1939 (1923); W. Borsche and E. Feske, *Ber. Deut. Chem. Ges.*, **59**, 815 (1926).

[170] J. M. Berkebile and A. H. Fries, *J. Chem. Educ.*, **25**, 617 (1948).

[171] H. E. Fierz-David and R. Sponagel, *Helv. Chim. Acta*, **26**, 98 (1943).

[172] H. H. Hodgson and E. Marsden, *J. Chem. Soc.*, **1944**, 22.

[173] C. Gassmann, *Ber. Deut. Chem. Ges.*, **29**, 1243, 1521 (1896).

[174] G. Schroeter, *Ann. Chem.*, **426**, 17 (1922).

[175] E. Hecker, R. Lattrell, and E. Meyer, *Chem. Ber.*, **95**, 985 (1962).

[176] C. E. Braun, C. D. Cook, C. Merrit Jr., and J. E. Rousseau, *Org. Syn.*, **31**, 77 (1951).

[177] W. E. Kuhn, *Org. Syn.*, Coll. Vol. II, 447 (1943).

with ethyl nitrate in the presence of potassium ethoxide, giving in an exothermic reaction more than 70% of potassium 9-*aci*-nitrofluorene.[178]

Chlorobenzene is nitrated almost quantitatively by mixed acid in 4 h even below room temperature, giving two-thirds *p*- and one-third *o*-chloronitrobenzene. Further nitration gives a mixture of, mainly, 2,4- with a small amount of 2,6-dinitro compound. Fluorobenzene is nitrated almost exclusively in the *para*-position.

Dinitration, to give **1-fluoro-2,4-dinitrobenzene,** is achieved in 87% yield by dropping fluorobenzene (40 g) into an ice-cold mixed acid composed of nitric acid (*d* 1.52; 120 g) and sulfuric acid (*d* 1.84; 280 g) and subsequent warming for 2 h on a boiling water-bath.[179]

This compound, which is important in peptide chemistry, can also be obtained from the readily accessible 1-chloro-2,4-dinitrobenzene by halogen exchange.[180,181] Halogen exchange is also the most convenient method for preparation of 1-iodo-2,4-dinitrobenzene.[182]

The ease of nitration of phenols[183] has been noted above, and because they are liable to oxidation it is necessary to use nitric acid in some suitable solvent (glacial acetic acid or chloroform) and to arrange for cooling. Better yields are obtained by means of dinitrogen tetroxide in a light petroleum–benzene mixture.[184,185] The product is always a mixture containing various amounts of *o*- and *p*-nitrophenol, from which it is easy to separate the steam-volatile *ortho*-compound; the proportion of *p*-nitrophenol increases with increase in the dielectric constant of the solvent used.[184] *p*-Nitrophenol is obtained exclusively if phenol is esterified with benzene- or toluene-sulfonic acid before nitration, the nitration product being then hydrolysed by alkali.

It is advisable, particularly for introduction of several nitro groups, to start from phenolsulfonic acids and to exchange their sulfo groups for nitro groups (see page 546). It is also possible to replace the chlorine of chloronitrobenzenes by a hydroxyl group by means of boiling aqueous alkali.

Aromatic amines, like phenols, are very easily nitrated. However, primary and secondary amines in particular readily undergo oxidative side reactions, so that it is advisable to protect the amino group by acylation or by conversion by an aldehyde into the Schiff base. Even using a large excess of sulfuric acid protects the amino group to a considerable extent, owing to formation of the ammonium salt, but then entry of the nitro group is directed to a considerable extent into the *meta*-position. The usual *N*-acyl derivative is the acetyl compound, but benzoyl, *p*-toluenesulfonyl, oxalyl, ethoxycarbonyl (from chloroformic ester), and phthaloyl derivatives are also used.

Nitration of aniline as the acetyl derivative by mixed acid gives *p*-nitroacetanilide as the main product, together with a little of the *ortho*-compound. The relative amounts are shifted very greatly in favor of the *ortho*-compound

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[178] W. Wislicenus and M. Waldmüller, *Ber. Deut. Chem. Ges.*, **41**, 3334 (1908).

[179] H. Zahn and A. Würz, *Angew. Chem.*, **63**, 147 (1951).

[180] N. N. Vorozhtzov Jr. and G. G. Yakobson, *Zh. Obshch. Khim.*, **27**, 1672 (1957); *Chem. Abstr.*, **52**, 2777 (1958).

[181] G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, **78**, 6034 (1956).

[182] J. F. Bunnett and R. M. Conner, *J. Org. Chem.*, **23**, 305 (1958); *Org. Syn.*, **40**, 34 (1960).

[183] C. A. Bunton, E. D. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff, and R. I. Reed, *J. Chem. Soc.*, **1950**, 2628.

[184] J. Podkova and A. Tarnavski, *Monatsh. Chem.*, **90**, 179 (1959).

[185] H. Wieland, *Ber. Deut. Chem. Ges.*, **54**, 1776 (1921).

by working with acetic anhydride–acetic acid mixtures not containing sulfuric acid.

This procedure may be briefly illustrated by one example:[109] A mixture of nitric acid (*d* 1.5; 23 g), urea (1 g), and glacial acetic acid (23 g) is prepared hot and then cooled. To this a solution of acetanilide (45 g) in acetic anhydride (34 g) and glacial acetic acid (22 g) is slowly added. After 24 hours' storage at room temperature precipitation is completed by addition of ice (360 g), and the crude product (52 g, 87%) is filtered off. This is then rubbed, at 0°, with a 1 : 4 : 1 (v/v) mixture of 50% aqueous potassium hydroxide solution, water, and ethanol, which dissolves only the *ortho*-compound. The *para*-compound is filtered off and washed with water until pure; it can be hydrolysed by warm dilute sodium hydroxide to ***p*-nitroaniline**. When the filtrate has been kept for a day at room temperature hydrolysis of the *ortho*-compound is complete and pure ***o*-nitroaniline** has separated in large crystals. The proportion of *ortho*- to *para*-compound is about 3 : 1.

Pure ***o*-nitroaniline** can also be obtained by blocking the *para*-position, namely, by starting with sulfanilic acid, acetylating this, treating that compound with mixed acid in the cold, and then removing the sulfo group by hot concentrated hydrochloric acid.

Another process starts from oxanilide, which is obtained from oxalic acid and aniline at 200°. Oxanilide is sulfonated by concentrated sulfuric acid on a water bath, cooled to 50°, and nitrated with mixed acid [equal parts of nitric acid (*d* 1.44) and concentrated sulfuric acid] at that temperature. The oxalyl and sulfo groups are successively removed by dilution of the reaction mixture with water and boiling for several hours.

Nitration of *N*-benzylideneaniline[186] or *N*-phenylphthalimide gives ***p*-nitroaniline** almost exclusively. The latter method[187] is particularly recommended and can be used for all aromatic amines that condense with phthalic anhydride.

N-Phenylphthalimide (2.23 parts) is dissolved in concentrated sulfuric acid (14 parts) by gentle warming and then cooled to 0°, whereupon part of the imide separates again. To this suspension is added sulfuric acid monohydrate containing 25% of nitric acid (total 2.55 parts) whilst the temperature is kept below 3°. The mixture is then poured on ice, and the precipitated *N*-(nitrophenyl)phthalimide is filtered off and washed with water. For transamidation the dried product is heated with aniline (1.1 parts) for 1 h in a pressure vessel at 170–180°. This gives a mixture of *N*-phenylphthalimide, *p*-nitroaniline, and aniline, from which the aniline is removed by distillation in steam; extracting the residue with hot water removes the desired *p*-nitroaniline; the *N*-phenylphthalimide remains behind and can be used for a further batch.[187]

The preparation of ***N,N*-dimethyl-*m*-nitroaniline**[188] illustrates *meta*-nitration under conditions where formation of an ammonium salt has been caused by presence of a strong acid:

A mixture of nitric acid (*d* 1.42; 200 ml) and concentrated sulfuric acid (200 ml) is dropped slowly into a stirred solution (prepared with cooling) of *N,N*-dimethylaniline (363 g) in concentrated sulfuric acid (1270 ml) at 5°. The mixture is stirred for a further 1 h at 5–10°, then poured into ice-water (6 l) and treated with concentrated aqueous ammonia until precipitation of the *p*-nitro compound is complete, this being recognized by a change in the color of the precipitate from yellow (*p*-nitro compound) to orange (*m*-nitro compound). The *p*-nitro compound is filtered off and further ammonia is added to the filtrate until the pH is 3; this precipitates the *N,N*-dimethyl-*m*-nitroaniline, which is obtained pure (m.p. 59–60°) in 56 to 63% yield (280–316 g) by recrystallization from ethanol (400 ml).

However, working in less strongly acidic solution gives mainly the *p*- and *o*-nitro compounds; the former of these particularly can be very easily further nitrated to give *N,N*-dimethyl-2,4-dinitroaniline.[189]

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[186] Ger. Pat. 72173; *Friedlander*, **3**, 48 (1890–1894).

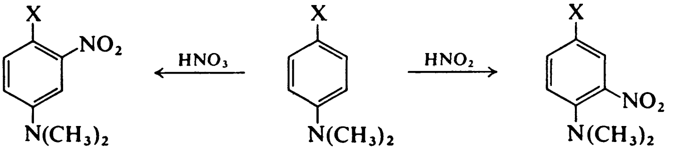
[187] Ger. Pat. 141893; *Friedlander*, **7**, 64 (1902–1904); cf. Ger. Pat. 148874; *Friedlander*, **7**, 65 (1902–1904).

[188] H. M. Fitch, *Org. Syn.*, Coll. Vol. III, 658 (1955).

[189] J. Glazer, E. D. Hughes, C. K. Ingold, A. T. James, G. T. Jones, and E. Roberts, *J. Chem. Soc.*, **1950**, 2657.

Introduction of more than two nitro groups into *N*,*N*-dimethylaniline is no longer a smooth reaction; demethylation and *N*-nitration lead eventually to *N*-methyl-2,4,6,*N*-tetranitroaniline which is used as an explosive under the name "Tetryl".

The reaction of some *para*-substituted tertiary aromatic amines with nitrous acid is also anomalous: treatment with an alkali nitrite in cold hydrochloric or sulfuric acid converts, *e.g.*, *N*,*N*-dimethyl-*p*-toluidine[190,191] or -*p*-anisidine[192] or *p*-(dimethylamino)acetanilide[193] into the corresponding *m*-nitro amines in good to high yield, whereas the *o*-nitro isomers are formed by nitration with nitric acid:



It should, however, be noted that aromatic amino-nitro compounds are often more conveniently prepared by heating a halo-nitro compound with ammonia or an amine (*e.g.*, *N*,*N*-dimethyl-*o*- and -*p*-nitroaniline[194]) or by partial reduction of a polynitro compound (cf. pp. 463 *et seq.* and 575).

Aldehydes are nitrated preferentially in the *meta*-position by cooled concentrated nitric or mixed acid. For example, benzaldehyde and mixed acid at 5–10° give *m*-nitrobenzaldehyde in about 80% yield together with a little of the *ortho*-compound.[195] Almost isomer-free ***m*-nitrobenzaldehyde** is obtained from hydrobenzamide, $C_6H_5CH(N{=}CHC_6H_5)_2$, and mixed acid.[196a]

Finely powdered hydrobenzamide (350 g) is added in portions to sulfuric acid monohydrate (1650 g) at 10–12°. When dissolution is complete the mixture is cooled to 0° and treated dropwise with nitrating acid (30% of nitric and 70% of sulfuric acid monohydrate) at such a rate (within 15 h) that the temperature remains below 15°. Then the temperature is allowed to rise to 15–18° during 10–12 h, after which the solution is poured into such a quantity (about 1500 g) of ice that a temperature of 45° is attained. After some hours the cooled solution is filtered and the *m*-nitrobenzaldehyde is washed until free from acid. It (450 g) melts at 58° and contains 0.5% of *o*-nitro isomer.

On the other hand, when aromatic aldehydes are treated with nitric acid at low temperatures, addition compounds (the so-called aldehyde nitrates) can be isolated, which pass into ring-nitrated aldehydes when brought into sulfuric acid.[197]

If benzaldehyde diacetate is the starting material, the amount of *ortho*- and *para*-nitration increases;[198] nevertheless *o*- and *p*-nitrobenzaldehyde are pre-

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[190] G. P. Crowley, G. J. G. Milton, T. H. Reade, and W. M. Todd, *J. Chem. Soc.*, **1940**, 1286.

[191] H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, **1930**, 277.

[192] H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, **1932**, 1812.

[193] H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, **1932**, 2976.

[194] T. W. Campbell, *J. Amer. Chem. Soc.*, **71**, 740 (1949).

[195] R. N. Icke, C. E. Redemann, B. B. Wisegarver, and G. A. Alles, *Org. Syn.*, **29**, 72 (1949).

[196] O. Bayer in Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1954, Vol. 7, Part 1, pp. (a) 407, (b) 465.

[197] G. Reddelien, *J. Prakt. Chem.*, [ii], **91**, 213 (1915); *Angew. Chem.*, **35**, 580 (1922).

[198] W. Davey and J. R. Gwilt. *J. Chem. Soc.*, **1950**, 204, 3348.

ferably prepared by indirect routes such as the oxidation of the respective nitrotoluenes[199,200] or nitrocinnamic acids.[198] The preparation of *o*-nitrocinnamic acid is described in *Organic Syntheses*.[201]

It is only in rare cases, *e.g.*, with anisaldehyde,[202] that more than one nitro group can be introduced into an aromatic aldehyde by direct nitration; here too it is usually an indirect route that is indicated.

It is usual to start with a nitrated toluene and convert this into the *N*-(nitrobenzylidene)-aniline, which is easily hydrolysed by concentrated hydrochloric acid to the nitro aldehyde and the amine. Toluenes are converted into benzylideneanilines either by treatment of the derived benzyl halide with aniline, followed by oxidation with potassium permanganate,[203] or by condensation of nitrotoluenes with *N,N*-dimethyl-*p*-nitrosoaniline[205-208] as first described by Sachs.[204] It should be specially noted that the condensation product of 2,4,6-trinitrotoluene with *N,N*-dimethyl-*p*-nitrosoaniline has a strong tendency to explode.[206] For similar compounds see also pages 447–448.

For acetophenone, only *meta*-nitration has preparative value. As for benzaldehyde, this is favored by a large excess of concentrated or, better, fuming sulfuric acid and by reaction at as low a temperature as possible;[209] yields of *m*-nitroacetophenone exceeding 90% have been obtained in this way.[210,211] Use of nitric acid alone or increase in the reaction temperature increases the amount of *ortho*-isomer formed,[212] but this is nevertheless not a satisfactory method of synthesis.

For the preparation of *o*- and *p*-nitroacetophenone by direct oximation of *o*- and *p*-ethylnitrobenzene see page 430,[213] and for synthesis by the malonic ester route from *o*- and *p*-nitrobenzoyl chloride see reference 214.

The preparation of ***m*-nitrobenzonitrile** exemplifies nitration of a nitrile:[112]

Benzonitrile (5 g) is dissolved in fuming nitric acid (25 ml) and warmed at 60° for 30 min. The mixture is then poured into water; crystallization of the precipitate from boiling water gives colorless needles (6 g), mp. 116°.

Nitro groups enter carboxylic acids almost exclusively at the *meta*-position, yet it is often difficult to obtain the products completely free from isomers. Thus, to prepare *m*-nitrobenzoic acid it is profitable to start from methyl benzoate, which with mixed acid and good cooling affords approximately

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[199] S. M. Tsang, E. H. Wood, and J. R. Johnson, *Org. Syn.*, **24**, 75 (1944).

[200] S. V. Lieberman and R. Connor, *Org. Syn.*, Coll. Vol. II, 441 (1943).

[201] R. E. Buckles and M. P. Bellis, *Org. Syn.*, **33**, 60 (1953).

[202] E. Wörner, *Ber. Deut. Chem. Ges.*, **29**, 157 (1896).

[203] K. von Auwers and E. Fense, *Ber. Deut. Chem. Ges.*, **58**, 1369 (1925).

[204] F. Sachs and R. Kempf, *Ber. Deut. Chem. Ges.*, **35**, 1224 (1902).

[205] A. Lowy and B. B. Wescott, *J. Amer. Chem. Soc.*, **42**, 849 (1920).

[206] S. Secareanu, *Ber. Deut. Chem. Ges.*, **64**, 834, 837 (1931).

[207] A. Lowy and E. H. Balz, *J. Amer. Chem. Soc.*, **43**, 341 (1921).

[208] (a) G. M. Bennett and E. V. Bell, *Org. Syn.*, Coll. Vol. II, 223 (1943); (b) for a criticism of their directions for 2,4-dinitrobenzaldehyde see, however, I. Tanasescu and V. Fărcăsan, *Acad. Rep. Pop. Rom., Filiala Cluj, Stud. Cercet. Chim.*, **8**, 169 (1957); *Chem. Abstr.*, **52**, 16270 (1958).

[209] J. W. Baker and W. G. Moffitt, *J. Chem. Soc.*, **1931**, 314.

[210] H. Rupe, A. Braun, and K. von Zembruski, *Ber. Deut. Chem. Ges.*, **34**, 3522 (1901).

[211] V. G. Morgan and H. B. Watson, *J. Soc. Chem. Ind. (London)*, **55**, 29T (1936).

[212] C. Engler, *Ber. Deut. Chem. Ges.*, **18**, 2238 (1885).

[213] A. H. Ford-Moore and H. N. Rydon, *J. Chem. Soc.*, **1946**, 679.

[214] G. A. Reynolds and C. R. Hauser, *Org. Syn.*, **30**, 70 (1950); H. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 1386 (1946).

80%-pure *m*-nitro ester,[215] whence hydrolysis[216] gives 90%-pure *m*-nitrobenzoic acid. Introducing a second nitro group is naturally very much more difficult; using the free acid and a mixed acid containing fuming nitric acid under fairly energetic conditions affords 3,5-dinitrobenzoic acid in 55% yield.[217] Benzoic acids nitrated in the *ortho*- and/or *para*-position must be prepared indirectly, *e.g.*, by chromic acid oxidation of the corresponding nitrotoluenes.

The following method[218] has proved its value for the **nitration of salicylic acid** and its esters: The substance (1 mole) is dissolved in no more than necessary of glacial acetic acid, nitric acid (*d* 1.42) dissolved in nine times its volume of glacial acetic acid is added rapidly at room temperature, and the mixture is warmed until it begins to darken. After cooling, precipitation with water gives about a 50% yield of product consisting wholly of the 5-nitro compound (COOH = 1).

1-Hydroxy-2-naphthoic acid and its esters give the 4-nitro compounds, yields being consistently somewhat higher than in the salicylic acid series.

Phthalic acid and its anhydride give on nitration a mixture of 3- and 4-nitrophthalic acid; the 3-nitro acid, being the less soluble in water, can be isolated from the mixture of isomers in about 30% yield.[219] 4-Nitrophthalic acid is better prepared by nitration of phthalimide[220] with fuming nitric acid and sulfuric acid with cooling; subsequent hydrolysis[221] affords about 50% overall yield.

The behavior of heterocyclic compounds towards nitrating agents varies very greatly from case to case.[222] For instance, pyridine is extremely resistant to nitric acid, but on attempted nitration pyrrole easily undergoes deep-seated changes which must be countered by using as low a reaction temperature as possible. In spite of this difficulty pyrrole was converted by nitric acid in acetic anhydride at $-10°$ to $-15°$ into 2-nitropyrrole in 21% yield, and further nitration thereof by fuming nitric acid (*d* 1.51) afforded a relatively high yield of a mixture containing 80 parts of 2,4- and 20 parts of 2,5-dinitropyrrole.[223] Nitration can become very much easier when substituents, particularly methyl groups, are present.[224] The literature[224-226] should be consulted for nitration of substituted pyrroles.

3-Nitropyrrole can be prepared by decarboxylation of 4-nitropyrrole-2-carboxylic acid, whose ethyl ester is simply accessible in 75% yield by condensation of the sodium derivative of nitromalondialdehyde with glycine ester.[227]

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[215] O. Kamm and J. B. Segur, *Org. Syn.*, **3**, 71 (1923).

[216] O. Kamm and J. B. Segur, *Org. Syn.*, **3**, 73 (1923).

[217] R. Q. Brewster, B. Williams, and R. Phillips, *Org. Syn.*, Coll. Vol. III, 337 (1955).

[218] H. C. Barany and M. Pianka, *J. Chem. Soc.*, **1946**, 965.

[219] P. J. Culhane and G. E. Woodward, *Org. Syn.*, **7**, 70 (1927); C. M. Moser and T. Gompf, *J. Org. Chem.*, **15**, 583 (1950).

[220] E. H. Huntress and R. L. Shriner, *Org. Syn.*, Coll. Vol. II, 459 (1943).

[221] E. H. Huntress, E. L. Shloss Jr., and P. Ehrlich, *Org. Syn.*, Coll. Vol. II, 457 (1943).

[222] K. Schofield, *Quart. Rev. (London)*, **4**, 382 (1950).

[223] I. J. Rinkes, *Rec. Trav. Chim.*, **53**, 1167 (1934).

[224] H. Fischer and W. Zerweck, *Ber. Deut. Chem. Ges.*, **55**, 1949 (1922).

[225] I. J. Rinkes, *Rec. Trav. Chim.*, **56**, 1142 (1937).

[226] H. J. Anderson, *Can. J. Chem.*, **35**, 21 (1957).

[227] W. J. Hale and W. V. Hoyt, *J. Amer. Chem. Soc.*, **37**, 2538 (1915).

Simple nitrofurans are also difficult to prepare. 2-Nitrofuran can be obtained from furan[228] or 2,5-furandicarboxylic acid[229] in acetic anhydride and nitric acid (*d* 1.51), though in the latter case the yield is only ca. 5%. Here too methyl substituents facilitate the reaction: 3–3.5 g of 2-methyl-5-nitrofuran were obtained from 10 g of 2-methylfuran under similar conditions to those cited.[230] The industrially important 5-nitro-2-furaldehyde can be prepared in 40–45% yield by direct nitration of 2-furaldehyde or its diacetate.[231]

5-Nitro-2-furaldehyde diacetate:[231] A mixture of acetic anhydride (143 g) and fuming nitric acid (*d* 1.5; 43.7 g) is prepared at 0° and a solution of 2-furaldehyde diacetate (49.5 g) in acetic anhydride (51 g) is dropped in within 30–40 min, the temperature not being allowed to rise above −5°. The mixture is stirred for 3 h, then added to ice (1 kg) and treated, with stirring, with ca. 40% sodium hydroxide solution until separation of an oil is complete. The aqueous layer is removed and to the oil an equal volume of pyridine is added cautiously in small portions, whereby the ring-opened intermediate is recyclized. After warming for some time and then dilution with 2–3 parts of ice-water by volume, the resulting precipitate is filtered off and washed with dilute acetic acid and then water until free from pyridine. Crude 5-nitro-2-furaldehyde diacetate (24.5 g, 40%; m.p. 85°) gives material of m.p. 92.5° on recrystallization from ethanol.

Thiophen is relatively easy to nitrate: when treated in acetic anhydride with a nitrating mixture composed of fuming nitric acid (*d* 1.51) and glacial acetic acid it affords the 2-nitro derivative in 70–85% yield;[232,233] small amounts of the 3-nitro derivative can be separated therefrom by recrystallization from light petroleum (b.p. 40–60°).[233] 3-Nitrothiophen is obtained in about 20% overall yield from thiophen by way of 2-thiophensulfonyl chloride, which is converted by nitration into its 4-nitro derivative whence the sulfur group can then be removed.[233] For the dinitration of thiophen also see Blatt *et al.*[233]

Pyridine is converted into a mixture of the 2- and the 3-nitro derivative under extreme conditions and in poor yield,[115b] and the three mononitropyridines are better obtained by oxidizing the appropriate aminopyridines with Caro's acid.[234–236] Nitration is appreciably smoother, although requiring equally drastic conditions, if substituents such as OH,[237] NH_2,[238] or CH_3[239] are present in the pyridine nucleus; *e.g.*, with potassium nitrate and fuming sulfuric acid 2,4,6-trimethyl- and 2,6-dimethyl-pyridine afford the 3-nitro derivatives in 90% and 66% yield, respectively.[239] For the preparation of **4-nitropyridine** it is better to start from pyridine 1-oxide:[240–242]

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[228] B. T. Freure and J. R. Johnson, *J. Amer. Chem. Soc.*, **53**, 1142 (1931).

[229] I. J. Rinkes, *Rec. Trav. Chim.*, **49**, 1169 (1930).

[230] I. J. Rinkes, *Rec. Trav. Chim.*, **49**, 1118 (1930).

[231] H. Gilmqa and G. F. Wright, *J. Amer. Chem. Soc.*, **52**, 2550, 4165 (1930); R. Behnisch in Ullmann's "Encyklopädie der Technischen Chemie," Urban & Scwarzenberg, Munich and Berlin, 3rd ed, 1954, Vol. 5, p.239.

[232] V. S. Babasinian, *Org. Syn.*, Coll. Vol. II, 466 (1943).

[233] A. H. Blatt, S. Bach, and L. W. Kresch, *J. Org. Chem.*, **22**, 1693 (1957).

[234] A. Kirpal and W. Böhm, *Ber. Deut. Chem. Ges.*, **64**, 767 (1931).

[235] O. von Schickh, A. Binz, and A. Schulz, *Ber. Deut. Chem. Ges.*, **69**, 2593 (1936).

[236] A. Kirpal and W. Böhm, *Ber. Deut. Chem. Ges.*, **65**, 680 (1932).

[237] E. Koenigs and K. Freter, *Ber. Deut. Chem. Ges.*, **57**, 1187 (1924).

[238] M. A. Phillips, *J. Chem. Soc.*, **1941**, 9.

[239] E. Plažek, *Ber. Deut. Chem. Ges.*, **72**, 577 (1939).

[240] E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

[241] K. Thomas and D. Jerchel, *Angew. Chem.*, **70**, 719 (1958).

[242] F. Kröhnke and H. Schäfer, *Chem. Ber.*, **95**, 1098 (1962).

Pyridine (26 g) is warmed with glacial acetic acid (100 ml) and perhydrol (50 ml) on a boiling water-bath for 24 h, then the acetic acid is removed in a vacuum. The residual oxide is dissolved with ice-cooling in concentrated sulfuric acid (70 ml), treated with a mixture of concentrated nitric acid (*d* 1.52; 110 ml) and concentrated sulfuric acid (70 ml), and heated in an oil-bath at 130° (internal temperature) for 2.5 h. Next, nitric oxide is led in while the temperature is raised slowly to 200°. When the evolution of nitrous fumes ceases, the mixture is allowed to cool in a stream of nitric oxide and then poured on ice. The pH is then adjusted to 6 with sodium carbonate, the precipitate is filtered off and dissolved in chloroform, and the filtrate is made weakly alkaline and shaken three times with chloroform. The united chloroform solutions are extracted with water, decolorised with animal charcoal, dried over sodium sulfate, and evaporated in a vacuum. When dissolved in light petroleum, brought to the boil, and allowed to crystallize with ice-cooling, the residue forms white flakes, m.p. 50° (26.4 g, 71%).

N.B.: 4-Nitropyridine can cause skin damage, *e.g.*, blisters.

2. Nitrosation

a. General

Electrophilic replacement of hydrogen by the nitroso group is restricted by the relatively slight electrophilicity of the nitrosyl cation to compounds containing mobile hydrogen (compounds containing active methylene groups, phenols, and tertiary amines). All *C*-nitroso compounds are unstable, and any reasonable degree of stability attaches only to compounds in which the nitroso group is bonded to a tertiary carbon atom or to a secondary carbon atom carrying also a stabilizing group such as NO_2, COOR, or halogen. Very many nitroso compounds exist as monomers only in solution or in the gas phase; they are then deeply colored and when they pass into the solid state form colorless dimers to which the structure of azo dioxides applies and which can sometimes be isolated in both *cis-* and *trans-*forms; a review by Gowenlock and Lüttke[243] is relevant.

Primary and secondary nitroso compounds usually stabilize themselves, even under the conditions of their preparation, by passing irreversibly into their isomers, the oximes. In tertiary aliphatic nitroso compounds this transformation is accompanied by fission of the neighboring carbon–carbon bond by hydrolysis or decarboxylation. Aromatic nitroso compounds are more stable, and when oxime formation does occur this is usually reversible within the framework of a true tautomeric equilibrium; for instance, the tautomeric pair *p*-nitrosophenol/*p*-benzoquinone monooxime is obtained both by nitrosation of phenol and by oximation of *p*-benzoquinone.

The customary nitrosating agents are nitrous acid (sodium nitrite and hydrochloric acid) or its esters, particularly ethyl and pentyl nitrite. Either a basic (alkoxide) or an acidic (hydrochloric acid) catalyst is generally used with the esters. The combination ethyl nitrite–hydrochloric acid has the advantage that all the by-products can be removed in a vacuum at room temperature. In special cases nitrosylsulfuric acid, nitrosyl chloride, and nitric oxide have been used, generally with success. Solvents are usually water, ethanol, glacial acetic acid, or diethyl ether. The reaction often occurs smoothly at 0°; less reactive compounds require gentle heat, up to 50–60°.

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[243] B. G. Gowenlock and W. Lüttke, *Quart. Rev.* (*London*), **12**, 321 (1958).

b. Nitrosation of aliphatic compounds

i, Preparation of oximes

In the aliphatic series, nitrosation is mainly used for preparation of oximes,[244] which are always obtained instead of the true nitroso compounds unless rearrangement can be avoided by choice of special conditions. In general, the reaction is more successful the more strongly the hydrogen to be replaced is activated by electron-attracting groups.

α-(Hydroxyimino) ketones are formed directly on nitrosation of ketones (see, for example, Karg[245]); α-chloro ketones give hydroxamoyl chlorides.[246] Biacetyl monooxime is obtained in about 60% yield when ethyl nitrite is led into ethyl methyl ketone containing a little concentrated hydrochloric acid at 40–55°.[247] In homologous unsymmetrical ketones nitrosation may occur on the longer and on the shorter carbon chain, and if the nitrosating agent is used in excess under acid catalysis both the α-positions may react, *e.g.*, in tropinone[248] or cyclohexanone.[249,250]

When a β-keto acid is used in place of the corresponding ketone, nitrosation is naturally easier because the methylene group is more strongly activated; working with sodium nitrite and dilute acid in an aqueous medium may lead to simultaneous decarboxylation, thus affording the same hydroxyimino ketone, but in better yield; in this way Diels[251] obtained a 94% yield of 3-(hydroxyimino)-2-pentanone from α-ethylacetoacetic acid. Acetonedicarboxylic acid can be either mononitrosated to give γ-(hydroxyimino)acetoacetic acid[252] or converted in a two-fold reaction into 1,3-bis(hydroxyimino)-acetone.[253,254]

Bis(hydroxyimino)acetone:[253] A solution of crude acetonedicarboxylic acid (150 g) in water (275 ml) is thoroughly cooled in an ice–salt bath and treated dropwise, with stirring, with a solution of sodium nitrite (100 g) in water (200 ml) whilst the temperature is not allowed to rise above 0°. The mixture is then cooled to −5° and the precipitate formed is collected at once and washed with small amounts of ice-water. An additional quantity is obtained by adding cold 6N-nitric acid (200 ml) to the filtrate. The white product is washed four times with small amounts of ice-water and dried over sulfuric acid in a vacuum-desiccator; it decomposes at 133°. The yield is 59 g (51%).

β-Keto esters and amides containing unsubstituted α-methylene groups can be nitrosated to give α-(hydroxyimino) β-keto esters and amides. For example, α-(hydroxyimino)acetoacetic ester is formed almost quantitatively on dropping an aqueous sodium nitrite solution into a cooled mixture of acetoacetic

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[244] O. Touster, *Org. Reactions*, **7**, 327 (1953).

[245] E. Karg, *Arch. Pharm.*, **282**, 49 (1944).

[246] G. Hesse and G. Krehbiel, *Chem. Ber.*, **88**, 130 (1955).

[247] W. L. Semon and V. R. Damerell, *Org. Syn.*, Coll. Vol. II, 204 (1943).

[248] R. Willstätter, *Ber. Deut. Chem. Ges.*, **30**, 2698 (1897).

[249] A. Treibs and A. Kuhn, *Chem. Ber.*, **90**, 1691 (1957).

[250] (a) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. K. Latourette, *J. Org. Chem.*, **25**, 492 (1960); (b) cf. D. C. Batesky and N. S. Moon, *J. Org. Chem.*, **24**, 1694 (1959).

[251] O. Diels and G. Plaut, *Ber. Deut. Chem. Ges.*, **38**, 1917 (1905).

[252] J. B. Neilands, A. Neuberger, and J. J. Scott, *J. Amer. Chem. Soc.*, **82**, 214 (1960).

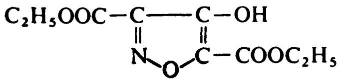
[253] T. A. Geissman, M. J. Schlatter, and J. D. Webb, *J. Org. Chem.*, **11**, 736 (1946).

[254] O. Achmatowicz and M. Leplawy, *Roczniki Chem.*, **32**, 1375 (1958).

ester and 18% sulfuric acid.[255, cf. 256] Most acyl-homologous esters react equally smoothly.

α-(Hydroxyimino)benzoylacetic ester [ethyl 2-(hydroxyimino)-2-oxo-3-phenylpropionate]:[257] Sodium nitrite (18.5 g), dissolved in a little water, is added slowly to a solution of benzoylacetic ester (50 g) in glacial acetic acid (125 g) at 5–8°. Part of the resultant oxime crystallizes; the remainder is precipitated when the solution is kept for 2–3 h below room temperature and then treated with ice-water. It crystallizes from hot ethanol in large tablets, m.p. 120 to 121° (52 g).

Diethyl acetonedicarboxylate can be only mononitrosated; when attempting dinitrosation with pentyl nitrite, von Pechmann[258] obtained diethyl 4-hydroxyisooxazole-3,5-dicarboxylate:



Nitrosation of α-substituted β-keto esters is accompanied by loss of the acyl group. α-Alkyl-α-(hydroxyimino)acetic esters, which are important for preparation of α-amino[259] and α-keto acids,[260] are obtained in this way from *C*-alkylacetoacetic esters:

$$\mathrm{CH_3CO{-}CHR{-}COOR'} \longrightarrow \mathrm{CH_3CO{-}CR(NO){-}COOR'} \longrightarrow \mathrm{HON{=}CR{-}COOR'}$$

In these reactions yields of the hydroxyimino compounds are particularly good if nitrosation is carried out with an alkyl nitrite in the presence of an alkoxide[261] or, better, in 85% sulfuric acid.[259,262]

The last method will be exemplified for a case which will serve also for analogous esters. **2-(Hydroxyimino)hexanoic acid:**[262] 85% Sulfuric acid (30 g), in 400-ml beaker, is cooled in ice–salt and to it is added slowly, with stirring, ethyl 2-butylacetoacetate (18.6 g, 0.1 mole), the temperature being kept below −5°. The butyl nitrite (0.1 mole + 5% excess; 11 g) is dropped in at about 0° at such a rate that there is gentle effervescence but no noticeable evolution of nitrogen oxides. The acid is then diluted by addition of small pieces of ice, whereupon the hydroxyimino ester separates as a white cheesy precipitate. Cold water is added and the mixture is extracted with ether. The ethereal solution is shaken with cold 10% sodium hydroxide solution, in which the hydroxyimino compound dissolves with a red color. The alkaline solution is heated for 15 min on a water-bath, then cooled and acidified. The 2-(hydroxyimino)hexanoic acid that separates is filtered off and the filtrate is extracted with ether. Recrystallization from light petroleum gives a product of m.p. 136° (dec.) in 86% yield.

The formation of α-(hydroxyimino) esters from cyclic β-keto esters is necessarily combined with ring opening. Thus ethyl 2-(hydroxyimino)adipate is obtained from ethyl 2-oxocyclopentanecarboxylate on its reaction with ethyl nitrite and sodium ethoxide.[263] If the ester group is hydrolysed under

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[255] M. Z. Jovichich, *Ber. Deut. Chem. Ges.*, **28**, 2683 (1895); **35**, 151 (1902).

[256] H. Adkins and E. W. Reeve, *J. Amer. Chem. Soc.*, **60**, 1328 (1938); N. F. Albertson, B. F. Tullar, J. A. King, B. B. Fishborn, and S. Archer, *J. Amer. Chem. Soc.*, **70**, 1150 (1948).

[257] L. Wolff and A. A. Hall, *Ber. Deut. Chem. Ges.*, **36**, 3612 (1903).

[258] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **24**, 857 (1891).

[259] K. E. Hamlin Jr. and W. H. Hartung, *J. Biol. Chem.*, **145**, 349 (1942).

[260] R. Fischer and T. Wieland, *Chem. Ber.*, **93**, 1387 (1960).

[261] J. C. Shivers and C. R. Hauser, *J. Amer. Chem. Soc.*, **69**, 1264 (1947).

[262] R. H. Barry and W. H. Hartung, *J. Org. Chem.*, **12**, 460 (1947).

[263] W. Dieckmann, *Ber. Deut. Chem. Ges.*, **33**, 579 (1900).

the reaction conditions the nitroso compound stabilizes itself by decarboxylation and there is no ring fission; *e.g.*, ethyl 2-oxocyclohexanecarboxylate affords 1,2-cyclohexanedione monooxime,[264] which is difficult to obtain from cyclohexanone.[250b]

Alkylmalonic esters are especially suitable starting materials for the preparation of β-(hydroxyimino) esters. Shivers and Hauser[261] obtained high yields in such cases by means of ethyl nitrite and an equimolar amount of sodium ethoxide. Barry and Hartung recommend carrying out the nitrosation in ethereal solution with sodium nitrite and hydrogen chloride.[262]

Cyanoacetic esters yield 2-cyano-2-(hydroxyimino)acetic esters on nitrosation,[265] but substituted cyanoacetic esters are hydrolysed and decarboxylated during the reaction, yielding β-(hydroxyimino) nitriles, and the free acids do not react.[266]

Alkyl groups in the *ortho*- or *para*-position of aromatic nitro compounds are also nitrosated, in the α-position. Thus *o*- and *p*-nitroacetophenone oxime are obtained in 73.5% and 67% yield, respectively, by nitrosating the corresponding ethylnitrobenzene with *tert*-butyl nitrite (for its preparation see Coe and Doumani[267]) in the presence of sodium *tert*-butoxide.[213]

Nitrosation of hydrocarbons — other than cyclopentadiene[268] and fluorene[269] — is not effected by the methods mentioned above, but can be achieved photochemically by nitrosyl chloride or by nitric oxide and chlorine. By the action of sunlight on a solution of nitrosyl chloride in toluene at or below room temperature for about 2 hours Lynn and Arkley[270] obtained β-benzaldoxime in almost quantitative yield (calculated on nitrosyl chloride); similarly, by passing gaseous nitrosyl chloride through cyclohexane under irradiation at a low temperature (0° to −30°) Naylor and Anderson[271] obtained cyclohexanone oxime in 71% yield (calculated on nitrosyl chloride). A disadvantage of this procedure is the great dilution at which the reaction is effected.

Replacing the nitrosyl chloride by a mixture of nitric oxide and chlorine has also proved successful in the nitrosation of irradiated saturated hydrocarbons. According to the conditions and the proportions in which the oxide and chlorine are used, cyclohexane affords as main product 1-chloro-1-nitrosocyclohexane, dimeric nitrosocyclohexane, or cyclohexanone oxime. Experimental details of this interesting reaction, which has industrial interest, will be found in a review by Müller *et al.*[272] and the papers cited therein.

ii, Preparation of true nitroso compounds

Up to the present, compounds containing active methylene groups have only seldom been converted into true nitroso compounds or their dimers.

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[264] T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).

[265] M. Conrad and A. Schulze, *Ber. Deut. Chem. Ges.*, **42**, 735 (1909).

[266] T. K. Walker, *J. Chem. Soc.*, **125**, 1622 (1924).

[267] C. S. Coe and T. F. Doumani, *J. Amer. Chem. Soc.*, **70**, 1516 (1948).

[268] J. Thiele, *Ber. Deut. Chem. Ges.*, **33**, 666 (1900).

[269] C. F. Koelsch, *J. Org. Chem.*, **26**, 1291 (1961).

[270] E. V. Lynn and H. L. Arkley, *J. Amer. Chem. Soc.*, **45**, 1045 (1923).

[271] M. A. Naylor and A. W. Anderson, *J. Org. Chem.*, **18**, 115 (1953).

[272] E. Müller and co-workers, *Angew. Chem.*, **71**, 229 (1959); *Chem. Ber.*, **98**, 1893 (1965).

To avoid immediate rearrangement to oximes, it is necessary to avoid the presence of traces of alkali during the reaction, which should if possible, be carried out without a solvent and particularly without a hydroxylic solvent.

Baeyer obtained some dimeric nitroso compounds in the terpene series by the action of ethyl or pentyl nitrite on terpene ketones in the presence of small amounts of acetyl chloride or by means of pentyl nitrite and a few drops of concentrated hydrochloric acid in light petroleum solution;[273] and similar procedures have been used by some other workers.[274,275]

Dimeric ethyl 1-nitroso-2-oxocyclopentanecarboxylate:[274] Ethyl 2-oxocyclopentanecarboxylate (10 g) is mixed with ethyl nitrite (6–7 g; theor. 5 g) with ice-cooling, and a few drops of acetyl chloride are added. After 10–15 h the colorless dimeric nitroso compound is filtered off and washed with ether. The yield is 60–80%.

Wieland and Bloch[276] obtained dimeric nitroso compounds by leading nitrogen oxides (from arsenic trioxide and nitric acid of *d* 1.38) into cooled ethereal solutions of 1,3-diketones. The dimeric nitroso compounds from dibenzoylmethane, benzoyl-*p*-anisoylmethane, and benzoylacetone were prepared in this way.

α-Substituted acetoacetic esters usually react some what differently with nitrogen oxides if there is at least one hydrogen atom in the α-position. On passing nitrogen oxides into the undiluted esters, Schmidt and Widmann[277] observed that introduction of the nitroso group was accompanied by hydrolysis of the acetyl group; monomeric, blue 2-nitroso derivatives of propionic, butyric, and hexanoic esters were thus obtained from the α-methyl, α-ethyl, and α-butyl derivatives, respectively, of acetoacetic esters; further examples have also been recorded.[278,279]

$$CH_3COCHRCOOR' \xrightarrow[(0^\circ)]{N_2O_3} CH_3COCR(NO)COOR' \longrightarrow ON{-}CHRCOOR'$$

$$[R = CH_3,\ C_2H_5,\ CH_2COOR'',\ C_4H_9,\ CH(COCH_3)COOR'']$$

Similarly, aliphatic α-nitro esters and nitrogen oxides do not give compounds resembling pseudonitrols but lose the nitro group and afford the aliphatic nitroso esters.[164,279,280] On nitrosation of ethyl 2-benzoylpropionate the hydrolysis can be avoided and ethyl 2-benzoyl-2-nitrosopropionate can be isolated.[281]

Nitroso derivatives of hydrocarbons cannot be obtained by direct nitrosation, except under irradiation as mentioned above. They are prepared by oxidation of other nitrogenous groups (see p. 591), photochemical or thermal decomposition of alkyl nitrites,[282] or, recently, by oxidative fission of oxaziridines.[283]

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[273] A. Baeyer, *Ber. Deut. Chem. Ges.*, **28**, 639, 1586 (1895); **29**, 1078 (1896).

[274] W. Dieckmann, *Ber. Deut. Chem. Ges.*, **33**, 590, 594 (1900); W. Dieckmann and A. Groeneveld, *Ber. Deut Chem. Ges.*, **33**, 604 (1900).

[275] W. Pritzkow and W. Rösler, *Ann. Chem.*, **703**, 66, (1967).

[276] H. Wieland and S. Bloch, *Ber. Deut. Chem. Ges.*, **37**, 1524 (1904).

[277] J. Schmidt and K. T. Widmann, *Ber. Deut. Chem. Ges.*, **42**, 497, 1886 (1909).

[278] J. Schmidt and A. Haid, *Ann. Chem.*, **377**, 23 (1910).

[279] J. Schmidt and H. Dieterle. *Ann. Chem.*, **377**, 30 (1910).

[280] N. Kornblum, R. K. Blackwood, and D. D. Mooberry, *J. Amer. Chem. Soc.*, **78**, 1501 (1956).

[281] J. Schmidt and E. Aeckerle, *Ann. Chem.*, **398**, 251 (1913).

[282] B. G. Gowenlock and co-workers, *J. Chem. Soc.*, **1955**, 4190; **1956**, 1670; **1960**, 2222.

[283] W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 6522 (1957).

c. Nitrosation of aromatic compounds

i, Nitrosation of phenols and tertiary amines

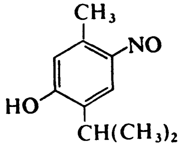
By far the most stable nitroso compounds are those of the aromatic series. The smoothest *C*-nitrosation is achieved with phenols and tertiary amines having a free *para*-position. In benzene derivatives the nitroso group enters almost exclusively[284] the *para*-position to the hydroxyl or amino group. In the naphthalene series the reaction is not always unidirectional: 1-nitroso-2-naphthol is obtained almost quantitatively from 2-naphthol,[285] but 1-naphthol gives a mixture of about equal parts of 2- and 4-nitroso-1-naphthol.[286]

The nitrosating agent most often used is nitrous acid itself. Phenols are usually dissolved in sodium hydroxide solution, aqueous sodium nitrite solution is added, and nitrous acid is developed by dropping in a dilute mineral acid. Tertiary amines are dissolved in an excess of mineral acid, and the calculated amount of sodium nitrite solution is dropped in. The reaction temperature should not exceed 10°.

Bridge's classical procedure[287] may be cited as an example of nitrosation of a phenol: Phenol (60 g), sodium hydroxide (27 g), and sodium nitrite (54 g) are dissolved in water (1500 ml) and treated gradually with a mixture of concentrated sulfuric acid (150 g) and water (400 ml) at 7–8° with cooling. After 2 h the precipitated nitrosophenol is filtered off, washed with ice-water, taken up in ether, and shaken with animal charcoal at room temperature. Evaporation of the ether affords an 80% yield of **p-nitrosophenol** as yellow needles that melt at 125° with decomposition. For purification it may be recrystallized from benzene or toluene.

It is sometimes better to work with an alcoholic solution.

According to *Organic Syntheses*[288] **nitrosothymol** is prepared by adding sodium nitrite (72 g) gradually, in portions, to a solution of thymol (100 g) in a mixture of 95% ethanol (500 ml) and concentrated hydrochloric acid (500 ml) at 0°. The crude product is precipitated by addition of much water and is recrystallized from benzene, then having m.p. 160–164°. The yield is 87%.



Nitrosothymol

Polyhydric phenols can also be doubly nitrosated. Heinrich[289] obtained 4-nitrosoresorcinol as potassium salt on dropping pentyl nitrite into a cooled solution of resorcinol and potassium hydroxide in absolute alcohol, but resorcinol is easily doubly nitrosated, at the 2,4-positions, by nitrous acid in an acid solution.[289,290] N.B.: preparation of trinitrosophloroglucinol may lead to an explosion.[291]

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[284] S. Veibel, *Ber. Deut. Chem. Soc.*, **63**, 1577 (1930).

[285] C. S. Marvel and P. K. Oorter, *Org. Syn.*, **2**, 61 (1922).

[286] R. Henriques and M. Ilinski, *Ber. Deut. Chem. Ges.*, **18**, 704 (1885).

[287] J. L. Bridge, *Ann. Chem.*, **277**, 85 (1893).

[288] E. Kremers, N. Wakeman, and R. M. Hixon, *Org. Syn.*, **6**, 92 (1926).

[289] F. Henrich, *Ber. Deut. Chem. Ges.*, **35**, 4191 (1902).

[290] W. R. Orndorff and M. L. Nichols, *J. Amer. Chem. Soc.*, **45**, 1536 (1923).

[291] H.-E. Freund, *Angew. Chem.*, **73**, 433 (1961).

Substituents in the *ortho*- or *meta*-position to a hydroxyl group usually do not interfere. Thus *o*- and *m*-cresol afford the 4-nitroso derivatives (OH = 1).[292] *para*-Substituted phenols react differently, if at all: *p*-cresol, for instance, is nitrated in the *ortho*-position to the hydroxyl group by nitrous acid.[292]

Nitrosophenols are also often prepared from *N,N*-dialkyl-*p*-nitrosoanilines. This reaction may be effected by boiling alkali hydroxide solutions[293] or by treatment with alkali hydrogen sulfite solutions.[294] It is used mainly for preparing the secondary amines that form the other product.

The Baudisch reaction[295] makes it possible simultaneously to introduce a nitroso and a hydroxyl group in the *ortho*-position to one another. In this reaction NOH radicals are produced by oxidation of hydroxylamine or reduction of nitrous acid; these radicals, in conjunction with an oxidizing agent and in the presence of a copper salt as catalyst attack the aromatic nucleus. Yields are seldom very high, but few *o*-nitrosophenols are easily prepared in other ways. Cronheim[296] has reported the first preparation of fifty mono- and di-substituted *o*-nitrosophenols by the Baudisch reaction.

Among tertiary aromatic amines, *N,N*-dimethyl-, *N,N*-diethyl-, and *N,N*-dipropyl-aniline can be nitrosated, but the reaction fails with *N,N*-dibutyl- and *N,N*-diisopentyl-aniline.[297]

Good directions for the nitrosation of *N,N*-dimethylaniline are given in *Organic Syntheses*[208a] (cf. Hodgson and Nicholson[298]):

For a good yield in nitrosation of tertiary amines it is important that no more, or only very slightly more, than the theoretical amount of nitrite should be used and that the concentration of mineral acid shall be such that the nitroso compound remains largely undissolved; otherwise, undesirable side reactions are to be expected, such as elimination of *N*-alkyl groups and subsequent *N*-nitrosation or nuclear nitration.[298,299] Nuclear nitration may also occur on attempted nitrosation of *p*-substituted amines[300] (cf. page 423). Also, substituents *ortho* to the nitrogen sometimes hinder nitrosation at the *para*-position,[301,302] but many exceptions to this action are known.

ii, Nitrosation of secondary amines

C-Nitroso derivatives of secondary aromatic amines can be prepared by the so-called Fischer–Hepp rearrangement,[303] which involves the action of a hydrogen halide on the corresponding *N*-nitroso amine. In this process the *N*-nitroso group is split off as nitrosyl halide which then nitrosates the ring

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[292] H. H. Hodgson and E. A. C. Crouch, *J. Chem. Soc.*, **1943**, 221.

[293] A. Baeyer and H. Caro, *Ber. Deut. Chem. Ges.*, **7**, 963 (1874).

[294] Ger. Pat. 74,628; *Friedländer*, **3**, 957 (1890–1894); J. von Braun, K. Heider, and E. Müller, *Ber. Deut. Chem. Ges.*, **51**, 737 (1918); R. Munch, G. T. Thannhauser, and D. L. Cottle, *J. Amer. Chem. Soc.*, **68**, 1297 (1946); W. R. Boon, *J. Chem. Soc.*, **1947**, 307.

[295] O. Baudisch, *Naturwissenschaften*, **27**, 768 (1939); *Science*, **92**, 336 (1940); O. Baudisch and S. H. Smith, *Naturwissenschaften*, **27**, 769 (1939); O. Baudisch, *J. Amer. Chem. Soc.*, **63**, 622 (1941); *Arch. Biochem.*, **5**, 401 (1944).

[296] G. Cronheim, *J. Org. Chem.*, **12**, 1, 7, 20 (1947).

[297] P. Carrer, *Ber. Deut. Chem. Ges.*, **48**, 1398 (1915).

[298] H. H. Hodgson and D. E. Nicholson, *J. Chem. Soc.*, **1941**, 470.

[299] W. G. Macmillan and T. H. Reade, *J. Chem. Soc.*, **1929**, 2863.

[300] H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, **1936**, 1500.

[301] J. Houben, *Ber. Deut. Chem. Ges.*, **42**, 3188 (1909).

[302] J. von Braun, Z. Arkuszewski, and Z. Köhler, *Ber. Deut. Chem. Ges.*, **51**, 282 (1918).

[303] O. Fischer and E. Hepp, *Ber. Deut. Chem. Ges.*, **19**, 2991 (1886).

of the secondary amine.[304] The rearrangement usually occurs merely on keeping the *N*-nitroso amine in alcoholic hydrochloric[303] or hydrobromic acid,[305] at room temperature, the yellow or orange crystalline hydrohalide of the *C*-nitroso compound separating after some time. Occasionally, however, concentrated hydrochloric acid[301,306] or glacial acetic acid and hydrogen chloride[307] are needed to effect the rearrangement.

Not only simple *N*-alkyl-*N*-nitrosoanilines[303,308] undergo this reaction, but also ring-substituted aniline derivatives with a free *para*-position, such as *N*-ethyl-*N*-nitroso-*o*-toluidine,[303] *m*-chloro- and *m*-bromo-*N*-methyl-*N*-nitrosoaniline,[310] and *N*-methyl-*N*-nitrosoanthranilic acid;[301,311] the *C*-nitroso derivative obtained from the last-mentioned compound can be hydrolysed to nitrosalicylic acid.[312] Rearrangements of the derivatives of 1- and 2-naphthylamine have been reported by several authors.[305,308,309,313]

N-Ethyl-4-nitroso-1-naphthylamine is also obtained on direct nitrosation, in 73% yield[314] (see the next Section).

iii, Nitrosation of primary amines

Blangey[314] obtained direct *C*-nitration of some primary amines when he added the amine to an ice-cold solution of sodium nitrite in concentrated sulfuric acid with exclusion of moisture. After complete consumption of the nitrous acid the products were precipitated by ice-water and proved in each case to be the *p*-nitroso amine. Thus were obtained the 4-nitroso derivatives of 1-naphthylamine and its 2-, 6-, 7-, and 8-monosulfonic acids, and in the benzene series those of *m*-anisidine, *m*-toluidine ($NH_2 = 1$), etc. The sulfo group was split off from naphthionic acid, which gave a good yield of the product obtained from 1-naphthylamine. For the preparation of *C*-nitroso derivatives of primary amines from nitrosophenols see page 529.

3. Azo coupling

a. General

The term, 'azo coupling' denotes all reactions of diazonium cations with anionic substances that lead to neutral molecules with removal of the charges on the reactants:[315]

$$[\mathrm{Ar{-}N{\equiv}N}]^+ + \mathrm{X}^- \longrightarrow \mathrm{Ar{-}N{=}N{-}X}$$

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[304] P. W. Neber and H. Rauscher, *Ann. Chem.*, **550**, 182 (1942).

[305] O. Fischer and E. Hepp, *Ber. Deut. Chem. Ges.*, **20**, 1247 (1887).

[306] J. Houben, *Ber. Deut. Chem. Ges.*, **46**, 3984 (1913).

[307] J. Houben and W. Brassert, *Ber. Deut. Chem. Ges.*, **40**, 4740 (1907).

[308] L. Wacker, *Ann. Chem.*, **243**, 290 (1888).

[309] E. Kock, *Ann. Chem.*, **243**, 307 (1888).

[310] M. Ikuta, *Ann. Chem.*, **243**, 272 (1888).

[311] J. Houben, W. Brassert, and L. Ettinger, *Ber. Deut. Chem. Ges.*, **42**, 2745 (1909).

[312] J. Houben and E. Kellner, *Ber. Deut. Chem. Ges.*, **42**, 2757 (1909); J. Houben and G. Schreiber, *Ber. Deut. Chem. Ges.*, **53**, 2352 (1920).

[313] O. Fischer and E. Hepp, *Ber. Deut. Chem. Ges.*, **20**, 2471 (1887).

[314] L. Blangey, *Helv. Chim. Acta*, **21**, 1579 (1938).

[315] K. Holzach, "Die aromatischen Diazoverbindungen," Ferdinand Enke, Stuttgart, 1947; K. H. Saunders, "The Aromatic Diazo-Compounds and their Technical Applications," Edward Arnold & Co, London, 2nd ed, 1949; H. Zollinger, "Chemie der Azofarbstoffe," Birkhäuser Verlag, Basle and Stuttgart, 1958.

Strictly speaking, therefore, it covers also the well-known rearrangement of diazonium salts to diazoates, *e.g.*, the formation of diazocyanides from diazonium cyanides.[316] According to the element with which the terminal nitrogen atom forms a new covalent bond in the coupling process, the product is called a C-, O-, N-, or S-azo compound. This Section is concerned only with C-azo compounds.

The diazo components used for coupling are almost exclusively diazonium salts. Because their instability usually precludes the use of energetic reaction conditions such as high temperatures, and because their electrophilicity is relatively low, C-azo coupling demands particularly reactive anionic components, *e.g.*, compounds containing active methylene groups, phenols, or aromatic amines.

However, the nature of the diazo component also has a great influence on the course of the coupling. Diazonium salts containing electron-attracting substituents couple particularly readily and even at fairly low pH. According to Raab[317] the ease of coupling by substituted diazotized anilines decreases in the following order: polynitroanilines, chloronitroanilines, nitroanilines, chloroanilines, anilinesulfonic acids, aniline, anisidine, aminophenols. The more the diazo component is activated by electron-attracting substituents the less activated does the coupling component need to be; thus, for instance, diazotized 2,4,6-trinitroaniline couples even with mesitylene, giving the deep red 2,4,6-trinitrobenzeneazomesitylene.[318, cf. 319] The two diazonium groups of tetrazotized diamines usually have different reactivities and can be brought into stepwise reaction with different coupling components.

Components that can undergo coupling are in general those that can undergo direct nitrosation. The analogy goes even further: just as aliphatic nitroso compounds readily rearrange to oximes, so the coupling products of aliphatic components readily undergo a similar rearrangement that gives hydrazones.[320,321] True azo compounds are thus rarely obtained on coupling with aliphatic components. Occasionally rearrangement to the hydrazone form is observed even with purely aromatic azo compounds, but in such cases there seems to be a true tautomeric equilibrium. For instance, it has long been known[322] that the coupling product of a benzenediazonium salt with α-naphthol is identical with 1,4-naphthoquinone monophenylhydrazone; by means of the absorption spectra Kuhn and Bär[323] showed that the nature of the solvent decided whether the azo or the hydrazone form predominated. This tautomerism of hydroxyazo compounds is, however, not general: in solutions of *o*-, *m*-, and *p*-(phenylazo)phenol only the azo form could be detected.[323]

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[316] D. Anderson, R. J. W. LeFèvre and J. Savage, *J. Chem. Soc.*, **1947**, 445; N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, **1947**, 453; D. Anderson, M. E. Bedwell, and R. J. W. LeFèvre, *J. Chem. Soc.*, **1947**, 457.

[317] H. Raab in Ullmann's "Enzyklopädie der Technischen Chemie," Urban & Schwarzenberg, Munich–Berlin, 3rd ed, 1953, Vol. 4, pp. 76ff.

[318] K. H. Meyer and H. Tochtermann, *Ber. Deut. Chem. Ges.*, **54**, 2283 (1921).

[319] L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.*, **60**, 1142 (1938).

[320] S. M. Parmenter, *Org. Reactions*, **10**, 1 (1959).

[321] R. R. Phillips, *Org. Reactions*, **10**, 143 (1959).

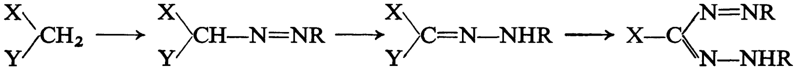
[322] T. Zincke and H. Bindewald, *Ber. Deut. Chem. Ges.*, **17**, 3026 (1884).

[323] R. Kuhn and F. Bär, *Ann. Chem.*, **516**, 143 (1935).

Formulating true azo compounds as derivatives of diimine, RN=NR, leads to the expectation of stereoisomeric forms, and in some cases conversion of the *trans*-isomers — the usual products — into the *cis*-forms by, *e.g.*, UV irradiation has been described.[324–328]

b. Coupling with compounds containing active methylene groups

Compounds **(1)** containing active methylene groups[320,321] usually couple smoothly with molar quantities of arenediazonium salts with formation of the appropriate arylhydrazone **(2)**; occasionally formazans **(3)** are formed as by-products:



(1) **(2)** **(3)**

The reactivity of a methylene group is greatly influenced by the activating efficiency of the neighboring groups X and Y, their effects being additive. Hünig and Boes[329] have arranged the common activating substituents in the following order: $NO_2 > CHO > COCH_3 > CN > COOC_2H_5 > CONH_2 > COOH > SOOCH_3 > C_6H_5$. This series enables one to state, for instance, that acetoacetic ester will couple more readily than malonic ester, and the latter more readily than malonic acid or phenylacetic acid. The more strongly activated the methylene group is, the lower can the pH of the medium be adjusted. It is customary to work with aqueous or aqueous-alcoholic solutions at 0–10°; when the acidity has to be reduced it usually suffices to add large amounts of sodium acetate; too high a pH, like an excess of the diazonium compound, favors two-fold coupling to give formazans (see page 473).

Bülow and Ganghofer[330] obtained **dimethyl mesoxalate phenylhydrazone** by adding a diazonium salt solution prepared from aniline (12 g), 30% hydrochloric acid (36 g), ice + water (150 g), and 98% sodium nitrite (10 g) to a cold solution of dimethyl malonate (20 g) in ethanol (100 g), followed by saturated aqueous sodium acetate solution slowly to incipient turbidity. The hydrazone crystallized during 24 hours' storage in a refrigerator and had m.p. 62° after recrystallization from ethanol.

Those compounds containing active methylene groups that, after rearrangement to oximes on nitrosation, undergo further structural transformations such as decarboxylation or loss of an acyl group, are also prone to further reaction after coupling with diazonium salts. Thus, as after nitrosation, so after coupling α-monosubstituted β-keto esters usually lose their acyl group, passing into derivatives of α-keto acids (the Japp–Klingemann reaction[321,331]):

$$\mathrm{RCO}\underset{\mathrm{H}}{\underset{|}{\mathrm{C}}}\mathrm{R'COOR''} \longrightarrow \mathrm{RCO}\underset{\mathrm{N{=}NR'''}}{\underset{|}{\mathrm{C}}}\mathrm{R'COOR''} \longrightarrow \underset{\mathrm{N{-}NHR'''}}{\underset{\|}{\mathrm{C}}}\mathrm{R'COOR''}$$

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[324] G. S. Hartley, *Nature*, **140**, 281 (1937); *J. Chem. Soc.*, **1938**, 633.

[325] A. H. Cook, *J. Chem. Soc.*, **1938**, 876.

[326] L. Zechmeister, O. Frehden, and P. F. Jörgensen, *Naturwissenschaften*, **26**, 495 (1938).

[327] A. H. Cook and D. G. Jones, *J. Chem. Soc.*, **1939**, 1309; A. H. Cook, D. G. Jones, and J. B. Polya, *J. Chem. Soc.*, **1939**, 1315.

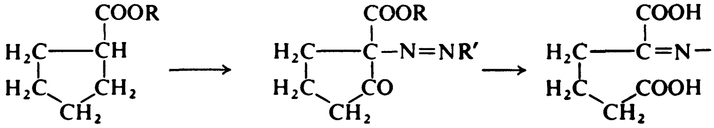
[328] H. H. Hodgson, *J. Chem. Soc.*, **1948**, 1097; W. R. Brode, J. H. Gould, and G. M. Wyman, *J. Amer. Chem. Soc.*, **74**, 4641 (1951).

[329] S. Hünig and O. Boes, *Ann. Chem.*, **579**, 28 (1953).

[330] C. Bülow and A. Ganghofer, *Ber. Deut. Chem. Ges.*, **37**, 4169 (1904).

[331] F. R. Japp and F. Klingemann, *Ber. Deut. Chem. Ges.*, **20**, 2942 (1887).

For example, coupling an ester (**4**) of 2-oxocyclopentanecarboxylic acid with benzenediazonium chloride and subsequent treatment with alkali gives a 73% yield of α-(phenylhydrazono)adipic acid (**6**):[332,333]



(4) **(5)** **(6)**

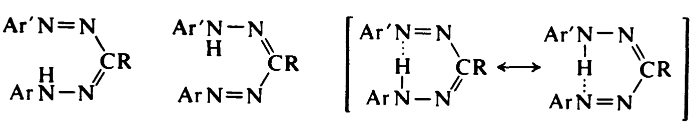
When the ester (**4**) is coupled with diazonium salts from *p*-nitroaniline, 3,4,5-triiodoaniline, or 3,5-diiodo-*p*-anisidine (NH_2 = 1), the unstable azo compounds (**5**) can be isolated as crystalline intermediates, which, however, pass into the hydrazones if warmed or treated with dilute alkali.[333,334] In recent years,[335] however, the isolation of various, relatively stable aliphatic arylazo compounds has been reported.

Most free β-keto acids undergo decarboxylation on coupling.

For example, with benzenediazonium chloride 2-oxocyclopentanecarboxylic acid gives 1,2-cyclopentanedione mono(phenylhydrazone),[336] and acetoacetic acid gives an 80% yield of methylglyoxal 1-(phenylhydrazone).[337]

In individual cases, also, aliphatic hydrocarbons can couple with diazonium salts; *e.g.*, Meyer[338] obtained crystalline azo compounds from butadiene and its homologs.

Formazans[339] occupy a special position among the coupling products of diazonium salts with compounds containing active methylene groups, though they are usually prepared by coupling aldehyde hydrazones with these salts. In accord with the latter method of preparation they have usually been formulated as compounds (**7**) or (**8**) containing an azo and a hydrazone group on the same carbon atom; however, all attempts to obtain isomeric pairs such as (**7**) and (**8**) with different aryl groups on the terminal nitrogen atoms have failed,[340] so that nowadays they are more correctly formulated as in (**9**).[341]



(7) **(8)** **(9)**

Independently of the order in which the different areneazo groups are introduced onto the central carbon atom the same products are obtained; on coupling benzaldehyde phenylhydrazone with *p*-toluenediazonium chloride,

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[332] L. Kalb, F. Schweizer, and G. Schimpf, *Ber. Deut. Chem. Ges.*, **59**, 1858 (1926).

[323] R. P. Linstead and A. B.-L. Wang, *J. Chem. Soc.*, **1937**, 807.

[324] L. Kalb, F. Schweizer, and H. Zellner, *Ber. Deut. Chem. Ges.*, **59**, 1860 (1926).

[325] B. Heath-Brown and P. G. Philpott, *J. Chem. Soc.*, **1965**, 7185; H. C. Yao and P. Resnick, *J. Amer. Chem. Soc.*, **84**, 3514 (1962).

[336] W. Dieckmann, *Ann. Chem.*, **317**, 63 (1901).

[337] G. A. Reynolds and J. A. Van Allan, *Org. Syn.*, **32**, 84 (1952).

[338] K. H. Meyer, *Ber. Deut. Chem. Ges.*, **52**, 1468 (1919).

[339] A. W. Nineham, *Chem. Rev.*, **55**, 355 (1955).

[340] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **27**, 1679 (1894).

[341] L. Hunter and C. B. Roberts, *J. Chem. Soc.*, **1941**, 820, 823.

von Pechmann[340] recognized that the product was the same formazan as was obtained from benzaldehyde *p*-tolylhydrazone and benzenediazonium chloride.[cf. 342]

For the older nomenclature of formazans see references [339, 340, 343,] and[344,] and for their stereochemistry see papers by Kuhn and his co-workers.[345,346]

Coupling of hydrazones with diazonium salts is usually conducted in weakly alkaline solution at about 0–10°. It is advantageous to add the diazonium salt solution, buffered if necessary with sodium acetate, to an alcoholic solution of the hydrazone that also contains sodium acetate; or pyridine may be used in place of sodium acetate.[347]

3-Ethyl-1,5-diphenylformazan:[345] A solution of propionaldehyde phenylhydrazone (3.2 g) in methanol (25 ml) was treated with crystalline sodium acetate (7 g) in methanol (35 ml) and then, at 0°, with a diazonium salt solution prepared from aniline (2 g in 9 ml of concentrated hydrochloric acid and 2 ml of water) and sodium nitrite (80%; 2 g in 3 ml of water). The formazan, which first separated as a red oil, had crystallized after 14 h.

The yields are often good, but occasionally surprisingly low. If the phenylhydrazone group has an electrophilic *meta-* or *para*-substituent, or if the aldehyde residue has a similarly substituted aromatic ring, this often has an adverse influence on the yield.[310,339] If the phenylhydrazone carries a hydroxyl or amino substituent in the ring, and also in the case of naphthylhydrazones,[348] the diazonium component may couple with the aromatic ring instead of with the central carbon atom. According to von Pechmann[340] hydrazones of the type $R_2N—N=CHR'$, which have no hydrogen on the hydrazone nitrogen, are incapable of yielding formazans. Busch and Pfeiffer,[349] therefore, assumed that the first step in formazan synthesis was formation of a tetrazene by replacement of the hydrazone-hydrogen. Recent work has demonstrated the influence of pH on the course of the reaction: benzaldehyde phenylhydrazone and benzenediazonium chloride at pH above 9 give the formazan, at pH between 4 and 8 give the tetrazene, and at pH 3 give benzaldehyde [*p*-(phenylazo)phenyl]hydrazone.[350]

Occasionally it is unnecessary to isolate the hydrazone since this is itself accessible by a coupling reaction. Numerous formazans can be obtained by treating compounds containing active methylene groups directly with 2 molar proportions of a diazonium salt. For example, pyruvic acid is converted into 3-oxalo-1,5-diphenylformazan ("formazylglyoxalic acid") in 94% yield by benzenediazonium chloride in potassium hydroxide solution.[351] Acyl groups (CH_3CO or COOH) are often eliminated in such reactions;[343,344,352] thus acetoacetic ester yields ethyl 1,5-diphenylformazan-3-carboxylate almost

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[342] R. Kuhn and D. Jerchel, *Ber. Deut. Chem. Ges.*, **74**, 941 (1941).

[343] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **25**, 3175 (1892).

[344] E. Bamberger and E. W. Wheelwright, *Ber. Deut. Chem. Ges.*, **25**, 3201 (1892).

[345] I. Hauser, D. Jerchel, and R. Kuhn, *Chem. Ber.*, **82**, 515 (1949).

[346] R. Kuhn and H. M. Weitz, *Chem. Ber.*, **86**, 1199 (1953).

[347] J. N. Ashley, B. M. Davis, A. W. Nineham, and R. Slack, *J. Chem. Soc.*, **1953**, 3881.

[348] I. Hausser, D. Jerchel, and R. Kuhn, *Chem. Ber.*, **84**, 651 (1951).

[349] M. Busch and H. Pfeiffer, *Ber. Deut. Chem. Ges.*, **59**, 1162 (1926).

[350] H. Hauptmann and A. Cid de Mello Perisse, *Chem. Ber.*, **89**, 1081 (1956).

[351] E. Bamberger and J. Müller, *J. Prakt. Chem.*, [ii], **64**, 199 (1901).

[352] E. Bamberger and E. W. Wheelwright, *J. prakt. Chem.*, [ii], **65**, 123 (1902).

quantitatively,[344,352] and Walker[353] obtained 3-ethyl-1,5-diphenylformazan in similar yield from ethylmalonic acid.

Sometimes, as in the preparation of 1,5-diphenylformazan ("formazylhydrogen") from malonic acid,[343] it is best to use only one molar equivalent of the diazonium compound, since otherwise three-fold coupling to yield (phenylazo)formazans may readily occur.

Finally, in strongly alkaline solution formazans containing removable substituents such as COOH, $COCH_3$, and COCOOH in position 3 can couple with a third diazonium component, giving the so-called 3-(phenylazo)formazans; for instance, 1,5-diphenyl-3-(phenylazo)formazan, $C_6H_5NH—N{=}C\cdot(N{=}NC_6H_5)_2$, is obtained as end-product of complete coupling of acetone,[344] acetaldehyde,[344,351,354] pyruvic acid,[344,351] acetoacetic acid,[344,352] malonic acid,[343] or acetonedicarboxylic acid,[343] etc.

c. Azo coupling with aromatic components

Much the most important application of azo coupling is that to aromatic or heterocyclic components, above all in relation to production of dyes.[355] It has, however, also preparative interest for the synthesis of primary amines, for these can be obtained by reductive cleavage of azo compounds (see page 568).

Azo coupling is strongly dependent on the pH of the medium. Couplings that occur readily can be carried out at lower pH than those that are more difficult. For phenols the coupling range is between pH 5 and pH 9 approximately, for amines between about pH 3.5 and pH 7, but these values are greatly affected by the presence of substituents in both the diazonium and the coupling component. It was mentioned above that diazonium compounds containing electron-attracting substituents, including tetrazonium compounds, couple with increased ease and at lower pH. The position is reversed for the coupling component (phenol or amine): electron-attracting substituents (NO_2, COOH, Cl, SO_3H) decrease their ease of coupling, electron-repelling substituents (CH_3, OH, NH_2) increase it. The weaker a coupling component, the narrower in general is the pH range in which the reaction succeeds.

Phenols. In the benzene series the azo group enters almost wholly at the *para*-position. The small amount of *ortho*-product can sometimes be removed by distillation in steam.[356] When the *para*-position is already occupied, coupling occurs at the *ortho*-position, *e.g.*, in *p*-chlorophenol[357] or *p*-cresol;[358] when the *ortho*-positions are also occupied, coupling either does not occur or, as with also *p*-hydroxybenzoic acid,[359] occurs with removal of the blocking substituent; in addition, O-azo coupling may then result, as with 2,4,6-tri-

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[353] T. K. Walker, *J. Chem. Soc.*, **124**, 2775 (1923).

[354] E. Bamberger and J. Müller, *Ber. Deut. Chem. Ges.*, **27**, 147 (1894).

[355] H. E. Fierz-David and L. Blangey, "Grundlegende Operationen der Farbenchemie," Springer Verlag, Vienna, 8th ed, 1952, pp. (a) 129, (b) 136, (c) 137, (d) 144, (e) 171, (f) 191, (g) 200, (h) 226, 228 (i) 246.

[356] E. Bamberger, *Ber. Deut. Chem. Ges.*, **33**, 3188 (1900).

[357] M. Krause, *Ber. Deut. Chem. Ges.*, **32**, 124 (1899).

[358] E. Nölting and O. Kohn, *Ber. Deut. Chem. Ges.*, **17**, 351 (1884).

[359] S. von Kostanecki and J. D. Zibell, *Ber. Deut. Chem. Ges.*, **24**, 1695 (1891).

methylphenol.[360] Sufficiently active coupling components can couple twice (at positions 2,4) or three times (at positions 2,4,6); however, three-fold coupling to the same ring, *e.g.*, formation of 2,4,6-tris(phenylazo)phenol[361] or 2,4,6-tris(phenylazo)resorcinol,[362] usually leads to only poor yields.

α-Naphthol couples more easily than its β-isomer, mostly at the 4-position; feebly activated diazonium salts often attack first at the 2-position. The 2- and 4-azo isomers can generally be separated by treatment with dilute alkali, which dissolves the 4-azo compound preferentially. β-Naphthol and its derivatives couple exclusively at position 1, if necessary with extrusion of another substituent such as COOH[363] (but not CH_3[364]). Coupling of 1-naphtholsulfonic acid takes place at position 2 or 4 according to the site of the sulfo group. Dihydric phenols, aminophenols, and diamines in which the substituents are in *ortho-* or *para*-position to one another, are easily oxidized to quinones by the diazonium components. Aryl ethers couple less easily, usually only with particularly reactive diazonium compounds; glacial acetic acid has proved valuable as solvent in such cases.[365]

For coupling, water-soluble phenols or phenolsulfonic acids are dissolved in sodium carbonate solution, and sparingly soluble ones in an equivalent of sodium hydroxide solution to which sodium carbonate is added; the amount of carbonate used should just suffice to convert all the acid in the diazonium solution into bicarbonate. Then the acid diazonium solution is run slowly and with efficient stirring into the alkaline solution of the coupling component. If coupling is rapid, it can be carried out at room temperature without special precautions. If coupling is slow it is advisable to use ice-cooling and diffuse illumination, so as to reduce decomposition of the diazonium compound. The end of the reaction is recognized when a sample, brought onto filter paper, no longer forms a dye with a strongly coupling component such as R salt or sodium 2-naphthyl oxide in aqueous solution. For diazo compounds that rearrange to diazoates even in a sodium carbonate medium (*e.g.*, *o*- or *p*-nitrodiazobenzene), the sodium carbonate is better replaced by sodium acetate, calcium carbonate, or pyridine.

Amines. When primary or secondary aromatic amines are treated with a diazonium salt, N-azo coupling, leading to triazenes,[366] may occur alongside, or instead of, coupling to the aromatic ring. However, increasing the acidity of the reaction medium depresses the triazene formation. It is in accord with this that powerful diazonium components and particularly reactive amines, which couple even in an acid medium, afford *p*-amino azo compounds directly.[367] The tendency for triazene formation decreases through the series: aniline, *o*-toluidine, *m*-toluidine, and 2,5-dimethoxyaniline.[317] Under the usual conditions 2,5-dimethylaniline, 2,5-dimethoxyaniline, and α- and β-naphthylamine almost always give amino azo compounds. Even with aniline

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[360] O. Dimroth, H. Leichtlin, and O. Friedemann, *Ber. Deut. Chem. Ges.*, **50**, 1534 (1917).

[361] E. Grandmougin and H. Freimann, *Ber. Deut. Chem. Ges.*, **40**, 2662 (1907); *J. Prakt. Chem.*, [ii], **78**, 384 (1908).

[362] W. R. Orndorff and B. J. Ray, *Ber. Deut. Chem. Ges.*, **40**, 3211 (1907).

[363] R. Nietzki and A. L. Guiterman, *Ber. Deut. Chem. Ges.*, **20**, 1274 (1887).

[364] K. Fries and E. Hübner, *Ber. Deut. Chem. Ges.*, **39**, 435 (1906).

[365] K. H. Meyer and S. Lenhardt, *Ann. Chem.*, **398**, 74 (1913); K. H. Meyer, A. Irschick, and H. Schlösser, *Ber. Deut. Chem. Ges.*, **47**, 1741 (1914); K. von Auwers and F. Michaelis, *Ber. Deut. Chem. Ges.*, **47**, 1275 (1914); K. von Auwers and E. Borsche, *Ber. Deut. Chem. Ges.*, **48**, 1716 (1915); J. F. Bunnett and G. B. Hoey, *J. Amer. Chem. Soc.*, **80**, 3142 (1958).

[366] T. W. Campbell and B. F. Day, *Chem. Rev.*, **48**, 299 (1951), where the structure and tautomerism of aromatic triazenes are discussed.

formation of the triazene can be almost wholly suppressed by using a suitable procedure such as coupling in formic acid solution.[367]

If formed, the triazene can often be converted into the amino azo compound by even gentle warming with dilute acid; this conversion is smoother if the triazene is warmed with the amine used for coupling and a small amount of its hydrochloride.[368] The acid-catalysed rearrangement of triazenes involves intermediate reformation of the diazonium salt and the amine.[369,370] So, if rearrangement of a triazene is carried out in the presence of a different, more readily coupling amine, the diazonium component reacts preferentially with the latter; *e.g.*, *N*,*N*-dimethyl-*p*-(phenylazo)aniline is obtained from diazoaminobenzene and *N*,*N*-dimethylaniline.[368]

Triazene formation can be avoided *ab initio* by using the *N*-(sulfomethyl) derivative instead of the free amine and subsequently hydrolysing off the sulfomethyl group;[372] these derivatives are easily obtained from the amine, formaldehyde, and sodium hydrogen sulfite:[371]

$$\mathrm{ArNH_2 + CH_2O + NaHSO_3 \longrightarrow ArNH{-}CH_2SO_3Na + H_2O}$$

Acylation of an amine generally hinders coupling, although some exceptions to this are known, *e.g.*, *N*-acetyl- and *N*-benzoyl-1-naphthylamine,[373] *N*-(*p*-toluenesulfonyl)-1-and -2-naphthylamine.[374]

Primary amines couple more slowly than the corresponding phenols, but the ease of coupling is notably increased by substitution on the nitrogen, being considerably greater for, *e.g.*, *N*,*N*-dimethylaniline and diphenylamine than for aniline. Holzach[375] and Philippi[376] and their co-workers contributed a series of examples of coupling of *N*,*N*-dialkylanilines. *para*-Substituted aniline derivatives can couple at the position *ortho* to the amino group, but the tendency for this is not great; for instance, *N*,*N*-dimethyl-*p*-toluidine and *p*-bromo-*N*,*N*-dimethylaniline do not react with diazotized sulfanilic acid, and *p*-(dimethylamino)benzoic acid affords *p*-[*p*′-dimethylamino)phenylazo]-benzenesulfonic acid (Helianthin) with extrusion of carbon dioxide.[377] 1-Naphthylamine usually couples in the 4-position but can also be attacked at the 2-position.[378] 2-Naphthylamine couples only at position 1 and, as with 2-naphthol, previous 1-substituents may be replaced by the azo group. For the coupling sites of the numerous technically important aromatic amino sulfonic acids the review by Raab[317] may be consulted.

Water-insoluble amines are dissolved in a dilute acid, or when necessary in methanol, ethanol, acetone, or even pyridine. Sulfonic acids are used as their sodium salts. If there is a danger that the amine may undergo more than single coupling when this is not desired, then,

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[367] K. H. Meyer, *Ber. Deut. Chem. Ges.*, **54**, 2265 (1921).

[368] E. Rosenhauer and H. Unger, *Ber. Deut. Chem. Ges.*, **61**, 392 (1928).

[369] H. V. Kidd, *J. Org. Chem.*, **2**, 198 (1938).

[370] O. Wallach, *Ann. Chem.*, **235**, 233 (1886).

[371] A. Eibner, *Ann. Chem.*, **316**, 89 (1901); H. Bucherer and A. Schwalbe, *Ber. Deut. Chem. Ges.*, **39**, 2796 (1906).

[372] Ger. Pat. 131,860; *Friedländer*, **6**, 872 (1900–1902).

[373] W. König and E. Köhler, *Ber. Deut. Chem. Ges.*, **54**, 981 (1921).

[374] O. N. Witt and G. Schmitt, *Ber. Deut. Chem. Ges.*, **27**, 2370 (1894); cf. W. König and E. Köhler, *Ber. Deut. Chem. Ges.*, **55**, 2139 (1922).

[375] K. Holzach and A. Simon, *Ber. Deut. Chem. Ges.*, **75**, 166 (1942).

[376] E. Philippi and G. Ulmer-Plenk, *Ber. Deut. Chem. Ges.*, **74**, 1529 (1941).

[377] W. Scharwin and Kaljanov, *Ber. Deut. Chem. Ges.*, **41**, 2056 (1908).

[378] H. S. Turner, *J. Chem. Soc.*, **1949**, 2282.

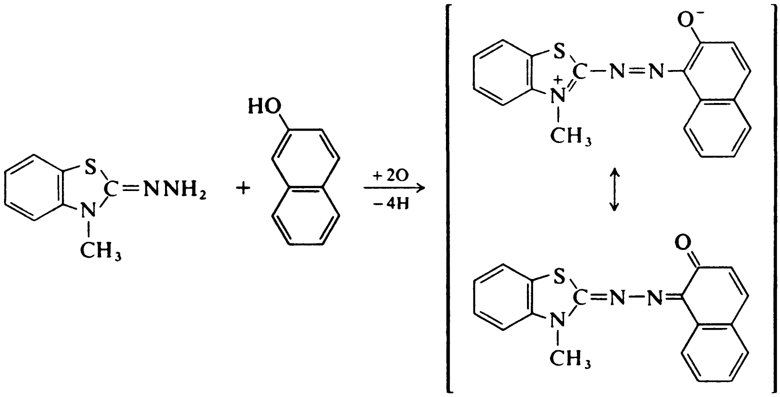
exceptionally, the diazonium solution may be stirred into the amine solution; in other cases the reverse procedure is used. If the reaction is too sluggish, the acid is buffered with sodium carbonate, or sodium carbonate is added very gradually until the solution is neutral but ensuring that this point is reached only towards the end of the reaction. In the coupling of tetrazonium compounds, to give mixed bisazo compounds, *e.g.*, from benzidine, it is essential to avoid conditions that can lead to the symmetrical bisazo product; therefore the weaker coupling component should be brought into reaction first, and the more strongly coupling one later, and the pH should be as low as convenient. If a compound contains both a hydroxyl and an amino group, the latter directs the coupling in acid solution and the former controls it in alkaline solution; this demands careful control of the pH in, *e.g.*, the industrially important coupling of aminonaphtholsulfonic acids; coupling is then carried out first in a solution acid to Congo Red, then, after the first equivalent of diazonium salt solution has been consumed, the reaction mixture is made alkaline with sodium carbonate and treated with the second equivalent of the diazonium solution or with a second coupling component.

Methods of working up the reaction mixtures vary greatly according to the nature of the azo compound. Acid dyes (sulfonic acids) can often be salted out as sodium salts by copious addition of sodium chloride. Basic dyes can in many cases be isolated as their hydrochlorides by addition of hydrochloric acid and sodium chloride. Hydroxy azo dyes are mostly sparingly soluble and are precipitated during the reaction.

Detailed prescriptions for synthesis of industrially important azo dyes are reported in the book by Fierz-David and Blangey.[355]

d. Oxidative azo coupling

Oxidative azo coupling makes it possible to prepare, in particular, heterocyclic azo compounds that cannot be obtained by direct coupling because of the instability of the requisite diazonium salts.[379,380] By the term "oxidative azo coupling" is meant the oxidative linkage of hydrazones to phenols, aromatic amines, or compounds containing reactive methylene groups, to give products that can be regarded formally as either azo compounds or azines. The example described below could be formulated as illustrated.



The hydrazone used must contain the structural unit of an amidrazone $[\rangle N{-}C{=}N{-}NH_2]$ or of a vinylog thereof $[\rangle N{-}(C{=}C)_n{-}C{=}N{-}NH_2]$.

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[379] S. Hünig and co-workers, *Angew. Chem.*, **70**, 215 (1958); **74**, 818 (1962).

[380] S. Hünig, H. Balli, H. Nöther, and H. Geiger, *Ann. Chem.*, **628**, 75 (1959).

The solvent used may be water in admixture with methanol, 2-methoxyethanol, or *N*,*N*-dimethylformamide; the customary oxidizing agent is $K_3[Fe(CN)_6]$, but Na_2CrO_4, H_2O_2, or Cu(II)Fe(III), and Ag salts are also suitable. The pH has a decisive influence on oxidative as on direct azo coupling: phenols are coupled in a weakly alkaline solution, amines in a mineral acid or acetate-buffered solution.

As an example of the procedure the coupling of 3-methyl-2(1*H*)benzothiazolone hydrazone to phenols or compounds containing a reactive methylene group will be described:[381] Potassium ferricyanide (22 mmoles) is dissolved in a mixture of water (50 ml), methanol (50 ml), and 25% aqueous ammonia solution (10 ml). A second solution is prepared from 3-methyl-2(1*H*)benzothiazolone hydrazone (5 mmoles) and the coupling component (5 mmoles) in a mixture of methanol (70 ml) and water (30 ml), and the ferricyanide solution is run into this at 25–30°, with stirring and cooling, during the course of 2–5 min. The dye is formed instantaneously. After 15 min the solution is diluted with water (250 ml), and the precipitated dye is filtered off, washed with water, and dried, in a vacuum over silica gel.

By this process 2-naphthol, for example, affords **1,2-dihydro-2-[3′-methyl-2′-(1′*H*)benzothiazolidinylidene]-2-naphthalenone** (crude yield 1.4 g, 88%; m.p. 237°), which on recrystallization from chlorobenzene forms fine red needles, m.p. 243–244°.

4. Other reactions

a. Introduction of amino groups[382]

Direct replacement of hydrogen by an amino group can be effected only in a few special cases but then has considerable preparative interest. Aminating agents requiring consideration are alkali amides, hydroxylamine, and *N*-halo amines.

In early work, Sachs[383] found that certain naphthalene derivatives, such as naphthylamines and naphthols, are aminated in the aromatic ring, preferentially at the 5-position, when melted with sodamide. This reaction, however, has greater importance for the preparation of amino derivatives of certain N-heterocycles.[384,385]

The best known example is Chichibabin' preparation of 2-pyridinamine[386] by heating of pyridine with sodamide in toluene or xylene at 120–150°. *N*,*N*-Dimethylaniline is an especially effective reaction medium.[387] Further amino groups can also be introduced, by using higher temperatures, leading to 2,6-pyridinediamine (150–180°, 82–90% yield[361]) and even to 2,4,6-pyridinetriamine.[387] Pyridine homologs such as 2-picoline[387,388] and quinoline derivatives[384] can also be aminated in good yield. The yields, however, are much lower if the sodamide is replaced by the sodio derivatives of primary or secondary amines.[389] Prerequisite for a smooth reaction is first-class quality of the sodamide; effective preparation of sodamide has

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[381] S. Hünig and K. H. Fritsch, *Ann. Chem.*, **609**, 143 (1957).

[382] P. Kovacic in G. A. Olah's "Friedel–Crafts and Related Reactions," Interscience Publishers, New York–London–Sydney, 1964, Vol. 3, Part 2, p. 1493.

[383] F. Sachs, *Ber. Deut. Chem. Ges.*, **39**, 3006 (1906).

[384] M. T. Leffler, *Org. Reactions*, **1**, 91 (1942).

[385] C. L. Deasy, *J. Org. Chem.*, **10**, 141 (1945).

[386] A. E. Chichibabin and O. A. Zeide, *J. Russ. Phys.-chem. Soc.*, **46**, 1216 (1914); *Chem. Abstr.*, **9**, 1901 (1915).

[387] Ger. Pat. 663,891; *Chem. Abstr.*, **33**, 175 (1939).

[388] E. D. Parker and W. Shive, *J. Amer. Chem. Soc.*, **69**, 63 (1947).

[389] K. Kovács and T. Vajda, *Chem. & Ind. (London)*, **1959**, 259.

been described several times,[384,390,391] as have the dangers of working with it.[390,392] For the amination of, in particular, quinoline and isoquinoline derivatives Bergstrom[393] found it preferable to use barium amide or potassium amide in liquid ammonia at room temperature.

The sodio derivatives of hydrazine or 1,2-dimethylhydrazine can be used in the same way as sodamide; thus Kauffmann and Schoeneck[394] obtained 2-pyridylhydrazine by heating pyridine in anhydrous hydrazine for 8 hours, the yield being about 40%. In the absence of free hydrazine hydrazo compounds are formed.[395]

Aromatic nitro compounds are comparable with pyridine derivatives in reactivity and can sometimes be aminated directly. 1-(4′-Nitro-1′-naphthyl)-piperidine was obtained from 1-nitronaphthalene and sodium piperidide (sodamide and piperidine).[396] Nitrobenzene and the alkali derivative of carbazole[397] or diphenylamine[398] gave the corresponding *p*-amino derivative, 9-(*p*-nitrophenyl)carbazole (70%) and 4-nitrotriphenylamine (45%). Huisgen and Rist[399] record the reaction of nitrobenzene with lithium piperidide.

Amination of aromatic nitro compounds often occurs smoothly and directly also on condensation with hydroxylamine in alkaline solution, the amino group normally entering *ortho* or *para* to the nitro group. One nitro group activates naphthalene derivatives sufficiently, but in the benzene series two are necessary to induce this reaction. 2-Nitro-1-naphthylamine was thus obtained (80%) from 2-nitronaphthalene,[400] and 4-nitro-1-naphthylamine (60%) from 1-nitronaphthylamine.[401] The amino group also enters the nitrated ring of quinoline derivatives.

Preparation of **6-nitro-5-quinolinamine**[402] will exemplify the technique: 6-Nitroquinoline (5 g) and hydroxylamine hydrochloride (6 g) are dissolved in hot 96% ethanol (90 ml) and allowed to cool whilst being shaken, so that the sparingly soluble nitroquinoline separates in very small crystals. Then 20% methyl-alcoholic potassium hydroxide (30 ml) is added in one portion at room temperature. Potassium chloride separates and after brief shaking the 6-nitroquinoline dissolves with a yellow coloration of the solution whilst the temperature rises within a few min by 20°. The nitroquinolinamine soon begins to separate and the solution sets to a crystalline mass. Luke-warm water (250 ml) is added and the whole is filtered. Drying the solid gives silky yellow needles (5.2 g, 94%), m.p. 272° (from much ethanol). The yellow hydrochloride is sparingly soluble in water.

Non-nitrated aromatic compounds can be directly aminated by hydroxylamine-*O*-sulfonic acid (aminyl hydrogen sulfate) or hydroxylammonium salts

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[390] H. Henecka in Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1952, Vol. 8, pp. 571–572; cf. G. Spielberger, *op. cit.*, Vol. 11, Part 1 (1957), p. 74.

[391] F. W. Bergstrom, *Org. Syn.*, Coll. Vol. III, 778 (1955).

[392] F. W. Bergstrom and W. C. Fernelius, *Chem. Rev.*, **12**, 43 (1933); **20**, 413 (1937).

[393] F. W. Bergstrom, *J. Amer. Chem. Soc.*, **56**, 1748 (1934); *Ann. Chem.*, **515**, 34 (1935); *J. Org. Chem.*, **2**, 411 (1938); **3**, 233, 424 (1939).

[394] T. Kauffmann and W. Schoeneck, *Angew. Chem.*, **71**, 285 (1959); cf. T. Kauffmann, J. Hansen, C. Kosel, and W. Schoeneck, *Ann. Chem.*, **656**, 103 (1962).

[395] T. Kauffmann, *Angew. Chem.*, **76**, 206 (1964).

[396] W. Bradley and R. Robinson, *J. Chem. Soc.*, **1932**, 1254.

[397] G. de Montmollin and M. de Montmollin, *Helv. Chim. Acta*, **6**, 94 (1923).

[398] F. W. Bergstrom, I. M. Granara, and V. Erickson, *J. Org. Chem.*, **7**, 98 (1942).

[399] R. Huisgen and H. Rist, *Ann. Chem.*, **594**, 159 (1955).

[400] J. Meisenheimer and E. Patzig, *Ber. Deut. Chem. Ges.*, **39**, 2533 (1906).

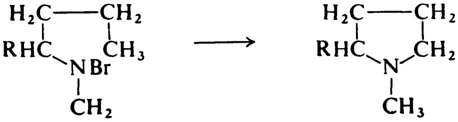
[401] C. C. Price and S.-T. Voong, *Org. Syn.*, Coll. Vol. III, 664 (1955).

[402] R. Huisgen, *Ann. Chem.*, **559**, 142 (1948).

in the presence of aluminum chloride,[403] but the importance of these reactions is restricted to special cases because their course is not unidirectional; toluene affords a mixture of toluidines in which the *ortho*- and *para*-compounds preponderate.[404]

Ring amination is achieved in high yield when aromatic compounds are treated with *N*-chlorodialkylamines either in concentrated sulfuric acid, hot or irradiated at 0°, or in the presence of Friedel–Crafts catalysts such as $AlCl_3$.[405]

The Hofmann–Löffler reaction, namely, cyclization of *N*-halo derivatives of secondary aliphatic amines,[406] is a method of intramolecular amination:



By the action of concentrated sulfuric acid on *N*-bromo-*N*-methylbutylamine and subsequent treatment with alkali Löffler[407] obtained 1-methylpyrrolidine, and he obtained 1-methyl-2-propylpyrrolidine analogously from the *N*-bromo derivative of *N*-methyl-1-propylbutylamine[408]

Coleman and Goheen[409] found it better to use *N*-chloro amines rather than the *N*-bromo compounds for synthesis of pyrrolidines and in this way achieved yields of around 75% of substituted pyrrolidines. The method has also proved valuable for synthesis of bicyclic tertiary amines.[410–412] Schmitz[413] applied it to *N,N*-dibromo derivatives of primary amines: from *N,N*-dibromo-1-propylbutylamine he obtained pyrrolizidine in 35% yield,[414] the best yields being obtained here, as in other cases,[412,415,416] when the reaction is carried out with irradiation in ultraviolet light. Recently ring closure was also achieved with *N*-monochloro derivatives of primary amines:[417] pyrrolidine (70%) was obtained from butylamine, 2-methylpyrrolidine (80%) from pentylamine, and 2-propylpyrrolidine (50% and 70%, respectively) from heptylamine or 1-propylbutylamine.[417] The mechanism of the Hofmann–Löffler reaction has been discussed by Wawzonek and Culbertson.[416]

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[403] R. N. Keller and P. A. S. Smith, *J. Amer. Chem. Soc.*, **66**, 1122 (1944); **68**, 899 (1946); P. Kovacic, R. P. Bennett, and J. L. Foote, *J. Amer. Chem. Soc.*, **84**, 759 (1962).

[404] P. Kovacic and R. P. Bennett, *J. Amer. Chem. Soc.*, **83**, 221 (1961); cf. P. Kovacic and J. L. Foote, *J. Amer. Chem. Soc.*, **83**, 743 (1961).

[405] H. Bock and K.-L. Kompa, *Chem. Ber.*, **99**, 1347, 1357, 1361 (1966).

[406] M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).

[407] K. Löffler and C. Freytag, *Ber. Deut. Chem. Ges.*, **42**, 3427 (1909).

[408] K. Löffler, *Ber. Deut. Chem. Ges.*, **43**, 2035 (1910).

[409] G. H. Coleman and G. E. Goheen, *J. Amer. Chem. Soc.*, **60**, 730 (1938).

[410] G. Menschikoff, *Ber. Deut. Chem. Ges.*, **69**, 1802 (1936).

[411] S. Wawzonek and P. J. Thelen, *J. Amer. Chem. Soc.*, **72**, 2118 (1950).

[412] S. Wawzonek, M. F. Nelson Jr., and P. J. Thelen, *J. Amer. Chem. Soc.*, **73**, 2806 (1951).

[413] E. Schmitz, *Angew. Chem.*, **73**, 23 (1961).

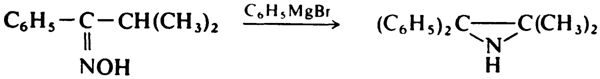
[414] E. Schmitz and D. Murawski, *Chem. Ber.*, **93**, 754 (1960).

[415] W. R. Hertler and E. J. Corey, *J. Org. Chem.*, **24**, 572 (1959).

[416] S. Wawzonek and T. P. Culbertson, *J. Amer. Chem. Soc.*, **81**, 3367 (1959).

[417] E. Schmitz and D. Murawski, *Z. Naturforsch.*, **17b**, 127 (1962); *Chem. Ber.*, **99**, 1493 (1966).

Finally a further method of cyclizing amination should be mentioned, in which oximes give oxirane derivatives under the action of Grignard reagents:[418,419]



$$C_6H_5-C(=NOH)-CH(CH_3)_2 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2C\overset{NH}{\text{——}}C(CH_3)_2$$

b. Introduction of ammonium groups

A hydrogen atom is replaced by an ammonium group when 1-4′-pyridylpyridinium salts are formed from pyridine and thionyl chloride. Since these salts are often applied to the preparation of 4-substituted pyridines that are hard to obtain by other methods,[241] the preparation of **1-4′-pyridylpyridinium chloride hydrochloride**[241] is described below:

A 1-l three-necked flask is fitted with a dropping funnel, KPG stirrer, and reflux condenser to which a calcium chloride tube is attached. In this, dry pyridine (300 ml) is treated with technical (!) thionyl chloride (900 g) with vigorous stirring; the internal temperature is easily maintained at about 20° by external cooling in running water and control of the rate of addition. When all the chloride has been added, the mixture is set aside at room temperature for three days. The excess of thionyl chloride is removed in a vacuum, the water-bath temperature being gradually raised to 110° and kept there for 2 h after removal of all the thionyl chloride. Boiling the solid residue in the flask with anhydrous methanol (ca. 200 ml) converts it into a homogeneous crystal slurry. Cooling to 0° and filtration gives a crude product which, when washed with a little ethanol and dried at 100°, has m.p. 145–148°; the yield at this stage is 260 g (60%). For further purification the crude product is dissolved in a little hot 2N-hydrochloric acid, and the filtered solution is treated several times with animal charcoal. Concentration in a vacuum and addition of alcohol affords almost colorless crystals which, when cooled, filtered off, washed with alcohol, dried, and recrystallized from methanol, have m.p. 151°. (For the mechanism of the reaction see Thomas and Jerchel.[241])

c. Introduction of diazo groups

Compounds, such as β-diketones, containing reactive methylene groups react with aromatic sulfonyl azides in the presence of bases, affording α-diazo compounds.[420,421]

2-Diazodimedone:[420] Dimedone (10 g) and triethylamine (7.3 g) are dissolved in ethanol (25 ml), cooled to 0°, and treated, with stirring, with *p*-toluenesulfonyl azide (14 g), whilst the temperature rises to 15–20°. 25 Minutes' stirring in the ice-bath yields a yellow crystal slurry, which is treated with ether (25 ml), left in the ice-bath for a further 15 min, and then filtered, affording a crude product (6.7 g) melting at 100–102°. A further amount (1.9 g) can be obtained by treating the filtrate with ether (200 ml), shaking this solution with potassium hydroxide (4 g) in water (200 ml), and drying and evaporating the ethereal solution. The total yield is 73%. Recrystallization from ethanol gives colorless needles, m.p. 108°.

Using half the above quantity of azide at the boiling point gives **2,2′-azodimedone** directly.

Sufficiently activated monoketones, such as benzyl phenyl ketone, are also converted into α-diazo ketones by sulfonyl azides.[422]

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[418] K. N. Campbell, B. K. Campbell, J. J. McKenna, and E. P. Chaput, *J. Org. Chem.*, **8**, 103 (1943); K. N. Campbell, B. K. Campbell, L. G. Hess, and I. J. Schaffner, *J. Org. Chem.*, **9**, 184, (1944).

[419] H. M. Kissman, D. S. Tarbell, and J. Williams, *J. Amer. Chem. Soc.*, **75**, 2959 (1953).

[420] M. Regitz, *Ann. Chem.*, **676**, 101 (1964); M. Regitz and D. Stadler, *Ann. Chem.*, **687**, 214 (1965); M. Regitz, *Chem. Ber.*, **99**, 3128 (1966).

[421] M. Regitz, *Angew. Chem. Int. Ed., Engl.*, **6**, 733 (1967).

[422] M. Regitz, *Chem. Ber.*, **98**, 1210 (1965).

d. Direct introduction of diazonium groups

Aromatic compounds can in many cases be converted directly into diazonium salts by means of nitrous acid and its derivatives:[423-428]

$$\mathrm{ArH + 2HNO_2 + HX \longrightarrow [ArN_2]^+X^- + 2H_2O + [2O]}$$

Nitroso compounds are formed as intermediates in this reaction. Yields from sulfonic acids, carboxylic acids, and nitro compounds, amongst others, are poor,[424] but those from tertiary amines and phenols are often very good,[423,426] although naphthols give only the nitroso derivatives; for example, yields are 70% from *N,N*-diethylaniline,[423] 96% from phenol,[426] 98% from *o*- or *m*-cresol,[426] 95% from chlorophenol,[426] and 75–85% from *o*-hydroxybenzenesulfonic acid; [428] the diazonium group enters *para* to the NR_2 or OH group.

Preparative value attaches to the **direct diazotization of phenols and heterocycles:**[429] For the preparation of hydroxybenzenediazonium salt solutions Tedder and Theaker[426] prescribe the use of very dilute aqueous solutions containing added acetone at 0° (or 20° for the less reactive phenols such as chloro- and nitrophenol), with a 14-fold excess of sodium nitrite and a 4-fold excess of hydrochloric acid (as 2N-HCl), the mixture being set aside for 20 h with exclusion of light.

e. Ehrlich–Sachs reaction*

Aromatic nitroso compounds are able to condense with numerous compounds containing reactive methylene groups; this, the Ehrlich–Sachs reaction,[430] affords Schiff bases, whence the corresponding carbonyl compound and amine can be obtained by hydrolysis:

$$\mathrm{RR'CH_2 + ONR'' \longrightarrow RR'C{=}NR'' \longrightarrow RR'C{=}O + H_2NR}$$

The methylene component may be provided by *β*-dicarbonyl compounds, phenyl- or cyano-acetic ester derivatives, nitrotoluenes, the methiodide of 1- or 3-picoline, etc.[430-435] (cf. page 424).

It is best to use an alkaline condensing agent such as an alkali hydroxide, sodium carbonate, pyridine, or an alkoxide.

***N*-(2,4-Dinitrobenzylidene)-*p*-(diethylamino)aniline:**[204] 2,4-Dinitrotoluene (91 g) and *N,N*-diethyl-*p*-nitrosoaniline (90 g) are dissolved in ethanol (ca. 500 ml) and heated under reflux for 5 h with crystalline sodium carbonate (150 g). After cooling, the product is filtered off and

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* Cf. p. 312.

[423] J. M. Tedder, *J. Chem. Soc.*, **1957**, 4003.

[424] J. M. Tedder and G. Theaker, *J. Chem. Soc.*, **1957**, 4008.

[425] J. M. Tedder, *J. Amer. Chem. Soc.*, **79**, 6090 (1957).

[426] J. M. Tedder and G. Theaker, *J. Chem. Soc.*, **1958**, 2573.

[427] J. M. Tedder and B. Webster, *J. Chem. Soc.*, **1960**, 3270.

[428] W. Rodionov and W. Matveev, *Ber. Deut. Chem. Ges.*, **57**, 1711 (1934).

[429] H. P. Patel, J. M. Tedder, and B. Webster, *Chem. & Ind.*, (*London*), **1961**, 1163.

[430] P. Ehrlich and F. Sachs, *Ber. Deut. Chem. Ges.*, **32**, 2341 (1899).

[431] F. Sachs, *Ber. Deut. Chem. Ges.*, **33**, 959 (1900); **34**, 494 (1901); F. Sachs and H. Barschall, *Ber. Deut. Chem. Ges.*, **34**, 3047 (1901); **35**, 1437 (1902); F. Sachs and E. Bry, *Ber. Deut. Chem. Ges.*, **34**, 118 (1901); F. Sachs and A. Röhmer, *Ber. Deut. Chem. Ges.*, **35**, 3307 (1902); F. Sachs and P. Becherescu, *Ber. Deut. Chem. Ges.*, **36**, 1132 (1903).

[432] A. Kaufmann and L. G. Valette, *Ber. Deut. Chem. Ges.*, **45**, 1736 (1912); **46**, 49 (1913).

[433] S. Skraup and K. Böhm, *Ber. Deut. Chem. Ges.*, **59**, 1007 (1926).

[434] F. Kröhnke, *Ber. Deut. Chem. Ges.*, **71**, 2583 (1928).

[435] F. Kröhnke, H. Leister, and I. Vogt, *Ber. Deut. Chem. Ges.*, **90**, 2792 (1957).

washed thoroughly with boiling water. The yield is 188 g (88%), and the m.p. is about 173° (dec.).

In some cases the condensation is such a violent reaction that it is preferable to mix the reactants portionwise or to add the condensing agent in very small portions. When reaction in an aqueous-alcoholic medium it unsatisfactory, it is better to use an anhydrous alcoholic solution containing an alkoxide.[311]

Azomethines are formed by way of addition products, RR′CH—NR″OH. In certain cases, however, these may be dehydrogenated by the nitroso compound to the nitrones, with simultaneous formation of azoxy compounds:[434,435]

$$\mathrm{RR'CH{-}NR''{-}OH + 2R''NO \longrightarrow RR'C{=}NR''(O) + R''N{=}NR''(O) + H_2O}$$

Formation of the nitrone can generally be prevented by using an excess of the methylene component. When a halogen atom is present on the methylene-carbon atom, nitrone may be formed without presence of an excess of the nitroso compound, since the primary adduct may be stabilized by loss of hydrogen halide, as occurs, for instance, in the reaction of 4-nitrobenzyl chloride with nitrosobenzene:[434]

$$\mathrm{NO_2C_6H_4CH_2Cl + ONR \longrightarrow NO_2C_6H_4CHCl{-}NR(OH) \longrightarrow}$$
$$\mathrm{NO_2C_6H_4CH{=}NR(O) + HCl}$$

II. Replacement of halogen by nitrogen

1. Reaction of halogen compounds with ammonia derivatives

a. Alkylation

Alkyl halides are the alkylating agents that come first to mind. As is well known, the iodides are the most reactive of such halides. Primary react more readily than secondary alkyl halides; tertiary alkyl halides are easily converted by amines into olefins, with loss of hydrogen halide. With vinyl halides the tendency to polymerization preponderates. Allyl halides, however, react normally, but with α-alkylated allyl halides the reaction with amines almost always involves an allylic rearrangement. Polar solvents accelerate alkylation; the solvents most used are water and alcohol, but benzyl alcohol and glycol ethers are also applied because of their higher boiling points. Acetonitrile and also nitromethane[436] have proved their worth for quaternizations with methyl iodide.

Treatment of ammonia or primary or secondary amines with alkyl halides almost always leads to a mixture of all the higher alkylation stages. Using an excess of the halide can thus afford the quaternary salt in one stage provided the formation of the hydrohalides is suppressed by addition of a base; nevertheless, alkylation of a tertiary base is preferable for preparation of quaternary salts.

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[436] F. G. Mann and J. Watson, *J. Org. Chem.*, **13**, 502 (1948).

It is essential to use a sufficient excess (at least ten-fold) of ammonia if primary amines are to be obtained in reasonable yield; the technique of working in liquid ammonia, proposed by von Braun,[437] also provides this excess. The ease with which the components can be separated out of the inevitable mixture naturally increases with increasing size of the alkyl group in the halide used, since this increases the differences in boiling point of the free bases. For this reason this method does not come into consideration for the first few members of the homologous monoalkylamines; but it also cannot be used for alkylamines containing very long chains as the requisite halides are then insoluble in liquid ammonia.[438]

Westphal and Jerchel[439] used alcoholic ammonia in a sealed tube but obtained mainly the secondary amine. Butylamine can be obtained in 47% yield by a somewhat involved procedure from butyl bromide and alcoholic ammonia at room temperature without the use of increased pressure.[440]

A series of ring-substituted primary phenethylamines has been prepared in 70–80% yield by a similar method: a solution of the requisite phenethyl bromide (15 g) in ethanol (500 ml) is saturated with ammonia at 5° and set aside for 5–8 days.[441]

Homologous ring-substituted α-methylphenethylamines can be prepared from the chlorides and alcoholic ammonia under pressure.[442] The following details are taken from a series of examples that include reaction with methylamine:

Benzedrine:[442] α-Methylphenethyl chloride (25 g) is dissolved in a saturated alcoholic solution of ammonia (450 ml containing 125 g/l) and heated in a shaking autoclave for 9 h at 160°. After cooling and filtration, the alcohol is distilled off and the residue is made alkaline with 6N-sodium hydroxide solution and extracted 4–5 times with benzene. The benzene solution is then shaken 3–4 times with 6N-hydrochloric acid (15-ml portions). The resulting solution of the hydrochloride is made alkaline with sodium hydroxide and extracted several times with benzene. Drying of the extracts over potassium carbonate and distillation afford benzedrine, b.p. 80–82°/11 mm (11.1 g, 51%).

Essentially the same difficulties arise when dihalides are treated with ammonia, but there is the further difficulty that the action of ammonia on α,ω-dihalides containing a chain of 4–6 carbon atoms readily results in ring closure; the N-heterocycles formed then rapidly react further, giving quaternary spirans.[437]

The most important method of preparing primary aliphatic amines is that due to Gabriel, in which the undesirable formation of secondary and tertiary amines is excluded.[443] It consists of treatment of potassium phthalimide with an alkyl halide and hydrolysis of the *N*-alkylphthalimide formed.

The procedure is capable of very wide variation. It can be applied to dihalides which may be treated with one or two equivalents of potassium phthalimide; almost all aliphatic halides react smoothly, even those of very

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[437] J. von Braun, *Ber. Deut. Chem. Ges.*, **70**, 979 (1937).

[438] J. von Braun and R. Klar, *Ber. Deut. Chem. Ges.*, **73**, 1417 (1940).

[439] O. Westphal and D. Jerchel, *Ber. Deut. Chem. Ges.*, **73**, 1002 (1940).

[440] F. C. Whitmore and D. P. Langlois, *J. Amer. Chem. Soc.*, **54**, 3441 (1932).

[441] J. H. Speer and A. J. Hill, *J. Org. Chem.*, **2**, 139 (1938).

[442] T. M. Patrick Jr., E. T. McBee, and H. B. Hass, *J. Amer. Chem. Soc.*, **68**, 1009 (1946).

[443] S. Gabriel, *Ber. Deut. Chem. Ges.*, **20**, 2224 (1887).

complex structure. When reactivity is slight it has proved a help to use a solvent such as acetone or, better, formamide, dimethylformamide, or acetamide.[444]

The substituted phthalimides can be cleaved by ca. 20% hydrochloric acid at the boiling point or in a sealed tube at higher temperatures; in some cases Posner's method may be used, in which the phthalimide is cleaved by potassium hydroxide solution to the phthalamic acid, whose hydrolysis is completed by hydrochloric acid.[445] The phthalimides are, however, more conveniently cleaved by short boiling with a stoichiometric amount of hydrazine hydrate in ethanol;[446] this gives the desired amine and phthalazone; the latter may be hydrolysed by hydrochloric acid. Carbonyl groups present in the *N*-alkyl group of a phthalimide may be protected as acetal from the hydrazine fission.[447] Phenylhydrazine is also useful for cleavage of phthalimido carboxylic acids.[448]

Phthalimido derivatives are stable and so can be used for further reactions, particularly when the *N*-alkyl group contains a substituent that can take part in a different reaction before the hydrolysis. For instance, if potassium phthalimide is treated with a halogenated acid chloride, the carbonyl-chlorine does not react; the product is a phthalimidoalkanoyl chloride, which can be treated with sodiomalonic ester or other alkali enolate, so that β-diketones or β-keto acids or, eventually, amino ketones can be obtained in this way. Subjecting phthalimido carbonyl chlorides to a Friedel–Crafts reaction with an aromatic compound gives alkylaryl amino ketones. Amino alcohols can also be obtained by Gabriel synthesis. Finally, the bromine atom of *N*-(bromoalkyl)phthalimides can be replaced by a thiol group through reaction with potassium hydrogen sulfide, the hydrolysis product then being an amino thiol.[449,450]

Potassium phthalimide:[451] Potassium hydroxide (7.6 g) in solution in 75% ethanol (30 ml) is added to a solution of phthalimide (20 g) in anhydrous ethanol (400 ml). The mixture is cooled rapidly, the precipitated potassium phthalimide is filtered off, and the filtrate is reheated. More phthalimide (20 g) is added, followed by potassium hydroxide (7.6 g) in 75% ethanol (30 ml), and the whole is cooled again and filtered. The potassium phthalimide is stirred with acetone, filtered off again, and dried in the air by gentle heat. The yield is 40–45 g. Considerable preparative advantage is gained by using pyridine as solvent.[452]

***N*-(2-Bromoethyl)phthalimide:**[449,cf.453] Potassium phthalimide (100 g) is heated with ethylene dibromide (300 g, 3 equivalents) under lively reflux with frequent shaking until, after about 7 h, a syrup has been formed. Unchanged ethylene dibromide is then removed in steam; the residual viscous mass solidifies on cooling under water. The water is decanted and the solid is dissolved in boiling 96% ethanol (ca. 150 ml), which is then filtered and allowed

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[444] J. C. Sheehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, **72**, 2786 (1950).

[445] T. Posner, *Ber. Deut. Chem. Ges.*, **26**, 1856 (1893).

[446] H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, **1926**, 2348.

[447] K. Balenović, N. Bregant, D. Cerar, D. Fles, and I. Jambresic, *J. Org. Chem.*, **18**, 297 (1953).

[448] I. Schumann and R. A. Boisonnas, *Nature*, **169**, 154 (1952); *Helv. Chim. Acta*, **35**, 2235 (1952).

[449] S. Gabriel, *Ber. Deut. Chem. Ges.*, **22**, 1137 (1889).

[450] S. Gabriel, *Ber. Deut. Chem. Ges.*, **24**, 1110 (1891).

[451] W. J. Hale and E. C. Britton, *J. Amer. Chem. Soc.*, **41**, 841 (1919).

[452] J. Reitmann in Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1952, Vol. 8, p. 658.

[453] P. L. Salzberg and J. P. Supniewski, *Org. Syn.*, **7**, 8 (1927).

to cool. When crystallization is complete the solid is collected, dried in the air (crude yield ca. 120 g), and extracted with boiling carbon disulfide (ca. 240 ml) which leaves a residue of *N,N'*-ethylenediphthalimide (about 8 g); the filtrate therefrom yields *N*-(2-bromoethyl)-phthalimide on cooling and a further amount on concentration of the mother-liquors. The total yield is 100 g (73%),[449] the m.p. is 79–80°, rising to 82–83° on recrystallization from dilute ethanol.[453]

2-Bromoethylamine:[454] *N*-(2-Bromoethyl)phthalimide (20 g) is heated with concentrated hydrobromic acid (*d* 1.49; 50–60 ml) in a bomb tube for 2 h at 180–200°. Cold water is added to the cooled product, residual phthalic acid is filtered off, and the filtrate is evaporated to dryness on a water-bath. The dark residue solidifies on cooling and is recrystallized from anhydrous ethanol (15–20 ml). 2-Bromoethylamine hydrobromide forms dense crystals on cooling, but these are accompanied by a fine powder; the latter is freed from mother liquor by decantation and crystallized again from ethanol. The hydrobromide, m.p. 155–160°, gives an unstable free base when treated with concentrated potassium hydroxide solution.

Cadaverine:[455] Molar amounts of 1-benzoylpiperidine and phosphorus pentachloride are warmed together in a distillation flask, the distillate is shaken with ice-water to destroy phosphorus oxychloride, and the resulting mixture of benzonitrile and 1,5-dichloropentane is dried over calcium chloride, mixed with an excess (2.5 moles, calculated on benzoylpiperidine) of potassium phthalimide, and heated rapidly to 190–200° with stirring in an open flask. The mixture melts to a brown viscous syrup, which is kept at 190–200° for 1-2 h and then allowed to cool. Next, unchanged potassium phthalimide is leached out with boiling water, and steam is passed through the residue, removing benzonitrile and unchanged 1,5-dichloropentane. The distillation residue is washed first with 50% and then with anhydrous ethanol, passing gradually into a pale powder, and this is boiled with not too little ethanol. After cooling, the crude product is collected, washed with a little alcohol, dissolved in hot chloroform, and reprecipitated by ethanol. This material is recrystallized from chloroform–ethanol and dried at 100°. This constitutes a 60–70% yield of *N,N'*-pentamethylenediphthalimide, m.p. 186°. This imide is heated with three times the amount of concentrated hydrochloric acid in a bomb tube at 200° for 2 h, filtered from the phthalic acid that separates on cooling, and evaporated to dryness on a water-bath. The residue is taken up again in water and evaporated until all the excess of hydrochloric acid is removed, and is finally washed with alcohol and ether. There results an almost quantitative yield of pure pentamethylenediamine dihydrochloride (cadaverine dihydrochloride), m.p. 255°.

Sometimes the separate preparation of potassium phthalimide can be dispensed with and the free imide can be treated with the halide in the presence of potassium carbonate. The following example of this procedure illustrates also the technique for cleavage by hydrazine.

Benzylamine:[446] An intimate mixture of phthalimide (300 g) and dry potassium carbonate (150 g) is heated with benzyl chloride (300 g, 20% excess) in an oil-bath for 3 h under reflux, whereafter the excess of benzyl chloride is removed in steam, and the *N*-benzylphthalimide is collected and washed with water (yield 360–375 g); the m.p. is 116° after recrystallization from glacial acetic acid.

For preparation of benzylamine the finely powdered *N*-benzylphthalimide is suspended in ethanol containing the theoretical amount of hydrazine hydrate. Warming causes separation of a gelatinous precipitate. This is decomposed by warming with an excess of hydrochloric acid; phthalhydrazide separates and is filtered off and washed with water. The alcohol is distilled off from the filtrate, which is then cooled, filtered from a small additional amount of phthalhydrazide, and made alkaline. This affords benzylamine which is removed in ether, dried over potassium hydroxide, and fractionated; this gives a 90–95% yield of amine, b.p. 185–187°.

Sörensen[456] has built on the basis of Gabriel's method a synthesis of α-amino acids whose first step is the preparation of diethyl phthalimidomalonate:[456,457]

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[454] S. Gabriel, *Ber. Deut. Chem. Ges.*, **21**, 566 (1888).

[455] J. von Braun, *Ber. Deut. Chem. Ges.*, **37**, 3583 (1904).

[456] S. P. L. Sörensen, *Compt. Rend. Trav. Lab. Carlsberg*, **6**, 1 (1903).

[457] A. E. Osterberg, *Org. Syn.*, **7**, 78 (1927).

Diethyl bromomalonate (210 g) is heated with potassium phthalimide (165 g) in an oil-bath at 100–120° until reaction sets in; this then continues spontaneously to completion. Cold water leaches potassium bromide and unchanged potassium phthalimide from the cooled products. The residue is dried and recrystallized first from benzene and then from anhydrous ethanol, affording **diethyl phthalimidomalonate** (70–80%), m.p. 74°.

Alkyl groups can be introduced in phthalimidomalonic esters by way of the sodio derivative. Hydrolysis then leads to α-amino carboxylic acids through various intermediates. A good synthesis of asparagine, for example, is described in *Organic Syntheses.*[458] Other examples are syntheses of lanthionine and ethionine,[459] also of kynurenine.[460]

According to Sörensen,[461] various precautions must be taken when preparing **diethyl phthalimidosodiomalonate.** The sodio derivative must not separate either as a gel or in large crystals: gelatinous products cannot be separated from an excess of alcohol without decomposition, and coarsely crystalline products are relatively unreactive.

Ethanol (80–100 ml), freshly, distilled from sodium, is placed in a 500-ml round-bottomed flask fitted with a reflux condenser and a calcium chloride tube, and sodium (4.6 g) is dissolved therein. This solution is treated at 60–70° with somewhat more than the calculated amount (62–63 g) of completely dry diethyl phthalimidomalonate, which dissolves to a yellow solution on shaking. If the temperature is kept within the stated limits the yellow crystalline sodio derivative soon begins to separate; continuous shaking and suitable cooling are used to ensure complete separation in as fine a crystalline form as possible. Then the alcohol is distilled off in a vacuum, with extreme precautions to exclude moisture, the bath temperature being finally raised to 140°. The last traces of alcohol are removed by introduction of dry air free from carbon dioxide and repeated evacuation.

ω-Amino acids can be prepared similarly: potassium phthalimide is first caused to react with an α,ω-dihalide and then the second halogen atom is caused to react with sodiomalonic ester. Emil Fischer[462] obtained ornithine in this way. Two amino groups can be introduced simultaneously, by starting with dihalo carboxylic acids; formamide is a particularly good solvent to use in this reaction. Sheehan and Bolhofer[444] converted 2,5-dibromoadipic acid into the corresponding diphthalimido acid (90%) and thence by hydrolysis with hydrogen bromide in glacial acetic acid into 2,5-diaminoadipic acid (91%).

Reaction with tetrachlorophthalimide has proved valuable for identification of alkyl halides and sulfonates because the alkylimides of this series have characteristic melting points.[463]

A further synthesis of primary aliphatic amines was developed by Delépine;[464] he alkylated urotropine to the monoquaternary salt and cleaved that by alcoholic hydrochloric acid. Chlorides and bromides often react very slowly with urotropine, but they can be converted *in situ* into the iodides by adding an equivalent amount of sodium iodide.

Galat and Elion[465] give a **simplified urotropine method,** which however often involves long periods of waiting (a few hours to several weeks) for complete separation of the quaternary urotropine salt. Yields are good.

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[458] M. S. Dunn and B. W. Smart, *Org. Syn.*, **30**, 7 (1950).

[459] R. Kuhn and G. Quadbeck, *Ber. Deut. Chem. Ges.*, **76**, 527, 529 (1943).

[460] A. Butenandt, W. Weidel, R. Weichert, and W. von Derjugin, *Z. Physiol. Chem.*, **279**, 27 (1943).

[461] S. P. L. Sörensen, *Z. Physiol. Chem.*, **44**, 454 (1905).

[462] E. Fischer, *Ber. Deut. Chem. Ges.*, **34**, 454, 2900 (1901).

[463] C. F. H. Allan, W. R. Adams, and C. L. Myers, *Anal. Chem.*, **37**, 158 (1965).

[464] M. Delépine, *C. R. Heb. Séances Acad. Sci.*, **120**, 501 (1895); **124**, 292 (1897); *Bull. Soc. Chim. France*, [iii], **17**, 290 (1897); [iv], **31**, 108 (1922).

[465] A. Galat and G. Elion, *J. Amer. Chem. Soc.*, **61**, 3585 (1939).

Urotropine (1 mole) is dissolved in 8–10 times its weight of hot 95% ethanol and treated slowly with sodium iodide (1 mole) and then with the alkyl chloride or bromide (1 mole). When precipitation is complete, the mixture is saturated with gaseous hydrogen chloride, whereupon the precipitate redissolves and ammonium chloride is precipitated. This is removed, the alcohol is distilled off from the filtrate, and the residue therefrom is treated with an excess of alkali; the liberated amine is distilled.

The urotropine method provides a convenient route to α-amino ketones.

ω-Aminoacetophenone:[466] Equimolar amounts of ω-chloroacetophenone and urotropine in chloroform give an approximately 60% yield of the quaternary salt, m.p. 145°, in 12 h at room temperature.

A cold mixture of 38% hydrochloric acid (30 ml) and ethanol (240 ml) is poured over the finely powdered quaternary salt (30g), and the mixture is set aside with occasional shaking for 3 days. Then the ammonium chloride is filtered off and the filtrate is evaporated to dryness in a vacuum. The residue is dissolved in hot water (4 ml); on cooling, the hydrochloride, m.p. 186–187° (9–10 g), crystallizes and a further amount (2–3 g) can be obtained from the mother-liquor.

This method has also found application in the synthesis of amino acids,[467,468] *p*-(aminoalkyl)benzoic acids,[469] and amines containing heterocyclic substituents.[470,471] For example, β-alanine was obtained in 85% yield from 3-bromopropionic acid.[468]

For the preparation of secondary and tertiary amines by monoalkylation of, respectively, primary and secondary amines by alkali halides there are as few satisfactory prescriptions in the literature as there are for the reaction with ammonia. The main difficulties have been mentioned above.

N-Alkyl- and *N*,*N*-dialkyl-phenethylamines are obtained in good to excellent yield when phenethyl bromide (1 mole) is heated with a primary (5 moles) or secondary (3 moles) amine, respectively, for 6–8 h at 100°;[441] and *N*-alkylallylamines are formed in good yield by treatment of allyl chloride with a large excess of an alkylamine under pressure.[472]

The preparation of 2-(diethylamino)ethanol from ethylene chlorohydrin and diethylamine (about 70% yield) is described in *Organic Syntheses*.[473]

Mention should also be made of the alkylation of diethylamine by isopropyl bromide, which cannot be effected in absence of a solvent at atmospheric pressure but occurs with astonishingly good yields in glycerol or ethylene glycol.[474] Isopropyl bromide (123 g), diethylamine (94.9 g), and glycerol (50 g) are boiled together under reflux for 72 h; the mixture is made alkaline and the liberated amine is dried over potassium hydroxide and fractionally distilled; this gives ***N*,*N*-diethylisopropylamine,** b.p. 108°, in 60% yield (67 g).

Primary aromatic amines are alkylated somewhat more cleanly; *e.g.*, *N*-benzylaniline is obtained in 95% yield from benzyl chloride and 4 equivalents of aniline in the presence of 1.25 equivalents of sodium hydrogen carbonate;[475] with a smaller excess of aniline the tertiary base becomes the main product.

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[466] C. Mannich and F. L. Hahn, *Ber. Deut. Chem. Ges.*, **44**, 1542 (1911).

[467] A. Baniel, M. Frankel, I. Friedrich, and A. Katschalsky, *J. Org. Chem.*, **13**, 791 (1948).

[468] N. L. Wendler, *J. Amer. Chem. Soc.*, **71**, 375 (1949).

[469] F. F. Blicke and W. M. Lilienfels, *J. Amer. Chem. Soc.*, **65**, 2281 (1943).

[470] F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, **64**, 477 (1942).

[471] H. Keskin, C. D. Mason, and F. F. Nord, *J. Org. Chem.*, **16**, 1333 (1951).

[472] J. Falbe, H.-J. Schulze-Steinen, and F. Korte, *Chem. Ber.*, **98**, 1923 (1965).

[473] W. W. Hartman, *Org. Syn.*, Coll. Vol. II, 183 (1943).

[474] S. Caspe, *J. Amer. Chem. Soc.*, **54**, 4457 (1932).

[475] F. G. Willson and T. S. Wheeler, *Org. Syn.*, **8**, 38 (1928).

It is often unnecessary to use a condensing agent. Hickinbottom[476] prepared monoalkylanilines in about 75% yield by boiling propyl, isopropyl, and butyl bromide for several hours with 2.5–4 times the quantity of aniline; to separate the excess of aniline from the resulting mixture of bases, an aqueous solution of zinc chloride is added, for this gives a water-resistant complex only with the primary amine; this complex can thus be filtered off after some hour's storage.

Secondary amines may be isolated from mixed amine products by separation as nitrosoamines. Erdmann's preparation of ***N*-ethylaniline**[477] will serve as an example:

Aniline (100 g) and ethyl bromide (130 g) are heated together under gentle reflux for 1 to 2 h. The mixture sets almost completely solid on cooling; it is dissolved in water and freed from a small amount of ethyl bromide by boiling. Then 20% sodium hydroxide solution (300 ml) is added, the oily layer of bases is separated, the aqueous solution is extracted with ether which is then added to the main portion of bases and evaporated on the water-bath. The residue is dissolved in a mixture of concentrated hydrochloric acid (200 ml) and water (1 l), thoroughly cooled in ice, and treated with sodium nitrite (60 g). *N*-Ethyl-*N*-nitrosoaniline separates as a dark oil which is taken up in ether. Unchanged aniline is converted into benzenediazonium chloride in the aqueous solution, but, as insurance, the ethereal extract may be shaken with dilute sodium hydroxide solution. Then the ether is removed and the oily residue is added to a solution of tin(II) chloride (350 g) in concentrated hydrochloric acid (400 ml), with cooling by water if necessary. The solution is then made alkaline with sodium hydroxide solution, steam is passed in, and the volatile *N*-ethylaniline is taken up in ether. The ethereal extract is dried over potassium hydroxide and on distillation gives the product (40–50 g), b.p. 205°. When pure, *N*-ethylaniline gives no color with bleaching powder.

The same principle was used more recently for monoalkylation of *m*-toluidine in good yield.[478] For the preparation of monoalkylarylamines free from the tertiary product see also pages 455 and 496.

Primary aliphatic[479] and aromatic amines[480–482] may undergo ring closure on reaction with α,ω-dihalides, affording *N*-alkylated and *N*-arylated heterocycles, respectively. When the formation of α,ω-diamines is regarded as a side reaction to be avoided, it is best to use equivalent amounts of amine and dihalide together with 1 equivalent of sodium carbonate.[482,483]

1-*o*-Tolylpiperidine:[482] A mixture of *o*-toluidine (10.7 g, 0.1 mole), pentamethylene dibromide (23 g, 0.1 mole), and anhydrous sodium carbonate (10.6 g, 0.1 mole) in toluene (30 ml) is stirred and heated under reflux for 24 h. Then the toluene solution is decanted and the residue is dissolved in water, made strongly alkaline with sodium hydroxide, and extracted with toluene. The united toluene solutions are distilled. Repeated fractionation in a vacuum gives a product (10.3 g, 59%), b.p. 65–66°/0.6 mm.

Complications arising during alkylation of amines owing to hydrohalide formation can often be very simply avoided by adding a sterically hindered amine to bind the acid, since such amines cannot be alkylated. 1,1′,1″-

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[476] W. J. Hickinbottom, *J. Chem. Soc.*, **1936**, 992.

[477] H. Erdmann, "Anleitung zur Darstellung organischer Präparate," Ferdinand Enke Verlag, Stuttgart, 1894, p. 428.

[478] J. S. Buck and C. W. Ferry, *Org. Syn.*, Coll. Vol. II, 290 (1943).

[479] R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949).

[480] J. von Braun, *Ber. Deut. Chem. Ges.*, **37**, 3210 (1904).

[481] M. Scholtz and E. Wassermann, *Ber. Deut. Chem. Ges.*, **40**, 852 (1907).

[482] A. H. Sommers and S. E. Aaland, *J. Amer. Chem. Soc.*, **75**, 5280 (1953).

[483] J. Sauer, R. Huisgen, and A. Hauser, *Chem. Ber.*, **91**, 1461 (1958).

Nitrilotri(propan-2-ol) (triisopropanolamine) is especially suitable for this purpose.

***N,N*-Dibutylaniline:**[484] Aniline (9.3 g, 0.1 mole), butyl bromide (30.14 g, 0.22 mole), and 1,1′,1″-nitrilotri(propan-2-ol) (57.3 g, 0.3 mole) are stirred and heated under reflux with rigorous exclusion of moisture at such a temperature that moderate refluxing of butyl bromide can be seen (100–110°). After 2 h, no refluxing butyl bromide can be seen even though the temperature has been raised gradually to 180°. The mixture is, however, kept at this temperature for a further 2 h, but then twice its volume of water is added with vigorous stirring. The resulting suspension deposits the crude product as an oil when kept for 2 h in a separatory funnel. A further small amount of product is obtained by stirring in more water and then potassium hydroxide (17 g, 0.3 mole) and a little ether. The combined crude products are washed with water, dried over potassium hydroxide and potassium carbonate, and distilled through a spinning band column, giving *N,N*-dibutylaniline (18.5 g), b.p. 151°/15 mm. The distillation residue contains a further 0.9 g, the total yield being 95%.

Exclusively secondary amines are obtained by alkylation and subsequent hydrolysis of acylated primary amines. The process is analogous to the Gabriel synthesis but not so universally applicable. The strongly acidic character of the amide-hydrogen atom and the need to avoid *O*-alkylation make it necessary to use the alkali derivatives. The older procedures direct metallic sodium for formation of the amide-alkali compounds.

As illustration Thielepape's directions for ***N*-methylacetanilide** are reproduced:[485] Sodium (11.5 g) is pressed as wire into dry benzene (400 ml) in a 2-l flask, the acetanilide (67.5 g) is added, and the mixture is warmed to dissolve the anilide. Vigorous evolution of hydrogen soon occurs and a white granular sodium salt is formed, this process being completed by 2 hours' stirring under vigorous reflux. Methyl iodide (80 g) is added in portions; the mixture is warmed for 1 h, then cooled and shaken with water (100 ml). The benzene solution is dried over sodium sulfate and concentrated (not quite to dryness); when cooled, it then yields *N*-methylacetanilide (60 g, after washing with 20 ml of benzene); a further amount (13.3 g) can be obtained from the mother liquor and washings, making a total yield of 98.3%. After recrystallization from light petroleum the product has m.p. 100° (corr.).

p-Methoxy-*N*-methylacetanilide is obtained analogously in 96% yield.

Metalation of *N*-acetyl-2-naphthylamine requires a somewhat higher temperature. For preparation of ***N*-methyl-2-naphthylamine**[486] the acetyl amine is boiled with the calculated amount of sodium in toluene. An equimolar amount of methyl iodide is added without isolation of the sodium salt; sodium iodide separates and is filtered off. The toluene solution is then boiled with dilute hydrochloric acid; the toluene is then extracted with ether, and the aqueous solution is made alkaline. The oil that separates distils in a vacuum at 165–170°/12 mm (yield 55%).

Attempts have been made[487] to replace the sodium by sodium hydride, but with only limited success. More recently[488] it has been shown that it is quite unnecessary to prepare the alkali derivative of the amide if acetone is used as solvent and an excess of potassium hydroxide is added; even amines that do not react with sodium hydride give good yields in this way.

***N*-Methyl-*p*-nitroacetanilide:** *p*-Nitroacetanilide (5 g) is dissolved in warm acetone (100 ml) and treated with powdered potassium hydroxide (6 g). A solution of methyl iodide (6 g) in acetone (15 ml) is then added with heating to give moderate reflux. After 1 min the mixture is filtered and the filtrate is concentrated, diluted with water, and cooled, giving 4.36 g of 81%-pure product, m.p. 153–154°; a further 0.67 g is obtained from the mother liquor.

Other amides require somewhat longer heating.

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[484] S. Hünig and M. Kiessel, *Chem. Ber.*, **91**, 380 (1958).

[485] E. Thielepape, *Ber. Deut. Chem. Ges.*, **68**, 751 (1935).

[486] R. Pschorr and W. Karo, *Ber. Deut. Chem. Ges.*, **39**, 3140 (1906).

[487] W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

[488] I. J. Pachter and M. C. Kloetzel, *J. Amer. Chem. Soc.*, **74**, 1321 (1952).

In early work Pictet and Crépieux[489] alkylated formanilide in the presence of alcoholic potassium hydroxide and obtained monoalkylanilines (methyl to pentyl) by hydrolysis (short warming with alcoholic potassium hydroxide or concentrated hydrochloric acid).

N-Alkylsulfonamides react more smoothly and more readily than the less strongly acidic carboxamides.[490] This difference is very evident in the following experiment where sulfonated and acetylated ethylenediamine becomes methylated only on the sulfonamide-nitrogen atom.

***N*-Methylethylenediamine:**[491] *N*-Acetylethylenediamine is prepared by keeping a mixture of ethyl acetate (528 g) and 70% aqueous ethylenediamine (1550 g) until homogeneous (several days) and then fractionating the mixture twice; the monoacetyl derivative has b.p. 125–130°/5 mm and is obtained in 60% yield (365 g).

To a solution of the acetyl derivative (306 g) in an equal weight of water are added simultaneously, but slowly and with stirring, benzenesulfonyl chloride (530 g) and 10% aqueous sodium hydroxide (1200 g). After several hours the mixture is acidified and the precipitated amide is collected. For recrystallization this is dissolved in diluted ethanol and filtered hot from small amounts of disulfonyl derivative; separation of the product as an oil can be avoided by using a sufficient amount of the solvent; the yield is 500 g (70%), and the m.p. 103° (corr.).

For methylation, *N*-acetyl-*N'*-(benzenesulfonyl)ethylenediamine (121 g) is dissolved in one equivalent of boiling alcoholic potassium hydroxide (35 g of 85% KOH in 200 ml of ethanol), methyl iodide (142 g) is dropped in during 15 min, and the whole is boiled for 2 h. After cooling, the precipitated potassium iodide (about 60 g) is filtered off and the methyl iodide and ethanol are removed in steam.

The residual methylated amide is hydrolysed by boiling concentrated hydrochloric acid (500 ml) in 12 h under reflux; more acid is occasionally added during this process. Then the hydrolysate is evaporated almost to dryness. Solid sodium hydroxide is added and the amine is distilled out of the concentrated aqueous solution. Solid sodium hydroxide is added to the distillate, and the amine that separates is dried over fresh sodium hydroxide and then by refluxing over metallic sodium. Finally, fractionation through a column affords 80% (28 g) of monomethylethylenediamine, b.p. 115–116°.

Cleavage of sulfonamides[492] generally needs more energetic conditions than even for carboxamides; it is effected either by many hours' refluxing with concentrated hydrochloric acid or, better, heating in a bomb tube at about 150°, or by prolonged heating with concentrated sulfuric acid. Toluenesulfonamides are said to be very smoothly cleaved by 2-3 hours' heating with chlorosulfonic acid at 130–150°;[493] these particular amides are also cleaved reductively by sodium in boiling butanol or by zinc and hydrochloric acid.[494] This reductive cleavage is so convenient that an example follows:

***N*-Methylallylamine:**[495] To powdered potassium hydroxide (43.29) under a little ethanol are added *N*-methyl-*p*-toluenesulfonamide (143 g) and then allyl chloride (85 g); the mixture spontaneously comes to the boil (reflux!). When the reaction slackens and most of the alkali has dissolved, the mixture is heated for 6 h on a steam-bath. Then the alcohol and allyl chloride are distilled off and the residual oil is decanted from the salt and distilled, giving *N*-allyl-*N*-methyl-*p*-toluenesulfonamide (155 g, 89%), b.p. 190–193°/12 mm, n_D^{20} 1.5340.

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[489] A. Pictet and P. Crépieux, *Ber. Deut. Chem. Ges.*, **21**, 1106 (1888).
[490] O. Hinsberg, *Ann. Chem.*, **265**, 178 (1891).
[491] S. R. Aspinall, *J. Amer. Chem. Soc.*, **63**, 852 (1941).
[492] S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).
[493] W. Marckwald and A. von Droste-Hülshoff, *Ber. Deut. Chem. Ges.*, **31**, 3261 (1898).
[494] D. Klamann and G. Hofbauer, *Chem. Ber.*, **86**, 1246 (1953).
[495] A. W. Weston, A. W. Ruddy, and C. M. Suter, *J. Amer. Chem. Soc.*, **65**, 674 (1943).

To a boiling solution of the preceding allylmethylamide (45 g) in butan-1-ol (500 ml), sodium (46 g in small pieces) is gradually added, and the mixture is then heated under reflux for 1 h. When cold, the solution is treated with water and is distilled into hydrochloric acid until the material that distils is neutral. The distillate is evaporated to dryness in a vacuum, then treated with concentrated sodium hydroxide solution, and the amine is distilled off; it has b.p. 65°, n_D^{20} 1.4065, and the yield is 48% (6.7 g).

Another unequivocal method of converting primary into secondary amines involves intermediate formation of Schiff bases and their quaternization. The quaternary salts are obtained almost quantitatively by heating the base with a lower alkyl halide in a sealed tube for several hours; they are readily hydrolysed to the secondary amine. Benzaldehyde is usually taken to form the Schiff base. A number of *N*-alkyl-β-methylphenethylamines have been prepared in excellent yield by this route.[496] Also the allylmethylamine described above was obtained from allylamine in 71% yield by way of the anil.[497]

For the preparation of **N-methylnonylamine** this method proved the only practicable one:[498] Nonylamine (9 g; b.p. 85°/13 mm) is heated with benzaldehyde (7 g) for 1 h on a water-bath and the anil is distilled off in a vacuum (b.p. 179°/14 mm). The anil obtained (13.6 g) is sealed with methyl iodide (8.4 g), set aside for 1 h and then heated for 3 h in a water-bath. The quaternary salt is precipitated as a deep red, viscous oil; it is kept in 90% ethanol (40 ml) for 1 h on a water-bath, after which the alcohol is distilled off, the residue is acidified, and the benzaldehyde is extracted with ether. Treating the acid solution with base liberates the amine, which is separated and distilled (b.p. 95°/14 mm; 6.6 g).

Secondary amines can occasionally be prepared by alkylation of cyanamide and hydrolysis of the product, and it is an advantage that the cheap commercial calcium cyanamide may be used as starting material.

Dibenzylamine:[499] Finely ground, commercial calcium cyanamide (14.6 g; 50% $CaCN_2$ content) is suspended in 70% alcohol (100 ml), treated with benzyl chloride (25.3 g), and heated under reflux for 12 h. The solid material is then filtered off and washed with alcohol, and the filtrate is saturated with gaseous hydrogen chloride and then heated in an autoclave at 140° for 4–5 h. Dibenzylamine hydrochloride separates as large plates (13 g, 55%).

Vliet[500] similarly obtained 52–56% of diallylcyanamide which was hydrolysed to diallylamine in about 85% yield by dilute sulfuric acid.

There is rarely any difficulty in quaternizing tertiary amines by alkyl halides unless the amine is insufficiently basic or sterically hindered. Equimolar amounts of the tertiary amine and halide, best in methanol or acetone, usually afford very good to quantitative yields often in the cold and otherwise under reflux. The products are isolated by concentration of the solution and treatment with ether.

Some recent papers[501,502] have been concerned with the preparation of simple quaternary ammonium salts containing differing groups. The varied preparative uses of 1-alkylpyridinium salts[503] may be noted.

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[497] A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, **1950**, 1478.

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[502] E. Grovenstein Jr., E. P. Blanchard Jr., D. A. Gordon, and R. W. Stevenson, *J. Amer. Chem. Soc.*, **81**, 4842 (1959).

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Halo derivatives of ketones, aldehydes, ethers, and carboxylic acids are stronger alkylating agents than are the simple alkyl halides.

Alkylation by α-halo ethers is of preparative interest only in special cases and is often accompanied by side reactions, *e.g.*, loss of hydrogen halide. The subject has been reviewed several times.[504]

With halo ketones and aldehydes it must be remembered that ammonia and primary amines may also react with the carbonyl group, but side reactions of that type can often be prevented by use of the acetal.

Aminoacetaldehyde diethyl acetal was obtained in 74% yield by heating a methanolic solution of chloroacetaldehyde diethyl acetal with 18 equivalents of anhydrous ammonia in a pressure vessel at 140° for 10 h.[505] 2-Amino- and 2-(methylamino)-propionaldehyde diethyl acetal were prepared in 55 %and 40 % yield, respectively, under similar conditions.[506] Aromatic amines are best brought to this reaction as *N*-metal derivatives.

However, for alkylation of secondary and tertiary amines by halo ketones or aldehydes it is often unnecessary to protect the carbonyl group.

Alexander[507] obtained **2-(dimethylamino)isobutyraldehyde** by dropping the 2-bromo aldehyde (40 g) into a cooled 35% aqueous solution (300 g) of dimethylamine, whilst the temperature was kept below 10°. One day later the solution was extracted with ether, and the extract was dried over magnesium sulfate and distilled through a column. The product (9.9 g, 32%) had b.p. 126–129°.

The preparation of **(dimethylamino)acetone** was described by Zaugg and Horrom[508] as follows: Chloroacetone (46.3 g), dissolved in dry ether (100 ml) was dropped, with stirring, during 15 min into a dry ethereal solution (1 l) of dimethylamine (45 g) at 2–10°. The mixture was stirred for 7 h at room temperature and set aside for 3 days. The precipitated dimethylamine hydrochloride was filtered off and washed with ether, and the filtrate and the wash liquor were dried over magnesium sulfate and evaporated. Fractionation of the residue gave the amino ketone, b.p. 35–36°/25 mm, n_D^{20} 1.4128, in 74% yield (37.5 g).

A series of other amino ketones was prepared in good yield, in some cases with warming.[509–511]

Alkylation by a halogenated nitrile will be exemplified by the preparation of **4-piperidinobutyronitrile:**[7]

A mixture of dry benzene (500 ml) and chloroform (100 ml) containing piperidine (600 g, 7 moles) is brought to the boil in a 5-l flask fitted with a stirrer, reflux condenser, and dropping funnel; 4-chlorobutyronitrile (310 g, 3 moles) is added during 30 min. The whole is heated under reflux for 5 h, then set aside overnight and filtered from the precipitated piperidine hydrochloride, which is washed with ether. The wash ether and the chloroform–benzene solution are united and distilled through a column until the temperature reaches 108°. The residue is cooled and more piperidine hydrochloride (total yield 350 g, 96%) is filtered off and washed with ether. This filtrate and the wash ether are then distilled, yielding 4-piperidinobutyronitrile (393 g, 86.2%), b.p. 129–131°/25 mm, n_D^{20} 1.4653.

4-Bromobutyronitrile and diethylamine give analogously 86% of 4-(diethylamino)butyraldehyde, b.p. 101–103°/21 mm, n_D^{20} 1.4351.

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[504] L. Summers, *Chem. Rev.*, **55**, 326 (1955); H. Baganz, *Angew. Chem.*, **71**, 366 (1959); H. Gross and E. Höft, *Z. Chem.*, **4**, 401 (1964).

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[511] R. C. Elderfield and C. Ressler, *J. Amer. Chem. Soc.*, **72**, 4059 (1950).

Clark and Mosher[512] obtained a 96.7% yield of 4-(diethylamino)butyronitrile from 4-bromobutyronitrile after addition of 0.05 mole-% of sodium iodide which aided reaction. Yields are usually lower from reactions in absence of a solvent,[513] but 90% of 6-(diethylamino)hexanenitrile, b.p. 102–102.5°/4 mm, was obtained from 6-bromohexanenitrile.[514]

Amino acids have often been prepared by treating halo aliphatic acids with ammonia. Occasionally a surprisingly large excess of ammonia has been used, but Fischer obtained good yields by short heating in a sealed tube with only the five-fold amount of ammonia.[515]

Alanylglycine:[515] *N*-(2-Bromopropionyl) glycine was heated with the five-fold amount of 25% aqueous ammonia in a sealed tube at 100° for 20 min. The solution was evaporated, ethanol was added, and evaporation repeated to remove all the water. When the residue was treated with hot anhydrous ethanol (60 ml/5g of starting material) the ammonium bromide all gradually dissolved. The residual dipeptide was dissolved in the smallest possible amount of hot 50% ethanol, and the solution was filtered and treated with anhydrous ethanol tot incipient turbidity. The product crystallizes slowly in short needles, m.p. ca. 228° (dec.) (87%).

Yields are usually less good on ammonolysis of simple halo aliphatic acids and then a large excess of ammonia appears desirable. Cheronis and Spitzmueller[516] found adding ammonium carbonate assisted formation of primary amino acids and gave directions for preparation of α-amino acids with 2–6 carbon atoms; details are illustrated in the following example.

2-Aminobutyric acid:[516] Ammonium carbonate (450 g, 8 moles of NH_3) is warmed to 55° with water (140 ml), cooled to 40°, and treated with aqueous ammonia (410 ml, 6 moles of NH_3). Still at this temperature 2-bromobutyric acid (167 g) is added gradually during 30 min. The whole is set aside for 24 h at 40–50°, then ammonia and carbon dioxide are removed on the water-bath, after which the solution is concentrated in an evaporating dish until the amino acid separates. After cooling, this product is filtered off and washed twice with a little methanol. Evaporation of the filtrate to 125 ml and addition of methanol (250 ml) give a second fraction. The total yield of pure amino acid is 59–62 g (57–60%).

For synthesis of amino acids from halo aliphatic acids and liquid ammonia a paper by Sisler and Cheronis[517] should be consulted.

N-Alkylated amino acids can be obtained analogously from halo aliphatic acids and alkylamines. For instance, keeping 5 g of L-2-bromopropionic acid in 15 ml of 33% aqueous methylamine solution for 2 days afforded 71% of L-*N*-methylalanine.[518] Alkylation of sulfonamido derivatives, mentioned above, can also be applied to the synthesis of alkylamino acids:[518,519] Fischer and Lipschitz[519] synthesized *N*-methylleucine from leucine by preparing and methylating the *N*-tosyl derivative.

The presence of ammonium salts either formed or added often makes it difficult to isolate free amino acids; their separation is aided by esterification.

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[517] H. H. Sisler and N. D. Cheronis, *J. Org. Chem.*, **6**, 467 (1941).

[518] E. Fischer and L. von Mechel, *Ber. Deut. Chem. Ges.*, **49**, 1335 (1916).

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[520] N. J. Leonard and W. V. Ruyle, *J. Amer. Chem. Soc.*, **71**, 3094 (1949).

Ethyl 2-(methylamino)butyrate:[520] A mixture of 2-bromobutyric acid (56 g) and 35% aqueous methylamine solution (1.5 l) is stirred at room temperature for 4 days. The excess of aqueous methylamine is then distilled off in a water-pump vacuum, whereby about 1.34 l of 29% methylamine solution are recovered. To the residue is added potassium hydroxide (39 g) as 50% aqueous solution together with 95% ethanol (200 ml), and the solution is evaporated to dryness in a vacuum. This process is repeated twice more. The mixture of syrup and crystals is stirred with anhydrous ethanol (500 ml) until the syrup has dissolved and the crystals remain undissolved. The solution is saturated with gaseous hydrogen chloride, set aside overnight, then heated for 1.5 h under reflux, and finally evaporated to dryness in a vacuum. The residue is covered with ether (300 ml) and cooled in an ice-bath. This mixture is stirred while a cold solution of potassium hydroxide (50 g) in water (50 ml) is slowly added, the temperature not being allowed to rise above 10°. The flask is then closed and thoroughly shaken. The yellow ether layer is separated, and the shaking with ether is repeated four times (once with 200 ml and three times each with 100 ml). The extracts are combined, dried over magnesium sulfate, and fractionated, yielding the amino ester (30.4 g, 63%), b.p. 64–65.5°/20 mm, n_D^{20} 1.4174.

Halogen in positions other than next to the carboxyl group of aliphatic acids is somewhat less reactive. For preparation of methyl 4-(diethylamino)-butyrate from the 4-chloro compound the detour through the 4-iodo compound was chosen, this being easily accessible by means of sodium iodide.[521]

The halo group of halogenated lactones can be replaced by an amino group without causing ring opening.[522,523]

Quaternization by halo carboxylic acid derivatives occurs especially smoothly, as an example of which the preparation of **(trimethylammonio)-acetohydrazide chloride**, known as Girard reagent T, will be described:[524]

$$(CH_3)_3N^+—CH_2CONHNH_2Cl^-$$

Ethyl chloroacetate (984 g) and well-cooled anhydrous trimethylamine (280 g) are dissolved in anhydrous ethanol (2 l). Next day, further trimethylamine (200 g) is added. On the third day hydrazine hydrate (400 g) is added in one portion with good stirring, and the mixture is kept in a refrigerator until the strongly exothermic reaction has ended. The material that has separated is collected with exclusion of moisture. A second crop is obtained by concentration of the mother liquor, giving a total yield of about 90%; the m.p. is 192° (dec.).

Further alkylation of mono- and di-alkylhydrazines is always easier than the initial alkylation of hydrazine. Of the various methods[525] for preparation of **monoalkylhydrazines**, one avails itself of the dilution principle for C_2–C_6 alkyl derivatives.[525]

A solution of the alkyl bromide (1 mole) in ethanol (100 ml) is added with vigorous stirring to 100% hydrazine hydrate (500 g) during 3 h, the temperature being kept below 30°. After being stirred for a further 2 h at room temperature the solution is extracted with dry ether for 24 h; the extract is evaporated and the residual alkylhydrazine is distilled from barium oxide through a Vigreux column. Yields for these hydrazines are: ethyl 41, propyl 66, butyl 71, pentyl 41, and hexyl 40%.

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The simplest derivatives to prepare are the 1,1,1-trialkylhydrazinium salts;[526,527] reaction of hydrazine hydrate with chlorohydrins in an alkaline medium is also relatively smooth; it gives hydrazino alcohols.[528]

Metalation of phenylhydrazine with sodium in liquid ammonia and then reaction with alkyl halides occur readily and give good yields of 1-alkyl-1-phenylhydrazines.[529] 1,2-Dialkylhydrazines cannot be obtained at all by direct alkylation of hydrazine, but they are quite smoothly prepared by alkylation of 1,2-diacylhydrazines and subsequent hydrolysis.[530-533] Alkylation of monoacylhydrazines has been discussed by Hinman and Flores.[534]

Reaction of α-halo carboxylic acids with hydrazine is a very smooth reaction:

Ethyl hydrazinoacetate:[535] Chloroacetic acid (94.5 g, 1 mole) is added in portions to aqueous 32% hydrazine solution (500 g, 5 moles), followed after 48 h by sodium hydroxide (8 5g, ca. 2 moles). Distillation in a vacuum then enables much (4 moles) of the hydrazine to be recovered. The distillation residue is heated with 30% alcoholic hydrochloric acid (650 ml) to gentle reflux, then cooled and saturated with gaseous hydrogen chloride (ca. 2 h). Next, dry ethanol (500 ml) is added and the mixture is boiled and filtered hot. The hydrazino ester hydrochloride (103 g, 66.5%), m.p. 150–153°, crystallizes.

Geminal dihalides and 1,1-dialkylhydrazines afford hydrazones.[536]

Finally it may be noted that alkylation of hydroxylamine by alkyl iodides gives the *N,N*-dialkyl derivatives as the first isolable products, and that, particularly with the lower homologs, it very easily proceeds further to give trialkylamine oxides.[537]

b. Arylation

It is difficult to bring into reaction a halogen atom that is bound to an aromatic ring. Unless activated by strongly negative substituents in the *ortho*- or *para*-position, halogen atoms have the same relative reactivities in aromatic as in alkyl halides; in practice, however, one is concerned only with chloro and bromo aromatic compounds. These compounds react with ammonia or amines only under energetic conditions and even then require catalytic assistance from copper powder or copper salts. Raney copper, prepared from Devarda alloy, is said to be particularly effective.[538] In this reaction, known as the Ullmann synthesis, the catalytic efficiency of copper is further increased by traces of iodine. Dry potassium carbonate is usually used to bind the acid formed; nitrobenzene has proved a suitable solvent. Under the conditions even diphenylamine can be arylated:

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[537] W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **75**, 792 (1899).

[538] K. Bauer, *Chem. Ber.*, **83**, 10 (1950).

Triphenylamine:[539] Powdered diphenylamine (176 g), iodobenzene (204 g), acid-free nitrobenzene (1 l), finely powdered potassium carbonate (138 g), and Naturkupfer C (a copper powder) (5 g) are placed in a 2-l round-bottomed flask fitted with an efficient stirrer and an air-condenser 65 cm long attached to a descending water-condenser. The mixture is heated with vigorous stirring so that the nitrobenzene condenses in the upper part of the air condenser and a small amount passes into the descending condenser. This distillate is dried from time to time by sodium sulfate and then returned to the reaction mixture. The reaction is complete when no more water distils over (ca. 12–24 h). The nitrobenzene is then distilled off, and unchanged diphenylamine is removed in steam from the residue in a 5-l flask. Distillate (8–10 l) is collected until it contains less than 5 g of insoluble material per liter. Crude triphenylamine crystallizes as the residue cools and is collected and washed with water (two 400-ml portions); it is then extracted with benzene (first 1 l, then three 75-ml portions). These extracts are freed from most of their water and then distilled until only benzene distils. Thereupon the residue is made up to 1.2 l with dry benzene and filtered, and gaseous hydrogen chloride is led in. The precipitated diphenylamine hydrochloride is filtered off after some hours and is washed with benzene. Benzene is removed from the filtrates, and the remaining, still crude triphenylamine is distilled in a vacuum through a short column into a not too narrow descending air-condenser. A small forerun of benzene and a colored impurity is followed by triphenylamine (220–235 g), b.p. 195–205°/10–12 mm, m.p. 120–124°. Recrystallization is from ethyl acetate (ca. 700 ml). The total yield, including material from the mother liquor, is 200–210 g (82–85%), the m.p. being 126°.

9-Phenylcarbazole is obtained analogously in 88% yield from carbazole.[539]

If *N*-phenylanthranilic acid is used in place of diphenylamine, a good yield of the *N*,*N*-diphenylanthranilic acid is obtained;[540] and the monophenyl derivative itself can be obtained by an Ullmann reaction from *o*-chlorobenzoic acid in about 90% yield.[538,541]

It is often more profitable to use an *N*-acetyl derivative instead of the free amine.

3-Nitrodiphenylamine:[542] 3-Nitroacetanilide (12 g) and bromobenzene (21 g) are dissolved in nitrobenzene and treated with potassium carbonate (5 g). The mixture is heated at 180° for 10 h with addition of small amounts of potassium iodide and copper powder, then gradually at up to 210° during a further 8 h. Steam-distillation leaves behind a brown oil that becomes viscous on cooling. After separation of the aqueous layer the oil is dissolved in ethanol, filtered, and, for hydrolysis, boiled for 3 h with concentrated hydrochloric acid (20–25 ml). Then adding water precipitates 3-nitrodiphenylamine as a brown oil that rapidly crystallizes (11.3 g, 80%). Recrystallization from ethanol gives brick-red crystals, m.p. 112°.

Prior metallation considerably facilitates reaction of unactivated aromatic halo compounds with amines. In the simplest cases it suffices to add an alkali amide to the reaction mixture.

1-Phenylpiperidine:[543] Sodamide (7.8 g) is heated with dry piperidine (30 ml) for 15 min under reflux. Then bromobenzene (15.7 g) is added dropwise through the reflux condenser, whereupon a vigorous reaction ensues with evolution of ammonia which slackens towards the end of the addition. The mixture is then heated for 2 h under reflux, cooled, and treated cautiously with water (25 ml) and benzene (25 ml). The benzene layer is separated and washed with 10% hydrochloric acid (three 25-ml portions). The acid extracts are united and made strongly alkaline with concentrated potassium hydroxide solution which precipitates an oil. This oil is taken up in ether (15 ml), the aqueous-alcoholic layer is extracted with its own volume of ether, the ethereal solutions are united and freed from ether, and the residue distilled, affording 1-phenylpiperidine (16 g, 99%), b.p. 93 to 97°/3–4 mm, n_D^{20} 1.5593.

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[540] I. Goldberg and M. Nimerovsky, *Ber. Deut. Chem. Ges.*, **40**, 2448 (1907).

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[542] I. Goldberg, *Ber. Deut. Chem. Ges.*, **40**, 4541 (1907).

[543] J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **22**, 832 (1957).

The technique for preparation of **N-cyclohexylaniline** is similar:[544] First, metallic potassium (12g) is dissolved in liquid ammonia (100 ml), then dry cyclohexylamine (100 ml) is added. The ammonia is allowed to evaporate and dry bromobenzene (47 g) is added to the residue, whereupon the mixture becomes warm and brown. The mixture is then stirred at 120–130° for 3 h after which it is treated with water (100 ml) and the organic phase is washed with a further amount (150 ml) of water. The two portions of wash-water are together shaken with ether (100 ml), which is then united with the organic phase, dried over sodium sulfate, and evaporated at atmospheric pressure. Fractionation of the residue in a vacuum affords cyclohexylaniline (22 g, 42%) at 142–147°/9 mm. A small fraction of b.p. 198–205°/9 mm, presumably cyclohexyldiphenylamine, remains in the residue.

The applicability of this process to halogen derivatives of substituted or polycyclic aromatic compounds is, however, very limited since the reaction usually proceeds through an aryne intermediate stage that normally leads to rearrangements.[545] Nevertheless the procedure has its preparative uses when the rearrangement is unidirectional.

***m*-Anisidine** from *o*-chloroanisole:[546] *o*-Chloroanisole (60 g) is dropped during 0.5 h into a stirred solution of sodamide (0.85 mole) in liquid ammonia (800 ml). After a further 0.5 hour's stirring, the excess of sodamide is destroyed by addition of ammonim chloride, the solvent is evaporated, and the residue is extracted with ether, from which the amine is precipitated as hydrochloride (30 g, 57.7%).

Halogen bound to an aromatic ring is rendered considerably more reactive by nitro groups in the *para*- or, especially, the *ortho*-position to it; carboxyl, sulfonyl, and cyano groups have considerably less effect. Among such activated halo aromatic compounds the relative reactivities of the halogens are reversed, and fluorine is much the most reactive. This is used for, *e.g.*, determination of *N*-terminal amino acids in peptides by means of 1-fluoro-2,4-dinitrobenzene.[547] The ease of reaction is illustrated in the following example:

***N*-(2-Hydroxyethyl)-2,4-dinitroaniline:**[548] Ethanolamine (0.5 g) is shaken at room temperature for 3 h with sodium hydrogen carbonate (1 g), water (10 g), and a solution of 1-fluoro-2,4-dinitrobenzene (0.8 g) in ethanol (20 ml). Then, to remove the excess of fluorodinitrobenzene, glycine (0.2 g) is added, shaking is continued for a further 2 h, the alcohol is removed in a vacuum, and the residue is treated with water. Extraction with ether, evaporation of the ether extract, and recrystallization of the residue from ethanol give reddish-yellow needles (1.62 g, 86.4%), m.p. 92°.

Bräuniger and Spangenberg[549] have described the treatment of a large number of amines with 1-fluoro-2,4-dinitrobenzene.

The reactivity naturally increases with increasing numbers of *ortho*- and *para*-nitro groups; thus reactions of *p*-chloronitrobenzene require relatively energetic conditions:

***N,N*-Diethyl-*p*-nitroaniline:**[550] Diethylamine (100 g, 1.4 moles) and *p*-chloronitrobenzene (97.8 g, 0.6 mole) are heated in a shaking autoclave for 8 h at 175°. The mixture is then poured into water (1 l), and the precipitate is collected, washed with water, and dissolved

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[546] H. Gilman and S. Avakian, *J. Amer. Chem. Soc.*, **67**, 349 (1945).

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[549] H. Bräuniger and K. Spangenberg, *Pharmazie*, **12**, 335 (1957).

[550] L. C. Behr, J. E. Kirby, R. N. McDonald, and C. W. Todd, *J. Amer. Chem. Soc.*, **68**, 1296 (1946).

in 20% hydrochloric acid (200 ml) at 60°. This solution is filtered through a glass frit and ammonia is added, which precipitates a crude product (114 g, 94%), m.p. 71–73°. Recrystallization from ethanol gives material (85 g) of m.p. 76°.

In the following case the use of pressure can be avoided by using the amine hydrochloride in the presence of a base:

N,N-Dimethyl-*p*-nitroaniline:[194] *p*-Bromonitrobenzene (42 g), pyridine (300 ml), and sodium hydrogen carbonate (50 g) are placed in a 500-ml flask, treated with a solution of dimethylamine hydrochloride (30 g) in warm water (10 ml), and heated under reflux for 10 h. Then the salt that separates is washed with acetone (200 ml). The acetone is combined with the filtrate from the salt, heated to the b.p., and treated with water to incipient turbidity. On cooling, needles separate, which, after recrystallization from methanol, have m.p. 164. A second fraction can be obtained by concentrating the mother liquor to about a third of its volume. The total yield is 32.4–33.6 g (94–97%).

o-Chloronitrobenzene gives an 85% yield of *N,N*-dimethyl-*o*-nitroaniline, b.p. 149°/20 mm, analogously.

Organic Syntheses[551] give good directions for the preparation of 2,4-dinitroaniline from chlorodinitrobenzene: to avoid the use of pressure, the chloride is melted with ammonium acetate at 170° and a stream of ammonia is passed over the melt for 6 h. Another method consists in melting the chlorodinitrobenzene with urea.[552]

The reactivity of picryl chloride has been raised by the three activating nitro groups to the level of that of alkyl halides. Linke[553] set a long series of aromatic amines aside for 15 hours at 7° in an alcoholic solution of picryl chloride and thereby obtained almost quantitative yields in every case; indeed, the reaction of picryl chloride with aniline in ethyl acetate in the presence of sodium hydrogen carbonate has been used for quantitative determination of that amine.[554]

Hydrazine too reacts with activated aryl halides as readily as ammonia or amines. The important carbonyl reagent 2,4-dinitrophenylhydrazine is obtained in 80% yield from an aqueous-alcoholic solution of 1-chloro-2,4-dinitrobenzene and hydrazine.[555] Moreover, hydrazones can be arylated in the same way, which can be of interest when the 2,4-dinitrophenylhydrazones cannot be prepared with ease directly from the ketone. The conversion of acetone hydrazone into the 2,4-dinitrophenylhydrazone[556] will be described here as a typical example:

Acetone hydrazone (1.5 g, 0.02 mole) is dissolved in 95% ethanol (10 ml) and treated with a solution of 1-chloro-2,4-dinitrobenzene (4.0 g, 0.019 mole) in 95% ethanol (30 ml). The mixture is heated for 1 h under reflux, then cooled and filtered. The solid product is freed from a little adhering chlorodinitrobenzene by washing with a little warm ethanol and is then dried. One recrystallization from 95% ethanol gives **acetone 2,4-dinitrophenylhydrazone**, m.p. 123°.

c. Acylation

Acyl halides, as a class, are among the most important derivatives of acids used for acylation of nitrogen compounds (see also pages 480–496).

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[551] F. B. Wells and C. F. H. Allen, *Org. Syn.*, Coll. Vol. II, 221 (1943).

[552] Brit. Pat. 263,552; *Chem. Abstr.*, **22**, 92 (1928).

[553] B. Linke, *Ber. Deut. Chem. Ges.*, **56**, 848 (1923).

[554] B. Linke, H. Preissecker, and J. Stadler, *Ber. Deut. Chem. Ges.*, **65**, 1280, 1282 (1932).

[555] C. F. H. Allen, *Org. Syn.*, Coll. Vol. II, 228 (1943).

[556] L. I. Braddock and M. L. Willard, *J. Org. Chem.*, **18**, 313 (1953).

Chlorides are the only halides used in practice, and the crude acyl halide obtained from the organic acid and phosphorus trichloride or thionyl chloride is often pure enough for this reaction.[557] For acylation of ammonia it is simplest to rub the acyl chloride with ammonium carbonate, warm the mixture until reaction is complete, and leach out the ammonium salts with cold water. Reaction of acid chlorides with ammonium acetate in acetone at room temperature has also been recommended.[558] Another method is to drop the chloride into ice-cooled, vigorously stirred, concentrated aqueous ammonia in excess, thereafter continuing the stirring for a short time before evaporating the whole to dryness; as the lower carboxamides are somewhat soluble in water, an organic solvent must be used to separate them from the ammonium chloride; anhydrous ethanol, for example, may be used; for isobutyramide[559] boiling ethyl acetate proved excellent, the amide separating on cooling in 80% yield. Use of aqueous ammonia is, of course, most convenient when the resulting amide is insoluble in water so that it is at once precipitated, as, *e.g.*, with 2-phenylbutyramide[560] or 2-naphthylacetamide.[561]

Separation of the amide from ammonium chloride by solvent extraction can be avoided by using an organic solvent for the main reaction. This solvent is usually benzene, light petroleum, or chloroform; lower yields are often obtained in ether. It is inadvisable to lead gaseous ammonia directly into the solution of acyl chloride as appreciable amounts of diacylated products are then sometimes formed; so the acyl chloride is added to the ammonia solution. After completion of a reaction in an organic solvent the ammonium chloride can be filtered off or, if the amide is insoluble in water, can be extracted with water. The anhydrous technique, which generally gives high yields and pure products, is illustrated in the following example; a long series of other amides can be similarly prepared in good to very good yields.

Butyramide:[562] Dry benzene (250 ml) is placed in a 500-ml three-necked flask fitted with reflux condenser, dropping funnel, and gas inlet tube. This solvent is warmed on a boiling water-bath while dry ammonia (ca. 250 ml per min) is led in with exclusion of moisture. At the same time a solution of butyryl chloride (21.3 g) in dry benzene (50 ml) is dropped in during 1 h. Passage of ammonia is then continued for a further 0.5 h, after which the ammonium chloride deposited is filtered off and washed twice with hot benzene (25-ml portions). The benzene solution and wash liquor are together evaporated to 75 ml and then, whilst hot, treated cautiously with light petroleum (b.p. 30–60°) to incipient crystallization. The mixture is reheated until clear, then cooled rapidly. The butyramide that separates is collected and recrystallized twice in the same way from benzene–light petroleum, affording white, odorless crystals, m.p. 115–116° (13.7 g, 78.7%).

Primary and secondary amines can in principle be acylated analogously to ammonia; a second molecule of the amine is then required to bind the hydrochloric acid and is lost.

Here again, so far as the solubility of the amine permits, the reaction may be in an aqueous or an anhydrous medium. For instance, *N*-methylamides of simple aliphatic acids have been prepared by dropping the acyl chloride into

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[557] O. Aschan, *Ber. Deut. Chem. Ges.*, **31**, 2344 (1898).

[558] P. A. Finan and G. A. Forthergill, *J. Chem. Soc.*, **1962**, 2824.

[559] R. E. Kent and S. M. McElvain, *Org. Syn.*, Coll. Vol. III, 490 (1955).

[560] S. M. McElvain and C. L. Stevens, *J. Amer. Chem. Soc.*, **69**, 2663 (1947).

[561] M. S. Newman, *J. Org. Chem.*, **9**, 518 (1944).

[562] G. E. Philbrook, *J. Org. Chem.*, **19**, 623 (1954).

an excess of aqueous methylamine solution at −10° to −20°.[563] The following general directions have proved valid for **preparation** of a large number of **diethylamides**, particularly those from aromatic acids:[564]

The acyl chloride (0.1 mole) is added slowly, with vigorous stirring, to a well-cooled solution of dry diethylamine (0.2 mole) in anhydrous ether (100 ml); the mixture is stirred for a further hour at room temperature, then sufficient water is added to dissolve all the precipitated amine hydrochloride. The organic phase is separated, washed successively with 100-ml portions of 5% hydrochloric acid, water, 5% sodium hydroxide solution, water, and saturated sodium chloride solution, then dried, filtered, and evaporated. Distillation in a vacuum affords the amide, usually in good yield.

Other anhydrous solvents, such as benzene and chloroform, may replace the ether; the acyl chloride and amine should be dissolved in the same solvent.

The hydrogen halide liberated may be removed by a base that is cheaper than the amine itself, particularly if the latter is valuable; this can be done by alkali carbonates for reactions in organic solvents.

2-(Benzoylamino)-1-butanol:[565] A mixture of benzene (500 ml), anhydrous sodium carbonate (25 g), and 2-amino-1-butanol (18.3 g) is cooled to 10° and stirred while a solution of benzoyl chloride (28.1 g) in benzene (100 ml) is added with stirring and cooling so that the temperature does not rise above 10°. After about 45 min more sodium carbonate (25 g) is added and the whole is stirred for a further 4 h at 10° and then for another 4 h at room temperature. Lastly, it is heated under reflux until the odor of benzoyl chloride disappears. The inorganic precipitate is filtered off and washed with hot benzene (two 100-ml portions). The united benzene solutions are concentrated to 400 ml and allowed to cool for crystallization. A second fraction is obtained on concentrating the mother liquor to 150 ml. The total yield is 90% (34–35 g). The m.p. is 97–98° after washing with benzene and 98–99° after recrystallization from toluene.

Amines can be almost quantitatively acylated even in the absence of an acid-binding material provided that their hydrochlorides are heated under reflux with the acid chloride in an inert solvent until evolution of hydrogen halide ceases, a process requiring a considerable time.[566–568]

Benzanilide:[566] Anilinium chloride (9 g), benzoyl chloride (9 g), and benzene (50 ml) are heated under reflux for 8 h, at the end of which no more hydrogen chloride is being evolved. The mixture is cooled, and the precipitated amide is washed with benzene and water and crystallized from ethanol. It has m.p. 162°. The yield is almost quantitative.

This process is successful with both aromatic[566] and aliphatic amines[567] and for large batches of the latter is preferable to the Schotten–Baumann acylation described below.[567] It can also be used for amino acids presented as internal salts.[566,568]

The well-known Schotten–Baumann method of acylation[569] is carried out in aqueous suspension, with an alkali hydroxide to bind the liberated acid.

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[563] G. F. D'Alelio and E. E. Reid, *J. Amer. Chem. Soc.*, **59**, 109 (1937).

[564] E. T. McCabe, W. F. Barthel, S. I. Gertler, and S. A. Hall, *J. Org. Chem.*, **19**, 493 (1954).

[565] J. H. Billman and E. E. Parker, *J. Amer. Chem. Soc.*, **66**, 538 (1944).

[566] H. Franzen, *Ber. Deut. Chem. Ges.*, **42**, 2465 (1909).

[587] H. Suida and F. Drahowzal, *Ber. Deut. Chem. Ges.*, **75**, 991 (1942).

[568] E. Ronwin, *J. Org. Chem.*, **18**, 127, 1546 (1953).

[569] C. Schotten, *Ber. Deut. Chem. Ges.*, **17**, 2544 (1884); **23**, 3430 (1890); E. Baumann, *Ber. Deut. Chem. Ges.*, **19**, 3218 (1886); L. von Udránsky and E. Baumann, *Ber. Deut. Chem. Ges.*, **21**, 2744 (1888); O. Hinsberg and L. von Udránsky, *Ann. Chem.*, **254**, 252 (1899).

It is thus particularly suitable for acylation by the more difficultly hydrolysable aromatic acyl chlorides. It usually suffices to shake a suspension of the amine in sodium hydroxide solution with the acid chloride for some time at room temperature; the mixture is then sometimes heated for a short time to complete the reaction and hydrolyse unchanged acyl chloride; the amide is finally filtered off or extracted with an organic solvent. Since the mixture should remain alkaline to the end of the reaction and a small proportion of the chloride will be hydrolysed, an approximately 25% excess of both the alkali and the chloride is usually used.

With aliphatic or other very reactive chlorides it is nevertheless advisable to work with cooling; yields are then also generally good.

***N*-Methylisobutyramide:**[570] Solutions of sodium hydroxide (320 g, 8 moles) in water (1 l) and of methylammonium chloride (278 g, 4 moles) in water (690 ml) are slowly mixed and cooled. To this mixture isobutyryl chloride (424 g, 4 moles) is slowly added with stirring whilst the temperature is not allowed to rise above 10°. Then the mixture is allowed to warm to room temperature, the amide layer is separated, and the aqueous phase is extracted with ether (three 200-ml portions). The amide layer and the ethereal solutions are united, dried, and distilled, giving an amide (303 g, 75%), b.p. 120–121°/27 mm, n_D^{20} 1.4350.

N-Ethylisobutyramide,[570] m.p. 65–67°, and *N*-methylmethacrylamide[571] have been obtained similarly.

The Schotten–Baumann technique has often been applied to acylation of amino acids, particularly for benzoylation and for introduction of the benzyloxycarbonyl group.

Steiger[572] has given a general prescription for benzoylation of amino acids by the Schotten–Baumann technique, and also a review of the older literature. Individual prescriptions for benzoylation of glycine[573] and 6-aminohexanoic acid[574] are to be found in *Organic Syntheses*.

Benzyloxycarbonylamino acids are important for peptide synthesis since, as is well-known, the acyl group is readily removed by hydrogenolysis;[575] an example of the preparation of such an amide is therefore provided:

***N*-(Benzyloxycarbonyl)glycine:**[576] Benzyl chloroformate (17 g) and 4N-sodium hydroxide solution (25 ml) are added separately but simultaneously, slowly and with stirring, within 20–25 min to an ice-cooled solution of glycine (7.5 g) in 2N-sodium hydroxide solution (50 ml). The mixture is then stirred for a further 10 min, whereafter it is extracted with ether. The aqeuous phase is acidified to Congo Red by concentrated hydrochloric acid under ice-cooling. The precipitated amide acid is filtered off, washed with a little water, dried in the air, and recrystallized from chloroform. The yield is 18–19 g and the m.p. 120°.

4-Nitro-[577] and 4-bromo-benzyloxycarbonylamino acids[578] usually crystallize more readily than the parent benzyloxy esters, and they too readily undergo hydrogenolysis. Colored N-protective groups are of particular interest for

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[570] S. M. McElvain and C. L. Stevens, *J. Amer. Chem. Soc.*, **69**, 2667 (1947).

[571] J. Heyboer and A. J. Staverman, *Rec. Trav. Chim.*, **69**, 787 (1950).

[572] R. Steiger, *J. Org. Chem.*, **9**, 396 (1944).

[573] A. W. Ingersoll and S. H. Babcock, *Org. Syn.*, Coll. Vol. II, 328 (1943).

[574] J. C. Eck and C. S. Marvel, *Org. Syn.*, Coll. Vol. II, 76 (1943).

[575] M. Bergmann and L. Zervas, *Ber. Deut. Chem. Ges.*, **65**, 1192 (1932).

[576] H. E. Carter, R. L. Frank, and H. W. Johnston, *Org. Syn.*, Coll. Vol. III, 167 (1955).

[577] F. H. Carpenter and D. T. Gish, *J. Amer. Chem. Soc.*, **74**, 3818 (1952); D. T. Gish and F. H. Carpenter, *J. Amer. Chem. Soc.*, **75**, 950 (1953).

[578] D. M. Channing, P. B. Turner, and G. T. Young, *Nature*, **167**, 487 (1951).

chromatographic purification of amino acids and peptides, and they have been discussed by Schwyzer *et al.*[579]

Magnesium hydroxide,[575] calcium hydroxide,[580] barium hydroxide,[581] sodium hydrogen carbonate,[582] or sodium acetate may be used in place of sodium or potassium hydroxide solution to bind the hydrogen halide liberated in a Schotten–Baumann reaction. Pyridine has also proved excellent for this purpose in countless cases, and it can also be used as solvent for the reaction (see, for instance, Walther and Wlodkowski[583]).

Methyl *p*-(*p'*-nitrobenzoylamino)benzoate:[584] A solution of methyl *p*-aminobenzoate (2.6 g) in methanol-free, dry chloroform (20 ml) is treated with a solution of *p*-nitrobenzoyl chloride (2.9 g) in chloroform (10 ml), followed by anhydrous pyridine (5 ml). The mixture becomes warm and a pale yellow compound begins to separate. After 15 h at 20° the mixture is filtered. Recrystallization of the solid (4.6 g, 98%) from ethyl acetate gives the acylamino ester, m.p. 244°.

Diethyl (benzoylamino)malonate:[585] Benzoyl chloride (48.5 g) is dropped into a stirred mixture of diethyl aminomalonate (58 g), pyridine (50 ml), and water (250 ml), the temperature being kept below 50°. After cooling to room temperature the precipitate is filtered off, dried in a vacuum, dissolved in the minimum amount of benzene, and reprecipitated by gradual addition of six times the volume of light petroleum. The amido ester (92.4 g, 90%) has m.p. 73–74°.

For acylation in pyridine by Einhorn's method it is not always necessary to start with preformed acyl chloride. Its preparation and reaction can be effected in one operation by dissolving the amine and carboxylic acid together in pyridine, adding the calculated amount of thionyl chloride with cooling, and after some time pouring the mixture into water; the amide is precipitated and is washed successively with dilute acid, dilute alkali hydroxide, and water.

Other tertiary amines, such as triethylamine[586] and *N*,*N*-diethylaniline[587] have sometimes been used instead of pyridine.

The possibility that ketene may be formed from a tertiary amine and an aliphatic acyl chloride should be noted.[588]

The reactivity of halogen attached to a carbonyl-carbon atom is so great that the methods of acylation described above can be applied to acyl halides carrying other functional groups. In some cases side reactions can be completely excluded by choosing a sufficiently low reaction temperature. Thus, bromoacetyl bromide,[589] 2-bromopropionyl bromide,[590] and dichloroacetyl chloride[591] give good yields of the halo amides on reaction with a wide variety of amines in ethylene chloride at −10° to −20°; an excess of the amine is here used to bind the acid formed.

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[579] R. Schwyzer, P. Sieber, and K. Zatskó, *Helv. Chim. Acta*, **41**, 491 (1958).

[580] J. Biehringer and A. Busch, *Ber. Deut. Chem. Ges.*, **36**, 137 (1903).

[581] A. Étard and A. Vila, *C. R. Hebd. Séances Acad. Sci.*, **135**, 698 (1902).

[582] E. Fischer, *Ber. Deut. Chem. Ges.*, **32**, 2454 (1899).

[583] R. Walther and S. Wlodkowski, *J. Prakt. Chem.*, [ii], **59**, 266 (1899).

[584] R. Kuhn, E. F. Möller, G. Wendt, and H. Beinert, *Ber. Deut. Chem. Ges.*, **75**, 717 (1942).

[585] C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 345 (1939).

[586] H. Suter, H. Zutter, and H. Widler, *Ann. Chem.*, **576**, 223 (1952).

[587] P. Ruggli and J. Rohner, *Helv. Chim. Acta*, **25**, 1533 (1942).

[588] W. E. Hanford and J. C. Sauer, *Org. Reactions*, **3**, 124 (1946).

[589] W. E. Weaver and W. M. Whaley, *J. Amer. Chem. Soc.*, **69**, 515 (1947).

[590] W. E. Weaver and W. M. Whaley, *J. Amer. Chem. Soc.*, **69**, 1144 (1947).

[591] A. D. Swensen and W. E. Weaver, *J. Amer. Chem. Soc.*, **70**, 4060 (1948).

Ester chlorides of dicarboxylic acids can be converted into ester amides without attack on the ester group. *E.g.*, the methyl ester chloride from sebacic acid gives, with aqueous ammonia, a 95% yield of the ester amide.[592] Treatment of chloroformic esters with ammonia[576,593] or a primary[594] or secondary amine[595] is a much used route to urethanes.

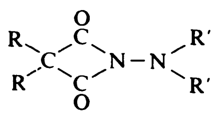
Diacyl chlorides can often be either singly or doubly amidated. Carbamoyl chlorides are obtained from phosgene and ammonia or an amine under conditions that must be rigidly adhered to;[596] they can then be applied to preparation of aromatic carboxamides by a Friedel–Crafts reaction or to the synthesis of unsymmetrically substituted ureas.

Double amidation of phosgene, to give symmetrical ureas, is considerably easier to perform. Considerable interest is attached to the recent reaction of imidazole with phosgene, which led to 1,1′-carbonyldiimidazole, an extremely reactive compound on account of the lability of its amide bonds;[597] The ease with which the imidazole group can be replaced by other groups offers the widest possibilities for synthesis of other carbonic acid derivatives, carboxylic esters, amides, and hydrazides, peptides, phosphoric esters, etc., all under the mildest conditions.[598] Since 1,1′-carbonyldiimidazole is hydrolysed even by atmospheric moisture, it must be prepared under the most strictly anhydrous conditions.

1,1′-Carbonyldiimidazole:[599] Imidazole (10 g) is dissolved in anhydrous tetrahydrofuran (120 ml) in a 250-ml flask with a ground neck. Phosgene (2.50 ml) is pipetted into this solution by means of a graduated acid pipette provided with a trap cooled in acetone–carbon dioxide. The precipitated imidazole hydrochloride is collected on a frit with a ground neck, so that water can be excluded. Evaporation of the tetrahydrofuran solution in a vacuum gives the carbonyldiimidazole (90–95%), m.p. 116–118°.

Other inert solvents, such as benzene,[600] are occasionally used instead of tetrahydrofuran. For the preparation of 1,1′-(thiocarbonyl)diimidazole a benzene solution of thiophosgene was dropped into a chloroform solution of imidazole.[601]

Malonyl dichloride and its disubstitution products react with strongly basic amines to give preferentially the diamides. Ring closure to cyclic imides occurs only between disubstituted malonyl dichlorides and weakly basic aromatic or heterocyclic-aromatic amines. 3,3-Disubstituted 1-(disubstituted-amino)-2,4-azetidinediones are obtained analogously from *N*,*N*-disubstituted hydrazines.[602]



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[592] W. S. Bishop, *Org. Syn.*, Coll. Vol. III, 613 (1955).

[593] W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

[594] W. W. Hartman and M. R. Brethen, *Org. Syn.*, Coll. Vol. II, 278 (1943).

[595] C. S. Marvel and W. A. Noyes, *J. Amer. Chem. Soc.*, **42**, 2276 (1920).

[596] H. Hopff and H. Ohlinger, *Angew. Chem.*, **61**, 183 (1949).

[597] H. A. Staab, *Ann. Chem.*, **609**, 75 (1957).

[598] H. A. Staab, *Angew. Chem.*, **74**, 407 (1962).

[599] H. A. Staab and K. Wendel, *Chem. Ber.*, **93**, 2902 (1960).

[600] R. Paul and G. W. Anderson, *J. Amer. Chem. Soc.*, **82**, 4596 (1960).

[601] H. A. Staab and G. Walther, *Ann. Chem.*, **657**, 98 (1962).

[602] A. Ebnöther, E. Jucker, E. Rissi, J. Rutschmann, E. Schreier, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta.*, **42**, 918 (1959).

Halides derived from hydrogen cyanide also react smoothly with primary amines. Reaction with cyanogen bromide is to be recommended as a method of preparing cyanamides, but it is advisable to arrange for good cooling so as to avoid formation of guanidines.

Benzylcyanamide:[603] A solution of cyanogen bromide (2.1 g) in dry ether (14 ml) is dropped slowly into a stirred, ice-cooled solution of benzylamine (4.3 g). Filtration from the benzylamine hydrobromide and evaporation in a vacuum gives a crude product (2.6 g, 95%), m.p. 42–44°.

For the preparation of disubstituted cyanamides it is often better, not to treat a secondary amine with cyanogen bromide, but, instead, to subject a tertiary amine to von Braun degradation[604] in which it is generally the smallest alkyl group that is split off as alkyl bromide.

***N*-Methyl-*N*-1-naphthylcyanamide:**[605] *N,N*-Dimethyl-1-naphthylamine (171 g) and cyanogen bromide (125 g) are heated together under reflux on a water-bath in a fume cupboard for 16 h, then the product is poured into dry ether (2.5 l). A little (ca. 10 g) trimethyl-1-naphthylammonium bromide, m.p. 160°, separates as by-product and is filtered off. The filtrate is extracted with ca. 15% hydrochloric acid (four 800-ml portions) and then with water (five 500-ml portions), after which it is dried over anhydrous calcium sulfate (30–35 g). After removal of the ether, fractionation in a vacuum affords a pale yellow oil (115–122 g, ca. 65%), b.p. 171°/1 mm, 185–187°/3 mm.

The three chlorine atoms of cyanuric chloride can be replaced stepwise by different amino groups.[606]

Acid chlorides react less smoothly with hydroxylamine, hydrazine, tertiary amines, or amides than with ammonia or primary or secondary amines.

Acyl chlorides are rarely used to convert hydroxylamine into hydroxamic acids;[607,608] it is more effective to acylate hydroxylamine with carboxylic esters.

Similarly carbohydrazides are best obtained by hydrazinolysis of esters, since acyl chlorides and hydrazine often give *N,N'*-diacyl derivatives, particularly in an aqueous medium.[609]

Thus, *N,N'*-dibenzoylhydrazine, which is important as starting material for *N,N'*-dialkylhydrazines, is obtained in 70% yield in a Schotten–Baumann reaction.[532] On the other hand, "benzyloxycarbonylhydrazine" (*i.e.*, benzyl hydrazinoformate), which is sometimes required for peptide syntheses, is prepared by treating benzyl chloroformate with an excess of hydrazine hydrate in chloroform,[610] whereas mainly dibenzyl hydrazodiformate, $(C_6H_5CH_2OCONH-)_2$, is formed in aqueous solution.[610]

Tertiary aliphatic amines cannot be acylated by the chlorides of simple carboxylic acids. When reaction occurs, the chlorides lose hydrogen halide, affording ketenes[588] which readily undergo further reaction; in individual cases of α,β-unsaturated acyl chlorides, acyltrialkylammonium salts can be

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[603] H. K. Nagy, A. J. Tomson, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **82**, 1609 (1960).

[604] H. A. Hageman, *Org. Reactions*, **7**, 198 (1953).

[605] H. W. J. Cressman, *Org. Syn.*, Coll. Vol. III, 608 (1955).

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[609] C. Naegeli and G. Stefanovitsch, *Helv. Chim. Acta*, **11**, 621 (1928).

[610] H. Böshagen and J. Ullrich, *Chem. Ber.*, **92**, 1478 (1959).

isolated as intermediates.[611] The reaction, however, has no real preparative value, although occasionally yields are good, as in the preparation of diphenylketene.[612] Acyl halides occasionally dealkylate tertiary amines.[613]

Acylation of tertiary aliphatic amines to acyltrialkylammonium salts by means of acyl chlorides has recently been achieved by Klages,[614] by adding antimony pentachloride to the reaction mixture so that the actual acylating agent is an acylium hexachloroantimonate:

$$\mathrm{RCOCl} + \mathrm{SbCl_5} \longrightarrow [\mathrm{RCO}]^+[\mathrm{SbCl_6}]^- \xrightarrow{+\mathrm{NR'_3}} [\mathrm{RCO{-}NR'_3}]^+[\mathrm{SbCl_6}]^-$$

These acyltrialkylammonium salts are stronger acylating agents than acyl chlorides themselves.

Unlike tertiary aliphatic amines, pyridine can be *N*-acylated even in the absence of complex-forming Lewis acids.[615,616] 1-Acylpyridinium salts have been studied by Kröhnke.[503]

Acylation of amides is naturally much harder to achieve, because of their lower basicity, but it is very greatly facilitated by the presence of pyridine.[583,617,618] The reason for this effect is, of course, the intermediate formation of 1-acylpyridinium salts as mentioned above.[619] For instance, dibenzamide is formed almost quantitatively from benzoyl chloride and benzamide in pyridine solution even at room temperature, whereas there is no reaction in the absence of pyridine.[620] Also, by the action of aromatic acid halides on aliphatic or aromatic amides in the presence of pyridine at temperatures as low as −60° to −70° Thompson[617] obtained high yields of triacyl derivatives.

Other methods for the acylation of amides without the use of pyridine generally call for considerably more energetic conditions than are required for amines. For instance, many hours' boiling under reflux are necessary for mono- or di-acylation of urea by fatty acid halides.[621,622]

Butyrylurea:[621] A mixture of urea (10 g), benzene (25 ml), and a little concentrated sulfuric acid (2 drops) is boiled under reflux while butyryl chloride (15 g) is added with stirring during 15 min. The mixture is boiled for a further 4 h, then cooled. The acylated urea separates and is collected and washed with sodium hydrogen carbonate solution and with water, then having m.p. 173–174° (75–85%).

Similar conditions are used for further acylation of monoacylureas, this occurring on the other nitrogen atom.[621,622]

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[611] G. B. Payne, *J. Org. Chem.*, **31**, 718 (1966).

[612] H. Staudinger, *Ber. Deut. Chem. Ges.*, **44**, 1619 (1911).

[613] O. Hess, *Ber. Deut. Chem. Ges.*, **18**, 685 (1885).

[614] F. Klages and E. Zange, *Ann. Chem.*, **607**, 35 (1957).

[615] V. Prey, *Ber. Deut. Chem. Ges.*, **75**, 537 (1942).

[616] H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949).

[617] Q. E. Thompson, *J. Amer. Chem. Soc.*, **73**, 5841 (1951).

[618] N. O. V. Sonntag, *Chem. Rev.*, **52**, 308 (1953).

[619] W. Hückel, *Ann. Chem.*, **540**, 283 (1939).

[620] A. W. Titherley, *J. Chem. Soc.*, **85**, 1673 (1904).

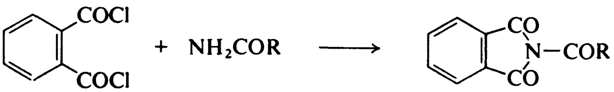
[621] R. W. Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

[622] R. W. Stoughton, H. L. Dickison, and O. G. Fitzhugh, *J. Amer. Chem. Soc.*, **61**, 408 (1939).

The heating can often be avoided by prior metalation of the amide. For example, using this method, Diels[623] diacylated ethyl carbamate (urethane) by two equivalents of ethyl chloroformate, obtaining triethyl nitrilotriformate (triethyl nitrogentricarboxylate):

$$NH_2COOR + 2ClCOOR + 2Na \xrightarrow{\text{Ether}} N(COOR)_3 + 2NaCl + H_2$$

Reaction of amides with phthaloyl dichloride to give ***N*****-acylphthalimides** has sometimes been used to characterize them:[624]



For this purpose the amide is heated with phthaloyl dichloride, either without a solvent or in toluene, until evolution of hydrogen chloride ceases.[624] This method is often superior to acylation of phthalimide[625] if it is a question of synthesizing *N*-acylphthalimides; *N*(*p*-toluenesulfonyl)phthalimide, for instance, can be obtained only by the phthaloyl dichloride method.[624]

Side reactions often interfere in the acylation of carboxamides by carbonyl chlorides; for example, exchange of acyl groups[626] or formation of amidines[627] may occur on treatment of anilides with acyl chlorides. Acyl chlorides may also dehydrate amides to nitriles.[617]

$$RCOCl + R'CONHC_6H_5 \longrightarrow R'COCl + RCONHC_6H_5$$

The original literature[628] should be consulted for acylation of cyanamide by acyl halides.

d. Other reactions

i, Isocyanates from phosgene and amino compounds[629,630]

Whereas the reaction of phosgene with an excess of a free amine leads to symmetrical urea derivatives, isocyanates can be prepared by the action of phosgene in excess on the hydrochlorides of primary amines. High temperatures are necessary for the latter reaction, which can be interpreted as preliminary loss of hydrogen chloride to give a carbamoyl chloride which decomposes, when heated, to isocyanate and hydrogen chloride:

$$RNH_2{\cdot}HCl + COCl_2 \xrightarrow{-2HCl} RNHCOCl \longrightarrow RNCO + HCl$$

This procedure is excellently suited to laboratory practice and fails only with the lowest members of the aliphatic series. It is customary to use an inert,

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[623] O. Diels, *Ber. Deut. Chem. Ges.*, **36**, 736 (1903); C. H. F. Allen and A. Bell, *Org. Syn.*, Coll. Vol. III, 415 (1955).

[624] T. W. Evans and W. M. Dehn, *J. Amer. Chem. Soc.*, **51**, 3651 (1929).

[625] C. D. Hurd and M. F. Dull, *J. Amer. Chem. Soc.*, **54**, 2432 (1932).

[626] A. Pictet, *Ber. Deut. Chem. Ges.*, **23**, 3011 (1890).

[627] C. A. Friedmann and O. G. Backeberg, *J. Chem. Soc.*, **1938**, 469.

[628] O. Diels and A. Wagner, *Ber. Deut. Chem. Ges.*, **45**, 874 (1912); A. F. Crowther, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, **1948**, 586.

[629] Review: W. Siefken, *Ann. Chem.*, **562**, 75 (1949).

[630] J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 203 (1948).

high-boiling solvent (toluene, xylene, chlorobenzene, or chloronaphthalene), whose boiling point should differ as much as possible from that of the isocyanate product. Reaction is easier if the amine salt is in as fine a form as possible, preferably freshly precipitated by gaseous hydrogen chloride from a solution of the amine in the reaction solvent. It is then stirred vigorously at 130–150°, or sometimes at higher temperatures, whilst phosgene is passed into or, better, over the suspension (or solution) until evolution of hydrogen chloride ceases.

Phenyl isocyanate:[631] A solution of aniline (93 g) in toluene (1 l) is saturated with dry gaseous hydrogen chloride at 70°, then phosgene is led into the boiling mixture until a clear solution is obtained. Distillation through an efficient column yields phenyl isocyanate (99 g, 83%), m.p. 158–168°.

Hexamethylene diisocyanate:[629] Very finely powdered hexamethylenediamine dihydrochloride (190 g) is suspended in dichlorobenzene (1 l), and phosgene is led in at 190–195°. A clear solution is obtained in 18 h. Separation from the solvent through a Widmer column affords hexamethylene diisocyanate (160 g, 95%), b.p. 132°/15 mm.

It is, however, also possible to start with the free amine, provided that reaction is first converted with an excess of phosgene in the cold. The amine, sometimes in solution, is usually added to a cooled solution of an excess of phosgene; the symmetrical urea derivative is not formed under these conditions, but instead a mixture of the amine hydrochloride and the carbamoyl chloride which then reacts further with phosgene as described above. For instance, the 4,4′-diisocyanate from diphenylmethane was prepared in this way.[629]

A further variant can be used with strongly basic aliphatic amines and has proved especially valuable for diamines whose hydrochlorides do not react with phosgene: first, dry carbon dioxide is led into a solution of the amine in a solvent suitable for the phosgene reaction, this giving a carbamic acid salt:

$$NH_2—R—NH_2 + CO_2 \longrightarrow {}^{+}NH_3—R—NH—COO^{-}$$

this is converted by phosgene, first in the cold into the carbamoyl chloride hydrochloride and then in the hot into the isocyanate:[629]

$$\begin{aligned} {}^{+}NH_3—R—NH—COO^{-} &\xrightarrow[-CO_2]{+COCl_2} [NH_3—R—NH—COCl]^{+}Cl^{-} \\ &\xrightarrow[-4HCl]{+COCl_2} OCN—R—NCO \end{aligned}$$

1,4-Cyclohexylene diisocyanate, for instance, was obtained in this way.[629]

In individual cases urea derivatives may be suitable as starting materials for preparation of isocyanates:

Phenyl isocyanate:[629] Diphenylurea (1.7 kg) is kept well mixed with 1-chloronaphthalene (4 kg) at 150° while phosgene (800 g) is led in during 4–5 h. Residual hydrogen chloride is then removed in a stream of air during 0.5 h. Fractional distillation gives pure phenyl isocyanate (1.6 kg), b.p. 55–57°/16 mm. The distillation residue can be used for further batches.

The simplest alkyl isocyanates are often best prepared by thermal fission of various urea or urethane derivatives.

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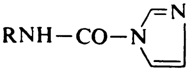
[631] D. V. N. Hardy, *J. Chem. Soc.*, **1934**, 2011.

For instance, **methyl isocyanate** can be prepared[629] by treating diphenylamine with phosgene, which gives diphenylcarbamoyl chloride; this can be converted by methylamine into the unsymmetrical urea derivative; this 3-methyl-1,1-diphenylurea (226 g), when heated at 240–290°, affords methyl isocyanate (57 g, 100%), b.p. 38–40°, and the distillation residue consists of diphenylamine.

The urea derivatives (**10**), obtained from equimolar amounts of 1,1′-carbonyldiimidazole and a primary amine, decompose into isocyanate and imidazole with especial ease, even merely on distillation.[632]



(**10**)

Cyclohexyl isocyanate:[632] Cyclohexylamine (6.15 g) is dropped gradually into a stirred solution of 1,1′-carbonyldiimidazole (10.06 g) in tetrahydrofuran. After removal of the solvent in a vacuum, distillation at 80–96°/45 mm (bath 170–185°) gives cyclohexyl isocyanate (6.41 g, 83%).

Recent work has considerably extended the synthesis of isocyanates from ureas, making isocyanates available that cannot be obtained by direct reaction of phosgene and amines.[633]

Isothiocyanates can be prepared by the analogous thermal fission of thioureas, and analogously the imidazole process using 1,1′-(thiocarbonyl)diimidazole[634] has been useful.

1-Naphthyl isothiocyanate:[635] 1-Naphthylthiourea (16.16 g) is heated in chlorobenzene (180 ml) at 150° under reflux for 8 h, then the chlorobenzene is distilled off, first at 20 mm, then at 1 mm. The residue is extracted with hexane (four 30-ml portions), which leaves a mixture of 1-naphthylthiourea and di-1-naphthylthiourea (0.65 g each) undissolved. The hexane solutions are united and evaporated, leaving 1-naphthyl isothiocyanate (12.75 g, 86%), needles, m.p. 58–58.5°.

Finally, acyl isocyanates have been prepared from carboxamides by use of oxalyl chloride in place of phosgene.[636]

ii, Isocyanides and formamides from chloroform and amines

Reaction of a primary amine with chloroform in the presence of an alkali hydroxide gives the isocyanide. This reaction has long been known for qualitative detection of primary amines but it often gives good yields on a preparative scale. It usually occurs exothermally on mere mixing of the components. By using benzene as solvent Malatesta[637] achieved yields of 80–85% from some aliphatic and arylalkyl amines (butyl, isopentyl, pentyl, benzyl).

Phenyl isocyanide, obtained from aniline, is difficult to free from unchanged aniline; samples containing aniline are generally colorless, but pure phenyl isocyanide polymerizes readily to blue indigo dianil.[638]

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[632] H. A. Staab and W. Benz, *Angew. Chem.*, **73**, 66 (1961); *Ann. Chem.*, **648**, 72 (1961).

[633] H. Ulrich and A. A. R. Sayigh, *Angew. Chem.*, **78**, 761 (1966).

[634] H. A. Staab and G. Walther, *Ann. Chem.*, **657**, 104 (1962).

[635] J. N. Baxter, J. Cymerman-Craig, M. Moyle, and R. A. White, *J. Chem. Soc.*, **1956**, 659.

[636] A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 3742 (1962); *Org. Syn.*, **46**, 16 (1966).

[637] L. Malatesta, *Gazz. Chim. Ital.*, **77**, 238 (1947).

[638] C. Grundmann, *Chem. Ber.*, **91**, 1380 (1958).

A carefully worked out procedure for preparation of **phenyl isocyanide** has been described by Grundmann:[638] A 3-l three-necked flask fitted with a KPG stirrer and two very efficient (Friedrich) condensers and containing a mixture of aniline (200 ml, 2.2 moles), chloroform (360 ml, 4.5 moles), and sodium hydroxide flakes (320 g, 8 moles) to which anhydrous ethanol (10 ml) has been added is warmed with stirring on a wire gauze until a spontaneous reaction sets in. This reaction soon becomes extremely violent but is held within the limits of the condensers by occasional cooling in a previously prepared ice-bath. Foaming may also occur and is only controlled by further reduction in the rate of reaction. When the spontaneous reaction is over, the mixture is heated and stirred under gentle reflux for a further hour, but as the batch becomes continuously more viscous care is needed to see that it does not set hard on the glass. The total reaction time is 1.5–3 h. After cooling, the mixture is filtered in a fume cupboard and the insoluble matter is washed with ether (250 ml). The dark brown filtrate is separated from a small amount of aqueous phase and then distilled at 100 mm from a water-bath whose temperature does not exceed 50°. The material remaining after removal of the solvent is at once fractionated in a vacuum through an efficient column; phenyl isocyanide (73–75 g) distils at 57–62°/14 mm; a second fraction, b.p. 62–73°/14 mm (89 g), consists mainly of aniline and can be reused for a further batch. Redistillation of the first fraction through the column gives completely pure phenyl isocyanide (71 g), b.p. 53.5 to 54°/13 mm, which at once becomes blue and is thus free from aniline. The yield is 55% after allowance for recovered aniline.

For further information about isocyanides see page 479. Their preparation by removal of water from substituted formamides should also be noted.[639] The chemistry of isocyanides has been reviewed by Ugi and his collaborators.[640]

Secondary amines react with chloroform under the same conditions as primary amines do, but the products are *N*,*N*-disubstituted formamides[641,642] and not isocyanides.

For example, dibutylamine (129.2 g) and chloroform (160 ml) were treated dropwise with a solution of sodium hydroxide (160 g) in methanol (1 l); after the exothermic reaction the mixture was heated for 24 h under reflux, then filtered, cooled, and distilled in a vacuum, yielding unchanged dibutylamine (19.9 g, 15%) and ***N*,*N*-dibutylformamide** (102 g, 65%), b.p. 63°/0.1 mm, n_D^{25} 1.4419.[641]

2. Reaction of halogen compounds with other nitrogen compounds

a. With nitrites

Alkyl halides can be converted into nitro compounds by treatment with metal nitrites (for a review see Kornblum[146]). The older directions almost all prescribe silver nitrite at elevated temperatures (ca. 80–110°). However, because of the numerous side reactions it is only for the simplest primary iodides (up to about C_5) that this reaction gives satisfactory yields (about 50%). Only in a few cases can bromides be used.[643] Recently, however, the process has been made economic by using considerably milder conditions. It is advisable

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[639] I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960); I. Ugi, W. Betz, U. Fetzer, and K. Offermann, *Chem. Ber.*, **94**, 2814 (1961).

[640] I. Ugi and co-workers, *Angew. Chem. Int. Ed., Engl.*, **4**, 472 (1965).

[641] M. B. Frankel, H. Feuer, and J. Bank, *Tetrahedron Lett.*, **1959**, No. 7, 5; cf. *Angew. Chem.*, **71**, 682 (1959).

[642] M. Saunders and R. W. Murray, *Tetrahedron*, **6**, 88 (1959).

[643] A. I. Vogel, *J. Chem.. Soc.*, **1948**, 1847.

to work at as low a temperature as possible and with ether as diluent. In this way primary nitroalkanes could be obtained in yields of around 80% from silver nitrite and alkyl iodides, or even bromides, with straight chains of up to eight carbon atoms.[644] Branched halides can also be used if the branching is not closer than β to the halogen atom,[644] but the method has no practical value for secondary or tertiary halides.[645] The directions below for 1-nitrooctane can be generalized for preparation of any of the lower primary nitro compounds from the iodide or bromide.

1-Nitrooctane:[644,646] A mixture of silver nitrite (100 g, 0.65 mole) and dry ether (150 ml) is cooled to 0° in a three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. Octyl iodide (120 g, 0.5 mole) is dropped in during 2 h, with stirring and exclusion of light. Stirring is continued for 24 h at 0° and for a further 36 h or more at room temperature — until the solvent no longer shows a positive Beilstein test for halogen. The silver salts are then filtered off and washed with much ether. The filtrate and washings are united and the ether is distilled off at atmospheric pressure through a column, and the residue is fractionated in a vacuum. Octyl nitrite (8.4 g) distils over first, at 51°/5 mm (n_D^{20} 1.4124-25); an intermediate fraction (b.p. 56–71°/3 mm) is followed by 1-nitrooctane (83%, 64.9 g), n_D^{20} 1.4321–1.4323, at 71.5–72°/3 mm. For the preparation of silver nitrite see *Organic Syntheses*.[646]

ω-Nitroalkylamines, *e.g.*, 5-nitropentylamine,[647] can be prepared similarly from *N*-(ω-haloalkyl)phthalimides.

Until recently there were few cases in which an alkali nitrite could replace silver nitrite in the synthesis of nitro compounds. Such a case was Kolbe's nitroalkane synthesis, in which an alkali salt of a 2-haloalkanoic acid was treated with a boiling aqueous solution of an alkali nitrite; the 2-nitroalkanoic acid formed lost carbon dioxide under the reaction conditions and the nitroalkane distilled over in the steam. The Kolbe synthesis is, however, of practical use only for the preparation of nitromethane (38% yield from chloroacetic acid[648]) and nitroethane (about 50% yield from 2-bromopropionic acid[649]): it is substantially valueless for higher fatty acids.[649,650]

If, however, 2-bromoalkanoic esters are kept for several days in an aqueous-alcoholic solution of sodium nitrite at room temperature, good yields of the 2-(hydroxyimino) ester can be isolated (the Lepercq reaction).[164]

Recently, however, Kornblum *et al.*[651] showed that alkali nitrites, in particular sodium nitrite, can replace silver nitrite in the preparation of nitro compounds if dimethylformamide is used as solvent. The method has the additional advantage that not merely primary but also secondary alkyl iodides and bromides react readily in this solvent. Yields are around 60% in both cases. It usually suffices to stir the halide with an excess of sodium nitrite in dimethylformamide for some hours at room temperature; primary iodides need about 2.5 hours, primary bromides about 6 hours for complete reaction. With secondary halides it is advisable to add urea as this raises the solubility

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[644] N. Kornblum, B. Taub, and H. E. Ungnade, *J. Amer. Chem. Soc.*, **76**, 3209 (1954).

[645] N. Kornblum, R. A. Smiley, H. E. Ungnade, A. M. White, B. Taub, and S. A. Herbert Jr., *J. Amer. Chem. Soc.*, **77**, 5528 (1955).

[646] N. Kornblum and H. E. Ungnade, *Org. Syn.*, **38**, 75 (1958).

[647] V. Prelog and co-workers, *Helv. Chim. Acta*, **43**, 901 (1960).

[648] F. C. Whitmore and M. G. Whitmore, *Org. Syn.*, **3**, 83 (1923).

[649] V. Auger, *Bull. Soc. Chim. France*, [iii], **23**, 333 (1900).

[650] W. Treibs and H. Reinheckel, *Chem. Ber.*, **87**, 341 (1954).

of sodium nitrite in dimethylformamide and accelerates the reaction.[651] It is further advisable to destroy the alkyl nitrite formed as by-product by means of phloroglucinol, since the nitrite can react with the nitro compound and thus lower the yield of the latter considerably.[164,651,652] The reaction time can be very appreciably shortened by using dimethyl sulfoxide as solvent; then too it is unnecessary to add urea or phloroglucinol.[651,653]

4-Nitroheptane:[651] 4-Iodoheptane (67.8 g, 0.3 mole) is poured into a stirred mixture of sodium nitrite (36 g, 0.52 mole), urea (40 g, 0.67 mole), and dimethylformamide (600 ml). Slight cooling keeps the reaction temperature at not more than 20–25°. Stirring is continued for 5.5 h, then the mixture is poured into ice-water (1.5 l), which is next extracted four times with light petroleum (100-ml portions, b. p. 35°). The united extracts are washed with 10% aqueous sodium thiosulfate solution, then four times with water (75-ml portions), and dried over magnesium sulfate. The petroleum is removed at room temperature and the residue is fractionated in a vacuum through a column, providing a forerun (ca. 10.9 g, 25%) of 1-propylbutyl nitrite, b.p. 44°/18 mm, n_D^{20} 1.4032, and then 4-nitroheptane (26.4 g, 60%), b.p. 59°/8 mm, n_D^{20} 1.4219.

α,ω-Dinitroalkanes, *e.g.*, 1,6-dinitrohexane,[654] are obtained analogously from α,ω-dibromoalkanes.

If the Kornblum synthesis is to be applied to halo carboxylic esters it is essential to add phloroglucinol whether dimethylformamide or dimethyl sulfoxide is used as solvent, because otherwise the α-(hydroxyimino) ester is the predominant product.[655,cf.164,652]

Organic Syntheses contains detailed directions[656] for preparation of ethyl 2-nitrobutyrate (75% yield), which can be applied also to other haloalkanoic esters. Ethyl nitroacetate cannot be prepared in this way,[657] but is obtained in 77% yield by the action of silver nitrite on ethyl iodoacetate during several days at room temperature;[658] oxidation of ethyl α-(hydroxyimino)acetoacetate by bichromate and sulfuric acid can also be recommended.[659]

b. With azides

Sodium azide can substitute an azide group for the halogen atom of alkyl or acyl halides.

N.B.: A number of serious accidents have occurred due to spontaneous explosion of organic azides. Statements in the literature about the supposed stability of individual azides, particularly those of low molecular weight, should not be implicitly trusted (see, for example, Grundmann and Haldenwanger[660]). All operations with azides must be carried out with extreme care and with safety precautions similar to those used in work with peroxides, as described on page 306. Particular attention is directed also to the toxicity of hydrogen azide (hydrazoic acid).

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[651] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Amer. Chem. Soc.*, **78**, 1497 (1956).

[652] N. Kornblum, R. K. Blackwood, and D. D. Mooberry, *J. Amer. Chem. Soc.*, **78**, 1501 (1956).

[653] N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).

[654] J. K. Stille and E. D. Vessel, *J. Org. Chem.*, **25**, 478 (1960).

[655] N. Kornblum, R. K. Blackwood, and J. W. Powers, *J. Amer. Chem. Soc.*, **79**, 2507 (1957).

[656] N. Kornblum and R. K. Blackwood, *Org. Syn.*, **37**, 44 (1957).

[657] N. Kornblum and W. M. Weaver, *J. Amer. Chem. Soc.*, **80**, 4333 (1958).

[658] N. Kornblum, M. E. Chalmers, and R. Daniels, *J. Amer. Chem. Soc.*, **77**, 6654 (1955).

[659] M. W. Rodionow, I. W. Matschinskaja, and W. M. Belikow in "Synthesen organischer Verbindungen," VEB Verlag Technik, Berlin, 1959, Vol. 1, p. 120.

[660] C. Grundmann and K. Haldenwanger, *Angew. Chem.*, **62**, 410 (1950).

Alkyl azides are usually prepared by warming alkyl iodides or bromides with an excess of sodium azide in an organic solvent.[661] Glycol ethers are recommended as solvents for the simple alkyl azides (C_3–C_{10}).[662]

Pentyl azide:[662] A mixture of activated sodium azide[663] (27 g), diethylene glycol monoethyl ether ("Carbitol") (450 ml), and water (75 ml) is placed in a 1-l three-necked flask fitted with a reflux condenser, thermometer, and stirrer; the mixture is stirred while pure pentyl iodide (60 g) is added in one portion. The solid dissolves within a few minutes. Whilst being continuously stirred, the mixture is heated during 3 h to 95° and then kept at that temperature for 20 h. It is then cooled and poured in two portions into separate portions of ice-water (each 800 ml). The aqueous phases are separated and extracted twice with ether (200-ml batches). The ether solutions are united with the previous organic phases, and the ether is evaporated. The residue (42 g) is fractionated in a vacuum, giving the azide, b.p. 77–78°/112 mm, n_D^{20} 1.4266 (27.8 g, 81.4%).

Further examples, where other solvents are used, are to be found in the literature.[664–666]

Carbonyl azides are usually obtained from the hydrazides, although in principle they can also be prepared directly from the carbonyl chlorides and sodium azide. They are frequently used as intermediates for synthesis of isocyanates, urethanes, ureas, amines, etc., and are often used in such work without isolation.

They can be prepared either in an inert organic solvent or, particularly when from an aromatic acid chloride, in an aqueous-organic medium. Cooling is necessary to avoid decomposition of the azide to the isocyanate.

***m*-Nitrobenzoyl azide:**[667] An ice-cold, concentrated aqueous solution of sodium azide (20 g) is stirred into a cooled acetone solution of *m*-nitrobenzoyl chloride (50 g). The azide crystallizes when the mixture is kept in the ice-bath. Purified by dissolution in acetone and precipitation by water, it melts at 68° (yield 53 g).

Ethyl azidoformate:[668] A solution of ethyl chloroformate (50 g) in pure ether (50 ml) is dropped, with stirring, into a solution, cooled in ice, of sodium azide (35 g) in distilled water (190 ml). Stirring is continued for a further 2.5 h with continued cooling, then the ether phase is separated, the aqueous phase is extracted with ether, and the combined ether solutions are dried over sodium sulfate. The ether is distilled off at atmospheric pressure and the residue is distilled in a vacuum through a short Vigreux column (87.4%; b.p. 39–41°/30 mm). Before use the product should be distilled again in a vacuum; it then has n_D^{25} 1.4180. It is best kept in a refrigerator, since it decomposes readily at room temperature, particularly in light. **(Caution: poisonous, explosive!)**

Owing to the insolubility of sodium azide in inert organic solvents its rate of reaction therein becomes reasonable only when the mixture is warmed to about 60–80°. To facilitate reaction it is advisable to activate the sodium azide in advance,[663] although the azides then often decompose to isocyanates with loss of nitrogen; methyl, hexyl, and phenyl isocyanate, *inter alia*, have indeed been prepared in this way.[669] *Organic Syntheses* contains a detailed

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[661] J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).

[662] E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, **22**, 238 (1957).

[663] P. A. S. Smith, *Org. Reactions*, **3**, 382 (1946); cf. J. Nelles, *Ber. Deut. Chem. Ges.*, **65**, 1345 (1932).

[664] J. H. Boyer and J. Hamer, *J. Amer. Chem. Soc.*, **77**, 951 (1955); J. H. Boyer, F. C. Canter, J. Hamer, and R. K. Putney, *J. Amer. Chem. Soc.*, **78**, 325 (1956).

[665] T. Wieland and H. J. Hennig, *Chem. Ber.*, **93**, 1236 (1960).

[666] L. Horner and A. Groß, *Ann. Chem.*, **591**, 117 (1955).

[667] C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **16**, 349 (1933).

[668] W. Lwowski and T. W. Mattingly, *J. Amer. Chem. Soc.*, **87**, 1947 (1965).

[669] G. Schroeter, *Ber. Deut. Chem. Ges.*, **42**, 3356 (1909).

description[670] of the preparation of undecyl isocyanate, in which the azide is obtained in aqueous acetone and then decomposed to the isocyanate in benzene. Isocyanates prepared in this way are often converted into urethanes, amines, etc., without isolation.

c. With cyanides

Alkylation and acylation of readily dissociable metal cyanides, *e.g.*, alkali cyanides, lead almost exclusively to linkage of carbon to carbon, as in formation of nitriles[671] or acyl cyanides,[672] respectively, but undissociated cyanides can also be alkylated on nitrogen.

To obtain isocyanides Gautier heated silver cyanide with 0.5–1.0 equivalent of alkyl iodide for several hours on a steam-bath; for low-boiling alkyl iodides a pressure vessel is used. The mixture should not become brown in this reaction. The isocyanide is precipitated as a complex with silver cyanide, which, after removal of the excess of alkyl iodide by distillation, is decomposed by addition of a concentrated solution of potassium cyanide. The isocyanide can then be isolated by distillation.

Detailed directions for preparation of ethyl isocyanide are to be found in *Organic Syntheses.*[673]

Nitriles can be *N*-alkylated and *N*-acylated, to give nitrilium salts, in inert solvents containing complex-forming metal chlorides such as antimony(V) chloride and iron(III) chloride.[674] These nitrilium salts afford *N*-alkylated and *N*-acylated amides in high yields on alkaline hydrolysis.[674]

d. With cyanates

Isocyanic esters have only rarely been prepared by alkylation of salts of cyanic acid by alkyl halides[674,675] (cf. pages 472 and 500).

Butyl isocyanate:[676] Potassium cyanate (40.5 g) is heated at ca. 90° under reflux for 15 min with butyl bromide (75 g) in anhydrous dimethylformamide (250 ml; dried over calcium hydride). Then distillation gives a crude product, b.p. 105–135° (98 g; isocyanate content 41 g, 82%), which on further fractionation gives material of b.p. 112–115° (37 g, 75%).

Acyl isocyanates can be prepared from silver cyanate and acid halides.

Because of their great sensitivity to water, acyl isocyanates must be rigidly protected therefrom.

When they are prepared in anhydrous ethereal solution, the reaction is usually complete in 1–3 h at room temperature or after gentle warming.[677,678] For preparation of benzoyl isocyanate, silver cyanate and benzoyl chloride were heated under reflux for 6 h in carbon tetrachloride.[679] Older preparations, *e.g.*, that of acetyl isocyanate,[680] were made also without solvent but under cooling.

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[670] C. F. H. Allen and A. Bell, *Org. Syn.*, Coll. Vol. III, 846 (1955).

[671] D. T. Mowry, *Chem. Rev.*, **42**, 189 (1948).

[672] J. Thesing, D. Witzel, and A. Brehm, *Angew. Chem.*, **68**, 425 (1956).

[673] H. L. Jackson and B. C. McKusick, *Org. Syn.*, **35**, 62 (1955).

[674] H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956).

[675] J. J. Donleavy and J. English Jr., *J. Amer. Chem. Soc.*, **62**, 218 (1940).

[676] C. M. Himel and L. M. Richards, U.S. Pat. 2,866,801; *Chem. Abstr.*, **53**, 9145 (1959); W. Gerhardt, *J. Prakt. Chem.*, **38**, 77 (1968).

[677] A. J. Hill and W. M. Degnan, *J. Amer. Chem. Soc.*, **62**, 1595 (1940).

[678] T. Lieser and K. Macura, *Ann. Chem.*, **548**, 243 (1941).

[679] C. L. Arcus and B. S. Prydal, *J. Chem. Soc.*, **1954**, 4018.

[680] O. C. Billeter, *Ber. Deut. Chem. Ges.*, **36**, 3213 (1903).

III. Replacement of oxygen by nitrogen

1. Reactions of acid derivatives with nitrogen compounds

a. Reactions of free acids with nitrogen compounds

Ammonia and primary and secondary amines can be acylated by heating them with carboxylic acids. The removal of water occurs within the framework of an equilibrium that affords worthwhile amounts of amide only at temperatures above 100° (usually at 180–200°). So one of the starting materials (acid or amine) is usually taken in excess and the water formed is removed continuously from the reaction mixture. For formylation only, aqueous acid can be used. Yields are mostly good.

To obtain unsubstituted amides it is often enough to distil the dry ammonium salt of the acid; the temperature required for this reaction can often be lowered by addition of ammonium hydrogen carbonate. An excess of glacial acetic acid has proved advantageous for preparation of acetamide.[681] Amides of the higher fatty acids (C_8–C_{18}) have been prepared by passing gaseous ammonia for 10–14 hours into the acid heated at 190–210°.[682,cf.683] A good preparation of unsubstituted amides is provided by melting the carboxylic acids with urea or thiourea.[684]

Heptanamide, for instance, was obtained in 70–80% yield by heating urea (1 mole) with heptanoic acid (0.5 mole) at 170–180° for 4 h.[685]

Urea may be replaced by an amide of a more volatile acid, *e.g.*, formamide was used to afford the amide of oleic acid.[686]

N-Substituted carboxamides can be obtained analogously, *e.g.*, the dimethylamides of simple aliphatic acids by passing dimethylamine into the hot acid.[683,687] For the preparation of benzanilide molar amounts of aniline and benzoic acid are heated at 180–190°, yields being 84%.[688] The urea method can also be applied for *N*-substituted amides, if appropriately substituted ureas or thioureas are used.[689,690] The following technique has proved useful for preparation of a variety of carboxanilides:

Carboxanilides:[689] An intimate mixture of equimolar amounts of the carboxylic acid and 1,3-diphenylurea is slowly heated in a Giesler flask in an oil-bath. After 20–30 min with a bath-temperature of about 200–205° the mixture begins to foam; foaming ceases after a further 0.5 h at about 210–220°, the reaction then being at an end. After cooling, the product is dissolved in ether, freed from the aniline produced by extraction twice with a slight excess of 6% hydrochloric acid, and washed with water. Drying over calcium chloride and evap-

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[681] G. H. Coleman and A. M. Alvarado, *Org. Syn.*, **3**, 3 (1923).

[682] A. W. Ralston, C. W. Hoerr, and W. O. Pool, *J. Org. Chem.*, **8**, 473 (1943).

[683] J. A. Mitchell and E. E. Reid, *J. Amer. Chem. Soc.*, **53**, 1879 (1931).

[684] E. Cherbuliez and F. Landolt, *Helv. Chim. Acta*, **29**, 1315, 1438 (1946); A.-U. Rahman, M. A. Medrano, and O. P. Mittal, *Rec. Trav. Chim.*, **79**, 188 (1960).

[685] J. L. Guthrie and N. Rabjohn, *Org. Syn.*, **37**, 50 (1957).

[686] E. T. Roe, J. T. Scanlon, and D. Swern, *J. Amer. Chem. Soc.*, **71**, 2215 (1949).

[687] J. R. Ruhoff and E. E. Reid, *J. Amer. Chem. Soc.*, **59**, 401 (1937).

[688] C. N. Webb, *Org. Syn.*, **7**, 6 (1927).

[689] A. Rahman and M. O. Farooq, *Chem. Ber.*, **86**, 945 (1953).

[690] A.-U. Rahman, M. A. Medrano, and B. E. Jeanneret, *J. Org. Chem.*, **27**, 3315 (1962).

oration of the ether leaves the crude anilide as residue. If the anilide is sparingly soluble in ether it suffices merely to wash out the aniline formed by means of ether. Yields are around 90%.

This procedure affords *N*-phenylsuccinimide from succinic acid.

Water can also be removed from ammonium salts by heating them in high-boiling inert solvents, the water being continuously removed as azeotrope. Nitrobenzene and xylene have been used for this purpose. Formylations occur relatively readily and for formylation of, *e.g.*, *N*-methylaniline it suffices to use boiling toluene.[691]

There have, of course, been many attempts to moderate the reaction conditions by various additions and to make the process usable for more sensitive substances. For instance, adding small amounts of concentrated sulfuric acid have been recommended for acylation of aromatic amines, or similarly addition of aluminum chloride. Phosphoric oxide has sometimes been added to bind the water formed. In other cases it proved valuable to add the anhydride of the acid in question, but its action is not limited to binding the water because, being a stronger acylating agent than the acid, it must itself perform much of the acylation of the ammonia.

***N*-Propylacetamide:**[692] Acetic acid (30 g) is added slowly to propylamine (25g) in a 250-ml flask fitted with a reflux condenser; reaction is violent. Acetic anhydride (50 ml) is next added and the mixture is heated under reflux for 0.5 h, after which the acetic acid is distilled off through a column. When this has been achieved (70 ml of distillate), distillation is continued without a column, giving a small forerun and then *N*-propylacetamide (34–35 g, about 90%), b.p. 208°/760 mm, 100°/16 mm.

In many cases the catalysts added have, however, a more deep-seated effect: they form very reactive intermediates with either the acid or the amine — intermediates that can often be isolated.

For instance, the reaction of amines with carboxylic acids occurs under appreciably milder conditions if phosphorus trichloride is added; the reaction does not proceed by way of the intermediate acid chloride, as previously assumed, but the amine and phosphorus trichloride first form a "phosphorazo compound" (phosphoramidic imide) which in turn reacts with the carboxylic acid to give the amide:[693]

$$5RNH_2 + PCl_3 \longrightarrow RN{=}P{-}NHR + 3RNH_3Cl$$

$$RN{=}P{-}NHR + 2RCOOH \longrightarrow 2RCONHR + [HPO_2]$$

The two steps can be realized separately,[693,694] but it is customary to work without isolating the phosphorazo compound. Recently the method has been much used for synthesis of peptides from amino esters and *N*-protected amino acids.[694–698] Benzene, dioxan, and pyridine are among the solvents used. The technique will be evident from an example:

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[691] L. F. Fieser and J. E. Jones, *Org. Syn.*, Coll. Vol. III, 590 (1955).

[692] K. Heyns and W. von Bebenburg, *Chem. Ber.*, **86**, 278 (1953).

[693] H. W. Grimmel, A. Guenther, and J. F. Morgan, *J. Amer. Chem. Soc.*, **68**, 539 (1946).

[694] S. Goldschmidt and H. Lautenschlager, *Ann. Chem.*, **580**, 68 (1953).

[695] S. Goldschmidt and C. Jutz, *Chem. Ber.*, **86**, 1116 (1953); **89**, 518 (1956); S. Goldschmidt and G. Rosculet, *Chem. Ber.*, **93**, 2387 (1960).

[696] O. Süs, *Ann. Chem.*, **572**, 96 (1951).

[697] W. Grassmann and E. Wünsch, *Chem. Ber.*, **91**, 449 (1958).

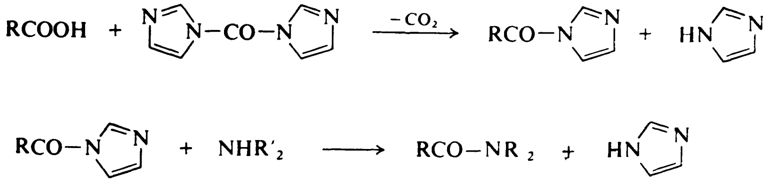
[698] W. Grassmann, E. Wünsch, and A. Riedel, *Chem. Ber.*, **91**, 455 (1958).

Benzyloxycarbonyl-L-alanylglycine ethyl ester:[697] Very pure phosphorus trichloride (4.36 ml) in pyridine (25 ml) is stirred dropwise into a cooled solution of glycine ethyl ester (10.3 g) in dry pyridine (150 ml), and the mixture is left for a short time at room temperature. Then benzyloxycarbonyl-L-alanine (22.5 g) is added in one portion and the mixture is stirred for 3 h whilst heated on a water-bath. After cooling, any polyphosphorous acid that has separated is filtered off, an operation that considerably helps later working up. The solvent is next removed in a vacuum at 40–50° and the residue is partitioned between ethyl acetate and dilute hydrochloric acid, the aqueous phase being kept acid to Congo Red. The organic phase is washed carefully with potassium hydrogen carbonate solution, to remove any unchanged benzyloxycarbonyl amino acid (or any slight excess thereof), then washed with water, dried over sodium sulfate, and freed from solvent by distillation. This gives the benzyloxycarbonyl peptide ester as long, snow-white needles (26.8 g, 87%), which after recrystallization from ethyl acetate–light petroleum have m.p. 100°.

Phosphorus oxychloride has been used for the same purpose, but less often than the trichloride. Klosa[699] has described a general process for using it in the preparation of carboxanilides. It was also used in preparation of (cyanoacetyl)urea as part of Traube's uric acid synthesis:

(Cyanoacetyl)urea:[700] Phosphorus oxychloride (1 mole) is dropped very slowly into a stirred mixture of urea (6 moles) and cyanoacetic acid (2 moles). The heat of reaction liquifies the mixture which, however, later solidifies again. More powerful heating is to be avoided (discoloration). Treatment with water leaves undissolved (cyanoacetyl)urea, m.p. 209–212° (dec.).

Acylation of amines by carboxylic acids occurs in excellent yield at room temperature if carried out in the presence of the calculated amount of 1,1′-carbonyldiimidazole in an inert solvent such as tetrahydrofuran.[701] It involves formation of the acylimidazole as intermediate which is transamidated by the amine.[702,703] It is necessary to use dry reagents and to exclude moisture.



The calculated amount of 1,1′-carbonyldiimidazole (see page 469) is added to the carboxylic acid in dry tetrahydrofuran. When evolution of carbon dioxide ceases, the calculated amount of amine is added. Reaction is quantitative after about an hour at 20°.[702]

This method is well suited for amino acid coupling because of the ease of formation of the amide link.[600]

1,1′-Thionyl-[704] and 1,1′-thiocarbonyl-diimidazole[705] have been used analogously to the carbonyl compound.

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[699] J. Klosa, *Arch. Pharm.*, **286**, 253 (1953).

[700] W. Traube, *Ber. Deut. Chem. Ges.*, **3T**, 3043 (1900).

[701] H. A. Staab, *Angew. Chem., Int. Ed., Engl.*, **1**, 351 (1962).

[702] H. A. Staab, *Angew. Chem.*, **71**, 164 (1959).

[703] H. A. Staab, M. Lüking, and F. H. Dürr, *Chem. Ber.*, **95**, 1275 (1962).

[704] H. A. Staab and K. Wendel, *Angew. Chem.*, **73**, 26 (1961).

[705] H. A. Staab and G. Walther, *Ann. Chem.*, **657**, 98 (1962).

Amides are also formed at room temperature if a mixture of a carboxylic acid and an amide is treated with a suitable carbodiimide, such as 1,3-dicyclohexylcarbodiimide.[706–710] This method can often be operated, moreover, in an aqueous medium:

$$\mathrm{RCOOH + NH_2R' + C_6H_{11}N{=}C{=}NC_6H_{11} \longrightarrow RCONHR' + C_6H_{11}NH{-}CO{-}NHC_6H_{11}}$$

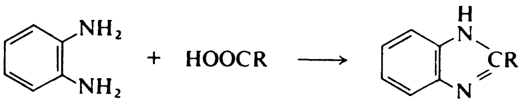
The 1,3-dicyclohexylurea formed as by-product is usually easy to separate because of its slight solubility in organic solvents.

Phthaloylleucylvaline ethyl ester:[710] DL-Valine ethyl ester hydrochloride (1.82 g, 10 mmoles) in dry tetrahydrofuran (20 ml) is treated at 0° with triethylamine (1.38 ml). The triethylamine hydrochloride is filtered off after an hour and washed well with tetrahydrofuran. Phthaloylleucine (2.57 g, 10 mmoles) is dissolved in the filtrate, and then at −8° dicyclohexylcarbodiimide (2.26 g, 11 mmoles). The mixture is left for 2 h at −5° and then at room temperature overnight. The separated 1,3-dicyclohexylurea is filtered off and the filtrate is evaporated in a vacuum, leaving a syrup which is dissolved in ethyl acetate (25 ml) and washed with 2N-hydrochloric acid (25 ml) and water (two 25-ml portions). The solution is dried over sodium sulfate, filtered, and evaporated in a vacuum, the residue (3.5 g, 90%) solidifying to a glass on storage; this product is very soluble in alcohols, chloroform, ethyl acetate, pyridine, or dimethylformamide, moderately soluble in benzene or toluene, but insoluble in ether, light petroleum, or water.

When applied to hydroxylamines, *e.g.*, *O*-benzylhydroxylamine,[711] the carbodiimide gives analogously hydroxamic acids.

It is impossible here to describe in detail the very many variants for acylation of amines by carboxylic acids, *e.g.*, the use of ethynyl ethers[712] or tetraethyl pyrophosphate;[713] these may be found in reviews of peptide syntheses by, *e.g.*, Wieland and others.[714,715]

The reaction of amines with carboxylic acids can also be used to build heterocyclic ring systems. Aliphatic 1,2-diamines and carboxylic acids or their derivatives give imidazolines;[716] boiling *o*-phenylenediamine with a carboxylic acid for 0.5 hour gives the 2-alkylbenzimidazole:[717]



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[706] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).

[707] H. G. Khorana, *Chem. & Ind.* (*London*), **1955**, 1087.

[708] J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, **21**, 439 (1956).

[709] J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Amer. Chem. Soc.*, **78**, 1367 (1956).

[710] B. Helferich and H. Böshagen, *Chem. Ber.*, **92**, 2813 (1959).

[711] P. A. Plattner and co-workers, *Helv. Chim. Acta*, **40**, 1545 (1957).

[712] J. F. Arens, *Rec. Trav. Chim.*, **74**, 769 (1955).

[713] J. Blodinger and G. W. Anderson, *J. Amer. Chem. Soc.*, **74**, 5514 (1952); cf. G. W. Anderson, J. Blodinger, R. W. Young, and A. D. Welcher, *J. Amer. Chem. Soc.*, **74**, 5304 (1952).

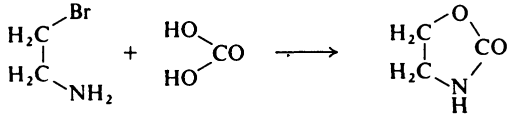
[714] T. Wieland and co-workers, *Angew. Chem.*, **63**, 7 (1951); 66, 507 (1954); **69**, 362 (1957); **71**, 417 (1959); **75**, 539 (1963).

[715] W. Grassmann and E. Wünsch, *Fortschr. Chem. Org. Naturstoffe*, **13**, 444 (1956).

[716] R. J. Ferm and J. L. Riebsomer, *Chem. Rev.*, **54**, 593 (1954).

[717] W. O. Pool, H. J. Harwood, and A. W. Ralston, *J. Amer. Chem. Soc.*, **59**, 178 (1937).

2-bromoethylamine and carbon dioxide (as $NaHCO_3$) give 2-oxazolidinone:[718]



Whereas all the reactions of carboxylic acids mentioned above lead to amides, *N*,*N'*-diarylformamidines are obtained directly from formic acid (cf. page 494). Equal amounts (by weight) of sodium formate and amine hydrochloride are allowed to react with a five-fold amount of a primary aromatic amine in absence of moisture; conversion is complete after 10–15 minutes under reflux and is used for detection of formic acid in admixture with other monobasic aliphatic acids.[719]

b. Reactions of acid anhydrides with nitrogen compounds

Carboxylic anhydrides are more powerful than the free acids as acylating agents and convert ammonia and primary and secondary amines into amides, generally smoothly and in very good yield. The equation

$$RCO—C—COR + NHR'_2 \longrightarrow RCONR'_2 + RCOOH$$

shows that only half the acid is utilized for acylation, which may be a disadvantage, particularly when the acid is valuable. Thus, in the aliphatic series it is generally only the cheap and readily accessible acetic anhydride that is used in practice, although most of the homologous anhydrides also give good yields. For acylation the anhydrides have the advantage over acids that they can be used at lower temperatures, and over acid halides that it is generally unnecessary to add an excess of the amine or another base to bind the acid formed.

Reaction conditions can be varied within wide limits. Merely mixing the amine and anhydride often sets off an exothermic reaction, but the mixture is usually heated subsequently for 1–2 hours on the steam-bath or under reflux. A solvent is not always needed when the reactants are liquid.

***N*-Acetylbenzylamine:**[692] Acetic anhydride (20 g) is dropped into benzylamine (21 g), the mixture is boiled for a short time under reflux, and the acetic acid formed is distilled off through a column. Then (after 9 ml has distilled) distillation is continued without a column but in a vacuum and with an air-condenser, yielding a small forerun and then *N*-acetylbenzylamine (95%), b.p. 191°/23 mm, m.p. 61°.

Normally, however, a solvent is not dispensed with. For acetylations it may be an excess of the anhydride; or glacial acetic acid may be used. Solvents of general utility are ether, light petroleum, benzene, and toluene; dimethylformamide and pyridine have been used but less often; use of alcohols is restricted to reactions at low temperatures.

***p*-Nitroacetanilide:**[720] A warm concentrated solution of *p*-nitroaniline (13.8 g) in benzene is treated with acetic anhydride (10.5 g). The heat of reaction causes the mixture to boil, but *p*-nitroacetanilide, m.p. 215–216°, crystallizes out immediately and almost quantitatively.

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[718] S. Gabriel and G. Eschenbach, *Ber. Deut. Chem. Ges.*, **30**, 2494 (1897).

[719] W. B. Whalley, *J. Chem. Soc.*, **1948**, 1014.

[720] A. Kaufmann, *Ber. Deut. Chem. Ges.*, **42**, 3480 (1909).

Formylation is best carried out with the readily accessible mixed anhydride of formic and acetic acid.[721]

Aromatic anhydrides mostly react more slowly than aliphatic ones. For the analogous benzoylation of *p*-nitroaniline the amine is boiled with benzoic anhydride in benzene for 1.5 hours.[720]

Carboxylic anhydrides are hydrolysed only slowly in the cold and water can therefore often be used as reaction medium for acylations by them:

***N*-Acetylglycine:**[722] Glycine (75 g) is dissolved in water (300 ml) and stirred while 95% acetic anhydride (215 g) is added in one portion. The mixture becomes warm but is stirred for a further 15–20 min. The crystallization that has begun is then completed by external cooling. The product is collected next day, washed with cold water, and dried at 100–110°; it has m.p. 207–208° (yield 75–85 g).

The filtrate and wash-water are evaporated to dryness at 50–60° in a vacuum; on crystallization from boiling water (75 ml) the residue affords a further amount (20–30 g) of the acetylglycine, and still a little more (4–6 g) can be isolated from the mother liquor therefrom. The total yield thus reaches 104–108 g (89–92%).

Even aromatic amines can be acylated in an aqueous medium. For example, *p*-anisidine was dissolved in dilute acetic acid for acetylation.[723,cf.724] Further, amines can often be brought to reaction as mineral salts in aqueous solution,[725] the mineral acid liberated being buffered by sodium acetate.[726]

Introduction of two acyl groups into an amine, and acylation of an amide, naturally require more drastic conditions.[727,728] For conversion into the diacetyl derivative, for instance, 2,6-dibromo-*p*-toluidine ($NH_2 = 1$) was heated with twice its volume of acetic anhydride at 150–160°.[729] Twelve hours' refluxing is required for preparation of *N*-propionylphthalimide from phthalimide and propionic anhydride.[625]

Dipropionamide, $(CH_3CH_2CO)_2NH$, is obtained in 74% yield when molar amounts of propionamide and propionic anhydride containing a little concentrated sulfuric acid are heated together for 1 h at 100°.[728]

Amines that are difficult to acylate, such as carbazole and diphenylamine, generally react more smoothly and under milder conditions if an acid catalyst is present such as concentrated sulfuric acid, perchloric acid, aluminum chloride, or iron(III) chloride.

For example, diphenylamine and acetic anhydride containing about 0.4% of perchloric acid at 80–90° give the *N*-acetyl derivative almost quantitatively in only 6–8 min.[730] Similarly, carbazole is converted into the 9-acetyl derivative in 95% yield by acetic anhydride containing one drop of 30% perchloric acid in 3–5 min at room temperature.[730]

When treated with ammonia or primary or secondary amines, cyclic anhydrides of dicarboxylic acids readily undergo ring cleavage with formation of the monoamide of the dicarboxylic acids. For instance, phthalanilic acid,

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[721] C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

[722] R. M. Herbst and D. Shemin, *Org. Syn.*, Coll. Vol. II, 11 (1943).

[723] P. E. Fanta and D. S. Tarbell, *Org. Syn.*, Coll. Vol. III, 661 (1955).

[724] H. Plieninger and C. E. Castro, *Chem. Ber.*, **87**, 1760 (1954).

[725] J. Pinnow, *Ber. Deut. Chem. Ges.*, **33**, 417 (1900).

[726] C. H. Roeder and A. R. Day, *J. Org. Chem.*, **6**, 25 (1941).

[727] J. B. Polya and T. M. Spotswood, *Rec. Trav. Chim.*, **67**, 927 (1948).

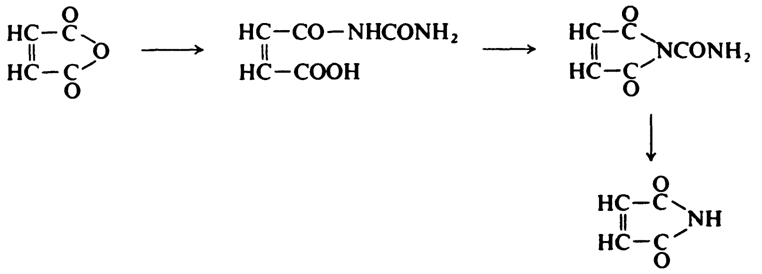
[728] D. Davidson and H. Skovronek, *J. Amer. Chem. Soc.*, **80**, 376 (1958).

[729] F. Ulffers and A. von Janson, *Ber. Deut. Chem. Ges.*, **27**, 93 (1894).

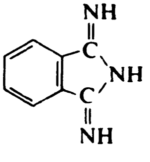
[730] A. A. Berlin, *Zh. Obshch. Khim.*, **14**, 438 (1944); *Chem. Abstr.*, **39**, 4606 (1945).

o-HOOC—C_6H_4—$CONHC_6H_5$, is obtained in an exothermic reaction on mere mixing of chloroform solutions of phthalic anhydride and aniline.[731] At higher temperatures, and if necessary after addition of some reagent to remove water, these monoamides cyclize again, yielding cyclic imides; and using more stringent conditions for acylation by the dicarboxylic anhydride leads directly to the cyclic imide. For instance, *N*-phenylsuccinimide is formed even on boiling succinic anhydride and aniline in aqueous solution;[732] succinimidoacetic acid is obtained by heating succinic anhydride and glycine at 170–180° in a vacuum for 2 hours;[733] and the analogous reaction with phthalic anhydride and amino acids (15 min at 180–185°) has been used for characterization of amino acids.[734] However, to obtain phthalimido acids on a preparative scale[735] it is better to use dioxan as a solvent at 105°;[709] and reaction of phthalic anhydride with amines occurs particularly smoothly and completely in glacial acetic acid.[736]

Maleimide is obtained easily and under mild conditions from the anhydride and urea, but it is possible to isolate the two intermediate stages:[737]



Phthalimide behaves analogously; further, the cyclic diamidine of phthalic acid (1,3-diiminoisoindoline) can be obtained in high yield by adding ammonium nitrate to a melt of the anhydride and urea:[738]



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[731] M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *J. Amer. Chem. Soc.*, **50**, 474 (1928).

[732] G. Koller, *Ber. Deut. Chem. Ges.*, **37**, 1598 (1904).

[733] J. Scheiber and H. Reckleben, *Ber. Deut. Chem. Ges.*, **46**, 2412 (1913).

[734] J. H. Billman and W. F. Harting, *J. Amer. Chem. Soc.*, **70**, 1473 (1948).

[735] F. Weygand and J. Kaelicke, *Chem. Ber.*, **95**, 1031 (1962), who give a literature review.

[736] G. Wanag and A. Veinbergs, *Ber. Deut. Chem. Ges.*, **75**, 1558 (1942).

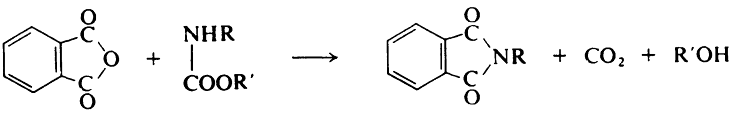
[737] P. O. Tawney, R. H. Snyder, C. E. Bryan, R. P. Conger, F. S. Dowell, R. J. Kelly, and C. H. Stiteler, *J. Org. Chem.*, **25**, 56 (1960).

[738] F. Baumann, B. Bienert, G. Rösch, H. Vollmann, and W. Wolf, *Angew. Chem.*, **68**, 137, (1956).

For the preparation also of *N*-alkylphthalimides, the corresponding alkylurea may replace the amine for heating with phthalic anhydride.[739]

***N-tert*-Butylphthalimide** is obtained in 75% yield by heating *tert*-butylurea for 15 min at about 220° with somehat more than twice the molar amount of phthalic anhydride.[740]

The analogous reaction of urethanes with phthalic anhydride has been recommended for cleavage of urethanes that are difficult to hydrolyse:[739]



N-Hydroxysuccinimide, which is of interest in connexion with peptide synthesis, is obtained from succinic anhydride and hydroxylamine.[741]

Cyclic compounds are formed by reaction of cyclic anhydrides with hydrazine more readily than in the corresponding reaction with amines, but the constitution of the anhydride and the method of effecting the reaction are of influence on the result. Succinic anhydride[742] gives only open-chain hydrazides; phthalic anhydride[743] and substituted phthalic anhydrides[744] give different cyclic hydrazides according to the reaction conditions;[745] maleic anhydride[746] gives open-chain compounds or the cyclic hydrazide according to the relative quantities of the reactants used.

Cyclic maleic hydrazide (1,2-dihydro-3,6-pyridazinedione):[746] Maleic anhydride (161.7 g) is dissolved by stirring under reflux in boiling glacial acetic acid (1 l) in a three-necked 2-l flask. When all is in solution, heating is interrupted, and 100% hydrazine hydrate (75 g) is dropped in during 10 min; this causes a transitory yellow precipitate. The mixture is heated for a further 0.5 h, then cooled, and the solid product is filtered off, washed with small amounts of alcohol and ether, and dried in the air, affording a colorless hydrazide (100 g). A second fraction is obtained by removal of much (800 ml) of solvent from the filtrate, addition of water (200 ml), and cooling; further dilution of that filtrate with water (400 ml) and concentration (to 100 ml) gives a third fraction. The total yield is 144 g (83%). The product melts above 300° with decomposition.

Schiff bases of the type $RCH_2CH{=}NR'$ react with acetic anhydride extremely easily, even in the cold, affording acetylated enamines:

$$RCH_2CH{=}NR' \xrightarrow[-CH_3COOH]{+(CH_3CO)_2O} RCH{=}CH{-}NR'{-}COCH_3$$

It is essential to neutralize the acetic acid formed, and triethylamine is very effective for this purpose.

***N*-Propyl-*N*-vinylacetamide:**[747] Acetic anhydride (79 g) is dropped with cooling into a mixture of *N*-ethylidenepropylamine (66 g) and triethylamine (78 g) in benzene (350 ml) at

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[739] R. H. F. Manske, *J. Amer. Chem. Soc.*, **51**, 1202 (1929).

[740] L. I. Smith and O. H. Emerson, *Org. Syn.*, Coll. Vol. III, 151 (1955).

[741] K.-T. Wang, D. N. Brattesani, and B. Weinstein, *J. Heterocycl. Chem.*, **3**, 98 (1966).

[742] H. Feuer, G. B. Bachman, and E. H. White, *J. Amer. Chem. Soc.*, **73**, 4716 (1951).

[743] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, **1937**, 16.

[744] H. D. K. Drew and F. H. Pearman, *J. Chem. Soc.*, **1937**, 26.

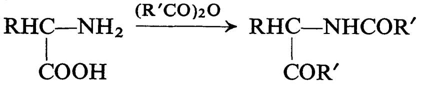
[745] W. R. Vaughan, *Chem. Rev.*, **43**, 447 (1948) (review of phthalhydrazides and related compounds).

[746] H. Feuer, E. H. White, and J. E. Wyman, *J. Amer. Chem. Soc.*, **80**, 3790 (1958).

[747] H. Breederveld, *Rec. Trav. Chim.*, **79**, 401 (1960).

5–8° in a three-necked 1-l flask fitted with a stirrer, dropping funnel, and thermometer. The mixture is then allowed to warm to room temperature and finally it is distilled in a vacuum. This gives *N*-propyl-*N*-vinylacetamide (59 g), b.p. 77–78°/14 mm, and a forerun, b.p. 40 to 77°/14 mm. Shaking the latter with a solution of sodium hydroxide (10 g) in water (40 ml) and distillation gives a further batch (8 g) of amide, bringing the total yield to 68 %. The product has n_D^{20} 1.4725.

When α-amino acids are heated with carboxylic anhydrides in pyridine, a reaction that includes decarboxylation leads to α-acylamino ketones (the Dakin–West reaction):[748–750]



$$\underset{\text{COOH}}{\text{RHC}}\text{—NH}_2 \xrightarrow{(\text{R}'\text{CO})_2\text{O}} \underset{\text{COR}'}{\text{RHC}}\text{—NHCOR}'$$

3-Acetylamino-4-phenyl-2-butanone:[750] A mixture of phenylalanine (12.4 g), pyridine (39.3 g), and acetic anhydride (65.2 g) is heated on the steam-bath for 5 h, then freed from pyridine by steam-distillation. The residue is treated with an excess of sodium hydrogen carbonate solution and then extracted with ether (six 100-ml portions). The extracts are dried and freed from ether, and the orange-yellow, waxy residue is crystallized twice from xylene, giving colorless needles (12.1 g, 79 %), m.p. 98–99° (corr.).

Aminoacetone has been obtained analogously from glycine.[751]

c. Reactions of esters with nitrogen compounds

Two fundamentally different types of reaction of esters with ammonia and its derivatives must be distinguished, although in both cases oxygen is replaced by nitrogen:

(*A*) (*B*)

With a few exceptions due to substitution,[752] carboxylic esters cause acylation on nitrogen (as in *A*), but many mineral acid esters as well as arenesulfonic esters are powerful alkylation agents (see *B*).

For the alkylation of amines by carboxylic esters in the presence of lithium tetrahydroaluminate see a paper by Wright.[753]

i, Acylation of nitrogen compounds

Acylation of nitrogen compounds by carboxylic esters. The action of carboxylic esters on ammonia or primary or secondary amines generally leads to carboxamides under relatively mild conditions, and the analogous treatment of carboxylic esters with hydrazine and hydroxylamine provides the most important methods of preparing simple carboxhydrazides and carbohydroxamic acids.

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[748] H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91, 757 (1928); P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **74**, 689 (1927); **79**, 95 (1928); M. Proštenik, N. Gerenčevič, J. Pluščec, and M. Šateva, *Naturwissenschaften*, **47**, 496 (1960).

[749] R. H. Wiley, *J. Org. Chem.*, **12**, 43 (1947); F. E. Lehmann and co-workers, *Helv. Chim. Acta*, **33**, 1217 (1950).

[750] G. H. Cleland and C. Niemann, *J. Amer. Chem. Soc.*, **71**, 841 (1949).

[751] J. D. Hepworth, *Org. Syn.*, **45**, 1 (1965).

[752] F. D. Chattaway, *J. Chem. Soc.*, **1936**, 355; cf. H. Irving, *J. Chem. Soc.*, **1936**, 797; A. C. Pierce and M. M. Joullié, *J. Org. Chem.*, **27**, 3968 (1962).

[753] W. B. Wright, *J. Org. Chem.*, **27**, 1042 (1962).

The reactivity of carboxylic esters towards ammonia derivatives is, however, more dependent than is that of other carboxylic acid derivatives on the structure of the acylating agent. For example, diethyl malonate and alkylmalonates react smoothly with ammonia, giving the corresponding amides, but diethyl diethylmalonate does not react under the usual conditions.[754] The nature of the amine component also has a great effect: methyl lactate, for instance, with dimethylamine gives the dimethylamide quite smoothly, but diethylamine and dibutylamine react only with difficulty.[755] These varying reactivities presumably have steric origin. In general, the rate of ester aminolysis parallels that of ester hydrolysis: methyl esters undergo aminolysis more easily than ethyl esters (cf. Gordon *et al.*[756] and Russel[757]), and esters of primary alcohols more easily than those of secondary alcohols;[756] primary amines usually react faster than ammonia[758], and secondary amines usually more slowly.[758,759] The reaction is catalysed by small amounts of water[760,761] and more strongly by alkoxides;[757,758,762] alkoxide catalysis is particularly advisable for acylation of aromatic amines.[763]

It often suffices for preparation of unsubstituted amides to stir or shake the ester with concentrated aqueous ammonia, but the conditions required vary widely from case to case. For example, ethyl cyanoacetate[754] and concentrated aqueous ammonia afford 88% of the amide in 1 hour without external heating, and methyl fluoroacetate reacts equally rapidly (**N.B.:** a potent poison):

Fluoroacetamide:[765] Methyl fluoroacetate (20 g) is cooled in ice-water and treated with an excess of aqueous ammonia (*d* 0.88; 20 ml). After 1 h the precipitate is filtered off (15 g) and dried; this product is almost pure. Evaporation of the mother-liquor makes the yield up to 100%. Recrystallization from chloroform or chloroform–light petroleum gives crystals of m.p. 108°.

Ethyl fumarate, however, requires 7 hours' stirring with concentrated aqueous ammonia at 25–30°,[766] and considerably longer time is necessary for aminolysis of methyl methacrylate:[767]

Methacrylamide: Methyl methacrylate (76 g) is shaken for 7 days with ammonia solution (*d* 0.885; 390 ml). The homogeneous solution is then evaporated in portions in a vacuum (19 mm) on a water-bath (78°), and the crude product is dried over calcium chloride to constant weight (65 g), broken into small pieces, and dissolved in methylene chloride (580 ml) boiling under reflux. The solution is filtered through a filter heated by hot water, and the residue is extracted again with methylene chloride (60 ml). When the filtrates are cooled in an ice-bath, monomeric methacrylamide crystallizes; two further fractions can be obtained from the mother liquors, bringing the total yield of material melting at 95–109° up to 48 g (75%). To obtain the pure amide, as thin tablets, m.p. 110–111°, requires repeated recrystallization.

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[754] E. Fischer and A. Dilthey, *Ber. Deut. Chem. Ges.*, **35**, 844 (1902).
[755] W. P. Ratchford and C. H. Fisher, *J. Org. Chem.*, **15**, 317 (1950).
[756] M. Gordon, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, **70**, 1946 (1948).
[757] P. B. Russel, *J. Amer. Chem. Soc.*, **72**, 1853 (1950).
[758] R. Baltzly, I. M. Berger, and A. A. Rothstein, *J. Amer. Chem. Soc.*, **72**, 4149 (1950).
[759] E. McC. Arnett, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, **73**, 5393 (1951).
[760] M. Gordon, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, **71**, 1245 (1949).
[761] P. K. Glasoe, L. D. Scott, and L. F. Audrieth, *J. Amer. Chem. Soc.*, **63**, 2965 (1941).
[762] R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1568 (1937).
[763] C. C. Price and B. H. Velzen, *J. Org. Chem.*, **12**, 386 (1947).
[764] B. B. Corson, R. W. Scott, and C. E. Vose, *Org. Syn.*, **9**, 36 (1929).
[765] F. J. Buckle, R. Heap, and B. C. Saunders, *J. Chem. Soc.*, **1949**, 912.
[766] D. T. Mowry and J. M. Butler, *Org. Syn.*, **30**, 46 (1950).
[767] C. L. Arcus, *J. Chem. Soc.*, **1949**, 2732.

In some cases liquid ammonia may replace aqueous ammonia.[768,769] Very good yields are also obtained when alcoholic, particularly methanolic, ammonia solutions are used.

For example, **acetamide** is obtained in 90% yield by allowing methyl acetate (0.5 mole) to react with ammonia (8 moles) in methanol at room temperature for 24 h and then distilling the mixture in a vacuum.[758]

Ethylmalonamide[757] is obtained in 91% yield when diethyl ethylmalonate (10 g) is set aside in a mixture of methanol (50 ml), methanolic ammonia solution (100 ml, saturated at 0°), and sodium (0.1 g) for 96 h at room temperature. The yield is lower if the sodium is omitted.

When both the ester and the amine are liquid they may be allowed to react without a solvent. Methyl lactate, for instance, gave a large number of mono- and di-alkylamides in consistently very high yield when treated with a 10% excess of the amine at room temperature.[755,770]

The preparation of ***N*-hexyllactamide**[755,770] may be described as a typical example: Methyl lactate (208 g, 2 moles) is shaken with hexylamine (222 g, 2.2 moles), and the mixture is set aside at room temperature for 15 days. Distillation through a Vigreux column gave first methanol (55 g) at atmospheric pressure, then in a vacuum an intermediate fraction (3 g) at 28–120°/1 mm, followed by the main fraction of *N*-hexyllactamide (341 g, 98%), b.p. 120–128°/0.3 mm. After three recrystallizations from ether–light petroleum the amide had m.p. 41–42°.

When the stability and relatively low volatility of the components permit, the long reaction time can, of course, be shortened by working at higher temperatures. The *N*-formyl derivatives of aniline, 2-naphthylamine, α-methylbenzylamine, and menthylamine were prepared almost quantitatively by heating the base with ethyl formate for 1 hour at 100–110°.[771]

***N*-Decylnicotinamide:**[772] Ethyl nicotinate (61.8 g) is heated for 190 min at 214–250° with decylamine (70.8 g) in a flask fitted with a column to which a condenser is attached. Ethanol (10.6 g) distils over. The residue is dissolved in chloroform (500 ml), and the solution is clarified by being boiled with charcoal and is then filtered and, whilst still hot, treated with light petroleum. This precipitates the amide which, collected from the cooled solution, has m.p. 69.8–70.4° (90.8 g, 82.7%). Several crystallizations from chloroform–light petroleum raise the m.p. to 72.2–72.6°.

Heating is essential for conversion of keto carboxylic esters into amides, as otherwise enamines are formed by reaction of the keto group with the amine[773] (cf. pages 507 and 517).

For preparation of, *e.g.*, **α-benzoylacetanilide,** aniline is dropped into a solution of ethyl benzoylacetate in xylene preheated at 145–150°, the alcohol formed thus distilling over.[774,cf.775] Acetoacetanilide is obtained analogously in 85% yield by reaction in boiling toluene.[355c]

Carboxylic acids and amines that normally react sluggishly can often be brought into smooth reaction by using the alkali or alkaline-earth derivatives

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[768] J. Kleinberg and L. F. Audrieth, *Org. Syn.*, Coll. Vol. III, 516 (1955).

[769] L. F. Audrieth and J. Kleinberg, *J. Org. Chem.*, **3**, 312 (1938).

[770] W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950).

[771] J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, **1948**, 1457.

[772] C. O. Badgett, R. C. Provost Jr., C. L. Ogg, and C. F. Woodward, *J. Amer. Chem. Soc.*, **67**, 1135 (1945).

[773] L. Limpach, *Ber. Deut. Chem. Ges.*, **64**, 970 (1931).

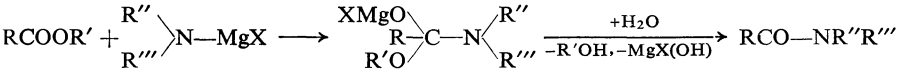
[774] C. J. Kibler and A. Weissberger, *Org. Syn.*, Coll. Vol. III, 108 (1955).

[775] C. H. F. Allen and W. J. Humphlett, *Org. Syn.*, **37**, 2 (1957).

in place of the free amines. In the aromatic series these derivatives are readily accessible from the amine and the metal in an inert solvent and can be used without isolation.[776]

Diethylmalonanilide is obtained, in accord with this method, in good yield by boiling diethyl diethylmalonate for 0.5 h with sodium anilide (2 moles) in toluene.[776] Analogously, *N,N*-diethylglycine ethyl ester and the sodio derivative of aniline, *N*-ethylaniline, or 2,6-dimethylaniline in boiling toluene give the corresponding anilides in 65–90% yield.[776]

The halomagnesium derivatives, NR_2—MgHal, may replace the alkali derivatives (the Boudroux reaction):[777]



$$\mathrm{RCOOR'} + \begin{matrix}\mathrm{R''}\\ \mathrm{R'''}\end{matrix}\!\!>\!\mathrm{N{-}MgX} \longrightarrow \begin{matrix}\mathrm{XMgO}\\ \mathrm{R}\\ \mathrm{R'O}\end{matrix}\!>\!\mathrm{C{-}N}\!<\!\begin{matrix}\mathrm{R''}\\ \mathrm{R'''}\end{matrix} \xrightarrow[-\mathrm{R'OH},\,-\mathrm{MgX(OH)}]{+\mathrm{H_2O}} \mathrm{RCO{-}NR''R'''}$$

Weygand[778] has prepared a number of *N*-methylcarboxanilides in this way; Kuhn and Morris[779] converted ethyl *β*-ionylideneacetate into the corresponding *o*-toluidide in 80% yield. The general directions below for the **Boudroux reaction** have been applied to, *inter alia*, *N,N*-diphenylacetamide (85%), *N,N*-diphenylbenzamide (88%), *N*-hexanoylaniline (87%), and dodecananilide (80%).[777]

A solution of the amine (0.1 mole) in ether (30 ml) is added slowly to methylmagnesium iodide (0.1 mole) in dry ether (50 ml). When the violent reaction is ended, the ester (0.05 mole) in ether (about 20 ml) is added and the whole is warmed for 2 h on the water-bath. The product is then decomposed cautiously with water (50 ml), the basic magnesium compounds are dissolved in 2N-hydrochloric acid, and the ethereal layer is separated, dried, and freed from ether and unchanged amine by distillation. The residual anilide is purified by recrystallization.[777]

Birkhofer and Frankus[780] similarly converted *β*-amino esters into the *N*-(aminoacyl) derivatives of *N*-methylaniline, carbazole, and indole.

The rate of reaction of carboxylic esters with amines can often be increased by using as acylating agents esters that exchange their alcohol residues with particular ease. With this in mind Schwyzer[781] recommends the use of cyanomethyl esters, $RCOOCH_2CN$. The cyanomethyl esters of N-protected amino acids react readily even at room temperature with amino esters and are thus particularly suitable for peptide synthesis. Also, phenyl trifluoroacetate has been recommended for trifluoroacetylation of amino acids and peptides.[782] The possibilities offered by such activated esters for peptide synthesis are reviewed in the monograph by Schröder and Lübke.[783]

Isopropenyl acetate, obtained from ketene and acetone, reacts as an activated ester of acetic acid and, like its generator ketene, acetylates amides highly exothermally at room temperature.[784] Even 1-acetylimidazole, which is difficult to prepare in other ways, is thus obtained from imidazole in 94% yield.[785]

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[776] E. S. Stern, *Chem. & Ind.* (*London*), **1956**, 277.

[777] H. L. Bassett and C. R. Thomas, *J. Chem. Soc.*, **1954**, 1188.

[778] F. Weygand and co-workers, *Angew. Chem.*, **65**, 530 (1953).

[779] R. Kuhn and C. J. O. R. Morris, *Ber. Deut. Chem. Ges.*, **70**, 853 (1937).

[780] L. Birkhofer and E. Frankus, *Chem. Ber.*, **94**, 216 (1961).

[781] R. Schwyzer and co-workers, *Helv. Chim. Acta*, **38**, 69, 80, 83 (1955).

[782] F. Weygand and A. Röpsch, *Chem. Ber.*, **92**, 2095 (1959).

[783] E. Schröder and K. Lübke, "The Peptides," Academic Press, New York-London, Vol. 1, 1965; Vol. 2, 1966.

[784] H. J. Hagemeyer Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

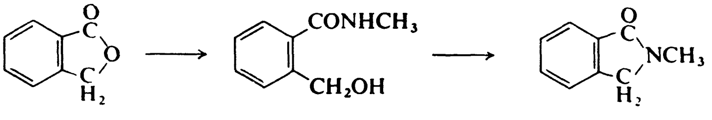
[785] J. H. Boyer, *J. Amer. Chem. Soc.*, **74**, 6274 (1952).

4-Acetylmorpholine:[784] Morpholine (87 g) is dropped slowly onto isopropenyl acetate (100 g), placed in a distillation flask. A vigorous reaction occurs and the acetone formed distils. Subsequent distillation of the residue in a vacuum affords 4-acetylmorpholine, b.p. 89°/1 mm, n_D^{20} 1.4337, in 80% yield.

Lactones act as acylating agents for ammonia and amines, in the manner of open-chain carboxylic esters:

***o*-(Hydroxymethyl)-*N*-methylbenzamide (2):**[786] Phthalide (1) (175 g) is dissolved by warming in 29% aqueous methylamine solution (140 g) and placed in ice, whereupon the product separates in colorless crystals, m.p. 122–123° (159 g, 74%).

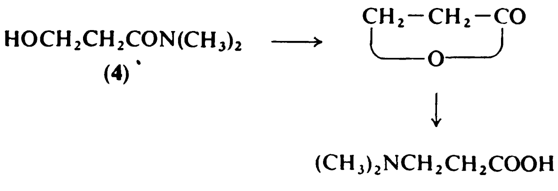
Less reactive amines can be used in this reaction as their *N*-metal derivatives.[787]



(1) (2) (3)

Provided that they have at least one hydrogen atom on the amide-nitrogen, the hydroxy carboxamides formed from lactones can be converted by heat into lactams. For example, the above *o*-(hydroxymethyl)-*N*-methylbenzamide (**2**) cyclizes to the lactam (**3**) at 160°; however, the removal of water involved in the change (**2**) → (**3**) competes with the loss of methylamine that leads back to phthalide, so that pressure is required in preparation of the lactam.[786]

Lactones, however, often act as alkylating agents, thus yielding amino acids. For instance, boiling 4-butyrolactone and potassium phthalimide in dimethylformamide gives 4-phthalimidobutyric acid[788] and phthalide (**1**) gives analogously *o*-(phthalimidomethyl)benzoic acid.[789] *β*-Lactones have a particularly enhanced tendency to alkylation, though it often depends on the conditions which course the reaction takes:[733] for instance, dropping propiolactone into an ethereal solution of dimethylamine at 0° gives 95% of 3-hydroxy-*N*,*N*-dimethylpropionamide (**4**), whereas 84% of *N*,*N*-dimethyl-*β*-alanine (**5**) can be obtained by the reverse procedure of passing dimethylamine into an ethereal solution of the lactone at 0°:[790]



$HOCH_2CH_2CON(CH_3)_2$ (4) $\longrightarrow$ $\downarrow$ $(CH_3)_2NCH_2CH_2COOH$

(5)

The solvent also has a great influence on the direction of the reaction.[790]

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[786] W. Theilacker and K. Kalenda, *Ann. Chem.*, **584**, 87 (1953).

[787] W. Reppe and co-workers, *Ann. Chem.*, **596**, 175 (1955).

[788] G. Talbot, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **36**, 593 (1958).

[789] J. Bornstein, P. E. Drummond, and S. F. Bedell, *Org. Syn.*, **38**, 81 (1958).

[790] T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Amer. Chem. Soc.*, **73**, 3168 (1951); cf. C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, **74**, 5889 (1952); **76**, 5562 (1954).

The most important reactions of carboxylic esters with amides are the cyclizations of urea with dicarboxylic esters. As required for an ester condensation, stoichiometric amounts of an alkoxide must be used. Simple directions for the synthesis of **barbituric acid** were given by Pfleiderer and Nübel:[791]

Ethyl malonate (320 g) is stirred into a solution of sodium (48 g) in anhydrous methanol (400 ml), and the mixture is then boiled for 10 min, after which a hot solution of urea (120 g) in anhydrous methanol (300 ml) is added; this affords a thick slurry. To complete the condensation the mixture is heated for a further 5 h under reflux. It is then poured into water (3 l) and acidified with concentrated hydrochloric acid (200 ml), which causes first dissolution of the solid material and then separation of barbituric acid in beautiful crystals. After recrystallization from water and drying for 2 days at 100° these have m.p. above 260° with decomposition. The yield is 210 g.

The use of ethanol is prescribed in *Organic Syntheses*,[792] but this needs more energetic conditions.

The analogous condensation of urea with cyanoacetic ester, by Traube's method,[793] proceeds equally smoothly.

It should be noted that the reverse route can be used for synthesis of barbituric acid, namely, condensation of malonamide (or a dialkylmalonamide) with diethyl carbonate. This reaction is carried out in liquid ammonia containing sodium hydroxide or amide as condensing agent but in most cases has no advantage over the conventional method.[794]

Reaction of carboxylic esters with hydrazines is generally easier than that with amines. Simple aliphatic esters often give the corresponding hydrazide exothermally at room temperature, though it is advisable to warm the mixture on the water-bath for a short time thereafter. In such reactions the formation of 1,2-diacylated hydrazines rarely proves troublesome although it is a frequent side reaction when acid chlorides or anhydrides are used. The following details exemplify the technique:

***p*-Nitrophenylacetohydrazide:**[795] Methyl *p*-nitrophenylacetate (34 g) and 42% hydrazine hydrate (50 g) are heated on a steam-bath for 30 min. A red color first develops but soon fades while the mixture sets to a hard yellow mass. This is washed with water and crystallized from anhydrous ethanol, forming needles, m.p. 167° (33 g, 97%).

Adipohydrazide:[796] A mixture of 85% aqueous hydrazine hydrate (120 ml, 2 moles) and anhydrous ethanol (25 ml) is heated under reflux and diethyl adipate (101 g, 0.5 mole) is added dropwise during 2 h. The hydrazide separates on cooling and is washed with alcohol and dried, then melting at about 174–181° (yield about 90%).

***p*-Ethoxybenzohydrazide:**[797] Ethyl *p*-ethoxybenzoate (1 mole) is boiled with hydrazine hydrate (1.25 moles) in 20% aqueous solution for at least 8 h. The hydrazide separates on cooling as colorless needles (95%), which on recrystallization from dilute ethanol form colorless, rectangular tablets, m.p. 126–127°.

Esters of acids having α-branches react more slowly than straight-chain esters with hydrazine, as in aminolysis. Reaction can be hastened by using alcohols of higher boiling point as solvent (*e.g.*, butanol) or by using anhydrous hydrazine.

Mixtures of isomeric hydrazines, AcylNH—NHR and AcylNR—NH_2, may be formed on reaction of carboxylic esters with alkylated hydrazines and

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[791] W. Pfleiderer and E. Nübel, *Ann. Chem.*, **631**, 168 (1960).

[792] J. B. Dickey and A. R. Gray, *Org. Syn.*, Coll. Vol. II, 60 (1943).

[793] W. R. Sherman and E. C. Taylor Jr., *Org. Syn.*, **37**, 15 (1957).

[794] K. Shimo and S. Wakamatsu, *J. Org. Chem.*, **24**, 19 (1959).

[795] R. L. Shriner and J. M. Cross, *J. Amer. Chem. Soc.*, **60**, 2338 (1938).

[796] P. A. S. Smith, *Org. Syn.*, **36**, 69 (1956).

[797] P. P. T. Sah and K.-S. Chang, *Ber. Deut. Chem. Soc.*, **69**, 2763 (1936).

they are not always easy to separate (cf. Hinman and Fulton[798]). The preparation of 1-acyl-2-methylhydrazines by way of oxadiazolinones has been described by Meyer.[799]

Hydroxylamine is acylated by carboxylic esters, giving hydroxamic acids. The reaction often occurs in a few hours at room temperature if the components are mixed in alcoholic solution, preferably with addition of an equivalent of an alkoxide. In the latter case the hydroxamic acids are obtained as salts, but are easily liberated therefrom.

Malonodihydroxamic acid:[800,cf.801] Diethyl malonate (80 g, 0.5 mole) is treated with an anhydrous ethanolic solution (1 l) containing hydroxylamine (1 mole) liberated from its hydrochloride by the calculated amount of sodium ethoxide in ethanol. To this is added a solution of sodium (25 g, 1.1 moles) in anhydrous ethanol (500 ml), whereupon the disodium salt of the product begins to separate, a process that is complete (78 g) after a few hours.

To provide the free acid, the salt (17 g) is treated with the calculated amount of alcoholic hydrogen chloride (50 ml, 2.8 n) and set aside for 2 h with occasional shaking. Filtration from the separated sodium chloride and removal of the alcohol in a vacuum (25°) afford the crude dihydroxamic acid, m.p. 144–147°; the pure acid melts at 155°.

Directions for essentially similar preparation of benzohydroxamic acid are given in *Organic Syntheses*,[802] and various ring-substituted benzohydroxamic acids have been reported by Stolberg *et al.*[607]

Acylation of nitrogen compounds by orthoesters. The formation of amidines from orthoesters (preferably orthoformates) and ammonia or an aromatic amine has been known for about 100 years (for a review see Post[803]). As an example for the acylation of ammonia a modern procedure is reproduced, in which acetamidine is obtained as acetate:[804]

Acetamidine acetate:[804] Ethyl orthoacetate (32.4 g) is heated under reflux for 45 min with ammonium acetate (15.4 g) whilst dry ammonia is led through the mixture. The product is distilled at a bath-temperature of 155–160° until the temperature of the condensing vapor falls to 75°. (This requires about 25 min with the above-mentioned quantities and gives 18.5 g of distillates.) The residue is then cooled to room temperature and filtered; the solid acetamidine acetate is washed with a little ethanol and dried, then amounting to 16.5 g and melting at 189–191°. A further fraction can be isolated from the filtrate (total yield 19.75 g, 84%).

Formamidine acetate was prepared in similar high yield by a similar procedure but with glacial acetic acid as solvent.[804] *N,N*-Disubstituted formamidine and acetamidine derivatives have been obtained analogously from orthoesters and alkylamines in the presence of glacial acetic acid[805] or boron trifluoride etherate.[806] In the reaction of orthoesters with secondary amines in the presence of toluenesulfonic acid the formation of ketene aminals (alkyl 1-aminovinyl ethers) was also observed.[807]

There was for some time uncertainty about the course of the reaction and the nature of the end products, but it now appears certain that imidic esters

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[798] R. L. Hinman and D. Fulton, *J. Amer. Chem. Soc.*, **80**, 1895 (1958).

[799] R. F. Meyer, *J. Heterocyl. Chem.*, **2**, 305 (1965).

[800] C. D. Hurd and D. G. Botteron, *J. Org. Chem.*, **11**, 207 (1946).

[801] A. Hantzsch, *Ber. Deut. Chem. Ges.*, **27**, 799 (1894).

[802] C. R. Hauser and W. B. Renfrow Jr., *Org. Syn.*, Coll. Vol. II, 67 (1943).

[803] H. W. Post, "The Chemistry of the Aliphatic Orthoesters," Reinhold Publ. Corp., New York, 1943, pp. 84 et seq.

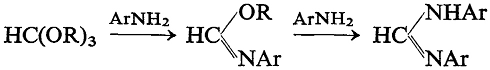
[804] E. C. Taylor and W. A. Ehrhart, *J. Amer. Chem. Soc.*, **82**, 3138 (1960); E. C. Taylor, W. A. Ehrhart, and M. Kawanisi, *Org. Syn.*, **46**, 39 (1966).

[805] E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.*, **28**, 1108 (1963).

[806] G. Lehmann, H. Seefluth, and G. Hilgetag, *Chem. Ber.*, **97**, 299 (1964).

[807] H. Baganz and L. Domaschke, *Chem. Ber.*, **95**, 2095 (1962).

are first formed,[808] which pass into the amidine when orthoformic ester and an excess of the amine are used:[809]



$$\mathrm{HC(OR)_3} \xrightarrow{\mathrm{ArNH_2}} \mathrm{HC}\begin{matrix}\diagup\mathrm{OR}\\ \diagdown\mathrm{NAr}\end{matrix} \xrightarrow{\mathrm{ArNH_2}} \mathrm{HC}\begin{matrix}\diagup\mathrm{NHAr}\\ \diagdown\mathrm{NAr}\end{matrix}$$

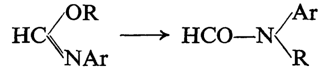
The following procedure may be generalized and applied also to the preparation of other aromatic formamidines:

***N,N′*-Bis(*o*-chlorophenyl)formamidine:**[810] Ethyl orthoformate (104 g, 0.7 mole) and *o*-chloroaniline (179 g, 1.4 moles) are placed in a 500-ml flask under an externally heated, filled column (about 40 cm long). The flask is heated for 1.5 h in a bath at 145° while the column is kept at 90–100°. The bath temperature is then raised to 180° for 0.5 h, which should complete the distillation of the ethanol released. The contents of the flask must then be poured rapidly into a porcelain dish as they quickly solidify on cooling. This gives a crude product of m.p. 137–141° in almost quantitative yield. Recrystallization from dry benzene gives colorless prisms (150 g, 81 %), m.p. 139–141°.

If the experiment is carried out with a 1 : 1 ratio of the reactants or with an excess of the orthester in presence of catalytic amounts of acid, then the reaction stops at the first stage and good yields of *N*-arylimidic esters are obtained.

Ethyl *N*-phenylformimidate:[811,cf.812] Aniline (1 mole), ethyl orthoformate (1.5 moles), and sulfuric acid (10 drops) are heated under reflux for 30 min, then ethanol (117 ml) is distilled off. The residue is neutralized with dry sodium *tert*-butoxide (3.5 g) and distilled in a vacuum. The excess of orthoester distils first, then the imidic ester (121.6 g, 82 %), b.p. 117–119°/40mm.

Acidic catalysts convert *N*-arylformimidic esters at elevated temperatures into the isomeric *N*-alkylformanilides:



$$\mathrm{HC}\begin{matrix}\diagup\mathrm{OR}\\ \diagdown\mathrm{NAr}\end{matrix} \longrightarrow \mathrm{HCO{-}N}\begin{matrix}\diagup\mathrm{Ar}\\ \diagdown\mathrm{R}\end{matrix}$$

so that a suitable technique enables these anilides to be obtained directly from the amine and the orthoester:[813,cf.814]

***N*-Ethylformanilide:**[813] Aniline (18.6 g, 0.2 mole), ethyl orthoformate (44.5 g, 0.3 mole), and concentrated sulfuric acid (0.78 g) are heated under reflux for 30 min. Then a filled column (about 30 cm long) is placed on the flask and the temperature of the bath is raised to 175° and kept there for 30 min, during which time the ethanol formed (21.8 g) distils off. After cooling, the residue is distilled in a vacuum, giving excess of orthoformate (9.1 g), b.p. 65 to 67°/40 mm, then imidic ester (a few drops, b.p. 118–120°/40 mm), and finally *N*-ethylformanilide (22.4 g, 75 %), b.p. 150–154°/40 mm.

The ease with which the formyl group is removed by hot dilute hydrochloric acid permits this reaction to be used for preparation of pure *N*-monoalkylanilines.[813,814]

A true orthoamide of formic acid is obtained from ethyl orthoformate and *N*-methylaniline,[815] namely $HC[N(CH_3)C_8H_5]_3$.

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[808] R. H. DeWolfe, *J. Org. Chem.*, **27**, 490 (1962).

[809] R. M. Roberts and R. H. DeWolfe, *J. Amer. Chem. Soc.*, **76**, 2411 (1954).

[810] R. M. Roberts, *J. Org. Chem.*, **14**, 277 (1949).

[811] R. M. Roberts, *J. Amer. Chem. Soc.*, **71**, 3848 (1949).

[812] R. M. Roberts and P. J. Vogt, *Org. Syn.*, **35**, 65 (1955).

[813] R. M. Roberts and P. J. Vogt, *J. Amer. Chem. Soc.*, **78**, 4778 (1956).

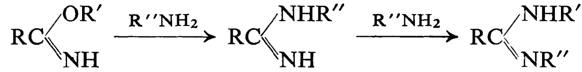
[814] R. M. Roberts and P. J. Vogt, *Org. Syn.*, **38**, 29 (1958).

[815] D. H. Clemens, E. Y. Shropshire, and W. D. Emmons, *J. Org. Chem.*, **27**, 3664 (1962).

Condensing ethyl orthoformate with arylhydrazines gives either *N*-heterocycles[816] or *N'*-arylformohydrazonic esters,[816,817] RO—CH=N—NHAr.

Tris(acylamino) methanes, HC(NHAcyl)$_3$, can be prepared from ethylorthoformate and carboxamides.[818]

Acylation of nitrogen compounds by imidic esters. It was mentioned above that synthesis of amidines from orthoesters proceeds through imidic esters, so that both classes of compound are normally treated together in reviews.[819-821] Accordingly, also, it is, of course, possible to use imidic ester hydrochlorides as usually prepared from nitriles and to treat these with ammonia or amines.[820] Care must be taken, however, with primary amines lest the imido group be also exchanged for the residue from the amine, particularly at higher temperatures:



$$RC\begin{matrix}\diagup OR' \\ \diagdown NH\end{matrix} \xrightarrow{R''NH_2} RC\begin{matrix}\diagup NHR'' \\ \diagdown NH\end{matrix} \xrightarrow{R''NH_2} RC\begin{matrix}\diagup NHR'' \\ \diagdown NR''\end{matrix}$$

this exchange is, of course, not possible with secondary amines. The more feebly basic aromatic amines generally undergo this reaction only with difficulty and not unidirectionally. In all cases moisture must be rigidly excluded.

The following general procedure is recommended for preparation of **unsubstituted amidine hydrochlorides**:[822]

An approximately 10% solution or suspension of 0.1 mole of an imidic ester hydrochloride in anhydrous ethanol containing 0.13 mole of ammonia is shaken in a closed vessel for 2 to 3 days at room temperature. The precipitated ammonium chloride is filtered off, the filtrate is diluted with ether, and the precipitated amidine hydrochloride is collected and recrystallized from ethyl methyl ketone and alcohol.

The preparation of acetamidine hydrochloride from acetonitrile is described in detail in *Organic Syntheses*.[823]

A number of **N-[2-(diethylamino)ethyl]amidines** have been obtained as follows:[824]

The imidic ester hydrochloride (1 mole) is dissolved in an eight- to ten-fold weight of anhydrous ethanol, treated with 2-(diethylamino)ethylamine (1.05 moles), and stirred for 8 h at 40–45°. The alcohol is then removed in a vacuum and the residue is dissolved in water and acidified to Congo Red by hydrochloric acid. After short warming the mixture is cooled and all non-basic material is removed by filtration or by extraction with ether. The solution is then evaporated to dryness at 40° in a vacuum and the last traces of water are distilled off azeotropically with benzene–ethanol. The yield is 75–80%.

The reaction with ethylenediamine[822] gives 2-substituted imidazolines, which can be regarded as cyclic amidines. The reaction with anthranilic acid also leads to ring closure, since the final products are quinazolines.[825]

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[816] C. Runti and C. Nisi, *J. Med. Chem.*, **7**, 814 (1964).
[817] G. Lehmann, H. Wehlan, and G. Hilgetag, *Chem. Ber.*, **100**, 2967 (1967).
[818] H. Bredereck, F. Effenberger, and H.-J. Treiber, *Chem. Ber.*, **96**, 1505 (1963).
[819] R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).
[820] A. Pinner, "Die Imidoäther und ihre Derivate," Verlag Oppenheim, Berlin, 1892.
[821] R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).
[822] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, **69**, 1688 (1947).
[823] A. W. Dox, *Org. Syn.*, **8**, 1 (1928).
[824] F. H. S. Curd and C. G. Raison, *J. Chem. Soc.*, **1947**, 160.
[825] W. Ried and W. Stephan, *Chem. Ber.*, **95**, 3042 (1962).

Cyclic imidic esters (lactim alkyl ethers) are also readily converted into cyclic amidine by amines[826] or amino acids.[827]

O-Alkylisoureas react as simple imidic esters: arginine was obtained in 94.5% yield from *O*-methylisourea and ornithine.[828]

Finally it may be mentioned that distillation of free formimidic or acetimidic esters in a vacuum leads to loss of alcohol, the remaining material giving a cyclic trimer, whereby a simple synthesis of *s*-triazine and its 2,4,6-derivative is provided.[829,830]

***s*-Triazine:**[830] Tributylamine (68 g) is added to ethyl formimidate hydrochloride[831] (40 g) at 10°. The mixture is stirred at room temperature for 1.5 h, then distilled at 25–30 mm, the internal temperature being gradually raised to 100°. The distillate is collected in a receiver cooled in Dry Ice and, when treated with light petroleum, gives crystalline *s*-triazine (7.8 g, (79%).

Hydrazine reacts analogously to amines with imidic ester hydrochlorides and requires the same conditions; they afford amidrazones.[820,832,833]

ii, Alkylation of nitrogen compounds

Alkylation of nitrogen compounds by sulfuric esters. The use of sulfuric esters as alkylating agents for ammonia derivatives is limited substantially to dimethyl and diethyl sulfate. Under not too drastic conditions only one alkyl group is transferred from the ester to the amine component; transfer of the second group usually occurs only at 160–200°.

Good yields of primary or secondary amines are rarely obtained by alkylation of ammonia or primary amines, respectively, as all possible more highly alkylated products are formed simultaneously. The best results are obtained on alkylation of primary to tertiary aromatic amines; the formation of quaternary salts is less objectionable in these cases because these salts are degraded to the tertiary amine by boiling alkoxide or subsequent distillation in steam from alkaline solution.

Hünig[834] recommends the following procedure for methylation of primary to tertiary aromatic amines:

The aromatic amine (1 mole) is added to an aqueous slurry of sodium hydrogen carbonate (3–4 moles); then the dimethyl sulfate (2.5–3.5 moles) is added in one portion. Stirring initiates the reaction involving evolution of carbon dioxide. Yields are excellent if the amine is sufficiently basic for methylation to occur below 35°; at higher temperatures the dimethyl sulfate is appreciably hydrolysed. Further the amine and dimethyl sulfate must possess at least some mutual solubility, a state that may on occasions be favored by addition of a water-immiscible solvent.

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[826] R. E. Benson and T. L. Cairns, *J. Amer. Chem. Soc.*, **70**, 2115 (1948).

[827] S. Petersen and E. Tietze, *Ann. Chem.*, **623**, 166 (1959).

[828] F. Turba and K. Schuster, *Z. Physiol. Chem.*, **283**, 27 (1948).

[829] F. Cramer, K. Pawelzik, and J. Kupper, *Angew. Chem.*, **68**, 649 (1956).

[830] F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

[831] R. Ohme and E. Schmitz, *Angew. Chem. Int. Ed., Engl.*, **6**, 566 (1967).

[832] D. Jerchel and H. Fischer, *Ann. Chem.*, **574**, 96 (1951).

[833] A. Pinner, *Ann. Chem.*, **297**, 221 (1897); **298**, 1 (1898).

[834] S. Hünig, *Chem. Ber.*, **85**, 1056 (1952).

***N,N*-Dimethyl-2-naphthylamine:**[834] 2-Naphthylamine (14.5 g), sodium hydrogen carbonate (34 g), and water (50 ml) are placed in a three-necked flask fitted with a stirrer, thermometer, and bubble-counter, and dimethyl sulfate (34 ml) is then added. Vigorous gas evolution begins at 10° and is complete in 45 min. The excess of dimethyl sulfate is hydrolysed by warming the mixture to 55–60°. The resulting solution is freed from residual sodium hydrogen carbonate, made very strongly alkaline with sodium hydroxide, and boiled under reflux for 1 h. The oil that is formed is taken up in chloroform. The chloroform is then removed from the organic layer and the residue is distilled, giving a colorless oil, b.p. 160–161°/12 mm (16.8 g, 98%).

The presence of the hydrogen carbonate is necessary to liberate the base from the amine (alkyl sulfate) salt, so that this also may be further methylated. Sodium hydrogen carbonate has the advantage over a stronger base for this purpose in that the pH that results permits selective alkylation of aminophenols on nitrogen.[834]

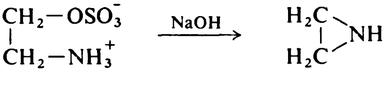
In older work aqueous sodium hydroxide was often used to bind the alkyl hydrogen sulfate that results, the medium being maintained alkaline by alternate addition of dialkyl sulfate and sodium hydroxide. However, the yields depended largely on the exact maintenance of prescribed reaction conditions and on the purity of the dialkyl sulfate.

***o*-Bromo-*N,N*-dimethylaniline:**[835] *o*-Bromoaniline (100 g) and water (100 g) are placed in a 1-l three-necked flask fitted with a stirrer and treated with three equivalents of dimethyl sulfate (219 g) as follows: one equivalent is stirred into the mixture which is then left until, homogeneous, whereupon it is neutralized carefully with 25% potassium hydroxide solution under cooling; the second equivalent of dimethyl sulfate is added in the same way, but a slight excess of potassium hydroxide is added after the neutralization; then the remainder of the dimethyl sulfate is stirred in and the mixture is left for 1 h before being extracted with ether. The ethereal phase is washed with water and dried over potassium carbonate. Distillation affords *o*-bromo-*N,N*-dimethylaniline, b.p. 100–101°/12 mm, in 70% yield (81.5%).

m-Bromo-*N,N*-dimethylaniline, b.p. 118–119°/8 mm, is obtained analogously in 54% yield.

In many cases amines are alkylated when merely heated with dialkyl sulfates. For instance, *N,N*-diethyl-*p*-anisidine was obtained (61% yield) by heating *p*-anisidine (1 mole) with diethyl sulfate (2.2 moles) for 4 h at 120–130°, *N,N*-diethyl-*p*-toluidine (91%) analogously after 6 hours' heating, and *N,N*-diethyl-*m*-phenetidine (52%) after 8 hours' heating.[836]

An important method for preparing aziridine (ethylene imine) and its derivatives is to cyclize the sulfuric esters of ethanolamines by heating them with alkali:[479, 837, 838]



Pure primary amines may also be obtained by alkylating urotropine with dialkyl sulfates and cleaving the resulting quaternary salt.[839]

Alkylation of cyanamide makes dialkylcyanamides accessible and, by their hydrolysis, also secondary amines. For instance, dimethylamine was obtained

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[835] H. Gilman and I. Banner, *J. Amer. Chem. Soc.*, **62**, 344 (1940).

[836] H. A. Fahim and A. M. Fleifel, *J. Chem. Soc.*, **1951**, 2761.

[837] C. H. F. Allen, F. W. Spangler, and E. R. Webster, *Org. Syn.*, **30**, 38 (1950).

[838] K. N. Campbell, A. H. Sommers, and B. K. Campbell, *Org. Syn.*, **27**, 12 (1947).

[839] F. L. Hahn and H. Walter, *Ber. Deut. Chem. Ges.*, **54**, 1531 (1921).

in 70–80% yield from calcium cyanamide and dimethyl sulfate.[499] This method has, however, no advantage over the use of alkyl halides.

When alkylating carboxamides and lactams it should be remembered that free amides can readily undergo *O*-alkylation which gives imidic esters. Hexanolactam, for instance, with dimethyl sulfate gives the *O*- or the *N*-methyl derivative according to the conditions applied.[826] To convert an amide exclusively into its *N*-alkyl derivative it is best to use the *N*-alkali derivative and conduct the alkylation in an inert solvent.

For example, in a preparation of *N*-methyl-*p*-anisidine, *N*-acetyl-*p*-anisidine was first metalated with sodamide in boiling toluene and then, in the same operation, methylated with dimethyl sulfate at 100° and finally hydrolysed by alkali.[724]

More importance attaches to alkylation of sulfonamides by dimethyl or diethyl sulfate. The following technique has proved useful for arenesulfonanilides:

The arenesulfonanilide (0.04 mole) is dissolved in 10% aqueous sodium hydroxide solution (0.042 mole), then the dialkyl sulfate (0.042 mole) is added, with stirring, at 25° during 30 min. A few minutes after this addition has begun, the *N*-alkylarenesulfonanilide begins to crystallize. The mixture is stirred for a further 1 h at 40°, then the product is collected and recrystallized from 95% ethanol.[840]

Hydrazine does not react unidirectionally with dialkyl sulfates. Acylhydrazines can be alkylated more smoothly; for example, for preparation of 1,2-dimethylhydrazine, 1,2-dibenzoylhydrazine was methylated in an alkaline medium by dimethyl sulfate and the alkylation product was finally hydrolysed.[532]

Alkylation of nitrogen compounds by phosphoric esters. There are few records of the alkylation of nitrogen compounds by phosphoric esters. Billman *et al.*[841] give the following general directions for alkylation of aromatic amines; the phosphoric ester is wholly dealkylated under these conditions.

A mixture of aniline (0.3 mole) and the requisite trialkyl phosphate (0.2 mole) is heated in a 500-ml flask for 2 h. The initial reaction is usually strongly exothermic, so that the temperature rises considerably. When the violent ebullition slackens the water-condenser is replaced by an air-condenser. The mixture is cooled to 50°, treated with a solution of sodium hydroxide (25 g) in water (100 ml), boiled for 1 h, and allowed to cool to room temperature in a beaker. The upper amine layer is separated from the precipitated sodium phosphate, and the latter is washed with ether. The amine and the ethereal solution are dried together over sodium sulfate, then freed from ether. The residue is set aside overnight with its own volume of acetic anhydride, then treated with a mixture of concentrated hydrochloric acid (20 ml) and water (30 ml), and shaken until all the amine has dissolved. The solution is then extracted with ether (two 30-ml portions), after which the amine is liberated by 25% sodium hydroxide solution and taken up in ether. This extract is dried over sodium sulfate and distilled. The following are examples of yields of *N,N*-dialkylanilines obtained by use of the appropriate trialkyl phosphate: dimethyl 68%, diethyl 99%, dipropyl 78%, and dibutyl 79%.

1- and 2-Naphthylamine[841] and a series of ring-substituted anilines[842] were similarly alkylated. *N,N*-Diethyl-2-fluorenamine was obtained almost quanti-

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[840] M. Neeman and A. Modiano, *J. Org. Chem.*, **21**, 667 (1956).

[841] J. H. Billman, A. Radike, and B. W. Mundy, *J. Amer. Chem. Soc.*, **64**, 2977 (1942).

[842] D. G. Thomas, J. H. Billman, and C. E. Davis, *J. Amer. Chem. Soc.*, **68**, 895 (1946).

tatively from 2-fluorenamine and triethyl phosphate at 205°;[843] and morpholine affords 4-ethylmorpholine in 70% yield under not quite such drastic conditions.[844]

For alkylation of alkali cyanates to give alkyl isocyanates the use of trialkyl phosphates[845] has advantages over that of sulfuric or sulfonic esters.[846]

Dialkyl chlorophosphates are occasionally used in place of the trialkyl esters; aniline was thus monoalkylated in 95% yield at 240–245°.[847]

Alkylation of nitrogen compounds by arenesulfonic esters. Arenesulfonic esters have found widespread application as alkylating agents; in particular, toluenesulfonic esters are potent alkylating agents for primary alcohols. When 2-chloroethyl toluenesulfonate is treated with potassium phthalimide it is the sulfonate group and not the halogen that becomes attached to the nitrogen atom.[848]

As in alkylation with sulfuric and phosphoric esters it is essential to use the free amine, since that of, *e.g.*, the amine hydrochlorides leads almost exclusively to alkylation of the chloride ion to alkyl chloride.

For example, heating octyl *p*-toluenesulfonate (0.05 mole) with diethylamine hydrochloride (0.1 mole) in chloroform (35 ml) for 6 h gives a 91% yield of **octyl chloride.**[849]

As when dialkyl sulfates are used, the products formed from free amines and sulfonic esters are almost always mixtures of all the possible alkylation stages of the amine. Nevertheless, formation of specific products can be favored by choice of techniques. When a solvent is needed alcohol or acetone is usually chosen.

***N*-Monopropylaniline:**[850] Aniline (18.8 g, 0.2 mole) and propyl *p*-toluenesulfonate (24 g, 0.1 mole) are heated for 5 h in an oil-bath at 110°. On cooling, the product solidifies owing to crystallization of aniline *p*-toluenesulfonate (m.p. 236°C). This salt dissolves on addition of water (70 ml), and a reddish-brown oil separates which is taken up in ether, washed with water, dried over sodium sulfate, and distilled, giving *N*-propylaniline (12 g, 87%) as a pale yellow oil, b.p. 95–105°/10 mm.

***N*,*N*-Dipropylaniline:**[850] Aniline (9.4 g, 0.1 mole) and propyl *p*-toluenesulfonate (48 g, 0.2 mole) are heated with potassium hydroxide (12.8 g, 0.2 mole) on a water-bath. Reaction begins with very violent foaming. When this ceases the mixture is heated for 2 h in an oil-bath at 110°. On cooling, potassium *p*-toluenesulfonate crystallizes out and is brought into solution by addition of water. The red oil that then separates is purified and dried by distillation with a little acetic anhydride; this gives a pale yellow, oily tertiary base (12.6 g, 70%), b.p. 127°/10 mm.

***N*,*N*,*N*′,*N*′-Tetrasubstituted diamines** are obtained from diol bissulfonates and secondary amines:[851]

$$\mathrm{RSO_2O-(CH_2)_{\mathit{n}}-OSO_2R + 4R'R''NH \longrightarrow}$$
$$\mathrm{R'R''N-(CH_2)_{\mathit{n}}-NR'R'' + 2(RSO_2OH \cdot NHR'R'')}$$

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[843] T. L. Fletcher, M. E. Taylor, and A. W. Dahl, *J. Org. Chem.*, **20**, 1021 (1955).

[844] W. H. C. Rueggeberg and J. Chernack, *J. Amer. Chem. Soc.*, **70**, 1802 (1958).

[845] T. I. Bieber, *J. Amer. Chem. Soc.*, **74**, 4700 (1952).

[846] K. H. Slotta and L. Lorenz, *Ber. Deut. Chem. Ges.*, **58**, 1320 (1925); K. H. Slotta and R. Tschesche, *Ber. Deut. Chem. Ges.*, **60**, 295 (1927).

[847] W. Gerrard and G. J. Jeacocke, *Chem. & Ind. (London)*, **1954**, 1538.

[848] E. J. Sakellarios, *Helv. Chim. Acta*, **29**, 1675 (1946).

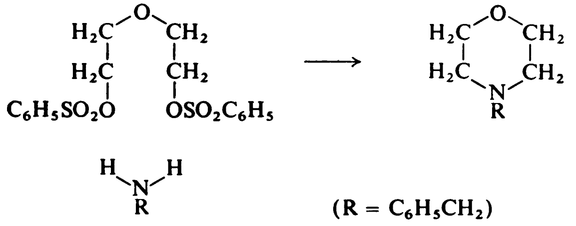
[849] D. Klamann, *Ann. Chem.*, **583**, 63 (1953).

[850] K. H. Slotta and W. Franke, *Ber. Deut. Chem. Ges.*, **63**, 678 (1930).

[851] T. M. Laakso and D. D. Reynolds, *J. Amer. Chem. Soc.*, **73**, 3518 (1951).

Technique:[851] The diol bissulfonate is heated and stirred with the secondary amine (20 equivalents) for 20 h under anhydrous conditions, then the secondary amine is distilled off and the solution is treated with an excess of 40% sodium hydroxide solution. The oily layer is separated and the aqueous phase is extracted with ether. The organic phases are united and dried over potassium carbonate. The ether is removed and the residue is distilled in a vacuum. In this way were prepared, *inter alia*: *N,N,N',N'*-tetracyclohexylethylenediamine (86%), m.p. 102–104°; *N,N,N',N'*-tetraethylenediamine (55%), b.p. 89°/31.5 mm; *N,N,N',N'*-tetraisopropyltrimethylenediamine (86%), b.p. 83°/10–11 mm; *N,N,N',N'*-tetrabutyltetramethylenediamine (78%), b.p. 107–108°/1 mm; *N,N,N',N'*-tetraphenyltrimethylenediamine (65%), b.p. 118–121°/0.3 mm; and bis[2-(diethylamino)ethyl] ether (13%), b.p. 69–70°/1 mm.

N-Alkylated heterocyclic compounds can be built up in one operation by treating diol bissulfonates with primary amines. For instance, 1-cyclohexylpiperidine, b.p. 234°, is obtained in 81% yield from 1,5-pentanediol bis(benzenesulfonate) and cyclohexylamine, and 4-benzylmorpholine, b.p. 79°/2 mm, from 2,2'-oxybis(ethyl benzenesulfonate) and benzylamine.[852]



(R = $C_6H_5CH_2$)

Such cyclizations are achieved by the following technique:[852] The primary amine (1.5 moles) is dropped within 2 h into a solution of the diol bisarenesulfonate (0.5 mole) in dry dioxan (500 ml) boiling under reflux. Then an aqueous solution of sodium hydroxide (60 g, 1.5 moles) is added and the mixture is concentrated to half its volume. The residue is cooled, stirred with ether, filtered, and fractionated.

In general it is not possible to perform arylations by aryl arenesulfonates, but some nitroaryl esters form exceptions, as was found by Ullmann.[853, 854]

For instance, passing ammonia into a boiling solution of 2,4-dinitro-1-naphthyl *p*-toluenesulfonate gives 2,4-dinitro-1-naphthylamine quantitatively, and 2,4-dinitro-*N*-phenyl-1-naphthylamine is obtained in 98% yield by use of aniline.[854]

Primary amines have occasionally been prepared, *e.g.*, allylamine,[839] by alkylation of urotropine and hydrolysis of the resulting quaternary urotropinium salt.

An important method of preparing pure primary or secondary amines is to alkylate sulfonamides and hydrolyse the products.

For monoalkylation of arenesulfonamides containing an unsubstituted SO_2NH_2 group it is best that the medium should contain sodium carbonate, since dialkylated products are readily formed in alkali hydroxide solutions.[855]

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[852] D. D. Reynolds and W. O. Kenyon, *J. Amer. Chem. Soc.*, **72**, 1597 (1950).

[853] F. Ullmann and G. Nádai, *Ber. Deut. Chem. Ges.*, **41**, 1870 (1908).

[854] F. Ullmann and W. Bruck, *Ber. Deut. Chem. Ges.*, **41**, 3932, 3939 (1908).

[855] D. Klamann, G. Hofbauer, and F. Drahowzal, *Monatsh. Chem.*, **83**, 870 (1952); cf. D. Klamann and H. Bertsch, *Chem. Ber.*, **89**, 2007 (1956).

N-Methyl-p-toluenesulfonamide:[855] *p*-Toluenesulfonamide (19 g, 0.11 mole) is added to a hot saturated solution of anhydrous sodium carbonate (21.1g, 0.2 mole) in water (25 ml), and the mixture is boiled under reflux until all is dissolved. Then methyl *p*-toluenesulfonate (18.6 g, 0.1 mole) is added, and boiling is continued with stirring for a further 2 h. The solution is then allowed to cool, treated with water, and filtered. On acidification of the filtrate some unchanged sulfonamide (1.4 g) is recovered (7.3% of the batch). The original precipitate (crude monomethylamide) is purified by boiling it with an excess of sodium hydroxide solution, filtering off the insoluble dimethylamide (2 g, 10%; m.p. 86.5°), and recovery by acidification with 17% hydrochloric acid. The *N*-methyl-*p*-toluenesulfonamide (13 g, 70.3%) thus obtained is nearly pure; it has m.p. 77°.

The *N*-monoethyl and the *N*-monobutyl derivatives are obtained analogously in 86% and 65% yield, respectively.

Dialkylation of sulfonamides, and further alkylation of *N*-alkyl- and *N*-arylsulfonamides, can be effected in alkali hydroxide solutions:[855,840]

N-Ethyl-p-toluenesulfonanilide:[855] *p*-Toluenesulfonanilide (74 g, 0.3 mole) is dissolved in 10% sodium hydroxide solution (108 ml, 0.3 mole), treated with methyl *p*-toluenesulfonate (60 g, 0.3 mole), and stirred under reflux at 100° for 2 h. At the end of the reaction, the mixture is stirred whilst cooling, so that the *N*-ethylanilide solidifies. When filtered off, washed with water, and dried, this has m.p. 88° (78,3 g, 94.8%). Acidification of the filtrate with hydrochloric acid permits unchanged anilide (3.2 g, 4.3% of the batch) to be recovered.

These directions can be generalized for the preparation of other *N,N*-disubstituted sulfonamides. If the starting material is an unsubstituted amide, then of course double the relative amounts of sodium hydroxide and ester are required. Extension of the process to long-chain alkyl groups also occurs smoothly.[840,855]

The preparation of amides from arenesulfonyl chlorides and their alkylation can be carried out in one operation.[855]

For the hydrolysis of sulfonamides see pages 456 and 683.

d. Reactions of amides with nitrogen compounds

Replacement of the carbonyl-oxygen atom of amides by the nitrogen of primary or secondary amines often leads relatively simply to amidines. The reaction requires the presence of an acid halide such as PCl_3, $POCl_3$, PCl_5, or $SOCl_2$ (in certain circumstances also an alkylating agent) and it occurs by way of addition compounds or amidoyl chlorides which can occasionally be isolated. It is mainly formamidines that have been prepared in this way. The technique of using PCl_5 in dry chloroform is shown in the following example:

N,N′-Diphenylformamidine:[856] Formanilide (2.4 g, 0.02 mole) is added slowly, in small portions, to a cooled solution of PCl_5 (4.8 g, 0.023 mole) in chloroform (20 ml). When the reaction subsides, a chloroform solution of freshly distilled aniline (1.9 ml, 0.02 mole) is added, causing an immediate precipitation. The mixture is heated under reflux for 2.5 h, then cooled in an ice-bath and filtered. The solid amidine salt is collected, washed with cold acetone, and dried in a vacuum. The free amidine base was obtained therefrom by treatment with alcoholic sodium ethoxide solution. The crude amidine crystallizes in an ice-bath and is filtered off, washed with cold alcohol, dried, and extracted with acetone. Pouring the acetone solution into water precipitates the amidine. One more precipitation from acetone by water gives material of m.p. 140–141° (2.6 g, 66%).

H. Bredereck and his co-workers[857,858] have prepared a number of amidines in good yield when using phosphorus oxychloride in benzene:

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[856] H. G. Mandel and A. J. Hill, *J. Amer. Chem. Soc.*, **76**, 3978 (1954).

[857] H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).

[858] H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2298 (1961).

N^1,N^1-Dimethyl-N^2-phenylformamidine: A mixture of dimethylformamide (27.4 g) and anhydrous benzene (50 ml) at 20–25° was treated, with stirring and exclusion of moisture, with phosphorus oxychloride (23.1 g) in anhydrous benzene (50 ml) dropwise, and then left overnight at room temperature. On the next day aniline (11.6 g) in anhydrous benzene (40 ml) was dropped in at approximately 35°, while the yellow oil that separated was kept in suspension by rapid stirring. Stirring was continued for a further 3–4 h, after which the supernatant benzene was decanted and the residue was kneaded with anhydrous benzene (50 ml); the benzene was decanted and the kneading and decantation were repeated. To convert this material into the free base it was dissolved in ice-water, the solution was covered with a layer of the equal amount of benzene, and the mixture was made strongly alkaline with cold 2N sodium hydroxide solution. The mixture was shaken, the benzene layer was separated, and the aqueous phase was extracted twice more with benzene. The benzene solutions were united, dried over potassium carbonate, and evaporated. The residue was purified by distillation in a vacuum, giving the amidine, b.p. 119–122°/10 mm, n_D^{20} 1.5955 (15.6 g, 85%).

N^1,N^1-Dimethyl-N^2-phenylacetamidine was obtained analogously from *N,N*-dimethylacetamide.

When ureas are used as the amide component, guanidines are formed analogously.[858] If the amine component contains a suitably reactive group, the amidine may on occasions react further to give a heterocycle: for instance, benzothiazole is obtained in 85% yield from *o*-aminothiophenol, dimethylformamide, and phosphorus oxychloride.[859]

To prepare N^1,N^2-dimethyl-N^1,N^2-diphenylamidinium salts one can proceed directly from the acid, instead of from the acid chloride, treating the acid with an excess of *N*-methylaniline and phosphorus oxychloride.[860]

Benzoic acid (9.15 g) is dissolved in *N*-methylaniline (32.1 g) with stirring and warming, then the mixture is cooled and treated dropwise with phosphorus oxychloride (15.3 g). The mixture is heated for 2 h at 130°, then dissolved in 50% aqueous methanol, shaken with charcoal, and filtered. Adding sodium perchlorate solution to the filtrate precipitates **N^1,N^2-dimethyl-N^1,N^2-diphenylbenzamidinium perchlorate,** which after recrystallization from methanol–ether has m.p. 216–218° (dec.) (25 g, 83%).

Formamidine formation gives a different result if carried out in the presence of alkylating agents; in that case a formimidic ester is formed as intermediate, which reacts with the excess of formamide to give first the formamidine and then **tris(formamido)methane [*N,N,N*-methylidynetris(formamide)]**;[861] which is an intermediate of manifold reactivity:

Dimethyl sulfate (126 g) and formamide (450 g) are heated together in a distillation flask at water-pump vacuum for 1.5 h at 70–80°. The trisamide (87 g, 60% calculated on dimethyl sulfate), m.p. 165–166°, crystallizes out overnight.

e. Reactions of isocyanates with nitrogen compounds

Although the addition of nitrogen compounds to the C=N bond of isocyanates offers a number of synthetic possibilities (see page 406), formal replacement of the isocyanate-oxygen by nitrogen has only recently become important and then only for one case. This case is the conversion of isocyanates into carbodiimides:

$$2RNCO \longrightarrow RN{=}C{=}NR + CO_2$$

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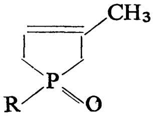
[859] C. S. Davis, A. M. Knevel, and G. L. Jenkins, *J. Org. Chem.*, **27**, 1919 (1962).

[860] C. Jutz and H. Amschler, *Chem. Ber.*, **96**, 2100 (1963).

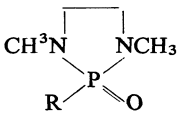
[861] H. Bredereck, R. Gompper, H. G. von Schuh, and G. Theilig, *Angew. Chem.*, **71**, 753 (1959).

which often occurs in high yield under mild conditions and is catalysed by phosphoryl compounds.

Aromatic isocyanates, particularly those containing electron-attracting substituents, react noticeably more easily than aliphatic isocyanates. In the former case it often suffices to leave the components for some hours at room temperature in a water-pump vacuum, whereas for aliphatic compounds boiling under reflux is usually necessary and sometimes use of a higher-boiling solvent such as decalin. The best catalysts are cyclic phosphine oxides of type (**1**) (phospholene oxides)[862] and cyclic phosphonic diamides of type (**2**) (1,3,2-diazaphospholidine oxides).[863] The best results were obtained with compound (**1**, R = C_2H_5) (for its preparation see Campbell *et al.*[862]); the phenyl compound, although more readily prepared,[864] is somewhat less reactive. The amounts of catalyst needed are 0.1% for (**1**) or 0.5% for (**2**).



(**1**)



(**2**)

Di-*o*-tolylcarbodiimide:[862] A mixture of *o*-tolyl isocyanate (25 ml) and 1-ethyl-3-methyl-3-phospholene oxide (**1**, R = C_2H_5) (0.25 g) is heated for 9.5 h at 50–55° with exclusion of water and then distilled in a vacuum, affording the carbodiimide (19.3 g, 87%), b.p. 118–122°/0.13 mm, n_D^{25} 1.6230.

Detailed directions for preparation of **diphenylcarbodiimide** are given in *Organic Syntheses.*[865]

2. Reactions of carbonyl compounds with nitrogen compounds

a. Preparation of simple derivatives of carbonyl compounds

Reaction of a carbonyl group with ammonia or its derivatives is always one of addition, leading to the so-called *O,N*-semiacetals (α-amino ethers) (see page 411). In most cases, however, these compounds cannot be isolated; they normally stabilize themselves by losing water and forming a C=N double bond (cf., however, pages 411 and 515), so that formally there is replacement of =O by =NR. These end products are often carbon derivatives of preparative or analytical value. If other functional groups or suitably orientated double bonds are present this type of C—N bond formation may have additional preparative importance by leading to heterocyclic systems in which new C—C bonds have been formed.

i, Preparation of imines, Schiff bases[866]

Aldimines, RCH=NH, cannot be prepared from the aldehyde and ammonia; some polymerize (*e.g.*, acetaldehyde gives 2,4,6-triethylhexahydro-*s*-triazine), some condense further with the carbonyl compound (hydrobenzamide from

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[862] T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Amer. Chem. Soc.*, **84**, 3673 (1962).
[863] H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Org. Chem.*, **32**, 1360 (1967).
[864] W. B. McCormack, *Org. Syn.*, **43**, 73 (1963).
[865] T. W. Campbell and J. J. Monagle, *Org. Syn.*, **43**, 31 (1963).
[866] M. M. Sprung, *Chem. Rev.*, **26**, 297 (1940); R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

benzaldehyde; secondary and tertiary aliphatic aldehydes behave differently[792a]), yet others react simultaneously in both ways (urotropine from formaldehyde[793]). A general method for preparing aldimines is to decompose the complex formed from a nitrile, hydrogen chloride, and stannous chloride.[869]

When aldehydes are subjected to simultaneous action of ammonia and lead(IV)acetate the imines formed as intermediates are dehydrogenated to nitriles.[870]

Ketimines, $R_2C{=}NH$, also cannot be prepared, as a general rule, from the ketone and ammonia; one of the few exceptions is 9-fluorenimine which is obtained in 66% yield when ammonia is led for several hours into fluorenone at 165°.[871] It has recently been shown that ketones are converted directly into their imines by phosphinimines:

Benzophenone imine:[872] Triphenylphosphine imine (5.85 g) and benzophenone (3.4 g) are dissolved in benzene (200 ml) and gently boiled for 2 h. Then the benzene is distilled off, leaving an oil which boils at 108°/1 mm. This is benzophenone imine (3.24 g). Leading gaseous hydrogen chloride into a benzene solution of the imine precipitates the iminium chloride, which sublimes at 230–250°.

The literature should be consulted for the preparation of ketimines from nitriles and Grignard compounds[873] and by the Hoesch synthesis.[874]

The *N*-alkyl and *N*-aryl derivatives (Schiff bases, azomethines, anils) that can be obtained from aldehydes and ketones by use of primary amines are considerably more important than the unsubstituted imines.

For preparation of purely aliphatic aldimines $RCH{=}NR'$ it is best to mix the aldehyde and amine at 0° without a solvent and bind the water formed by means of solid potassium hydroxide.[875] The following directions show a process that can be generalized:

***N*-Propylbutyraldimine:**[875] Propylamine (23.6 g, 0.4 mole) is placed in a 250-ml three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel and is cooled while butyraldehyde (28.4 g, 0.4 mole) is dropped in during 2 h. After 2 hours' further stirring, solid potassium hydroxide is added. Two phases are formed during about 10 min. The organic layer is kept overnight in the refrigerator over crushed potassium hydroxide and then distilled from fresh potassium hydroxide. The main fraction (70%) boils at 120–124° and has n_D^{20} 1.4149.

It should be noted that Schiff bases of this type, like the parent imines unsubstituted on nitrogen, are also relatively unstable: they still possess the pronounced tendency to trimerization with formation of hexahydrotriazine

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[867] R. H. Hasek, E. N. Elam, and J. C. Martin, *J. Org. Chem.*, **26**, 1822 (1961).

[868] H. H. Richmond, G. S. Myers, and G. F. Wright, *J. Amer. Chem. Soc.*, **70**, 3659 (1948).

[869] T. L. Tolbert and B. Houston, *J. Org. Chem.*, **28**, 695 (1963).

[870] K. N. Parameswaran and O. M. Friedman, *Chem. & Ind.* (*London*), **1965**, 988; cf. H. M. Blatter, H. Lukaszewski, and G. de Stevens, *J. Amer. Chem. Soc.*, **83**, 2203 (1961).

[871] G. H. Harris, B. R. Harriman, and K. W. Wheeler, *J. Amer. Chem. Soc.*, **68**, 846 (1946).

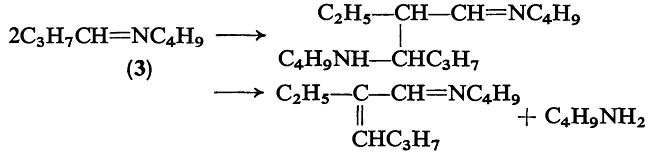
[872] R. Appel and A. Hauss, *Chem. Ber.*, **93**, 405 (1960).

[873] P. L. Pickard and D. J. Vaughan, *J. Amer. Chem. Soc.*, **72**, 876, 5017 (1950); P. L. Pickard and T. L. Tolbert, *J. Org. Chem.*, **26**, 4886 (1961).

[874] P. E. Spoerri and A. S. Du Bois, *Org. Reactions*, **5**, 387 (1949).

[875] K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Amer. Chem. Soc.*, **66**, 82 (1944).

derivatives; and purely aliphatic Schiff bases readily undergo, when heated, a kind of aldol condensation, as when 3 hours' refluxing (140–150°) of *N*-butylidenebutylamine (3) gives 65% of the different Schiff base (4):[876]



$$\underset{(3)}{2C_3H_7CH{=}NC_4H_9} \longrightarrow \begin{array}{l} C_2H_5\text{—}CH\text{—}CH{=}NC_4H_9 \\ \qquad\quad | \\ C_4H_9NH\text{—}CHC_3H_7 \end{array} \longrightarrow \begin{array}{l} C_2H_5\text{—}C\text{—}CH{=}NC_4H_9 \\ \qquad\;\, \| \\ \qquad CHC_3H_7 \end{array} + C_4H_9NH_2$$

(4)

Further, the reaction between an aldehyde and an amine can be carried out in such a way that the condensation product is obtained directly instead of the simple Schiff base.[877]

When α,β-unsaturated aldehydes react with amines there is usually simultaneous addition to the C=O and the C=C double bond. To obtain the compound retaining the C=C double bond, the aldehyde can be treated with an *N*-alkylketimine:[878,879]

$$RCHO + R'R''C{=}NR''' \longrightarrow RCH{=}NR''' + R'R''CO$$

Unlike purely aliphatic Schiff bases, the condensation products of aromatic aldehydes with primary amines and, particularly, with primary aromatic amines are very stable compounds. They usually crystallize well and can thus be used to characterize amines or aldehydes. They are often formed on merely mixing the components but with gentle warming (*e.g.*, in alcoholic solution) if necessary, and yields are in most cases very good. The tendency to condensation is often so great that it occurs even in an aqueous medium.

***N*-Methylbenzaldimine:**[880] Benzaldehyde (106 g) is treated with 33% aqueous methylamine solution (150 g) during 20 min. The reaction is strongly exothermic. The mixture is then left for 12 h at room temperature, after which it is saturated with sodium chloride and extracted with ether. The extract is dried and distilled through an efficient column. This affords the Schiff base as a colorless liquid (83 g, 70%), b.p. 183–185°.

***N*-Benzylideneaniline:**[881] Aniline (93 g) is added, with efficient stirring, to benzaldehyde (106 g) in a 500-ml flask. Reaction sets in exothermally after a few seconds, water separating. The mixture is set aside for 15 min, then poured into 95% ethanol (165 ml) in a 600-ml beaker. Crystallization starts after a few minutes and is completed by ice-cooling. The product is filtered off and dried in the air (152–158 g, 84–87%; m.p. 52°). A further 10 g can be obtained by concentration of the mother liquor in a vacuum. The benzaldehyde and aniline used should preferably be freshly distilled.

Benzylideneaniline is polymorphous and melting points found lie between 42° and 56°.

Unlike aldehydes, many ketones — and, in particular, aromatic ketones — do not react readily with amines to give ketimines. The reaction usually requires higher temperatures and addition of a condensing agent, for which Reddelien[882] recommends zinc chloride or the zinc chloride–amine adducts.

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[876] W. S. Emerson, S. M. Hess, and F. C. Uhle, *J. Amer. Chem. Soc.*, **63**, 872 (1941).

[877] A. M. Paquin, *Chem. Ber.*, **82**, 316 (1949).

[878] C. W. Smith, D. G. Norton, and S. A. Ballard, *J. Amer. Chem. Soc.*, **75**, 3316 (1953).

[879] U.S. Pat. 2,513,996; *Chem. Abstr.*, **44**, 8361 (1950).

[880] N. H. Cromwell, R. D. Babson, and C. E. Harris, *J. Amer. Chem. Soc.*, **65**, 312 (1943).

[881] L. A. Bigelow and H. Eatnough, *Org. Syn.*, **8**, 22 (1928).

[882] G. Reddelien, *Ber. Deut. Chem. Ges.*, **43**, 2476 (1910); **42**, 4759 (1909); cf. J. H. Billman and K. M. Tai, *J. Org. Chem.*, **23**, 535 (1958).

Benzophenone anil:[882] Benzophenone (10 g) and aniline (10 g) at 160° are treated during 0.5 h with freshly crushed, anhydrous zinc chloride (1–2 g). After cooling, the yellow melt is boiled with a little benzene or ether. The yellow anil (12 g, 85%), m.p. 117°, crystallizes from the solution.

A similar condensation has been carried out, but with toluene as solvent, for 2-methylcyclohexanone and aniline, and for cyclohexanone with aniline and *o*-toluidine.[883]

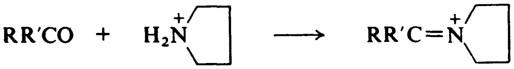
Phosphorus oxychloride may be used in place of zinc chloride, and this is recommended for cases where the latter has not sufficient condensing action owing to the low solubility of its amine adduct.[884] Boron trifluoride etherate was found to be a particularly active catalyst for condensation of 9-fluorenone with aromatic amines.[885]

Norton[886] has given the following simple method for preparation of purely **aliphatic ketimines**:

The amine and the ketone are heated with azeotropic removal of the water formed, the carrier being benzene, toluene, xylene, or an excess of the ketone. Water-soluble amines and ketones, which cannot be treated in this way, are kept together at room temperature for 24 h after addition of concentrated hydrochloric acid (3 g per 5 moles of amine and ketone), after which the water produced is removed by solid sodium hydroxide and the organic phase is distilled. Very good yields of about 40 aliphatic ketimines were obtained by these two methods.[886]

Acetone anil cannot be obtained by direct reaction of the components: mesityl oxide is formed and this reacts with the aniline to give 1,2-dihydro-2,2,4-trimethylquinoline.[887] However, the anil is formed smoothly when acetone diethyl ketal is condensed with aniline.[888] The latter reaction is, however, not generally applicable because many acetals and ketals are unusually resistant to attack by ammonia or amines.[505]

Condensation of carbonyl compounds with secondary amines such as morpholine and pyrrolidine, introduced as perchlorates, gives the iminium salts in high yield:[890]



β-Keto carboxylic esters usually react with ammonia or primary or secondary aliphatic amines exothermally as soon as the components are mixed; the products, however, are not the imino acids but the unsaturated amino acids tautomeric therewith: thus derivatives of *β*-aminoacrylic esters are formed:

$$\mathrm{RCOCH_2COOR'} \xrightarrow[-\mathrm{H_2O}]{+\mathrm{NH_3}} \mathrm{NH_2CR{=}CHCOOR'}$$

Ethyl 3-aminocrotonate:[891] A rapid stream of dry ammonia is passed, with stirring, into ethyl acetoacetate (97.5 g) for 5 h. The temperature rises to 40° during the first hour and is

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[883] C. Hansch, F. Gschwend, and J. Bamesberger, *J. Amer. Chem. Soc.*, **74**, 4554 (1952).

[884] A. W. Weston and R. J. Michaelis Jr., *J. Amer. Chem. Soc.*, **73**, 1381 (1951).

[885] M. E. Taylor and T. L. Fletcher, *J. Org. Chem.*, **26**, 940 (1961).

[886] D. G. Norton, V. E. Haury, F. C. Davis, L. J. Mitchell, and S. A. Ballard, *J. Org. Chem.*, **19**, 1054 (1954).

[887] G. Reddelien and A. Thurm, *Ber. Deut. Chem. Ges.*, **65**, 1511 (1932); I. W. Elliot Jr. and P. Yates, *J. Org. Chem.*, **26**, 1287 (1961).

[888] L. Claisen, *Ber. Deut. Chem. Ges.*, **29**, 2931 (1896).

[889] J. R. Johnson and co-workers, *J. Amer. Chem. Soc.*, **69**, 2364 (1947).

[890] N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

[891] S. A. Glickman and A. C. Cope, *J. Amer. Chem. Soc.*, **67**, 1017 (1945).

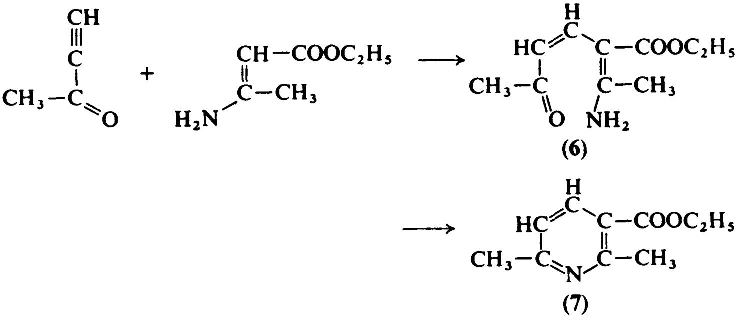
kept at 35–40° by cooling. Then ether (100 ml) is added and the water produced is separated. Vacuum-distillation through a Widmer column affords the amino ester (88.2 g, 90%), b.p. 91–93°/8–9 mm, n_D^{25} 1.4980, m.p. 18°.

The 3-(methylamino)- and 3-(dimethylamino)-crotonic ester were obtained analogously.

Aromatic amines often react only when warmed or when an acid catalyst is added, *e.g.*, the amine hydrochloride;[892] for condensation of ethyl acetacetate with aniline a solution in benzene containing a little glacial acetic acid is boiled.[893] Too high a reaction temperature must, however, be avoided lest the ester group react to form the amide[773,894] (cf. page 490).

The tendency of 1,4-diketones to cyclize with ammonia or primary amines, yielding pyrrole derivatives (the Paal–Knorr synthesis[895]), can only be mentioned here.

It is also impossible here to go into detail about the numerous syntheses of heterocycles that include formation of C—N bonds as well as new C—C bonds: only rarely does the C—N bonding occur as an isolated partial step in the reaction. A recent example of such separation is the unusually smooth synthesis of pyridine derivatives discovered by Bohlmann and Rahtz;[896] in this, an activated enamine, *e.g.*, ethyl 3-aminocrotonate, adds to an acyl acetylene, and the resulting amino carbonyl compound is then converted into the pyridine derivative by heat.



(6)

(7)

Ethyl 2,6-dimethylnicotinate (7):[896] 3-Butyn-2-one (6.8 g) is added to a solution of ethyl 3-aminocrotonate (12.9 g) in ethanol (30 ml). When reaction has ceased the mixture is warmed for 15 min on a water-bath, then allowed to cool. The adduct (6) is obtained as colorless prisms, m.p. 135° (90% yield), on recrystallization of the product from methanol. When this adduct is heated in a vacuum at 120–140°, ethyl 2,6-dimethylnicotinate distils at 60°/0.1 mm in 90% yield.

ii, Preparation of hydrazones, semicarbazones, etc.

Hydrazine and, more so, its 1,1-substitution products form with aldehydes and ketones derivatives that are often valuable from an analytical or preparative point of view.

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[892] S. Coffey, J. K. Thomson, and F. J. Wilson, *J. Chem. Soc.*, **1936**, 856.

[893] G. A. Reynolds and C. R. Hauser, *Org. Syn.*, Coll. Vol. III, 374 (1955).

[894] L. Knorr, *Ber. Deut. Chem. Ges.*, **25**, 775 (1892).

[895] L. Lederer and C. Paal, *Ber. Deut. Chem. Ges.*, **18**, 2591 (1885); L. Knorr, *Ber. Deut. Chem. Ges.*, **18**, 299 (1885).

[896] F. Bohlmann and D. Rahtz, *Chem. Ber.*, **90**, 2265 (1957).

Hydrazones derived from unsubstituted hydrazine are mostly rather unstable and have only specialized preparative interest, *e.g.*, in Wolff–Kishner reduction[897] and synthesis of heterocycles. In many cases it is difficult to prepare them because hydrazine tends to react with both amino groups, thereby yielding azines; an excess of hydrazine is usually used so as to avoid this azine formation. The condensing agent may be triethylamine, barium oxide, or sodium hydroxide, sometimes in alcohol. Diethyl phosphonate[898] has been recommended as an excellent solvent that is said also to catalyse formation of the hydrazone.

Hydrazine sulfate may replace the hydrate as reactant; the sulfuric acid is buffered with sodium acetate, and the resulting sodium sulfate is precipitated by ethanol. The condensation occurs at room temperature or on gentle warming. Ketones require a somewhat longer reaction time than aldehydes.

Acetone hydrazone:[556,899] Acetone (15 g) is added to hydrazine hydrate (15 g) containing a few pieces of barium oxide, whereby considerable heat is generated. The mixture is set aside for a few days, then filtered and fractionated, giving a yield of about 31% of the hydrazone, b.p. 124–125°. The hydrazone decomposes slowly when kept, generating ammonia and nitrogen.

To avoid azine formation it has also been proposed[900] that the carbonyl compound should first be converted into a 1,1-dialkylhydrazone and that this be then treated with hydrazine.

Details for the preparation of benzil hydrazone are given in *Organic Syntheses*,[901] and for preparation of benzophenone hydrazone by Barton *et al.*[902]

Aliphatic ketazines are obtained by reaction of stoichiometric amounts of the components.

Dimethylketazine, $(CH_3)_2C{=}N{-}N{=}C(CH_3)_2$:[903] 20% Sodium hydroxide solution (somewhat more than 2 equivalents) is added, with shaking, portionwise, to a mixture of hydrazine sulfate (1 equivalent) and acetone (2 equivalents). The resulting ketazine is extracted in ether, dried, and distilled (b.p. 131°).

This method of synthesis is not suitable for aliphatic aldazines.

The preparation of benzaldazine is described in detail in *Organic Syntheses.*[904]

Formaldehyde behaves differently to other carbonyl compounds in reacting with hydrazine to give more highly condensed products, *e.g.*, "tetraformaltrisazine" (octahydro-*s*-tetrazino[1,2-*a*]-*s*-tetrazine) (**8**),[905] from which, however, monomeric formaldazine can be obtained by thermal depolymerization.[906] Similarly formaldehyde does not give a simple phenylhydrazone; hexahydro-

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[897] D. Todd, *Org. Reactions*, **4**, 378 (1948).

[898] J. A. Maynard, *Austr. J. Chem.*, **15**, 867 (1962).

[899] T. Curtius and L. Pflug, *J. Prakt. Chem.*, [ii], **44**, 535 (1891).

[900] G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, **31**, 677 (1966).

[901] C. H. F. Allen, *Org. Syn.*, Coll. Vol. II, 497 (1943).

[902] D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, **1962**, 470.

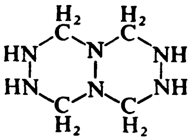
[903] T. Curtius and E. Zinkeisen, *J. Prakt. Chem.*, [ii], **58**, 315 (1898); cf. T. Curtius and K. Thun, *J. Prakt. Chem.*, [ii], **44**, 161 (1891).

[904] H. H. Hatt, *Org. Syn.*, Coll. Vol. II, 395 (1943).

[905] K. A. Hofmann and D. Storm, *Ber. Deut. Chem. Ges.*, **45**, 1725 (1912).

[906] N. P. Neureiter, *J. Amer. Chem. Soc.*, **81**, 2910 (1959).

1,4-diphenyl-*s*-tetrazine is the main product formed in acetic acid solution, but other condensation products have also been isolated.[907]



(8)

Phenylhydrazones and their *p*-nitro and 2,4-dinitro derivatives are considerably more important than their parent unsubstituted hydrazones and are often used for separation and characterization of carbonyl compounds.

Phenylhydrazones are best prepared in dilute acetic acid solution; use of more concentrated acetic acid can lead to formation of 1-acetyl-1-phenylhydrazine, m.p. 130–131° (corr.); if there is a neighboring hydroxyl group, which can lead to osazone formation, and if this is to be avoided, then any acidity is unfavorable and the reaction should be carried out as near the neutral point as possible. Condensation usually occurs in the cold, and almost always on short warming on the water-bath. A solvent is often unnecessary. α,β-Unsaturated aldehydes and ketones may cyclize to pyrazole derivatives on reaction with phenylhydrazine.

Acetophenone phenylhydrazone:[908] Equimolar amounts of acetophenone (40 g) and phenylhydrazine (36 g) are heated for 1 h on the water-bath, and the product is dissolved in hot ethanol (80 ml). On rubbing and cooling in ice, the phenylhydrazone crystallizes, amounting to 54–57 g after washing with 25 ml of ethanol; a further 4–10 g are provided by concentration of the mother liquor and washings. When dried over calcium chloride in a vacuum-desiccator, the phenylhydrazone (total yield 61–64 g, 87–91 %) has m.p. 105–106°.

The carbonyl compounds can be regenerated by warming the phenylhydrazones with hydrochloric acid or, in many cases, with benzaldehyde or formaldehyde.

Most 2,4-dinitrophenylhydrazones crystallize well and have sharp melting points. However, they tend to form mixed crystals, which may lead to errors in identification of the carbonyl compound. They are most suitable for separation and identification of the simple ketones. Their use with α-hydroxy ketones is not recommended.[909]

Condensation of 2,4-dinitrophenylhydrazine with carbonyl compounds is carried out in mineral acid solution (HCl, H_2SO_4, H_3PO_4).[909–911] Sometimes it is difficult to remove sulfuric acid from the product.[911] In the presence of acetic acid, 2,4-dinitrophenylhydrazine may also be acetylated, which also may lead to false identifications.[910] It is sometimes difficult to separate the 2,4-dinitrophenylhydrazone products from the unchanged reagent, wherefore it is advisable to use an excess of the carbonyl compound.[911]

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[907] E. Schmitz and R. Ohme, *Ann. Chem.*, **635**, 82 (1960).

[908] R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syn.*, Coll. Vol. III, 726 (1955).

[909] C. F. H. Allen, *J. Amer. Chem. Soc.*, **52**, 2955 (1930).

[910] H. H. Strain, *J. Amer. Chem. Soc.*, **57**, 758 (1935).

[911] C. F. H. Allen and J. H. Richmond, *J. Org. Chem.*, **2**, 222 (1938).

The customary reagent is a solution of 2,4-dinitrophenylhydrazine (1 g) in concentrated sulfuric acid (3 ml) and ethanol (10 ml). It is added to an alcoholic solution of the carbonyl compound and gently warmed.[910,196b] It reacts with many carbonyl groups that are indifferent to other reagents.[196b]

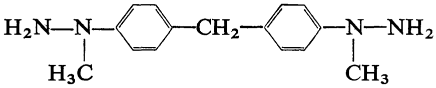
Johnson[912] recommends a phosphoric acid solution: 2,4-dinitrophenylhydrazine (50 g) is dissolved in 85% phosphoric acid (600 ml) on a steam-bath and treated with 95% ethanol (395 ml).

Shine[913] treats an alcoholic solution of the carbonyl compound with a solution of 2,4-dinitrophenylhydrazine in diethylene glycol dimethyl ether ("diglyme") and adds a few drops of concentrated hydrochloric acid as catalyst.

A detour often leads easily to 2,4-dinitrophenylhydrazones of sterically hindered ketones when these derivatives cannot be prepared directly or only so with difficulty (*e.g.*, dibutyl, dipentyl, or dinonyl ketone): the unsubstituted hydrazone is prepared and treated with 1-chloro-2,4-dinitrobenzene (see page 464).

Besides phenylhydrazine and its nitro derivatives, many other arylhydrazines with free NH_2 groups have been applied to separation or characterization of carbonyl compounds, but it is rare that they have more to offer than 2,4-dinitrophenylhydrazine. However, there are a few hydrazines that are of interest because of their specific action on certain types of carbonyl compound.

Stroh[914] has reviewed the influence of substituents on the reaction of phenylhydrazines with sugars and their selectivity in reaction with sugar mixtures. The so-called diphenylmethanedimethylhydrazine [*p,p'*-methylenedi(*N*^{1}-methylphenylhydrazine)], for instance, is sometimes useful for separating sugar mixtures as it condenses more easily with most aldoses than with ketoses.[915] 1-Methyl-1-phenylhydrazine can also be used to differentiate aldoses from ketoses: with aldoses it forms the hydrazone but with ketoses the osazone.[916]



p-Hydrazinobenzoic acid gives carbonyl derivatives that can be titrated.[917] Hydrazones from alkylhydrazines are of less interest although a large number have recently been prepared,[918] *e.g.*, from methyl- and 1,1-dimethylhydrazine.

Hydrazides condense with carbonyl compounds analogously to alkyl- and aryl-hydrazines. Among these compounds, the semicarbazones have achieved special analytical importance because they crystallize readily and have sharp melting points. They are particularly useful for characterizing lower aliphatic aldehydes.

Semicarbazones can be prepared in an aqueous medium by allowing the carbonyl compound (if necessary in alcohol) to react with an aqueous solution of semicarbazide hydrochloride buffered with an alkali acetate.[919]

The carbonyl compound may be regenerated by warm dilute mineral acid or may be replaced in the semicarbazone by benzaldehyde or 2,4-dinitrobenzaldehyde.

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[912] G. D. Johnson, *J. Amer. Chem. Soc.*, **73**, 5888 (1951); **75**, 2720 (1953).

[913] H. J. Shine, *J. Org. Chem.*, **24**, 252 (1959).

[914] H. H. Stroh, *Chem. Ber.*, **91**, 2645, 2657 (1958); **90**, 352 (1957).

[915] J. von Braun, *Ber. Deut. Chem. Ges.*, **41**, 2169, 2604 (1908); **43**, 1495 (1910).

[916] C. Neuberg, *Ber. Deut. Chem. Ges.*, **35**, 959 (1902).

[917] S. Veibel, *Acta Chem. Scand.*, **1**, 54 (1947); S. Veibel and H. W. Schmidt, *Acta Chem. Scand.*, 2, 545 (1948).

[918] R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957); R. H. Wiley and G. Irick, *J. Org. Chem.*, **24**, 1925 (1959).

[919] N. Zelinsky, *Ber. Deut. Chem. Ges.*, **30**, 1541 (1897).

Thiosemicarbazones are also mostly sparingly soluble and crystallize well. They are obtained from thiosemicarbazide in alcoholic solution.

***p*-Nitrobenzaldehyde thiosemicarbazone:**[920] Warm solutions of *p*-nitrobenzaldehyde (30.2 g, 0.2 mole) in 95% ethanol (300 ml) and of thiosemicarbazide (18.2 g, 0.2 mole) in water (300 ml) are mixed. Crystallization begins at once. After cooling, the thiosemicarbazone (38 g, 85%), m.p. 232–233° (dec.), is collected.

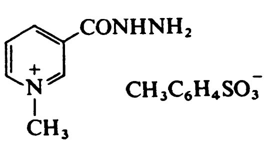
Schiff bases, arylhydrazones, semicarbazones, and oximes are almost all converted into the corresponding thiosemicarbazones when warmed with thiosemicarbazide in alcohol. Thiosemicarbazones are quite extraordinarily stable and, unlike other carbonyl derivatives, can rarely be cleaved to regenerate the aldehyde or ketone (see, however, acetone thiosemicarbazone, page 410).

Aldehydes and ketones are separated, even from very dilute solution, particularly rapidly by reaction with 1-amino-3-nitroguanidine, $NH_2NHC(=NH)—NHNO_2$;[921-923] This is effected in aqueous or aqueous-alcoholic solution containing a little acetic acid.[921] The reagent is unsuitable for separation of carbohydrates.[921]

For derivatives that can be very easily cleaved back to the carbonyl compound Leonard and Boyer[924] recommend oxalic (α-methylbenzyl)amide hydrazide, $C_6H_5CH(CH_3)—NH—COCO—NHNH_2$; these derivatives must be prepared in a completely anhydrous medium: the components are heated for a few minutes in anhydrous benzene containing a minute amount of iodine.[924]

Racemic carbonyl compounds can be separated into their enantiomers by means of the chiral forms of this reagent.[924] D-Tartaric amide hydrazide,[925] $NH_2COCH(OH)CH(OH).CONHNH_2$, and 4-(—)-menthylsemicarbazide,[926] $C_{10}H_{19}—NHCONHNH_2$, can be used for the same purpose. (—)-Menthyl carbazinate, [927]$C_{10}H_{19}O—CO—NHNH_2$, proved useful for resolution of camphor.

Water-soluble hydrazones of aldehydes and ketones are obtained by means of *N*-methylnicotinhydrazide *p*-toluenesulfonate (9),[928] the components being boiled for 15 min in anhydrous ethanol; the products have sharp melting points and can be purified easily; it is also easy to cleave them by acid and to convert them into the 2,4-dinitrophenylhydrazones in acid solution.



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[920] J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, and W. A. Lott, *J. Amer. Chem. Soc.*, **73**, 906 (1951).

[921] W. F. Whitmore, A. J. Revukas, and G. B. L. Smith, *J. Amer. Chem. Soc.*, **57**, 706 (1935).

[922] G. B. L. Smith and E. P. Shoub, *J. Amer. Chem. Soc.*, **59**, 2077 (1937).

[923] R. A. Henry and G. B. L. Smith, *J. Amer. Chem. Soc.*, **74**, 278 (1952).

[924] N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, **15**, 42 (1950).

[925] F. Nerdel and E. Henkel, *Chem. Ber.*, **85**, 1138 (1952).

[626] A. B. Crawford and F. J. Wilson, *J. Chem. Soc.*, **1934**, 1122.

[927] R. B. Woodward, T. B. Kohman, and G. C. Harris, *J. Amer. Chem. Soc.*, **63**, 120 (1941).

[928] C. F. H. Allen and J. W. Gates Jr., *J. Org. Chem.*, **6**, 596 (1941).

Water-soluble hydrazones are also provided by the Girard reagents P and T,[524,929] which have proved their worth for separation of mixtures of natural products.[930, 931] The condensation is usually effected in aqueous methanol buffered with acetate.[524]

Girard reagent P

$$[(CH_3)_3\overset{+}{N}-CH_2CONHNH_2]Cl^-$$

Girard reagent T

When the presence of acetic acid hinders reaction or when it is difficult to separate it later, the condensation can be effected by using a weakly acidic cation-exchanger such as Amberlite IRC 50 (comparable German products are Permutit B and Wofatit CP 300), which are simply filtered off later.[932]

It is usually unnecessary to isolate such hydrazones during the working up; the mixture is partitioned between water and a water-insoluble solvent such as ether. The hydrazones then remain in the aqueous phase, and the other organic substances are removed in the organic phase. The carbonyl components are finally regenerated from the aqueous hydrazone phase by acid hydrolysis. Considerable fractionation of mixed carbonyl compounds can be achieved by varying the reaction conditions, notably the temperature or pH, of either the condensation or the hydrolysis. Acid-sensitive carbonyl compounds, *e.g.*, citral, may be isolated by exchange from the hydrazone by an excess of formaldehyde.[932]

Mono(*p*-toluenesulfonyl)hydrazones formed from α-dicarbonyl compounds and *p*-toluenesulfonohydrazide split off the toluenesulfonyl group when treated with alkali or, in some cases, spontaneously, and thus yield α-diazo carbonyl compounds.[933,934]

10-Diazo-9-phenanthrone:[934] Finely powdered phenthraquinone (5.5 g) is stirred in a solution of *p*-toluenesulfonohydrazide (5 g) in 95% ethanol (60 ml) at 65° for 5 h. If the diazo compound has not yet crystallized, this is effected by cooling in an ice-salt bath. Filtration and washing with a little methanol gives the product in 74% yield (4.3 g). Recrystallization from methanol affords yellow needles, m.p. 113–114° (dec.).

*iii, Preparation of oximes**

Conversion of carbonyl compounds into oximes is usually carried out in an aqueous-alcoholic medium with an excess of hydroxylamine hydrochloride, the acid being buffered by sodium acetate or sodium carbonate.[935, 936] A pH around 4.7 is considered optimal. Aldehydes and simple ketones usually react at room temperature.

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* For the preparation of oximes by nitrosation of compounds containing active methylene groups see page 428.

[929] O. H. Wheeler, *Chem. Rev.*, **62**, 205 (1962).

[930] A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **22**, 640 (1939).

[931] T. Reichstein, *Helv. Chim. Acta*, **19**, 1107 (1936).

[932] C. L. Teitelbaum, *J. Org. Chem.*, **23**, 646 (1958).

[933] M. P. Cava, R. L. Litle, and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2257 (1958).

[934] O. Süs, H. Steppan, and R. Dietrich, *Ann. Chem.*, **617**, 20 (1958).

Heptanal oxime:[937] A solution of sodium carbonate (265 g, 2.5 moles) in water (500 ml) is stirred, dropwise, into a mixture of hydroxylamine hydrochloride (348 g, 5 moles), water (600 ml), and heptanal (460 g, 4 moles), the temperature being kept at not more than 45°. The whole is then stirred for a further hour at room temperature, then the oily layer is separated, washed with water (two 100-ml portions), and fractionated in a vacuum; the oxime (420–480 g), b.p. 103–107°/6 mm, distils at a bath temperature of 140–147° and gradually crystallizes (m.p. 44–46°). Recrystallized from 60% ethanol it has m.p. 53–55°.

According to Hückel,[935] the method often used for higher ketones (*e.g.*, camphor[938] or aceto-,[939] propio-,[939] or benzo-phenone[940]), namely, warming in an alkali hydroxide solution, has no advantage over the acetate buffer method; for instance, 98.5% of the oxime was obtained from 7-nitro-1-tetralone and hydroxylamine hydrochloride in aqueous alcohol containing sodium acetate.[941]

The combination hydroxylamine–pyridine[942] is an extremely powerful oximating agent. Ketones containing large alkyl groups, which do not react under more normal conditions, react smoothly when warmed with this reagent, if necessary in alcoholic solution.[943,944] The pyridine method has indeed been applied to quantitative determination of carbonyl compounds.[945]

Diaryl ketoximes:[944] The ketone (0.01 mole) and hydroxylamine hydrochloride (0.011 mole) are warmed in a mixture of pyridine and anhydrous ethanol until a clear solution is obtained; 4–5 ml of each solvent usually suffice. The mixture is warmed for 2 h on the steam-bath, then the solvent is removed, and the residue (usually forming good crystals) is washed with water.

Some sterically hindered ketones, *e.g.*, aryl *o*-tolyl ketones, require very long heating (about 40 h).

The sugar oximes needed for degradation by Wohl's method are best obtained by using hydroxylamine hydrochloride and pyridine.[946]

If an aldehyde is treated with hydroxylamine hydrochloride in presence of acetic anhydride[946] or formic acid and sodium formate,[947] concomitant loss of water leads to the nitrile.

***o*-Benzonitrile:**[946] *o*-Nitrobenzaldehyde (m.p. 42.5°; 5.0 g) and hydroxylamine chloride (4.0 g) are dissolved in pyridine (30 ml) in a 100-ml flask and treated with acetic anhydride (13 ml) in portions. The temperature rises thereby to 80°. The mixture is heated for a further 1 h on a boiling water-bath, then allowed to cool and poured on ice (about 500 g). When the ice has melted, the precipitated nitrile is filtered off, washed with water, and recrystallized from ethanol; it forms needles (4.1 g), m.p. 110°.

The cheaper sodium hydroxylamine-*N*,*N*-disulfonate may be used for preparation of oximes in place of the relatively expensive hydroxylamine. This salt is readily obtained from sodium nitrite, sodium hydrogen sulfite,

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[935] W. Hückel and M. Sachs, *Ann. Chem.*, **498**, 176 (1932).

[936] F. Nerdel and I. Huldschinsky, *Chem. Ber.*, **86**, 1005 (1953).

[937] E. W. Bousquet, *Org. Syn.*, Coll. Vol. II, 313 (1943).

[938] K. von Auwers, *Ber. Deut. Chem. Ges.*, **22**, 604 (1889).

[939] K. N. Campbell, B. K. Campbell, and E. P. Chaput, *J. Org. Chem.*, **8**, 99 (1943).

[940] A. Lachman, *Org. Syn.*, Coll. Vol. II, 70 (1943).

[941] H. J. Shine, *J. Org. Chem.*, **23**, 318 (1958).

[942] J. Meisenheimer and E. Mahler, *Ann. Chem.*, **508**, 191 (1934).

[943] W. E. Bachmann and C. H. Boatner, *J. Amer. Chem. Soc.*, **58**, 2097 (1936).

[944] W. E. Bachmann and M. X. Barton, *J. Org. Chem.*, **3**, 300 (1939).

[945] W. M. D. Bryant and D. M. Smith, *J. Amer. Chem. Soc.*, **57**, 57 (1935).

[946] C. H. Trabert, *Arch. Pharm.*, **294**, 246 (1961).

[947] T. van Es, *J. Chem. Soc.*, **1965**, 1564.

and sulfur dioxide[948] and can be brought into reaction with the carbonyl compound without being isolated. The technique is described in detail in *Organic Syntheses* for the oximes of acetone[948] and cyclohexanone.[574] The sodium salt of hydroxylamine-*N*-monosulfonic acid has also been used occasionally.[247,949]

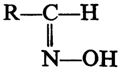
Oximes of sterically hindered ketones can be obtained, in very slow reactions but often in quantitative yield, by treatment with hydroxylamine hydrochloride in the presence of an excess of potassium *tert*-pentyl oxide at room temperature.[950]

2,4,6-Trimethylacetophenone oxime:[950] Hydroxylamine hydrochloride (5.5 g) and 2,4,6-trimethylacetophenone (10 g) are added to a solution (125 ml) of potassium *tert*-pentyl oxide (prepared from 98 g of potassium in 1250 ml of anhydrous *tert*-pentyl alcohol), and the mixture is kept for 32 days in a closed vessel. The pentyl alcohol is then removed in a rotary evaporator and the residue is shaken with a solution of ammonium chloride (5.3 g) in water (100 ml). If the oxime is precipitated as an oil, more water must be added. The yield is 10.8 g, 98%, of a product melting at 98–101°; after sublimation the m.p. is 101.5–102.5°.

Owing to their low melting points oximes are not very suitable for characterization of carbonyl compounds. They are often precipitated as oils and crystallize only slowly. Oximes of carbonyl compounds of low molecular weight can often be conveniently purified by distillation in a vacuum.

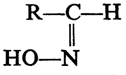
Fission by aqueous-alcoholic sodium hydrogen sulfite solution is recommended as an elegant method for regenerating carbonyl compounds from their oximes in high yield.[951]

Stereoisomers are known for a very large number of oximes.[952,953] Aromatic carbonyl compounds usually give the *syn*-oximes (also called α-oximes) in which the hydroxyl group is *cis* to the aldehyde-hydrogen atom or, in ketones, to the smaller group, but in the alipatic series the more reactive *anti*-oximes (also called β-oximes), with the *trans*-configuration are more commonly formed. Recently *Chemical Abstracts* and the Nomenclature Rules of the International Union of Pure and Applied Chemistry designate these so-called *syn*-oximes as *E*-oximes, and the so-called *anti*-oximes as *Z*-oximes, where *E* is derived from the German "entgegen" (= opposite) and *Z* from "zusammen" (= together, same side) with reference to the aromatic group of the aldehyde residue or the ketone group that is most preferred by the sequence rule.



$$\begin{array}{l} R\text{—}C\text{—}H \\ \quad\ \| \\ \quad N\text{—}OH \end{array}$$

syn- or α-Oxime
E-oxime



$$\begin{array}{r} R\text{—}C\text{—}H \\ \| \quad\ \ \\ HO\text{—}N \quad\ \ \end{array}$$

anti- or β-Oxime
Z-Oxime

It is not rare for both isomers to be formed side by side; such mixtures have unsharp melting points; they can either be separated by fractional crystallization or converted into a single, sterically homogeneous isomer by isomerization.[953]

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[948] W. L. Semon, *Org. Syn.*, **3**, 61 (1923).

[949] W. L. Semon and V. R. Damerell, *J. Amer. Chem. Soc.*, **46**, 1290 (1924).

[950] D. E. Pearson and O. D. Keaton, *J. Org. Chem.*, **28**, 1557 (1963).

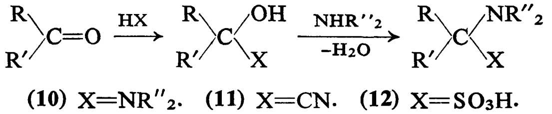
[951] S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).

[952] K. Freudenberg, "Stereochemie," Verlag F. Deuticke, Leipzig and Vienna, 1933, pp. 963 et seq.

[953] G. Wittig, "Stereochemie", Akademische Verlagsgesellschaft m. b. H., Leipzig, 1930, pp. 128 et seq.

b. Preparation of amines with functional groups in the α-position

In some cases, *O*,*N*-semiacetals (α-hydroxy amines) become stabilized by replacement of their hydroxyl group by a second nitrogen-containing group, instead of by the formation of a C=N double bond that was discussed in Sub-section a above; this gives compounds of type **(10)**. Analogous types of reaction occur on treatment of carbonyl compounds with amines and hydrocyanic acid or bisulfite, which give compounds of types **(11)** and **(12)**, respectively; here too the primary reaction is addition to the C=O double bond, and the adduct (cyanohydrin or bisulfite compound) corresponding to the *O*,*N*-semiacetal exchanges its hydroxyl group for a nitrogen-containing group.



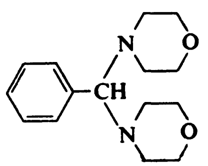
(10) $X{=}NR''_2$. **(11)** $X{=}CN$. **(12)** $X{=}SO_3H$.

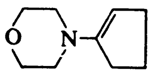
i, Preparation of N,N-acetals, etc.

The *O*,*N*-semiacetals that are the first products of addition of secondary amines to carbonyl compounds differ from the primary amine adducts in that they cannot achieve stabilization by loss of water to give a Schiff base (cf. page 411). Instead, the hydroxyl group is replaced by a second amine group, which yields an *N*,*N*-acetal (*i.e.*, a *gem*-diamine).[954,955]

N,*N*-Acetals (also called aminals[956]) are more stable than *O*,*N*-semiacetals; most of them can be isolated smoothly provided that a deficiency of the amine is used. When the reaction is sluggish the water formed should be removed by potassium carbonate; *N*,*N*-acetals are at once hydrolysed by acids.

4,4′-Benzylidenedimorpholine:[955] Morpholine (17.4 g, 0.2 mole) is added with cooling to benzaldehyde (21.2 g, 0.2 mole). The solution becomes turbid and a white substance begins to separate after an hour. The mixture is left overnight and then filtered. The filtrate consists of the excess of benzaldehyde (about 10 ml); the crystals constitute the crude product and, when dried, amount to 77% (20.4 g) calculated on the morpholine; after recrystallization from 95% ethanol they form white crystals melting at 101–101.5°.





Aminals containing hydrogen in the β-position to a nitrogen atom lose one equivalent of the amine when heated, thus yielding enamines:[957–959]

$$RCH_2{-}CH(NHR'_2)_2 \xrightarrow{-NHR'_2} RCH{=}CHNR'_2$$

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[954] R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, **71**, 2271 (1949).

[955] M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

[956] H. Böhme, *Angew. Chem.*, **68**, 224 (1956).

[957] C. Mannich and H. Davidsen, *Ber. Deut. Chem. Ges.*, **69**, 2106 (1936).

[958] E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

[959] G. Opitz, H. Hellmann, and H. W. Schubert, *Ann. Chem.*, **623**, 112 (1959).

This provides a simple method of preparing enamines from carbonyl compounds and secondary amines, and sometimes it is not necessary to isolate the aminal.

4-(1′-Cyclopentenyl)morpholine:[960] Cyclopentanone (42 g, 0.5 mole) and morpholine (65.4 g, 0.75 mole) in benzene (200 ml) are brought to the boiling point in a 500-ml round-bottomed flask fitted with a reflux condenser and a water-separator. Separation of water begins at once and is completed in 4–5 h. After a total of 5.5 h the benzene is distilled off and the residue is fractionated in a vacuum; this gives the enamine (67.3 g, 88%), b.p. 105 to 109°/13 mm.

The enamine is formed even in the cold from acetaldehyde and diethylamine.[961] Adding a stoichiometric amount of titanium tetrachloride appears to provide a generally applicable method of preparing enamines in the cold; even sterically hindered ketones then afford remarkably high yields.[962]

Enamines from morpholine and cyclopentanone[875] or cyclohexanone[963a] have been applied by Hünig in an elegant method of lengthening the chain of aliphatic carboxylic acids by, respectively, 5 or 10, or 6 or 12, carbon atoms.[963]

The chemistry of enamines has been reviewed by Szmuszkovicz.[964]

α,β-Unsaturated aldehydes can add the amine simultaneously at the C=O and the C=C double bond:

$$RCH_2CH{=}CHCHO + 3NHR'_2 \longrightarrow RCH_2{-}CH(NH_2){-}CH_2CH(NR'_2)_2 + H_2O$$

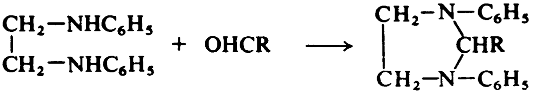
These adducts afford 3-amino-1-enamines, which in turn lose a further amino group with formation of conjugated C=C double bonds:[965]

$$RCH_2{-}CH(NR'_2){-}CH{=}CH{-}NR'_2 \longrightarrow RCH{=}CH{-}CH{=}CH{-}NR'_2 + NHR'_2$$

Reaction of disecondary amines and carbonyl compounds affords cyclic aminals if the amino groups are in suitable positions relative to one another (1,2-, 1,3-, or 1,4-). For example, 1,3-diamines condense readily with aldehydes or ketones to give hexahydropyrimidine derivatives,[966,967] and disecondary ethylenediamine derivatives give imidazolidines.[968]

1,3-Diarylimidazolidines are obtained by treating a solution of an *N,N′*-diarylethylenediamine in methanol or ethyl acetate with an excess of 30% formaldehyde solution and then acidifying the mixture with acetic acid.[968]

Condensation of *N,N*-diphenylethylenediamine with aldehydes is so smooth that it can be used for separation and characterization of aliphatic and aromatic aldehydes:[969]



$$\begin{matrix} CH_2{-}NHC_6H_5 \\ | \\ CH_2{-}NHC_6H_5 \end{matrix} + OHCR \longrightarrow \begin{matrix} CH_2{-}N{-}C_6H_5 \\ |\quad\quad \backslash \\ |\quad\quad CHR \\ |\quad\quad / \\ CH_2{-}N{-}C_6H_5 \end{matrix}$$

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[960] S. Hünig and W. Lendle, *Chem. Ber.*, **93**, 909 (1960).

[961] G. Laban and R. Mayer, *Z. Chem.*, **7**, 12 (1967).

[962] W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

[963] S. Hünig and co-workers, *Chem. Ber.*, (a) **90**, 2833 (1957); (b) **91**, 129 (1958); **92**, 652 (1959); **93**, 909, 913 (1960).

[964] J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

[965] C. Mannich, K. Handke, and K. Roth, *Ber. Deut. Chem. Ges.*, **69**, 2112 (1936); W. Langenbeck, O. Gödde, L. Weschky, and R. Schaller, *Ber. Deut. Chem. Ges.*, **75**, 232 (1942); H. Finch, E. A. Peterson, and S. A. Ballard, *J. Amer. Chem. Soc.*, **74**, 2016 (1952).

[966] E. Bergmann, D. Herman, and E. Zimkin, *J. Org. Chem.*, **13**, 353 (1948).

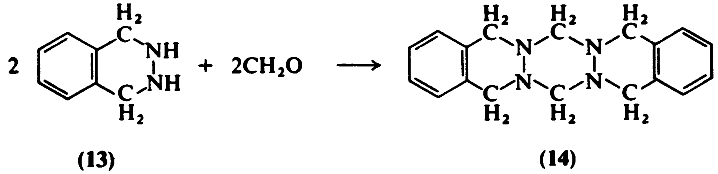
[967] J. L. Riebsomer and G. H. Morey, *J. Org. Chem.*, **15**, 245 (1950).

[968] L. Jaenicke and E. Brode, *Ann. Chem.*, **624**, 134 (1959).

[969] H.-W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).

It is best to conduct this reaction in methanol solution containing a few drops of acetic acid, with warming when necessary. The resulting 2-substituted 1,3-diphenylimidazolidines crystallize well and have sharp melting points.[969]

Condensing certain hydrazine derivatives with carbonyl derivatives may, further, lead to heterocycles containing the structural unit of *N*,*N*-acetals (aminals): for instance, 1,2,3,4-tetrahydrophthalazine (**13**) and formaldehyde give 5,7,9,14,16,18-hexahydrodiphthalazino[2,3-*a*: 2′,3′-*d*]-*s*-tetrazine (**14**):[970]



This reaction fails with higher aldehydes and can thus be used for quantitative determination of formaldehyde in the presence of other aldehydes (sensitivity $3.4 \cdot 10^{-6}$ g of CH_2O per ml).

The reagent used is a solution of tetrahydrophthalazine hydrochloride (0.7 g) in water (20 ml). The pH of the solution to be tested should be between 4.5 and 6 (acetate buffer). The precipitate of the product (**13**) is formed within 5 min and affords white prisms from water or leaflets from hot chlorobenzene; the m.p. is 265–270° (dec.).

Reactions of formaldehyde with hydrazine and phenylhydrazine that can lead to similar ring closures are mentioned on page 509.

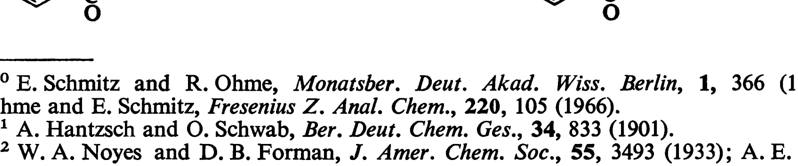
Primary amines seldom give rise to aminals; their tendency to afford Schiff bases predominates and aminals are observed only occasionally and as by-products. Nevertheless benzaldehyde and *p*-nitroaniline give the aminal as the main product.[971]

N-Acylated aminals are obtained somewhat more easily from aldehydes and unsubstituted amides:[972]

$$RCHO + 2NH_2{-}COR' \longrightarrow RCH(NHCOR')_2$$

When heated at 220–280° they lose one equivalent of the amide and give enamides.[973]

Mixed *N*,*N*-acetals from amides and amines are also known.[83,974,975] When formaldehyde, phthalimide, and a primary aromatic amine are boiled



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[970] E. Schmitz and R. Ohme, *Monatsber. Deut. Akad. Wiss. Berlin*, **1**, 366 (1959); R. Ohme and E. Schmitz, *Fresenius Z. Anal. Chem.*, **220**, 105 (1966).

[971] A. Hantzsch and O. Schwab, *Ber. Deut. Chem. Ges.*, **34**, 833 (1901).

[972] W. A. Noyes and D. B. Forman, *J. Amer. Chem. Soc.*, **55**, 3493 (1933); A. E. Martell and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (1941); T. R. Lewis Jr., F. R. Butler, and A. E. Martell, *J. Org. Chem.*, **10**, 145 (1945).

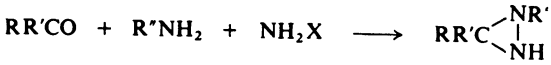
[973] D. Ben-Ishai and R. Giger, *Tetrahedron Lett.*, **1965**, 4523.

[974] H. W. Heine, M. B. Winstead, and R. P. Blair, *J. Amer. Chem. Soc.*, **78**, 672 (1956).

[975] H. Zinner, H. Herbig, and H. Wigert, *Chem. Ber.*, **89**, 2131 (1956).

in alcohol for 0.5 hour, they give a high yield of the *N*-[(arylamino)methyl]-phthalimide, and these products have sharp melting points, so that they can be used to characterize amines.[83] Secondary aromatic and aliphatic amines react analogously.[974]

Reaction of ketones with ammonia or primary amines and chloramine or hydroxylamine-*O*-sulfonic acid affords diaziridines:[87]



(X = Cl or OSO_3H)

ii, Preparation of α-amino nitriles, hydantoins, etc.

The hydroxyl groups of the hydrogen sulfite and hydrogen cyanide adducts of carbonyl compounds can be replaced by amino groups with very great ease.

A large number of α-amino sulfonic acids have been prepared from the hydrogen sulfite adducts (α-hydroxy sulfonic acids) and ammonia or amines at or slightly above room temperature. [976]They are very important intermediates in the Knoevenagel–Bucherer form of the Strecker amino acid synthesis (cf. page 877). In this synthesis the aldehyde-bisulfite compounds are converted by ammonia or amines into α-amino sulfonic acids and thence by alkali cyanide or hydrogen cyanide into α-amino nitriles, which are then hydrolysed:

$$\text{RCHO} \longrightarrow \text{HO—CHR—SO}_3\text{Na} \longrightarrow \text{NH}_2\text{—CHR—SO}_3\text{Na} \longrightarrow$$

$$\text{NH}_2\text{—CHR—CH} \longrightarrow \text{NH}_2\text{—CHR—COOH}$$

Luten[977] gives a general procedure for preparation of α-amino nitriles by these reactions; the sodium α-amino sulfonates may be isolated when necessary.

A detailed description of the preparation of (diethylamino)acetonitrile from formaldehyde-bisulfite, diethylamine, and sodium cyanide is to be found in *Organic Syntheses.*[978]

The conversion of cyanohydrins into α-amino nitriles is an analogous step in the Tiemann form of the Strecker synthesis and also takes place at or slightly above room temperature:

2-Amino-2-methylpropionitrile:[979,cf.980] Dry ammonia is led into freshly prepared acetone cyanohydrin, the temperature not being allowed to rise above 65°. The solution is kept for some time at 60°, then the amino nitrile formed is taken up in ether. Because of the ease with which this compound decomposes, the solution must next be very thoroughly dried over calcium chloride. Then distillation in a vacuum affords a 64% yield of the amino nitrile, b.p. 48–50°/11 mm. It is, however, better to add a drying agent (sodium sulfate) to the mixture while the ammonia is being passed in; the yield is then greater (up to 85%).

The preparation of *N*-substituted derivatives of this nitrile is described by Exner *et al.*[981]

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[976] *E.g.*, L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959).

[977] D. B. Luten Jr., *J. Org. Chem.*, **3**, 594 (1939).

[978] C. H. F. Allen and J. A. Van Allan, *Org. Syn.*, Coll. Vol. III, 275 (1955).

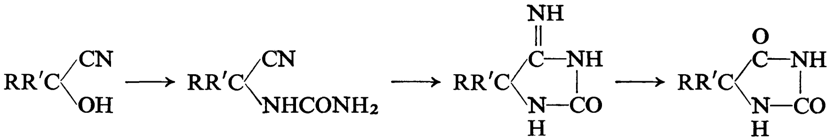
[979] H. T. Bucherer and W. Steiner, *J. Prakt. Chem.*, [ii], **140**, 291 (1934).

[980] H. T. Clarke and H. J. Bean, *Org. Syn.*, Coll. Vol. II, 29 (1943).

[981] L. J. Exner, L. S. Luskin, and P. L. DeBenneville, *J. Amer. Chem. Soc.*, **75**, 4841 (1953).

Organic Syntheses contains applications of the Strecker–Tiemann synthesis with other components that yield 2-amino-2-ethylbutyric acid[982] and 2-amino-2-phenyl-acetic[983] and -propionic acid.[984]

If cyanohydrins are treated with ammonium carbonate instead of ammonia, 5-substituted hydantoins are obtained, usually in very good yield (the Bucherer–Henze synthesis):[979]



This reaction is so smooth that it can be used for identification of carbonyl compounds.[985]

5,5-Dimethylhydantoin:[979] Acetone cyanohydrin (0.1 mole) and ammonium carbonate (0.2 mole) are warmed in water (80 ml) at 30–40°. A lively reaction sets in, complete in 30 min, the mixture becoming homogeneous. Evaporation in a vacuum gives the hydantoin in almost quantitative yield. After recrystallization from ligroin or ethanol it has m.p. 174–175°.

Instead of the cyanohydrin's being isolated, the carbonyl compound may be treated directly with cyanide and ammonium carbonate.

Hydrolysis of the hydantoins gives the α-amino acids, often in better yield than can be obtained from the α-amino nitriles. Among the amino acids that have been prepared from cyanohydrins and hydantoins are methionine,[986] lysine,[987,988] alanine,[989] and phenylalanine.[989]

Further, acylals can sometimes replace cyanohydrins in amino acid syntheses; for example, the acylal of acetylated glycolaldehyde ("glycolaldehyde triacetate"),

$$CH_3COCH_2CH(COCH_3)_2,$$

which is readily obtainable from vinyl acetate, affords D,L-serine in a smooth reaction.[990]

c. Preparation of amines by reductive alkylation

An important method of preparing amines is to treat ammonia or an amine with an aldehyde or a ketone in the presence of a suitable reducing agent. These reducing agents are usually hydrogen and a catalyst[991] or formic acid or a derivative thereof (the Leuckart–Wallach reaction).[992] When formaldehyde is the carbonyl component it often acts also as reducing agent.

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[982] R. E. Steiger, *Org. Syn.*, Coll. Vol. III, 66 (1955).

[983] R. E. Steiger, *Org. Syn.*, Coll. Vol. III, 84 (1955).

[984] R. E. Steiger, *Org. Syn.*, Coll. Vol. III, 88 (1955).

[985] H. R. Henze and R. J. Speer, *J. Amer. Chem. Soc.*, **64**, 522 (1942).

[986] E. Pierson, M. Giella, and M. Tishler, *J. Amer. Chem. Soc.*, **70**, 1450 (1948); D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, **1952**, 3403.

[987] O. A. Rogers, R. D. Emmick, J. W. Tyran, L. B. Phillips, A. A. Levine, and N. D. Scott, *J. Amer. Chem. Soc.*, **71**, 1837 (1949).

[988] R. Gaudry, *Can. J. Res.*, *B*, **26**, 387 (1948).

[989] R. Gaudry, *Can. J. Res.*, *B*, **26**, 773 (1948).

[990] H. Geipel, J. Gloede, K.-P. Hilgetag, and H. Gross, *Chem. Ber.*, **98**, 1677 (1965).

[991] W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).

[992] M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

Organic Syntheses contains detailed descriptions of the preparation of methylamine[993] (50% yield) and trimethylamine[994] (89% yield) from ammonium chloride and formaldehyde.

Reductive alkylation does not differ in principle from hydrogenation of a Schiff base but has the advantage that preparation and hydrogenation take place in one operation (cf. page 554).

i, Catalytically excited hydrogen as reducing agent

In most cases reductive alkylation involving hydrogen and a catalyst is carried out in an autoclave. The catalysts usually used for hydrogenations of this type are Raney nickel (more rarely Raney cobalt) and platinum metals. The hydrogen pressure and the reaction temperature needed depend largely on the activity of the carbonyl compound and the catalyst, and generalization is impossible. With nickel catalysts, hydrogen pressures of the order of 20 to 150 atm and reaction temperatures between 40° and 150° are required, but there are as many cases where reaction takes place smoothly at room temperature with pressures of 1–3 atm.

The greatest importance of reductive alkylation is for preparation of primary amines from aldehydes and ketones. This is mostly effected in alcoholic solution with Raney nickel and an excess of ammonia.

Formaldehyde is unsuitable for alkylation of ammonia as it yields urotropine. Lower aliphatic aldehydes are added only gradually to the reaction mixture to avoid aldol condensations. Higher aliphatic aldehydes and aromatic aldehydes react smoothly and special precautions are generally unnecessary.

Heptylamine:[995] Heptanal (113 g, 1 mole), methanol (150 ml), Raney nickel (10 g), and anhydrous ammonia (50 ml) are mixed in a stirring autoclave and then heated at 90° under a hydrogen pressure of 100 atm. Hydrogen uptake is complete in about 30 min. The catalyst is filtered off and ammonia and methanol are distilled off through a 20-cm column until the bath-temperature reaches 100°. The residue is freed from water by azeotropic distillation with benzene. After removal of the benzene, heptylamine (93.5 g, 81%) distils at 50°/14 mm.

Benzylamine:[996] A solution of ammonia (51 g, 3 moles) in cold ethanol (300 ml) is treated with benzaldehyde (3 moles) and Raney nickel (10 g). Under an initial hydrogen pressure of 90 atm hydrogenation begins at 40° and is complete after 30 min at a final temperature of 70°. Distillation of the filtered product gives benzylamine (287 g, 89.4%), b.p. 70–80°/8 mm, and dibenzylamine (21.7 g, 7.1%), b.p. 140–150°/7 mm.

Good yields are obtained also from alkyl methyl ketones, as from aldehydes; for instance, 2-heptanone affords 2-heptanamine in 75–80% yield.[997] However, higher ketones, particularly those branched at the α-position to the carbonyl group, are readily reduced to secondary alcohols even if an excess of ammonia is used, although adding ammonium chloride or acetic acid (1% of the amount of ketone) raises the yields of amine in such cases.[998]

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[993] C. S. Marvel and R. L. Jenkins, *Org. Syn.*, **3**, 67 (1923).

[994] R. Adams and C. S. Marvel, *Org. Syn.*, **1**, 79 (1921); R. Adams and B. K. Brown, *Org. Syn.*, **1**, 75 (1921).

[995] F. Möller in Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1957, Vol. 11, Part 1, pp. (a) 312, (b) 605.

[996] C. F. Winans, *J. Amer. Chem. Soc.*, **6,1** 3566 (1939).

[997] E. Rohrmann and H. A. Shoule, *J. Amer. Chem. Soc.*, **66**, 1516 (1944).

[998] H. Wilms in Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1957, Vol. 11, Part 1, p. 611.

Norton and his co-workers[886] obtained very good yields of primary amines by hydrogenating an equimolar mixture of ketones and anhydrous ammonia (without a solvent) in the presence of Raney nickel at 150°/35–70 atm.

Isopropylamine:[886] Acetone (696 g, 12 moles) and liquid ammonia (204 g, 12 moles) are heated at 140° in a shaking autoclave containing Raney nickel (50 g) under a hydrogen pressure of 52 atm. Distillation then gives a 77% yield (545 g) of isopropylamine, b.p. 31.5 to 32.5°, n_D^{15} 1.377.

Under similar conditions ethyl methyl ketone gives 90% of *sec*-butylamine, 2-heptanone gives 90% of 2-heptanamine, and at 150°/70 atm even diisobutyl ketone gives 48% of the corresponding amine.[886]

Alkylation of ammonia has also, but more rarely, been effected at lower hydrogen pressures. Haskelberg[999] succeeded in converting some ketones, *e.g.*, phenylacetone and 5-(diethylamino)-2-pentanone, into the primary amines in good yield (85%) by alcoholic ammonia in the presence of Raney nickel at room temperature and without hydrogen over-pressure. In the presence of platinum catalysts at lower hydrogen pressures secondary amines are apparently formed preferentially;[1000] however, according to Alexander and Misegades[1001] primary amines can be obtained in satisfactory yields in the presence of platinum catalysts at low pressures if somewhat more than a molar amount of ammonium chloride is also added:

Platinum oxide (0.2 g) is suspended in water (10 ml) and reduced by hydrogen, then the ketone (0.3 mole), ammonium chloride (20 g, 0.37 mole), saturated methanolic ammonia solution (225 ml), and aqueous ammonia (25 ml) are added, and the mixture is hydrogenated at 1–3 atm. The following are among the amines prepared from the corresponding ketones, in the yields stated, by this method: **4-methyl-2-pentanamine** (57–65%), **4-heptanamine** (40 to 60%), **2,4-dimethyl-3-pentanamine** (55%), and **α-methylbenzylamine** (69%).[1002]

Preparation of secondary amines by reductive alkylation of ammonia is not such a general reaction as that of primary amines. In the aliphatic series treating ammonia with 2 moles of a carbonyl compound usually affords a mixture of mono-, di-, and tri-alkylamines. However, 80–90% yields of the corresponding dibenzylamine are obtained from benzaldehyde or its *o*-chloro or *o*-methyl derivative.[996]

The technique for preparation of **dibenzylamine** is that described above (page 521) for benzylamine except that 3 equivalents of benzaldehyde and 1.5 equivalents of ammonia are used; yields are dibenzylamine 81% and benzylamine 12%.[996]

Monoalkylation of primary amines proceeds more smoothly than dialkylation of ammonia. Only formaldehyde readily reacts further to give the tertiary amines. Other aliphatic aldehydes afford good yields of secondary amine if aldol condensation is avoided by adding the aldehyde gradually to the reaction mixture.

Primary aromatic amines can be reductively alkylated in satisfactory yields by aliphatic aldehydes in alcoholic solution containing a platinum or nickel catalyst at 3 atm hydrogen pressure if sodium acetate is also present.[1002]

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[999] L. Haskelberg, *J. Amer. Chem. Soc.*, **70**, 2811 (1948).

[1000] A. Skita and F. Keil, *Ber. Deut. Chem. Ges.*, **61**, 1452 (1928).

[1001] E. R. Alexander and A. L. Misegades, *J. Amer. Chem. Soc.*, **70**, 1315 (1948).

[1002] W. S. Emerson and P. M. Walters, *J. Amer. Chem. Soc.*, **60**, 2023 (1938); W. S. Emerson and W. D. Robb, *J. Amer. Chem. Soc.*, **61**, 3145 (1939).

Good yields of secondary amine are obtained from aromatic aldehydes and either primary aliphatic or primary aromatic aldehydes in either high- or low-pressure procedures.[1003]

N-Benzyl-m-toluidine, b.p. 153–157°/4 mm, is formed in 89–94% yield when a mixture of 1 mole each of benzaldehyde and *m*-toluidine is hydrogenated in ether (200 ml) containing Raney nickel (8–10 g) at room temperature and about 70 atm hydrogen pressure.[1004]

N-Methylbenzylamine:[1005] A catalyst is prepared by hydrogenating a mixture of palladium chloride (0.5 g) and active charcoal (5 g) in dilute hydrochloric acid, and the water is then replaced by decantation several times with methanol. Benzaldehyde (45 g) and a solution of methylamine (31 g) in methanol are added and the mixture is hydrogenated at atmospheric pressure. Hydrogen uptake is rapid — about 1 l per 5 min. The product (44 g) boils at 78°/14 mm.

In reductive alkylation of aromatic amines the water formed is often removed by azeotropic distillation before the hydrogenation; or a preformed Schiff base may be reduced (cf. page 554). These procedures are particularly suitable for reductive alkylation of ketones[886,1006] in order to counter reduction of the ketone to the secondary alcohol. Here too formation of the alcohol can be repressed by adding a catalytic amount of ammonium chloride or acetic acid to the ketone–amine mixture (cf. page 521).

Reductive alkylation of 2-hydroxyethylamine by ketones or aldehydes in the presence of a platinum catalyst at a hydrogen pressure of 2 atm is an extremely smooth operation.[1007]

Attempts to prepare tertiary amines by reductive alkylation have in general proved unsatisfactory: the only significant reactions are the methylation of secondary and the dimethylation of primary amines by formaldehyde. Bowman and Stroud[1008] described the preparation of a series of aliphatic dimethylamino acids by hydrogenation of mixtures of amino acids and formaldehyde in the presence of palladium–charcoal at atmospheric pressure. In most cases results are improved if the aldehyde is added gradually to the reaction mixture. In the methylation of aromatic amines special precautions are necessary to prevent condensation of the formaldehyde with the aromatic ring.[1009]

It is often possible to replace a primary amine in a reductive alkylation by a nitrogen compound such as a nitro or nitroso compound or nitrile that can be converted into the primary amine by the reduction. For example, *N*-alkyl- and *N,N*-dialkyl-anilines can be prepared from nitrobenzene in a single operation.[1010,1011] Directions for the preparation of *N*-alkylarylamines from aromatic nitro compounds are given on page 555.

Cyclic secondary amines may be obtained by hydrogenating carbonyl compounds that contain, at a suitable position, a group that is reducible to a

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[1003] D. M. Balcom and C. R. Noller, *Org. Syn.*, **30**, 59 (1950); K. Bodendorf and H. Raff, *Arzneimittel-Forsch.*, **5**, 695 (1955).

[1004] C. H. F. Allen and J. Van Allan, *Org. Syn.*, Coll. Vol. III, 827 (1955).

[1005] R. Wegler and W. Frank, *Chem. Ber.*, **69**, 2071 (1936).

[1006] R. E. Lutz and co-workers, *J. Org. Chem.*, **12**, 760 (1947); J. S. Buck, *J. Amer. Chem. Soc.*, **53**, 2192 (1931).

[1007] A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **64**, 1503 (1942).

[1008] R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, **1950**, 1342.

[1009] D. E. Pearson and J. D. Bruton, *J. Amer. Chem. Soc.*, **73**, 864 (1951).

[1010] W. S. Emerson and H. W. Mohrman, *J. Amer. Chem. Soc.*, **62**, 69 (1940).

[1011] W. S. Emerson and C. A. Uraneck, *J. Amer. Chem. Soc.*, **63**, 749 (1941).

primary amino group.[1012,1013] For instance, on hydrogenation of 3-oxo-4-phenylbutyronitrile in methanol in the presence of Raney nickel at atmospheric pressure, cyclization leads to a 77.5% yield of 2-phenylpyrrolidine.[1012]

Reductive alkylation has occasionally been applied to hydrazine, analogously to that of ammonia, as when acetone and hydrazine in acid solution containing a platinum catalyst at 2 atm hydrogen pressure afforded 1,2-diisopropylhydrazine in almost quantitative yield.[1014]

ii, Leuckart–Wallach reaction

The Leuckart–Wallach reaction[992] consists of the reductive alkylation of ammonia or an amine by a carbonyl compound with formic acid or a derivative thereof as reducing agent:

$$RR'CO + NHR''_2 + HCOOH \longrightarrow RR'CH{-}NR''_2 + CO_2 + H_2O$$

The best results are achieved with formaldehyde or a higher ketone, *i.e.*, one boiling above 120°. The reaction affords primary and secondary amines as their *N*-formyl derivatives from which the free bases can be obtained by hydrolysis. The Leuckart–Wallach reaction is of more limited applicability than the reductive alkylation described above; however, the use of formic acid as reducing agent often permits alkylation to occur on reaction of components that contain reducible groups such as double bonds or nitro or nitrile groups; such groups are reduced by catalytic hydrogenation but are unaffected under the conditions of the Leuckart–Wallach reaction.

Primary and secondary amines can be methylated in good yield to tertiary amines when formaldehyde is added: about 1.0–1.25 moles of formaldehyde and 2–4 moles of formic acid are used for each methyl group to be introduced.

Methylation of aliphatic amines to tertiary amines:[1015] 1 mole of a primary amine is added with cooling to a mixture of 5 moles of 90% formic acid and 2.2 moles of 35% formaldehyde solution. Secondary amines require only half of these amounts of formic acid and formaldehyde, but an excess is not disadvantageous. Reaction begins when the mixture is heated on a steam-bath. When the initial vigorous evolution of carbon dioxide ceases, the mixture must be heated for a further 2–4 h, in all for 8–12 h. Then somewhat more than 1 mole of hydrochloric acid is added and the formic acid and formaldehyde are distilled off. The colorless residue is dissolved in water and basified with 25% sodium hydroxide solution, and the amine is distilled off in steam. The distillate is saturated with solid potassium hydroxide, and the oil that separates is dried over potassium hydroxide and distilled from sodium. The following tertiary amines were thus obtained in more than 80% yield: **N,N-dimethylbutylamine**, b.p. 94°; **N,N-dimethylbenzylamine**, b.p. 176–180°; and **1-methylpiperidine**, b.p. 106°.

Methylated hydrazines cannot be obtained from hydrazine hydrate in this way.[1016]

Because of the tendency of formaldehyde to react with the ring of aromatic amines, this procedure cannot be used satisfactorily with compounds such as

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[1012] E. B. Knott, *J. Chem. Soc.*, **1948**, 186.

[1013] H. Henecka, *Chem. Ber.*, **82**, 104 (1949).

[1014] H. L. Lochte, J. R. Bailey, and W. A. Noyes, *J. Amer. Chem. Soc.*, **43**, 2597 (1921); H. L. Lochte, W. A. Noyes, and J. R. Bailey, *J. Amer. Chem. Soc.*, **44**, 2556 (1922).

[1015] H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

[1016] F. Klages, G. Nober, F. Kircher, and M. Bock, *Ann. Chem.*, **547**, 1 (1941).

aniline unless reaction in the ring is precluded by the presence of substituents at positions 2, 4, and 6. Nevertheless, Borkowski and Wagner[1017] worked out a procedure by which aromatic amines can be *N*-methylated in good yield if they contain only one or two *ortho-* or *para*-substituents, as follows:

Paraformaldehyde (2.5 moles) and 98% formic acid (at least 3 moles) are heated on a steam-bath, stirred vigorously while a primary aromatic amine is added within 10–15 min, and then heated for a further 5 min. If there is a tendency for the methylated amine to react in the ring, the primary amine is added in half the stated time and subsequent heating is omitted. The mixture is then poured into cooled sodium hydroxide solution (1.3 equivalents referred to the formic acid) and distilled in steam. The oil that passes over is taken up in ether and dried over potassium carbonate, and the amine is isolated by distillation.

Higher aliphatic aldehydes are relatively seldom applied as alkylating agents. Secondary aliphatic amines are converted into tertiary amines by aliphatic aldehydes under relatively mild conditions: *N,N*-dimethyl-propylamine, -isopropylamine, and -1-heptanamine, amongst others, are thus obtained from dimethylamine in 60% yield.[1018] Cyclic secondary amines such as morpholine[1018] and piperazine[1019] can also be *N*-alkylated by aliphatic aldehydes. Conversion of benzaldehyde into benzylamine (60% yield) requires more energetic conditions (3 hours at 190°), but ring-substituted benzylamines (except the 4-methyl derivative) are obtained only in poor yield.[1020] On the other hand, benzylation of secondary amines such as piperazine[1019] and piperidine[1021] by benzylaldehyde is quite a smooth reaction.

The Leuckart–Wallach procedure is not very suitable for use with lower aliphatic ketones. However, acetophenone and similar higher-boiling ketones afford the primary amines in 70–80% yield when treated with the mixture of ammonium formate and formamide (the Ingersoll reagent) that is formed when ammonium formate or an ammonium carbonate–carbamate mixture is heated with formic acid at 165°.[1022]

Alkylation by ketones:[1022–1024] Commercial ammonium carbonate–carbamate (215 g, equivalent to 4 moles of ammonia) is treated gradually with 85–90% formic acid (215–230 g, 4.1 moles) in a 1-l three-necked flask fitted with a thermometer reaching almost to the bottom of the flask, a wide descending condenser, and a dropping funnel. The mixture is heated cautiously and gradually to 165°, water being continually distilled off. The ketone (1 mole) is then added to the hot reagent and the flask is further heated over a small flame. Water, carbon dioxide, ammonia, and some of the ketone are evolved through the condenser. Any ketone that distils over is returned to the flask from time to time; for volatile ketones a reflux condenser and water separator should be used. When the internal temperature reaches 175–185° hardly any more water distils and the mixture is kept at that temperature for a further 3–4 h, but this period should be extended to 10 h for ketones such as camphor and fenchone that react slowly for steric reasons. The reaction is complete when hardly any more ammonium carbonate separates in the condenser; the mixture is then cooled and stirred with twice its volume of water. The crude, water-insoluble product is collected and boiled with concentrated hydrochloric acid (100 ml) for 30–50 min, after which any excess of ketone and condensation

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[1017] W. L. Borkowski and E. C. Wagner, *J. Org. Chem.*, **17**, 1128 (1952).

[1018] P. L. DeBenneville and J. H. Macarthney, *J. Amer. Chem. Soc.*, **72**, 3073 (1950).

[1019] W. T. Forsee Jr. and C. B. Pollard, *J. Amer. Chem. Soc.*, **57**, 1788 (1935).

[1020] K. G. Lewis, *J. Chem. Soc.*, **1950**, 2249.

[1021] E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

[1022] A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp, and G. Jennings, *J. Amer. Chem. Soc.*, **58**, 1808 (1936).

[1023] F. Nerdel and H. Liebig, *Chem. Ber.*, **87**, 221 (1954).

[1024] A. W. Ingersoll and H. D. DeWitt, *J. Amer. Chem. Soc.*, **73**, 3360 (1951).

products are removed by shaking several times with benzene. Ketones that readily resinify may alternatively be removed by steam-distillation before the acid hydrolysis. The amine is liberated from the hydrochloric acid solution by alkali hydroxide and is purified as usual.

Many variants of the Leuckart–Wallach method have been proposed for conversion of ketones into primary amines, but they cannot be considered in detail here; they should be sought in the various publications on the best techniques for individual ketones[1025–1027] and on the use of catalysts.[1027–1029] However, as examples it may be noted that aliphatic[1030] and arylaliphatic ketones with more than short alkyl side chains[941] can be converted into primary amines under the following conditions:

1-Phenyl-1-dodecanamine:[992,1026] A mixture of 28% aqueous ammonia (105 g, 1.72 moles) and 90% formic acid (88 g, 1.72 moles) is heated slowly to 160° in a 500-ml three-necked flask fitted with a dropping funnel, thermometer, and descending condenser. Water distils off. Then dodecanophenone (89.5 g, 0.344 mole) is added in one portion and the mixture is kept at 160–170° for 24 h. Ketone that distils over is returned to the batch from time to time. The resulting *N*-formyl amine is hydrolysed by boiling the reaction mixture with concentrated hydrochloric acid (120 ml) under reflux for 8 h. Then the solution is set aside for 12 h, after which it is treated with water (200 ml). The crystalline mass of amine hydrochloride is broken up, filtered off, and washed with cold water. Recrystallization from hot water gives a salt (76 g, 78%) which, when recrystallized from ethanol, has m.p. 115–116°. The free amine boils at 170–172°/1–2 mm and has n_D^{25} 1.4903.

Secondary[1005,1031–1033] and tertiary amines[1021,1029,1033–1035] are obtained analogously from ketones, by using the amine formate or *N*-alkyl- or *N*,*N*-dialkyl-formamide in place of ammonia (or ammonium formate) or formamide. In this way *N*-methyl- and *N*,*N*-dimethyl-cyclohexylamine are obtained from cyclohexanone and formic acid by methyl- and dimethyl-formamide, respectively, whereas formamide and formic acid give cyclohexylamine.[1033]

1-Cyclohexylpiperidine:[1034] Piperidine (43 g, 0.5 mole) is added rapidly to 98% formic acid (23 g, 0.5 mole) with gentle cooling in running water. The mixture is treated whilst still hot with cyclohexanone (25 g, 0.25 mole) and then boiled under reflux (pumice) for 5.5 h. The solution is next cooled, poured into several times its volume of water, acidified with concentrated hydrochloric acid (50 ml), and extracted three times with benzene. The aqueous solution is set aside for 6 h for hydrolysis of the 1-formylpiperidine, then a concentrated aqueous solution of sodium hydroxide (30 g) is added and the whole is distilled in steam (until there are 400 ml of distillate). The oily amine layer in the distillate is separated and the aqueous layer is extracted with light petroleum. The amine and the petroleum extract are united, dried, and fractionated in a vacuum, yielding 1-cyclohexylpiperidine (25.4 g, 61%), b.p. 114–118°/25 mm, n_D^{20} 1.4862.

[1025] C. B. Pollard and D. C. Young Jr., *J. Org. Chem.*, **16**, 661 (1951).

[1026] F. S. Crossley and M. L. Moore, *J. Org. Chem.*, **9**, 529 (1944).

[1027] V. J. Webers and W. F. Bruce, *J. Amer. Chem. Soc.*, **70**, 1422 (1948).

[1028] A. N. Kost, A. P. Terent'ev and G. A. Shvekhgeimer, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, **1951**, 150; *Chem. Abstr.*, **45**, 10194 (1951).

[1029] J. F. Bunnett and J. L. Marks, *J. Amer. Chem. Soc.*, **71**, 1587 (1949).

[1030] B. L. Murr and C. T. Lester, *J. Amer. Chem. Soc.*, **77**, 1684 (1955).

[1031] A. Novelli, *J. Amer. Chem. Soc.*, **61**, 520 (1939).

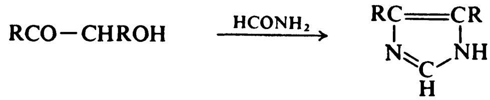
[1032] H. Suter and H. Zutter, *Ann. Chem.*, **576**, 220 (1952).

[1033] M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. Soc. Chim. France*, **1952**, 197.

[1034] P. A. S. Smith and A. J. Macdonald, *J. Amer. Chem. Soc.*, **72**, 1037 (1950).

[1035] J. F. Bunnett, J. L. Marks, and H. Moe, *J. Amer. Chem. Soc.*, **75**, 985 (1953).

α,β-Diketones or acyloins with an excess of formamide give good yields of 4,5-disubstituted imidazoles,[861] and not the amino alcohols; and α-halo and α-amino ketones react analogously.[861]



4,5-Dipropylimidazole:[1036] Butyroin (20 g) and formamide (40 ml) are gently boiled (175–190°) for 3 h under an air-condenser. Distillation in a vacuum then affords the imidazole as a yellowish oil (17 g, 81 %), b.p. 168°/10 mm, that solidifies (m.p. 66°). The hydrochloride has m.p. 163° (from ethyl malonate).

3. Reaction of alcohols and phenols with nitrogen compounds

a. Replacement of alcoholic hydroxyl groups by amino groups

Replacement of an unactivated hydroxyl group in an aliphatic compound by an amino group requires energetic conditions and use of a catalyst.

The necessary dehydrating catalysts such as aluminum oxide, kaolin, bauxite, aluminum phosphate, and mixed catalysts of similar composition require temperatures of 250–500° and pressures of several hundred atmospheres. The special apparatus and catalysts needed render this method of only industrial interest, the more so as only compounds of simple structure can be submitted to such drastic conditions and, on a laboratory scale, the amines that can be obtained in this way can be prepared more conveniently by other methods.

Somewhat milder conditions — a temperature region of 100–250° and pressures up to 25 atm (rarely 100–150 atm) — suffice for alkylation of ammonia or primary or secondary amines by primary or secondary alcohols in the presence of hydrogenation catalysts such as platinum, palladium, nickel, and copper chromite. In these cases the temperature required for reaction depends largely on the catalyst. Noble-metal catalysts can be effective from about 100°, nickel catalysts usually have a working temperature in the region 150–200°, but copper chromite catalysts need 190–250°. Frequently the reaction is carried out in an atmosphere of hydrogen.

Alkylation of ammonia usually affords mixtures of primary, secondary, and tertiary amines. Cyclohexylamine is obtained relatively smoothly (91 % yield) from cyclohexanol in the presence of reduced nickel at 150° under hydrogen at 20 atm.[1037] Adkins and his co-workers have described many cases of alkylation of amines by alcohols, for choice on nickel catalysts under pressure.[1038–1041]

Compounds with several hydroxyl groups at suitable distances from one another may cyclize to cyclic amines in these reactions.[1040,1041] For instance, 1-benzylpyrrolidine is obtained in 76% yield from 1,4-butanediol and benzylamine in the presence of copper chromite in an autoclave at 250°,[1040] and

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[1036] H. Bredereck and G. Theilig, *Chem. Ber.*, **86**, 88 (1953).
[1037] A. Guyot and M. Fournier, *Bull. Soc. Chim. France*, [iv], **47**, 203 (1930).
[1038] C. F. Winans and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 306 (1932).
[1039] E. J. Schwoegler and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 3499 (1939).
[1040] J. H. Paden and H. Adkins, *J. Amer. Chem. Soc.*, **58**, 2487 (1936).
[1041] R. M. Hill and H. Adkins, *J. Amer. Chem. Soc.*, **60**, 1033 (1938).

under similar conditions 1,5-hexanediol and pentylamine give 75% of 2-methyl-1-pentylpiperidine.[1041]

Of particular interest for laboratory practice are those reactions that can be carried out without pressure. Most of these are reactions between high-boiling alcohols and amines, but there have also been reports of alkylations by lower alcohols (other than methanol) that give good yields at atmospheric pressure. For example, aniline and benzidine can be monoalkylated by aliphatic alcohols with 2–6 carbon atoms or by benzyl alcohol in the presence of Raney nickel.[1042]

N-Propylaniline:[1042] A mixture of aniline (25ml), Raney nickel (15 g, well washed with 1-propanol), and 1-propanol (100 ml) is heated and stirred under reflux for 16 h. The catalyst is filtered from the cold solution and is well washed with alcohol. The filtrate and alcoholic washings are distilled in a vacuum through a Vigreux column, giving 82% (30.3 g) of the product, b.p. 98.5–100°/11 mm, n_D^{22} 1.5406.

Yields from other unbranched primary alcohols are of the same order, but from isobutyl and isopentyl alcohol are only 41% and 49%, respectively.[1042]

N-Ethyl-2-naphthylamine:[1043] A mixture of 2-naphthylamine (14.3 g), 95% ethanol (100ml), and moist Raney nickel (40 g) is heated under reflux for 4 h. Filtration and fractionation in a vacuum then afford *N*-ethyl-2-naphthylamine (14 g, 82%), b.p. 162°/12 mm, n_D^{25} 1.6402.

Mineral acids (HCl, H_2SO_4) and their salts [$ZnCl_2$, $Zn(NH_3)_2Cl_2$, $CuCl_2$, $FeCl_3$, etc.] also catalyse reactions between alcohols and amines. In this connexion alkylation of aromatic amines is of special interest for laboratory practice; it can be carried out in the temperature range of 180° to 250° under pressure.

N,N-Dimethylaniline:[355,cf.1044] A mixture of aniline (93 g), pure methanol (105 g), and 94% sulfuric acid (9.4 g) is heated at 215° for 6 h in an autoclave with a cast-iron lining. Some of the amine is alkylated thereby to the quaternary salt, and to cleave this to the tertiary base the reaction product is treated, after cooling, with 30% sodium hydroxide solution (25 g) and heated again in the autoclave for 5 h at 170°. The autoclave contents are then distilled in steam, and the amine is salted out of the distillate, separated in a separatory funnel, and distilled through a column. This gives almost pure *N,N*-dimethylaniline (117 g, 96%), b.p. 192°.

Similarly heating aniline hydrochloride and ethanol for 8 h at 180–200° affords a good yield of **N,N-diethylaniline** and some monoethylaniline, the latter being separable by means of *p*-toluenesulfonyl chloride. Catalysis by sulfuric acid is not suitable in this case owing to formation of ethylene.[355a]

Knoevenagel[1045] used iodine as catalyst and obtained an 87% yield of pure diethylaniline by heating aniline (18.6 g), ethanol (36.8 g), and iodine (0.5 g) at 220–230° for 10 h. Numerous further examples are recorded in the same paper.[1045]

Amines have also, but more rarely, been treated with alcohols in the presence of alkaline condensing agents (NaOH, MgO, alkoxides). Sprinzak[1046] has shown by a number of examples that this procedure gives particularly good yields in monobenzylation of primary aromatic and heterocyclic amines:

[1042] R. G. Rice and E. J. Kohn, *J. Amer. Chem. Soc.*, **77**, 4052 (1955); *Org. Syn.*, **36**, 21 (1956).

[1043] C. Ainsworth, *J. Amer. Chem. Soc.*, **78**, 1635 (1956).

[1044] R. N. Shreve, G. N. Vriens, and D. A. Vogel, *Ind. Eng. Chem.*, **42**, 791 (1950).

[1045] E. Knoevenagel, *J. Prakt. Chem.*, [ii], **89**, 1 (1914).

[1046] Y. Sprinzak, *J. Amer. Chem. Soc.*, **78**, 3207 (1956).

N-Benzyl-1-naphthylamine:[1046] 1-Naphthylamine (35.8 g), benzyl alcohol (40 g), and dry potassium hydroxide (3 g) are heated under reflux while the water formed is continuously removed through a separator. The boiling point reaches 267° in 15 min, at which stage the mixture is allowed to cool. On addition of an equal volume of water the amine crystallizes in 95% yield.

Directions for the preparation of 2-(benzylamino)pyridine in 99% yield from 2-pyridinamine and benzyl alcohol are given in *Organic Syntheses.*[1047]

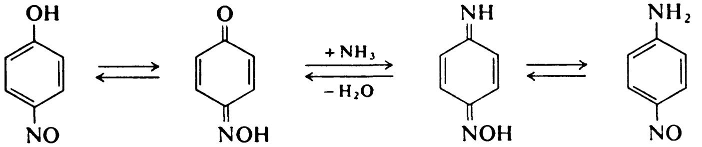
If a hydroxyl group is activated by a neighboring electron-repelling group it is replaced by an amino group under considerably milder conditions. Bodendorf,[1048] for instance, obtained 4-piperidino-2-butanone from 4-hydroxy-2-butanone by means of piperidine even in the cold, and 4-(dimethylamino)-2-butanone analogously by means of dimethylamine.

The reactions of enolized keto carboxylic esters with ammonia and amines are described on page 507, and those of α-amino alcohols, cyanohydrins, and α-hydroxy sulfonic acids on pages 516–520.

b. Reaction of phenols with ammonia, amines, and hydrazines

Acid catalysts must be used if substitution of an amino group for a hydroxyl group on an aromatic ring is to be fast enough for preparative purposes and even then it usually requires energetic conditions.

Certain nitroso phenols and polyhydroxy compounds are exceptions where the exchange takes place under relatively mild conditions and sometimes without the need for a catalyst. For example, *p*-nitrosophenol and ammonium salts, when heated on a steam-bath for 0.5 hour, give 50% of *p*-nitrosoaniline, [1049,cf.1050] and 1-nitroso-2-naphthol and aqueous methylamine solution at 35° give 90% of N,N-dimethyl-1-nitroso-2-naphthylamine.[1051] The easier reaction is due to the tautomerism of these phenols with the ketonic isomers, *e.g.*, for nitrosophenol:



and similarly phloroglucinol, which with hydroxylamine even gives a trioxime,[1052] reacts with ammonia and ammonium chloride even at room temperature to give 5-aminoresorcinol.[1053]

Nitro groups also increase the reactivity of phenols, but replacement of the hydroxyl by an amino group still needs temperatures of 150–200° and thus usually the use of pressure vessels.[1054] Primary amines can be obtained at normal pressures from di- and tri-nitrated phenols and naphthols by melting them with urea;[1055,1056] picramide, m.p. 188°, for instance, was formed in 88% yield by heating picric acid with 3 equivalents of urea at 173° for 36 h.[1056]

[1047] Y. Sprinzak, *Org. Syn.*, **38**, 3 (1958).

[1048] K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 113 (1933).

[1049] O. Fischer and E. Hepp, *Ber. Deut. Chem. Ges.*, **20**, 2475 (1887); **21**, 684 (1888).

[1050] J. Willenz, *J. Chem. Soc.*, **1955**, 2049.

[1051] E. W. Malmberg and C. S. Hamilton, *J. Amer. Chem. Soc.*, **70**, 2415 (1948).

[1052] A. Baeyer, *Ber. Deut. Chem. Ges.*, **19**, 159 (1886).

[1053] J. Pollak, *Monatsh. Chem.*, **14**, 401 (1893).

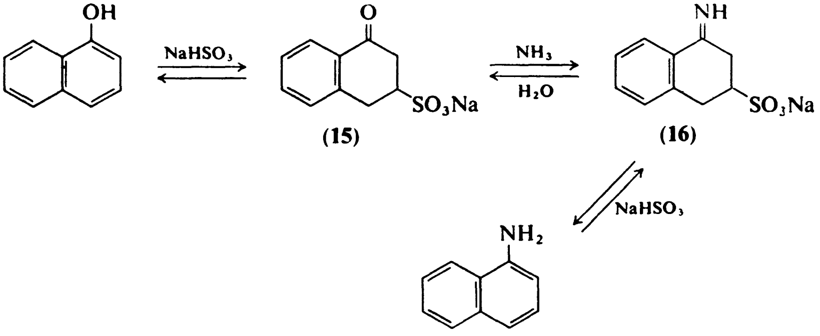
[1054] V. Merz and C. Ris, *Ber. Deut. Chem. Ges.*, **19**, 1749 (1886); O. N. Witt, *Ber. Deut. Chem. Ges.*, **19**, 2032 (1886); A. Barr, *Ber. Deut. Chem. Ges.*, **21**, 1541 (1888); E. Diepolder, *Ber. Deut. Chem. Ges.*, **42**, 2916 (1909).

[1055] O. Kym, *J. Prakt. Chem.*, [ii], **75**, 323 (1907).

[1056] E. Y. Spencer and G. F. Wright, *Can. J. Res.*, *B*, **24**, 204 (1946).

In spite of its limited applicability the Bucherer reaction[1057] is the most important method of preparing aromatic amines from phenols. This consists of the conversion of phenols into amines, and the reverse conversion of amines into phenols, as well as transamination of aromatic amines (cf. page 538), each in the presence of hydrogen sulfite ions.

The mechanism of this interesting reaction, long disputed, was recently clarified by Rieche and Seeboth.[1057,1058] It involves a series of reversible reactions, that can be formulated as follows for the case of 1-napthol–1-naphthylamine:



(15) **(16)**

The position of the decisive equilibrium **(15)** ⇄ **(16)** is determined by the concentrations of the reactants and by the tendency of the imine **(16)** either to split off sodium hydrogen sulfite or to undergo hydrolysis.[1059]

The principal applications of the Bucherer reaction have been in the naphthalene series.[1060–1064] 1- and 2-Naphthol give their respective primary amines smoothly, and substituents in position 5, 6, 7, or 8 have little influence on the reaction; however, 1-naphthol-2- and 3-sulfonic acids and 2-naphthols with substituents (particularly carboxyl groups) at position 3 do not, in general, exchange their hydroxyl groups. The 1-position of 1-naphthol-4-sulfonic acids is particularly reactive, so that if further hydroxyl groups are present the 1-hydroxyl group is replaced preferentially. In the benzene series substantially only resorcinol and its homologs undergo the reaction.[1065,1066] In the quinoline and isoquinoline series only hydroxyl groups attached to the benzene ring can be replaced by amino groups.[1067]

[1057] N. L. Drake, *Org. Reactions*, **1**, 105 (1942); H. Seeboth, *Angew. Chem.*, **79**, 329 (1967).

[1058] A. Rieche and H. Seeboth, *Ann. Chem.*, **638**, 43 (1960).

[1059] H. Seeboth, *Monatsber. Deut. Akad. Wiss. Berlin*, **3**, 43 (1961).

[1060] H. T. Bucherer, *J. Prakt. Chem.*, [ii], **69**, 49 (1904); *Z. Farben- u. Textilchem.*, **2** 193 (1903).

[1061] H. T. Bucherer and A. Stohmann, *J. Prakt. Chem.*, [ii], **71**, 433 (1905); *Z. Farben- u. Textilchem.*, **3**, 57 (1904).

[1062] H. T. Bucherer and F. Seyde, *J. Prakt. Chem.*, [ii], **75**, 249 (1907).

[1063] H. T. Bucherer and M. Schmidt, *J. Prakt. Chem.*, [ii], **79**, 369 (1909).

[1064] H. T. Bucherer and A. Uhlmann, *J. Prakt. Chem.*, [ii], **80**, 201 (1909).

[1065] H. T. Bucherer and E. Hoffmann, *J. Prakt. Chem.*, [ii], **121**, 113 (1929).

[1066] W. H. Hartung, L. J. Minnick, and H. F. Koehler, *J. Amer. Chem. Soc.*, **63**, 507 (1941).

[1067] N. N. Woroshtzow and J. M. Kogan, *Ber. Deut. Chem. Ges.*, **65**, 142 (1932); R. A. Robinson, *J. Amer. Chem. Soc.*, **69**, 1944 (1947); R. H. F. Manske and M. Kulka, *J. Amer. Chem. Soc.*, **72**, 4997 (1950).

To convert naphthols into the corresponding primary amines they are heated with ammonium sulfite and aqueous ammonia solution (molar ratios $ArOH : SO_2 : NH_3$ = ca. 1 : 1.5–2 : 5–8) in an autoclave at 130–160°; the reaction times required are in the range of 6–30 hours.

2-Naphthylamine:[1068] 2-Naphthol (144 g, 1 mole) is heated in a stirring autoclave at 140° for 8 h with an ammonium sulfite solution prepared by passing sulfur dioxide (100 g) into aqueous ammonia solution (*d* 0.880; 400 ml). A pressure of 5–7 atm is developed. After cooling, the product is a stiff paste; this is made into a slurry with water, filtered off, washed with water, and dissolved in hot water (1.5 l) containing concentrated hydrochloric acid (150 ml). To remove any turbidity (due to unchanged naphthol and small amounts of secondary amine), the solution is boiled with animal charcoal (10 g), filtered, and, whilst still hot, treated with 20% sodium hydroxide solution until alkaline to phenolphthalein. After cooling, the amine is collected, washed, and then dried in a vacuum at 30–50°. This gives a crude reddish product (130–140 g) of m.p. 109–111°. For further purification it is distilled in a vacuum (metal-bath at 210°) into a wide sabre-shaped receiver, yielding a pure-white amine (125–135 g), m.p. 112°.

The preparation of the technically important 2-naphthylamine-1-sulfonic acid from 2-naphthol-1-sulfonic acid is described by Fierz-David and Blangey.[355f]

Both phenols and primary amines have been used as starting materials for synthesis of secondary amines. 2-Naphthylamines react with amines more easily than do 2-naphthols, and these easier than 1-naphthols. If a hydroxyl group is to be replaced by a strongly basic amino group, this can be done, as for primary amines, by using the appropriate alkylammonium sulfite and alkylamine (molar ratios $ArOH : SO_2 : RNH_2$ = ca. 1 : 2 : 2–3). If longer reaction times can be considered, phenols can also be used; they should be boiled under reflux with 2–3 moles of the amine and sodium hydrogen sulfite, if necessary with addition of ammonium sulfite (total SO_2 4–12 moles). Any aromatic amine may be used, but few except naphthalene derivative react smoothly. For the preparation of *N*-aryl-1-naphthylamines see a paper by Rieche and Seeboth[1058] and page 537.

Symmetrical diarylamines, *e.g.*, di-2-naphthylamine,[1069] can be prepared by treating the primary amine with a hydrogen sulfite only.

Aryl hydrazines can also be prepared according to the principles of the Bucherer reaction, namely by treating appropriate phenols with hydrazine hydrate and sulfur dioxide.[1070–1073] Thus 2,3-naphthalenediol affords 57% of 2,3-naphthylenedihydrazine,[1070,1071] and 2,7-naphthalenediol affords 82% of 7-hydrazino-2-naphthol.[1072] However, no great importance attaches to these reactions.

Arylhydrazines do not give the derived hydrazo compounds when treated with naphthols in the presence of sulfurous acid. 1-Naphthol, phenylhydrazine,

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[1068] R. Schröter in Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1957, Vol. 11, Part 1, p. 150.

[1069] Ger. Pat. 114,974; *Friedländer*, **6**, 198 (1900–1902).

[1070] H. Franzen, *Ber. Deut. Chem. Ges.*, **38**, 266 (1905).

[1071] H. Franzen, *J. Prakt. Chem.*, [ii], **76**, 205 (1907).

[1072] H. Franzen and W. Deibel, *J. Prakt. Chem.*, [ii], **78**, 143 (1908).

[1073] H. Franzen and T. Eichler, *J. Prakt. Chem.*, [ii], **78**, 157 (1908).

and sodium hydrogen sulfite afford 1,2,3,4-tetrahydro-4-(phenylhydrazono)-2-naphthalenesulfonic acid, which is cyclized by acid to benzo[*a*]carbazole (85% yield) in analogy to the Fischer indole synthesis; and benzo[*c*]carbazole is obtained similarly from 2-naphthol.[1058]

The preparation of amines from phenols that are neither activated by suitable groups (see page 529) nor amenable to the Bucherer reactions requires higher temperatures (180–300°) and thus in most cases the use of pressure. Zinc chloride and diamminodichlorozinc[1074] have often proved their worth as catalysts; calcium chloride, sodium hydrogen sulfate, iron(III) chloride, and sulfanilic acid have also been used, but less often. Knoevenagel[1045] obtained very good yields in the arylation of aromatic amines by naphthols when adding catalytic amounts of iodine. It is often useful to use amine hydrochlorides instead of the free base. Most of the directions for laboratory-scale work with simple components are to be found in the older literature.[1074,1075]

Two more recent examples may be cited: **3-Amino-2-naphthoic aicd,** which cannot be obtained in 70% yield by the Bucherer reaction, has been prepared by heating 3-hydroxy-2-naphthoic acid with aqueous ammonia and zinc chloride for 36 h in an autoclave at 195°.[1076]

For the preparation of **2-phenyl-7-quinolinamine** (80% yield), 2-phenyl-7-quinolinol (6.6 g) was heated with calcium chloride ammoniate (25 g) in a sealed tube at 250° for 3 h and then at 280–290° for a further 7 h.[1077]

An amino group can be introduced in place of a phenolic hydroxyl group in, *e.g.*, alkylphenols[1078,1079] or steroids[1078,1080] by various very effective processes that depend on oxidizing the phenol by lead tetraacetate to a *p*-[1078,1080] or *o*-quinol[1079] acetate and treating this with a carbonyl reagent such as semicarbazide,[1078] dinitrophenylhydrazine,[1078,1079] or benzylamine;[1080] the nitrogenous carbonyl derivative becomes aromatic again by ejecting an acetoxyl group and can then be cleaved to the free amine by reduction[1078,1079] or by hydrolysis.[1080]

4. Reaction of ethers and oxonium salts with nitrogen compounds

Substitution of an amino for the alkoxyl group of simple aliphatic ethers has little preparative importance: the ether linkage must be weakened by a carbonyl, carboxyl, or nitrile group in the β-position if the reaction is to occur under not too drastic conditions. Certain β-methoxy ketones of type **(17)** can be converted into β-amino ketones below 100°.[1081] Cleavage of the ether group in activated enol ethers is still easier; for instance, 2-(acetoxymethylene)-

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[1074] V. Merz and P. Müller, *Ber. Deut. Chem. Ges.*, **19**, 2901 (1886).

[1075] V. Merz and P. Müller, *Ber. Deut. Chem. Ges.*, **20**, 544 (1887); R. Lloyd, *Ber. Deut. Chem. Ges.*, **20**, 1254 (1887); K. Buch, *Ber. Deut. Chem. Ges.*, **17**, 2634 (1884).

[1076] C. H. F. Allen and A. Bell, *Org. Syn.*, Coll. Vol. III, 78 (1955).

[1077] W. Borsche and M. Wagner-Roemmich, *Ann. Chem.*, **544**, 294 (1940).

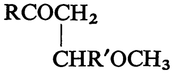
[1078] E. Hecker, *Chem. Ber.*, **92**, 3198 (1959); E. Hecker and E. Walk, *Chem. Ber.*, **93**, 2928 (1960).

[1079] H. Budzikiewicz, F. Wessely, and O. S. Ibrahim, *Monatsh. Chem.*, **95**, 1396 (1964).

[1080] A. M. Gold and E. Schwenk, *J. Amer. Chem. Soc.*, **81**, 2198 (1959).

[1081] I. N. Nazarow and S. A. Vartanyan, *Zh. Obshch. Khim.*, **22**, 1668, 1794 (1952); *Chem. Abstr.*, **47**, 9968, 9969 (1953).

acetoacetic esters (**18**), -malonic esters* (**19**), and -acetylacetylacetone (**20**) give the aminomethylene compounds in very good yields when treated with



$\begin{array}{l} RCOCH_2 \\ | \\ CHR'OCH_3 \end{array}$

(17)

$\begin{array}{c} CH_3COCCOOR \\ \| \\ CHOC_2H_5 \end{array}$

(18)

$\begin{array}{c} ROOCCCOOR \\ \| \\ CHOC_2H_5 \end{array}$

(19)

$\begin{array}{c} CH_3COCCOCH_3 \\ \| \\ CHOC_2H_5 \end{array}$

(20)

ammonia on primary aliphatic amines at room temperature,[1082] and these products are used for numerous syntheses of N-heterocyclic compounds, such as 4-quinolinols.[1084–1088]

Ethyl 2-(aminomethylene)oxaloacetate:[1089] 18% Anhydrous alcoholic ammonia solution (26 g, 0.27 mole of NH_3) is added in one portion to a stirred solution of 2-(ethoxymethylene)-oxaloacetate (61 g, 0.25 mole) in dry ether (250 ml) that is cooled in ice–salt. The mixture is shaken and set aside for 20 h in a closed vessel. The gelatinous precipitate is then filtered off and washed thoroughly with dry ether. Evaporating the combined filtrates in a vacuum affords a syrup, which soon crystallizes [45–49 g, 84–91%; m.p. 68–69° (from ether–light petroleum)].

It is not always necessary to start from the pre-formed alkoxymethylene compound (2, 3, 4, etc.); they can be prepared from an orthformic ester and a compound containing a reactive methylene group and treated with the amine in one operation.[1088]

Most aromatic amines[1084–1088,1090,1091] and amides,[1082,1090,1092] *e.g.*, ureas, give good yields only at 100–150°.

When alkoxymethylene compounds are treated with hydroxylamines, hydrazines, or diamines, replacement of the hydroxyl by the nitrogenous group is accompanied by ring closure, and this allows various types of N-heterocycle to be built up, as described by numerous authors.[1082,1092–1095]

Not merely alkoxymethylene derivatives from compounds containing reactive methylene groups, but also other enol ethers can be cleaved by amines, *e.g.*, 3-alkoxyacrylic esters,[1096] 4-pyrones,[1097,1098] and furfuraldehyde.[1099]

1,2,6-Trimethyl-4-pyridone:[1098] A solution of 2,6-dimethyl-4-pyrone (70 g) in water (200 ml) is added during 1 h to a stirred 40% aqueous methylamine solution (150 ml), the

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* Preparation of these compounds from malonic esters, orthoformic esters, and acetic anhydride is described by Parham[1083] and Duffin[1084] and their co-workers.

[1082] L. Claisen, *Ann. Chem.*, **297**, 1 (1897).

[1083] W. E. Parham and L. J. Reed, *Org. Syn.*, Coll. Vol. III, 395 (1955).

[1084] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, **1948**, 893.

[1085] C. C. Price and R. M. Roberts, *Org. Syn.*, Coll. Vol. III, 272 (1955).

[1086] C. C. Price, N. J. Leonard, and H. F. Herbrandson, *J. Amer. Chem. Soc.*, **68**, 1251 (1946).

[1087] C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204 (1946).

[1088] H. R. Snyder and R. E. Jones, *J. Amer. Chem. Soc.*, **68**, 1253 (1946).

[1089] R. G. Jones, *J. Amer. Chem. Soc.*, **73**, 3684 (1951).

[1090] R. H. Baker and A. H. Schlesinger, *J. Amer. Chem. Soc.*, **68**, 2009 (1946).

[1091] R. H. Baker, J. G. Van Oot, S. W. Tinsley Jr., D. Butler, and B. Riegel, *J. Amer. Chem. Soc.*, **71**, 3060 (1949).

[1092] C. W. Whitehead, *J. Amer. Chem. Soc.*, **74**, 4267 (1952).

[1093] P. Schmidt, K. Eichenberger, and W. Wilhelm, *Angew. Chem.*, **73**, 15 (1961).

[1094] A. Dornow and co-workers, *Chem. Ber.*, **91**, 1830 (1958); **93**, 1103 (1960).

[1095] A. Kreutzberger and C. Grundmann, *J. Org. Chem.*, **26**, 1121 (1961).

[1096] P. L. DeBenneville and J. H. Macarthney, *J. Amer. Chem. Soc.*, **72**, 3725 (1950).

[1097] J. W. Armit and T. J. Nolan, *J. Chem. Soc.*, **1931**, 3023.

[1098] K. N. Campbell, J. F. Ackerman, and B. K. Campbell, *J. Org. Chem.*, **15**, 337 (1950).

temperature being kept below 40°. The mixture is kept for 1–2 h, then cooled to 0°, after which the product is filtered off and crystallized from hot water. It gives an 88% yield of pyridone, m.p. 245–246°.

Boiling an acidic, aqueous-methanolic solution of furfuraldehyde with *p*-nitroaniline under reflux for 2–3 h gives an almost quantitative yield of **1-(*p*-nitrophenyl)-2-pyrrolecarbaldehyde.**[1099]

In the aromatic series it is only for certain nitro derivatives that this ether cleavage by ammonia or amines has preparative value. Di- and tri-nitrophenyl ethers react with ammonia, primary amines, hydrazine hydrate, or hydroxylamine at temperatures that range from 50° to 200° according to the degree of activation of the ether. Diaryl ethers mostly react more smoothly than alkyl aryl ethers; in the latter case the new nitrogenous group replaces the alkyl group; in the diaryl ethers it replaces the less nitrated aryloxy group.

For example, Borsche[1100] obtained 2,4-dinitroaniline anr 2,4-dinitrodiphenylamine from 2,4-dinitrophenyl phenyl ether and ammonia or aniline, respectively, at 40–50°. Boiling 2,4-dinitrophenyl 2-naphthyl ether with aniline affords 2,4-dinitrodiphenylamine (97%), m.p. 156–157°.[1101]

Reactions of nitroaryl ethers with hydrazine[1100] and hydroxylamine[1102] proceed analogously. Warming 2,4-dinitroanisole with 90% hydrazine on a water-bath for 0.5 h gives 2,4-dinitrophenylhydrazine almost quantitatively.[1100]

Ether fission in the pyridine and quinoline series is mainly of interest for introduction of an amino group in position 4. Simpson and Wright[1103] obtained 6-nitro-4-quinolinamine in 84% yield by heating the 4-phenoxy compound with an excess of ammonium acetate at 170–180° for 25 min.

In the pyridine series it is not necessary to activate the ether linkage by a nitro group if an amine hydrochloride is used instead of the free base. Jerchel and Jakob[1104] obtained a number of *N*-substituted 4-pyridinamines in good yield from 4-pyridyl phenyl ethers and amine hydrochlorides.

For example, *N*-phenyl-4-pyridinamine is formed in 89% yield when 4-phenoxypyridine is heated with an excess of aniline hydrochloride for 3 h at 180°.[1104]

Reaction of ammonia or amines with saturated cyclic ethers containing five or six ring members causes the ether oxygen atom to be replaced by an NH or NR group, but the conditions needed are so drastic that this is rarely of interest for laboratory practice.

A temperature of 330–340° and use of an aluminum oxide catalyst are necessary for conversion of tetrahydropyran into 1-phenylpiperidine by means of aniline;[1105] tetrahydrofuran gives pyrrolidine under similar conditions.[1106]

[1099] L. A. Janowskaja in "Synthesen organischer Verbindungen," VEB Verlag Technik, Berlin, 1959, Vol. 1, p. 123.

[1100] W. Borsche, *Ber. Deut. Chem. Ges.*, **56**, 1488 (1923).

[1101] Y. Ogata and M. Okano, *J. Amer. Chem. Soc.*, **71**, 3211 (1949).

[1102] W. Borsche, *Ber. Deut. Chem. Ges.*, **56**, 1494, 1939 (1923); W. Borsche and E. Feske, *Ber. Deut. Chem. Ges.*, **59**, 683 (1926).

[1103] J. C. E. Simpson and P. H. Wright, *J. Chem. Soc.*, **1948**, 1707.

[1104] D. Jerchel and L. Jakob, *Chem. Ber.*, **91**, 1266 (1958).

[1105] A. N. Bourns, H. W. Embleton, and M. K. Hansuld, *Org. Syn.*, **34**, 79 (1954).

[1106] W. Reppe and co-workers, *Ann. Chem.*, **596**, 143 et seq. (1955).

Cyclic ethers with smaller rings react at lower temperatures, but the products are all acyclic (amino alcohols). Oxetane (trimethylene oxide) is converted into *N*-substituted 3-amino-1-propanols when heated with an amine and a little water in a sealed tube at 150° for several hours.[1107]

Ethylene oxides (oxiranes) react exothermally at room temperature with ammonia and most strongly basic amines; presence of water or an alcohol accelerates the reaction. N.B.: There is danger of explosions when working with oxirane.

Ammonia and oxirane itself give various proportions of mono-, di-, and tri-ethanolamine according to the proportions of the reactants used; the products can be separated by distillation.[1108] Reaction with primary or, more so, secondary amines is more clear-cut. **2-(Diethylamino)ethanol** is best obtained in this way:

Oxirane (220 g, 5 moles) is led into a stirred mixture of diethylamine (880 g, 12 moles) and methanol (440 g) at such a rate that the temperature does not rise above 60°. Then the methanol and unchanged dimethylamine are distilled off at atmospheric pressure, followed by the 2-(diethylamino)ethanol at 54–55°/12 mm (550 g, 94%).[995a]

Directions for preparation of 2-(dialkylamino)ethanols in general are given by Rohrmann and Shonle.[1109]

Tertiary amines may also be used: thus trimethylamine and oxirane give choline at room temperature.[1110]

Most primary aromatic amines also react at room temperature or on gentle warming,[1111] but weakly basic amines require temperatures of 100–140° (pressure vessel).

Substituted oxiranes generally react the more slowly the greater the number of substituents. The amino group usually becomes attached to unsymmetrically substituted oxiranes at the carbon atom that carried the larger number of hydrogen atoms.

Hydroxylamine reacts with oxirane at room temperature or below, giving *N*,*N*-bis(2-hydroxyethyl)hydroxylamine, but interaction for longer times leads to tris(2-hydroxyethyl)amine oxide [2,2′,2″-nitrilotri(ethanol) oxide].[1112]

With hydrazine hydrate substituted oxiranes give hydrazino alcohols,[1113] and with sodium azide give azido alcohols,[1114] in both cases in good yields.

Nitrogen dioxide and oxirane in chloroform at 0–20° give an almost quantitative yield of 2-nitroethyl nitrate, which can be hydrolysed to 2-nitroethanol by 10% sodium carbonate solution at 35–45°.[1115] The latter product can also be obtained in 85% yield directly by allowing oxirane and carbon dioxide to react with aqueous sodium nitrite solution at 25–30°.[1116]

[1107] S. Searles and V. P. Gregory, *J. Amer. Chem. Soc.*, **76**, 2789 (1954).

[1108] L. Knorr, *Ber. Deut. Chem. Ges.*, **30**, 909, 915, 918 (1897).

[1109] E. Rohrmann and H. A. Shonle, *J. Amer. Chem. Soc.*, **66**, 1641 (1944).

[1110] K. H. Meyer and H. Hopff, *Ber. Deut. Chem. Ges.*, **54**, 2279 (1921).

[1111] Yu. K. Jurev, K. Yu. Novitskii, and L. G. Liberov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1951**, 317; *Chem. Abstr.*, **46**, 932 (1952).

[1112] L. W. Jones and G. R. Burns, *J. Amer. Chem. Soc.*, **47**, 2966 (1925).

[1113] G. Gever, *J. Amer. Chem. Soc.*, **76**, 1283 (1954).

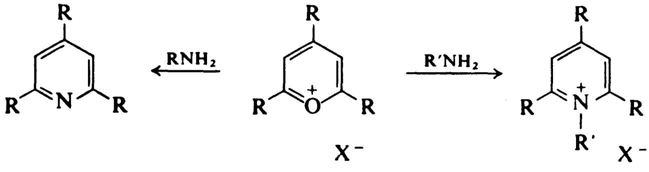
[1114] C. A. VanderWerf, R. Y. Heisler, and W. E. McEwen, *J. Amer. Chem. Soc.*, **76**, 1231 (1954); W. E. McEwen, W. E. Conrad, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **74**, 1168 (1952).

[1115] G. Darzens, *C. R. Hebd. Séances Acad. Sci.*, **229**, 1148 (1949).

[1116] Jap. Pat. 6,910; *Chem. Abstr.*, **48**, 1412 (1954).

Interaction of substituted oxiranes and sodium azide in dimethyl sulfoxide affords azido alcohols.[1117]

An important method of preparing pyridine derivatives is to treat pyrylium salts[1118] with ammonia, primary amines, hydroxylamine, or hydrazines:



(R = Alkyl or aryl; R′ = alkyl, aryl, acyl, —NHC_6H_5, —$NHCONH_2$, or —OH.)

Use of ammonia in this reaction has led to numerous pyridine derivatives that are difficult to obtain in other ways, particularly those with alkyl or aryl groups at positions 2, 4, and 6, these being readily prepared from the pyrylium salts. The older directions prescribe an aqueous medium, but Dimroth recommends suspending the pyrylium salt in anhydrous *tert*-butyl alcohol and passing in dry gaseous ammonia (the preparation and reactions of pyrylium salts have been reviewed by him and by Schroth and Fischer[1118]); the salt dissolves and the solution becomes warm; on cooling, the ammonium salt of the inorganic acid originally bound in the pyrylium salt separates (*e.g.*, ammonium perchlorate or tetrafluoroborate), and adding water to the filtrate therefrom precipitates the pyridine derivative.

2,4,6-Triphenylpyridine:[1118] 2,4,6-Triphenylpyrylium tetrafluoroborate (10 g) is suspended in anhydrous *tert*-butyl alcohol (100 ml). The suspension is heated to the boiling point and anhydrous ammonia is led in as a rapid stream, causing the salt to dissolve. After 30 min the precipiated ammonium tetrafluoroborate is filtered off and the filtrate is treated with a little water (to turbidity). Storage in a refrigerator for a short time then affords the product (ca. 8 g, 90%) as colorless leaflets, m.p. 138°.

N-Alkyl- and *N*-aryl-pyridinium salts are obtained analogously from 2,4,6-trisubstituted pyrylium salts and primary aliphatic or aromatic amines, generally in excellent yields.[1028]

Using hydroxylamine leads to pyridine 1-oxides provided that the 2- and 6-substituents are not too bulky;[1119] using semicarbazide leads to 1-ureidopyridines,[1119] and using phenylhydrazine leads to the interesting [1120] 1-(arylamino)pyridines[1120,1121] which cannot be obtained at all in other ways.

However, with a few exceptions, chromylium and xanthylium salts cannot be converted in such ways into quinoline or acridine derivatives.

[1117] K. Ponsold, *Chem. Ber.*, **95**, 1727 (1962).

[1118] K. Dimroth, *Angew. Chem.*, **72**, 331 (1960); W. Schroth and G. Fischer, *Z. Chem.*, **4**, 281 (1964).

[1119] A. T. Balaban and C. D. Nenitzescu, *Ann. Chem.*, **625**, 74 (1959); E. Schmitz, *Chem. Ber.*, **91**, 1488 (1958).

[1120] K. Dimroth, G. Arnoldy, S. von Eicken, and G. Schiffler, *Ann. Chem.*, **604**, 221 (1957).

IV. Replacement of other elements by nitrogen

1. Replacement of nitrogen by nitrogen

The greatest interest in such replacements attaches to transamination and transamidation and to the various methods of forming C—N bonds by means of diazonium salts and diazo compounds. Substitution of amino for nitro groups is almost wholly restricted to *o*- and *p*-dinitro compounds and is of little importance. Preparation of α-nitroso and α-hydroxyimino esters from α-nitro esters and sodium nitrite has been discussed above (pages 431, 478 and 479).

a. Transamination (amine exchange reactions)

The terms transamination and amine exchange reactions denote reactions between ammonia and an amine, or between two amines, in which formally the amino group of one amine is replaced by that of another,* *e.g.*:

$$RNH_2 + R'NR''_2 \longrightarrow RNR''_2 + R'NH_2$$

In this type of reaction, when heated in the presence of acid catalysts (hydrochloric, phosphoric, or *p*-toluenesulfonic acid), primary aromatic amines often condense smoothly with loss of ammonia to afford diamines. Diphenylamine, for example, can be obtained by heating aniline and aniline hydrochloride for 20 hours at 230°/6 atm.[355b]

***N*-Phenyl-1-naphthylamine:**[355e] This amine, which cannot be prepared smoothly by the Bucherer reaction, is obtained as follows. 1-Napthylamine (143 g), aniline (175 g), and sulfanilic acid (3 g) are heated for 40–48 h under reflux in a flask fitted with a thermometer and a long air-condenser. Ammonia is evolved and the boiling point of the mixture rises from about 195° to 215°. Then, on fractionation in a vacuum, aniline (80–85 g) distils at 70°/12 mm, followed with bumping an dfoaming by an intermediate fraction (8–10 g) that contains a little *N*-phenyl-1-naphthylamine. The bulk of the latter (190–195 g) boils at 212 to 216°/12 mm; the residue distils up to 225°/12 mm. The total yield is 91% (about 200 g) of colorless needles, m.p. 62° (from a little ethanol).

Good yields of *N*-aryl-1-naphthylamines are also obtained by using catalytic amounts of iodine with, *e.g.*, 1-naphthylamine and aniline, the toluidines, *m*- and *p*-chloroaniline, *o*- and *p*-anisidine,[1045] 2,3- or 3,4-dimethylaniline.[1122] Di-(2-naphthylamine) is obtained almost quantitatively when 2-naphthylamine is heated for 4 hours at 230° in the presence of 0.5–1.0% of iodine, and 4,4'-dihydroxydiphenylamine in 70% yield from *p*-aminophenol under similar conditions.[1045]

2,2'-Biphenyldiamine is converted almost quantitatively into carbazole when heated with phosphoric acid.[1123]

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* Some examples of the exchange of nitrogen components in Schiff bases, hydrazones, etc., have been mentioned in the Section dealing with their preparation (see pages 504 *et. seq.*).

[1121] W. Schneider and co-workers, *Ber. Deut. Chem. Ges.*, **54**, 2285 (1921); **61**, 2445 (1928); **74**, 1252 (1941); *Ann. Chem.*, **438**, 115, 147 (1924).

[1122] N. P. Buu-Hoï, *J. Chem. Soc.*, **1949**, 670.

[1123] H. Leditschke, *Chem. Ber.*, **86**, 522 (1953).

Carbazole:[1123] 2,2′-Biphenyldiamine (50 g) is thoroughly stirred while being heated with phosphoric acid (*d* 1.85; 278 g) in an open vessel at 200–210°. Carbazole begins to separate after 15 min. After 5 h the hot solution is filtered from the solid carbazole, which is washed with water until neutral. This gives a quantitative yield (45 g) of carbazole, m.p. 238°.

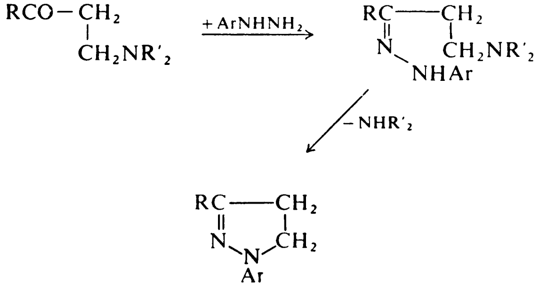
Pyrrolidine and piperidine are obtained by similar ring closures in the aliphatic series.[523,1124,cf.1125]

With 2-naphthylamine and its derivatives there is a further possible method of transamination: they can be converted into *N*-alkyl- and *N*-aryl-2-naphthylamines reversibly by a type of Bucherer reaction (cf. page 531).

4-Hydroxy-6-(phenylamino)-2-naphthalenesulfonic acid ("phenyl-γ-acid"):[355g] 6-Amino-4-hydroxy-2-naphthalenesulfonic acid ("γ-acid") (239 g of pure material), sodium hydrogen sulfite solution (25% SO_2 content; 750 g), water (750 ml), and aniline (200 g) are heated together under reflux for 24 h. The mixture is then made alkaline with concentrated sodium carbonate solution, and the aniline is removed in steam. Acidification of the residue with hydrochloric acid precipitates the phenyl-γ-acid in an almost pure state in 75–80% yield.

Tertiary and quaternary Mannich bases often undergo transamination readily and under mild conditions if the exchange amine is used in excess and the secondary or tertiary amine formed is sufficiently volatile (cf. reviews by Hellmann[82,1126]). Primary amines can also be prepared in this way, the amine group of the Mannich base being replaced by phthalimide[1127] and the product then hydrolysed.

The amino group of Mannich bases can also be exchanged against sulfonamides,[1128] hydroxylamines,[1129] or phenylhydrazine.[1130] Interaction of hydrazines and Mannich bases from ketones gives first the hydrazones and then pyrazolines by amine exchange involving cyclization:[1131]



Quaternary pyridinium salts[503] having electron-attracting substituents on nitrogen — *e.g.*, 1-(2,4-dinitrophenyl)- or 1-(4′-pyridyl)-pyridinium salts — can react in two ways with nucleophilic reagents such as amines. Either the quaternary pyridinium nucleus is replaced by the new amine group (reaction

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[1124] A. Ladenburg, *Ber. Deut. Chem. Ges.*, **18**, 3100 (1885); **20**, 442 (1887).

[1125] K. Kindler and D. Matthies, *Chem. Ber.*, **95**, 1992 (1962).

[1126] H. Hellmann, *Angew. Chem.*, **65**, 473 (1953).

[1127] R. O. Atkinson, *J. Chem. Soc.*, **1954**, 1329; A. Butenandt and U. Renner, *Z. Naturforsch.*, **8 B**, 454 (1953); Ger. Pat. 933,339; *Chem. Abstr.*, **52**, 16303 (1958).

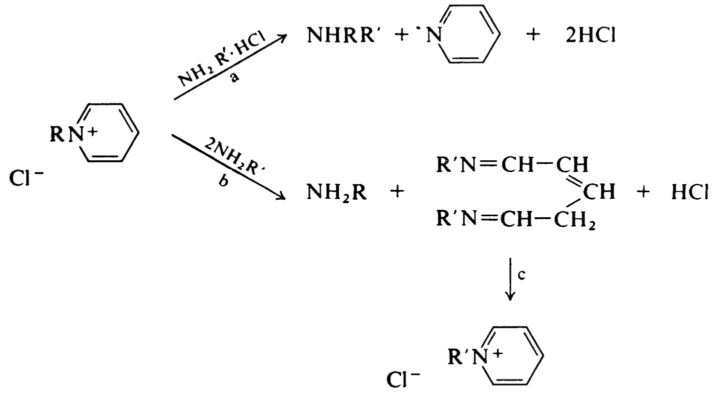
[1128] J. J. Licari and G. Dougherty, *J. Amer. Chem. Soc.*, **76**, 4039 (1954); J. J. Licari, L. W. Hartzel, G. Dougherty, and F. R. Benson, *J. Amer. Chem. Soc.*, **77**, 5386 (1955).

[1129] J. Thesing, *Chem. Ber.*, **87**, 507 (1954); J. Thesing, A. Müller, and G. Michel, *Chem. Ber.*, **88**, 1027 (1955).

[1130] J. Thesing and C.-H. Willersinn, *Chem. Ber.*, **89**, 1195 (1956).

[1131] M. Stamper and B. F. Aycock, *J. Amer. Chem. Soc.*, **76**, 2786 (1954); H. B. Nisbet, *J. Chem. Soc.*, **1945**, 126.

a); or a glutacondialdehyde derivative is formed by ring fission (Zincke fission),[1132] in which the pyridine nitrogen appears as a primary amine containing its original substituent (reaction b); the glutacondialdehyde derivative then recyclizes to a pyridine derivative (reaction c), so that the final result shows exchange of the substituents on the pyridine nitrogen:[1132,1133]



Whether it is reaction (a) or (b) that occurs depends on the substituents on the pyridine ring and on the reaction conditions (see the reviews[241,503]).

If 1-(2,4-dinitrophenyl)pyridinium chloride is heated with aniline hydrochloride in benzoic acid for some time at 200°, 2,4-dinitrodiphenylamine is formed in accord with reaction (a); other examples are given by Vompe and Turitsyna.[1134]

This reaction (a) has considerable preparative interest in the case of 1-(4-pyridyl)pyridinium salts since it permits introduction of an amino group at position 4 of pyridine. For example, 4-aminopyridine is formed when 1-(4-pyridyl)pyridinium chloride hydrochloride is heated with aqueous ammonia for 8 hours at 150°[1136] or when ammonia is led into a solution of this salt in phenol for 3 hours at 180–190° (80% yield).[1137] Analogously, passing dimethylamine into a phenol melt of the salt gives 4-(dimethylamino)pyridine.[1138] Under these conditions the quaternary pyridine ring is easily cleaved by aromatic amines, so that 4-(arylamino)pyridines are better synthesized from the pyridylpyridinium salts by means of the hydrochloride of aromatic amines.[1139]

4-(Phenylamino)pyridine:[241] 1-(4-Pyridyl)pyridinium chloride hydrochloride (2.3 g) and aniline hydrochloride (2.6 g) are heated at 180° for 90 min, then cooled, taken up in water, and warmed with animal charcoal. The solution is filtered, made strongly alkaline with

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[1132] T. Zincke, *Ann. Chem.*, **330**, 361 (1903); **333**, 296 (1904); T. Zincke and W. Würker, *Ann. Chem.*, **341**, 365 (1905).

[1133] H. Lettré, W. Haede, and E. Ruhbaum, *Ann. Chem.*, **579**, 123 (1953).

[1134] F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953) (especially p. 624).

[1135] A. F. Vompe and N. F. Turitsyna, *Doklady Akad. Nauk S.S.S.R.*, **64**, 341 (1949); *Chem. Abstr.*, **43**, 4671 (1949).

[1136] E. Koenigs and H. Greiner, *Ber. Deut. Chem. Ges.*, **64**, 1049 (1931); J. P. Wibaut, S. Herzberg, and J. Schlatmann, *Rec. Trav. Chim.*, **73**, 140 (1954).

[1137] A. Albert, *J. Chem. Soc.*, **1951**, 1376.

[1138] D. Jerchel, H. Fischer, and K. Thomas, *Chem. Ber.*, **89**, 2921 (1956).

[1139] D. Jerchel and L. Jakob, *Chem. Ber.*, **91**, 1266 (1958).

sodium hydroxide solution, and heated to the boil. Crystals separate, which, when collected and recrystallized from aqueous methanol, afford 4-(phenylamino)pyridine, m.p. 172°, in quantitative yield.

Ring fission similar to Zincke fission is occasionally applied to other N-heterocycles to afford aldehydes. For instance, in an alkaline medium containing hydroxylamine pyrrole is converted into succindialdehyde dioxime,[1140] and dihydropyridine (prepared from pyridine by sodium and methanol) affords glutardialdehyde dioxime analogously.[1141]

The ethylenimine (aziridine) ring is much harder than the oxirane ring to open by ammonia or amines; catalysts such as ammonium chloride[1142] and aluminum chloride[1143] have been added.

b. Transamidation and related reactions

The NH_2 group of carboxamides, particularly if unsubstituted, can be exchanged for residues from other amines, hydrazines, etc. Thus *N*-formylamines are often obtained quite smoothly by heating the amine with formamide in a vacuum at as low as 70°.[1144] Higher carboxamides react analogously at temperatures of 150–200°.[1145] Transamidation occurs more readily if the carboxamide is melted with the amine hydrochloride;[692,1146] and diacylamides, including cyclic dicarboximides such as succinimide and phthalimide are more reactive than simple carboxamides.[1147]

Interesting transamidations can be carried out with the very reactive 1-acylimidazoles.[597,598,702,703] 1,1'-Carbonyldiimidazole (readily accessible from phosgene and imidazole; see page 469) reacts with amines to give the corresponding ureas, in some cases even at room temperature. 1,3-Diphenylurea, for instance, is obtained in 91% yield by its reaction with aniline in tetrahydrofuran at room temperature for 30 min. 1-Acylimidazoles, readily obtained from 1,1'-carbonyldiimidazole and carboxylic acids also in tetrahydrofuran at room temperature (see formula scheme on page 482), can be converted, without isolation, into other carboxamides by means of amines at room temperature; the anilides and diethylamides of *p*-alkylbenzoic acids, for example, were prepared in 90–95% yields in this way. The method can also be applied in peptide syntheses with good results.[600] 1-Imidazole- and 1-triazole-carboxylic esters, obtained from imidazole and triazole by the action of chloroformic esters, are readily converted by amines into carbamic esters (urethanes).[1148] 1-Aroyl-imidazoles and -triazoles are less reactive than their

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[1140] R. Willstätter and W. Heubner, *Ber. Deut. Chem. Ges.*, **40**, 3871 (1907); L. C. Keagle and W. H. Hartung, *J. Amer. Chem. Soc.*, **68**, 1608 (1946).

[1141] A. C. Cope, H. L. Dryden Jr., C. G. Overberger, and A. A. D'Addieco, *J. Amer. Chem. Soc.*, **73**, 3416 (1951).

[1142] L. B. Clapp, *J. Amer. Chem. Soc.*, **70**, 184 (1948).

[1143] G. H. Coleman and J. H. Callen, *J. Amer. Chem. Soc.*, **68**, 2006 (1946).

[1144] B. Lachowicz, *Monatsh. Chem.*, **9**, 695 (1888); Ger. Pat. 449,112; *Friedländer*, **15**, 234 (1925–1927).

[1145] J. H. McGregor and F. Werd, *J. Soc. Chem. Ind. (London)*, **66**, 344 (1947).

[1146] A. Galat and G. Elison, *J. Amer. Chem. Soc.*, **65**, 1566 (1943); D. Klamann, *Monatsh. Chem.*, **84**, 925 (1953).

[1147] F. S. Spring and J. C. Woods, *J. Chem. Soc.*, **1945**, 625.

[1148] H. A. Staab, *Ann. Chem.*, **609**, 83 (1957).

aliphatic analogs; thus 15 minutes' heating with aniline at 120° suffices to convert the diimidazole amide of adipic acid into the dianilide, but 3 hours heating at 150° is necessary for the terephthalic analog.[1149]

Transamidation has often been used also as a convenient method of converting urea into *N*- or *N,N'*-substituted ureas and hydrazides. The amine and urea are melted together[1150] or heated together for some time in glacial acetic acid.[1151] The reaction temperature and the proportions of the reactants determine whether the monosubstituted or symmetrically disubstituted urea is produced, but mixtures of the two are frequently formed. Amide hydrochlorides can also be used, being boiled with the urea in aqueous solution; a well-known example is the conversion of urea into methylurea by 3 hours' boiling with methylamine hydrochloride, which is a step in the preparation of 1-methyl-1-nitrosourea.[1152]

Conversion of urea into phenyl- and 1,3-diphenyl-urea by aqueous aniline hydrochloride solution is described in *Organic Syntheses*[1153].

Very good yields are almost always obtained by starting with nitrourea.[1154–1157] In these cases the NO_2NH group is exchanged almost exclusively, so that this method is especially suitable for preparation of monosubstituted ureas and is in many cases superior even to the route from isocyanates.[1155]

Ethylurea:[1158] Ethylamine (44 g) is dissolved in a mixture of water (200 ml) and ice (100 g) in a 2-l flask, nitrourea (104 g) is added, and the whole is heated on a water-bath until lively evolution of nitrogen begins. The reaction is moderated by ice-cooling, but the mixture is eventually heated to the boiling point to complete the transformation. After evaporation in a vacuum ethylurea crystallizes; the mixture is cooled to 0° and the product (55 g; m.p. 90–92°) is filtered off and washed with ice-water. A second crop (15.7 g; m.p. 89–92°) is obtained by evaporating the mother-liquor and washings; and, when dissolved in anhydrous ethanol and precipitated with ether, the residue affords a third crop (7–8 g). The total yield is 90% (78 g).

The reaction of nitroguanidine with amines has been reviewed by McKay.[1159]

Carbohydrazides can be obtained from amides and hydrazine hydrate or substituted hydrazines. The products are mono- or di-acyl derivatives of hydrazine according to the reaction conditions, the proportions of the reactants, and the nature of any substituents already present on the hydrazine.

1,2-Diformylhydrazine:[1160] A solution of hydrazine hydrate (25 ml, 0.5 mole) in formamide (45 g, 1 mole) is heated on a water-bath for 2 h. Any unchanged material is distilled off in a vacuum. Then treating the residue with ethanol (100 ml) gives 1,2-diformylhydrazine (80%), m.p. 160°.

[1149] H. A. Staab, *Chem. Ber.*, **90**, 1326 (1957).

[1150] T. L. Davis and H. W. Underwood Jr., *J. Amer. Chem. Soc.*, **44**, 2595 (1922).

[1151] A. Sonn, *Ber. Deut. Chem. Ges.*, **47**, 2437 (1914).

[1152] F. Arndt, L. Loewe, and S. Avan, *Ber. Deut. Chem. Ges.*, **73**, 606 (1940).

[1153] T. L. Davis and K. C. Blanchard, *Org. Syn.*, **3**, 95 (1923).

[1154] T. L. Davis and K. C. Blanchard, *J. Amer. Chem. Soc.*, **51**, 1790 (1929).

[1155] J. S. Buck and C. W. Ferry, *J. Amer. Chem. Soc.*, **58**, 854 (1936).

[1156] R. W. Charlton and A. R. Day, *J. Org. Chem.*, **1**, 552 (1936).

[1157] J. K. Shillington and co-workers, *J. Amer. Chem. Soc.*, **80**, 6551 (1958).

[1158] E. Billmann and A. Klit, *Ber. Deut. Chem. Ges.*, **63**, 2205 (1930).

[1159] A. F. McKay, *Chem. Rev.*, **51**, 301 (1952).

[1160] C. Ainsworth and R. G. Jones, *J. Amer. Chem. Soc.*, **77**, 621 (1955).

Benzohydrazide:[1161] This is obtained when benzamide is heated in three parts of water with one equivalent of hydrazine hydrate until evolution of ammonia ceases. When the solution cools, the product crystallizes; it is recrystallized from hot water. Formation of hydrazide is smoother and faster from the amide than from ethyl benzoate.

A remarkable application of this reaction is the treatment of peptides with hydrazine (8–10 hours at 100°). All the amino acid residues except the terminal one are thereby converted into their hydrazides. Since it is easy to separate the C-terminal amino acid from the hydrazides, this method permits determination of the amino acid sequence (see, for example, Braunitzer[1162]).

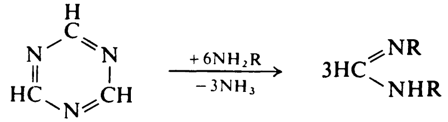
Semicarbazide, m.p. 96°, is obtained by heating molar amounts of urea and hydrazine hydrate for 3 hours at 100° (sealed tube);[1163] and heating phenylurea (0.5 mole) with 42% hydrazine hydrate solution (1 mole) for 12 hours in a steam-bath gives 4-phenylsemicarbazide, $C_6H_5NHCONHNH_2$.[1164]

4-Substituted semicarbazides can also be prepared from semicarbazones as the latter exchange the free NH_2 group for a substituted NHR group when heated with high-boiling amines.[1165]

The synthesis of carbohydrazides from the corresponding 1-acylimidazoles by Staab's method[703,1166] proceeds under very mild conditions: an equimolar mixture of carboxylic acid and 1,1'carbonyldiimidazole is heated in anhydrous tetrahydrofuran until evolution of carbon dioxide ceases and is then treated with the requisite hydrazine derivative. Hydrazine hydrate can be used to provide unsubstituted hydrazides since hydrazinolysis of the acylimidazole is faster than its hydrolysis.[703,1166]

If the reverse change, of a hydrazide into an amide, is to be effected it is often better to convert the hydrazide into the azide by nitrous acid and then to convert the azide into the amide, for the azide group is more easily replaced than an amino group. Replacement of hydrazide-nitrogen by amide-nitrogen plays its most important part in peptide chemistry.[783]

An interesting N—N exchange is undergone by *s*-triazine (for its preparation see Grundmann and others[829,830,1167]) with primary amines:[1168] each methine group condenses with two molecules of the primary amine, giving the *N*,*N'* disubstituted formamidine, while the three ring nitrogen atoms are eliminated as ammonia; excellent yields are obtained by reaction without a solvent or in an anhydrous inert medium (benzene, tetrahydrofuran, or dioxan); lower aliphatic amines react at room temperature, higher ones on gentle warming. For a review see Grundmann.[1169]



[1161] T. Curtius and G. Struve, *J. Prakt. Chem.*, [ii], **50**, 296 (1894).
[1162] G. Braunitzer, *Chem. Ber.*, **88**, 2025 (1955).
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[1164] A. S. Wheeler, *Org. Syn.*, **6**, 74 (1926).
[1165] W. Borsche, *Ber. Deut. Chem. Ges.*, **38**, 831 (1905).
[1166] H. A. Staab, *Angew. Chem.*, **71**, 385 (1959).
[1167] C. Grundmann and A. Kreutzberger, *J. Amer. Chem. Soc.*, **76**, 5646 (1954).
[1168] C. Grundmann and A. Kreutzberger, *J. Amer. Chem. Soc.*, **77**, 6559 (1955); *J. Polymer Sci.*, **38**, 425 (1959).
[1169] C. Grundmann, *Angew. Chem. Int. Ed., Engl.*, **2**, 309 (1963).

Interesting heterocyclic ring closures can be achieved by using diamines, aminophenols, amino(thiophenols), etc., for both the functional groups of these compounds become attached to the methine group and substantially the only by-product is ammonia.[1168] *s*-Triazine and hydrazine hydrate afford 1,2-bis(hydrazonomethyl)hydrazine, $H_2NN{=}CH{-}NHNH{-}CH{=}NNH_2$, which also forms the starting point of interesting syntheses of heterocyclic compounds;[1170] substituted hydrazines such as phenylhydrazine react analogously to primary amines, giving formazans.[1170]

c. Replacement of diazonium and diazo nitrogen

Aromatic amino groups can be replaced by other nitrogen-containing groups through the derived diazonium salts.

The main interest of this reaction lies in the possibility of converting amines into nitro compounds. Many nitro compounds that cannot be prepared by direct nitration can be obtained easily in this way through neutral or weakly alkaline diazonium salt solutions in satisfactory and sometimes excellent yield. Success depends largely on choice of a suitable transfer agent for the nitro group.[1171] Hodgson and Marsden[172] state that diazonium hexanitritocobaltates are particularly suitable for production of the nitro compounds:

The amine (0.1 mole) is diazotized in hydrochloric or sulfuric acid solution by sodium nitrite (7 g), the volume of solution being kept as small as possible. The diazonium salt solution is neutralized with calcium carbonate and filtered, and trisodium hexanitritocobaltate (15 g) is stirred into the filtrate, whereupon the trisdiazonium salt usually separates as a solid. For conversion into the nitro compound this salt (10 g), finely powdered, is added in portions, at room temparature, with good stirring, to a solution of sodium nitrite (10 g) and copper sulfate (10 g) in water (60 ml) in which copper(I) oxide (4 g) is suspended. When evolution of nitrogen ceases the nitro compound is isolated either by extraction with a solvent, *e.g.*, chloroform, or by basification of the solution and steam-distillation.[172]

The following yields were obtained by this method: **1-nitronaphthalene** 68%, **2-nitronaphthalene** 60%, ***p*-nitrotoluene** 69%, ***p*-nitroanisole** 68%, and ***o*-nitrotoluene** 61%.[172]

A number of dinitronaphthalenes have also been prepared similarly, but in less good yields.[1172]

Solid diazonium sulfates (for their preparation see Hodgson and Mahadevan[1173]) can also be used as starting material. They are washed free from adhering acid by alcohol or ether and added in aqueous solution or as solids to aqueous sodium sulfite solution containing suspended copper(I,II) sulfite.[1174] This sulfite is obtained by treating aqueous copper sulfate solution with aqueous sodium sulfite solution (equal weights of the two salts) and washing the precipitate.[1174,cf.1175] This method is indicated in particular for preparation of dinitronaphthalenes. Detailed description, suitable also for analogous cases, is to be found in *Organic Syntheses*[1175] for the preparation of 1,4-dinitronaphthalene from 4-nitro-1-naphthylamine. Also, diazonium nitritocobaltates may be used in place of diazonium sulfates with this technique.[1174]

[1170] C. Grundmann and A. Kreutzberger, *J. Amer. Chem. Soc.*, **79**, 2839 (1957); C. Grundmann and R. Rätz, *J. Org. Chem.*, **21**, 1037 (1956).

[1171] A. Hantzsch and J. W. Blagden, *Ber. Deut. Chem. Ges.*, **33**, 2544 (1900).

[1172] H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, **1947**, 127.

[1173] H. H. Hodgson and A. P. Mahadevan, *J. Chem. Soc.*, **1947**, 325.

[1174] H. H. Hodgson, A. P. Mahadevan, and E. R. Ward, *J. Chem. Soc.*, **1947**, 1392.

[1175] H. H. Hodgson, A. P. Mahadevan, and E. R. Ward, *Org. Syn.*, Coll. Vol. III, 341 (1955).

Further simplification of the technique, as shown in the following example, is possible whenever the amine can be diazotized in aqueous solution and the diazonium salt is stable in neutral solution.[1176,1177]

***o*-Dinitrobenzene:**[1177] *p*-Nitroaniline (10 g) is dissolved in a warm mixture of sulfuric acid (*d* 1.84; 12 ml) and water (30 ml), and the solution is poured into ice-water (50 ml) with vigorous stirring. Crushed ice (20 g) is added and then a solution of sodium nitrite (8 g) in water (13 ml) very rapidly (!) with good stirring. The mixture is stirred for 5 min, then added in portions but very rapidly through a wide glass tube to a well stirred, warm (60°) mixture of sodium nitrite (100 g) and sodium hydrogen carbonate (45 g) in water (1 l) containing some silicone anti-foaming agent. The glass tube should dip below the surface of the solution. Five minutes after this addition the product is filtered off, washed with 2N-hydrochloric acid and then with much water. The yield of almost pure *o*-dinitrobenzene, m.p. 116–118°, is 97% (11.8 g). Completely pure *o*-dinitrobenzene, m.p. 118°, is obtained in 90% overall yield by chromatography of a benzene solution of the crude product on aluminum oxide.

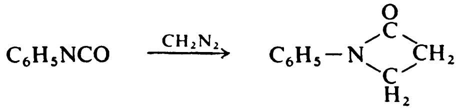
***p*-Dinitrobenzene** is obtained analogously in similar yield; in this case half the stated amounts of sulfuric acid and sodium hydrogen carbonate suffice.[1177]

The catalyst cannot be completely dispensed with for similar reactions of other diazonium salts, but it suffices to add a few grams of copper sulfate and copper(I) oxide to the hot nitrite solution.[1176]

Other nitrogen-containing groups besides nitro groups may be introduced to replace diazonium salt groups in the same general type of reaction. For example, aryl isocyanates can be prepared by using alkali cyanates,[1178] and aryl azides by using sodium azide or hydrogen azide.[661,1179]

It should also be mentioned that aliphatic and aromatic amines can be alkylated by means of diazomethane in the presence of boron trifluoride[1180] by means of diazo ketones in the presence of copper powder;[1181] but the preparative value of these reactions is small.

β-Lactams can be prepared from aromatic isocyanates by means of diazomethane:[1182]



$$C_6H_5NCO \xrightarrow{CH_2N_2} C_6H_5{-}N\langle C(=O)CH_2CH_2 \rangle$$

2. Replacement of carbon by nitrogen

Formation of a C–N bond with cleavage of a C–C bond occurs occasionally as undesired side reaction during nitration,[166,1183] nitrosation, or azo coupling. Some examples of this have been mentioned in the respective Sections. Such reactions have preparative interest only when they form the main reaction, as in the Japp–Klingemann reaction (see page 436) and in certain oximations by nitrous acid (see page 429).

[1176] H. H. Hodgson, F. Heyworth, and E. R. Ward, *J. Chem. Soc.*, **1948**, 1512.

[1177] E. R. Ward, C. D. Johnson, and J. G. Hawkins, *J. Chem. Soc.*, **1960**, 894.

[1178] L. Gattermann and A. Cantzler, *Ber. Deut. Chem. Ges.*, **23**, 1225 (1890); **25**, 1086 (1892).

[1179] O. Noelting and O. Michel, *Ber. Deut. Chem. Ges.*, **26**, 86 (1893).

[1180] E. Müller, H. Huber-Emden, and W. Rundel, *Ann. Chem.*, **623**, 34 (1959).

[1181] P. Yates, *J. Amer. Chem. Soc.*, **74**, 5376 (1957).

[1182] J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, **70**, 1985 (1948); **71**, 4059 (1949).

[1183] R. A. Henry, *J. Org. Chem.*, **23**, 648 (1958).

Nitration of *p*-cymene by fuming nitric acid leads to 2,4-dinitrotoluene.[1184] Heating 1,6-dihydro-1-methyl-6-oxonicotinic acid with nitric acid (*d* 1.52) under reflux gives 1-methyl-3,5-dinitro-2(1*H*)-pyridone in good yield.[1185] 2,6-Dibromo-4-nitrosophenol is formed quantitatively from 3,5-dibromo-4-hydroxybenzoic acid and sodium nitrite in aqueous alcohol.[166,1183] Nitrous acid replaces hydroxymethyl groups in phenols by nitro groups,[1186] and diazonium salts replace them by diazo groups.[1187]

An elegant method of acylation for not too weakly basic amines consists of treatment with acyl cyanides.[1097a] The process[1188,1189] has the advantage

$$\mathrm{RCOCN + R'NH_2 \longrightarrow RCONHR' + HCN}$$

over the customary Schotten–Baumann and Einhorn acylation that it can be used with amines that are sensitive to water, acid, or alkali. It is carried out in an indifferent solvent at room temperature; no acid-binding agent is needed. Amino alcohols react only at the nitrogen, even when an excess of the reagent is used; it requires a temperature above 100°, *e.g.*, reaction in boiling dimenthylformamide, before the hydroxyl group is attacked.

***N*-Benzoyl-L-ephedrine:**[1189] L-Ephedrine (1 g, 6 mmoles) is dissolved in ether (ca. 100 ml) and treated gradually with a solution of benzoyl cyanide (0.9 g, 7 mmoles) in ether (ca. 50ml). The solution is later considerably concentrated, whereupon the pure *N*-benzoyl-L-ephedrine, m.p. 110°, crystallizes in 74.5% yield (1.2 g) after some hours.

Chloromycetin has been prepared analogously,[1189] starting from dichloroacetyl cyanide, which may be produced *in situ* from chloral and sodium cyanide.[1190]

The ready cleavage of the carbon–carbon bond in chloral by strongly basic amines finds excellent application for *N*-formylation, particularly as the reaction usually affords very good yields under mild conditions.[1191–1193]

A chloroform solution of the amine is treated dropwise with an equimolar amount of chloral, water being excluded. The mixture is stirred for several hours, then heated for 0.5 h on a steam-bath.[1192]

Formylation by chloral hydrate can also be carried out in aqueous solution.[1194]

Also, if chloral is replaced by a Schiff base derived therefrom, formamidines are formed:[1195]

$$\mathrm{CCl_3CCH{=}NR + NHR'R'' \xrightarrow{-CHCl_3} R'R''N{-}CH{=}NR}$$

Two carbon–carbon bonds are cleaved when diethyl acetonedicarboxylate is heated with three times the amount of an amine. Substituted phenethylamines thus yield the corresponding ureas.[1196]

[1184] J. Alfthan, *Ber. Deut. Chem. Ges.*, **53**, 78 (1920).

[1185] A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, **1951**, 2590.

[1186] E. Ziegler and K. Gartler, *Monatsh. Chem.*, **80**, 634 (1949).

[1187] E. Marder and I. W. Ruderman, *J. Amer. Chem. Soc.*, **73**, 5475 (1951); E. Ziegler and G. Zigeuner, *Monatsh. Chem.*, **79**, 42, 89, 358 (1948).

[1188] A. Dornow and H. Theidel, *Angew. Chem.*, **66**, 605 (1954).

[1189] A. Dornow and H. Theidel, *Chem. Ber.*, **88**, 1267 (1955).

[1190] Brit. Pat. 712,745; *Chem. Abstr.*, **50**, 1083 (1956).

[1191] G. B. L. Smith, M. Silver, and E. S. Becker, *J. Amer. Chem. Soc.*, **70**, 4254 (1948).

[1192] F. F. Blicke and Chi-Jung Lu, *J. Amer. Chem. Soc.*, **74**, 3933 (1952).

[1193] F. F. Blicke and Chi-Jung Lu, *J. Amer. Chem. Soc.*, **77**, 29 (1955).

[1194] E. J. Poziomek, *J. Org. Chem.*, **28**, 243 (1963).

[1195] D. Borrmann and R. Wegler, *Chem. Ber.*, **100**, 1814 (1967).

[1196] M. I. Moyer and W. E. McEwen, *J. Amer. Chem. Soc.*, **73**, 3075 (1951).

3. Replacement of sulfur by nitrogen

a. Replacement of sulfo groups by nitrogen

Because aromatic sulfonic acids are readily accessible replacement of sulfo groups by other groups is often the simplest way to introduce substituents into an aromatic ring. This is of particular importance for preparation of amines in the anthraquinone series. 1- and 2-Aminoanthraquinone and 1,5-, 1,8-, and 2,6-diaminoanthraquinone are obtained by heating the respective sulfonic acids with ammonia under pressure; it is important to remove the sulfite formed out of the equilibrium mixture either by precipitation with, *e.g.*, barium chloride or by oxidation to sulfate with arsenic acid or sodium *m*-nitrobenzenesulfonate.

1-Aminoanthraquinone:[355h] Potassium anthraquinone-1-sulfonate (60 g) is heated with 24% ammonia solution (120 g) and sodium *m*-nitrobenzenesulfonate (21 g) in a stirring autoclave up to 170–175° during 4 h and then kept at this temperature for a further 12 h (pressure ca. 25 atm). After cooling, the precipitate is filtered off, sucked dry, washed with a little hot water, boiled with acidified (HCl) water (300 ml), filtered off again, washed with hot water, and dried at 90°. This gives the technically pure product, m.p. 238°, in about 95% yield (39 g). Recrystallization from xylene affords a 75% yield of pure 1-aminoanthraquinone, m.p. 241°.

2-Aminoanthraquinone is obtained in exactly the same way.[355h] Analogous directions for preparation of 1-(methylamino)anthraquinone in *Organic Syntheses* prescribe sodium chlorate as oxidizing agent.[1197]

1,3-Naphthalenediamine and its derivatives are obtained by heating 4-aminonaphthalene-2-sulfonic acid with ammonia or an amine at 160–180° under pressure; any sulfo groups in the other ring are unaffected. 4-Hydroxynaphthalene-2-sulfonic acid exchanges both its sulfo and its hydroxyl group.[1198]

A sodamide melt can be used at atmospheric pressure but gives poorer yields.[383] However, use of sodamide in boiling piperidine has proved an excellent method of preparing 1-arylpiperidines from aromatic sulfonic acids.[1191]

Alkyl- and aryl-sulfonyl groups can also be replaced by amino groups, analogously to sulfo groups; these sulfone fissions are effected by cyclic secondary amines in the presence of sodamide and often give high yields of the tertiary amine.[1199,1200,cf.1201]

Further, replacement of sulfo by diazo groups has been observed. It occurs extraordinarily easily on occasions when *o*- or *p*-amino- or *o*- or *p*-hydroxybenzenesulfonic acids are coupled with diazonium salts.[367]

Substitution of nitro for sulfo groups[1202] has special importance. The too easy oxidation of phenols during direct nitration can often be elegantly avoided by first sulfonating the phenol and then removing the sulfo group by nitric acid.[1203] Many industrially important nitro compounds are prepared in this

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[1197] C. V. Wilson, J. B. Dickey, and C. H. F. Allen, *Org. Syn.*, **29**, 66 (1949).

[1198] Ger. Pat. 89,061, 90,905, 90,906, 94,075; *Friedländer*, **4**, 598–600 (1894–1897).

[1199] T. K. Brotherton and J. F. Bunnett, *Chem. & Ind.* (*London*), **1957**, 80; *J. Amer. Chem. Soc.*, **78**, 155 (1956); J. F. Bunnett, T. K. Brotherton, and S. M. Williamson, *Org. Syn.*, **40**, 74 (1960).

[1200] W. Bradley, *J. Chem. Soc.*, **1938**, 458.

[1201] H.-J. Nitzschke and H. Budka, *Chem. Ber.*, **88**, 264 (1955).

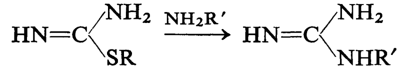
[1202] C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons Inc., New York, 1944, pp. 406 et seq.

[1203] R. King, *J. Chem. Soc.*, **119**, 2105 (1921).

way on a large scale. A laboratory prescription for picric acid has been given[355d,cf.1204] that can be extended analogously to the preparation of 8-hydroxy-5,7-dinitro-2-naphthalenesulfonic acid (Naphthol Yellow S) and nitrocresols. In addition, some phenol-, cresol-, and xylenol-sulfonic acids have been converted into the corresponding nitrophenols by nitrous gases.[1205]

b. Replacement of other sulfur groups by nitrogen

A method often used for preparation of guanidines is to treat *S*-alkylthiuronium salts with ammonia or amines:[1206–1208]



$$HN{=}C\begin{matrix}\diagup NH_2\\ \diagdown SR\end{matrix} \xrightarrow{NH_2R'} HN{=}C\begin{matrix}\diagup NH_2\\ \diagdown NHR'\end{matrix}$$

The reaction usually occurs in the cold if the thiuronium salt is not substituted on nitrogen.

Guanidinoacetic acid ("glycocyamine"):[1209] 2N-Sodium hydroxide solution (252 ml) is poured over *S*-ethylthiouronium bromide (92.5 g) with ice-cooling, and the mixture is treated rapidly with a hot (80°) solution of glycine (41 g) in water (90 ml). The flask is removed from the ice-bath when the temperature of the mixture reaches 25°. After about 30 min crystallization begins, then ether (100 ml) is added and the mixture is set aside overnight. On the next day the mixture is cooled for 2 h in an ice-bath, then the ether is decanted and the product that has separated is filtered off, washed with ice-water (2 × 20 ml), ethanol (2 × 150 ml), and ether (2 × 150 ml), and dried in the air. This affords an 80–90% yield (47–53 g) of guanidinoacetic acid, m.p. 280–284°.

N-Substituted thiouronium salts require higher temperatures. Nitroguanidines are prepared analogously from *N*-nitrothiouronium salts,[1210] and aminoguanidines particularly smoothly from thiouronium salts and hydrazine hydrate.[1212] It is also possible to start from thioureas instead of thiouronium salts, treating these with ammonia or an amine in the presence of a desulfurizing agent such as lead oxide.[1212,1213]

Cleavage of thiiranes (ethylene sulfides) with amines is suitable for preparation of 2-aminoethanethiols.[1214] Aliphatic amines undergo this reaction in

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[1204] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Walter de Gruyter & Co., Berlin, 35th ed, 1953, p. 172.

[1205] R. L. Datta and P. S. Varma, *J. Amer. Chem. Soc.*, **41**, 2039 (1919).

[1206] C. E. Braun, *J. Amer. Chem. Soc.*, **55**, 1280 (1933).

[1207] H. King and S. M. Tonkin, *J. Chem. Soc.*, **1946**, 1063.

[1208] A. F. McKay, W. G. Hatton, and R. O. Braun, *J. Amer. Chem. Soc.*, **78**, 6144 (1956).

[1209] E. Brand and F. C. Brand, *Org. Syn.*, Coll. Vol. III, 440 (1955).

[1210] L. Fishbein and J. A. Gallaghan, *J. Amer. Chem. Soc.*, **76**, 1877 (1954).

[1211] G. W. Kirsten and G. B. L. Smith, *J. Amer. Chem. Soc.*, **58**, 800 (1936); R. A. Henry and G. B. L. Smith, *J. Amer. Chem. Soc.*, **73**, 1858 (1951); W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953); E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, **19**, 1231 (1954).

[1212] S. Petersen in Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1952, Vol. 8, p. 183.

[1213] J. Macholdt-Erdniss, *Chem. Ber.*. **91**, 1992 (1958).

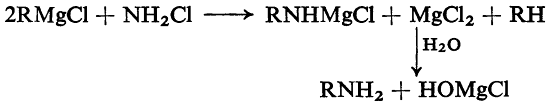
[1214] R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962), who give a literature review.

refluxing benzene,[1214] but aromatic amines require more energetic conditions (heating under pressure at at least 100°).[1215]

4. Replacement of metals by nitrogen

Of the many organometallic compounds, only Grignard reagents are used for formation of C–N bonds. Alkyl- and aryl-magnesium halides undergo various types of reaction with nitrogen compounds,[1216] but few of these have major importance.

Among these few is the formation of aliphatic and arylaliphatic amines by reaction of Grignard reagents with chloramine according to the scheme:



$$\begin{array}{rl} 2\mathrm{RMgCl} + \mathrm{NH_2Cl} \longrightarrow & \mathrm{RNHMgCl} + \mathrm{MgCl_2} + \mathrm{RH} \\ & \qquad\qquad \downarrow \mathrm{H_2O} \\ & \mathrm{RNH_2} + \mathrm{HOMgCl} \end{array}$$

The reaction is carried out in ethereal solution; it gives the best yields when alkylmagnesium chlorides are used; the corresponding alkyl chlorides are by-products. The process has its main interest for preparation of primary amines whose amino group is attached to a secondary or tertiary carbon atom. Examples of its use and a tested method of preparing chloramine are given in a review by Theilacker.[1217] Also the unstable chloramine may be replaced by methoxylamine, which is easier to handle.[1218]

cis-Azo compounds can be obtained in good yield by reaction of diarylzincs with arenediazonium salts.[1219]

[1215] H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947); Ger. Pat. 631,016; *Chem. Abstr.*, **30**, 6008 (1930); Brit. Pat. 445,805.

[1216] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., New York, 1954, pp. 1199 et seq.

[1217] W. Theilacker and E. Wegner, *Angew. Chem.*, **72**, 127 (1960).

[1218] R. Brown and W. E. Jones, *J. Chem. Soc.*, **1946**, 781.

[1219] D. Y. Custin and J. L. Tveten, *J. Org. Chem.*, **26**, 1764 (1961).

CHAPTER 7

Alteration of Nitrogen Groups in Carbon-Nitrogen Compounds

Compiled by
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I. Formation of the N–H bond

An N–H bond can be formed by addition or exchange. All the methods coming in question for this purpose are reducing methods.

1. Formation of the N–H bond by addition

a. Preparation of hydrazo compounds from azo compounds

$(\mathrm{R{-}N{=}N{-}R'} \longrightarrow \mathrm{R{-}NH{-}NH{-}R'})$

Azo compounds are readily reduced to hydrazo compounds, *i.e.*, *N*,*N*′-disubstituted hydrazines. The simplest aromatic representative of the series, hydrazobenzene, is usually prepared by reducing nitrobenzene with zinc dust and alkali[1] or electrolytically,[2] passing through the azo stage. The following reducing agents, amongst others, are suitable for direct reduction of azobenzene to hydrazobenzene: zinc dust and alcoholic potassium hydroxide, aluminum amalgam,[3] iron in alkaline suspension, and diimine,[4] as well as electrochemical reduction of azobenzene in alkaline suspension.[5] Hydrazo compounds are also obtained in good yield by adding ethylmagnesium bromide to azo compounds and decomposing the adducts by water.[6]

Negative substituents in the ring facilitate the reduction. Azo compounds are resistant to reduction by lithium tetrahydridoaluminate or, after longer reaction therewith, are converted into the dihydro derivatives.[7]

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[1] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Walter de Gruyter & Co., Berlin, 35th ed, 1953, pp. (a) 158, (b) 162, (c) 168, (d) 235, (e) 241, (f) 250, (g) 273.

[2] E. Müller, "Elektrochemisches Praktikum," Verlag Theodor Steinkopf, Dresden and Leipzig, 1947, p. 248.

[3] H. Wislicenus, *J. Prakt. Chem.*, [ii], **54**, 65 (1896).

[4] E. J. Corey, W. W. Mock, and D. J. Pasto, *Tetrahedron Lett.*, **1961**, 347; S. Hünig, H. R. Müller, and W. Thier, *Tetrahedron Lett.*, **1961**, 353; E. E. Van Tamelen, R. S. Dewey, and R. J. Timmons, *J. Amer. Chem. Soc.*, **83**, 3725 (1961); E. Schmitz, R. Ohme, and G. Kozakiewicz, *Z. Anorg. Allg. Chem.*, **339**, 44 (1965); S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem. Int. Ed., Engl.*, **4**, 271 (1965).

[5] F. Darmstädter, Ger. Pat. 196,979; *Chem. Abstr.*, **2**, 2307 (1908).

[6] H. Franzen and W. Deibel, *Ber. Deut. Chem. Ges.*, **38**, 2716 (1905).

[7] F. Bohlmann, *Chem. Ber.*, **85**, 390 (1952).

The procedure for preparation of hydrazobenzene and other hydrazo compounds must be uninterrupted and must involve exclusion of air, as these compounds are autoxidizable and are dehydrogenated to azo compounds by atmospheric oxygen.

Ruggli and Hölzle[8] describe partial reduction of bisazo compounds by zinc dust in pyridine containing some glacial acetic acid. Sensitive azo compounds can be reduced under mild conditions by means of zinc dust and ammonia under nitrogen.[8] Nitro-azo compounds can be converted into hydrazo compounds without reduction of the nitro group by treating them in ammoniacal or alkaline suspension with hydrogen sulfide.

Aliphatic azo compounds can also be reduced to *N,N′*-dialkylhydrazines in good yield. Thiele[9] described the reduction of azomethane to 1,2-dimethylhydrazine by zinc dust in 8% sodium hydroxide solution at 0°; this reduction can also be effected by sodium amalgam.

b. Preparation of hydrazines from diazonium salts

$$(R{-}N_2X \longrightarrow R{-}NH{-}NH_2)$$

Reduction of arenediazonium salts to arylhydrazines is generally effected by alkali sulfites (Emil Fischer's method) or tin(II) chloride (Victor Meyer's method). The action of alkali sulfites on arenediazonium salts in neutral or alkaline solution gives diazosulfonates, $RN{=}NSO_3Na$, as primary products which are then reduced by zinc dust and acetic acid or by sulfurous acid; this converts them into salts of the arylhydrazinesulfonic acid, from which the sulfo group is removed when they are heated with dilute mineral acid. When ammonium sulfite is used as the reducing agent, the resulting arylhydrazinesulfonic acids can be isolated as their ammonium salts.[10]

Failure has repeatedly attended attempts to repeat the older procedures, and improvements have recently been proposed which may be useful also in analogous cases. It has been recommended[11] that the diazonium salt solution should be heated for several hours after treatment with sodium sulfite solution and acidification.

Tin(II) chloride has often been used for reduction of arenediazonium salts in acid solution, a procedure that usually gives the tin double salt of the arylhydrazine hydrochloride, these salts being readily decomposed by alkali. This process is simpler than the sulfite method and is very suitable for laboratory purposes; the reduction occurs at a low temperature (about 0°), but it fails with diazonium salts of the anthraquinone series, with *p*-nitrobenzenediazonium chloride, and with *o*-benzenetetrazonium dichloride. Victor Meyer exemplifies the use of tin(II) chloride by the reduction of benzenediazonium chloride to phenylhydrazine.[12]

1-Naphthylhydrazine:[13] 1-Naphthylamine (50 g) is finely ground under concentrated hydrochloric acid (50 g), then the mixture is treated with hydrochloric acid of *d* 1.1 (400 g) and, with good cooling, with the calculated amount of sodium nitrite. The resulting solution is

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[8] P. Ruggli and K. Hölzle, *Helv. Chim. Acta*, **26**, 814, 1190 (1943).

[9] J. Thiele, *Ber. Deut. Chem. Ges.*, **42**, 2578 (1909).

[10] W. Davies, *J. Chem. Soc.*, **121**, 715 (1922).

[11] G. H. Coleman, *Org. Syn.*, Coll. Vol. I, 442 (2nd edw., 1941).

[12] V. Meyer, *Ber. Deut. Chem. Ges.*, **16**, 2976 (1883).

[13] E. Fischer and M. T. Lecco, *Ann. Chem.*, **232**, 237 (1885).

filtered at once into a vigorously stirred solution of tin(II) chloride (250 g) in hydrochloric acid. The solution thus obtained is warmed until it is colorless, then cooled and filtered from the crystalline hydrochloride, which is decomposed with sodium hydroxide solution. The free 1-naphthylhydrazine is recrystallized from ether–alcohol and then from water, then having m.p. 116–117° (yield 66%).

p-Nitrophenylhydrazine:[14,10] *p*-Nitroaniline (20 g) is dissolved in concentrated hydrochloric acid (42 ml) and water (40 ml), poured on crushed ice (100 g), and diazotized, with cooling and stirring, by a solution of sodium nitrite (12 g) in water (12 ml). After being cooled in ice for 3 h, the diazonium salt solution is filtered from undissolved material and allowed to flow during 15 min into a vigorously stirred solution, at 0°, of anhydrous sodium sulfite (45 g) and sodium hydroxide (4 g) in water (100 ml). After a further 5 min the deep red solution is treated with concentrated hydrochloric acid (140 ml) and then set aside for 12 h. The crystalline *p*-nitrobenzenediazosulfonate that has then separated is filtered off and heated for 20 min with concentrated hydrochloric acid (40 ml) on the water-bath. After cooling the mixture of sodium chloride and *p*-nitrophenylhydrazinium chloride is collected and the latter is dissolved out of it in ethanol. The mixture is filtered and the alcohol is removed from the filtrate, giving the product (9–12 g) with m.p. 157° (dec.).

The following methods of reduction have also been recommended for conversion of arenediazonium salts into arylhydrazines: Electrolytic reduction of benzenediazonium chloride has been carried out,[15] giving a 100% yield of phenylhydrazinium chloride. Reduction with triphenylphosphine has been recommended[16] as a general method of preparing arylhydrazines from arenediazonium salts. Good results were also obtained by using sulfur dioxide as reductant,[17] and sodium dithionite in hydrochloric acid solution has also proved useful.[18]

Phenylhydrazine and its homologs are potent blood poisons that can lead to chronic poisoning. In many people phenylhydrazine causes skin excema.

c. Preparation of amines from nitriles

($RCN \rightarrow RCH_2NH_2$)

Reduction of nitriles is an important method of preparing amines. It is, however, not always easy to carry out in spite of the unsaturated character of the nitrile group; three methods are available: (i) catalytic reduction, (ii) reduction by metal hydrides, and (iii) reduction by sodium in an alcohol.

i, Catalytic reduction

Catalytic hydrogenation of nitriles to amines had at first little preparative importance since a mixture of primary, secondary, and tertiary amines was always formed. Only when methods were found of conducting the reaction so that primary amines became the preponderant product did the method

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[14] L. Reichel (Berlin), personal communication.

[15] P. Rüetschie and G. Trümpler, *Helv. Chim. Acta*, **36**, 1649 (1953).

[16] L. Horner and H. Hofmann, *Angew. Chem.*, **68**, 484 (1956).

[17] K. Pfannenstiel and J. Janecke, *Ber. Deut. Chem. Ges.*, **75**, 1096 (1942).

[18] E. Knecht and L. Thompson, *J. Soc. Dyers Colour.*, **36**, 217 (1920); L. Thompson, *J. Soc. Dyers Colour.*, **37**, 7 (1921).

achieve significance for the laboratory and industry.[19j,20e] The following catalysts have proved suitable: Raney nickel, Raney cobalt, platinum, palladium rhodium, and platinized nickel. Raney nickel, which is most commonly chosen, is used not only in ammoniacal or neutral solution, but also, with excellent results, for acylating hydrogenation in acetic anhydride containing anhydrous sodium acetate. Platinum and palladium have optimal properties in an acid medium, but rhodium can also be used for hydrogenations where ammonia is added to the medium.

The following methods have proved useful to control the direction of the reaction:

(a) Trapping of the amine product as salt. The nitrile is hydrogenated in alcoholic solution containing 3 moles of hydrochloric, sulfuric, or perchloric acid per mole, in a shaking autoclave under pressure in the presence of a palladium catalyst.

2-Pyridinemethylamine:[21] 2-Pyridinecarbonitrile (70 g) is hydrogenated in anhydrous ethanol (1300 ml) containing hydrogen chloride (26 g) and a 15% palladium–charcoal catalyst (20 g), the calculated amount of hydrogen (30 l) being absorbed in 6 h. The catalyst is filtered off and washed with water. The filtrate and washings are united, treated with an excess (100 ml) of 10N-hydrochloric acid, and freed from ethanol in a vacuum. A concentrated aqueous solution of sodium hydroxide (170 g) is added, with ice-cooling, to the residual aqueous solution which is then extracted six times with ether (300-ml portions). After drying and removal of the solvent 2-pyridinemethylamine distils at 86–87°/14 mm as a colorless, strongly basic liquid (45 g, 62%).

(b) Trapping of the amine product as amide.[22] When hydrogenated in the presence of acid anhydrides or esters, nitriles afford the derived amides in good yield. Noble-metal or (dehydrated) Raney catalysts are used. Hydrogenation is effected under pressure — about 3 atm and room temperature with a platinum catalyst, 100 atm and about 100° with Raney nickel.

D, L-Lysine dihydrochloride:[23] Diethyl α-(acetylamino)-α-(3-cyanopropyl)malonate (15 g) is dissolved in freshly distilled acetic anhydride (100 ml), platinum dioxide (0.5 g) is added, and hydrogenation carried out at an initial pressure of 3 atm. Absorption is complete in 3 h. The catalyst is removed, and the acetic anhydride is hydrolysed by cautious addition of water (25 ml). The *N,N*-diacetyllysine is then cleaved by boiling it for 18 h in acetic acid solution containing concentrated hydrochloric acid (*d* 1.19; 100 ml). Evaporation then affords D,L-lysine dihydrochloride (9 g, 77%), m.p. 175–180°, which, after dissolution in anhydrous ethanol and precipitation by ether, melts at 187–188°.

(c) Reduction in the presence of ammonia[19d,k] has found the widest use. It can be carried out at atmospheric pressure and room temperature or at higher pressure and room temperature or above. For work at atmospheric pressure a large amount of catalyst (Raney nickel or Raney cobalt) is used, always with a solvent, *e.g.*, water or ethanol. In work under pressure ammonia

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[19] Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, (a) Vol. 5, Part 3 (1962), pp. 31, 69; (b) Vol. 10, Part 3 (1957), p. 755; Vol. 11, Part 1 (1957), pp. (c) 341, (d) 348, (e) 360, (f) 399, (g) 500, (h) 533, (i) 536, (j) 545, (k) 557.

[20] F. Zymalkowski, "Katalytische Hydrierung im organisch-chemischen Laboratorium," F. Enke-Verlag, Stuttgart, 1965, pp. (a) 234, (b) 242, (c) 244, (d) 250, (e) 256), (f) 290, (g) 305, (h) 311.

[21] K. Winterfeld and G. Gierenz, *Chem. Ber.*, **92**, 240 (1959).

[22] W. H. Carothers and co-workers, *J. Amer. Chem. Soc.*, **49**, 2912 (1927).

[23] E. F. Degering and L. G. Boatright, *J. Amer. Chem. Soc.*, **72**, 5137 (1950).

can play the role of solvent, wholly or partially; the amount of ammonia needed varies from 1.2 moles (aromatic nitriles) to 5 moles (dinitriles of lower molecular weight) per nitrile group.

Albert and Magrath[24] give the preparation of *p*-(aminomethyl)benzoic acid from *p*-cyanobenzoic acid as example of the reduction of a nitrile in the presence of ammonia under atmospheric conditions (Raney nickel). Pressure hydrogenation in the presence of ammonia is carried out as follows:

Phenethylamine from benzyl cyanide:[25] A 2-l autoclave is charged with benzyl cyanide (1 kg; distilled over Raney nickel) and Raney nickel (one tablespoonful) and is then closed. Liquid ammonia (180 ml) is introduced and then hydrogen to a pressure of 140 atm. The autoclave is then heated at 120–130° and shaken for 1 h, after which it is cooled and the product is freed from catalyst by filtration and distilled in a vacuum, giving the amine (83 to 87%), b.p. 90–93°/15 mm.

Catalytic hydrogenation of nitriles is often accompanied by hydrogenolysis, *e.g.*, debenzylation; such side reactions can be avoided by use of rhodium–aluminum catalysts; these are applied in the presence of ammonia at room temperature and low pressures.[26]

ii, Reduction by metal hydrides[27a,g]

Nitriles can be converted into primary amines by lithium tetrahydridoaluminate or diborane. The products of such reactions, unlike those of catalytic hydrogenation, contain only small amounts of secondary and primary amines, so that these processes are particularly suitable for small batches in the laboratory. Alkali hydridoborates do not effect this reduction. 0.5 mole of lithium tetrahydridoaluminate is necessary for reduction of 1 mole of nitrile, but using an excess of reductant leads to better yields; a 1 : 1 ratio is generally applied. Amundsen and his coworkers[28] studied the optimal conditions for this reduction and describe reduction of heptyl cyanide as an example of a generally applicable procedure:

Octylamine:[28] A solution of heptyl cyanide (12.5 g, 0.10 mole) in ether (20 ml) is dropped slowly into one of lithium tetrahydridoaluminate (3.8 g, 0.12 mole) in anhydrous ethanol (200 ml) at 0° (ice-bath). Then, with continued cooling and vigorous stirring, are added successively water (4 ml), 20% sodium hydroxide solution (3 ml), and again water (14 ml). The ethereal solution is decanted from the white inorganic residue, the latter is washed with a little ether, the combined ethereal solutions are evaporated, and the residue is distilled in a vacuum, giving octylamine (11.5–11.9 g, 89–92%), b.p. 53°/6 mm.

iii, Reduction by sodium

Primary alkanenitriles can be reduced to the amines by sodium in alcohol. Nitrile groups attached to an aromatic ring or to a secondary carbon atom in α-position to a benzene ring (ArCHRCN) are not reduced by sodium,

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[24] A. Albert and D. Magrath, *J. Chem. Soc.*, **1944**, 678.

[25] J. C. Robinson Jr. and H. R. Snyder, *Org. Syn.*, Coll. Vol. III, 720 (1955).

[26] M. Freifelder, *J. Amer. Chem. Soc.*, **82**, 2386 (1960).

[27] A. Hajós, "Komplexe Hydride," VEB Deutscher Verlag der Wissenschaften, Berlin, 1966, pp. (a) 180, (b) 189, (c) 192, (d) 194, (e) 196, (f) 202, (g) 318.

[28] L. H. Amundsen and co-workers, *J. Amer. Chem. Soc.*, 73, 243 (1951).

since in these cases the nitrile group is usually split off ($RCN + H_2 \rightarrow RH + HCN$). The reduction is usually carried out with 1-butanol as solvent, and always with an excess of sodium, but using more than seven atoms of sodium per nitrile group does not increase the yield further; somewhat more than 3 moles of butanol suffice for complete dissolution of 1 mole of sodium; mechanical stirring during the reduction has been recommended. Suter and Moffett[29] describe the following procedure, which is suitable for many cases:

A solution of the nitrile (or oxime) (1 mole) in 1-butanol (2300 ml) is heated to boiling in a 5-l two-necked flask fitted with a wide condenser (2.5 × 100 cm), and sodium (161 g in 10–20-g portions) is then added during 20 min. When the reaction slackens, heating under reflux is continued until almost all the sodium is dissolved, then the solution is allowed to cool, water (1.5 l) is added, and the butanol and amine are distilled off (the distillate is tested for amine, and if necessary more water is added and distillation continued). The distillate is made weakly acidic and concentrated (to 300 ml), then water (500 ml) is again added and distillation is continued until no more butanol passes over. The resulting concentrated butanol-free solution of the amine hydrochloride is supersaturated with alkali, and the amine is separated (if necessary with addition of ether) and dried first with solid alkali and then with sodium, after which distillation affords the pure amine without forerun or subsequent fraction. (The reaction is said to fail if sodium containing 0.1–0.01 % of potassium is used.[30])

d. Preparation of secondary amines from Schiff bases

Schiff bases can usually be hydrogenated easily and in satisfactory yield. Schiff bases from aliphatic aldehydes and aliphatic or aromatic primary amines, as well as those from aromatic aldehydes and aromatic amines, are amenable to this reduction. Hydrogenation is carried out either catalytically (Raney nickel, Adams catalyst, palladium–charcoal, or rhodium–aluminum oxide) or, especially in the laboratory, by metal hydride complexes; for reviews of the latter see Houben–Weyl[19c] or Zymalkowski.[20f] In many cases the Schiff base is not isolated, the mixture of amine and carbonyl compound being hydrogenated at once; for example, *N*-methylaniline is obtained in 90% yield by hydrogenating a mixture of formaldehyde and aniline in presence of a nickel–kieselguhr catalyst.[19c,20f] If the aldehyde to be used is unstable or has too great a tendency to undergo aldol condensation, it is added gradually to a mixture of the primary amine, hydrogen, and catalyst. In special cases the amine may be first formed in the reaction solution; in place of the amine a compound is taken that is readily reduced to a primary amine, *e.g.*, a nitro or nitroso compound, oxime, or nitrile; cf. the Leukardt–Wallach reaction.

When noble-metal catalysts are used the secondary amine may reduce the activity of the catalyst, leading often to incomplete absorption of hydrogen. However, the activity of the catalyst is sustained in the presence of acid, which should be strong enough to provide a mixture with pH in the region 2.88–4.64.[31]

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[29] C. M. Suter and E. W. Moffett, *J. Amer. Chem. Soc.*, **56**, 487 (1934).

[30] A. N. Kost and A. D. Terent'iev, *Zh. Obshch. Khim.*, **17**, 105 (1947); *Chem. Abstr.*, **42**, 112 (1948).

[31] M. Freifelder, *J. Org. Chem.*, **26**, 1835 (1961).

Catalytic hydrogenation of the C=N double bond as component of a heteroaromatic ring generally requires more vigorous conditions.[32]

The following examples illustrate such catalytic reduction.

***N*-Methylbenzylamine:**[33] Distilled *N*-benzylidenemethylamine (83 g) in anhydrous ethanol (100 ml) containing Raney nickel (7 g) is shaken with hydrogen at room temperature and a pressure of 3 atm. Reduction is almost complete after 2 h. The product obtained by distillation through an efficient column has b.p. 184–186°/760 mm (60 g).

***N*-Alkylarylamines:**[34] An aromatic nitro compound (0.1 mole), an aldehyde (0.3 mole), and sodium acetate (2.0 g) are dissolved in ethanol (150 ml). Raney nickel (3–6 g) is added and hydrogenation is effected at an initial pressure of 3 atm. Hydrogenation is complete after 12–24 h. The catalyst is filtered off, the filtrate is acidified with hydrochloric acid, and the solvent is distilled off on a water-bath. The residue is made alkaline with sodium hydroxide solution and extracted with ether, and the secondary amine is isolated by distillation.

In this way were prepared ***N*-ethylaniline** (57–63%), ***N*-butylaniline** (94–96%), and ***N*-butyl-*p*-toluidine** (88%), etc.

Hydrogenation of Schiff bases by metal hydride complexes[27c] is a valuable laboratory procedure since selective reductions can be achieved. For example, *N*-benzylideneaniline can be hydrogenated by lithium tetrahydridoaluminate to *N*-benzylaniline without hydrogenolytic removal of the benzyl group.[35] Reduction of one mole of an azomethine to the secondary amine theoretically requires 0.25 mole of lithium tetrahydridoaluminate, but in practice 0.5–1.0 mole of the reductant is generally used. Suitable solvents are diethyl ether, dioxan, and tetrahydrofuran. Reduction of Schiff bases by sodium tetrahydridoborate is still simpler, and moreover nitro groups are not affected by this reagent. Billman and Diesing[36] give the following general directions:

Secondary amines from Schiff bases: A 2–10% methanolic solution of sodium tetrahydridoborate (100% excess) is dropped, with stirring, into a 5–10% methanolic solution of the Schiff base. The mixture is heated for 15 min under reflux, then cooled and treated with an equal volume of water, which precipitates the secondary amine produced. Thus were obtained, *inter alia*, ***N*-benzyl-*p*-nitroaniline** (90%), ***N*-(*p*-nitrobenzyl)aniline** (87%), and ***N*-benzylaniline** (97%).

e. Preparation of substituted hydrazines from hydrazones or azines

$$(\mathrm{RNH{-}N{=}CHR'} \longrightarrow \mathrm{RNH{-}NHCH_2R'})$$

$$(\mathrm{RCH{=}N{-}N{=}CHR'} \longrightarrow \mathrm{RCH_2NH{-}NHCH_2R'})$$

Hydrazones and azines can be reduced to *N,N'*-disubstituted hydrazines either catalytically or by metal hydride complexes.[27d] Sodium amalgam has also been applied successfully in a few cases to reduction of the C=N double bond of hydrazones.[37,38] In general, hydrazones and azines of ketones are reduced more easily than their aldehyde analogs.

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[32] F. Zymalkowski, "Katalytische Hydrierung im organisch-chemischen Laboratorium," F. Enke-Verlag, Stuttgart, 1965, p. 203.

[33] N. H. Cromwell and co-workers, *J. Amer. Chem. Soc.*, **65**, 312 (1943).

[34] W. S. Emerson and H. W. Mohrmann, *J. Amer. Chem. Soc.*, **62**, 69 (1940).

[35] R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).

[36] I. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).

[37] P. Jacobson, *Ann. Chem.*, **427**, 220 (1922).

[38] T. Curtius, *Ber. Deut. Chem., Ges.*, **33**, 2459 (1900).

(i) Catalytic hydrogenation: For catalytic hydrogenation platinum is the commonest catalyst, used in an acid medium, but palladium has also been applied.[39] Raney nickel and Raney cobalt cannot be used since they cause hydrogenolysis of the N–N bond. 1,2-Dibenzylhydrazine has been obtained in excellent yield by hydrogenation of benzaldehyde azine in ethanolic hydrochloric acid with a platinum catalyst;[40] 1,2-diisopropylhydrazine can be prepared under similar conditions.[41] *N'*-Benzyl- and *N'*-phenethyl-hydrazones of ketones are hydrogenated in glacial acetic acid in the presence of platinum catalysts at room temperature and atmospheric pressure.[42] 1-Acyl-2-alkylidene- or -arylalkylidene-hydrazines can be converted into the corresponding 1-acyl-2-alkyl- or -arylalkyl-hydrazines in 70–80% yield by hydrogenation with a platinum catalyst in glacial acetic acid at atmospheric pressure and room temperature.[43]

1-(*p*-Chlorobenzoyl)-2-isopropylhydrazine:[44] 1-*p*-(Chlorobenzoyl)-1-isopropylidenehydrazine (20 g) is suspended in 95% ethanol (250 ml), a 5% platinum–charcoal catalyst (1.5 g) is added, and the mixture is hydrogenated at 2 atm of hydrogen. The theoretical amount of hydrogen is absorbed in 1 h. The catalyst is filtered off and the solution is evaporated to dryness. When recrystallized from dilute ethanol the product (94.3%) has m.p. 135°.

(ii) Reduction with metal hydride complexes: Lithium tetrahydridoaluminate has been used for reduction of benzophenone azine,[45] but similar reduction of 1-acyl-2-alkylidenehydrazines leads either to the 1-acyl-2-alkylhydrazines[46] or, with reduction of the acyl group, to 1,2-dialkylhydrazines.[42]

Sodium tetrahydridoborate has proved particularly valuable for reduction of 2,2-bis-(2-chloroethyl)hydrazones of aliphatic ketones:[48]

A solution of sodium tetrahydridoborate (0.5 mole per mole of hydrazone) in a few ml of water and a little alcohol is dropped rapidly, with stirring, into a solution of a hydrazone (5 g) in ethanol (50 g) cooled to $-15°$. Stirring is continued at $-15°$ to $-10°$ for a further 2 h, then methanolic hydrochloric acid is added until the mixture is acidic. The solution is filtered from sodium chloride and evaporated, and the hydrochloride obtained is recrystallized from ethanol. Yields amount to 75–95%.

N,N'-Disubstituted hydrazines are stable only as their salts; the free bases are dehydrogenated to azo compounds even by atmospheric oxygen. For the preparation of pure 1,2-diisopropylhydrazine it has been proposed that the free base should be dried over sodium amalgam, then distilled in a stream of inert gas, and that the last traces of azo compound should be removed by passing a stream of pure dry nitrogen through the product.[49]

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[39] C. Simon, Ger. Pat. 951,503; *Chem. Abstr.*, **53**, 3060 (1959).

[40] H. H. Fox and J. P. Gibas, *J. Org. Chem.*, **20**, 67 (1955).

[41] H. L. Lochte and co-workers, *J. Amer. Chem. Soc.*, **43**, 2600 (1921).

[42] H. Röhnert, *Arch. Pharm.*, **296**, 296 (1963).

[43] H. Röhnert, *Z. Chem.*, **5**, 302 (1965).

[44] M. Freifelder and co-workers, *J. Org. Chem.*, **26**, 383 (1961).

[45] S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **77**, 2460 (1955).

[46] R. L. Hinman, *J. Amer. Chem. Soc.*, **79**, 414 (1957).

[47] L. Spialter and co-workers, *J. Org. Chem.*, **30**, 3278 (1965).

[48] W. Schulze and co-workers, *J. Prakt. Chem.*, [iv], **33**, 96 (1966).

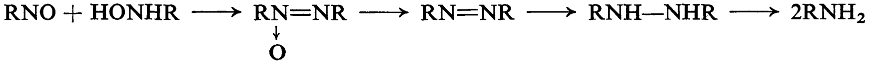
[49] H. L. Lochte and co-workers, *J. Amer. Chem. Soc.*, **44**, 2556 (1922).

2. Preparation of the N–H bond by exchange

a. Preparation of amines by reduction of nitro compounds

($RNO_2 \longrightarrow RNH_2$)

Reduction of a nitro to an amino group is one of the most important reactions in organic chemistry and can be effected in all cases and with very good yields.[19e] The detailed course of the reaction depends on the structure of the nitro compound and on the natures of the reducing agent and medium used. In every case the nitro group is first reduced to a nitroso group, independently of the constitution of the nitro compound and of the reaction conditions. If produced from a nitro group attached to a primary or secondary carbon atom, this nitroso group usually reacts further in the iso-form; like an oxime group it is reduced to an amino group by way of a hydroxyamino or an imino group; the intermediate isonitroso group causes a certain degree of sensitivity to acid hydrolysis, so that only a few of the reducing agents applicable to aromatic nitro compounds can be used also for aliphatic nitro compounds. If the nitroso group produced is attached to a tertiary carbon atom, then either it is converted directly into an amino group by way of the hydroxyamino stage or the amine is formed by condensation of the nitroso group with the hydroxyamino group that is also produced, resulting in azoxy and hydrazo intermediates:



$$RNO + HONHR \longrightarrow \underset{\underset{O}{\downarrow}}{RN{=}NR} \longrightarrow RN{=}NR \longrightarrow RNH{-}NHR \longrightarrow 2RNH_2$$

The former of the two reaction routes is followed preferentially in an acid medium, whereas reaction through the azoxy stage is favored in an alkaline medium; nitro-phenols and -anilines, however, are reduced directly under alkaline conditions. All the intermediates of both routes can be isolated on appropriate choice of conditions and, of course, all these intermediates can be reduced to amines, although in this connexion only the azo compounds produced by coupling are important.

(i) Methods of reduction. A large number of methods can be used for reduction of the nitro group, of which the following are among the more important: catalytic reduction (with platinum, palladium, copper, Raney nickel, or in industry with special mixed catalysts), reduction with iron, tin, tin(II) chloride, sodium dithionite, iron(II) hydroxide, metal hydrides, hydrogen sulfide and its derivatives, hydrazine, sulfites, zinc, or aluminum, and electrochemical reduction.

(ii) Choice of reducing agent. If the nitro group is the sole functional group in the molecule, the method required for working up the product becomes the main factor in choice of the reducing agent. Temperatures up to 100° almost always suffice; concentrations are chosen so that the strongly exothermic reaction can be controlled.

The choice of reducing agent is also largely free when other functional groups present in the nitro group are not easily affected by hydrolytic or reducing conditions, such as alkoxy, sulfonyl, carboxy, carboxamido, sulfo, and sulfonamido groups; if one of the last three of these other groups is present, then the properties of the end product determine whether reduction is to be carried out in an acid or an alkaline medium. Tin and tin(II) chloride may lead to cleavage of alkoxy groups and to decarboxylation and must therefore be used with caution. When labile groups are present the following points must be considered: the resistance of these groups to acid and alkaline hydrolysis and to reduction, as well as their liability to undergo other types of reaction with the reducing agent; it may be necessary to depart from the normal, usually optimal conditions, and in such cases the specialist literature should always be consulted since the present account of the reduction of nitro compounds can mention only selected general methods.

(iii) Catalytic reduction. As a continuous process in the liquid or the gas phase, catalytic reduction of nitro compounds finds its principal application in industry. Discontinuous processes are favored for laboratory work;[20a,50] these are effected at atmospheric pressure or above, but when a choice is available working under pressure (up to 50 atm) is preferable.

Industry uses mainly combinations of catalysts; laboratory processes employ mainly Raney nickel, platinum, platinum dioxide, or palladium, the last of these often on a carrier such as charcoal or barium sulfate. Since it is only the reduced surface of a platinum dioxide catalyst that is active and reduction of the oxide to the metal is checked by adsorption of nitro compounds (particularly if aromatic), it is advisable to reduce this catalyst in a preliminary operation. When platinum dioxide is used in solvents of differing acidities, the rate of reaction increases in the following order: neutral > alkaline > acid solution > glacial acetic acid.

A 'silk catalyst' of especial efficiency has been developed for hydrogenation of aromatic nitro compounds.[51] Boiling silk fibroin fibres with an aqueous solution of potassium tetrachloroplatinate affords a brown, hair-like silk–platinum chelate from which the actual black 'silk catalyst' is obtained by hydrogenation at 9 atm in the presence of 1% acetic acid. Its activity, calculated on platinum content, for hydrogenation of nitrobenzene to aniline, is 250 times that of platinum dioxide.

The reducing agent used is generally molecular hydrogen, but in special cases it may be chemically bound hydrogen, *e.g.*, that in hydrazine, formic acid, or unsaturated hydroaromatic compounds (cyclohexene). The solvent should be miscible with the water formed, because otherwise the catalyst aggregates to clumps and is inactivated; also it must be a sufficiently good solvent for the intermediate products as otherwise the latter may be precipitated and become the end products of the hydrogenation. Lower alcohols, glycol monoethers, tetrahydrofuran, dioxan, pyridine, dimethylformamide, and glacial acetic acid have all proved suitable as solvents; ethyl formate formylates the amines produced by the hydrogenation; ethyl acetate can be used as solvent in the aromatic series but readily acetylates primary aliphatic amines. Water is to be recommended for soluble salts, *e.g.*, those of nitro carboxylic acids. In all hydrogenations of nitro compounds a solvent of some kind must be used in order to retain control of the reaction.

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[50] P. H. Emmett, "Catalysis," Reinhold Publ. Corpn., New York, 1955, Vol. III, pp. 149–170.

[51] A. Akamatsu, Y. Izumi, and S. Akabori, *Bull. Chem. Soc. Japan*, **34**, 1067, 1302 (1961).

The conditions require firm control because catalytic reduction of nitro compounds is strongly exothermic; in the case of nitrobenzene 132 kcal/mole are liberated. If the heat is not removed fast enough the reaction becomes explosive.[52] This danger is best removed by using a small amount of catalyst at low pressures and temperatures. Dilutions given in the literature range from 1 : 1 to 1 : 20. Loss of control of the reaction is least to be feared for hydrogenation at atmospheric pressure, and the non-technical literature contains only few directions for high-pressure hydrogenation of nitro compounds in the laboratory; caution is essential when repeating any such experiments and in any case a small batch should be tried before carrying out such a reduction on a large scale.

5-Quinolinamine:[53] A suspension of 5-nitroquinoline (34.8 g) in anhydrous ethanol (200ml) is shaken with hydrogen in the presence of Adams catalyst (platinum dioxide) (0.4 g). The reaction is complete in about 2 h, there being a marked rise in temperature. The solution is clarified with charcoal, the solvent is removed in a vacuum, and the residue is distilled, giving a product (27 g, 95%) having b.p. 180–181°/7 mm and m.p. 100–107°. Recrystallization from ether gives material (23.5 g, 82%) of m.p. 108–110°.

8-Quinolinamine, b.p. 140.5–141.5°/7 mm, m.p. 64–65°, is obtained analogously in 96% yield.

***m*-Chloroaniline:**[54] A solution of *m*-chloronitrobenzene (30 g) in anhydrous ethanol (100 ml) containing Raney nickel (2.5 g) is reduced by hydrogen at room temperature and a pressure of 2–3 atm. The product is worked up by filtration and distillation, being obtained with b.p. 113°/18 mm in 98.5% yield (24 g). The tosyl derivative, recrystallized from ethanol, has m.p. 134°.

(iv) Catalytic hydrogenation with bound hydrogen. A particularly elegant method of reducing nitro compounds has recently assumed increasing importance. In this, the molecular hydrogen used in classical catalytic hydrogenation is replaced by compounds such as cyclohexene[20b,55] and hydrazine[55] from which hydrogen can be removed in the presence of metallic catalysts. The process occurs at atmospheric pressure and can be carried out in a beaker. An alcoholic solution of the nitro compound is treated with 3–4 times the theoretical amount of hydrazine hydrate, and a small quantity of metal catalyst is added; the reaction begins immediately, with evolution of heat and foaming, and it is completed by gentle warming until decomposition of the excess of hydrogen is finished (if necessary with addition of more catalyst). If the amine produced is sparingly soluble in cold alcohol it is unnecessary to destroy the excess of hydrazine; the procedure then is to mix the reactants in alcohol, await the reaction (5–60 min), filter off the catalyst, and cool the solution. Such hydrogenations are often very selective; for instance, when platinum or palladium catalysts are used with hydrazine, nitro groups are reduced whilst carbonyl groups and not specially activated C=C double bonds are unaffected.

The classical hydrogenation catalysts nickel, platinum, and palladium have proved useful in such reactions also; in special cases ruthenium[56] and iron[57]

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[52] C. F. H. Allen and J. V. Allen, *Org. Syn.*, Coll. Vol. III, 63 (1955).

[53] L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **62**, 1640 (1940).

[54] N. Löfgren, *Acta Chem. Scand.*, **9**, 1079 (1955).

[55] A. Fursch and co-workers, *Chem. Rev.*, **65**, 51 (1965).

[56] S. Pietra, *Ann. Chim.* (*Rome*), **26**, 699 (1956).

[57] S. Kubota and co-workers, *J. Pharm. Soc. Japan*, **76**, 801 (1956); *Chem. Abstr.*, **51**, 1086 (1957).

have been used. Solvents applicable are methanol, ethanol, dioxan, xylene, and ethylene glycol and its ethers.

The following amines, *inter alia*, have been prepared by use of nickel and hydrazine hydrate:[58] *p*-aminophenyl phenyl ether, 4-aminocinnamic acid, 3-aminobenzophenone, and bis-*p*-(aminophenyl) ether. Palladium and hydrazine hydrate were used successfully in reduction of 2-nitrofluorene.[59]

2-Aminoacetophenone:[60] Palladium black (50 mg) is added to a mixture of 2-nitroacetophenone (0.54 g), cyclohexene (5 ml; freshly distilled over sodium), and tetrahydrofuran (25 ml), and the mixture is heated under reflux for 17 h. The catalyst is then filtered off, the solution is evaporated, and the residue is dissolved in ether. The ethereal solution is dried over magnesium sulfate, and dry hydrogen chloride is led into it, affording 2-aminoacetophenone hydrochloride (0.5 g), m.p. 167°.

General procedure for reduction of nitro compounds with Raney nickel and hydrazine:[58] The nitro compound (1 g) is dissolved in ethanol (10 ml) and treated with a two- to three-fold molar amount of 100% hydrazine hydrate. The mixture is warmed on a water-bath, and a small amount of Raney nickel is added. Reaction is complete in 5–60 min, as can be recognized from the facts that gas evolution stops and the previously yellow solution becomes colorless. Then fresh catalyst is added and the mixture is boiled to destroy the excess of hydrazine. The catalyst is filtered off and the filtrate is boiled with charcoal, filtered again, and, after cooling, poured into cold water.

Reduction with iron in acid solution is used principally in industry. It requires only a very small amount of hydrochloric acid. The iron(III) chloride formed reacts with the excess of iron, forming iron(II) chloride, which takes over further reduction leading to separation of hydrated iron oxide. The product is a mixture of a small amount of amine hydrochloride with much free base, so that very little alkali is needed to liberate the amine, which makes the process very much cheaper. Also the formation of chlorinated products is much repressed.

General procedure:[19f] The nitro compound (1 mole) is heated on a water-bath to the boiling point with ethanol (500 ml) and concentrated hydrochloric acid (10 ml). Then iron filings (170 g per nitro group) are added in four portions at intervals of 5 min. The mixture should boil vigorously so as to prevent agglomeration of the iron. When all the iron has been added, the batch is boiled for a further 2 h. The method of working up depends on the nature of the amine.

Steam-volatile amines are distilled in steam after addition of sodium carbonate (10 g), the alcohol that passes over first being collected separately from the later turbid distillate. Alternatively, the calculated amount of sodium hydroxide is added, the mixture is filtered hot, and the iron paste is washed with ethanol; most of the alcohol is then distilled off and the amine is precipitated from the residue as hydrochloride by means of concentrated hydrochloric acid. If the hydrochloride is too soluble for this procedure, most of the alcohol is distilled off, the remaining solution is saturated with hydrogen chloride, and the product is precipitated by ether.

In spite of some disadvantages, reduction with tin has found widespread use for preparative purposes, as has reduction by tin(II) chloride which is superior to use of the metal. Both reagents are nowadays being more and more replaced by modern catalytic methods.

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[58] D. Balcom and A. Furst, *J. Amer. Chem. Soc.*, **75**, 4334 (1953).

[59] P. M. G. Bavin, *Org. Syn.*, **40**, 5 (1960).

[60] E. A. Braude and co-workers, *J. Chem. Soc.*, **1954**, 3578, 3586, 3595; cf. Y. Ahmad and D. H. Hey, *J. Chem. Soc.*, **1954**, 4516.

When these reducing agents are used, various side reactions are occasionally observed, these being partly due to the strongly acid medium required; they include removal of halogen, sulfo, or carboxy groups in the *ortho-* or *para-*position to the nitro group, formation of halogenated derivatives of the amine product, and hydrolytic conversion of the amino into a hydroxyl group.

When these reducing agents are used, tin double salts of the amine hydrochlorides are usually obtained, from which the amines are liberated by alkali hydroxide or hydrogen sulfide.[61]

(v) Alkaline reduction by sulfur derivatives. Alcoholic ammonium sulfide solutions are often used for converting nitro into amino groups under alkaline conditions. When hydrogen sulfide is led into an alcoholic ammoniacal solution of the nitro compound, the reaction proceeds smoothly and quantitatively at a moderate temperature [*e.g.*, with (*p*-nitrophenyl)acetic acid[62]), but in some cases working under pressure cannot be avoided. Willstätter[63] observed that reduction in the cold often stops at the hydroxylamine stage.

Sodium sulfide and sodium hydrogen sulfide have also been used as reducing agents. If in the *ortho*-position to a nitro group there is a second nitro group or a halogen atom, sulfur-containing products may be formed by replacement of the *ortho*-substituent. In special cases disodium disulfide is effective; it reacts as follows:

$$RNO_2 + H_2O + Na_2S_2 \longrightarrow RNH_2 + Na_2S_2O_3$$

Since no sulfur is formed, the amine is easily separable from the thiosulfate solution.

Hydrogen sulfide derivatives can also be used for partial reduction of polynitro compounds.

Sometimes a combination of sodium hydrogen carbonate with sodium sulfide gives better yields owing to formation of sodium hydrogen sulfide which is considered to be the effective reducing agent. Aqueous methanol is prefererd to aqueous ethanol.[64] 1,5-Dinitronaphthalene is reduced to 5-nitro-1-naphthylamine by aqueous sodium sulfide solution.[65]

Aniline:[66] Sulfur (32 g) is dissolved in a stirred, boiling solution of sodium sulfide (78 g) in water (360 ml) [or sodium sulfide nonahydrate (240 g) in water (200 ml)], and then nitrobenzene (123 g) is run in. The reaction is complete (pale aqueous liquid) after about 12 hours' boiling and stirring. The mixture is set aside for a short time, then the aniline is separated from the aqueous phase and purified by drying and distillation.

***m*-Nitroaniline:**[67] A solution of *m*-dinitrobenzene (10 g) in methanol (74 g) is mixed with one of sodium hydrogen sulfide (5.5 g; calc. 5 g) in aqueous methanol (150 ml) and heated under reflux for 25 min. Then part (150 ml) of the methanol is distilled off and the residual solution is poured into ice-water (500 ml). This gives about 90% (8.3 g) of *m*-nitroaniline.

Reduction of nitro compounds by sodium dithionite:

$$RNO_2 + 3Na_2S_2O_4 + 4H_2O \longrightarrow RNH_2 + 6NaHSO_3$$

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[61] R. B. Woodward, *Org. Syn.*, Coll. Vol. III, 453 (1955).

[62] H. P. Clarke and J. H. Bishop, *Org. Syn.*, Coll. Vol. I, 52 (2nd edn., 1941).

[63] R. Willstätter, *Ber. Deut. Chem. Ges.*, **41**, 1936 (1908).

[64] H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, **1945**, 663, 794.

[65] H. H. Hodgson and H. S. Turner, *J. Chem. Soc.*, **1943**, 318.

[66] J. Kunz, Ger. Pat. 144,809; *Friedländer*, **7**, 57.

[67] H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, **1949**, 1316.

is carried out in a neutral or weakly alkaline medium; it usually proceeds smoothly, but side reactions (formation of amino sulfonic acids) sometimes intrude. A favorable weakly basic medium is produced by tertiary aromatic or heterocyclic bases. The solvent may be ethanol, acetone, water, or formamide. The reducing agent can be used in excess (120% of the theoretical amount).

2-Amino-*p*-cresol (OH = 1):[68] A solution of 2-nitro-*p*-cresol (10 g) in water (200 ml) and concentrated ammonia solution (50 ml) is added slowly to one of sodium dithionite (75 g) in water (300 ml). A white, crystalline but flocculent precipitate appears in 5 min, the red color of the solution changing to pale yellow. The whole mixture (unfiltered) is extracted with ether. The extract is dried, treated with charcoal, and evaporated, yielding yellowish-brown crystals (6.8 g, 81%), m.p. 134–135°.

Other methods of reduction are said to fail. The above method leads to partial reduction of 2,4-dinitrophenol, to 2-amino-4-nitrophenol, in good yield.[69]

(vi) Reduction by other methods. Reduction of nitro compounds by iron(II) hydroxide is more rarely used; but it has considerable advantages in some special cases. It finds use when a molecule contains, next to a nitro group, other groups than are reducible or are hydrolysed by acids. Since the reduction is effected in an alkaline medium it is suitable also for reduction of alkali-soluble nitro compounds.

Hydrocarbon nitro derivatives can also be reduced by this reagent: Allen[70] obtained up to 100% of aniline from nitrobenzene. Bimolecular intermediates are rarely obtained in spite of the alkalinity of the reaction medium. The proportions of reactants used are in accord with the reaction:

$$RNO_2 + 6Fe(OH)_2 + 4H_2O \longrightarrow RNH_2 + 6Fe(OH)_3$$

A general prescription has been given by Jakobs and Heidelberger.[71]

A series of nitro compounds has been reduced in good yield by warming them with a powdered copper–magnesium alloy (Arndt alloy) in the presence of water and a little ammonium chloride,[72] examples being *p*-nitroaniline (93%), bis-(*p*-nitrophenyl) sulfone (70%), and 1-nitroanthraquinone (70%).

Metal hydrides such as lithium tetrahydridoaluminate have been used for reduction of aliphatic and alicyclic nitro to amino compounds; in general, 2 moles of this aluminate are applied per mole of nitro compound. However, aromatic nitro compounds are usually reduced thereby only to the azo stage. Indeed, apart from special cases, the reduction of nitro compounds by lithium tetrahydridoaluminate has only slight practical importance.[27e] Sodium tetrahydridoborate had been recommended for reduction of *o*-nitrophenol in the presence of a palladium–charcoal catalyst.[73]

(vii) Reduction of aliphatic nitro compounds to amines. This has recently assumed increasing importance, but the choice of conditions is strictly limited because of the great reactivity of the aliphatic nitro group. In an alkaline medium condensation may occur, and in a strongly acid medium primary nitro groups may be removed by hydrolysis.

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[68] H. M. Woodburn and C. F. Stuntz, *J. Amer. Chem. Soc.*, **72**, 1361 (1950).

[69] W. W. Hartmann and H. L. Silloway, *Org. Syn.*, Coll. Vol. III, 82 (1955).

[70] H. C. Allen, *J. Phys. Chem.*, **16**, 131 (1912).

[71] W. A. Jakobs and M. Heidelberger, *J. Amer. Chem. Soc.*, **39**, 1435 (1917).

[72] G. Faust, *J. Prakt. Chem.*, [iv], **6**, 14 (1958).

[73] T. Neilson and co-workers, *J. Chem. Soc.*, **1962**, 371.

Oximes are formed as intermediates in this reduction[74] and this may be the reason why secondary amines can also be obtained. In an acid medium oximes may be hydrolysed to carbonyl compounds, and aldoximes may undergo the Beckmann rearrangement.

α-Nitro alcohols may be formed from carbonyl compounds and nitroalkanes under catalysis by bases and decompose into these compounds by the reverse reaction, so that cleavage often occurs during their hydrogenation owing to the base produced;[20c] the solution must therefore be prevented from becoming basic during a hydrogenation. The following methods have been used for catalytic hydrogenation of aliphatic nitro compounds to amines: nitroalkanes have been hydrogenated with Raney nickel[75] or platinum oxide;[76] 2-nitro-1,3-propanediol with palladium–barium sulfate in oxalic acid solution;[77] α-nitrostyrene with a palladium catalyst in glacial acetic and sulfuric acid, the C=C double bond being also reduced.[78] Aliphatic nitro groups can also be reduced to amino groups by iron in glacial acetic or hydrochloric acid,[75] by lithium tetrahydridoaluminate,[79] or by sodium ethoxytrihydridoaluminate.[80] Nitrourea has been reduced electrolytically to semicarbazide.[81]

b. Reduction of nitro compounds and oximes to hydroxylamines

$$(\mathrm{RNO_2} \longrightarrow \mathrm{RNHOH})$$

$$(\mathrm{RR'C{=}NOH} \longrightarrow \mathrm{RR'CHNHOH})$$

Under suitable conditions it is possible to isolate the *N*-substituted hydroxylamines that are formed as intermediates in the reduction of nitro compounds. For this purpose it is essential in the reduction of aromatic nitro compounds to work with neutral or nearly neutral solutions; suitable reducing agents are hydrogen and platinum oxide catalysts in glacial acetic acid,[82,83] zinc dust in ammonium chloride solution,[84] aluminum amalgam,[85] and ammonium sulfide.[86] Aliphatic nitro compounds may be reduced as their alkali salts (nitronates) by diborane in tetrahydrofuran, then giving *N*-alkylhydroxylamines;[87] for instance, *N*-cyclohexylhydroxylamine is thus obtained from nitrocyclohexane in 53% yield. However, aliphatic nitro compounds are converted into *N*-alkylhydroxylamines more simply by catalytic hydrogenation in the presence of palladium–barium sulfate; unlike aromatic nitro compounds, aliphatic nitro compounds require an acid medium for reduction to hydroxylamines; an oxalic acid medium has proved the most suitable.

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[74] C. Grundmann, *Angew. Chem.*, **62**, 558 (1950).
[75] K. I. Johnson and E. F. Degering, *J. Amer. Chem. Soc.*, **61**, 3194 (1939).
[76] D. C. Iffland and F. A. Cassis, *J. Amer. Chem. Soc.*, **74**, 6284 (1952).
[77] E. Schmidt and R. Wilkendorf, *Ber. Deut. Chem. Ges.*, **52**, 389 (1919).
[78] O. Schales, *Ber. Deut. Chem. Ges.*, **68**, 1579 (1935).
[79] A. Dornow and F. Boberg, *Ann. Chem.*, **578**, 94 (1952).
[80] G. Hesse and R. Schrödel, *Ann. Chem.*, **607**, 24 (1957).
[81] A. W. Ingersoll and L. J. Bircher, *Org. Syn.*, Coll. Vol. I, 485 (2nd edn., 1941).
[82] L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **62**, 1643 (1940).
[83] K. Michel and M. Matter, *Helv. Chim. Acta*, **44**, 2204 (1961).
[84] C. S. Marvel and O. Kamm, *J. Amer. Chem. Soc.*, **41**, 279 (1919).
[85] V. Migridichian, *Org. Syn.*, Coll. Vol. I, 490 (1957).
[86] O. Neunhoeffer and H. G. Liebich, *Ber. Deut. Chem. Ges.*, **71**, 2248 (1938).
[87] H. Feuer and co-workers, *J. Org. Chem.*, **30**, 2880 (1965).

***N*-Methylhydroxylamine oxalate:**[88] Nitromethane (40 g) and a palladium–barium sulfate catalyst[89] (6.5 g) are added to a solution of oxalic acid dihydrate (42 g) in water (500 ml), and the mixture is reduced at room temperature in a 1-l autoclave with an initial hydrogen pressure of 100 atm. Absorption of hydrogen ceases after about 4 h. The catalyst is filtered off and the filtrate is evaporated to dryness in a vacuum, giving *N*-methylhydroxylamine oxalate (96%), m.p. 158°.

When a mixed catalyst containing silver is used, the hydrogenation of nitroalkanes can be conducted so that reduction stops at the oxime stage; this has been studied in detail for nitrocyclohexane.[74]

Oximes of aliphatic aldehydes and ketones are hydrogenated to *N*-alkylhydroxylamines in the presence of platinum black in aqueous-alcoholic hydrochloric acid;[90] also a mixture of the ketone and hydroxylamine hydrochloride may be hydrogenated.[91] However, with arylalkyl and aryl ketones the latter method yields amines.

A reducing agent that converts all types of oximes equally into *N*-monosubstituted hydroxylamines is diborane;[92] for example, diborane reduces cyclohexanone oxime to *N*-cyclohexylhydroxylamine in 82% yield and similarly affords *N*-heptyl- (81%), *N*-(*p*-nitrobenzyl-(68%), and *N*(-α-methylbenzyl)-hydroxylamine (55%).

c. Preparation of amines by reduction of oximes and hydroxylamines

$(R{=}NOH \longrightarrow RNH_2;\ RNHOH \longrightarrow RNH_2)$

The hydroxyimino group attached to carbon (C=NOH) may be converted into an amino group by way of the intermediate hydroxyamino or imino group. The reduction of oximes can be conducted so as to yield (1) a synthesis of amines from carbonyl compounds, (2) introduction of amino groups into a compound containing active methylene groups (by way of the isonitroso compounds obtained by nitrosation), or (3) production of amines from the adducts of nitrogen oxides or nitrosyl chloride to olefins.

The following reagents are suitable for reduction of the hydroxyimino group: catalytically activated hydrogen (noble-metal catalysts alone or on a carrier, also nickel and copper catalysts); hydrazine in combination with a metal catalyst; lithium tetrahydridoaluminate. The following methods have been used for special cases: Sodium amalgam in acid has been applied to the reduction of oximes of benzaldehyde, benzophenone, camphor, benzoin, and isobutyraldehyde.[93] Lithium amalgam reduces oximes to amines but does not attack nitriles.[94] Oximes can also be reduced by sodium in alcohol; the method given for preparation of heptylamine may be considered a general technique.[95] For reduction of an oxime group attached to a four-membered ring it has proved valuable to add sodium very rapidly to a boiling alcoholic solution.[96]

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[88] E. Schmidt and co-workers, *Ber. Deut. Chem. Ges.*, **58**, 2430 (1925).

[89] E. Schmidt, *Ber. Deut. Chem. Ges.*, **52**, 409 (1919).

[90] G. Vavon and co-workers, *Bull. Soc. Chim. France*, **43**, 231 (1928).

[91] G. Vavon and co-workers, *Bull. Soc., Chim. France*, **37**, 301 (1925).

[92] H. Feuer and co-workers, *J. Org. Chem.*, **30**, 2877 (1965).

[93] H. Goldschmidt, *Ber. Deut. Chem. Ges.*, **19**, 3232 (1896); **20**, 492 (1897).

[94] T. Kametani and J. Nomura, *J. Pharm. Soc. Japan*, **74**, 1037 (1954).

[95] W. H. Lycan and co-workers, *Org. Syn.*, Coll. Vol. II, **318** (1950).

[96] V. Prelog and co-workers, *Helv. Chim. Acta*, **28**, 178, 576 (1945).

Reduction of the hydroxyimino group with acetylation of the resulting amino group can be effected by zinc dust in the presence of acetic acid and acetic anhydride; diethyl (acetylamino)malonate, which is important for amino acid syntheses, has been prepared in this way.[97] Zinc dust reduces oximes of diaryl and arylalkyl ketones better in concentrated ammoniacal than in acid solution, giving the amines as very pure free bases whilst hardly any higher alkylated product is formed.[98] Aminoacetone,[99] diaminoacetone,[100] and 2-amino-3-pentanone[99] have been obtained by reducing oximes with tin or tin(II) chloride in alcoholic hydrochloric acid solution. In individual cases oximes have been reduced by sodium dithionite or aluminum amalgam.[19g] Further, the patent literature contains examples of electrolytic reduction of oximes.[19g]

Catalytic hydrogenation of oximes to amines requires conditions resembling those for catalytic hydrogenation of nitro compounds and nitriles.[20d] The catalyst should be as active as possible, *e.g.*, Raney nickel[101] (if necessary, platinized), platinum oxide,[102] palladium–charcoal,[103] palladium–barium sulfate,[104] or rhodium–alumina.[105] This rhodium catalyst also serves for reduction of an amidoxime to the amidine.[106] Hydrogenation may be effected under pressure, but the temperature should be kept as low as possible to avoid formation of secondary amines.

The following conditions have proved their worth by avoidance of side reactions: a strongly ammoniacal medium; an acid medium (alcoholic hydrochloric acid, or if necessary acetic acid); acylating conditions (presence of acetic anhydride or formic esters as solvent); high dilution.

Diethyl (formylamino)malonate:[107] A solution of diethyl (hydroxyimino)malonate (5.7 g) in ethyl formate (24 ml) is hydrogenated over palladium–charcoal (0.5 g) at 105 atm. The catalyst is filtered off, the solvent is evaporated, and the residue is distilled in a vacuum. Diethyl (formylamino)malonate is obtained (5.5 g, 90%) as an oil, b.p. 130–140°/1.5 mm, which rapidly crystallizes (m.p. 50–52°).

It should be noted that aldoximes may undergo the Beckmann rearrangement when Raney nickel is used for their hydrogenation.[108]

Hydrogenation with hydrazine and Raney nickel is smooth only for ketoximes;[109] yields are often comparable with those obtained by reduction with lithium tetrahydridoaluminate. The oxime and 64% hydrazine hydrate are dissolved in alcohol, and the reaction is started by addition of a little Raney

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[97] A. J. Zambito and E. E. Howe, *Org. Syn.*, **40**, 21 (1960).

[98] J. C. Jochims, *Monatsh. Chem.*, **94**, 677 (1963).

[99] S. Gabriel and G. Pinkus, *Ber. Deut. Chem. Ges.*, **26**, 2197 (1893).

[100] K. K. Koessler and M. T. Hanke, *J. Amer. Chem. Soc.*, **40**, 1716 (1918).

[101] D. C. Iffland and Teh-Fu-Yen, *J. Amer. Chem. Soc.*, **76**, 4180 (1954).

[102] A. Dornow and K. Bruncken, *Chem. Ber.*, **83**, 189 (1950); M. Fields and co-workers, *J. Amer. Chem. Soc.*, **73**, 1000 (1951).

[103] G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1885 (1954).

[104] F. Zymalkowski and H. J. Rimek, *Arch. Pharm.*, **294**, 581 (1961).

[105] M. Freifelder and co-workers, *J. Org. Chem.*, **27**, 2209 (1962).

[106] R. P. Mull and co-workers, *J. Med. Pharm. Chem.*, **5**, 651 (1962).

[107] A. Ek and B. Witkop, *J. Amer. Chem. Soc.*, **76**, 5579 (1954).

[108] R. Paul, *Bull. Soc. Chim. France*, [v], **4**, 1115 (1937); A. G. Caldwell and E.R.H. Jones, *J. Chem. Soc.*, **1946**, 599.

[109] D. Lloyd and co-workers, *J. Chem. Soc.*, **1965**, 822.

nickel at room temperature; when the reaction ceases, the excess of hydrazine is destroyed by warming, and gaseous hydrogen chloride is led in so that the amine produced is isolated as hydrochloride. Oximes reduced in this way include fluorenone oxime (94% yield), menthone oxime (90%), cyclohexanone oxime (65%), and acetone oxime (36%). Aldoximes do not react under these conditions.

Primary amines can be prepared from aldehydes and ketones by reducing their oximes with lithium tetrahydridoaluminate.[27b,40a] One mole of oxime requires 0.75 mole of the aluminate, and the presence of the active hydrogen atom leads to evolution of 1 mole of gaseous hydrogen; however, the best results are obtained by using 2.2–4.0 moles of aluminate per mole of oxime.[111] Ethers such as tetrahydrofuran can be used as solvent. This method is used especially when mild conditions are required owing to presence of labile groups or when carboxyl groups are to be reduced simultaneously. Beckmann rearrangement has, however, been observed during reduction of acetophenone and propiophenone oxime by lithium tetrahydridoaluminate.[112] Oximes may also be reduced to amines by diborane after preliminary *O*-acetylation.[113]

General procedure:[114] 80% lithium tetrahydridoaluminate (15 g, 0,25 mole) is stirred with anhydrous ether (400 ml) and to the resulting slurry is added a solution of an oxime (0.2 mole) in anhydrous ether (100–200 ml), dropwise with vigorous stirring. After this addition the mixture is stirred on the water-bath for a further 3–4 h, then it is cooled and treated with water and dilute sulfuric acid until the aqueous layer reacts distinctly acid. The ethereal layer is separated, and the aqueous solution is first shaken several times with ether to remove neutral ingredients and then treated with water and sodium hydroxide solution, with cooling, until it reacts strongly alkaline and is only slightly turbid. This mixture is extracted with ether, this ethereal extract is dried, and the amine is obtained from it by distillation. Yields are 50–70%.

Reduction of unsaturated oximes without effect on the C=C double bond is best carried out by sodium amalgam at not too high a temperature. Quinone dioximes are best converted into the amines by use of sodium sulfide in boiling alcohol.[115] Amino carboxylic acids are prepared from the corresponding oxo carboxylic acid oximes, catalytic reduction being in these cases the method of choice.

Hydroxyamino groups are reduced to amino groups, in principle, by the same methods as are used for the oxime group. Aromatic hydroxylamines, which can rearrange to aminophenols in an acid medium, are advantageously reduced by aluminum amalgam.[116]

d. Reduction of nitroso compounds to amines

$$(\mathrm{RNO} \longrightarrow \mathrm{RNH_2})$$

Since the nitroso group is the first stage in reduction of a nitro group, the conditions under which the former is reduced to an amino group differ, as might be expected, little from those used for reduction of nitro compounds.

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[110] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York–London, 1956, pp. (a) 751, (b) 761–762.

[111] D. R. Smith and co-workers, *J. Org. Chem.*, **17**, 294 (1952).

[112] R. E. Lyle and H. J. Proscianec, *J. Org. Chem.*, **20**, 1757 (1955).

[113] A. Hassner and P. Catsonlacos, *Chem. Commun.*, **1967**, 590.

[114] E. Larson, *Svenks Kem. Tidskr.*, **61**, 242 (1949).

[115] P. D. Bartlett and co-workers, *J. Amer. Chem. Soc.*, **72**, 1003 (1950).

[116] H. Wislicenus, *Ber. Deut. Chem. Ges.*, **29**, 495 (1896).

Primary and secondary aliphatic nitroso compounds are usually present as dimers which can be converted into isonitroso compounds thermally or by irradiation.[119] Thus aliphatic nitroso compounds are reduced in practice under the conditions described above for oximes.

In the aromatic series practical importance is restricted to reduction of the compounds readily obtained by nitrosation of phenols[118] and tertiary amines. They are reduced analogously to nitro compounds, in either acid or alkaline solution. For work in acid solution catalytic hydrogenation is generally used (palladium or Raney nickel); in an alkaline medium sodium dithionite gives good yields.[118,119] In isolated cases recourse has been had to reduction by ammonium hydrogen sulfide,[120] iron, tin,[121] zinc,[122] and hydrogen iodide.[123] Reducing *N*,*N*-dimethyl-*p*-nitrosoaniline by tin(II) chloride in acid solution gives *N*,*N*-dimethyl-*p*-phenylenediamine,[1g] but 4,4′-bis(dimethylamino)azobenzene is obtained when lithium tetrahydridoaluminate is used.[110b]

e. Reduction of nitrosamines to asymmetrically disubstituted hydrazines

Asymmetrically disubstituted hydrazines can be obtained by reduction of nitrosamines. Singly substituted hydrazines can be prepared, in principle, analogously through the intermediacy of alkylnitrosoureas. These reductions are usually carried out by zinc in acetic acid; if mineral acid is used the nitroso group is split off. The method goes back to work by Emil Fischer.[124]

1,2-Diphenylhydrazine: *N*-Nitrosodiphenylamine (50 g) is dissolved in ethanol (250 ml), and zinc dust (75 g) is added, followed, gradually, with good cooling and continuous shaking, by glacial acetic acid until heat is no longer evolved and a filtered sample is no longer colored bluish-green by concentrated hydrochloric acid. The hot mixture is filtered from zinc dust, concentrated to a quarter of its volume, diluted with an equal volume of water, and treated, with cooling and stirring, with a plentiful excess of fuming hydrochloric acid. As the solution cools, a mixture of 1,2-diphenylhydrazine hydrochloride and diphenylamine hydrochloride separates as blue needles. The crude product is treated with hot, very dilute hydrochloric acid, and the oily diphenylamine produced by hydrolysis is filtered off. The diphenylhydrazine hydrochloride is reprecipitated from the filtrate by adding fuming hydrochloric acid. If necessary these two operations must be repeated several times. A final crystallization from ethanol gives the diphenylhydrazine hydrochloride as thin, colourless needles. The free base is obtained as a pale yellow oil by treating the hydrochloride with an excess of sodium hydroxide solution.

1,2-Dimethylhydrazine[125] and 1-methyl-2-phenylhydrazine[126] are obtained similarly. A preparation of ethylhydrazine by way of 1,3-diethyl-1-nitrourea is due to Fischer.[127] Ethyl 3-(ethylnitrosoamino)propionates can also be reduced

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[117] E. Müller and co-workers, *Chem. Ber.*, **88**, 165, 1891 (1955).
[118] A. E. Albert, *J. Amer. Chem. Soc.*, **76**, 4985 (1954).
[119] J. B. Conant and B. B. Corson, *Org. Syn.*, Coll. Vol. II, 33 (1943).
[120] W. A. Jakobs and M. Heidelberger, *J. Amer. Chem. Soc.*, **39**, 2188 (1917).
[121] J. Lindner, *Monatsh. Chem.*, **42**, 421 (1921).
[122] W. Pfleiderer and G. Nübel, *Ann. Chem.*, **631**, 168 (1960).
[123] J. H. Boyer and W. Schoen, *J. Amer. Chem. Soc.*, **78**, 423 (1954).
[124] E. Fischer, *Ann. Chem.*, **190**, 175 (1878).
[125] H. H. Hatt, *Org. Syn.*, Coll. Vol. II, 211 (1943).
[126] W. W. Hartmann and L. J. Roll, *Org. Syn.*, Coll. Vol. II, 418 (1943).
[127] E. Fischer, *Ann. Chem.*, **199**, 287 (1879).

in good yields by zinc and acetic acid, the resulting hydrazines cyclizing to 1-alkyl-3-pyrazolidones under the reaction conditions.[128]

Reducing nitrosamines by one mole of lithium tetrahydridoaluminate per mole of nitrosamine in ether or tetrahydrofuran[27f,129,130] has led to, *e.g.*, 1-methyl-1-phenylhydrazine (77%), 1,1-dicyclohexylhydrazine (48%), and 1-aminopiperidine (75%), but if too great an excess of the aluminate is used the N–N bond may be cleaved and to avoid this it is recommended that the aluminate be added gradually to the nitrosamine.[129]

Nitrosamines can also be reduced electrolytically. 1-Deoxy-1-(methylnitrosoamino) sugar alcohols in hydrochloric acid solution are reduced to 1-methyl-1-(pentahydroxyhexyl)hydrazines in very good yield at a stirred mercury cathode of large surface area.[131] Reduction by this method does not require addition of substances that are later hard to separate; about 8 hours are required for reduction of 50 mmoles at constant potential.

Catalytic hydrogenation of nitrosamines to *N*,*N*-disubstituted hydrazines is effected in water or aqueous alcohol with 10% palladium–charcoal, 10% platinum–charcoal, or 5% rhodium–charcoal as catalyst,[132] in the presence of a salt (*e.g.*, calcium chloride, ammonium acetate, or lithium chloride) at temperatures between 25° and 60°; for example, 0.2 mole of 4-nitrosomorpholine in a solution of 30 g of calcium chloride in 150 ml of water is stirred with 2 g of 10% palladium–charcoal under a hydrogen pressure of 3–4 atm for 22 hours at 60°, thereby affording an 82.7% yield of 4-aminomorpholine.

By another procedure palladium–charcoal catalysts are used with iron(II) sulfate.[133] Use of Raney nickel catalysts generally leads to hydrogenolysis of the N–N bond, but hydrogenation of nitrosamines with Raney nickel is nevertheless possible if the nitrosamine is stirred for an hour with the catalyst at atmospheric pressure and the hydrogen is admitted later.[134]

Sodium amalgam,[135] aluminum in weakly alkaline aqueous suspension,[136] and sodium in alcohol or liquid ammonia[130] have also been used for reduction of nitrosamines.

f. Reduction of azo compounds to amines

Reduction of azo compounds to amines, with fission of the N=N double bond, assumes practical importance because so many azo compounds are readily accessible, even on an industrial scale, by coupling of diazonium salts with reactive molecules. In this way a large number of primary amines can be obtained free from isomers, which is not always easy to achieve by other

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[128] H. Dorn and co-workers, *Chem. Ber.*, **98**, 3377 (1965).

[129] C. Hanna and F. W. Schueler, *J. Amer. Chem. Soc.*, **74**, 3693 (1952).

[130] H. Zimmer and co-workers, *J. Amer. Chem. Soc.*, **77**, 790 (1955).

[131] H. Dorn and co-workers, *Chem. Ber.*, **99**, 2620 (1966).

[132] L. N. Smith and D. N. Thatcher, *Ind. Eng. Chem., Prod. Res. Develop.*, **1**, 117 (1962).

[133] N. B. Tuemmler and H. Winkler, U.S. Pat. 2,976,505 (1961); *Chem. Abstr.*, **55**, 15349 (1961).

[134] O. Mathieson, Brit. Pat. 881,339 (1960); *Chem. Abstr.*, **56**, 9962 (1962).

[135] H. Jonas and H. J. Abendroth, Ger. Pat. 1,130,821 (1962); *Chem. Abstr.*, **57**, 12320 (1962).

[136] H. G. Kazmirowski and co-workers, D.D.R. Pat. 23,001 (1962); *Chem. Abstr.*, **58**, 6746 (1963).

methods. In principle, the same reducing agents are suitable as for conversion of nitro into amino groups. Because of the great stability of the azo group, azo compounds can be subjected to many reactions that lead to difficulties with amino compounds. The use of azo compounds as having protected amino groups opens a route to a variety of ring-substituted primary amines; and, further, reductive fission of the azo group is a valuable technique for determination of the constitution of azo dyes.

However, the benzidine and semidine rearrangements may occur in acid solution if the hydrazo stage is not further reduced sufficiently fast, and in such cases it is preferable to carry out the reduction in an alkaline medium.

When reducing azo compounds it is generally possible to use the solutions or pastes that result directly from the coupling reaction, although it is advisable to purify the azo compound before catalytic hydrogenation.

The reagents most commonly used for reducing azo compounds are sodium dithionite,[137] zinc,[138] tin(II) chloride,[139] hydrogen iodide,[140] and activated hydrogen.

Reduction by sodium dithionite always gives good yields and is preferred here over all other methods because the technique required is simple. Two moles of sodium dithionite are added to a warm (40–60°) neutral or alkaline, aqueous or alcoholic solution of one mole of the azo compound, and the solution is warmed for a short time (until decolorized).

2-Amino-4-methoxyphenol:[141] 4-Methoxy-2-(phenylazo)phenol (100 g) is dissolved in a solution of sodium hydroxide (100 g) in water (1 l), warmed on the water-bath, and treated, with stirring, with portions of sodium dithionite until the solution is decolorized. The aniline produced is extracted with ether, and the aqueous-alcoholic phase therefrom is neutralized, whereupon the aminophenol is precipitated. This is at once filtered off, dried, and immediately converted into its hydrochloride by ethereal hydrogen chloride. The yield is 57.5 g and the m.p. 205–212° (dec.). A further 7.8 g of somewhat lower m.p. are obtained by extracting the aqueous mother-liquor with ether, the total yield being 85%.

Any active hydrogenation catalyst can be used for hydrogenation of azo compounds.[20g] It is unnecessary to use pressure since the rate of reduction can be accelerated by raising the temperature. Azobenzene is reduced to aniline under atmospheric pressure at 180–200°. Azo compounds can be converted into hydroaromatic amines in one operation by using catalysts that also hydrogenate aromatic rings. Reduction of azo compounds with Raney nickel has been studied in detail;[142] hydrogenation is carried out under normal conditions and always gives good yields. Water, alcohol, or dioxan can be used as solvent; the solution should be neutral or weakly alkaline.

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[137] E. Grandmougin, *Ber. Deut. Chem. Ges.*, **39**, 2494, 2561 (1906); *J. Prakt. Chem.*, [ii], **76**, 124 (1907); H. Fischer, *Z. Physiol. Chem.*, **60**, 69 (1909); H. E. Fierz-David, and L. Blangey, "Grundlegende Operationen der Farbenchemie," Springer-Verlag, Vienna, 1952, p. 151.

[138] O. N. Witt, *Ber. Deut. Chem. Ges.*, **19**, 1719 (1896).

[139] O. N. Witt, *Friedländer*, **4**, 67 (1894–1897); C. Liebermann, *Ann. Chem.*, **211**, 53 (1882).

[140] R. Meyer, *Ber. Deut. Chem. Ges.*, **53**, 1265 (1920).

[141] W. I. Close and co-workers, *J. Amer. Chem. Soc.*, **71**, 1265 (1949).

[142] W. F. Withmore and A. J. Rerukas, *J. Amer. Chem. Soc.*, **59**, 1500 (1937); **62**, 1687 (1940).

p-Phenylenediamine:[143] A solution of p-(phenylazo)aniline (9.85 g) in 95% ethanol (100ml) containing platinum oxide (0.1 g) is shaken with hydrogen at 3 atm. Absorption is complete in 20 min. Working up gives p-phenylenediamine (5.12 g) and aniline (2.92 g).

g. Reduction of azines, hydrazones, hydrazines, and hydrazides

$$(\mathrm{R{=}N{-}N{=}R} \longrightarrow 2\mathrm{RNH_2})$$

$$(\mathrm{RCONH{-}NHR} \longrightarrow \mathrm{RCONH_2} + \mathrm{RNH_2})$$

Mild reduction converts azines and hydrazines into disubstituted hydrazines, but under vigorous conditions reductive cleavage of the N–N bond affords amines. Reduction of oximes thus affords a further but seldom used method of converting carbonyl compounds into amines.

Catalysts that are active for hydrogenation can be used equally for hydrogenolysis of an N–N bond; Raney nickel is the catalyst of choice for this purpose;[162] use of platinum or palladium catalysts generally leads only to the substituted hydrazine,[144,145] N–N fission being rare in these cases.[146] Experience to date does not permit prediction with certainty as to which compounds will suffer N–N fission on noble-metal catalysts; it has been observed mainly with hydrazones and azines of aromatic aldehydes, but such catalysts have often been used in acid solution for reduction of hydrazones and azines to the corresponding hydrazines.

Hydrogenolysis of the N–N bond is best achieved directly by use of Raney nickel alloy in an alkaline medium,[147] and this reaction has been used to clarify the constitution of hydrazine derivatives.[128]

Hydrazides of carboxylic[144,148] and sulfonic acids[144,148,149] are cleaved to amides by hydrogenation over Raney nickel in boiling alcohol:

General procedure: A mixture of a hydrazide (1–2 g), 95% ethanol (100 ml), and Raney nickel (10 g) is stirred and heated under reflux for 3 h, then filtered and evaporated. The residue is extracted with hot water or benzene. As the extract cools, the amide is obtained in 60–80% yield.

1,2-Diacylhydrazines are hydrogenolysed by hydrazine hydrate and Raney nickel.[150]

Hydrogenolysis of the N–N bond may be coupled with hydrogenation of a C=C double bond.[151] Sodium amalgam in an acid medium can also be used for this cleavage.[152] Zinc in an acid solution converts arylhydrazones of α-oxo carboxylic acids into α-amino acids.[19h] Recently, N–N cleavage of 1,2-dialkylhydrazines has been observed when merely boiling them in N-hydrochloric acid.[153]

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[143] L. H. Andrews and A. Lowy, *J. Amer. Chem. Soc.*, **56**, 1411 (1934).

[144] C. Ainsworth, *J. Amer. Chem. Soc.*, **76**, 5774 (1954).

[145] H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **20**, 60 (1955).

[146] K. Bodendorf and W. Wössner, *Ann. Chem.*, **623**, 109 (1959); W. G. Laves and co-workers, *J. Chem. Soc.*, **1959**, 1474, 1480.

[147] von Eudokimoff, *Gazz. Chim. Ital.*, **81**, (1951) 725.

[148] R. L. Hinman, *J. Org. Chem.*, **22**, 148 (1957).

[149] T. Ueda and T. Tsuji, *Chem. Pharm. Bull.* (*Tokyo*), **9**, 71 (1961).

[150] F. P. Robinson and R. K. Brown, *Can. J. Chem.*, **39**, 1171 (1961).

[151] G. Losse and J. Müller, *J. Prakt. Chem.*, [iv], **12**, 285 (1964).

[152] J. Tafel, *Ber. Deut. Chem. Ges.*, **19**, 1924 (1886); **20**, 398 (1887); **22**, 1854 (1889).

[153] E. F. Elslager and co-workers, *J. Med. Chem.*, **7**, 493 (1964).

h. Reduction of azides

$$(RN_3 \longrightarrow RNH_2)$$

Amines can be obtained by the action of reducing agents on azides in a reaction involving evolution of elemental nitrogen but whose mechanism has not been fully clarified. The reaction is relatively seldom used as azides are always explosive and (**N.B.**) must thus be handled with particular caution. The method can be used, for example, to afford primary aliphatic amines since the requisite azides can be prepared in simple reactions from alkyl halides and sodium azide (see pp. 477 *et seq.*) or by addition of hydrogen azide to ethylene oxides. The reducing agents used are nearly always those used also for reduction of nitro groups.

Aryl azides can, however, also be converted into amines. Thus aniline is obtained in 88% yield by catalytic hydrogenation of phenyl azide,[154] and indeed catalytic hydrogenation of azides on platinum or palladium catalysts is a general reaction.[154] Helferich and Mitrowsky,[155] moreover, obtained a 95% yield of tetra-*O*-acetyl-1-amino-1-deoxyglucose by reducing tetra-*O*-acetylglucosyl azide on a nickel catalyst; and reduction by lithium tetrahydridoaluminate also generally affords amines in good yields; phenethylamine has been prepared in 89% yield from phenethyl azide.[156] Horner and Hofmann[157] converted azides into phosphinimines by reaction with triphenylphosphine:

$$R_3P + RN_3 \longrightarrow R_3P{=}NR + N_2$$

and these products are hydrolysed to amines by hydrogen bromide in glacial acetic acid.

i. Preparation of amines by cleavge of N-nitrosamines

Secondary amines can be identified as nitrosamines, and several methods have proved their value for regeneration of the secondary amine therefrom. One such method is reductive cleavage by iron(II) chloride in hydrochloric acid:

$$R_2NNO + HCl + FeCl_2 \longrightarrow R_2NH + NO + FeCl_3$$

The nitric oxide formed can be determined volumetrically, so that the reaction can be used for quantitative determination of nitrosamines.[158] Reductive cleavage by copper(I) chloride and hydrochloric acid proceeds analogously.

The nitrosamine is treated with an excess of a cold solution of copper(I) chloride in hydrochloric acid (*d* 1.17).Nitric oxide is evolved at once. The reaction is completed by warming. Secondary amines are thus obtained from their nitroso derivatives in good yield.

Whereas mild reducing agents (sodium amalgam, zinc dust in hydrochloric acid) convert nitrosamines into *N,N*-disubstituted hydrazines, reduction by zinc and sulfuric acid or tin and hydrochloric acid cleaves with regeneration of the secondary amine.[159] Nitrosamines are also cleaved smoothly by dilute sulfuric acid containing urea.[160]

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[154] A. Bertho and J. Maier, *Ann. Chem.*, **498**, 50 (1932).

[155] B. Helferich and A. Mitrowsky, *Chem. Ber.*, **85**, 1 (1952).

[156] I. H. Boyer, *J. Amer. Chem. Soc.*, **73**, 5865 (1959).

[157] L. Horner and H. Hofmann, *Angew. Chem.*, **68**, 485 (1956).

[158] K. Lehmstedt, *Ber. Deut. Chem. Ges.*, **60**, 1910 (1927).

[159] E. Fischer, *Ann. Chem.*, **190**, 152 (1878).

[160] N. G. Macmillan and T. Reade, *J. Chem. Soc.*, **1929**, 585.

***N*-Methyl-*m*-nitroaniline:** *N*-Methyl-*N*-nitroso-*m*-nitroaniline (20 g) is added to a warm (50°) solution of urea (15 g) in water (75 ml) and sulfuric acid (75 ml), whereupon nitrogen, carbon dioxide, and nitric oxide are at once evolved. The mixture is then heated for a further 15 min at 100°, and finally allowed to cool. The secondary amine is precipitated by ammonia and recrystallized from light petroleum. The yield is 15.5 g, and the m.p. 67.5°.

Simply boiling nitrosamines with hydrochloric acid affords the secondary amine and nitrous acid:

$$R_2NNO + H_2O \longrightarrow R_2NH \quad \text{and} \quad HNO_2$$

The N–N bond of *N*-nitroso amides is also easily cleaved by hydrochloric acid.[161]

II. Reduction of *N*-oxides

The present Section deals with reductive alteration of a nitrogenous group without formation of an N–H bond, *e.g.*, reduction of amine oxides and azoxy compounds.

The discovery that electrophilic substitutents can be introduced into the *N*-oxides of nitrogenous heterocycles more easily than into the heterocycles themselves considerably increased the importance of this group of compounds, and several reviews[162–164] treat the large number of papers in that field. Addition and later removal of oxygen has been much used as an aid to the study of nitrogenous natural products.

Aliphatic and aliphatic-aromatic *N*-oxides are converted into the parent amines by mild reducing agents, but powerful reducing agents are generally needed in the aromatic heterocyclic series. Good results have been obtained by using Raney nickel with glacial acetic acid and acetic anhydride as solvent; catalytic hydrogenation of *N*-oxides in the pyridine series by reaction is rapid and the pyridine ring is not attacked. An acid medium is also usually required when a platinum or palladium catalyst is used, although 3- and 4-methylpyridine *N*-oxide, for instance, are smoothly hydrogenated on platinum dioxide in methanol.[164] *N*-Oxides can also be reduced by hydrazine hydrate in the presence of Raney nickel, but the yields are then very variable.[165] Iron in acetic acid also affords the tertiary amines.[166] Reduction is also effected by sodium or sulfur in liquid ammonia. When other reducible groups are present, phosphorus trichloride in chloroform can be used; *e.g.*, 4-nitropyridine was obtained in 70–80% yield from its *N*-oxide in this way.[163] Aliphatic *N*-oxides can be reduced by triphenylphosphine in boiling glacial acetic acid,[167] and aromatic *N*-oxides by this reagent at 200° in absence of a solvent.[168] Pyridine oxide and its homologs can be reduced by dropping them into thionyl chloride at 50–70°.[169]

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[161] I. K. Barben and H. Suschitzky, *J. Chem. Soc.*, **1960**, 2735.

[162] T. R. Emerson and C. W. Rees, *Proc. Chem. Soc.*, **1960**, 418; A. R. Katritzky, *Quart. Rev.*, **10**, 395 (1956).

[163] E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

[164] K. Tjomas and D. Jerchel, *Angew. Chem.*, **70**, 731 (1958).

[165] A. Furst and co-workers, *Chem. Rev.*, **65**, 61 (1965).

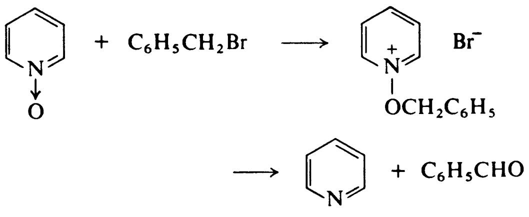
[166] I. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).

[167] L. Horner and H. Hofmann, *Angew. Chem.*, **68**, 480 (1956).

[168] E. Howard and N. F. Olszewski, *J. Amer. Chem. Soc.*, **81**, 1483 (1959).

[169] W. Hoefling and co-workers, D.D.R. Pat. 36,422 (1965); *Chem. Abstr.*, **63**, 18047 (1965).

Since amine oxides react with alkyl halides to give *O*-alkyl compounds which are cleaved by alkali to the tertiary amine and an aldehyde, this reaction also can be used to eliminate the oxygen from *N*-oxides.[163]



4-Methylpyridine from its oxide:[164] Raney nickel (ca. 1 g) is added to a solution of the amine oxide (20 g) in glacial acetic acid (60 ml) and acetic anhydride (10 ml) and the mixture is shaken vigorously under hydrogen at room temperature. When hydrogen absorption ceases most of the nickel can be simply filtered off; the filtrate is treated with concentrated hydrochloric acid (about 20 ml) and concentrated to a syrup at 80° under water-pump vacuum. Addition of dilute sodium hydroxide to the residue precipitates nickel hydroxide. After a short time the free base is distilled in steam, separated from the distillate by addition of sodium hydroxide, and dried for several days over solid sodium hydroxide. The residue of base in the aqueous phase is isolated by extraction with ether. Distillation of the united fractions of base affords pure 4-methylpyridine, b.p. 144–145°/760 mm (39.2 g, 84%).

Reduction of amine oxides affords the tertiary amines in a very pure state. Jerchel and Melloh[170] have described the isolation of pure methylpyridines from methylpyridine mixtures by way of the *N*-oxides.

Tin or tin(II) chloride,[171] zinc in an acid medium,[172] sodium dithionite,[173] and sulfur dioxide[174] are also effective for reducing *N*-oxides. Azoxy compounds are converted into azo or hydrazo compounds by relatively mild reducing agents; azoxybenzene is reduced to hydrazobenzene by zinc in alkaline solution[1c] and to azobenzene (99% yield) by lithium tetrahydridoaluminate.[35]

III. Formation of the N–O bond

The N–O bond can be formed by addition or exchange; in all cases the process is one of oxidation.

1. Formation of the N–O bond by addition

a. Preparation of *N*-oxides

$$(R_3N \longrightarrow R_3N{-}O)$$

The study of *N*-oxides is a recent development and, as set out in the preceding Section, the importance of these derivatives is increasing, particularly in the nitrogenous heterocyclic series. The semipolar N–O bond confers the character of salts on these oxides: they are readily soluble in water and difficultly soluble in benzene or ether. Pyridine 1-oxide is very hygroscopic, like pyridinium salts.

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[170] D. Jerchel and W. Melloh, *Ann. Chem.*, **613**, 144 (1958).

[171] G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, **1948**, 1864.

[172] P. Friedländer and H. Ostermaier, *Ber. Deut. Chem. Ges.*, **14**, 1916 (1881).

[173] D. L. Vivian, *J. Amer. Chem. Soc.*, **73**, 457 (1951).

[174] H. Z. Lecher and W. D. Hardy, *J. Amer. Chem. Soc.*, **70**, 3789 (1948); F. A. Daniker and B. E. Hackley, *J. Org. Chem.*, **31**, 4267 (1966).

The melting points and boiling points are always higher than those of the corresponding bases. They have a basic reaction and afford salts.

The most important methods of preparing *N*-oxides are by oxidation of tertiary bases, which is effected by means of hydrogen peroxide, peroxyacids, or ozone.

(i) Oxidation by hydrogen peroxide. For the preparation of *N*-oxides by hydrogen peroxide it is customary to use a 30% solution of the reagent. The amount of oxidant and the reaction temperature naturally depend on the reactivity of the amine used. It has been recommended that platinum foil should be added to destroy the excess of hydrogen peroxide at the end of the reaction so as to avoid the possibility of its explosive decomposition.[175]

Trimethylamine oxide hydrate:[176] A 33% aqueous solution (100 ml) of trimethylamine and a pure 3% solution (600 ml) of hydrogen peroxide are allowed to react at room temperature. If the odor of trimethylamine has not disappeared after 24 h, more hydrogen peroxide solution (100–200 ml) is added. When trimethylamine can no longer be detected, the solution is evaporated in a vacuum and the residue is recrystallized from ethanol–ether. This gives the oxide hydrate as needles, m.p. 96° in yields up to 95%.

Anhydrous trimethylamine oxide is obtained by removing the water from the hydrate at 120–150°/12 mm.[176] Industrially, trimethylamine oxide hydrate is prepared at a lower temperature (−40°) than that mentioned above.[177]

(ii) Oxidation by peroxyacids: Meisenheimer[178] prepared *N*-ethyl-*N*-methylaniline oxide by oxidation with peroxybenzoic acid, although it could not be obtained by means of aqueous hydrogen peroxide, and *N*-oxides of other *N,N*-dialkylanilines can also be obtained by this method.[179] For preparing a variety of *N*-oxides Stahmann and Bergmann[180] used peroxyacetic acid and monoperoxyphthalic acid as well as perbenzoic acid. The prescriptions of pyridine 1-oxide[181] and nicotinamide 1-oxide[182] may serve as general directions for preparation of *N*-oxides. Caro's acid has been used for preparation of *p*-bromo-*N,N*-dimethylaniline oxide.[183]

Pyridine 1-oxide: A solution of pyridine in glacial acetic acid is warmed with an excess of 30% hydrogen peroxide at 70–80° for several hours and then concentrated in a vacuum, basified, and extracted with chloroform. The product is purified by distillation under diminished pressure.

Amine oxide of pyridine homologs and many other pyridine derivatives can be prepared by this method, usually in very good yield.[163]

(iii) Oxidation by ozone. Strecker and Baltes[184] oxidized trialkylamines in chloroform at −80° by means of ozone. When oxidation was complete, hydrogen chloride was led into the solution, and the oxide hydrochloride was isolated. yields of up to 90% were obtained.

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[175] A. C. Cope and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3426 (1949).

[176] J. Meisenheimer and K. Bratring, *Ann. Chem.*, **397**, 286 (1913).

[177] E. Rotter and E. Haaver, Ger. Pat. 937,058 (1952); *Chem. Abstr.*, **53**, 220 (1959).

[178] J. Meisenheimer, *Ber. Deut. Chem. Ges.*, **52**, 1667 (1919).

[179] J. Meisenheimer, *Ann. Chem.*, **449**, 188 (1926).

[180] M. A. Stahmann and M. Bergmann, *J. Org. Chem.*, **11**, 586 (1946).

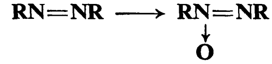
[181] H. S. Mosher and co-workers, *Org. Syn.*, Coll. Vol. IV, 828 (1963).

[182] E. C. Taylor Jr. and A. J. Crovetti, *Org. Syn.*, Coll. Vol. IV, 704 (1963).

[183] L. W. Jones and E. B. Hartshorn, *J. Amer. Chem. Soc.*, **46**, 1840 (1924).

[184] W. Strecker and M. Baltes, *Ber. Deut. Chem. Ges.*, **56**, 2693 (1921); cf. H. B. Henbest and M. J. W. Stratford, *J. Chem. Soc.*, **1964**, 711.

b. Azoxy compounds from azo compounds



$$RN{=}NR \longrightarrow \underset{\substack{\downarrow\\ O}}{RN{=}NR}$$

Hydrogen peroxide in glacial acetic acid oxidizes azo compounds to azoxy compounds smoothly and almost quantitatively. Reaction normally occurs at room temperature, but in a few cases warming on a water-bath for a fairly long time is needed.[185] Polyazoxy compounds can also be obtained by this method.[210] However, organic peroxyacids are generally used for this oxidation, the reaction being almost quantitative under mild conditions; azoxy compounds prepared in this way have been the subject of a review by Swern.[186] Aliphatic azo compounds cannot be oxidized to azoxy compounds by aliphatic peroxyacids as these reagents cause the azo–hydrazone rearrangement, but this oxidation is effected smoothly by peroxybenzoic acid.[187] Badger and his colleagues have made a detailed study of the oxidation of azo compounds by peroxybenzoic acid.[188] α-(Phenyl-*NNO*-azoxy)toluene has been obtained by oxidizing benzaldehyde phenylhydrazone with peroxyphthalic acid:[189]

$$C_6H_5CH{=}NNHC_6H_5 \rightleftarrows C_6H_5CH_2N{=}NC_6H_5 \longrightarrow C_6H_5CH_2N(O){—}NC_6H_5$$

c. Oxidation of the nitroso and the oxime group to the nitro group

Oxidation of nitroso to nitro compounds is particularly important when introduction of a nitroso group (by oxidation of an amino group) is easier than direct nitration. For example, amino-pyridine and -quinolines and some *o*-nitroanilines are prepared relatively easily in this way; oxidation to nitroso compounds and further oxidation thereof leads to the desired nitro derivatives.

Kuhn and von Klaveren[190] recommend a mixture of nitric acid and 100% hydrogen peroxide for oxidation of *o*-nitronitroso compounds.

1,2-Dimethyl-4,5-dinitrobenzene: 1,2-Dimethyl-5-nitro-4-nitrosobenzene (10 g) is dissolved in glacial acetic acid (300 ml) and treated with a mixture of glacial acetic acid (150 ml) and 33% hydrogen peroxide (150 ml), followed by nitric acid (*d* 1.40; 10 ml). The whole is warmed on the water-bath, whereupon the dark green color of the solution changes to orange within a few minutes. Oxidation of the nitroso compound is complete when extraction of a sample with chloroform no longer gives a green color. Then the product (9 g, 83%) is precipitated by addition of water (600 ml).

Aminopyridines can be oxidized in one operation to nitropyridine, by way of the nitroso compounds, by using a mixture of 100% hydrogen peroxide and sulfuric acid.[191]

Koelsch[192] used a mixture of nitric acid and water at 40–50° for oxidation of the nitroso group. Simultaneous oxidation of a nitroso to a nitro group and of a methyl to a carboxyl group is described in *Organic Syntheses*[193] for the

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[185] P. Ruggli and G. Bartusch, *Helv. Chim. Acta*, **27**, 1371 (1944).

[186] D. Swern, *Chem. Rev.*, **45**, 38 (1919).

[187] B. W. Langley and co-workers, *J. Chem. Soc.*, **1952**, 4191.

[188] G. M. Badger and co-workers, *J. Chem. Soc.*, **1953**, 2143; B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 95 (1967).

[189] J. N. Brough and co-workers, *J. Chem. Soc.*, **1954**, 4069, 4079; B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962).

[190] R. Kuhn and W. von Klaveren, *Ber. Deut. Chem. Ges.*, **71**, 779 (1938).

[191] A. Kirpal and W. Böhm, *Ber. Deut. Chem. Ges.*, **65**, 680 (1932).

[192] C. F. Koelsch, *J. Amer. Chem. Soc.*, **66**, 2019 (1944).

[193] W. D. Langley, *Org. Syn.*, Coll. Vol. III, 334 (1955).

case of 2-nitroso-5-nitrotoluene, the oxidant being potassium dichromate in sulfuric acid. Heptafluoronitrosopropane was converted into the corresponding nitro compound by oxygen in a pressure tube at 70°.[194] Gowenlock[195] has reviewed *C*-nitroso compounds.

The hydroxyimino (oxime) group can also be oxidized to a nitro group. For example, diethyl nitrosomalonate gives diethyl nitromalonate in 88% yield on treatment with manganese dioxide in glacial acetic acid for 24 hours at 30°.[196]

Oximes of carbocyclic ketones in hydrogen carbonate solution are oxidized by *N*-bromosuccinimide to 1-bromo-1-nitrosocycloalkenes, which are converted by nitric acid into 1-bromo-1-nitrocycloalkanes in 40–70% yield, and the latter products can be reduced by potassium iodide in methanol or by sodium tetrahydridoborate to the corresponding nitrocycloalkanes.[197] Oximes of aromatic aldehydes may be converted by dinitrogen tetraoxide into the dinitro compounds.[198] α-Nitrobenzaldehyde oxime is converted by dinitrogen tetraoxide into α,α,α-trinitrotoluene (phenyltrinitromethane) in 77% yield.[199]

2. Formation of the N–O bond by exchange

a. Oxidation of amines, hydroxylamines, and oximes to nitroso compounds

Amines can be oxidized to nitroso compounds ($RNH_2 \rightarrow RNHOH \rightarrow RNO$) through the hydroxyamino stage, suitable reagents being Caro's acid (potassium peroxydisulfate),[193] dichromate–sulfuric acid,[1a] iron(II) chloride,[200,201] and peroxybenzoic and peroxyacetic acid.[202] Oxidation of arylhydroxylamines to nitroso compounds is usually effected by dichromate–sulfuric acid. Bamberger and Seligmann[203] have studied the oxidation of aliphatic amines in detail; the type of product depends on the surroundings of the carbon atom to which the amino group is attached; if this is a tertiary carbon atom, nitroso compounds are obtained, but if it is primary or secondary the products are oximes; for example, oxidation of *tert*-butylamine by Caro's acid (H_2SO_5) gives tertiary nitrosobutane (2-methyl-2-nitrosopropane), but that of isopropylamine gives acetone oxime. Kahr and Berther obtained oximes by catalytic oxidation of primary amines;[204] aliphatic, arylaliphatic, and carbocyclic mono- and di-amines can be oxidized to the corresponding oximes by hydrogen peroxide under catalysis by soluble salts of tungstic, molybdic, or uranic acid.

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[194] D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, **1956**, 3416.

[195] B. C. Gowenlock, *Quart. Rev.*, **12**, 321 (1958).

[196] L. Canonica, *Gazz. Chim. Ital.*, **77**, 92 (1947).

[197] D. C. Iffland and G.X. Criner, *J. Amer. Chem. Soc.*, **75**, 4047 (1953).

[198] L. I. Khmel'nitskii, S. S. Novikov, and O. V. Lebedev, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1961**, 477; *Chem. Abstr.*, **55**, 23389 (1961); cf. *Chem. Rev.*, **64**, 25 (1964).

[199] S. S. Novikov and co-workers, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1960**, 1783, 2019.

[200] R. E. Lutz and M. Lytton, *J. Org. Chem.*, **2**, 73 (1937).

[201] F. Barrow and F. J. Thorneycroft, *J. Chem. Soc.*, **1939**, 773, 775.

[202] J. D'Ans and A. Kneip, *Ber. Deut. Chem. Ges.*, **48**, 1144 (1915).

[203] E. Bamberger and R. Seligmann, *Ber. Deut. Chem. Ges.*, **36**, 685, 701 (1903).

[204] K. Kahr and C. Berther, *Chem. Ber.*, **93**, 132 (1960).

5-Nitro-2-nitrosotoluene:[193] 4-Nitro-*o*-toluidine ($NH_2 = 1$) (50 g, 0.33 mole) is treated with an ice-cold mixture of concentrated sulfuric acid (200 ml) and water (50 ml). The whole is stirred at room temperature. Meanwhile Caro's acid is prepared as follows: potassium peroxydisulfate (300 g) is stirred into ice-cold sulfuric acid (*d* 1.84; 175 ml), and the mixture is treated with ice (800 g) and water (300 ml) and vigorously stirred. This solution of Caro's acid is added, with stirring, to the suspension of nitrotoluidine, stirring is continued for a further 2 h at 40°, and then more powdered potassium peroxydisulfate (100 g) is added in one portion. The mixture is stirred at 40° for yet a further 2 h, then diluted with water (to 4 l). The precipitate is filtered off and washed with water, and the 5-nitro-2-nitrosotoluene is purified by distillation in steam, the yield being 30–39 g.

The preparation of nitrosobenzene by oxidation of phenylhydroxylamine with dichromate–sulfuric acid has been described by Gattermann and Wieland.[1a] 2,6-Dihaloanilines can be oxidized to nitroso compounds in good yield by a mixture of 30% hydrogen peroxide and glacial acetic acid.[205] Nitroso compounds are also obtained in good yield by oxidation of arylhydroxylamines with diethyl azodicarboxylate.[206]

b. Oxidation of amines to nitro compounds

Whereas peroxyacetic acid oxidizes aromatic amines at room temperature to nitroso compounds, further oxidation to nitro compounds occurs in boiling chloroform.[207] Trifluoroperoxyacetic acid[208] and a mixture of maleic anhydride and hydrogen peroxide[209] are valuable reagents for oxidizing aromatic amines in general to nitro compounds.

Aliphatic amines containing a tertiary alkyl group are oxidized to tertiary nitroalkanes in good yield by potassium permanganate.[210]

2-Methyl-2-nitropropane: *tert*-Butylamine (100 g) is added during 15 min to a stirred solution of potassium permanganate (650 g) in water (3 l), the temperature rising to 45°. After being stirred for 8 h without external heating, the mixture is heated at 50–60° for a further 8 h. Then the 2-methyl-2-nitropropane formed is distilled off in steam and freed from traces of amine by washing with dilute hydrochloric acid. The product (117 g, 83%) has b.p. 127–128°, m.p. 25–26°.

c. Oxidation of nitrosamines to nitramines

Because of their ready availability, nitrosamines are useful starting points for preparation of nitramines by oxidation. Trifluoroperoxyacetic acid is a suitable reagent for this purpose.[211]

IV. Formation of the N–N bond by exchange

1. Preparation of nitrosamines and nitrosamides

Nitroso derivatives are valuable for characterizing secondary amines and can be used as starting points for the synthesis of *N*,*N*-disubstituted hydrazines. Nitrosamines are usually prepared by the action of nitrous acid on aliphatic

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[205] R. R. Holmes and R. P. Bayer, *J. Amer. Chem. Soc.*, **82**, 3454 (1960).

[206] E. C. Taylor and F. Yoneda, *Chem. Commun.*, **1967**, 4, 199.

[207] W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5528 (1957).

[208] W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3470 (1954).

[209] R. W. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1961).

[210] N. Kornblum and co-workers, *J. Amer. Chem. Soc.*, **78**, 4003 (1956).

[211] W. D. Emmons and A. F. Ferris, *J. Amer. Chem. Soc.*, **75**, 4623 (1953); **76**, 3468 (1954).

or aromatic secondary amines in acidic aqueous solution; the customary technique is to add the amine in acidic aqueous solution (often hydrochloric, less often acetic acid) to a slight excess of sodium nitrite; for the preparation of aliphatic nitrosamines the mixture may be heated.[125] *N*-Nitroso derivatives of amides, sulfonamides, or urethanes are advantageously obtained by using sodium nitrite with acetic anhydride as solvent,[212] but dinitrogen tetraoxide has also proved very suitable for nitrosation of amide groups.[212,213] Amines that are sparingly soluble in aqueous acid are nitrosated in glacial acetic acid[214] or alcohol, and in the former solvent alkyl nitrites may be used as the nitrosating agent.[215] Nitrous gases have been applied for nitrosation of hexanolactam, again in glacial acetic acid.[216] Certain nitroso compounds, *e.g.*, 3-nitro-9-nitrosocarbazole, can transfer their nitroso groups to other secondary amines.[217]

Most nitrosamines have a neutral reaction and are sparingly soluble in water. However, dimethylnitrosamine is feebly basic, and its hydrochloride can be obtained from its solution in ether. Nitrosamines can usually be distilled in steam or in a vacuum, but explosive decomposition has been observed in such operations.[218]

The preparation of a large number of important *N*-nitroso compounds is described in *Organic Syntheses*, *e.g.*, *N*-nitrosodimethylamine,[125] 1-methyl-1-nitrosourea,[219] *N*-methyl-*N*-nitrosourethane (ethyl *N*-methyl-*N*-nitroso-carbamate),[230] and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide.[221] The last three of these are intermediates in the preparation of diazomethane.

Mono-*N*-nitrosation of 1,2-dialkylhydrazines can be effected in the same way as nitrosation of secondary amines. For instance, 1,2-diisopropyl-1-nitrosohydrazine is obtained by using sodium nitrite in either glacial acetic or hydrochloric acid.[222]

A rather large number of nitrosamines are carcinogenic; *e.g.*, *N*-nitrosodimethylamine causes liver cancer.[223] **Care** is thus advisable when working with *N*-nitroso compounds.

2. Preparation of nitramines and nitramides

$$(\mathrm{RR'NH} \rightarrow \mathrm{RR'NNO_2})$$

The paragraphs below describe only the preparations of *N*-nitro compounds that involve formation of an N–N bond: (i) the preparation of primary aliphatic nitramines and nitramides by direct nitration or by nitrolysis of *N*,*N*-

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[212] E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008 (1955).

[213] W. M. Jones and D. L. Muck, *J. Amer. Chem. Soc.*, **88**, 3798 (1966).

[214] E. J. Forbes, *J. Chem. Soc.*, **1956**, 513.

[215] P. Quitt and co-workers, *Helv. Chim. Acta*, **47**, 166 (1964).

[216] R. Huisgen and R. Reinertshofer, *Ann. Chem.*, **575**, 174 (1952).

[217] C. L. Baumgardener and co-workers, *J. Amer. Chem. Soc.*, **83**, 4417 (1961).

[218] C. E. Redemann and co-workers, *Org. Syn.*, Coll. Vol. III, 244 (1955).

[219] F. Arndt, *Org. Syn.*, Coll. Vol. II, 461 (1943).

[220] W. W. Hartmann and R. Phillips, *Org. Syn.*, Coll. Vol. II, 464 (1943).

[221] T. J. deBoes and H. J. Baker, *Org. Syn.*, Coll. Vol. IV, 943 (1963).

[222] H. L. Lochte and co-workers, *J. Amer. Chem. Soc.*, **44**, 2565 (1922).

[223] P. N. Magee and J. M. Barnes, *Brit. J. Cancer*, **10**, 114 (1956); H. Druckrey and co-workers, *Z. Krebsforsch.*, **66**, 138 (1964).

dichloro amines; (ii) the preparation of secondary aliphatic nitramines and nitramides; and (iii) the preparation of aromatic nitramines.

Properties and reactions of nitramines: Secondary nitramines are neutral, primary nitramines form salts with bases, but an excess of alkali often causes decomposition to the carbonyl compound, nitrogen, and water. Secondary nitramines and aqueous alkali afford nitrous acid, aldehyde, and primary amine. Acids decompose primary aliphatic nitramines with formation of nitrous oxide in a reaction that has not yet been clarified; thus these compounds cannot be hydrolysed by acid to amines in the same way as nitrosamines, although, like the latter, they can be reduced to hydrazines. Primary and secondary aromatic nitramines readily rearrange to *C*-nitroarylamines in acid solution. Most nitramines decompose explosively when heated, but the lower aliphatic secondary nitramines can be distilled in a vacuum.

N.B. Particular care is required with the nitrations by acetic anhydride–nitric acid mixtures described below, since the acetyl nitrate formed has repeatedly caused violent **explosions**. Alkyl nitrates may also explode unexpectedly.

(i) Before nitration, amines are converted into suitable amides, these are nitrated by anhydrous or fuming nitric acid or by nitric and sulfuric acid, and the nitramide produced is hydrolysed to the nitramine by alkali. Nitric acid–acetic anhydride,[224] nitric acid–sulfur trioxide,[224] ethyl nitrate,[225] and dinitrogen pentoxide[226,227] have also proved valuable reagents for *N*-nitration. Nitration of guanidine is effected by adding guanidine nitrate to cooled sulfuric acid;[228] and nitrourea is obtained analogously from urea nitrate.

***N*-Nitromethylamine:**[229] *N*-Methyl-*p*-toluenesulfonamide (23 g) is added portionwise, with stirring, to 70% nitric acid (130 ml) at 5°. When all the amide has dissolved, 98% nitric acid (130 ml) is added at 0° with stirring which is then continued for a further 10 min at 0°. Finally the mixture is poured into ice-water, and the *N*-methyl-*N*-nitro-*p*-toluenesulfonamide is filtered off and crystallized from ethanol; it then has m.p. 57° (21 g, 73%).

Piperidine (10 g) is added to a solution of the nitramide (10 g) in acetonitrile (35 ml) stirred at 5–10°; the mixture becomes distinctly warm; it is boiled under reflux for 30 min and then poured into 10% sodium hydroxide solution (100 ml). The precipitated 1-tosylpiperidine is filtered off and the filtrate is acidified cautiously and extracted with ether. The extract is dried and evaporated and the nitramine is distilled in a vacuum. Yields are between 81% and 96%.

Priamary aliphatic nitramines can also obtained by converting the amine by butyllithium into its lithium salt and nitrating this with ethyl nitrate. *N*-Nitromethylamine and -*tert*-butylamine, for example, have been prepared by this method.[230]

Nitrolysis of dichloramines affords *N*-chloro-*N*-nitro amines, from which the chlorine may be removed to give the nitramines in useful yields.[231] The technique is to add the dichloramine and 99% nitric acid simultaneously to acetic

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[224] E. H. White and D. N. Grisley Jr., *J. Amer. Chem. Soc.*, **83**, 1191 (1961).

[225] E. H. White and co-workers, *J. Org. Chem.*, **31**, 3038 (1966).

[226] J. Runge and W. Treibs, *J. Prakt. Chem.* [iv], **15**, 223 (1962).

[227] E. H. White and co-workers, *J. Org. Chem.*, **31**, 3030 (1966).

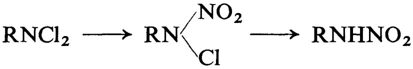
[228] Z. W. Davies, *Org. Syn.*, Coll. Vol. I, 399 (1948).

[229] M. I. Gillibrand and A. H. Lamberton, *J. Chem. Soc.*, **1949**, 1883; W. D. Emmons and J. P. Freeman, *J. Amer. Chem. Soc.*, **77**, 6061 (1955).

[230] L. J. Winters and co-workers, *J. Org. Chem.*, **30**, 2471 (1965).

[231] G. N. R. Smart and G. F. Wright, *J. Amer. Chem. Soc.*, **70**, 3141 (1948).

anhydride in proportions such that a 5% excess of nitric acid is always present; the mixture is then concentrated to one-third of its volume, poured into cold water, and treated with sufficient sodium hydroxide solution to dissolve the nitramine product as its sodium salt; oily by-products are removed by extraction with ether, the aqueous phase is acidified with acetic acid, and the free nitramine is taken up in ether and distilled in a vaccum. The reaction may be expressed as:



$$RNCl_2 \longrightarrow RN\begin{matrix}\nearrow NO_2\\ \searrow Cl\end{matrix} \longrightarrow RNHNO_2$$

(ii) Only weakly basic secondary amines can be converted into nitramines by nitric acid. More strongly basic amines, such as dimethylamine, can be nitrated by nitric acid in acetic anhydride only in presence of hydrogen chloride or an acyl chloride.[232] This nitration may also be effected by acyl nitrates.[233] Nitric acid esters of ketone cyanohydrins are especially valuable nitrating agents for such cases;[234] 4-nitromorpholine, for example, has been prepared by their aid.[235] Dinitrogen pentoxide has also been much used for *N*-nitration, the general technique being illustrated by the following example.

***N*-Nitroglutarimide:**[226] A solution of glutarimide (25 g) and dinitrogen pentoxide (32 g) in chloroform (150 ml) is prepared at −15° and allowed to warm slowly to room temperature. After 15 h it is evaporated in a vacuum and the oily residue is caused to crystallize by addition of a little water. This gives an 88% yield (32 g) of the product, m.p. 98–99° (after recrystallization from benzene).

(iii) Nitration of aromatic amines often occurs in the ring instead of giving the desired nitramine; aromatic nitramines are, as a rule, obtained only when the amine has a negative substituent at the *ortho*- or *para*-position. 100% nitric acid is used for these nitrations, alone or in acetic anhydride;[236] mixtures of nitric and sulfuric acid are unsuitable because the latter acid favors rearrangement of the nitramines to *C*-nitroarylamines.

Tertiary amines can be used for synthesis of certain nitramines. For example, "Tetryl" (*N*-methyl-2,4,6,*N*-tetranitroaniline) is obtained by nitration of *N*,*N*-dimethylaniline, one methyl group being replaced by a nitro group.[237] Benzoyl nitrate[238] and dinitrogen pentaoxide[239] have also been used with success in such reactions. Further, heterocycles nitrated on a ring-nitrogen atom are known.[240]

Nitramines have use especially as explosives ("Hexogen," "Tetryl," nitroguanidine).

In an elegant process, *N*-alkyl-*N′*-nitro-*N*-nitrosoguanidines afford diazoalkanes on treatment with strong aqueous alkali.[241] Nitramines have been reviewed by Lamberton,[242] and nitroguanidines by McKay.[243]

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[232] W. J. Chute and co-workers, *Can. J. Res.*, **26**, *B*, 114 (1948).

[233] W. D. Emmons and J. P. Freeman, *J. Amer. Chem. Soc.*, **77**, 4387 (1955).

[234] W. D. Emmons and J. P. Freeman, *Angew. Chem.*, **67**, 349 (1955).

[235] J. P. Freeman and I. G. Shepard, *Org. Syn.*, **43**, 83 (1963).

[236] A. E. Bradfield and J. K. P. Orton, *J. Chem. Soc.*, **1929**, 915.

[237] C. E. Clarkson and co-workers, *J. Chem. Soc.*, **1950**, 1556.

[238] F. E. Francis, *J. Chem. Soc.*, **89**, 1 (1906).

[239] E. Hoff, *Ann. Chem.*, **311**, 91 (1900).

[240] R. Hüttel and F. Büchele, *Chem. Ber.*, **88**, 1586 (1955).

[241] A. F. McKay, *J. Amer. Chem. Soc.*, **70**, 1974 (1948).

[242] A. H. Lamberton, *Quart. Rev.*, **5**, 75 (1951).

[243] A. F. McKay, *Chem. Rev.*, **51**, 301 (1952).

3. Diazotization of aromatic amines

Salts of primary aromatic amines react with nitrous acid to give diazonium salts:

$$ArNH_2 + HCl + HNO_2 \longrightarrow ArN_2^+Cl^- + 2H_2O$$

The so-called "direct method" can be used with any amine that dissolves in aqueous acid. A cold solution of sodium nitrite is dropped into a cold solution of the arylamine in aqueous mineral acid. Diazotization is usually carried out at 0° because free nitrous acid is most soluble at low temperatures; also the diazonium salts produced are most stable at low temperatures. When these salts are relatively stable, diazotization may be conducted at somewhat higher temperatures, sulfanilic acid, for instance, even at 10–15°; in special cases even temperatures of 30–40° may be used. The higher temperatures are permissible when the diazonium salt is sufficiently stable and the base to be diazotized is too sparingly soluble at 0°.

The optimum temperature for simple arylamines is 0–2°, for *m*-haloarylamines 0–5°, and for benzidines, naphthylamines, and *o*- and *p*-haloarylamines 10–12°. In isolated cases higher temperatures are used, *e.g.*, 34° for *p*-nitroaniline and 40° for *o*-anisidine. The end-point of the reaction is determined by testing for an excess of nitrous acid with potassium iodide–starch paper. Amino sulfonic acids are no longer used to remove the excess of nitrous acid since they react with reactive diazo compounds.[244]

An excess (about 3 moles) of mineral acid is used to prevent coupling of the diazonium salt with unchanged amine to yield the diazoamino compound. Sparingly soluble amine salts may be added in the solid state[245] or, better, may be diazotized by Claus's method in anhydrous acid (sulfuric acid, where nitrosylsulfuric acid is considered to be the effective reagent). Claus's method is applied in particular for weakly basic amines containing negative substituents, examples being 4-nitro-1-naphthylamine,[246] picramide, and 2,6-diiodo-4-nitroaniline.[247] Amines that are unaffected by concentrated nitric acid (*d* 1.48) are advantageously diazotized by Witt's method;[248] in this, the amine (*e.g.*, dinitroaniline) is dissolved in concentrated nitric acid and treated with potassium disulfite which reduces part of the nitric to nitrous acid ($K_2S_2O_5 + 2\,HNO_3 \longrightarrow K_2S_2O_7 + 2\,HNO_2$); the resulting nitrous acid then converts the amine into the diazonium salt.

Arylamines that contain an acid group (sulfo or carboxyl) are diazotized by the so-called "indirect method". They are dissolved in aqueous alkali, treated with a solution of the calculated amount of sodium nitrite, and dropped into an excess of acid; the diazonium salt then usually separates as a solid. This method has been used with success for diazotizing aminobenzoic acid and aniline- and naphthylamine-sulfonic acids; weakly basic amines such

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[244] H. W. Grimmel and J. F. Morgan, *J. Amer. Chem. Soc.*, **70**, 1750 (1948).

[245] M. Gomberg and W. E. Bachmann, *Org. Syn.*, Coll. Vol. I, 113 (1943).

[246] A. Claus and C. Beysen, *Ann. Chem.*, **266**, 224 (1891); H. H. Hodgson and co-workers, *Org. Syn.*, **28**, 52 (1955).

[247] C. Niemann and C. E. Redemann, *J. Amer. Chem. Soc.*, **63**, 1550 (1941).

[248] O. N. Witt, *Ber. Deut. Chem. Ges.*, **42**, 2953 (1909).

as nitroanilines, 4-ethoxy-2-nitroaniline, and aminoazobenzene can be similarly diazotized.[249b]

According to Hantzsch and Jochem[250] solid diazonium salts are prepared as follows:

The amine hydrochloride is dissolved or suspended in a three-fold amount of glacial acetic acid and treated at 10° with the calculated amount of pentyl nitrite, with stirring; when all is dissolved, the mixture is treated cautiously with ether, which precipitates the diazonium salt.

Solid benzenediazonium chloride:[251] Aniline hydrochloride (5 g) is suspended in a mixture of glacial acetic acid (30 ml) and dry, peroxide-free dioxan (30 ml). The suspension is cooled in an ice–salt bath, and ethyl nitrite is led in until all the solid has dissolved (an excess is detected by coloration of starch–iodide paper). Dry dioxan (150 ml) is then added in one portion, whereupon the benzenediazonium chloride separates as fine, white crystals. They are filtered off and washed twice with dioxan (25-ml portions).

The "direct method": 2-Naphthalenediazonium chloride solution:[252] 2-Naphthylamine (143 g, 1 mole) is added to a mixture of concentrated hydrochloric acid (450 ml) and water (500 ml). The resulting suspension of amine hydrochloride is cooled to 5° by addition of ice (500 g). Then solid sodium nitrite (ca. 69 g) is added, with vigorous stirring, until presence of a slight excess is indicated by a color on starch–iodide paper. Additional ice (ca. 600 g) is added gradually during the preceding reaction so that the temperature does not exceed 5°. At the end of the reaction small amounts of insoluble matter are filtered off.

The "indirect method": Diazotization of sulfanilic acid:[249b] A solution of sodium sulfanilate (23 g) and sodium nitrite (7 g) in water (120 ml) is cooled to 0° and dropped with stirring into an ice-cold solution of concentrated sulfuric acid (17 ml) in water (100 ml). The diazonium salt separates instantaneously.

Claus's method; general procedure:[249c] A solution of a weakly basic amine in hot glacial acetic acid (12 ml per gram of amine) is cooled rapidly to room temperature and treated gradually, with stirring, with a solution of sodium nitrite in sulfuric acid [7 ml of sulfuric acid (*d* 1.84) per gram of sodium nitrite]. The sulfuric acid solution of nitrite is prepared by adding finely powdered sodium nitrite to the acid with very vigorous stirring, warming the mixture to 70°, and, when dissolution is complete, cooling the solution to room temperature. An approximately 10% excess of sodium nitrite is used, calculated on the amine.

A continuous process for the preparation of diazonium salts has been described by Hupfer.[253]

The kinetics and mechanism of diazotization have been studied in depth (cf. Schmidt[254]). Diazonium salts are unstable, both in the solid state and in solution. Solid diazonium salts should be handled only in small quantities and with very great **caution** as they decompose explosively with extreme violence on warming, on shock, or even without recognizable cause.[255] The nature of the anion influences the liability to decomposition: chlorides and sulfates are generally less dangerous than nitrates or perchlorates. Diazonium solutions are not so dangerous, although they decompose slowly (often even if the temperature exceeds 5°); for reactions they are thus always freshly prepared. Methods for stabilizing diazonium salts have, however, been perfected in recent times; it is achieved by, *e.g.*, salt formation with 1,5-naphthalenedisul-

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[249] (a) K. H. Saunders, "The Aromatic Diazo-Compounds and Their Technical Applications," E. Arnold & Co., 2nd ed., 1949, pp. (b) 10, (c) 13, (d) 21.

[250] A. Hantzsch and E. Jochem, *Ber. Deut. Chem. Ges.*, **34**, 3337 (1901).

[251] W. Smith and C. E. Waring, *J. Amer. Chem. Soc.*, **64**, 469 (1942).

[252] A. N. Nesmayanov, *Org. Syn.*, Coll. Vol. II, 432 (1943).

[253] H. Hupfer, *Angew. Chem.*, **70**, 244 (1958).

[254] H. Schmidt, *Chemiker-Ztg.*, **78**, 565 (1954).

[255] E. Bamberger, *Ber. Deut. Chem. Ges.*, **28**, 538 (1895).

fonic acid or 2-hydroxynaphthalene-1-sulfonic acid,[256] by double-salt formation with mercury(II) chloride,[252] or by treatment of 2 moles of the diazonium salt with 1 mole of piperazine;[257] diazonium tetrafluoroborates have also often been used.[258]

Diamino compounds can be tetrazotized.[249d] Some ring substituents in the *ortho*-position to the newly formed diazonium group may cyclize with it, with or without elimination of nitrogen; for instance, 1,2,3-benzotriazole is obtained in 51% yield on diazotization of *o*-phenylenediamine.[259] If the *ortho*-substituent is a methyl group an indazole is formed.[260]

Two monographs deal in detail with the preparation, properties, reactions, and constitution of aromatic diazonium compounds.[249a] The diazotization of proteins has been described by Rohrlich.[261]

4. Preparation of azides

Particular care is required when working with azides as they are unusually **treacherous explosives.** The tendency of any one material to explode varies from batch to batch; and, if possible, no attempt should be made to isolate azides of low molecular weight. Storage of, and reactions involving, azides should be confined to solutions of less than 10% concentration. When working with volatile azides it is essential to avoid breathing the vapors; like hydrogen azide, organic azides have, *inter alia*, the property of expanding the blood vessels (similarity to alkyl nitrites; danger of circulatory collapse); azidoformic esters are especially active in this respect.

Only those azide syntheses are treated below that involve formation of an N-N bond, namely:

(i) by the action of ammonia on diazonium perbromides:[262]

$$\mathrm{ArN_2Br_3 + NH_3 \longrightarrow ArN_3 + 3HBr} \quad \text{(yield 55\%)}$$

(ii) by reaction of hydrazines with nitrous acid:[263]

$$\mathrm{ArNHNH_2 + HONO \longrightarrow ArN_3 + 2H_2O} \quad \text{(yield 65–68\%)}$$

(iii) from diazo compounds and hydrazine hydrate:[264]

$$\mathrm{ArN_2X + H_2NNH_2 \longrightarrow H_2O + ArN_2{-}NHNH_2 \longrightarrow ArN_3 + NH_3} \quad \text{(yield ca. 70\%)}$$

(iv) from arenediazonium salts and *O*-alkylhydroxylamines:[265]

$$\mathrm{ArN_2Cl + RONH_2 \longrightarrow ArN_3 + ROH + HCl} \quad \text{(yield good)}$$

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[256] N. Kornblum, *Org. Reactions*, **2**, 285 (1944).

[257] P. I. Drumm and co-workers, *Sci. Proc. Roy. Dublin Soc.*, **22**, 223 (1940).

[258] G. Schiemann and W. Winkelmüller, *Org. Syn.*, Coll. Vol. II, 188, 225 (1943); A. Wayne and co-workers, *J. Amer. Chem. Soc.*, **64**, 828 (1942).

[259] R. E. Darmschroder and W. D. Peterson, *Org. Syn.*, Coll. Vol. III, 106 (1955).

[260] H. D. Porter and W. D. Peterson, *Org. Syn.*, Coll. Vol. III, 660 (1955).

[261] M. Rohrlich, *Chemiker-Ztg.*, **80**, 847 (1956).

[262] K. Clusius and H. Hürzeler, *Helv. Chim. Acta*, **37**, 383 (1954).

[263] R. O. Lindsay and C. F. H. Allen, *Org. Syn.*, Coll. Vol. III, 710 (1955).

[264] C. K. Banks and O. M. Gruhzit, *J. Amer. Chem. Soc.*, **70**, 1268 (1948).

[265] A. B. Boese and co-workers, *J. Amer. Chem. Soc.*, **53**, 3530 (1931).

(v) from diazonium salts and sulfonamides:[266]

$$ArN_2Cl + Ar'SO_2NH_2 \longrightarrow ArN_3 + Ar'SO_2H + HCl \qquad \text{(yield 60–80\%)}$$

(vi) by oxidation of phenylsemicarbazide:[267]

$$C_6H_5NHNHCONH_2 \longrightarrow C_6H_5N{=}NCONH_2 \longrightarrow C_6H_5N{=}NNH_2 \longrightarrow C_6H_5N_3 \qquad \text{(yield 53\%)}$$

(vii) from arenediazonium salts and halo amines[268] in yields between 50% and 80%.

Phenyl azide from benzenediazonium perbromide and ammonia:[262] A 21% solution (15 ml) of ammonia is covered with a layer of ether (10 ml) and to it is added, with ice-cooling and good stirring, the diazonium perbromide (4.05 g) in small portions; a surface reaction between the perbromide and the ammonia leads to immediate and quantitative production of phenyl azide which is taken up by the ether phase. Then the ether is evaporated and the two-phase residue is subjected to steam-distillation. The distillate, which contains ammonia, is acidified with dilute sulfuric acid, and the phenyl azide is extracted in ether and then distilled in a high vacuum into a receiver cooled in solid carbon dioxide. The yield is 55% (0.775 g).

The diazonium perbromide is prepared as described in Gattermann and Wieland's book.[1f]

Phenyl azide from phenylhydrazine and nitrous acid:[263] Very pure phenylhydrazine (33.5 g) is added in 10 min, dropwise and with stirring and cooling in ice–salt, to a mixture of water (300 ml) and concentrated hydrochloric acid (58.5 ml). Whilst stirring is continued, the solution is covered with ether (100 ml) at 0° and a freshly prepared solution of sodium nitrite (25 g) in water (30 ml) is dropped in slowly (20–30 min) at a rate such that the temperature does not exceed 5°. The mixture is then distilled in steam (400 ml collected), the ether layer is separated, and the aqueous phase is extracted with ether (28 ml). The ether layers are combined, dried over calcium chloride (10 g), and distilled under reduced pressure in the water-bath (26–30°); the phenyl azide is distilled off cautiously at 65° (bath-temperature)/5 mm; it has b.p. 49–50°/5 mm; the yield is 24–25 g (65–68%).

Aryl azides from diazonium salts and *p*-toluenesulfonamide:[266] An aromatic monoamine (1 mole) or diamine (0.5 mole) is dissolved in concentrated hydrochloric acid (2.5 moles), and the resulting solution or suspension of the amine hydrochloride is diazotized with the calculated amount of sodium nitrite. The diazonium salt solution is mixed with a solution of *p*-toluenesulfonamide (1 mole) and sodium hydroxide (5 moles) at −5° and set aside for 24–48 h, then brought to pH 8 and extracted with ether. The azide is distilled as above. Solid azides, however, are filtered off and washed with ether.

Acyl azides are obtained from hydrazides by the action of nitrous acid or alkyl nitrites:[269]

$$RCONHNH_2 + HNO_2 \longrightarrow RCON_3 + 2H_2O$$

The reaction is carried out analogously to the diazotization of primary amines. A review by Lieber and Minnis[270] deals with carbamoyl azides.

(*p*-Nitrophenyl)acetyl azide:[271] The hydrazide (12 g) is dissolved in water (2 l) containing concentrated hydrochloric acid (8 ml) and treated, with stirring, with sodium nitrite (5 g) at 20°. The azide separates and is filtered off (yield 83.5%).

***tert*-Butyl azidoformate:**[272] Sodium nitrite (47 g) is added to an ice-cold mixture of *tert*-butyl hydrazinoformate (82 g), glacial acetic acid (72 g), and water (100 ml) within 40–50 min,

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[266] A. Key and P. K. Dutt, *J. Chem. Soc.*, **119**, 2088 (1921); **1928**, 2035; H. Brettschneider and H. Rager, *Monatsh. Chem.*, **81**, 970 (1950).

[267] A. Darapski, *Ber. Deut. Chem. Ges.*, **40**, 3033 (1907).

[268] Skraup and K. Steinruck, Ger. Pat. **456** 857; *Friedländer*, **16**, 452 (1931).

[269] I. Honzl and J. Rudinger, *Coll. Czech. Chem. Commun.*, **26**, 2333 (1961).

[270] E. Lieber and R. L. Minnis Jr., *Chem. Rev.*, **65**, 377 (1965).

[271] R. L. Shriner and J. M. Cross, *J. Amer. Chem. Soc.*, **60**, 2339 (1938).

[272] L. A. Carpino and co-workers, *Org. Syn.*, **44**, 15 (1964).

the temperature being kept between 10° and 15°. The whole is set aside for 30 min in the ice-bath, then treated with water (100 ml) and extracted four times with ether (40-ml portions). The united ethereal extracts are washed with water (4 × 50 ml) and with sodium hydrogen carbonate solution (3 × 40 ml), then dried over magnesium sulfate and freed from ether at 140–150 mm. The residual azide is distilled cautiously in small portions at a bath-temperature of 90–95°; it has b.p. 73–74°/70 mm, n_D^{24} 1.4227 (yield up to 82%). It must be handled in an efficient draught chamber.

5. Syntheses of hydrazines

In this Section only those hydrazine syntheses are discussed that occur with formation of an N–N bond (*N*-amination). For syntheses of substituted hydrazines by reduction of hydrazones, azines, *N*-nitroso compounds, and diazonium salts the Sections relevant thereto should be consulted.

The synthesis of substituted hydrazines has been extensively studied in recent years, with emphasis on alkylhydrazines, and the voluminous literature has been the subject of several reviews.[273,274]

N-Amination can be effected with compounds of type NH_2X where X is chlorine or OSO_3H. It was application of the Raschig synthesis to alkylamines that first made available a larger number of mono-[275] and *N*,*N*-di-alkylhydrazines,[276] as well as *N*,*N*,*N*-trialkylhydrazinium salts.[277] Attempts to replace the chlorine atom of *N*-chloroalkylamines by an amino group by the Raschig method all failed; only *N*-chloro-tetramethylenediamine and -tetramethylenediamine were amenable to intramolecular amination.[278]

Hydroxylamine-*O*-sulfonic acid (aminyl hydrogen sulfate) has often proved superior to chloramine for amination; the former is a stable crystalline substance that can be easily handled and weighed. It aminates primary[279,280] and secondary amines[280] to hydrazines, and tertiary amines to hydrazinium salts.[280] It is a stronger aminating agent than chloramine as it converts pyridine into the 1-aminopyridinium salt, a reaction that cannot be carried out by chloramine.[281] Other heterocycles, *e.g.*, uracil,[282] can also be converted into hydrazines by hydroxylamine-*O*-sulfonic acid.

1,1-Diethylhydrazine can be usefully prepared by aminating triethylamine with hydroxylamine-*O*-sulfonic acid and decomposing the resulting 1,1,1-triethylhydrazinium salt by alkali to ethylene and the diethylhydrazine; this method is better than amination of diethylamine.[280]

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[273] R. Ohme and A. Zubek, *Z. Chem.*, **8**, 41 (1968).

[274] C. C. Clark, "Hydrazine," Mathieson Chem. Corp., Baltimore, Maryland, 1953; R. F. Evans, *Rev. Pure Appl. Chem.*, **12**, 146 (1962); A. N. Kost and R. S. Sagitulin, *Usp. Khim.*, **33**, 361 (1964); C. G. Overberger, I. P. Anselme, and I. J. Lombardino, "Organic Compounds with Nitrogen–Nitrogen Bonds," The Ronald Press Company, New York, 1966.

[275] L. F. Audrieth and L. H. Diamond, *J. Amer. Chem. Soc.*, **76**, 4869 (1954); **77**, 3131 (1955); G. M. Omietanski and co-workers, *J. Amer. Chem. Soc.*, **78**, 3874 (1956).

[276] R. A. Rowe and L. F. Audrieth, *J. Amer. Chem. Soc.*, **78**, 563 (1956); F. R. Hurley, U.S. Pat. 3,015,675 (1962); *Chem. Abstr.*, **57**, 4543 (1962).

[277] G. M. Omietanski and H. H. Sisler, *J. Amer. Chem. Soc.*, **78**, 1211 (1956).

[278] A. Lüttringhaus and co-workers, *Chem. Ber.*, **92**, 1756 (1959).

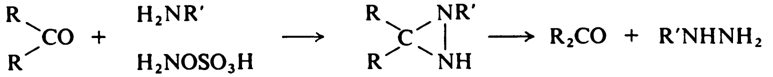
[279] G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949).

[280] R. Gösl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959).

[281] R. Gösl and A. Meuwsen, *Org. Syn.*, **43**, 1 (1963).

[282] W. Klötzer, *Monatsh. Chem.*, **97**, 1120 (1966).

The *N*-amination is particularly smooth when formation of a diaziridine ring occurs simultaneously with that of the N–N bond.[283,284] The diaziridine ring is formed when chloramine, an *N*-chloroalkylamine, or hydroxylamine-*O*-sulfonic acid reacts with a Schiff base or when hydroxylamine-*O*-sulfonic acid reacts with an aqueous solution of a ketone and an amine; warming the diaziridines with aqueous acid then cleaves them to the carbonyl compounds and the substituted hydrazine:



The end-product from synthesis of a diaziridine and its fission to alkylhydrazine is the same as is obtained by direct treatment of an amine with chloramine or hydroxylamine-*O*-sulfonic acid, as the carbonyl component of the Schiff base is recovered; however, the detour through the diaziridine is worthwhile because in the direct reaction a considerable excess of the amine must be used to suppress further reaction of the alkylhydrazine product with the aminating agent, whereas the diaziridines are unaffected thereby; moreover, the diaziridine route is more widely applicable. Even further, the diaziridine route avoids both the requirement for an excess of alkali and the production of the hydrazine as a very dilute aqueous solution, both of which characterize the direct reaction. Indeed it provides an effective and generally applicable synthesis of mono-[284,285] and 1,1-dialkyl-hydrazines.[286]

Monoalkylhydrazines can also be prepared by hydrolysis of diaziridines that are obtained from diazirines and Grignard reagents.[287] Pentamethylenediazirine (2,3-diazaspiro[2.5]oct-2-ene)[288] is a particularly suitable starting material for this synthetic route, which is of special value when the alkyl halide is more accessible than the amine.

Addition of aryl ethylenesulfonates to 1-alkylaziridines and subsequent hydrolysis makes available 1,2-disubstituted hydrazines of the type[289]

$$RNHNHCH_2CH_2SO_3Ar.$$

Hydroxylamine-*O*-sulfonic acid (aminyl hydrogen sulfate):[290] 60% oleum (300 ml) is added to hydroxylamine sulfate (250 g) during 1 h with stirring and exclusion of moisture, much heat being evolved. The mixture is stirred for a further 1 h, then the thick paste is set aside overnight. The crude acid is then filtered off as rapidly as possible and added to ether 600ml cooled in ice; the temperature should not exceed 20° during this addition. Filtration under goods uction and washing with more ether (400 ml) affords 99%-pure hydroxylamine-*O*-sulfonic acid (240–260 g); it is dried over phosphorus pentoxide and stored over that reagent.

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[283] E. Schmitz, *Adv. Heterocyclic Chem.*, **2**, 104 (1963); "Dreiringe mit zwei Heteroatomen," (Organische Chemie in Einzeldarstellungen, Vol. 9), Springer-Verlag, Berlin–Heidelberg, 1967.

[284] E. Schmitz, *Angew. Chem. Int. Ed., Engl.* **3**, 333 (1964); R. Ohme, E. Schmitz, and L. Sterk, *J. Prakt. Chem.*, [iv], **37**, 257 (1968).

[285] E. Schmitz and D. Habisch, *Chem. Ber.*, **95**, 680 (1962); E. Schmitz, D.D.R. Pat. 24,622; *Chem. Zentralbl.*, **1964**, 39-2385.

[286] E. Schmitz and K. Schinkowski, *Chem. Ber.*, **97**, 49 (1964).

[287] E. Schmitz and R. Ohme, *Chem. Ber.*, **94**, 2166 (1961); Ger. Pat. 1,134,083; *Chem. Abstr.*, **57**, 14936 (1963).

[288] E. Schmitz and R. Ohme, *Org. Syn.*, **45**, 83 (1965).

[289] H. Dorn and K.-H. Walter, *Ann. Chem.*, **720**, 98 (1968).

[290] E. Schmitz and co-workers, *Ann. Chem.*, **702**, 131 (1967).

Methylhydrazine oxalate:[291] Hydroxylamine-*O*-sulfonic acid (1 mole) is added in 45 min, with good cooling (0° to, at most, 10°) and stirring, to a solution of cyclohexanone (103 ml) in 36% methylamine solution (515 g). After a further hour's cooling, the mixture is extracted with toluene (400 ml). The toluene layer is at first shaken with an aqueous solution of crystalline oxalic acid (19 g), then separated therefrom and placed over an aqueous solution of oxalic acid (76 g of dihydrate). This mixture is heated under reflux until a sample of the toluene layer no longer liberates iodine from a dilute sulfuric acid solution of potassium iodide. The aqueous layer is then evaporated in a vacuum, giving methylhydrazine oxalate (80 g), m.p. 150–155°.

Pentylhydrazine:[279] Water (180 ml), pentylamine (47.5 g, 0.55 mole), and potassium hydroxide (9.4 g) are mixed, giving two layers. The mixture is heated under reflux and hydroxylamine-*O*-sulfonic acid[280] (9.9 g, 0.083 mole) in ice-water (50 ml) is added dropwise during 30 min. The whole is cooled and acidified with glacial acetic acid (70 ml), and some of it (50 ml) is distilled off at atmospheric pressure. Inorganic salts are then filtered off after cooling, and the filtrate is warmed to 50° and stirred for 10 min with benzaldehyde (9 g). The resulting emulsion is cooled and extracted with ether (3 × 50 ml). The united extracts are mixed with a solution of oxalic acid dihydrate (20 g) in water (100 ml), a little charcoal is added, and the whole subjected to steam-distillation until no more benzaldehyde passes over. The residue is filtered and cooled, whereupon a white precipitate of pentylhydrazine oxalate separates.

General procedure for *N*-amination with chloramine: A cold solution (250 ml) of chloramine (0.04 mole; prepared from sodium hypochlorite and ammonia) is treated with gelatine (0.25 g) and an alkylamine (0.32 mole), and the whole is left for 1 h at room temperature and then heated on a water-bath for 10–30 min. The alkylhydrazine is isolated in one of two ways: (a) The excess of amine and part of the water are distilled off and the hydrochloride or sulfate of the alkylhydrazine is obtained by acidification. Or (b) the mixture is neutralized with acetic acid, treated with benzaldehyde, and extracted with ether; aqueous oxalic acid is added to the ethereal layer and the whole distilled in steam until the benzaldehyde is removed; the alkylhydrazine oxalate is obtained by concentration of the residual liquid. Yields range between 40% and 60%.

1,1-Diethylhydrazine:[280] A mixture of triethylamine (4 g, 40 mmoles), potassium hydroxide (5.6 g, 100 mmoles), and hydroxylamine-*O*-sulfonic acid (5.3 g, 47 mmoles) in water (120 ml) is distilled, all the material that distils up to 100° being collected. The content of 1,1-diethylhydrazine in the distillate is determined by means of N/40-potassium iodate. The yield is 2.87 g (82%). The product gives a picrate, m.p. 84°.

The N–N linkage of tetraarylhydrazines is readily obtained by oxidation of diarylamines, suitable oxidizing agents being lead dioxide in ether,[292] potassium permanganate,[293] or, best, silver oxide in pyridine–ether.[294] Tetraalkylhydrazines are obtained in very good yield by oxidizing copper(I) amides of secondary amines with oxygen.[295]

6. Diazoamino compounds (triazenes)

Diazonium salts react with primary or secondary aromatic amines to give diazoamino compounds:

$$RN_2X + NH_2R' \longrightarrow RN{=}NNHR' + HX$$

They may be formed when not desired, during diazotization in insufficiently strongly acidic solution. Diazoamino compounds crystallize well and are yellow and feebly basic; they form salts with acids but they also give metal

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[291] R. Ohme and E. Schmitz, unpublished work.

[292] H. Wieland, *Ber. Deut. Chem. Ges.*, **45**, 2602 (1912).

[293] E. Lieber and S. Somasekhara, *J. Org. Chem.*, **24**, 1775 (1959).

[294] H. Wieland, *Ber. Deut. Chem. Ges.*, **53**, 1322 (1920).

[295] T. Kaufmann and co-workers, *Angew. Chem. Int. Ed., Engl.*, **6**, 633 (1967).

salts on reaction with Cu(II), Ag, or Hg(II) salts, the hydrogen atom attached to nitrogen being replaced.

The pale yellow diazoamino compounds often contain red impurities that can be removed by chromatography on alumina.[296] They are stable at room temperature but, when heated, usually decompose, sometimes explosively. Mineral acids split them to the amine and diazonium salts.

Diazoamino compounds can be prepared, essentially by two methods:

(i) By coupling of diazonium salts with primary or secondary amines in buffered solution.[297,298] In the coupling with aliphatic primary amines the diazoamino compound formed reacts further with the diazonium salt to give 3-alkyl-1,5-diarylpentaza-1,4-dienes (bisdiazonium compounds); to suppress this, a water-immiscible solvent is added which withdraws the diazoamino product from the aqueous layer, thus preventing the further reaction.[297] Benzenediazonium salts and ammonia give only the pentazadiene.[299] On the other hand, 1-triazenoanthraquinone can be obtained by reaction of 1-diazoanthraquinone with ammonium carbonate.[300] Nevertheless, secondary aliphatic amines and primary or secondary aromatic amines usually give good yields; for example, reaction of a benzenediazonium salt with dimethylamine gives a 93% yield of 3,3-dimethyl-1-phenyltriazene.[301]

(ii) By the action of amines on *N*-acyl-*N*-nitrosoamines.[302] Reaction of *N*-nitroso amides in place of diazonium salts has the advantage that the triazene is prepared in an organic solvent.

Diazoamino compounds can rearrange to aminoazo compounds under feebly acidic conditions.[303]

1,3,5-Triarylpentaza-1,4-dienes can be prepared in useful yield by the action of diazonium salts with 1,3-diaryltriazenes in alcoholic alkoxide solution.[304]

7. Azo compounds

Azo compounds can be regarded as substitution products of diimine HN=NH, but, unlike this parent, azo compounds of general formula RN=NR′ are stable. R and R′ may be the same or different aromatic or heteroaromatic groups; or R may be aromatic and R′ aliphatic; however, wholly aliphatic azo compounds are also known. Further, the azo group may be linked to an aromatic or aliphatic acyl group (giving an acylazo compound). Finally, R and R′ may be secondary amino groups (1,1,4,4-tetrasubstituted 2-tetrazenes).

Aromatic azo compounds differ in methods of preparation and in properties from other azo compounds. Aromatic azo compounds, which are all colored, are the most stable members of this class; they are used in large quantities as

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[296] T. W. Campbell and B. F. Day, *Chem. Rev.*, **48**, 299 (1951).

[297] O. Dimroth, *Ber. Deut. Chem. Ges.*, **38**, 2328 (1905).

[298] W. W. Hartmann and I. B. Dickey, *Org. Syn.*, Coll. Vol. II, 163 (1955).

[299] H. von Pechmann and L. Frobenius, *Ber. Deut. Chem. Ges.*, **28**, 170 (1895).

[300] L. Wacker, *Ber. Deut. Chem. Ges.*, **35**, 3922 (1902).

[301] J. Elks and D. H. Hey, *J. Chem. Soc.*, **1943**, 441.

[302] R. Huisgen, *Ann. Chem.*, **573**, 177 (1951).

[303] P. Ruggli and A. Courtin, *Helv. Chim. Acta*, **15**, 90 (1932).

[304] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **27**, 703 (1894).

dyes. Aliphatic azo compounds, on the other hand, are colorless and less stable; at elevated temperatures they have a tendency towards homolytic decomposition and thus find industrial use as radical formers. This decomposition may even become explosive among the lower aliphatic members such as azomethane, $CH_3N{=}NCH_3$;[305] compounds in which the azo group forms part of a three-membered ring (*i.e.*, diazirines) are particularly **explosive.**[288,306] Under acid conditions aliphatic azo compounds rearrange readily to hydrazones.[307] Azo compounds can exist in *cis*- and *trans*-forms, the more stable *trans*-forms being converted into the *cis*-isomers by irradiation with light of short wavelength;[308] the *cis*- and *trans*-forms of aromatic azo compounds can be separated by chromatography on alumina.[309]

The following paragraphs describe the methods of forming azo compounds in which an N–N bond is created (for preparation by coupling see the Section on "Preparation of the C–N bond by replacement".) These methods can be classified as: (a) oxidative junction of amines; (b) oxidation of hydrazo compounds; (c) disproportionation of hydrazo compounds; (d) action of hypochlorite on *N,N′*-diarylsulfamides; (e) condensation of nitroso compounds with amines; (f) reaction of nitro compounds with amines; (g) reduction of nitro and nitroso compounds; and (h) reaction of *N*-arylhydroxylamines with sulfinylimines.

(a) Two arylamine molecules can be joined together at the oxygen atom to give an azo compound by means of the following oxidizing agents: active manganese dioxide, peroxyboric or peroxyacetic acid, molecular oxygen in the presence of alkoxides or pyridine–copper(I) complexes, sulfur or selenium in the presence of mercury–carboxamide complexes,[310] iodosobenzene diacetate in benzene[311] or glacial acetic acid,[312] lead tetraacetate in glacial acetic acid,[313] or chromium trioxide.[314]

Active manganese dioxide seems to be the reagent of choice, having been used for conversion of many arylamines (*e.g.*, aniline, *m*- and *p*-chloroaniline, *o*- and *p*-anisidine, *o*-ethylaniline) into azo compounds in 90% yield.

General procedure:[315] An arylamine (0.01 mole) and dry active manganese dioxide (0.05 to 0.06 mole) are boiled in benzene for 6 h under a water-separator. Then the mixture is filtered, the manganese dioxide is washed with benzene, the benzene is evaporated, and the residual azo compound is crystallized by addition of hexane.

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[305] F. P. Jahn, *J. Amer. Chem. Soc.*, **59**, 1761 (1937).

[306] R. Ohme and E. Schmitz, *Chem. Ber.*, **97**, (1964).

[307] E. Fischer, *Ber. Deut. Chem. Ges.*, **29**, 794 (1897); A. Elbers, *Ann. Chem.*, **227**, 354 (1885); J. Thiele, *Ann. Chem.*, **376**, 267 (1910); D. W. Neighbors and co-workers, *J. Amer. Chem. Soc.*, **44**, 1561 (1922).

[308] R. F. Hutton and C. Steel, *J. Amer. Chem. Soc.*, **86**, 745 (1964); G. O. Schenck and co-workers, *Z. Naturforsch.*, **20a**, 637 (1965); F. Aylward and M. H. Sawstowska, *J. Chem. Soc.*, **1964**, 1435.

[309] A. H. Cook and D. G. Jones, *J. Chem. Soc.*, **1939**, 1309.

[310] P. S. Pishimuka, *Zh. Obshch. Khim.*, **21**, 1689 (1951); *Chem. Abstr.*, **46**, 8030 (1952); L. F. Shpeier, *Trans. Khar'kovsk. Sel'skokhoz. Inst.*, **35**, 138 (1961); *Chem. Abstr.*, **59**, 3799 (1963).

[311] K. H. Pausacker, *J. Chem. Soc.*, **1953**, 1889; H. H. Szmant and R. Infante, *J. Org. Chem.*, **26**, 4173 (1961).

[312] G. B. Barlin and co-workers, *J. Chem. Soc.*, **1954**, 3122.

[313] K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.*, **1954**, 4004.

[314] P. Ruggli and B. Hegedüs, *Helv. Chim. Acta*, **24**, 703 (1941).

[315] O. H. Wheeler and D. Gonzales, *Tetrahedron*, **20**, 189 (1964).

Perborate in glacial acetic acid also gives good results, *e.g.*, converting *p*-aminoacetanilide into 4,4′-bis(acetylamino)azobenzene in 57% yield,[316] and affording 4,4′-dihaloazobenzenes in about 50% yield.[317] Oxidation of arylamines by other peracids does not give homogeneous products, azo and azoxy compounds being formed side by side; in the presence of copper salts, however, the formation of azo compounds is favored, as when *m*-nitroaniline is oxidized by peracetic in glacial acetic acid containing copper(II) chloride to 3,3′-dinitroazobenzene in 72% yield.[318]

In the presence of potassium *tert*-butoxide, molecular oxygen converts certain substituted primary arylamines into azo compounds through radical intermediates; 4,4′-dimethoxyazobenzene is obtained in 65% yield from *p*-anisidine in toluene at room temperature.[319] Oxidation by oxygen is more effective with a pyridine solution of the arylamine containing copper(I) chloride: an 81% yield of 4,4′-bis(dimethylamino)azobenzene was obtained in this way.[320] Results are particularly good with potassium *tert*-butoxide in dimethyl sulfoxide,[321] giving, for instance, 87% of azobenzene from aniline and also being useful for various haloanilines.

(b) Hydrazo compounds can be oxidized to azo compounds by any of the usual reagents, such as mercuric oxide, potassium permanganate, or hypobromite; oxidation of hydrazo compounds by molecular oxygen in the presence of an alkali alkoxide has a particular use, for, besides the azo compound, it gives the alkali peroxide which can then be decomposed to hydrogen peroxide, and this process has been carried out industrially for manufacture of hydrogen peroxide.[322] Oxidation by air also succeeds well with compounds that contain the hydrazo group as component in a heterocyclic ring.[83]

(c) Hydrazo compounds disproportionate to azo compounds and arylamines thermally[323] and on ultraviolet irradiation, (2300–2700 Å),[324] but this reaction is without preparative value.

(d) The action of hypochlorite on *N*,*N*′-dialkylsulfamides affords azoalkanes in good yield,[325,326] and can be adapted for preparation also of 4,4′-disubstituted aromatic azo compounds:

4,4′-Dinitroazobenzene:[326] *N*,*N*′-Bis-(*p*-nitrophenyl)sulfamide[327] (10 g) is dissolved in water (100 ml) containing 2N-sodium hydroxide solution (30 ml). It is then poured, with stirring, into a hot mixture of 2N-sodium hydroxide solution (30 ml) and 1.4M-sodium hypochlorite solution (100 ml). When the mixture is warmed at 90° the azo compound is precipitated; it is collected, washed with alcohol, and crystallized from glacial acetic acid containing a little chromic acid. This gives red needles, m.p. 216°, in 31% yield (2.5 g).

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[317] S. M. Mehta and M. V. Vakilwala, *J. Amer. Chem. Soc.*, **74**, 563 (1952).

[318] E. Pfeil and K. H. Schmidt, *Ann. Chem.*, **675**, 36 (1964).

[319] L. Horner and J. Dehnert, *Chem. Ber.*, **96**, 786 (1963).

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[321] G. A. Russell, E. G. Janzen, H.-D. Becker, and F. J. Smentowski, *J. Amer. Chem. Soc.*, **84**, 2652 (1962).

[322] French Pat. 790,497; *Chem. Abstr.*, **30**, 3175 (1936); U.S. Pat. 2,908,552; *Chem. Abstr.*, **54**, 3882 (1960); D. A. Blackadder and C. Hinshelwood, *J. Chem. Soc.*, **1957**, 2898.

[323] P. F. Holt and B. P. Hughes, *J. Chem. Soc.*, **1953**, 1666.

[324] P. F. Holt and B. P. Hughes, *J. Chem. Soc.*, **1955**, 98.

[325] R. Ohme and E. Schmitz, *Angew. Chem. Int. Ed., Engl.*, **4**, 433 (1965).

[326] R. Ohme and H. Preuschhof, *Ann. Chem.*, **713**, 74 (1968).

[327] E. W. Parnell, *J. Chem. Soc.*, **1960**, 3466.

(e) Condensation of aromatic nitroso compounds with arylamines is a valuable method of preparing asymmetric diarylazo compounds. It gives high yields in an acid medium (glacial acetic acid with or without an organic solvent), for example, 95% of azobenzene;[328] it can be carried out also in an alkaline medium, but yields are then lower.[329] This reaction is also useful for ^{15}N labelling of azo compounds.[323]

Ethyl 4′-nitroazobenzene-4-carboxylate:[330] Ethyl *p*-nitrosobenzoate (5 g) and *p*-nitroaniline (4.2 g) are heated in glacial acetic acid (100 ml) containing trichloroacetic acid (15 g) on a water-bath for 4 h, then the mixture is cooled and poured into water, and the precipitated ester is taken up in benzene–ether (1 : 1). This solution is concentrated (to 250 ml) and poured through alumina (Brockmann, neutral, activity 1–2; 100 g), giving a product, m.p. 162–163° (from benzene) (7.26 g, 87%).

(f) Reaction of aromatic nitro compounds with arylamines is usually smooth[331] but requires more drastic conditions (200° in presence of sodium hydroxide) than does that of nitroso compounds. Its course is not clear-cut as part of the arylamine is oxidized. 3-Methoxyazobenzene has, *inter alia*, been prepared by this method (55% yield).[332]

(g) The reduction of aromatic nitro and nitroso compounds by a series of reagents under alkaline conditions can be so arranged as to produce the azo compounds by way of the nitroso and azoxy intermediates; for instance, azobenzene is formed in 86% yield by reduction of nitrobenzene with zinc dust and alkali.[333] Halogenated nitro compounds are converted into azo compounds by hydrazine in alcoholic solution containing a palladium catalyst.[334] Lithium tetrahydridoaluminate also gives good yields of azo compounds,[35] as do sodium tetrahydridoaluminate[335] and ethoxytrihydridoaluminate.[80] Nitro compounds can be smoothly reduced by silicon or ferrosilicon in an aqueous-alcoholic alkaline medium, azoxy, azo, and hydrazo compounds being formed depending on the amount of silicon used.[336]

Azobenzene: Nitrobenzene (15 g) in ethanol (50 ml) is stirred into a solution of sodium hydroxide (70 g) in water (200 ml), then silicon powder (25 g) is added to the boiling mixture in portions such that evolution of hydrogen continues brisk. The whole is then boiled for 1.5 h and the azobenzene (10.3 g, 98%) is driven over in steam.

In individual cases nitro compounds are reduced to azo compounds by glucose in aqueous or alcoholic alkali.[337] Tin(II) chloride,[338] alkali sulfides,[339] and sodium amalgam[386] have been used for the same reduction.

(h) Azo compounds can be prepared in very good yields (90%) by treating *N*-arylhydroxylamines with *N*-arylsulfinimines:[340]

$$3\mathrm{ArNHOH} + \mathrm{Ar'N{=}S{=}O} \longrightarrow \mathrm{ArN{=}NAr'} + \mathrm{ArNHSO_3H} + \mathrm{ArNH_2} + \mathrm{H_2O}$$

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[328] Y. Ogata and Y. Takagi, *J. Amer. Chem. Soc.*, **80**, 3591 (1958).

[329] N. Campbell and co-workers, *J. Chem. Soc.*, **1953**, 1281.

[330] E. Hecker, *Chem. Ber.*, **88**, 1666 (1955).

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[335] A. E. Finhold and co-workers, *J. Amer. Chem. Soc.*, **77**, 4163 (1955).

[336] R. Meier and F. Böhler, *Chem. Ber.*, **89**, 2303 (1956).

[337] R. B. Johns and K. R. Markham, *J. Chem. Soc.*, **1962**, 3712.

[338] O. N. Witt, *Ber. Deut. Chem. Ges.*, **18**, 2912 (1885).

[339] Ger. Pat. 216,246; *Chem. Abstr.*, **4**, 813 (1910).

[340] A. Michaelis and K. Peton, *Ber. Deut. Chem. Ges.*, **31**, 984 (1898); H. E. Fierz-David and co-workers, *Helv. Chim. Acta*, **34**, 846 (1951).

Aromatic-aliphatic azo compounds can without exception be prepared by oxidation of the corresponding *N*-alkyl-*N'*-arylhydrazines. The oxidant must be one that reacts in neutral or alkaline conditions since the azo product rearranges to arylhydrazone in an acid medium. Mercury(II) oxide, introduced by Emil Fischer[341] as oxidant, is almost always used for this reaction. 30% Hydrogen peroxide in hydrogen carbonate solution has been applied to dehydrogenation of *N*-aryl-*N'*-(triphenylmethyl)hydrazines with good results.[342]

Azoalkanes are mostly prepared by dehydrogenating *N,N'*-dialkylhydrazines, but also by methods that newly form the N–N bond, for example by the action of alkaline hypochlorite solution on *N,N'*-dialkylsulfamides.[325,326] In isolated cases azoalkanes have been obtained from alkyl isocyanates and hydrogen peroxide (azooctadecane in 38% yield).[343] 2,2'-Azoisobutane (1,1,1',1'-tetramethylazoethane) was prepared from *N*-bromo-*tert*-butylamine and silver oxide in 13% yield.[344]

Any of many oxidants can be used for dehydrogenation of *N,N'*-dialkylhydrazines to azoalkanes since these hydrines are powerful reducing agents; an acid reaction medium is essential as otherwise the azoalkanes rearrange very quickly to alkylhydrazones.

Azomethane was prepared by oxidizing 1,2-dimethylhydrazine with neutral potassium chromate solution.[9] Mercuric oxide is often used as dehydrogenating agent;[47] silver oxide proved best for converting diaziridines into diazirines;[288] 1-isopropyl-2-methylhydrazine was oxidized to the azo compounds by an excess of 30% hydrogen peroxide;[345] when 1,2-dimethyl- or 1,2-diethylhydrazine is treated with copper(II) chloride or[305,346] with hydrazine hydrochloride and copper oxide[49] the azoalkanes are obtained as red, crystalline copper complexes[347] which afford very pure azoalkanes on thermal decomposition. Alcoholic iodine solution has also been found to be a useful oxidant for such reactions.[348]

Hydrazines of the general formula RR'(NC)C–NHNH–C(CN)RR', obtained by addition of hydrogen cyanide to ketazines, can be dehydrogenated to azo compounds under acid conditions, best by bromine in aloholic hydrogen chloride;[349] attempts to use nitrous acid gave poorer yields.[350]

1,1'-Dicyanoazoalkanes:[350] A 1,2-bis-(1-cyanoalkyl)hydrazine (0.04–0.08 mole) is dissolved in saturated alcoholic hydrogen chloride, cooled in ice, and treated dropwise with a solution of bromine (4 g) in ethanol (100 ml). The mixture becomes homogeneous, then more bromine is added until its absorption is only slow. The whole is then poured into water, and the azo compound is filtered off, washed with water (crude yield 70–90%), and recrystallized from ether or ethanol.

Azoalkanes can also be obtained in good yield by treating *N,N'*-dialkylsulfamides with alcoholic sodium hypochlorite solution:[325,326]

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[341] E. Fischer, *Ber. Deut. Chem. Ges.*, **29**, 793 (1896).

[342] S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **75**, 5504 (1963).

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[348] G. Fodor and J. Wein, *J. Chem. Soc.*, **1948**, 890.

[349] C. G. Overberger and co-workers, *Org. Syn.*, Coll. Vol. IV, 66, 274 (1963).

[350] C. G. Overberger and co-workers, *J. Amer. Chem. Soc.*, **71**, 2661 (1949).

Azocyclohexane: *N,N'*-Dicyclohexylsulfamide (13 g, 0.05 mole) in methanol (150 ml) containing 2N-sodium hydroxide (50 ml) is treated slowly at 40–50° with sodium hypochlorite solution (0.1 mole). Then the methanol is removed in a vacuum and the residue is extracted with ether. Evaporation of the extract gives azocyclohexane (5.1 g, 58%), having m.p. 33–34° after recrystallization from ether.

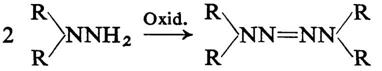
2,2'-Azoisobutane (1,1,1',1'-tetramethylazoethane) is obtained in 48% yield on oxidation of *tert*-butylamine with iodine pentachloride.[351]

Acylazo compounds: Acylazo compounds contain one or two carbonyl groups adjacent to the azo group. They differ from aliphatic and aromatic azo compounds in having pronounced reactivity at the N=N group.[352]

Acylazo compounds are prepared by oxidizing acyl- and diacyl-hydrazines, reagents of proved value being chlorine,[353] bromine,[354] *N*-bromosuccinimide,[355] concentrated nitric acid,[356] and silver oxide.[354] Lower aliphatic diacylazo compounds have been obtained by treating the diacylhydrazines with mercury(II) chloride and oxidizing the resulting metal salts with iodine.[357] Cyclic diacylazo compounds are formed on dehydrogenation of acid hydrazides with lead tetraacetate[358] or *tert*-butyl hypochlorite,[359] but because of their instability they are not isolated.

8. Tetraalkyl-2-tetrazenes

N,N-Dialkylhydrazines can be oxidized to tetraalkyl-2-tetrazenes in good yield by potassium bromate in hydrochloric acid solution:



$$2\ R_2NNH_2 \xrightarrow{\text{Oxid.}} R_2NN{=}NNR_2$$

Tetramethyl-, tetraethyl, and tetrapropyl-2-tetrazene can be prepared as follows:

Tetraalkyl-2-tetrazenes:[360] The 1,1-dialkylhydrazine (3 moles) is added to 37% hydrochloric acid (4.6 moles) at 0° and then treated with potassium bromate (1 mole) slowly whilst the temperature is kept below 10°. Neutralization with 10N-sodium hydroxide solution (4.75 moles) then affords 85% of the tetraalkyl-2-tetrazene.

This oxidation can also be effected by bromine in the presence of calcium carbonate or by mercuric oxide. When 1,1-dibenzylhydrazine is oxidized by potassium permanganate, air, or Fehling's solution, it yields bibenzyl with loss of the nitrogen; tetrabenzyl-2-tetrazene is obtained only, and in moderate yield, by means of mercury(II) acetate or benzoquinone.[361]

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[356] J. C. Kauer, *Org. Syn.*, Coll. Vol. IV, 411 (1963).

[357] H. H. Inhoffen and co-workers, *Chem. Ber.*, **81**, 507 (1948).

[358] R. A. Clement, *J. Org. Chem.*, **27**, 1115 (1962).

[359] T. J. Kealy, *J. Amer. Soc.*, **84**, 966 (1962).

[360] W. R. McBride and H. W. Kruse, U.S. Pat. 3,135,800; *Chem. Abstr.*, **61**, 4215 (1964); *J. Amer. Chem. Soc.*, **79**, 572 (1957).

[361] R. L. Hinman and K. L. Hamm, *J. Amer. Chem. Soc.*, **81**, 3294 (1959).

9. Azoxy compounds

The most important synthesis of aromatic azoxy compounds is by reduction of aromatic nitro compounds by specific reagents; nitroso and hydroxyamino compounds, which are intermediates in this reduction, can combine to give azoxy compounds with formation of the N–N bond; this reaction is favored by alkaline conditions.[19b]

Proved reductants are alcoholic sodium hydroxide, glucose in an alkaline aqueous medium,[362] and hydrazine in the presence of palladinized calcium carbonate.[334] Azoxy compounds that contain nitro groups are prepared by catalytic hydrogenation in an alkaline medium in the presence of a palladium–charcoal catalyst;[363] sodium arsenite[364] and stannite[365] have also been used for this reduction. A general method has been worked out for reduction by potassium tetrahydridoborate.[366] Individual azoxy compounds have been prepared by reduction of aromatic nitro compounds by magnesium in methanol,[367] tin(II) chloride,[368] phosphine in sodium hydroxide solution,[369] or electrolytically on graphite electrodes in sodium carbonate solution.[370]

Azoxybenzene:[371] Nitrobenzene (10 g) is added during 40 min to a stirred solution of sodium hydroxide (66 g) in methanol (200 ml) placed in a bath at 80–84°. More nitrobenzene (40 g) is added during the next 10 min, the internal temperature rising to 92° and a small amount of hydrogen (ca. 0.3 l) being evolved. The mixture is stirred for a further 2.5 h at a bath-temperature of 84°, then poured into water (1.5 l). The precipitated azoxybenzene is washed with water, then dilute hydrochloric acid and again water and dried in the air. This gives 96% (38.6 g) of material of m.p. 33–34° (not recrystallized).

Treating aromatic nitroso compounds with arylhydroxylamines under mild conditions often affords quantitative yields of the azoxy compounds;[372] when alcoholic solutions of the components are mixed (if necessary with addition of a little acetic acid), the azoxy compound soon crystallizes or, if not, is precipitated by water.

Azoxy compounds can also be obtained by oxidizing arylamines with peroxy compounds. Aniline is oxidized to azoxybenzene by hydrogen peroxide in acetonitrile–methanol at 50°, the yield being 62%;[373] and 3,3′-dinitroazoxybenzene is obtained in 79% yield from *m*-nitroaniline and peroxyacetic acid in glacial acetic acid.[318]

10. Preparation of aliphatic diazo compounds

Since, unlike arylamines, alkylamines cannot be diazotized, special processes are needed for synthesis of aliphatic diazo compounds; these mostly involve a

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[362] H. W. Galbraith and co-workers, *J. Amer. Chem. Soc.*, **73**, 1323 (1951).

[363] K. Brand and J. Steiner, *Ber. Deut. Chem. Ges.*, **55**, 875 (1922).

[364] H. E. Bigelow and A. Palmer, *Org. Syn.*, Coll. Vol. II, 58 (1943).

[365] G. Lock and E. Bayer, *Ber. Deut. Chem. Ges.*, **69**, 2666 (1936).

[366] H. I. Heine and H. E. Mallory, *J. Org. Chem.*, **27**, 2390 (1962).

[367] L. Zechmeister, *Ann. Chem.*, **468**, 117 (1929).

[368] B. Flürscheim, *J. Prakt. Chem.*, [ii], **71**, 497 (1905); B. Flürscheim and P. Simon, *J. Chem. Soc.*, **93**, 1463 (1908).

[369] S. A. Buckler and co-workers, *J. Org. Chem.*, **27**, 794 (1962).

[370] M. V. King, *J. Org. Chem.*, **26**, 3323 (1961).

[371] D. Habisch and co-workers, unpublished work.

[372] G. A. Russell and E. J. Guls, *J. Amer. Chem. Soc.*, **87**, 122 (1965), who discuss mechanism and report references.

[373] G. B. Payne and co-workers, *J. Org. Chem.*, **26**, 659 (1961).

detour through *N*-nitroso alkylamines, whence an acyl group can be removed in an alkaline medium.[216] Aliphatic diazo compounds may be prepared as follows:

(a) from *N*-alkyl-*N*-nitrosourethanes:[374]

$$\mathrm{CH_3N(NO)COOC_2H_5 + KOH \longrightarrow CH_2N_2 + K_2CO_3 + C_2H_5OH + H_2O}$$

(b) from *N*-alkyl-*N*-nitrosoureas:[375]

$$\mathrm{CH_3N(NO)CONH_2 + KOH \longrightarrow CH_2N_2 + KOCN + 2H_2O}$$

(c) from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide:[376]

$$\mathrm{CH_3N(NO)SO_2C_7H_7 + C_2H_5O^- \longrightarrow CH_2N_2 + C_7H_7SO_2C_2H_5 + HO^-}$$

(d) from *N*-alkyl-*N*-nitroso-*N'*-nitroguanidines:[241,377]

$$\mathrm{CH_3N(NO)C({=}NH)NHNO_2 + KOH \longrightarrow CH_2N_2 + K[NCNNO_2] + H_2O}$$

(e) from methyl-4-(*N*-methyl-*N*-nitrosoamino)-2-pentanone:[218]

$$\mathrm{CH_3N(NO)C(CH_3)_2CH_2COCH_3 \xrightarrow[RONa]{} CH_2N_2 + (CH_3)_2C{=}CHCOCH_3 + H_2O}$$

(f) from *N,N'*-dimethyl-*N,N'*-dinitrosoterephthaldiamide:[378]

$$\mathrm{CH_3N(NO){-}COC_6H_4CO{-}N(NO)CH_3 \xrightarrow[NaOH]{} 2CH_2N_2 + C_6H_4(COOH)_2}$$

(g) from aldehyde and ketone hydrazones by oxidation:[379]

$$\mathrm{R_2C{=}NNH_2 \xrightarrow[HgO]{} R_2CN_2 + H_2O + Hg}$$

(h) by vacuum-pyrolysis of alkali salts of aldehyde *N'*-tosylhydrazones. The method is valuable when the aldehyde precursor is more easily accessible than the amine[380] (the Bamford–Stevens reaction):

$$\mathrm{RCH{=}NN(CH_3)SO_2C_7H_7 \longrightarrow RCHN_2 + CH_3SO_2C_7H_7}$$

(i) by reaction of oximes with chloramines or hydroxylamine-*O*-sulfonic acid (Forster reaction).[381]

There are excellent reviews, by Eistert,[382] Gutsche,[383] and Huisgen,[384] covering the theoretical and practical aspects of the important field of diazoalkanes.

Aliphatic diazo compounds are all poisonous and colored — colors range from yellow or purplish-red. The lower diazoalkanes are gaseous and **explosive**, higher members are liquid to solid and much more stable. Comparative studies of the rate of decomposition by acid

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[374] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **27**, 1888 (1894).

[375] J. R. Dyer and co-workers, *J. Org. Chem.*, **29**, 3423 (1964); F. Arndt and H. Scholz, *Angew. Chem.*, **46**, 47 (1933).

[376] T. J. DeBoer and H. J. Backer, *Org. Syn.*, Coll. Vol. IV, 250 (1963).

[377] A. F. McKay, *Chem. Rev.*, **51**, 331 (1952); *J. Amer. Chem. Soc.*, **71**, 1968 (1949).

[378] J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

[379] L. I. Smith and K. L. Howard, *Org. Syn.*, Coll. Vol. III, 351 (1950); R. Hüttel and co-workers, *Chem. Ber.*, **93**, 1425 (1960); R. Baltzly and co-workers, *J. Org. Chem.*, **26**, 3669 (1961); A. Schönberg and E. Freese, *Chem. Ber.*, **95**, 2810 (1962); A. C. Day and co-workers, *J. Chem. Soc., C*, **1966**, 467.

[380] G. M. Kaufman and co-workers, *J. Amer. Chem. Soc.*, **87**, 935 (1965).

[381] J. Meinwald and co-workers, *J. Amer. Chem. Soc.*, **81**, 4751 (1959).

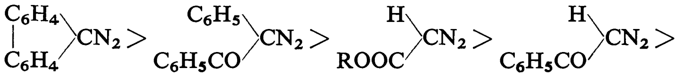
[382] B. Eistert, *Angew. Chem.*, **54**, 99, 124, 308 (1941); **55**, 118 (1942); **61**, 185 (1949).

[383] C. D. Gutsche, *Org. Reactions*, **8**, 364 (1954).

[384] R. Huisgen, *Angew. Chem.*, **67**, 439 (1955).

led to a basicity scale for diazoalkanes, *i.e.*, permitted the compounds to be arranged in a series of decreasing activity, as follows:[385]

$$CH_2N_2,\ CH_3CHN_2 > C_6H_5(CH_3)CN_2 > (C_6H_5)_2CN_2 >$$



$$\begin{matrix}C_6H_4\\|\\C_6H_4\end{matrix}\!\!>CN_2 > \begin{matrix}C_6H_5\\C_6H_5CO\end{matrix}\!\!>CN_2 > \begin{matrix}H\\ROOC\end{matrix}\!\!>CN_2 > \begin{matrix}H\\C_6H_5CO\end{matrix}\!\!>CN_2 >$$

$$(C_6H_5CO)_2CN_2,\ (ROOC)_2CN_2$$

As end-members of the series, diazodicarbonyl compounds are characterized by their resistance to attack by acid. Diazomethane is decomposed quantitatively by weak acids, *e.g.*:

$$C_6H_5COOH + CH_2N_2 \longrightarrow C_6H_5COOCH_3 + N_2$$

and this reaction can be used for determination of the diazomethane content of solutions.[1d] The acid causing the decomposition has also a catalytic effect when it does not enter into the main reaction. This is always the case when the intermediate carbonium ion does not combine with the acid anion but reacts instead with, say, the hydroxilic solvent. Since water is a stronger nucleophile than the sulfate or perchlorate ion, the reaction of, *e.g.*, diazoacetic ester with aqueous perchloric acid occurs wholly according to the catalytic scheme:

$$HClO_4 + H_2O \longrightarrow H_3O^+ + ClO_4^+;$$

$$H_3O^+ + N{\equiv}\overset{+}{N}{-}\overset{-}{C}HCOOR \rightleftarrows H_2O + N{\equiv}\overset{+}{N}{-}CH_2COOR \xrightarrow{-N_2}$$

$$H_2O + \overset{+}{C}CH_2COOR \longrightarrow H_2\overset{+}{O}{-}CH_2COOR;$$

$$H_2\overset{+}{O}{-}CH_2COOR + HO^- \rightleftarrows HOCH_2COOR + H_2O$$

Diazomethane from *N*-methyl-*N*-nitrosourea:[385] The methylnitrosourea (10 g) is added in small portions to ether (100 ml) which is placed over strongly cooled 40% potassium hydroxide solution (30 ml). The temperature is kept at +5° while the mixture is continuously shaken. After 10 min the deep yellow ethereal layer is decanted and dried for 3 h over solid potassium hydroxide. The diazomethane solution can be kept for some time if cold and in the dark with the flask closed by a capillary tube; it decomposes slowly with evolution of nitrogen [cf. the preparation as described in *Organic Syntheses*, Coll. Vol. III, 244 (1955)].

Diphenyldiazomethane:[386] A mixture of benzophenone hydrazone (13 g, 0.066 mole), anhydrous sodium sulfate (15 g), ether (200 ml), ethanol saturated with potassium hydroxide (5 ml; or 10 ml if red mercuric oxide is used), and yellow (or red) mercuric oxide (35 g) is shaken in a pressure flask for 75 min. The solids are then filtered off and the solvents are removed in a vacuum at room temperature. The dark red oily product is dissolved in light petroleum (b.p. 30–60°) and this solution is filtered and the solvent is again removed in a vacuum at room temperature. The oil produced is frozen in Dry Ice and gradually allowed to warm to room temperature, whereupon dark red crystals, of m.p. 29–32°, are obtained in 89% yield [cf. also *Organic Syntheses*, **24**, 53 (1944)].

Ethyl diazoacetate:[387] Great care is necessary in work with the poisonous and explosive ethyl diazoacetate. A solution of glycine ethyl ester hydrochloride (140 g, 1 mole) in water (250 ml) is placed in a 2-l four-necked flask fitted with stirrer, dropping funnel, thermometer, and gas inlet tube. Methylene dichloride (600 ml) is added and the mixture cooled to −5°. Nitrogen is led in while the mixture is stirred and an ice-cold solution of sodium nitrite (83 g, 1.2 moles) in water (250 ml) is added; the temperature is next lowered to −9° and 5% sulfuric acid (95 g) is dropped in during 3 min. The temperature must not rise above +1° (cooling-bath at −23°). The reaction is complete in 10 min. The mixture is transferred to a cooled 2-l separatory funnel, and the golden-yellow methylene dichloride layer is mixed with cold 5% sodium hydrogen carbonate solution (1 l) and shaken thoroughly. The original aqueous layer is shaken with methylene dichloride (75 ml). When all the methylene dichloride has been extracted with hydrogen carbonate, that phase is dried over anhydrous sodium sulfate (15 g). Most of the solvent is removed through a column at 350 mm and the rest at 20 mm; at no time shall the temperature of the heating bath exceed 35°. The yield is 79–88% (90–100 g) of a yellow oil, n_D^{25} 1.462, which is pure enough for most synthetic purposes but can be

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[385] H. Staudinger and A. Gaule, *Ber. Deut. Chem. Ges.*, **49**, 1897 (1916).

[386] I. B. Müller, *J. Org. Chem.*, **24**, 561 (1959).

[387] N. E. Searle, *Org. Syn.*, **36**, 25 (1956).

subjected to steam-distillation in a vacuum.[1e] Reimlinger[388] has described a safe method of preparing larger amounts of ethyl diazoacetate from *N*-acetyl-*N*-nitrosoglycine ethyl ester.

Diethyl diazomalonate:[389] A mixture of diethyl mesoxalate hydrazone (20 g), dry, freshly precipitated silver oxide (100 g), magnesium sulfate (45 g), and tetrahydrofuran (300 ml) is shaken vigorously at room temperature for 4 h and then filtered. The solids are washed with tetrahydrofuran and the filtrates are united and concentrated in a rotary evaporator. Finally distillation affords diethyl diazomalonate (17.6 g, 89 %), b.p. 58°/0.3 mm, m.p. 9°, n_D^{24} 1.4650. The methyl ester is obtained analogously.

Diazirines, containing an unsaturated three-membered ring, are cyclic isomers of aliphatic diazo compounds; they are colorless and stable to acids.[390] The parent diazirine itself (cyclodiazomethane) is prepared by the action of sodium hypochlorite on methylenediamine.[306]

V. Formation of the nitrogen–halogen bond

N-Halo amines and *N*-halo amides are among the strongest oxidizing agents in organic chemistry. *N*-Halo amines are liquids with an unpleasant smell, that irritate the skin and mucous membranes; they are rarely isolated but are brought into reactions as solutions; **explosive decomposition** may occur during their distillation in a vacuum. *N*-Haloarylamines are stable for an appreciable time only in solution at −70°;[391] *N*-monohaloalkylamines also decompose relatively easily, first undergoing disproportionation to *N*,*N*-dihaloalkylamine and amine. This disproportionation occurs particularly fast in dilute mineral acid, but not at all in concentrated sulfuric acid.[392] Concentrated hydrochloric acid is oxidized to chlorine by *N*-chloroalkylamines. The stability of *N*,*N*-dihaloalkylamines and of *N*-halodialkylamines is greatest near the neutral point, so that they are often prepared in buffered solutions,[393] *e.g.*, in the presence of sodium hydrogen carbonate or acetate. Ether, ligroin, chloroform, carbon tetrachloride, and toluene have been used for extraction of halo amines from reaction mixtures.

Elemental chlorine and bromine, and alkali and alkaline-earth hypochlorides are used for *N*-halogenation of amines or amides; or *tert*-butyl hypochlorite[394,395] may be used for halogenation in an organic solvent. The Table on p. 598 illustrates uses of the individual halogenating agents.

N-Iodo amides are prepared exclusively by reaction of *N*-silver salts with iodine. Occasionally the nitrogen–halogen bond has been created by transhalogenation from, *e.g.*, dichlorourea[396] or *N*-bromo amides.[397] *N*-Chlorosuccinimide has been recommended for halogenation of sensitive amines in the steroid series.[398]

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[388] H. Reimlinger, *Angew. Chem.*, **72**, 33 (1960); *Chem. Ber.*, **93**, 2162 (1960).

[389] E. Ciganek, *J. Org. Chem.*, **30**, 4366 (1965).

[390] E. Schmitz, *Adv. Heterocyclic Chem.*, **2**, 125 (1963).

[391] H. Goldschmidt, *Ber. Deut. Chem. Ges.*, **46**, 2728 (1913); **55**, 2450 (1922).

[392] E. Schmitz and D. Murawski, *Z. Naturforsch.*, **17 b**, 127 (1962).

[393] I. Weil and I. C. Morris, *J. Amer. Chem. Soc.*, **71**, 3123 (1949); L. K. Jackson and co-workers, *J. Amer. Chem. Soc.*, **69**, 1539 (1947); F. D. Chattaway, *J. Chem. Soc.*, **87**, 381 (1905).

[394] H. Zimmer and L. F. Audrieth, *J. Amer. Chem. Soc.*, **76**, 3856 (1954).

[395] C. M. Teeter and E. W. Bell, *Org. Syn.*, Coll. Vol. IV, 125 (1963) (prep. of But OCl), but cf. *Org. Syn.*, **44**, 26 (1964).

[396] R. L. Datta, *J. Chem. Soc.*, **101**, 166 (1912).

[397] T. Seliwanov, *Ber. Deut. Chem. Ges.*, **26**, 423 (1893).

[398] H. Ruschig and co-workers, Ger. Pat. 896,803; *Chem. Zentralbl.*, **1955**, 5606.

All *N*-halo compounds can be readily determined by analysis based on their oxidizing action. They liberate two equivalents of iodine from acidified potassium iodide solution almost instantaneously (1 mmole of *N*-monohalo compound is equivalent to 20 ml of 0.1N-thiosulfate solution). The liberation of iodine from hydrogen iodide involves production of the amine or amide parent of the halo compound. Sodium sulfite and hydrogen sulfide also reduce N-halo compounds. UV and IR spectroscopic methods have been worked out for determination of *N*-halo compounds.[399]

N-Halo amides are stronger halogenating agents than the corresponding *N*-halo amines; they are mostly solid, easily accessible, and pleasant to handle. *N*-Bromosuccinimide has found manifold uses as brominating agent, being characterized in that it is more selective than other *N*-bromo amides.[400,401] There are various reviews of the preparative uses of *N*-halo amines.[402,403]

Preparation of *N*-haloamines and *N*-halo amides

Halogenated product	Halogenating agent	Ref.
Chloramine	NaOCl	402
N-Chlorocyclohexylamine	NaOCl	404
N-Chlorosuccinimide	$KOCl–CH_3COOH$	405
N-Chlorodibutylamine	$Cl_2–NaOH$	406
Tetrachloroglycoluril	$Cl_2–NaOH$	407
Benzophenone *N*-chloroimine	$Cl_2–NaHCO_3$	408
N,*N*-Dichloro-*O*-propylurethane	$Cl_2–H_2O$	409
N-Chlorohexanolactam	$Cl_2–H_2O$	410
N-Chloro-*O*-ethylurethane	$Cl_2–H_2O$	411
N-Chloroaniline	*tert*-BuOCl	412
N,*N*-Dichlorocyclohexylamine	*tert*-BuOCl	413
N-Chlorophthalimide	*tert*-BuOCl	394
N-Bromohexanolactam	$Br_2–KOH$	414
N-Bromoacetamide	$Br_2–NaOH$	415
N-Bromophthalimide	$Br_2–NaOH$	416
Benzophenone *N*-bromoimine	$Br_2–NaHCO_3$	408
N-Iodosuccinimide	I_2–acetone	417
N-Iodosuccinimide	I_2–dioxan	418

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[399] V. L. Hensley and co-workers, *J. Org. Chem.*, **31**, 3050 (1966).
[400] L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1939).
[401] R. Filler, *Chem. Rev.*, **63**, 21 (1963).
[402] W. Theilacker and E. Wegener, *Angew. Chem.*, **72**, 127 (1960).
[403] E. Schmitz, *Angew. Chem.*, **73**, 23 (1961).
[404] G. E. P. Smith and co-workers, *J. Org. Chem.*, **14**, 935 (1949).
[405] J. Tscherniac, *Ber. Deut. Chem. Ges.*, **34**, 4213 (1901).
[406] H. Colman and co-workers, *Org. Syn.*, Coll. Vol. III, 159 (1955).
[407] F. B. Slezak and co-workers, *J. Org. Chem.*, **25**, 660 (1960).
[408] D. Y. Curtin and C. G. McCarty, *J. Org. Chem.*, **32**, 223 (1967).
[409] R. L. Datta and S. D. Gupta, *J. Amer. Chem. Soc.*, **37**, 569 (1915).
[410] H. Beyer and J. Kőrősi, *Chem. Ber.*, **94**, 480 (1961).
[411] W. Traube and H. Gockel, *Ber. Deut. Chem. Ges.*, **56**, 387 (1923).
[412] S. S. Israelstam, *J. S. Afr. Chem. Inst.*, **9**, 30 (1956).
[413] G. H. Alt and W. S. Knowles, *Org. Syn.*, **45**, 16 (1965).
[414] B. Taub and I. B. Hino, *J. Org. Chem.*, **25**, 263 (1960).
[415] E. P. Oliveto and C. Gerold, *Org. Syn.*, Coll. Vol. IV, 104 (1963).
[416] I. Bredt and H. Hof, *Ber. Deut. Chem. Ges.*, **33**, 23 (1900).
[417] C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.*, **75**, 3494 (1953).
[418] W. R. Benson and co-workers, *Org. Syn.*, **42**, 73 (1962).

***N*-Chloroalkylamines:**[286] A 10–20% aqueous solution of a primary alkylamine is cooled in ice–salt and stirred while being treated during 5–10 min with a 1.5M-sodium hypochlorite solution (0.9 mole). The product is obtained by extraction with ether (several times for *N*-chloroethylamine) and drying over potassium carbonate. yields are 90–98%, determined iodometrically.

***N*-Bromocyclohexylamine:**[419] Cyclohexylamine (22.8 g) is dissolved in water (30 ml) and treated with 2N-potassium hydroxide solution (200 ml). Then bromine (31.9 g) is added during 4 min to the solution which is stirred in ice–salt. The mixture is shaken with cold ether (100 ml), separated, and extracted with more ether (100 ml). The ethereal extracts are washed with cold sodium hydrogen carbonate solution and with ice-water. This leads to a 91.4% yield.

***N,N'*-Dichlorourea:**[420] A rapid stream of chlorine is led into a solution of urea (6 g) in water (50 ml) containing finely divided zinc oxide (10 g) at −5°; the zinc oxide dissolves rapidly and the dichlorourea soon crystallizes from the solution. It is collected and washed with water and chloroform. Its yield is 10 g and the m.p. is 83°.

***N,N*-Dichloro-*O*-ethylurethane:**[421] Chlorine is led into a stirred, ice-cold solution of ethyl carbamate (10 g) in water (500 ml). A yellow oil that separates after some hours is separated (yield 12 g). Addition of calcium carbonate before chlorination leads to a higher yield (14 g). The dichlorourethane can be purified by cautious distillation in a vacuum (not more than 10-g batches), then having b.p. 66–67°/18 mm.

Directions for *N*-bromosuccinimide[400] are given in the Chapter on "Formation of carbon–halogen bonds."

***N,N*-Dibromobenzenesulfonamide:**[422] Bromine (255 g) is added gradually to a vigorously stirred mixture of benzenesulfonamide (125 g), sodium carbonate (90 g), and water (600 ml) placed in a 2-l three-necked flask. The resulting bromo sulfonamide is filtered off and washed with water (yield 245 g, 98%; m.p. 115°). *N,N*-Dichlorobenzenesulfonamide is obtained analogously in quantitative yield by passing chlorine into the mixture.

Little importance attaches as yet to *N*-fluoro compounds. Attempts to prepare them have usually given mixtures or perfluoro compounds.[19a,423]

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[419] D. Murawski, Diplomarbeit, Humboldt University, Berlin, 1960.

[420] F. D. Chattaway, *J. Chem. Soc.*, **95**, 464 (1909).

[421] J. Hauben, *J. Prakt. Chem.*, [ii], **105**, 16 (1922).

[422] S. Akiyooshi and K. Okuno, *J. Amer. Chem. Soc.*, **76**, 693 (1954).

[423] M. Hudlicky, "Chemie der organischen Fluorverbindungen," VEB Deutscher Verlag der Wissenschaften, Berlin, 1960, p. 131; R. N. Haszeldine, *J. Chem. Soc.*, **1950**, 1966; J. M. Tedder, *Adv. Fluorine Chem.*, **2**, 104 (1961); C. J. Hoffmann and R. G. Neville, *Chem. Rev.*, **62**, 1 (1962).

CHAPTER 8

Formation of Carbon–Sulfur Bonds

Compiled by
D. Martin

8.1. Formation of the carbon–sulfur bond by addition

I. Addition of sulfur compounds to C–C multiple bonds

1. Addition of hydrogen sulfide and its derivatives

In the absence of radical-forming catalysts addition of hydrogen sulfide and thiols (mercaptans) to a carbon–carbon double bond occurs preferentially in accord with the Markovnikov rule:

$$RR'C{=}CR''H + H_2S \longrightarrow HS{-}CRR'{-}CR''H_2$$

However, the addition occurs contrary to the Markovnikov rule under irradiation by ultraviolet light or in the presence of peroxides;[1] for instance, allylamine hydrochloride or a derivative thereof in alcoholic solution is thiolated by an excess of hydrogen sulfide under UV-irradiation, exclusively (yields up to 57%), to give 3-aminoalkanethiols.[2] Addition of hydrogen sulfide is of use in the laboratory only when the reaction can be carried out in the liquid phase and is then preferably effected under the influence of a basic catalyst; Dahlbom,[3] for instance, obtained 3-mercapto-butyric acid from crotonic acid hydrogen sulfide in the presence of diethylamine in a closed vessel at 70°; and 4-mercapto-4-methyl-2-pentanone is obtained in 80% yield from mesityl oxide and hydrogen sulfide with triethylamine as catalyst.[4]

The first step in the addition of hydrogen sulfide to unsaturated compounds is the formation of thiols, but further reaction can occur, yielding sulfides (thioethers), the latter being favored by using an excess of the olefin.[5]

3,3'-Thiodipropionic acid:[6] A solution of sodium hydroxide (40 parts) in water (100 parts) is saturated with hydrogen sulfide and then treated with a solution of sodium acrylate (94 parts) in water (130 parts). A little (0.1 part) of hydroquinone is added and the mixture is heated at 100° for 20 hours. Acidification then affords 3,3'-thiodipropionic acid.

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[1] W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **7**, 472 (1942).

[2] S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **27**, 2846 1962).

[3] R. Dahlbom, *Acta Chem. Scand.*, **5**, 697 (1951).

[4] Z. Földi and J. Kollonitsch, *J. Chem. Soc.*, **1948**, 1683.

[5] V. N. Ipatieff and B. S. Friedmann, *J. Amer. Chem. Soc.*, **61**, 71 (1939).

[6] French Pat. 845,793 (1938); *Chem. Abstr.*, **35**, 1186 (1941).

Dimethyl 3,3'-thiodipropionate (yield 71–81%)[7] and bis-(2-cyanoethyl) sulfide (yield 86–93%)[8] are respectively obtained analogously by adding hydrogen sulfide to methyl acrylate in the presence of sodium acetate and to acrylonitrile with catalysis by Triton B (benzyltrimethylammonium hydroxide).

Hydrogen sulfide can be added to diethyl 2,6-octadienedioate to give diethyl tetrahydro-2,5-thiophenediacetate in 77% yield.[9]

Addition of alkanethiols and thiophenols to a carbon–carbon double bond is easier than that of hydrogen sulfide; the reactivity decreases in the order thiophenols, primary, secondary, tertiary alkanethiols.[10]

Since the S–H bond is only slightly polarized and heterolysis to a proton and a mercaptide ion is thus difficult,[19] the addition to olefins is preferably carried out by a radical route induced by benzoyl peroxide[12] by irradiation with UV light.[13] Alkanethiols and thiophenols can be added under the influence of basic catalysts to strongly polar double bonds such as those in unsaturated carbonyl compounds, nitriles, and carboxylic acids, the C–S bond then being formed to the cationic β-carbon atom:

$$RS^-H^+ + R'\overset{+}{C}H-\overset{-}{C}HCOR'' \longrightarrow RS-CHR'CH_2COR''$$

In this way benzylideneacetone and thiophenol afford 4-phenyl-4-(phenylthio)-2-butanone,[14] and methanethiol and methyl vinyl ketone afford 4-(methylthio)-2-butanone.[15]

4-(Methylthio)-2-butanone:[15] Methyl vinyl ketone (5.6 g) is cooled in ice–salt, and methanethiol (9 g) and anhydrous potassium carbonate (0.5 g) are added. When reaction ceases, the mixture is left for 15 min at room temperature, then filtered from the potassium carbonate and distilled. The product, b.p. 72–74°/18 mm, is obtained in 77% yield (7.3 g).

Addition of thiols to α,β-unsaturated aldehydes is best carried out with triethylamine as catalyst,[16] but Brzozowski[17] achieved a 94% yield of 3-(methylthio)propionaldehyde from acrylaldehyde and methanethiol when using copper acetate.

Alkanethiols and thiophenols can also be added to α,β-unsaturated anhydrides,[18] carboxylic acids,[19] and esters[20] of the latter:

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[7] E. A. Fehnel and M. Carmack, *Org. Syn.*, **30**, 65 (1950).

[8] L. L. Gershbein and C. D. Hurd, *J. Amer. Chem. Soc.*, **69**, 241 (1947).

[9] A. Lüttringhaus and H. Merz, *Arch. Pharm.*, **293**, 881 (1960).

[10] M. S. Kharasch, W. Nudenberg, and G. J. Mantell, *J. Org. Chem.*, **16**, 524 (1951); C. S. Marvel and R. R. Chambers, *J. Amer. Chem. Soc.*, **70**, 993 (1948).

[11] I. L. Knunyants and A. V. Fokin, *Usp. Khim.*, **19**, 545 (1950); *Chem. Abstr.*, **45**, 6568 (1951).

[12] C. T. Lester, G. F. Rodgers, and E. E. Reid, *J. Amer. Chem. Soc.*, **66**, 1674 (1944).

[13] B. Weibull, *Arkiv Kemi*, **23 A**, No. 18 (1947).

[14] S. Ruhemann, *J. Chem. Soc.*, **87**, 17 (1905).

[15] H. Böhme and P. Heller, *Chem. Ber.*, **86**, 443 (1953).

[16] J. R. Catch, A. H. Cook, A. R. Graham, and I. Heilbron, *J. Chem. Soc.*, **1947**, 1609.

[17] H. Brzozowski, *Ann. Soc. Chim. Pol.*, **33**, 217 (1959); *Chem. Zentralbl.*, **1961**, 3293.

[18] F. B. Zienty, B. D. Vineyard, and A. A. Schleppnik, *J. Org. Chem.*, **27**, 3140 (1962).

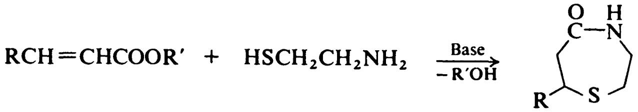
[19] A. A. Schleppnik and F. B. Zienty, *J. Org. Chem.*, **29**, 1910 (1964).

[20] C. D. Hurd and L. L. Gershbein, *J. Amer. Chem. Soc.*, **69**, 2328 (1947).

3-Phenyl-3-(phenylthio)propionic acid:[21] Cinnamic acid (10 g), thiophenol (8 g), and glacial acetic acid (10 g) saturated with hydrogen bromide are heated in a pressure flask for 9 h at 100°, then diluted with much water. Unchanged thiophenol is removed by distillation in steam. The oil that separates is removed; it crystallizes when cooled and seeded and, after recrystallization from light petroleum, has m.p. 85–86° (yield about 75%).

(Butylthio)succinic anhydride:[18] First triethylamine (0.5 ml) and then 1-butanethiol (28.8 g, 0.3 mole) are added during 5 min to a warm (60°) solution of maleic anhydride (29.4 g, 0.3 mole) in benzene (150 ml). The mixture is heated for 30 min at 65–70°, then treated with concentrated sulfuric acid (0.3 ml), filtered, and distilled, giving the sulfide, b.p. 122–124°, in 85–89% yield.

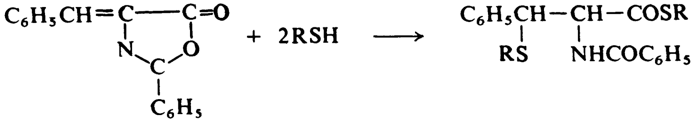
When β-amino thiols and α,β-unsaturated esters are used, addition is accompanied by condensation and ring closure to afford seven-membered thiolactams [tetrahydro-1,4-thiazepin-5(2*H*)-ones] in yields of up to 96%:[22]



Use of aqueous alkali is sufficient to bring about addition of thiols to unsaturated dicarboxylic acids[23] and of mercapto carboxylic acids to acrylic acid.[24]

Alkanethiols and thiophenols add to α,β-unsaturated nitriles with very great ease in the presence of traces of alkali, sometimes even in the cold;[25] the reaction is termed cyanoalkylation. 3-Alkyl derivatives of 3-(phenylthio)-propionic acid are thus obtained from 3-alkyl derivatives of acrylonitrile,[26] 2-(alkylthio-)1-cyclohexanecarbonitriles from 1-cyclohexene-1-carbonitrile and alkanethiols,[27] and alkyl or aryl 2- or 4-cyanophenethyl sulfides from *o*- or *p*-vinylbenzonitrile.[28]

Vinyl chloride,[29] vinyl acetate,[30] α-nitro olefins,[31] and azlactones[32] also add alkanethiols. The reaction of azlactones is accompanied by ring fission to yield *N*-acyl β-alkylthio α-amino thioesters, this being a good preparative route to such compounds:



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[21] F. Arndt, *Ber. Deut. Chem. Ges.*, **56**, 1269 (1923).

[22] F. Jakob and P. Schlack, *Chem. Ber.*, **96**, 88 (1963).

[23] E. J. Morgan and E. Friedmann, *Biochem. J.*, **32**, 733 (1938).

[24] A. Schöberl and A. Wagner, *Chem. Ber.*, **80**, 379 (1947).

[25] O. Bayer, *Angew. Chem.*, **61**, 229 (1949).

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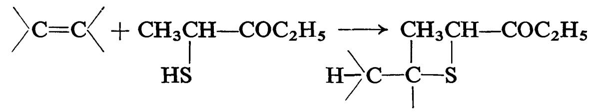
[31] R. L. Heath and A. Lambert, *J. Chem. Soc.*, **1947**, 1477.

[32] R. Ruhemann, *J. Chem. Soc.*, **87**, 461 (1905); B. H. Nicolet, *J. Biol. Chem.*, **95**, 389 (1932); R. Neher, M. Spillmann, L. H. Werner, H. Wettstein, and K. Miescher, *Helv. Chim. Acta*, **29**, 1874 (1946); A. Butenandt, H. Jatzkewitz and, P. Fouche, *Z. Physiol. Chem.*, **282**, 268 (1947).

Reaction of quinones with thiols gives (alkylthio)hydroquinones,[33,36] which are dehydrated to (alkylthio)quinones by an excess of the original quinone or by addition of another oxidant.

2-(Methylthio)-1,4-naphthoquinone:[35] 1,4-Naphthoquinone (16.5 g) is dissolved in anhydrous ethanol (1 l) at 40° and the solution is filtered after it has cooled to room temperature. The filtrate is cooled to 15° and cold methanethiol (10 g) is stirred in all at once. The mixture is left for 30 min at room temperature, then a 70% iron(III) chloride solution (calculated on $FeCl_3 \cdot 6H_2O$; 15 ml) is added and after a further 15 min more (22 ml) of this solution is added. The resulting suspension is cooled to 7° and filtered, and the solid is dried on the filter with light petroleum. This gives yellow crystals (11.9 g, 56%) which after recrystallization from ethanol have m.p. 186.5–187°.

α-Mercapto ketones behave similarly to thiols; although the polarity of the SH group is increased by the neighboring carbonyl group, radical addition is easier to achieve. Rühlmann and his co-workers[36] added 2-mercapto-3-pentanone[37] to various symmetrical and unsymmetrical olefins in the presence of catalysts that caused ionic and radical addition; they obtained α-(alkylthio) sulfides:



2-(Cyclohexylthio)-3-pentanone: This sulfide was obtained by heating 2-mercapto-3-pentanone (0.5 mole), freshly distilled cyclohexene (0.5 mole), and benzoyl peroxide (400 mg) under reflux for 8 h and then fractionating the mixture in a vacuum. The product has b.p. 89°/2 mm, the yield being 44%.

2-Mercapto-3-pentanone and other thiols have also been added to styrene, 2-methyl-2-butene, 1-methyl-1-cyclohexene, and olefins containing functional groups[38] such as vinyl chloride, 1-chlorocyclohexene, 2-chlorocrotonaldehyde, allylamine, allyl alcohol, bromide and chloride, and cinnamyl alcohol.

Sulfenyl chlorides can be added to olefins with great ease, affording β-halo sulfides,[39] *e.g.*:

$$RSCl + CH_2{=}CH_2 \longrightarrow RS{-}CH_2CH_2Cl$$

Lecher and his co-workers[39,40] obtained pure **2-chloroethyl phenyl sulfide,** b.p. 122°/13 mm (14.6 g), by leading ethylene, with exclusion of moisture, into a solution of benzenesulfenyl chloride (15 g) in carbon tetrachloride (80 ml) until this was decolorized and then distilling the product in a vacuum.

If the C–C double bond is flanked by electron-attracting groups the addition may be hindered or prevented. Turner and Connor[41] have reviewed the applicability of this reaction.

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[33] O. Dimroth, L. Kraft, and K. Aichinger, *Ann. Chem.*, **545**, 124 (1940).

[34] M. Schubert, *J. Amer. Chem. Soc.*, **69**, 712 (1947).

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[37] F. Asinger, M. Thiel, and E. Pallas, *Ann. Chem.*, **602**, 37 (1957).

[38] K. Rühlmann, U. Schräpler, and D. Gramer, *J. Prakt. Chem.*, [iv], **10**, 325 (1960).

[39] H. Lecher, F. Holschneider, K. Köberle, W. Speer, and P. Stöcklin, *Ber. Deut. Chem. Ges.*, **58**, 414 (1925).

[40] H. Baganz and G. Dransch, *Chem. Ber.*, **93**, 782 (1960); W. H. Mueller and P. E. Butler, *Chem. Commun.*, **1966**, 646.

[41] R. A. Turner and R. Connor, *J. Amer. Chem. Soc.*, **69**, 1009 (1947).

Substituted 2-chloroalkanesulfenyl chlorides can be prepared analogously by addition of sulfur dichloride to methacrylonitrile or methacrylic esters.[42]

Thiocarboxylic acids add to unsaturated compounds, affording *S*-alkyl thiocarboxylates, which can be hydrolysed to mercapto carboxylic acids.[43] Thioacetic acid always adds in such a way that the acetylthio group becomes attached to the carbon atom in β-position to the carboxylate group:

$$\mathrm{RCH{=}CHCOOH + CH_3COSH \longrightarrow CH_3CO{-}S{-}CHRCH_2COOH}$$

2-Mercaptovaleric acid:[44] Thioacetic acid (25 g) is added to 2-pentenoic acid (25 g), and next day a crystalline substance (39.5 g; m.p. 43–45°) is obtained by distillation at 133–134°/2 mm. This acetylthio compound is hydrolysed by treatment with sodium hydroxide (25 g) in water (200 ml) and on the following day the solution is acidified with concentrated sulfuric acid (60 g) in water (60 ml) and extracted with ether. The extracts are dried by calcium chloride, whereafter distillation affords the 2-mercaptovaleric acid, b.p. 108–110°/4 mm (22.5 g).

Thiocarboxylic acids also add under radical conditions to almost all the olefinic systems mentioned above. Brown and his co-workers give a general review of this reaction.[45]

Neureiter and Bordwell[46] report that addition of thioacetic acid to *cis*- and *trans*-2-chloro-2-butene is almost sterically homogeneous, giving 90% of *threo*- and 10% of *erythro*-2-(acetylthio)-3-chlorobutane.

Addition of thiols can also be effected to acetylenes, but this gives usually a sterically inhomogeneous mixture of *cis*- and *trans*-vinyl sulfides.[47]

Di-, tri-, and tetra-ynes add hydrogen sulfide in a weakly alkaline medium at temperatures between 20° and 80°, affording thiophenes in 51–85% yield:[48]

This reaction is common to butadiynes containing alkyl, aryl, or heterocyclic groups and to primary, secondary, and tertiary diacetylenic alcohols.

Thiophenes from alkynes:[48] The alkyne is dissolved in methanol, ethanol, or acetone and the solution is adjusted to pH 9–10 by adding N-sodium hydroxide solution in the proportion 9 : 1. Hydrogen sulfide is then led in at 20–80° until a sample of the mixture no longer shows acetylene bands in its UV spectrum (4–20 h). The mixture is then treated with water, and the product is taken up in ether, dried over sodium sulfate, freed from solvent, and distilled or recrystallized. Thus were prepared **2,5-dimethylthiophene**, b.p. 134–136° (70%), **2,5-diethylthiophene**, b.p. 180–181° (65%), and **2,5-diphenylthiophene**, m.p. 152–153° (85%).

Sulfur dichloride is taken up by acetylenes even at −15°, giving bis-(2-chloro-1-alkenyl) sulfides:[49]

$$\mathrm{2RCH_2C{\equiv}CH + SCl_2 \longrightarrow (RCH_2CCl{=}CH)_2S}$$

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[42] U. Hasserodt, *Chem. Ber.*, **100**, 1482 (1967).

[43] B. Holmberg and E. Schjånberg, *Arkiv Kemi*, **14 A**, No. 7 (1940); E. Schjånberg, *Svensk Kem. Tidskr.*, **53**, 282 (1941).

[44] E. Schjånberg, *Ber. Deut. Chem. Ges.*, **74**, 1751 (1941).

[45] R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, **1951**, 2123.

[46] N. P. Neureiter and F. G. Bordwell, *J. Amer. Chem. Soc.*, **82**, 5354 (1960).

[47] E. P. Kohler and H. Potter, *J. Amer. Chem. Soc.*, **57**, 1316 (1935); L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, **1949**, 3109.

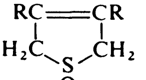
[48] K. E. Schulte, J. Reisch, and L. Hörner, *Chem. Ber.*, **95**, 1943 (1962); K. E. Schulte, J. Reisch, W. Herrmann, and G. Bohn, *Arch. Pharm.*, **292**, 456 (1963).

[49] L. Brandsma and J. F. Arens, *Rec. Trav. Chim.*, **80**, 241 (1961).

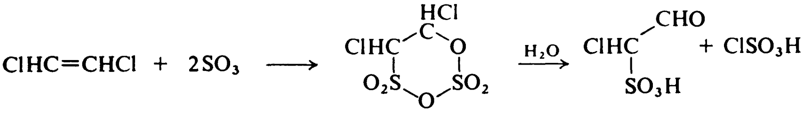
Truce[50] has reviewed the nucleophilic additions of thiols, and Oswald and Griesbaum[51] have collated the radical reactions of thiols with olefins and acetylenes.

2. Addition of other sulfur compounds

Sulfur dioxide reacts with olefins in the presence of radical-forming catalysts to yield polysulfones,[52] but cyclic sulfones can be obtained from butadiene, 2,3-dimethylbutadiene, isoprene, and hexadiene under specific conditions:[53]



Sulfur trioxide and oleum add to olefins to give β-hydroxy sulfonic acids by way of carbyl sulfates (1,3,2,4-dioxadithianes).[54,55] According to Sperling,[56] both the adduct *cis*-2-hydroxycyclohexanesulfonic acid and the substitution product 1-cyclohexenesulfonic acid are formed on treatment of cyclohexene with sulfuric acid in glacial acetic acid. 1,2-Dichloroethylene[57] and the corresponding dibromo compound[58] also react with sulfur trioxide, and cleavage of the resulting carbyl sulfate ring affords, respectively, 1-chloro- and 1-bromo-2-oxoethanesulfonic acid:



Reaction of acetylene with sulfur trioxide gives 2-oxo-1,1-ethanedisulfonic acid, $OHC{-}CH(SO_3H)_2$.[59]

Sodium hydrogen sulfite can be added to olefins under pressure but also at a useful rate at atmospheric pressure in the presence of tertiary peroxides.[60] The course of the addition depends considerably on the reaction conditions and on the nature of the solvent. Kharasch and his co-workers[61] have reviewed the applicability of this reaction in relation to the nature of the olefin and the reaction conditions. α-Nitro olefins add sodium hydrogen sulfite even in aqueous solution at 0°, yielding 1-nitroalkane-2-sulfonates.

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[50] W. E. Truce in N. Kharasch, "Organic Sulfur Compounds," Pergamon Press, Oxford-London-New York, 1961, Vol. 1, p. 112.

[51] A. A. Oswald and K. Griesbaum in N. Kharasch and C. Y. Meyers, "The Chemistry of Organic Sulfur Compounds," Pergamon Press, Oxford–London–New York, 1966, Vol. 2, p. 233.

[52] H. Staudinger and B. Ritzenthaler, *Ber. Deut. Chem. Ges.*, **68**, 455 (1935).

[53] Ger. Pat. 236,386; *Chem. Abstr.*, **5**, 3611 (1911); H. J. Backer, J. Strating, and C. M. H. Kool, *Rec. Trav. Chim.*, **58**, 778 (1939).

[54] A. Michael and N. Weiner, *J. Amer. Chem. Soc.*, **58**, 294 (1936).

[55] C. M. Suter, P. B. Evans, and J. M. Kiefer, *J. Amer. Chem. Soc.*, **60**, 538 (1938).

[56] R. Sperling, *J. Chem. Soc.*, **1949**, 1938.

[57] *Ger. Pat.* 362,744; *Chem. Abstr.*, **18**, 1129 (1924).

[58] C. S. Rondestvedt Jr. and J. C. Wygant, *J. Amer. Chem. Soc.*, **76**, 509 (1954).

[59] U.S. Pat. 2,552,421; *Chem. Abstr.*, **46**, 2565 (1952).

[60] U.S. Pat. 2,504,411; *Chem. Abstr.*, **44**, 5897 (1950).

[61] M. S. Kharasch, E. M. May, and F. R. Mayo, *J. Org. Chem.*, **3**, 175 (1939).

2-Nitroethanesulfonic acid:[62] Nitroethylene (27.5 g) is added dropwise, with vigorous stirring, to a solution of sodium hydrogen sulfite (39.2 g) in water (70 ml) at −5° to 0°. The mixture is stirred for a further 2 h at this temperature and for 4 h at 20°, then concentrated under diminished pressure at 40°, and the residue is extracted with anhydrous ethanol. This affords sodium 2-nitroethanesulfonate (75%), which can be recrystallized from ethanol.

With sodium or potassium hydrogen sulfite allyl alcohol gives the salt of 3-hydroxypropanesulfonic acid,[63] the free acid from which gives a 90% yield of propanesultone when heated gradually to 200°. Hydrogen sulfites can also be added to unsaturated fatty acids,[64] acrylonitrile,[29] and alkenedicarboxylic acids and their esters.[65]

A convenient method of preparing β-chloro sulfones (yields 60–97%) is to add sulfonyl chlorides to olefins under catalysis by copper(II) chloride:[66]

$$RSO_2Cl + CH_2{=}CHR' \longrightarrow RSO_2CH_2CHR'Cl$$

Sulfones are obtained very smoothly and without the need for a catalyst by adding sulfinic acids to a C–C double bond that is activated by a neighboring carbonyl or cyano group.

Thus, Schjånberg[67] obtained **3-(phenylsulfonyl)butyric acid** by dissolving crotonic acid (7 g) in 0.4N-benzenesulfinic acid (200 ml) and allowing the solution to evaporate spontaneously; the air-dried crystals obtained (14 g) melted at 102.5–103.5° after recrystallization from water (15 ml).

$$C_6H_5SO_2H + CH_3CH{=}CHCOOH \longrightarrow C_6H_5SO_2CH(CH_3)CH_2COOH$$

In such reactions the arylsulfonyl group always adds at the β-position to the carboxyl group; addition to the *trans*-alkenesulfonic acid is appreciably slower than to the *cis*-isomers.

α,β-Unsaturated ketones[68] and sulfinic acids afford γ-oxo sulfones; and (arylsulfonyl)hydroquinones are formed from quinones and arenesulfinic acids by 1,4-addition. According to work by Hinsberg and others[69] occurrence of this reaction is direct evidence of a quinonoid structure if *ortho-* or *para-*positions are free and neither hydroxyl nor amino groups are present as substituents in the quinone.

Further sodium thiosulfate can add to quinones; and the resulting *S*-aryl thiosulfate can be reduced to an *o*-mercaptohydroquinone.

Mercaptohydroquinone:[70,71] *p*-Benzoquinone (43.2 g) is dissolved in glacial acetic acid (150 parts) and, whilst still warm (40–50°) is added to a solution of sodium thiosulfate (150 parts) in water (200 parts) at such a rate that the temperature of the mixture does not exceed 10°. After being stirred for a short time the clear, almost colorless solution is saturated with potassium chloride, which precipitates potassium *S*-(2,5-dihydroxyphenyl) thiosulfate.

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[62] R. L. Heath and H. A. Piggott, *J. Chem. Soc.*, **1947**, 1481.

[63] J. H. Helberger, *Ann. Chem.* **588**, 71 (1954).

[64] R. T. E. Schenck and I. Danishefsky, *J. Org. Chem.*, **16**, 1683 (1953).

[65] U.S. Pat. 2,028,091; *Chem. Abstr.*, **30**, 1466 (1936).

[66] M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1964, 4962.

[67] E. Schjånberg, *Ber. Deut. Chem. Ges.*, **76**, 287 (1943).

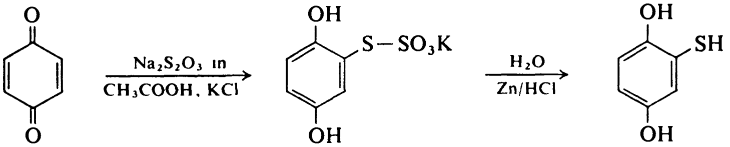
[68] H. Gilman and L. F. Cason, *J. Amer. Chem. Soc.*, **72**, 3469 (1950); D. Vorländer and A. Friedberg, *Ber. Deut. Chem. Ges.*, **56**, 1144 (1923).

[69] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **36**, 107 (1903), and references cited therein; J. Walker, *J. Chem. Soc.*, **1945**, 630; I. H. Spinner, J. Yannopoulos, and W. Metanomski, *Can. J. Chem.*, **39**, 2529 (1961).

[70] W. Alcalay, *Helv. Chim. Acta*, **30**, 578 (1947).

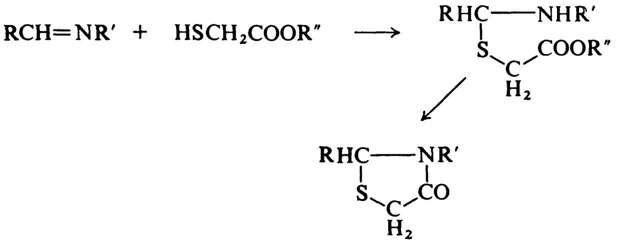
[71] Ger. Pat. 175,070; *Chem. Abstr.*, **1**, 1085 (1907).

A solution of this salt (2.6 g) in water (10 ml) is treated with concentrated hydrochloric acid (20 ml) and then gradually with zinc dust (5 g). The temperature is kept at 40–50° until gas evolution ceases; then extraction with ether and working up gives mercaptohydroquinone as long needles, m.p. 118°.



II. Addition of sulfur compounds to C–N multiple bonds

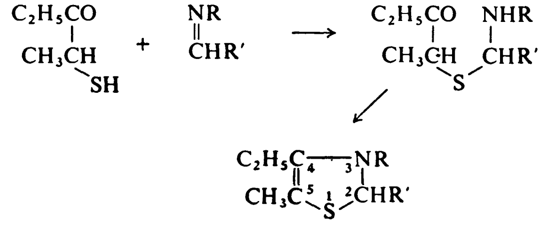
The C–N double bond of Schiff bases reacts with mercaptoacetic esters to give, first a new C–S bond and then ring closure to 2,3-disubstituted 4-thiazolidones:[72]



Addition of thiols to *N*-benzylideneanthranilic acid has been described by Stacy and Morath.[73]

According to Asinger and his co-workers, addition of α-mercapto ketones to aldimines affords 4-thiazolines.[74]

4-Thiazolines:[58] One mole each of an aldimine and 2-mercapto-3-pentanone are boiled in benzene (300 ml) under a Dean and Stark apparatus until no more water appears in the separator. Then the solvent is evaporated and the residue is distilled in a vacuum or recrystallized. The 4-thiazolines recorded in the Table below were prepared by this method.



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[72] H. D. Troutman and L. M. Long, *J. Amer. Chem. Soc.*, **70**, 3436 (1948); A. R. Surrey, *J. Amer. Chem. Soc.*, **71**, 3354 (1949); **74**, 3450 (1952).

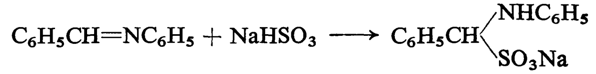
[73] G. W. Stacy and R. J. Morath, *J. Amer. Chem. Soc.*, **74**, 3885 (1952).

[74] K. Rühlmann, M. Thiel, and F. Asinger, *Ann. Chem.* **622**, 94 (1959), and references cited therein.

R	R′	Yield (%)	B.p. (°/mm)
CH_3	C_6H_5	85	138–139/3 (m.p. 58°)
C_6H_5	C_6H_5	70	197–198/5
Cyclohexyl	C_2H_5	29	140/5
Butyl	C_3H_7	70.5	120/4
C_6H_5	C_3H_7	72	155/4

α-Mercapto ketones and 2-aminovinyl ketones similarly give 3-thiazolines.[75]

Sodium hydrogen sulfite adds smoothly to aromatic aldimines in aqueous solution; *e.g.*, *N*-benzylideneaniline affords α-(phenylamino)-α-toluenesulfonate:[76]



$$C_6H_5CH{=}NC_6H_5 + NaHSO_3 \longrightarrow C_6H_5CH\begin{cases}NHC_6H_5\\SO_3Na\end{cases}$$

However, reaction of aldehyde bisulfite compounds is more widely applicable for preparation of 1-amino-1-alkanesulfonic acids.[76]

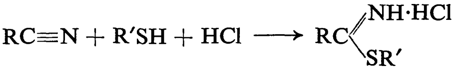
Addition of sulfur compounds to a cyano group is of preparative importance since it leads to thioamides. This reaction occurs particularly readily with aromatic nitriles or when the cyano group is activated by an unsaturated system. Aliphatic nitriles and hydrogen sulfide give thioamides only in the presence of basic catalysts.[77] It is customary to use an alkali hydrogen sulfide or ammonium hydrogen sulfide with dimethylamine, triethylamine, or other strong base, whilst exclusion of water and a maximal concentration of hydrogen sulfide favor the reaction.

Peak and his co-workers[78] give the following general directions for the preparation of **thioamides:** The nitrile is dissolved in an equal weight of pyridine, triethylamine (1 equivalent) is added, and dry hydrogen sulfide is led into the solution for 2–4 h. Pouring the mixture into water then precipitates the thioamide.

A large number of variously substituted benzonitriles have been treated in this way.

If the nitrile contains also a nitro group, the latter is reduced to an amino group at the same time as the hydrogen sulfide is added. The hydroxyl group of α-hydroxy nitriles should be protected by acylation.[79] Hurd and De LaMater[80] as well as Walter and Bode[81] give comprehensive reports of the preparation and chemical properties of thioamines.

In the presence of hydrogen chloride but absence of water, thiols add to nitriles[82] or to hydrogen cyanide,[83] yielding thiocarbimidic ester hydrochlorides:



$$RC{\equiv}N + R'SH + HCl \longrightarrow RC\begin{cases}NH{\cdot}HCl\\SR'\end{cases}$$

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[75] F. Asinger, L. Schröder, and S. Hoffmann, *Ann. Chem.*, **648**, 83 (1961).

[76] L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959); M. Frankel and P. Moses, *Tetrahedron*, **9**, 289 (1960).

[77] K. Kindler, *Ann. Chem.*, **431**, 187 (1923).

[78] A. E. S. Fairfull, J. L. Lowe, and D. A. Peak, *J. Chem. Soc.*, **1952**, 742, and references cited therein.

[79] A. Albert, *Ber. Deut. Chem. Ges.*, **48**, 470 (1915).

[80] R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 45 (1961).

[81] W. Walter and K.-D. Bode, *Angew. Chem. Int. Ed., Engl.*, **5**, 447 (1966).

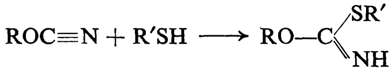
[82] E. Schmidt, *Ber. Deut. Chem. Ges.*, **47**, 2545 (1914); S. Scheithauer and R. Mayer, *Chem. Ber.*, **100**, 1413 (1967).

[83] J. Houben and R. Zivadinovitsch, *Ber. Deut. Chem. Ges.*, **69**, 2352 (1936).

Phenyl thiobenzimidate hydrochloride is formed in this way[84] in almost quantitative yield as white crystals, m.p. 178°, when hydrogen chloride is led into an ice-cooled mixture of equal parts of benzonitrile and thiophenol and the resulting solid material is thoroughly stirred with ether.

Mercaptoacetic acid adds very readily to nitriles and, according to Condo and his co-workers[85] can be used for direct identification of nitriles; it gives the adducts in 80–90% yield when a solution of the nitrile and mercaptoacetic acid in anhydrous ether is saturated at 0° with dry hydrogen chloride. Hydrogen sulfide and thiols add to cyanic esters, giving respectively thiocarbamic esters and (alkylthio)formimidic esters homogeneously, under mild conditions, and in almost quantitative yield:[86]

$$\mathrm{ROC{\equiv}N + H_2S \longrightarrow ROCSNH_2}$$



$$\mathrm{ROC{\equiv}N + R'SH \longrightarrow RO{-}C\begin{smallmatrix}\nearrow SR' \\ \searrow NH\end{smallmatrix}}$$

The reaction of cyanic esters with sodium thiosulfate in acid solution occurs particularly readily.

***O*-(2,4-Dimethylphenyl) thiocarbamate:**[87] 2,4-Dimethylphenyl cyanate (7.35 g, 50 mmoles) is added to a solution of sodium thiosulfate pentahydrate (12.4 g, 50 mmoles) in water (30 ml) and ethanol (20 ml); then 1% sulfuric acid (25 mmoles) is dropped in. After a short while the thiocarbamic ester, m.p. 139–140°; 85 g, 93.5%), crystallizes.

III. Addition of sulfur compounds to C=O bonds

α-Hydroxy α-thiols, *e.g.*, X_3C—CH(OH)—SH or $(X_3C)_2C$(OH)—SH, are formed as intermediates when hydrogen sulfide reacts with carbonyl compounds (see page 648); some of these products can be isolated in high yield, namely when carbonyl compounds containing strongly electron-attracting substituents (such as chloral or fluorinated aldehydes or ketones) are treated with hydrogen sulfide under pressure.[88]

Treating aldehydes or ketones with thiols gives, as first product, semithioacetals, but these can be isolated without difficulty only when there are strongly electron-attracting groups on the carbon atom next to the carbonyl group; it is therefore not unexpected that the semithioacetals of chloral,[89] isatin,[90] phenanthrenequinone,[91] and pyruvic acid[90] have been known for a considerable time.

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[84] W. Autenrieth and A. Brüning, *Ber. Deut. Chem. Ges.*, **36**, 3464 (1903).

[85] F. E. Condo, E. T. Hinkel, A. Fassero, and R. L. Shriner, *J. Amer. Chem. Soc.*, **59**, 230 (1937).

[86] E. Grigat and R. Pütter, *Chem. Ber.*, **97**, 3022 (1964); D. Martin and W. Mucke, *Chem. Ber.*, **98**, 2059 (1965); K. A. Jensen and H. Holm, *Acta Chem. Scand.*, **18**, 826 (1964); **19**, 438 (1965); W. Walter and K.-D. Bode, *Annalen*, **681**, 64 (1965).

[87] E. Grigat, R. Pütter, and E. Mühlbauer, *Chem. Ber.*, **98**, 3777 (1965).

[88] J. F. Harris, *J. Org. Chem.*, **30**, 2190 (1965).

[89] C. A. Martius and P. Mendelsohn-Bartholdy, *Ber. Deut. Chem. Ges.*, **3**, 443 (1870).

[90] E. Baumann, *Ber. Deut. Chem. Ges.*, **18**, 883 (1885).

[91] A. Schönberg, O. Schütz, G. Arend, and J. Peter, *Ber. Deut. Chem. Ges.*, **60**, 2344 (1927).

The **methyl semithioacetal of chloral [2,2,2-trichloro-1-(methylthio)ethanol]** is prepared[92] simply by adding chloral (24.5 g) to an ethereal solution of methanethiol (8 g) at −10°. Evaporation of the ether and recrystallization of the residue from light petroleum gives the semithioacetal, m.p. 56° (26.6 g, 82%).

Trichloroacetone, however, with methanethiol and hydrogen chloride immediately gives 1,1,1-trichloro-2,2-bis(methylthio)propane.

The preparative importance of semithioacetals lies in the possibility of converting them into α-halo sulfides, so that the latter can be obtained in one step from, *e.g.*, formaldehyde, a thiol, and hydrogen halide:

$$CH_2O + RSH \longrightarrow [RSCH_2OH] \xrightarrow{HCl} RSCH_2Cl$$

Chloromethyl ethyl sulfide:[93] Hydrogen chloride is led into a slurry of polyoxymethylene (15 g) in ethanethiol (31 g), cooled in ice–salt, until dissolution is complete, calcium chloride is added and the flask is closed except for a capillary opening and is set aside for 24 h. The upper layer is separated, freed from residual hydrogen chloride by passing in a stream of dry air, and distilled with exclusion of moisture. The product (60–70 g, 60%) boils at 128–131°.

α-Halo sulfides can also be obtained from acetaldehyde or benzaldehyde.

Campaigne[94] has reviewed the addition of hydrogen sulfide and thiols to carbonyl compounds.

Unless the carbonyl group is sterically strongly hindered by α-substituents, as in aromatic ketones, the C–O double bond of most aldehydes and ketones readily adds hydrogen sulfite in an exothermic reaction, to give bisulfite compounds (geminal hydroxy sulfonic acids); these are easily reconverted into their components by acid or alkali.

$$RR'CO + NaHSO_3 \longrightarrow RR'C(OH)SO_3Na$$

Bisulfite compounds are mostly sparingly soluble in an excess of hydrogen sulfite solution or in ethanol and can thus be readily separated.

Bisulfite compounds are usually prepared by simply shaking the carbonyl compound, alone or in solution, with a concentrated solution of sodium hydrogen sulfite, but it is often advisable to add a little alcohol as co-solvent and soap as emulsifier.

Complications arise in the formation of bisulfite compounds from unsaturated carbonyl compounds since sodium hydrogen sulfite may add also to the C–C double bond (see page 605). The type of adduct obtained varies, depending on the reactivities of the C–C and C–O double bonds; but it is usually possible to avoid simultaneous addition to the C–C double bond by using hydrogen sulfite solution freshly prepared from 1 mole of pure crystalline sodium sulfite and 1 mole of acetic acid and, if possible, working at neutrality (buffers) and avoiding long reaction times and elevated temperatures. With these precautions Tiemann[95] prepared the "normal" bisulfite compounds of, *e.g.*, cinnamaldehyde, citronellal, and citral.

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[92] H. Böhme, H. D. Lohmeyer, and J. Wickop, *Ann. Chem.*, **587**, 51 (1954).

[93] H. Böhme, *Ber. Deut. Chem. Ges.*, **69**, 1610 (1936).

[94] E. Campaigne in N. Kharasch, "Organic Sulfur Compounds," Pergamon Press, Oxford–London–New York, 1961, Vol. 1, p. 134.

[95] F. Tiemann, *Ber. Deut. Chem. Ges.*, **31**, 3297 (1898).

Addition of sulfinic acids to aldehydes affords α-hydroxy sulfones:

$$\mathrm{RCHO + R'SO_2H \longrightarrow HO{-}CHR{-}SO_2R'}$$

except for the lower aliphatic members, these crystallize readily, but they decompose more or less readily depending on the nature of the components.

Bredereck and Bäder,[96] amongst others, have prepared a large number of α-hydroxy sulfones, their directions for **hydroxymethyl sulfones** being as follows: A few grams of a magnesium alkanesulfinate are warmed with 35% formaldehyde solution to 40–50° and ca. 12N-sulfuric acid is dropped in with vigorous stirring. After 0.5–2 h the alkyl hydroxymethyl sulfone is separated from the formaldehyde solution. Isopentyl and hexyl hydroxymethyl sulfone are liquids; heptyl and higher hydroxymethyl sulfones are solids.

α-Hydroxy sulfones from higher aliphatic aldehydes are obtained by boiling an ethereal solution of the sulfinic acid for 0.25–1.0 h with an excess of aldehyde whilst nitrogen is passed in. The nitrogen atmosphere is unnecessary when working with aromatic aldehydes as the derived adducts are more stable than those from aliphatic aldehydes.

8.2. Formation of the carbon–sulfur bond by exchange

I. Replacement of hydrogen by sulfur groups

1. Introduction of the sulfonic acid group

a. Aliphatic sulfonation

Introduction of the sulfonic acid group by replacement of hydrogen is much less important in the aliphatic than in the aromatic series. On direct sulfonation of alkanes by sulfuric acid, oleum, or sulfur trioxide side reactions (isomerization, dehydrogenation, oxidation, and formation of sulfone bonds) occur to such an extent that this process has found hardly any practical applications.

A more straightforward formation of sulfonic acids by means of sulfuric acid has been observed with aliphatic carbonyl compounds, acids, etc.

Rewald[97] treated (±)-camphor (100 g) with a mixture of acetic anhydride (135 g) and concentrated sulfuric acid (98 g) and after 4 days obtained optically inactive **camphorsulfonic acid** in a yield that amounted to 40% after recrystallization from glacial acetic acid.

Sulfonation of fatty acids by sulfuric acid usually affords α-sulfo carboxylic acids in only moderate yield; but the yield is said to be almost quantitative if a little pyridine is present during the reaction.[98]

Chlorosulfonic acid, and in particular adducts of sulfur trioxide with dioxan or pyridine have been used for aliphatic sulfonation. These adducts, which are to be considered as betaine-like internal oxonium salts, very easily transfer

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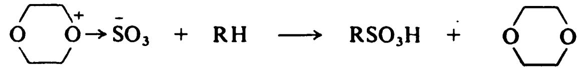
[96] H. Bredereck and E. Bäder, *Chem. Ber.*, **87**, 129 (1954); H. Bredereck, E. Bäder, and G. Höschele, *Chem. Ber.*, **87**, 784 (1954); K. Schank, *Chem. Ber.*, **99**, 48 (1966).

[97] B. Rewald, *Ber. Deut. Chem. Ges.*, **42**, 3136 (1909); cf. P. Lipp and H. Knapp, *Ber. Deut. Chem. Ges.*, **73**, 915 (1940).

[98] U.S. Pat. 2,268,443; *Chem. Abstr.*, **36**, 2564 (1962).

the sulfur trioxide to the other reactant, thus making it possible to conduct the sulfonation in an inert organic solvent under very mild conditions:



The conversion of aldehydes and ketones into α-formyl and α-oxo sulfonic acids in this way is a particularly smooth operation.[100]

The **dioxane–sulfur trioxide adduct** is prepared as follows:[101] In an all-glass apparatus sulfur trioxide is distilled out of 60% oleum into a tared flask containing dry ethylene dichloride and cooled in cold water. To this solution is added, with vigorous stirring, an equivalent amount of dioxane (previously boiled over sodium and distilled) while the internal temperature is kept always below 5°.

Acetophenone-ω-sulfonic acid:[100] Acetophenone (42 g, 0.35 mole) is added to the dioxane–sulfur trioxide reagent (exactly 0.35 mole) whilst the temperature is not allowed to rise above 35°. Addition is complete in 1 h, and after a further 2 hours' stirring the mixture is hydrolysed by being poured into water (300 ml). The organic layer is removed and the aqueous layer is brought to pH 7 by cold sodium hydroxide solution and evaporated in a stream of air. The solid residue is extracted with a boiling 60% ethanol–water mixture. Sodium acetophenone-ω-sulfonate (54 g, 70%) crystallizes from the extract as it cools.

The following sodium sulfonates, $RCOCH_2SO_3Na$, have been prepared similarly: 2′,4′,6′-trimethylacetophenone-2-, propiophenone-2-, isobutyrophenone-2-sulfonate;acetonaphthone-2-sulfonate; 3,3-dimethyl-2-oxo-1-butanesulfonate; and 2-oxo-2-(2′-thienyl)ethanesulfonate. Aldehydes such as phenylacetaldehyde, isobutyraldehyde, and heptanal can also be converted into their α-sulfonic acids, R—CO—SO_3H, in this way.

Phenylalkanoic acids and dioxan–sulfur trioxide afford their α-sulfonic acids,[102] whereas direct sulfonation by sulfuric acid leads to substitution in the ring.

The literature[103] should be consulted for a sulfonation procedure utilizing sulfur dioxide and oxygen (termed sulfoxidation) that has invoked considerable industrial interest and proceeds as a radical-induced chain reaction.

b. Aromatic sulfonation by sulfuric acid or oleum

i, General

Sulfonation if of great practical importance as one of the fundamental operations of aromatic chemistry, and there are many methods of carrying it out. The term "sulfonation" denotes introduction of an SO_3H group into a molecule, in the simplest case by means of sulfuric acid:[104]

$$RH + HO—SO_3H \rightleftharpoons RSO_3H + H_2O$$

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* The literature of theoretical organic chemistry[99] should be consulted with regard to the bonding of sulfur in such compounds.

[99] C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, 1962.

[100] W. E. Truce and C. C. Alfieri, *J. Amer. Chem. Soc.*, **72**, 2740 (1950).

[101] F. G. Bordwell and C. S. Rondestvedt Jr., *J. Amer. Chem. Soc.*, **70**, 2432 (1948).

[102] W. E. Truce and C. E. Olson, *J. Amer. Chem. Soc.*, **75**, 1651 (1953).

[103] R. Graf, *Ann. Chem.*, **578**, 80 (1952); L. Orthner, *Angew. Chem.*, **62**, 302 (1950).

[104] C. C. Price, *Chem. Rev.*, **29**, 37 (1941); E. S. Gould, "Mechanismus und Struktur in der organischen Chemie," Verlag Chemie, Weinheim/Bergstraße, 1962, p. 528.

For the reaction mechanism see reviews by Price and by Gould.[104] The reaction converts a compound into a water-soluble derivative which may be the free sulfonic acid or, more often, a salt thereof. Moreover, sulfonic acids are extremely important intermediates for the preparation of phenols, particularly those of the naphthalene series.

Free sulfonic acids rarely have characteristic melting points. They are all appreciably stronger acids than the corresponding carboxylic acids.

The decisive factors in successful sulfonation of specific compounds are the nature of the sulfonating agent, reaction conditions such as acid concentration, temperature, and time of reaction, and the influence of the solvent.

Use of the various reagents for preparation of sulfonic acids is described in the following Sub-sections; the present Sub-section gives only a brief account of the influence of conditions on the course of the reaction.

The usual reagents are ordinary concentrated (98%) sulfuric acid, 100% (monohydrate) acid, and oleum containing 5–70% of sulfur trioxide. Since water is formed during sulfonation, dilution may gradually become appreciable, so that reaction may cease prematurely. It is thus often necessary to start with an appropriate excess of sulfuric acid, to restore the original concentration by adding oleum (with cooling if there is too much heat evolved), or to remove the water formed by means of azeotropic distillation.[105] Meyer's instructions for the preparation of *p*-toluenesulfonic acid with azeotropic dehydration of the sulfonation mixture are reproduced in Gattermann and Wieland's textbook;[106d] and a further method, namely, removal of the water by working in a vacuum, was reported by Terrisse[107] for the preparation of 4-hydroxy-2-methylbenzoic acid.

The water produced may direct the sulfo group to other positions; or it may shift the equilibrium between the hydrocarbon and the sulfonic acid greatly towards the former, so the sulfo group is removed by acid catalysis. On the other hand, too high a concentration of oleum may lead to introduction of further sulfo groups.

The temperature to be maintained during sulfonation varies widely—from 0° to 200° approximately—according to the reactivity of the starting material; increase in the temperature increases the rate of reaction but it also increases the dangers of isomerization of further substitution.

It is impossible to generalize about the time required for sulfonation: many compounds, *e.g.*, thiophene, are sulfonated within a few minutes; others, however, require several days for complete reaction.

For sensitive compounds that may be resinified by sulfuric acid it is advisable to use a solvent, chosen to suit the solubility of the starting material or the sulfonic acid: acetonitrile, glacial acetic acid, acetic anhydride, liquid sulfur dioxide, light petroleum, and carbon tetrachloride have been suggested, amongst others; 1-naphthol-2-sulfonic acid, for instance, is obtained from 1-naphthol and sulfuric acid in glacial acetic acid.[108]

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[105] H. Meyer, *Ann. Chem.*, **433**, 327 (1928).

[106] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Verlag Walter de Gruyter & Co., Berlin, 35th ed., 1953, pp. (a) 151, (b) 168, (c) 169, (d) 170, (e) 171, (f) 172.

[107] Ger. Pat. 281,054; *Friedlander*, **12**, 160 (1914–1916).

[108] M. Conrad and W. Fischer, *Ann. Chem.*, **273**, 107 (1893).

Catalysis can be achieved to a much greater extent in sulfonation than in nitration, the following being the most important of the catalysts mentioned: alkali disulfates at elevated temperatures, vanadium pentaoxide,[109] iodine[110] (though this has been disputed),[111] boron trifluoride,[112] and hydrogen fluoride (which probably exerts its effect as the intermediate fluorosulfuric acid). In the presence of mercury salts the sulfo group is often introduced contrary to the substitution rules; for instance, with sulfuric acid alone anthraquinone gives almost exclusively the 2-sulfonic acid, but in presence of small amounts of mercury gives little except the 1-sulfonic acid, 0.5% of mercury sufficing for this change according to Iljinsky;[113] nevertheless, such cases are extremely rare, as shown in systematic studies by Holdermann.[114]

The method of isolating the sulfonic acids from the sulfonation mixture plays an extremely important role in all cases. Separation of the excess of sulfuric acid from the sulfonic acid product is simplest for amino sulfonic acids; those that contain as many sulfo as amino groups are mostly so sparingly soluble in water—and still less soluble in dilute sulfuric acid—that they separate almost quantitatively on dilution of the sulfonation mixture and have merely to be filtered off and washed. Free aromatic sulfonic acids are less soluble in dilute mineral acids (*e.g.*, sulfuric and hydrochloric acid) than in water, so that they can often be separated by addition of dilute sulfuric acid or gradual treatment with water or ice; in this way, for example, *p*-toluenesulfonic acid, which is sparingly soluble in 66–71% sulfuric acid, can be separated from the *ortho*-isomer which is precipitated from 45–55% acid.[115]

In some cases the free sulfonic acid may be precipitated by adding the sulfonation mixture to an organic solvent that is miscible with sulfuric acid, such as acetone or ethanol;[116] or continuous extraction by benzene or toluene may be effective.

Isolation of the sulfonic acids as salts is usually carried out in one of two ways. In one the sulfonation mixture is taken up in water, neutralized with slaked lime, and filtered from the precipitated calcium sulfate, whereafter the filtrate, which contains the calcium salt of the sulfonic acid, is treated with sodium carbonate which converts the calcium into the sodium salt; after filtration from calcium carbonate the solution is concentrated until crystallization occurs or, if necessary, evaporated to dryness. This procedure, termed "chalking" in industry, can be applied to all sulfonic acids except for the few cases such as 1-amino-4-hydroxynaphthalene-2-sulfonic acid that give sparingly soluble calcium salts; however, it is inconvenient because of the large volumes of liquid that must later be evaporated; to avoid this precipitation of

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[109] Ger. Pat. 214,156; *Chem. Abstr.*, **4**, 519 (1910).

[110] E. Knoevenagel, *J. Prakt. Chem.*, [ii], **89**, 1 (1914).

[111] V. Auger and M. Vary, *C. R. Hebd. Séances Acad. Sci.*, **173**, 239 (1921).

[112] R. J. Thomas, W. F. Anzilotti, and G. F. Hennion, *Ind. Eng. Chem.*, **32**, 408 (1940); G. F. Hennion and C. J. Schmidle, *J. Amer. Chem. Soc.*, **65**, 2468 (1943).

[113] M. Iljinsky, *Ber. Deut. Chem. Ges.*, **36**, 4197 (1903).

[114] K. Holdermann, *Ber. Deut. Chem. Ges.*, **39**, 1250 (1906); cf. O. Dimroth and W. von Schmaedel, *Ber. Deut. Chem. Ges.*, **40**, 2411 (1907).

[115] Ger. Pat. 137,935; *Friedländer*, **7**, 53 (1901–1904).

[116] G. V. Shirolkar, I. S. Uppal, and V. Venkataraman, *J. Indian Chem. Soc.*, **17**, 443 (1940).

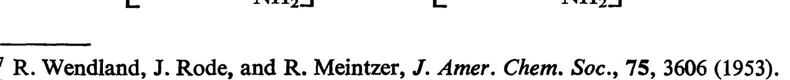
the alkali sulfonate may be attempted with alcohol. The second method consists in diluting the sulfonation mixture with water and adding an alkali salt (usually sodium chloride or sulfate, less often potassium chloride or ammonium sulfate) to salt out the corresponding salt of the sulfonic acid. This method is usually applicable, but not always since some sulfonates are not precipitated sufficiently completely in this way; it should be noted also that the sulfonate isolated is usually contaminated with the inorganic salt, although this is often not deleterious for further reactions. Sulfonates can sometimes be obtained with little or no inorganic salt content by adding first saturated and then dilute sodium chloride solution and, if the product is not too soluble, washing it with ice–water. Separation from the inorganic salt may also be attempted by crystallization from an organic solvent such as aqueous methanol or ethanol.

To obtain free sulfonic acids from their sodium salts it is usual to stir the solid sodium salt with concentrated hydrochloric acid, filter off the precipitated sodium chloride on a sinter, and evaporate the filtrate in a vacuum; the residue consists of the free sulfonic acid as a syrup or a hygroscopic crystal mass which can be freed from small amounts of salt and impurities by dissolution in ethanol. Free sulfonic acids can be obtained with certainty by treating the barium salts with sulfuric acid or the lead salts with sulfuric acid or hydrogen sulfide.

Arenesulfonic acids and organic bases often form salts that crystallize readily and have sharp melting points, so that these can be used for identification of the acid.[117] Forster and Keyworth,[118] for example, describe a process for separating the different naphthalenesulfonic acids by way of their arylamine salts. Benzidine and bianisidine salts are also mostly sparingly soluble and can be used for separation and quantitative determination of sulfonic acid mixtures.[119]

Toluidine arenemonosulfonates can be prepared by the following general procedure:[120] Solutions of equivalent amounts of the potassium arenesulfonate and of *p*-toluidine hydrochloride in the minimal amounts of water at 60° are thoroughly mixed under rapid cooling. The *p*-toluidine salt is filtered off, washed with a little ice–water, and recrystallized from water, if necessary with addition of charcoal.

S-Benzyl- and *S*-(1-naphthylmethyl)-thiouronium chloride and sulfonates also form crystalline salts (thiouronium sulfonates) that are very suitable for characterization of sulfonic acids and often for their separation:[121]



$$RSO_3Na + \left[R'CH_2SC\begin{smallmatrix}NH_2\\ NH_2\end{smallmatrix}\right]^+ Cl^- \longrightarrow \left[R'CH_2SC\begin{smallmatrix}NH_2\\ NH_2\end{smallmatrix}\right]^+ {}^-O_3SR + NaCl$$

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[117] R. Wendland, J. Rode, and R. Meintzer, *J. Amer. Chem. Soc.*, **75**, 3606 (1953).

[118] R. B. Forster and C. M. Keyworth, *J. Soc. Chem. Ind.* (*London*), **46**, T 25 (1927).

[119] H. Erdmann, *Ber. Deut. Chem. Ges.*, **32**, 3186 (1899); V. F. Borodkin and T. V. Mal'kova, *Zh. Anal. Khim.*, **3**, 186 (1948); *Chem. Abstr.*, **42**, 8714 (1948); A. A. Spryskov and B. I. Karavaev, *Zh. Obshch. Khim.*, **22**, 1620 (1952); *Chem. Abstr.*, **47**, 8709 (1953).

[120] A. D. Barton and L. Young, *J. Amer. Chem. Soc.*, **65**, 294 (1943).

[121] E. Chambers and G. W. Watt, *J. Org. Chem.*, **6**, 376 (1941); W. A. Bonner, *J. Amer. Chem. Soc.*, **70**, 3508 (1948).

Sulfonic acids from the simplest members of the benzene series can be purified by distillation in a high vacuum,[122] but purification is usually undertaken through the sulfonyl chlorides or sulfonamides.

ii, Sulfonation and the influence of substituents in the benzene series

In the benzene series any substituents already present influence the rate of sulfonation and the point of entry of the sulfo group. Sulfonation is facilitated by the presence of hydroxyl groups, to a smaller extent by alkoxy, amino, and acylamino groups, and to a still smaller extent by alkyl groups; it is made more difficult by halogen atoms, carboxyl and carbonyl groups, any sulfo groups already present, and, especially, by nitro groups. Dinitrated hydrocarbons cannot be sulfonated at all.

The position of substitution is governed almost without exception by the ordinary rules of substitution:[123] *ortho/para*-directing groups (which have a $+M$ effect) cause sulfonation mainly at the *ortho*-position at low temperatures and at the *para*-position at higher temperatures; *meta*-directing groups (which have a $-M$ effect) cause *meta*-sulfonation.

Benzenesulfonic acid: A simple method of preparation is described in Gattermann and Wieland's textbook.[106b] Larger amounts can be prepared as follows:[124b] Benzene (200 g) is cautiously mixed with oleum (450 g) containing 10% of sulfur trioxide, during about 0.5 h, in an iron, porcelain, or enamel vessel fitted with a stirrer and a reflux condenser, the temperature not being allowed to rise above 75°. When mixing is complete, the whole is heated to 110° (at higher temperatures the disulfonic acid is relatively readily formed). All the benzene reacts in about 1.5–2 h, then the mixture is poured into water (1 l), neutralized at the boiling point, with good stirring, with powdered chalk (about 450 g), and filtered from the calcium sulfate through a large filter. This precipitate is washed with water, then the calcium sulfonate in the solution (about 1.5 l) is converted at the boiling point into the sodium salt by adding anhydrous sodium carbonate (about 110 g) until the mixture is alkaline to phenolphthalein. The precipitated calcium carbonate is filtered off and the clear filtrate is evaporated over a free flame until crystals of sodium benzenesulfonate begin to separate. On cooling, a wet paste is formed containing about 15% of solids which consist of benzenesulfonate (about 90%, calculated on dry weight), sodium sulfate and carbonate (7%), and calcium salts (a little). This can be converted directly into phenol, or the benzenesulfonate can be isolated by evaporation to dryness. If the product is desired to be as free as possible from inorganic salts, the paste can be filtered and the solid dried, a procedure that, however, involves considerable loss.

Benzenesulfonic acid monohydrate, m.p. 45–46°, can be obtained by azeotropic distillation with an excess of benzene, as described by Meyer.[105]

Further sulfonation of benzenesulfonic acid occurs in the *meta*-position:

***m*-Benzenedisulfonic acid:**[124e] 20% Oleum (250 g) is added, with good stirring, to benzene (78 g, 1 mole) during 2 h at such a rate that the temperature does not exceed 40–50°. Then, during a further 2 h, 66% oleum (200 g) is similarly added, the temperature rising to about 75°. Finally the mixture is heated at 90° for a further hour, poured into water (2 l), and neutralized hot, with stirring, by chalk (about 400 g). Working up is as described above, by filtration, washing, and treatment with sodium carbonate; the evaporation residue is dried at 130–140° (yield, ca. 250 g, 90%).

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[122] F. Krafft and W. Wilke, *Ber. Deut. Chem. Ges.*, **33**, 3207 (1900); J. von Braun and K. Weissbach, *Ber. Deut. Chem. Ges.*, **63**, 2839 (footnote) (1930).

[123] K. Lauer, *J. Prakt. Chem.*, [ii], **143**, 130 (1935).

[124] H. E. Fierz-David and L. Blangey, "Grundlegende Operationen der Farbenchemie," Springer Verlag, Vienna, 8th ed., 1952, pp. (a) 79, (b) 116, (c) 122, (d) 131, (e) 138, (f) 161, (g) 173 (laboratory apparatus), (h) 190, (i) 192, (j) 207, (k) 225, (l) 227, (m) 296, (n) 324.

Toluene is sulfonated more easily than benzene, giving *o*- and *p*-toluenesulfonic acid;[115] the latter is the main product at elevated temperature[125] (cf. page 614). A procedure for preparation of 2,4-toluenedisulfonic acid is described in Fierz-David and Blangey's book.[124m] Higher homologs of benzene are sulfonated almost wholly in the *para*-position, probably as a result of steric hindrance.[126] Of the three isomeric xylenes the *meta*-compound is the most easily sulfonated; their varying behaviors can be utilized for separation of the isomers by fractional sulfonation.[127]

A halogen atom in the benzene ring directs the sulfo group almost completely into the *para*-position.[105,128]

Baxter and Chattaway[129] described the preparation of *p*-bromo-and *p*-iodo-benzenesulfonic acid.

Chlorobenzenedisulfonic acid: This is best prepared by heating *p*-chlorobenzenesulfonyl chloride and sulfuric acid monohydrate (4 parts) slowly to 160–180°, and then until evolution of hydrogen chloride ceases. The mixture is poured into water and worked up by "chalking" as described above.

Phenol is extremely easily sulfonated; at low temperatures the *ortho*- and at higher temperatures (ca. 100°) the *para*-compound with about 10% of the phenyl ester is the main product.

o-Hydroxybenzenesulfonic acid:[130] Phenol (200 g) is melted and sulfuric acid monohydrate (100 g) is added with good stirring; the mixture, which no longer readily solidifies, is cooled to below 20° and more of the monohydrate acid (200 g) is stirred in. Stirring is continued for a further 6–8 h whilst the temperature is kept continuously below 20°. Then the mixture is poured into water (1.5 l), most of the excess of sulfuric acid is neutralized with lead carbonate (about 500 g needed), and barium carbonate is added in portions and cautiously until the reaction of the mixture to Congo paper just changes from blue to red, this maintaining the sulfonic acids in solutions as acid barium salts. (Prolonged heating with an excess of carbonate must be avoided as that precipitates the sparingly soluble neutral barium sulfonates.) The lead sulfate–barium sulfate mixture is filtered off and well washed, the filtrate is filtered from any further precipitate, and the liquid is evaporated until the mother-liquor above the resultant crystals has a specific weight of 1.18–1.20 (measured cold). Care must be taken that the compact, crust-forming crystals of the *o*-sulfonate are not accompanied by the fine, felted needles of the isomer; if the latter appear they should be redissolved by means of cold water. The crude *o*-sulfonate that separates is filtered off and washed until the wash-water has a specific weight of 1.08–1.09. This gives about 25% of the theoretical yield of crude barium *o*-hydroxybenzenesulfonate.

***p*-Hydroxybenzenesulfonate:**[130] The mixture obtained as in the above paragraph consists to about two-fifths of *o*- and three-fifths of *p*-sulfonate. The mother-liquor from the crude *o*-sulfonate contains about 80% of the *p*-sulfonate that is formed and this crystallizes as magnesium *p*-hydroxybenzenesulfonate when magnesium sulfate is added.

If only the *p*-sulfonic acid is required, phenol (200 g) is heated with 95% sulfuric acid (220 g) at 90–100° with good stirring (6–8 h), then allowed to cool to 70–75°, treated with water (50 ml) to prevent solidification, and further cooled to room temperature. The product then contains more than 80% of the *p*-sulfonate and can be worked up directly for this as described above.

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[125] Ger. Pat. 57,391; *Friedländer*, **3**, 905 (1890–1894); E. E. Gilbert and E. P. Jones, *Ind. Eng. Chem.*, **43**, 2030 (1951).

[126] M. Senkowski, *Ber. Deut. Chem. Ges.*, **23**, 2417 (1890); R. L. Frank, R. E. Berry, and O. L. Shotwell, *J .Amer. Chem. Soc.*, **71**, 3891 (1949).

[127] T. S. Patterson, A. McMillan, and R. S. Somerville, *J. Chem. Soc.*, **125**, 2488 (1924).

[128] G. F. Lisk, *Ind. Eng. Chem.*, **41**, 1925 (1949); Ger. Pat. 116,759; *Friedländer*, **5**, 931 (1897–1900); Ger. Pat. 260,563; *Chem. Abstr.*, **7**, 3198 (1913).

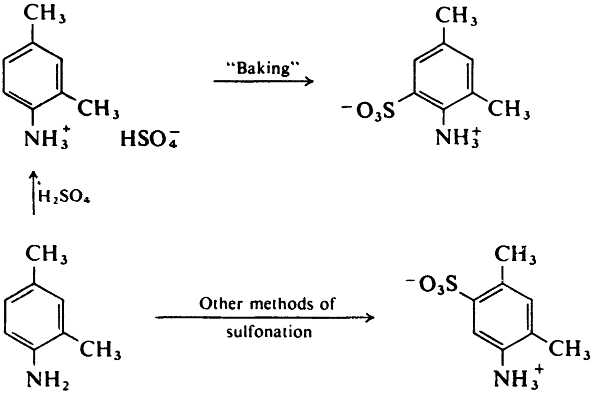
[129] R. R. Baxter and F. D. Chattaway, *J. Chem. Soc.*, **107**, 1815 (1915).

[130] J. Obermiller, *Ber. Deut. Chem. Ges.*, **40**, 3637 (1907).

o-Cresol is converted by concentrated sulfuric acid into 4-hydroxy-3-methylbenzenesulfonic acid,[131] and guaiacol into 4-hydroxy-2-methoxybenzenesulfonic acid.

An amino group controls sulfonation so that the sulfo group enters the *ortho*- and *para*-positions to it, but formation of *m*-sulfonic acids is favored increasingly by use of oleum with increasing sulfur trioxide contents. At low temperatures aniline gives mainly *o*-aminobenzenesulfonic acid, but at higher temperatures mainly sulfanilic acid.[132] Aniline and concentrated sulfuric acid at 180–190° give good yields of sulfanilic acid in 4–5 hours.[106c,124f]

Aromatic bases such as the toluidines, xylidines, chloroanilines, 1-naphthylamine, benzidine, and tertiary amines can be simply converted into their sulfonic acids by heating ("baking") with ammonium hydrogen sulfate. This method has the advantage over normal sulfonation by sulfuric acid that exactly theoretical amounts can be used so that no higher sulfonation product is obtained. Further, isomers are rarely obtained, since the sulfo group almost always enters exclusively at the *para*-position or, if that is occupied, at the *ortho*-position, and never at the *meta*-position.



It is important for the "baking" process that the ammonium hydrogen sulfate shall have as large a surface area as possible, and this is achieved by spreading it in a thin layer on a metal sheet, crushing the crusts formed, and placing them in a vacuum. The best reaction temperature is between 170° and 220° but it varies from case to case and must be determined for each specific amine. It is advantageous to carry out the reaction in a vacuum (for a laboratory vacuum apparatus see reference [124g]) as sulfonation is then faster and smoother and there is no danger of carbonization. The arylammonium hydrogen sulfate used for the "baking" must be as pure as possible since any included sulfuric acid will cause sulfonation of a different type; the best procedure is to dissolve the amine in glacial acetic acid, run in the calculated amount of concentrated sulfuric acid, and distil off the acetic acid in a vacuum; the residue consists wholly of the acid sulfate.

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[131] M. E. Hultquist and co-workers, *J. Amer. Chem. Soc.*, **73**, 2558 (1951).

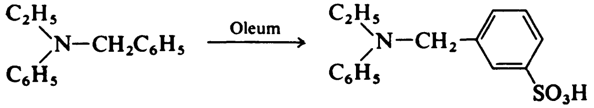
[132] E. R. Alexander, *J. Amer. Chem. Soc.*, **68**, 969 (1946); **69**, 1599 (1947).

Huber[133] has given several examples in a review of preparation of aromatic amine sulfonic acids by the "baking" process.

The following have also been prepared by the "baking" method: 2-amino-3,5-dimethyl-[134] and 4-amino-3-methyl-benzenesulfonic acid[135], 2-amino-5-sulfobenzoic acid.[136] Rearrangement of acid sulfates can also be effected by heating them in inert high-boiling solvents.[137]

Direct sulfonation of amines by sulfuric acid or oleum is not as clear-cut as the "baking" process. *p*-(Ethylamino)benzenesulfonic acid is formed from *N*-ethylaniline,[116] but both *m*- and *p*-(dimethylamino)benzenesulfonic acid are formed from *N*,*N*-dimethylaniline.[138] According to Blangey and his coworkers,[124d,139] *m*-[(*N*-ethyl-*N*-phenylamino)methyl]benzenesulfonic acid is obtained from *N*-benzyl-*N*-ethylaniline.

***m*-[(*N*-ethyl-*N*-phenylamino)methyl]benzenesulfonic acid:**[139] *N*-Benzyl-*N*-ethylaniline (150 g) is dropped during 15 min, with stirring, into sulfuric acid monohydrate (150 g), the temperature being kept below 50° by external cooling. Then 60% oleum (150 g) is added and the mixture is heated at 60° until, after about 3 h, a sample no longer gives a turbidity when diluted with water and poured into dilute sodium carbonate solution. The whole is next poured into water (1 l), and the precipitated sulfonic acid is filtered off and washed with water (yield 72%). The mother-liquor may be neutralized with lime, treated with sodium sulfate (to give the sodium sulfonate), filtered, and evaporated (to 400 ml); acidification then affords a second fraction, but often only after scratching and seeding (yield about 5%). The sodium salt of the *p*-acid may be obtained (about 15%) from the final mother-liquor by addition of sodium chloride.



Acylated amines can be sulfonated in the *para*-position with retention, loss, or alteration of the acyl group. *N*-Methylacetanilide affords *p*-(methylamino)benzenesulfonic acid.[140]

o- and *p*-Aminophenol are harder to sulfonate than phenol itself. The sulfo group enters at the *ortho*- or *para*-position to the hydroxyl group. *o*-Aminophenol gives solely 3-amino-4-hydroxybenzenesulfonic acid,[141] *m*-aminophenol gives 4-amino-2-hydroxybenzenesulfonic acid,[142] and *p*-aminophenol gives 5-amino-2-hydroxybenzenesulfonic acid.[143]

Nitrobenzenesulfonic acids are usually prepared by nitration of the aromatic sulfonic acids, the reverse procedure being used only when sulfonation gives more homogeneous products than nitration does. Sulfonation of nitro comp-

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[133] W. Huber, *Helv. Chim. Acta*, **15**, 1372 (1932); cf. A. F. Holleman, *Helv. Chim. Acta*, **16**, 245 (1933).

[134] A. Junghahn, *Ber. Deut. Chem. Ges.*, **35**, 3750 (1902).

[135] C. F. H. Allen and J. A. VanAllan, *Org. Syn.*, **27**, 88 (1947).

[136] U.S. Pat. 2,353,351; *Chem. Abstr.*, **38**, 5845 (1944).

[137] Ger. Pat. 549,136; *Chem. Abstr.*, **27**, 513 (1933).

[138] E. A. Shilov and A. N. Kurakin, *Zh. Obshch. Khim.*, **18**, 2092 (1948); *Chem. Abstr.*, **43**, 3803 (1949).

[139] L. Blangey, H. E. Fierz-David, and G. Stamm, *Helv. Chim. Acta*, **25**, 1162 (1942); Ger. Pat. 69,777; *Friedländer*, **3**, 39 (1890–1894).

[140] J. Halberkann, *Ber. Deut. Chem. Ges.*, **54**, 1836 (1921); G. A. Smyth, *Ber. Deut. Chem. Ges.*, **7**, 1241 (1874).

[141] J. Post, *Ann. Chem.*, **205**, 51 (1880).

[142] A. L. Miller, H. S. Mosher, F. W. Gray, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **71**, 3559 (1949); Ger. Pat. 70,788 (1892); *Friedländer*, **3**, 59 (1890–1894).

[143] R. Bauer, *Ber. Deut. Chem. Ges.*, **42**, 2107 (1909).

ounds requires great care since explosive decomposition may occur. As ex amples of the sulphonation may be cited the preparation of *m*-nitrobenzenesulfonic acid from nitrobenzene,[124b] and of 2-methyl-5-nitrobenzenesulfonic acid from *p*-nitrotoluene.[124f]

Carboxyl and formyl groups direct a sulfo group to the *meta*-position, as in *m*-sulfobenzoic acid[144] and 5-formyl-1,3-benzenedisulfonic acid.[124m]

iii, Sulfonation and the influence of substituents in the naphthalene, anthracene, and phenanthrene series

In the naphthalene series introduction of even the first substituent can lead to two isomers, α and β (or 1 and 2). Sulfonation usually leads to mixtures, whose composition depends on the temperature of the reaction: α-sulfonic acid predominates in the cold, and the β-isomer at 120–130°. The point of entry of the sulfo group is also influenced by any substituents already present, although not to such a pronounced extent as in the benzene series. *ortho-and para*-directing substituents facilitate the usual electrophilic substitution, mainly at the *ortho*- and *para*-positions to themselves, *meta*-directing substituents, however, hinder substitution, though least at the *meta*-position to themselves; sulfonation then occurs preferentially in the unsubstituted ring. According to Armstrong and Wynne's rule direct sulfonation never places two sulfo groups in the *ortho*-, *para*-, or *peri*-position to one another.

1-Naphthalenesulfonic acid:[124j] Naphthalene, very finely ground (128 g), is added with stirring to sulfuric acid monohydrate (260 g) at 0°. To avoid sudden separation of the sulfonic acid from a supersaturated solution, a seed of the 1-sulfonic acid is added after the naphthalene (the seed is obtained by warming a sample of naphthalene in sulfuric acid on the water-bath and cooling the product). If the naphthalene has not all been sulfonated, naphthalene will separate when a sample of the reaction mixture is added to water; if that happens the reaction mixture should be warmed for a short time at 60°.

2-Naphthalenesulfonic acid:[106e,145] Naphthalene (100 g) is melted in a flask fitted with a thermometer, dropping funnel, and stirrer, and to it is added concentrated sulfuric acid (160 g) dropwise during 15 min, the temperature being kept at 160°. Stirring is continued for a further 5 min at that temperature, then the solution is poured into cold water (120 ml), and the crystals that separate are collected and pressed on porous plate. For purification, portions (10 g) of the crude product are dissolved in water (5 ml), filtered hot, and treated hot (above 70°) with concentrated hydrochloric acid (about 2 ml). These processes yield about 160 g of the sulfonic acid trihydrate; it may be dried on porous plate or placed in a desiccator above sodium hydroxide.

Naphthalene-di- and/or -tri-sulfonic acids are obtained when oleum reacts with naphthalene at elevated temperatures and for an extended time; directions for the preparation of 1,5-, 1,6-,[146] and 2,7-naphthalenedisulfonic acid[147] and of 1,3,5- and 1,3,6-naphthalenetrisulfonic acid are given in Fierz-David and Blangey's book.[124a]

In the naphthol series direct sulfonation is usually restricted to β-naphthols, since α-naphtholsulfonic acids are generally obtained in other ways, such as from naphthalene-di- and -tri-sulfonic acids in an alkali melt or from 1-aminonaphthalenesulfonic acids by the Bucherer reaction.

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[144] H. Offermann, *Ann. Chem.*, **280**, 5 (1894).

[145] O. N. Witt, *Ber. Deut. Chem. Ges.*, **48**, 751 (1915).

[146] Ger. Pat. 45,229; *Friedländer*, **2**, 244 (1887–1890).

[147] Ger. Pat. 48,053; *Friedländer*, **2**, 243 (1887–1890).

Occasionally, however, direct sulfonation is applied also to α-naphthol; for instance, 4-hydroxy-1,3-naphthalenedisulfonic acid is obtained as acid sodium salt in 95% yield by means of sulfuric acid at 50° for 2 hours[148] or of sulfuric acid monohydrate at 20° for 36–48 hours and then at 40° for a day.[149b]

The site at which the sulfo group appears in β-naphthol depends very markedly on the temperature. At low temperatures 2-hydroxy-1-naphthalenesulfonic acid is obtained;[150] at higher temperatures or when an excess of sulfuric acid is used, migration of the sulfo group leads to 7-hydroxy-1-naphthalenesulfonic acid (croceic acid), and finally at 110° almost exclusively to 7-hydroxy-2-naphthalenesulfonic acid (Schäffer acid). Further treatment with an excess of sulfuric acid leads to β-naphthol-di- and -tri-sulfonic acids, which are important for the dyestuffs industry but which will not be discussed in detail here.[151,152]

Sulfonation of α-naphthylamine always gives mixed sulfonic acids, the first sulfo group entering at position 4, 5, or 6. Most of the sulfonic acids of α-naphthylamine are, however, not prepared by sulfonation of this amine but rather by other methods, such as reduction of nitronaphthalenesulfonic acids.

The "baking" process affords 4-amino-1-naphthalenesulfonic acid homogeneously.[124g]

4-Amino-1-naphthalenesulfonic acid:[153] Preparation of the acid sulfate: 70% Sulfuric acid (73.5 g) is heated to 120–125° in a three-necked flask fitted with a dropping funnel, stirrer, and descending condenser. A warm (50°) solution of 1-naphthylamine (75 g) in benzene (about 15 g) is then dropped in, with stirring, in 0.5 h; the benzene distils off continuously. The solid residue is dried for 18 h at 120°.

"Baking": The finely powdered acid sulfate (75 g) is heated for 8 h at 180°/10–15 mm. The pale grey cake obtained on cooling is dissolved in water (about 500 ml) containing anhydrous sodium carbonate (20 g), heated to the boiling point, filtered, freed from unchanged naphthylamine by means of benzene, and treated with hydrochloric acid to incipient turbidity. Charcoal is added and the mixture is filtered hot. After cooling, the filtrate is acidified with hydrochloric acid, and the naphthionic acid is collected and dried at 100° (yield 60 to 65 g, 85–95%).

Sulfonation of β-naphthylamine leads to somewhat more precise orientation of the substituents. When special attention is paid to conditions such as temperature and SO_3 content of the sulfonation mixture, either 6- and 7-amino-1-naphthalenesulfonic acid or 6- and 7-amino-2-naphthylaminesulfonic acid can be obtained. When the concentration of SO_3 is increased, di- and trisulfonic acids of β-naphthylamine are formed from the monosulfonic acids.[151,152]

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[148] M. Conrad and W. Fischer, *Ann. Chem.*, **273**, 105 (1893).

[149] Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed., 1955, Vol. 9, pp. (a) 19, (b) 485.

[150] Ger. Pat. 74,688; *Friedländer*, 3, 440 (1890–1894); R. Nietzki, *Ber. Deut. Chem. Ges.*, **15**, 305 (1882).

[151] H. E. Fierz-David and L. Blangey, "Grundlegende Operationen der Farbenchemie," Springer Verlag, 8th ed., 1952, p. 79; *Friedländer*, **4**, 623–643 (1894–1897); K. Venkataraman, "The Chemistry of Synthetic Dyes," Academic Press, Inc., New York, 1952, Vol. 1, p. 55; Ullmann's "Encyklopädie der technischen Chemie," Urban & Schwarzenberg, Munich–Berlin, 3rd ed., 1960, Vol. 12, pp. 593, 609.

[152] C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, New York, London 1944, (a) 268ff., (b) 458, (c) 573, (d) 660, (e) 668.

[153] R. H. C. Nevile and A. Winther, *Ber. Deut. Chem. Ges.*, **13**, 1948 (1880).

2-Amino-1-naphthalenesulfonic acid (Tobias acid) can be prepared homogeneously in 90% yield by using sulfur trioxide in tetrachloroethane.[154]

The 2-sulfonic acid as well as disulfonic acid is formed on sulfonation of anthracene.[155] Sulfonation of anthraquinone[156] and of phenanthrene[157] has been examined in more detail; the latter affords 2- and 3-phenanthrenesulfonic acid, which can be separated as described by Fieser.[158]

c. Sulfonation by sulfuric acid and oleum in the presence of catalysts*

Metal salts such as sodium and ammonium sulfate exert a dilution effect that effectively weakens the aggressive action of sulfuric acid. Thus, Tietze and Bayer,[159] sulfonating pyrene in the presence of sodium sulfate, weakened the oxidizing action of the pure acid on this hydrocarbon; in fact, heating pyrene, sulfuric acid, and sodium sulfate in the molar proportions 1 : 3 : 3 at 180° for 6 hours gives a 100% yield of 1-pyrenesulfonic acid.[160] Adding sodium sulfate is also advantageous in preparation of 1-aminoanthraquinone-2-sulfonic acid.[161]

The longest known influence of catalysts on sulfonation is that of mercury and mercury salts, which not only accelerates the reaction but also determines the site of substitution owing to intermediate formation of organometallic compounds.[156] Thus, whereas anthraquinone-2-sulfonic acid is formed from anthraquinone and oleum,[124k,l] the 1-sulfonic acid is obtained when mercury salts are present.[124k,l]

Anthraquinone-1-sulfonic acid:[124k,l] Pure, dry anthraquinone (208 g) is intimately mixed by grinding with washed mercuric oxide for sulfate (4 g) and then added, with stirring, to oleum (200 ml) containing 20% of sulfur trioxide. The mixture is stirred at 50° until all the solid is dissolved, then heated to 130–135° during 1 h, and oleum (50 g) containing 60% of sulfur trioxide is dropped in during a further 2 h. The whole is stirred for a further hour at 135°, then cooled, poured into ice-water (2 l), heated to the boiling point, and filtered from unchanged anthraquinone (ca. 60 g). The filtrate is heated again to the boiling point and then treated, with stirring, with a hot solution of potassium chloride (80 g) in a little water. This mixture is allowed to cool to 60°, maintained at that temperature for 6 h, and filtered through a funnel preheated to 60°. The solid product is washed with saturated potassium chloride solution and a little water and constitutes potassium anthraquinone-1-sulfonate (190 g, 58%).

4-Sulfophthalic anhydride is formed on sulfonation of phthalic anhydride by oleum, but presence of mercury(I) sulfate leads to the 3,5-disulfonic acid.[162] The catalytic effect of mercury and mercury salts is also applied to the conversion of 4-methylpyridine into 4-methyl-3-pyridinesulfonic acid[163] and of

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* Cf. page 612.

[154] U.S. Pat. 1,969,189; *Chem. Abstr.*, **28**, 6160 (1934).

[155] Ger. Pat. 77,311; *Friedländer*, **4**, 271 (1894–1897).

[156] K. Lauer, *J. Prakt. Chem.*, [ii], **135**, 173 (1932); **138**, 81 (1933).

[157] L. F. Fieser, *J. Amer. Chem. Soc.*, **51**, 2460, 2471 (1929); cf. F. L. Cohen and U. Cormier, *J. Amer. Chem. Soc.*, **52**, 4363 (1930).

[158] L. F. Fieser, *Org. Syn.*, Coll. Vol. 2, 482 (1955).

[159] E. Tietze and O. Bayer, *Ann. Chem.*, **540**, 189 (1939).

[160] Y. Abe and Y. Nagai, *Kogyo Kagaku Zasshi*, **62**, 1025 (1959); *Chem. Abstr.*, **57**, 8520 (1962).

[161] Ger. Pat. 484,997; *Chem. Abstr.*, **24**, 1124 (1930).

[162] H. Waldmann and E. Schwenk, *Ann. Chem.*, **487**, 287 (1931).

[163] J. L. Webb and A. H. Crowin, *J. Amer. Chem. Soc.*, **66**, 1456 (1944).

pyridine itself into 3-pyridinesulfonic acid,[164] both in appreciably increased yield. In the presence of 0.2–3.0% of mercury quinoline affords 5-quinolinesulfonic acid without any of the 8-sulfonic acid.[165]

Sulfonation is also easier in the presence of hydrogen fluoride, boron trifluoride[112] (*e.g.*, for benzene, toluene, naphthalene, naphthylamine, naphthol, phenol, carbazole, and biphenyl), or boric acid[166] (*e.g.*, for 6-quinizarinsulfonic acid), but iodine is reported[111] not to influence the course of a sulfonation.

d. Sulfonation with sulfur trioxide and its addition compounds

Direct introduction of the sulfo group by means of sulfur trioxide[167,168] has the advantage over sulfonation by sulfuric acid that no water is formed, so that the site of sulfonation is fixed more cleanly.[169] The reaction is generally very violent, often even leading to carbonization, so that it is wise to use a low temperature or a solvent. The reaction may be performed by passing gaseous sulfur trioxide into the reactant or in solution.

Methyl 5-sulfosalicylate ($COOCH_3$ = 1),[170] for example, is obtained by passing sulfur trioxide into methyl salicylate until the reaction mass is solid, during which process the temperature rises slowly from 25° to 107°.

Liquid sulfur dioxide is particularly suitable as solvent for sulfonation by sulfur trioxide.[171]

The powerful oxidizing action of sulfur trioxide can be overcome by using the sulfur trioxide addition compounds mentioned above (page 612); their activity in sulfonation depends on their stability.[167] Disulfur hexaoxide or its adducts to mineral acids (*e.g.*, $H_2S_2O_7$) are more powerful sulfonating agents than the stable adducts to dioxan[55,101] or tertiary amines; very mild conditions can be used with the latter;[172] compounds that are especially sensitive to acids can be sulfonated by the pyridine-sulfur trioxide adduct without decomposition.

Pyridine–sulfur trioxide adduct:[173] Pyridine (1 mole) is added, with stirring and good cooling, to sulfur trioxide (1 mole) in three parts of carbon tetrachloride. The adduct produced is filtered off, washed with a little ice-water (to remove small amounts of pyridinium sulfate), and dried. The yield is about 90%.

These directions can also be used if the sulfur trioxide is replaced by chlorosulfuric acid.

Heterocyclic compounds, in particular, are readily sulfonated by the pyridine–sulfur trioxide adduct: 2-pyrrolesulfonic acid is formed from pyrrole,[174] and 5-acetyl-3-pyrrolesulfonic acid from 2-acetylpyrrole.[175]

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[164] S. M. McElvain and M. A. Goese, *J. Amer. Chem. Soc.*, **65**, 2233 (1943).

[165] U.S. Pat. 2,689,850; *Chem. Abstr.*, **49**, 11725 (1955).

[166] Ger. Pat. 492,000; *Chem. Abstr.*, **24**, 2473 (1930).

[167] C. M. Suter and A. W. Weston, *Org. Reactions*, **3**, 141 (1946).

[168] G. F. Lisk, *Ind. Eng. Chem.*, **40**, 1671 (1948); **41**, 1923 (1949); **42**, 1746 (1950).

[169] K. Lauer, *J. Prakt. Chem.*, [ii], **143**, 127 (1935).

[170] U.S. Pat. 2,527,880; *Chem. Abstr.*, **45**, 1164 (1951).

[171] L. Leiserson, R. W. Bost, and R. LeBaron, *Ind. Eng. Chem.*, **40**, 508 (1948); W. H. C. Rueggeberg, T. W. Sauls, and S. L. Norwood, *J. Org. Chem.*, **20**, 455 (1955).

[172] P. Baumgarten, *Ber. Deut. Chem. Ges.*, **59**, 1976 (1926).

[173] Ger. Pat. 514,821; *Chem. Abstr.*, **25**, 2156 (1931).

[174] A. P. Terent'ev, L. A. Yanovskaya, and V. G. Yashunskii, *Zh. Qbshch. Khim.*, **20**, 510 (1950); *Chem. Abstr.*, **44**, 7828 (1950); cf. *Chem. Abstr.*, **43**, 7015 (1949).

[175] A. P. Terent'ev and L. A. Yanovskaya, *Zh. Obshch. Khim.*, **19**, 2118 (1949); *Chem. Abstr.*, **44**, 3973 (1950).

2-Furansulfonic acid[176] provides an example: Pure furan, b.p. 31.2–31.5°, is prepared from technical furan by way of the maleic anhydride adduct, which is then decomposed at 140 to 150°. This furan is treated with the pyridine–sulfur trioxide adduct in a bomb-tube for 8–10 h at 100°. This product is treated with a paste of barium carbonate in water for 30–40 min, then filtered hot, and concentrated, and the barium sulfonate is precipitated by ethanol. The following yields are obtained from 1.9 g of furan: with 4.4 g of pyridine–sulfur trioxide 30%, with 8.8 g 56%, and with 13.4 g 90%. *S*-Benzylthiouronium 2-furansulfonate melts at 205°.

Similarly 2-acetylfuran (2 g) and pyridine–sulfur trioxide (5.8 g) in dichloroethane (10 ml), heated for 10 h at 140° and then treated with barium carbonate, give **barium 5-acetyl-2-furansulfonate**[177] (2.5 g, 82.5%; recrystallized from aqueous ethanol) and some (0.8 g) starting material. 3-Methylindole gives its 2-sulfonic acid.[178]

Some aromatic compounds, *e.g.*, aniline, phenol, and naphthalene, can be sulfonated by pyridine–sulfur trioxide at 170°.[172]

Aromatic hydrocarbons such as toluene, xylenes, mesitylene, and methylnaphthalenes can be sulfonated in dichloroethane almost quantitatively by the dioxan–sulfur trioxide complex under very mild conditions (2 h at 20°).[179]

e. Aromatic sulfonation by halosulfuric acids and other sulfonating agents

When aromatic compounds are sulfonated by chlorosulfuric acid side reactions such as formation of the sulfonyl chloride or even the sulfone occur to a greater extent than in the procedures described above. For example, *o*- and *p*-toluenesulfonyl chloride are produced industrially from toluene and an excess of chlorosulfuric acid. Nevertheless, this acid can be used for introducing the sulfonic acid group if the proportions of the reactants, the temperature, and the solvent are selected correctly.

It is best to sulfonate by chlorosulfuric acid in an inert solvent such as carbon disulfide, carbon tetrachloride, chloroform, chlorobenzene, dichlorobenzene, or nitrobenzene.

Using chlorosulfuric acid has the advantage over using sulfuric acid that milder conditions can generally be applied, so that the products are purer and substitution is more confined to one site; also substituents that are affected by sulfuric acid, such as the cyano group, remain intact during sulfonation by chlorosulfuric acid.

Examples of sulfonation by chlorosulfuric acid are the preparation of 2-hydroxy-1-naphthalenesulfonic acid,[124h] 6-chrysenesulfonic acid,[180] 4-hydroxy-2-methylbenzenesulfonic acid.[181] Aromatic amines are sulfonated with particular ease by this reagent.

4-Amino-3-(trifluoromethyl)benzenesulfonic acid:[182] *m*-(Trifluoromethyl)aniline (161 g) is dissolved in carefully dried *o*-dichlorobenzene (1 l), freshly distilled chlorosulfuric acid (120 g) is added with stirring, and the mixture is heated slowly to 180°, whereupon there is lively

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[176] A. P. Terent'ev and L. A. Kazitsyna, *Zh. Obshch. Khim.*, **18**, 723 (1948); *Chem. Abstr.*, **43**, 214 (1949).

[177] A. P. Terent'ev, L. A. Kazitsyna, and A. M. Turovskaya, *Zh. Obshch. Khim.*, **20**, 185 (1950); *Chem. Abstr.*, **44**, 5862 (1950).

[178] A. P. Terent'ev, S. K. Golubeva, and L. V. Tsymbal, *Zh Obshch. Khim.*, **19**, 781 (1949); *Chem. Abstr.*, **44**, 1095 (1950).

[179] Y. T. Gordash, E. A. Laryutima, and R. Y. Semyachko, *Dokl. Akad. Nauk Beloruss. SSR*, **6**, 237 (1962); *Chem. Abstr.*, **59**, 1546 (1963).

[180] M. S. Newman and J. A. Cathcart, *J. Org. Chem.*, **5**, 621 (1940).

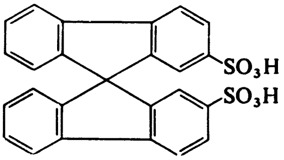
[181] R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **125**, 1303 (1924).

[182] Ger. Pat. 629,257; *Chem. Abstr.*, **30**, 5051 (1936).

evolution of hydrogen chloride for 3–4 h. After cooling, the solid product is filtered off, washed with ether, and, when dry, dissolved in warm 2N-sodium carbonate solution (600 ml) and water (1 l). The acid is freed from unsulfonated base by extraction with ether and is precipitated on subsequent acidification to Congo Red with hydrochloric acid.

Various substituted (trifluoromethyl)anilines can be sulfonated similarly.

9,9′-Spirobifluorene-2,2′-disulfonic acid:[183] Distilled chlorosulfuric acid (5.4 ml) in chloroform (20 ml) is added during 1.25 h to a boiling solution of 9,9′-spirobifluorene (12.8 g) in chloroform (80 ml). The mixture is heated for a further 3 h, then cooled, and the product is filtered off, washed with chloroform, and dried in a vacuum over potassium hydroxide (yield 17.9 g; m.p. 225°).



Aromatic hydrocarbons can also be sulfonated by fluorosulfuric acid, if necessary under pressure.[184] The dichloride of disulfuric acid has been used occasionally for sulfonation of terpenes,[185] and thionyl chloride for that of tertiary aromatic amines.[186]

For quinonoidal compounds a further possibility is direct introduction of the sulfo group by means of sodium sulfite or sodium hydrogen sulfite (the sulfite reaction). Sodium 1,3-dihydroxy-1,3,5-cyclohexanetrisulfonic acid is obtained from resorcinol and on subsequent treatment with alkali loses two moles of sodium hydrogen sulfite and one of water with formation of *m*-hydroxybenzenesulfonic acid.[187]

Sodium *m*-hydroxybenzenesulfonate:[188] Resorcinol (100 g) and sodium hydrogen sulfite solution (*d* 1.32; 1 l) are heated together for 22 h, then freed from sulfite and sulfate ions by addition of barium acetate, filtered, and concentrated to 500 ml. Addition of 85% ethanol (1 l) precipitates trisodium 1,3-dihydroxy-1,3,5-cyclohexanetrisulfonate (242.8 g). This salt (100 g) is dissolved in water (100 ml), treated with 50% sodium hydroxide solution (40 ml), and set aside overnight. The mixture is next neutralized with sulfuric acid, treated with hot 85% ethanol (400 ml), filtered, and evaporated. The residue is extracted with hot 99% ethanol. Adding ether (500 ml) affords sodium *m*-hydroxybenzenesulfonate (23.55 g), which has m.p. 314° after recrystallization from ethanol.

Further examples of the sulfonation of phenols by this method are the preparation of 1,4-dihydroxyanthraquinone-2-sulfonic acid from quinazirin[189] and of 1,3,4-trihydroxyanthraquinone-2-sulfonic acid from purpurin.[190]

Amines, polyamines, and aminophenols that can quinonize are similarly amenable to this reaction if an oxidizing agent is added:[191] 4-amino-3-hydroxy-1-naphthalenesulfonic acid was obtained from 1-naphthylamine,[192] and a monosulfonic acid from *p*-phenylenediamine.[193]

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[183] J. H. Weisburger, E. K. Weisburger, and F. E. Ray, *J. Amer. Chem. Soc.*, **72**, 4253 (1950).

[184] J. H. Simons, H. J. Passino, and S. Archer, *J. Amer. Chem. Soc.*, **63**, 608 (1941).

[185] U.S. Pat. 2,220,678; *Chem. Abstr.*, **35**, 1412 (1941).

[186] A. Michaelis and E. Godchaux, *Ber. Deut. Chem. Ges.*, **23**, 553 (1890).

[187] W. M. Lauer and C. M. Langkammerer, *J. Amer. Chem. Soc.*, **56**, 1628 (1934).

[188] V. N. Ufimtsev, *Zh. Prikl. Khim.*, **20**, 1199 (1947); *Chem., Abstr.*, **43**, 2595 (1949).

[189] Ger. Pat. 287,867; *Chem. Abstr.*, **10**, 2305 (1916).

[190] Ger. Pat. 288,474; *Chem. Abstr.*, **10**, 2306 (1916).

[191] A. Seyewetz, 4th Congr. Chim. Ind. Paris, 1934, Commun. 2, 1935.

[192] E. Bamann, K. Schriever, and G. Müller, *Arch. Pharm.*, **287**, 570 (1954).

[193] Ger. Pat. 64,908; *Friedländer*, **3**, 40 (1890–1894).

Sulfonation of nitroso compounds by sodium hydrogen sulfite leads to amino sulfonic acids by simultaneous reduction.[124c,194] When aromatic nitro compounds are subjected to this reaction, sulfonation in the ring is accompanied by formation of arylamine-*N*-sulfonic acids (arylsulfamic acids), which on acid fission also give amino sulfonic acids; this reaction, known in the literature as the Piria reaction, has been reviewed in papers by Hunter and his co-workers.[195]

Sodium dithionite can also be used as sulfonating agent in special cases, *e.g.*, for *N*-heterocyclic nitro compounds whose nitro groups are then simultaneously reduced to amino groups. 5-Amino-4-uracilsulfonic acid was thus prepared from 5-nitrouracil, and 3-amino-4-hydroxy-2-pyridinesulfonic acid from 3-nitro-4-pyridinol.[196]

2. Introduction of the sulfonyl chloride group

In aliphatic chemistry replacement of a hydrogen atom by the sulfonyl chloride group is achieved mainly by Reed's process,[197] which involves simultaneous action of sulfur dioxide and chlorine ("sulfochlorination")[198] on the hydrocarbon according to the total reaction:

$$\mathrm{RH + SO_2 + Cl_2 \longrightarrow RSO_2Cl + HCl}$$

This reaction (whose course was incorrectly interpreted by its discoverer) is effected under irradiation by ultraviolet light or in the presence of a catalyst at 20–25° and occurs as a radical chain reaction:[198b]

$$\begin{array}{rll}
\mathrm{Cl_2} + h\nu & \longrightarrow \mathrm{Cl^{\bullet} + Cl^{\bullet}} & \text{Start} \\
\left.\begin{array}{r} \mathrm{RH + Cl^{\bullet}} \\ \mathrm{R^{\bullet} + SO_2} \\ \mathrm{RSO_2^{\bullet} + Cl_2} \end{array}\right. & \left.\begin{array}{l} \longrightarrow \mathrm{R^{\bullet} + HCl} \\ \longrightarrow \mathrm{RSO_2^{\bullet}} \\ \longrightarrow \mathrm{RSO_2Cl + Cl^{\bullet}} \end{array}\right\} & \text{Reaction chain} \\
\mathrm{Cl^{\bullet} + Cl^{\bullet}} & \longrightarrow \mathrm{Cl_2} & \text{Termination}
\end{array}$$

The sulfochlorination, involving simultaneous entry of sulfur dioxide and chlorine, is accompanied by a usual chlorination in which no sulfur is bound:

$$\mathrm{RH + Cl_2 \longrightarrow RCl + HCl}$$

Surprisingly, however, this competitive reaction retires almost completely into the background when sulfochlorination is carried out under UV irradiation.[199] It can also be suppressed by adjusting the temperature and the proportions of sulfur dioxide and chlorine. Optimal conditions for sulfochlorination are irradiation with light of wavelength 3000–3600 Å, a reaction temperature of 20–25° after initiation at 35–40°, and a $Cl_2 : SO_2$ ratio of 1 : 1.3. There is practically no reaction if chlorine and sulfur dioxide are led into a

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[194] J. M. Kogan, *Ber. Deut. Chem. Ges.*, **64**, 2150 (1931).

[195] W. H. Hunter and M. M. Sprung, *J. Amer. Chem. Soc.*, **53**, 1432, 1443 (1931).

[196] F. G. Fischer, H. Eilingsfeld, and W. P. Neumann, *Ann. Chem.*, **651**, 49 (1962), and references cited therein.

[197] U.S. Pat. 2,046,090, 2,174,110, 2,174,492, 2,263,312, 2,370,421; *Chem. Abstr.*, **30**, 5593 (1936); **34**, 554, 778 (1940); **36**, 1408 (1942); **39**, 3420 (1945).

[198] Reviews: (a) J. H. Helberger, *Angew. Chem.*, **55**, 172 (1942); (b) H. J. Schumacher and J. Stauff, *Angew. Chem.*, **55**, 341 (1942); (c) F. Asinger, "Chemie und Technologie der Paraffinkohlenwasserstoffe," Akademie-Verlag, Berlin, 1956, Chapter 5.

[199] H. Kroepelin, W. Opitz, and W. Freiss, *Erdöl und Kohle*, **2**, 498 (1949); *Angew. Chem.*, **64**, 273 (1952).

mixture of completely pure hydrocarbons in the dark, but a dark reaction is induced by organic peroxides[168] or other radical-forming catalyst;[200] suitable catalysts have proved to be acetone peroxide, oxygen-treated turpentine oil, benzoyl peroxide, di-*tert*-butyl peroxide,[201] and acetyl cyclohexanesulfonyl peroxide.[202]

Sulfochlorination under the above conditions is smoothest and most unambiguous for normal alkanes and for cycloalkanes of simple structure; branched alkanes and alkylated cycloalkanes are less suitable because the hydrogen on tertiary carbon atoms is not replaced.

Contrary to statements in the patent literature,[197] sulfochlorination cannot be established for aromatic compounds subjected to the above treatment:[198,199] toluene, for example, is only chlorinated, and ethyl- and propyl-benzene are side-chain sulfochlorinated to the extent of 8% and 20%, respectively.

Similar treatment of oxygen-containing compounds, such as alcohols,[203] aldehydes, acids, esters,[197] ethers, and acetals, is almost always less successful than that of aliphatic hydrocarbons: in most cases only chlorine, and no sulfur, enters the molecule.

1-Chlorobutane gives 1- and 4-chloro-2-butanesulfonyl chloride and 4-chloro-1-butanesulfonyl chloride,[204] hydrolysis of which affords the corresponding sulfonic acids; 4-chloro-2- and -1-butanesulfonic acid lose hydrogen chloride when heated, passing into sultones[205] (internal anhydrides of hydroxy sulfonic acids).

The following products are usually contained in the reaction mixture produced by sulfochlorination:[198c] mono-, di-, and poly-sulfonyl chlorides; chloro-mono-, -di-, and -poly-sulfonyl chlorides; alkyl chloride; and unchanged starting material; of which the last two are unhydrolysable neutral oils. The individual products obtained on sulfochlorination of aliphatic hydrocarbons of low molecular weight can be separated by distillation, but it has also been found that the mono- can be separated from the poly-sulfonyl portions by treating the mixture with at least a five-fold amount of pentane and cooling to −30°.[206]

According to Asinger and his co-workers,[207,209–211] the ingredients of the monosulfonyl chloride mixture can be estimated by Hass's rule,[208] according

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[200] Ger. Pat. 765,790; *Chem. Abstr.*, **49**, 3336 (1955); Brit. Pat. 628,014; *Chem. Abstr.*, **44**, 2556 (1950); Ger. Pat. 833,808, 839,351; *Chem. Abstr.*, **47**, 3336, 5432 (1953); U.S. Pat. 2,503,253; *Chem. Abstr.*, **44**, 5896 (1950); K. Ziegler, *Brennstoffchemie*, **30**, 181 (1949).

[201] U.S. Pat. 2,536,008, 2,542,578; *Chem. Abstr.*, **45**, 4262, 8027 (1951).

[202] Ger. Pat. 841,147; *Chem. Abstr.*, **47**, 4897 (1953); cf. R. Graf, *Ann. Chem.*, **578**, 50 (1952).

[203] French. Pat. 870,163; *Chem. Zentralbl.*, **1942**, II, 478; Brit. Pat. 538,407; *Chem. Abstr.*, **36**, 1335 (1942).

[204] Brit. Pat. 516,214; *Chem. Abstr.*, **35**, 5911 (1941).

[205] J. H. Helberger, G. Nanecke, and H. M. Fischer, *Ann. Chem.*, **562**, 23 (1949).

[206] Ger. Pat. 711,821, 734,562; *Chem. Abstr.*, **37**, 4405 (1943); **38**, 1247 (1944).

[207] Cf. F. Asinger, *Ber. Deut. Chem. Ges.*, **75**, 668 (1942).

[208] H. B. Hass, E. T. McBee, and P. Weber, *Ind. Eng. Chem.*, **27**, 1190 (1935); **28**, 333 (1936); H. B. Hass, E. T. McBee, and L. F. Hatch, *Ind. Eng. Chem.*, **29**, 1335 (1937).

[209] F. Asinger, W. Schmidt, and F. Ebeneder, *Ber. Deut. Chem. Ges.*, **75**, 34 (1942).

[210] F. Asinger, F. Ebeneder, and E. Böck, *Ber. Deut. Chem. Ges.*, **75**, 42 (1942); F. Asinger and F. Ebeneder, *Ber. Deut. Chem. Ges.*, **75**, 344 (1942).

[211] F. Asinger, *Ber. Deut. Chem. Ges.*, **77**, 191 (1944).

to which sulfochlorination occurs about 3.25 times as fast on secondary as on primary carbon atoms. Thus, on sulfochlorination propane gives 50% each of 1- and 2-propanesulfonyl chloride,[209] butane gives 33% of 1- and 67% of 2-butanesulfonyl chloride,[210] and dodecane gives (after removal of polysulfonyl chlorides and neutral portions) 8.5% of 1- and 18.3% each of 2-, 3-, 4-, 5-, and 6-dodecanesulfonyl chloride.[211]

In the laboratory sulfonation of liquid hydrocarbons is generally carried out in a vertical quartz tube (or, if necessary, in a glass tube) of about 60-mm diameter, inside which is a thermometer and a cooling coil. For gaseous hydrocarbons the tube is filled with carbon tetrachloride, and the hydrocarbon, as well as the sulfur dioxide and chlorine, are led in through a frit. Irradiation is by a mercury vapor lamp at a distance of about 25 cm.

Sulfochlorination of propane:[209,212] A mixture of propane (2.5 parts by vol.), sulfur dioxide (1.1 parts by vol.), and chlorine (1 part by vol.) is passed into carbon tetrachloride under illumination by a quartz lamp until an approximately 20% solution of the products in carbon tetrachloride is obtained. Then the solvent is removed. The residue (1000-g batch) is distilled at 15 mm, whereupon 85% of it passes over at 70–150° (mainly at 70–90°). This distillate contains mainly propanemonosulfonyl chlorides, with small amounts of mono- and di-chloropropanemonosulfonyl chlorides; the residue contains disulfonyl chlorides. Redistillation through a 50-cm Raschig column (reflux ratio 1 : 5) gives 88% of a mixture of propanemonosulfonyl chlorides, b.p. 72–79°/15 mm, d^{20} 1.268, $n_D{}^0$ 1.452; the residue therefrom being mono- and di-chloropropanesulfonyl chlorides.

As mentioned above, the chlorosulfonyl group cannot be introduced into aromatic hydrocarbons by Reed's process, but this can be achieved by means of the chlorides from sulfuric acid.[213] Preparation of sulfonyl chlorides by means of chlorosulfuric acid depends on using a sufficient excess and on the purity of the acid; sulfones may be formed as by-products, and these can be further sulfochlorinated.[214] Benzenesulfonyl chloride has been prepared from benzene in 75–77% yield in this way.[215]

***p*-Chlorobenzenesulfonyl chloride:**[216] Chlorobenzene (20 g) is added from a dropping funnel, during 2 h, to chlorosulfuric acid (60 g), which is cooled to −15°. The mixture is set aside with occasional shaking for 2 h at −5° to −10° and then for 12 h at room temperature, after which it is poured on ice. The oil is separated and distilled in a vacuum. The sulfonyl chloride (22 g; m.p. 53°) passes over at 144°/15 mm; recrystallization of the residue from glacial acetic acid gives pure bis-(*p*-chlorophenyl) sulfone (5 g).

Various substituted aromatic compounds can be converted into sulfonyl chlorides by dissolution in five parts of chloroform, dropwise addition of five parts of chlorosulfuric acid at 0°, and keeping for 20 minutes at room temperature. The products are isolated by decomposition with ice, washing of the chloroform layer with water, removal of the solvent, recrystallization of the residue from dry low-boiling light petroleum or from chloroform, and drying in a vacuum over concentrated sulfuric acid. The following benzene- and naphthalene-sulfonyl chlorides were obtained in this way:[217]

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[212] French Pat. 842,509; *Chem. Abstr.*, **34**, 5466 (1940).

[213] E. E. Gilbert and E. P. Jones, *Ind. Eng. Chem.*, **51**, 1151 (1959); **50**, 1410 (1958); **49**, 1553 (1957) (annual reviews).

[214] J. Pollak, M. Heimberg-Krauss, E. Katscher, and O. Lustig, *Monatsh. Chem.*, **55**, 363 (1930).

[215] H. T. Clarke, G. S. Babcock, and T. F. Murray, *Org. Syn.*, Coll. Vol. 1, 78 (1937).

[216] F. Ullmann and J. Korselt, *Ber. Deut. Chem. Ges.*, **40**, 641 (1907).

[217] E. H. Huntress and F. H. Carten, *J. Amer. Chem. Soc.*, **62**, 511 (1940).

Benzene series	M.p. (°)	Naphthalene series	M.p. (°)
p-Fluoro-	35–36[a]	4-Chloro-	92– 93
p-Chloro-	53.5[a]	7-Chloro-	124–126
p-Bromo-	75.4	4-Bromo-	81– 83
3,4-Dichloro-	18–19	7-Bromo-	142–143
2,5-Dibromo-	71[b]		
4-Fluoro-3-methyl-	Oil		
4-Chloro-2-methyl-	52–53[c]		

[a] From benzene or ether. [b] After 1 hours' heating.
[c] After 10minutes' heating at 50°.

Pollak and his co-workers reported the preparation of hydroxybenzene-[218] and hydroxynaphthalene-sulfonyl chlorides.[219]

For the preparation of aminoarenesulfonyl chlorides it is advisable to protect the amino group by acylation,[220–222] but this is unnecessary when 2-aminopyridine is converted into 6-amino-2,5-pyridinedisulfonyl chloride (79% yield) by hot chlorosulfuric acid.[223]

Sulfonyl chlorides of aromatic carboxylic acids can be obtained from chlorides of the latter by treatment with sulfonating agents that do not produce water during the reaction.[224]

m-Chlorosulfonylbenzoic acid:[224] Sulfur trioxide is passed into benzoyl chloride (100 g) at 110° until a weight increase of 71.3 g has been achieved. The mixture is kept at 130° for a further 2 h, taken up in chloroform, and washed with ice-water. After removal of the chloroform by distillation and recrystallization of the residue from toluene the product has m.p. 133°.

To avoid side reactions and multiple chlorosulfonation it is often advisable to use an inert solvent such as chloroform or carbon tetrachloride. Side reactions can also be produced by the water formed, and this can be bound by an excess of chlorosulfuric acid or, better, oleum, phosphorus pentaoxide, or thionyl chloride.

The chlorosulfonyl group can, finally, be introduced into aromatic compounds by using the chloride of disulfuric acid[225] or sulfuryl chloride,[226] the latter in the presence of condensing agents such as aluminum chloride.

3. Direct introduction of the sulfone and sulfoxide group

Direct introduction of a sulfone group RSO_2 into aromatic compounds in place of a hydrogen atom occurs during sulfonation by sulfuric acid, but

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[218] J. Pollak and E. Gebauer-Fülnegg, *Monatsh. Chem.*, **47**, 537 (1927).

[219] J. Pollak, E. Gebauer-Fülnegg, and E. Blumenstock-Halward, *Monatsh. Chem.*, **49**, 187 (1928); J. Pollak and E. Blumenstock-Halward, *Monatsh. Chem.*, **49**, 203 (1928).

[220] Cf. G. F. Lisk, *Ind. Eng. Chem.*, **42**, 1751 (1950).

[221] Ger. Pat. 573,193; *Chem. Abstr.*, **27**, 2966 (1933).

[222] R. N. Johnson and S. Smiles, *J. Chem. Soc.*, **123**, 2384 (1923).

[223] E. J. Cragoe, J. A. Nicholson, and J. M. Sprague, *J. Med. Pharm. Chem.*, **4**, 369 (1961).

[224] French Pat. 872,771; *Chem. Zentralbl.*, **1942**, II, 2219.

[225] W. Steinkopf and K. Buchheim, *Ber. Deut. Chem. Ges.*, **54**, 2963 (1921).

[226] H. C. Brown, *Ind. Eng. Chem.*, **36**, 788 (1944).

always as a side reaction. However, it can be made into one that gives satisfactory yields by changing the reaction conditions, *e.g.*, by raising the temperature[227] or by adding agents that remove water.[228] It is particularly relevant to note a very generally applicable process due to Meyer,[105] according to which simple and mixed sulfones[229] can be prepared by continuously removing the water from the equilibrium mixture; this method has been used for the synthesis of, *e.g.*, diphenyl, di-*p*-tolyl, di-*m*-xylyl, bis-(*p*-chlorophenyl), bis-(tetrahydronaphthyl), phenyl tolyl, *p*-tolyl *m*-xylyl, *p*-chlorophenyl phenyl, 2-naphthyl tolyl, and tetrahydronaphthyl tolyl sulfone.

Aryl methyl sulfones can be obtained in average yields of 60% by heating aromatic hydrocarbons with methanesulfonic anhydride:[230]

$$\mathrm{ArH} + (\mathrm{CH_3SO_2})_2\mathrm{O} \longrightarrow \mathrm{ArSO_2CH_3} + \mathrm{CH_3SO_3H}$$

***p*-Methoxyphenyl methyl sulfone:**[230] A mixture of anisole (60 g, 0.056 mole), methanesulfonic anhydride (9.0 g, 0.052 mole), and tetrachloroethylene (50 ml) is boiled for 16 h, then treated with two successive portions (each 25 ml) of warm water. The aqeuous extracts are cooled and extracted with ether. The solvents are removed in a current of air from the combined tetrachloroethylene and ether phases, and the residue is recrystallized from 1-butanol or from water, giving the sulfone (70% yield), m.p. 120°.

p-Toluenesulfonyl perchlorate (which is formed from 5–10% solutions of *p*-toluenesulfonyl bromide and silver perchlorate in nitromethane at 0°) is the strongest sulfonylating agent known.[231] For instance, it sulfonylates the relatively unreactive halobenzenes in satisfactory yield at room temperature: *p*-bromo- and *p*-chloro-phenyl *p*-tolyl sulfone were obtained in 66.5% and 63% yield, respectively:[231]

$$\mathrm{C_7H_7SO_2^+ClO_4^-} + \mathrm{ArH} \longrightarrow \mathrm{C_7H_7SO_2Ar} + \mathrm{HClO_4}$$

Synthesis of aromatic sulfoxides is usually effected preparatively by one of the two following methods. First, aromatic compounds can be treated with thionyl chloride under Friedel–Crafts conditions: di-*p*-tolyl sulfoxide has thus been obtained from toluene,[232] diphenyl sulfoxide from benzene,[233,234] and bis-(*p*-hydroxyphenyl) sulfoxide from phenol.[235]

Diphenyl sulfoxide: Finely powdered aluminum chloride (30 g) is added in portions to benzene (50 g) and thionyl chloride (16 g) cooled in cold water. Then more benzene (20 g) is added and the whole is heated for 30 min on a water-bath, cooled, and poured into water. The benzene layer, when separated, washed, dried, and evaporated, provides diphenyl sulfoxide (21 g), which after recrystallization from light petroleum has m.p. 70–71°.

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[227] L. E. Hinkel and G. H. R. Summers, *J. Chem. Soc.*, **1949**, 2854.

[228] R. Otto, *Ber. Deut. Chem. Ges.*, **19**, 2421 (1886); G. Machek and H. Haas, *J. Prakt. Chem.*, [ii], **160**, 41 (1942); A. Michael and A. Adair, *Ber. Deut. Chem. Ges.*, **10**, 583 (1877)

[229] H. Drews, S. Meyerson, and E. K. Fields, *Angew. Chem.*, **72**, 493 (1960); W. F. Hart, M. E. McGreal, and P. E. Thurston, *J. Org. Chem.*, **27**, 338 (1962).

[230] E. E. Gilbert, *J. Org. Chem.*, **28**, 1945 (1963).

[231] F. Klages and F. E. Malecki, *Ann. Chem.*, **691**, 15 (1966).

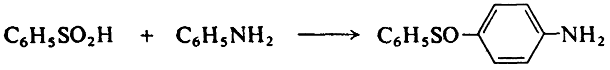
[232] C. Parker, *Ber. Deut. Chem. Ges.*, **23**, 1884 (1890).

[233] A. Schönberg, *Ber. Deut. Chem. Ges.*, **56**, 2275 (1923).

[234] R. L. Shriner, H. C. Struck, and W. J. Jorison, *J. Amer. Chem. Soc.*, **52**, 2065 (1930).

[235] L. N. Nikolenko and N. I. Krizhechkovskaya, *Zh. Obshch. Khim.*, **33**, 3731 (1963); *Chem. Abstr.*, **60**, 7964 (1964).

The second method is to treat aromatic amines with benzenesulfinic acid:[236,237]



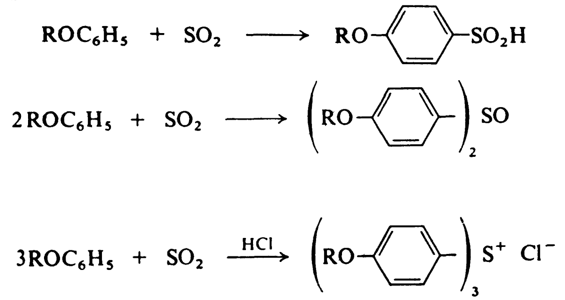
4. Direct introduction of the sulfinic acid group

Hydrocarbons react with sulfur dioxide in the presence of Friedel–Crafts catalysts with formation of sulfinic acids:

$$RH + SO_2 \xrightarrow[AlCl_3]{} RSO_2H$$

Saturated aliphatic hydrocarbons undergo this reaction most satisfactorily under pressure and at elevated temperatures,[238] but alkenes give sulfinic acids even at atmospheric pressure.[239]

Aromatic hydrocarbons and aryl halides can be converted into sulfinic acids in yields averaging 80% if the reaction is carried out at low temperature, if, as in the Gattermann aldehyde synthesis, reaction is initiated by passing in dry hydrogen chloride, and if the tetrachloroaluminum sulfinate formed is decomposed, not by acid, but by alkali, and acid is used for the first time to decompose the alkali sulfinites thus formed.[240] Aryl ethers give sulfinic acids even in the cold, but reaction readily proceeds further to give sulfoxides and sulfonium compounds:[241]



Benzenesulfinic acid:[240] Dry hydrogen chloride (5 g) and thereafter dry sulfur dioxide (126 g) are passed into a suspension of aluminum chloride (200 g) in benzene (400 g) cooled in ice. The mixture is set aside at room temperature for 12 h, then poured on ice, treated with a solution of sodium hydroxide (260 g) in water (1 l), and heated on the water-bath under reflux until all the "aluminum chloride salt" is decomposed. The excess of benzene is removed in steam, the precipitate is filtered off, and the filtrate is freed from residual aluminum by saturation with carbon dioxide. Filtration again, concentration, and treatment with concentrated hydrochloric acid give pure benzenesulfinic acid, m.p. 83° (170 g, 80% calculated on aluminum chloride).

p-Toluenesulfinic acid can be obtained (m.p. 84°) in 94% yield in the same way.

Involatile hydrocarbons and their derivatives are best diluted with carbon disulfide.

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[236] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **36**, 113 (1903).

[237] P. W. B. Harrison, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, **1926**, 2079.

[238] Brit. Pat. 321,843; *Chem. Abstr.*, **24**, 2759 (1930).

[239] Ger. Pat. 727,205; *Chem. Abstr.*, **37**, 6279 (1943).

[240] E. Knoevenagel and J. Kenner, *Ber. Deut. Chem. Ges.*, **41**, 3315 (1908).

[241] Cf. C. E. Colby and C. S. McLoughlin, *Ber. Deut. Chem. Ges.*, **20**, 195 (1887).

2,5-Dimethylbenzenesulfinic acid:[240] Treating *p*-xylene (10 g), carbon disulfide (40 g), and aluminum chloride (12.6 g) with hydrogen chloride and sulfur dioxide at 0° and keeping the mixture for 2 h afford this acid, 12,5 g, m.p. 84–85°.

Mesitylene-, pseudocumene-, *p*-chlorobenzene, *p*-bromobenzene- and 1-naphthalenesulfinic acid have been prepared by the same method.

5. Introduction of thioxo, thio, and mercapto groups: preparation of sulfur ylides

It is sometimes possible to replace two hydrogen atoms in a molecule directly by a thioxo group (=S), leading to thioketones (RR'C=S); examples are the treatment of diphenylmethane and acridine derivatives with sulfur[242,243] or sodium sulfide.[244]

In the presence of Friedel–Crafts catalysts, sulfur may replace an atom of hydrogen in each of two molecules, yielding sulfides (thioethers, RSR'); this method was used, for example, for preparation of diphenyl sulfide[245] and of phenothiazine[246] and its derivatives.[247]

Sulfides may also be prepared by using sulfur halides instead of elemental sulfur:

$$SCl_2 + 2C_6H_6 \xrightarrow{AlCl_3} (C_6H_5)_2S{\cdot}AlCl_3 + 2HCl$$

$$S_2Cl_2 + 2C_6H_6 \longrightarrow (C_6H_5)_2S{\cdot}AlCl_3 + 2HCl + S$$

Diphenyl sulfide:[248] Dry benzene (980 ml) and aluminum chloride (464 g) are placed in a 5-l round-bottomed flask fitted with a stirrer, dropping funnel, and reflux condenser with an attached outlet tube for hydrogen chloride. The mixture is placed in an ice-bath, and disulfur dichloride (405.1 g) in benzene (450 ml) is added at 10° during 1 h; the reaction begins suddenly, with evolution of hydrogen chloride and separation of a yellow, viscous aluminum complex. When addition is complete, the whole is stirred for a further 2 h at room temperature and then at 30° until after about 1 h no more hydrogen chloride is evolved. The mixture is then poured on ice (1 kg), the organic layer is separated, and the benzene is distilled off from it on the water-bath. The residue is cooled to 0° and filtered through a Buchner funnel (sulfur). The solid is stirred with methanol (500 ml) at 0° for 3 h, then filtered off and distilled, a yellow oil (470–490 g) passing over at 155–170°/18 mm. To obtain a colorless product, the distillate is stirred with zinc dust (70 g) and hot 40% sodium hydroxide solution (200 g) for 1 h, separated again, washed with water (2 × 500 ml), dried over sodium sulfate, and distilled. Colorless diphenyl sulfide, b.p. 162–163°/18 mm, is thus obtained in 81–83% yield (450–464 g).

When phenols are treated in carbon tetrachloride with sulfur dichloride at −10°, sulfides are formed as colorless or yellow precipitates that can be recrystallized from benzene.[249]

Holzmann[250] has described the reaction of *N*,*N*-dialkylanilines with sulfur chlorides, which gives sulfides and disulfides. In the presence of lead oxide, aniline and sulfur afford **bis-(*p*-aminophenyl) sulfide** as follows:[251]

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[242] A. E. Tschitschibabin and I. L. Knunjanz, *Ber. Deut. Chem. Ges.*, **62**, 3051 (1929).

[243] E. F. Elslager, *J. Org. Chem.*, **27**, 4346 (1962).

[244] Ger. Pat. 287,994; *Chem. Abstr.*, **10**, 2522 (1916).

[245] W. Dilthey, L. Neuhaus, E. Reis, and W. Schommer, *J. Prakt. Chem.*, [ii], **124**, 108 (1930).

[246] Ger. Pat. 222,879; *Chem. Abstr.*, **4**, 2882 (1910).

[247] Ger. Pat. 224,348; *Chem. Abstr.*, **5**, 210 (1911).

[248] W. W. Hartmann, L. A. Smith, and J. B. Dickey, *Org. Syn.*, Coll. Vol. II, 242 (1955).

[249] F. Dunning, B. Dunning Jr., and W. E. Drake, *J. Amer. Chem. Soc.*, **53**, 3466 (1931).

[250] E. Holzmann, *Ber. Deut. Chem. Ges.*, **20**, 1636 (1887); **21**, 2056 (1888).

[251] M. L. Moore and T. B. Johnson, *J. Amer. Chem. Soc.*, **57**, 1287 (1935).

Freshly distilled aniline (93 g) and sulfur (32 g) are stirred in an oil-bath at 135–145° while lead oxide (160 g) is added during 5.5 h. Stirring is continued for a further 0.5 h, after which the dark oily product is cooled, treated with 20% sodium hydroxide solution (30 ml), and extracted three times with boiling alcohol. The alcohol is distilled off and the excess of aniline is removed in steam. Treatment with dilute hydrochloric acid affords the hydrochloride, which is dissolved in water, treated with charcoal, and reconverted into the base by alkali. The base can be further purified by way of the sulfate and after final recrystallization from 35% alcohol has m.p. 107–108°.

Treating the hydrochlorides of primary aromatic amines with an excess of disulfur dichloride (the Herz reaction)[252] and hydrolysing the resulting "thiazthionium chlorides" with alkali afford *o*-aminothiophenols.[253] If the amine has the *para*-position free, the product is a 5-chloro-2-aminothiophenol.

Mercapto derivatives of purines[254] and thiophenes[232b] can be obtained in good yield by reaction with sulfur, which converts a C–H directly into a C–SH bond in these cases.

The preparation of sulfides by reaction of sulfenyl chlorides with compounds containing acidic hydrogen has been reported by Brintzinger and his co-workers in a series of papers.[256] Sulfides of the indole series[257] as well as (alkylthio)phenols and (alkylthio)phenyl ethers[258] have been prepared by this method.

Condensing sulfoxides with compounds containing reactive methylene groups gives sulfur ylides in good yields:

$$\mathrm{RR'SO} + \mathrm{H_2CXY} \xrightarrow{(-\mathrm{H_2O})} \mathrm{RR'\overset{+}{S}{—}\overset{-}{C}XY}$$

Suitable condensing agents for this reaction are acetic anhydride,[259,260] hydrogen chloride and thionyl chloride,[261] dicyclohexylcarbodiimide,[262] and phosphorus pentaoxide.[263] For example, barbituric acids, 2-hydroxy-1,4-naphthoquinone, and methylene di(phenyl sulfone),[259] malonodinitrile,[261] Meldrum acid and 2,3-indenedione,[262] dinitromethane and dihydroresorcinol[260] yield ylides by this method.

Dimethylsulfonium bis(phenylsulfonyl)methylide:[259] Methylene di(phenylsulfone) (14.8 g) is heated with dimethyl sulfoxide (39 g) and acetic anhydride (25 g) until reaction sets in. The violent reaction is moderated by gentle cooling, then more acetic anhydride (25 g) is added and the mixture is gently heated again. After cooling, the colorless crystals are filtered off and washed with benzene. When recrystallized from dimethylformamide–water this methylide (12 g, 67%) has m.p. 214–215°.

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[252] Ger. Pat. 367,346, 360,690; *Friedländer*, **14**, 918, 908 (1921–1925); L. D. Huestis M. L. Walsh, and N. Hahn, *J. Org. Chem.*, **30**, 2763 (1965); W. Ried and J. Valentin, *Annalen*, **699**, 183 (1966).

[253] J. M. F. Leaper, *J. Amer. Chem. Soc.*, **53**, 1891 (1931).

[254] A. Giner-Sorolla, E. Thom, and A. Bendich, *J. Org. Chem.*, **29**, 3209 (1964).

[255] Ya. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *Zh. Obshch. Khim.*, **32**, 222 (1962); *Chem. Abstr.*, **57**, 16529 (1962).

[256] H. Brintzinger and co-workers, *Chem. Ber.*, (a) **86**, 557 (1953); (b) **87**, 300, 314, 320, 325 (1954).

[257] T. Wieland and D. Grimm, *Chem. Ber.*, **98**, 1727 (1965).

[258] R. T. Wragg, *J. Chem. Soc.*, **1964**, 5482.

[259] G. Compper and H. Euchner, *Chem. Ber.*, **99**, 527 (1966).

[260] A. Hochrainer, *Monatsh. Chem.*, **97**, 823 (1966).

[261] W. J. Middleton, E. L. Buhle, J. G. McNally, and M. Zanger, *J. Org. Chem.*, **30**, 2384 (1965).

[262] A. Hochrainer and F. Wessely, *Monatsh. Chem.*, **97**, 1 (1966).

[263] H. Nozaki, Z. Morita, and K. Kondô, *Tetrahedron Lett.*, **1966**, 2913.

II. Replacement of halogen by sulfur groups

1. Reaction of alkyl and aryl halides with salts and derivatives of hydrogen sulfide

a. Preparation of thiols and disulfides

The method most commonly used for preparation of thiols is reaction of alkali hydrogen sulfide with an alkyl or suitable aryl halide. Sulfides may be formed in this reaction owing to the equilibrium $2NaSH \rightleftarrows Na_2S + H_2S$ that is characteristic of alkali hydrogen sulfides; however, sulfide formation can be repressed by passing in H_2S during the reaction or by conducting the operation at not more than 50–60° or in an autoclave and at the same time excluding water so far as possible. Ellis and Reid,[264] using these conditions, prepared a series of low alkanethiols (up to nonanethiol) in yields of 36–74%.

For such reactions to succeed with aryl halides the halogen must be particularly reactive. For example, *o*-halobenzoic acids give *o*-mercaptobenzoic acid when heated with an alkali hydrogen sulfide in the presence of copper powder under pressure;[265] and *p*-chloronitrobenzene gives *p*-aminothiophenol when heated with an excess of sodium sulfide in aqueous solution, the nitro group being simultaneously reduced.[266]

Mercaptoacetic acid:[267] This is formed very smoothly, even in aqueous solution, as follows. A solution of chloroacetic acid (100 g) is added gradually to a stirred solution (ca. 15%) of potassium hydrogen sulfide (2 moles) in water (500 ml). The mixture is heated for 15 min on a water-bath, then treated with a concentrated solution of barium chloride, followed by 25% ammonia solution (ca. 1.25 mole). The barium salt is caused to separate by scratching and shaking and is collected and treated with a three-fold amount of 12% hydrochloric acid. The acid liberated is taken up in ether and purified by distillation (b.p. 107–108°/16 mm).

A method of preparing alkanethiols and thiophenols by means of thiocarboxylic acids consists of converting, preferably, thioacetic or thiobenzoic acid by an alkyl (or aryl) halide into an *S*-alkyl (or *S*-aryl) thiocarboxylate and hydrolysing this by acid or alkali; this method, and that described in the following paragraphs, have the advantage that the thiols can be obtained free from sulfide.[268]

$$C_6H_5CHBrCOCH_3 + CH_3COSK \longrightarrow KBr + CH_3CO{-}S{-}CH(C_6H_5)COCH_3$$

$$\xrightarrow{H_2O} HS{-}CH(C_6H_5)COCH_3$$

1-(Acetylthio)-1-phenylacetone: A solution of thioacetic acid (29 g) in ethanol (200 ml) is exactly neutralized with the most concentrated possible potassium hydroxide solution and to it is added at not more than 50°, dropwise, somewhat less than one equivalent (70 g) of 1-bromo-1-phenylacetone. Potassium bromide is at once precipitated. After cooling, the mixture is treated with water, and the precipitated oil is taken up in ether, dried over sodium sulfate, and distilled in a vacuum. The fraction passing over between 140° and 160° at 12 mm is redistilled through a Widmer column, giving the acetylthio ketone, b.p. 157–158°/12 mm, in 50% yield (36 g).

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[264] L. M. Ellis Jr. and E. E. Reid, *J. Amer. Chem. Soc.*, **54**, 1674 (1932).

[265] Ger. Pat. 189,200; *Friedländer*, **8**, 474 (1905–1907).

[266] H. Gilman and G. C. Gainer, *J. Amer. Chem. Soc.*, **71**, 1747 (1949).

[267] P. Klason and T. Carlson, *Ber. Deut. Chem. Ges.*, **39**, 732 (1906).

[268] A. von Wacek, K. Kratzl, and A. von Bézard, *Ber. Deut. Chem. Ges.*, **75**, 1352 (1942).

1-Mercapto-1-phenylacetone: The above acetylthio derivative (14.5 g) is shaken vigorously with 5% sodium hydroxide solution (180 ml) until after about 0.75 h it has all dissolved. The solution is then rapidly extracted with ether, and the thiol is precipitated by acidification. This product is taken up in ether and dried over sodium sulfate, and the ether is distilled off, leaving an oil that slowly crystallizes. Recrystallization from aqueous ethanol gives the thiol as pale yellow crystals, m.p. 108–110°, in 80% yield (10–11 g).

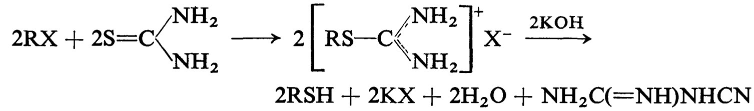
Replacement of halogen leads to formation of a C–S bond in many cases when alkyl or aryl halides are allowed to react with thiocarbonic acid derivatives such as thiocarbamates, thiourea, dithiocarbamates, or xanthates. The importance of this method is due to the fact that the intermediates are readily converted into thiols by hydrolysis:

$$RX + NH_4S{-}CSNH_2 \longrightarrow RS{-}CSNH_2 + NH_4X$$

$$RS{-}CSNH_2 \xrightarrow{OH^-} RSH + HSCN$$

For the xanthate method see page 654. In the aliphatic series dithiols[269] and unsaturated thiols[270] are best prepared by Braun's dithiourethane method.

The value of thiourea for the preparation of thiols is that on reaction with alkyl halides,[271] mixtures of hydrogen bromide and alcohols,[272] or suitable aromatic[273] or heterocyclic halides[274] it readily yields *S*-alkyl- or *S*-aryl-thiouronium salts,* from which the thiols are usually obtained in good yield by alkaline hydrolysis or by aminolysis with high-boiling, strongly nucleophilic amines:[275]



$$2RX + 2S{=}C\begin{matrix}NH_2\\NH_2\end{matrix} \longrightarrow 2\left[RS{-}C\begin{matrix}NH_2\\NH_2\end{matrix}\right]^+ X^- \xrightarrow{2KOH}$$

$$2RSH + 2KX + 2H_2O + NH_2C({=}NH)NHCN$$

1-Dodecanethiol:[271] A mixture of dodecyl bromide (125 g, 0.5 mole), thiourea (38 g, 0.5 mole), and 95% ethanol (250 ml) is heated for 3 h on the steam-bath, then treated with a solution of sodium hydroxide (30 g, 0.75 mole) in water (300 ml) and heated for a further 2 h at the b.p. Some of the thiol separates and is removed from the aqueous layer, which is then acidified with dilute sulfuric acid (7 ml of concentrated acid in 50 ml of water), and extracted with benzene. The benzene (75 ml) extract and the previous layer of crude thiol are united, washed with two portions (each 200 ml), of water dried over anhydrous sodium sulfate (20 g), and fractionated. This gives 79–83% (80–84 g) of 1-dodecanethiol, b.p. 165–169°/39 mm.

Sodium thiosulfate can also be used for preparation of thiols: it is treated with an alkyl halide which converts it into the *S*-alkyl thiosulfate (Bunte salt), and this affords the thiol under reducing conditions (required to suppress formation of the disulfide); the Bunte salt need not be isolated.

$$ClCH_2COONa + Na_2S_2O_3 \longrightarrow NaO_3S{-}S{-}CH_2COONa \longrightarrow HSCH_2COOH$$

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* For alkylation by dimethyl sulfate and for arylation by diazonium salts see reference 276.

[269] J. von Braun, *Ber. Deut. Chem. Ges.*, **42**, 4568 (1909).

[270] J. von Braun and T. Plate, *Ber. Deut. Chem. Ges.*, **67**, 281 (1934); J. von Braun and R. Murjahn, *Ber. Deut. Chem. Ges.*, **59**, 1208 (1926).

[271] G. G. Urquhart, J. W. Gates Jr., and R. Connor, *Org. Syn.*, **21**, 36 (1941); A. J. Speziale, *Org. Syn.*, **30**, 35 (1950).

[272] R. L. Frank and P. V. Smith, *J. Amer. Chem. Soc.*, **68**, 2103 (1946).

[273] C. Price and G. W. Stacy, *J. Amer. Chem. Soc.*, **68**, 498 (1946).

[274] M. A. Phillips and H. Chapiro, *J. Chem. Soc.*, **1942**, 584.

[275] B. C. Cossar, J. O. Fournier, D. L. Fields, and D. D. Reynolds, *J. Org. Chem.*, **27**, 93 (1962).

[276] F. Arndt, *Ber. Deut. Chem. Ges.*, **54**, 2236 (1921); M. Busch and K. Schulz, *J. Prakt. Chem.*, [ii], **150**, 173, 180 (1938).

Mercaptoacetic acid:[149a,277] Monochloroacetic acid is neutralized with 3N-sodium hydroxide solution, treated with the equivalent amount of sodium thiosulfate, and heated for an hour on the water-bath. The end of the reaction is recognized when a sample no longer becomes turbid (separation of sulfur) when acid is added. Hydrolysis of the reaction mixture with 25% hydrochloric acid for 2 h affords a 95% yield of mercaptoacetic acid, which can be isolated by extraction with ether and subsequent distillation in a vacuum.

S-Alkyl thiosulfates are oxidized by elemental iodine to disulfides in excellent yield, probably without formation of the thiols as intermediates:[278]

$$2RS{-}SO_3Na + 2H_2O + I_2 \longrightarrow RS{-}SR + 2NaHSO_4 + 2HI$$

It is unnecessary to isolate the thiosulfate ester; for instance, methyl bromoacetate affords dimethyl dithiodiglycolate,[278] and benzyl chloride affords dibenzyl disulfide in 99% yield.[278] The following exemplifies the technique.

Dibutyl disulfide:[279] *n*-Butyl bromide (38.1 g) and sodium thiosulfate (74.4 g) are dissolved by warming in 50% ethanol (450 ml), then iodine is added in small portions until its color remains permanently. The aqueous layer is separated and extracted with ether; the residue obtained on evaporation of the extract is united with the previous oily layer, washed with sodium hydrogen sulfite solution, dried over sodium sulfate, and distilled in a vacuum, giving the disulfide (57%), b.p. 90–100°/3 mm.

Disulfides are also formed in good yield when alkyl or aryl halides react with sodium disulfide. According to Blanksma,[280] who prepared many aliphatic and aromatic disulfides by this method, the halide is heated with an equivalent amount of sodium disulfide in alcoholic solution. In this way have been prepared, *inter alia,* bis-(*o*-nitrophenyl) disulfide (62%),[281] dithiodi(malonic acid),[250] and 2,2′-diphenyl-2,2′-dithiodi(acetic acid).[251]

Lecher[284] was the first to prepare unsymmetrical disulfides by the action of sulfenyl chlorides on thiols. The reaction is carried out in an anhydrous solvent (ether or carbon tetrachloride) with exclusion of moisture and, if necessary, addition of copper bronze as catalyst.[285]

Ethyl phenyl disulfide:[256a] Ethanesulfenyl chloride (9.6 g) is dropped into a stirred solution of thiophenol (11 g) in ether (50 ml) at 0°. The mixture is warmed gently on the water-bath, the solvent is removed, and the residue is distilled in a vacuum. The product boils at 126°/15 mm.

The reaction of chloromethanesulfenyl chloride with aliphatic thiols or thiophenols gives products that contain both disulfide and sulfide groups:[256b]

$$ClCH_2SCl + 2RSH \longrightarrow RS{-}CH_2{-}S{-}SR$$

b. Preparation of sulfides and sulfonium salts

Sulfides (thioethers) can be obtained by replacing the halogen of alkyl and suitable aryl halides in a reaction with sodium sulfide, this being analogous to the preparation of thiols and disulfides. The reaction is usually carried out

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[277] A. Wagner, Dissertation, Hannover, 1951; *Chem. Zentralbl.*, **1953**, 4954.

[278] T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **95**, 1489 (1909).

[279] H. E. Westlake Jr. and G. Dougherty, *J. Amer. Chem. Soc.*, **64**, 149 (1942).

[280] J. J. Blanksma, *Rec. Trav. Chim.*, **20**, 132 (1901).

[281] M. T. Bogert and A. Stull, *Org. Syn.*, Coll. Vol. I, 213 (1937).

[282] A. Schöberl and H. Eck, *Ann. Chem.*, **522**, 107 (1936).

[283] A. Schöberl, E. Berninger, and F. Harren, *Ber. Deut. Chem. Ges.*, **67**, 1548 (1934).

[284] H. Lecher, *Ber. Deut. Chem. Ges.*, **53**, 577, 591 (1920).

[285] S. Magnusson, J. E. Christian, and G. L. Jenkins, *J. Amer. Pharm. Ass. Sci. Ed.*, **36**, 257 (1947); *Chem. Abstr.*, **42**, 877 (1948).

in alcoholic, aqueous-alcoholic, or aqueous solution, and in most cases with stoichiometric amounts of the two reactants.

Preparation of the lower dialkyl sulfides by the following general procedure has been described by McAllan and his co-workers:[286] Sodium sulfide nonahydrate (1.5 moles) is dissolved in water (250 ml) in a three-necked flask fitted with a reflux condenser, dropping funnel, and stirrer, then the alkyl halide (2 moles) is added slowly with vigorous stirring. When the very exothermic reaction ceases, the mixture is heated under reflux for a further 3 h and the sulfide is distilled over in steam, separated, washed with water, 10% sodium hydroxide solution, and again water, dried over calcium chloride, and distilled. In this way were obtained: **dimethyl** (b.p. 37.3°), **diethyl** (b.p. 92°),[287] **diisopropyl** (b.p. 119.8°), **dipropyl** (b.p. 142.8°),[288] and **bis-(2-cyanovinyl) sulfide** (m.p. 142–143°, from ethyl acetate–cyclohexane).[289]

Arylalkyl and aryl halides containing sufficiently reactive halogen also yield sulfides by this method.

Bis-(2-naphthylmethyl) sulfide:[290] Sodium sulfide nonahydrate (25), dissolved in water (15 ml) and anhydrous ethanol (230 ml), is added to 2-(chloromethyl)naphthalene (36 g), and the whole is heated under reflux for 6 h, allowed to cool, and poured into water. The precipitate is collected and recrystallized from alcohol, giving the sulfide (84.4%, 26.5 g), m.p. 123–124°.

Bis-(4-chlorobenzyl) sulfide is obtained in 85.7% yield analogously from 4-chlorobenzyl chloride.[290]

p-Chloronitrobenzene and chlorodinitrobenzene can also be converted into the aryl sulfides by means of sodium sulfide in the above manner; but with *o*-chloronitrobenzene[291] the sodium sulfide solution must be dropped into the aryl halide, and with the less reactive *m*-chloronitrobenzene reduction precedes reaction of the chlorine atom.

Bis-(2,4-dinitrophenyl) sulfide:[292] 1-Chloro-1,4-dinitrobenzene (100 g) is dissolved in ethanol (1 l), and a melt of sodium sulfide nonahydrate (65.5 g) and sulfur (9 g) is added in small portions. A violent reaction occurs, which is completed by 3 hours' boiling on a sand-bath. After cooling, the product is filtered off and washed, first, with ethanol and then with warm water to remove the sodium chloride. The product (86 g) has m.p. 280° (dec.).

Lower dialkyl sulfides and vinyl sulfides[293] are advantageously prepared by alkaline hydrolysis of *S*-alkylthiouronium salts, the resulting thiolate being alkylated, without isolation, by an alkyl halide or dialkyl sulfate.[294]

Diethyl sulfide: Finely powdered thiourea (86g, 1.1 moles) is boiled with ethanol (50ml) and ethyl bromide (109 g, 1 mole) under reflux for 6 h; towards the end of this time the thiourea dissolves. The solution is evaporated in a vacuum on the water-bath and, without waiting for the residue to crystallize, water (100 ml) is added through a dropping funnel, followed by a solution of sodium or potassium hydroxide (4 moles) in water (200 ml) during 10 min with stirring. This mixture is boiled for an hour under a very efficient reflux condenser; it

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[286] D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Amer. Chem. Soc.*, **73**, 3627 (1951).

[287] H. Böhme and H. J. Gran, *Ann. Chem.*, **577**, 68 (1952).

[288] R. W. Bost and M. W. Conn, *Org. Syn.*, Coll. Vol. II, 547 (1955).

[289] F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).

[290] C. G. Overberger, S. P. Ligthelm, and A. E. Swire, *J. Amer. Chem. Soc.*, **72**, 2856 (1950).

[291] R. Nietzki and H. Bothof, *Ber. Deut. Chem. Ges.*, **29**, 2774 (1896); F. Kehrmann and E. Bauer, *Ber. Deut. Chem. Ges.*, **29**, 2362 (1896).

[292] J. Teppema and L. B. Sebrell, *J. Amer. Chem. Soc.*, **49**, 1755 (1927).

[293] A. J. Schneider, J. J. Bagnell, and G. C. Murdoch, *J. Org. Chem.*, **26**, 1980 (1961).

[294] G. Drefahl and H. Schick, *Z. Chem.*, **4**, 347 (1964).

is then cooled, ethyl bromide (164 g, 1.5 moles) is dropped in during 30 min, and gentle boiling is renewed for 5 h. The reflux condenser is replaced by a descending condenser, and the mixture is distilled until 1 l of distillate has collected; the volume of liquid in the distillation flask must be kept constant by continual addition of water, so as to avoid separation of potassium or sodium bromide. The distillate is acidified, with cooling, by concentrated hydrochloric acid and again similarly distilled (1 l of distillate). The diethyl sulfide is separated in a separatory funnel, washed with 10% sodium hydroxide solution and then with water, dried over calcium chloride, and distilled through a 20-cm Vigreux c olumn, then havin gb.p. 90–92° (65% yield).

Dimethyl and **dipropyl sulfide** are obtained similarly in 60% yield.

Mixed sulfides can be prepared by reaction of alkyl or aryl halides with thiols[295] or better, because of their greater reactivity, with thiolates:

$$\mathrm{RSNa + R'Cl \longrightarrow RSR' + NaCl}$$

The reaction is most satisfactory with alkyl and aryl bromides, since the chlorides are mostly insufficiently reactive. However, when more reactive halogen compounds, and particularly, iodides, are used a redox reaction leading to disulfides interferes:[296]

$$\mathrm{2RSH + R'I \longrightarrow RS{-}SR + R'H + HI}$$

(Butylthio)acetic acid:[297] Crude 1-butanethiol (360 g) is added to a solution of sodium hydroxide (120 g) in water (600 ml), and this solution is stirred and cooled while being treated with chloroacetic acid (285 g), previously neutralized with sodium carbonate. After some hours the solution is heated and then distilled in steam to remove impurities. The residue is acidified with dilute sulfuric acid, and the (butylthio)acetic acid, which separates as an oil, is fractionated in a vacuum; it has b.p. 140–144°/10–15 mm, the yield being 245 g.

o-(Carboxymethylthio)benzoic acid is obtained in 80% yield from thiosalicyclic acid in the same way.[124n]

The conversion of 2,4-dinitrothiophenol into the sulfides by alkyl halides is particularly smooth, so that this reaction can be used for characterization of organic halogen compounds. The following general directions have been given[298] for **characterization of alkyl bromides and iodides**:

28% Potassium hydroxide solution (5 ml), followed by the halogen compound (0.025 mole), are added to a solution of 2,4-dinitrothiophenol (5 g, 0.025 mole) in Butylcarbitol (diethylene glycol monobutyl ether) (50 ml). In a few cases, when reaction does not occur at once, the mixture is heated at 70° for 10–30 min or, often better, left at room temperature for a considerable time. When reaction is complete, the cold mixture is treated with ice-water, and the product that seperates is collected and recrystallized; solvents used were alcohol, 1-butanol, dioxan, benzene, and acetone.

This technique is also successful with alkyl chlorides if potassium iodide (3 g) is added to the batch.

"*S*-Glycosides" are obtained when acetobromoglucose is used for sulfide formation.[299] For instance, Wagner and Kühmstedt[300] obtained *S*-(*o*-, *m*-, and *p*-hydroxyphenyl) tetra-*O*-acetyl-1-deoxy-1-thio-β-D-glucoside from *o*-, *m*-, and *p*-mercaptophenol and α-acetobromoglucose in aqueous acetone containing potassium hydroxide.

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[295] W. Nekrassow and N. N. Melnikow, *Ber. Deut. Chem. Ges.*, **62**, 2091 (1929).

[296] N. Hellström, *Z. Phys. Chem.*, *A*, **163**, 33 (1933).

[297] Y. Uyeda and E. E. Reid, *J. Amer. Chem. Soc.*, **42**, 2385 (1920).

[298] R. W. Bost, P. K. Starnes, and E. L. Wood, *J. Amer. Chem. Soc.*, **73**, 1968 (1951).

[299] Cf. T. Sabalitschka, *Arch. Pharm.*, **267**, 675 (1929).

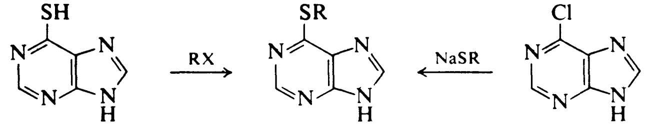
[300] G. Wagner and H. Kühmstedt, *Arch. Pharm.*, **294**, 117 (1961).

Aryl halides containing less reactive halogen can also be converted into sulfides by thiols if heavy-metal (lead, zinc, mercury) thiols are used at 225–230°; 1-naphthyl, 2-naphthyl sulfide,[301] 1- and 2-naphthyl phenyl sulfide,[302] and 1- and 2-naphthyl *o*-, *m*-, and *p*-tolyl sulfide[303] have been obtained in this way. When the heavy-metal thiolates are too stable and do not react with aryl bromides even at 240°, the aryl sulfides can nevertheless often be prepared by a generally applicable reaction of aryl iodides with sodium thiolates under the influence of copper as catalyst.[304]

Diphenyl sulfide:[304] Thiophenol (7 g) is added to a solution of sodium (1.2 g) in ethanol (7 ml), the alcohol is removed by heat, copper powder (Naturkupfer C) (0.2 g) and iodobenzene (12.9 g) are added, and the whole is heated for 2.5 h in an oil-bath at 235–240° (bath-temperature). After cooling, the product is taken up in a little ethanol and acidified with dilute sulfuric acid, zinc dust is added, and the mixture is distilled in steam. Unchanged iodobenzene passes over and some diphenyl sulfide produced as by-product is reduced to thiophenol. After cooling, the residue in the distillation flask is filtered, the zinc-containing precipitate is filtered off and extracted with ether, and the extract is dried over calcium chloride and fractionated, giving diphenyl sulfide (6.1 g), b.p. 295°.

Further examples of this procedure are the preparation of variously substituted diphenyl sulfides, such as methyl-, methoxy-, and nitro-phenyl phenyl sulfide and *o*-bis(butylthio)benzene.[305]

In a detailed study Johnston and his co-workers[306] described the preparation of 6-(alkylthio)purines; they were obtained by reaction either of 6-mercaptopurines with alkyl halides or of 6-chloropurine with sodium thiolates:



Further reaction of organic sulfides with alkyl halides leads to sulfonium compounds:

$$RSR' + R''X \longrightarrow [RR'R''S]^+X^-$$

In accord with their character as salts, these products are soluble in water but insoluble in ether. The reaction is general in the aliphatic series, but aromatic sulfides behave differently; for instance, methyl tolyl sulfide is methylated to the sulfonium salt by dimethyl sulfate but not by methyl iodide.[307,308] Alcohol, acetone, benzene, or nitromethane is often used as solvent. Reaction of sufficiently reactive components occurs at room temperature. Formation of sulfonium salts is often appreciably increased by adding an equivalent amount of a metal salt:[309]

$$R_2S + R'Cl + FeCl_3 \longrightarrow [R_2R'S]^+[FeCl_4]^-$$

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[301] F. Krafft, *Ber. Deut. Chem. Ges.*, **23**, 2364 (1890).

[302] F. Krafft and E. Bourgeois, *Ber. Deut. Chem. Ges.*, **23**, 3045 (1890).

[303] E. Bourgeois, *Ber. Deut. Chem. Ges.*, **24**, 2264 (1891).

[304] F. Mauthner, *Ber. Deut. Chem. Ges.*, **39**, 3594 (1906).

[305] R. Adams, W. Reitschneider, and A. Terretti, *Org. Syn.*, **42**, 22 (1962).

[306] T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Amer. Chem. Soc.*, **80**, 6265 (1958).

[307] K. von Auwers and F. Arndt, *Ber. Deut. Chem. Ges.*, **42**, 2713 (1909).

[308] F. Kehrmann and A. Duttenhöfer, *Ber. Deut. Chem. Ges.*, **38**, 4197 (1905).

[309] K. A. Hofmann and K. Ott, *Ber. Deut. Chem. Ges.*, **40**, 4930 (1907); R. R. Renshaw and D. A. Searle, *J. Amer. Chem. Soc.*, **55**, 4951 (1933).

When the sulfonium salt is sensitive to water, as are butyl-, dodecyl-, and hexadecyl-dimethylsulfonium iodide and dimethyloctylsulfonium iodide, the reaction is best carried out under nitrogen in a Schlenk vessel.[310]

***S*-Methylmethioninium iodide:**[311] Methionine (7.45 g, 0.05 mole) and methyl iodide (7.8 g, 0.055 mole) are heated in water (40 ml) for 6 h at 45°, then evaporated to a syrup in a vacuum, and rubbed with hot alcohol. The salt is filtered off and recrystallized from aqueous ethanol, then having m.p. 150° (dec.) (10.4 g, 75%).

Böhme and Krause[312] describe the preparation of various dialkylphenacylsulfonium salts, *e.g.*, **dimethylphenacylsulfonium bromide:** ω-Bromoacetophenone (9 g) is dissolved in a mixture of water (1 volume) and acetone (20 volumes), and dimethyl sulfide (3 g) is added. After about 0.5 h the sulfonium salt separates as long, colorless needles, m.p. 145° (10.2 g, 85%).

Under more energetic conditions disulfides can also be converted into sulfonium salts;[313-315] here too reaction is facilitated by addition of metal salts.[316,317]

c. Preparation of thioketones, mercaptals, and mercaptols

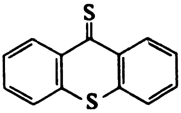
The halogen atoms of the geminal dihalo derivatives of diaryl diketones and of heterocyclic ketones can be replaced in reactions with sulfur compounds (*e.g.*, sodium hydrogen sulfide, thioacetic acid, phosphorus pentasulfide), thioketones being formed.[318,319] Staudinger and Freudenberger,[320] for instance, obtained thiobenzophenone in 46% yield from benzophenone dichloride (dichlorophenylmethane) and a hot alcoholic solution of sodium hydrogen sulfide:

$$(C_6H_5)_2CCl_2 + 2NaSH \longrightarrow (C_6H_5)_2CS + 2NaCl + H_2S$$

In a generally applicable reaction numerous derivatives of the thiobenzophenone series have been obtained by the action of thioacetic acid on aromatic ketone dichlorides:[321]

$$Ar_2CO \xrightarrow[\text{or } (COCl)_2]{PCl_5} Ar_2CCl_2 \xrightarrow{HSCOCH_3} Ar_2CCl(SH) \longrightarrow Ar_2CS$$

The preparation of **10-thioxanthene-9-thione** provides an example:



10-Thioxanthone[322] (5.7 g) is boiled with oxalyl chloride, with exclusion of moisture, for 20 h on a water-bath, and the mixture a is then evaporated to dryness in a vacuum at 100°. The residue is dissolved in dry benzene (75 ml) and treated with thioacetic acid (10 g) in

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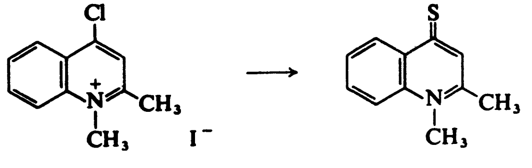
[310] R. Kuhn and O. Dann, *Ber. Deut. Chem. Ges.*, **73**, 1092 (1940).
[311] R. O. Atkinson and F. Poppelsdorf, *J. Chem. Soc.*, **1951**, 1378.
[312] H. Böhme and W. Krause, *Chem. Ber.*, **82**, 426 (1949).
[313] S. H. Davies, *Ber. Deut. Chem. Ges.*, **24**, 3548 (1891).
[314] W. Steinkopf and S. Müller, *Ber. Deut. Chem. Ges.*, **56**, 1926 (1923).
[315] M. L. Selker, *Ind. Eng. Chem.*, **40**, 1467 (1948).
[316] D. P. Hilditch and S. Smiles, *J. Chem. Soc.*, **91**, 1394 (1907).
[317] P. C. Rây and N. Adhikary, *J. Indian Chem. Soc.*, **7**, 297 (1930).
[318] L. Gattermann and H. Schulze, *Ber. Deut. Chem. Ges.*, **29**, 2944 (1896).
[319] W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.*, **30**, 1375 (1965).
[320] H. Staudinger and F. Freudenberger, *Org. Syn.*, Coll. Vol. II, 573 (1955).
[321] A. Schönberg, O. Schütz, and S. Nickel, *Ber. Deut. Chem. Ges.*, **61**, 1375 (1928).
[322] E. G. Davis and S. Smiles, *J. Chem. Soc.*, **97**, 1296 (1910).

small portions under a stream of carbon dioxide. This mixture is heated on a boiling water-bath until evolution of hydrogen chloride ceases (about 5 h), then evaporated to dryness in a vacuum. The residue is recrystallized from light petroleum (b.p. 80–90°) and then from xylene, yielding black needles with a green sheen, that have m.p. 168°.

As additional method of preparing thioketones the reaction of aromatic compounds with thiophosgene under Friedel–Crafts conditions deserves mention.[323,324]

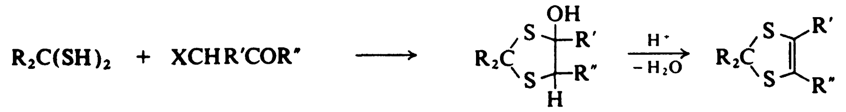
Further, thiopyridones and quinaldinethiones can be obtained by the action of alkali hydrogen sulfides on halopyridinium and haloquinaldinium salts:[325,326]



Mercaptals' (dithioacetals)[327] or mercaptols (ketone dithioacetals)[328,329] are obtained by reaction of geminal dihalogen compounds with thiolates, usually in a smooth reaction when hydrogen halide cannot be split off from the halogen compound:

$$RHCCl_2 + 2R'SH \longrightarrow \underset{\text{Mercaptal}}{RHC(SR')_2} \qquad RR'CCl_2 + 2R''SH \longrightarrow \underset{\text{Mercaptol}}{RR'C(SR'')_2}$$

1,3-Dithioles of mercaptol type can be prepared from *gem*-dithiols and α-halo ketones. The 1,3-dithiolan-4-ols first formed are dehydrated to 1,3-dithioles in the presence of acid:[330]



2,2-Dibenzyl-4-phenyl-1,3-dithiole:[330] A suspension of 1,3-diphenyl-2,2-propanedithiol (5.2 g, 0.02 mole), sodium hydrogen carbonate (4.0 g), and phenacyl bromide (4.0 g, 0.02mole) in ethanol (100 ml) is stirred at room temperature for 48 h, then cooled to −10°, treated with concentrated sulfuric acid (35 ml), and kept overnight at room temperature. Water then precipitates the dithiole which, on recrystallization from glacial acetic acid, forms yellow needles, m.p. 126.5–127.5° (4.4 g, 61%).

Mixed mercaptals are formed from α-halo sulfides and thiols in yields up to 90%.[331]

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[323] Ger. Pat. 37,730; *Friedländer*, **1**, 94 (1877–1887).

[324] L. Gattermann, *Ber. Deut. Chem. Ges.*, **28**, 2869 (1895).

[325] A. Michaelis and A. Hölken, *Ann. Chem.*, **331**, 245 (1904).

[326] E. Champaigne, R. E. Cline, and C. E. Kaslow, *J. Org. Chem.*, **15**, 600 (1950).

[327] E. Fromm, *Ann. Chem.*, **253**, 155 (1889); cf. R. Otto and K. Mühle, *Ber. Deut. Chem. Ges.*, **28**, 1120 (1895).

[328] A. Schönberg and O. Schütz, *Ann. Chem.*, **454**, 47 (1927).

[329] A. Schönberg, O. Schütz, V. Bruckner, and J. Peter, *Ber. Deut. Chem. Ges.*, **62**, 2550 (1929).

[330] E. Campaigne and F. Haaf, *J. Heterocycl. Chem.*, **1**, 163 (1964).

[331] H. Böhme, H. Fischer, and R. Frank, *Ann. Chem.*, **563**, 54 (1949).

Formaldehyde benzyl ethyl dithioacetal: Chloromethyl ethyl sulfide (11 g) and α-toluenethiol (12.4 g) react very vigorously, with evolution of hydrogen chloride, and control by cooling is necessary. After being kept overnight, the mixture is fractionated in a vacuum, affording the dithioacetal, b.p. 165°/19 mm, in 60% yield.

Formaldehyde dibenzyl dithioacetal, m.p. 55° (from 2-propanol), is formed analogously in 90% yield (4.8 g) from benzyl chloromethyl sulfide (3.5 g) and α-toluenethiol (3 g).

2. Reaction of acyl halides with hydrogen sulfide and its derivatives

Replacement of the halogen of acyl halides by a sulfur-containing group leads to thiocarboxylic acids or derivatives thereof. For instance, acylation of hydrogen sulfide is the most important method of preparing thiocarboxylic acids. The reaction is carried out in anhydrous pyridine and seems to be generally applicable.[332] For good yields it is important that cooling shall suffice to prevent too high a reaction temperature and that any local excess of acid chloride be prevented by using a rapid stream of hydrogen sulfide and vigorous stirring. The simple thio acids up to thiononanoic acid have been prepared by this method.[332]

Thioacetic[333] **and thiobenzoic acid:**[333,334] In a 1-l flask fitted with a stirrer and reflux condenser, anhydrous pyridine (200 ml) is saturated by a stream of hydrogen sulfide that has been washed by iodine solution and dried through calcium chloride. It is then treated with acetyl chloride (40 g) with stirring and cooling to below 15° for 2-3 h; alternatively, benzoyl chloride (40 g) is similarly added at 5°. Thereafter the mixture is acidified with the calculated amount of 5N-sulfuric acid and extracted with ether. The extract is dried over sodium sulfate and fractionated in a stream of nitrogen, giving thioacetic, b.p. 87.5–88°, or thiobenzoic acid, b.p. 85–87°/10 mm, in 60–65% yield.

S-Esters of thiocarboxylic acids are obtained on acylation of thiols; this reaction, which is often very smooth even in the absence of a base,[335] is generally carried out by the Schotten–Baumann technique[336,337] or in the presence of pyridine.[338]

***S*-Benzoylcysteamine hydrochloride:**[339] Cysteamine hydrochloride (2 g) is heated with benzoyl chloride (3 ml) until evolution of hydrogen chloride begins (at 155–170°); the reaction then goes to completion without further heating. The product, which solidifies, is triturated with anhydrous ether, washed several times with that solvent, and recrystallized from dimethylformamide containing a few drops of concentrated hydrochloric acid. A second fraction can be obtained from the mother-liquors by extraction with ether, making the total yield 70% (2.7 g). The m.p. is 167° (dec.).

When shaken with benzoyl chloride and an excess of sodium hydroxide solution, 1,5-pentanedithiol gives an almost quantitative yield of ***S,S*-pentamethylene bis(thiobenzoate),** m.p. 45° (after recrystallization from ethanol).[336]

3. Reaction of alkyl halides with sulfites and sulfinic acids

Replacement of the halogen of alkyl halides by treatment with alkali sulfites was first used by Strecker[340] in his preparation of aliphatic sulfonic acids:

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[332] A. Fredga and H. Bauer, *Arkiv Kemi*, **2**, 113 (1950).

[333] S. Sunner and T. Nilson, *Svensk Kem. Tidskr.*, **54**, 163 (1942).

[334] P. Noble Jr. and D. S. Tarbell, *Org. Syn.*, **32**, 101 (1952).

[335] R. B. Baker and E. E. Reid, *J. Amer. Chem. Soc.*, **51**, 1567 (1929).

[336] W. Autenrieth and A. Geyer, *Ber. Deut. Chem. Ges.*, **41**, 4253 (1908).

[337] C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.*, **1947**, 559.

[338] P. N. Rylander and D. S. Tarbell, *J. Amer. Chem. Soc.*, **72**, 3021 (1950).

[339] T. Wieland and E. Bokelmann, *Ann. Chem.*, **576**, 20 (1952).

[340] A. Strecker, *Ann. Chem.*, **148**, 90 (1868).

Hemilian[341] used ammonium sulfite: on heating ethyl iodide (20 g) with a solution of crystalline ammonium sulfite (20 g) in water (40 ml) he obtained, after cooling, **ammonium ethanesulfonate.** To convert this into the barium salt he diluted it with water and heated it with lead oxide until evolution of ammonia ceased; he filtered the mixture and removed the lead from the filtrate by hydrogen sulfide; after renewed filtration he digested the filtrate with barium carbonate, filtered again, and evaporated that filtrate to dryness.

Particularly good yields are obtained from *n*-alkyl halides, but only up to about 25% of the halide can be replaced from secondary carbon atoms, and tertiary halogen compounds give olefins.

1,2-Ethanedisulfonic acid is obtained from ethylene dibromide and concentrated aqueous sodium sulfite solution,[342] but using a deficiency of sulfite leads to sodium 2-bromoethanesulfonate.[343] A general prescription for preparation of α,ω-alkanedisulfonates has been given by Stone.[344]

1,4-Butanedisulfonic acid was obtained by Weygand as follows: Tetramethylene dibromide (100 g, 0.46 mole), anhydrous sodium sulfite (150 g, 1.15 moles), and water (400 ml) are vigorously stirred for 20 h in a two-necked 1-l flask fitted with a stirrer and reflux condenser and placed on a boiling water-bath. The mixture is then diluted to 1 l and, whilst still warm, shaken with charcoal until the leek-like smell has disappeared; it is then left overnight, after which the charcoal is filtered off and hydrogen chloride is led in. When sodium chloride begins to separate, the flask is cooled in ice-water and hydrogen chloride is passed into the mixture until no more sodium chloride separates. The precipitate is removed, the filtrate is concentrated (to 300 ml), and introduction of hydrogen chloride is resumed, with cooling; 1,4-butanedisulfonic acid dihydrate separates; when this is collected and dried in a vacuum over solid sodium hydroxide it melts at 86–93°; treating the dihydrate with acetic anhydride and removing the acetic acid formed affords the anhydrous acid, m.p. 136°, in 92% yield.

Of arylalkyl halides the bromide[152,345] reacts more readily than the chloride with sodium sulfite; for benzyl chloride addition of sodium hydroxide solution has proved useful.

α-Toluenesulfonic acid:[346] Finely powdered, crystalline sodium sulfite (250 g) is boiled with benzyl chloride (125 g) and 10% sodium hydroxide solution (200 ml) for 1.5 h under reflux. The hot solution is subjected to steam-distillation which removes the excess of benzyl chloride and the benzyl alcohol. Concentration affords a 97% yield of sodium α-toluenesulfonate; this crystallizes with 1 mole of water of crystallization, but disintegrates readily in the air.

Halo carboxylic acids and their derivatives,[347] halo alcohols,[348] halo ketones,[349,350] and halo ethers[351] react similarly with sodium sulfite, giving the corresponding sulfonic acids.

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[341] W. Hemilian, *Ann. Chem.*, **168**, 145 (1873); cf. F. C. Wagner and E. E. Reid, *J. Amer. Chem. Soc.*, **53**, 3409 (1931).

[342] B. C. Saunders, *J. Chem. Soc.*, **1950**, 686.

[343] C. G. Overberger, D. E. Baldwin, and H. P. Gregor, *J. Amer. Chem. Soc.*, **72**, 4864 (1950).

[344] G. C. H. Stone, *J. Amer. Chem. Soc.*, **58**, 488 (1936); cf. B. Helferich and H. Grünert, *Ber. Deut. Chem. Ges.*, **74**, 1531 (1941).

[345] C. A. Bunton and E. A. Halevi, *J. Chem. Soc.*, **1952**, 4541.

[346] E. Fromm and J. de Seixas Palma, *Ber. Deut. Chem. Ges.*, **39**, 3312 (1906).

[347] French Pat. 788,748; *Chem. Abstr.*, **30**, 1809 (1936).

[348] J. M. Stewart and H. P. Cordts, *J. Amer. Chem. Soc.*, **74**, 5884 (1952).

[349] G. D. Parkes and S. G. Tinsley, *J. Chem. Soc.*, **1934**, 1861.

[350] F. Püschel and C. Kaiser, *Chem. Ber.*, **97**, 2903 (1964).

[351] U.S. Pat. 2,394,834; *Chem. Abstr.*, **40**, 2658 (1946).

3- and 4-Hydroxyalkanesulfonic acids, which are accessible by the Strecker synthesis, can be dehydrated by heat to 1,3- and 1,4-sultones,[352,353] respectively, but azeotropic dehydration by xylene has proved a particularly useful method.

Sulfonic acids can also be obtained by the Strecker synthesis from sodium sulfite and aryl halides that contain reactive halogen. Thus *o*-formylbenzenesulfonic acid is formed in very good yield when *o*-chlorobenzaldehyde is heated under pressure with sodium sulfite,[354] 2-formyl-4-nitrobenzenesulfonic acid is formed on merely boiling 2-chloro-5-nitrobenzaldehyde with alcoholic sodium sulfite solution.[355] The nitro group of nitroaryl halides may also be reduced to an amino group (cf. page 626); using polyhalo compounds leads to polysulfonic acids.[356]

A reaction also known for a long time is the formation of sulfones from alkyl halides and alkali sulfinates,[357] which is usually effected in aqueous or alcoholic solution at water-bath temperatures:

$$RSO_2^-Na^+ + R'X \longrightarrow R{-}SO_2{-}R' + NaX$$

Suitable halogen compounds are primary and secondary alkyl halides and benzyl or aryl halides, the last-mentioned provided that the halogen is activated by an *o*- or *p*-nitro group. Aliphatic sulfinates usually give lower yields than aromatic sulfinates.

Benzyl methyl and ethyl sulfone[358] are formed when sodium α-toluenesulfinate is boiled under reflux for some hours with a slight excess of methyl or ethyl iodide in aqueous sodium hydroxide; when isolated by means of ether and recrystallized from water they melt at 127° (methyl) and 84° (ethyl).

The reaction can also be carried out in alcoholic solution. **Benzyl phenyl sulfone**[359] is formed when sodium benzenesulfinate (178 g) and benzyl chloride (127 g) are boiled in anhydrous ethanol (500 ml) for 7–8 h; pouring the hot solution into ice-water (1 l) gives the sulfone, which is collected, dried, and recrystallized from ethanol, then having m.p. 146–146.5° (120 g, 52%).

More vigorous conditions are needed for successful reaction of aryl halides — the temperature or the pressure must be raised.

Heating *p*-chloronitrobenzene with sodium *p*-(acetylamino)benzenesulfinate for 3.5 h in ethylene glycol and Methylcarbitol (diethylene glycol monomethyl ether) at 142° affords a 51% yield of **p-(acetylamino)phenyl p-nitrophenylsulfone,** from which bis-(*p*-aminophenyl) sulfone can be obtained by reduction.[360]

For the preparation of **o- and p-nitrophenyl phenyl sulfone,**[361] (i) benzenesulfinic acid (4 g), *o*-chloronitrobenzene (4.5 g), and sodium acetate (2.5 g), or (ii) benzenesulfinic acid (5 g), *p*-chloronitrobenzene (5.5 g), and sodium acetate (3.5 g), are heated in a sealed tube for 3 at 160° together with sufficient ethanol for dissolution (about 10 ml). After cooling, the product is filtered off and washed with water. Yields and m.p.s are: *ortho*-compound, 4.5 g, m.p. 147.5°; *para*-compound, 5.5 g, m.p. 143°.

A large number of sulfones prepared by this method are tabulated in Suter's "The Organic Chemistry of Sulfur."[152e]

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[352] J. H. Helberger and H. Lautermann, *Ann. Chem.*, **586**, 158 (1954).

[353] F. Püschel and C. Kaiser, *Chem. Ber.*, **97**, 2917 (1964).

[354] Ger. Pat. 88,952; *Friedländer*, **4**, 133 (1894–1897).

[355] Ger. Pat. 165,613; *Friedländer*, **8**, 158 (1905–1907).

[356] Ger. Pat. 98,321; *Friedländer*, **5**, 207 (1897–1900).

[357] R. Otto, *Ber. Deut. Chem. Ges.*, **13**, 1272 (1880); *Ann. Chem.*, **283**, 181 (1894).

[358] E. Fromm and J. de Seixas Palma, *Ber. Deut. Chem. Ges.*, **39**, 3308 (1906).

[359] R. L. Shriner, H. C. Struck, and W. J. Jorison, *J. Amer. Chem. Soc.*, **52**, 2067 (1930).

[360] C. W. Ferry, J. S. Buck, and R. Baltzly, *Org. Syn.*, **22**, 31 (1942).

[361] F. Ullmann and G. Pasdermadjian, *Ber. Deut. Chem. Ges.*, **34**, 1150 (1901).

4. Preparation of thiocyanic and isothiocyanic esters

Treatment of alkyl halides with alkali thiocyanates leads to replacement of the halogen with formation of thiocyanic esters (organic thiocyanates). However, it is impossible to foretell whether thiocyanic esters or the isothiocyanic esters ("mustard oils") will be products by this method; but in all cases the latter is the more stable, so that thiocyanates can be converted into isothiocyanates by heat.

There are also preparatively important methods for preparation of thiocyanic esters that start from dithiocyanogen, which behaves in its reactions as a pseudohalogen, so that it can add to olefinic double-bond systems and substitute aromatic compounds. Kaufmann[362] and also Wood[363] have reviewed the preparation of organic thiocyanates, which has been described previously (pages 203, 213) in the present volume.

Thiocyanic esters can also be obtained by treating arene-[364] or alkanesulfenyl chlorides,[365] including trichloromethanesulfenyl chloride,[366] with potassium cyanide:

$$\mathrm{RSCl + KCN \longrightarrow RSCN + KCl}$$

III. Replacement of oxygen by sulfur groups

1. Reaction of alcohols with sulfur compounds

a. With hydrogen sulfide and its derivatives

Formal replacement of the oxygen of an alcoholic hydroxyl group by sulfur, with formation of a thiol, can often be effected in good yield by passing the alcohol vapor in admixture with hydrogen sulfide over thorium oxide at 350–380°. Kramer and Reid[367] have reported the optimum operating technique for simple alkanethiols from methanethiol to 3-methyl-1-butanethiol. Binz and Pence[368] have shown that this replacement may occur under milder conditions: 1-(hydroxymethyl)piperidine (1-piperidinemethanol), which is easily accessible from piperidine and formaldehyde, reacts readily with hydrogen sulfide to give the derived thiol in an exothermic reaction.

Alcoholic hydroxyl groups are replaced when treated with thiols, water being split off and organic sulfides formed. Thus, for example, **(desylthio)-acetic acid** is obtained from benzoin and mercaptoacetic acid:[369]

$$\mathrm{C_6H_5COCH(C_6H_5)OH + HSCH_2COOH \xrightarrow{HCl} C_6H_5COCH(C_6H_5){-}S{-}CH_2COOH + H_2O}$$

Benzoin (5 g) and mercaptoacetic acid (6.5 g) are warmed for 0.5 h on a water-bath while hydrogen chloride is passed in. The mixture is then treated with cold sodium carbonate

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[362] H. P. Kaufmann, *Angew. Chem.*, **54**, 195 (1941); "Neuere Methoden der präparativen organischen Chemie," Verlag Chemie, Berlin, 1944, p. 237.

[363] J. L. Wood, *Org. Reactions*, **3**, 240 (1949).

[364] T. Zincke and K. Eismayer, *Ber. Deut. Chem. Ges.*, **51**, 751 (1918).

[365] H. Brintzinger and M. Langheck, *Chem. Ber.*, **86**, 560 (1953).

[366] U.S. Pat. 2,650,240; *Chem. Abstr.*, **48**, 8819 (1954).

[367] R. L. Kramer and E. E. Reid, *J. Amer. Chem. Soc.*, **43**, 880 (1921).

[368] A. Binz and L. H. Pence, *J. Amer. Chem. Soc.*, **61**, 3134 (1939).

[369] O. Behaghel and E. Schneider, *Ber. Deut. Chem. Ges.*, **68**, 1588 (1935).

solution and filtered into dilute hydrochloric acid. The product that separates soon crystallizes and can be recrystallized from carbon tetrachloride or aqueous methanol, then having m.p. 105°.

A further example is the preparation of *p*-tolyl triphenylmethyl sulfide from triphenylmethanol and thio-*p*-cresol.[370]

Alkyl *tert*-alkyl sulfides are obtained in 20–68% yield from tertiary alcohols and thiols in glacial acetic acid containing perchloric acid.[371]

Under suitable conditions aromatic hydroxyl groups are also replaced in excellent yield by alkylthio groups by means of thiols.[372]

Dodecyl 2-naphthyl sulfide:[372] 2-Naphthol (28.8 g, 0.2 mole), dodecanethiol (40.4 g, 0.2 mole), *p*-toluenesulfonic acid (10 g, 0.06 mole), and toluene (5 ml) are stirred at 110° for 24 h under nitrogen. The product is washed successively with water (200 ml), 2% sodium hydroxide solution (200 ml), and water (200 ml). The residue (63 g, 96%; m.p. 39–45°) gives the sulfide, m.p. 44–46° (79%, 52 g), on recrystallization from ethanol.

Methyl (99%) and ethyl 2-naphthyl sulfide (68%), (2-naphthylthio)acetic acid (87%), and 2-naphthyl phenyl sulfide (43%) have been prepared by the same method.

Formal replacement of an aromatic hydroxyl group by a thiol group is shown in the preparation of thiophenols by way of *O*-aryl *N*,*N*-dialkylthiocarbamates, which undergo rearrangement to the *S*-esters, whence hydrolysis gives the thiophenols.[373] The same reaction occurs in the heterocyclic series. Good yields are obtained in all the steps.

$$\mathrm{ArOH + NR_2C(S)Cl \xrightarrow{-HCl} ArOCSNR_2 \longrightarrow ArSCONR_2 \xrightarrow{HO^-} ArSH}$$

Primary alcohols in admixture with acids can act as alkylating agents, their reaction with sulfides leading to loss of water and formation of sulfonium salts:

$$\mathrm{R_2S + R'OH + H^+X^- \longrightarrow [R_2R'S]^+X^- + H_2O}$$

The preparation of **dimethylphenylsulfonium perchlorate**[374] will serve as an example: A mixture of methyl phenyl sulfide (2 g), methanol (6 ml), and 70% perchloric acid (3 ml) is heated to the boiling point, the excess of methanol is evaporated, and the residue is poured into water. The sulfonium salt that separates melts at 160° after recrystallization from water.

b. With sodium hydrogen sulfite

In some cases replacement of an alcoholic hydroxyl group, leading to sulfonic acid salts, can be effected by means of sodium hydrogen sulfite:

$$\mathrm{CR_3OH + NaHSO_3 \longrightarrow CR_3SO_3Na + H_2O}$$

For example, sodium tris-(*p*-tolyl)methanesulfonate[375] and triphenylmethanesulfonate[376] have been obtained from tris-(*p*-tolyl)methanol and triphenylmethanol, respectively.

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[370] M. P. Balfe, J. Kenyon, and C. E. Searle, *J. Chem. Soc.*, **1950**, 3309.

[371] M. E. Cain, M. B. Evans, and D. F. Lee, *J. Chem. Soc.*, **1962**, 1694.

[372] F. M. Furman, J. H. Thelin, D. W. Hein, and W. B. Hardy, *J. Amer. Chem. Soc.*, **82**, 1450 (1960).

[373] M. S. Newman and H. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).

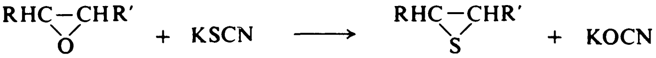
[374] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **69**, 492 (1936).

[375] A. Mothwurf, *Ber. Deut. Chem. Ges.*, **37**, 3158 (1904).

[376] A. Baeyer and V. Villiger, *Ber. Deut. Chem. Ges.*, **35**, 3016 (1902).

2. Reaction of alkene oxides (oxiranes) with sulfur compounds

Alkene oxides (oxiranes) can be converted into the corresponding sulfides (thiiranes) with replacement of the oxygen by sulfur under the action of sulfur-containing compounds such as, *e.g.*, thiocyanates, sodium thiosulfate, or thiourea:[377–381]



$$\underset{\diagdown\,O\,\diagup}{RHC{-}CHR'} + KSCN \longrightarrow \underset{\diagdown\,S\,\diagup}{RHC{-}CHR'} + KOCN$$

The reaction is often very violent and good cooling is required.

The preparation of **cyclohexene sulfide (7-thiobicyclo[4.1.0]heptane)**[378,382] may be described as an example: Cyclohexene oxide (7-oxabicyclo[4.1.0]heptane) (5 g) in methanol (20 ml) is treated with thiourea (5 g) at 60° for 1.5 h. The mixture is poured into water (150ml) and extracted with chloroform. Fractionation affords the sulfide, b.p. 67–68°/16 mm, in 58% yield.

Sander[383] has reviewed the methods for preparation of thiiranes.

Treating oxiranes with hydrogen sulfide cleaves the ether linkage and gives β-mercapto alcohols; (hydroxymethyl)oxirane (from glycerol), for instance, affords α-thioglycerol when treated with barium hydroxide solution that is saturated with hydrogen sulfide;[384] and passing oxirane itself with a slight excess of moist hydrogen sulfide through a porcelain tube heated at 150–160° affords 2-mercaptoethanol.[385,386]

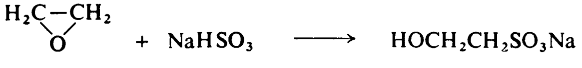
Oxiranes can also be cleaved by mercaptanes, this yielding β-hydroxy sulfides. This reaction has been carried out[386] with oxirane, 7-oxabicyclo[4.2.1]heptane, and epichlorohydrin [(chloromethyl)oxirane] and, as sulfur components, ethane-, 1-propane-, benzene-, and α-toluene-thiol in the presence of a little active charcoal as catalyst.

For example, **1-(ethylthio)-3-chloro-2-propanol** is obtained in 90% yield when epichlorohydrin (46 g) is warmed with ethanethiol (31 g) at 50° for 4 h; the product has b.p. 114 to 115°/16 mm.

2-(Phenylthio)ethanol is obtained (b.p. 119–120°/4 mm, 12 g) when thiophenol (11 g), oxirane (4.4 g), and a little active charcoal are kept in a closed vessel for 24 h.

Potassium thiolates in alcoholic solution cleave oxiranes without the need for a catalyst, yields being very good.[387,388]

A method that is important preparatively and is based on replacement of oxygen by sulfur consists of treating oxiranes with sodium hydrogen sulfite;[389] it leads to sodium β-hydroxy sulfonates:[390]



$$\underset{\diagdown\,O\,\diagup}{H_2C{-}CH_2} + NaHSO_3 \longrightarrow HOCH_2CH_2SO_3Na$$

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[377] French Pat. 797,621; *Chem. Abstr.*, **30**, 7122 (1936).

[378] C. C. J. Culvenor, W. Davies, and K. H. Pausacker, *J. Chem. Soc.*, **1946**, 1050.

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[380] B. Ketcham and V. P. Shah, *J. Org. Chem.*, **28**, 229 (1963).

[381] D. A. Lighitner and C. Djerassi, *Tetrahedron*, **21**, 583 (1965).

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[383] M. Sander, *Chem. Rev.*, **66**, 297 (1966).

[384] L. Smith and B. Sjöberg, *Ber. Deut. Chem. Ges.*, **69**, 678 (1936).

[385] French Pat. 769,216; *Chem. Abstr.*, **29**, 481 (1935).

[386] C. D. Nenitzescu and N. Scărlătescu, *Ber. Deut. Chem. Ges.*, **68**, 587 (1935).

[387] C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, **1949**, 278.

[388] D. J. Drain, *J. Med. Chem.*, **6**, 63 (1963).

[389] Ger. Pat. 569,148 (1931); *Chem. Abstr.*, **27**, 2457 (1933).

[390] R. Ten Eyck Schenck and S. Kaizerman, *J. Amer. Chem. Soc.*, **75**, 1636 (1953).

Sodium 2-hydroxy-1-propanesulfonate:[348] A mixture of sodium metabisulfite (95 g, 0.5 mole) with methyloxirane (67 g, 1.16 moles) in water (200 ml) is stirred at room temperature for 8 h and then evaporated to dryness. Recrystallization from 90% ethanol affords sodium 2-hydroxy-1-propanesulfonate (138 g, 85.2%), which after two recrystallizations from 95% ethanol has m.p. 225–227°.

3. Reaction of carbonyl compounds with sulfur compounds

Thiols can be obtained from carbonyl compounds, the oxygen atom of the latter being replaced by SH and H, if hydrogen sulfide or sulfur is used in the presence of hydrogen and a catalyst that is not poisoned by sulfur:[391]

$$\mathrm{RCOR'} + \mathrm{H_2S} + \mathrm{H_2} \xrightarrow{\text{Catal.}} \mathrm{HSCHRR'} + \mathrm{H_2O} \qquad (\mathrm{R'}\ \text{may be H})$$

The reaction occurs at 150–200° and about 140 atm in the presence of cobalt sulfide or nickel sulfide catalysts, yields averaging 70%.

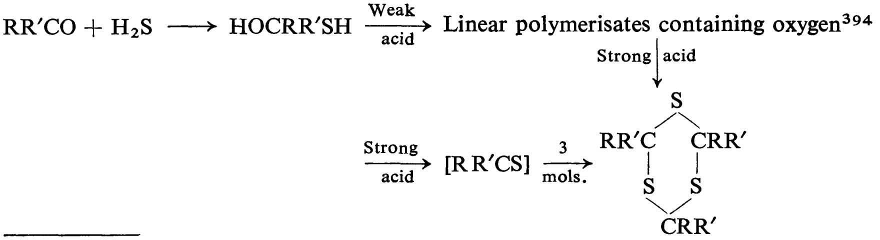
With hydrogen sulfide in the absence of hydrogen, however, aldehydes and ketones give geminal dithiols, the pressures required varying from 35 to 8500 atm according to the nature of the carbonyl compound;[392] these dithiols can also be obtained without use of pressure and at room temperature in dimethylformamide as solvent containing a basic catalyst such as morpholine or butylamine.[393]

Preparation of geminal dithiols:[393] A rapid stream of hydrogen sulfide is led for 7 h into an ice-cooled solution of a ketone (0.5 mole) in dimethylformamide (100 ml) containing an amine catalyst (0.05 mole). The mixture is acidified with dilute hydrochloric acid and extracted with light petroleum. The extract is washed with water until free from acid, dried over sodium sulfate, and distilled through a 30-cm Vigreux column at a pressure such that the liquid boils below 100°. All operations must be conducted in a fume cupboard, and the extracted air and waste water must be purified chemically.

The following were converted into geminal dithiols in this way: dimethyl (34%, b.p. 57°/100 mm; morpholine), ethyl methyl (44%, b.p. 73°/73 mm; morpholine), and diethyl ketone (31%, b.p. 72°/30 mm; butylamine), and cyclopentanone (72%, b.p. 63°/10 mm; morpholine).

$$\mathrm{RCOR'} + 2\mathrm{H_2S} \longrightarrow \mathrm{(HS)_2CRR'} + \mathrm{H_2O} \qquad (\mathrm{R'}\ \text{may be H})$$

A third synthesis leads, initially, to thioaldehydes and thioketones containing sulfur doubly bonded to carbon. The action of hydrogen sulfide and hydrochloric acid or other condensing agents on carbonyl compounds is the most general method of preparing thioaldehydes and thioketones; however, these products tend even more than do the oxygen analogs to polymerize, the favored polymers being the trimeric cyclic *s*-trithianes.



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[391] M. W. Farlow, W. A. Lazier, and F. K. Signaigo, *Ind. Eng. Chem.*, **42**, 2547 (1950).

[392] T. L. Cairns, G. L. Evans, A. W. Larchar, and B. C. McKusick, *J. Amer. Chem. Soc.*, **74**, 3982 (1952).

[393] R. Mayer, G. Hiller, M. Nitzschke, and J. Jentzsch, *Angew. Chem. Int. Ed., Engl.*, **2**, 370 (1963).

[394] S. W. Lebedew and M. Platonow, *Ber. Deut. Chem. Ges.*, **69**, 762 (1926); E. Müller and G. Schiller, *J. Prakt. Chem.*, [ii], **116**, 175 (1927); J. H. Wood and R. W. Bost, *J. Amer. Chem. Soc.*, **59**, 1011 (1937).

Thioformaldehyde and symmetrical thioketones can be obtained in only one trimeric form, but unsymmetrical thioketones are obtained in two isomeric forms: In the α- or *cis*-form all three groups R (and, of course, similarly R′) lie on one side of the ring; in the β- or *trans*-form two of a kind lie on one side with the third on the other. This isomerism is naturally prevented if these substituents are too bulky. The *cis*-compounds can be rearranged catalytically to the more favored, higher-melting β-forms.[395–397]

Thioaldehydes have acquired preparative importance since they yield olefins, or polymers thereof, when the sulfur is removed as hydrogen sulfide by reducing agents:[398]

$$2RCHS + [4H] \longrightarrow RCH{=}CHR + 2H_2S$$

Bost and Constable[399] give details for the preparation of trithioformaldehyde (*s*-trithiane).

α-Trithioacetaldehyde (*cis*-2,4,6-trimethyl-s-trithiane) is obtained, according to Baumann and Fromm,[400] by passing hydrogen sulfide into a mixture of equal parts of water, acetaldehyde, and concentrated hydrochloric acid; the oil that separates solidifies gradually and is collected after 24 h; when crystallized several times from acetone it has m.p. 101°.

β-Trithioacetaldehyde (*trans*-2,4,6-trimethyl-*s*-trithiane)[400] is formed when 1 part of acetaldehyde is mixed with 3 parts of ethanol saturated with hydrogen chloride and the mixture is saturated with hydrogen sulfide; after recrystallization from alcohol it melts at 125–126°.

β-Trithiobenzaldehyde (*trans*-2,4,6-triphenyl-s-triazine)[400] is obtained by passing hydrogen sulfide into a mixture of benzaldehyde and alcoholic hydrochloric acid. The resulting precipitate is boiled with benzene. The β-trithiane separates from the solution on cooling; it contains a molecule of benzene of crystallization and softens at about 140°; it melts at 225°.

The preparation of α-trithiobenzaldehyde (the *cis*-trithiane) is described by Klinger.[401]

Monohalobenzaldehydes are converted into the derived trimeric thioaldehydes (trithianes) by passing hydrogen chloride and hydrogen sulfide into their solution in anhydrous ethyl acetate.[402]

Thioketones are without exception colored but have a strong tendency to pass into the colorless trithianes, particularly the dialkyl and alkyl aryl thioketones. For instance, thioacetone exists only as the trimer at room temperature but, when heated, is converted into violet vapors of the monomer.[403] On the other hand, Baumann and Fromm[403] found that acetophenone gives, not only the trimer, but also the monomeric thioketone as an unstable blue oil from which the trimer is formed by pyrolysis.

Trithiocyclopentanone and **trithiohexanone (trispiro-[*s*-trithiane-2,1′:4,1″:6,1‴-tri(cyclopentane) and -tri(cyclohexane)]:)**[404] Gaseous hydrogen chloride, followed by hydrogen sulfide to saturation, is passed into a solution of cyclopentanone or cyclohexanone in five times the amount of anhydrous ethanol. A mass of crystals soon separates, which is filtered off and washed with dilute ethanol. When recrystallized from ethanol, trithiocyclopentanone melts at 99°; when dissolved in chloroform and precipitated by ethanol, trithiocyclohexanone melts at 101–102°.

The monomers were obtained by Sen,[405] as was thiocamphor.

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[395] O. Hassel and H. Viervoll, *Acta Chem. Scand.*, **1**, 149 (1947).

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[398] R. Kuhn, *Angew. Chem.*, **50**, 703 (1937).

[399] R. W. Bost and E. W. Constable, *Org. Syn.*, **16**, 81 (1936).

[400] E. Baumann and E. Fromm, *Ber. Deut. Chem. Ges.*, **22**, 2600 (1889).

[401] H. Klinger, *Ber. Deut. Chem. Ges.*, **9**, 1895 (1876); **10**, 1877 (1887).

[402] J. A. Stanfield and L. B. Reynolds Jr., *J. Amer. Chem. Soc.*, **74**, 2878 (1952).

[403] E. Baumann and E. Fromm, *Ber. Deut. Chem. Ges.*, **28**, 895 (1895).

[404] E. Fromm, *Ber. Deut. Chem. Ges.*, **60**, 2090 (1927).

[405] D. C. Sen, *J. Indian Chem. Soc.*, **13**, 268 (1936); **12**, 647 (1935).

Pure monomeric thioketones have only recently become accessible[406] but can now be prepared in any desired amount. The following methods have proved suitable: catalytic removal of hydrogen sulfide from geminal dithiols at 200°;[407] thermolysis of 2*H*,6*H*-1,3-dithiins[408] (obtained from geminal dithiols and malonodinitrile or its alkylidene or benzylidene derivatives);[409] and treatment of ketals with hydrogen sulfide in the presence of acid catalysts.[410] The last method in particular is widely variable and very effective; it is only necessary to see that overdosage with hydrogen sulfide does not convert the thione into the geminal dithiol by addition.

$$R'R''C(OR)_2 + H_2S \longrightarrow R'R''CS + 2ROH$$

Enol ethers react similarly, giving a mixture of enethiols and thioketones:

$$—CH{=}C(OR)— \xrightarrow[-ROH]{H_2S} —CH{=}C(SH)— \rightleftharpoons —CH_2—CS—$$

It is best to carry out the operation under an inert gas and in the presence of a little hydroquinone.

General preparation of monomeric thioketones:[410] One mole of the desired ketal or enol ether is treated with twice the amount by weight of glacial acetic acid and about 1 gram of hydroquinone, then 3 drops of concentrated sulfuric acid are added and a rapid stream of hydrogen sulfide is passed in until the theroretical amount has been absorbed. The reaction is usually complete in 15–20 min. The final temperature is about 35°. The mixture is poured into ice-water, and the organic phase is taken up rapidly in light petroleum, purified, and distilled through a column. The thioketones are unstable deep red oils with an extremely unpleasant and penetrating odor.

This method has given: **2-butanethione,** 43–45% yield, b.p. 120–124°; **3-pentanethione,** 80–85%, b.p. 55–56°/57 mm; **4-heptanethione,** 50–55%, b.p. 52–62°/12 mm; **cyclopentanethione,** 30–35%, b.p. 60–67°/18 mm; and **cyclohexanethione,** 50%, b.p. 81–84°/17 mm.

Aromatic and heterocyclic thioketones show no tendency to polymerize and with few exceptions they crystallize well. For their preparation the oxygen analogs are treated (i) with hydrogen sulfide in anhydrous hydrogen fluoride [*e.g.*, thiobenzophenone, 4,4'-dimethylthiobenzophenone, 1-naphthyl phenyl thioketone, or 4-(dimethylamino)thiobenzophenone[411]] or in the presence of hydrogen chloride (*e.g.*, thiobenzophenone[412] or thiofluorenone[413]) or (ii) with phosphorus pentasulfide (*e.g.*, dimethylthiochromone[361], 4-thioflavone,[414] or thiophthalimide[416]).

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[406] Review: R. Mayer, J. Morgenstern, and J. Fabian, *Angew. Chem. Int. Ed., Engl.*, **3**, 277 (1964).

[407] S. Bleisch and R. Mayer, *Chem. Ber.*, **99**, 1771 (1966).

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[410] R. Mayer and H. Berthold, *Chem. Ber.*, **96**, 3096 (1963).

[411] R. M. Elofson, L. A. Baker, F. F. Gadallah, and R. A. Sikstrom, *J. Org. Chem.*, **29**, 1355 (1964).

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[414] H. Simonis and S. Rosenberg, *Ber. Deut. Chem. Ges.*, **47**, 1232 (1914).

[415] W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, **1952**, 1303.

[416] R. J. W. Cremlyn, *J. Chem. Soc.*, **1961**, 5055.

4-Thio-4-pyrone:[417] 4-Pyrone is boiled for 0.5 h with twice the amount of pure yellow phosphorus pentasulfide and then filtered; the filtrate and a benzene extract of the residue are evaporated in a vacuum; recrystallization of the product from low-boiling light petroleum gives ochre-yellow needles, m.p. 49°.

Reaction of thiols with aldehydes or ketones leads to formation of water and geminal bis(alkylthio) compounds, which, when derived from aldehydes, are known as mercaptals or, when derived from ketones, as mercaptols:

$$RR'CO + 2R''SH \longrightarrow RR'C(SR'')_2 + H_2O \qquad \text{Mercaptol (if } R'{=}H\text{, mercaptal)}$$

In general, aldehydes react more readily than ketones: of thiols, α-toluenethiol condenses more easily than ethane-, pentane-, or benzene-thiol.[418]

General preparation of mercaptals:[90] Dry hydrogen chloride is led into a mixture of a thiol (2 moles) and an aldehyde (1 mole), reaction occurring in a short time with evolution of heat and separation of water. The solid mercaptal is recrystallized from ether, light petroleum, or benzene. The following are examples: benzaldehyde bis-(*p*-bromophenyl) mercaptal, m.p. 79–80° (from ether); cinnamaldehyde diphenyl mercaptal, m.p. 80–81° (from light petroleum); piperonaldehyde diphenyl mercaptal, m.p. 48° (from acetone).

A general prescription for the preparation of dibutyl mercaptols and mercaptals has been given by Whitner and Reid.[419]

Fischer[420] reported the preparation of mercaptals from carbohydrates; the reaction can be applied to all aldoses and aliphatic thiols, but fails with thiophenols and also with fructose and sorbose,[421] so that it can be used to separate, *e.g.*, glucose from a mixture with fructose and sorbose.

Glucose diethyl mercaptal:[420] Finely powdered, pure glucose (70 g) is shaken with fuming hydrochloric acid (*d* 1,19; 70 g) at room temperature in a glass-stoppered flask until dissolved, then cooled, and ethanethiol is added in portions (4 × 10 g) with vigorous shaking. Most of the thiol dissolves in a short time, the mixture becoming warm. The thick crystal mass is filtered off and pressed as dry as possible. The crude mercaptal (59 g) is recrystallized from four times the amount of ethanol, then twice from water, and again from ethanol, to give pure material, m.p. 127–128°.

Mercaptals from α-toluenethiol[422] and mercapto carboxylic acids[423] are particularly suitable for identification and isolation of carbonyl compounds.

Ketones and thiols form mercaptols, in general under the above conditions but with greater difficulty;[90] addition of zinc chloride as catalyst is frequently recommended.[424]

When acetals of aldehydes or ketones are heated with thiols in a bomb tube at 100–130° the OR groups are replaced by SR, this process having been used to provide acetaldehyde diethyl mercaptal (84% yield), acetone diethyl mercaptol (81%), and triethyl trithioorthoformate (87%).[425]

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[425] M. F. Shostakovskii, A. V. Bogdanova, and G. I. Plotnikova, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1960**, 1524, 1901; *Chem. Abstr.*, **55**, 371, 16407 (1961).

4. Reaction of carboxylic acid derivatives with sulfur compounds

Thiocarboxylic acids are obtained by acylation of hydrogen sulfide (cf. page 642). For example, thiobenzoic acid is formed (61–76% yield) from benzoyl chloride and potassium hydrogen sulfide,[426] and thioacetic acid (74% yield) when hydrogen sulfide is passed into acetic anhydride.[427,428] This method can also be applied to other anhydrides.[429]

S-Esters of thiocarboxylic acids are formed on acylation of thiols by acid anhydrides. For the preparation of the **lower *S*-esters** the following Schotten–Baumann procedure is used:[430,431]

A mixture of sodium hydroxide (40 g), water (75 ml), and thiol (1.2 moles) is poured on crushed ice (500 g), and the whole is stirred vigorously while acetic anhydride (1.25 moles) is added. After a further 5 minutes' stirring, the ester is separated, washed, dried, and distilled.

The C_4 to C_8 *S*-alkyl thioacetates are prepared[431] by heating the thiol (1 mole), acetic anhydride (1.2 moles), and anhydrous sodium acetate (one-fifth of the weight of the anhydride) under reflux for 1 h in an oil-bath whose temperature is raised from an initial 130° to 150°; the reaction is usually so violent that the flask must be removed from the heating-bath for a short time. After cooling, the mixture is poured into water, and the ester is isolated as above.

S-Methyl to *S*-octyl thioacetates are obtained in this way in yields averaging 90%. Thiophenol has been acylated by a mixed anhydride composed from the desired acylating acid and ethyl hydrogen carbonate.[432]

Orthothioformic esters are the most easily prepared orthothiocarboxylic esters, being obtained from formic acid and a thiol.[433]

Another preparatively important method of replacing the oxygen of carboxylic acid derivatives by sulfur is provided by sulfuration of amides by means of phosphorus sulfides; this gives thioamides:[434]

$$5RCONR'_2 + P_2S_5 \longrightarrow 5RCSNR'_2 + P_2O_5$$

The reaction is usually effected in boiling benzene, toluene, or dioxan and is fairly widely applicable;[435] it is in general appreciably smoother for secondary and tertiary[436] than for primary amides, since primary amides are easily dehydrated to nitriles by the phosphorus pentoxide produced.

Kindler[437] obtained thioamides by the action of a mixture of phosphorus pentasulfide and potassium sulfide on amides, first at room temperature and finally at 70–80°; this process has afforded, *e.g.*, thioacetamide, thiobenzamide, phenyl(thioacetamide), 3-phenyl(thiopropionamide), and their *N*-methyl derivatives.

Thiobenzanilide is best prepared with pyridine as solvent.[438]

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[426] P. Noble Jr. and D. S. Tarbell, *Org. Syn.*, Coll. Vol. IV, 924 (1963).

[427] E. K. Ellingboe, *Org. Syn.*, **31**, 105 (1951).

[428] B. Sjöberg, *Svensk Kem. Tidskr.*, **63**, 90 (1951).

[429] U.S. Pat. 2,587,580; *Chem. Abstr.*, **46**, 10192 (1952).

[430] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **39**, 2433 (1906).

[431] F. W. Wenzel Jr. and E. E. Reid, *J. Amer. Chem. Soc.*, **59**, 1089 (1937).

[432] T. Wieland, W. Schäfer, and E. Bokelmann, *Ann. Chem.*, **573**, 99 (1951).

[433] J. Houben and K. L. M. Schultze, *Ber. Deut. Chem. Ges.*, **44**, 3235 (1911); J. Houben, *Ber. Deut. Chem. Ges.*, **45**, 2942 (1912); cf. H. Gross and A. Rieche, *Chem. Ber.*, **94**, 543 (1961).

[434] A. W. Hofmann, *Ber. Deut. Chem. Ges.*, **11**, 340 (1878).

[435] K. Jakopčić and V. Hahn, *Naturwissenschaften*, **51**, 482 (1964).

[436] A. Reissert, *Ber. Deut. Chem. Ges.*, **37**, 3708 (1904).

[437] K. Kindler, *Ann. Chem.*, **431**, 209 (1923).

[438] E. Klingsberg and D. Papa, *J. Amer. Chem. Soc.*, **73**, 4989 (1951).

The sulfuration of amides has been reviewed, with a large number of examples, by Hurd and DeLaMater.[439]

5. Reaction of alkyl and dialkyl sulfates with sulfur compounds

The lower alkyl sulfides can be prepared by alkylation of alkali sulfides with either mono-*O*-alkylsulfuric acid salts[440,441] or dialkyl sulfates.[442-444]

Diethyl sulfide:[445] Sodium sulfide nonahydrate (120 g) in water (120 ml) is heated to the boiling point in a distillation flask (750-ml capacity) fitted to a very efficient descending condenser leading to a receiver that is cooled in ice. To this is added diethyl sulfate (155 g) at such a rate that the lively reaction proceeds without external heating. The distillate is saturated with sodium chloride, and the sulfide is separated in a separatory funnel, dried over calcium chloride, and distilled; it has b.p. 90–92°, the yield being 78% (35 g).

Organic sulfides can also be alkylated to afford sulfonium alkyl sulfates. Use of dialkyl sulfates is sometimes essential, as, for instance, diaryl sulfides[308] and methyl *p*-tolyl sulfide are not converted into sulfonium salts by alkyl halides.

Dimethyl-*p*-tolylsulfonium methyl sulfate[307] is obtained when equivalent amounts of methyl *p*-tolyl sulfide and dimethyl sulfate are heated on a water-bath for 15–20 min. The product separates as a viscous oil but on cooling solidifies to a crystal mass having m.p. 97°.

Methylation with dimethyl sulfate also converts thiocarboxylic acids into their methyl esters,[446] and sulfites into aliphatic sulfonic acids.

Barium methanesulfonate:[447] Pure dimethyl sulfate (126 g) is added slowly to 26% ammonium sulfite solution (600 ml) at 10°. When the dimethyl sulfate has dissolved, crystalline ammonium sulfite (75 g) that has been rubbed to a paste with water (75 ml) is added and the whole is heated on the water-bath for a few hours. Next the mixture is diluted whilst still hot to three times its volume, a small excess of sulfite is destroyed by sulfuric acid, the calculated amount of barium hydroxide is added, and the ammonia is boiled off. The excess of barium hydroxide is carefully removed by sulfuric acid, and the solution is neutralized with barium carbonate and filtered. Evaporating the filtrate yields barium methanesulfonate as residue.

IV. Replacement of nitrogen by sulfur

1. Replacement of the amino group by sulfur groups

Removal of an amino group with formation of a C–S bond cannot be achieved directly; it is effected by way of the diazonium salts that are readily obtained from aromatic amines. Nevertheless, to overcome the always present, great or slight, tendency for formation of organic sulfides — as in analogous alkylations — it is customary here, too, to use as aryl acceptors only those

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[439] R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 47 (1961).

[440] P. Klason, *Ber. Deut. Chem. Ges.*, **20**, 3407 (1887).

[441] H. Hepworth, *J. Chem. Soc.*, **119**, 1254 (1921).

[442] H. Böhme and W. Krause, *Chem. Ber.*, **82**, 426 (1949).

[443] H. L. Gray and G. O. Gutekunst, *J. Amer. Chem. Soc.*, **42**, 856 (1920).

[444] W. Strecker and R. Spitaler, *Ber. Deut. Chem. Ges.*, **59**, 1763 (1926).

[445] H. Böhme and H. J. Gran, *Ann. Chem.*, **577**, 72 (1952).

[446] L. S. Pratt and E. E. Reid, *J. Amer. Chem. Soc.*, **37**, 1934 (1915).

[447] C. Weygand, unpublished work.

alkali hydrogen sulfides in which formally the hydrogen is replaced by a readily removable group, usually by an acyl group. For this reason alkali xanthates are the reagents of choice for preparation of thiophenols by this method. The diazonium xanthates first formed readily lose nitrogen, giving aryl xanthates from which the thiophenols are obtained by alkaline hydrolysis:[448,449]

$$[C_6H_5{-}N{\equiv}N]^+Cl^- + KS{-}C({=}S){-}OC_2H_5 \longrightarrow C_6H_5{-}N_2{}^+S{-}C({=}S){-}OC_6H_5 \xrightarrow{-N_2}$$

$$C_6H_5{-}S{-}C({=}S){-}OC_2H_5 \xrightarrow{HO^-} C_6H_5SH$$

To avoid explosions[450] it is recommended to carry out the diazonium salt reaction very cautiously with stirring — best by adding the cold diazonium salt solution to the xanthate solution pre-warmed to 60–70°. For each mole of diazonium compound it is advisable to use 1.4 moles of xanthate in the tenfold amount of water.[451]

***p*-Mercaptophenol (thiohydroquinone):**[452] *p*-Aminophenol (110 g, 1 mole) is dissolved in an excess (2.25 moles) of 10% hydrochloric acid, cooled to below 15°, and diazotized by gradual addition of sodium nitrite (70 g, 1 mole) at 15–20°. The diazonium salt solution is then added slowly and with stirring below the surface of a solution of potassium ethylxanthate (224 g, 1.4 moles) in water (650 ml) at 70–75°. After addition is complete the mixture is warmed for a further 0.5 h at 90°, sodium hydroxide (160 g, 4 moles) is added, and the whole is boiled for some hours to decompose the xanthate ester. Finally this solution is acidified with an excess of 50% sulfuric acid, zinc and benzene are added, and the whole is heated further to reduce any disulfide fromed. The crude oily product is separated, washed with dilute hydrochloric acid and then with water, and distilled in a vacuum. The thiol (61 g) has b.p. 133 to 137°/11 mm.

The reaction of diazonium salts with sodium disulfide proceeds in the same way, nitrogen being split off and organic disulfides formed:

$$2[RN_2]^+Cl^- + Na_2S_2 \longrightarrow RSSR + 2NaCl + 2N_2$$

For example, Chmelewsky and Friedlander[453] obtained **2,2′-dithiodi(cinnamic acid)** by pouring *o*-diazocinnamic acid into an excess of warm, concentrated, aqueous sodium disulfide and acidifying the mixture. For purification, a solution of the crude product in cold sodium carbonate solution is filtered and acidified; the precipitate melts at 221° after recrystallization from ethanol.

The preparation of 2,2′-dithiodi(benzoic acid) (dithiosalicylic acid)[454] may be cited as a further example.

Aromatic sulfides are often obtained by treating diazonium salts with alkali thiolates; to avoid explosions it is best to operate under the conditions described above.[455,456] The following have been obtained by this process:

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[448] R. Leuckart, *J. Prakt. Chem.*, [ii], **41**, 187 (1890).

[449] D. S. Tarbell and D. K. Fukushima, *Org. Syn.*, **27**, 81 (1947).

[450] K. Holzach, "Die aromatischen Diazoverbindungen," F. Enke, Stuttgart, 1947, p. 216.

[451] K. H. Saunders, "The Aromatic Diazo-Compounds and their Technical Applications," E. Arnold & Co., London, 1949, p. 326.

[452] E. Miller and R. R. Read, *J. Amer. Chem. Soc.*, **55**, 1224 (1933).

[453] C. Chmelewsky and P. Friedländer, *Ber. Deut. Chem. Ges.*, **46**, 1903 (1913).

[454] C. F. H. Allen and D. D. McKay, *Org. Syn.*, Coll. Vol. II, 580 (1955).

[455] J. H. Ziegler, *Ber. Deut. Chem. Ges.*, **23**, 2469 (1890).

[456] F. Mayer, *Ber. Deut. Chem. Ges.*, **42**, 3046 (1909).

(1- and 2-naphthylthio)acetic acid,[857] 1-(9,10-anthraquinon-2-ylthio)-9,10-anthraquinone-2-carboxylic acid,[458] and *p*-(butylthio)phenetole;[452] diphenyl sulfide was prepared in the presence of copper powder which catalyses the decomposition of the diazo sulfide.[459]

The action of sulfur dioxide in the presence of copper powder or copper(I) oxide, which act as reducing agents, provides a useful and generally applicable method of replacing a diazonium by a sulfinic acid group.[460]

The following general directions for preparation of **sulfinic acids** have been recommended by Gattermann:[461] The diazonium salt solution obtained from an amine in sulfuric acid, if necessary (see below) treated with an excess of sulfuric acid, is thoroughly cooled whilst being saturated with sulfur dioxide; at least 15 g of the dioxide are absorbed per 100 ml of solution; the solution must remain completely clear (precipitates are formed if the solution is insufficiently acid or insufficiently cooled). Copper powder[462,463] is then added whilst cooling and passage of sulfur dioxide are continued, the mixture being stirred until no more nitrogen is evolved. The precipitate is extracted with ether, the ethereal extract is extracted with sodium carbonate solution, and this aqueous phase is acidified. Depending on its solubility the sulfinic acid is finally filtered off or isolated by means of ether. This process has afforded benzene-, toluene-, xylene-, halobenzene-, methoxybenzene-, ethoxybenzene-, and naphthalene-sulfinic acid as well as sulfinobenzoic acids in yields averaging 90%.

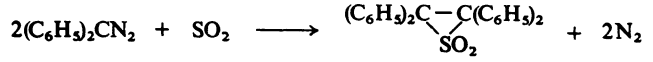
The preparation of various halobenzenesulfinic acids by this method has also been described by Hanke,[464] and by Silvester and Wynne.[465]

For the preparation of aromatic sulfinic acids the copper reducing agent may be replaced by iron(II) salts with advantage.

For example, **2,4-dinitrobenzenesulfinic acid** is obtained in 74.1% yield from diazotized 2,4-dinitroaniline and sulfur dioxide on addition of iron(II) sulfate.[466]

Truce and Murphy[467] have reviewed, with a large number of examples, the methods for preparation of sulfinic acids from diazonium salts.

Diazodiphenylmethane reacts with sulfur dioxide with elimination of nitrogen and formation of a cyclic sulfone, namely, 2,2,3,3-tetraphenylthiirane 1,1-dioxide:[468]



$$2(C_6H_5)_2CN_2 + SO_2 \longrightarrow \underset{SO_2}{(C_6H_5)_2C{-}C(C_6H_5)_2} + 2N_2$$

Meerwein and his co-workers[469] found that *p*-chlorobenzenesulfonyl chloride[476] can be obtained from *p*-chlorobenzenediazonium chloride in liquid sulfur dioxide containing copper(I) chloride, and his school later elaborated

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[457] Ger. Pat. 194,040; *Chem. Abstr.*, **2**, 2162 (1908).

[458] Ger. Pat. 460,087; Friedländer, **16**, 1250 (1931); Ger. Pat. 475,688; *Chem. Abstr.*, **23**, 3815 (1929).

[459] G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **51**, 1526 (1929).

[460] Ger. Pat. 100,702; *Friedländer*, **5**, 44 (1897–1900).

[461] L. Gattermann, *Ber. Deut. Chem. Ges.*, **32**, 1136 (1899).

[462] L. Gattermann, *Ber. Deut. Chem. Ges.*, **23**, 1219 (1890).

[463] F. Ullmann, *Ber. Deut. Chem. Ges.*, **29**, 1878 (1896).

[464] M. E. Hanke, *J. Amer. Chem. Soc.*, **45**, 1325 (1923).

[465] W. A. Silvester and W. P. Wynne, *J. Chem. Soc.*, **1936**, 691.

[466] H. Meerwein, G. Dittmar, G. Kaufmann, and R. Raue, *Chem. Ber.*, **90**, 859 (1957).

[467] W. E. Truce and A. M. Murphy, *Chem. Rev.*, **48**, 86 (1951).

[468] H. Staudinger and F. Pfenninger, *Ber. Deut. Chem. Ges.*, **49**, 1941 (1916).

[469] H. Meerwein, E. Büchner, and K. van Emster, *J. Prakt. Chem.*, [ii], **152**, 251 (1939).

[470] Ger. Pat. 859,461; *Chem. Abstr.*, **50**, 2668 (1956).

this to a general synthesis of aromatic sulfonyl chlorides:[471]

$$[ArN_2]^+Cl^- + SO_2 \longrightarrow ArSO_2Cl + N_2$$

The liquid sulfur dioxide can with advantage and more conveniently be replaced by a saturated (about 30%) solution of the gas in glacial acetic acid, and the solid diazonium salt by as concentrated as possible a solution thereof in hydrochloric acid. Copper(II) chloride dihydrate is a particularly useful catalyst as it is reduced during the reaction to finely divided and partially dissolved copper(I) chloride which is the effective agent. In the absence of catalyst only diazonium chlorides, such as dinitrobenzenediazonium chloride, having strongly negative substituents react with sulfur dioxide. The reaction temperature must be adjusted so that nitrogen is evolved rapidly, ensuring that the reaction proceeds fast, because then fewer side reactions occur and thus yields are improved. In many cases the rate of reaction can be increased by adding a water-immiscible solvent of lower dielectric constant (carbon tetrachloride or benzene) or by increasing the chloride ion concentration, notably by adding magnesium chloride. In this way benzene-, toluene-, naphthalene-, halobenzene-, and methoxybenzene-sulfonyl chloride and chlorosulfonylbenzoic acid were obtained in yields averaging 70–80%.

The preparation of **p-bromobenzenesulfonyl chloride** will serve as example: A freshly prepared solution of *p*-bromobenzenediazonium chloride [from *p*-bromoaniline (43 g, 0.25 mole), 36% hydrochloric acid (85 ml), and sodium nitrite (19 g, 0.275 mole, in 30 ml of water)] containing 9.5% of free hydrochloric acid is run into a 30% solution (200 ml) of sulfur dioxide in glacial acetic acid to which a concentrated aqueous solution of copper(II) chloride dihydrate (10 g) has been added. Lively evolution of nitrogen occurs and the temperature rises from 12° to 35°; further rise in temperature is avoided by cooling in ice-water. The reaction is complete in 3–4 min; then a three-fold amount of ice-water is added and the precipitate is collected, washed, and dried (yield 58.6 g, 92%). After recrystallization from benzene the chloride has m.p. 76.3–76.5° and b.p. 153°/15 mm.

When diazobenzene- or diazonaphthalene-sulfonic acid is treated analogously with sulfur dioxide in glacial acetic acid containing copper(I) chloride, the products are the disulfonic acids, owing to the instability of chlorosulfonyl sulphonic acids in aqueous solution.[471] The reaction is a smooth one and yields are good. For example, 2-hydroxy-1,4-naphthalenedisulfonic acid was obtained in this way from 4-diazo-3-hydroxy-1-naphthalenesulfonic acid.[472]

p-Benzenedisulfonic acid: A solution of diazosulfanilic acid (18.4 g, 0.1 mole) in concentrated sulfuric acid (100 ml) is poured into a suspension of copper(I) chloride in sulfur dioxide–glacial acetic acid (150 ml). The temperature rises by itself from 18° to 23° and is gradually increased to 42° by heating. Evolution of nitrogen (2.3 l at NTP) is complete in 4 h. The mixture is evaporated to dryness in a vacuum; addition of saturated sodium chloride solution to the residue causes separation of a crystalline mass of sodium *p*-benzenedisulfonate. This is filtered off, washed several times with methanol, recrystallized from saturated sodium chloride solution, and freed from adhering sodium chloride by washing with methanol. The yield is 76.3% (21.5%).

o- and *m*-Benzenedisulfonic acid, 1,4- and 1,6-naphthalenedisulfonic acid and *p*-arsonobenzenesulfonic acid were prepared in the same way[471]

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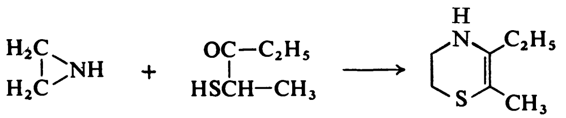
[471] H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

[472] French Pat. 826,402; *Chem. Abstr.*, **32**, 7479 (1938).

2. Replacement of the imino group by sulfur groups

When aziridines (ethyleneimines) are treated with hydrogen sulfide or thiols one C–N bond is broken and β-aminoalkanethiols or β-(alkylthio)alkylamines, respectively, are formed:[473]

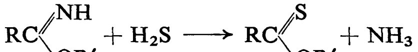
The reaction can be extended to other mercapto derivatives such as α-mercapto ketones[474] and α-mercapto carboxylic acids.[475] For example, 3-ethyl-5,6-dihydro-2-methyl-4*H*-1,4-thiazine is obtained in 85–90% yield from aziridine and 2-mercapto-3-pentanone:[474]



The preparation of cysteamine has been reported by Mills and Bogert.[476] **S-Methyl-** and **S-ethylcysteamine**[477] are obtained when aziridine is added gradually to a methanolic solution of methane- or ethane-thiol, respectively, at −15° and the mixture is set aside at room temperature.

N-Acetylcysteamine is obtained when aziridine (142 g) is added dropwise to a solution of mercaptoacetic acid (250 g) in anhydrous methanol (1700 ml) at 5–10° and then boiled under reflux for 30 min.[478] Isolation is by distillation; a small amount of *S*-acetylcysteamine distils first, solidifying in the receiver; the *N*-acetyl derivative follows as a colorless oil, b.p. 138 to 140°/7 mm (175 g, 45%).

An important method of preparing *O*-esters of thiocarboxylic acids is to treat imidic esters with hydrogen sulfide:



A large number of such *O*-esters have been obtained by this method.[479-482]

3. Replacement of tertiary-bonded nitrogen and of the ammonium group by sulfur groups

The replacement of tertiary-bonded nitrogen of certain Schiff bases by sulfur leads to thioketones. Reddelien and Danilof give the following directions for preparation of **thiobenzophenone** by this method:[483]

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[473] H. Bestian, *Ann. Chem.*, **566**, 210 (1949).

[474] F. Asinger, H. Diem, and W. Schäfer, *Monatsh. Chem.*, **95**, 1335 (1964).

[475] H. Lehr, S. Karlan, and M. W. Goldberg, *J. Med. Chem.*, **6**, 136 (1963).

[476] E. J. Mills and M. T. Bogert, *J. Amer. Chem. Soc.*, **62**, 1173 (1940).

[477] T. Wieland, E. F. Möller, and G. Dieckelmann, *Chem. Ber.*, **85**, 1041 (1952).

[478] R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

[479] Y. Sakurada, *Mem. Coll. Eng., Kyoto Imp. Univ., A*, **10**, 67, 79 (1926); *Chem. Abstr.*, **21**, 3609 (1927).

[480] J. P. Jepson, A. Lawson, and V. D. Lawton, *J. Chem. Soc.*, **1955**, 1791.

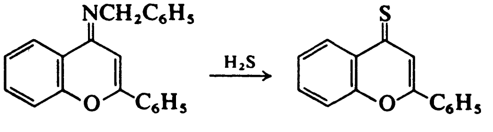
[481] U. Schmidt, E. Heymann, and K. Kabitzke, *Chem. Ber.*, **96**, 1478 (1963).

[482] G. Barnikow and G. Strickmann, *Chem. Ber.*, **100**, 1428 (1967).

[483] G. Reddelien and H. Danilof, *Ber. Deut. Chem. Ges.*, **54**, 3141 (1921).

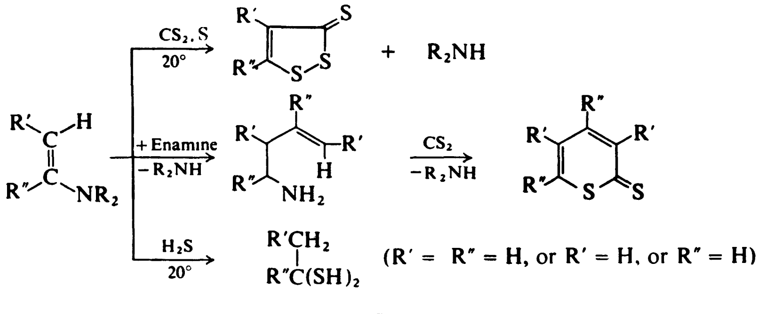
Benzophenone anil (7 g) is dissolved in benzene (50 ml) in a hydrogenation vessel and treated with dry hydrogen chloride, which precipitates the yellow hydrochloride. The hydrogen chloride is then replaced by hydrogen sulfide, and the vessel is shaken for 6 days under the pressure from a Kipps apparatus. The resulting deep blue solution is filtered under carbon dioxide from the precipitated aniline hydrochloride and unchanged benzophenone anil hydrochloride, the benzene is evaporated in a stream of carbon dioxide, and the residue is fractionated. Thiobenzophenone (3 g) distils at 176–178°/18 mm as a deep blue oil, which solidifies on cooling but remelts in the warmth of a hand.

Passing hydrogen sulfide into a solution of flavone benzylimine (0.5 g) in ethanol (15 ml) for 30 min gives **4-thioflavone**[484], which, after 2 h, is filtered off, washed with water, dried (yield 0.277 g, 72%), and recrystallized from light petroleum (b.p. 60–80°), then having m.p. 88°.



Under certain conditions the reaction can be stopped at the 1,1-dithiol stage.[485]

Studies by Mayer and his school have shown that replacement of the nitrogen group of enamines provides a synthetic method capable of considerable variation and especially useful for the preparation of sulfur heterocycles.[486] For example, 3*H*-1,2-dithiol-3-thiones are obtained by the action of hydrogen sulfide and sulfur on enamines, particularly in a polar solvent, at room temperature.[487] If the sulfur is omitted, then at higher temperatures and in an apolar solvent 2*H*-thiopyrone-2-thiones are formed preferentially.[488] Also, enamines can be cleaved to 1,1-dithiols by sulfur:[489] enamines obtained from *β*-oxo carboxylic esters thus give 60–90% yields of *β*-thioxo carboxylic esters.[490]



$$\begin{array}{l} NR_2\text{—}CR''\text{=}CR'\text{—}COOR''' \xrightarrow[-R_2NH]{H_2S,20^\circ} HS\text{—}CR''\text{=}CR'\text{—}COOR''' \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \updownarrow \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad S\text{=}CR''\text{—}CHR'\text{—}COOR''' \end{array}$$

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[484] W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, **1952**, 1299.

[485] B. Magnusson, *Acta Chem. Scand.*, **16**, 1536 (1962); **17**, 273 (1963).

[486] Review: R. Mayer and K. Gewald, *Angew. Chem. Int. Ed., Engl.*, **6**, 294 (1967).

[487] R. Mayer, P. Wittig, J. Fabian, and R. Heitmüller, *Chem. Ber.*, **97**, 654 (1964).

[488] R. Mayer, G. Laban, and M. Wirth, *Ann. Chem.*, **703**, 140 (1967).

[489] M. Demuynk and J. Vialle, *Bull. Soc. Chim. France*, **1962**, 2126.

[490] S. Bleisch and R. Mayer, *Z. Chem.*, **4**, 146 (1964).

General method for preparation of 3*H*-1,2-dithiol-3-thiones:[487] Sulfur powder (6 g, 0.19 mole) is distributed in pure dimethylformamide (40 ml) and carbon disulfide (45.5 g, 0.6 mole), contained in a three-necked flask (250 ml) fitted with a stirrer, thermometer, and dropping funnel. The desired enamine (0.2 mole) is dropped in with vigorous stirring at 15°. The sulfur dissolves when stirring is continued for a further 2–4 h, whereafter the mixture is stirred into water (400 ml). The dithiolthione crystallizes in a few minutes and is filtered off and warmed with 50% (by weight) sulfuric acid to decompose adhering dithiocarbamate. The dithiolthione obtained by cooling and dilution with water is collected on a fritted filter and washed until free from acid. It is purified, if necessary, by recrystallization, sublimation, or chromatography. Liquid dithiolthiones are taken up in chloroform and purified by distillation.

Organic sulfides are obtained by treating quaternary ammonium salts with sodium sulfide, the corresponding tertiary amines being by-products. The reaction is, however, smooth only if a benzyl or an allyl group is present as well as an aryl group, since only the two first are transferable for alkylation of sodium sulfide.[491]

4. Replacement of the nitro group by sulfur groups

One nitro group of *o*-dinitrobenzene and its derivatives is reactive and can be replaced by a mercapto, alkylthio, or sulfo group under the influence of sodium sulfide, sodium thiolates, or sodium sulfite, respectively. For preparative purposes this reaction is, however, restricted to a few examples. *o*-Dinitrobenzene and sodium sulfide give bis-(*o*-nitrophenyl) sulfide,[492] and trinitroanisole gives the bis(methoxydinitrophenyl) sulfide.[493]

[(*o*-Nitrophenyl)thio]acetic acid is obtained from *o*-dinitrobenzene and mercaptoacetic acid.[494]

Replacement of the nitro group by a sulfo group is particularly easy in the nitroanthraquinone series, when these compounds are boiled for several hours with sodium or potassium sulfite in aqueous solution.[495,496]

V. Replacement of other elements by sulfur groups

1. Reactions of Grignard reagents

The extreme reactivity of Grignard compounds has been utilized over a very wide field for the synthesis of organic sulfur compounds. Although the action of elemental sulfur on Grignard compounds is one of the less important methods of preparing thiols owing to the incidence of side reactions,[497] the reaction with sulfenyl chlorides can in general be used for synthesis of organic sulfides:

$$RMgBr + R'SCl \longrightarrow RSR' + MgClBr$$

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[491] H. R. Snyder and J. C. Speck, *J. Amer. Chem. Soc.*, **61**, 668, 2895 (1939).

[492] C. A. Lobry de Bruyn and J. J. Blanksma, *Rec. Trav. Chim.*, **20**, 115 (1901).

[493] J. J. Blanksma, *Rec. Trav. Chim.*, **23**, 114 (1904).

[494] P. Friedländer, *Ber. Deut. Chem. Ges.*, **39**, 1065 (1906).

[495] Ger. Pat. 164,292; *Friedländer*, **8**, 231 (1905–1907).

[496] U.S. Pat. 2,499,003; *Chem. Abstr.*, **44**, 7883 (1950).

[497] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, 1954, p. 1274.

Lecher and his co-workers, for instance, obtained diphenyl sulfide and phenyl *p*-tolyl sulfide from benzene- and *p*-toluene-sulfenyl chloride, respectively.[39]

Benzyl phenyl sulfide:[256b] Chloromethanesulfenyl chloride (5.85 g) in anhydrous ether (50 ml) is added, with stirring and cooling, to a phenylmagnesium bromide solution prepared from magnesium turnings (2.8 g) and bromobenzene (17 g) in anhydrous ether (50 ml). After being warmed for 30 min under reflux, the mixture is cooled and poured on ice. Concentrated hydrochloric acid (10 ml) is added and the ethereal layer is separated, dried over calcium chloride, and fractionated. After a rather large forerun at 60–90°/14 mm, benzyl phenyl sulfide (2.4 g, 55%) is obtained at 145–155°/14 mm.

Sulfinic acids are formed by reaction of sulfur dioxide[498] or sulfuryl chloride[499] with Grignard compounds, but yields rarely exceed 60%. Side reactions that may occur can be repressed by passing in the sulfur dioxide at temperatures below 0° and by not using an excess thereof.

$$2RMgBr + 2SO_2 \longrightarrow 2RSO_2MgBr \longrightarrow (RSO_2)_2Mg + MgBr_2$$

General directions for preparation of sulfinic acids:[498,500] Sulfur dioxide is led into a well cooled ethereal solution of the alkylmagnesium halide until no more precipitation occurs. After removal of the ether, the white crystalline residue of the magnesium sulfinate can be recrystallized directly from water, and the magnesium salts of ethane-, propane-, butane-, isopentane-, cyclohexane-, and benzene-sulfinite were prepared in this way; magnesium 1-dodecanesulfinite[501] was prepared at −35° to −40°.

For preparation of the free sulfinic acids[498] the magnesium sulfinite is suspended in a little water and treated under good cooling with concentrated hydrochloric or sulfuric acid. The oil that separates is taken up in ether, the sulfinic acid is removed from the ether by sodium carbonate solution, liberated again by acid, and taken up again in ether. Finally the ether is removed in a current of air at a low temperature.

Other examples of the preparation of sulfinic acids have been described by Allen,[502] Houben and Doescher,[503] and, in a general review, by Truce and Murphy.[467]

In some cases it proved possible to convert sulfoxides into sulfonium salts by the action of arylmagnesium bromides:[504]

$$(C_6H_5)_2SO + ArMgBr \longrightarrow [(C_6H_5)_2SAr]^+[OMgBr]^- \xrightarrow{2HBr}$$
$$[(C_6H_5)_2SAr]^+Br^- + MgBr_2 + H_2O$$

A reaction of Grignard compounds with carbonyl sulfide can be used to obtain thiocarboxylic acids,[505] which can be isolated in about 70% yield alongside the alcohols:

$$RMgX + COS \longrightarrow RCO{-}S{-}MgX \xrightarrow{H_2O} RCOSH + HOMgX$$

Thiopropionic, thiobenzoic, and thio-*p*- and thio-*o*-toluic acid have been synthesized by this process.

Carbon disulfide gives dithiocarboxylic acids when treated with Grignard compounds,[503,506] but, although the reaction is generally applicable, yields

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[498] J. von Braun and K. Weissbach, *Ber. Deut. Chem. Ges.*, **63**, 2838 (1939).

[499] B. Oddo, *Gazz. Chim. Ital.*, **35**, II, 136 (1905).

[500] A. Rosenheim and L. Singer, *Ber. Deut. Chem. Ges.*, **37**, 2152 (1904).

[501] C. S. Marvel and R. S. Johnson, *J. Org. Chem.*, **13**, 824 (1948).

[502] P. Allen Jr., *J. Org. Chem.*, **7**, 23 (1942).

[503] J. Houben and H. Doescher, *Ber. Deut. Chem. Ges.*, **39**, 3503 (1906).

[504] B. S. Wildi, S. W. Taylor, and H. A. Potratz, *J. Amer. Chem. Soc.*, **73**, 1965 (1951).

[505] F. Weigert, *Ber. Deut. Chem. Ges.*, **36**, 1007 (1903).

[506] J. Houben and co-workers, *Ber. Deut. Chem. Ges.*, **35**, 3695 (1902); **40**, 1303, 1725 (1907).

are better in the aromatic than in other series. Finally, *O*-esters of thiocarboxylic acids can be prepared from Grignard compounds and *O*-esters of chloro(thioformic acid):[507]

$$\text{RMgX} + \text{ClCS—OR}' \longrightarrow \text{RCS—OR}' + \text{MgXCl}$$

and thioamides can be prepared by the action of Grignard reagents on isothiocyanates:[508-510]

$$\text{RNCS} + \text{R}'\text{MgX} \longrightarrow \text{RN=CR}'\text{—SMgX} \longrightarrow \text{RN=CR}'\text{SH} \longrightarrow \text{R}'\text{CSNHR}$$

The latter reaction affords over 90% yields if the Grignard reagent is used in 50% excess.

***N*-Cyclohexylthiobenzamide:**[509] Cyclohexyl isothiocyanate (10.89 g, 0.077 mole) in ether (50 ml) is added with stirring to phenylmagnesium bromide (0.08 mole) in ether (200 ml) at 5°. Stirring is continued for a further hour at 5°, then the solution is allowed to warm gradually to room temperature and poured on ice. The mixture is acidified and the ethereal layer is dried over sodium sulfate and evaporated. The solid residue (15 g, 88%) is recrystallized several times from light petroleum, then melting at 90–92°.

2. Reactions of other organometallic compounds

Addition to the C–S double bond of isothiocyanates, for the preparation of thioamides, is not limited to Grignard reagents but is general for organometallic compounds;[511,512] there have been descriptions, in particular, of the reaction of isothiocyanates with phenylsodium and phenyllithium,[513] and with the sodium salts of acetoacetic ester,[514] acetylacetone (2,4-pentanedione),[515] and malonic ester.[516] The reaction is so smooth that it can be used for detection of organoalkali compounds.[517] For the preparation of sulfinic acids from sulfur dioxide and organometallic compounds, organolithium[518] and organosodium compounds[519] are especially suitable.

Finally, the reaction of phenyllithium with elemental sulfur to give thiophenol,[520] and the preparation of (alkylthio)acetylenes from lithium acetylides and disulfides, should be mentioned.[521]

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[507] M. Delépine, *C. R. Hebd. Séances Acad. Sci.*, **153**, 279 (1911); *Bull. Soc. Chim. France*, [iv], **9**, 904 (1911).

[508] D. E. Worrall, *J. Amer. Chem. Soc.*, **47**, 2974 (1925).

[509] G. Allinger, G. E. P. Smith Jr., E. L. Carr, and H. P. Stevens, *J. Org. Chem.*, **14**, 962 (1949).

[510] R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 54 (1961).

[511] W. Schlenk and E. Bergmann, *Ann. Chem.*, **463**, 1 (1928).

[512] W. Schlenk, H. Hillemann, and I. Rudloff, *Ann. Chem.*, **487**, 135 (1931).

[513] H. Gilman and F. Breuer, *J. Amer. Chem. Soc.*, **55**, 1262 (1933).

[514] D. E. Worral, *J. Amer. Chem. Soc.*, **40**, 415 (1918).

[515] D. E. Worral, *J. Amer. Chem. Soc.*, **42**, 1055 (1920).

[516] D. E. Worral, *J. Amer. Chem. Soc.*, **50**, 1456 (1928).

[517] Cf. A. A. Morton, A. R. Olson, and J. W. Blattenberger, *J. Amer. Chem. Soc.*, **63**, 314 (1941).

[518] W. E. Truce and J. F. Lyons, *J. Amer. Chem. Soc.*, **73**, 126 (1951).

[519] W. Schlenk and R. Ochs, *Ber. Deut. Chem. Ges.*, **49**, 613 (1916).

[520] H. Gilman and L. Fullhart, *J. Amer. Chem. Soc.*, **71**, 1480 (1949).

[521] J. R. Novi and J. F. Arens, *Rec. Trav. Chim.*, **80**, 244 (1961).

8.3. Preparation of organic sulfur compounds by alteration of sulfur groups

Methods for the preparation of organic sulfur compounds by alteration of sulfur-containing groups already present include reduction, oxidation, and cleavage. The preparation of thiocarbonic acid and its derivatives is treated at the end of the present Chapter. For the rearrangement of sulfur compounds see the Section on p. 1074.

I. Reduction of sulfur groups

Reduction is a possible reaction of almost all sulfur-containing organic compounds. According to the conditions used it leads either to thiols or to disulfides. For these purposes importance attaches primarily to reduction of aromatic sulfonyl chlorides and hydrogenating cleavage of disulfides.

Aromatic sulfonyl chlorides can be converted into thiophenols by many types of reducing agent, but most simply by zinc dust in hydrochloric or sulfuric acid, yields being mostly very good.[522] Preparatively the most rewarding process is their reduction in boiling glacial acetic acid by red phosphorus in the presence of catalytic amounts of iodine.[523]

General directions for the preparation of thiophenols: Glacial acetic acid (1 l), red phosphorus (250 g, 8 moles), and iodine (12 g, 95 mmoles) are heated to the boiling point on an oil-bath in a three-necked flask (2 l) fitted with a reflux condenser, stirrer, and dropping funnel (or, for solid sulfonyl chlorides, an air-condenser). The sulfonyl chloride (0.1 mole) is then dropped in portionwise or added through the air condenser. Reaction starts with ebullition of the solution and evolution of iodine vapors, and the heating bath is then removed. The remainder of the sulfonyl chloride (3.3 moles) is then added at a rate such that the mixture boils but no iodine vapor escapes through the reflux condenser. When addition is complete, the mixture is boiled for a further 2–3 h, then treated cautiously with water (1800 ml), boiled for a further hour, and finally, distilled in steam. Liquid thiophenols constituting the organic phase of the distillate are taken up in chloroform, dried over sodium sulfate, recovered by evaporation of the chloroform, and fractionated in a vacuum. Solid thiophenols are filtered off from the distillate and recrystallized from aqueous methanol. Thus have been prepared **thiophenol** (91%), **thio-*p*-cresol** (90%), ***p*-chloro-** (91%) and ***p*-methoxy-thiophenol** (63%), and **thio-2-naphthol** (89%).

Other reducing agents proposed are tin (for the preparation of *p*-chlorothiophenol,[524] tin(II) chloride (for the preparation of 4,4′-biphenyldithiol),[525] iron powder (for the preparation of *o*- and *p*-thiocresol),[526] and lithium tetrahydroaluminate (for the preparation of 1-butanethiol).[527]

Sulfonyl chlorides can also be reduced by one hour's heating with a 1.5-fold amount of aluminum amalgam[528] in alcoholic-ethereal solution and subsequent gradual dilution with water.[529] 2,5-Dichlorothiophenol, thio-2-

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[522] E. Bourgeois, *Ber. Deut. Chem. Ges.*, **28**, 2319 (1895); *Rec. Trav. Chim.*, **18**, 432 (1899); R. Adams and C. S. Marvel, *Org. Syn.*, Coll. Vol. I, 505 (1937).

[523] A. W. Wagner, *Chem. Ber.*, **99**, 375 (1966).

[524] H. J. Backer and J. Kramer, *Rec. Trav. Chim.*, **53**, 1101 (1934).

[525] C. S. Marvel and P. D. Caesar, *J. Amer. Chem. Soc.*, **73**, 1097 (1951).

[526] E. Profft, *Chem. Tech.*, **5**, 239 (1953).

[527] C. S. Marvel and P. D. Caesar, *J. Amer. Chem. Soc.*, **72**, 1033 (1950).

[528] H. Wislicenus, *J. Prakt. Chem.*, [ii], **54**, 18 (1896).

[529] E. Gebauer–Fülnegg, *J. Amer. Chem. Soc.*, **49**, 1386 (1927).

naphthol, and *p*-(acetylamino)thiophenol have been obtained in 50–70% yield in this way.

Alkali sulfites have proved valuable for reduction of sulfonyl chlorides in the anthraquinone series.[530]

Conditions can be arranged so that reduction of sulfonyl chlorides stops at the sulfinic acid or disulfide stage.[531] This reaction has been used on a very wide scale for the preparation of sulfinic acids although account must always be taken of further reduction to thiols or disulfides.[532] The reducing agents have been metals, such as zinc in a neutral, basic aqueous, or alcoholic medium,[533–535] sodium amalgam in anhydrous ether or benzene,[536–538] magnesium in ether,[539] and iron or zinc in glacial acetic acid.[540]

2-Thiophenesulfinic acid:[541,542] 2-Thiophenesulfonyl chloride is dissolved in several parts of water and cooled whilst being treated gradually with zinc dust. When the odor of the sulfonyl chloride has disappeared the pasty mixture is filtered and the solid is washed free from zinc chloride by water. The residue consisting of zinc thiophenesulfinite and the excess of zinc dust is treated with sodium carbonate solution which converts the zinc salt into the sodium salt which is readily soluble in water. The solution is filtered, greatly concentrated on a water-bath, and acidified. The sulfinic acid is taken up in ether. On removal of the ether it is obtained as an oil that solidifies to needles, m.p. 67°, when kept in a vacuum over sulfuric acid.

Except when sensitive to alkali, aromatic sulfonyl chlorides are almost all reduced to sulfinic acids by sodium sulfite in alcoholic or neutral aqueous solution, but best in aqueous solution made alkaline by sodium hydrogen carbonate:

$$RSO_2Cl + Na_2SO_3 + 2NaOH \longrightarrow RSO_2Na + NaCl + Na_2SO_4 + H_2O$$

General directions for reduction of sulfonyl chlorides to sulfinic acids:[543] A mixture of the sulfonyl chloride (20 g), sodium sulfite nonahydrate (50 g), and crushed ice (100 g) is shaken until the chloride has dissolved (about 3 h); the mixture is tested for alkalinity from time to time and dilute sodium hydroxide solution is added as necessary to prevent evolution of sulfur dioxide, whilst cooling by ice is maintained. Finally the mixture is filtered and the sulfinic acid is precipitated from the filtrate by gradual addition of concentrated hydrochloric acid. Yields average 80–90%.

Benzene-, toluene-, and halobenzene-sulfinic acids, as well as sulfinobenzoic acids, amongst others, have been prepared by this procedure.

Of the many other reducing agents applicable for preparation of sulfinic acids mention may be made of tin(II) chloride,[544] alkali sulfides,[545,546] alkali

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[530] Ger. Pat. 292,457; *Chem. Abstr.*, **11**, 1554 (1917).
[531] W. A. Sheppard, *Org. Syn.*, **40**, 80 (1960).
[532] W. E. Truce and A. M. Murphy, *Chem. Rev.*, **48**, 69 (1951).
[533] M. Bazlen, *Ber. Deut. Chem. Ges.*, **60**, 1470 (1927).
[534] C. Pauly, *Ber. Deut. Chem. Ges.*, **9**, 1595 (1876).
[535] F. C. Whitmore and F. H. Hamilton, *Org. Syn.*, Coll. Vol. I, 493 (1937).
[536] R. Otto, *Ann. Chem.*, **143**, 207 (1867).
[537] R. Otto and O. von Gruber, *Ann. Chem.*, **142**, 93 (1867).
[538] S. Gabriel and A. Deutsch, *Ber. Deut. Chem. Ges.*, **13**, 388 (1880).
[539] H. Gilman and R. E. Fothergill, *J. Amer. Chem. Soc.*, **50**, 804 (1928).
[540] W. Kalle, *Ann. Chem.*, **119**, 160 (1861).
[541] L. Weitz, *Ber. Deut. Chem. Ges.*, **17**, 800 (1884).
[542] A. Biedermann, *Ber. Deut. Chem. Ges.*, **19**, 1616 (1886).
[543] S. Krishna and H. Sing, *J. Amer. Chem. Soc.*, **50**, 794 (1928).
[544] M. Claasz, *Ann. Chem.*, **380**, 314 (1911).
[545] Ger. Pat. 224,019; *Chem. Abstr.*, **4**, 3282 (1910).
[546] Ger. Pat. 263,340; *Chem. Abstr.*, **7**, 4048 (1913).

arsenites,[547] thiophenoxides,[548] and organometallic compounds such as those of zinc,[549] lead,[550] and magnesium.[551]

Also sulfinic acids can be reduced to thiols and disulfides, preferably by zinc and acid.[552–554]

General directions for reduction of sulfinic acids to thiols:[461] The crude sulfinic acid is dissolved in water, four to five parts of zinc dust are added, and steam is passed through the mixture while 30% sulfuric acid (somewhat more than equivalent to the zinc) is added gradually. The thiol distilling in the steam is taken up in ether, dried over sodium sulfate, recovered, and fractionated.

Alkyl- and alkoxy-thiophenols and mercaptobenzoic acids have been obtained in this way.

Disulfides are obtained from sulfinic acids on reduction by hydrogen bromide in acetic acid solution:[553,555–557]

$$2RSO_2H + 6HBr \longrightarrow RSSR + 4H_2O + 3Br_2$$

Finally, thiols are also obtained by reductive fission of sulfides by sodium in liquid ammonia,[558] or by reduction of disulfides, the latter being generally applicable. Since sensitivity to oxidation is typical of thiols, the formation of disulfides cannot be avoided during the customary syntheses of thiols, and a wide variety of reducing agents has been studied for reversal of this reaction; reagents recommended include zinc in glacial acetic acid for preparation of *o*-mercaptobenzoic acid,[454] zinc in hydrochloric acid for *p*-bromothiophenol,[559] metallic sodium in ether for the lower alkanethiols,[560] sodium in liquid ammonia for cysteine,[561] lithium tetrahydroaluminate in ether or tetrahydrofuran for butane-, pentane-, benzene-, α-toluene-, and dodecane-thiol,[562] and finally potassium sulfide for various alkane- and arenethiols.[563]

2-Mercaptoethanol:[564] 2,2′-Dithiodiethanol is dissolved in alcohol and treated with an excess of somewhat diluted sulfuric acid. Zinc dust is added gradually and the mixture is kept overnight at about 40°. After filtration the mineral acid is neutralized with sodium carbonate and, after filtration again, the product is fractionated in a vacuum; it boils at 61°/18 mm.

1-Butanethiol:[565] Metallic sodium (1.25 g) and dibutyl disulfide (5 g) are added to dry xylene (100 ml). After 12 hours' heating on a steam-bath the sodium thiolate is filtered off and washed with ether.

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[547] A. Gutmann, *Ber. Deut. Chem. Ges.*, **42**, 480 (1909).

[548] R. Otto, *Ber. Deut. Chem. Ges.*, **24**, 713 (1891).

[549] W. Kalle, *Ann. Chem.*, **119**, 158, 161 (1861).

[550] R. Schiller and R. Otto, *Ber. Deut. Chem. Ges.*, **9**, 1636, 1637 (1876).

[551] H. Burton and W. A. Davy, *J. Chem. Soc.*, **1948**, 529.

[552] K. Fries and W. Vogt, *Ann. Chem.*, **381**, 331 (1911).

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[554] W. B. Price and S. Smiles, *J. Chem. Soc.*, **1928**, 2372.

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[556] K. Fries and E. Engelbertz, *Ann. Chem.*, **407**, 217 (1915).

[557] K. Fries, H. Koch, and H. Stukenbrock, *Ann. Chem.*, **468**, 177 (1929).

[558] F. E. Williams and E. Gebauer-Fülnegg, *J. Amer. Chem. Soc.*, **53**, 353 (1931).

[559] E. Bourgeois and A. Abrahàm, *Rec. Trav. Chim.*, **30**, 407 (1911).

[560] C. G. Moses and E. E. Reid, *J. Amer. Chem. Soc.*, **48**, 776 (1926).

[561] V. du Vigneaud, L. F. Audrieth, and H. S. Loring, *J. Amer. Chem. Soc.*, **52**, 4500 (1930).

[562] R. C. Arnold, A. P. Lien, and R. M. Alm, *J. Amer. Chem. Soc.*, **72**, 731 (1950); F. O. Bobbio and P. A. Bobbio, *Chem. Ber.*, **98**, 998 (1965).

[563] R. Otto and A. Rössing, *Ber. Deut. Chem. Ges.*, **19**, 3129 (1886).

[564] E. Fromm and H. Jörg, *Ber. Deut. Chem. Ges.*, **58**, 305 (1925).

[565] R. E. Stutz and R. L. Shriner, *J. Amer. Chem. Soc.*, **55**, 1244 (1933).

o-Nitrothiophenol:[566] Finely powdered bis-(*o*-nitrophenyl) disulfide (30 g) is heated to the boiling point in ethanol (100 ml) and treated gradually with an aqueous solution of sodium hydrogen sulfide (from 2.2–2.5 g of sodium hydroxide and hydrogen sulfide) and sodium hydroxide (8 g). After a short time all the disulfide is dissolved and the solution is brown. The mixture is diluted with water, and the *o*-nitrothiophenol can be precipitated by hydrochloric acid.

Cysteine hydrochloride:[567] Tin foil is added to a solution of cystine in hydrochloric acid, the metal at first dissolving without evolution of hydrogen. When gas evolution becomes prominent the mixture is diluted and the tin is precipitated by hydrogen sulfide. The filtrate therefrom is evaporated to dryness.

Sulfoxides can be reduced to sulfides by triphenylphosphine in boiling carbon tetrachloride, yields usually exceeding 80%.[568]

General directions for reduction of sulfoxides to sulfides: A mixture of the sulfoxide (0.01 mole) and triphenylphosphine (0.02 mole) in carbon tetrachloride (100 ml) is boiled for 2 h, then evaporated. The sulfide is obtained from the residue either by extraction with light petroleum (b.p. 35–37°) or by recrystallization from ethanol (in which the triphenylphosphine is readily soluble).

Thus have been obtained, *inter alia*, **dimethyl** (82%), **di-*p*-tolyl** (100%), **bis-(*p*-hydroxyphenyl)** (27%), **bis-(*p*-methoxyphenyl)** (90%), **bis-(*p*-bromophenyl)** (94%), and **bis-(*p*-nitrophenyl) sulfide** (83%).

II. Oxidation of sulfur groups

1. Oxidation of thiols

Disulfides, which are in the redox equilibrium:

$$\mathrm{RSSR} + 2\mathrm{H} \rightleftarrows 2\mathrm{RSH}$$

can usually be obtained very easily from the thiols. The choice of oxidant depends on the ease of oxidation, which increases from tertiary through secondary and then primary aliphatic thiols to thiophenols.[10] If the oxidant is too powerful the reaction can proceed through the disulfide stage to yield sulfonic acids. Suitable oxidants are atmospheric oxygen (2,2′-dithiodiacetophenone[569,570]), preferably in aqueous-ammoniacal solution, hydrogen peroxide [bis-(*o*-cinnamoylaminophenyl) disulfide,[571] dihexadecyl disulfide[572]], iodine [α,α'-dithiodi(styrenecarboxylic acid)[573]], hypohalites (lower dialkyl disulfides[286]), iron(III) chloride [4,4′-dithiobis-(1-naphthoic acid)[574]], potassium hexacyanoferrate(III) [bis-(2-cyanobenzyl) disulfide[575]], and dimethyl sulfoxide.[576,577]

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[566] K. Brand, *Ber. Deut. Chem. Ges.*, **42**, 3465 (1909).
[567] E. Baumann, *Z. Physiol. Chem.*, **8**, 300 (1884).
[568] J. P. A. Castrillón and H. H. Szmant, *J. Org. Chem.*, **30**, 1338 (1965).
[569] Ger. Pat. 198,509; *Chem. Abstr.*, **2**, 2629 (1908).
[570] Ger. Pat. 565,967; *Chem. Abstr.*, **27**, 2538 (1933).
[571] W. H. Mills and J. B. Whitworth, *J. Chem. Soc.*, **1927**, 2747.
[572] J. E. Hesse and F. K. Truby, *Chem. & Ind. (London)*, **1965**, 680.
[573] A. Schöberl and H. Eck, *Ann. Chem.*, **522**, 97 (1936).
[574] T. Zincke and J. Ruppersberg, *Ber. Deut. Chem. Ges.*, **48**, 120 (1915).
[575] A. W. Day and S. Gabriel, *Ber. Deut. Chem. Ges.*, **23**, 2478 (1890).
[576] C. N. Yinnios and J. V. Karabinos, *J. Org. Chem.*, **28**, 3246 (1963).
[577] T. J. Wallace, *Chem. & Ind. (London)*, **1964**, 501.

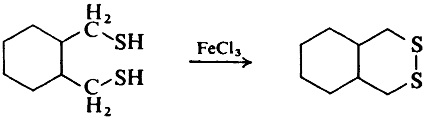
General method for oxidation of thiols to disulfides:[576] The thiol (0.1 mole) is dissolved in dimethyl sulfoxide (50 ml) and stirred at 80–90° for 8 h. Then charcoal is added and the mixture is cooled, filtered, and stirred into 10 parts of ice-water. After 3 h the disulfide is isolated by filtration or extraction with ether, yields being 80–100%.

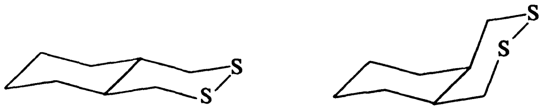
Bis-(4-cyanobenzyl) disulfide:[578] *p*-(Mercaptomethyl)benzonitrile (5 g) is dissolved in 95% ethanol (100 ml), treated with concentrated ammonia solution (25 ml), and exposed to the air for 4 days. The pale yellow needles that separate are recrystallized from 95% ethanol; the yield is 70.4% (3.5 g), and the m.p. 148°.

Bis-(*o*- and *p*-methoxy- and -ethoxy-phenyl) disulfide:[461] The alkoxythiophenol is dissolved in somewhat more than the calculated amount of 10% sodium hydroxide solution, and the theoretical amount of finely powdered iodine is added, whereupon the disulfide separates in crystalline form. After addition of a little sulfur dioxide solution the product is collected and recrystallized from ethanol.

Bis(benzothiazol-2-yl) disulfide:[579,580] A solution of benzothiazole-2-thiol in the calculated amount of dilute sodium hydroxide solution is treated with the calculated amount of aqueous potassium hexacyanoferrate(III) solution. The precipitated disulfide is collected, washed with water, and recrystallized from benzene, the m.p. then being 186°.

Cyclic disulfides are obtained from dithiols of suitable structure. Lüttringhaus and Hägele[581] used iron(III) chloride as oxidant for the preparation of 2,3-dihydro-1,2-benzodithiol and 1,2,3,4-tetrahydro-2,3-benzodithiin. *cis*- and *trans*-1,2-Cyclohexanedimethanethiol can be oxidized in the same way, yielding, respectively, *cis*- and *trans*-perhydro-2,3-benzodithiin (2,3-dithiadecalin), both of which exist in the preferred chair conformation:





trans *cis*

Perhydro-2,3-benzodithiin

***cis*- and *trans*-Perhydro-2,3-benzodithiin:**[582] *cis*- or *trans*-1,2-Cyclohexanedimethanol (1 g), dissolved in 1 : 1 methanol–glacial acetic acid (50 ml), is allowed to run slowly into a stirred solution of iron(III) chloride (2 g) in methanol (12 ml) and glacial acetic acid (5 g) and, after some time, is diluted with three times its volume of water; the oil that separates, milky at first but later clearing, solidifies to pale yellow needles when kept at 0°. Recrystallization from methanol gives the *cis*-product, m.p. 41.5°, in 71% yield or the *trans*-product, m.p. 56.5–57°, in 77.5% yield.

Thiols can be oxidized to sulfonic acids by stronger oxidizing agents. This method is generally applicable and has often been used for preparation of specific sulfonic acids. Nitric acid[583,584] or potassium permanganate[585]

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[578] C. Barkenbus, E. B. Friedman, and R. K. Flege, *J. Amer. Chem. Soc.*, **49**, 2552 (1927).

[579] P. Jakobson, *Ber. Deut. Chem. Ges.*, **21**, 2626 (1888).

[580] Ger. Pat. 613,300; *Chem. Abstr.*, **29**, 6251 (1935).

[581] A. Lüttringhaus and K. Hägele, *Angew. Chem.*, **67**, 304 (1955).

[582] A. Lüttringhaus and A. Brechlin, *Chem. Ber.*, **92**, 2271 (1959).

[583] D. L. Vivian and E. E. Reid, *J. Amer. Chem. Soc.*, **57**, 2559 (1935).

[584] E. Koenigs and G. Kinne, *Ber. Dem. Chem. Ges.*, **54**, 1357 (1921).

[585] B. Flaschenträger and G. Wannschaff, *Ber. Deut. Chem. Ges.*, **67**, 1121 (1934).

are suitable oxidizing agents for preparation of aliphatic sulfonic acids and of 4-pyridinesulfonic acid. **Benzothiazole-2-sulfonic acid** can be obtained in excellent yield from benzothiazole-2-thiol and alkaline hydrogen peroxide or hypochlorite solution.[586]

A solution of benzothiazole-2-thiol (8.4 parts) in dilute (40 g per l) sodium hydroxide solution (150 parts) is submitted to the action of hydrogen peroxide (6 parts) in concentrated aqueous solution; the sulfonic acid formed can be salted out by sodium chloride.

Oxidation of lead[587] or barium[583] thiolates often gives good yields of sulfonic acids.

Disulfides can be oxidized specifically to sulfinic esters in about 70% yields by lead tetraacetate in chloroform-methanol solution.[588]

2. Oxidation of disulfides

Disulfides can be oxidized to sulfonic acids in the same way as thiols:[589-593]

$$2RSSR + 5O_2 + 2H_2O \longrightarrow 4RSO_3H$$

In laboratory work the oxidation of disulfides has been applied particularly to the preparation of thiosulfinic and thiosulfonic esters:

$$RSSR \xrightarrow{\text{Peracids}} RS(O)\text{—}SR \qquad \text{Thiosulfinic esters}$$

$$RSSR \xrightarrow{H_2O_2} RS(O)_2\text{—}SR \qquad \text{Thiosulfonic esters}$$

Oxidation to thiosulfinic esters is best effected by an equivalent amount of perbenzoic acid or peracetic acid in chloroform,[594] and the preparation of thiosulfonic esters by a slight excess of hydrogen peroxide in acetic acid or by chlorine in the presence of glacial acetic acid with subsequent treatment by water.[595-597]

3. Oxidation of sulfides

Oxidation of sulfides gives sulfoxides or sulfones according to the strength of the reagent:

$$R_2S \longrightarrow R_2SO \longrightarrow R_2SO_2$$

Preparation of sulfoxides can be achieved by use of various oxidants: diphenyl,[898] dibenzyl,[596] bis-(4-acetylaminophenyl),[596] and diethyl sulf-

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[586] Ger. Pat. 615,132; *Chem. Abstr.*, **29**, 6251 (1935).

[587] J. W. McBain and R. C. Williams, *J. Amer. Chem. Soc.*, **55**, 2250 (1933).

[588] L. Field, C. B. Hoelzel, J. M. Locke, and J. E. Lawson, *J. Amer. Chem. Soc.*, **83**, 1256 (1961); **84**, 847 (1962).

[589] W. A. Proell, C. E. Adams, and B. H. Shoemaker. *Ind. Eng. Chem.*, **40**, 1129 (1948).

[590] U.S. Pat. 2,489,318; *Chem. Abstr.*, **44**, 1528 (1950).

[591] W. T. Caldwell and A. N. Sayin, *J. Amer. Chem. Soc.*, **73**, 5127 (1951).

[592] F. Fichter and W. Wenk, *Ber. Deut. Chem. Ges.*, **45**, 1373 (1912).

[593] T. H. Chao and W. B. Hardy, *Chem. & Ind.* (*London*), **1965**, 81.

[594] L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Amer. Chem. Soc.*, **69**, 1710 (1947).

[595] L. Field and T. F. Parsons, *J. Org. Chem.*, **30**, 657 (1965).

[596] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **41**, 2836, 4294 (1908); cf. J. Cymerman-Craig and J. B. Willis, *J. Chem. Soc.*, **1951**, 1332.

[597] G. Leandri and A. Tundo, *Ann. Chim.* (*Rome*), **44**, 63 (1954).

[598] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **43**, 289 (1910).

oxide,[599] amongst others, have been obtained by use of the calculated amount of hydrogen peroxide in glacial acetic acid or acetone.

Benzyl phenyl sulfoxide:[600] Benzyl phenyl sulfide (52 g) is dissolved in acetone (250 ml), filtered, and treated with 30% hydrogen peroxide (40 g), then thoroughly shaken and set aside for 72 h. The acetone is evaporated and the residue is caused to crystallize by moderate cooling and then recrystallized (yield 40 g; m.p. 122–123°) from 60% ethanol.

Dicyclopentyl sulfoxide:[601] Dicyclopentyl sulfide (3.4 g) is dissolved in glacial acetic acid (30 ml), treated with 100% hydrogen peroxide (2.5 g), and heated on a water-bath for 3 h, then the acetic acid is removed in a vacuum. Recrystallization of the crystalline residue affords the sulfoxide, m.p. 71.5°.

The more important of the other oxidizing agents reported for the preparation of sulfoxides are peracids[602,603] (in equivalent amounts), sodium metaperiodate,[604] chromic acid in glacial acetic acid,[605] and nitric acid.[606]

General directions for oxidation of sulfides to sulfoxides:[604] A mixture of a 0.5M-solution (210 ml, 0.105 mole) of sodium metaperiodate in water and of the sulfide (0.1 mole) is stirred at 0° for 12 h. The precipitated sodium iodate is filtered off and the solution is extracted with chloroform. The chloroform is removed in a vacuum and the residual product is purified by distillation, crystallization, or sublimation. Yields of sulfoxide are about 90%.

The action of stronger oxidizing agents on sulfides leads to sulfones, and in accord with the reaction scheme outlined above these can also be obtained by oxidation of sulfoxides. Oxidants used have been potassium permanganate, chromic acid, and nitric acid, as well as hydrogen peroxide, but the experimental conditions depend to a great extent on the nature of the sulfide in question and on the choice of oxidizing agent. Use of hydrogen peroxide has the advantage that no inorganic contaminant can be formed by the reaction, whereby isolation of the product is greatly simplified. Glacial acetic acid is usually preferred as solvent.

Diphenyl sulfone:[598] Diphenyl sulfide in glacial acetic acid is treated with an excess (about 2.5 equivalents) of hydrogen peroxide. After several day's storage at room temperature colorless crystals, m.p. 124°, begin to separate and the amount of them is increased by addition of water.

Other examples are the preparation of methyl *p*-nitrophenyl sulfone,[607] various alkyl tolyl sulfones, and 2-chloroethyl tolyl sulfone.[608]

Oxidation to sulfones can also be effected by peracids:[602,609]

Thus **dichloromethyl methyl sulfone** (2.02 g, 84%) is formed when dichloromethyl methyl sulfide (1.93 g) and monoperphthalic acid (6.3 g) are kept in ether (200 ml) for several days. The sulfone, m.p. 71–72.5°, is isolated by removal of the ether, extraction with chloroform, and final recrystallization from chloroform–light petroleum or benzene–cyclohexane.

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[599] R. Pummerer, *Ber. Deut. Chem. Ges.*, **43**, 1407 (1910).

[600] R. L. Shriner, H. C. Struck, and W. J. Jorison, *J. Amer. Chem. Soc.*, **52**, 2066 (1930).

[601] S. Loevenich, H. Utsch, P. Moldrickx, and E. Schaefer, *Ber. Deut. Chem. Ges.*, **62**, 3092 (1929).

[602] H. Böhme, *Ber. Deut. Chem. Ges.*, **70**, 379 (1937).

[603] L. N. Lewin and J. Tschulkoff, *J. Prakt. Chem.*, [ii], **128**, 171 (1930).

[604] N. J. Leonard and C. R. Johnson, *J. Amer. Chem. Soc.*, **84**, 3701 (1962); *J. Org. Chem.*, **27**, 282 (1962).

[605] F. Mayer, *Ber. Deut. Chem. Ges.*, **43**, 584 (1910).

[606] L. Gattermann, *Ann. Chem.*, **393**, 140 (1912).

[607] T. Zincke, *Ann. Chem.*, **400**, 16 (1913).

[608] H. Gilman and N. J. Beaber, *J. Amer. Chem. Soc.*, **47**, 1449 (1925).

[609] H. Richtzenhain and B. Alfredson, *Chem. Ber.*, **86**, 142 (1953).

Oxidation by potassium permanganate is usually carried out in acetic or sulfuric acid solution. Isolation of the sulfone must include separation from the precipitate of manganese(IV) oxide hydrate, which, in the case of sparingly soluble sulfones, is effected by reduction of this precipitate by just sufficient sodium hydrogen sulfite solution or by sulfur dioxide; soluble sulfones can be isolated by addition of water after filtration from the hydrated manganese oxide or by acidification and extraction with ether.

Ethyl 2,2-bis(ethylsulfonyl)propionate:[610]

$$CH_3C(SO_2C_2H_5)_2COOC_2H_5$$

Ethyl pyruvate diethyl mercaptol [2,2-bis(ethylthio)propionate] is shaken with an excess of cold permanganate solution after several additions of dilute sulfuric acid. The liquid is then decolorized by passing in sulfur dioxide, and the sulfone, part of which is precipitated, is extracted with ether. If the substance isolated is not solid the oxidation must be repeated. After recrystallization from 50% ethanol the disulfone melts at 60–62°.

Bost and his co-workers[611] have reported a generally applicable procedure for the preparation of alkyl 2,4-dinitrophenyl sulfones by use of potassium permanganate in glacial acetic acid.

Alkyl and aryl *p*-nitrophenyl sulfones have been obtained in yields averaging 80% by oxidizing the appropriate sulfides with chromic acid in glacial acetic acid[612] according to the following general directions:

A solution of the sulfide (10 g) in 80% acetic acid (100 ml) is heated to the boiling point and treated with a saturated aqueous chromic acid solution until an orange color indicates presence of an excess of the oxidant. The mixture is boiled for a further 15 min, then treated with an equal volume of water and cooled. The sulfone is recrystallized from 50% acetic acid.

Application of nitric acid as oxidizing agent for this purpose is restricted mainly to aliphatic sulfides because of possible nitration.[613]

Suter[152a] and Barnard and his co-workers[614] have both reviewed the preparation of sulfones by oxidation of sulfides.

4. Oxidative halogenation of sulfur compounds; sulfonyl chlorides

Various organic compounds of bivalent sulfur, such as sulfides, disulfides, xanthates, and thiouronium salts, can be converted into sulfonyl chlorides by chlorine. Haloalkanesulfonyl chlorides are obtained from cyclic sulfides in this way, for example, 1-chloro-2-propanesulfonyl chloride from methylthiirane.[615]

Higher α-chlorinated sulfonyl chlorides[616] can be prepared in good yield by saturating aldehydes with hydrogen sulfide and treating the product with chlorine in the presence of water.

Lee and Dougherty[617] have reported the oxidative chlorination of dialkyl and bis(arylalkyl) sulfides.

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[610] T. Posner, *Ber. Deut. Chem. Ges.*, **32**, 2801 (1899).

[611] R. W. Bost, J. O. Turner, and R. D. Norton, *J. Amer. Chem. Soc.*, **54**, 1986 (1932).

[612] W. R. Waldron and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 2399 (1923).

[613] D. W. Goheen and C. F. Bennet, *J. Org. Chem.*, **26**, 1331 (1961).

[614] D. Barnard, L. Bateman, and J. I. Cunneen in N. Kharasch, "Organic Sulfur Compounds," Pergamon Press, Oxford–London–New York–Paris, 1961, Vol. 1, p. 229.

[615] J. M. Stewart and H. P. Cordts, *J. Amer. Chem. Soc.*, **74**, 5880 (1952).

[616] Ger. Pat. 836,492; *Chem. Abstr.*, **47**, 4896 (1953).

[617] S. W. Lee and G. Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

This reaction of sulfides, and also of disulfides, is carried out in the two- to five-fold volume of acetic acid that contains sufficient water to provide the necessary oxygen. Chlorine is led in until the product no longer decolorizes potassium permanganate solution. **1-Butanesulfonyl chloride** is obtained in this way in 80% yield from dibutyl sulfide, and **α-toluenesulfonyl chloride** from dibenzyl sulfide.

Other examples are the preparation of ethanesulfonyl and pentanesulfonyl chloride.

Further, alkyl thiocyanates[618] and thiosulfates[619] are converted into aliphatic sulfonyl chlorides by chlorination.

Ethanesulfonyl chloride:[618] A suspension of ethyl thiocyanate (20 g) in water (200 ml) is vigorously stirred while a stream of chlorine (2–3 l per h) is led in, the temperature being kept between 0° and 5°. Passage of chlorine is stopped when the mixture assumes a permanent green color which indicates presence of an excess of chlorine, and this excess is then removed in a slow stream of air. The oil that separates is taken up in ether, and that solution is washed with sodium bisulfite and sodium hydrogen carbonate solutions and dried over calcium chloride. Removal of the ether and distillation in a vacuum afford the sulfonyl chloride (79% yield), b.p. 71–72°/20 mm.

Studies by Johnson and Sprague[619,620] have shown that the action of chlorine or bromine on aqueous solutions of alkylthiouronium salts affords sulfonyl chlorides or bromides, respectively, and this process is particularly useful because isothiourea derivatives are very easily accessible from alkyl halides and thiourea (see page 692).

In the aromatic series disulfides are the preferred starting material for oxidative chlorination to sulfonyl halides:

$$\mathrm{RSSR + 5Cl_2 + 4H_2O \longrightarrow 2RSO_2Cl + 8HCl}$$

4-Methyl-2-nitrobenzenesulfonyl chloride:[621] Bis-(2-nitrotolyl) disulfide (2 g) is dissolved in glacial acetic acid (10 ml), water (2 ml) is added, and the solution is saturated with chlorine whilst being allowed to become warm. On cooling, part of the sulfonyl chloride separates as colorless crystals and the remainder is obtained by evaporation; for purification it is recrystallized from benzene–light petroleum, then having m.p. 98–99°.

The sulfonyl bromide,[622] m.p. 115°, is obtained similarly on treatment with bromine.

Chlorination has been carried out also in hydrochloric acid solution containing nitric acid, *e.g.*, for preparation of *o*-nitrobenzenesulfonyl chloride.[623] Also, thiophenols[624] and heterocyclic thiols[625] can be converted into sulfonyl chlorides by chlorination.

For instance, Zincke and Frohneberg[624] obtained ***p*-toluenesulfonyl chloride,** m.p. 69°, by passing chlorine to saturation into a solution of thio-*p*-cresol in 5 parts of glacial acetic acid, setting the mixture aside for a short time, and then evaporating it.

***p*-Toluenesulfonyl bromide,** prepared from thio-*p*-cresol (3 g), glacial acetic acid (15 g), and bromine (6 g), melts at 93–94° after recrystallization from a little light petroleum.

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[618] T. B. Johnson and I. B. Douglass, *J. Amer. Chem. Soc.*, **61**, 2548 (1939).

[619] C. Ziegler and J. M. Sprague, *J. Org. Chem.*, **16**, 621 (1951).

[620] T. B. Johnson and J. M. Sprague, *J. Amer. Chem. Soc.*, **58**, 1348 (1936); **59**, 1837, 2439 (1937); **61**, 176 (1939); see also K. Winterfeld and W. Häring, *Arch. Pharm.*, **295**, 615 (1962).

[621] T. Zincke and H. Röse, *Ann. Chem.*, **406**, 134 (1914).

[622] T. Zincke and H. Röse, *Ann. Chem.*, **406**, 108 (1914).

[623] E. Wertheim, *Org. Syn.*, Coll. Vol. II, 471 (1955).

[624] T. Zincke and W. Frohneberg, *Ber. Deut. Chem. Ges.*, **42**, 2728 (1909); **43**, 840 (1910).

[625] R. O. Roblin Jr. and J. W. Clapp, *J. Amer. Chem. Soc.*, **72**, 4890 (1950).

A simple method of preparing sulfinic esters consists of oxidative chlorination of aliphatic thiols, thiophenols, or disulfides with chlorine in glacial acetic acid, followed by alcoholysis of the resulting sulfinyl chlorides:[626]

$$\mathrm{RSSR + 2CH_3COOH + 3Cl_2 \longrightarrow 2RS(O)Cl + 2CH_3COCl + 2HCl}$$

$$\mathrm{RS(O)Cl + R'OH \longrightarrow RS(O)OR' + HCl}$$

Chloro(dimethyl)sulfonium salts are readily formed in 92% yield by the action of chlorine on the dimethyl sulfide–antimony chloride adduct[627] in methylene dichloride solution:

$$\mathrm{(CH_3)_2S \rightarrow SbCl_5 + Cl_2 \longrightarrow [(CH_3)_2SCl]^+SbCl_6^-}$$

The chlorine in this reaction may be equally well replaced by sulfuryl chloride or by an excess of the antimony pentachloride:

Chloro(dimethyl)sulfonium hexachloroantimonate:[627] A solution of dimethyl sulfide (5 g, 80.5 mmoles) in methylene dichloride (20 ml) is dropped, with stirring, during 35 min into a solution or suspension of antimony pentachloride (25 ml, 195 mmoles) in methylene dichloride (40 ml) that is cooled in a mixture of methanol and Dry Ice. The mixture is stirred in the cooling-bath for 24 h, then filtered, and the solid is washed with methylene dichloride (200 ml). The product (30.6 g, 88%) has m.p. 185–186° (dec.).

Chloro(dimethyl)sulfonium salts are extremely reactive, usually losing the chlorine as anion and thus able to transfer the dimethylsulfonium group readily to nucleophilic compounds such as alcohols, compounds containing acidic CH groups, organic sulfides, and disulfides.[627]

III. Cleavage of sulfur bonds

1. Cleavage of the C–S bond[628]

Fission of the C–S bond of thiols can occasionally be utilized for preparation of sulfides:

$$\mathrm{2RSH \longrightarrow RSR + H_2S}$$

The reaction occurs merely on heating, for instance with 2-mercaptoanthraquinones,[629] but better in the presence of substances that bind hydrogen sulfide; a mixed catalyst composed of cadmium sulfide, zinc sulfide, and aluminum oxide has been used.[630]

Thiiranes can be cleaved by alcohols in the presence of boron trifluoride and glacial acetic acid, yielding β-alkoxy thiols; and using thiols affords 2-(alkylthio)ethanethiols.[631] The general procedure is as follows:

A mixture of the thiol (0.11 mole) and boron trifluoride–ether (2 drops) are stirred and heated on a steam-bath while the sulfide (0.05 mole) is dropped in during about 45 min.

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[626] I. B. Douglass, *J. Org. Chem.*, **30**, 633 (1965).

[627] H. Meerwein, K.-F. Zenner, and R. Gipp, *Ann. Chem.*, **688**, 67 (1965).

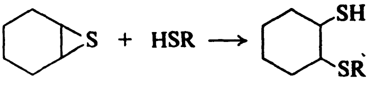
[628] D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).

[629] Ger. Pat. 254,561; *Chem. Abstr.*, **7**, 1618 (1913).

[630] P. J. Wiezevich, L. B. Turner, and P. K. Frohlich, *Ind. Eng. Chem.*, **25**, 295 (1933).

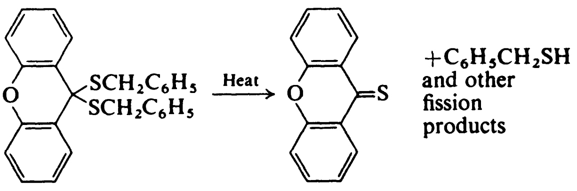
[631] H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2675 (1947).

The mixture is then heated for 2 h, after which it is extracted with ether. The extract is washed with water and with saturated sodium chloride solution, dried, and distilled under diminished pressure. The following **2-(alkylthio)cyclohexanethiols** have been obtained from 7-thiabicyclo[4.1.0]heptane (cyclohexene sulfide) and 1-alkanethiols: alkyl = butyl, b.p. 109–111°/2.5 mm; pentyl, b.p. 123–126°/3.5 mm; hexyl, b.p. 130–133°/3 mm; and heptyl, b.p. 141 to 144°/3 mm.



Carboxylic acids,[632] acid chlorides,[633] and amines[634] have also been used for cleavage of the C–S bond of cyclic sulfides.

The low thermal stability of mercaptols can be utilized for their thermal fission to yield thioketones:



9-Xanthenethione (0.5 g) has been obtained[635] from xanthone dibenzyl mercaptol[636] (4 g) by 15 minutes' heating at 205° in a vacuum, extraction of the residue with hot benzene (10 ml), and subsequent cooling of the extract; on recrystallization from benzene it melts at 156°.

The thermally unstable benzyl mercaptols of aromatic ketones undergo this fission particularly readily, yielding the thioketone and α-toluenethiol as well as a series of other decomposition products.[635] Purely aromatic mercaptols of the type $Ar_2C(SAr')_2$ also decompose when heated, but yield the corresponding disulfide and thioketone together with other, inhomogeneous decomposition products, as Schönberg and his co-workers have shown in extensive studies of the relation between the structure and the thermal stability of mercaptols.[329,635]

Monomeric aliphatic thioketones can be obtained by passing geminal dithiols $RR'S(SH)_2$ in an inert gas over sea-sand, clay tiles, kieselguhr, active charcoal, or other porous material at 150–200°/5–10 mm.[407] The thiones are formed in 60–96% in such high purity that in most cases they need not be distilled again before being used for further reactions.

Disulfides are formed, with elimination of the cyano group, when the C–S bond of thiocyanic esters is cleaved by alkali;[637–639] and sulfides are obtained,

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[632] C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, **1949**, 282.

[633] W. Davies and W. E. Savige, *J. Chem. Soc.*, **1950**, 317.

[634] H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947).

[635] A. Schönberg and O. Schütz, *Ber. Deut. Chem. Ges.*, **62**, 2322 (1929).

[636] A. Schönberg and O. Schütz, *Ann. Chem.*, **454**, 52 (1927).

[637] A. Maggiolo and G. H. Hitchings, *J. Amer. Chem. Soc.*, **73**, 4226, 5815 (1951).

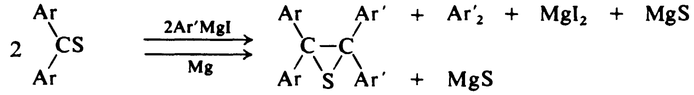
[638] P. A. S. Smith and T.-Y. Yu, *J. Org. Chem.*, **17**, 1281 (1952).

[639] P. W. Feit, *Acta Chem. Scand.*, **16**, 297 (1962).

with elimination of the cyanato group, when alcoholic potassium hydroxide is used;[640] but these reactions have little preparative value.

For formation of thiols and sulfides on fission of the C–S bond of thiocarbonic acid derivatives see pages 635 and 637.

Work by Schönberg and by Staudinger and their collaborators has shown that aromatic ketones can be converted into tetraarylthiiranes by the action of Grignard reagents[641] or of magnesium iodide in the presence of magnesium[642] as well as through diazo compounds:[643,644]



The following, amongst others, have been prepared by these methods: 2,2,3,3-tetrakis-(*p*-methoxyphenyl)-, tetraphenyl-, 2,2-bis(methoxyphenyl)-3,3-diphenyl-, and 2,2-diphenyl-3,3-bis-[*p*-(dimethylamino)phenyl]-thiirane.

Sulfinic acids can be prepared by alkaline fission of sulfones, best by alkoxides or thiolates;[645] for example, benzenesulfinic acid has been obtained in 72% yield from phenethyl phenyl sulfone[646] and in 79% yield from 2,4-dinitrophenyl phenyl sulfone:[647]

$$C_6H_5SO_2CH_2C_6H_5 + KOH \longrightarrow C_6H_5SO_2K + CH_2{=}CHC_6H_5 + H_2O$$

Many sulfones, *e.g.*, diaryl, alkyl aryl, and alkyl benzyl sulfones, but not dialkyl sulfones, are cleaved to sulfinates and compounds RH with surprising ease and under mild conditions and in good yield when treated with tetraalkylammonium generated from the tetramethylammonium ion on a mercury cathode.[648]

When chlorine reacts with diacyl disulfides it is not the disulfide link that is broken but a carbon–sulfur bond, and 1-acyl-2-disulfanes are formed:[649]

$$RCO{-}S{-}S{-}COR + Cl_2 \longrightarrow RCO{-}S{-}SCl + RCOCl$$

Diacyl monosulfides are cleaved analogously to acylsulfur chlorides, which with thiols form 1-acyl-2-alkyldisulfanes, whence alcoholysis affords alkyl-

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[640] R. K. Olsen and H. R. Snyder, *J. Org. Chem.*, **30**, 187 (1965).

[641] A. Schönberg, *Ann. Chem.*, **454**, 37 (1927).

[642] A. Schönberg and O. Schütz, *Ber. Deut. Chem. Ges.*, **60**, 2351 (1927).

[643] H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 833 (1920).

[644] Cf. H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920).

[645] W. E. Truce and F. E. Roberts, *J. Org. Chem.*, **28**, 593 (1963); see also F. Weygand and W. Steglich, *Chem. Ber.*, **98**, 487 (1965).

[646] G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, **1930**, 705.

[647] N. Kharasch and R. Swidler, *J. Org. Chem.*, **19**, 1706 (1954).

[648] L. Horner and H. Neumann, *Chem. Ber.*, **98**, 1715 (1965).

[649] H. Böhme and M. Clement, *Ann. Chem.*, **576**, 61 (1952).

disulfanes (alkyl hydrogen disulfides):[650]

$$(RCO)_2S \xrightarrow{Cl_2} RCO\text{—}SCl \xrightarrow{RSH} RCO\text{—}S\text{—}SR \longrightarrow HS\text{—}SR$$

Arenesulfenyl chlorides can be prepared by chlorinating cleavage of aryl benzyl sulfides by means of sulfuryl chloride,[651] and thiocarbonyl chlorides similarly from dithiocarboxylic acids and thionyl chloride.[652]

Preparative importance attaches to chlorinating cleavage of carbon disulfide, which leads to trichloromethanesulfenyl chloride (the so-called "perchloromethylmercaptan"); this is an important step in the preparation of thiophosgene.[653]

$$2CS_2 + 5Cl_2 \longrightarrow 2CCl_3\text{—}SCl + S_2Cl_2$$

Trichloromethanesulfenyl chloride:[654] Carbon disulfide (1.8 kg) containing a little (3 g) iodine is placed in a three-necked flask (4 l) fitted with a thermometer and with gas inlet and outlet tubes. Chlorine is led in while the temperature of the liquid is kept at 10–20° by external cooling in ice-water, being continued until a sample shows the solution to have a density of 1.61 (time required, 30–40 h; chlorine consumption about 3.5 kg). The resulting mixture of trichloromethanesulfenyl chloride and sulfur chlorides is separated by distillation through a Vigreux column; first, at normal pressure a forerun consisting of sulfur chlorides is obtained up to 100°; then, after evacuation to 12–13 mm, a small forerun, followed at 56–58° by pure trichloromethanesulfenyl chloride. Care must be taken during the vacuum-distillation that the connexions, and particularly the valve of the water-pump, do not become blocked by sulfur; it is helpful to place, between the pump and the distillation apparatus, a flask filled with water, which decomposes the evolving gases and thus prevents deposition of sulfur in the pump. Trichloromethanesulfenyl chloride (yield 2.6 kg, 60%) is a yellow to reddish-brown oil with a very unpleasant odor.

Since sulfonation of aromatic compounds is a reversible process, sulfonic acids can be cleaved to starting materials by hydrolysis. The differing ease of removal of sulfo groups from different compounds can be used for separations, *e.g.*, of *m*- from *o*- and *p*-xylene since *m*-xylenesulfonic acid is the most easily hydrolysed;[655] biphenyl homologs in coal-tar heavy oil can also be separated in this way.[656] Partial removal of sulfonic acid groups from polysulfonic acids is also possible, often merely by heating in acid solution.[657] Finally, removal of sulfonic acid groups has preparative interest when directed substitution is required or when it is desired to improve the mobility of an atom or group; for example, if a nitro group is to be introduced at a position other than that accessible by direct substitution, a sulfo group can be placed at the favored position, the nitro group being then introduced and the sulfo group finally removed hydrolytically; thus 2,6-dinitroaniline is obtained in 30–36% yield

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[650] H. Böhme and G. Zinner, *Ann. Chem.*, **585**, 142 (1954).

[651] N. Kharasch and R. B. Langford, *J. Org. Chem.*, **28**, 1903 (1963); *Org. Syn.*, **44**, 47 (1964).

[652] R. Mayer and S. Scheithauer, *Chem. Ber.*, **98**, 829 (1965).

[653] P. Klason, *Ber. Deut. Chem. Ges.*, **20**, 2376 (1887); G. Sosnovsky, *Chem. Rev.*, **58**, 509 (1958).

[654] G. M. Dyson, *Org. Syn.*, Coll. Vol. I, 507 (1937); P. Klason, *Ber. Deut. Chem. Ges.*, **28**, ref. 942 (1896); Ger. Pat. 83,124.

[655] N. Kizner and G. Vendelshtein, *Russ. Phys. Chem. Soc. Chem. Part*, **59**, 1 (1925); *Chem. Abstr.*, **20**, 2316 (1926).

[656] O. Kruber, *Ber. Deut. Chem. Ges.*, **65**, 1382 (1932).

[657] Brit. Pat. 285,488; *Chem. Abstr.*, **22**, 4540 (1928).

from chlorobenzene by successive sulfonation at the *para*-position, nitration, amination, and removal of the sulfo group.[658]

2. Cleavage of the S–H bond

Chlorination of thiophenols leads, with cleavage of the S–H bond, to arenesulfenyl chlorides,[659–661] the first example of the series having been prepared by Zincke as early as 1911:[662]

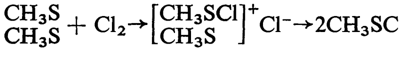
$$\mathrm{RSH} + \mathrm{Cl_2} \longrightarrow \mathrm{RSCl} + \mathrm{HCl}$$

According to investigations by Lecher and Holschneider,[663] the arenesulfenyl chloride that is first formed from the thiophenol reacts with unchanged thiol to give the disulfide, which in a third step undergoes chlorolysis to 2 moles of arenesulfenyl chloride. In general, electron-attracting substituents increase the stability of arenesulfenyl chlorides since they lower the electron density at the Cl–S bond and thus make removal of the chlorine atom more difficult. In such preparations it is important to exclude moisture, so as to avoid hydrolysis, and to work at low temperatures with shielding from light, so as to avoid *C*-halogenation.

General directions for preparation of sulfenyl chlorides:[664] The required thiophenol (0.1 mole) is added to anhydrous carbon tetrachloride (50 ml) in a three-necked flask fitted with a stirrer, dropping funnel, calcium chloride tube, and thermometer. Then a solution of chlorine (7.09 g, 0.01 mole) in anhydrous carbon tetrachloride (100 ml) is dropped in, with stirring, whilst the temperature is not allowed to rise above −1° (−12° for compounds having two methyl groups on an aromatic ring). Stirring is continued for a further 1 h, then the solvent is removed in a vacuum and the residue is distilled at reduced pressure. Yields are 80–90%.

Benzene-, halobenzene-, toluene-, xylene-, and halotoluene-sulfenyl chlorides have been obtained according to these instructions.

This synthesis of sulfenyl chlorides can also be used in the aliphatic series although here the limitation applies that most alkylsulfur halides are too unstable to be isolated from solution. In general, and also in the aromatic series, sulfenyl chlorides are easier to prepare than the bromides, whilst the iodides are known only in a few cases and the fluorides not at all. As an example, Schneider,[665] chlorinating methanethiol in anhydrous carbon tetrachloride at −15°, obtained dimethyl disulfide dichloride [chloro(methyl)(methylthio)-sulfonium chloride] which passed into methanesulfenyl chloride when allowed to warm slowly to room temperature:



$$\begin{matrix}\mathrm{CH_3S}\\ \mathrm{CH_3S}\end{matrix} + \mathrm{Cl_2} \rightarrow \begin{bmatrix}\mathrm{CH_3SCl}\\ \mathrm{CH_3S}\end{bmatrix}^{+}\mathrm{Cl^-} \rightarrow 2\mathrm{CH_3SCl}$$

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[658] H. P. Schultz, *Org. Syn.*, **31**, 45 (1951).

[659] N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946).

[660] M. B. Sparke, J. L. Cameron, and N. Kharasch, *J. Amer. Chem. Soc.*, **75**, 4907 (1953).

[661] W. E. Truce and M. F. Amos, *J. Amer. Chem. Soc.*, **73**, 3013 (1951).

[662] T. Zincke, *Ber. Deut. Chem. Ges.*, **44**, 769 (1911).

[663] H. Lecher and F. Holschneider, *Ber. Deut. Chem. Ges.*, **57**, 755 (1924).

[664] L. Almasi and A. Hantz, *Chem. Ber.*, **94**, 728 (1961).

[665] E. Schneider, *Chem. Ber.*, **84**, 911 (1951).

3. Cleavage of the S–S bond[666]

Cleavage of the S–S bond of disulfides has considerable preparative interest also for the preparation of sulfenyl chlorides. The details for general reaction conditions given in the preceding Section apply here also. The following examples will illustrate the procedure:

o-Nitrobenzenesulfenyl chloride:[662] Carbon tetrachloride (10 parts) is poured over bis-(*o*-nitrophenyl) disulfide and chlorine is passed in to saturation. Introduction of chlorine is repeated some hours later and the mixture is set aside in a closed flask. Yellow needles of the sulfenyl chloride separate after some time and are filtered off. When recrystallized from light petroleum they melt at 75°.

p-Nitro-,[667] m.p. 52°, and 4-methyl-2-nitro-benzenesulfenyl chloride,[668] m.p. 90°, were obtained in the same way.

For the preparation of **4-chloro-2-nitrobenzenesulfenyl bromide** Zincke[669] heated the corresponding disulfide in chloroform (10 parts) under reflux with somewhat more than the calculated amount of bromine until dissolution was complete. The solution was then allowed to cool and the precipitated bromide was recrystallized from light petroleum. The final m.p. was 111°.

The alkyl groups of aliphatic disulfides are chlorinated particularly easily by elemental chlorine. For example, although dimethyl disulfide affords methanesulfenyl chloride[670] at −15° to −20°, **chloromethanesulfenyl chloride** is formed even at 0°:

A slow stream of dry chlorine is led into dimethyl disulfide (23.6 g) at −15° to −20° until about 17 g have been taken up. Then more chlorine is introduced while the solution warms gradually to 0°, until a further 17 g are absorbed. After being kept for a short time at room temperature the product is distilled at about 40 mm; it has b.p. 50°/14 mm.

Chloromethanesulfenyl can also be obtained by chlorinating bis(chloromethyl) disulfide with chlorine or dimethyl disulfide with sulfuryl chloride. Sulfuryl chloride has also been used as chlorinating agent in the preparation of **1-chloroethanesulfenyl chloride:**[671]

Sulfuryl chloride (68 g) is dropped slowly into a stirred solution of diethyl disulfide (61.5 g) in carbon tetrachloride (150 ml) at −20°. More sulfuryl chloride (123 g) is added gradually at −15°, then the solution is warmed slowly to room temperature and set aside overnight. The carbon tetrachloride is then removed and the residue is distilled at 38°/27 mm. Repeated fractional distillation permits further amounts to be isolated from the forerun, the total yield being 90%.

2-Chloroethanesulfenyl chloride is obtained in 79% yield by the action of elemental chlorine on bis-(2-chloroethyl) disulfide.[672]

Thioanisole (methyl phenyl sulfide) and aromatic disulfides can be cleaved at the C–S bond by *N*-bromosuccinimide, whereby good yields af *N*-(arylthio)-

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[666] A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959); O. Foss in N. Kharasch, "Organic Sulfur Compounds," Pergamon Press, Oxford–London–New-York–Paris, 1961, Vol. 1, p. 83.

[667] T. Zincke, *Ann. Chem.*, **400**, 9 (1913).

[668] T. Zincke, *Ann. Chem.*, **406**, 110 (1914).

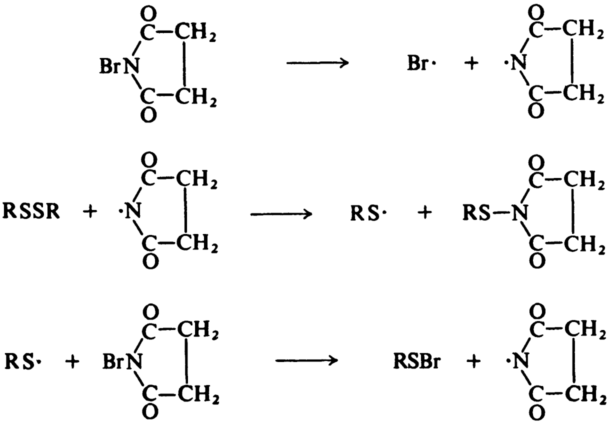
[669] T. Zincke, *Ann. Chem.*, **416**, 95 (1918).

[670] H. Brintzinger, K. Pfannstiel, H. Roddebusch, and K. E. Kling, *Chem. Ber.*, **83**, 89 (1950).

[671] H. Brintzinger and H. Ellwanger, *Chem. Ber.*, **87**, 307 (1954).

[672] R. C. Fuson and co-workers, *J. Org. Chem.*, **11**, 471 (1946).

succinimides (sulfenamides) are obtained.[673] The reaction proceeds through radical intermediates, according to the following mechanism:


(1)

N-(Arylthio)succinimides: The disulfide (0.025 mole) is dissolved in anhydrous carbon tetrachloride (25 ml), treated first with dibenzoyl peroxide (0.1 g) and then with N-bromosuccinimide (0.025 mole), with exclusion of moisture, and is finally boiled until the solution is clear. After cooling, the precipitate is collected, washed with a little carbon tetrachloride, and recrystallized from ethanol. The following products (**1**) were thus obtained (yields and m.p.s in parentheses) in which R was phenyl (94%, 116°), *p*-chlorophenyl (86%, 142.5–143.5°), *o*- (60%, 85.5–86°) and *p*-tolyl (62%, 113.5°), *o*-(methoxycarbonyl) (86%, 186–187°), and benzyl (74%, 162°).

In the presence of aromatic hydrocarbons, primary aliphatic disulfides are cleaved under Friedel–Crafts conditions to alkyl aryl sulfides:[674]

$$\mathrm{ArH + RSSR \xrightarrow[AlCl_3]{} ArSR + RSH}$$

Schönberg and his co-workers[675] obtained sulfides by cleaving disulfides with organo-lithium or -sodium compounds; *e.g.*, he obtained phenyl triphenylmethyl sulfide from diphenyl disulfide and (triphenylmethyl)sodium.

The thiocyanato group of sulfenyl thiocyanates can be removed by thiols, a reaction that leads to unsymmetrical disulfides:[676]

$$\mathrm{RSH \xrightarrow{(SCN)_2} RS{-}SCN \xrightarrow{R'SH} RSSR' + HSCN}$$

The preparation of sulfinic acids by fission of the S–S bond of thiosulfonic salts or esters is useful when other methods are excluded by the presence of sensitive substituents. Arenethiosulfonic acid salts, which are formed from arenesulfonyl chlorides and alkali sulfides:

$$\mathrm{RSO_2Cl + Na_2S \longrightarrow RSO_2SNa + NaCl}$$

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[673] W. Groebel, *Chem. Ber.*, **92**, 2887 (1959); **93**, 284 (1960).

[674] H. Behringer and K. Kuchinka, *Angew. Chem.*, **72**, 348 (1960).

[675] A. Schönberg, A. Stephenson, H. Kaltschmitt, E. Petersen, and H. Schulten, *Ber. Deut. Chem. Ges.*, **66**, 237 (1933).

[676] R. G. Hiskey and co-workers, *J. Org. Chem.*, **26**, 1152 (1961).

can be cleaved by acid[677] or alkali,[678] reductively by sodium amalgam,[679] or by reagents such as alkali sulfides,[678] cyanides,[680] or arsenites[680] that bind sulfur:

$$RSO_2SNa \longrightarrow RSO_2Na + S$$

Gutmann[680] thus obtained **potassium *p*-toluenesulfinate** by evaporating a mixture of potassium *p*-toluenethiosulfonate (4.5 g), potassium cyanide (2.5 g), 20% potassium hydroxide solution (2 g), and water (10 ml).

Arenethiosulfonic esters can be cleaved to sulfinic acid salts and disulfides by alkali[681] or by thiolates.[682]

4. Cleavage of the S–Cl bond

a. Cleavage of sulfonyl chlorides

Hydrolysis of sulfonyl chlorides to sulfonic acids is often important because many of these acids can best be obtained pure by first preparing and then hydrolysing their chlorides; and moreover sulfonyl chlorides are accessible by a variety of routes.

The most elegant method of converting alkanesulfonyl chlorides into the sulfonic acids is alcoholysis:[683] no ester is formed in the absence of acid-binding agents:

$$RSO_2Cl + R'OH \longrightarrow RSO_3H + R'Cl$$

Most arenesulfonyl chlorides are readily hydrolysed to the sulfonic acids by boiling with water, alkali, aqueous alcohol, aqueous acetic acid, or concentrated formic acid. Sulfonic esters are formed when alcohols or phenols are used with an acid-binding agent.[684,685]

Alkyl benzenesulfonates:[686] 20–30% sodium hydroxide solution is added dropwise, with vigorous shaking, to benzenesulfonyl chloride (1 part) and the alcohol (1 part), until the alkaline reaction is permanent after considerable shaking and the oil that separates is completely free from chlorine. Benzene and water are added, the two layers are separated, the organic layer is washed and dried, and the solvent and alcohol are removed in a vacuum by means of a water-bath at 30–40° (not higher). This process has afforded the allyl (explosive decomposition on distillation), 2-chloroethyl, b.p. 184°/9 mm, 2-bromoethyl, b.p. 185–187°/16 mm, and 2-chloro-1-(chloromethyl)ethyl ester, b.p. 200–205°/20 mm, m.p. 50° (from benzene).

Roos and his co-workers[687] have described a general method of preparing simple alkyl toluenesulfonates. Pyridine has been used as acid-binding agent in the preparation of alkyl methanesulfonates,[688] yields averaging 80%.

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[677] J. Perl, *Ber. Deut. Chem. Ges.*, **18**, 67 (1885).

[678] R. Otto and J. Tröger, *Ber. Deut. Chem. Ges.*, **24**, 494 (1891).

[679] H. Limpricht, *Ann. Chem.*, **221**, 347, 361 (1883).

[680] A. Gutmann, *Ber. Deut. Chem. Ges.*, **41**, 3351 (1908).

[681] E. Fromm, *Ber. Deut. Chem. Ges.*, **41**, 3409 (1908).

[682] H. Gilman, L. E. Smith, and H. H. Parker, *J. Amer. Chem. Soc.*, **47**, 854 (1925); S. Smiles and D. T. Gibson, *J. Chem. Soc.*, **125**, 180 (1924).

[683] U.S. Pat. 2,319,121; Ger. Pat. 742,927; *Chem. Abstr.*, **37**, 5986 (1943); **40**, 903 (1946).

[684] Ger. Pat. 715,846; *Chem. Abstr.*, **38**, 2050 (1944).

[685] S. S. Rossander and C. S. Marvel, *J. Amer. Chem. Soc.*, **50**, 1493 (1928).

[686] Z. Földi, *Ber. Deut. Chem. Ges.*, **53**, 1836 (1920).

[687] A. T. Roos, H. Gilman, and N. J. Beaber, *Org. Syn.*, Coll. Vol. I, 138 (1937).

[688] H. R. Williams and H. S. Mosher, *J. Amer. Chem. Soc.*, **76**, 2985 (1954).

Aryl arenesulfonates mostly crystallize readily and are useful for identification of phenols or sulfonic acids; they are easily obtained from the acid chlorides and phenols in the presence of alkali[689] or a tertiary base[690] by the Schotten–Baumann procedure.

For the **preparation of aryl esters of substituted benzenesulfonic acids** Slagh and Britton[691] give the following general directions: The arenesulfonyl chloride (1 mole) and the phenol (1 mole) are stirred at 60–70° and treated during 0.5 h with 0.7N-sodium hydroxide solution at 60–80°. The mixture is stirred for a further hour at 60–80°, then cooled, and the ester is filtered off, washed with water, and recrystallized several times from ethanol containing a little benzene. Yields average 90%.

Sulfonic anhydrides are prepared from acid chlorides, in principle, by the same methods as are used for the corresponding carboxylic anhydrides. Thus Billeter[692] obtained alkanesulfonic anhydrides by the action of the sulfonyl chlorides on silver alkanesulfonates; benzenesulfonic anhydride is best obtained by heating 2 moles of benzenesulfonyl chloride and 1 mole of anhydrous oxalic acid slowly to 200°.[693]

Sulfonamides can in general be obtained very smoothly by treating sulfonyl chlorides with ammonia[694] or dry, powdered ammonium carbonate.[217,695] The reaction with ammonia is carried out in aqueous solution or better in an inert organic solvent in the cold; it is advisable to use an excess of ammonia so as to avoid hydrolysis to the ammonium sulfonate or formation of the disulfonylamide, $(RSO_2)_2NH$.

For the **preparation of arenesulfonamides from the sulfonyl chlorides** by aqueous ammonia Huntress and Carten[217] give the following general directions: The arenesulfonyl chloride (0.5 g) is heated for 10 min with ammonia solution of *d* 0.9 (5 ml), then cooled to room temperature and treated with water (10 ml). The amide that separates is collected, washed thoroughly, recrystallized to constant m.p. from aqueous ethanol, and dried at 105°.

Series of halo- and alkyl-substituted benzene- and naphthalene-sulfonamides have been obtained by this method.

When the sulfonyl chloride is hydrolysed under the above experimental conditions it is advisable to pass dry ammonia into its cooled ethereal solution.

The corresponding reaction with amines can be carried out in alkaline solution by the Schotten–Baumann procedure,[696] or, to avoid formation of disulfonyl compounds,[697] in a weakly alkaline, neutral, or weakly acidic medium,[698] or in the presence of an organic base as acid-binding agent.[131,699] N^4-Acetyl-N^1-arylsulfanilamides, p-$CH_3CONHC_6H_4SO_2NHAr$, are prepared, according to Shepherd,[693] in glacial acetic acid containing sodium acetate.

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[689] O. Hinsberg, *Ber. Deut. Chem. Ges.*, **23**, 2962 (1890).

[690] S. E. Hazlet, *J. Amer. Chem. Soc.*, **59**, 287 (1937).

[691] H. R. Slagh and E. C. Britton, *J. Amer. Chem. Soc.*, **72**, 2808 (1950).

[692] O. C. Billeter, *Ber. Deut. Chem. Ges.*, **38**, 2018 (1905).

[693] R. G. Shepherd, *J. Org. Chem.*, **12**, 275 (1947).

[694] F. H. Bergheim and W. Braker, *J. Amer. Chem. Soc.*, **66**, 1459 (1944).

[695] E. H. Huntress and J. S. Autenrieth, *J. Amer. Chem. Soc.*, **63**, 3446 (1941).

[696] L. Knorr and P. Rössler, *Ber. Deut. Chem. Ges.*, **36**, 1279 (1903); O. Hinsberg and J. Kessler, *Ber. Deut. Chem. Ges.*, **38**, 906 (1905).

[697] N. N. Dykhanov, *Zh. Obshch. Khim.*, **29**, 3602 (1959); *Chem. Abstr.*, **54**, 19577 (1960).

[698] F. Reverdin, *Ber. Deut. Chem. Ges.*, **42**, 1523 (1909); H. Feichtinger, *Chem. Ber.*, **96**, 3068 (1963).

[699] R. Adams and J. H. Looker, *J. Amer. Chem. Soc.*, **73**, 1147 (1951).

Hultquist and his co-workers[131] used pyridine as both condensing agent and solvent in the preparation of a large number of sulfonamides containing heterocyclic *N*-substituents.

1-(Arenesulfonyl)imidazoles are obtained by reaction of the corresponding sulfonyl chloride (1 mole) with imidazole (2 moles) in anhydrous tetrahydrofuran, yields being almost quantitative.[700] These compounds can be used to transfer the sulfonyl group to nucleophilic compounds.

The substituted benzenesulfonyl chloride (1 mole) is added portionwise to a mixture of the amino heterocycle (1–2-moles) and pyridine (500 ml) and heated for 1–2 h at 55–60°. For isolation of the product the mixture is poured into cold water, an excess of cold dilute hydrochloric acid, or dilute alcoholic hydrochloric acid.

Space does not allow details to be given here for the preparation of sulfonamides, for which reviews and the original literature should be consulted.[152c,701–705]

Sulfonyl azides can be obtained smoothly by stirring an anhydrous methyl-alcoholic solution of the sulfonyl chloride for 1–2 hours with sodium azide and precipitating the product by addition of ice-water.[706]

The preparative importance of *N*-sulfinyl compounds — for addition and cycloaddition reactions — has increased in recent years.[707] Most of the *N*-sulfinyl compounds known to date are derived from amines or hydrazines, from which they are prepared by reaction with thionyl chloride:

$$RNH_2 + SOCl_2 \longrightarrow RN{=}S{=}O + 2HCl$$

Yields of the aniline derivatives are usually almost quantitative; for aliphatic amines they lie between 35% and 65% if pyridine is added to bind the hydrogen chloride evolved. Sulfinylation of sulfonamides is considerably slower but gives good yields after several days' refluxing.

***N*-Sulfinylaniline:**[707] Aniline is dissolved in five times the amount of dry benzene, and a slight excess of thionyl chloride in twice the amount of benzene is dropped in slowly with stirring and cooling. The mixture is then boiled on the water-bath until the aniline hydrochloride that is first precipitated has redissolved (3–6 h). The benzene and the excess of sulfonyl chloride are distilled off and the *N*-sulfinylaniline (95% yield) is distilled in a vacuum (b.p. 80°/12 mm).

1-Phenyl-2-sulfinylhydrazine:[708] Thionyl chloride (35.7 g, 0.3 mole) in chloroform (50 ml) is added during 2 h to a rapidly stirred solution of phenylhydrazine (32.4 g, 0.3 mole) in chloroform (200 ml) and pyridine (47.5 g, 0.6 mole) that is cooled in ice. Stirring is continued

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[700] H. A. Staab and K. Wendel, *Chem. Ber.*, **93**, 2902 (1960).

[701] E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, 1948.

[702] F. Hawking and J. S. Lawrence, "The Sulfonamides," H. K. Lewis & Co., London, 1950.

[703] H. Herbst, "Schwefelorganische Verbindungen und ihre Verwendung in der Therapie," Akademische Verlagsgesellschaft Geest & Portig K.G., Leipzig, 1953.

[704] F. Mietzsch and R. Behnisch, "Therapeutisch verwendbare Sulfonamid- und Sulfonverbindungen," Verlag Chemie, Weinheim/Bergstraße, 2nd edn., 1955.

[705] F. Mietzsch, "Therapeutisch verwendbare Sulfonamid- und Sulfonverbindungen," Verlag Chemie, Berlin, 1945.

[706] J. H. Boyer, C. H. Mack, N. Goebel, and J. R. Morgan Jr., *J. Org. Chem.*, **23**, 1051 (1958); J. Goerdeler and H. Ullmann, *Chem. Ber.*, **94**, 1067 (1961).

[707] G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem. Int. Ed., Engl.*, **1**, 89 (1962).

[708] D. Klamann, U. Krämer, and P. Weyerstahl, *Chem. Ber.*, **95**, 2694 (1962).

for a further 1 h, then the precipitate is filtered off and the filtrate is washed with water, dilute hydrochloric acid, and again water, and dried over sodium sulfate. Evaporation of the chloroform leaves the sulfinyl derivative (37.8 g, 82%), which melts at 76.5° after crystallization from ethanol.

***p*-Chloro-*N*-sulfinylbenzenesulfonamide:**[707] *p*-Chlorobenzenesulfonamide (31 g) and thionyl chloride (13.5 ml) are boiled in dry benzene (50 ml), with exclusion of moisture, until, after about 3 days, the sulfonamide has completely dissolved and does not separate again on cooling. Removing the solvent in a vacuum and distilling the brown residue (34 g, 88%) then gives the product as yellow oil, b.p. 122–125°/10^{-4} mm, which crystallizes and then has m.p. 52–53°.

Elimination of hydrogen chloride from sulfinyl chlorides by means of triethylamine[709] has been used in a few cases to afford sulfines (an alternative method is the oxidation of diaryl thioketones by peracids[710]):

$$R_2CHSOCl + (C_6H_5)_3N \longrightarrow R_2C{=}S{=}O + (C_6H_5)_3NHCl$$

Application of this reaction to sulfonyl chlorides leads to sulfenes, which, however, cannot be isolated although they can be used in trapping reactions of various types to afford cyclic sulfones.[711]

b. Cleavage of sulfinyl and sulfenyl chlorides

Sulfinyl chlorides, analogously to sulfonyl chlorides, are important starting materials for the preparation of other sulfinic acid derivatives. Thus, when warmed with alcohols they give sulfinic esters,[712,713] and esterification can also be carried out by the Schotten–Baumann procedure in the presence of pyridine or potassium carbonate.[714]

The racemization of optically active sulfinic esters has been described by Ziegler and Wenz,[715] with particular reference to laevorotatory 1-methylheptyl toluenesulfinite.

Also, reaction of sulfinyl chlorides with ammonia or amines in ethereal solution affords sulfinamides.

Benzenesulfinamides:[716,717] Benzenesulfinyl chloride is dissolved in five times the amount of ether and treated with 2 moles of amine at 0°. The precipitate is collected, washed with water, dissolved in ethanol, and reprecipitated by addition of a little water. Thus were obtained benzenesulfinamide, m.p. 121°, and its *N,N*-dimethyl derivative (readily soluble in ether), b.p. 90°/2–3 mm, benzenesulfinanilide, m.p. 112–114°, and 1-(benzenesulfinyl)piperidine, m.p. 83°.

Amides of *p*-toluenesulfinic acid can be prepared in the same way.

Sulfenyl chlorides are extremely reactive and give sulfenic esters when treated with sodium alkoxides or phenoxides, but the reaction is often not quite smooth.[364,621,718]

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[709] W. A. Sheppard and J. Diekmann, *J. Amer. Chem. Soc.*, **86**, 1891 (1964); J. Starting, L. Thijs, and B. Zwanenburg, *Rec. Trav. Chim.*, **83**, 631 (1964).

[710] J. Starting, L. Thijs, and B. Zwanenburg, *Tetrahedron Lett.*, **1966**, 65.

[711] G. Opitz, *Angew. Chem. Int. Ed., Engl.*, **6**, 107 (1967).

[712] J. von Braun and K. Weissbach, *Ber. Deut. Chem. Ges.*, **63**, 2840 (1930).

[713] Cf. R. Otto and A. Rössing, *Ber. Deut. Chem. Ges.*, **18**, 2506 (1885).

[714] H. Phillips, *J. Chem. Soc.*, **127**, 2553 (1925).

[715] K. Ziegler and A. Wenz, *Ann. Chem.*, **511**, 109 (1934).

[716] Cf. T. P. Hilditch and S. Smiles, *Ber. Deut. Chem. Ges.*, **41**, 4115 (1908).

[717] J. von Braun and W. Kaiser, *Ber. Deut. Chem. Ges.*, **56**, 549 (1923).

[718] H. Lecher, *Ber. Deut. Chem. Ges.*, **58**, 409 (1925).

Methyl triphenylmethanesulfenate[719] is formed when a mixture of the sulfenyl chloride (3 g) in methanol (50 ml) with a solution of sodium (0.3 g) in methanol (10 ml) is boiled for a short time. On cooling, the ester separates in colorless needles, and a second fraction is obtained by diluting the filtrate with water and extraction with ether. After recrystallization from chloroform–methanol the ester has m.p. 124°.

Sulfenic esters are formed much more smoothly and homogeneously from primary, secondary, or tertiary alcohols and 2,4-dinitrobenzenesulfenyl chloride in the presence of pyridine, so that this reaction can be used for characterization of alcoholic hydroxyl groups.[720]

Treating sulfenyl chlorides with ammonia or amines gives the sulfenamides in a particularly smooth reaction whose yields are good;[721] according to Lecher[718] this is best effected in ethereal solution.

***N,N*-Dimethylbenzenesulfenamide:** A solution of benzenesulfenyl chloride (5 g) in anhydrous ether (30 ml) is dropped into one of dimethylamine (from 9 g of the hydrochloride) in anhydrous ether (100 ml) that is cooled in ice–salt. After removal of the precipitated dimethylamine hydrochloride distillation affords the amide (4.9 g), b.p. 63.5–64°/3 mm.

Other examples are the preparation of 1-chloro-2-naphthalenesulfenamide and *p*-nitro-,[667] 2-nitro-4-methyl-,[668] and 4-chloro-2-nitro-benzenesulfenamide.[669]

5. Cleavage of the S–O bond

Cleavage of the S–O bond of sulfonic acids and its salts by the action of halogenating agents is one of the most important methods of preparing sulfonyl halides; it is effected by treating the free acid with thionyl chloride[722,723] or phosphorus trichloride,[589] or a salt with phosphorus pentachloride.[690,724]

Methanesulfonyl chloride:[692] Well dried sodium methanesulfonate is treated gradually with phosphorus pentachloride, and the volatile products are distilled off. When the distillate is fractionated, pure methanesulfonyl chloride distils at 161–161.5°/730 mm.

In other cases it is often necessary to warm the mixture to some necessary reaction temperature after addition of the phosphorus pentachloride. When the sulfonyl chloride is resistant to hydrolysis the reaction mixture may be poured on ice, the sulfonyl chloride then being isolated by extraction with ether. If the reaction mixture tends to solidify, an inert solvent such as benzene, xylene, or carbon tetrachloride may be added.

This method has also been used for preparation of benzenesulfonyl chloride,[106c] 1,5-naphthalenedisulfonyl chloride,[725] and the 3-sulfonyl chlorides of pyridine and alkylpyridines.[726]

Sulfonyl chlorides can also often be prepared in good yield by treating the sodium sulfonate (dried for 3 hours at 130–200°) with 93–96% chlorosulfuric

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[719] D. Vorländer and E. Mittag, *Ber. Deut. Chem. Ges.*, **52**, 413 (1919).

[720] N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Amer. Chem. Soc.*, **75**, 2658 (1953).

[721] J. H. Billman and E. O'Mahony, *J. Amer. Chem. Soc.*, **61**, 2340 (1939); J. H. Billman, J. Garrison, R. Anderson, and B. Wolnak, *J. Amer. Chem. Soc.*, **63**, 1920 (1941).

[722] C. R. Noller and P. J. Hearst, *J. Amer. Chem. Soc.*, **70**, 3955 (1948).

[723] P. J. Hearst and C. R. Noller, *Org. Syn.*, **30**, 58 (1950).

[724] C. S. Marvel, M. D. Helfrick, and J. P. Belsley, *J. Amer. Chem. Soc.*, **51**, 1272 (1929); P. D. Bartlett and L. H. Knox, *Org. Syn.*, **45**, 14 (1965).

[725] P. D. Caesar, *Org. Syn.*, **32**, 88 (1952).

[726] Ger. Pat. Appl. I 201/30 (1930); Friedländer, **19**, 815 (1934).

acid.[727] For isolation the reaction mixture is poured on ice, and the precipitated sulfonyl chloride is separated and dried over sodium hydroxide in a vacuum. Benzenesulfonyl chloride and its 3-chloro-4-methyl and *m*-nitro derivatives, as well as *p*-toluene- and 1-naphthalene-sulfonyl chloride, amongst others, have been obtained in this way.

***p*-Chlorobenzenesulfonyl chloride:**[728] Chlorosulfuric acid (370 g) is added during about 15 min to a stirred suspension of dry sodium *p*-chlorobenzenesulfonate (335 g) in chloroform (700 ml), the temperature not being allowed to exceed 60°. The resulting thick slurry is stirred at 55–60° for 6 h, then poured into ice-water. The organic phase is separated, washed three times with cold water, dried over calcium chloride, and fractionated. The product (293 g, 89%) has b.p. 140°/12 mm and m.p. 52–53°.

Preparation of many other sulfonyl chlorides from the sulfonic acids is covered in a review by Suter.[152b]

Arenesulfonic anhydrides can be obtained by removal of water from the sulfonic acids by thionyl chloride according to directions given by Meyer *et al.*[729] Phosphorus pentaoxide,[730] di-*p*-tolylcarbodiimide,[731] or aryl cyanates[732] may also be used for this purpose.

***p*-Toluenesulfonic anhydride:**[732] Anhydrous *p*-toluenesulfonic acid (3.44 g, 20 mmoles) is heated in benzene (10 ml) with phenyl cyanate (1.2 g, 10 mmoles) at the boiling point until the odor of cyanate has disappeared. The mixture is then cooled, phenyl carbamate (1.34 g, 98%) is filtered off, and the solvent is removed from the filtrate in a vacuum. The residue of *p*-toluenesulfonic anhydride has m.p. 123–124° when recrystallized from 1 : 1 benzene–ethanol, the yield being 83% (2.7 g). If *p*-toluenesulfonic acid monohydrate (3.8 g) is used with phenyl cyanate (3.6 g, 30 mmoles) the yield of anhydride is 77%.

Knoevenagel and Polack[733] have given directions for the preparation of aromatic sulfinic anhydrides by the action of acetic anhydride on a suspension of the dry sulfinic acid in a little acetic acid. The reaction is catalysed by sulfuric acid or a 0.1% solution of iron(III) chloride in glacial acetic acid or acetic anhydride. Benzene-, *p*-toluene-, *p*-xylene-, pseudocumene-, mesitylene-, and *p*-bromo- and *p*-iodo-benzene-sulfinic anhydride have been obtained in this way.

6. Cleavage of the S–N bond

Cleavage of the S–N bond[734] of sulfonamides, yielding sulfonic acids, has preparative interest when purification of the sulfonic acid by way of the chloride is difficult and is better achieved by recrystallization of the amide prepared from the chloride. The amide is hydrolysed in a hydrochloric acid medium.[735]

$$RSO_2NHR' + H_2O \xrightarrow{HCl} RSO_3H + R'NH_2$$

$$RSO_3H + H_2O \longrightarrow RH + H_2SO_4 \qquad \text{(side reaction)}$$

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[727] A. A. Spryskov and N. V. Aparjeva, *Zh. Obshch. Khim.*, **20**, 1818 (1950); *Chem. Abstr.*, 44, 9367 (1950).

[728] M. Kulka, *J. Amer. Chem. Soc.*, **72**, 1216 (1950).

[729] H. Meyer and K. Schlegl, *Monatsh. Chem.*, **34**, 561 (1913); H. Meyer, *Ann. Chem.*, **433**, 334 (1923); A. L. Bernoulli and H. Stauffer, *Helv. Chim. Acta*, **23**, 640 (1940).

[730] L. Field, *J. Amer. Chem. Soc.*, **74**, 394 (1952).

[731] H. G. Khorana, *Can. J. Chem.*, **31**, 585 (1953).

[732] D. Martin, *Chem. Ber.*, **98**, 3286 (1965).

[733] E. Knoevenagel and L. Polack, *Ber. Deut. Chem. Ges.*, **41**, 3323 (1908).

[734] D. Klamann and G. Hofbauer, *Ann. Chem.*, **581**, 182 (1952).

[735] R. S. Schrieber and R. L. Shriner, *J. Amer. Chem. Soc.*, **56**, 1618 (1934).

General directions for hydrolysis of sulfonamides to the acids: The sulfonamide (25 g) is boiled in 25% hydrochloric acid (125 g) until hydrolysis is complete, which is usually indicated by total dissolution of the amide; 10–36 h are needed. Then the small amount of hydrocarbon formed is removed in steam, the residual solution is made alkaline with sodium hydroxide, and the amine liberated is also distilled off in steam. The residual mixture is filtered and evaporated almost to dryness; the sodium sulfonate is isolated by extracting with ethanol the salts that have separated.

IV. Preparation of thiocarbonic acid derivatives

This Section consists of a review of the most important methods of preparing thiocarbonic acid derivatives. The space available suffices for details of the processes in only a few cases, and for others the literature cited must be consulted.

Since carbonyl sulfide and thiophosgene are used particularly often for preparation of these compounds, convenient methods of obtaining them in the laboratory will be described first. For the preparation of dicyanogen see page 105.

Carbonyl sulfide:[763–738] from potassium thiocyanate: A cold mixture of concentrated sulfuric acid (1 kg) and water (500 g) is placed in a flask (3-l capacity) with a saturated aqueous solution (100 ml) of potassium thiocyanate (70 g). As the mixture warms to 20° a vigorous evolution of gas begins, which is occasionally regulated by cooling in ice-water and later by warming to 40°. The moist gas, which contains carbon dioxide, hydrogen sulfide, and carbon disulfide as impurities, is passed through an empty flask at 0°, through concentrated sulfuric acid, through 30% sodium hydroxide solution (in a ten-bulb assembly, also cooled at 0°), and over calcium chloride and phosphorus pentaoxide, all in that order. For complete purification from traces of carbon disulfide and carbon dioxide the original literature should be consulted.

When pure, carbonyl chloride is a colorless, odorless, easily flammable gas with a strong narcotic action. It is soluble in organic solvents, and water dissolves about its own volume of the gas. Carbonyl sulfide decomposes gradually in aqueous solution to carbon dioxide and hydrogen sulfide.

The most satisfactory method (tested in the author's laboratory) of preparing **thiophosgene** is reduction of trichloromethanethiol by tetralin:[739] A 0.5-l flask (A) is fitted with a wide-bore adapter comprising a vertical tube with a side arm. The vertical tube is connected to an ascending bulb condenser which, in turn, is connected to a Liebig condenser that slopes downwards; the bulb condenser is heated by steam. The side arm of the adaptor carries a dropping funnel of 250-ml capacity with a pressure-equalization device. The Liebig condenser is attached to a 0.5-l receiver (B) that is placed in ice–salt. The effluent gases from B pass seriatim into two Erlenmeyer flasks of about 750-ml capacity, through leads dipping to the surface of about 300 ml of water, these flasks being cooled in ice-water. Final venting is to a fume cupboard. The reaction flask A is heated preferably in an air-bath or an heating mantle.

Dry tetrahydronaphthalene (182 g) is heated in flask A to 195–200°. Then dry trichloromethanethiol (465 g) is added from the dropping funnel at a steady rate during 4–5 h; a gentle, regular reaction ensues, with evolution of a stream of brown vapors of which hydrogen chloride forms part. Most of the thiophosgene condenses in flask B; the hydrogen chloride

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[736] P. Klason, *J. Prakt. Chem.*, [ii], **36**, 64 (1887); R. J. Ferm, *Chem. Rev.*, **57**, 621 (1957).

[737] Cf. A. Stock and E. Kuss, *Ber. Deut. Chem. Ges.*, **50**, 159 (1917).

[738] A. Stock, W. Siecke, and E. Pohland, *Ber. Deut. Chem. Ges.*, **57**, 719 (1924).

[739] Ger. Pat. 853,162; *Chem. Zentralbl.*, **1953**, 9314.

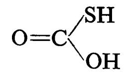
is absorbed by the water in the two Erlenmeyer flasks, and the remainder of the thiophosgene condenses there. The reaction is complete when no more brown fumes are visible on further addition of trichloromethanethiol and continued heating at 200°. Napthalene separates as the brown contents of the reaction flask A cool. The thiophosgene separating in the two Erlenmeyer flasks is removed from the aqueous hydrochloric acid by means of a separatory funnel and is added to the main quantity of thiophosgene in the receiver B. The crude product thus obtained is fractionally distilled, pure thiophosgene passing over at 71–75°/760 mm in 65% yield (185 g). Thiophosgene is a red, poisonous liquid with a suffocating odor and is moderately stable towards water and dilute alkali.

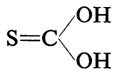
Reduction of trichloromethanethiol by sulfur dioxide is preparatively very simple[740] and has the advantage that it is unnecessary to isolate the thiophosgene:

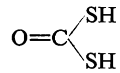
Thiophosgene solution: This preparation has been tested in the author's laboratory. A mixture of water (450 ml), a water-immiscible inert solvent (150 ml) such as benzene or carbon tetrachloride, freshly distilled trichloromethanethiol (88 ml), and potassium iodide (0.15 g) is cooled to −5° in a three-necked flask (2 l) fitted with a stirrer, thermometer, and gas inlet and outlet tubes. The flask is removed from the cooling bath, and the mixture is stirred while sulfur dioxide is led in until the temperature ceases to rise (about 45–50°). Then the organic phase is separated, washed with water, and dried over calcium chloride. The solution, which contains about 90% (about 42 g) of the theoretical amount of thiophosgene can be used directly for further reactions. If the thiophosgene is to be isolated it is advisable to use a higher-boiling solvent (*e.g.*, tetrachloroethane) from which the thiophosgene can be separated by distillation.

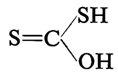
1. Thiocarbonic acids

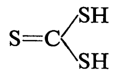
Replacing the various oxygen atoms of carbonic acid H_2CO_3 by sulfur leads formally to the following types of acid:


$O{=}C\begin{array}{l}\diagup SH\\ \diagdown OH\end{array}$


$S{=}C\begin{array}{l}\diagup OH\\ \diagdown OH\end{array}$


$O{=}C\begin{array}{l}\diagup SH\\ \diagdown SH\end{array}$


$S{=}C\begin{array}{l}\diagup SH\\ \diagdown OH\end{array}$


$S{=}C\begin{array}{l}\diagup SH\\ \diagdown SH\end{array}$

Only the last of these, trithiocarbonic acid, is known in the free state,[741] the others existing only as salts, chlorides, esters, and amides. In the light of modern practice, these acids are here named thio-, dithio-, and trithio-carbonic acid according to the number of sulfur atoms present in the molecule; the hypothetical acids may be distinguished by *S*- and/or *O*-prefixes, *e.g.*, the first is thiocarbonic *O,S*-acid and the third is dithiocarbonic *S,S*-acid; for derivatives of these acids, *O*- and *S*-prefixes are also used, when necessary, before the names of atoms or groups replacing hydrogen of the acid.

2. Chlorothioformic esters

Chlorothioformic esters are prepared by treating thiophosgene or phosgene with alcohols or phenols or with thiols in the presence of sufficient aqueous

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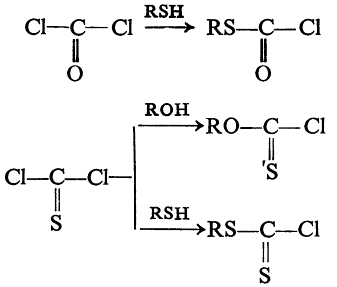
[740] M. Zbirovsky and J. Horak, ČSSR Pat. 103,963; *Chem. Abstr.*, **59**, 11258 (1963).

[741] H. Mills and P. L. Robinson, *J. Chem. Soc.*, **1928**, 2330.

alkali hydroxide to bind the hydrochloric acid liberated:



$$\mathrm{Cl{-}\underset{\underset{O}{\|}}{C}{-}Cl} \xrightarrow{\mathrm{RSH}} \mathrm{RS{-}\underset{\underset{O}{\|}}{C}{-}Cl}$$

S—R chlorothioformate[747,748]

$$\mathrm{Cl{-}\underset{\underset{S}{\|}}{C}{-}Cl} \xrightarrow{\mathrm{ROH}} \mathrm{RO{-}\underset{\underset{S}{\|}}{C}{-}Cl}$$

O—R chlorothioformate[742–746]

$$\mathrm{Cl{-}\underset{\underset{S}{\|}}{C}{-}Cl} \xrightarrow{\mathrm{RSH}} \mathrm{RS{-}\underset{\underset{S}{\|}}{C}{-}Cl}$$

R chlorodithioformate[748,749]

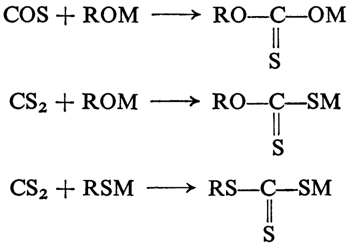
***O*-Aryl chlorothioformates:**[744] A solution of sodium hydroxide (40 g) in water (500 ml) is dropped during 1 h into one of a phenol (1 mole) and thiophosgene (115 g) in chloroform (500 ml) at 15–20°. After a further hour's stirring, the chloroform layer is separated, washed with water, dried over calcium chloride, freed from solvent, and fractionated in a vacuum. This process has afforded, amongst other esters, *O*-phenyl, b.p. 92.5°/10 mm (80%), *O*-*p*-tolyl, b.p. 115 to 119°/13 mm (73%), *O*-*p*-chlorophenyl, b.p. 123–126°/12 mm (67%), *O*-*p*-methoxyphenyl, b.p. 141–143°/13 mm (74%), *O*-3,4-dichlorophenyl, b.p. 98–100°/1.3 mm, m.p. 58–60° (83%), *O*-2,6-dichlorophenyl, b.p. 135–137°/11 mm (60%), and *O*-2,6-diethylphenyl chlorothioformate, b.p. 130–136°/13 mm (56%).

Such esters have also been obtained by chlorination of bis(alkyl xanthates) [dialkyl dithio(dithioformates)].[750]

3. Thiocarbonic esters

a. Thiocarbonic half esters

For the preparation of thiocarbonic half esters, alkoxides or thiolates are added to carbon disulfide or carbonyl sulfide to the following scheme (where M = a metal):



$$\mathrm{COS + ROM \longrightarrow RO{-}\underset{\underset{S}{\|}}{C}{-}OM}$$

O—M *O*—R thiocarbonate[751,752]

$$\mathrm{CS_2 + ROM \longrightarrow RO{-}\underset{\underset{S}{\|}}{C}{-}SM}$$

S—M *O*—R dithiocarbonate
or M R xanthate[753]

$$\mathrm{CS_2 + RSM \longrightarrow RS{-}\underset{\underset{S}{\|}}{C}{-}SM}$$

M R trithiocarbonate[754]

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[742] H. Rivier, *Bull. Soc. Chim. France*, [iii], **35**, 837 (1906).

[743] H. Rivier and J. Schalch, *Helv. Chim. Acta*, **6**, 612 (1923).

[744] P. Reich and D. Martin, *Chem. Ber.*, **98**, 2068 (1965).

[745] L. Garmaise, A. Uchiyama, and A. F. McKay, *J. Org. Chem.*, **27**, 4509 (1962).

[746] W. Walter and K.-D. Bode, *Ann. Chem.*, **698**, 108, 122 (1966).

[747] R. Riemschneider and O. Lorenz, *Monatsh. Chem.*, **84**, 518 (1953).

[748] H. Rivier, *Bull. Soc. Chim. France*, [iv], **1**, 733, 737 (1907).

[749] P. Klason, *Ber. Deut. Chem. Ges.*, **20**, 2384 (1887).

[750] Ger. Pat. 1,018,054; *Chem. Abstr.*, **54**, 5480 (1960).

[751] C. Bender, *Ann. Chem.*, **148**, 137 (1868).

[752] F. Salomon, *J. Prakt. Chem.*, [ii], **5**, 476 (1872).

[753] M. Ragg, *Chem.-Ztg.*, **34**, 83 (1910).

[754] B. Holmberg, *J. Prakt. Chem.*, [ii], **73**, 239 (1906).

The xanthates are formed with extreme ease, so that almost all alcoholic hydroxyl groups can be brought into reaction in this way.

General directions for preparation of xanthates:[755] Finely powdered potassium hydroxide (56 g, 1 mole) is dissolved in the requisite amount of an alcohol, the solution is cooled to room temperature, and carbon disulfide (76 g, 1 mole) is added with stirring during 30 min. After a further hour's stirring, ether is added to complete the precipitation of the xanthate, which is then filtered off and recrystallized from ethanol. Yields are 80–95%.

b. Thiocarbonic diesters

Thiocarbonic diesters are prepared by treating 2 moles of an alcohol or thiolate with one mole of phosgene or thiophosgene or by treating an alkoxide or thiolate with a chlorothioformic ester in 1 : 1 molar ratio, according to the following reactions where M = metal:

$$\mathrm{CSCl_2} \xrightarrow{\mathrm{2ROM}} \mathrm{RO{-}CS{-}OR} \xleftarrow{\mathrm{ROM}} \mathrm{ClCS{-}OR}$$

O, *O*—di—R

thiocarbonate[745,756,757]

$$\mathrm{RS{-}CO{-}OR} \xleftarrow{\mathrm{RSM}} \mathrm{ClCO{-}OR}$$

O, *S*—di—R

thiocarbonate[758]

$$\mathrm{CSCl_2} \xrightarrow{\mathrm{2RSM}} \mathrm{RS{-}CS{-}SR} \xleftarrow{\mathrm{RCl}} \mathrm{K_2CS_3}$$

di—R

trithiocarbonate[749,759-762]

$$\mathrm{COCl_2} \xrightarrow{\mathrm{2RSM}} \mathrm{RS{-}CO{-}SR} \xleftarrow{\mathrm{RSM}} \mathrm{ClCO{-}SR}$$

S, *S*—di—R

dithiocarbonate[758,763]

$$\mathrm{RO{-}CS{-}SR} \xleftarrow[\mathrm{[RN_2]^+Cl^-}]{\mathrm{RCl}} \mathrm{RO{-}CS{-}SK}$$

O, *S*—di—R

dithiocarbonate[763-765]

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[755] F. Drawert, K. H. Reuther, and F. Born, *Chem. Ber.*, **93**, 3064 (1960).

[756] H. Eckenroth and K. Kock, *Ber. Deut. Chem. Ges.*, **27**, 1368 (1894).

[757] M. M. Delépine, *Ann. Chim.* (*Paris*), [viii], **25**, 546 (1912).

[758] F. Salomon, *J. Prakt. Chem.*, [ii], **6**, 433 (1873); E. Mylius, *Ber. Deut. Chem. Ges.*, **6**, 312 (1873).

[759] W. Autenrieth and H. Hefner, *Ber. Deut. Chem. Ges.*, **58**, 2151 (1925).

[760] Cf. J. A. Durden Jr., H. A. Stansbury Jr., and W. H. Catlette, *J. Amer. Chem. Soc.*, **82**, 3082 (1960).

[761] F. Runge, Z. El-Hewehi, H.-J. Renner, and E. Taeger, *J. Prakt. Chem.*, [iv], **11**, 284 (1960).

[762] M. Kiessel and D. Braun, *Chem. Ber.*, **98**, 1350 (1965).

[763] R. Leuckart, *J. Prakt. Chem.*, [ii], **41**, 179 (1890).

[764] W. Fomin and N. Sochanski, *Ber. Deut. Chem. Ges.*, **46**, 244 (1913).

[765] L. Tschugaeff, *Ber. Deut. Chem. Ges.*, **32**, 3334 (1899); D. Martin, *J. Prakt. Chem.*, [iv], **9**, 222 (1963).

***O,O*-Diaryl thiocarbonates:**[756,759] A monohydric phenol (2 moles) is dissolved in a small excess of 10% sodium hydroxide solution, diluted with the four- to five-fold amount of water, and treated gradually, with vigorous shaking, with thiophosgene (1 mole). If the mixture becomes too warm it must be cooled. The aryl ester produced separates as a white precipitate and is washed free from alkali by water and recrystallized, generally from ethanol.

Diphenyl thiocarbonate obtained in this way in almost quantitative yield has m.p. 106°.

4. Thiocarbamic acid derivatives

a. Salts

The preparation of alkali and ammonium salts of *N*-substituted thiocarbamic acids is usually effected by addition of primary or secondary amines to carbonyl sulfide of carbon disulfide in the presence of ammonia or an alkali hydroxide. Using a strongly basic amine in place of the inorganic base affords the amine salt of the thiocarbamic acid:[766,767]

$RNH_2 + COS + MOH \longrightarrow RNH—CO—SM$ *S*—metal *N*—alkylthiocarbamate[768,769]

$RNH_2 + CS_2 + MOH \longrightarrow RNH—CS—SM$ Metal *N*—alkyl dithiocarbamate[768,770-772]

Potassium *N*-phenyldithiocarbamate:[773] An ethereal solution containing equimolar amounts of carbon disulfide and aniline is treated an with alcoholic solution containing an equivalent amount of potassium hydroxide. The colorless needles produced are readily soluble in water or alcohol but insoluble in ether.

b. Thiocarbamoyl chlorides

Thiocarbamoyl chloride itself is produced by addition of hydrogen chloride to thiocyanic acid in anhydrous ether:[774]

$$HNCS + HCl \longrightarrow NH_2—CSCl$$

N-Substituted derivatives thereof are obtained from primary or secondary amines and thiophosgene in anhydrous ether:[775-778]

$$RR'NH + CSCl_2 \longrightarrow RR'N—CSCl \qquad (R' \text{ may be H})$$

Whilst primary amines undergo this reaction only in complete absence of water, the hydrochlorides of secondary amines can be acylated in aqueous solution by means of thiophosgene in chloroform.[777]

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[766] A. Rieche, G. Hilgetag, A. Martini, O. Nejedly, and H. Schlegel, *Arch. Pharm.*, **293**, 957 (1960).

[767] Ger. Pat. 531,007; *Chem. Abstr.*, **25**, 5434 (1939).

[768] K. H. Slotta and H. Dressler, *Ber. Deut. Chem. Ges.*, **63**, 888 (1930).

[769] S. Kallenberg, *Ber. Deut. Chem. Ges.*, **56**, 320 (1923).

[770] C. E. Redemann, R. N. Icke, and G. A. Alles, *Org. Syn.*, **27**, 73 (1947).

[771] F. B. Dains, R. Q. Brewster, and C. P. Olander, *Org. Syn.*, Coll. Vol. I, 446 (1937).

[772] M. L. Moore and F. S. Crossley, *Org. Syn.*, **21**, 81 (1941).

[773] S. M. Losanitsch, *Ber. Deut. Chem. Ges.*, **24**, 3021 (1891).

[774] M. Battegay and E. Hégazi, *Helv. Chim. Acta*, **16**, 1003 (1933).

[775] G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

[776] O. C. Billeter, *Ber. Deut. Chem. Ges.*, **20**, 1629 (1887).

[777] O. C. Billeter and H. Rivier, *Ber. Deut. Chem. Ges.*, **37**, 4317 (1904).

[778] J. von Braun, *Ber. Deut. Chem. Ges.*, **36**, 2274 (1903).

c. Thiocarbamic esters (thiourethanes)[779]

A variety of methods is available for preparation of *O*-esters of thiocarbamic acid:

$$\left.\begin{array}{l} (1)\ R'O\text{—}CS\text{—}SR'' + NH_2R \\ (2)\ RNCS + R'OH \\ (3)\ NR_2\text{—}CSCl + NaOR' \\ (4)\ R'O\text{—}CSCl + NH_2R \end{array}\right] \longrightarrow R'O\text{—}CS\text{—}NHR \quad \text{or} \quad R'O\text{—}CS\text{—}NR_2$$

Reaction (1) is advantageous only when R' = alkyl,[781] (2) gives good yields with alcohols but not with phenols,[782-785] results with (3) are good only for disubstituted carbamoyl chlorides,[786] and (4) is by far the most generally applicable.[783,787,788]

***O*-Aryl *N*-substituted thiocarbamates:**[787] An *O*-aryl chlorothioformate (1 mole) is dropped slowly into a solution of an amine (2 moles) in acetone or ethanol at 20–30°, with stirring. After a further hour's stirring, the mixture is poured into water, and the precipitated ester is collected, dried, and recrystallized from ethanol.

S-esters of thiocarbamic acid can be obtained by modification of the methods indicated above, namely, from carbamoyl chlorides and thiolates[789] from *S*-esters of chlorothioformic acid and amines,[790] or by addition of water to thiocyanic esters.[791]

Dithiocarbamic esters can generally be obtained easily by alkylation or arylation of the corresponding dithiocarbamic salts;[792-798] other methods are addition of thiols to isothiocyanic esters,[792] treatment of chlorodithioformic esters with amines,[792] and reaction of thiocarbamoyl chlorides with thiolates.[786]

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[779] W. Walter and K.-D. Bode, *Angew. Chem. Int. Ed., Engl.*, **6**, 281 (1967).

[780] G. D. Thorn and R. A. Ludwig, "The Dithiocarbamates and Related Compounds," Elsevier Publishing Co., Amsterdam–New York, 1962.

[781] E. Biilmann, *Ann. Chem.*, **348**, 140 (1906).

[782] R. W. Bost and E. R. Andrews, *J. Amer. Chem. Soc.*, **65**, 900 (1943).

[783] R. P. Mull, *J. Amer. Chem. Soc.*, **77**, 581 (1955).

[784] W. Schneider and F. Wrede, *Ber. Deut. Chem. Ges.*, **47**, 2038 (1914).

[785] D. Martin, A. Rieche, and R. N. Iyer, *Arch. Pharm.*, **296**, 641 (1963).

[786] O. C. Billeter and A. Strohl, *Ber. Deut. Chem. Ges.*, **43**, 1856 (1910); **21**, 102 (1888).

[787] A. Rieche, G. Hilgetag, A. Martini, and R. Philippson, *Arch. Pharm.*, **294**, 201 (1961).

[788] A. Rieche, D. Martin, and W. Schade, *Arch. Pharm.*, **296**, 770 (1963).

[789] U.S. Pat. 2,642,428; *Chem. Abstr.*, **48**, 5210 (1954); R. G. Hiskey, F. J. Carroll, R. F. Smith, and R. T. Corbett, *J. Org. Chem.*, **26**, 4756 (1961).

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[794] A. M. Clifford and J. G. Lichty, *J. Amer. Chem. Soc.*, **54**, 1163 (1932).

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[797] A. Rieche, G. Hilgetag, D. Martin, and I. Kreyzi, *Arch. Pharm.*, **296**, 310 (1963).

[798] J. Krsek and Z. Štota, *Collect. Czech. Chem. Commun.*, **28**, 3159 (1963).

5. Bi(alkyl xanthates) and thiuram disulfides

Bi(alkyl xanthates) [dithiodi(thioformates)], (RO—CS—S—)$_2$, and thiuram disulfides [dithiodi(formamides)], (NH$_2$—CS—S—)$_2$, are formed by oxidation of xanthates and salts of dithiocarbamic acid, respectively. Thioureas can be dehydrogenated analogously to di(amidino) disulfide salts, [$^+$NH$_2$=C(NH$_2$)—S—)$_2$ 2X$^-$, by a wide variety of oxidizing agents. Reaction with bromine in chloroform is particularly satisfactory for these reactions.[799]

Dithiodi(thioformates [bi(ethyl xanthates)]):[800] The potassium alkyl xanthate is dissolved in water and cooled in ice while a rapid stream of air containing 5–10% of chlorine is led through until treating a sample of the liquid with copper sulfate no longer gives a precipitate of copper xanthate. The precipitate or oil produced is separated, taken up in ether, dried, recovered, and distilled.

Iron(III) chloride,[801] iodide,[802] and potassium hexacyanoferrate(III)[803] are among other oxidants proposed for use with dithiocarbamates.

6. Isothiocyanic esters (mustard oils)[780,804]

Dithiocarbamic salts are suitable starting materials for the preparation of isothiocyanic esters (mustard oils), their reactions with heavy-metal salts,[771] chloroformic esters,[772] phosgene,[768] carbodiimides,[805] phosphorus oxychloride,[806] aryl cyanates,[732] or sodium hypochlorite[807] usually giving good yields. Reaction of amines [808,809] or their hydrochlorides with thiophosgene[810] is also generally applicable.

Preparation of isothiocyanic esters from dithiocarbamic salts:

(1) Reaction with carbodiimides:[805] A primary aliphatic amine (0.1 mole) is added to a solution of dicyclohexylcarbodiimide (0.1 mole) and carbon disulfide (40 ml) in ether or tetrahydrofuran (100–200 ml) stirred at −10°. The temperature is allowed to rise to 20° during 3 h. The mixture is then set aside at room temperature for 12 h, after which the dicyclohexylurea, is filtered off and washed with a little ether, the filtrate is evaporated, and the residual isothiocyanate is distilled in a vacuum or recrystallized. Yields are about 80%.

(2) Reaction with phosphorus oxychloride:[806] Carbon disulfide (18 ml, 0.3 mole) is dropped into a stirred solution of an amine (0.3 mole) and anhydrous triethylamine (126 ml, 0.9 mole) in anhydrous ether (150 ml) at −5°; with aromatic amines the mixture is set aside overnight. Then a solution of phosphorus oxychloride (28 ml, 0.3 mole) in anhydrous ether (30 ml) is dropped in, with stirring, at −10° to −5°. Next day the precipitated triethylammonium chloride is filtered off and stirred thoroughly with two portions of ether. The ethereal solutions are extracted with sodium hydrogen carbonate solution and with water, dried over sodium sulfate, concentrated, and fractionated. Yields are about 60%.

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[802] J. von Braun, *Ber. Deut. Chem. Ges.*, **35**, 819 (1902).

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[804] S. J. Assony in N. Kharasch, "Organic Sulfur Compounds," Pergamon Press, Oxford–London–New York–Amsterdam, 1961, Vol. 1, p. 326.

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[807] E. Schmidt, F. Zaller, F. Moosmüller, and E. Kammerl, *Annalen*, **585**, 230 (1954).

[808] G. M. Dyson, *Chem. & Ind. (London)*, **1954**, 934.

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[810] E. Tietze, S. Peterson, and G. Domagk, *Chem. Ber.*, **86**, 312 (1953).

(3) Reaction with cyanic esters:[732] Carbon disulfide (2.28 g, 30 mmoles) in ether (5 ml) is dropped into a solution of the amine (30 mmoles) and triethylamine (3.03 g, 30 mmoles) in ether (20 ml) which is stirred and cooled in ice-water. The mixture is then left at room temperature for 1 h (or 24 h for aromatic amines), treated with phenyl cyanate (3.57 g, 30 mmoles), and diluted with ether (5 ml). The clear solution that results is extracted with dilute hydrochloric acid, with sodium hydrogen carbonate solution, and with water, concentrated, filtered from the precipitated phenyl thiocarbamate, and fractionated. Yields are about 60%.

2-Chloroethyl isothiocyanate:[811] 2-Chloroethylammonium chloride (50 g), dissolved in water (100 ml), and chloroform (200 ml) are stirred together and cooled in ice while a concentrated aqueous solution of calcined sodium carbonate (130 g) and a solution of thiophosgene (50 g) in chloroform (50 ml) are dropped in simultaneously; the solution must remain alkaline throughout this addition. After a further 0.5 hour's stirring, the chloroform layer is separated, dried over sodium sulfate, and fractionated. The product boils at 80°/13 mm.

Isothiocanic esters are also readily accessible by acid fission of diarylureas,[106a] reaction of arylamines with *N,N*-diethylthiocarbamoyl chloride,[812] and by treatment of *N*-metalated amidophosphates with carbon disulfide.[813]

Acyl isothiocyanates are prepared from carbonyl chlorides and thiocyanic salts:

$$\mathrm{RCOCl + MSCN \longrightarrow RCO{-}NCS + MCl}$$

Because of their great reactivity these products are often not isolated but are used in solution for further reactions.

Benzoyl isothiocyanate:[814] A mixture of dry lead thiocyanate (65 g; prepared from lead acetate and potassium thiocyanate), benzoyl chloride (55 g), and benzene (100 ml) is boiled for 1 h, then filtered and distilled in a vacuum. The product (30 g) boils at 119°/10 mm.

Numerous carbonyl chlorides[815,816] and chloroformic esters[817,818] have been subjected to this reaction.

The most reactive compounds of this series, namely, sulfonyl isothiocyanates, can be prepared by either of two syntheses, both satisfactory in practice; these are thermolysis of *N*-sulfonyldithiourethanes (yields 30 to 50%):[819]

$$\mathrm{RSO_2NH{-}CS{-}SCH_3 \xrightarrow{150-160^\circ} RSO_2{-}NCS + CH_3SH}$$

and treatment of salts of (sulfonylimino)dithiocarbonic acid with acylating agents such as phosgene,[820,821] chloroformic esters,[7181] and phosphorus pentachloride[820] (yields 60–80%):

$$\mathrm{RSO_2N{=}C(SK)_2 + COCl_2 \longrightarrow RSO_2{-}NCS + COS + 2KCl}$$

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[811] H. Brintzinger, K. Pfannenstiel, and H. Koddebusch, *Chem. Ber.*, **82**, 399 (1949).

[812] A. A. R. Sayigh, H. Ulrich, and J. S. Potts, *J. Org. Chem.*, **30**, 2465 (1965).

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[815] A. E. Dixon and co-workers, *J. Chem. Soc.*, **67**, 565, 1040 (1895); **69**, 855, 1593 (1896).

[816] P. A. Smith and R. O. Kan, *Org. Syn.*, **44**, 91 (1964).

[817] J. Goerdeler and H. Horn, *Chem. Ber.*, **96**, 1551 (1963).

[818] R. E. Doran, *J. Chem. Soc.*, **69**, 324 (1896); **79**, 906 (1901).

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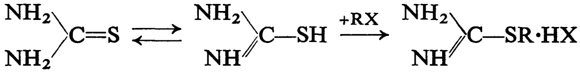
[820] K. Dickoré and E. Kühle, *Angew. Chem. Int. Ed., Engl.*, **4**, 430 (1965).

[821] K. Hartke, *Arch. Pharm.*, **299**, 175 (1966).

7. Isothiourea salts*

The chemical behavior of thiourea and its *N*-derivatives is determined by the existence of tautomeric forms; the mercapto group is almost always the point of attack in chemical reactions.



$$(NH_2)_2C{=}S \rightleftarrows NH_2(NH{=})C{-}SH \xrightarrow{+RX} NH_2(NH{=})C{-}SR{\cdot}HX$$

Thiourea Isothiourea

The usual alkylating agents, such as alkyl halides,[822-824] dimethyl sulfate,[825, 826] sulfonic esters,[827] and vinyl compounds in the presence of acid,[828,829] thus yield *S*-alkylisothiourea salts (thiouronium salts).

General directions for preparation of thiouronium salts:[620] Equimolar amounts of thiourea and alkyl halide are heated on the water-bath in a volume of alcohol equal to that of the halide, until treatment of a sample with ammoniacal silver nitrate no longer gives a precipitate of silver sulfide.

When ethylene dibromide or dichloride is used the amount of alcohol must be increased four- to five-fold; the resulting *S,S'*-ethylenedithiouronium salts are insoluble in ethanol and can be filtered off.

In some cases,[272] particularly in the preparation of *S*-cyclohexylthiouronium salts,[620] it proved useful to have hydrogen bromide present during alkylation of the alcohols.

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* See also page 635.

[822] E. Brand and F. C. Brand, *Org. Syn.*, **22**, 59 (1942).

[823] A. Bertram, *Ber. Deut. Chem. Ges.*, **25**, 48 (1892).

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CHAPTER 9

Formation of Carbon-Phosphorus Bonds

Compiled by
H. Teichmann

9.1. Formation of the carbon–phosphorus bond by addition

I. Addition of phosphorus compounds to C—C multiple bonds

1. Addition of compounds containing P–H bonds[1]

a. Addition of phosphine and primary and secondary phosphines[2a]

Phosphine and primary and secondary phosphines add to non-activated olefins in the presence of radical-formers[3,4] or if irradiated by ultraviolet light.[3,5] Azodi(isobutyronitrile) as initiator gives better yields than does di-*tert*-butyl peroxide.[4] The experimental conditions (temperature and, if necessary, pressure) required vary according to the nature of the compounds used. Phosphine in excess gives the primary phosphine as main product; but taking the olefin in excess leads to high yields of tertiary phosphine only if the double bond is not too strongly sterically hindered; for example, with 1-butene phosphine gives 67% of tributylphosphine,[3] but with isobutene gives little and with cyclohexene no tertiary phosphine and only the primary and secondary products.[4] Phosphine also gives good yields with olefins that polymerize readily in the absence of phosphine, only minimal amounts of telomer being formed during the additions. Radical addition is reversible, as is shown by isomerization of *cis*- to *trans*-2-butene in its reaction with phenyl- or dibutylphosphine.[6]

A variety of processes is available for preparation of **phosphine** (**N.B.**: very poisonous and flammable): hydrolysis of calcium phosphide[7] or aluminum phosphide[8] (best if suspended in an inert solvent[9,10]), white phosphorus,[7] a mixture of phosphorus and diphosphorus tetraiodide,[11] or phosphonium iodide;[7] thermal disproportionation of phosphorus acid;[3,5] or reduction of phosphorus trichloride by lithium tetrahydroaluminate.[5]

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[1] F. W. Stacey and J. F. Harris, *Org. Reactions,* **13**, 218 (1963).

[2] L. Maier, *Progr. Inorg. Chem.*, **5**, (a) 179, (b) 184 (1963).

[3] A. R. Stiles, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **74**, 3282 (1952).

[4] M. M. Rauhut and co-workers, *J. Org. Chem.*, **26**, 5138 (1961).

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[6] J. Pellon, *J. Amer. Chem. Soc.*, **83**, 1915 (1961).

[7] G. Bauer, "Handbuch der Präparativen Anorganischen Chemie," Verlag Ferdinand Enke, Stuttgart, 2nd ed., 1960, Vol. 1, p. 471.

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[10] USSR Pat. 125,551; *Chem. Abstr.*, **54**, 15,874 (1960).

[11] W. C. Fernelius, *Inorg. Synth.*, **2**, 41 (1946).

Primary phosphines are also obtained in good yield by an acid-catalysed reaction of non-activated olefins with 20–40 atm of phosphine at 30–60°;[12] those olefins react most readily that yield a tertiary carbonium ion.

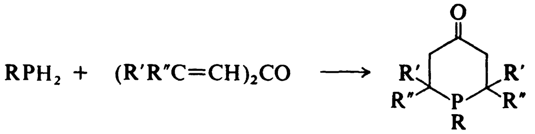
Olefins that are activated by electron-attracting substituents add phosphine and primary or secondary phosphines extremely readily in the presence of strong bases (potassium hydroxide or organic bases such as heptamethylbiguanide).

Bis-(2-cyanoethyl)phenylphosphine:[9] Acrylonitrile (24 g) is dropped during 15 min into a vigorously stirred mixture of phenylphosphine [25 g; prepared from dichloro(phenyl)-phosphine[13]], acetonitrile (25 ml), and aqueous 10N-potassium hydroxide solution (5 ml) under nitrogen. The initial reaction is very violent, and the mixture should be kept at 25 to 30° by cooling in ice. The whole is stirred for an additional 2.5 h, then the organic phase is separated, washed with saturated sodium chloride solution (3 × 10 ml), dried over sodium sulfate and distilled. The main fraction (38.2 g, 77%), b.p. 215–233°/0.2 mm, crystallizes, when kept (m.p. 73–74°). A further amount (5 g) can be obtained by crystallizing the small forerun from ethanol (m.p. 72–73°).

Many activated olefins, *e.g.*, acrylonitrile[14] and ethyl acrylate,[15] also add phosphines in the absence of a catalyst, but higher temperatures are then needed.

(2-Cyanoethyl)diphenylphosphine:[14] Diphenylphosphine [3.3 g; from chloro(diphenyl)-phosphine[14]] and acrylonitrile (1.9 g) are placed under nitrogen in a tube cooled in Dry Ice. The tube is then sealed and heated for 7 h at 130°. Removing the unchanged nitrile by distillation leaves a residue that crystallizes; two recrystallizations from methanol gives the product, m.p. 64–64.5°, in 71% yield (3 g).

Under the same conditions, doubly α,β-unsaturated ketones such as dibenzylideneacetone and phorone are converted into cyclic phosphorinan-4-ones, which yield the corresponding phosphorinanes on Huang–Minlon reduction:[16]



2,2,6,6-Tetramethyl-1-phenylphosphorinan-4-one:[16] Phorone (7 g) and phenylphosphine (5.6 g) are heated under nitrogen for 6 h at 130°. The product, which crystallizes on cooling, is distilled (b.p. 130–140°/0.5 mm) and then sublimed at 100°/0.3 mm. It has m.p. 91–92° (yield 77%).

Secondary phosphines may be replaced by their alkali salts; these add more easily even to non-activated olefins and afford tertiary phosphines on hydrolytic working up.[17]

An elegant method of preparing tertiary phosphine oxides starts from elemental phosphorus and consists of using acrylonitrile or acrylamide to trap

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[12] M. C. Hoff and P. Hill, *J. Org. Chem.*, **24**, 356 (1959).

[13] F. G. Mann and I. T. Millar, *J. Chem. Soc.*, **1952**, 3039.

[14] F. G. Mann and I. T. Millar, *J. Chem. Soc.*, **1952**, 4453.

[15] B. A. Arbuzov and co-workers, *Dokl. Akad. Nauk SSSR*, **127**, 1217 (1959); *Chem. Abstr.*, **54**, 1377 (1960).

[16] R. P. Welcher and N. E. Day, *J. Org. Chem.*, **27**, 1824 (1962).

[17] A. A. Petrov and V. A. Kormer, *Dokl. Akad. Nauk SSSR*, **132**, 1905 (1960); *Chem; Abstr.*, **54**, 22 327 (1960); K. Issleib and K. Jasche, *Chem. Ber.*, **100**, 412 (1967).

the intermediate stages in the alkaline hydrolysis that leads to phosphine:[18,19]

$$P_4 + 2KOH + 4H_2O + 9CH_2{=}CHR \longrightarrow 3(RCH_2CH_2)_3PO + K_2HPO_3$$

Tris-(2-cyanoethyl)phosphine oxide:[19] White phosphorus (7.7 g) is melted at 50° under nitrogen in a mixture of acetonitrile (75 ml) and acrylonitrile (29.7 g). On cooling to 30° the phosphorus solidifies in finely divided form if continuous rapid stirring is provided. The suspension is stirred rapidly while 10N-potassium hydroxide solution (18 ml) is added during 20 min with the temperature held at 30–35° by external cooling. The mixture is stirred for a further hour, during which a thick white precipitate is formed, but this dissolves when dilute hydrochloric acid (from 10 ml of concentrated acid and 300 ml of water) is added. For removal, any unchanged phosphorus is melted by warming to 50° and, after cooling, is filtered off through kieselguhr under nitrogen. The filtrate is evaporated in a vacuum and the residue is extracted with methanol (200 ml). The phosphine oxide, m.p. 165–169° (23.5 g, 45%), crystallizes from the methanol, and a further amount (4.5 g, 9%) is obtained by concentration of the mother-liquors. Recrystallization from aqueous 2-propanol gives material of m.p. 172–173°.

Tris-(2-carbamoylethyl)phosphine oxide is obtained analogously in 74% yield by use of acrylamide.

b. Addition of dialkyl phosphites

Addition of phosphorous diesters to olefins is an important method of preparing phosphonic diesters and thence, by hydrolysis, of phosphonic acids. This addition to non-activated olefins, like that of phosphines, is a radical reaction: peroxides, azodi(isobutyronitrile), or UV-irradiation initiates it. Except for the photochemical addition, which occurs at room temperature in the presence of acetone as senzitizer,[20] it is necessary to heat the reactants under nitrogen for several hours at temperatures above 100°. Lower telomers are by-products, the amounts formed increasing with the concentration of the olefin. Yields are mostly in the region of 40–60%. Dialkyl thiophosphites[23] and phosphonous monoesters[22,23] react in the same way as dialkyl phosphites.[20–22] Phosphorous acid itself gives poor yields,[24] but good results have been reported with hypophosphorous acid, H_2POOH, and its salts.[22]

Base-catalysed addition of dialkyl phosphites to activated olefins such as α,β-unsaturated ketones and carboxylic acid derivatives[25–27] is appreciably easier, the reaction being exothermic and often giving high yields. Here too it is essential that there be no more than slight steric hindrance around the double bond because otherwise the phosphite may add to the carbonyl double

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[18] M. M. Rauhut and A. M. Semsel, U.S. Pat 3,067,251, 3,148,206; *Chem. Abstr.*, **58**, 9139 (1963); **61**, 14,711 (1964).

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[20] A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Amer. Chem. Soc.*, **80**, 714 (1958).

[21] M. S. Kharasch, R. A. Mosher, and I. S. Bengelsdorf, *J. Org. Chem.*, **25**, 1000 (1960); R. Sasin and co-workers, *J. Amer. Chem. Soc.*, **81**, 6275 (1959); G. H. Barnes and M. P. David, *J. Org. Chem.*, **25**, 1191 (1960); U.S. Pat. 3,029,273; *Chem. Abstr.*, **57**, 9741 (1962).

[22] U.S. Pat. 2,724,718; *Chem. Abstr.*, **50**, 10,124 (1956).

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[25] A. N. Pudovik and B. A. Arbuzov, *Dokl. Akad. Nauk SSSR*, **73**, 327 (1950); *Chem. Abstr.*, **45**, 2853 (1951).

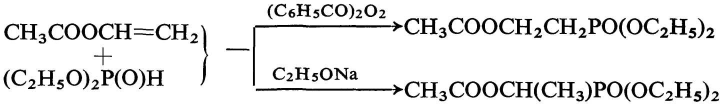
[26] B. Bochwic and J. Michalski, *Rocz. Chem.*, **25**, 338 (1951); *Chem. Abstr.*, **48**, 12,013 (1954).

[27] N. Kreutzkamp and H. Schindler, *Arch. Pharm.*, **295**, 28 (1962).

bond of, *e.g.*, mesityl oxide; also, addition to α,β-unsaturated aldehydes occurs at the carbonyl double bond. The most convenient basic catalyst is an alcoholic alkoxide solution, where the alkyl group of the latter should be the same as that of the phosphite so as to avoid transesterification.

Dibutyl 2-cyanoethylphosphonate:[27] A saturated solution of sodium butoxide in 1-butanol is added dropwise to a stirred and cooled mixture of dibutyl phosphite (97 g) and acrylonitrile (26.5 g) until the temperature ceases to rise. The mixture is then heated under reflux on a water-bath for a further 30 min, after which distillation affords the phosphonate (106 g, 80%), b.p. 143–144°/0.8 mm, n_D^{23} 1.4420.

Unlike radical addition of dialkyl phosphites to vinyl esters, which occurs at the β-position,[28,29] the base-catalysed addition takes place at the α-position:[29]



$$\left.\begin{array}{c} CH_3COOCH{=}CH_2 \\ + \\ (C_2H_5O)_2P(O)H \end{array}\right\} \begin{array}{l} \xrightarrow{(C_6H_5CO)_2O_2} CH_3COOCH_2CH_2PO(OC_2H_5)_2 \\ \xrightarrow{C_2H_5ONa} CH_3COOCH(CH_3)PO(OC_2H_5)_2 \end{array}$$

Enamines add dialkyl phosphites with unusual ease; no catalyst is needed and addition is at the α-position.[30]

Like dialkyl phosphites, dialkyl phosphinites R_2PHO can be added under basic catalysis to α,β-unsaturated nitriles, esters, and amides.[31]

2. Addition of compounds containing P–halogen bonds

a. Addition of phosphorus trihalides and halophosphines

Phosphorus trichloride adds to olefins both in a radical reaction[32] and in presence of $AlCl_3$.[33] The former type of reaction gives alkyldichlorophosphines, but, after hydrolytic working up, the latter affords cyclic phosphinic chlorides or phosphinic acids. Neither reaction has been studied in detail.

Phosphonic dichlorides are obtained when oxygen is led into a mixture of PCl_3 and an olefin.[34] This reaction sometimes occurs at temperatures much below 0°; the yields vary greatly but are particularly poor for the lower olefins. Haloolefins and acrylic acid derivatives often give good yields, but usually of mixed isomers.

Phosphinic chlorides are obtained analogously from alkyl- or aryl-dichlorophosphines[35,36] (cf. page 735).

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[28] S. Preis, T. C. Myers, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 6225 (1955).

[29] R. L. McConnell and H. W. Coover, *J. Amer. Chem. Soc.*, **79**, 1961 (1957).

[30] G. Opitz and co-workers, *Ann. Chem.*, **665**, 91 (1963).

[31] R. C. Miller, J. S. Bradley, and L. A. Hamilton, *J. Amer. Chem. Soc.*, **78**, 5299 (1956).

[32] M. S. Kharasch and co-workers, *J. Amer. Chem. Soc.*, **67**, 1864 (1945); B. Fontal and H. Goldwhite, *J. Org. Chem.*, **31**, 3804 (1966).

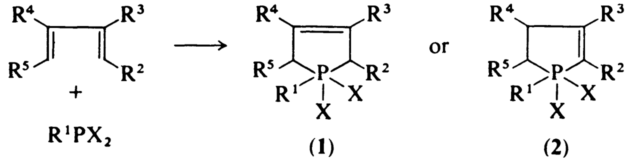
[33] E. Jungermann and co-workers, *J. Org. Chem.*, **27**, 606, 1833 (1962); *Ind. Eng. Chem., Prod. Res. Develop.*, **2**, 315 (1963); Ger. Pat. 1,183,080; *Chem. Zentralbl.*, **1965**, 34–2504.

[34] Yu. M. Zinov'ev, L. Z. Soborovskii, and co-workers, *Zh. Obshch. Khim.*, **28**, 317 (1958); 29, 1139, 3947 (1959); *Chem. Abstr.*, **52**, 13613 (1958); **54**, 1270, 20844 (1960); F. Rochlitz and H. Vilsczek, *Angew. Chem. Int. Ed., Engl.*, **1**, 652 (1962).

[35] L. Z. Soborovskii, Yu. M. Zinov'ev, and co-workers, *Zh. Obshch. Khim.*, **24**, 516 (1954); *Chem. Abstr.*, **49**, 6086 (1955).

[36] Yu. M. Zinov'ev and L. Z. Soborovskii, *Zh. Obshch. Khim.*, **26**, 3030 (1956); *Chem. Abstr.*, **51**, 8662 (1957).

1,3-Dienes add alkyl- or aryl-dihalophosphines[37] in a kind of Diels–Alder reaction. According to the structures of the diene and phosphorus components either the expected 1-alkyl- or 1-aryl-3-phospholene 1,1-dihalide (**1**) or the isomeric 2-phospholene derivative (**2**) is formed.[38,39]



Since the double-bond isomerization was at first unrecognized and later recognized only in the hydrolysis products, the position of the double bond in most of the compounds described in the literature must be regarded as uncertain. The only proved facts seem to be that with isoprene dichloro(phenyl)-phosphine gives the 2-phospholene derivative, that dichloro(methyl)phosphine and dibromo(phenyl)phosphine give the 3-phospholene, whereas also with 2,3-dimethylbutadiene dichloro(phenyl)phosphine gives the non-isomerized product of type (**1**).[38,39]

The 1,1-dihalides are rarely isolated but instead are hydrolysed to the 1-oxides,[40-45] the position of the double bond being apparently unaltered thereby.[39] The 1-sulfides can be obtained from (**1**) or (**2**) by means of H_2S,[46] and the phospholenes themselves by reduction with Mg or $LiAlH_4$.[47] Hydrogenation of the phospholene 1-oxides over Raney nickel leads to the saturated phospholane 1-oxides.[48]

The addition occurs in the presence of polymerization inhibitors such as copper stearate, aromatic polynitro compounds, or sterically hindered phenols and then sometimes requires days or weeks. In spite of the often tedious procedure the method is of great interest since, from cheap materials, it often affords good yields of compounds containing the phospholene ring system which is otherwise difficultly accessible. Compounds of type (**1**) and (**2**) have also considerable interest as efficient catalysts for the carbodiimide synthesis (cf. page 504).

1-Ethyl-3-methyl-3(?)-phospholene 1-oxide[42] (**1**; $R^1 = C_2H_5$; $R^3 = CH_3$; $R^2 = R^4 = R^5 = H$): A 2-l four-necked flask is fitted with a thermometer, dropping funnel, stirrer, and efficient condenser, then to this condenser is attached one cooled by Dry Ice. Dichloro(ethyl)-

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[37] U.S. Pat. 2,663,736; *Chem. Abstr.*, **49**, 7602 (1955).

[38] K. Hunger, U. Hasserodt, and F. Korte, *Tetrahedron*, **20**, 1593 (1964).

[39] L. D. Quin and T. P. Barket, *Chem. Commun.*, **1967**, 914.

[40] U.S. Pat. 2,663,737; *Chem. Abstr.*, **49**, 7601 (1955).

[41] B. A. Arbuzov and L. A. Shapshinskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 65; *Chem. Abstr.*, **57**, 13,791 (1962).

[42] T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Amer. Chem. Soc.*, **84**, 3673 (1962).

[43] W. B. McCormack, *Org. Syn.*, **43**, 73 (1963).

[44] L. D. Quin and co-workers, *Tetrahedron Lett.*, **1964**, 3689.

[45] I. G. M. Campbell and co-workers, *J. Chem. Soc.*, **1965**, 2184.

[46] U.S. Pat. 2,663,738; *Chem. Abstr.*, **49**, 7602 (1955).

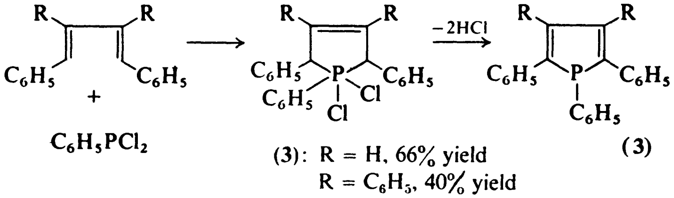
[47] L. D. Quin and co-workers, *J. Org. Chem.*, **29**, 836 (1964); *Tetrahedron Lett.*, **1965**, 2187.

[48] U.S. Pat. 2,663,739; *Chem. Abstr.*, **49**, 7602 (1955).

phosphine (780 g) and copper stearate (1 g) are placed in the flask and freshly distilled isoprene (447 g) is dropped in under nitrogen. The mixture is stirred at reflux temperature for 42 h, then at room temperature for 2 days, and is finally refluxed for a further 5 days without stirring. The excess of isoprene is then distilled off and water (850 ml) is dropped in with stirring and ice-cooling. The dark brown solution is treated in a 5-l flask with 30% sodium hydroxide solution (ca. 1250 ml; to pH 8), filtered, and extracted for 12 days with chloroform. After removal of the chloroform by distillation, vacuum-distillation of the residue through a 25-cm Vigreux column affords a water-clear liquid (453 g, 51%) with a weak smell of phosphine. This is treated for 6 h with 3% hydrogen peroxide solution at 50°, then extracted with benzene. Final working up by distillation gives a product of b.p. 115–116°/1.2–1.3 mm, n_D^{25} 1.5050.

The 1-phenyl derivative,[43] which possesses structure (2),[38,39] is obtained somewhat more conveniently (5–7 days at room temperature) in about 60% yield from dichloro(phenyl)-phosphine.

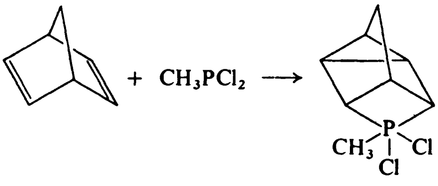
Isoprene and particularly 2,3-dimethylbutadiene react more readily than butadiene itself. 1,4-Diphenyl- and 1,2,3,4-tetraphenyl-butadiene require temperatures in excess of 200°, and loss of HCl begins already under these conditions so that the phospholes (3) are obtained directly without isolation of the phospholene dihalides.[45]



(3)

(3): R = H, 66% yield
R = C_6H_5, 40% yield

Bicyclo[2.2.1]heptadiene behaves analogously to the conjugated dienes, affording with dichloro(methyl)phosphine at room temperature the tetracyclic compound (4).[49]



(4)

Whereas cyclization of 1,3-dienes with alkyl- or aryl-dihalophosphines leads to derivatives of tertiary phosphines, use of phosphorus trihalides[50–54] provides entry to the phosphinic acid series by way of the very hygroscopic 1,1,1-trihalo-3-phospholenes. Phosphorus tribromide in particular reacts extremely readily,

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[49] M. Green, *J. Chem. Soc.*, **1965**, 541.

[50] Belg. Pat. 631,416; *Chem. Abstr.*, **61**, 688 (1964).

[51] USSR Pat. 162,845; *Chem. Zentralbl.*, **1965**, 52-2848.

[52] B. A. Arbuzov and A. O. Vizel, *Dokl. Akad. Nauk SSSR*, **158**, 1105 (1954); *Chem. Abstr.*, **62**, 2791 (1965).

[53] B. A. Arbuzov and co-workers, *Dokl. Akad. Nauk SSSR*, **159**, 582 (1964); *Chem. Abstr.*, **62**, 6505 (1965).

[54] U. Hasserodt, K. Hunger, and F. Korte, *Tetrahedron*, **19**, 1563 (1963); **20**, 1593 (1964).

affording, for instance, with 2,3-dimethylbutadiene an 85% yield of the 1,1,1-tribromide derived from 3,4-dimethyl-3-phospholene in 1 h even at −10°.[54] The trichloro, but not the tribromo, derivatives from 3-phospholenes suffer much double-bond isomerization on hydrolysis or alcoholysis, yielding the 2-phospholene derivatives.[53,54] Phosphorous ester dihalides[41,53] and diester halides[55,56] cyclize with 1,3-dienes similarly to phosphorus trihalides and give the corresponding phosphinic chlorides or esters with loss of alkyl halides.

b. Addition of phosphorus pentachloride

Phosphorus pentachloride adds exothermally to numerous 1-alkenes, giving products that usually afford alkenyltrichlorophosphonium hexachlorophosphates by loss of HCl. These extremely hygroscopic products can be converted into phosphonic chlorides by phosphorus(v) oxide or, better, by sulfur dioxide.

$$\mathrm{RCH{=}CH_2 + 2PCl_5 \longrightarrow [RCHClCH_2PCl_3]PCl_6 \xrightarrow{-HCl}}$$

$$\mathrm{[RCH{=}CHPCl_3]PCl_6 \xrightarrow[-POCl_3]{SO_2} RCH{=}CHP(O)Cl_2}$$

The yields are often good. β-Branched olefins, styrenes,[57] and vinyl ethers,[58] for instance, react in this way; but vinyl esters react differently.[59] Dienes, alkynes, and alkenynes also add PCl_5, although the reaction does not always take an unambiguous course. PCl_3 may replace the PCl_5 if chlorine is led into the reacting mixture.[57]

Styrylphosphonic dichloride:[60] A solution of styrene (26 g) in benzene (50 ml) is dropped within 30 min, with stirring and exclusion of moisture, into an ice-cooled mixture of phosphorus(v) chloride (104 g) and dry benzene (150 ml). The mixture is then stirred for 30 min at room temperature, after which sulfur dioxide is led until the first crystalline product has dissolved, cooling being sometimes necessary at that stage. The benzene is finally removed and the residual liquid is distilled in a vacuum, affording about 90% (about 50 g) of a product, b.p. 107–110°/0.2 mm, that later solidifies (m.p. 71–72°).

3. Addition of tertiary phosphines and phosphites

Olefins with electrophilic substituents, but not those with electron-donating substituents, add tertiary phosphines;[61] the phosphonium betaines first formed stabilize themselves under some circumstanes by forming their tautomers, the alkylidenephosphoranes. Thus, for example, the ylide (5) is obtained in more

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[55] B. A. Arbuzov and co-workers, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.* **1962**, 2074; *Chem. Abstr.*, **58**, 11396 (1963).

[56] N. A. Razumova and A. A. Petrov, *Zh. Obshch. Khim.*, **31**, 3144 (1961); **33**, 783, 3858 (1963); **34**, 1886 (1964); *Chem. Abstr.*, **56**, 12720 (1962); **59**, 8783 (1963); **60**, 10711 (1964); **61**, 8836 (1964).

[57] G. M. Kosolapoff and W. F. Huber, *J. Amer. Chem. Soc.*, **68**, 2540 (1946).

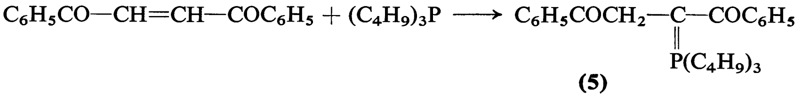
[58] K. N. Anisimov and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1954**, 610; *Chem. Abstr.*, **49**, 11540 (1955).

[59] I. F. Lutsenko and M. Kirilov, *Zh. Obshch. Khim.*, **31**, 3594 (1961); *Chem. Abstr.*, **57**, 8606 (1962).

[60] R. Schmutzler, *Org. Syn.*, **45**, 99 (1965).

[61] L. Horner and K. Klüpfel, *Ann. Chem.*, **591**, 69 (1955).

than 80% yield from *trans*-1,2-dibenzoylethylene (1,4-diphenyl-2-butene-1,4-dione) and tributylphosphine in methylene chloride at 0°:[62]



$$C_6H_5CO{-}CH{=}CH{-}COC_6H_5 + (C_4H_9)_3P \longrightarrow C_6H_5COCH_2{-}\underset{\underset{\displaystyle P(C_4H_9)_3}{\|}}{C}{-}COC_6H_5$$

(5)

Quinones also add tertiary phosphines, but give partly *C*- and partly *O*-phosphonium compounds.[63] A series of phosphonium bromides has been prepared in high yields by warming triphenylphosphine with activated olefins such as acrylic acid derivatives in 48% hydrobromic acid at 100°:[64]

$$(C_6H_5)_3P + RCH{=}CHX \xrightarrow{HBR} [(C_6H_5)_3\overset{+}{P}{-}CHRCHX]Br^-$$

Electronegatively substituted acetylenes afford triphenylvinylphosphonium salts analogously in high yields but under somewhat more energetic conditions.[65] In the absence of acid the primary adducts of aromatic phosphines to acetylenes readily undergo further reactions.[66,67]

(1,2-Diphenylethyl)diphenylphosphine oxide:[67] A solution of triphenylphosphine (10 g), phenylacetylene (9 g), and water (3 ml) in bis-(2-hydroxyethyl) ether (75 ml) is heated under reflux for 8 h, then the solvent is removed in a vacuum and the residue is recrystallized from benzene (yield 7.2 g, 50%). After several recrystallizations from benzene the product has m.p. 233–234°.

When trialkyl phosphites are heated with acrylic acids to about 120° [2-(alkoxycarbonyl)ethyl]phosphinic esters are formed, sometimes in satisfactory yield:[68]

$$(RO)_3P + R'CH{=}CHCOOH \longrightarrow (RO)_3\overset{+}{P}CHRCH_2COO^- \longrightarrow$$
$$(RO)_2P(O)CHR'CH_2COOR$$

Acraldehyde and crotonaldehyde react more readily and when warmed in dioxan at 70° afford (3-alkoxyallyl)phosphonic esters analogously:[69]

$$(RO)_3P + R'CH{=}CH{-}CHO \longrightarrow (RO)_2P(O)CHR'CH{=}CH{-}OR$$

This reaction becomes more generally applicable if a proton donor such as methanol, ethanol, or, better, phenol is added:[70] substituents have the same effect as in Michael addition:

$$(RO)_3P + R'CH{=}CHX + R''OH \longrightarrow (RO)_2P(O)CHR'CH_2X + ROR''$$

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[62] F. Ramirez and co-corkers, *Tetrahedron Lett.*, **1965**, 201.

[63] F. Ramirez and co-workers, *J. Amer. Chem. Soc.*, **78**, 5614 (1956); *Tetrahedron*, **21**, 1941 (1965).

[64] H. Hoffmann, *Chem. Ber.*, **94**, 1331 (1961).

[65] H. Hoffmann and H. J. Diehr, *Chem. Ber.*, **98**, 363 (1965).

[66] J. C. Tebby and co-workers, *J. Chem. Soc.*, **1961**, 2126; *C*, **1967**, 944; *Tetrahedron Lett.*, **1965**, 2361.

[67] D. W. Allen and J. C. Tebby, *Tetrahedron*, **23**, 2795 (1967).

[68] G. Kamai and V. A. Kukhtin, *Zh. Obshch. Khim.*, **27**, 2372 (1957); *Chem. Abstr.*, **52**, 7127 (1958).

[69] G. Kamai and V. A. Kukhtin, *Zh. Obshch. Khim.*, **27**, 2376 (1957); *Chem. Abstr.*, **52**, 7127 (1958).

[70] R. G. Harvey, *Tetrahedron*, **22**, 2561 (1966).

α,β-Unsaturated aldehydes and vinyl ketones undergo this reaction particularly easily (even at 0°), the carbonyl group being simultaneously largely acetalized by the hydroxy compound. Alkynes such as propiolic esters also add trialkyl phosphites, with simultaneous saturation of the resulting double bond by addition of the alcohol.

This reaction is a welcome expansion of the base-catalysed addition of dialkyl phosphites which fails with sterically hindered olefins and with unsaturated aldehydes occurs at the carbonyl group. An example of the efficiency of the method with sterically hindered alkenes is afforded by the reaction of mesityl oxide which leads to **diethyl (1,1-dimethyl-3-oxobutyl)phosphonate**:[70]

Mesityl oxide (0.1 mole), triethyl phosphite (0.125 mole), and phenol (25 g) under nitrogen are heated and stirred for 24 h in an oil bath at 100°. Distillation of the crude product affords a 96% yield of material having b.p. 98°/1.6 mm, n_D^{28} 1.4384.

The same conditions are used for α,β-unsaturated esters, amides, and nitriles.

II. Addition of phosphorus compounds to C=O bonds

1. Addition of compounds containing P–H bonds

a. Addition of phosphine and primary or secondary phosphines

Addition of phosphine or its derivatives to carbonyl compounds offers manifold possibilites for the preparation of organophosphorus compounds. It usually occurs under acid catalysis and normally does not stop at the 1 : 1 adduct stage since the reactivity of phosphines increases progressively from PH_3 up to the tertiary phosphine stage. For example, high yields of tetrakis-(1-hydroxyalkyl)phosphonium salts are obtained from PH_3 and formaldehyde[8,71] or other unbranched aliphatic aldehydes[72,73] in the presence of hydrochloric acid:

$$4RCHO + PH_3 + HCl \longrightarrow [RCH(OH)]_4P^+Cl^-$$

Well-tested laboratory directions for the preparation of the hydroxymethyl compound have been provided by Reeves and his co-workers.[8]

It follows further that primary, secondary, and tertiary phosphines give α-hydroxy phosphonium salts analogously;[74–77] only in the absence of acid are tertiary phosphines obtained.[75,78]

Bis(hydroxymethyl)diphenylphosphonium chloride:[77] To a solution of concentrated hydrochloric acid (100 ml) in tetrahydrofuran (200 ml) under nitrogen at room temperature are

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[71] E. V. Kuznetsov, R. K. Valetdinov, Ts. Ya. Roithard, and L. B. Zakharova, *Tr. Kazan. Khim.-Tekhnol. Inst.*, **1960**, No. 29, 20; *Chem. Abstr.*, **58**, 547 (1963); Kh, R. Raver, A. B. Bruker, and L. Z. Soborovskii, *Zh. Obshch. Khim.*, **32**, 588 (1962); *Chem. Abstr.*, **58**, 6857 (1963).

[72] Brit. Pat. 885,440 (1960); U.S. Pat. 3,013,085; *Chem. Abstr.*, **57**, 11240 (1962).

[73] S. A. Buckler and V. P. Wystrach. *J. Amer. Chem. Soc.*, **83**, 168 (1961).

[74] S. Trippett, *J. Chem. Soc.*, **1961**, 2813.

[75] H. Hellmann and co-workers, *Ann. Chem.*, **659**, 49 (1962).

[76] K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **31**, 2729, 3411, 3417 (1961); *Chem. Zentralbl.*, **1965**, 40-0847, 47-0921, 47-0922.

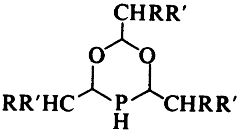
[77] M. Grayson, *J. Amer. Chem. Soc.*, **85**, 79 (1963).

[78] Ger. Pat. 1,035,135; *Chem. Abstr.*, **54**, 14125 (1960).

added diphenylphosphine (27 g) and then, dropwise during 30 min, a solution of 37% aqueous formaldehyde (40 g) in tetrahydrofuran (50 ml). The reaction is feebly exothermic. The mixture is stirred for 2 h at room temperature, then the solvent is removed in a vacuum at 50° (bath temperature). The product, which crystallizes on cooling, is washed with a little acetone (yield 36 g, 88%; m.p. 161–162°) and after recrystallization from 2-propanol has m.p. 161°.

On treatment with aqueous or alcoholic alkali hydroxide or with tertiary amines the quaternary (hydroxymethyl)phosphonium salts are cleaved with loss of one equivalent of formaldehyde and formation of the tertiary phosphine;[74–77,79,80] if the phosphonium salt contains more than one hydroxymethyl group, the amount of base used must not exceed one equivalent; the fission occurs more easily the less basic is the resulting phosphine.[75] As the tertiary (hydroxymethyl)phosphine quaternizes again with alkyl halides, any desired tertiary phosphine can be built up by successive quaternizations and basic fissions.[75,77,79]

α-Halo aldehydes such as chloral and dichloroacetaldehyde react with PH_3 only so far as to give secondary phosphines.[73,81] α-Branched aliphatic aldehydes and PH_3 also give secondary aldehydes, these products cyclizing by acetalization to form 1,3,5-dioxaphosphacyclohexanes (1,3,5-dioxaphosphanes) (**6**).[73,82] Dialdehydes such as glutar- and succin-dialdehyde with PH_3 afford spirophosphonium salts.[73,82]



(**6**)

Aromatic aldehydes behave differently: with PH_3 they form minor amounts of compounds of type (**6**), but the main products are tertiary phosphine oxides resulting from deoxygenation of the carbonyl compound:[83,84]

$$PH_3 + ArCHO \longrightarrow ArCH_2P(O)H_2 \xrightarrow{2ArCHO} ArCH_2P(O)[CHAr(OH)]_2$$

This type of reaction is also observed on treatment of aliphatic aldehydes (except formaldehyde) with secondary phosphines containing electron-attracting substituents in strongly acidic solution at elevated temperature.[85] It thus affords a method for preparing tertiary phosphine oxides.

(1-Naphthylmethyl)diphenylphosphine oxide:[85] Diphenylphosphine (10.5 g), 1-naphthaldehyde (8.9 g), and concentrated hydrochloric acid (50 ml) are heated under reflux and stirred under nitrogen for 8 h. After cooling, the mixture is then diluted with water and extracted

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[79] K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, (a) **31**, 3421 (1961); (b) **32**, 553 (1962); (c) **35**, 1602 (1965); *Chem. Abstr.*, **57**, 4693 (1962); **58**, 5714 (1963); **63**, 18145 (1965).

[80] Ger. Pat. 1,151,255; *Chem. Abstr.*, **60**, 54 (1965); E. Steininger, *Chem. Ber.*, **95**, 2541 (1962).

[81] V. Ettel and J. Horák, *Collect. Czech. Chem. Commun.*, **26**, 2087 (1961).

[82] S. A. Buckler and V. P. Wystrach. *J. Amer. Chem. Soc.*, **80**, 6454 (1958).

[83] S. A. Buckler, *J. Amer. Chem. Soc.*, **82**, 4215 (1960).

[84] V. Ettel and J. Horák, *Collect. Czech. Chem. Commun.*, **25**, 2191 (1960); **26**, 1949 (1961).

[85] M. Epstein and S. A. Buckler, *Tetrahedron*, **18**, 1231 (1962).

with chloroform. Drying over sodium sulfate and evaporation of the chloroform extracts affords a white residue which is washed with ether (yield 18.1 g, 83%; m.p. 161–162°) and after recrystallization from ethanol has m.p. 161–163°.

Under mild conditions some of the primary products, the α-hydroxy phosphines, can be isolated and then, when heated, isomerize to the phosphine oxides.[85]

Addition of PH_3 and phosphines to ketones is less clear-cut; here also deoxygenation to form phosphine oxide derivatives predominates.[86] Polycyclic systems can be obtained from β-diketones[87] and pyruvic acid.[88]

b. Addition of dialkyl phosphites

Aldehydes and ketones add dialkyl phosphites under base catalysis, yielding α-hydroxy phosphonic esters;[29,89] and dialkyl thiophosphites afford α-hydroxy thiophosphonic esters analogously.[90]

Diethyl (1-hydroxybutyl)phosphonate:[29] A mixture of butyraldehyde (36 g), diethyl phosphite (69 g), and triethylamine (5 ml) is stirred whilst heated at 90° for 1.5 h. Subsequent distillation through a short Vigreux column yields the adduct ester (53 g, 50%), b.p. 125 to 129°/1.3–1.5 mm, n_D^{20} 1.4358.

Another procedure is to treat an equimolar mixture of the components dropwise with a saturated alcoholic alkoxide solution (preferably one containing the same alkyl group as that in the ester) until the exothermic reaction moderates; after subsequent heating if necessary, the mixture is neutralized with acetic acid before distillation.[29,91]

Addition of diphenyl phosphite to acetone can be effected also with acid catalysis.[92]

Reactivities and yields are said to increase with increasing size of the alkyl group of the aldehyde.[89] Addition to α,β-unsaturated aldehydes occurs selectively to the carbonyl group,[91] this behavior differing from that of α,β-unsaturated ketones (cf. page 695); of the unsaturated ketones it is only those, such as mesityl oxide, that carry two alkyl groups at the β-position, that add phosphites to the carbonyl group.[93]

Like the adducts of phosphines to carbonyl compounds, α-hydroxy phosphonic esters are readily cleaved to their components, particularly by alkali.[94]

Addition of dialkyl phosphites to α-halo ketones[95] and aldehydes[96–98] occurs especially easily, no catalyst being needed. The phosphonate derived from

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[86] S. A. Buckler and M. Epstein, *J. Amer. Chem. Soc.*, **82**, 2076 (1960); *Tetrahedron*, **18**, 1211 (1962).

[87] M. Epstein and S. A. Buckler, *J. Amer. Chem. Soc.*, **83**, 3279 (1961).

[88] S. A. Buckler, *J. Amer. Chem. Soc.*, **82**, 4215 (1960).

[89] V. S. Abramov and N. A. Il'jina, *Zh. Obshch. Khim.*, **24**, 124 (1954); *Chem. Abstr.*, **49**, 2997 (1955).

[90] A. B. Pudovik and G. A. Zametaeva, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, **1952**, 932; *Chem. Abstr.*, **47**, 10467 (1953).

[91] A. N. Pudovik and Yu. P. Kitaev, *Zh. Obshch. Khim.*, **22**, 46 (1952); *Chem. Abstr.*, **47**, 2687 (1953).

[92] E. N. Walsh, *J. Amer. Chem. Soc.*, **81**, 3023 (1959).

[93] A. N. Pudovik, *Dokl. Akad. Nauk SSSR*, **73**, 499 (1950); *Chem. Abstr.*, **45**, 2856 (1951).

[94] V. S. Abramov and co-workers, *Dokl. Akad. Nauk SSSR*, **84**, 281 (1952); *Chem. Abstr.*, **47**, 3227 (1953).

chloral and dimethyl phosphite has achieved great importance because of its insecticidal properties.

Dimethyl (2,2,2-trichloro-1-hydroxyethyl)phosphonate:[97] Freshly distilled chloral (74 g) is dropped into dimethyl phosphite (60 g) with stirring whilst the temperature is kept at 50–60° by cooling. When cold, the product is taken up in benzene (300 ml), washed with 4% sodium hydrogen carbonate solution (50 ml), and dried over sodium sulfate. The solvent is then distilled off and the residue is recrystallized from water, yielding colorless needles, m.p. 81° (115.8 g, 90%).

1-Hydroxyalkylidenediphosphonates can be prepared by using an α-keto phosphonate as the carbonyl component in the presence of an alkoxide[99] or a tertiary amine:[100]

$$\mathrm{RCO{-}P(O)(OR')_2 + (R'O)_2P(O)H \longrightarrow RC(OH)[P(O)(OR')_2]_2}$$

Tetraethyl 1-hydroxy-2-methylpropylidenediphosphonate:[100] Diethyl isobutyroylphosphonate (20.8 g) is dropped, with stirring, into a mixture of diethyl phosphite (20 g) and triethylamine (7 g), and the whole is then stirred for 2 h, after which fractional distillation affords the tetraethyl ester (25.2 g, 73%), b.p. 142–145°/1.2 mm, n_D^{20} 1.4359.

Addition of secondary phosphine oxides, which are structurally analogous to dialkyl phosphites, to aldehydes and ketones was mentioned in the preceding Section.[cf.101] Secondary phosphine oxides are, however, not always easy to prepare and can be replaced by their salts which are prepared from the phosphinic chlorides and sodium or Grignard solutions.[102] The same salts are obtained from dialkyl phosphites (cf. page 746).

$$\mathrm{(RO)_2P(O)H \xrightarrow{R'MgX} R'_2P(O)MgX \xrightarrow[Hydrol.]{R''CHO} R'_2P(O)CHR''OH}$$

Dibenzyl-(α-hydroxybenzyl)phosphine oxide:[103] A solution of dibutyl phosphite (27.9 g) in benzene (100 ml) is dropped under nitrogen, with stirring, during 45 min into a Grignard solution prepared from magnesium (10 g), benzyl chloride (52 g), and ether (100 ml). A further amount (200 ml) of benzene is then added and the whole is heated under reflux for 30 min. Benzaldehyde (15 g), dissolved in benzene (100 ml), is then added during 30 min, the gelatinous mass that had been formed then dissolving in a feebly exothermic reaction. The solution is next heated under reflux for 90 min and set aside overnight, and the product is hydrolysed with dilute (3 : 1) sulfuric acid (250 ml). The organic phase is washed with sodium carbonate solution and then water, dried, and concentrated to 150 ml. Addition of heptane (350 ml) and cooling causes crystallization of the phosphine oxide (31 g; m.p. 161–163°). Two recrystallizations from aqueous ethanol give material (23.9 g) of m.p. 162.5–163°.

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[95] V. S. Abramov and A. L. Shalman, *Zh. Obshch. Khim.*, **32**, 827 (1962); *Chem. Abstr.*, **58**, 9129 (1963).

[96] F. W. Barthel and co-workers, *J. Amer. Chem. Soc.*, **76**, 4186 (1954); **77**, 2424 (1955).

[97] U.S. Pat. 2,701,225 (1952); *Chem. Abstr.*, **49**, 7180 (1955); W. Lorenz, A. Henglein, and G. Schrader, *J. Amer. Chem. Soc.*, **77**, 2554 (1955); G. Schrader, "Die Entwicklung neuer insektizider Phosphorsäureester," Verlag Chemie, Weinheim, 3rd ed, 1963, p. 31.

[98] B. Teichmann, *J. Prakt. Chem.*, [iv], **28**, 94 (1965).

[99] A. E. Arbuzov and M. M. Azanovskaya, *Dokl. Akad. Nauk SSSR*, **58**, 1961 (1947); *Chem. Abstr.*, **46**, 8606 (1952); J. A. Cade, *J. Chem. Soc.*, **1959**, 2272.

[100] R. L. McConnell and H. W. Coover, *J. Amer. Chem. Soc.*, **78**, 4450 (1956).

[101] M. M. Rauhut and H. A. Currier, *J. Org. Chem.*, **26**, (a) 4626, (b) 4628 (1961); L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **28**, 3315 (1963).

[102] L. Horner, P. Beck, and V. G. Toscano, *Chem. Ber.*, **94**, 1317 (1961).

[103] R. C. Miller, D. C. Miller, W. Rogers, and L. A. Hamilton, *J. Amer. Chem. Soc.*, **79**, 424 (1957).

2. Addition of compounds containing P–Cl bonds

Addition of phosphorus trichloride to aldehydes or ketones occurs with deoxygenation of the carbonyl compound. It thus provides a simple entry to the phosphonic acid series. After phosphorus trichloride has reacted with 3 moles of a carbonyl compound hydrolytic working up affords α-hydroxy phosphonic acids, often in good yield. Directions for the preparation of the hydroxymethyl compound from paraformaldehyde have been given by Bannard and his co-workers.[104]

The primary formaldehyde adduct, (chloromethyl)phosphonic dichloride, can be isolated by a suitable technique including exclusion of moisture:

$$PCl_3 + CH_2O \longrightarrow ClCH_2P(O)Cl_2$$

(Chloromethyl)phosphonic dichloride:[105] Phosphorus trichloride (200 g) and carefully dried, finely powdered paraformaldehyde (30 g) are heated in a 1-l autoclave for 10 h at 250°. Two fractional distillations of the product afford the dichloride (100–108 g, 60–65%), b.p. 87 to 88°/15 mm.

Phosphonic chlorides can be prepared analogously from dichlorophosphines, and phosphine oxides from monochlorophosphines.[106]

In a different technique for preparation of α-hydroxy phosphonic acids equimolar amounts of the components are used with glacial acetic acid as solvent.

General directions for preparation of α-hydroxy phosphonic acids:[107] Phosphorus trichloride (10% excess) is added with exclusion of moisture to the carbonyl compound, the temperature not being allowed to rise above 35°, and the mixture is set aside for 2–3 h. Glacial acetic acid (3 moles) is then added, the temperature being kept below 30°. After a further 12 h the mixture is poured into well-stirred ice-water (300 ml), and the whole is evaporated to dryness.

Benzophenone and other aromatic ketones do not react in these conditions; their reaction is effected in a benzoic acid melt.

A new procedure is exemplified by the following:

(1-Hydroxycyclohexyl)phosphonic acid:[108] Cyclohexanone (98 g) is added slowly, with stirring and cooling, to a solution of phosphorus trichloride (154 g) in glacial acetic acid (243 g). The reaction soon becomes violent and cooling in ice is then required. The mixture is kept for 24 h below 30°, then filtered, poured into water (1 l), and evaporated. The residue is redissolved in water (500 ml). Evaporation of this solution yields a product that crystallizes on cooling (m.p. 170–181°; 174 g, 86%). On recrystallization from ethanol, the phosphonic acid is obtained as colorless crystals, m.p. 191–192°.

3. Addition of tertiary phosphines and phosphites

It has already been mentioned (page 701) that aldehydes react more readily with tertiary than with primary or secondary phosphines; for experimental

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[104] R. A. B. Bannard, J. R. Gilpin, G. R. Vavasour, and A. F. McKay, *Can. J. Chem.*, **31**, 976 (1953).

[105] M. I. Kabatschnik and Je. S. Schepelewa, "Synthesen organischer Verbindungen," VEB Verlag Technik Berlin–Porta Verlag, Munich, 1956, Vol. 2, p. 146.

[106] M. I. Kabatchnik and Ye. S. Shepeleva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1953**, 826; *Chem. Abstr.*, **49**, 843 (1955).

[107] J. B. Conant and co-workers, *J. Amer. Chem. Soc.*, **43**, 1929 (1921).

[108] P. Fay and H. P. Lankelma, *J. Amer. Chem. Soc.*, **74**, 4933 (1952).

details see Wittig[109] and Hellmann[110] and their co-workers. The reaction of triphenylphosphine with aldehydes in the presence of hydrochloric acid has been recommended for the separation of aldehydes from mixtures because the resulting (1-hydroxyalkyl)triphenylphosphonium salts regenerate the components quantitatively on decomposition by alkali.[111]

Trialkyl phosphites add to aldehydes when heated with them for several hours in a sealed tube, yielding α-alkoxy phosphonic esters in moderate yields:[112]

$$(RO)_3P + R'CHO \longrightarrow (RO)_2P(O)CHR'OR$$

α,β-Unsaturated aldehydes give 1,4-addition products.[113]

Benzophenone and *p*-chlorobenzophenone react with triisopropyl phosphite in excess when refluxed for many hours; the carbonyl compound is deoxygenated and phosphonic diesters are formed:

$$2[(CH_3)_2CHO]_3P + Ar_2CO \longrightarrow Ar_2CHP(O)[OCH(CH_3)_2]_2 + [(CH_3)_2CHO]_3PO + C_3H_6$$

Trimethyl and triethyl phosphite do not undergo this reaction.

[Bis-(*p*-chlorophenyl)methyl]phosphonic acid:[114] 4,4′-Dichlorobenzophenone (12.5 g) is heated under reflux with triisopropyl phosphite (52 g) under nitrogen for 72 h. The product is extracted with water, and the water-insoluble residue is taken up in aqueous sodium hydroxide solution. Acidification of this solution precipitates the phosphonic acid (13.9 g), which after recrystallization from ethanol has m.p. 253–254°.

III. Addition of phosphorus compounds to C=N bonds

The reactions to be treated in this Section are almost exclusively those of compounds containing P–H bonds, once more mainly dialkyl phosphites; the subject matter is therefore best assembled according to the structural characteristics of the nitrogenous component.

Isocyanates add PH_3[115] or primary[116] or secondary phosphines[101b] in the presence of catalytic amounts of triethylamine under mild conditions, the products being tertiary carbamoyl phosphines. *p*-Nitrophenyl isocyanate with 2–4 atm of PH_3 at room temperature gives an almost quantitative yield of tris-[*N*-(*p*-nitrophenyl)carbamoyl]phosphine; yields are considerably lower from isocyanates containing less negative substituents. Primary[116] and secondary[101b,117,118] phosphine oxides give tertiary carbamoyl phosphine oxides in analogous reactions. Vinyl isocyanate also adds to the C=N double bond.

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[109] G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

[110] H. Hellmann and co-workers, *Ann. Chem.*, **659**, 49 (1962).

[111] H. Hoffmann, *Angew. Chem.*, **72**, 77 (1960).

[112] V. S. Abramov, *Dokl. Akad. Nauk SSSR*, **95**, 991 (1954); *Chem. Abstr.*, **49**, 6084 (1955).

[113] V. A. Ginsburg and A. Ya. Yakubovich, *Zh. Obshch. Khim.*, **30**, 3979 (1960); *Chem. Abstr.*, **55**, 22099 (1961).

[114] A. C. Poshkus and J. E. Herweh, *J. Org. Chem.*, **29**, 2567 (1964).

[115] S. A. Buckler, *J. Org. Chem.*, **24**, 1460 (1959).

[116] S. A. Buckler and M. Epstein, *Tetrahedron*, **18**, 1221 (1962).

[117] N. Kreutzkamp and K. Storck, *Naturwissenschaften*, **47**, 497 (1960).

[118] R. C. Schulz and H. Hartmann, *Monatsh. Chem.*, **93**, 905 (1962).

Diphenyl-(*N*-vinylcarbamoyl)phosphine oxide:[118] Diphenylphosphine oxide (2 g) is dissolved in acetone (15 ml) and treated with vinyl isocyanate (1.1 g) and then triethylamine (5 drops). The solution becomes somewhat warm and after about 15 min separation of needle-shaped crystals begins. The mixture is set aside for several hours for completion of the crystallization (2.15 g, 80%). After recrystallization from methanol or ethanol the product has m.p. 179–180° (dec.).

The addition of dialkyl phosphites to isocyanates has been studied more often.[118-122] The uncatalysed reaction gives poor yields[119] (addition of dimethyl thiophosphite to phenyl isocyanate does not require a catalyst[120]), and weak bases such as sodium carbonate, sodium cyanide, and tributylamine are poor catalysts, and the reaction proceeds best on addition of sodium, sodium dialkyl phosphites, or triethylamine.[122] A typical example is the preparation of **diisopropyl [*N*-(*p*-chlorophenyl)carbamoyl]phosphonate**:[122]

A solution of diisopropyl phosphite (3.32 g) in dry hexane (20 ml) is treated with sodium (5 mg). When the metal has dissolved, a solution of *p*-chlorophenyl isocyanate (3.3 g) in hexane (10 ml) is added rapidly at about 30° with stirring and exclusion of moisture. The temperature then rises to about 40°. After 10 min the mixture is heated under reflux for 1.5 h, then filtered and concentrated. The product (4.4 g, 69%; m.p. 122–127°) crystallizes and after several recrystallizations from hexane has m.p. 128–128.7°.

Approximately the same yield is obtained if the sodium is replaced by triethylamine (2 drops).

Addition to aromatic isocyanates,[122] like that to diphenylcarbodiimide,[123] has been recommended for identification of dialkyl phosphites.

Addition of dialkyl phosphites to aldimines and ketimines leads to α-amino phosphonic esters:

$$R^1N{=}CR^2R^3 + (R^4O)_2P(O)H \longrightarrow R^1HN{-}CR^2R^3{-}P(O)(OR^4)_2$$

These reactions have been sometimes carried out with catalysis by alkoxides,[124] but they occur also, often with high yield, in the absence of a catalyst.[125] The reaction gains interest because the imine can be replaced by a mixture of carbonyl compound and amine. It is true that reaction of an aldehyde and ammonia (which requires use of a sealed tube or an autoclave) gives only moderate yields,[126] but these are higher from aliphatic ketones, ammonia, and dialkyl phosphites — it suffices in some cases to pass dry ammonia into an equimolar mixture of the ketone and phosphite with subsequent heating at

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[119] T. Reetz and co-workers, *J. Amer. Chem. Soc.*, **77**, 3813 (1955).

[120] A. N. Pudovik and A. V. Kuznetsova, *Zh. Obshch. Khim.*, **25**, 1369 (1955); *Chem. Abstr.*, **50**, 4808 (1956).

[121] E. V. Kuznetsov and M. I. Bakhitov, *Zh. Obshch. Khim.*, **31**, 3015 (1961); *Chem. Zentralbl.*, **1965**, 15-0861; U.S. Pat. 3,048,613; *Chem. Abstr.*, **57**, 15154 (1962).

[122] R. B. Fox and D. L. Venetzky, *J. Amer. Chem. Soc.*, **78**, 1661 (1956).

[123] J. Kennedy, *Chem. & Ind. (London)*, **1956**, 1348.

[124] A. N. Pudovik and co-workers, *Dokl. Akad. Nauk SSSR*, **83**, 865 (1952); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1952**, 940; *Zh. Obshch. Khim.*, **31**, 4053 (1961); *Chem. Abstr.*, **47**, 4300, 10468 (1953); **57**, 9878 (1962).

[125] E. K. Fields, *J. Amer. Chem. Soc.*, **74**, 1529 (1952).

[126] M. I. Kabatchnik and T. Ya. Medved, *Dokl. Akad. Nauk SSSR*, **83**, 689 (1952); *Chem. Abstr.*, **47**, 2724 (1953); M. E. Chalmers and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 5278 (1953).

atmospheric pressure.[127] Aromatic aldehydes and amines often react very easily, as is illustrated by the following directions:[128]

> Equimolar amounts of aldehyde and amine are dissolved separately in the minimum amount of hot ethanol and are then mixed with cooling. The Schiff base crystallizes. Next an ethanolic solution of an equimolar amount of the dialkyl phosphite is added in portions with cooling and shaking. When the mixture is diluted with a 4–5-fold amount of ether and, if necessary, stored in a refrigerator overnight, the **α-amino phosphonic ester** crystallizes and can be filtered off and washed with cold ether. Yields of 70–80% are obtained from benzaldehyde with aromatic amines containing electron-attracting substituents or with aminopyridines.

Addition of hypophosphorous acid, $PH(OH)_2$ to Schiff bases, yielding (1-aminoalkyl)phosphorous acids, can also be effected by mixing the three reactants.[129] Further, Schiff bases have also been added to dialkyl thiophosphites,[130] phosphonous monoesters,[130] secondary phosphine oxides,[117] and metal derivatives of secondary phosphines;[131] these phosphides, however, give well-defined products only after hydrolytic working up to phosphine oxides.

Hydrochlorides of enamines add as iminium salts to dialkyl phosphites with formation of α-amino phosphonic esters.[132]

IV. Addition of phosphorus compounds to C=S bonds

Reaction of trialkylphosphines with carbon disulfide has long been known;[133] it leads to red zwitterionic adducts[134] which can be alkylated on the sulfur atom to give quaternary phosphonium salts:

$$R_3P + CS_2 \longrightarrow R_3\overset{+}{P}\text{—}CSS^- \xrightarrow{R'Hal} R_3\overset{+}{P}\text{—}CSSR'Hal^-$$

Alkali salts of dialkyl phosphites[135] and thiophosphites[136] add similarly to carbon disulfide and carbon oxysulfide. In these cases the adducts are not isolated but are converted directly, by alkylation, into dialkyl [(alkyloxy)-carbonyl]-phosphonates or -thiophosphonates or (alkylthio)carbonyl analogs thereof:

$$\underset{(X=O\text{ or }S)}{(RO)_2P(X)Na + CSX} \longrightarrow (RO)_2P(X)\text{—}CX\text{—}SNa \xrightarrow{R'Hal} (RO)_2P(X)\text{—}CX\text{—}SR'$$

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[127] T. Ya. Medved and M. I. Kabatchnik, *Dokl. Akad. Nauk SSSR*, **84**, 717 (1952); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1954**, 314; *Chem. Abstr.*, **47**, 3226 (1953); **48**, 10541 (1954).

[128] H. Zimmer and J. P. Bercz, *Ann. Chem.*, **686**, 107 (1965).

[129] H. Schmidt, *Chem. Ber.*, **81**, 477 (1948); F. D. Popp and W. Kirsch, *J. Org. Chem.*, **26**, 3858 (1961); W. M. Linfield and co-workers, *J. Org. Chem.*, **26**, 4088 (1961).

[130] A. N. Pudovik, *Dokl. Akad. Nauk SSSR*, **92**, 773 (1953); *Chem. Abstr.*, **49**, 3050 (1955).

[131] K. Issleib and R.-D. Bleck, *Z. Anorg. Allg. Chem.*, **336**, 234 (1965).

[132] G. Opitz and co-workers, *Ann. Chem.*, **665**, 91 (1963).

[133] A. W. Hofmann, *Ann. Chem. Pharm., Suppl.*, **1**, 1 (1861).

[134] T. N. Margulis and D. H. Templeton, *J. Amer. Chem. Soc.*, **83**, 995 (1961); K. A. Jensen and P. H. Nielsen, *Acta Chem. Scand.*, **17**, 547 (1963).

[135] D. W. Grisley, *J. Org. Chem.*, **26**, 2544 (1961); U.S. Pat. 3,033,891; *Chem. Abstr.*, **58**, 3458 (1963).

[136] L. Almasi and L. Paskucz, *Rev. Roum. Chim.*, **10**, 301 (1965); *Chem. Abstr.*, **63**, 11604 (1965).

If the reaction is carried out at elevated temperatures the expected products are replaced by *O,O,S*-trialkyl thiophosphates[137] or *O,O,S*-trialkyl dithiophosphates.[136]

Diisopropyl [(methylthio)thiocarbonyl]phosphonate:[135] Diisopropyl phosphite (33.2 g, 0.2 mole) is converted into its sodium salt by heating its solution in dry tetrahydrofuran (200 ml) under reflux, with exclusion of moisture, together with the calculated amount of sodium hydride until evolution of hydrogen ceases. The mixture is then cooled and treated dropwise with carbon disulfide (76 g) during 15 min while the temperature is kept between 2° and 8°. Methyl iodide (30 g) is then added during 5 min to the red solution at the same temperature, after which the whole is stirred for a further 5 min at about 5° and then poured into ice-water (750 ml). Extraction with ether (300 ml), washing of the ether extract four times with water (500-ml portions), drying over magnesium sulfate, and removal of the ether afford a residue which is fractionated through a Vigreux column in a vacuum. The product (38 g, 60%) is a dark red oil, b.p. 116–117°/0.4 mm, n_D^{25} 1.5168.

Stannylphosphines react like tertiary phosphines with carbon disulfide, a P–C bond being formed; the zwitterionic adducts, however, cannot be isolated and stabilize themselves by migration of the stannyl group to sulfur:[138]

$$(C_6H_5)_2P\text{—}Sn(C_6H_5)_3 + CS_2 \longrightarrow (C_6H_5)_2P\text{—}CS\text{—}SSn(C_6H_5)_3$$

However, with amino phosphines the insertion of CS_2 occurs in the reverse direction, giving [(thiocarbamoyl)thio]phosphines:[139]

$$R_2P\text{—}NR'_2 + CS_2 \longrightarrow R_2P\text{—}S\text{—}CS\text{—}NR'_2$$

Phosphonous[140] and phosphorous amides behave analogously.[140,141]

9.2. Formation of the carbon–phosphorus bond by exchange

I. Replacement of hydrogen by phosphorus

1. Replacement of hydrogen by phosphorus by means of phosphorus halides

a. Direct reaction

Direct reaction of phosphorus halides with hydrocarbons in the absence of catalysts requires drastic conditions and is not really suitable for laboratory purposes. For example, phosphorus trichloride reacts with methane or ethane only at about 600°; this affords moderate yields of alkyldichlorophosphines.[142] The corresponding reaction with benzene at 550° is said to give good yields of dichloro(phenyl)phosphine.[143]

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[137] B. A. Arbuzov and co-workers, *Zh. Obshch. Khim.*, **31**, 4015 (1961); *Chem. Abstr.*, **57**, 9642 (1962).

[138] H. Schumann, P. Jutzi, and M. Schmidt, *Angew. Chem. Int. Ed., Engl.*, **4**, 787 (1965).

[139] USSR Pat. 164,281; *Chem. Abstr.*, **61**, 16095 (1964).

[140] G. Oertel, H. Malz, and H. Holtschmidt, *Chem. Ber.*, **97**, 891 (1964).

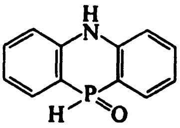
[141] H.-J. Vetter and H. Nöth, *Chem. Ber.*, **96**, 1308 (1963).

[142] J. A. Pianfetti and L. D. Quin, *J. Amer. Chem. Soc.*, **84**, 851 (1962).

[143] U.S. Pat. 3,029,282; *Chem. Zentralbl.*, **1965**, 23-2523.

Dialkylanilines are much more reactive, all three chlorine atoms of PCl_3 or $POCl_3$ being replaced at considerably lower temperatures. However, the older literature concerning these reactions must be treated with caution as it was shown recently[144] that the supposed tri-[*p*-(dimethylamino)phenyl]phosphine obtained[145] from dimethylamine and phosphorus trichloride is really the phosphine oxide.

The reaction of diphenylamine with phosphorus trichloride is interesting because after hydrolysis it leads to the *ortho*-substitution product, namely the phenophosphazine derivative (7):



(7)

5,10-Dihydrophenophosphazine 10-oxide:[146] Diphenylamine (676 g) is added in portions during 2 h, with stirring, to phosphorus trichloride (578 g), the temprature rising to about 50°. The mixture is then heated slowly under reflux to 200–210° and this temperature is maintained until evolution of hydrogen chloride ceases (about 4 h). The product is cooled to 100–120° and treated with water (1 l) (temporary inflammation sometimes occurs), after which it is left to cool overnight. The hard mass is then broken up (the flask being usually fractured thereby) and powdered as fine as possible whilst being stirred under water. The aqueous suspension is then stirred on a hot water-bath until the solid agglomerates; after cooling, the product is filtered off, sucked as dry as possible, and recrystallized with charcoal from dimethylformamide (1.6–2.0 l). Cooling in ice causes separation of very fine crystals which are collected and washed with, successively, dimethylformamide, acetone, and ether. This crude product (40% yield) is recrystallized from glacial acetic acid (1.8 l), giving hard prisms (214 g), m.p. 214–216°. A further amount (21.5 g; m.p. 214.5–216.5°) separates on long storage of the mother-liquor after it has been concentrated to the consistency of honey; the total yield amounts to 27.3%.

b. Reactions of Friedel–Crafts type

The reaction of phosphorus trichloride with aromatic hydrocarbons in the presence of aluminum chloride, yielding aryldichlorophosphines, has been known since Michaelis' time, but until very recently there were great experimental difficulties in separating the products. One method of overcoming these difficulties is to oxidize the aryldichlorophosphines *in situ* by chlorine[147] or sulfuryl chloride[148] and to convert these oxidation products by means of an alcohol into the phosphonic diesters; these esters can be relatively easily

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[144] G. P. Schiemenz, *Chem. Ber.*, **98**, 65 (1965).

[145] H. Raudnitz, *Ber. Deut. Chem. Ges.*, **60**, 743 (1927); E. Koenigs and H. Friedrich, *Ann. Chem.*, **509**, 138 (1934).

[146] M. Häring, *Helf. Chim. Acta*, **43**, 1816 (1960).

[147] G. M. Kosolapoff and W. F. Huber, *J. Amer. Chem. Soc.*, **69**, 2020 (1947); G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **74**, 4119 (1952).

[148] K. A. Petrov and co-workers, *Zh. Prikl. Khim.*, **37**, 429 (1964); *Chem. Abstr.*, **60**, 12049 (1964).

separated and can, if necessary, be hydrolysed to the phosphonic acids:

$$\mathrm{ArH} \xrightarrow[\mathrm{AlCl_3}]{\mathrm{PCl_3}} \mathrm{ArPCl_2} \xrightarrow[\mathrm{SO_2Cl_2}]{\mathrm{Cl_2\ or}} \mathrm{ArPCl_4} \xrightarrow{\mathrm{ROH}} \mathrm{ArP(O)(OR)_2} \xrightarrow[\mathrm{H^+}]{\mathrm{H_2O}} \mathrm{ArP(O)(OH)_2}$$

Another method is oxidation *in situ* to thiophosphonic chlorides.

Phenyl(thiophosphonic) dichloride:[149] Benzene (23 g), phosphorus trichloride (124 g), and aluminum chloride (40 g) are heated and stirred together under reflux for 3 h. The product is cooled to 30° and treated with sulfur (10 g), the temperature then rising to 60° and the color darkening. When the exothermic reaction ceases the mixture is heated for a few min at 80°, then the excess of phosphorus trichloride is removed in a vacuum. The residue is poured on ice and twice extracted with light petroleum. The extracts are washed with water and dried over calcium chloride. After removal of the solvent fractionation in a vacuum affords the dichloride (46.7 g, 73.8% calculated on benzene), b.p. 128–130°/12 mm, 95–110°/2–3 mm, 72–75°/0.5 mm, n_D^{20} 1.6227.

The aryldichlorophosphines themselves first became readily accessible when it was found that the aluminum chloride could be precipitated quantitatively from the product by addition of phosphorus oxychloride[150] or pyridine.[151] Optimum yields are obtained with the ratios hydrocarbon: $PCl_3 : AlCl_3 = 0.3 : 1.2 : 0.4$ with subsequent addition of an amount of phosphorus oxychloride equivalent to the aluminum chloride.[152]

Dichloro(phenyl)phosphine:[152] Phosphorus trichloride (165 g, 105 ml), benzene (23.4 g), and aluminum chloride (53 g) are slowly warmed, with stirring, to reflux; the reflux condenser is connected first to a drying tube and thence to a wash-bottle containing aqueous sodium hydroxide to absorb the hydrogen chloride. To complete the reaction, the resulting homogeneous mixture is heated after 2 h as vigorously as possible, until evolution of hydrogen chloride almost ceases (in all about 3 h); during this operation it is advisable to pump ice-water through the condenser. The source of heat is then removed and the mixture, whilst still hot, is treated dropwise with phosphorus oxychloride (62 g, 37 ml); this causes an exothermic reaction and separation of the adduct as solid lumps. The whole is cooled and then stirred with light petroleum (6–8 × 100 ml), and the solid is washed on a filter also with light petroleum. The combined petroleum extracts are freed from solvent, whereafter fractional distillation through a 20-cm Raschig column affords the product (38.5–42 g, 72–78%), b.p. 68–70°/1 mm, 90–92°/10 mm, n_D^{25} 1.5962.

Alkylbenzenes react analogously; isomer proportions in the products are reported by Baldwin and his co-workers.[153] The yield of aryldichlorophosphine decreases rapidly with increasing alkyl substitution of the ring; it is already zero with mesitylene. As a variation of the process, the diarylphosphine oxides, together with small amounts of the diarylphosphinic acids, can be obtained by hydrolysis of the insoluble $POCl_3/AlCl_3$ complex.

General procedure for the preparation of **diarylphosphine oxides** from mesitylene, durene and pentamethylbenzene:[154] The hydrocarbon (0.3 mole) is treated with phosphorus trichloride and aluminum chloride as in the preceding prescription. After addition of the phos-

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[149] U.S. Pat. 2,662,917; *Chem. Abstr.*, **48**, 13711 (1954).

[150] W. T. Dye, *J. Amer. Chem. Soc.*, **70**, 2595 (1948).

[151] E. L. Gefter, *Zh. Obshch. Khim.*, **28**, 1338 (1958); *Chem. Abstr.*, **52**, 19999 (1958); Je. K. Gefter, "Organophosphorus Monomers and Polymers," Pergamon Press, Oxford, 1962, p. 99.

[152] B. Buchner and L. B. Lockhart, *J. Amer. Chem. Soc.*, **73**, 755 (1951); *Org. Syn.*, Coll. Vol. IV, 784 (1963).

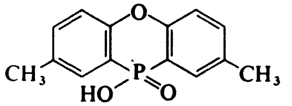
[153] R. A. Baldwin, K. A. Smitheman, and R. M. Washburn, *J. Org. Chem.*, **26**, 3547 (1961).

[154] A. W. Frank, *J. Org. Chem.*, **24**, 966 (1959).

phorus trichloride, the mixture is boiled for a further 0.5 h, then cooled and diluted with light petroleum (300 ml, b.p. 30–60°). The liquid is decanted and the solid is rapidly filtered off, washed with light petroleum (2 × 100 ml), and then added cautiously, in portions, to water (1 l). When the violent reaction is ended, an insoluble rubbery residue is obtained. The liquid is decanted, extracted with benzene (3 × 100 ml), and then discarded. The resinous residue is rubbed in portions with benzene until dissolved therein. This solution is united with the benzene extracts and washed successively with water (three times), dilute sodium hydroxide solution, and water (acidification of the alkaline extract provides 4–5% of the diarylphosphinic acid). The washed benzene solution is dried, filtered, and evaporated, yielding the secondary phosphine oxide as residue in the following yields: bis-(2,4,6-trimethylphenyl)- 59% (an oil), bis-(2,3,5,6-tetramethylphenyl)- 43% (m.p. about 150°, from benzene), and bis(pentamethylphenyl)-phosphine oxide 27% (m.p. 240°, from benzene).

Ethylbenzene gives no diarylphosphine oxide, but instead 52 % of dichlorophosphine and 36 % of diarylphosphinic acid.

Reaction of di-*p*-tolyl ether with $PCl_3/AlCl_3$ gives the cyclic phosphinic acid (**8**) in high yield. Ring closure does not occur with diphenyl ether.



(**8**)

2,8-Dimethylphenoxaphosphin-10-ol 10-oxide (8):[155] Di-*p*-tolyl ether (9.9 g), phosphorus trichloride (17.4 ml), and aluminum chloride (8.5 g) are heated under reflux for 22 h with stirring and exclusion of moisture, then cooled and poured on ice. The oily product soon solidifies and is then filtered off, washed with water, and reprecipitated from 5% sodium hydroxide solution by acidification. Recrystallization from ethanol provides it with m.p. > 300° (yield 73%).

Ferrocene reacts with $PCl_3/AlCl_3$ with replacement of all three chlorine atoms, but the tertiary phosphine is sensitive to air and difficult to isolate. However, diferrocenylphenylphosphine [from dichloro(phenyl)phosphine] and ferrocenyldiphenylphosphine [from chloro(diphenyl)phosphine] are obtained analogously as stable compounds in 52% and 37% yield, respectively.[156]

Zinc chloride has been used in place of aluminum chloride for the reaction of polyhydric phenol ethers with phosphorus trichloride, suitable working up again giving the tertiary phosphines. The resulting $ZnCl_2$ complexes are successfully decomposed by aqueous ammonia.[157]

Phosphorus oxychloride, which forms stable and often insoluble complexes with Friedel–Crafts catalysts, appears not yet to have been used with success in reactions of this type. The analogous reaction of thiophosphoryl chloride has been studied in detail, but only recently:[158] its use has made phenyl(thiophosphonic) dichloride, diphenyl(thiophosphinic) chloride, and triphenylphosphine sulfide conveniently accessible. The dichloride is obtained in about 45% yield, together with about 33% of the monochloride, when a mixture in the molar proportions $PSCl_3 : AlCl_3 : C_6H_6 = 1:2:1$ is heated at 80° for 15 min; the ratios $1:2:4$ are most favorable for preparation of the mono-

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[155] L. D. Freedman, G. O. Doak, and J. E. Edmisten, *J. org. Chem.*, **26**, 284 (1961).

[156] G. P. Sollott and co-workers, *J. Org. Chem.*, **27**, 4034 (1962); **28**, 1090 (1963).

[157] I. S. Protopopov and M. Ya. Kraft, *Zh. Obshch. Khim.*, **33**, 30850 (1963); *Chem. Abstr.*, **60**, 1789 (1964).

[158] L. Maier, *Helv. Chim. Acta*, **47**, 120 (1964).

chloride (refluxing for 0.5 h; about 86% yield); longer reaction periods are needed for replacement of the three chlorine atoms.

Triphenylphosphine sulfide:[158] A mixture of thiophosphoryl chloride (50.7 g, 0.3 mole), aluminum chloride (133 g, 1 mole), and benzene (150 g, 1.92 moles) is heated, with stirring, to reflux. Evolution of hydrogen chloride begins at once and is complete after about 8 h. The mixture is poured on ice, and the aqueous phase is washed three times with benzene. The benzene phase and the benzene extracts are united and dried over sodium sulfate. After removal of the solvent there remains a residue (91 g) which, on two recrystallizations from aqueous acetone, gives the sulfide (75.5 g, 85.8% calculated on $PSCl_3$), m.p. 158–158.5°.

Toluene and fluorobenzene undergo mainly *para*-substitution but chlorobenzene gives *ortho*- and *para*-substitution products in about equal proportions. Trimethoxybenzene, thiophene, and furfuraldehyde do not react.

Thiophosphonic and thiophosphinic chlorides are also amenable to the reaction, and this permits preparation of unsymmetrical phosphine sulfides. Thiophosphonic and thiophosphinic bromides can be obtained analogously from thiophosphoryl bromide and aluminum bromide.

c. Oxidative phosphonylation

Although phosphorus trichloride does not react with aliphatic hydrocarbons alone under the usual conditions, yet in the presence of oxygen these components undergo a violent reaction even at low temperatures: phosphonic dichlorides are thereby formed together with phosphorus oxychloride:

$$RH + 2PCl_3 + O_2 \longrightarrow RP(O)Cl_2 + HCl + POCl_3$$

The reaction was apparently discovered independently by three schools.[159-161] It occurs by a radical process,[162] but requires neither irradiation nor initiators and is inhibited by numerous substances (amongst others, iodine, iron powder, and boron trifluoride). Isomer proportions in the products are similar to those obtained on chlorination or sulfochlorination of hydrocarbons.[163]

Experimental conditions can often be varied within wide limits. For instance, yields from cyclohexane (which has been favored for study because it does not produce isomers) are substantially constant between −40° and +70° if the ratio of the reactants is invariant.[164] Also presence of the products has no influence on the yield. Use of air in place of oxygen greatly reduces the rate of reaction. However, the temperature and partial pressure of oxygen do appear to influence the occasional formation of phosphoric ester dichlorides.[159,162] Small amounts of diphosphorylated compounds may also appear as by-products.[165]

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[159] R. Graf, *Chem. Ber.*, **85**, 9 (1952).

[160] J. O. Clayton and W. L. Jensen, *J. Amer. Chem. Soc.*, **70**, 3880 (1948).

[161] L. Z. Soborovskii, Yu. M. Zinov'ev, and M. A. Englin, *Dokl. Akad. Nauk SSSR*, **67**, 293 (1949); *Chem. Abstr.*, **44**, 1401 (1950).

[162] F. R. Mayo, L. J. Durham, and K. S. Griggs, *J. Amer. Chem. Soc.*, **85**, 3156 (1963); R. L. Flurry and C. E. Boozer, *J. Org. Chem.*, **31**, 2076 (1966).

[163] G. Geiseler, F. Asinger, and M. Fedtke, *Chem. Ber.*, **93**, 765 (1960).

[164] A. F. Isabell and F. T. Wadsworth, *J. Amer. Chem. Soc.*, **78**, 6042 (1956).

[165] W. L. Jensen and C. R. Noller, *J. Amer. Chem. Soc.*, **71**, 2348 (1949).

The technique is to pass oxygen into a mixture of phosphorus trichloride and an excess of the hydrocarbon, if necessary with cooling. Gaseous hydrocarbons can be treated either in an autoclave[159] or by passing their mixture with oxygen into phosphorus trichloride.[161] Methane does not react,[159] nor does cumene,[164] but other alkylated aromatic hydrocarbons such as toluene, ethylbenzene,[163] and *p*-xylene[166] give ω-substitution products. Phosphinic chlorides are obtained analogously from alkyl-[35] or aryl-dichlorophosphines.[36]

Cyclohexylphosphonic dichloride:[159] Oxygen is passed into a vigorously stirred mixture of cyclohexane (2 moles) and phosphorus trichloride (1 mole) under a reflux condenser. The mixture heats up immediately. The stirrer should be adjusted to throw as much liquid as possible up into the gas space. The reaction is ended when the temperature, which has been held between 20° and 30° by external cooling, falls materially. With an oxygen stream of 6–8 l/h this usually occurs after about 2 h. The unchanged components are distilled off and the residue is fractionated in a vacuum. The fraction distilling at 140–150°/15 mm solidifies rapidly and is redistilled in a vacuum; this affords 60–70% (calculated on PCl_3; 60–70 g) of the dichloride, m.p. 41°.

2. Replacement of hydrogen by phosphorus by means of other phosphorus compounds

a. Replacement by means of P–H compounds

Dialkyl phosphites can effect radical substitution of an aromatic ring. The following compounds have been thus substituted by heating them with diethyl phosphite in the presence of di-*tert*-butyl peroxide, the products being subsequently hydrolysed to phosphonic acids (figures in parentheses are the percentage yields and conversions):[167] naphthalene (51, 25), anthracene (96, 50), phenanthrene (60, 58), dibenzofuran (69, 58), and carbazole (80, 15); however, pyridine and ferrocene do not react;[167] methyl benzoate gave 65% of *p*-phosphobenzoic acid.[168] Mixtures of isomers are obtained except in the cases of anthracene and phenanthrene. Considerable amounts of diethyl isobutylphosphonate are formed as by-product.

9-Anthrylphosphonic acid:[167] Anthracene (53.6 g, 0.3 mole), diethyl phosphite (170 ml, 1.33 moles), and di-*tert*-butyl peroxide (30.1 ml, 0.168 mole) are heated for 4 h at 150°, whereafter much (120 ml) of the diethyl phosphite is recovered by distillation in a vacuum. The residue is treated with water (200 ml), collected, washed with water, and, for hydrolysis, heated under reflux for 72 h with a mixture of ethanol (500 ml) and concentrated hydrochloric acid (150 ml). The resulting solution is evaporated and the solid residue is heated with 5% aqueous potassium hydroxide (500 ml). Filtration and acidification then precipitate a yellow crude product (38.6 g), m.p. 279–282°, which is washed with water. For purification this product (6.5 g) is stirred with charcoal in a solution of sodium acetate (10 g) in water (100 ml) for 0.5 h at 70°. Filtration and acidification precipitate the white acid which, after drying at 120° in a vacuum, has m.p. 282–283° (dec.) (6.2 g).

A different method was worked out for radical substitution by cyclohexane.[169] Irradiation of this hydrocarbon together with a dialkyl phosphite, phosphonous

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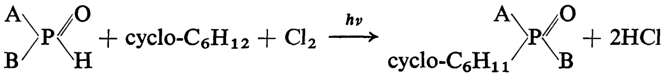
[166] S. R. Rafikov and M. E. Ergebekov, *Zh. Obshch. Khim.*, **34**. 2230 (1964); *Chem. Abstr.*, **61**, 10705 (1964).

[167] E. F. Jason and E. K. Fields, *J. Org. Chem.*, **27**, 1402 (1962).

[168] E. K. Fields and R. J. Rolih, *Chem. & Ind. (London)*, **1960**, 999.

[169] E. Müller and H. G. Padeken, *Chem. Ber.*, **100**, 521 (1967).

monoester, or secondary phosphine oxide in the presence of chlorine by means of a high-pressure mercury lamp affords good yields of, respectively, the phosphonic ester, phosphinic ester, or phosphine oxide:

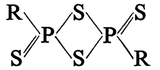


$$\begin{matrix}A & & O\\ & P & \\ B & & H\end{matrix} + \text{cyclo-}C_6H_{12} + Cl_2 \xrightarrow{h\nu} \begin{matrix} & A & & O\\ & & P & \\ \text{cyclo-}C_6H_{11} & & & B\end{matrix} + 2HCl$$

The chloride ABP(O)Cl formed in the absence of cyclohexane is an unimportant by-product. Use of chlorine can be avoided if it is replaced by the chloride ABP(O)Cl, although then short-wavelength light (deuterium lamp, $\lambda < 200$ mμ) is necessary.

b. Replacement by means of phosphorus(v) oxide or sulfide

Phosphorus(v) oxide reacts at 275–325° with aromatic hydrocarbons such as benzene, toluene, and naphthalene, and also with chlorobenzene, giving phosphonic anhydrides which are preferably worked up by hydrolysis to the phosphonic acids.[170] Phosphorus(v) sulfides react at appreciably lower temperatures, yielding dithiophosphonic anhydrides (9); the optimal temperatures vary greatly from one compound to another but must not be exceeded for fear of resinification.[171] These thioanhydrides are obtained in better yield from phosphonic dichlorides and hydrogen sulfide.[172]



(9)

Cyclohexene reacts in the same way as aromatic compounds with phosphorus(v) sulfide.[108]

2-Cyclohexenyldithiophosphonic cyclic anhydride [di-μ-thio-1,2-di-(2′-cyclohexenyl)1,2-dithiodiphosphorus(v)] (9; R = cyclohexenyl): Cyclohexene (721 g) and P_4S_{10} (60 g) (molar proportions 10 : 1!) are heated under reflux for 108 h and then filtered. Unchanged P_4S_{10} (19 g) is then removed by filtration and the excess of cyclohexene by evaporation at room temperature until crystallization begins. Refrigeration and filtration afford a product (38 g, 58%) having m.p. 113–115°. Recrystallization from carbon disulfide gives colorless, hygroscopic crystals, m.p. 118–120°.

Reaction of phosphorus(v) sulfide with aromatic hydrocarbons in the presence of aluminum chloride affords a simple method of preparing aromatic dithiophosphinic acids;[173] or the P_4S_{10} can be replaced by the dithiophosphonic anhydride (9).[172]

Diphenyldithiophosphonic acid:[173] A mixture of benzene (6630 g) and P_4S_{10} (1887 g) is vigorously stirred at 50° while aluminum chloride (4540 g) is added in portions during 3 h the rate of addition being adjusted so that the temperature is kept at 60–63°. This mixture is then heated under reflux for 5 h, set aside overnight, and poured with vigorous stirring on ice. The benzene layer is separated, the aqueous layer is stirred again with benzene, and the

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[170] H. Z. Lecher and co-workers, *J. Amer. Chem. Soc.*, **76**, 1045 (1954); U.S. Pat. 2,717,906; *Chem. Abstr.*, **50**, 6508 (1956).

[171] H. Z. Lecher and co-workers, *J. Amer. Chem. Soc.*, **78**, 5018 (1956).

[172] P. E. Newallis, J. P. Chupp, and L. D. Groeneweghe, *J. Org Chem.*, **27**, 3829 (1962).

[173] W. A. Higgins, P. W. Vogel, and W. G. Craig, *J. Amer., Chem. Soc.* **77**, 1864 (1955); U.S. Pat. 2,809,979; *Chem. Abstr.*, **52**, 3859 (1958).

benzene layers are united, washed with water, dried over magnesium sulfate, and freed from solvent. The residual dark green viscous liquid becomes semisolid when kept. For purification it is dissolved in 10% sodium hydroxide solution, washed with benzene and then acidified with hydrochloric acid. The precipitated phosphinic acid is collected, dried in a vacuum, and recrystallized twice from 2-propanol, then having m.p. 55–56° (yield 54%).

II. Replacement of halogen by phosphorus

1. Replacement of halogen by phosphorus by means of elemental phosphorus

Elemental phosphorus reacts with alkyl and aryl halides to give products that vary according to the experimental conditions. When heated with white phosphorus in a bomb tube at 250–300°, benzyl chloride, bromobenzene, *m*-bromotoluene, and octyl bromide give mixtures of halo and dihalo phosphines, sometimes in appreciable yield:

$$P_4 + 6RHal \longrightarrow 2RPHal_2 + 2R_2PHal$$

by-products are hydrocarbons and sometimes more highly substituted phosphorus compounds.[174] Benzyl bromide is said[175] to react even at 150° and to give benzyldibromophosphine together with considerable amounts of the quaternary phosphonium salt. With either white or red phosphorus at 200–220° perfluoroalkyl iodides give iodo and diiodo phosphines and sometimes tertiary phosphines.[176]

Dibromo(phenyl)phosphine and (bromo)diphenylphosphine:[177] White phosphorus (10 g) and bromobenzene (79 g) are sealed in a thick-walled Pyrex tube and heated at 250° for 20 h and then at 310–315° for 4 h. The product is filtered and fractionated, giving successively bromobenzene (18 g), dibromo(phenyl)phosphine (31.2 g), b.p. 75–80°/0.005 mm, n_D^{20} 1.6719, and (bromo)diphenylphosphine (27.3 g), b.p. 111–115°/0.005 mm, n_D^{20} 1.6649 (total yield 68% calculated on P).

A rational process involving a copper catalyst in a flow tube at 360° has been worked out for the preparation of dibromo(methyl)phosphine and (bromo)dimethylphosphine and the corresponding chloro compounds; ethyl halides give only poor yields by this technique, and butyl bromide does not react at all.[177,178] Dichloro(trichloromethyl)phosphine has also been obtained on γ-irradiation of white phosphorus in carbon tetrachloride, yields being up to 41% at 130°.[179]

When white phosphorus and methyl chloride in molar proportions 1 : 1 to 1 : 2 are heated at 250–260° for about 5 h, good yields of tetramethylphos-

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[174] USSR Pat. 130,512; *Chem. Abstr.*, **55**, 7356 (1961); K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **31**, 3027 (1961); *Chem. Abstr.*, **56**, 12934 (1962).

[175] A. I. Titov and P. O. Gitel, *Dokl. Akad. Nauk SSSR*, **158**, 1380 (1964); *Chem. Abstr.*, **62**, 2791 (1965).

[176] F. W. Bennett, H. J. Emeléus, and R. N. Haszeldine, *J. Chem. Soc.*, **1953**, 1565; H. J. Emeléus and J. D. Smith, *J. Chem. Soc.*, **1959**, 375; A. B. Burg and co-workers, *J. Amer. Chem. Soc.*, **79**, 247 (1957).

[177] L. Maier, *Helv. Chim. Acta*, **46**, 2026 (1963).

[178] Ger. Pat. 1,122,522; *Chem. Abstr.*, **57**, 16660 E (1962); L. Maier, *Angew. Chem.*, **71**, 574 (1959).

[179] D. Perner and A. Henglein, *Z. Naturforsch.*, **17b**, 703 (1962); K. D. Asmus, A. Henglein, G. Meissner, and D. Perner, *Z. Naturforsch.*, **19b**, 549 (1964).

phonium chloride are obtained;[180] methyl bromide[180] and iodide and ethyl bromide and iodide[181] also give the quaternary salts.

Tetramethylphosphonium chloride:[180] White phosphorus is introduced into each of two thick-walled Pyrex tubes (4 g into each), and traces of moisture are removed by heating at 50° in a vacuum — the phosphorus melts. With cooling, finally in liquid nitrogen, methyl chloride (7.5 g) is added to each of the tubes, which are then sealed in a vacuum. After being allowed to reach room temperature the tubes are heated slowly (during 2 h) to 250° and kept at that temperature for a further 3 h. Next the tubes are opened under cooling and all the volatile products are removed by heating at 100° in a high vacuum (9.8 g of distillate consisting of PCl_3 and CH_3PCl_2) (if the distillation is omitted the phosphonium salt is very difficult to separate from the oily product). The distillation residue from both tubes is extracted with ethanol; treating the extract with ether precipitates tetramethylphosphonium chloride (8.4 g), m.p. > 345°.

Phosphinic chlorides are obtained by alkylation of white phosphorus in solution in carbon disulfide in the presence of aluminum chloride and hydrogen chloride,[181] followed by oxidation.[182] Successive action of sodium and an alkyl halide on red phosphorus in liquid ammonia leads to tetraalkyldiphosphanes R_2P_4 and trialkylphosphines, or, after addition of sulfur, to their sulfides.[183]

More important is the alkylation of red phosphorus in the presence of catalytic amounts of iodine or diphosphorus tetraiodide, which after hydrolytic working up leads to trialkylphosphine oxides, sometimes in high yield. Lower alkyl iodides are treated at 200–220° in a sealed tube or an autoclave,[184] higher-boiling iodides at atmospheric pressure.[185,186]

General directions for preparation of **tri-*n*-alkylphosphine oxides** (alkyl = hexyl to decyl):[186] The alkyl iodide (0.2 mole), red phosphorus (0.1 mole), and iodine or diphosphorus tetraiodide (0.0007 mole) are heated, with stirring, at 205–215° (internal temperature) for 5–9 h. For the lower-boiling hexyl iodide the heating is for 30 h at 180°. The dark brown mass produced is stirred twice with hot saturated sodium sulfite solution (100-ml portions) and then extracted with boiling benzene (300 ml). The benzene solution is washed three times with water (150-ml portions) and dried over sodium sulfate. After removal of the benzene, distillation in a vacuum gives the crude phosphine oxide. The following were thus prepared (yields in parentheses refer to the P_2I_4 procedure):

$(C_6H_{13})_3PO$, 62% (82%), b.p. 180–181°/2 mm, m.p. 31–34°
$(C_7H_{15})_3PO$, 66% (53%), b.p. 198–200°/2 mm, m.p. 37–38°
$(C_8H_{17})_3PO$, 78% (43%), b.p. 237–238°/3 mm, m.p. 50–52°
$(C_9H_{19})_3PO$, 50% (57%), b.p. 228–230°/2 mm, m.p. 36–37°
$(C_{10}H_{21})_3PO$, 45% (77%), b.p. 270–271°/2 mm, m.p. 41–42°.

The above reaction clearly occurs by way of P_2I_4, which can readily be formed from the elements and can with advantage replace elemental phosphorus.[185-187]

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[180] L. Maier, *Helv. Chim. Acta*, **49**, 2458 (1966).

[181] W. Gee, R. A. Shaw, and B. C. Smith, *J. Chem. Soc.*, **1965**, 3355.

[182] H. P. Angstadt, *J. Amer. Chem. Soc.*, **86**, 5040 (1964).

[183] G. M. Bogolyubov and A. A. Petrov, *Zh. Obshch. Khim.*, **36**, 1505 (1966); *Chem. Abstr.*, **66**, 10995 (1967).

[184] E. S. Levchenko, Yu. V. Piven, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **30**, 1976 (1960); *Chem. Abstr.*, **55**, 6418 (1961).

[185] USSR Pat. 149,776 (1961); *Chem. Zentralbl.*, **1964**, 12-2240.

[186] N. G. Feshchenko, T. I. Alekseeva, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **33**, 1013 (1963); *Chem. Abstr.*, **59**, 8782 (1963).

[187] H. Hoffmann, R. Grünewald, and L. Horner, *Chem. Ber.*, **93**, 861 (1960).

Tribenzylphosphine oxide:[184] A mixture of diphosphorus tetraiodide (10 mmoles) and benzyl iodide (60 mmoles) is heated gradually in an oil-bath. At 110° (internal temperature) a violent exothermic reaction sets in, the temperature rising to 170°. When the temperature has fallen again to 120° the mixture is heated at that temperature for a further 20 min. The dark mass, which solidifies, is stirred, with gentle warming, with saturated sodium sulfite solution or 2N-sodium hydroxide solution. The tribenzylphosphine oxide separates; it is washed liberally with water (yield 95%, m.p. 206–208°), and after recrystallization from ethanol has m.p. 212–213°.

Recently it has been shown[188] that red phosphorus can combine directly with iodine and higher alcohols, yielding about 50% of the alkylphosphonic acid and 25–30% of the trialkylphosphine oxide.

2. Replacement of halogen by phosphorus by means of phosphorus halides

An elegant entry into the phosphonic acid series is provided by the reaction of phosphorus trichloride with alkyl chlorides in the presence of anhydrous aluminum chloride, as discovered by American[189] and British investigators.[190,191] The alkyl chloride is added in up to 25% excess, with exclusion of moisture and if necessary with cooling, to an equimolar mixture of phosphorus trichloride and aluminum chloride; the alkyltrichlorophosphonium tetrachloroaluminate, generally in crystalline form, is obtained and is then dissolved in methylene dichloride and hydrolysed cautiously to the phosphonic dichloride:

$$PCl_3 + AlCl_3 + RCl \longrightarrow [RPCl_3]AlCl_4 \xrightarrow{H_2O} RP(O)Cl_2$$

***tert*-Butylphosphonic dichloride:**[163] *tert*-Butyl chloride (140 g) is dropped, with ice-cooling, into a mixture of phosphorus trichloride (137 g) and aluminum chloride (133 g); the temperature should not rise above 15°. The resulting precipitate is dissolved in methylene dichloride or chloroform and added to a mixture of ice and concentrated hydrochloric acid. The organic layer is dried over calcium chloride. Removal of the solvent in a vacuum leaves as residue a solid, colorless product (131 g, 75%) with an odor of camphor; purification by sublimation at 84°/14 mm gives material melting at 118–120°.

Detailed directions for preparation of trichloromethylphosphonic dichloride are to be found in *Organic Syntheses.*[192]

Isomerization is observed with higher alkyl halides, as in Friedel–Crafts reactions; isopropylphosphonic dichloride is stated to be the sole product from *n*-propyl chloride,[190,191] and *tert*-pentyl chloride undergoes C–C fission, yielding the *tert*-butyl acid.[193] On reduction by lithium tetrahydroaluminate the phosphonic chloride formed from *n*-butyl chloride gives a primary phosphine that is shown by ^{31}P-nuclear magnetic resonance to consist of *n*- and *sec*-butylphosphine in the proportions 5:95; and the product from *n*-octyl chloride was similarly shown to contain all four position isomers.[194]

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[188] N. G. Feshchenko and A. V. Kirsanov, *Zh. Obshch. Khim.*, **36**, 586 (1966); N. G. Feshchenko, T. I. Alekseeva, L. F. Irodinova, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **37**, 473 (1967); *Chem. Abstr.*, **65**, 742 (1966); **67**, 32705w (1967).

[189] J. B. Clay, *J. Org. Chem.*, **16**, 892 (1951); U.S. Pat. 2,744,132; *Chem. Abstr.*, **51**, 1246 (1957).

[190] A. M. Kinnear and E. A. Perren, *J. Chem. Soc.*, **1952**, 3437.

[191] Brit. Pat. 707,961; *Chem. Abstr.*, **49**, 7588 (1954).

[192] K. C. Kennard and C. S. Hamilton, *Org. Syn.*, **37**, 82 (1957); *J. Amer. Chem. Soc.*, 77, 1156 (1955).

[193] P. C. Crofts and G. M. Kosolopoff, *J. Amer. Chem. Soc.*, **75**, 3379 (1953).

[194] L. Maier, *Helv. Chim. Acta*, **48**, 1190 (1965).

Allyl chloride reacts without rearrangement. Vinyl chloride does not react. The various polyhaloalkanes behave differently from each other: carbon tetrachloride is almost as reactive as alkyl halides, chloroform requires heating under reflux, methylene dichloride reacts only on prolonged heating at 100°; diphosphonylation is not observed even with 1,4-dichloroalkanes.[190,191]

Higher alkyl chlorides have also been brought into reaction in methylene dichloride[195] although the reaction is usually effected without a solvent. It is sometimes advisable to use a two-molar amount of aluminum chloride, which leads to formation of a liquid complex $[RPCl_3]Al_2Cl_7$.[196] A phosphonic dibromide has been obtained from dibromomethane, phosphorus tribromide, and aluminum bromide.[197] Phosphorous ester dichlorides give the same phosphonic dichlorides as PCl_3, as they undergo O–alkyl fission.[190] Phosphonous dichlorides afford phosphinic chlorides;[198] and the complex $C_6H_5PCl_2 \cdot AlCl_3$ obtained from benzene, phosphorus trichloride, and aluminum chloride (see page 709) affords phosphinic chlorides directly from alkyl halides.[199]

According to the reaction conditions, phosphonic ester chlorides or phosphonic diesters are obtained directly on alcoholysis of the alkyltrichlorophosphonium complexes.[195]

Diethyl isopropylphosphate:[195] Phosphorus trichloride (137 g) is dissolved in methylene dichloride (400 ml), and powdered aluminum chloride (128 g) is added followed by isopropyl chloride (88 g) dropwise with ice-cooling; the temperature must be kept below 15°. When all the aluminum chloride has dissolved, dry alcohol (322 g) is dropped in, with stirring, at such a rate that the mixture remains boiling gently. The mixture is then stirred at the boiling point for a further 3 h, then cooled to 20° and, whilst stirring is continued, treated at 20–25°, dropwise with water (500 ml). A white precipitate is formed initially but gradually dissolves. The upper (aqueous) layer is washed three times with methylene dichloride (50-ml portions). The extracts and the organic phase are dried and evaporated to dryness at room temperature. Distillation of the liquid residue affords the ester (127.8 g, 71%), b.p. 58°/2.5 mm, n_D^{25} 1.4161.

Alkyldichlorophosphines are produced by reducing alkyltrichlorophosphonium salts with phosphorus,[200,201] aluminum,[201] or sodium.[201] The most convenient procedure is to start with two moles of aluminum chloride and reduce the liquid adduct with aluminum turnings;[196,202] the aluminum chloride is bound by addition of potassium chloride or sodium chloride.[196,201,202] Dialkylchlorophosphines are prepared analogously by starting from alkyldichlorophosphines.[201] Another method consists of binding the aluminum chloride by diethyl phthalate and reducing with antimony.[203]

If, after the reduction and before addition of alkali chloride, sulfur is added to the reaction mixture, high yields of alkyl(thiophosphonic) dichlorides are

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[195] F. W. Hoffmann, T. C. Simmons, and L. J. Glunz, *J. Amer. Chem. Soc.*, **79**, 3570 (1957).

[196] Ger. Pat. 1,119,860; *Chem. Abstr.*, **58**, 6863 (1963).

[197] J. A. Cade, *J. Chem. Soc.*, **1959**, 2266.

[198] J. L. Ferron, *Can. J. Chem.*, **39**, 842 (1961).

[199] P. Biddle, J. Kennedy, and J. L. Willians, *Chem. & Ind. (London)*, **1957**, 1481.

[200] U.S. Pat. 2,875,224; *Chem. Abstr.*, **53**, 13054 (1959).

[201] I. P. Komkov, K. V. Karavanov, and S. Z. Ivin, *Zh. Obshch. Khim.*, **28**, 2963 (1958); *Chem. Abstr.*, **53**, 9035 (1959).

[202] Ger. Pat. 1,119,861; *Chem. Abstr.*, **58**, 3125 (1963).

[203] B. J. Perry, J. B. Reason, and J. L. Ferron, *Can. J. Chem.*, **41**, 2299 (1963).

formed.[204] Addition of sulfur and reduction can be carried out in one step by sulfur or a metal sulfide, but yields are then somewhat lower.[205] In this manner also, dialkyl(thiophosphinic) chlorides can be prepared from alkyldichlorophosphines in substantially similar manner.[206]

Methyl(thiophosphonic) dichloride:[207] Coarsely powdered aluminum chloride (390 g) and phosphorus trichloride (128 ml) are placed in a 1-l three-necked flask fitted with a thermometer, stirrer, reflux condenser, and gas-inlet tube. Into this suspension is led methyl chloride (dried by sulfuric acid) from a steel bottle, with stirring and exclusion of moisture. All the aluminum chloride dissolves within 5 h. Next, aluminum turnings (26 g) are added in portions and the whole is warmed to 100°, whereupon the temperature rises spontaneously to about 150°. The whole is allowed to cool to room temperature and then treated with sulfur (42 g) (slight evolution of heat) and set aside overnight. Well-dried sodium chloride (343 g) is stirred into this mixture and the thiophosphonyl dichloride is distilled off through a descending condenser, heating being by a free flame; most (160 g) of the crude product distils between 150° and 167° at normal pressure and a further amount (10 g) is obtained by use of a vacuum (b.p. 40–52°/15 mm); the total crude yield is 98%. Fractionation of the united distillates in a vacuum through Vigreux column gives 75% (130 g) of chloride, b.p. 39.5°/12 mm, n_D^{20} 1.5484.

3. Replacement of halogen by phosphorus by means of phosphines

a. Replacement of halogen by phosphorus by means of phosphine, primary or secondary phosphines, or their salts

For alkylation of phosphines containing C–H bonds their alkali salts are usually treated with alkyl halides. Thus primary and secondary phosphines can be obtained by metalation of phosphine itself with sodium in liquid ammonia and subsequent alkylation;[208] phosphirane, which is unstable, is also prepared in this way, from sodium phosphide and ethylene dichloride.[209] High yields of primary phosphines are afforded by alkylating lithium phosphide, which is formed almost quantitatively by metalating phosphine with butyllithium.[210] Since the hydrogen can be replaced stepwise by metal, unsymmetrical secondary and tertiary phosphines can be built up from PH_3 or a primary phosphine.[211] Use of alkali phosphides is not limited to alkylation: potassium diphenylphosphide reacts quantitatively with iodobenzene, yielding triphenylphosphine.[212]

The preparative value of alkali phosphides for formation of a P–C bond does not rest solely on the high reactivity of the strongly polar P–metal bond — the reactivity increases in the order Li < Na < K. Of equal importance is the fact that, not only the P–H bond, but also P–C, P–P, and P–halogen bonds can

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[204] Ger. Pat. 1,119,862; *Chem. Abstr.*, **58**, 6862 (1963).

[205] I. P. Komkov, S. Z. Ivin, and K. V. Karavanov, *Zh. Obsch. Khim.*, **28**, 2960 (1958); *Chem. Abstr.*, **53**, 9035 (1959).

[206] S. Z. Ivin and K. V. Karavanov, *Zh. Obshch. Khim.*, **28**, 2958 (1958); *Chem. Abstr.*, **53**, 9035 (1959).

[207] H. Teichmann, unpublished work.

[208] R. I. Wagner and A. B. Burg, *J. Amer. Chem. Soc.*, **75**, 3869 (1953).

[209] R. I. Wagner, L. D. Freeman, H. Goldwhite, and D. G. Roswell, *J. Amer. Chem. Soc.*, **89**, 1102 (1967).

[210] N. Kreutzkamp, *Chem. Ber.*, **87**, 919 (1954).

[211] F. Pass, E. Steininger, and H. Schindlbauer, *Monatsh. Chem.*, **90**, 792 (1959).

[212] W. Kuchen and H. Buchwald, *Chem. Ber.*, **92**, 227 (1959).

be cleaved by alkali metals or organoalkali compounds, so that alkali phosphides can be prepared from a large number of compounds of trivalent phosphorus.[213] However, working with metal phosphides, like that with organometallic compounds, requires strict exclusion of moisture and atmospheric oxygen.

Further, elemental phosphorus can be converted by Grignard reagents or organolithium compounds into metal phosphides which afford primary phosphines on hydrolysis; phenylphosphine was obtained in this way in yields of up to 40% from phenyllithium and white phosphorus.[214] In some circumstances cyclophosphines are formed on reaction of alkyl halides with the phosphide solutions obtained from elemental phosphorus.[215]

Treatment of the appropriate polyfunctional halide with metal phosphides is almost the only method of obtaining di-, tri-, or tetra-tertiary phosphines.

***P,P,P′,P′*-Tetraphenylmethylenediphosphine:**[216] Triphenylphosphine (131 g) is added within 10 min to a well-stirred solution of sodium (23 g; molar ratio 1 : 2) in liquid ammonia (1.5 l) at −75° under nitrogen. Reaction occurs at once, the color changing to deep orange. Ammonium bromide (49 g) is then added to destroy the phenylsodium and sodium amide (exothermal reaction — care!). After 1 h, methylene dichloride (21.5 g), dissolved in ether (20 ml), is added, whereupon the orange color fades. The solution is allowed to come to room temperature, and, when the ammonia has evaporated, the solid residue is washed with water (1.2 l) and then with methanol (four times with 50 ml) and crystallized from propanol (yield 74 g, 77%); one more crystallization gives the pure compound, m.p. 120.5–121.5°.

Tetrakis[(diphenylphosphino)methyl]methane has been similarly prepared from pentaerythritol tetrabromide.[217] The more reactive potassium diphenylphosphide permits the preparation also of ditertiary aromatic phosphines.[218]

***P,P,P′,P′*-Tetraphenyl-*p*-phenylenediphosphine:**[218] (Chloro)diphenylphosphine (46 g, 0.2 mole) is dropped slowly into a dispersion of potassium (16 g, 0.4 mole) in dry tetrahydrofuran (250 ml) under nitrogen. The resulting deep red solution is treated, dropwise at room temperature, with a solution of *p*-dibromobenzene (24 g, 0.1 mole) in tetrahydrofuran (50 ml), and the mixture is heated for 8 h at 67°. After cooling, the product is hydrolysed with water (100 ml) and the organic phase is dried and freed from solvent. The residue is made into a slurry with ethanol and filtered off. The yield is 68% and the m.p. 170–171° (after recrystallization from propanol).

Besides the phosphide method there is another method for alkylation of phosphine; this depends on the intermediate formation of a complex $PH_3 \cdot AlCl_3$ and leads, particularly with long-chain alkyl halides, to satisfactory or high yields of primary phosphines.[219]

Hays[220] has obtained high yields of tertiary phosphines by direct alkylation of decyl- and dodecyl-phosphine with alkyl iodides in an alcohol containing the same alkyl group.

Acylation to triacylphosphines is achieved when phosphine is passed into a pyridine solution of an aromatic acid chloride.[221]

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[213] K. Issleib, *Z. Chem.*, **2**, 163 (1962) (review).

[214] M. M. Rauhut and A. M. Semsel, *J. Org. Chem.*, **28**, 471 (1963).

[215] M. M. Rauhut and A. M. Semsel, *J. Org. Chem.*, **28**, 473 (1963).

[216] W. Hewertson and H. R. Watson, *J. Chem. Soc.*, **1962**, 1490.

[217] J. Ellermann and K. Dorn, *Chem. Ber.*, **99**, 653 (1966).

[218] H. Zorn, H. Schindlbauer, and H. Hagen, *Monatsh. Chem.*, **95**, 422 (1964).

[219] F. Pass, E. Steininger, and H. Zorn, *Monatsh. Chem.*, **93**, 230 (1963).

[220] H. R. Hays, *J. Org. Chem.*, **31**, 3817 (1966).

[221] R. Tyka and E. Plazek, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, **9**, 577 (1961); *Chem. Zentralbl.*, **1965**, 39-0924.

b. Replacement of halogen by phosphorus by means of tertiary phosphines

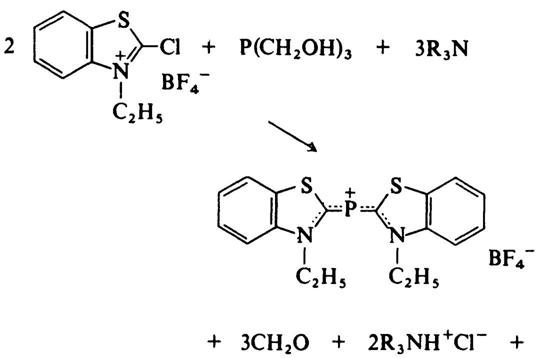
Alkylation of tertiary phosphines to quaternary phosphonium salts by alkyl halides is usually a smooth reaction that gives high to quantitative yields.[222] For unsubstituted and higher alkyl halides (up to C_3) it is best not to use a solvent.

Secondary and tertiary alkyl halides give olefins on occasions,[223] and β-unsaturated alkyl halides give products of allylic rearrangement.[224] α,ω-Dibromoalkanes give bisphosphonium salts in satisfactory to high yield.[225] Unlike dibromomethane, tribromomethane reacts with triphenylphosphine only to the monoquaternary salt stage, the reaction being radical in nature.[226]

Preparation of quaternary phosphonium salts is of great importance as it leads to the phosphorus ylides that are needed for Wittig olefination (see page 996). Further, quaternary phosphonium salts are intermediates in the methods of preparation of unsymmetrical phosphines that depend on successive alkylation of tertiary phosphines and degradation of the resulting quaternary salts. Three processes have been developed for the last-mentioned reaction:

(1) Use of the hydroxymethyl group, which is easily removed as formaldehyde from quaternary salts by means of alkali or triethylamine[227] (cf. page 702). Tetrakis(hydroxymethyl)phosphonium chloride, being commercially available, is a suitable starting material for preparation of symmetrical tertiary phosphines (*e.g.*, tripropylphosphine) by alternate fission and alkylation.[79b]

Because of the ease of its removal the hydroxymethyl group can even be used for synthesis of phospha analogs of cyanine dyes: 2-chloro-benzothiazolium or -quinolinium salts are treated with 0.5 equivalent of tris(hydroxymethyl)phosphine in the presence of 1.5 equivalents of a tertiary amine:[228]



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[222] W. A. Henderson and S. A. Buckler, *J. Amer. Chem. Soc.*, **82**, 5794 (1960).

[223] S. Trippett, *Quart. Rev.*, **17**, 406 (1963).

[224] H. H. Inhoffen and co-workers, *Chem. Ber.*, **88**, 1415 (1955).

[225] G. Wittig, H. Eggers, and P. Duffner, *Ann. Chem.*, **619**, 10 (1958); F. Ramirez and co-workers, *J. Amer. Chem. Soc.*, **83**, 3539 (1961).

[226] F. Ramirez and N. McKelvie, *J. Amer. Chem. Soc.*, **79**, 5831 (1957).

[227] K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **35**, 2062 (1965); *Chem. Sbstr.*, **64**, 6682 (1966).

[228] K. Dimroth and P. Hoffmann, *Chem. Ber.*, **99**, 1325 (1966).

(2) Use of the 2-cyanoethyl group, which is removed analogously by strong bases (sodium ethoxide).[229]

(3) Cathodic reduction of phosphonium salts. The ease of removal decreases in the series $C_6H_5CH_2$, $HOCH_2CH_2$, *tert*-$C_4H_9 >$ iso-$C_3H_7 >$ *n*-C_4H_9 $> C_2H_5 > C_6H_5 > CH_3$. This selective fission makes the process of alternate quaternization and reduction generally applicable to the synthesis of asymmetric phosphines, and moreover the yield and purity of the products are both high.[230] Also, both the cathodic reduction and the quaternization proceed with retention of configuration, so that the process is valuable for preparation of optically active phosphines.[231]

Arylation of tertiary phosphines cannot be achieved directly by means of aryl halides, but it can be effected photochemically[232] or under irradiation[233] or above 200° in the presence of aluminum chloride[234] or other anhydrous metal halides.

Bis(tetraphenylphosphonium) tetrabromoniccolate:[235] Triphenylphosphine (10 g), nickel bromide (4 g), and bromobenzene (15 g) are heated in a sealed tube for 2 h at 250°. The resulting dark blue crystals are washed from the tube with bromobenzene. Extraction with hot bromobenzene removes unchanged starting material. The product (12 g, 63%) melts at 273° after drying for 2 days in a vacuum at 130°.

Another method of arylating tertiary phosphines is provided by the "cobalt salt method", in which the aryl halide reacts in the presence of cobalt(II) chloride and a Grignard reagent. The process has radical character and the alkyl group of the Grignard reagent does not become attached to the phosphorus.

General directions for the preparation of **quaternary arylphosphonium salts** by the cobalt salt method:[236] Anhydrous cobaltous chloride (5 mmoles) is suspended in a solution of a tertiary phosphine (50 mmoles) and an aryl halide (100 mmoles) in ether (75 ml); into this is dropped a 2N-solution of phenylmagnesium bromide (50 mmoles) in ether under nitrogen. The mixture is stirred vigorously for 0.5 h, then boiled for 3 h, after which it is hydrolysed with 2N-hydrochloric acid (100 ml). Filtration removes at most a small precipitate — if present it is boiled out with water. Addition of sodium iodide to the aqueous phase precipitates the phosphonium iodide. After recrystallization from water or aqueous ethanol, yields are around 50%.

Diaryliodonium salts can also be used for arylating tertiary phosphines.[237] The supposed arylation of tertiary phosphines by bromophenols[238] does

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[229] M. Grayson, P. T. Keough, and G. A. Johnson, *J. Amer. Chem. Soc.*, **81**, 4803 (1959).

[230] L. Horner and A. Mentrup, *Ann. Chem.*, **646**, 65 (1961).

[231] L. Horner and co-workers, *Tetrahedron Lett.*, **1963**, 965; **1964**, 1421.

[232] J. B. Plumb and C. E. Griffin, *J. Org. Chem.*, **27**, 4711 (1962).

[233] H. Drawe and G. Caspari, *Angew. Chem. Int. Ed., Engl.*, **5**, 317 (1966).

[234] J. Chatt and F. C. Mann, *J. Chem. Soc.*, **1940**, 1192.

[235] F. A. Cotton, O. D. Faut, and D. M. L. Goodgame, *J. Amer. Chem. Soc.*, **83**, 344 (1961).

[236] L. Horner and H. Hoffmann, *Chem. Ber.*, **91**, 50 (1958).

[237] L. G. Makarowa and A. N. Nesmejanow, "Synthesen organischer Verbindungen", VEB Verlag Technik, Berlin, 1959, Vol. 1, p. 143.

[238] R. N. McDonald and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 4669 (1960).

not lead to formation of a P–C bond.[239] Like very many other compounds containing potentially positive halogen, bromophenols and also bromoarylamines[239] are, instead, attacked on the halogen atom by tertiary phosphines.[240] The halophosphonium salts formed as intermediates are solvolysed in solvents containing hydroxyl groups, thus yielding the phosphine oxide, hydrogen halide, and dehalogenated compound; in aprotic solvents the products vary according to the nature of the halogen compound used. Halogen compounds that do not give the expected alkylation products of tertiary phosphines include α-bromo ketones,[241] α-bromo nitro compounds,[242] and trichloroacetamide.[243] Some other polyhalo compounds, such as ethyl trichloro- and tribromo-acetate, and trichloroacetonitrile,[244] — also carbon tetrachloride and tetrabromide — on reaction with triphenylphosphine afford the dihalophosphorane and alkylidenephosphorane according to the overall reaction:

$$\mathrm{Hal_3CX + 2(C_6H_5)_3P \longrightarrow (C_6H_5)_3PHal_2 + (C_6H_5)_3P{=}CXHal}$$

In such reactions the ylide is not isolated but is consumed *in situ* for Wittig olefinations. However, the ylide was isolated after reaction of triphenylphosphine with α-bromo sulfones[247] and with 2,3-dibromopropionamide (other 2,3-dibromo carboxamides were smoothly dehalogenated by triphenylphosphine to the dibromophosphorane and acrylamide):[248]

$$\mathrm{BrCH_2CHBrCONH_2 + 2(C_6H_5)_3P \longrightarrow [(C_6H_5)_3PH]Br + BrCH_2\underset{\underset{P(C_6H_5)_3}{\|}}{C}CONH_2}$$

(10)

(2-Bromo-1-carbamoylethylidene)triphenylphosphorane(10):[248] 2,3-Dibromopropionamide (11.6 g 50 mmoles) is dissolved in dioxan (70 ml) and treated dropwise at room temperature during 1 h with a solution of triphenylphosphine (26.2 g, 100 mmoles) in dioxan (80 ml), the temperature being kept at 20–25° by external cooling. The mixture is stirred for a further 3 h, then the colorless precipitate is filtered off, dried in a vacuum, and recrystallized from chloroform–hexane. There is obtained an 85% yield (17.6 g) of the colorless, water-soluble compound (**10**), m.p. 241–242°.

The formation of ylides by use of the carbenes from chloroform[249] or methylene dichloride[109,250] and a base require only a mention here since such ylides are always used for Wittig olefinations without isolation.

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[239] H. Hoffmann, L. Horner, H. G. Wippel, and D. Michael, *Chem. Ber.*, **95**, 523 (1962).

[240] H. Hoffmann and H. J. Diehr, *Angew. Chem. Int. Ed., Engl.*, **3**, 737 (1964).

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[242] S. Trippett and D. M. Walker, *J. Chem. Soc.*, **1960**, 2976.

[243] A. J. Speziale and co-workers, *J. Amer. Chem. Soc.*, **82**, 903 (1960); **84**, 1868 (1962).

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[245] R. Rabinowitz and R. Marcus, *J. Amer. Chem. Soc.*, **84**, 1312 (1962).

[246] F. Ramirez and co-workers, *J. Amer. Chem. Soc.*, **84**, 1745 (1962).

[247] H. Hoffmann and H. Förster, *Tetrahedron Lett.*, **1963**, 1547.

[248] C. C. Tung and A. J. Speziale, *J. Org. Chem.*, **28**, 1521 (1963).

[249] A. J. Speziale and co-workers, *J. Amer. Chem. Soc.*, **82**, 1260 (1960); **84**, 854 (1962).

[250] D. Seyfarth and co-workers, *J. Amer. Chem. Soc.*, **82**, 1510 (1960); **83**, 1617 (1961).

4. Replacement of halogen by phosphorus by means of phosphites

a. Replacement of halogen by phosphorus by means of phosphorous triesters

When heated with alkyl halides at temperatures between 100° and 200°, phosphorous triesters containing at least one P–Oalkyl group afford phosphonic diesters:

$$(RO)_3P + R'Hal \longrightarrow R'P(O)(OR) + R_2Hal$$

This procedure, known as the Michaelis–Arbuzov reaction,[251] is one of the oldest but still one of the most important methods of forming P–C bonds.

When R = R′ the reaction amounts to isomerization of the phosphite to phosphonate, and then catalytic amounts of alkyl halide suffice.

Dimethyl methylphosphonate:[352] Trimethyl phosphite (0.1 mole) is heated with methyl iodide (10 mmoles) at 100° for 30 min. After a short induction period a violent reaction sets in which is complete in a few minutes. Distillation in a vacuum gives a 93% yield of the phosphonate, b.p. 63°/10 mm. When only 1 mmole of methyl iodide is used, the yield of phosphonate amounts to about 80%.

If the alkyl group that is to be introduced differs from the ester-alkyl group, then a competing reaction due to the newly formed alkyl halide will occur. Conditions are most favorable when the newly formed alkyl halide is more volatile than the other or is less reactive in S_N2 substitution; the halide formed can then, if necessary, be distilled off as formed or removed in a current of nitrogen. When the reaction requires long heating or high temperatures or — in exceptional cases (see below) — has radical character, it is advisable to use nitrogen as protecting agent against oxidative reactions.

The nucleophilicity of the trivalent phosphorus and thus the reactivity increases with increasing $+I$ effect of substituents on the phosphorus atom. The phosphonous esters and, more so, phosphinous esters undergo the Arbuzov reaction more readily than do phosphorous esters.[253] Methyl diphenylphosphinite, for instance, reacts exothermally with methyl iodide even at room temperature, giving the isomeric phosphine oxide;[254] although it is usual to work without a solvent, it is advisable to moderate the often very exothermic reaction of phosphonites by dilution with the reaction product and by carefully controlled portionwise addition of phosphonite.

Methyl methyl(phenyl)phosphinite:[255] Dimethyl phenylphosphonite (100 g) is dropped slowly into a stirred solution of a few drops of methyl iodide in methyl methyl(phenyl)-phosphinite (9 g) at 100–120°. Occasionally a few further drops of methyl idoide must be added later. When the addition is complete, distillation in a vacuum affords the product (100 g, 92%), b.p. 119°/3.5 mm, $n_D^{25.8}$ 1.5260 (the refractive index decreases sharply on storage in air).

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[251] G. M. Kosolapoff, *Org. Reactions*, **6**, 273 (1951); B. A. Arbuzov, *Pure Appl. Chem.*, **9**, 307 (1964); R. G. Harvey and E. R. DeSombre, "Topics in Phosphorus Chemistry," Interscience Publ., New York, Vol. 1 (1964), p. 57.

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[253] A. I. Razumov, *Zh. Obshch. Khim.*, **29**, 1635 (1959); *Chem. Abstr.*, **54**, 8608 (1960).

[254] A. E. Arbuzov and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948); *Chem. Abstr.*, **43**, 3801 (1949).

[255] H. J. Harwood and D. W. Grisley, *J. Amer. Chem. Soc.*, **82**, 423 (1960).

sec-Alkyl phosphites react faster than their primary analogs.[256,257] It is difficult to cause alkyl diphenyl phosphites with higher alkyl groups to enter the reaction, and that of triaryl phosphites with alkyl halides stops at the alkyltri(aryloxy)phosphonium salt stage.[258] The Arbuzov reaction fails with phosphites containing strongly electron-attracting substituents, *e.g.*, with tris-(2-cyanoethyl)[259] and tris-(2,2,2-trichloroethyl) phosphite.[260] 2-Chloroethyl phosphite[261] and phosphonite[262] function as alkylating agents of themselves, giving the isomerization product when merely heated:

$$P(OCH_2CH_2Cl)_3 \longrightarrow ClCH_2CH_2P(O)(OCH_2CH_2Cl)_2$$

(4-Chlorobutyl)phosphonous esters cyclize to 1-alkoxyphospholane 1-oxides in an intramolecular Arbuzov reaction.[263]

Primary react more readily than secondary alkyl halides; tertiary alkyl halides, except triphenylmethyl halides, normally do not react or give olefins. Formation of propene is observed on reaction of triisopropyl phosphite with isopropyl iodide, which leads to diisopropyl phosphite, whereas ethyl iodide and the same ester give the expected phosphonate.[257] The reactivity decreases, as usual, in progressing from iodide to chloride; simple alkyl fluorides do not react, nor do vinyl or aryl halides. Aryl halides, however, react with trialkyl phosphites, giving dialkyl esters of the aromatic phosphonic acid in high yield, if illuminated by ultraviolet light in the cold with very rigid exclusion of oxygen,[264,265] and this constitutes a valuable extension of the Arbuzov reaction which otherwise is strictly ionic.

A large number of substituted alkyl halides, for instance, chloro ethers,[266] chloro sulfides,[267] and halo carboxylic esters,[268] provide syntheses of phosphonic esters containing also other functional groups. *N*-(2-Bromoethyl)-phthalimide leads, after hydrolysis, to β-amino phosphonic esters.[269]

Diethyl [(benzyloxycarbonyl)methyl]phosphonate:[268] A mixture of benzyl chloroacetate (18.5 g, 0.1 mole) and triethyl phosphite (18.3 g, 0.11 mole) is heated at 175°; the internal temperature then rises somewhat and ethyl chloride distils off. When the exothermal reaction ceases, the mixture is heated for 1 h at 200° and then distilled in a vacuum; this affords 87% (25.1 g) of a product, b.p. 148–169°/1 mm. Redistillation gives analytically pure material having b.p. 174–179°/1.5 mm, n_D^{24} 1.4932.

Diethyl [(ethylthio)methyl]phosphonate:[267] Chloromethyl ethyl sulfide (22 g, 0.2 mole) is placed in a flask fitted with a dropping funnel, thermometer, and reflux condenser and con-

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[256] A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, **1947**, 1465.

[257] G. Aksnes and D. Aksnes, *Acta Chem. Scand.*, **19**, 898 (1965).

[258] A. E. Arbuzov and L. V. Nesterov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1954**, 427; *Chem. Abstr.*, **49**, 9541 (1955).

[259] E. V. Kuznetsov and R. K. Valetdinov, *Trudy Kazan. Khim. Tekhnol. Inst. im. S. M. Kirova*, **23**, 161 (1957); *Chem. Abstr.*, **52**, 8938 (1958).

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[261] M. I. Kabachnik and P. A. Rossiiskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1946**, 403; *Chem. Abstr.*, **42**, 7242 (1948).

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[266] G. K. Helmkamp, B. A. Olsen, and D. J. Pettitt, J. *Org. Chem.*, **30**, 676 (1965).

[267] N. Kreutzkamp and J. Pluhatsch, *Arch. Pharm.*, **292**, 159 (1959).

[268] D. J. Martin and C. E. Griffin, *J. Org. Chem.*, **30**, 4034 (1965).

[269] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 2112 (1947).

taining a piece of porous pot. The flask is heated at 90° while triethyl phosphite (33.2 g, 0.2 mole) is dropped in, and then at 150° for 5 h. Vacuum-distillation affords the phosphonate (34.6 g, 84%), b.p. 130°/10 mm, $n_D^{21.5}$ 1.4640.

Details directions for reactions of triethyl and triisopropyl phosphite with simple alkyl halides are to be found in *Organic Syntheses*.[270]

α,ω-Dihalides give reasonable to good yields of diphosphonates if an excess of the phosphite is used.[271] If no such excess is used, considerable amounts of monophosphonate are obtained;[256] with ethylene dibromide[256] and with 3-bromopropionic esters[272] olefin formation is observed as well as the competing reaction due to the newly formed alkyl bromide. 2-Hydroxyethyl chlorides are first transesterified by trialkyl phosphites and only then, at higher temperatures, undergo an intramolecular Arbuzov reaction.[273] A further side reaction that is occasionally met is competing alkylation of the phosphoryl-oxygen of the primary product.[274]

Chloroform reacts with triethyl phosphite in a peroxide-catalysed reaction that leads exclusively to the competing product diethyl ethylphosphonate.[275] On the other hand, carbon tetrachloride and the same ester give a high yield of the expected (trichloromethyl)phosphonate if boiled in the absence of radical-formers[276] or subjected to UV-irradiation in the cold.[277]

Chlorides of carboxylic acids, being strongly electrophilic reagents, react with trialkyl phosphites even at room temperature, yielding α-oxo phosphonic diesters.[278-280] The analogous imidoyl chlorides require higher temperatures.[281]

Diethyl propionylphosphonate:[280] Triethyl phosphite (35.9 g) is placed in a 100-ml flask and, whilst stirred under nitrogen with exclusion of moisture, is treated dropwise with freshly distilled propionyl chloride (20 g). When the exothermic reaction ceases, the mixture is set aside under nitrogen for 1 day and then distilled in a vacuum. This gives an 85.7% yield (36 g) of product, b.p. 105°/7 mm.

General procedure for the preparation of **dialkyl aroylphosphonates:**[279] The aroyl chloride (0.03 mole) is treated under nitrogen dropwise with the trialkyl phosphite (0.04 mole) at such a rate that the internal temperature does not exceed 35°. The resulting mixture is fractionated in a vacuum. As example, dimethyl benzoylphosphonate, b.p. 146°/2.5 mm, is obtained in 81% yield from benzoyl chloride and trimethyl phosphite.

When α-halo carbonyl compounds are used, the Arbuzov reaction (a) has as competitor the formation of an enol phosphate (*i.e.*, formation of a P–O

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[270] A. H. Ford-Moore and B. J. Perry, *Org. Syn.*, **31**, 33 (1951).

[271] G. M. Kosolapoff, *J. Chem. Soc.*, **1955**, 3092.

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[273] H.-G. Henning, *Z. Chem.*, **6**, 463 (1966).

[274] R. G. Laughlin, *J. Org. Chem.*, **27**, 1005 (1962).

[275] A. J. Burn, J. I. G. Cadogan, and P. J. Bunyan, *J. Chem. Soc.*, **1964**, 4369.

[276] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 1002 (1947).

[277] J. I. G. Cadogan and W. R. Foster, *J. Chem. Soc.*, **1961**, 3071.

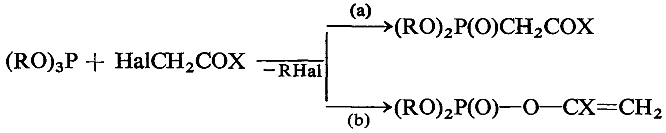
[278] M. I. Kabachnik and P. A. Rossiiskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1945**, 364; *Chem. Abstr.*, **40**, 4688 (1946); B. Ackerman and co-workers, *J. Amer. Chem. Soc.*, **78**, 4444 (1956).

[279] K. D. Berlin and H. A. Taylor, *J. Amer. Chem. Soc.*, **86**, 3862 (1964).

[280] K. D. Berlin, D. M. Hellwege, and M. Nagabhushanam, *J. Org. Chem.*, **30**, 1265 (1965).

[281] H. Zieloff, H. Paul, and G. Hilgetag, *Chem. Ber.*, **99**, 357 (1966).

bond), known as the Perkow reaction (b):[282,283]



$$(RO)_3P + HalCH_2COX \xrightarrow[-RHal]{} \begin{cases} \xrightarrow{(a)} (RO)_2P(O)CH_2COX \\ \xrightarrow[(b)]{} (RO)_2P(O){-}O{-}CX{=}CH_2 \end{cases}$$

Although α-halo carboxylic esters usually undergo the Arbuzov reaction smoothly (see above), α-halo aldehydes give exclusively the enol phosphate.[284] α-Halo ketones show intermediate behavior: the proportion of keto phosphonate to enol phosphate formed increases sharply in the series chloro-,[283,285] bromo-,[283,285,286] iodoacetone;[287] and the reaction temperature and the solvent also influence the direction of the reaction.[283,285] A vinyl phosphate was the sole product from a vinylogous α-chloro ketone.[288] 2-Bromo-4-butyrolactone behaves as an α-halo carboxylic ester, but α-chloro α-acyl γ-lactones give exclusively the products of the Perkow reaction.[289]

2-(Diethoxyphosphinyl)-4-butyrolactone:[289] 2-Bromo-4-butyrolactone (16 g, 0.1 mole) is stirred for 5 h with triethyl phosphite (20 g, 0.12 mole) at 140°, then the ethyl bromide is distilled off in a stream of nitrogen. After the mixture has cooled, distillation in a vacuum yields the product (19 g, 86%), b.p. 115°/0.02 mm.

α-Halo nitro compounds and trialkyl phosphites give *O*-phosphorylated oximes with deoxygenation,[290] this resembling the Perkow reaction.

b. Replacement of halogen by phosphorus by means of phosphorous diesters

The more readily accessible diesters can replace the triesters of phosphorous acid in the preparation of phosphonic diesters. The alkylation of the diesters, which must be presented as anions, by primary alkyl halides occurs exclusively on the phosphorus atom (Michaelis–Becker reaction).

The phosphorous diester is usually used as sodium salt. The oldest technique is to treat the dialkyl phosphite with an equivalent amount of sodium[291] in an inert solvent (toluene, xylene, dioxan, tetrahydrofuran, or ether) before adding the alkyl halide. Dibutyl phosphite has the advantage over the more frequently used diethyl phosphite that its sodium salt is soluble in hydrocarbons.[292] Complete conversion into the sodium salt requires several hours' heating unless the metal is finely divided; for the preparation of stable dis-

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[282] F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); R. F. Hudson, Chem. Soc. Special Publ. No. 19 (1964), p. 93, H.-G. Henning and G. Hilgetag, *Z. Chem.*, **7**, 169 (1967); I. J. Borowitz and co-workers, *J. Org. Chem.*, **32**, 1723 (1967).

[283] P. A. Chopard and co-workers, *Tetrahedron*, **21**, 1961 (1965).

[284] W. Perkow, *Chem. Ber.*, **87**, 755 (1954).

[285] A. N. Pudovik and V. P. Aver'yanova, *Zh. Obshch. Khim.*, **26**, 1426 (1956); *Chem. Abstr.*, **50**, 14512 (1956).

[286] N. Kreutzkamp and H. Kayser, *Chem. Ber.*, **89**, 1614 (1956).

[287] H. J. Jacobson and co-workers, *J. Amer. Chem. Soc.*, **79**. 2608 (1957).

[288] J. F. Allen and O. H. Johnson, *J. Amer. Chem. Soc.*, **77**, 2871 (1955).

[289] K.-H. Büchel, H. Röchling, and F. Korte, *Ann. Chem.*, **685**, 10 (1965).

[290] J. F. Allen, *J. Amer. Chem. Soc.*, **79**, 3071 (1957).

[291] A. Michaelis and T. Becker, *Ber. Deut. Chem. Ges.*, **30**, 1003 (1897).

[292] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **67**, 1180 (1945).

persions of sodium see Pass and Schindlbauer.[293] Sodium ethoxide may replace the metallic sodium.[294] However, sodium dialkyl phosphite solutions are most conveniently prepared by means of sodium hydride in tetrahydrofuran.[295]

A further elegant method involves a solution of sodium in liquid ammonia, which gives a sharp end-point (disappearance of the blue color) on addition of the equivalent amount of dialkyl phosphite; subsequent reaction with the halogen compound can be performed in the same solution. After a further 2 hours' stirring, evaporation of the ammonia generally provides a good yield of the product. However, side reactions occur with halo alkynes, which are reduced to alkynes, and with benzyl halides, which may yield diphenylethane derivatives; formation of amides of phosphoric acid has also been observed alongside dehalogenation.[296]

A prescription for the preparation of α-keto phosphonic diesters avoids use of the bases mentioned; above: in this, triethylamine is dropped into a mixture of the acid chloride and dialkyl phosphite in benzene.[297]

The Michaelis–Becker reaction can, by its nature, be carried out at lower temperatures than are required for the Arbuzov reaction and thus its use can provide some compounds that cannot be prepared by the latter method; for example, 2-chloro-*N*,*N*-diethylethylamine affords the required phosphonate on reaction with sodium diethyl phosphite but not with triethyl phosphite.[298] However, side reactions often lead to lower yields than those from the Arbuzov reaction; for instance, the halide ion produced can readily dealkylate the resulting phosphonate to the monoester,[299] so that it is essential to remove the sodium halide before working the product up by distillation.

The dialkyl phosphite ion, however, can itself dealkylate the phosphonate product;[300] and finally one may have to reckon with a competitive alkylation of the dialkyl phosphite ion by still unchanged phosphorous diester;[301] and the use of allyl halides in the Michaelis–Becker reaction may lead also to diphosphonates owing to the ability of dialkyl phosphite ions to add to unsaturated systems (see Section 9.1).[302]

Dialkyl thiophosphites $(RO)_2P(S)H$ are also alkylated exclusively on the phosphorus in the Michaelis–Becker reaction, thus affording thiophosphonic esters.[303]

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[293] F. Pass and H. Schindlbauer, *Monatsh. Chem.*, **90**, 148 (1959).

[294] P. Nylen, *Ber. Deut. Chem. Ges.*, **69**, 1119 (1926).

[295] R. G. Harvey, T. C. Myers, H. I. Jacobson, and E. V. Jensen, *J. Amer. Chem. Soc.*, **79**, 2612 (1957).

[296] A. Meisters and J. M. Swan, *Aust. J. Chem.*, **18**, 163 (1965).

[297] USSR Pat. 162,142; *Chem. Zentralbl.*, **1965**, 44-2443.

[298] J. I. G. Cadogan, *J. Chem. Soc.*, **1957**, 4154.

[299] V. S. Abramov and co-workers, *Zh. Obshch. Khim.*, **14**, 1030 (1944); **22**, 252, 257 (1952); *Chem. Abstr.*, **41**, 700 (1947); **46**, 11099 (1952).

[300] K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **29**, 3407 (1959); **30**, 1308 (1960); *Chem. Abstr.*, **54**, 17245 (1960); **55**, 1414 (1961).

[301] Z. Pelchowicz, S. Brukson, and E. D. Bergmann, *J. Chem. Soc.*, **1961**, 4348; R. E. Zimmerer and R. G. Laughlin, *J. Org. Chem.*, **27**, 3576 (1962); U.S. Pat. 3,064,031; *Chem. Abstr.*, **58**, 9142 (1963).

[302] W. H. Rueggeberg, J. Chernack, and I. M. Rose, *J. Amer. Chem. Soc.*, **72**, 5336 (1950).

[303] M. I. Kabachnik and T. A. Mastryukova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1953**, 163; *Chem. Abstr.*, **48**, 3243 (1954).

III. Replacement of oxygen by phosphorus

1. Replacement of oxygen by phosphorus by means of elemental phosphorus

White phosphorus can be aminomethylated in aqueous ethanol to mixtures of phosphonic acids, phosphinic acids, and phosphine oxides, the oxides usually constituting the main product, approximately in accord with the reaction:

$$\begin{aligned} 2P_4 + 20NR_2CH_2OH \longrightarrow\ & NR_2CH_2P(O)(OH)_2 + 2(NR_2CH_2)_2P(O)OH \\ & + 5(NR_2CH_2)_3PO + 8H_2O \end{aligned}$$

Tris[(dimethylamino)methyl]phosphine oxide:[304] 40% aqueous formaldehyde solution (99.8 ml) is dropped, with ice-cooling into a solution of dimethylamine (56.2 g, 1.25 moles) in ethanol (150 ml). Then white phosphorus (15 g, 0.483 mole) is added under nitrogen, and the mixture is heated under reflux for 15 h. The resulting clear yellow solution is evaporated on a rotary evaporator and the semisolid residue (165.3 g) is extracted with ether. Removing the ether gives the phosphine oxide (47.8 g, 44.6%), m.p. 154–157°. This can be further purified by sublimation at atmospheric pressure and is thus obtained as transparent needles.

2. Replacement of oxygen by phosphorus by means of phosphorus halides

Halides of trivalent phosphorus are usually converted into esters by alcohols in the presence of a tertiary amine. However, in some cases, notably in the phosphinous series, the expected products are obtained only by careful working in the cold; even distillation can then lead to isomerization, as in the reaction of (chloro)diphenylphosphine with benzyl alcohol in pyridine which, on distillation, leads to isolation of the phosphine oxide in place of its isomer, the phosphinite.[254] This behavior is the rule for α-hydroxy alkynes, where also prototropy is involved; it led to the production of a series of (allenyl)-diphenylphosphine oxides in good yield from (chloro)diphenylphosphine and α-hydroxy alkynes.[305] Phosphorus trichloride and dialkyl chlorophosphites react analogously.[306] Sometimes the prototropy leads beyond the allenyl stage, as when reaction of dialkyl chlorophosphites with, *e. g.*, propargyl chloride leads through the propargyl phosphite and propadienylphosphonate to the propynylphosphonate:[307]

$$\begin{aligned} (RO)_2PCl + CH{\equiv}CCH_2OH \longrightarrow\ & (RO)_2P{-}OCH_2C{\equiv}CH \longrightarrow \\ & (RO)_2P(O)CH{=}C{=}CH_2 \longrightarrow (RO)_2P(O)C{\equiv}CCH_3 \end{aligned}$$

Further, 2-chloroethyl phosphites tend to undergo an intramolecular Arbuzov reaction and thus may isomerize spontaneously during their preparation; a convenient synthesis of **(2-chloroethyl)phosphonic dichloride** utilizes this behavior:[308]

Ethylene oxide (dried over potassium hydroxide pellets in a tower) is led with stringent exclusion of moisture into 137.5 g of phosphorus trichloride until a weight increase of at least 132 g is attained; the temperature must be kept at 20° by external cooling. The mixture

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[304] L. Maier, *Helv. Chim. Acta*, **50**, 1723 (1967).

[305] A. P. Boisselle and N. A. Meinhardt, *J. Org. Chem.*, **27**, 1828 (1962).

[306] E. Cherbuliez and co-workers, *Helv. Chim. Acta*, **48**, 632 (1965).

[307] A. N. Pudovik and I. M. Aladzheva, *Zh. Obshch. Khim.*, **33**, 707 (1963); *Chem. Abstr.*, **59**, 2851 (1963).

[308] M. I. Kabatschnik and P. A. Rossijskaja, "Synthesen organischer Verbindungen," VEB Verlag Technik, Berlin und Porta-Verlag, Munich, Vol. 2 (1956), p. 138.

is set aside overnight and then heated cautiously at 150° for 5 h under a long, broad air-condenser carrying at the top a calcium chloride tube. 20-g portions of the product are placed in bomb-tubes, 32 g of phosphorus pentachloride are added to each, and the tubes are then sealed and heated at 150° for 2.5 h. Distillation of the combined products through a column gives the dichloride (90–95 g, 50–52%), b.p. 82–84°/5.5 mm.

An ether fission of tetrahydrofuran by (chloro)diphenylphosphine and lithium or magnesium has been described; this obviously proceeds by way of the metal phosphide. However, other ethers do not react in this way.[309]

(4-Hydroxybutyl)diphenylphosphine: A tetrahydrofuran solution of (chloro)diphenylphosphine (29.8 g, 0.135 mole) is added under nitrogen to a slurry of magnesium turnings (3.3 g, 0.135 mole) in tetrahydrofuran (100 ml), an immediate reaction occurring which raises the temperature to the boiling point. The magnesium is all consumed in 4 h. After cooling, the mixture is treated with water, and the organic layer is dried over magnesium sulfate. Removing the solvent leaves a viscous oil which is distilled through a 6-inch Vigreux column, yielding the cleaved product (29 g, 83%), b.p. 170°/0.16 mm, n_D^{25} 1.6103.

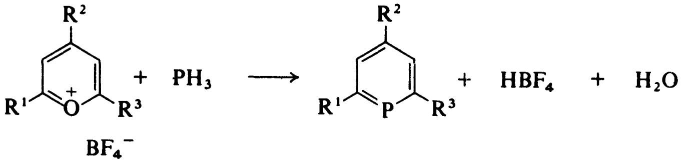
3. Replacement of oxygen by phosphorus by means of phosphines

Metal salts of primary and secondary phosphines cleave cyclic ethers to ω-hydroxyalkylphosphines.[310] In addition, lithium diphenylphosphide has been recommended for fission of alkyl aryl ethers.[311]

(Methyl)diphenylphosphine:[311] An ice-cold solution of diphenylphosphine (9.1 g) in dry tetrahydrofuran (110 ml) is treated under nitrogen with a 1.2M-solution (45 ml) of butyllithium and then with anisole (5.8 g). The deep red solution is heated under reflux for 4 h, then the solvent is distilled off completely and the residue is treated, with ice-cooling, with ether (150 ml) and boiled out water (50 ml). The aqueous phase is extracted with ether (two 50-ml portions). The united ether extracts are dried and evaporated, leaving a pale yellow oil (11.2 g) which distils at 90–108°/0.2 mm (yield 8.5 g, 87%). A second distillation gives a product boiling at 87–90°/0.2 mm.

Reaction of secondary phosphines with ethylene carbonate (1,3-dioxolan-2-one) at 150–200° affords *P,P,P′,P′*-tetraalkylethylenediphosphine dioxides.[312] With triphenylcyanurate they afford tristertiary phosphines in high yield with replacement of all three phenoxy groups.[313]

Phosphorus replaces the oxygen of pyrylium salts in reactions with phenylphosphine or phosphine itself. The former reaction gives products whose structure has not been completely clarified,[314] but in the presence of mineral acids the latter gives unambiguously derivatives of phosphorin (phosphabenzene):[315]



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[309] A. Y. Garner and A. R. Tedeschi, *J. Amer. Chem. Soc.*, **84**, 4734 (1962).
[310] K. Issleib and H.-R. Roloff, *Chem. Ber.*, **98**, 2091 (1965).
[311] F. G. Mann and M. J. Pragnell, *J. Chem. Soc.*, **1965**, 4120.
[312] P. T. Keough and M. Grayson, *J. Org. Chem.*, **27**, 1817 (1962).
[313] W. Hewertson, R. A. Shaw, and B. C. Smith, *J. Chem. Soc.*, **1964**, 1020.
[314] C. T. Price and co-workers, *J. Amer. Chem. Soc.*, **88**, 1034 (1966).
[315] G. Märkl, F. Lieb, and A. Merz, *Angew. Chem. Int. Ed., Engl.*, **6**, 944 (1967).

2-Methyl-4,6-diphenylphosphorin: A suspension of 2-methyl-4,6-diphenylpyrylium fluoroborate (2.1 g, 6.3 mmoles) in 1-butanol (50 ml) is heated with phosphonium iodide (2.6 g, 16 mmoles) at 110–120° for 24 h. The solvent is removed, the residue taken up in benzene, and this solution is washed several times with water, dried over calcium chloride, and concentrated. When the residue is rubbed with ethanol and cooled the product crystallizes; recrystallization from a little ethanol gives material (945 mg) melting at 79–81°.

Tris(hydroxymethyl)- or tris(trimethylsilyl)-phosphine may be used in place of phosphonium iodide.[316]

Tertiary phosphines can be quaternized by sulfonic esters[317] or carboxonium salts.[318] More important for synthesis is that they can be quaternized even by alcohols in the presence of mineral acid:[319,320]

$$(C_6H_5)_3P + ROH + HBr \longrightarrow (C_6H_5)_3\overset{+}{P}RBr^- + H_2O$$

A series of alkyltriphenylphosphonium salts has been prepared in this way in good yield with dimethylformamide as solvent and hydrogen bromide as acid and, after deprotonation, can be used in the same solution for Wittig olefination.[319]

4. Replacement of oxygen by phosphorus by means of phosphites and related compounds

a. Replacement of oxygen by phosphorus by means of phosphites and other compounds containing P–H bonds

Dialkyl phosphites react with (hydroxymethyl)amines, giving α-amino phosphonic esters; the same products can often be obtained by reaction of the phosphite with aminals, Schiff bases, or an aldehyde plus an amine[321] (cf. page 708). Free phosphorous acid can itself be α-aminoalkylated in an acid medium, when according to the amine selected (ammonia can also be used) up to three methylenephosphonic acid groups can be attached to one nitrogen atom:[322]

$$\underset{n=1-3}{R_{3-n}NH_n} + nCH_2O + nHP(O)(OH)_2 \longrightarrow \underset{\textbf{(11)}}{R_{3-n}N[CH_2P(O)(OH)_2]_n} + nH_2O$$

Nitrilotris(methylenephosphonic acid) (11; $n = 3$):[322] Ammonium chloride (17.8 g, 0.33 mole), crystalline phosphorous acid (82 g, 1 mole), water (100 ml), and concentrated hydrochloric acid (100 ml) are heated together to the boiling point in a flask fitted with a thermometer, stirrer, reflux condenser, and dropping funnel. 37% aqueous formaldehyde (160 ml, 2 moles, 100% excess) is added dropwise during 1 h and the whole is heated under reflux for a further hour. When the solution is then kept overnight most of the product crystallizes. Collection, washing with aqueous acetone, and drying at 120° affords it (74.9 g, 75%) with m.p. 210–215°. Concentration of the mother-liquor provides a second fraction.

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[316] G. Märkl and co-workers, *Angew. Chem. Int. Ed., Engl.*, **5**, 846 (1966); **6**, 458 (1967).

[317] D. Klamann and P. Weyerstahl, *Chem. Ber.*, **97**, 2534 (1964).

[318] L. Horner and B. Nippe, *Chem. Ber.*, **91**, 67 (1958).

[319] H. Pommer, *Angew. Chem.*, **72**, 811 (1960).

[320] J. D. Surmatis and A. Ofner, *J. Org. Chem.*, **28**, 2735 (1963).

[321] E. K. Fields, *J. Amer. Chem. Soc.*, **74**, 1528 (1952).

[322] K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).

Hypophosphorous acid can also be aminoalkylated; in the absence of mineral acid, (aminomethyl)phosphorous acids (**12**) are formed but in the presence of acid the second P–H group can also be substituted with formation of bis(aminomethyl)-phosphonic acids:[323]

$$R_2NH + CH_2O + H_2P(O)OH \longrightarrow \underset{(\mathbf{12})}{NR_2CH_2PH(O)OH}$$

(Piperidinomethyl)phosphonous acid monohydrate:[323] Into 40% aqueous formaldehyde (15 g of aldehyde, 0.5 mole) are added dropwise, with ice-cooling, first piperidine (42.5 g, 0.5 mole) and then hypophosphorous acid (33 g, 0.5 mole) as 60% aqueous solution. The mixture is then evaporated in a rotary evaporator at 80° under water-pump vacuum. The residual colorless oil crystallizes when kept for a short time. After recrystallization from ethanol–ether, the yield is 68.5% (62 g) and the m.p. 146–147°.

Secondary phosphine oxides[324] and sulfides[325] can be aminoalkylated to the tertiary compounds.

The alkyl halides used in the Michaelis–Becker reaction (cf. page 728) may be replaced by other alkylating agents such as dialkyl sulfates[326] or alkyl sulfonates;[295,327] even the use of carboxylic esters for alkylation of sodium dialkyl phosphites is the subject of a patent.[328] It is noteworthy that *p*-toluenesulfonates often have advantages over alkyl halides in that alcohols are readily converted into these esters and, further, that the *p*-toluenesulfonate ion liberated, being a weak nucleophile, causes fewer side reactions. Alkyl *p*-toluenesulfonates rank between alkyl chlorides and bromides in their reactivity towards sodium dialkyl phosphites.[286] *p*-Toluenesulfonates of secondary alcohols give poor yields of phosphonate.

Diethyl butylphosphonate:[327] Butyl *p*-toluenesulfonate (24.7 g, 0.11 mole) is dissolved in dry tetrahydrofuran (50 ml) and then stirred whilst being treated with a 1.5M-solution (82ml) of sodium diethyl phosphite (0.12 mole) in tetrahydrofuran. After 6 hours' stirring at room temperature the mixture is heated under reflux for some hours, then cooled and filtered. Evaporation of the filtrate and distillation of the residual oil in a vacuum affords the product (17.3 g, 82%), b.p. 53–55°/0.1 mm, n_D^{25} 1.4213.

Alkylation of dialkylphosphorous salts by dialkyl phosphites and by phosphonic diesters has been mentioned above (page 729). The latter reaction can be used for nearly quantitative preparation of salts of alkylphosphonic monoesters, by converting the dialkyl phosphite into its sodium salt and heating this in a sealed tube with a catalytic amount of a phosphonic diester containing the same alkyl group.[329] Further, when heated alone, sodium dialkyl phosphites afford, according to the conditions, sodium alkylphosphonates or disodium phosphonates and dialkyl phosphonates.[330]

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[323] L. Maier, *Helv. Chim. Acta*, **50**, 1742 (1967).

[324] M. M. Rauhut and H. A. Currier, *J. Org. Chem.*, **26**, 4629 (1961).

[325] L. Maier, *Helv. Chim. Acta*, **49**, 1249 (1966).

[326] A. Simon and W. Schulze, *Chem. Ber.*, **94**, 3251 (1961); U.S. Pat. 3,067,231; *Chem. Abstr.*, **58**, 7976 (1963).

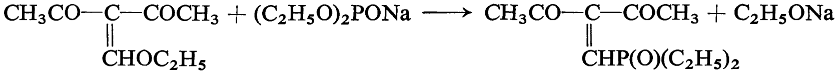
[327] T. C. Myers, S. Preis, and E. V. Jensen, *J. Amer. Chem. Soc.*, **76**, 4172 (1954).

[328] U.S. Pat. 2,681,920; *Chem. Abstr.*, **49**, 6989 (1955).

[329] K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **29**, 3407 (1959); *Chem. Abstr.*, **54**, 17245 (1960).

[330] A. N. Pudovik and R. I. Tarasova, *Zh. Obshch. Khim.*, **34**, 1151 (1964); *Chem. Abstr.*, **61**, 1888 (1964).

Finally, *O,O*-dialkylphosphorites can also be alkylated by epoxides[331,332] or lactones;[332] more than one product is usually formed; however, a smooth reaction occurs with enol ethers as 3-(ethoxymethylene)-2,4-pentanedione (**13**), the alkoxy group being replaced:[333]



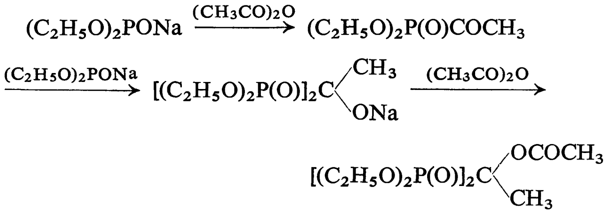
$$CH_3CO-\underset{\underset{CHOC_2H_5}{\|}}{C}-COCH_3 + (C_2H_5O)_2PONa \longrightarrow CH_3CO-\underset{\underset{CHP(O)(C_2H_5)_2}{\|}}{C}-COCH_3 + C_2H_5ONa$$

(13) **(14)**

3-[(Diethoxyphosphinyl)methylene]-2,4-pentanedione [diethyl (2-acetyl-3-oxo-2-butenyl)-phosphonate] (14): A solution of the enol ether (**13**) (0.1 mole) in ether (100 ml) is treated with a suspension of sodium diethyl phosphite (0.1 mole) in ether (100 ml) and heated under reflux, with stirring, for 2 h. After cooling, the mixture is extracted with 20% hydrochloric acid (19 g). The ethereal phase is dried and freed from ether and unchanged enol ether in a vacuum. Two fractionations of the residue in a vacuum afford the product (61%; crude yield before distillation 80%), b.p. 127°/0.01 mm, n_D^{20} 1.4622.

This process can be generalized.

Acylphosphonates, expected to be the primary products from reaction of dialkyl phosphites with acid anhydrides, add a further equivalent of the phosphite, thus yielding α-acyloxy diphosphonates which can be isolated in good yield after acylation:[334]



$$(C_2H_5O)_2PONa \xrightarrow{(CH_3CO)_2O} (C_2H_5O)_2P(O)COCH_3$$

$$\xrightarrow{(C_2H_5O)_2PONa} [(C_2H_5O)_2P(O)]_2C{<}^{CH_3}_{ONa} \xrightarrow{(CH_3CO)_2O}$$

$$[(C_2H_5O)_2P(O)]_2C{<}^{OCOCH_3}_{CH_3}$$

b. Replacement of oxygen by phosphorus by means of tertiary phosphites

Not only the Michaelis–Becker but also the Michaelis–Arbuzov reaction (cf. page 725) can be effected with alkylating agents other than alkyl halides. Sulfonic esters are the most important reagents for this reaction also. If the alkyl group of the phosphite and the sulfonate are the same, catalytic amounts of sulfonate suffice to afford high yields of phosphonate. If these alkyl groups are not the same, mixed products are obtained.[335] Surprisingly, even triphenyl phosphite reacts with methyl *p*-toluenesulfonate (72 hours at 130°), giving good yields of diphenyl methylphosphonate, which indicates formation of an intermediate containing quinquecovalent phosphorus.[336]

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[331] N. Kreutzkamp, *Naturwissenschaften*, **43**, 81 (1956).

[332] R. L. McConnell and H. W. Coover, *J. Amer. Chem. Soc.*, **78**, (a) 4450, (b) 4453 (1956).

[333] N. Kreutzkamp and H. Schindler, *Chem. Ber.*, **92**, 1695 (1959).

[334] G. Kamai and W. A. Kukhtin, *Zh. Obshch. Khim.*, **27**, 949 (1957); *Chem. Abstr.*, **52**, 3665 (1958).

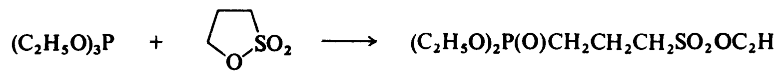
[335] R. A. Baldwin, C. O. Wilson, and R. I. Wagner, *J. Org. Chem.*, **32**, 2172 (1967).

[336] D. B. Denney and J. Giacin, *Tetrahedron Lett.*, **1964**, 1747.

Diethyl ethylphosphonate:[335] A mixture of triethyl phosphite (83 g, 0.5 mole) and ethyl *p*-toluenesulfonate (10 g, 0.05 mole) is heated slowly under nitrogen until an exothermic reaction begins. After cooling, the product is fractionated through a Vigreux column, giving the phosphonate (76.1 g, 91.6%), b.p. 90–92°/18 mm, n_D^{20} 1.4156–1.4160.

Dimethyl methylphosphonate is obtained analogously in 98–100% yield from trimethyl phosphite and methyl *p*-toluene- or benzene-sulfonate.

Catalytic amounts of dialkyl sulfates can also be used for preparation of phosphonates.[252] The Arbuzov reaction with sultones affords phosphonylated sulfonic esters:[337]



Lactones react analogously [although with dialkyl phosphites they give ω-(hydroxyacyl)phosphonates if catalysed by base], but telomers are always formed as well as the monomers.[332b] Unlike triethyl phosphite, triphenyl phosphite reacts with ethylene carbonate (1,3-dioxolan-2-one) in the presence of small amounts of copper powder to yield tetraphenyl ethylenebisphosphonate.[312]

Tetraphenyl ethylenebisphosphonate: Triphenyl phosphite (16.5 g) 1,3-dioxolan-2-one (4.4 g), and copper powder (0.5 g) are heated for 5 h at 200–260°. After cooling, the mixture is extracted with benzene, whence, after concentration, the diphosphonate (m.p. 145–146°; 5 g, 40.5%) crystallizes. Recrystallization from benzene gives material melting at 152–153°.

Alkyl trialkoxyphosphonium salts, which are intermediates in the Arbuzov reaction, can be prepared by alkylation of trialkyl phosphites with trialkyloxonium salts.[338]

A convenient method of obtaining diphenyl alkylphosphonates is to heat triphenyl phosphite with an alcohol at 220–250° in the presence of a catalytic amount of the corresponding alkyl iodide; sodium iodide or iodine may also be used as the catalyst. The best results are obtained when the alcohol used boils appreciably higher than phenol (180°), so that the phenol distils off continuously.[339]

General method for preparation of **diphenyl esters of (long-chain alkyl)phosphonic acids:** Equivalent amounts of the alcohol and triphenyl phosphite, together with 10 moles-% of sodium iodide, are placed in a flask fitted with a thermometer, gas-inlet tube, stirrer, and distillation head; water at about 50° is circulated through the attached condenser to prevent crystallization of the phenol. Nitrogen is led into the flask while the mixture is heated at the required temperature by a radiant heater until no more phenol distils (about 20 h). The remaining material is distilled at < 0.05 mm and the distillate is taken up in ether. The ethereal solution is washed with 2N-sodium hydroxide solution, dried and evaporated, and the residue is redistilled.

For example, 2.08 moles each of triphenyl phosphite and 1-dodecanol at 220–225° afford, after 19 h, a 71% yield of diphenyl dodecylphosphonate, b.p. 165°/0.01 mm.

Trialkyl phosphites which are unable to undergo intramolecular Arbuzov rearrangement can be isomerized by heating them at about 80° with an equimolar amount of a trialkylaluminum; *e. g.*, triethyl phosphite and triiso-

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[337] Ger. Pat. 938,186; *Chem. Zentralbl.*, **1956**, 14479.

[338] K. Dimroth and A. Nürrenbach, *Chem. Ber.*, **93**, 1649 (1960).

[339] R. G. Laughlin, *J. Org. Chem.*, **27**, 3644 (1962).

propylaluminum give a phosphonate adduct which on hydrolysis provides diethyl ethylphosphonate in about 70% yield.[340] Alkyl phosphinites are similarly isomerized to trialkylphosphine oxide adducts by trialkyltin halides.[342]

IV. Replacement of other non-metals by phosphorus

1. Replacement of nitrogen by phosphorus

a. Replacement of nitrogen by phosphorus by means of phosphorus halides

Provided moisture is rigidly excluded, phosphorus trichloride or tribromide and a diazoalkane at low temperatures afford α-halo alkyldihalophosphines:[342]

$$RCHN_2 + PCl_3 \longrightarrow RCHCl{-}PCl_2$$

More important is the reaction of phosphorus trichloride with arenediazonium salts, presented as fluoroborates, which causes introduction of an aryl group. The reaction was originally used for the preparation of phosphonic acids, the products being hydrolysed:

$$ArN_2{}^+BF_4{}^- + PCl_3 \longrightarrow Ar\overset{+}{P}Cl_3BF_4{}^- \xrightarrow{H_2O} ArPO(OH)_2$$

In spite of the moderate yields (generally 20–50%), the process is of great interest because, unlike the reaction of $PCl_3/AlCl_3$ with aromatic compounds (page 711), it gives products that are free from isomers. Small amounts of diarylphosphinic acids are formed as by-products.

General directions for the preparation of **arylphosphonic acids:**[343] Phosphorus trichloride (0.2 mole) and copper(I) chloride (4 g) are added to a suspension of the dry arenediazonium tetrafluoroborate (0.2 mole) in ethyl acetate (250 ml, dried over phosphorus pentaoxide) whilst the mixture is stirred and nitrogen is led in. After initial slight evolution of heat there is no sign of reaction for a considerable time (15 min to 2 h), then evolution of nitrogen and rise in temperature occur suddenly; in the latter phase cooling may be necessary; occasionally the mixture must be warmed to 50° to induce reaction. When gas evolution ceases, water (50 ml) is stirred in cautiously and the solvent and volatile by-products are removed by distillation in steam. When considerable (1 l) distillate has collected, the residual mixture is concentrated (to 200 ml) and filtered from the sparingly soluble phosphinic acid (sometimes this crystallizes only after cooling.) The filtrate is then further evaporated (to about 50 ml), so that the phosphonic acid separates on cooling. For purification this acid is dissolved in sufficient 20% sodium hydroxide solution to give pH 8, and the mixture is boiled with charcoal, filtered, and acidified to Congo Red; this precipitates the monosodium salt.

o-Toluenediazonium tetrafluoroborate does not react, although the *m*- and *p*-compounds give good yields;[344] ethylbenzenediazonium salts give poor yields.[345] Diazonium fluorosilicates may be used in place of the fluoroborates

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[340] M. Sander, *Angew. Chem.*, **73**, 67 (1961).

[341] A. N. Pudovik and co-workers, *Zh. Obshch. Khim.*, **33**, 3350 (1963); *Chem. Abstr.*, **60**, 4175 (1964).

[342] A. Ya. Yakubovich and V. A. Ginsburg, *Zh. Obshch. Khim.*, **22**, 1534 (1952); *Chem. Abstr.*, **47**, 9254 (1953).

[343] G. O. Doak and L. D. Freedman, *J. Amer. Chem. Soc.*, **73**, 5658 (1951); **74**, 753 (1952); **75**, 683 (1953).

[344] E. C. Ashby and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 4903 (1953).

[345] L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, **77**, 173 (1955).

with equal success.[346] Unsymmetrical phosphinic acids are obtained analogously from alkyl- or aryl-dichlorophosphines.[347]

Later it was found that the chlorophosphonium tetrafluoroborates formed by the reaction of the diazonium salts can be reduced to chlorophosphines by magnesium or aluminum. In this way phosphorus trichloride yields aryldichlorophosphines,[348,349] and the latter yield diarylchlorophosphines;[349] yields are of the same order as on hydrolytic working up.

Chloro-(*p*-cyanophenyl)phenylphosphine:[349] Dichloro(phenyl)phosphine (60 g) is added to a slurry of *p*-cyanobenzenediazonium tetrafluoroborate (72 g) and copper(I) bromide (2.4 g) in dry isopropyl acetate (300 ml). After about 20 min a violent reaction sets in which is moderated by external cooling so that the temperature remains between 20° and 40°. When gas evolution ceases, aluminum turnings (8 g) are added and the mixture is stirred for 2 h at 40–50°. Then the liquid is decanted from unused aluminum, and phosphorus oxychloride (51 g) is added to decompose the aluminum chloride complex. Distillation then affords a forerun (5 g), followed by the main fraction (39 g, 47%) between 158°/0.7 mm and 195°/3.1 mm (owing to unavoidable decomposition the pressure does not remain constant during the distillation). Further distillation gives a product boiling at 162°/0.2 mm.

When *ortho*-substituted arenediazonium salts are used, *e.g.*, derivatives of biphenyl or diphenyl ether, the reaction proceeds further to yield benzo-fused phospho heterocycles by cyclization.[350]

b. Replacement of nitrogen by phosphorus by means of phosphines

Buffered diazonium salts can be used to quaternize tertiary phosphines with an additional aryl group.[351]

General directions for the preparation of **tetraarylphosphonium iodides:** An approximately 0.5M-diazonium salt solution is filtered into a three-necked flask fitted with a stirrer, gas-outlet tube, and a dropping funnel. For each mole of excess acid three moles of sodium acetate are added (if the solution was very acid, the acidity may be first moderated by sodium hydroxide). Then the triarylphosphine (in amount equivalent to the diazonium salt) in solution in ethyl acetate is dropped in with stirring, the rate being adjusted to the evolution of nitrogen; it is helpful to measure the amount of nitrogen evolved. When gas evolution ceases (usually 80–100% of the theoretical amount is collected), the mixture is acidified and the aqueous layer is separated and extracted several times with ether. The ethyl acetate layer (and any oil that separates) is washed exhaustively with water, and the aqueous washings are united with the preceding aqueous phase. Addition of sodium iodide to the aqueous solutions precipitates the phosphonium iodide which is sparingly soluble in the cold and is recrystallized, with charcoal, from hot water or aqueous ethanol. Yields are 40–80%.

Quaternary salts of Mannich bases are useful for the preparation of quaternary phosphonium salts containing heterocyclic substituents, which are inaccessible or difficultly accessible by other routes:[352,353]

$$[RCH_2N(CH_3)_3]X + R'_3P \longrightarrow [RCH_2PR'_3]X + (CH_3)_3N$$

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[346] L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, **75**, 405 (1953).

[347] L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, **74**, 2885 (1952); *J. Org. Chem.*, **23**, 769 (1958); P. Malasterz, *Rocz. Chem.*, **37**, 187 (1963); *Chem. Zentralbl.*, **1965**, 25/26-0982.

[348] L. D. Quin and J. S. Humphrey, *J. Amer. Chem. Soc.*, **82**, 3795 (1960); **83**, 4124 (1961).

[349] L. D. Quin and R. E. Montgomery, *J. Org. Chem.*, **27**, 4120 (1962); **28**, 3315 (1963).

[350] G. O. Doak, L. D. Freedman, and J. B. Levy, *J. Org. Chem.*, **29**, 2382 (1964); **30**, 660 (1965).

[351] L. Horner and H. Hoffmann, *Chem. Ber.*, **91**, 45 (1958).

[352] H. Hellmann and O. Schumacher, *Ann. Chem.*, **640**, 79 (1961).

[353] P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, **1963**, 2990.

(Antipyrinylmethyl)triphenylphosphonium iodide:[352] (Dimethylaminomethyl)antipyrine methiodide (3.87 g, 0.01 mole) and triphenylphosphine (3.93 g, 0.015 mole) in dimethylformamide (25 ml) are boiled under reflux for 3 h while nitrogen is passed through the solution, the trimethylamine evolved (95%) being absorbed in 0.1N-hydrochloric acid. The reaction mixture is then freed from solvent, and the residue is powdered and boiled with benzene which removes unchanged phosphine. There remains a crude product (5.6 g, 96%) which after recrystallization from water has m.p. 193–194° (3.9 g, 67%).

c. Replacement of nitrogen by phosphorus by means of phosphites

Like tertiary phosphines, trialkyl phosphites can be alkylated by quaternary salts or hydrohalides of Mannich bases, this reaction widening the applicability of the Michaelis–Arbuzov reaction (cf. page 725); analogous alkylation of sodium dialkyl phosphites (cf. page 728) gives poorer yields of phosphonic esters.[354,355]

Diethyl (3-oxobutyl)phosphonate:[354] The methiodide obtained from 4-(diethylamino)-2-butanone (7.15 g, 0.05 mole) and methyl iodide (7.15 g) is heated with triethyl phosphite (0.25 mole, 41.5 g) for 1 h at 130°. After cooling, the triethylmethylammonium iodide formed (10.6 g, 87%) is filtered off and washed with benzene. On evaporation the filtrate and wash-benzene leave a pale yellow oil which is distilled in a vacuum (yield 8.4 g, 81%; b.p. 89–97°/0.08 mm) and on redistillation gives the phosphonic ester (7.5 g, 72%), b.p. 96–98°/0.14 mm, n_D^{25} 1.4352.

The preparation of α-amino phosphonic esters from aminals and dialkyl phosphites was mentioned above (page 732); tetraalkyl pyrophosphites and aminals also yield α-amino phosphonic esters as well as amino phosphites.[356]

2. Replacement of phosphorus by phosphorus

The most convenient method of preparing (chloro)diphenylphosphine is by disproportionation of the readily accessible dichloro(phenyl)phosphine:

$$2C_6H_5PCl_2 \rightleftarrows (C_6H_5)_2PCl + PCl_3$$

Yields of 70–80% are achieved by adding catalytic amounts of aluminum chloride and continuously distilling off the phosphorus trichloride.[357-359]

(Chloro)diphenylphosphine:[357] Dichloro(phenyl)phosphine (390.5 g) and anhydrous aluminum chloride (10 g) are heated under reflux in a flask carrying a Vigreux column under a distillation head. The phosphorus trichloride (136 g) distils in 12 h. The residue is then distilled at 130–156°/2–3 mm and the distillate is fractionated in a vacuum, giving dichloro(phenyl)phosphine (168 g, 70%), b.p. 110–112°/0.35 mm, n_D^{20} 1.6356.

Other diarylchlorophosphines can be obtained in the same way. Since aryldichlorophosphines are obtained from the aromatic hydrocarbons, phosphorus trichloride, and aluminum chloride (cf. page 710), the two steps can be combined into a single experiment.

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[354] T. C. Myers, R. G. Harvey, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 3101 (1955).

[355] A. F. Torralba and T. C. Myers, *J. Org. Chem.*, **22**, 972 (1957).

[356] H. Böhme and K.-H. Meyer-Dulheuer, *Ann. Chem.*, **688**, 78 (1965).

[357] M. P. Brown and H. B. Silver, *Chem. & Ind* (*London*), **1961**, 24.

[358] A. E. Senear, W. Valient, and J. Wirth, *J. Org. Chem.*, **25**, 2001 (1960).

[359] L. Horner, P. Beck, and V. G. Toscano, *Chem. Ber.*, **94**, 2122 (1961).

3. Replacement of sulfur by phosphorus

Aromatic phosphines that are difficult to obtain by other methods can be prepared by heating alkali phosphides with arenesulfonic acid salts, best in ethylene glycol ethers:

$$R_2PNa + ArSO_3Na \longrightarrow R_2PAr + Na_2SO_3$$

1-Naphthyldiphenylphosphine:[360] Potassium (7.8 g) is dispersed in dry 1,2-diethoxyethane (250 ml) by means of a vibrator and treated dropwise under nitrogen with (chloro)diphenylphosphine (21.5 g). After 1 hours' warming at 65° the resulting deep red solution is treated with completely dried sodium 1-naphthalenesulfonate (23 g) and heated at 180° for 3 h, whereupon the color fades. The mixture is allowed to cool and hydrolysed carefully with water (100 ml). The ethereal layer is dried and evaporated and the residue is heated on a water-bath with methanol. This leaves the tertiary phosphine undissolved (23.8 g, 75%), m.p. 124°.

V. Replacement of metals by phosphorus

1. Replacement of metals by phosphorus by means of elemental phosphorus

White phosphorus reacts with Grignard reagents and organolithium compounds, generating phosphides which give phosphines on hydrolysis; phenyllithium yields up to 40% of phenylphosphine in this way.[361] Alkylation by alkyl halides before hydrolysis leads to unsymmetrical tertiary phosphines.[215]

2. Replacement of metals by phosphorus by means of phosphines and phosphonium salts

Triphenylphosphine can be quaternized by a phenylmagnesium bromide solution to tetraphenylphosphonium salts in good yield if oxygen is led into the mixture.[362] Since triphenylphosphine itself can be obtained by a Grignard reaction, the tetraphenylphosphonium salts can be prepared directly by treating phosphorus trichloride with an excess of the phenyl Grignard reagent in a stream of oxygen (yield 91%).[363] The fourth P–C bond is presumably formed by way of a phosphine oxide–Grignard adduct, since tetraphenylphosphonium salts are obtained also from triphenylphosphine oxide and phenyllithium after treatment with acid.[364]

Wittig and his collaborators[364-366] prepared pentaarylphosphoranes from tetraphenylphosphonium iodide and aryllithium compounds.

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[360] H. Zorn, H. Schindlbauer, and H. Hagen, *Chem. Ber.*, **98**, 2431 (1965).

[361] U.S. Pat. 3,060,241; *Chem. Abstr.*, **58**, 6862 (1963); M. M. Rauhut and A. M. Semsel, *J. Org. Chem.*, **28**, 471 (1963).

[362] J. Dodonow and H. Medox, *Ber. Deut. Chem. Ges.*, **61**, 907 (1928).

[363] H. H. Willard and co-workers, *J. Amer. Chem. Soc.*, **70**, 737 (1948).

[364] G. Wittig and M. Rieber, *Ann. Chem.*, **562**, 187 (1949).

[365] G. Wittig and G. Geisler, *Ann. Chem.*, **580**, 44 (1953).

[366] G. Wittig and E. Kochendörfer, *Chem. Ber.*, **97**, 741 (1964).

3. Replacement of metals by phosphorus by means of phosphorus halides

a. Replacement of metals by phosphorus by means of halides of trivalent phosphorus

Treating phosphorus trichloride with alkyl-[367,368] or aryl-magnesium halides[369] constitutes a useful method of preparing tertiary phosphines.

All the lower trialkylphosphines are so sensitive to oxidation that all operations with them must be conducted with scrupulous exclusion of oxygen. Reliable directions for synthesis of the low-boiling, readily flammable trimethylphosphine has been provided by Zingaro and McGlothlin.[370] To obtain optimal yields of triethylphosphine it is advisable to distil it directly out of the reaction mixture under a protecting gas instead of, as usual, working up the Grignard mixture by hydrolysis.[370] The phosphine may also be isolated by precipitation as the carbon disulfide adduct, which is illustrated in the following example.

Tricyclohexylphosphine:[371] Phosphorus trichloride (54 g) in ether (100 ml) is dropped, with vigorous stirring and cooling in ice–salt, into a Grignard solution from magnesium turnings (32 g) and cyclohexyl bromide (220 g) in ether (500 ml) kept in a stream of nitrogen. After being stirred for 1 h at room temperature and a further 2 h under reflux, the batch is hydrolysed by a solution of ammonium chloride (50 g) in water (280 ml). The ethereal layer is dried over sodium sulfate and freed from solvent under nitrogen. Carbon disulfide (15 ml) is added to the residue, and the adduct that separates is collected and washed 2–3 times with light petroleum (b.p. 50–60°; 100-ml portions) (yield 66 g, 47.2%). Recrystallization of the adduct from ethanol, methanol, or dioxan (with protection from the atmosphere) gives a product of m.p. 118° (loss on recrystallization 5–10%).

For decomposition the carbon disulfide adduct is suspended in ethanol (400 ml per 66 g of adduct) and heated to the boiling point. The adduct passes into solution. The ethanol is then distilled off completely, carrying with it most of the carbon disulfide (the red initial color of the solution disappears). If the residual material is not quite colorless the distillation is repeated with fresh ethanol. The finally colorless residue crystallizes from acetone as white needles, m.p. 76–78°. Decomposition of the adduct is almost quantitative.

When dry, tricyclohexylphosphine is relatively stable in air.

Trialkylphosphine sulfides are obtained by adding sulfur to the hydrolysed Grignard mixture, yields being higher than those of the phosphine.

Tributylphosphine sulfide:[207] A Grignard solution is prepared in a 2.5-l sulfuration flask from magnesium (40 g), butyl bromide (168 ml) and ether (600 ml). This is kept under nitrogen, with cooling by ice-water and vigorous stirring, while freshly distilled phosphorus trichloride (36 ml) in ether (200 ml) is dropped in during 90 min. Refluxing for 45 min completes the reaction. The whole is set aside overnight, then hydrolysed under nitrogen, with stirring and ice-cooling, by dropwise addition of ammonium chloride (200 g) dissolved in water (1 l) during 90 min. Next sulfur (16 g) is added in portions and stirring continued for 30 min. The ethereal layer is dried over sodium sulfate, the ether is removed, and the residue is distilled at oil-pump vacuum, giving the sulfide (67.5 g, 70%, calculated on PCl_3), b.p. 122 to 125°/0.1 mm, n_D^{25} 1.5001.

Alkyl-[372] and aryl-lithiums[373] react like Grignard reagents, giving tertiary phosphines. Trialkylaluminums, however, even if in excess, give only poor yields of tertiary phosphines together with chlorophosphines as the main

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[367] W. J. Jones and co-workers, *J. Chem. Soc.*, **1929**, 33, 1262; **1947**, 1446.

[368] M. C. Browning and co-workers, *J. Chem. Soc.*, **1962**, 693.

[369] O. Neunhoeffer and L. Lamza, *Chem. Ber.*, **94**, 2514 (1961); L. Lamza, *J. Prakt. Chem.*, [4], **25**, 294 (1964).

[370] R. A. Zingaro and R. E. McGlothlin, *J. Chem. Eng. Data.* **8**, 226 (1963).

[371] K. Issleib and A. Brack, *Z. Anorg. Allg. Chem.*, **277**, 258 (1954).

[372] C. Screttas and A. F. Isbell, *J. Org. Chem.*, **27**, 2573 (1962).

product.[374,375] Tetraalkylleads behave similarly, for, when heated for several hours with phosphorus trichloride at >100°, they afford alkyldichlorophosphines in high yield.[376] Also, ethylphosphonic dichloride was obtained when oxygen was passed into tetraethyllead and phosphorus trichloride at 1–5°.[377]

Unsymmetrical tertiary phosphines can be synthesized from dichloro-[358, 368,378] or chloro-phosphines[358,379] and Grignard reagents.

(*p*-Methoxyphenyl)diphenylphosphine:[358] A Grignard solution from *p*-bromoanisole (112 g, 0.6 mole) in tetrahydrofuran (250 ml) is treated dropwise, with stirring and cooling, with a solution of (chloro)diphenylphosphine (90 g, 0.4 mole), in tetrahydrofuran (50 ml). After boiling for 1 h the product is hydrolysed by being poured on ice and dilute hydrochloric acid. The aqueous phase is extracted with benzene. The organic phases are united, washed, dried, and freed from solvent. Distillation of the residue gives a yellow oil (97 g), b.p. 195–225°/5 mm, which crystallizes when rubbed with methanol. Recrystallization from methanol (1 l) affords the tertiary phosphine (82 g, 70%), m.p. 78–79°.

Unsymmetrical alkylarylchlorophosphines can be prepared in good yield from aryldichlorophosphines and tetraethyllead.[380] 1,4-Dilithiotetraphenylbutadiene, which is relatively easily accessible from diphenylacetylene, reacts with dichloro(phenyl)phosphine to give pentaphenylphosphole (cf. page 698) in 84% yield.[381]

When a Grignard reagent is added to a phosphorous ester dichloride[382–384] or diester chloride[384–385] (not the phosphorus derivative to the reagent), the ester groups are retained and the products are phosphinous esters and phosphonous diesters, respectively. Unlike the bromides, organomagnesium chlorides give good yields only in the presence of pyridine, which must be mixed with the phosphite before the Grignard reagent is added; however, methyl phosphinites cannot be obtained, even by this special technique, from methylmagnesium chloride, bromide, or iodide.[382,383]

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[373] B. M. Mikhailov and N. F. Kucherova, *Zh. Obshch. Khim.*, **22**, 792 (1952); *Chem. Abstr.*, **47**, 5388 (1953); W. Tefteller, R. A. Zingaro, and A. F. Isbell, *J. Chem. Eng. Data.* **10**, 301 (1965).

[374] O. Yu. Okhlobystin and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1958**, 1006; *Chem. Abstr.*, **53**, 1122 (1959).

[375] L. Maier, *Helv. Chim. Acta*, **47**, 2129 (1964).

[376] M. S. Kharasch, E. V. Jensen, and S. Weinhouse, *J. Org. Chem.*, **14**, 429 (1949); L. Maier, *J. Inorg. Nucl. Chem.*, **24**, 1073 (1962).

[377] Yu. M. Zinov'ev and L. Z. Soborovski, *Zh. Obshch. Khim.*, **34**, 929 (1964); *Chem. Zentralbl.*, **1966**, 17-0626.

[378] H. D. Kaesz and F. G. A. Stone, *J. Org. Chem.*, **24**, 635 (1959); O. Neunhoeffer and L. Lamza, *Chem. Ber.*, **94**, 2519 (1960).

[379] C. Stuebe, W. M. Le Suer, and G. R. Norman, *J. Amer. Chem. Soc.*, **77**, 3526 (1955); L. Lamza, *J. Prakt. Chem.*, [4], **25**, 294 (1964); S. O. Grim, W. McFarlane, and E. F. Divadoff, *J. Org. Chem.*, **32**, 781 (1967).

[380] G. Kamai and G. M. Rusetskaya, *Zh. Obshch. Khim.*, **32**, 2848, 2854 (1962); *Chem. Abstr.*, **58**, 7965 (1963).

[381] E. H. Braye, W. Hübel, and I. Caplier, *J. Amer. Chem. Soc.*, **83**, 4406 (1961).

[382] M. I. Kabachnik and E. N. Tsvetkov, *Dokl. Akad. Nauk SSSR*, **135**, 323 (1960); *Chem. Abstr.*, **55**, 14288 (1960); K. A. Petrov, E. E. Nifant'ev, and L. V. Khorkhoyanu, *Zh. Obshch. Khim.*, **31**, 2889 (1961); *Chem. Abstr.*, **57**, 860 (1962).

[383] B. N. Strunin, O. Yu. Okhlobystin, and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1963**, 1373; *Chem. Abstr.*, **59**, 14018 (1963).

[384] M. Sander, *Chem. Ber.*, **93**, 1220 (1960).

[385] M. I. Kabachnik and co-workers, *Zh. Obshch. Khim.*, **29**, 1450 (1959); *Chem. Abstr.*, **54**, 9729 (1960); *Zh. Obshch. Khim.*, **32**, 3351 (1962); *Chem. Abstr.*, **58**, 9126 (1963); *Dokl. Akad. Nauk SSSR*, **117**, 817 (1957); *Chem. Zentralbl.*, **1959**, 1094.

Ethyl dibutylphosphinite:[384] A Grignard solution from magnesium (23.4 g) and butyl chloride (92.6 g) in ether (300 ml) is added within 2 h to a stirred and ice-cooled solution of ethyl phosphorodichloridite (73.3 g) in ether (200 ml). The mixture is heated under reflux for 1 h, then filtered, and freed from ether. Vacuum-distillation of the residue gives the product (50 g, 63%), b.p. 88–92°/12 mm, n_D^{20} 1.4465.

Organolithium compounds give higher yields of phosphonous diesters from dialkyl chlorophosphites than when Grignard reagents are used.[386]

Dialkylamino groups, like alkoxy groups, attached to trivalent phosphorus are readily removed by organometallic compounds. Therefore, for the preparation of dialkyl(dialkylamino)phosphines from (dialkylamino)dichlorophosphines the Grignard[387,388] or organolithium reagent[389] must again be added to the phosphorus compound. It has been shown[375] that in the reaction with organoaluminum compounds the yields are better if the amino group is bulky.

Diethyl(diethylamino)phosphine:[388] A Grignard solution, prepared from magnesium (12.6 g), ethyl bromide (57 g), and ether (250 ml) and filtered through glass wool, is dropped into one of dichloro(diethylamino)phosphine (45 g) in ether (250 ml) that is vigorously stirred at about −20° in a three-necked flask (1 l). After a further hour's stirring at room temperature, the mixture is heated for 1 h on the water-bath, and then the precipitate is filtered off under nitrogen and washed with ether. Removal of the ether and distillation of the residue in a vacuum gives the product (27 g, 64.8%), b.p. 181°/760 mm.

This product is sensitive to moisture and lachrymatory.

b. Replacement of metals by phosphorus by means of phosphoryl halides

Reaction of phosphorus oxychloride with Grignard reagents gives tertiary phosphine oxides and/or phosphinic acids; phosphonic acids appear not to be formed in this way. Trimethylphosphine oxide has been obtained in about 50% yield in this way,[390] and for the preparation of phosphinic acids (where replacement of the third chlorine atom is to be avoided) special techniques have been proposed such as addition of the Grignard reagent to the phosphorus oxychloride[391] or blocking of one chlorine atom by pyridine[392] or a dialkylamine;[393] nevertheless, newer findings are clear that in normal cases the phosphinic acid is the main product and that only small amounts of phosphine oxide are formed.[394]

Dicyclohexylphosphinic acid:[371] Phosphoryl chloride (85 g) in ether (100 ml) is dropped slowly and with vigorous stirring and good cooling into a Grignard solution prepared from magnesium (32 g) and cyclohexyl chloride (150 g) in ether (500 ml). The mixture is stirred for 1 h at room temperature, then boiled under reflux for a further 1 h. It is cooled and hydrolysed with water (300–400 ml) containing N-hydrochloric acid (50 ml). The ethereal layer is separated, dried, and evaporated and the residue is heated at 180–190°/12 mm. There remains a viscous oil, which is dissolved in hot acetone (50 ml). On cooling, most of the product

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[386] M. I. Kabachnik and E. N. Zvetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1960**, 133; *Chem. Abstr.*, **54**, 20822 (1960).

[387] A. B. Burg and P. J. Slota, *J. Amer. Chem. Soc.*, **80**, 1107 (1958); E. M. Evleth and co-workers, *J. Org. Chem.*, **27**, 2192 (1962).

[388] K. Issleib and W. Seidel, *Chem. Ber.*, **92**, 2681 (1959).

[389] H. Nöth and H.-J. Vetter, *Chem. Ber.*, **96**, 1109 (1963).

[390] A. B. Burg and W. E. McKee, *J. Amer. Chem. Soc.*, **73**, 4590 (1951); J. Goubeau and W. Berger, *Z. Anorg. Allg. Chem.*, **304**, 147 (1960).

[391] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **64**, 2982 (1942).

[392] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **72**, 5508 (1950).

[393] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **71**, 369 (1949); **77**, 6658 (1955).

[394] K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **30**, 2995 (1960); *Chem. Abstr.*, **55**, 18561 (1961).

separates but a further fraction can be obtained by concentrating the mother-liquor. After two recrystallizations from acetone or light petroleum the substance (95 g, 74.5%) has m.p. 143°.

Partial reaction of phosphoryl chloride with amines can be used for synthesis of phosphonic acids;[392,393] if applied to phosphonic dichlorides it affords unsymmetrical phosphinic acids.[396]

Tertiary phosphine oxides are obtained from phosphinic chlorides and Grignard reagents,[397] and ditertiary phosphine oxides similarly from di-Grignard reagents.[398]

Ethyldiphenylphosphine oxide:[397] Diphenylphosphinic acid (0.22 g) is converted into the acid chloride by 1–2 hours' boiling under reflux with thionyl chloride (0.5 ml) in toluene. About half the solvent is then distilled off and the residual solution is diluted with benzene and dropped at room temperature into a Grignard solution prepared from magnesium (0.25 g) and ethyl bromide (2.5 ml). The reaction is complete after half an hour's boiling under reflux. The product is hydrolysed by ice and hydrochloric acid, the aqueous layer is washed with ether, and ether phases are united, dried, and evaporated. The residue is subjected to steam-distillation and then extracted several times with ether. The residue left on evaporation of these extracts crystallizes at once or on short storage and is decolorized in acetone by charcoal. Recrystallization from ether–light petroleum or aqueous acetone affords the oxide, m.p. 123–124° (67%).

The Grignard reaction with phosphoric diester chlorides, like that with phosphoryl chloride, does not give homogenous products. With sterically hindered Grignard reagents such as (*o*-methoxyphenyl)magnesium bromide the ester group is retained and good yields of phosphonic diesters are obtained,[399,400] but with sterically unhindered Grignard reagents tertiary phosphine oxides are formed by the normal mode of addition[400] although both products are isolated after reversed addition.[401]

c. Replacement of metals by phosphorus by means of thiophosphoryl halides

Unlike the phosphorus chlorides mentioned above, thiophosphoryl chloride reacts with alkylmagnesium halides to form tetraalkyldiphosphane disulfides which contain a P–P bond:[402–411]

$$2PSCl_3 + 6RMgHal \longrightarrow R_2P(S)\text{—}P(S)R_2 + R\text{—}R + 6MgHalX$$

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[395] D. C. Morrison, *J. Amer. Chem. Soc.*, **73**, 5896 (1951).

[396] P. C. Crofts and I. S. Fox, *J. Chem. Soc.*, **1958**, 2995.

[397] D. C. Morrison, *J. Amer. Chem. Soc.*, **72**, 4820 (1950).

[398] G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, **1959**, 3950.

[399] N. D. Dawson and A. Burger, *J. Org. Chem.*, **18**, 207 (1953).

[400] A. Burger and N. D. Dawson, *J. Org. Chem.*, **16**, 1250 (1951).

[401] R. S. Edmundson and J. O. L. Wrigley, *Tetrahedron*, **23**, 283 (1967).

[402] M. I. Kabachnik and E. S. Shepeleva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1949**, 56 *Chem. Abstr.*, **43**, 5739 (1949); H. Reinhardt, D. Bianchi, and D. Mölle, *Chem. Ber.*, **90**, 1656 (1957).

[403] K. A. Pollart and H. J. Harwood, *J. Org. Chem.*, **27**, 4444 (1962).

[404] H. Niebergall and B. Lengenfeld, *Chem. Ber.*, **95**, 64 (1962).

[405] P. J. Christen, L. M. van der Linde, and F. N. Hooge, *Rec. Trav. Chim.*, **78**, 161 (1959).

[406] K. Issleib and A. Tzschach, *Chem. Ber.*, **92**, 704 (1959).

[407] W. Kuchen and co-workers, *Ann. Chem.*, **652**, 28 (1962).

[408] P. J. Christen and L. M. van der Linde, *Rec. Trav. Chem.*, **78**, 543 (1959).

[409] G. M. Kosolapoff and R. M. Watson, *J. Amer. Chem. Soc.*, **73** 5466 (1951).

[410] R. Schmutzler, *Inorg. Chem.*, **3**, 421 (1964).

[411] G. W. Parshall, *Org. Syn.*, **45**, 102 (1965).

Since, particularly for the lower homologs, yields are good and the P–P bond can be cleaved readily, this reaction provides a preparatively important route to the phosphinic acid series.

The most satisfactory conditions are a $PSCl_3$: Grignard ratio of 1 : 3.2 and temperatures slightly below room temperature; higher temperatures favor the production of trialkylphosphine sulfides which may in any case be formed as by-products and which become the main products when thiophosphoryl bromide is used.[404] Alkylmagnesium bromides give appreciably higher yields than the chlorides or iodides.[404] Yields decrease as the chain length increases,[404–407] and long-chain halides such as hexadecyl bromide give only the trialkylphosphine sulfide.[407] When yields of diphosphane disulfide are low or non-existent, as from isoalkylmagnesium halides, phosphinic acids can be isolated if oxidation is included in the working-up procedure of the hydrolysed Grignard product.[408,409] Cyclic diphosphane disulfides such as 1,1′-biphosphole disulfide and 1,1′-biphosphorinane disulfide can be obtained, although in poor yield, by using di-Grignard reagents at low temperatures.[410]

Tetraethyldiphosphane disulfide, $(C_2H_5)_2P(S)—P(S)C_2H_5$:[407] A Grignard solution is prepared from ethyl bromide (545 g), magnesium (120 g), and ether (2 l) in a flask (5 l) fitted with a very efficient condenser, a stirrer, and a dropping funnel. Thiophosphoryl chloride (256 g) in ether (300 ml) is added, with stirring and water-cooling, while the temperature is kept at not more than 25°. The reaction, initially lively, is complete after 6 h. The product is then hydrolysed by 2N-sulfuric acid (1 l), added slowly with ice-cooling, and the ethereal layer is separated and evaporated. The off-white residue crystallizes and, on recrystallization several times from isobutyl alcohol, gives the disulfide (131 g, 71.5%) as colorless needles, m.p. 77°.

Organic Syntheses[411] includes directions for the preparation of **tetramethyldiphosphane disulfide.**

Unlike that of their aliphatic analogs, reaction of aryl Grignard reagents with thiophosphoryl chloride yields tertiary phosphine sulfides;[412] and trialkylphosphine sulfides are formed from thiophosphoryl chloride and organolithium compounds;[372] further, there is no production of a P–P bond from alkyl derivatives of lead[413] or aluminum[414] and thiophosphoryl chloride, which afford thiophosphonic dichlorides (from R_4Pb) or thiophosphinyl chlorides and phosphine sulfides (from R_3Al).

Thiophosphinic dichlorides react like thiophosphoryl chloride with alkyl Grignard reagents, giving diphosphane disulfides[403,415] and thus affording a good route to unsymmetrical phosphinic acid derivatives. An exception seems to be provided by alkynyl Grignard reagents, which afford tertiary phosphine sulfides;[416] and cyclic tertiary phosphine sulfides are obtained in moderate yield from methyl(thiophosphonic) dibromide and di-Grignard reagents.[417]

Thiophosphinic halides behave differently: purely aliphatic members of this series give only tertiary phosphine sulfides with either alkyl or aryl Grignard

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[412] W. Strecker and C. Grossmann, *Ber. Deut. Chem. Ges.*, **49**, 63 (1916).

[413] L. Maier, *J. Inorg. Nucl. Chem.*, **24**, 1073 (1962).

[414] L. Maier, *Helv. Chim. Acta*, **47**, 27 (1964).

[415] L. Maier, *Chem. Ber.*, **94**, 3043 (1961); P. C. Crofts and K. Gosling, *J. Chem. Soc.*, **1964**, 2486.

[416] G. M. Bogolyubov and A. A. Petrov, *Zh. Obshch. Khim.*, **35**, 988 (1965); *Chem. Abstr.*, **63**, 9981 (1965).

[417] L. Maier, *Helv. Chim. Acta*, **48**, 133 (1965).

reagents,[416,418,419] but alkylaryl- and diaryl-thiophosphinic chlorides give also the diphosphane disulfides containing a P–P bond.[419] Since thiophosphinic halides can be obtained conveniently and in high yield by fission of diphosphane disulfides with chlorine, bromine, or sulfuryl chloride, an indirect route is provided from thiophosphoryl chloride to tertiary phosphine sulfides. Ditertiary phosphine sulfides can also be obtained, by using a di-Grignard reagent.[417]

Dimethyl(phenyl)phosphine sulfide:[418] Dimethylthiophosphinic bromide (16.4 g, 95 mmoles) in ether (75 ml) is added during 15 min, with stirring at 0–10°, to a solution of phenylmagnesium bromide (0.1 mole) in ether (110 ml). The mixture is set aside overnight and then poured into a mixture of ice and 10% sulfuric acid. The aqueous layer is washed with ether, and the ethereal washings and the original ether layer are washed with water, dried over sodium sulfate, and evaporated. The residual oil crystallizes when cooled and rubbed, and on recrystallization from hexane–benzene gives the sulfide as colorless needles (14.2 g, 88%), m.p. 47–47.7°.

Trimethylphosphine sulfide is obtained analogously in 90% yield.

d. Replacement of metals by phosphorus by means of phosphorus(v) chloride

Phosphorus(v) chloride exists in the crystalline state as $PCl_4^+PCl_6^-$; all its halogen atoms can be replaced by carbon in reaction with a suitable bidentate aryllithium compound.[420,421]

5,5′-Spirobis(dibenzophosphol)ium 5,5′,5″-spirotris(dibenzophosphol)ate(IV):[420] 2,2′-Diiodobiphenyl (12.2 g, 30 mmoles), dissolved in ether (200 ml), is metalated to 2,2′-dilithiobiphenyl by addition of butyllithium (60 mmoles) in ether, with ice-cooling. After 4 h the mixture is cooled to −70° and treated with finely powdered phosphorus(v) chloride (12 mmoles). The whole is stirred overnight, then allowed to come to room temperature. Hydrolysis affords a yellow precipitate which is purified by extraction with boiling alcohol, then having m.p. 254–256° (dec.) (2.37 g, 48%). This product can be recrystallized from ethanol–dimethylformamide.

4. Replacement of metals by phosphorus by means of esters

a. Replacement of metals by phosphorus by means of phosphorous esters

The alkoxy groups of dialkyl phosphites can be replaced by alkyl groups through the medium of Grignard compounds, secondary phosphine oxides containing alkyl groups from C_5 to C_{18} being thus available in moderate to good yields.[422]

Dibenzylphosphine oxide:[31] A solution of dibutyl phosphite (235.5 g) is dropped in 2 h into a Grignard solution prepared from benzyl chloride (500 g) and magnesium (96 g) in ether (700 ml). Towards the end of the addition the gently boiling solution becomes gelatinous. The mixture is boiled under reflux for a further 0.5 h, then hydrolysed by dilute (1 : 3) sulfuric acid (1.5 l). Two organic phases are formed but these become homogeneous on addition of benzene (750 ml). When the organic layer is concentrated (to 1 l) the product separates as

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[418] U.S. Pat 3,053,900; *Chem. Abstr.*, **58**, 1493 (1963); H. J. Harwood and K. A. Pollart, *J. Org. Chem.*, **28**, 3430 (1963).

[419] N. K. Patel and H. J. Harwood, *J. Org. Chem.*, **32**, 2999 (1967).

[420] D. Hellwinkel, *Chem. Ber.*, **98**, 576 (1965).

[421] D. Hellwinkel, *Chem. Ber.*, **99**, 3628 (1966).

[422] R. H. Williams and L. A. Hamilton, *J. Amer. Chem. Soc.*, **74**, 5418 (1952); **77**, 3411 (1955).

white plates (102 g), m.p. 107.5–109.5°; a further amount (101 g), m.p. 108–110°, crystallizes when the mother-liquor is diluted with heptane (2 l), the total yield thus becoming 68%. Recrystallization from 3 : 1 hexane–benzene raises the m.p. to 109.3–110.1°.

Oxidation of the hydrolysed Grignard mixture with hydrogen peroxide or bromine provides phosphinic acids;[383,398,423] however, the methyl and ethyl derivatives are difficult to isolate because of their great solubility in water, and these are better obtained by way of the diphosphane disulfides.[409] Thiophosphinic acids are obtained analogously in good yield by addition of sulfur.[424]

A simple method of preparing tertiary phosphine oxides is to alkylate, by alkyl halides, the metalated secondary phosphine oxides which are intermediates:[425,426]

$$(RO)_2P(O)H \xrightarrow{R'MgHal} R'_2P(O)MgHal \xrightarrow{R''Hal} R'_2R''PO$$

***n*-Butyldi-*sec*-butylphosphine oxide:**[426] Diethyl phosphite (0.25 mole) is added to a solution of *sec*-butylmagnesium bromide (1 mole) in ether (250 ml) at such a rate that the ether boils continuously. The resulting slurry is stirred for some time further and then treated with *n*-butyl bromide (0.3 mole). The mixture is boiled under reflux overnight, then hydrolysed by being poured on ice and hydrochloric acid. The ethereal layer is washed with successively water, 10% sodium carbonate solution, and again water. After removal of the ether, distillation in a vacuum through a Vigreux column gives the oxide (29 g, 50%), b.p. 100°/0.3 mm.

Tri-*n*-butylphosphine oxide is obtained analogously in 70% yield.

Dialkyl thiophosphites are converted into dithiophosphinic acids by Grignard reactions followed by addition of sulfur,[427] and into diphenylphosphine sulfides after reaction with phenyllithium.[325]

The products formed from trialkyl phosphites and Grignard reagents depend greatly on the reaction conditions and apparently also on the nature of the reactants. Quantitative yields of triphenylphosphine are obtained from trimethyl phosphite and phenylmagnesium bromide (molar ratio 1 : 4) under oxygen-free nitrogen[428] (cf. Morgan and Herr[429]); phosphonous diesters are formed on use of butylmagnesium bromide (molar ratio 1 : 1).[384] It is, however, often difficult to obtain homogeneous products in satisfactory yield since all three replacement products and, on occasions, their oxidation products may arise. Phosphonous di-[430] and phosphinous mono-esters[431] are converted into tertiary phosphines by Grignard reagents.

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[423] G. M. Kosolapoff and R. M. Watson, *J. Amer. Chem. Soc.*, **73**, 4101 (1951); K. A. Petrov and co-workers, *Zh. Obshch. Khim.*, **30**, 1964 (1960); *Chem. Abstr.*, **55**, 6362 (1967).

[424] T. A. Mastryukova, A. E. Shipov, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **29**, 1450 (1959); *Chem. Abstr.*, **54**, 1729 (1960).

[425] J. J. Richard and C. V. Banks, *J. Org. Chem.*, **28**, 123 (1963); M. I. Kabatchnik and co-workers, *Zh. Obshch. Khim.*, **35**, 1574 (1965); *Chem. Abstr.*, **63**, 18145 (1965); I. M. Downie and G. M. Morris, *J. Chem. Soc.*, **1965**, 5771.

[426] T. H. Siddall and M. A. Davis, *J. Chem. Eng. Data*, **10**, 303 (1965).

[427] T. A. Mastryukova, A. E. Shipov, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **31**, 507 (1961); *Chem. Abstr.*, **65**, 22101 (1961).

[428] K. D. Berlin and co-workers, *J. Amer. Chem. Soc.*, **86**, 1787 (1964).

[429] P. W. Morgan and B. C. Herr, *J. Amer. Chem. Soc.*, **74**, 4526 (1952).

[430] M. I. Kabachnik and co-workers, *Zh. Obshch. Khim.*, **32**, 3340 (1962); *Chem. Abstr.*, **58**, 9120 (1963).

[431] M. I. Kabachnik and co-workers, *Dokl. Akad. Nauk SSSR*, **135**, 603 (1960); *Chem. Abstr.*, **55**, 12272 (1961).

b. Replacement of metals by phosphorus by means of phosphoric and phosphonic esters

The reaction of phosphoric triesters with Grignard compounds has not so far proved a satisfactory method of forming a P–C bond: it can lead to mixtures of phosphonic and phosphinic esters[432] and also of phosphinic esters and phosphine oxides;[433] moreover, with trialkyl phosphates *C*-alkylation of the Grignard reagent may occur,[433] and this even becomes the main reaction with sterically hindered Grignard reagents, as also with analogous organolithium compounds.[434]

However, phosphonic diesters are suitable starting materials on the way to tertiary phosphine oxides,[399,428,429,435,436] and yields of 80–90% of dialkyl- and diaryl-phenylphosphine oxides have been achieved on treatment of diphenyl phenylphosphonate with an excess of the Grignard reagent.[436]

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[432] H. Gilman and co-workers, *J. Amer. Chem. Soc.*, **48**, 1063 (1926); *Rec. Trav. Chim.*, **48**, 328 (1929).

[433] K. D. Berlin and M. E. Peterson, *J. Org. Chem.*, **32**, 125 (1967).

[434] H. Gilman and B. J. Gaj, *J. Amer. Chem. Soc.*, **82**, 6326 (1960).

[435] R. G. Lauglin, *J. Org. Chem.*, **30**, 1322 (1965).

[436] K. D. Berlin and M. Nagabhushanam, *Chem. & Ind. (London)*, **1964**, 964.

CHAPTER 10

Formation of Metal-Carbon Bonds (Organometallic Compounds)

Compiled by
J. Dahlmann

Introduction

The term "organometallic compounds" is applied to those compounds that contain an organic residue such as an alkyl or aryl group attached directly to a metal atom, *i.e.*, to compounds containing a direct carbon–metal bond. The term "metal" is here used in a very wide sense, including "metalloids" and elements that have only slight metallic character. Organometallic compounds do not include metal derivatives in which the metal is bound to carbon through another atom such as oxygen or nitrogen.

This extremely wide field has been the subject of many books and reviews, *e.g.*, the book by Krause and von Grosse[1] (which includes almost all work published up to 1936) and that by Runge (1944).[2] The main feature of organometallic chemistry, with many valuable literature references, are given in books by Coates (1956),[3] Rochow, Hurd, and Lewis (1957),[4] and Rochow (1964).[5] A review by Coates (1950)[3] treats the organometallic compounds of the first three Groups of the Periodic System.

There are also reviews of many important areas of organometallic chemistry, such as fluorocarbon derivatives of metals,[7] alkynylmetal derivatives of groups 3–5,[8] etc.

Attention must also be drawn to some more recent accounts of the organic derivatives of transition metals,[9] including cyclopentadienyl-,[10] allyl-,[11] and cyclobutadienyl-metal com-

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[1] E. Krause and A. von Grosse, "Die Chemie der metallorganischen Verbindungen," Borntraeger, Berlin 1937.

[2] F. Runge, "Organo-Metallverbindungen," Wissenschaftliche Verlagsgesellschaft m.b.H., Stuttgart, 1944.

[3] G. E. Coates, "Organo-Metallic Compounds," Methuen Co. Ltd., London, and John Wiley & Sons, New York, 1956.

[4] E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry or Organometallic Compounds," John Wiley Sons, New York, 1957.

[5] E. G. Rochow, "Organometallic Chemistry," Reinhold Publ. Corp., New York, 1964.

[6] G. E. Coates, *Quart. Rev. (London)*, **4**, 217 (1950).

[7] P. M. Teichel, *Advan. Organometal. Chem.*, **1**, 143 (1964); R. D. Chambers, and T. Chivers, *Organometal. Chem. Rev.*, **1**, 279 (1966); R. N. Haszeldine, *Angew. Chem.*, **66**, 693 (1954).

[8] W. E. Davidsohn and M. C. Henry, *Chem. Rev.*, **67**, 73 (1967).

[9] M. Dub, "Organometallic Compounds; Methods of Synthesis, Physical Constants, and Chemical Reactions," Vol. 1, "Compounds of Transition Metals," Springer-Verlag, Berlin–Heidelberg–New York, 1966; E. O. Fischer and H. Werner, "Metall-π-Komplexe mit di- und oligoolefinischen Liganden" Verlag Chemie, Weinheim/Bergstraße, 1963.

[10] J. M. Birmingham, *Advan. Organometal. Chem.*, **2**, 365 (1964).

[11] M. L. H. Green, and P. L. I. Nagy, *Advan. Organometal. Chem.*, **2**, 325 (1964); G. Wilke, B. Bogdanovič, P. Hardt, P. Heimbach, W. Keim, M. Kröner, W. Oberkirch, K. Tanaka, E. Steinbrücke, D. Walter, and H. Zimmermann, *Angew. Chem. Internat. Ed., Engl.*, **5**, 151 (1966).

plexes,[12] the more so because this extremely rich specialist area of organometallic chemistry cannot be treated in detail in the text below. Directions for the preparation of numerous such transition-metal derivatives have been collected by King.[13]

Reviews of this and other areas of organometallic chemistry that have been intensively studied in recent years are to be found in, *e.g.*, Zeiss's book,[14] and the series *Advances in Organometallic Chemistry*[15] (issued by Stone and West starting in 1964) and *Organometallic Chemistry Reviews*[16] (issued since 1966 by Seyferth, Andrianov, Eaborn, Fischer, and Normant). An annual review of organometallic compounds is given by Seyferth and King in the *Annual Survey of Organometallic Chemistry*[16] (Volume 1 covers 1964).

In 1964 there was founded the international *Journal of Organometallic Chemistry*,[16] to deal with this field which has developed so very quickly in recent times and extends ever wider.

A collection of many organo-metallic compounds, together with their most important properties and references, will be found in Kaufman's "Handbook of Organometallic Compounds" (1961).[17]

The properties of completely alkylated or arylated metal compounds often differ widely from those of the usual derivatives of metals and resemble those of wholly organic compounds in many respects. For instance, very many of them are volatile, insoluble in water, and miscible with organic solvents and do not conduct an electric current. The derivatives of strongly electropositive elements, however, such as those of alkali metals, are markedly ionic, involatile, solid, almost insoluble in organic solvents, and moreover, good electrolytes.

It is, nevertheless, not possible to classify organometallic compounds strictly into different types such as homopolar and heteropolar, since the physical and chemical properties of these compounds alter continuously within a given Period or Group. In a given main Group the polarity of the metal–carbon bond and thus the salt-like character of the compounds increase slowly from top to bottom, and in a given Period from left to right.

Metals hydrides present a similar picture: hydrides of the alkali metals are salts, those of the alkaline-earth metals are salt-like, and those of silicon are gases or liquids resembling hydrocarbons.

The degree of polarity of the metal–carbon bond has, however, a marked effect, not only on the physical, but also on the chemical behavior of an organometallic compound. Thus the reactivity is found to be greater the more polar is the metal–carbon bond. This depends mainly on the difference in electronegativity between the central atom and carbon: the smaller the Pauling electronegativity of a metal the greater is the reactivity of its carbon derivatives.

In agreement with this principle, Gilman,[18] studying the addition of organometallic compounds to C–O and C–N multiple bonds and to C=C bonds of unsymmetrical olefins, found the reactivity of carbon compounds of the

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[12] P. M. Maithis, *Advan. Organometal. Chem.*, **4**, 95 (1966).

[13] R. B. King, "Organometallic Syntheses," Vol. 1, Academic Press, New York and London, 1965.

[14] H. Zeiss, "Organometallic Chemistry," Reinhold Publ. Corp., New York, 1960.

[15] *Adv. Organometal. Chem.*, Academic Press, New York and London.

[16] *Organometal. Chem. Rev.*, "Annual Survey of Organometallic Chemistry," and *J. Organometal. Chem.*, Elsevier Publ. Co., Amsterdam.

[17] H. C. Kaufman, "Handbook of Organometallic Compounds," D. Van Nostrand Co., Inc., Princeton, New Jersey, 1961.

[18] H. Gilman, "Organic Chemistry," John Wiley & Sons, New York, 2nd ed., 1943, Vol. 1, p. 520.

main-group elements in a given Period to decrease with increasing atomic number: RLi > RBe > RB and RNa > RMg > RAl > RSi; within one main group it increases in the opposite direction, *i.e.*, with increasing atomic number of the central atom: RLi < RNa < RK < RRb < RCs, and RBe < RMg < RCa, etc.

The order or reactivity is reversed for sub-group elements: RCu > RAg > RAu. Moreover the most inert element of that or the following main group is always more reactive than the most reactive element of a given sub-group: RLi > RCu, RBe > RZn, RBe > RCu, RB > RZn. It was also observed that among organic derivatives of a given metal the unsymmetrical compounds are always more reactive than the symmetrical analogs.

These differences in reactivity of the various organometallic compounds also appear on their hydrolysis, which affords a hydrocarbon and a metal hydroxide. For instance, alkyl derivatives of alkali or alkaline-earth metals undergo rapid and violent reaction with water, whereas the quite weakly polar alkylsilicons do not react at all under these conditions.

Other polar reagents such as hydrogen halides react analogously with organometallic compounds and in these cases quite small differences in the polarity of the carbon–metal bond have evident effect: for example, phenyl groups are removed from silicon by aqueous hydrochloric acid, but methyl groups are unaffected thereby.

The polarity and thus the reactivity of the carbon–metal bond are influenced also by the electronegativity of the carbon atom. They are but little affected by the structure of the hydrocarbon group, but the difference between methyl and phenyl groups is clearly recognizable. This effect is much increased if the hydrocarbon group carries strongly electronegative substituents such as chlorine; they cause a marked increase in the electronegativity of the carbon atom and thus of the metal–carbon bond. The opposite result is observed with electropositive substituents on the carbon or electronegative substituents on the metal: these decrease the polarity of the metal–carbon bond and thus also lower the reactivity.

When assessing the reactivity of an organometallic compound it is also necessary to take account of the fact that reactions normally take place in solution. Solvated species differ from non-solvated in reactivity properties. Thus, for instance, the nucleophilic reactivity of the metal–carbon bond is increased in solvating solvents such as ether.[19]

There is no direct connexion between the reactivity and thermal stability of organometallic compounds. It would be quite invalid to generalize that very reactive compounds are particularly unstable thermally and less reactive ones thermally more stable.

It is true that the stability of carbon derivatives from the heavier elements of a main group is in general less than that of the lighter elements: it is well known that tetraethylsilicon is much more stable than tetraethyllead; however, carbon derivatives of elements of the first sub-group are much less stable than the much more reactive ones of the alkali metals.

Similar remarks apply to the sensitivity of organometallic compounds to oxygen. The polarity of the metal–carbon bond certainly plays an important

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[19] L. I. Zakharkin, O. Yu. Okhlobystin, and K. A. Bilevitch, *Tetrahedron*, **21**, 881 (1965).

part: *e. g.*, alkyl derivatives of the alkali metals inflame spontaneously in atmospheric oxygen whereas those of mercury and silicon are not attacked. But other factors such as the presence of an electron deficiency or a free electron pair may be of decisive importance; for instance, trialkyl derivatives of metals of the third and fifth main group, in which the metal–carbon bond is almost wholly covalent, react extremely violently with oxygen; the lower alkyl derivatives inflame at once in air.

Furthermore, alkyl- and aryl-metals of the third and fifth main group react very readily with other electron-donors or -acceptors, respectively: thus alkylmetals of the third group (electron acceptors) react with those of the fifth group (electron donors) to form addition compounds, for example, $(CH_3)_3B \cdot As(CH_3)_3$. A detailed review of this aspect has been published by Stone.[20]

Very many organic derivatives of metals of other groups also show a great tendency to form addition and complex compounds with the most varied types of organic and inorganic compound, including compounds with themselves or other organometallic compounds. For instance, organolithium compounds associate with themselves:[21] in ether, phenyllithium exists as the "dimer" $Li[Li(C_6H_5)_2]$ over a wide range of concentrations; well-crystalline complexes are formed on treatment of phenyllithium with organometallic compounds whose central atom follows lithium in the first short period, i.e. beryllium or boron, the stability increasing in the order $Li[Li(C_6H_5)_2] < Li[Be(C_6H_5)_3] < Li[B(C_6H_5)_4]$.

The properties of complex compounds often differ very greatly from those of the components; phenyllithium and triphenylboron react readily with oxygen, and phenyllithium is decomposed violently by water, but lithium tetraphenylborate is stable to oxygen and dissolves unchanged in water.

Extensive studies of complex formation by, and reactivity of, organometallic compounds have been carried out by Wittig and his collaborators.[22]

Review of methods for preparation of organometallic compounds

Many methods are now known for the preparation of organometallic compounds, some being highly specialized, others generally applicable. This Section describes the most important of them.

1. Direct alkylation or arylation of metals by alkyl or aryl halides in accord with the general equation:

$$2M + RX \longrightarrow RM + MX$$

is one of the most important reactions in the chemistry of organometallic compounds, for it provides directly or indirectly a synthesis of almost all organometallic compounds.

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[20] F. G. Stone, *Chem. Rev.*, **58**, 101 (1958).

[21] T. L. Brown, *Advan. Organometal. Chem.*, 3, 365 (1965).

[22] G. Wittig, *Angew. Chem.*, **62**, 231 (1950); **70**, 65 (1958).

When the metal reacts only slowly or not at all, alloys with an alkali or alkaline-earth metal, especially with sodium, have proved useful:

$$\text{M—Na} + \text{RX} \longrightarrow \text{RM} + \text{NaX}$$

A similar reaction, cleavage of ethers by metals:

$$\text{ROR} + 2\text{M} \longrightarrow \text{RM} + \text{ROM}$$

can be effected only with certain ethers and only with alkali metals.

2. Replacement of a metal in an organometallic compound by another metal:

$$\text{M} + \text{RM}' \rightleftarrows \text{RM} + \text{M}'$$

is suitable for preparation of a very reactive from an unreactive compound. For instance, treatment of metallic lithium or sodium with a dialkyl- or diarylmercury gives the corresponding organic derivative of lithium or sodium.

3. Reaction of metals with hydrocarbons:

(a) with replacement of hydrogen by the metal:

$$\text{RH} + \text{M} \longrightarrow \text{RM} + \text{H}$$

this can be effected only with very reactive metals and with hydrocarbons containing activated hydrogen;

(b) with addition of reactive metals (alkali metals) to C=C bonds;

(c) with fission of C–C bonds by alkali metals.

4. Reaction of metal salts with other (organo)metallic compounds:

$$\text{RM} + \text{M}'\text{X} \rightleftarrows \text{RM}' + \text{MX}$$

is the most important and most widely applicable method of obtaining organometallic compounds. It can be used for the synthesis of almost all types of organometallic compound. The equilibrium lies towards the side of the less reactive organometallic component. Grignard compounds and organolithium compounds are the most widely used starting materials.

5. Reaction of metal halides and organic halides with metallic sodium in a kind of Wurtz synthesis:

$$\text{MX} + \text{RX} + 2\text{Na} \longrightarrow \text{RM} + 2\text{NaX}$$

provides a method of preparing organo-silicon, -tin, -arsenic, and -antimony compounds.

6. Reaction of metal salts with hydrocarbons:

$$\text{MX} + \text{RH} \longrightarrow \text{RM} + \text{HX}$$

may occur, particularly with aromatic compounds. For instance, the most varied types of organic compound can be mercurated by mercury(II) acetate, and copper and silver salts react with acetylenes to gives acetylides.

7. Reaction of metal salts with diazo compounds: Arylmetal compounds are formed when arenediazonium salts are decomposed in the presence of metal salts or when arenediazonium–metal salt complexes are decomposed

(the Nesmeyanov reaction), *e.g.*:

$$RN_2Cl{\cdot}HgCl_2 + 2Cu \longrightarrow RHgCl + 2CuCl + N_2$$

The mechanism of this reaction has been discussed by Reutow.[23]

A similar reaction consists of decomposition of the double salt of a diphenylhalonium salt and a heavy-metal halide by a powdered metal (Reutow). It can be used for synthesis of aryl derivatives of a wide variety of metals such as mercury, tin, antimony, and bismuth.[23]

One of the principal syntheses of the pharmacologically interesting arylarsonic acids is provided by treatment of arenediazonium chlorides with sodium arsenites (the Bart reaction), *e.g.*:

$$C_6H_5N_2Cl + Na_2HAsO_3 \longrightarrow C_6H_5AsO_3HNa + NaCl + N_2$$

Arylantimony compounds can be prepared similarly.

Many metal halides react with diazomethane, giving the corresponding halomethyl derivatives:[24]

$$MX + CH_2N_2 \longrightarrow M{-}CH_2X + N_2$$

8. Action of free radicals on metals: Schlenk and Marcus[25] investigated the action of triarylmethyl radicals on metallic sodium, whereby compounds of the type R_3CNa were formed. Paneth and Loleit[26] studied the formation of organometallic compounds by reaction of methyl and ethyl radicals with arsenic, antimony, and bismuth.

According to Waters' results,[27,28] the formation of aryl–metal compounds on decomposition of arenediazonium chlorides in the presence of metals such as mercury, antimony, bismuth, lead, and tin also occurs by way of radicals, in contrast to the Nesmeyanov reaction.

9. Certain organometallic compounds can be obtained by interaction of preformed organometallic compounds with other organic or organometallic compounds. The following reactions, for instance, are possible:

(a) with other organometallic compounds according to the general equation:

$$RM + R'M' \rightleftarrows RM' + R'M$$

the more negative organic group usually migrating to the more positive metal. Apart from this, the reaction is especially successful when one of the products is sparingly soluble in the solvent used and is thus precipitated.

(b) with hydrocarbons, whereupon, with very reactive organometallic compounds, hydrogen may be replaced by the metal, *e.g.*:

$$RNa + C_6H_6 \longrightarrow C_6H_5Na + RH$$

Further, organoalkali compounds may add to the C=C bond of unsymmetrical olefins.

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[23] O. A. Reutow, *Angew. Chem.*, **72**, 198 (1960); *Tetrahedron*, **1**, 67 (1957).

[24] D. Seyferth, *Chem. Rev.*, **55**, 1155 (1955).

[25] W. Schlenk and E. Marcus, *Ber. Deut. Chem. Ges.*, **47**, 1664 (1914).

[26] F. A. Paneth and H. Loleit, *J. Chem. Soc.*, **1935**, 366.

[27] F. B. Makin and W. A. Waters, *J. Chem. Soc.*, **1938**, 843.

[28] W. A. Waters, *J. Chem. Soc.*, **1937**, 2007.

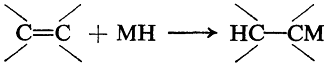
(c) the halogen of organic halides may be replaced by the metal: for example, butyllithium and some aromatic bromides and iodides afford aromatic lithium derivatives:

$$C_4H_9Li + RBr \longrightarrow RLi + C_4H_9Br$$

Also, organic halides may add to an organometallic compound to give a product in which the metal has a higher valence, *e.g.*:

$$R_3As + R'I \longrightarrow R_3R'AsI$$

10. An example of the addition of an inorganic or organometal hydride to a C=C bond:



is provided by the addition of trichlorosilane to olefins.[29]

A notable synthesis of this type is that developed on an industrial scale for the preparation of alkylaluminums from aluminum and hydrogen, or an aluminum hydride, and olefins, especially ethylene.

Most of the methods for preparing organometallic compounds have been reviewed and discussed by Jones and Gilman.[30]

I. Organic derivatives of elements of the First Group[31]

As the alkali metals are the most electropositive elements the carbon–metal bond of their organic derivatives is the most strongly polarized of any such. Organoalkali compounds are thus among the most reactive compounds known in chemistry. Alkyl derivatives of sodium and potassium react with all organic compounds except saturated aliphatic hydrocarbons. The less reactive lithium compounds have found wide use in synthesis. In accord with the diagonal relationship in the Periodic Table their behavior resembles that of Grignard reagents in most respects, but they are more reactive than these and moreover they do not cause the undesirable side reactions that are often met when organo-sodium or -potassium compounds are used. Further, organic derivatives of lithium are mostly soluble in inert organic media whereas the remaining alkali-metal derivatives are insoluble therein. Alkyl derivatives of lithium are the exception to the rule that simple alkyl and aryl derivatives of the alkali metals are solid, salt-like compounds[32] which neither melt nor volatilize without decomposition. In some special solvents such as dimethylzinc and trimethylaluminum they dissolve with formation of complex anions, *e.g.*, $Me^{2+}[Zn(CH_3)_2R_2]^{2-}$, and such solutions conduct an electric current.

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[29] E. W. Pietrusza, L. H. Sommer, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **70**, 484 (1948).

[30] R. G. Jones and H. Gilman, *Chem. Rev.*, **54**, 835 (1954).

[31] C. B. Wooster, *Chem. Rev.*, **11**, 1 (1932).

[32] A. A. Morton, "Solid Organoalkali Metal Reagents; a New Chemical Theory for Ionic Aggregates," Gordon and Breach, New York, 1965.

1. Organolithium compounds[33]

The method now most often used for preparing organolithium compounds is to treat metallic lithium with the appropriate organic halides:

$$2Li + RX \longrightarrow LiR + LiX$$

It was Ziegler and Colonius who first showed that the primary products in a Wurtz synthesis are organoalkali compounds which, under suitable conditions, do not react further and can be obtained as the main product of the reaction.[34]

Gilman and his co-workers prepared a large number of organolithium compounds by this method.[35] An analogous reaction occurs with chloro ethers, yielding, *e.g.*, from chloromethyl ether and lithium in methylal at −25° to −30° (methoxymethyl)lithium, which is stable for days at −70° but decomposes in a few hours at 0°.[36]

The course of the reaction is greatly influenced by the nature of the halide and the solvent used. Also, the ease with which it occurs depends appreciably on the sodium content of the lithium;[37] direct synthesis of vinyllithium, for instance, is impossible unless the lithium contains sodium (Na content about 2%).[38]

Iodides, except methyl iodide, cannot be used because they undergo the Wurtz reaction too easily and thus give low yields of the organolithium compound. In the aliphatic series it is best to use chlorides, and in the aromatic series bromides. It is important that the halide be very pure.

Suitable solvents for the preparation of alkyl derivatives of lithium are hydrocarbons such as benzene, cyclohexane, light petroleum, and, when the alkyllithium is to be brought into immediate further reaction, also diethyl ether or tetrahydrofuran, as in the last two the reaction is appreciably faster. A paper by Gilman and Schwebke[39] should be consulted concerning the stability of *n*-alkyl derivatives of lithium in mixtures of diethyl ether and tetrahydrofuran. Aryl derivatives of lithium are almost always prepared in diethyl ether since they do not react with ethers. All solvents should, of course, be completely anhydrous: they should have been kept over sodium for a considerable time.

The lithium used must be in small pieces so as to present a sufficient surface for reaction. Gilman *et al.*[40] describe various methods, more or less satisfactory, for effecting this.

A useful method is to prepare a lithium ribbon, about 1 cm broad and 1 mm thick, by means of a sodium press, passing this ribbon immediately into anhydrous ether and cutting the ribbon by scissors into pieces which are allowed to fall directly into the reaction solution.

An excess of the metal is not needed; 2–2.2 moles of lithium are used per mole of halide.

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[33] E. A. Braude, *Progr. Org. Chem.*, **3**, 172 (1955); D. L. Esmay, *Advan. Chem. Ser.*, **23**, 46 (1959).

[34] K. Ziegler and H. Colonius, *Ann. Chem.*, **479**, 135 (1930).

[35] H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Amer. Chem. Soc.*, **54**, 1957 (1932); **55**, 1252 (1933).

[36] U. Schöllkopf, H. Küppers, H.-J. Traenckner, and W. Pitteroff, *Ann. Chem.*, **704**, 120 (1967).

[37] C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 1807 (1960).

[38] R. West and W. H. Glaze, *J. Org. Chem.*, **26**, 2096 (1961).

[39] H. Gilman and G. L. Schwebke, *J. Organometal. Chem.*, **4**, 483 (1965).

[40] H. Gilman, W. Langham, and F. W. Moore, *J. Amer. Chem. Soc.*, **62**, 2327 (1940).

Oxygen and carbon dioxide must be rigidly excluded during preparation and reaction of organolithium compounds. It is customary to work under an atmosphere of nitrogen or argon. Before use, nitrogen from a bottle must be freed from oxygen by passage through alkaline pyrogallol solution and dried by passage through a calcium chloride tower and a phosphorus pentoxide tube.

The reaction vessels first used, by Ziegler and Colonius,[34] were Schlenk tubes;[41] Wittig[42] later used Kjeldahl flasks with an attached side arm. However, conventional apparatus can also be used, consisting of a three-necked flask fitted with a gas-tight stirrer, reflux condenser, and dropping funnel.[40] When all the air has been replaced by nitrogen and the solvent and lithium pieces have been added, the apparatus is closed by a mercury valve on top of the reflux condenser. A five-necked flask may also be used,[43] so that additionally the reaction temperature can be controlled on insertion of a thermometer and an inlet tube for continuous passage of nitrogen can be provided.

Adams *et al.*[44] have described another apparatus suitable for preparation and further reaction of organolithium compounds.

General directions for preparation of **alkyllithiums** in light petroleum:[45] Dry light petroleum (50 ml; free from unsaturated compounds; b.p. 28–38°) is placed in an apparatus consisting of a three-necked flask, a stirrer, a reflux condenser, and a dropping funnel, then nitrogen is passed in and lithium (slightly more than 0.7 g, 0.1 mole) is cut directly into the flask. The liquid is then gently boiled and vigorously stirred while a solution of the alkyl halide (0.05 mole) in light petroleum (50 ml) is added; reaction soon sets in and addition can be completed within 1 h. The mixture is boiled and stirred (0.5–1 h) until no further reaction is visible. The solution is cooled and transferred under nitrogen to a graduated flask. Yields are between 50% and 85%.

Phenyllithium:[46] Anhydrous ether (500 ml) is placed in a three-necked flask carrying a gas-tight stirrer, dropping funnel, and reflux condenser, and nitrogen is passed in. Lithium pieces (29.4 g) are then added, followed by a little (about 40 drops) of a solution of bromobenzene (314 g) in anhydrous ether (1 l). When the beginning of the reaction is indicated by appearance of a slight turbidity, addition of the bromobenzene solution is continued. If evolution becomes too lively, the mixture is cooled in an ice-bath but only so that it remains boiling continuously. Towards the end of the reaction the ice-bath is removed and the soluhion stirred until ebullition ceases. The reaction time amounts to 2 h. The solution is decanted through glass wool, under nitrogen, into a dropping funnel pre-filled with nitrogen.

For the preparation of **butyllithium** (often required in the laboratory) Gilman and his collaborators[47] have worked out directions which are also suitable for other alkyllithiums:

Anhydrous ether (200 ml) is placed in a three-necked flask (500 ml) fitted with a stirrer, low-temperature thermometer, and dropping funnel. The apparatus is filled with oxygen-free nitrogen, and lithium wire (8.6 g, 1.25 moles) is cut directly into the ether with continued passage of nitrogen. Then a little (about 30 drops) of a solution of butyl bromide (68.5 g,

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[41] W. Schlenk and A. Thal, *Ber. Deut. Chem. Ges.*, **46**, 2843 (1913).

[42] G. Wittig, *Angew. Chem.*, **53**, 241 (1940).

[43] E. Terres, U. von Felde, K. Hubbuch, H. Frank, and W. Meyer, *Erdöl u. Kohle*, **13**, 84 (1960).

[44] R. Adams, H. Wolff, C. K. Cain, and J. H. Clark, *J. Amer. Chem. Soc.*, **62**, 1770 (1940).

[45] H. Gilman, F. W. Moore, and O. Baine, *J. Amer. Chem. Soc.*, **63**, 2479 (1941).

[46] R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).

[47] H. Gilman, I. A. Beelm, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Amer. Chem. Soc.*, **71**, 1499 (1949).

0.5 mole) in ether (100 ml) is added from the dropping funnel with stirring, and the mixture is cooled to −10° by a Dry Ice–acetone bath (−30° to −40°). When the reaction begins, the liquid becomes slightly turbid and pale spots appear on the lithium. The remainder of the butyl bromide solution is then added in portions during 0.5 h while the internal temperature is kept at −10°. When this addition is complete the mixture is allowed to warm to 0–10° during 1–2 h, then decanted through a narrow tube containing glass wool into a graduated dropping funnel that has been washed out with nitrogen. The yield is 75–90%.

The ethereal butyllithium solution obtained has only limited stability and should thus be used as soon as possible.

For the preparation and properties of *n*- and *sec*-butyllithium see also Lewis *et al.*[48]

When necessary, the solution can be filtered under nitrogen from separated lithium halide and unchanged lithium; apparatus for this has been described by various authors.[40,42,43]

Some ethers react with metallic lithium in the same way as alkyl and aryl halides; *e.g.*, benzyllithium is obtained in good yield from alkyl benzyl ethers in tetrahydrofuran.[49]

The concentration of an organolithium solution can be determined by adding an aliquot part to water and titrating the resulting lithium hydroxide by 0.1N-hydrochloric acid to Methyl Orange. The amount required for a reaction can then be determined.

A different method of preparation is advisable if the pure, solvent-free organolithium compound is required. In a procedure due to Schlenk and Holtz[50] the organolithium compound is prepared from metallic lithium and the organomercury compound in an indifferent solvent; since most organolithium compounds, in particular the higher alkyl derivatives, are very readily soluble in hydrocarbons, they can be easily separated from the separating mercury and then obtained pure by evaporation of the solution.

$$\mathrm{RM} + \mathrm{Li} \longrightarrow \mathrm{RLi} + \mathrm{M}$$

Ethyllithium:[50] Clean metallic lithium (5 g; cut as fine as possible) is added in a nitrogen atmosphere to a solution of diethylmercury (10 g) in benzene or high-boiling light petroleum (60 ml). The vessel is then sealed and warmed to 65°. The reaction is complete in 3 days if the mixture is meanwhile repeatedly shaken. The mixture is heated to 70° and filtered with exclusion of air. When the filtrate cools, the ethyllithium separates in large crystals. Crystallization is completed by cooling in ice, and the product is collected under nitrogen, washed with a little ice-cold light petroleum, and dried in a stream of nitrogen.

This method can often be used for synthesis of organolithium compounds that are difficultly accessible by other means; *e.g.*, *o*-dilithiobenzene is formed in good yield when *o*-phenylenemercury is shaken for 3 days with lithium pieces in anhydrous ether.[51]

An analogous method, namely, the action of lithium on benzylmagnesium chloride, was used by Ziegler and Dersch for preparation of benzyllithium:[52]

$$\mathrm{C_6H_5CH_2MgCl} + 2\mathrm{Li} \longrightarrow \mathrm{LiCl} + \mathrm{Mg} + \mathrm{C_6H_5CH_2Li}$$

A further procedure depends on the differing solubilities of certain organometallic compounds in inert organic solvents. For instance, when solutions

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[48] D. M. Lewis, W. S. Leonhardt, and C. W. Kamienski, *Chimia* (*Aarau*), **18**, 134 (1964).

[49] H. Gilman and H. A. McNinch, *J. Org. Chem.*, **26**, 3723 (1961); H. Gilman and G. L. Schwebke, *J. Org. Chem.*, **27**, 4259 (1962).

[50] W. Schlenk and J. Holtz, *Ber. Deut. Chem. Ges.*, **50**, 262 (1917).

[51] G. Wittig and F. Bickelhaupt, *Chem. Ber.*, **91**, 883 (1958).

[52] K. Ziegler and F. Dersch, *Ber. Deut. Chem. Ges.*, **64**, 448 (1931).

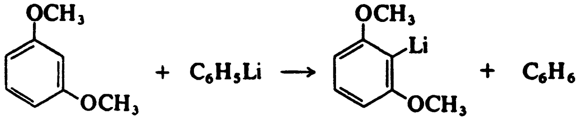
of ethyllithium and dimethylmercury in benzene or light petroleum are mixed, this leads to precipitation of methyllithium which is very sparingly soluble in these solvents:[50]

$$2C_2H_5Li + Hg(CH_3)_2 \longrightarrow 2CH_3Li\downarrow + Hg(C_2H_5)_2$$

Other transmetalations, between lithium and particularly tin derivatives, have also been examined in detail and have been utilized for synthesis of, *e.g.*, vinyl-,[53] propenyl-,[54] allyl-,[55] styryl-,[56] cyclopropyl-,[57] and benzyl-lithium.[58]

Metallation of certain reactive hydrocarbons provides yet another route to several otherwise difficultly accessible lithium derivatives.[59] Thus when a hydrogen atom on carbon has aryl or vinyl groups as neighbors it may be replaced by lithium under the action of organolithium compounds. Further, an *o*-hydrogen atom of, *inter alia*, aryl ethers and sulfides can be replaced by lithium in reactions with butyllithium or phenyllithium.[60]

2-Lithioresorcinol dimethyl ether:[42] This is obtained, for instance, by the following simple reaction. A mixture of resorcinol dimethyl ether (13.8 g, 0.1 mole) and phenyllithium (0.1 mole) in anhydrous ether (100.ml) is set aside at room temperature for 60 h, whereupon 2-lithioresorcinol dimethyl ether separates in large transparent crystals.



Heterocyclic compounds containing O, S, or N as ring members behave similarly,[61] and the resulting organolithium compounds can be used as, for example, intermediates for introduction of substituents into the heterocyclic ring.

Lithio derivatives of carbocycles can be obtained by reaction of alkyllithiums at −65° to −70° with polyhalohydrocarbons such as tetra- and pentachlorobenzene[62] and 1,3,3,4,4,5,5,6,6-nonafluorocyclohexene.[63]

When an organolithium compound reacts with an organic halide the product is usually a hydrocarbon, reaction being analogous to a Wurtz–Fittig synthesis. However, the action of alkyl- or aryl-lithiums replaces the halogen by lithium in several halogenated heterocycles, aromatic ethers, and alkyl

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[53] D. Seyferth and M. A. Weiner, *J. Amer. Chem. Soc.*, **84**, 361 (1962).

[54] D. Seyferth and L. G. Vaughan, *J. Amer. Chem. Soc.*, **86**, 883 (1964).

[55] D. Seyferth and M. A. Weiner, *J. Org. Chem.*, **24**, 1395 (1959).

[56] D. Seyferth, L. G. Vaughan, and R. Suzuki, *J. Organometal. Chem.*, **1**, 437 (1964).

[57] D. Seyferth and H. M. Cohen, *Inorg. Chem.*, **2**, 625 (1963).

[58] H. Gilman and S. D. Rosenberg, *J. Org. Chem.*, **24**, 2063 (1959); D. Seyferth, R. Suzuki, C. J. Murphy, and C. R. Sabet, *J. Organometal. Chem.*, **2**, 431 (1964).

[59] H. Gilman and J. W. Morton, *Org. Reactions*, **8**, 258 (1954).

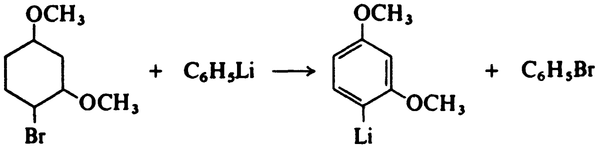
[60] G. Wittig, U. Pockels, and H. Dröge, *Ber. Deut. Chem. Ges.*, **71**, 1903 (1938); H. Gilman and F. J. Webb, *J. Amer. Chem. Soc.*, **71**, 4062 (1949).

[61] H. Gilman and R. V. Young, *J. Amer. Chem. Soc.*, **56**, 1415 (1934); **57**, 1121 (1935); H. Gilman and R. L. Bebb, *J. Amer. Chem. Soc.*, **61**, 109 (1939); H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1939); H. Gilman and D. A. Shirley, *J. Amer. Chem. Soc.*, **71**, 1870 (1949).

[62] C. Tamborski, E. J. Soloki, and C. E. Dill, *Chem. & Ind.* (*London*), **1965**, 2067.

[63] S. F. Campbell, R. Stephens, and J. C. Tatlow, *Chem. Commun.*, **1967**, 151.

benzyl ethers.[40,64] Wittig and Pockels,[65] for instance, observed instantaneous and almost complete formation of 4-lithioresorcinol dimethyl ether on mixing an ethereal solution of 4-bromoresorcinol dimethyl ether with an equivalent amount of phenyllithium:



This type of halogen–lithium exchange can also be effected with many halogenated aliphatic and aromatic hydrocarbons; for example, pure aryllithiums can be obtained from aryl iodides and butyllithium in benzene.[66]

Equilibria in mutual halogen–lithium exchanges have been measured[67] to determine the relative stabilities of various alkyl-, cycloalkyl-, alkenyl-, and aryl-lithium reagents.

Dihalogen compounds can also be converted into the corresponding organolithium reagents by this method,[68,69] a subject that has been reviewed by Jones and Gilman.[46]

Preparation of cross-linked poly-*p*-lithiostyrene and its use as lithium-transfer agent for halogen–lithium exchange and for metalations have been described by Braun and Seelig.[70]

2. Organo-sodium and -potassium compounds[71]

Organosodium compounds can, in principle, be prepared by the same methods as the corresponding lithium compounds. However, reaction of organic halides (usually chlorides) with metallic sodium in an inert solvent has been introduced recently:

$$RX + 2Na \longrightarrow RNa + NaX$$

Since alkyl- and aryl-sodiums are still more reactive than their lithium analogs — they react much more easily with organic halides in the sense of a Wurtz–Fittig reaction and with certain solvents — their preparation requires very exact control of reaction conditions. As for the organolithium analogs a nitrogen atmosphere is necessary during their preparation. Reactions are carried out in anhydrous, olefin-free hydrocarbons such as pentane, light petroleum, etc., and as the alkyl- and aryl-sodiums formed are insoluble therein the sodium used must be divided as finely as possible and there must be vigorous stirring.

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[64] W. Langham, R. Q. Brewster, and H. Gilman, *J. Amer. Chem. Soc.*, **63**, 545 (1941); H. Gilman, H. B. Willis, and J. Swislowsky, *J. Amer. Chem. Soc.*, **61**, 1371 (1939); H. Gilman *et al.*, *J. Amer. Chem. Soc.*, **62**, 1843, 2327 (1940); R. C. Fuson and B. Freedman, *J. Org. Chem.*, **23**, 1161 (1958).

[65] G. Wittig and U. Pockels, *Ber. Deut. Chem. Ges.*, **72**, 89 (1939).

[66] M. Schlosser and V. Ladenberger, *J. Organometal. Chem.*, **8**, 193 (1967).

[67] D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963).

[68] R. L. Letsinger, J. A. Gilpin, and W. J. Vullo, *J. Org. Chem.*, **27**, 672 (1962).

[69] I. T. Millar and H. Heaney, *Quart. Rev. (London)*, **11**, 109 (1957).

[70] D. Braun and E. Seelig, *Chem. Ber.*, **97**, 3098 (1964).

[71] M. Schlosser, *Angew. Chem. Int. Ed., Engl.*, **3**, 287, 362 (1964).

A fine sodium dust or, better, a suspension of sodium with particle size less than 25 microns is prepared and treated with the alkyl or aryl halide; the necessary apparatus has been described by various authors.[72,73] The preparation of pentylsodium (often required for further reaction)[74] and of phenylsodium[75,76] has been studied in especial detail.

Pentylsodium:[77] Sodium dust is prepared by stirring the metal in olefin-free decane under nitrogen for 1 min at 110–130° with a high-speed stirrer (10,000 rpm). The suspension is then cooled and the liquid is syphoned off under a nitrogen pressure. The residual sodium dust is washed several times with dry pentane.

The sodium dust (23 g, 1 mole) in pentane (ca. 300 ml) is placed under nitrogen in a flask (500 ml) fitted with a high-speed stirrer and is cooled to −10° to 0°. Then pure pentyl chloride is added (53 g, 0.5 mole) during 1 h. The yield is about 80%.

An excess of sodium may be used in many cases, and to start the reaction rapidly the metal may be activated by initial addition of a little pentyl alcohol (about 2 ml per 30 g of sodium).

Phenylsodium:[73] Finely divided sodium (average particle size below 25 microns; 54 g, 2.35 moles), suspended in toluene (275 g) under nitrogen, is treated at 25–30°, with gentle shaking, with a solution (10–15 ml) of chlorobenzene (112.6 g, 1 mole) in toluene (100 g). Reaction usually begins after 1–5 min and causes a rapid rise in temperature. Further chlorobenzene must never be added until the first exothermal reaction has occurred and has been brought under control by means of a cooling-bath (−20°). The internal temperature should not be allowed to exceed 40°. (If reaction has not begun after 20 min, 2–4 ml of pentyl alcohol may be added, but the mixture must then be cooled immediately as the reaction starts at once.) Finally the chlorobenzene–toluene mixture is dropped in, the rate of addition and the cooling being regulated so that formation of phenylsodium is complete in 20–30 min. The yield is 94–99%.

A laboratory apparatus for continuous preparation of phenylsodium has been described by Ruschig *et al.*[78]

A further method of preparing organosodium compounds, indeed that most used previously, was by the action of metallic sodium on organometallic compounds of zinc, cadmium, lead, or, above all, mercury in an indifferent solvent:[50,79]

$$R_2Hg + 2Na \longrightarrow Hg + 2NaR$$

Ethylsodium:[50] So much clean sodium is cut up and placed in dry petroleum ether (40 ml, b. p. 100–150°) that the liquid just covers the metal. The air is then completely replaced by dry, oxygen-free nitrogen, and diethylmercury (2 g) is added. Reaction begins at once, and after 1–2 h a translucent greenish-grey precipitate has settled on the sodium. For working up, the mixture is cooled for about 10 min in a freezing mixture and then shaken, whereupon the product separates from the metal. The precipitate and the liquid are poured together, under nitrogen, from the excess of sodium and the sodium amalgam, and the ethylsodium is filtered off, washed several times with dry light petroleum, and dried in a stream of nitrogen.

Direct treatment with sodium can lead to replacement of hydrogen by the metal in compounds such as alkynes, fluorenes, and triarylmethanes; dimethyl

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[72] A. A. Morton and L. M. Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).

[73] I. F. Nobis and L. F. Moormeier, *Ind. Eng. Chem.*, **46**, 539 (1954).

[74] A. A. Morton and co-workers, *J. Amer. Chem. Soc.*, **58**, 1697 (1936); **62**, 1301 (1940); **64**, 2242, 2247, 2250 (1942); **68**, 93 (1946); **69**, 172 (1947).

[75] Ger. Pat. 622,875, 633,083, 644,486; *Chem. Abstr.*, **30**, 2991, 7582; **31**, 5381 (1937); A. A. Morton and I. T. Massengale, *J. Amer. Chem. Soc.*, **62**, 120 (1940).

[76] H. Gilman, H. A. Pacevitz, and O. Baine, *J. Amer. Chem. Soc.*, **62**, 1514 (1940).

[77] A. A. Morton and co-workers, *J. Amer. Chem. Soc.*, **62**, 123 (1940); **72**, 3785 (1950).

[78] H. Ruschig, R. Fugmann, and W. Meixner, *Angew. Chem.*, **70**, 71 (1958).

[79] J. A. Wanklyn, *Ann. Chem.*, **107**, 125 (1858); **108**, 67 (1858); S. F. Acree, *Amer. Chem. J.*, **29**, 588 (1903); F. Hein, E. Petzchner, K. Wagler, and F. A. Segitz, *Z. Anorg. Allg. Chem.*, **141**, 161 (1924); F. Hein and H. Schramm, *Z. Phys. Chem.*, **A**, **151**, 234 (1930).

sulfoxide yields sodium methylsulfinylmethanide, CH_3SOCH_2Na, in this way.[80]

Reaction with sodium methylsulfinylmethanide with alkynes in dimethyl sulfoxide provides a convenient method of preparing sodium acetylides:[81]

$$CH_3SOCH_2Na + RC{\equiv}CH \longrightarrow (CH_3)_2SO + RC{\equiv}CNa$$

and analogous metallations of hydrocarbons by organosodium compounds offer a further possible method of preparing certain otherwise difficultly accessible organosodium compounds. Metalation by organosodium compounds proceeds very much more readily than by the corresponding organolithium compounds; thus Schorigin[82] observed many years ago that phenylsodium was formed when benzene was treated with ethylsodium:

$$C_2H_5Na + C_6H_6 \longrightarrow C_2H_6 + C_6H_5Na$$

Some of the factors controlling orientation and reactivity in metallation of aromatic compounds have been discussed[83] in the light of reactions of alkylsodiums and -potassiums with isopropylbenzene.

Benkeser *et al.*[84] have reviewed the metallation of organic compounds by organosodium derivatives.

Organopotassium compounds are still more reactive than the corresponding derivatives of sodium. Whereas phenylsodium can be obtained after reaction of sodium with chlorobenzene in toluene, reaction of potassium with chlorobenzene in toluene affords benzylpotassium in good yield, even at low temperatures;[76] benzylpotassium is also formed in about 90% yield by direct metalation of toluene by potassium in the presence of Na_2O, CaO, or MgO.[85]

$$2K + C_6H_5Cl \longrightarrow C_6H_5K + KCl$$

$$C_6H_5K + C_6H_5CH_3 \longrightarrow C_6H_5CH_2K + C_6H_6$$

The reactivity of alkyl potassiums is so much greater than that of the corresponding lithium and sodium derivatives, that interaction of alkyl halides and potassium gives a very complex mixture containing only a small proportion of the desired alkylpotassiums.[86]

Unlike alkyl derivatives of lithium and sodium, those of potassium attack inert alkanes such as pentane and hexane even at room temperature; metalation occurs mainly on the primary but also on the secondary carbon atoms, as shown in experiments with cyclohexane.[87]

Comparative investigations of alkylpotassiums and alkylsodiums as reagents for metalation of terminal olefins have been carried out by Broaddus.[88]

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[80] A. Ledwith and N. McFarlane, *Proc. Chem. Soc.*, **1964**, 108.

[81] J. Kříž, M. J. Beneš, and J. Peška, *Collect. Czech. Chem. Commun.*, **32**, 398 (1967).

[82] P. Schorigin, *Ber. Deut. Chem. Ges.*, **41**, 2723 (1908).

[83] R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *J. Amer. Chem. Soc.*, **85**, 3984 (1963); D. Bryce-Smith, *J. Chem. Soc.*, **1963**, 5983.

[84] R. A. Benkeser, D. J. Foster, D. M. Sauve, and J. F. Nobis, *Chem. Rev.*, **57**, 867 (1957).

[85] C. E. Claff and A. A. Morton, *J. Org. Chem.*, **20**, 440 (1955); A. A. Morton and C. E. Claff, *Angew. Chem.*, **67**, 349 (1955).

[86] R. A. Finnegan, *Tetrahedron Lett.*, **1962**, 1303.

[87] R. A. Finnegan, *Tetrahedron Lett.*, **1963**, 429.

[88] C. D. Broaddus, *J. Org. Chem.*, **29**, 2689 (1964).

II. Organic derivatives of elements of the Second Group

As the first element of the Second Group, beryllium occupies a special place, just as lithium does in the First Group. Dialkyl derivatives of beryllium differ markedly from those of the alkaline-earth metals and form a transition to those of elements of the Third Group. Although highly associated, dialkylberylliums are volatile, soluble in apolar organic solvents such as benzene, and, except for dimethylberyllium, all liquid; the corresponding magnesium compounds have a very much more salt-like character — they are infusible and almost involatile solids.

Very little is yet known about the physical properties of organo-calcium, -strontium, or -barium compounds. The preparation and properties of organic derivatives of the Second Group have been reviewed by Baluyeva and Ioffe[89] and by Ioffe and Nesmeyanov.[90]

Dialkyl derivatives of elements of the Second sub-Group, namely, zinc, cadmium, and mercury, contain an almost completely covalent metal–carbon bond. These compounds are normal, unassociated liquids with low boiling points; *e.g.*, the dimethyl derivative of zinc boils at 46°, that of cadmium at 105.5°, and that of mercury at 92°.

As for all other organometallic compounds, the reactivity of organic derivatives of Group II elements towards C–O and C–N multiple bonds decreases with increasing electronegativity of the metal. The behavior towards atmospheric oxygen and towards water is similar; thus the lower alkyl, *e.g.*, methyl, derivatives of beryllium, magnesium, and zinc are so violently attacked by atmospheric oxygen that they inflame spontaneously in air; their reaction with water is also extremely violent. Dimethylcadmium reacts less rapidly, and dimethylmercury is almost wholly unaffected by atmospheric oxygen or water at room temperature.

1. Organomagnesium compounds

Organomagnesium halides (the Grignard reagents) are still the organometallic compounds most widely used in preparative organic chemistry, owing this to the relative ease of their preparation and handling.

The method applied almost exclusively to their preparation is direct reaction of an alkyl or aryl halide with metallic magnesium, in accordance with the equation:

$$RX + Mg \rightarrow RMgX$$

It is extremely widely applicable, for Grignard reagents can be prepared from almost every type of alkyl and aryl halide except the fluorides.

The magnesium is used in the form of commercial turnings. It is usually unnecessary to purify this material, but, if desired, it may be washed in the reaction vessel with a little pure dry ether; occasionally there are advantages in using magnesium powder of defined grain size. Metals present as impurities in the magnesium do not interfere with the reactions, remaining as a dark

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[89] G. A. Baluyeva and S. T. Ioffe, *Uspekhi Khim.*, **31**, 940 (1962).

[90] S. T. Ioffe and A. N. Nesmeyanov, "The Organic Compounds of Magnesium, Beryllium, Calcium, Strontium, and Barium," North-Holland, Amsterdam, 1967.

powdery residue; the effect of such small amounts of impurity on the yield of Grignard reagent has been investigated by Chaudron.[91]

The amount of magnesium used is normally that equivalent to the halide, but sometimes an excess must be taken.

The halide most often used is the bromide. Bromides have the advantage over chlorides that they react more readily with the magnesium, although the latter sometimes give better yields. Iodides, which react still more readily, are seldom used as they are more expensive and tend to favor side reactions (Wurtz syntheses); they are, however, used when they are the most easily accessible halide, also for reactions of aliphatic compounds of high molecular weight where the cost of iodine is of relatively little importance, and when high reactivity is required.

The same techniques are used for the various types of halide. The halide must be as pure as possible, in particular free from acids, alcohols, and water; the impurities not only reduce the yield but also may prevent or greatly hinder initiation of the reaction. The halide is best dried over calcium chloride and distilled immediately before the reaction.

Grignard's fundamental investigations,[92] as well as subsequent very extensive studies, have shown that the solvent plays an important part in the reaction of organic halides with magnesium. Diethyl ether has proved the most serviceable solvent in the majority of cases, but dipropyl, dibutyl, and diisopentyl ether, as well as dioxan and tetrahydrofuran have been used in special cases; formals, *e.g.*, diisopropoxy- and diisobutoxy-methane, may also be invoked in the synthesis of organomagnesium compounds.[93]

The ether should contain no alcohol or water and should thus be stored for a considerable time over sodium wire; diisopentyl ether is best distilled several times from sodium. The amount of ether is usually chosen to give a final solution containing 1–2 moles of Grignard reagent per liter.

In the reaction the ether functions primarily as solvent for the organomagnesium halide, since this is insoluble in most solvents; the ether thus keeps the magnesium surface free from reaction products, enabling the reaction to proceed. In fact, the organomagnesium halides dissolve as ether adducts whose considerable heat of formation accelerates the main reaction.

The etherates formed may be isolated as white crystalline substances having the general composition $R_2Mg \cdot MgX_2 \cdot 4R'_2O$.

The structure of Grignard reagents and the position of the equilibria in ethereal solutions:

$$[RMgX]_2 \rightleftarrows 2RMgX \rightleftarrows R_2Mg + MgX_2 \rightleftarrows R_2Mg \cdot MgX_2$$

have been subjects widely studied in recent years;[94] the structure of unsolvated Grignard compounds has also been determined.[95]

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[91] T. Chaudron, *C. R. Hebd. Séances Acad. Sci.*, *C*, **264**, 1093 (1967).

[92] V. Grignard, *C. R. Hebd. Séances Acad. Sci.*, **130**, 1322 (1900).

[93] M. F. Shostakovskii, M. R. Kulibekov, A. K. Gorban, and S. M. Shostakovskii, *Zh. Obshch. Khim.*, **34**, 760 (1964); *Chem. Abstr.*, **61**, 566 (1964).

[94] E. C. Ashby and M. B. Smith, *J. Amer. Chem. Soc.*, **86**, 4363 (1964); A. D. Vreugdenhil and C. Blomberg, *Rec. Trav. Chim.*, **82**, 453, 461 (1963); R. E. Dessy, S. E. I. Green, and R. M. Salinger, *Tetrahedron Lett.*, **1964**, 1369.

[95] E. Weiss, *Chem. Ber.*, **98**, 2805 (1965).

Besides ethers, other compounds that form similar adducts accelerate the reaction of magnesium with an alkyl halide; examples are dialkyl derivatives of elements of the Sixth Group (sulfur, selenium, and tellurium) and tertiary amines such as dimethylaniline, diethylaniline, pyridine, and quinoline.

In older work, *e.g.*, that of Löhr,[96] attempts to cause methyl, ethyl, and propyl iodide to react with magnesium gave very unsatisfactory results, although Spencer[97] later showed that the reaction is smoother with iodides of higher molecular weight, such as pentyl iodide. Also, phenylmagnesium chloride can be obtained in good yield (up to 85%) by heating chlorobenzene with magnesium in an autoclave at 150–170°.

According to reports by Chelinzev[99] and Schlenk, Jr.,[100] metallic magnesium also reacts with alkyl halides in hydrocarbons such as benzene, toluene, and light petroleum, although the resulting alkylmagnesium halides do not form adducts with these solvents and thus do not dissolve. Very good yields of organomagnesium halides are obtained in dodecane, isooctane, or tetralin, the necessary rate of reaction being achieved by working at 80–100° for alkyl halides and at 160–170° for phenyl halides.[101]

Drahowzal *et al.*[102] obtained good yields of the so-called "individual Grignard compounds" by carrying out the reaction in benzene to which a small amount of a 10% solution of anhydrous aluminum chloride in tetrahydrofuran had been added.

Grignard solutions from alkyl or aryl halides can be obtained in yields almost as good as in ether by using a hydrocarbon such as benzene, toluene, xylene, or tetralin containing 1 mole of tetrahydrofuran[103] or of triethylamine[104] per mole of magnesium.

The apparatus used for preparation of Grignard solutions is usually a two-necked flask carrying a reflux condenser (wide bulb condenser or Dimroth condenser) and a dropping funnel, but there are advantages in using a three-necked flask as a stirrer can then be incorporated.

Grignard solutions are sensitive to moisture, carbon dioxide, and oxygen, which must thus be excluded. However, in simple operations which are not too protracted it generally suffices to exclude moisture by a calcium chloride tube on the condenser, although it is better to add a CO_2-absorbent such as soda-lime.

Special precautions to exclude oxygen are rarely taken: the ether vapor present over the solution usually suffices to keep the access of air within acceptable limits. Nevertheless, it is sometimes better to replace the air by nitrogen and add a mercury valve, at least at the start of the reaction. An apparatus for carrying out Grignard reactions with exclusion of oxygen has been described by Gilman and Hewlett.[105]

Grignard reactions are carried out as follows: The whole of the magnesium to be used is placed in the reaction flask and covered with anhydrous ether. Then a small amount of the

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[96] P. Löhr, *Ann. Chem.*, **261**, 48 (1891).

[97] I. F. Spencer, *Ber. Deut. Chem. Ges.*, **41**, 2302 (1908).

[98] H. Gilman and R. E. Brown, *J. Amer. Chem. Soc.*, **52**, 3330 (1930); P. Schorigin, W. Issaguljanz, A. Gussewa, O. Ossipowa, and C. Poljakowa, *Ber. Deut. Chem. Ges.*, **64**, 2584 (1931).

[99] W. Chelinzev, *Ber. Deut. Chem. Ges.*, **37**, 2081, 4534 (1904); **38**, 3664 (1905); **40**, 1487 (1907).

[100] W. Schlenk, Jr., *Ber. Deut. Chem. Ges.*, **64**, 739 (1931).

[101] L. I. Zakharkin, O. Yu. Okhlobystin, and B. N. Strunin, *Dokl. Akad. Nauk S.S.S.R.*, **147**, 108 (1962); *Chem. Abstr.*, **63**, 14622 (1965); *Tetrahedron Lett.*, **1962**, 631.

[102] F. Drahowzal, H. König, and H. Pöll, *Monatsh. Chem.*, **86**, 419 (1955).

[103] T. Leigh, *Chem. & Ind.* (*London*), **1965**, 426.

[104] E. C. Ashby and R. Reed, *J. Org. Chem.*, **31**, 971 (1966).

[105] H. Gilman and P. Hewlett, *Rec. Trav. Chim.*, **48**, 1124 (1929).

halide is added; starting with a large amount of halide is not advisable, for, once reaction starts, it can then become so fast that the ether boils too vigorously for the heat evolved to be carried away by cooling. It is best to allow the dense organic halide to flow down the side of the flask so that it lies under the ether and presents a concentrated solution to the magnesium; one should then wait patiently for the reaction to start. If necessary, the reaction can be started by adding a small grain of iodine and placing the mixture on a water-bath until the ether boils gently. After a little practice, start of the reaction is easily recognized by spontaneous refluxing of the ether and fragmentation of the magnesium, and at that point more halide (usually in ethereal solution) is added slowly from the dropping funnel. The drop rate is adjusted so that the ether remains boiling without the refluxing's becoming too rapid. If ebullition becomes too violent, the flask should be cooled in ice-water or cold water — and, if this is in any case done, the halide can be added faster and duration of the reaction thus shortened; nevertheless, too violent reaction must be avoided under all circumstances. When the main reaction is over, the mixture must be warmed for some time further on the water-bath so as to bring the small remaining amount of halide into reaction with the residual magnesium.

If a gaseous alkyl halide such as methyl or ethyl chloride or methyl bromide is to be brought into reaction, the dropping funnel is replaced by a gas inlet tube; in other respects the technique is essentially unchanged. The halide is taken from a steel bottle or is prepared in a parallel experiment; before being passed into the reaction solution it should be washed with water or dilute alkali and dried by passage through two wash-bottles containing concentrated sulfuric acid and, if necessary, thereafter through calcium chloride.

The Grignard solutions obtained in this way can be used for immediate reaction with a third component. They may, however, also be stored if air and light are excluded. Ethyl- and phenyl-magnesium bromide solutions, for instance, were found by Gilman and Meyers[106] to be unchanged after storage for months.

There is no difficulty in effecting Grignard reactions with aryl iodides or bromides or with primary or secondary alkyl iodides, bromides, or chlorides; halides of alkylic and benzylic type also react well, but there is some difficulty with tertiary alkyl halides.

Aryl chlorides react so slowly with magnesium in ether that such mixtures have no preparative use.

When reaction in ether is undesirably slow, better results can be obtained by using higher temperatures, *i.e.*, by choosing a higher-boiling solvent such as dibutyl ether or dimethylaniline, or by using a solvent such as tetrahydrofuran or ethylene glycol dimethyl ether that has a more pronounced donor character than diethyl ether. For instance, vinylmagnesium halides can be prepared if tetrahydrofuran is used as solvent.[107]

Grignard reagents can also be prepared from unreactive halides such as chlorobenzene and vinyl halides if the unreactive halide is mixed with a reactive one and the amount of magnesium taken suffices for reaction with both; this gives a mixture of the two Grignard reagents. Even sterically hindered halides such as bromopentamethylbenzene can often be brought into reaction in this way. The added reactive halide must, of course, be so chosen that the by-products produced in the subsequent reaction are easily separated; ethyl bromide is often a suitable choice.

Similar activation may be achieved by adding a small amount of pre-formed Grignard solution to a mixture of ether, magnesium, and halide.

A further method of bringing unreactive halides into a Grignard reaction, recommended by von Bayer as early as 1905,[108] was to use an activated mag-

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[106] H. Gilman and C. Meyers, *Ind. Eng. Chem.*, **15**, 61 (1923).

[107] H. Normant, *C. R. Hebd. Séances Acad. Sci.*, **239**, 1510 (1954); *Bull. Soc. Chim. France*, **1957**, 728.

[108] A. von Bayer, *Ber. Deut. Chem. Ges.*, **38**, 2759 (1905).

nesium that he obtained by heating magnesium filings with iodine. A still more effective product was prepared by Gilman *et al.*[109] who activated a magnesium–copper alloy by iodine. Magnesium powder can also be substantially activated by mechanical stirring for 24 hours in an atmosphere of oxygen-free nitrogen. With such a pre-treated, finely divided magnesium there is almost complete reaction of, *e. g.*, *p*-bromo-*N*,*N*-dimethylaniline in boiling tetrahydrofuran.[110]

A side-reaction that occurs to a greater or less extent in all Grignard reactions is an organometallic synthesis according to the scheme:

$$\mathrm{RX + RMgX \longrightarrow R{-}R + MgX_2}$$

As mentioned above, organic iodides undergo this undesirable side reaction much more than do the corresponding bromides and the still less reactive chlorides. This Wurtz-type competing reaction occurs particularly with compounds that contain mobile halogen atoms, such as 3-bromo-alkenes and -alkynes and tertiary alkyl halides. To hinder it, Groizeleau-Miginiac[111] proposed the use of 3,4-dihydro-2*H*-pyran or furan as solvent in place of ether, and in this way increased yields were obtained of, *inter alia*, allyl-,*tert*-butyl-, and propargyl-magnesium bromide [above 10° the last-mentioned (2-propynyl) gave 1-propynylmagnesium bromide]. Further, experience has shown that the side reaction occurs to a greater extent the more violent is the reaction, so that the mildest useful conditions must be observed in order to get maximal yields of the Grignard reagent. Therefore the organic halide is added only just fast enough to keep the reaction in progress, and the mixture is stirred vigorously so as to keep the local concentration of halide low — a feature which also diminishes the amount of hydrocarbon formed; and for the same reason it is often an advantage to increase the amount of solvent.

Another side reaction, observed particularly with tertiary halides, is loss of hydrogen halide:

$$\mathrm{2CHR_2{-}CR_2X + Mg \longrightarrow 2CR_2{=}CR_2 + H_2 + MgX_2}$$

A generally applicable color reaction for *qualitative detection* of Grignard reagents has been given by Gilman (see page 879).

Determination of the concentration of Grignard reagents is often important for their further preparative use and is best effected by titration with acid as elaborated by Gilman's school:[112]

An aliquot part (about 20 ml), measured to ±0.1 ml in a measuring cylinder, of a Grignard solution is poured slowly into an Erlenmeyer flask (400 ml) containing distilled water (50 ml). The measuring cylinder is washed out, first with a few ml of sulfuric acid of known strength (about 0.25N) and then several times with distilled water; the washings are added to the Erlenmeyer flask. Then sulfuric acid (about 20 ml) is added until an excess is present, and the mixture is placed on a hot-plate to complete the reaction, after which it is cooled and the excess of sulfuric acid is back-titrated with sodium hydroxide solution to Methyl Orange. Calculation proceeds according to the reaction:

$$\mathrm{2RMgX + H_2SO_4 \longrightarrow 2RH + MgSO_4 + MgX_2}$$

The results are usually somewhat too high, but normally within the limits essential for preparative purposes.

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[109] H. Gilman, J. M. Peterson, and F. Schulze, *Rec. Trav. Chim.*, **47**, 19 (1928).

[110] A. Mendel, *J. Organometal. Chem.*, **6**, 97 (1966).

[111] L. Groizeleau-Miginiac, *C. R. Hebd. Séances Acad. Sci.*, **250**, 3204 (1960).

[112] H. Gilman and co-workers, *J. Amer. Chem. Soc.*, **45**, 150 (1923).

The preparation of Grignard reagents has been described in detail by, *e. g.*, Kharasch and Reinmuth in their book "Grignard Reactions of Nonmetallic Substances".[113]

Grignard solutions cannot always be obtained from compounds containing more than one halogen atom. If the halogen atoms are separated by two or three carbon atoms, as in ethylene or trimethylene dibromide, then mostly magnesium halide is eliminated. Methylene dibromide and diiodide, however, give quite good yields of methylenebis(magnesium halide),[114] and dimagnesium compounds can also be obtained from dihalides whose halogen atoms are separated by four or more carbon atoms.[115] Nevertheless, higher homologs show some tendency to form coupling products: *e.g.*, even pentamethylene dibromide gives decamethylenebis(magnesium bromide) to some extent. It is also of importance that the differing reactivity of the halogens in compounds of the type $Cl(CH_2)_nBr$ suffices for preparation of (ω-chloroalkyl)magnesium bromides in tetrahydrofuran.[116]

Reaction of aromatic dihalides with magnesium does not occur very readily but can be induced by use of the magnesium–copper alloy activated by iodine mentioned above; for example, (*p*-bromophenyl)magnesium bromide and *p*-phenylenebis(magnesium bromide) can be obtained from *p*-dibromobenzene in this way.[117] *m*- and *p*-Phenylenebis(magnesium bromide) are formed in good yield if tetrahydrofuran is used as solvent.[118] The preparation of Grignard reagents from dihalogen compounds has been reviewed by Millar and Heaney.[69]

Perhalogenated aromatic compounds also yield Grignard reagents on reaction with magnesium: *e.g.*, (pentachlorophenyl)magnesium chloride is formed from hexachlorobenzene in tetrahydrofuran,[119] and (pentafluorophenyl)magnesium bromide from bromopentafluorobenzene.[120]

Further, at low temperatures (−30° to −65°) perfluoroalkyl iodides and bromides can be converted into the (perfluoroalkyl)magnesium halides by magnesium or magnesium amalgam.[121,122]

An interesting, different type of Grignard compound, the (alkoxymethyl)magnesium chlorides, can be obtained from alkyl chloromethyl ethers. These products decompose very easily thus:

$$2ROCH_2MgCl \longrightarrow 2ROMgCl + CH_2{=}CH_2$$

but they are stable for some time at low temperatures and can be used, like other Grignard reagents, for further reactions.[123]

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[113] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., New York, 1954.

[114] G. Emschwiller, *C. R. Hebd. Séances Acad. Sci.*, **183**, 665 (1926).

[115] J. von Braun and W. Sobecki, *Ber. Deut. Chem. Ges.*, **44**, 1918 (1911); E. Buchta and H. Weidinger, *Ann. Chem.*, **580**, 109 (1953).

[116] H. Normant and M. Noel, *C. R. Hebd. Séances Acad. Sci.*, **256**, 4230 (1963).

[117] H. Gilman and J. M. Peterson, *Proc. Acad. Iowa Sci.*, **33**, 173 (1926); *Chem. Abstr.*, **21**, 3901 (1927).

[118] M. Sander, *Chem. Ber.*, **95**, 473 (1962).

[119] H. Gilman and S.-Y. Sim, *J. Organometal. Chem.*, **7**, 249 (1967).

[120] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, **1959**, 166.

[121] R. N. Haszeldine, *J. Chem. Soc.*, **1952**, 3423; **1953**, 1748.

[122] E. T. McBee, R. D. Battershell, and H. P. Braendlin, *J. Org. Chem.*, **28**, 1131 (1963).

[123] H. Normant and B. Castro, *C. R. Hebd. Séances Acad. Sci.*, **257**, 2115 (1963); **259**, 830 (1964); B. Castro, *C. R., Hebd. Séances Acad. Sci.*, **261**, 1876 (1965); *Bull. Soc. Chim. France*, **1967**, 1533, 1540, 1547.

The same is true for the so-called *gem*-halo-Grignard reagents, CX_3—MgCl, CHX_2—MgCl, and CH_2X—MgCl, where X = Cl or Br; these compounds are obtained only by halogen–magnesium exchange between isopropylmagnesium chloride and a halogenated methane in tetrahydrofuran at low temperature.[124]

Alkoxides RMgOR′, analogous to Grignard reagents, can also sometimes be prepared directly, *e.g.*, butylmagnesium isopropoxide by reaction of magnesium with butyl chloride and isopropyl alcohol or sodium isopropoxide:[125]

$$2\text{-}C_4H_9Cl + 2Mg + CH(CH_3)_2OH \longrightarrow C_4H_9MgOCH(CH_3)_2 + C_4H_{10} + MgCl_2$$

$$C_4H_9Cl + Mg + CH(CH_3)_2ONa \longrightarrow C_4H_9MgOCH(CH_3)_2 + NaCl$$

Halogen-free organomagnesium compounds are most simply prepared by adding dioxan to the corresponding ethereal Grignard solution, whereby magnesium halide and some of the organomagnesium halide are precipitated while the MgR_2 compound remains in solution:[126]

$$MgR_2 \cdot MgX_2 \longrightarrow MgR_2 + MgX_2\downarrow$$

Immediate filtration affords yields of MgR_2 ranging between 6% from ethylmagnesium iodide to 84% from butylmagnesium chloride.[127] Shaking the precipitate in the solution for several hours increases the yield,[128] as also does adding the dioxan gradually in small portions during three days.[129]

The pure dialkylmagnesiums can be obtained from the solutions by evaporation and heating of the residual dioxanates in a high vacuum.[130]

A different synthesis of dialkyl- and diaryl-magnesiums involves treating magnesium with the corresponding organomercury compounds:[131]

$$HgR_2 + Mg \longrightarrow MgR_2 + Hg$$

The dialkyl- and diaryl-magnesiums are white, crystalline, infusible, insoluble in hydrocarbons, and almost involatile. However, all these compounds dissolve in ether and in those solvents that can form coordination complexes, *e.g.*, dioxan and pyridine. Diphenylmagnesium etherate is soluble also in benzene, but the unsolvated compound is insoluble therein.

In spite of their high reactivity, magnesium alkyls are fairly stable; *e.g.*, diethylmagnesium decomposes only above 175°, then slowly yielding magnesium hydride and ethylene with small amounts of polymeric ethylenemagnesium $(\text{—}C_2H_4Mg\text{—})_n$ and ethane:[132]

$$Mg(C_2H_5)_2 \xrightarrow[\text{vacuum}]{175\text{–}200°} 2C_2H_4 + MgH_2$$

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[124] H. Normant and J. Villieras, *C. R. Hebd. Séances Acad. Sci.*, **260**, 4535 (1965); J. Villieras, *Bull. Soc. Chim. France*, **1967**, 1511, 1520.

[125] D. Bryce-Smith and B. J. Wakefield, *Proc. Chem. Soc.*, **1963**, 376.

[126] W. Schlenk, Jr., *Ber. Deut. Chem. Ges.*, **64**, 734 (1931).

[127] G. O. Johnson and H. Adkins, *J. Amer. Chem. Soc.*, **54**, 1943 (1932).

[128] C. R. Noller and W. R. White, *J. Amer. Chem. Soc.*, **59**, 1354 (1937).

[129] R. Kullman, *C. R. Hebd. Séances Acad. Sci.*, **231**, 866 (1950).

[130] W. Strohmeier and F. Seifert, *Chem. Ber.*, **94**, 2356 (1961).

[131] H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **49**, 2328 (1927); W. Schlenk, Jr., *Ber. Deut. Chem. Ges.*, **64**, 736 (1931).

[132] E. Wiberg and R. Bauer, *Chem. Ber.*, **85**, 593 (1952).

2. Organozinc compounds

Zinc alkyls are among the longest known organometallic compounds. They were discoved in the year 1849 by Frankland when he tried to prepare what we now call ethyl radicals by the action of ethyl iodide on zinc.[133] This discovery marks the beginning of the chemistry of organometallic compounds.

Treatment of alkyl iodides with zinc, modified somewhat from Frankland's technique,[134] is still used for preparation of alkylzinc iodides. The metallic zinc is, however, replaced by a zinc–copper couple (midway between an alloy and a true mixture) that is obtained by heating zinc turnings with copper powder.[135]

A material still more active than the zinc–copper couple is obtained, according to Krug and Tang,[136] by heating a mixture of zinc dust and copper citrate until the latter is completely decomposed.

Detailed directions for the preparation of diethylzinc by treatment of ethyl iodide with a zinc–copper couple are to be found in *Organic Syntheses*.[137]

$$RI + Zn(Cu) \longrightarrow RZnI$$

$$2RZnI \xrightarrow{\text{Heat}} ZnR_2 + ZnI_2$$

The alkylzinc halides formed in this reaction are white crystalline compounds which are rarely isolated and which decompose to the dialkyl compounds when heated. Good results are obtained on use of primary or secondary alkyl iodides (sometimes mixed with the bromides). The reaction is carried out in an atmosphere of nitrogen or carbon dioxide.

Dialkylzincs can also be obtained directly, by treating alkyl iodides with a simple mixture of finely divided zinc powder and copper powder at 110°.[138]

It is usually unnecessary to use a solvent in such reactions, but one is sometimes used so that the product is obtained in solution. Ethyl acetate, often in admixture with toluene, is the solvent of choice since it accelerates the reaction appreciably. Diethyl ether can also be used, although it does not increase the rate of reaction and in some cases a little iodine must then be added to start the reaction. When higher reaction temperatures are necessary, diisopropyl or dibutyl ether is used[139] (in this connexion see the Reformatzky reaction, page 884).

Alkylzinc iodides can also be prepared in good yield from the alkyl iodide and zinc powder in a strongly solvating solvent; the accelerating action of the solvent increases in the order: isooctane < dibutyl ether < diethylene glycol dimethyl ether (diglyme) < 1,2-dimethoxyethane < dimethylformamide, dimethyl sulfoxide. In such solvents alkyl bromides also react with the zinc–copper pair, giving the alkylzinc bromide in yields of up to 80%; in dimethyl

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[133] E. Frankland, *Ann. Chem.*, **71**, 171, 213 (1849).

[134] E. Frankland, *Ann. Chem.*, **95**, 28 (1855); **111**, 44 (1859).

[135] A. Job. and R. Reich, *Bull. Soc. Chim. France*, [iv], **33**, 1414 (1923).

[136] R. C. Krug and P. J. C. Tang, *J. Amer. Chem. Soc.*, **76**, 2262 (1954).

[137] C. R. Noller, *Org. Syn.*, Coll. Vol. II, 184 (1943).

[138] N. K. Hota and C. J. Willis, *J. Organometal. Chem.*, **9**, 169 (1967).

[139] L. F. Hatch, G. Sutherland, and W. J. Ross, *J. Org. Chem.*, **14**, 1130 (1930).

sulfoxide the organozinc chloride is obtained even from benzyl or allyl chloride and zinc.[140]

Solutions of alkenyl- and alkynyl-zinc bromides suitable for further syntheses can be prepared from 2-alkenyl and 2-alkynyl bromides by zinc in tetrahydrofuran.[141]

Dialkyl- and diaryl-zincs and organozinc halides are obtained in solution when ethereal Grignard solutions are treated with anhydrous zinc chloride:[142]

$$ZnCl_2 + RMgX \longrightarrow RZnCl + MgXCl$$

$$ZnCl_2 + 2RMgX \longrightarrow ZnR_2 + 2MgXCl$$

This method can also be used to provide divinylzinc[143] and diallylzinc,[144] as well as mixed compounds of the type RZnR′ [145] (by reaction of an organozinc halide with the appropriate Grignard reagent).

The lower, more volatile dialkylzincs, such as dimethyl- and diethyl-zinc, can then be readily isolated by distillation, but their isolation in a pure state is rarely necessary as their solutions can be used directly in many cases.

Like the dialkylmagnesiums, the dialkylzincs can also be formed by the action of metallic zinc on the corresponding organomercury compounds:

$$Zn + HgR_2 \longrightarrow ZnR_2 + Hg$$

Pure diarylzincs, including nuclear-substituted ones, are best prepared either by this method, heating zinc and the diarylmercury in, *e.g.*, boiling xylene,[146,147] or from zinc chloride and phenyllithium.[148] Diarylzincs can, however, also be obtained by transmetallation, *e.g.*, by interaction of diethylzinc and the appropriate triarylboron.[149]

A special method for preparing bis(halomethyl)zincs is by the action of diazomethane on zinc halides, the mono(halomethyl)zinc halides forming intermediates:[150]

$$ZnX_2 + CH_2N_2 \longrightarrow XCH_2ZnX + N_2$$

$$XCH_2ZnX + CH_2N_2 \longrightarrow Zn(CH_2X)_2 + N_2$$

Organozinc compounds do not have the preparative importance of Grignard reagents because they are less reactive and more difficult to handle. However, they supplement the latter when, for instance, a less reactive reagent is useful. Thus reaction of acid chlorides and organozinc compounds gives ketones

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[140] L. I. Zakharkin and O. Yu. Okhlobystin, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1963**, 193; *Chem. Abstr.*, **58**, 12589 (1963).

[141] M. Gaudemar, *C. R. Hebd. Séances Acad. Sci.*, **246**, 1229 (1958).

[142] N. I. Sheverdina, I. E. Paleeva, N. A. Zaitseva, and K. A. Kocheshkov, *Dokl. Akad. Nauk S.S.S.R.*, **155**, 623 (1964); *Chem. Abstr.*, **60**, 14531 (1964).

[143] B. Bartocha, H. D. Kaesz, and F. G. A. Stone, *Z. Naturforsch.*, **14b**, 352 (1959).

[144] K.-H. Thiele and P. Zdunneck, *J. Organometal. Chem.*, **4**, 10 (1965).

[145] I. E. Paleeva, N. I. Sheverdina, and K. A. Kocheshkov, *Dokl. Akad. Nauk. S.S.S.R.*, **157**, 626 (1964); *Chem. Abstr.*, **61**, 9520 (1964).

[146] K. A. Kozeschkow, A. N. Nesmejanow, and W. I. Potrosow, *Ber. Deut. Chem. Ges.*, **67**, 1138 (1934).

[147] V. F. Martynova, *Zh. Obshch. Khim.*, **32**, 2702 (1962); *Chem. Abstr.*, **58**, 10233 (1963).

[148] W. Strohmeier, *Chem. Ber.*, **88**, 1218 (1955).

[149] K.-H. Thiele and J. Köhler, *J. Prakt. Chem.*, [iv], **32**, 54 (1966).

[150] G. Wittig and K. Schwarzenbach, *Ann. Chem.*, **650**, 1 (1961).

(see page 910):

$$(RCOCl + R'ZnI \text{ (or } ZnR'_2) \longrightarrow RCOR'$$

whereas when Grignard reagents are used the ketone that forms the primary product is partly converted into the tertiary alcohol.

Dialkylzincs are essentially stable, colorless liquids; in the absence of oxygen they can be kept indefinitely without decomposition and can be distilled at temperatures up to about 200°. At room temperature, diarylzincs are crystalline substances that have a sharp melting point.

3. Organocadmium compounds

It was a long time before the first alkylcadmiums could be obtained in satisfactory yield and with adequate purity, for, remarkably, they are much less stable thermally than the organic derivatives of the other elements of Group II. Of the alkyl derivatives, only the dimethyl compound can be kept for any length of time. The higher homologs decompose gradually even at room temperature and particularly when exposed to light. The solid diphenylcadmium is more stable.

When alkyl halides react with metallic cadmium[96,151] the primary product is probably the compound of type RCdX, as with the other elements of Group II, but so far such compounds have been obtained pure only by the action of anhydrous cadmium salts on dialkylcadmiums in anhydrous ether.[152]

When alkyl iodides react with metallic cadmium in tris(dimethylamino)-phosphorus, compounds of the composition $R_2Cd\{P[N(CH_3)_2]_3\}_2$ are obtained.[153]

Dialkyl- and diaryl-cadmiums are best prepared by reaction of an anhydrous cadmium halide with the appropriate Grignard reagent or organolithium compound;[154] perhalo compounds such as bis(pentafluorophenyl)cadmium can also be obtained in this way:[155]

$$2RMgX + CdCl_2 \longrightarrow CdR_2 + 2MgXCl$$

Dimethylcadmium: A solution of methylmagnesium bromide (0.3 mole) is prepared as usual from methyl bromide and magnesium. It is then cooled in ice and treated slowly with finely powdered, anhydrous cadmium chloride (0.16 mole). The ice-bath is then removed and the mixture is stirred for 0.5 h. Finally the color test (page 879) is applied to make sure that the Grignard reagent has been wholly consumed.

Dialkylcadmiums can be isolated by cautious distillation from a water-bath or oil-bath under diminished pressure; and diphenylcadmium can be purified by sublimation in a high vacuum.[148] In many cases, however, the organocadmium compound is not isolated, the solution obtained by reaction as above being used directly for further reaction.

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[151] I. A. Wanklyn, *J. Chem. Soc.*, **9**, 193 (1857).

[152] N. I. Sheverdina, I. E. Paleeva, Y. D. Dekinskaya, and K. A. Kocheshkov, *Dolk. Akad. Nauk S.S.S.R.*, **125**, 348 (1959); *Chem. Abstr.*, **53**, 19853 (1959).

[153] J. Chenault and F. Tatibouët, *C. R. Hebd. Séances Acad. Sci.*, *C*, **264**, 213 (1967).

[154] H. Gilman and J. F. Nelson, *Rec. Trav. Chim.*, **55**, 518 (1936); E. Krause, *Ber. Deut. Chem. Ges.*, **50**, 1813 (1917).

[155] M. Schmeisser and M. Weidenbruch, *Chem. Ber.*, **100**, 2306 (1967).

Some specific organocadmium compounds have recently become accessible by transmetallation: some very unstable compounds — they decompose above 0° with deposition of cadmium — such as diallyl-, dimethallyl-, and di-(2-butenyl)-cadmium have been prepared from the corresponding trialkenylborons and dimethylcadmium at $-10°$ to $-20°$.[156]

Organocadmium compounds are relatively unreactive towards carbonyl groups and thus, like organozinc compounds, can be used for synthesis of ketones from acid chlorides (see page 911). This matter has been reviewed by Cason.[157]

Recent investigations have shown that the reactivity of organocadmium compounds is increased by the presence of magnesium salts: if prepared in solution from a Grignard reagent and a cadmium halide, dialkylcadmiums — the members most studied — are appreciably more reactive than pure dialkylcadmiums in ether.[158]

4. Organomercury compounds

Much study has been devoted to organomercury compounds, particularly in the search for compounds of pharmacological value. They find wide use in horticulture and the number of individual members of the class is therefore extremely great; correspondingly a very large number of preparative methods have been developed covering widely varying types of organomercury compounds.

Their extreme toxicity necessitates stringent **precautions** during their preparation and handling. The toxicity of organomercury compounds is often greater than that of the mercury in them; the volatile alkylmercury class is particularly dangerous.

Organomercury compounds have only slight reactivity. They are also completely indifferent to atmospheric oxygen and to water under normal conditions and can thus be prepared and used under conditions that are not permissible for the more reactive organometallic compounds discussed above.

Some alkyl iodides react with metallic mercury in sunlight and in presence of a little elemental iodine, yielding alkylmercury iodides,[159] but the reaction is very slow.

A generally applicable method of preparing dialkyl- and diaryl-mercury compounds is by treatment of alkyl or aryl halides or alkyl sulfates with sodium amalgam:[160]

$$2RX + 2Na + Hg \longrightarrow HgR_2 + 2NaX$$

Dimethylmercury:[161] A mixture of methyl iodide (10 parts by wt.) and anhydrous methyl acetate (1 part by wt.) is placed in a round-bottomed flask carrying an efficient condenser

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[156] K.-H. Thiele and J. Köhler, *J. Organometal. Chem.*, **7**, 365 (1967).

[157] J. Cason, *Chem. Rev.*, **40**, 15 (1947).

[158] E. Henry-Basch, J. Michel, F. Huet, B. Marx, and P. Fréon, *Bull. Soc. Chim. France.*, **1965**, 927; E. Henry-Basch, J. Deniau, G. Emptoz, F. Huet, B. Marx, and J. Michel, *C. R. Hebd. Séances Acad. Sci.*, *C*, **262**, 598 (1966); J. Kollonitsch, *J. Chem. Soc.*, *A*, **1966**. 453, 456.

[159] J. L. Maynard, *J. Amer. Chem. Soc.*, **54**, 2108 (1932).

[160] K. Fuchs, *J. Prakt. Chem.*, [ii], **119**, 209 (1928).

[161] W. Schlenk, in Houben-Weyl, "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, 2nd ed, 1924, p. 924.

and is treated with 0.2% sodium amalgam (1.2 moles of sodium per mole of methyl iodide). The flask is alternately shaken and cooled in cold water (not ice, which renders the reaction too sluggish). The reaction is ended when the temperature falls and a few drops give only a trace of iodine when boiled with nitric acid. If the precipitated sodium iodide makes the mixture too pasty for adequate contact of the methyl iodide and the amalgam, it is best to distil off the remaining methyl iodide and methyl acetate on a water-bath and to treat the distillate with fresh amalgam in another flask. When reaction is complete, water is added and the mixture is distilled from an oil-bath whose temperature is not allowed to exceed 110°. The ether-like distillate is separated from the water, shaken with alcoholic potassium hydroxide solution (to remove the methyl acetate), washed well with water, dried, and fractionated. The product boils at 95°.

The simple dialkyl and diaryl mercury derivatives are, however, most conveniently prepared by reaction of mercury(II) chloride with the appropriate Grignard reagent[162,163] or other reactive organometallic compounds:[164]

$$\mathrm{RMgX + HgCl_2 \longrightarrow RHgCl + MgXCl}$$

$$\mathrm{RMgX + RHgCl \longrightarrow HgR_2 + MgXCl}$$

Perhalogenated compounds such as bis(pentachlorophenyl)mercury can also be obtained in this way.[165]

When mercury(I) salts are used, the same products result and metallic mercury separates.

The preparation of **diphenylmercury**[166] illustrates the procedure: Bromobenzene (50 g) in ether (200 ml) is converted into its Grignard compound. The residual magnesium is filtered off through glass wool, and the flask is connected to a small Soxhlet apparatus. Finely powdered mercuric chloride (26 g) is placed in the Soxhlet thimble (previously dried in an evacuated desiccator), and the Grignard solution is heated on a water-bath until the chloride has all dissolved. After a further hour's heating, the mixture is allowed to cool, then ice-water and dilute acetic acid are added, and the ethereal layer is separated (after addition of benzene if necessary) and dried. When the solvent is next removed, the residue consists of diphenylmercury mixed with some phenylmercuric chloride which may be separated because the latter is very sparingly soluble in ether. Recrystallization from ethanol gives pure diphenylmercury, m.p. 125° (25 g, more than 75% calculated on the mercuric chloride). The phenylmercuric chloride amounts to 6 g.

In this reaction the first stage is considerably faster than the second, so that organomercuric halides can be isolated. There have, for instance, been reports of the preparation of alkyl-,[167] vinyl-,[168] allyl-, propargyl-, and benzyl-mercuric halides[169] from the corresponding organo-aluminum, -magnesium, and -zinc compounds. However, most organomercuric halides are obtained more easily

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[162] C. S. Marvel and H. O. Calvery, *J. Amer. Chem. Soc.*, **45**, 820 (1923); H. Gilman and R. E. Brown, *J. Amer. Chem. Soc.*, **52**, 3314 (1930); R. E. Dessy and J.-Y. Kim, *J. Amer. Chem. Soc.*, **82**, 686 (1960); A. E. Borisov, I. S. Savel'eva, and S. R. Serdyuk, *Izv. Akad. Nauk. S.S.S.R.*, *Otd. Khim. Nauk*, **1965**, 924; *Chem. Abstr.*, **63**, 5667 (1965).

[163] P. Pfeiffer and P. Truskier, *Ber. Deut. Chem. Ges.*, **37**, 1125 (1904).

[164] G. B. Buckton, *Ann. Chem.*, **109**, 218 (1859); R. C. Friedlina, A. N. Nesmejanow, and K. A. Kozeschkow, *Ber. Deut. Chem. Ges.*, **68**, 565 (1935).

[165] F. E. Paulik, S. I. E. Green, and R. E. Dessy, *J. Organometal. Chem.*, **3**, 229 (1965).

[166] W. Schlenk, in Houben–Weyl, "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, 2nd ed, 1924, p. 927.

[167] Z. Eckstein, W. Dahllig, B. Hetnarski, and S. Pasynkiewicz, *Bull. Acad. Pol. Sci.*, *Ser. Sci. Chim. Géol.*, *Géogr.*, **8**, 161 (1960).

[168] A. N. Nesmeyanov, A. E. Borisov, I. S. Savel'eva, and E. I. Goleva, *Izv. Akad. Nauk S.S.S.R.*, *Otd. Khim. Nauk*, **1958**, 1490; *Chem. Abstr.*, **53**, 7973 (1959).

[169] M. Gaudemar, *C. R. Hebd. Séances Acad. Sci.*, **254**, 1100 (1962).

by the reaction:

$$HgR_2 + HgX_2 \longrightarrow 2RHgX$$

Unsymmetrical diaryl-, dialkyl-, and alkyl(aryl)-mercury compounds are conveniently prepared by reaction of organomercuric halides with the necessary Grignard reagent:[170]

$$RHgX + R'MgX \longrightarrow HgRR' + MgX_2$$

Alkylmercuric halides react analogously with ethynylmagnesium bromide, yielding alkyl(ethynyl) compounds of the type $RHgC{\equiv}CH$.[171]

Diarylmercury compounds can also be obtained by reduction of the arylmercuric halides or other salts obtained as above. This reduction can be effected by means of hydrazine hydrate,[172] sodium stannite,[173-175] magnesium,[176] or copper in pyridine[177] or electrolytically, *e.g.*:

$$2C_6H_5HgX + Na_2SnO_2 + 2NaOH \longrightarrow Hg(C_6H_5)_2 + Hg + 2NaX + Na_2SnO_3 + H_2O$$

Organomercuric halides can also be caused to disproportionate to HgR_2 and HgX_2 if the mercury halide is bound into a complex K_2HgX_4 by addition of potassium iodide, cyanide, or thiocyanate:[178]

$$2RHgI + 2KI \longrightarrow HgR_2 + K_2HgI_4$$

There are two main processes for direct preparation of arylmercuric salts, namely, mercuration of aromatic compounds and the so-called Nesmeyanov reaction.

In the Nesmeyanov reaction double salts of arenediazonium salts with mercuric chloride are decomposed by copper powder in cold acetone[179] or cold water:[180]

$$ArN_2Cl \cdot HgCl_2 + 2Cu \longrightarrow ArHgCl + 2CuCl + N_2$$

If an excess of copper powder is used and ammonia is finally added, the ArHgCl is reduced and a good yield of $HgAr_2$ is obtained.

Diphenylmercury: The diazonium–mercuric chloride double salt, $C_6H_5N_2Cl \cdot HgCl_2$, is first prepared: aniline is diazotized, as usual, with cooling in hydrochloric acid and, if necessary the solution is filtered rapidly through sintered glass. The filtrate is poured at once, with continuous stirring, into an equimolar solution of mercuric chloride in the same weight of concentrated hydrochloric acid containing the same amount of ice as was used in the diazotization. The precipitate is filtered off, washed with, successively, water, alcohol, and ether, and dried in the air.

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[170] S. Hilpert and G. Grüttner, *Ber. Deut. Chem. Ges.*, **48**, 906 (1915).

[171] M. Kraut and L. C. Leitch, *Can. J. Chem.*, **41**, 549 (1963).

[172] H. Gilman and M. M. Barnett, *Rec. Trav. Chim.*, **55**, 563 (1936).

[173] O. Dimroth, *Ber. Deut. Chem. Ges.*, **35**, 2853 (1902).

[174] W. Steinkopf, W. Bielenberg, and H. Augestad-Jensen, *Ann. Chem.*, **430**, 41 (1923).

[175] J. L. Maynard, *J. Amer. Chem. Soc.*, **46**, 1510 (1924).

[176] F. R. Jensen and J. A. Landgrebe, *J. Amer. Chem. Soc.*, **82**, 1004 (1960).

[177] F. Hein and K. Wagler, *Ber. Deut. Chem. Ges.*, **58**, 1499 (1925).

[178] F. C. Whitmore and R. J. Sobatzki, *J. Amer. Chem. Soc.*, **55**, 1128 (1933); R. W. Beattie and F. C. Whitmore, *J. Amer. Chem. Soc.*, **55**, 1567 (1933).

[179] A. N. Nesmejanow, *Ber. Deut. Chem. Ges.*, **62**, 1010, 1018 (1929); *Org. Syn.*, Coll. Vol. II, 432 (1943); A. N. Nesmejanow, N. T. Gluschnew, P. T. Epifansky, and A. I. Flegontow, *Ber. Deut. Chem. Ges.*, **67**, 130 (1934).

[180] A. N. Nesmeyanov, L. G. Makarova, and I. V. Polovyanyuk, *Zh. Obshch. Khim.*, **35**, 681 (1965).

The double salt (10 g) is mixed with Gattermann copper powder (8 g), and then acetone (50 ml), pre-cooled in a freezing-mixture, is poured over it. When the first energetic stage of the reaction is over, an equal volume of 25% aqueous ammonia solution is added with careful stirring and the whole is set aside for 12–24 h. An excess of water is added next, to precipitate all the organomercury compound. The precipitate is filtered off and washed with a little ether, then the symmetrical organomercury compound contained in it is extracted in benzene and recrystallized; this has m.p. 125°; the yield is 65%. If the material still contains halogen, this is removed completely by boiling with pyridine and copper.

In a variant of this process arenediazonium chlorides are decomposed directly by finely divided metallic mercury at 0–5°:[181]

$$\mathrm{ArN_2Cl + Hg \longrightarrow ArHgCl + N_2}$$

A subvariant of this is treatment of arenediazonium tetrafluoroborates with mercuric chloride and zinc(II) chloride, in which very finely divided mercury is formed as intermediate in the reaction mixture.[182]

Arylmercuric salts can be obtained with extraordinary ease by mercuration of aromatic compounds with mercury salts, the reaction involving direct replacement of hydrogen by mercury:

$$\mathrm{ArH + HgX_2 \longrightarrow ArHgX + HX}$$

The reaction is applicable to benzene, benzene derivatives,[174–176,183,184] polycyclic aromatic hydrocarbons,[185] and also heterocyclic compounds of aromatic character such as thiophen, furan, and pyridine; Volhard, for instance, in 1892 mercurated thiophen directly with mercuric chloride.[186]

Incidentally this method permits thiophen to be separated from benzene: if technical benzene is boiled with aqueous mercuric acetate solution a dimercurated thiophen derivative, 2-(acetoxymercuri)-5-(hydroxymercuri)thiophen,[187] is precipitated and after 30 minutes the benzene, which is hardly attacked at all, is free from thiophen.

This shows that aromatic compounds are not all mercurated at the same speed; in fact, amines, phenols, and aromatic ethers react especially readily, aromatic hydrocarbons such as benzene more slowly, and halo- and nitrobenzenes particularly slowly.

The rates of mercuration of halobenzenes by mercuric acetate in acetic acid, and the proportions of the isomers formed have been studied by Brown and Goldman.[188]

Aromatic hydrocarbons can be brought into reaction with mercuric acetate by boiling the mixture for several hours under reflux, which gives, for instance, an 80% yield of phenylmercuric acetate; and the yield is increased to 92% if these components are heated in glacial acetic acid under pressure at 110°.[189]

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[181] R. E. McClure and E. Lowy, *J. Amer. Chem. Soc.*, **53**, 319 (1931).

[182] M. F. W. Dunker, E. B. Starkey, and G. L. Jenkins, *J. Amer. Chem. Soc.*, **58**, 2308 (1936).

[183] O. Dimroth, *Ber. Deut. Chem. Ges.*, **31**, 2154 (1898); **25**, 2853 (1902).

[184] M. S. Kharasch and L. Chalkley, Jr., *J. Amer. Chem. Soc.*, **46**, 1211 (1924); M. S. Kharasch and J. M. Jacobsohn, *J. Amer. Chem. Soc.*, **43**, 1894 (1921).

[185] J. G. Carey and I. T. Millar, *J. Chem. Soc.*, **1962**, 3278.

[186] J. Volhard, *Ann. Chem.*, **276**, 172 (1892).

[187] O. Dimroth, *Ber. Deut. Chem. Ges.*, **32**, 759 (1899).

[188] H. C. Brown and G. Goldman, *J. Amer. Chem. Soc.*, **84**, 1650 (1962).

[189] K. A. Kobe and P. F. Lueth, Jr., *Ind. Eng. Chem.*, **34**, 309 (1942).

Phenylmercuric acetate:[175] Mercuric acetate (15 g), benzene (80 ml), and ethanol (20 ml) are boiled on a water-bath under reflux. After 5 h, further ethanol (20 ml) is added. The resulting yellow precipitate is brought into solution by adding a few ml of glacial acetic acid. After 55 h, the mixture is filtered, the filtrate is evaporated, and the residue is recrystallized from ethanol, affording phenylmercuric acetate, m.p. 149°, in 80% yield (12.6 g).

For conversion into **diphenylmercury**, a solution of the acetate (30 g) in water (300 ml) is mixed with 40% sodium hydroxide solution (125 ml) and a solution of tin(II) dichloride dihydrate (50 g) in water (125 ml) and stirred for 1 h. The mixture is then filtered and the grey residue consisting of metallic mercury and the mercury compound is extracted twice with acetone (75-ml portions), zinc powder being added to amalgamate the mercury. The diphenylmercury is precipitated from the acetone solution by water and is recrystallized, then having m.p. 124.5° (13.2 g, 95.6%).

Contrary to earlier views, the effect of substituents in the aromatic nucleus on the point of entry of the mercury is the same as in other electrophilic substitutions. For instance, mercuration of toluene gives mainly the *ortho*- and the *para*-compound, and that of nitrobenzene gives mainly the *meta*-derivative. However, at elevated temperatures mercuric acetate is not very selective and mixtures of the possible isomers are obtained. Mercuric perchlorate is much more specific; *e.g.*, in 60% perchloric acid at 23° nitrobenzene is mercurated to the extent of 89% in the *meta*-position.[190]

Mercuric perchlorate is a very much more powerful mercurating agent than the more covalent mercuric acetate: toluene is only very slowly mercurated by mercuric acetate at room temperature but addition of a little perchloric acid accelerates the reaction by a factor of about 2000.[191]

Thiophen and furan are both very readily mercurated; the mercury enters at the 2-position or, if that is occupied, at the 3-position; if an excess of mercuric acetate is used, further hydrogen atoms can be replaced by acetoxymercuri groups, in fact all four in the case of furan.

Polymercuration occurs only as an unimportant side reaction when an excess of the aromatic compound is used; and under these conditions no diorganomercury compound is obtained since in the presence of the liberated acid the HgR_2 compounds are unstable, being cleaved by acid to RHgX compounds.

Other types of organic mercury derivative are formed by addition of mercury salts to olefins;[192] for example, when ethylene is passed into an aqueous mercuric acetate solution, a basic mercury salt adds to the C=C double bond:

$$CH_2{=}CH_2 + Hg(OOCCH_3)_2 + H_2O \longrightarrow HOCH_2CH_2HgOOCCH_3 + CH_3COOH$$

The mechanism and stereochemistry of this 'hydroxymercuration' has been investigated by Traylor and Baker.[193]

Replacing the water in the above reaction by methanol leads to "methoxymercuration". A suspension of mercuric acetate in methanol absorbs a mole of ethylene within an hour, giving (2-methoxyethyl)mercuric acetate:[194]

$$CH_2{=}CH_2 + Hg(OOCCH_3)_2 + CH_3OH \longrightarrow CH_3OCH_2{-}CH_2HgOOCCH_3 + CH_3COOH$$

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[190] W. J. Klapproth and F. H. Westheimer, *J. Amer. Chem. Soc.*, **72**, 4461 (1950).

[191] H. C. Brown and C. W. McGary, Jr., *J. Amer. Chem. Soc.*, **77**, 2300, 2306, 2310 (1955).

[192] J. Chatt, *Chem. Rev.*, **48**, 7 (1951).

[193] T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963).

[194] W. Schoeller, W. Schrauth, and W. Esser, *Ber. Deut. Chem. Ges.*, **46**, 2864 (1913).

Cycloalkenes[195] and unsaturated carboxylic esters such as ethyl acrylate[196] react analogously.

Additions similar to those in water and methanol can be effected with other alcohols and with organic acids as solvent and yield the corresponding alkoxy and acyloxy derivatives as, for example, Spengler and Weber[197] have shown for styrene and ethyl cinnamate.

Mercurations of this type can be used for separation of olefins from saturated hydrocarbons[198] and of unsaturated from saturated aliphatic acids.[199]

Not only mercuric acetate but also other mercury salts such as the nitrate, sulfate, and chloride can be used, but then a base must be added to neutralize the strong acid liberated in the reaction. Without such an addition an equilibrium is reached because the adducts are decomposed to the starting materials by strong acids.

Acetylenes add mercury salts similarly to olefins, but in these cases even in the presence of strong acids; *e.g.*, (*trans*-2-chlorovinyl)mercuric chloride is obtained by passing acetylene into a solution of mercuric chloride in 15% hydrochloric acid.[200]

These adducts must not be confused with mercury acetyleides, which have the structure $(RC{\equiv}C)_2Hg$ and are obtained from mercuric oxide and the acetylene $RC{\equiv}CH$.

Mercuric chloride reacts with dehydrobenzene giving bis(chlorophenyl)-mercury.[201]

Organomercury compounds can also be obtained in preparatively useful quantitites by the action of radicals on metallic mercury. For example, arylmercuric compounds are formed on decomposition of arenediazonium salts in the presence of metallic mercury;[28] and when 3-iodopropionitrile is reduced electrolytically at a mercury cathode, the radicals produced react with the cathode material forming bis-(2-cyanoethyl)mercury.[202] Organomercury compounds are also obtained analogously on reduction of ketones at a mercury cathode.[203]

III. Organic derivatives of elements of the Third Group

Organic derivatives of the general formula R_3M can be prepared from all the elements of Group III. In these compounds the metal–carbon bond is more covalent than in the corresponding compounds of Group II elements, so that the Group III compounds are much less reactive. For instance, only

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[195] V. I. Sokolov, L. L. Troitskaya, and O. A. Reutov, *Zh. Org. Khim.*, **1**, 1579 (1965); *Chem. Abstr.*, **64**, 752 (1966).

[196] K. L. Mallik and M. N. Das, *J. Amer. Chem. Soc.*, **82**, 4269 (1960).

[197] G. Spengler and A. Weber, *Brennstoff-Chem.*, **40**, 22, 55 (1959).

[198] G. Spengler, H. Frömmel, R. Schäff, P. Faul, and P. Lonsky, *Brennstoff-Chem.*, **37**, 47 (1956).

[199] E. Jantzen and H. Andreas, *Chem. Ber.*, **92**, 1427 (1959).

[200] A. N. Nesmeyanov and R. Kh. Freidlina, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1945**, 150; *Chem. Abstr.*, **40**, 3451 (1946).

[201] C. Tseng, S. Tung, and K. Chang, *Scientia Sinica*, **13**, 1170 (1964).

[202] A. P. Tomilov, Yu. D. Smirnov, and S. Varshavskii, *Zh. Obshch. Khim.*, **35**, 391 (1965); *Chem. Abstr.*, **63**, 5238 (1965).

[203] T. Arai, *Bull. Chem. Soc. Japan*, **32**, 184 (1959).

one alkyl group of trialkylaluminums enters into the reaction with carbonyl compounds:

$$R_2CO + AlR'_3 \longrightarrow R_2R'C\text{—}O\text{—}AlR'_2$$

The chemical behavior of Group III elements carrying three organic groups is very greatly influenced by the electron deficiency of the aluminum valency shell. The absence of one electron pair has the result that trialkyl derivatives of these elements react extremely easily with oxygen and other electron donors.

1. Organoboron compounds

Interest in organoboron compounds has intensified in recent years; numerous reviews have appeared of the whole field[204] and, more so, of the intensively studied areas of the organoboron heterocycles[205] and carboranes.[206]

Trialkyl- and triaryl-borons have often been prepared from a boron halide or boric ester by means of a more reactive organometallic compound, usually a Grignard reagent. The halide that is most convenient in use is boron trifluoride as its stable etherate:[207]

$$BF_3 + 3RMgX \longrightarrow BR_3 + 3MgFX$$

The reaction can be extended to yield tris(pentafluorophenyl)boron from (pentafluorophenyl)magnesium bromide.[208]

Other methods of preparing trialkylborons are by treatment of trialkylaluminums or dialkylzincs with boric triesters,[209] metaboric ester $(RBO_2)_n$,[210] or mixtures of boric esters and diboron trioxide.[211]

Alkylboron halides of the types RBX_2 and R_2BX can be obtained by reaction of boron trihalides with dialkylzincs[212] or tetraalkyltins:[213]

$$2BX_3 + R_4Sn \longrightarrow 2RBX_2 + R_2SnX_2$$

$$BX_3 + R_4Sn \longrightarrow R_2BX + R_2SnX_2$$

but methylboron chlorides are not stable, disproportionating readily into trimethylboron and boron trichloride. Boron trichloride and tetravinyltin

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[204] M. F. Lappert, *Chem. Rev.*, **56**, 959 (1956); R. M. Adams, Advances in Chemistry Series No. **23**, 87 (1959).

[205] P. M. Maitlis, *Chem. Rev.*, **62**, 223 (1962); M. J. S. Dewar, Advances in Chemistry Series No. **42**, 227 (1964); *Progr. Boron Chem.*, **1**, 235 (1964); R. Köster, *Advan. Organometal. Chem.*, **2**, 257 (1964); *Progr. Boron Chem.*, **1**, 289 (1964).

[206] T. Onak, *Advan. Organometal. Chem.*, **3**, 263 (1965); K. Issleib, R. Lindner, and A. Tzschach, *Z. Chem.*, **6**, 1 (1966); R. Köster and M. A. Grassberger, *Angew. Chem. Int. Ed., Engl.*, **6**, 218 (1967).

[207] E. Krause and R. Nitsche, *Ber. Deut. Chem. Ges.*, **54**, 2784 (1921); **55**, 1261 (1922); J. R. Johnson, H. R. Snyder, and M. G. Van Campen, Jr., *J. Amer. Chem. Soc.*, **60**, 115 (1938); E. Krause and H. Polack, *Ber. Deut. Chem. Ges.*, **61**, 271 (1928); H. C. Brown, *J. Amer. Chem. Soc.*, **67**, 374 (1945); J.-P. Laurent, *Bull. Soc. Chim. France.* **1963**, 558.

[208] J. L. W. Pohlmann and F. E. Brinckman, *Z. Naturforsch.*, **20b**, 5 (1965).

[209] Austrian Patent 201,073; East German Pat. 19,083.

[210] L. I. Zakharkin and O. Yu. Okhlobystin, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1959**, 1135; *Chem. Abstr.*, **54**, 1269 (1960).

[211] Ger. Pat. 1,067,814; *Chem. Abstr.*, **55**, 13291 (1961).

[212] E. Wiberg and W. Ruschmann, *Ber. Deut. Chem. Ges.*, **70**, 1583 (1937).

[213] W. Gerrard, E. F. Mooney, and R. G. Rees, *J. Chem. Soc.*, **1964**, 740.

give vinylboron dichloride analogously.[214] Diaryl derivatives of mercury can be used in the same way for preparation of arylboron halides,[215] *e.g.*:

$$BCl_3 + (C_6H_5)_2Hg \longrightarrow C_6H_5BCl_2 + C_6H_5HgCl$$

$$C_6H_5BCl_2 + (C_6H_5)_2Hg \longrightarrow (C_6H_5)_2BCl + C_6H_5HgCl$$

Esters of alkyl- and aryl-boron acids can be obtained analogously by reaction of a trialkyl borate with an appropriate Grignard reagent:[216]

$$B(OR)_3 + R'MgX \longrightarrow R'B(OR)_2 + MgX(OR)$$

Two further methods of preparing organoboron compounds have been the subject of fairly recent detailed study, namely, reaction of boron halides with hydrocarbons and addition of boron hydrides to olefins. For instance, arylboron dihalides are formed when boron trihalides are heated with aromatic hydrocarbons, aluminum chloride, and aluminum powder,[217] and phenylboron dibromide has been prepared analogously.[218] Further, boron halides such as diboron tetrachloride and tetrafluoride add to olefins, yielding bis(dichloroboryl) and bis(difluoroboryl) compounds:[219]

$$CHR{=}CHR' + B_2X_4 \longrightarrow X_2B{-}CHR{-}CHR'{-}BX_2$$

Triethylboron is formed when diborane is heated with an excess of ethylene at 100°:[220]

$$6C_2H_6 + B_2H_6 \longrightarrow 2B(C_2H_5)_3$$

This very interesting reaction[221] can be extended to other olefins, to which the diborane often adds at or only slightly above room temperature.[222] Brown and his co-workers used a variant to prepare trialkylborons by reactions of ethylene, its homologs, and cycloalkenes with sodium tetrahydroborate–aluminum chloride or similar reagents, in some cases at room temperature.[223] A similar synthesis of trialkylborons was found by Ashby when he heated *N,N,N*-trialkylborazanes with olefins for 4 hours at 200°:[224]

$$H_3B{\cdot}NR_3 + 3R'CH{=}CH_2 \longrightarrow NR_3 + B(CH_2CH_2R')_3$$

Further, cyclic organoboron compounds are formed on treatment of diborane or *N,N,N*-trialkylborazanes with diolefins;[225] and substituted boron hydrides such as tetraalkyldiboranes react with olefins and diolefins in analogous ways.[226]

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[214] G. C. Brown, B. E. Deuters, W. Gerrard, and D. B. Green, *Chem. & Ind* (*London*) **1965**, 1634.

[215] A. Michaelis, *Ber. Deut. Chem. Ges.*, **27**, 244 (1894); *Ann. Chem.*, **315**, 19 (1901).

[216] E. Khotinsky and M. Melamed, *Ber. Deut. Chem. Ges.*, **42**, 3090 (1909); H. R. Snyder, J. A. Kuck, and J. R. Johnson, *J. Amer. Chem. Soc.*, **60**, 105 (1938); **82**, 4163 (1960).

[217] E. L. Muetterties, *J. Amer. Chem. Soc.*, **81**, 2597 (1959).

[218] Z. J. Bujwid, W. Gerrard, and M. F. Lappert, *Chem. & Ind.* (*London*), **1959**, 1091.

[219] P. Ceron, A. Finch, J. Frey, T. Parsons, G. Urry, and H. I. Schlesinger, *J. Amer. Chem. Soc.*, **81**, 6368 (1959).

[220] D. P. Hurd, *J. Amer. Chem. Soc.*, **70**, 2053 (1948).

[221] R. S. Brokaw and R. N. Pease, *J. Amer. Chem. Soc.*, **72**, 3237 (1950); A. T. Whatley and R. N. Pease, *J. Amer. Chem. Soc.*, **76**, 835 (1954).

[222] F. G. Stone and H. J. Emeléus, *J. Chem. Soc.*, **1950**, 2755.

[223] H. C. Brown and co-workers, *J. Amer. Chem. Soc.*, **78**, 5694 (1956); **82**, 4233 (1960); *J. Org. Chem.*, **22**, 1136, 1137 (1957).

[224] E. C. Ashby, *J. Amer. Chem. Soc.*, **81**, 4791 (1959).

[225] R. Köster, *Angew. Chem.*, **71**, 520 (1959); **72**, 626 (1960).

[226] R. Köster, G. Griasnow, W. Larbig, and P. Binger, *Ann. Chem.*, **672**, 1 (1964).

Heating an alkylated diborane such as tetraethyldiborane with a large excess of benzene in an autoclave at 180–200° affords triphenylboron, hydrogen and the alkyl groups being split off, the latter as saturated hydrocarbon;[227] the excess of benzene is required to avoid formation of more complex boron compounds.

Some organoboron compounds can also be obtained by transmetallations; for example, the alkyl groups of trialkylborons are replaced stepwise by benzyl groups on treatment of the compounds with benzylmagnesium bromide.[228]

Except for trimethylboron, which is a gas at room temperature, the trialkylborons are colorless liquids, but the triarylborons are crystalline. Unlike the alkyl derivatives of other elements of the Third Group, alkylborons are monomeric; they are unaffected by water but react with halogens and hydrogen halides, yielding organic boron halides.

Trialkylborons are extremely sensitive to oxygen; the lower members inflame in air and burn with a green flame; controlled oxidation affords the derived boric esters R_2BOR and $RB(OR)_2$, but under suitable conditions the alkyl boron peroxides R_2BOOR and $RB(OOR)_2$ that are the primary products can also be isolated.[229]

Organoboron compounds form a very wide variety of coordination compounds with electron-donors, including uncharged molecules such as amines that contain an electron-donor atom; amines give adducts of the type $R_3B \leftarrow NR'_3$; however, unlike alkylaluminums, they do not give stable etherates at room temperature.

Carbanions can also function as electron-donors to organoboron compounds; the products are complex ions. Thus reaction of trimethylboron with methyllithium in ethereal solution affords lithium tetramethylborate. The aromatic analog, sodium tetraphenylborate $Na[B(C_6H_5)_4]$, is an important reagent for gravimetric determination of potassium and a number of other ions, because lithium and sodium tetraphenylborate are soluble in water whereas the potassium, rubidium, cesium, and ammonium salts are almost completely insoluble therein.

2. Organoaluminum compounds

In a process that served for the preparation of the first organoaluminum compound (1865),[230] the trialkyl and, more so, the triaryl compounds can be conveniently obtained by treating metallic aluminum with the relevant organomercury compound.[147,231,232] This method is too expensive when large

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[227] R. Köster, K. Reinert, and K. H. Müller, *Angew. Chem.*, **72**, 78 (1960).

[228] G. E. Kacheishvili, N. I. Pirtskhalava, and G. D. Dzhiashvili, *Zh. Obshch. Khim.* **35**, 484 (1965); *Chem. Abstr.*, **63**, 622 (1965).

[229] M. H. Abraham and A. G. Davies, *J. Chem. Soc.*, **1959**, 429; A. G. Davies, *Progr. Boron Chem.*, **1**, 265 (1964).

[230] G. B. Buckton and W. Odling, *Ann. Chem.*, Suppl. **4**, 109 (1865).

[231] E. Krause and P. Dittmar, *Ber. Deut. Chem. Ges.*, **63**, 2401 (1930); S. Hilpert and G. Grüttner, *Ber. Deut. Chem. Ges.*, **45**, 2828 (1912); A. N. Nesmeyanov and N. N. Novikova, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1942**, 372; *Chem. Abstr.*, **39**, 1637 (1945); C. G. Bamford, D. L. Levi, and D. M. Newett, *J. Chem. Soc.*, **1946**, 468.

[232] K. S. Pitzer and H. S. Gutowski, *J. Amer. Chem. Soc.*, **68**, 2204 (1946).

quantitites of the organoaluminum compound are required, but it has the advantage that it provides the products free from solvent.

The action of alkyl halides on metallic aluminum leads to organoaluminum halides:[233]

$$2Al + 3RX \longrightarrow R_2AlX + RAlX_2$$

The corresponding arylaluminum halides can be obtained if aluminum is activated by grinding it with a little aluminum chloride in a percussion mill before being treated with the aryl halide.[234]

On treatment with methyl iodide and iodine, aluminum gives a good yield of pure methylaluminum diiodide:[235]

$$2Al + 2CH_3I + I_2 \longrightarrow 2CH_3AlI_2$$

Of the alkylaluminum halides, the chlorides are very stable, but the bromides and particularly the iodides disproportionate readily when heated, affording the trialkyl and trihalo compounds. Thus trimethylaluminum is obtained directly when aluminum is heated with methyl iodide:[232]

$$2Al + 3CH_3I \longrightarrow Al(CH_3)_3 + AlI_3$$

Organoaluminum halides, obtained as above, can also be converted into trialkylaluminums by reduction with alkali metals; and, conversely, alkylaluminum chlorides can be obtained from trialkylaluminums and aluminum chloride.[236]

Dialkylaluminum halides react with diazomethane at low temperatures, yielding nitrogen and very unstable dialkyl(halomethyl)aluminums.[237]

Trialkylaluminums can be obtained by direct reaction with an alkyl halide if an alloy of aluminum with a more electropositive metal (magnesium) is used:[238]

$$Al_2Mg_3 + 6RX \longrightarrow 2AlR_3 + 3MgX_2$$

Organoaluminum compounds are also formed on reaction of Grignard reagents with aluminum halides, this method having afforded, for instance, perhalo compounds such as tris(pentafluorophenyl)aluminum[208] and unsaturated compounds such as tris-(4-pentenyl)- and tris-(2-butenyl)-aluminum.[239] These reactions are effected in the usual way, in ether, but the products are always obtained as their very stable etherates $R_3Al \cdot O(C_2H_5)_2$; these adducts can be isolated from the reaction solution and can be purified, sometimes by distillation, and sometimes, as in the case of the crystalline tri-*tert*-butylaluminum-1-diethyl ether,[240] by sublimation in a vacuum. Trialkyl- and

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[233] A. von Grosse and I. M. Mavity, *J. Org. Chem.*, **5**, 106 (1940); V. Grignard and R. J. Jenkins, *C. R. Hebd. Séances Acad. Sci.*, **179**, 89 (1924); V. F. Hnizda and C. A. Kraus, *J. Amer. Chem. Soc.*, **60**, 2276 (1938).

[234] D. Wittenberg, *Ann. Chem.*, **654**, 23 (1962).

[235] D. Lehmkuhl, *Ann. Chem.*, **705**, 40 (1967).

[236] H. Reinheckel and K. Haage, *J. Prakt. Chem.*, [iv], **33**, 70 (1966).

[237] H. Hoberg, *Angew. Chem.*, **73**, 114 (1961).

[238] E. Krause and B. Wendt, *Ber. Deut. Chem. Ges.*, **56**, 466 (1923).

[239] L. I. Zakharkin and L. A. Savina, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1964**, 1222; *Chem. Abstr.*, **61**, 12023 (1964).

[240] H. Lehmkuhl, *Angew. Chem. Int. Ed., Engl.*, 3, 640 (1964).

triaryl-aluminums can be prepared free from ether if the organomagnesium derivative is prepared in a hydrocarbon solvent such as isooctane or dodecane.[241,242]

The less reactive organometallic compounds of silicon and lead also convert aluminum chloride into organoaluminum chlorides.[243]

The syntheses discovered by Ziegler and his colleagues have made organoaluminum compounds readily accessible on a large scale. Starting from the observation that ethylene and its higher homologs add smoothly to aluminum hydride, yielding triethylaluminum and its homologs with the aluminum bound exclusively to a primary carbon atom,[244] they developed a process that affords trialkylaluminums directly on bringing together an olefin, hydrogen, and aluminum under specified, easily maintainable conditions:[245]

$$\mathrm{Al} + 3\mathrm{C}_n\mathrm{H}_{2n} + 1.5\mathrm{H}_2 \longrightarrow (\mathrm{C}_n\mathrm{H}_{2n+1})_3\mathrm{Al}$$

The reaction concerns primarily olefins containing a $\mathrm{CH_2{=}C}\langle$ group, *i.e.*, ethylene and its mono- and di-substituted derivatives, but, as Bruno showed,[246] is also applicable to non-terminal olefins, then yielding secondary-organic derivatives. Of the terminal olefins, 1,1-disubstituted ethylenes, *e.g.*, isobutene, are converted directly into trialkylaluminums by activated aluminum and hydrogen in the presence of a little pre-formed trialkylaluminum. With other olefins, particularly with ethylene itself, the synthesis cannot be carried out in this way because at the requisite temperature of about 120° the primary product reacts further to give a mixture of higher alkylaluminums. To get round this difficulty the synthesis is divided into two stages:

$$2(\mathrm{C}_n\mathrm{H}_{2n+1})_3\mathrm{Al} + \mathrm{Al} + 1.5\mathrm{H}_2 \longrightarrow 3(\mathrm{C}_n\mathrm{H}_{2n+1})_2\mathrm{AlH}$$

$$3(\mathrm{C}_n\mathrm{H}_{2n+1})_2\mathrm{AlH} + 3\mathrm{C}_n\mathrm{H}_{2n} \longrightarrow 3(\mathrm{C}_n\mathrm{H}_{2n+1})_3\mathrm{Al}$$

The first of these reactions is carried out at 110–140°/50–200 atm; the second occurs at 80–100° or, in the case of ethylene at even lower temperature. For the synthesis of ethylene a pressure of at most 10 atm is used.[247]

The process can thus be made to yield the trialkylaluminum or the dialkylaluminum hydride at will. The latter are also obtained if the trialkylaluminum is heated with hydrogen under pressure at 140–160°:[248]

$$\mathrm{R_3Al} + \mathrm{H_2} \longrightarrow \mathrm{RH} + \mathrm{R_2AlH}$$

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[241] L. I. Zakharkin, O. Yu. Okhlobystin, and B. N. Strunin, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1961**, 2254; **1962**, 2002; *Chem. Abstr.*, **57**, 13799 (1962); **58**, 9131 (1963).

[242] L. I. Zakharkin, O. Yu. Okhlobystin, and B. N. Strunin, *Dokl. Akad. Nauk S.S.S.R.*, **144**, 1299 (1962); *Chem. Abstr.*, **57**, 12515 (1962).

[243] W. E. Evison and F. S. Kipping, *J. Chem. Soc.*, **1931**, 2774; H. Gilman and L. D. Apperson, *J. Org. Chem.*, **4**, 162 (1939).

[244] K. Ziegler, *Angew. Chem.*, **64**, 323 (1952); K. Ziegler, H. G. Gellert, H. Martin, K. Nagel, and J. Schneider, *Ann. Chem.*, **589**, 91 (1954).

[245] K. Ziegler, H. G. Gellert, K. Zosel, W. Lehmkuhl, and W. Pfohl, *Angew. Chem.*, **67**, 424 (1955).

[246] G. Bruno, *J. Org. Chem.*, **30**, 623 (1965).

[247] K. Ziegler, H. G. Gellert, H. Lehmkuhl, W. Pfohl, and K. Zosel, *Ann. Chem.*, **629**, 1 (1960).

[248] R. Köster, *Angew. Chem.*, **68**, 383 (1956); R. Köster, H. Lehmkuhl, and G. Bruno, East German Pat 16,560; Austrian Pat. 202,566.

A further synthesis of certain trialkylaluminums and dialkylaluminum hydrides is afforded by the observation that trialkylaluminums, *e.g.*, the triisobutylaluminum that is readily available by the above process, undergoes exchange reactions when warmed with other olefins:[246,249]

$$(\text{iso-}C_4H_9]_3Al + 3C_nH_{2n} \longrightarrow (C_nH_{2n+1})_3Al + 3\text{-iso-}C_4H_8$$

In principle the reaction is carried out by treating the triisobutylaluminum with the desired olefin, a little benzene, toluene, or heptane being added, if necessary, to obtain a defined boiling point, and the mixture is then simply boiled. A temperature above 100° is needed for smooth reaction; however, for terminal olefins $RCH{=}CH_2$ the temperature must not appreciably exceed 110° as then a certain amount of catalytic dimerization occurs.

For low-boiling or sensitive olefins it is advisable to divide the "replacement reaction" into two steps: the first step, carried out above 100°, is fission of the triisobutylaluminum into isobutene and diisobutylaluminum hydride; then 1 mole of the new olefin is added at 70–80°; by repeating both operations twice more, namely, removal of isobutene at the higher temperature (up to 150°) and addition of the new olefin at the lower temperature, all the isobutyl groups are finally replaced by the new alkyl group.

The procedure can also be varied so that the olefin is added slowly; then at any one moment more isobutene is split off than olefin is added, and the solution always contains free dialkylaluminum hydride, whereby secondary reactions are avoided. Finally the temperature is lowered to 70–80° and the remaining Al–H bonds are broken by adding the remainder of the olefin.

An excess of the olefin must be used when it does not react completely with dialkylaluminum hydrides but instead enters into an equilibrium:

$$R_2AlH + C_nH_{2n} \rightleftarrows R_2(C_nH_{2n+1})Al$$

the excess is finally removed by distillation in a vacuum, the temperature being kept as low as possible so as to avoid the reverse fission.

As mentioned above, at higher than a certain temperature a trialkylaluminum reacts with olefins of the general formula $RCH{=}CH_2$, and in particular with ethylene, in such a way that addition to the double bond occurs. With ethylene this leads to a "build-up" reaction in which a mixture of higher alkylaluminums is formed.

This addition of alkylaluminums to ethylene occurs smoothly at 90–120° according to the reaction:[250]

$$R\text{—al} + nC_2H_4 \longrightarrow R\text{—}(C_2H_4)_n\text{—al} \qquad \text{al} = Al/3$$

starting from ethylene, aluminum, and some hydrogen then leads to synthesis of almost all even-membered primary aliphatic compounds, *e.g.*, primary alcohols,[251] and equally to all even-membered *n*-alkanes and terminal olefins.[252] Synthesis of the corresponding compounds with an odd number of carbon atoms is achieved analogously by starting from tripropylaluminum and ethylene.

The "build-up" reaction, *i.e.*, smooth stepwise addition of ethylene, always overlaps the "replacement reaction", thus:

$$R(CH_2CH_2)_n\text{—al} + C_2H_4 \longrightarrow R(CH_2CH_2)_{n-1}\text{—}CH{=}CH_2 + C_2H_5\text{—al}$$

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[249] K. Ziegler, H. Martin, and F. Krupp, *Ann. Chem.*, **629**, 14 (1960); K. Ziegler, W. R. Kroll, W. Larbig, and O. W. Steudel, *Ann. Chem.*, **629**, 53 (1960).

[250] K. Ziegler, H. G. Gellert, K. Zosel, E. Holzkamp, J. Schneider, M. Söll, and W.-R. Kroll, *Ann. Chem.*, **629**, 121 (1960).

[251] K. Ziegler, F. Krupp, and K. Zosel, *Ann. Chem.*, **629**, 241 (1960).

[252] K. Ziegler, H. G. Gellert, E. Holzkamp, G. Wilke, E. W. Duck, and W. R. Kroll, *Ann. Chem.*, **629**, 172 (1960).

in which an olefin is split off. This side reaction becomes unimportant if the pressure is high enough; an ethylene pressure of about 100 atm has proved satisfactory.

With higher terminal olefins the "build-up" reaction leads only to a catalytic dimerization, since in such cases the replacement follows immediately on the addition:

$$\mathrm{RCH_2CH_2{-}al + R{-}CH{=}CH_2 \longrightarrow}$$

$$\mathrm{RCH_2CH_2CHRCH_2{-}al} \qquad \text{(addition)}$$

$$\mathrm{RCH_2CH_2CHRCH_2{-}al + RCH{=}CH_2 \longrightarrow}$$

$$\mathrm{RCH_2CH_2CR{=}CH_2 + RCH_2CH_2{-}al} \qquad \text{(replacement)}$$

Trialkylaluminums can also be added to acetylenes, giving further types of organoaluminum compound. For example, at temperatures as low as 40–60° 1 mole each of triethylaluminum and acetylene afford diethyl-(1-butenyl)aluminum:[253]

$$\mathrm{(C_2H_5)_3Al + CH{\equiv}CH \longrightarrow (C_2H_5)_2Al{-}CH{=}CHC_2H_5}$$

When organoaluminum hydrides react with acetylenes, a variety of products is formed: not only mono- and di-addition to the triple bond, but also replacement of the ethynyl-hydrogen with removal of hydrogen, take place.[254] The last of these reactions, which is a metallation, becomes the main reaction when a complex aluminum hydride $MAlH_4$ (M = Li, Na, or K) reacts with an acetylene, so that complex acetylenylaluminates $MAl(C{\equiv}CR)_4$ can be obtained in this way.[255]

With electron-donor molecules organoaluminum compounds form coordination compounds that are much more stable than those of boron. For example, with ethers such as diethyl ether,[238,256] anisole,[257] and the like they give extremely stable etherates, and some of these can be distilled without decomposition even though they boil at higher temperatures than the solvent-free compounds.

Carbon ions also add as electron donors; *e.g.*, the appropriate organolithium and -aluminum compounds give the salts, lithium tetramethylaluminate $Li[Al(CH_3)_4]$ and lithium tetraphenylaluminate $Li[Al(C_6H_5)_4]$.[258] Similarly, with trialkylaluminums many alkali halides and cyanides afford complex compounds containing coordinatively quadrivalent aluminum and having the composition $M[AlR_3X]$ or $MX \cdot 2AlR_3$ where M is an alkali metal and X is a halide or cyanide;[259] and salts $K[AlR_2X_2]$ are formed analogously from a dialkylaluminum chloride and potassium chloride.[260]

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[253] G. Wilke and H. Müller, *Ann. Chem.*, **629**, 222 (1960).

[254] J. R. Surtees, *Aust. J. Chem.*, **18**, 14 (1965); V. V. Markova, V. A. Kormer, and A. A. Petrov, *Zh. Obshch. Khim.*, **35**, 447 (1965); *Chem. Abstr.*, **63**, 1688 (1965).

[255] L. I. Zakharkin and V. V. Gavrilenko, *Izv. Akad. Nauk S.S.S.R.*, *Otd. Khim. Nauk*, **1963**, 1146; Chem. Abstr., 59, 8772 (1963); P. Chini, A. Baradel, E. Pauluzzi, and M. de Maldé, *Chim. e Ind.* (*Milan*), **44**, 1220 (1962).

[256] E. A. Baker and H. H. Sisler, *J. Amer. Chem. Soc.*, **75**, 4828 (1953).

[257] G. Geiseler and W. Knothe, *Chem. Ber.*, **91**, 2446 (1958).

[258] D. T. Hurd, *J. Org. Chem.*, **13**, 711 (1948); G. Wittig and co-workers, *Ann. Chem.*, **563**, 110 (1949); **573**, 195 (1951).

[259] K. Ziegler, R. Köster, H. Lehmkuhl, and K. Reinert, *Ann. Chem.*, **629**, 33 (1960).

[260] R. Köster and W. R. Kroll, *Ann. Chem.*, **629**, 50 (1960).

An interesting reaction is that of the salt Na[Al$(C_2H_5)_4$Cl] with benzene in the presence of sodium alkoxide; this gives ethane and sodium tetraphenylaluminate Na[Al$(C_6H_5)_4$], from which triphenylaluminum can be obtained by means of dimethylaluminum chloride. This opens the way to obtain phenylaluminum compounds from the ethylaluminum compounds that are readily accessible by direct synthesis.[261]

The tendency of various types of organoaluminum compounds to form complexes with various Lewis bases, and the replacement reactions that can lead to new complex compounds, have been reviewed by Lehmkuhl.[262]

Alkylaluminums have become very important as mixed catalysts for low-pressure polymerization of olefins (especially ethylene), a reaction discovered by Ziegler and his colleagues.[263] Numerous investigations have been devoted to a study of the mechanism of this reaction; *e.g.*, it has been shown that an important role in the polymerization is played by the organotitanium compounds formed from mixtures of alkylaluminums and titanium tetrachloride.[264]

The alkylaluminums that are now readily accessible by direct synthesis can also be used for preparation of alkyl derivatives of other metals and metalloids.[265]

IV. Organic derivatives of elements of the Fourth Group

The organic derivatives of silicon, germanium, tin, and lead belong among the most stable and unreactive of organometallic compounds. They enjoy very great industrial importance, *e.g.*, the Silicones, certain organotin compounds (as stabilizers for polyvinyl chloride), tetraethyllead (as anti-knock), etc.[266]

Petrov and Mironov[267] have reviewed recent investigations of organo-silicon, -germanium, and -tin compounds, especially those containing unsaturated hydrocarbon groups such as vinyl and ethynyl, including their preparation and reactions.

1. Organosilicon compounds[268]

Organosilicon chemistry is an extremely extensive field; it includes, besides the tetraalkyl- and tetraaryl-silanes, the most varied types of organosilicon

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[261] H. Lehmkuhl and R. Schäfer, *Ann. Chem.*, **705**, 33 (1967).

[262] H. Lehmkuhl, *Angew. Chem.*, **75**, 1090 (1963).

[263] K. Ziegler, E. Holzkamp, H. Briel, and H. Martin, *Angew. Chem.*, **67**, 541 (1955).

[264] C. Beermann and H. Bestian, *Angew. Chem.*, **71**, 618 (1959).

[265] H. Jenker, *Chem.-Ztg.*, **86**, 527, 563 (1962).

[266] M. Dub, "Organometallic Compounds; Methods of Synthesis, Physical Constants, and Chemical Reactions." Vol. 2. "Compounds of Germanium, Tin, and Lead, including Biological Activity and Commercial Application," Springer Verlag, Berlin–Heidelberg–New York, 1967.

[267] A. D. Petrov and V. F. Mironow, *Angew. Chem.*, **73**, 59 (1961).

[268] H. W. Post, "Silicones and Other Silicon Compounds," Reinhold Publ. Corp., New York, 1949; E. G. Rochow, "An Introduction to the Chemistry of the Silicones," John Wiley and Sons, New York, 2nd ed, 1951; A. Hunyar, "Chemie der Silikone," Verlag Technik, Berlin, 1952; R. R. McGregor, "Silikones and Their Uses," McGraw-Hill Publ. Co., London, 1954; C. Eaborn, "Organosilicon Compounds," Butterworths Scientific Publications, London, 1960.

halides, hydrides, and alkoxides, and silanols, siloxanes, etc.; polysiloxanes in particular have been very intensively studied.

Gilman and Dunn[269] have considered the relations between the organic compounds of silicon and those of carbon.

Organosilicon compounds can be prepared by reaction of silicon halides with other organometallic compounds. The first such synthesis (1865) was that by Friedel and Crafts[270] who heated silicon tetrachloride with dimethylzinc in a sealed tube at 200°:

$$SiCl_4 + 2(CH_3)_2Zn \longrightarrow Si(CH_3)_4 + 2ZnCl_2$$

Stock and Somieski[271] much later prepared the methylsilanes CH_3SiH_3 and $(CH_3)_2SiH_2$ from mono- and di-chlorosilane, respectively, at room temperature.

The action of diaryl derivatives of mercury on silicon tetrachloride affords aryltrichlorosilanes:[272]

$$SiCl_4 + HgAr_2 \longrightarrow ArSiCl_3 + ArHgCl$$

Certain mixed organosilicon compounds can also be obtained in this way, *e.g.*, (trialkylsilyl)acetic esters from trialkyliodosilanes and (iodomercuri)-acetic esters.[273]

However, the most far-reaching and almost universally applicable method for synthesis of organosilicon compounds is by the action of Grignard reagents on silicon halides. With silicon tetrachloride this gives a mixture of products in which one to four chlorine atoms have been replaced by hydrocarbon groups:

$$SiCl_4 \xrightarrow{RMgX} RSiCl_3 \xrightarrow{RMgX} R_2SiCl_2 \xrightarrow{RMgX} R_3SiCl \xrightarrow{RMgX} SiR_4$$

It is often difficult to separate such mixtures, but if defined conditions are observed and particularly if the appropriate amount of Grignard reagent is used then any desired component of the product can be obtained in good yield. Kipping[274] was the first to use this method to prepare compounds of the general formulae SiR_4, R_3SiCl, R_2SiCl_2, and $RSiCl_3$. Immediate hydrolysis of the organic chlorosilanes first formed leads directly to organic silanols[275] or siloxanes.[276]

Tetramethylsilane:[277] Magnesium (30 g) is placed under anhydrous ether (500 ml) in a 1-l flask and brought into solution by passing in methyl bromide, then treated dropwise with silicon tetrachloride (50 g) mixed with the same volume of anhydrous ether. To complete the reaction, the mixture is heated for at least 2 h under reflux, a long bulb condenser or a more efficient type being used since tetramethylsilicon boils even lower than ether and may otherwise be lost. The whole mixture is then distilled from a water-bath into an ice-cooled receiver. The resulting mixture of tetramethylsilane and ether cannot be separated by distillation because the boiling points of the components are too close together (26° and 35°); so use is made of the insolubility of the silicon derivative in concentrated sulfuric acid: the total distillate is

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[269] H. Gilman and G. E. Dunn, *Chem. Rev.*, **52**, 77 (1953).

[270] C. Friedel and J. M. Crafts, *Ann. Chem.*, **136**, 203 (1965).

[271] A. Stock and C. Somieski, *Ber. Deut. Chem. Ges.*, **52**, 695 (1919).

[272] A. Ladenburg, *Ann. Chem.*, **173**, 143 (1874).

[273] Yu. I. Baukov, G. S. Burlachenko, and I. F. Lutsenko, *Zh. Obshch. Khim.*, **35**, 1173 (1965); *Chem. Abstr.*, **63**, 11602 (1965).

[274] F. S. Kipping, *Proc. Chem. Soc.*, **20**, 15 (1904); **21**, 65 (1905); *J. Chem. Soc.*, **91**, 209, 717 (1907).

[275] S. Kohama, *J. Chem. Soc., Japan. Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **82**, 69 (1961).

poured into sulfuric acid (500 ml) that is cooled in a freezing mixture. The ether dissolves in the acid, and the tetramethylsilane separates as a colorless upper layer. The latter is distilled from a slightly warm water-bath through an efficient condenser into an ice-cooled receiver. Shaking this distillate with concentrated sulfuric acid and a final fractional distillation afford a pure product, b.p. 26–27°/760 mm.

Perfluorinated organosilicon compounds such as tetrakis(pentafluorophenyl)silane can be prepared from silicon tetrachloride and (pentafluorophenyl)-magnesium bromide or -lithium.[278]

For such syntheses one can use Grignard reagents prepared either in ether or in a hydrocarbon solvent (*e.g.*, isooctane)[241] and, quite generally, the corresponding organolithium compound.[279]

Organolithium compounds have been applied to afford, *e.g.*, tetrakis(methoxymethyl)-[280] and tetrakis(cyclohexylethynyl)-silane[281] as well as *para*-substituted tetrakis(phenylethynyl)silanes.[282]

Further, methyl and ethyl orthosilicate[279,283] and sodium hexafluorosilicate[284] can be caused to react with Grignard reagents or organolithium compounds, yielding organosilicon derivatives.

A large number of symmetrical and of unsymmetrical mixed organosilicon compounds has been prepared by reaction of organosilicon halides with various Grignard reagents or organolithium compounds; suitable combinations of starting materials have led to, *e.g.*, symmetrical and unsymmetrical tetraalkylsilanes,[285] trialkyl(chloromethyl)silanes,[286] trialkyl(aryl)- and alkyl(triaryl)-silanes,[287] cyclohexyl(triphenyl)silane,[288] alkenyl(trialkyl)silanes,[289] dialkenyl-(dialkyl)silanes,[290] dialkenyl(alkyl)(aryl)silanes,[290] dialkenyl(diaryl)silanes,[290] alkenyl(triaryl)silanes,[291] alkynyl(trialkyl)silanes,[292] trialkyl(arylalkynyl)-silanes,[293] dialkyl(dialkynyl)silanes,[294] and dialkynyl(diaryl)silanes.[294] Trial-

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[276] Y. Takami, *J. Soc. Org. Syn. Chem., Japan*, **19**, 449 (1961).

[277] A. Bygden, *Ber. Deut. Chem. Ges.*, **44**, 2640 (1911).

[278] C. Tamborski, E. J. Soloski, and S. M. Dec, *J. Organometal. Chem.*, **4**, 446 (1965).

[279] H. Gilman and R. N. Clark, *J. Amer. Chem. Soc.*, **68**, 1675 (1946).

[280] U. Schöllkopf and H.-J. Traenckner, *J. Organometal. Chem.*, **5**, 300 (1966).

[281] H. Hartmann and K. Meyer, *Naturwissenschaften*, **52**, 303 (1965).

[282] H. Hartmann and M. K. El A'ssar, *Naturwissenschaften*, **52**, 304 (1965).

[283] P. A. DiGiorgio, W. A. Strong, L. H. Sommer, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **68**, 1380 (1946); E. Khotinsky and B. Seregenkoff, *Ber. Deut. Chem. Ges.*, **41**, 2946 (1908); P. D. George, L. H. Sommer, and F. C. Withmore, *J. Amer. Chem. Soc.*, **77**, 6647 (1955).

[284] E. M. Soshestvenskaya, *Zh. Obshch. Khim.*, **10**, 1689 (1940); *Chem. Abstr.*, **35**, 3240 (1941).

[286] B. N. Dolgov, D. N. Andreev, and V. P. Lyutyi, *Dokl. Akad. Nauk S.S.S.R.*, **118**, 501 (1958); *Chem. Abstr.*, **52**, 10870 (1958).

[287] H. Gilman, D. H. Miles, L. O. Moore, and C. W. Gerow, J. *Org. Chem.*, **24**, 219 (1959).

[288] H. Gilman and D. H. Miles, *J. Amer. Chem. Soc.*, **80**, 611 (1958).

[289] A. D. Petrov and G. I. Nikishin, *Zh. Obshch. Khim.*, **26**, 1233 (1956); *Chem. Abstr.*, **50**, 14515 (1956); D. Seyferth and L. G. Vaughan, *J. Organomet. Chem.*, **1**, 138 (1963).

[290] L. D. Nasiak and H. W. Post, *J. Org. Chem.*, **24**, 489 (1959).

[291] M. C. Henry and J. G. Noltes, *J. Amer. Chem. Soc.*, **82**, 555 (1960).

[292] B. G. Shakhovskoi, M. D. Stadnichuk, and A. A. Petrov, *Zh. Obshch. Khim.*, **34**, (1964); *Chem. Abstr.*, **61**, 16087 (1964).

[293] C. Eaborn and D. R. M. Walton, *J. Organometal. Chem.*, **2**, 95 (1964).

[294] A. M. Sladkov and L. K. Luneva, *Zh. Obshch. Khim.*, **36**, 553 (1966); *Chem. Abstr.*, **65**, 744 (1966).

kyl(phenyl)silanes carrying substituents in the ring can also be prepared in this way.[295,296]

Analogously, starting from appropriate silicon halides or alkoxides and introducing various alkyl, aryl, or alkenyl groups stepwise leads to racemic organosilicon compounds such as methyl-(1-naphthyl)(phenyl)silane[297] and methoxy-(1-naphthyl)(phenyl)(vinyl)silane[298] which can be separated into their enantiomers.

When bifunctional Grignard reagents or organolithium compounds are treated with silicon halides containing three organic groups, bissilyl compounds such as *p*-bis(trimethylsilyl)benzene[299] and *o*-bis[methyl(diphenyl)silyl]benzene[300] are formed. Cyclic silanes can be obtained by using silicon di-, tri-, or tetra-halides, *e.g.*, 5,10-dihydro-5,5,10,10-tetraphenylsilanthrene from *o*-dilithiobenzene and dichloro(diphenyl)silane,[300] and 1,1-dichlorosilacyclohexane from 1,5-dibromopentane and silicon tetrabromide.[301]

Disilanes R_3SiSiR_3 and disiloxanes $R_3SiOSiR_3$ can be prepared directly from the corresponding halides $Cl_3SiSiCl_3$ and $Cl_3SiOSiCl_3$ by means of Grignard reagents or organosodium compounds.[302] Such disilanes are also formed by the action of metals (Na, K, Li, or Mg) on chlorosilanes containing three organic groups, and in the same way compounds $R_3Si—SiR_2—SiR_3$ are formed by the action of sodium on $R_3Si—SiR_2Cl$ and R_3SiCl, and so on; analogous reactions of dichlorosilanes carrying two organic groups afford cyclosilanes. Reference should be made to reviews on cyclosilanes[303] and chains of silicon atoms[304] carrying organic substituents.

If the silicon tetrachloride is replaced by trichlorosilane there is direct access to trialkylsilanes R_3SiH in good yield by means of an alkyl-Grignard reagent or an organolithium compound.[287,305] Further than this, hydrogen bound to silicon is replaced by organic groups in reactions with organolithium or -sodium compounds,[306] *e.g.*:

$$SiH_4 + 4C_6H_5Na \longrightarrow Si(C_6H_5)_4 + 4NaH$$

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[295] D. W. Lewis, *J. Org. Chem.*, **23**, 1893 (1958).

[296] R. S. Sorokina, E. M. Panov, and K. A. Kozeshkov, *Zh. Obshch. Khim.*, **35**, 1625 (1965).

[297] L. H. Sommer, C. L. Frye, G. A. Parker, and K. W. Michael, *J. Amer. Chem. Soc.*, **86**, 3271 (1964).

[298] R. Corriu, I. Massé, and G. Royo, *C. R. Hebd. Séances Acad. Sci., C*, **264**, 987 (1967).

[299] V. E. Nikitenkov, *Zh. Obshch. Khim.*, **33**, 641 (1963); *Chem. Abstr.*, **59**, 653 (1963).

[300] H. Gilman and E. A. Zuech, *J. Amer. Chem. Soc.*, **82**, 3605 (1960).

[301] R. West, *J. Amer. Chem. Soc.*, **76**, 6012 (1954); C. Tamborski and H. Rosenberg, *J. Org. Chem.*, **25**, 246 (1960).

[302] W. C. Schumb and C. M. Saffer, Jr., *J. Amer. Chem. Soc.*, **61**, 363 (1939); **63**, 93 (1941).

[303] H. Gilman and G. L. Schwebke, *Advan. Organometal. Chem.*, **1**, 89 (1964).

[304] H. Gilman, W. H. Atwell, and F. K. Cartledge, *Advan. Organometal. Chem.*, **4**, 1 (1966).

[305] A. G. Taylor and B. V. de G. Walden, *J. Amer. Chem. Soc.*, **66**, 842 (1944); F. P. Price, *J. Amer. Chem. Soc.*, **69**, 2600 (1947); H. Gilman and R. N. Clark, *J. Amer. Chem. Soc.*, **69**, 1499 (1947); F. C. Whitmore, E. W. Pietrusza, and L. H. Sommer, *J. Amer. Chem. Soc.*, **69**, 2108 (1947).

[306] J. S. Peake, W. H. Nebergall, and Yun Ti Chen, *J. Amer. Chem. Soc.*, **74**, 1526 (1952); R. N. Meals, *J. Amer. Chem. Soc.*, **68**, 1880 (1946).

Grignard reagents react analogously with mono-, di-, and tri-phenylsilanes, and unsymmetrical silane derivatives can be obtained in this way.[307]

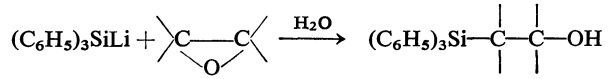
In the processes described above a silicon halide, ethoxide, or hydride is brought into reaction always with an organic derivative of another metal; however, a Si–C bond can also be formed by treating a silylmetal compound, *e.g.*, (triphenylsilyl)-potassium[308] or -lithium[309] with an aryl or alkyl halide, thus:

$$(C_6H_5)_3SiK + C_6H_5Br \longrightarrow Si(C_6H_5)_4 + KBr$$

$$(C_6H_5)_3SiLi + RCl \longrightarrow Si(C_6H_5)_3R + LiCl$$

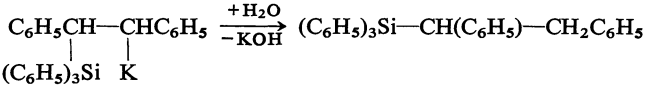
Reaction of (triphenylsilyl)lithium with polyhalomethanes such as CH_2Cl_2, CH_2Br_2, $CHCl_3$, $CHBr_3$, CHI_3, CCl_4, and CBr_4 is very complex, leading to a variety of products; this has been studied in detail by Gilman and Aoki.[310]

Silylmetal compounds react also with epoxides: for example, (triphenylsilyl)lithium and oxirane, its methyl derivative, or styrene oxide afford, after hydrolysis, the corresponding vicinal (triphenylsilyl)alkanols:[311]



Silylmetal derivatives add to olefins in reactions such as:[312]

$$(C_6H_5)_3SiK + C_6H_5CH{=}CHC_6H_5 \longrightarrow$$



$$\underset{(C_6H_5)_3Si}{C_6H_5CH}{-}\underset{K}{CHC_6H_5} \xrightarrow[-KOH]{+H_2O} (C_6H_5)_3Si{-}CH(C_6H_5){-}CH_2C_6H_5$$

A further method often used for preparation of organosilicon compounds is a Wurtz-type synthesis in which a silicon tetrahalide is condensed with an alkyl or aryl halide by means of metallic sodium in ether or a hydrocarbon solvent:[313]

$$SiX_4 + 4RX + 8Na \longrightarrow SiR_4 + 8NaX$$

If an alkyl- or aryl-silicon halide is used in place of the silicon tetrahalide, unsymmetrical organosilicon compounds can be synthesized in this way.[314]

When an alkoxychlorosilane is treated with an alkyl or aryl halide and sodium, the more reactive Si–Cl bond is mainly involved, so that organic

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[307] H. Gilman and E. A. Zuech, *J. Amer. Chem. Soc.*, **81**, 5925 (1959).

[308] R. A. Benkeser and R. G. Severson, *J. Amer. Chem. Soc.*, **73**, 1424 (1951).

[309] H. Gilman and D. Aoki, *J. Org. Chem.*, **24**, 426 (1959).

[310] H. Gilman and D. Aoki, *J. Organometal. Chem.*, **1**, 449 (1964).

[311] H. Gilman, D. Aoki, and D. Wittenberg, *J. Amer. Chem. Soc.*, **81**, 1107 (1959).

[312] T. C. Wu, D. Wittenberg, and H. Gilman, *J. Org. Chem.*, **25**, 596 (1960).

[313] A. Polis, *Ber. Deut. Chem. Ges.*, **18**, 1540 (1885); F. S. Kipping and L. L. Lloyd, *J. Chem. Soc.*, **79**, 449 (1901); F. Taurke, *Ber. Deut. Chem. Ges.*, **38**, 1661 (1905); E. A. Bassett, H. G. Emblem, M. Frankel, and D. Ridge, *J. Soc. Chem. Ind.* (*London*), **67**, 177 (1949); W. C. Schumb, J. Ackerman, and C. M. Saffer, *J. Amer. Chem. Soc.*, **60**, 2486 (1938).

[314] L. Spilater, D. C. Priest, and C. W. Harris, *J. Amer. Chem. Soc.*, **77**, 6227 (1955); M. Kanazashi, *Bull. Chem. Soc. Japan*, **26**, 493 (1956); A. D. Petrov, V. F. Mironov, and V. G. Glukhovstsev, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1956**, 461; *Chem. Abstr.*, **50**, 16663 (1956).

silyl alkoxides are obtained.[315] *e.g.*:

$$(C_2H_5O)_3SiCl + n\text{-}C_4H_9Cl + 2Na \longrightarrow n\text{-}C_4H_9Si(OC_2H_5)_3 + 2NaCl$$

$$(CH_3O)_2SiCl_2 + 2C_6H_5Cl + 4Na \longrightarrow (C_6H_5)_2Si(OCH_3)_2 + 4NaCl$$

However, Si–OR bonds can also be involved in a Wurtz–Fittig reaction; for instance, treating tetraalkoxysilanes with *tert*-butyl chloride and sodium affords alkoxy-*tert*-butylsilane.[316]

Methylsilyl chloride has acquired considerable industrial importance as a precursor for the preparation of silicon; it is prepared directly by reaction of methyl chloride with silicon in the presence of copper as catalyst at high temperatures.[317] Details for direct synthesis of methylsilyl chlorides have been given by Rochow.[318] The main product is dichloro(dimethyl)silane in accordance with a reaction $2CH_3Cl + Si \rightarrow (CH_3)_2SiCl_2$, but trichloro(methyl)silane, trimethylsilyl chloride, tetramethylsilane, silicon tetrachloride, and other products are also formed.

The method of preparing the silicon–copper catalyst has considerable influence on the course of the reaction,[319] and many suggestions have been made for increasing its activity by altering the method of its preparation[320] or by addition of a further metal.[321] Other metals than copper are also effective catalysts, *e.g.*, silver and gold;[322] silver is a particularly good catalyst for the analogous reaction of phenyl halides with silicon.[323]

Halo(vinyl)silanes can also be obtained by direct synthesis,[324] but for them tin[325] and nickel[326] prove better catalysts than copper.

Of the alkylhalosilanes the ethyl as well as the methyl compounds[323,327] can be obtained by the direct synthesis; with higher homologs decomposition of the alkyl groups increases greatly at the higher reaction temperatures required, and many by-products with little of the organosilicon compound are formed.

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[315] Jap. Pat. 5330 (1951); *Chem. Abstr.*, **47**, 9345 (1953); C. C. Chappelow, R. L. Elliott, and J. T. Goodwin, *J. Org. Chem.*, **25**, 435 (1960).

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Polyhalo compounds such as CH_2Cl_2, $CHCl_3$, and CCl_4 usually give a very complex mixture of various organosilicon compounds on reaction at a silicon–copper catalyst.[328] However, 1,1-dichloro-1-silacyclopentane (1,1-dichlorosilole) is obtained with other products from 1,4-dichlorobutane.[329]

More recently importance has attached to the hydrosilation of olefins, *i.e.*, addition of silanes of very varied types, such as H_nSiX_{4-n}, $HSiRX_2$, $HSiR_2X$, and H_nSiR_{4-n} ($n = 1$–4, R = alkyl or aryl, X = Cl, Br, or OR), to mono- and di-olefins. This addition can be carried out in the gaseous or the liquid phase. A simple example for a monoolefin is addition of trichlorosilane to ethylene at 160–400°:[330]

$$CH_2{=}CH_2 + SiHCl_3 \longrightarrow CH_3CH_2SiCl_3$$

Silanes such as $SiHCl_3$, CH_3SiHCl_2, $C_6H_5SiHCl_2$, $(CH_3)(C_6H_5)SiHCl$, and $(C_6H_5)_2SiHCl$ also add, at 160–400°, to olefins such as propene, 1- and 2-butene, hexene, and cyclohexene.[330] Vinylsilicon compounds add such types of silane in the same way at about 300°, *e.g.*,[331]

$$CH_2{=}CHSiCl_3 + SiHCl_3 \longrightarrow SiCl_3CH_2CH_2SiCl_3$$

Mono- and di-addition products can be obtained from diolefins.[330]

According to the conditions silanes containing more than one Si–H bond may add one or more moles of olefin per mole of silane, *e.g.*:[332]

$$SiH_4 + C_2H_4 \xrightarrow{120^\circ} C_2H_5SiH_3$$

$$C_2H_5SiH_3 + C_2H_4 \xrightarrow{370^\circ} (C_2H_5)_2SiH_2$$

Since this addition occurs stepwise, silanes of the type $RR'SiH_2$ can be obtained, *e.g.*:[333]

$$SiH_4 + C_2H_4 \xrightarrow{120^\circ} C_2H_5SiH_3$$

$$C_2H_5SiH_3 + CH_2{=}CHCH_3 \xrightarrow{370^\circ} C_2H_5SiH_2{-}CH_2CH_2CH_3$$

In the thermal addition, telomerization intervenes, even though only to a small extent. An appreciable amount of telomerization products is obtained if an excess of olefin is used at high pressure; *e.g.*, $SiHCl_3$ and an excess of ethylene at 285°/200 atm give products of the composition $SiCl_3{-}(CH_2CH_2){-}H$ where $n = 1$–5;[331] and CH_3SiHCl_2 with an excess of ethylene or propene at 260–270° and an initial pressure of 560 atm afford telomers

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[328] U.S. Pat. 2,381,000; *Chem. Abstr.*, **39**, 4889 (1945); A. V. Topchiev, N. S. Nametkin, and V. I. Zetkin, *Dokl. Akad. Nauk, S.S.S.R.*, **82**, 927 (1952); *Chem. Abstr.*, **47**, 4281 (1953); R. Muller and G. Seitz, *Chem. Ber.*, **91**, 22 (1958).

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[331] Brit. Pat. 771,587; *Chem. Abstr.*, **51**, 13,904 (1957).

[332] U.S. Pat. 2,786,862; *Chem. Abstr.*, **51**, 13,904 (1957).

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respectively of the composition CH_3SiCl_2—$(CH_2CH_2)_n$ —H (n = 1–6) and CH_3SiCl_2—(C_3H_6) —H.[333–335]

The tendency to telomerization is very much less in the, clearly radical, addition that occurs at considerably lower temperatures (100–140°) in the presence of catalytic amounts of peroxide. Under catalysis by peroxides — those most used are diacetyl, dibenzoyl, and di-*tert*-butyl peroxide and *tert*-butyl perbenzoate — or under UV or γ-irradiation, silanes such as $SiHCl_3$, $SiHBr_3$, CH_3SiHCl_2, CH_3SiHBr_2, n-$C_3H_7SiHCl_2$, $(C_2H_5)_3SiH$, and $(C_6H_5)_3SiH$ add under relatively mild conditions to very varied types of straight-chain, branched-chain, and cyclic olefins.[336–339] Analogous additions can be effected with, *e.g.*, alkenylsilicon compounds,[339,340] vinyl and allyl ethers and esters,[337,341,342] unsaturated carboxylic acids and their esters,[343,344] and halogenated olefins such as $CClF{=}CF_2$ and $CF_2{=}CF_2$.[345,346]

Olefins such as styrene, α-methylstyrene, acrylonitrile, and methacrylic esters that polymerize very readily give polymers containing silicon end-groups in the reaction carried out with peroxide catalysis just as in that involving γ-irradiation.[337,341]

Such polymerization can be avoided by using a catalyst composed of a Group VIII metal or a derivative thereof, *e.g.*, platinum (as platinum black or platinized asbestos or charcoal), hydrogen hexachloroplatinate, or ruthenium chloride; then the 1 : 1 adducts can be obtained in good yield from olefins such as styrene, acrylonitrile, and methacrylic esters with, *e.g.*, dichloro(methyl)-silane;[347–349] nevertheless it is advantageous to exclude oxygen and add a polymerization inhibitor such as *tert*-butylpyrocatechol or 2,6-di-*tert*-butyl-4-methylphenol.

Use of such catalysts permits addition of very varied silane derivatives to

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[334] A. N. Nesmeyanov, R. Kh. Freidlina, and E. Ts. Chukovskaya, *Dokl. Akad. Nauk S.S.S.R.*, **113**, 120 (1957); *Chem. Abstr.*, **51**, 14,541 (1957); *Tetrahedron*, **1**, 248 (1957).

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[348] J. W. Ryan and J. L. Speier, *J. Org. Chem.*, **24**, 2052 (1959).

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very varied unsaturated compounds under very mild conditions; as catalyst, platinum on charcoal or hydrogen hexachloroplatinate is usually used; silanes used include $SiHCl_3$, CH_3SiHCl_2, $C_2H_5SiHCl_2$, $SiH(OR)_3$, $CH_3SiH(OC_2H_5)_2$, $(CH_3)_2SiHCl$, $(C_2H_5)_3SiH$, $(C_6H_5CH_2)_3SiH$, SiH_2Cl_2, $(C_2H_5)_2SiH_2$, and $(C_6H_5)_2SiH_2$; unsaturated components include ethylene,[335, 350,351] propene,[351,352] pentene,[347,350,353] hexene,[353] heptene,[354] octene,[353] nonene,[353,355] decene,[353,355] unsaturated ethers,[349,351,356] esters and nitriles from unsaturated carboxylic acids,[349,357] carboxylic esters of unsaturated alcohols,[347,349] vinylsilanes,[358] vinyl[359] and allyl chloride,[360] and other halogenated olefins[359,361,362] (with these last, however, considerable amounts of other products are formed).

1,4-Addition occurs between diolefins, *e.g.*, butadiene, and $SiHCl_3$ in the presence of platinum on charcoal:[361,363]

$$SiHCl_3 + CH_2{=}CHCH{=}CH_2 \longrightarrow SiCl_3CH_2CH{=}CHCH_3$$

Hydrosilation of olefins in the presence of metallic or metal-salt catalysts clearly occurs by an ionic mechanism, in contrast to the radical reaction that occurs at high temperatures and under UV or γ-irradiation; the former is not decelerated by polymerization inhibitors, and the direction of addition corresponds to that of, *e.g.*, ionic addition of halogen; the following are examples:[347,349]

$$Cl_3Si^+H^- + CH_2{=}CHCOOCH_3 \longrightarrow Cl_3Si{-}CH(CH_3)COOCH_3$$

$$Cl_3Si^+H^- + CH_2{=}CHOOCCH_3 \longrightarrow Cl_3Si{-}CH_2CH_2OOCCH_3$$

$$Cl_3Si^+H^- + CH_2{=}CHCH_2CH_2CH_3 \longrightarrow Cl_3Si{-}CH_2CH_2CH_2CH_2CH_3$$

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[350] U.S. Pat. 2,632,013; *Chem. Abstr.*, **48**, 2760 (1954).

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[356] V. A. Ponomarenko, G. V. Odabashyan, I. N. Lifanova, and A. D. Petrov, *Zh. Prikl. Khim.*, **33**, 2751 (1960); A. D. Petrov, V. A. Ponomarenko, G. V. Odabashyan, and S. I. Krockmalev, *Dokl. Akad. Nauk S.S.S.R.*, **124**, 838 (1959); *Chem., Abstr.*, **55**, 11,340 (1961); **53**, 15,956 (1959).

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Chalk and Harrod[364] have investigated the mechanism of this hydrosilation of olefins under catalysis by complexes of metals of Group VIII.

Addition of trichlorosilane or dichloro(methyl)silane to olefins can also be effected in the presence of tertiary amines such as pyridine, *N,N,N′,N′*-tetramethylethylenediamine, and tributylamine or in the presence of tertiary phosphines such as triphenylphosphine.[365] Amides such as dimethylformamide, *N,N*-diethylbenzamide, and *N,N*-dibutylacetamide exert a similar catalytic effect.[366] The mechanism of these base-catalyzed hydrosilations is probably also ionic.

Silanes can also be added to acetylenes, alkylacetylenes, acetylenic alcohols and their derivatives, etc., under conditions very similar to those effective with olefins, *i.e.*, at high temperatures,[367] with catalysis by peroxides,[339,368] or in the presence of platinum[361,369] or hydrogen hexachloroplatinate;[370] palladium has proved a particularly effective catalyst for this reaction with acetylenes.[371] The corresponding vinylsilicon compounds are formed, *e.g.*:

$$\mathrm{RC{\equiv}CH + SiHCl_3 \longrightarrow RCH{=}CHSiCl_3}$$

trans-Addition occurs stereospecifically in the presence of dibenzoyl peroxide, and *cis*-addition stereospecifically in the presence of platinum. The reaction can be carried beyond the vinyl stage, by addition of a second molecule of the silane and formation of a saturated product, *e.g.*:

$$\mathrm{CH{\equiv}CH + SiHCl_3 \longrightarrow CH_2{=}CHSiCl_3 \xrightarrow{+SiHCl_3} Cl_3SiCH_2CH_2SiCl_3}$$

There is another synthesis of organosilicon halides, not generally applicable, but important in industry because the starting materials are cheap; this is the treatment of silicon halides with hydrocarbons at high temperatures. As examples, tetrachlorosilane and benzene in the gas phase at 840° give dichloro(diphenyl)silane;[372] tetrachlorosilane and methane in the gas phase give trichloro(methyl)silane at 960° in the presence of an iron catalyst[372] and at 500° in the presence of a brick or pumice catalyst.[373]

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[372] U.S. Pat. 2,405,019; *Chem. Abstr.*, **40**, 7235 (1946).

[373] Brit. Pat. 596,800; *Chem. Abstr.*, **42**, 5465 (1948).

Chlorohydrosilanes also react with hydrocarbons at high temperatures, *e.g.*, trichlorosilane and benzene in the gas phase at 600–850° give chloro(triphenyl)silane.[374] However, the yield is much improved by carrying out the reaction at a lower temperature in an autoclave under pressure and in presence of a catalyst, *e.g.*, boron trichloride:[375]

$$SiHCl_3 + C_6H_6 \xrightarrow[\text{pressure}]{BCl_3, 275°} C_6H_5SiCl_3 + H_2$$

The analogous reaction with CH_4 affords trichloro(methyl)silane.[376]

Trichlorosilane and dichloro(methyl)silane[375,377] react in the same way, not only with benzene, but also with other aromatic hydrocarbons such as toluene, biphenyl, and naphthalene, with boric acid, aluminum chloride, or Raney nickel as well as boron trichloride reported as catalysts. Barry *et al.*[378] have reviewed this direct process for synthesis of arylhalosilanes.

Yet another direct synthesis for a series of organosilicon compounds is to treat compounds containing an SiH group with organic halides under conditions similar to those mentioned above. Thus organic trihalosilanes are obtained by reaction of trichloro- or tribromo-silane with chloro- or bromobenzene, 1-bromonaphthalene, or allyl bromide in the gas phase at a high temperature;[379] analogously, dichlorosilane with vinyl chloride gives dichloro(vinyl)silane, and with chlorobenzene gives dichloro(phenyl)silane with some dichloro(diphenyl)silane.[355] This reaction also can be carried out at a lower temperature under pressure in an autoclave[380] if a Friedel–Crafts catalyst, *e.g.*, BCl_3,[381] is added.

An interesting method, reviewed by Seyferth,[382] for obtaining chloromethyl derivatives directly is to treat metal halides with diazomethane. If, for instance, diazomethane is allowed to act on tetrachlorosilane in ether at −55° to −45°, a very good yield of trichloro(chloromethyl)silane is obtained:[382–386]

$$SiCl_4 + CH_2N_2 \longrightarrow SiCl_3CH_2Cl + N_2$$

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[374] U.S. Pat. 2,379,821; *Chem. Abstr.*, **39**, 4619 (1945).

[375] Brit. Pat. 751,370; *Chem. Abstr.*, **51**, 5828 (1957).

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[380] U.S. Pat. 2,469,355; 2,511,820; *Chem. Abstr.*, **43**, 5791 (1949); **44**, 8370 (1950).

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[385] D. Seyferth and E. G. Rochow, *J. Amer. Chem. Soc.*, **77**, 907 (1955).

[386] D. Seyferth and E. G. Rochow, *Inorg. Syn.*, **6**, 37 (1960).

A second and a third chloromethyl group can be introduced in the presence of copper sulfate:

$$SiCl_3CH_2Cl + CH_2N_2 \longrightarrow SiCl_2(CH_2Cl)_2 + N_2$$

$$SiCl_2(CH_2Cl)_2 + CH_2N_2 \longrightarrow SiCl(CH_2Cl)_3 + N_2$$

However, a fourth chloromethyl group cannot be introduced.

Use of the more reactive tetrabromosilane leads to the bis- and tris-(chloromethyl) compounds without the necessity for a catalyst.[383] Diazomethane reacts with trichlorosilane or trichloro(methyl)silane in the presence of copper powder to yield, respectively, dichloro(chloromethyl)silane[385,386] and dichloro(chloromethyl)(methyl)silane,[383] but no chloromethyl derivative can be obtained in this way from chlorosilanes carrying three organic groups, such as chloro-(trimethyl), -(triethyl)-, and -(triphenyl)-silane.

Reaction of tetrachlorosilane with diazoethane is similar to that with diazomethane:[383]

$$SiCl_4 + CH_3CHN_2 \longrightarrow CH_3CHClSiCl_3 + N_2$$

George *et al.*[387] have reviewed the preparation and properties of organosilicon compounds in which the organic group bound to silicon contains functional groups, *e.g.*, $CH_3SiCl_2(CH_2Cl)$, $CH_2{=}CHSiCl_3$, $(CH_3)_3Si(CH_2SO_2CH_3)$, etc.

Other reviews[388] deal with the application of organosilicon compounds to the synthesis of purely carbon compounds.

Organogermanium compounds can be synthesized by methods closely resembling those for organosilicon compounds; various reviews[389] treat this subject.

2. Organotin compounds[390]

Tin forms organic derivatives of the same type as are obtained from silicon and germanium. However, the tin–carbon bond is very much more polar than that to silicon or germanium, so that attached organic groups are much more easily detached or replaced. Also the tendency to form complex compounds is greater.[391]

For the preparation of organotin compounds the procedure most widely applicable and that most often used in the laboratory is to treat tin tetra-

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[388] L. Birkhofer and A. Ritter, *Angew. Chem. Int. Ed., Engl.*, **4**, 417 (1965); K. Rühlmann, *Z. Chem.*, **5**, 130 (1965).

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halides with Grignard reagents; the technique is usually adjusted to give tetraalkyl or tetraaryl compounds:[241,392]

$$SnCl_4 + 4RMgX \longrightarrow SnR_4 + 4MgXCl$$

Tetraethyltin:[393] Tin tetrachloride (45 g) is dropped slowly, with cooling, into an ethereal solution of ethylmagnesium bromide (from magnesium turnings 24.5 g, ethyl bromide 136 g, and ether 500 ml). The mixture is boiled for a further 1 h, then the ether is removed completely on a water-bath. The residue is heated for 0.5 h in a boiling water-bath, after which the ether that distilled off is returned to the product. This mixture is treated with water and 5% hydrochloric acid until a sharp separation into two layers is obtained. The ethereal solution is separated, dried, and distilled, the final fractionation being best effected at water-pump vacuum because of the rather high boiling point of the product. About 75% of tetraethyltin, b.p. 78°/13 mm, is obtained.

For synthesis of certain organotin compounds the Grignard reagent is often replaced by an organolithium compound.[394,395]

The reaction of a tin tetrahalide with a Grignard reagent or an organolithium compound has been used also for synthesis of the following compounds SnR_4: R = cycloalkyl, alkenyl, or alkynyl, *e.g.*, cyclopropyl,[396] vinyl,[397,398] trifluorovinyl,[399] *cis*- and *trans*-propenyl,[400] (cyclohexylethynyl);[281] substituted and unsubstituted (phenylethynyl);[282,401] ring-substituted aryl of very various types, *e.g.*, *m*-(trifluoromethyl)phenyl, *p*-fluorophenyl,[402] and pentafluorophenyl.[278]

Such tetrasubstituted stannanes can then be readily converted into organic tin halides by a Kozeschkow disproportionation, thus:[403]

$$3SnR_4 + SnCl_4 \longrightarrow 4R_3SnCl$$

$$SnR_4 + SnCl_4 \longrightarrow 2R_2SnCl_2$$

$$SnR_4 + 3SnCl_4 \longrightarrow 4RSnCl_3$$

Organotin compounds of this type can be further treated with Grignard reagents or organo-lithium or -sodium compounds, thus yielding a variety of mixed organotin derivatives; for example, trialkyl- and tri(cyclohexyl)-tin

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[392] W. J. Pope and S. J. Peachey, *Proc. Chem. Soc.*, **19**, 290 (1903); P. Pfeiffer and K. Schnurmann, *Ber. Deut. Chem. Ges.*, **37**, 319 (1904); G. J. M. van der Kerk and J. G. A. Luijten, *Org. Syn.*, **36**, 86 (1956).

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chloride with an aryllithium or an aryl-Grignard reagent afford the corresponding trialkyl(aryl)tin or aryl[tri(cyclohexyl)]tin compound;[404] compounds with substituents in the ring,[404,405] *e.g.*, alkenyl groups,[406] and those with perfluorinated rings,[407] can also be synthesized by this route.

Analogous reactions afford other compounds of the type R_3SnR', such as alkyl(tri(cycloalkyl)]tin,[408] alkyl(triphenyl)tin,[409] alkenyl-(trialkyl)tin and -(triaryl)tin,[398,410] and alkynyl(triaryl)tin compounds;[411] also compounds of the general formula $R_2SnR'_2$, such as dialkyl- and diaryl-bis(perfluorovinyl)-tin[412] and dialkynyl(diaryl)tin compounds.[413]

Organotin hydroxides R_3SnOH and oxides R_2SnO react like the halides with organomagnesium compounds and yield products of the general formula SnR_4, SnR_3R', or $SnR_2R'_2$ according to the nature of the starting materials.[414]

A Sn–O bond may be replaced by a Sn–C bond in the same way in other tin compounds, such as alkoxy derivatives; thus tetralkyltins can be prepared from tetramethoxytin and an alkylmagnesium halide:[415]

$$Sn(OCH_3)_4 + 4RMgX \longrightarrow SnR_4 + 4CH_3OMgX$$

Organometallic derivatives other than those of lithium and magnesium can also be used in syntheses of organotin compounds; these include the alkylaluminum compounds that are readily accessible by direct synthesis on an industrial scale, and their reaction with tin tetrahalides has been studied in detail.[416]

Salts of bivalent tin can also be used: reaction of the dichloride or dibromide with dialkyl- or diaryl-thallium halides gives tin dihalides carrying two organic

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groups:[417]

$$SnX_2 + R_2TlX \longrightarrow R_2SnX_2 + TlX$$

and there is an analogous result between tin dihalides and dialkyl- or diarylmercury compounds, in which metallic mercury separates.[418]

Treating stannylmetals with organic halides also leads to a new Sn–C bond; *e.g.*, methyl(triphenyl)tin is obtained from sodium triphenylstannate and methyl iodide:[419]

$$(C_6H_5)_3SnNa + CH_3I \longrightarrow (C_6H_5)_3SnCH_3 + NaI$$

Sodium trialkylstannates react analogously with bromoacetylenes.[420]

Very similar reactions are also undergone by compounds containing a Sn–Sn bond; thus trifluoromethyl(trimethyl)tin and trimethyltin iodide are formed when hexamethylditin and trifluoroiodomethane are heated in a Carius tube;[421] and dibutyltin and alkyl halides afford alkyldibutyltin halides.[422]

Condensation of tin tetrachloride and organic halides by means of metallic sodium,[423–425] analogous to a Wurtz–Fittig synthesis, is very widely applicable to synthesis of tetraalkyl- and tetraaryl-tins:

$$SnCl_4 + 4RX + 8Na \longrightarrow SnR_4 + 4NaCl + 4NaX$$

Moreover, the process can be made to yield mixed organic tin compounds, tri(cyclohexyl)tin bromide and 2-chlorobiphenyl, for example, giving 2-biphenylyl[tri(cyclohexyl)]tin when boiled with sodium in light petroleum.[405]

Direct action of alkyl halides on metallic tin also gives organotin compounds; thus Frankland (1853)[426] prepared diethyltin diiodide, and Cahours (1860)[427] prepared dimethyltin diiodide. The possibilities have come into more recent attention and, *inter alia*, the effect of catalysts such as magnesium, zinc, alcohols, esters, and ethers has been studied;[428] organic ammonium salts, and mixtures of organic bases with iodine, particularly have proved effective catalysts for reaction of alkyl chlorides with tin powder;[429] and use of a solvating solvent such as diethylene glycol dimethyl ether (diglyme) has been proposed.[430]

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Benzyl halides react with tin powder, *e.g.*, in aqueous suspension at 100°, giving very good yields of tribenzyltin halides;[431] and reaction with 4-isopropylbenzyl chloride is similar.[432] The influence of the solvent on interaction of benzyl chloride with tin powder has been investigated in detail.[433]

Smith and Rochow[434] describe the preparation of dichloro-dimethyltin and -diethyltin by interaction of molten tin and methyl and ethyl chloride, respectively, and also reaction of methyl chloride, bromide, and iodide with a mixture of tin(II) oxide and copper above 300°:

$$3SnO + 2CH_3Cl \longrightarrow Sn(CH_3)_2 + SnOCl_2 + SnO_2$$
$$Sn(CH_3)_2 + CH_3Cl \longrightarrow (CH_3)_3SnCl$$

Organic halides react more readily with an alloy containing a non-noble metal than with pure tin;[435] tetraalkyl- and tetraaryl-stannanes have been obtained from the appropriate alkyl and aryl halides and the alloy SnNa:

$$4SnNa + 4RX \longrightarrow SnR_4 + 4NaX + 3Sn$$

In a newer variant the tin–sodium alloy is replaced by the magnesium–tin alloy Mg_2Sn which is much easier to handle:[436]

$$Mg_2Sn + 4RX \longrightarrow SnR_4 + 2MgX_2$$

Many organotin compounds, and in particular those that contain special substituents and are in some cases difficult to obtain in other ways, can be prepared by addition of organic tin hydrides to compounds containing double or triple carbon–carbon bonds. Tin hydrides containing three organic groups add to reactive double bonds and to acetylenes even on mere heating at 80 to 100°;[437] *e.g.*:

$$(C_6H_5)_3SnH + CH_2{=}CHC_6H_5 \longrightarrow (C_6H_5)_3SnCH_2CH_2C_6H_5$$

Very nearly quantitative reaction occurs within a few hours. Moreover, tin hydrides containing two organic groups add under the same conditions to terminal C≡CH groups, giving polymers of the type $—(SnR_2CH_2CHR')_n—$, and to α,ω-dienes and α,ω-diynes, giving linear and cyclic polymers of the types:[438]

$$—(SnR_2CH_2CH_2—R'—CH_2CH_2)—$$
$$\text{and}\quad —(SnR_2CH{=}CH—R'—CH{=}CH)_n—$$

In many cases, *e.g.*, with *o*-divinylbenzene or *o*-diethynylbenzene, monomeric as well as polymeric cyclic adducts can be isolated.[439]

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Organic tin hydrides carrying three organic groups can also be added smoothly at 70–80° to unsaturated organometallic derivatives of elements of the fourth main Group, such as vinyl-silanes, -germanes, and -stannanes, *e.g.*:[440]

$$(C_6H_5)_3SnH + CH_2{=}CHSi(C_6H_5)_3 \longrightarrow (C_6H_5)_3SnCH_2CH_2Si(C_6H_5)_3$$

Trialkyltin hydrides react with fluoroacetylenes even below 20°: thus hexafluoro-2-butyne affords trialkyl-[*trans*-3,3,3-trifluoro-1-(trifluoromethyl)propenyl]tins.[441]

Under UV irradiation compounds such as dimethylstannane can be added to simple olefins (*e.g.*, ethylene) at 25–30°:

$$(CH_3)_2SnH_2 + CH_2{=}CH_2 \longrightarrow (CH_3)_2SnHCH_2CH_3 \xrightarrow{CH_2=CH_2} (CH_3)_2Sn(CH_2CH_3)_2$$

Under these conditions conjugated dienes (*e.g.*, butadiene) afford monomeric 1,4-adducts, *e.g.*,

$$(CH_3)_2SnHCH_2CH{=}CHCH_3 \text{ and } (CH_3)_2Sn(CH_2CH{=}CHCH_3)_2.^{442}$$

The synthesis of alkyltins from olefins and organic tin halides becomes particularly smooth in the presence of compounds that decompose to radicals at relatively low temperatures; use of azoisobutyronitrile and azoisobutyric esters have proved valuable. Many different types of terminal alkene can be hydrostannated at 30–80° in a very short time by hydrides of types R_3SnH, R_2SnH_2, and $RSnH_3$:[443]

$$R_3SnH + CH_2{=}CHR' \longrightarrow R_3SnCH_2CH_2R'$$

$$R_2SnH_2 + 2CH_2{=}CHR' \longrightarrow R_2Sn(CH_2CH_2R')_2$$

$$RSnH_3 + 3CH_2{=}CHR' \longrightarrow RSn(CH_2CH_2R')_3$$

All the products have the organotin group attached at the terminal position, and yields amount to 75–95%.

Acetylenes and allenes can also be smoothly hydrostannated under these conditions;[444] for example, tributyltin hydride and acetylene give tributyl(vinyl)tin in very good yield.[445] Conjugated dienes afford mainly the 1,4-adducts.[446]

It has been shown[447] that hydrostannation of terminal and non-terminal olefins and of acetylenes occurs by a radical and not by a polar mechanism.

Reviews of the addition of organic tin hydrides to compounds containing double and triple carbon–carbon bonds have been published by Neumann[448] and by Kuivila.[449]

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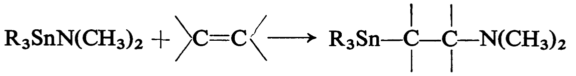
Radical reactions are also involved when compounds containing a Sn–Sn bond add to fluoroolefins under UV irradiation,[450] *e.g.*:

$$(CH_3)_3Sn{-}Sn(CH_3)_3 + CF_2{=}CF_2 \longrightarrow (CH_3)_3Sn{-}CF_2CF_2{-}Sn(CH_3)_3$$

and Sn–P compounds such as diphenyl(triphenylstannyl)phosphine add similarly to allyl chloride, styrene, or phenylacetylene in boiling benzene in the presence of azoisobutyronitrile.[451]

Tin amines of the type $R_3SnN(CH_3)_2$ also add to olefins or disubstituted acetylenes in ether or light petroleum at 35–60°:[452]



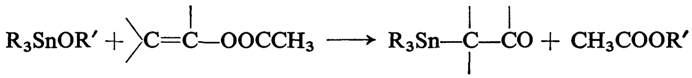
$$R_3SnN(CH_3)_2 + \mathrm{>C{=}C<} \longrightarrow R_3Sn{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}N(CH_3)_2$$

$$R_3SnN(CH_3)_2 + R'C{\equiv}CR'' \longrightarrow R_3Sn{-}CR'{=}CR''{-}N(CH_3)_2$$

Alkoxy(trialkyl)stannanes, which also add by various polar mechanisms,[453] do not react with styrene or with methacrylic or maleic esters, but with ketene undergo smooth addition to give stannylacetic esters:[454]

$$R_3SnOR' + CH_2{=}CO \longrightarrow R_3SnCH_2COOR'$$

and α-(trialkylstannyl) ketones are obtained in 70–95% yield from enol acetates:[455]



$$R_3SnOR' + \mathrm{>C{=}}\overset{|}{C}{-}OOCCH_3 \longrightarrow R_3Sn{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{C}O + CH_3COOR'$$

Terminal acetylenes RC≡CH, however, yield trialkyl(alkynyl)tin compounds on reaction with trialkyltin amides[456] or alkoxides[457] or with trialkyltin hydroxides[458] or bis(trialkyltin) oxides:[459]

$$R_3SnX + HC{\equiv}CR \longrightarrow R_3Sn{-}C{\equiv}CR + HX$$

$$(X = NR_2,\ OR,\ OH,\ \text{or}\ O{-}SnR_3)$$

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[458] M. F. Shostakovskii, N. V. Komarov, I. S. Guseva, and V. K. Misjunas, *Dokl. Akad. Nauk S.S.S.R.*, **158**, 918 (1964); *Chem. Abstr.*, **62**, 2788 (1965).

[459] M. F. Shostakovskii and co-workers, *Dokl. Akad. Nauk S.S.S.R.*, **163**, 390 (1965); *Zh. Obshch. Khim.*, **35**, 47 (1965); *Chem. Abstr.*, **63**, 11,601 (1965); **62**, 13,169 (1965).

A special process for the synthesis of aryltin halides was developed by Nesmeyanov and his colleagues; they found that the crystalline double salt of arenediazonium salts and tin tetrachloride decompose as follows in boiling ethyl acetate in the presence of powdered copper, zinc, or tin:[460]

$$(ArN_2Cl)_2 \cdot SnCl_4 + 2M^{II} \longrightarrow Ar_2SnCl_2 + 2N_2 + 2MCl_2$$

aromatic groups can be introduced by this method in cases when the Grignard reaction fails.

Diaryltin dihalides can also be obtained, by way of diaryltin oxides, when arenediazonium tetrafluoroborates are treated with stannous chloride dihydrate and zinc dust.[461]

Tin chlorides react with diazomethane to give chloromethyl derivatives, *e.g.*, (chloromethyl)dimethyltin chloride in good yield from dimethyltin dichloride:[386]

$$(CH_3)_2SnCl_2 + CH_2N_2 \longrightarrow (CH_3)_2SnCl(CH_2Cl) + N_2$$

3. Organolead compounds[462]

Organic derivatives of lead are less stable to heat and light and more readily decomposed than those of other elements of the fourth main Group; also the lead–carbon bond is considerably more easily broken by acids and oxidizing agents.

The method most used for preparation of organolead compounds in the laboratory is treatment of lead(II) chloride with alkyl-, aryl-, or vinyl-Grignard or -lithium reagents, the main products being as shown in the following summary for magnesium:[163,395,463,464]

$$2PbCl_2 + 4RMgX \longrightarrow PbR_4 + Pb + 2MgCl_2 + 2MgX_2$$

The lead products shown are accompanied by their homologs Pb_2R_6.

Lead salts of other inorganic and of organic acids may replace the lead chloride, as also may lead oxide or sulfide, and these may be brought into reaction with organo-lithium, -magnesium, -zinc, or -aluminum compounds; methods for obtaining tetraethyllead have been studied in particular detail.[465]

In these reactions half the lead is reduced to metallic lead and may thus be considered a loss. To avoid this, compounds of quadrivalent lead such as lead(IV) acetate, and potassium or ammonium hexachloroplumbate, may replace the lead(II) salts,[466] and their use with Grignard reagents or organo-

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[460] A. N. Nesmejanow, K. A. Kozeschkow, and W. A. Klimowa, *Ber. Deut. Chem. Ges.*, **68**, 1877 (1935).

[461] A. N. Nesmeyanov and L. G. Makarova, *Dokl. Akad. Nauk S.S.S.R.*, **87**, 421 (1952); *Chem. Abstr.*, **48**, 623 (1954).

[462] R. W. Leeper, L. Summers, and H. Gilman, *Chem. Rev.*, **54**, 101 (1954); G. J. M. van der Kerk, *Ind. Eng. Chem.*, **58**, No. 10, 29 (1966).

[463] G. Grüttner and E. Krause, *Ber. Deut. Chem. Ges.*, **49**, 1415 (1916).

[464] E. C. Juenge and S. E. Cook, *J. Amer. Chem. Soc.*, **81**, 3578 (1959).

[465] T. H. Pearson, S. M. Blitzer, D. R. Carley, T. W. McKay, R. L. Ray, L. L. Sims, and J. R. Zietz, Advances in Chemistry Series No. 23, 299 (1959).

[466] F. W. Frey and S. E. Cook, *J. Amer. Chem. Soc.*, **82**, 530 (1960).

lithium compounds has led to synthesis of products such as tetravinyl-,[467] tetrakis(cyclohexylethynyl)-, tetrakis-(*p*-bromophenylethynyl),[281,282] and tetrakis(pentafluorophenyl)-lead.[468]

Gilman and his co-workers, however, found[469] that all the lead of lead(II) salts can be converted into tetraalkyl or tetraaryl derivatives if the corresponding organic iodide (RI) was present during the reaction with the organometallic compound; the metallic lead formed in the reaction is finely divided and reacts with the iodide thus:

$$\mathrm{Pb + 2RI \longrightarrow R_2PbI_2}$$

The compound R_2PbI_2 can be converted into PbR_4 by an organolithium or Grignard reagent, so that, for instance, tetramethyllead is obtained when methyllithium or methylmagnesium iodide is added to a boiling solution of lead(II) chloride in ether which contains also methyl iodide; the reaction may be represented as:

$$\mathrm{PbCl_2 + 3CH_3Li + CH_3I \longrightarrow Pb(CH_3)_4 + 2LiCl + LiI}$$

An attempt to prepare tetrakis(pentafluorophenyl)lead analogously from lead dichloride, pentafluorophenyllithium, and pentafluoroiodobenzene failed, although the action of pentafluorophenylmagnesium bromide on lead dichloride in the presence of benzyl chloride gave the mixed organolead compound:

$$\mathrm{3C_6F_5MgBr + PbCl_2 + C_6H_5CH_2Cl \longrightarrow (C_6F_5)_3PbCH_2C_6H_5 + 3MgBrCl}$$

and tetrakis(pentafluorophenyl)lead was obtained in very good yield when pentafluorophenyl-magnesium bromide or -lithium was treated with lead dichloride in presence of the appropriate amount of bromine:[470]

$$\mathrm{4C_6F_5MgBr + PbCl_2 + Br_2 \longrightarrow Pb(C_6F_5)_4 + 2MgBr_2 + 2MgBrCl}$$

Mixed organolead compounds R_3PbR' and $R_2PbR'_2$, *e.g.*, triethyl- and triphenyl-vinyllead[464,471] or -styryllead,[472] diethyl- and diphenyl-divinyllead,[464,471] and alkynyl-triethyllead and -triphenyllead,[473] can be obtained from the relevant halides R_3PbCl or R_2PbCl_2 with an organomagnesium or organoalkali-metal compound.

Alkynyltriethylleads are also obtained by the action of terminal alkynes $RC{\equiv}CH$ on triethylmethoxylead.[474]

Organic halides also afford tetraalkyl- and teraaryl-leads on reaction with a lead–sodium alloy, sometimes with catalysis by a base such as pyridine.

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[467] L. Maier, *Angew. Chem.*, **71**, 161 (1959).

[468] C. Tamborski, E. J. Soloski, and St. M. Dec, *J. Organometal. Chem.*, **4**, 446 (1965).

[469] H. Gilman and R. G. Jones, *J. Amer. Chem. Soc.*, **72**, 1760 (1950); H. Gilman, L. Summers, and R. W. Leeper, *J. Org. Chem.*, **17**, 630 (1952).

[470] K. Hills and M. C. Henry, *J. Organometal. Chem.*, **9**, 180 (1967).

[471] V. V. Korchak, A. M. Polyakova, and M. D. Suchkova, *High-molecular Compounds* (*S.S.S.R.*), **2**, 13 (1960).

[472] H. G. Pars, W. A. G. Graham, E. R. Atkinson, and C. R. Morgan, *Chem. & Ind.* (*London*), **1960**, 693.

[473] J.-C. Masson, M. LeQuan, W. Chodkiewicz, and P. Cadiot, *C. R. Hebd. Séances Acad. Sci.*, **257**, 1111 (1963).

[474] A. G. Davies and R. J. Puddephatt, *Tetrahedron Lett.*, **1967**, 2265.

Thus Cahours (1862) prepared tetramethyllead from methyl iodide,[475] and Polis[476] prepared tetraphenyllead from bromobenzene. Industrial importance attaches to the preparation of tetraethyllead from ethyl chloride and a lead–sodium alloy at a low or moderate temperature.[477]

High yields of alkyllead compounds are obtained by reaction of alkyl halides with mixtures of lead and magnesium.[478]

Shapiro[479] has reviewed the synthesis of tetraalkylleads from lead and its alloys.

Ziegler and his co-workers have described a synthesis specially designed for tetraethyllead.[245,480] It starts from triethylaluminum; the complex $NaF \cdot 2Al(C_2H_5)_3$ or $Na[R_3AlC_2H_5]$ (both good conductors) is electrolyzed at a lead anode, then giving tetraethyllead readily in quantitative yield.

A further method of forming a Pb–C bond is by hydroplumbation of unsaturated organic compounds.[481] For example, tributyllead hydride adds, even at 0° in absence of a catalyst, to terminal olefins such as acrylonitrile, vinyl acetate, and styrene:

$$(C_4H_9)_3PbH + CH_2{=}CHR \longrightarrow (C_4H_9)_3PbCH_2CH_2R$$

$$(R = CN,\ OOCCH_3,\ \text{or}\ C_6H_5)$$

This reaction occurs very readily also with alkynes; for example with phenylacetylene at −20° it affords tributyl(*trans*-styryl)lead.

V. Organic derivatives of elements of the Fifth Group[482]

In their organic derivatives arsenic, antimony, and bismuth occur in the valence state +3 and +5. The derivatives of the trivalent metal have a free electron pair, and some of them thus react extremely violently with electron acceptors.

Thus the lower trialkyl compounds inflame spontaneously in the air. However, in contrast to the behavior of other alkylmetals, the reaction with oxygen does not occur first at the metal–carbon bond: cautious oxidation gives instead oxides of composition R_3MO. The triaryl compounds are stable to atmospheric oxygen and yield their oxides only when subjected to strong oxidizing agents.

The trialkyl and triaryl compounds react very rapidly with chlorine, bromine, or iodine, yielding halides R_3MX_2. Compounds R_2MX and RMX_2 give R_2MX_3 and RMX_4 analogously.

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[475] A. Cahours, *Ann. Chem.*, **122**, 67 (1862).

[476] A. Polis, *Ber. Deut. Chem. Ges.*, **20**, 716 (1887).

[477] J. Edgar, *Ind. Eng. Chem.*, **31**, 1439 (1939).

[478] U.S. Pat. 2,535,190; *Chem. Abstr.*, **45**, 3864 (1951).

[479] H. Shapiro, Advances in Chemistry Series No. **23**, 290 (1959).

[480] K. Ziegler and co-workers, *Angew. Chem.*, **71**, 628 (1959).

[481] W. P. Neumann and K. Kühlein, *Angew. Chem. Int. Ed., Engl.*, **4**, 784 (1965).

[482] M. Dub, "Organometallic Compounds; Methods of Syntheses, Physical Constants, and Chemical Reactions," Vol. 3. "Organic Compounds of Arsenic, Antimony, and Bismuth," Springer Verlag, Berlin–Heidelberg–New York, 1962.

Trialkyl-arsines and -stibines, and triarylarsines, add alkyl iodides, yielding quaternary arsonium and stibonium iodides, R_4MI or $R_3R'MI$.

Organic derivatives of the quinquevalent metals include examples of the following types: halides, RMX_4, R_2MX_3, R_3MX_2, and R_4MX; oxygen compounds, $RMO(OH)_2$, $R_2MO(OH)$, R_3MO, R_4MOH; and pentaalkyl and pentaaryl derivatives MR_5.

Organic halide derivatives of the quinquevalent metals lose alkyl or aryl halide when heated, and thus pass into derivatives of the trivalent element, *e.g.*:

$$R_3MX_2 \longrightarrow R_2MX + RX$$

This reaction occurs particularly readily with the compounds RMX_4 and R_2MX_3, some of which decompose in this way even at room temperature.

1. Organoarsenic compounds[483]

A great deal of work has been devoted to organic derivatives of arsenic, particularly in the search for pharmacologically useful substances.

Organoarsenic compounds can be prepared from arsenic trihalides and organic derivatives of other metals. For example, trialkylarsines are obtained in good yield from dialkylzincs and arsenic trichloride,[484] and dichloro(ethyl)arsine can be prepared from diethylmercury and arsenic trichloride:[485]

$$Hg(C_2H_5)_2 + AsCl_3 \longrightarrow C_2H_5HgCl + C_2H_5AsCl_2$$

Dichloro(ethyl)arsine:[485] Diethylmercury (150 g) is dropped into ice-cooled arsenic trichloride (150 g); a strongly exothermic reaction occurs and crystals separate. The mixture is finally heated for 0.5 h on a water-bath, then treated with anhydrous ether, filtered from the precipitated ethylmercuric chloride, and freed from ether. By repeated fractional distillation the dichloro(ethyl)arsine is separated from the excess of arsenic trichloride; the yield of the former, b.p. 145–150°/760 mm, is 90 g.

The most convenient method, and thus that most often used, is treatment of arsenic halides with alkyl- or aryl-Grignard reagents or organolithium compounds.[486,487]

Triethylarsine:[488] Arsenic trichloride (50 g), diluted with anhydrous ether (120 ml), is added to a cooled Grignard solution from ethyl bromide (93 g) and magnesium (21 g); then ice and dilute hydrochloric acid are added until there is clear separation of two layers. The ether layer is removed, dried over calcium chloride, and freed from ether cautiously below 38° in a stream of carbon dioxide. The residue of the ether is removed in a vacuum and the arsine is distilled in a vacuum into a distilling flask from which it is refractionated in a stream of carbon dioxide. The b.p. is 140°/736 mm and the yield is 40% (18 g).

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[483] W. R. Cullen, *Advan. Organometal. Chem.*, **4**, 145 (1966).

[484] A. W. Hofmann, *Ann. Chem.*, **103**, 357 (1857); R. R. Renshaw and G. E. Holm, *J. Amer. Chem. Soc.*, **42**, 1468 (1920).

[485] W. Steinkopf and W. Mieg, *Ber. Deut. Chem. Ges.*, **53**, 1013 (1920).

[486] H. Hibbert, *Ber. Deut. Chem. Ges.*, **39**, 160 (1906); P. Pfeiffer, *Ber. Deut. Chem. Ges.*, **37**, 4620 (1904).

[487] J. Seifter, *J. Amer. Chem. Soc.*, **61**, 530 (1939); W. R. Cullen and P. E. Yates, *Can. J. Chem.*, **41**, 1625 (1963).

[488] Ref. 1, pp. 456–457.

The yield is decreased by the considerable volatility of the arsine in ether; the ether that was distilled off can be worked up for triethylarsine dihalide.

Analogous syntheses can be effected for tris(perfluorovinyl)arsine[489] and trialkynylarsines.[401,490]

Arsenious oxide (As_2O_3) may replace the trihalide in its reaction with Grignard reagents, and triarylarsines can be prepared in good yield in this way.[491]

Grignard reagents can replace the chlorine of arsenic trichloride stepwise; *e.g.*, reaction with the appropriate amounts of *tert*-butylmagnesium chloride affords *tert*-butyldichloroarsine and di-*tert*-butylchloroarsine.[492]

Dialkyl- and diaryl-chloroarsines are formed in good yield from dichloro-(*N*,*N*-dialkylamino)arsines and organo-magnesium or -lithium compounds.[493] Dichloro(pentafluorophenyl)arsine and chlorobis(pentafluorophenyl)arsine are obtained analogously from pentafluorophenylmagnesium bromide and arsenic trichloride or dichloro-(*N*,*N*-dimethylamino)arsine.[494]

Arsenic derivatives of the types $R_2R'As$ and $RR'R''As$,[495] including very varied dialkyl- and diaryl-alkynylarsines,[401,496] have been synthesized by stepwise Grignard reagents or by isolated reactions of organic arsenic halides with organo-sodium, -lithium, or -magnesium derivatives.

Mixed arsines such as alkyl(diaryl)arsines can also be obtained in the "reverse" reaction, namely that of potassium diarylarsenides with alkyl bromides.[497] Similarly potassium diphenylarsenide and dihaloalkanes afford compounds of the type $(C_6H_5)_2AsCH_2CH_2As(C_6H_5)_2$.[498]

Wittig and Clauss[499] obtained pentaphenylarsenic by the action of phenyl lithium on triphenylarsine dichloride or tetraphenylarsonium bromide. The analogous reaction of methyllithium with trimethylarsine dibromide or tetramethylarsonium iodide gave no isolable amount of pentamethylarsine, although the formation of small amounts of this product could be demonstrated among the others.[500]

Condensation of arsenic trihalides with alkyl or aryl halides in the presence of metallic sodium, analogous to a Wurtz–Fittig reaction, leads to trialkyl- and triaryl-arsines. *E.g.*, tribenzylarsine is obtained by prolonged boiling of benzyl chloride and arsenic trichloride in ether containing sodium and a little ethyl acetate;[501] tripropylarsine is obtained similarly from propyl chloride, arsenic

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[489] R. N. Sterlin, L. N. Pinkina, R. D. Yatsenko, and I. L. Knunyants, *Khim. Nauka i Prom.*, **4**, 800 (1959); *Chem. Abstr.*, **54**, 14,103 (1959).

[490] W. Voskuil and J. F. Arens, *Rec. Trav. Chim.*, **83**, 1301 (1964).

[491] F. F. Blicke and F. D. Smith, *J. Amer. Chem. Soc.*, **51**, 1558 (1929); F. Sachs and H. Kantorowicz, *Ber. Deut. Chem. Ges.*, **41**, 2767 (1908).

[492] A. Tzschach and W. Deylig, *Z. Anorg. Allg. Chem.*, **336**, 36 (1965).

[493] N. K. Bliznyuk, G. S. Levskaya, and E. N. Matynkhina, *Zh. Obshch. Khim.*, **35**, 1247 (1965); *Chem. Abstr.*, **63**, 11,611 (1965).

[494] M. Green and D. Kirkpatrick, *Chem. Commun.*, **1967**, 57.

[495] W. Jones, W. J. C. Dyke, G. Davies, D. C. Griffiths, and J. H. E. Webb, *J. Chem. Soc.*, **1932**, 2284; W. Steinkopf, H. Donat, and P. Jäger, *Ber. Deut. Chem. Ges.*, **55**, 2607 (1922).

[496] J. Benain, *C. R. Hebd. Séances Acad. Sci.*, **261**, 1996 (1965).

[497] A. Tzschach and W. Lange, *Z. Anorg. Allg. Chem.*, **330**, 317 (1964).

[498] A. Tzschach and W. Lange, *Chem,. Ber.*, **95**, 1360 (1962).

[499] G. Wittig and K. Clauss, *Ann. Chem.*, **577**, 26 (1952).

[500] G. Wittig and K. Torssell, *Acta Chem. Scand.*, **7**, 1293 (1953).

[501] A. Michaelis and U. Paetow, *Ber. Deut. Chem. Ges.*, **18**, 41 (1885).

trichloride, and sodium,[502] and triarylarsines from aryl bromides, arsenic trichloride, and sodium in ether.[503]

Triphenylarsine:[504] Ether (600 ml; anhydrous) is poured over metallic sodium (146 g; fine pieces or, better, wire of diameter about 1 mm), a bulb reflux condenser is placed on the flask, and the whole transferred to a fume cupboard. A mixture of arsenic trichloride (100 g) and bromobenzene (260 g) is added fairly fast; then the reaction is allowed to proceed unaided for at least 12 h, with occasional shaking, after which the solution is decanted from residual sodium and precipitated sodium halides and freed from ether. The residual oil is fractionated; the arsine fraction of b.p. 220–230°/14 mm is crystallized (m.p. 59°) when rubbed with ethanol.

Trialkylarsines are also obtained by the action of alkyl iodides on arsenic alloys or compounds of arsenic with strongly electropositive metals such as sodium and potassium.[505]

For the synthesis of the important arylarsonic acids the Bart reaction is the first to be considered;[506,507] it consists of reaction of an arenediazonium salt with an alkali arsenite, *e.g.*:[508]

$$C_6H_5N_2Cl + Na_3AsO_3 \longrightarrow C_6H_5AsO(ONa)_2 + N_2$$

The Bart reaction can also be used for preparation of diarylarsinic acids, *e.g.*:

$$C_6H_5N_2Cl + C_6H_5As(ONa)_2 \longrightarrow (C_6H_5)_2AsO(ONa) + NaCl + N_2$$

Diarylarsinic acids containing two different aryl groups can be obtained by this method.

Arylarsenic compounds may also be obtained by the Nesmeyanov reaction: decomposition of the double salts of arenediazonium halides and iron(III) chloride or zinc chloride in the presence of arsenic trichloride and metallic iron leads to aryldichloroarsines and diarylchloroarsines among other products:[509]

$$ArN_2Cl{\cdot}FeCl_3 + AsCl_3 + Fe \longrightarrow ArAsCl_2 + FeCl_3 + FeCl_2 + N_2$$

$$2ArN_2Cl{\cdot}FeCl_3 + AsCl_3 + 2Fe \longrightarrow Ar_2AsCl + 2FeCl_3 + 2FeCl_2 + 2N_2$$

These products are readily converted in arylarsonic and diarylarsinic acids by nitric acid.

Good yields of triarylarsines are further obtained when arenediazonium chlorides or their double salts $(ArN_2)_2ZnCl_4$ decompose in the presence of arsenic trichloride or chloroarsines in a suspension of zinc dust in acetone:[510]

$$3ArN_2Cl + AsCl_3 + 3Zn \longrightarrow Ar_3As + 3N_2 + 3ZnCl_2$$

Also the Bechamp reaction, although not generally applicable, is useful for synthesis of certain arylarsonic acids:[507] aromatic hydrocarbons activated

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[502] W. M. Dehn, *Amer. Chem. J.*, **40**, 115 (1908).

[503] A. Michaelis and A. Reese, *Ber. Deut. Chem. Ges.*, **15**, 2876 (1882); *Ann. Chem.*, **321**, 160 (1902); G. T. Morgan and D. C. Vining, *J. Chem. Soc.*, **117**, 777 (1920).

[504] Ref. 1, pp. 497–498.

[505] A. Cahours and A. Riche, *Ann. Chem.*, **92**, 361 (1854); H. Landolt, *Ann. Chem.*, **89**, 301 (1854).

[506] Ger. Pat. 250,264; *Chem. Abstr.*, **6**, 3312 (1912).

[507] C. S. Hamilton and J. F. Morgan, *Org. Reactions*, **2**, 415.

[508] H. Schmidt, *Ann. Chem.*, **421**, 159 (1920).

[509] O. A. Reutov and Yu. G. Bundel, *Zh. Obshch. Khim.*, **25**, 2324 (1955); *Chem. Abstr.*, **50**, 9318 (1956).

[510] W. E. Hanby and W. A. Waters, *J. Chem. Soc.*, **1946**, 1029.

by hydroxyl or amino groups react with arsenic acid, *e.g.*, aniline and arsenic acid afford *p*-aminophenylarsonic acid (arsanilic acid) when heated together at about 160°:

$$C_6H_5NH_2 + H_3AsO_4 \longrightarrow NH_2C_6H_4AsO(OH)_2 + H_2O$$

Phenol gives (*p*-hydroxyphenyl)arsonic acid analogously.

The Meyer reaction is a general reaction particularly suitable for preparation of aliphatic arsonic acids;[507,511] here an alkyl halide is treated with sodium arsenite:

$$RX + Na_3AsO_3 \longrightarrow RAsO(ONa)_2 + NaX$$

Methylarsonic acid: Arsenious oxide, As_2O_3 (99 g), is dissolved in water (250 ml) by means of sodium hydroxide (3 moles), then methanol (50 ml) and methyl iodide (145 g) are added, and the whole is shaken mechanically for 24 h, at first with periodic cooling. The resulting sodium salt affords the free acid in 95% yield either directly or by way of the calcium salt.

The sodium salt of a dialkylarsinic acid is obtained similarly when the sodium salt of an alkylarsonous acid reacts with an alkyl halide:

$$RX + RAs(ONa)_2 \longrightarrow R_2AsO(ONa) + NaX$$

2. Organoantimony compounds

Organic derivatives of antimony can be prepared in essentials in the same way as the arsenic analogs; *e.g.*, trialkylstibines are formed by the action of alkyl iodides on antimony–potassium alloy:[512]

$$3RX + K_3Sb \longrightarrow SbR_3 + 3KX$$

More suitable for, especially, the triarylstibines of higher molecular weight, is the reaction of aryl halides, antimony trichloride, and an excess of sodium in benzene or xylene, as discovered by Michaelis and Reese;[513] ether cannot be used as solvent as the necessary reaction temperature cannot then be attained.[514]

Tris-(4-*m*-xylyl)stibine:[514] 4-Bromo-*m*-xylene (56 g) and antimony trichloride (23 g) are dissolved in dry benzene (150 ml), and then metallic sodium (50 g; in pieces) is added. When the reaction is complete (usually after warming) the solution is set aside overnight and then filtered. The residue is extracted three times with boiling benzene. All the liquids are united and the benzene is removed, whereafter the oily residue is poured into anhydrous ethanol. In a few minutes the stibine separates as long needles (25 g, 57%).

Many organoantimony compounds can be prepared by reaction of antimony halides with reactive organometallic compounds, principally Grignard reagents but also organolithium and organozinc compounds. Almost all the trialkyl- and triaryl-stibines were obtained from antimony chloride and the Grignard reagent:[486,515]

$$SbCl_3 + 3RMgX \longrightarrow SbR_3 + 3MgXCl$$

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[511] G. Meyer, *Ber. Deut. Chem. Ges.*, **16**, 1439 (1883); R. Pietsch, *Monatsh. Chem.*, **96**, 138 (1965).

[512] H. Landolt, *Ann. Chem.*, **78**, 91 (1851); C. Löwig and E. Schweizer, *Ann. Chem.*, **75**, 315 (1850).

[513] A. Michaelis and A. Reese, *Ann. Chem.*, **233**, 42 (1886).

[514] A. E. Goddard, *J. Chem. Soc.*, **124**, 2315 (1923).

[515] W. J. C. Dyke, W. C. Davies, and W. J. Jones, *J. Chem. Soc.*, **1930**, 463; L. H. Long and J. F. Sackman, *Trans. Faraday Soc.*, **51**, 1062 (1955); J. I. Harris, S. T. Bowden, and W. J. Jones, *J. Chem. Soc.*, **1947**, 1568; A. N. Tatarenko and Z. M. Manulkin, *Zh. Obshch. Chem.*, **34**, 3462 (1964); *Chem. Abstr.*, **62**, 2792 (1965).

Trialkenyl- and trialkynyl-stibines, *e.g.*, tris(perfluorovinyl)-,[489] triethynyl-,[490] and tris(phenylethynyl)-stibine,[401] have been synthesized by this method.

Since organoaluminum compounds have become industrially available by Ziegler's direct synthesis, they have appeared to offer opportunities for synthesis of organoantimony compounds; for example, the preparation of trialkylstibines by treatment of antimony(III) oxide with trialkylaluminums has been proposed:[516]

$$Sb_2O_3 + 3AlR_3 \longrightarrow 2SbR_3 + 3(RAlO)_n$$

Organolithium compounds are used also for the synthesis of pentaaryl- and pentaalkyl-antimony compounds; thus, pentaphenylantimony is obtained from phenyllithium and triphenylstibine dichloride or tetraphenylstibonium bromide:[499]

$$(C_6H_5)_3SbCl_2 + 2C_6H_5Li \longrightarrow (C_6H_5)_5Sb + 2LiCl$$

$$(C_6H_5)_4SbBr + C_6H_5Li \longrightarrow (C_6H_5)_5Sb + LiBr$$

It is also formed by interaction of phenyllithium and *Sb*-(*p*-toluenesulfonylamino)triphenylantimony.[517]

Pentaphenylantimony readily reacts further with phenyllithium, then forming lithium hexaphenylantimonate:

$$(C_6H_5)_5Sb + C_6H_5Li \longrightarrow Li[Sb(C_6H_5)_6]$$

In analogy with these reactions Wittig and Torsell[500] prepared pentamethylantimony by interaction of methyllithium and trimethylstibine dibromide or tetramethylstibonium iodide.

Unusual organoantimony compounds have been obtained by reaction of alkali-metal derivatives of organoantimony compounds with certain organic halides; *e.g.*, compounds of the series $(C_6H_{11})_2Sb—(CH_2)_n—Sb(C_6H_{11})_2$ have been prepared from lithium di(cyclohexyl)stibide and α,ω-dihaloalkanes.[518]

Arylantimony compounds can be obtained from arenediazonium salts by a variety of methods:

Arylstibonic acids are formed when arenediazonium salts are decomposed by an alkali antimonite (Sb_2O_3 + alkali).[519,520] The procedure can be varied by preparing a double salt, *e.g.*, $C_6H_5N_2Cl \cdot SbCl_3$ by adding antimony trichloride in acid solution and decomposing the salt by sodium hydroxide solution.

Analogously, decomposing an arenediazonium salt in the presence of an arylantimony oxide by potassium hydroxide solution affords the diarylstibinic acid:[519]

$$RN_2X + RSbO + 2KOH \longrightarrow R_2SbO(OK) + H_2O + N_2$$

There are also the syntheses of arylantimony compounds from arenediazonium salts by the Nesmeyanov reaction, which has been very extensively investigated in just this field and shown to have manifold applications.

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[516] W. Stamm, *Trans. New York Acad. Sci.*, [2], **28**, 396 (1966).

[517] G. Wittig and D. Hellwinkel, *Chem. Ber.*, **97**, 789 (1964).

[518] K. Issleib and B. Hamann, *Z. Anorg. Allg. Chem.*, **332**, 179 (1964).

[519] H. Schmidt, *Ann. Chem.*, **421**, 174 (1920).

[520] A. B. Bruker, *Zh. Obshch. Khim.*, **18**, 1297 (1948); *Chem. Abstr.*, **43**, 4647 (1949).

Many double salts are known to be composed of various antimony halides and arenediazonium salts, *e.g.*, $ArN_2Cl \cdot SbCl_3$, $ArN_2Cl \cdot SbCl_5$,[521,522] $ArN_2Cl \cdot Ar'SbCl_4$,[523] $ArN_2Cl \cdot Ar_2SbCl_3$;[524] decomposition of these with metal powders gives various kinds of arylantimony compound, as follows:

Decomposing double salts of the type $ArN_2Cl \cdot SbCl_3$ with zinc dust in acetone gives mixtures of products $ArSbCl_2$, Ar_2SbCl, Ar_3Sb, and Ar_3SbCl_2.[520,525] Decomposing these double salts by iron powder in acetone at 0° gives diarylantimony trichloride as main product alongside usually small amounts of the products just mentioned:[526]

$$2ArN_2Cl{\cdot}SbCl_3 + Fe \longrightarrow Ar_2SbCl_3 + 2N_2 + FeCl_2 + SbCl_3$$

Bis-(*p*-nitrophenyl)antimony trichloride:[526] Iron powder (2 g, 0.036 mole) is added at 0°, during 35–40 min, with vigorous stirring, to a solution of *p*-nitrobenzenediazonium chloride-1-antimony trichloride (15 g, 0.036 mole) in anhydrous acetone (45 ml), and the whole is then stirred for a further 40 min. The inorganic solid is removed and the filtrate is evaporated. The residual product is treated with 5N-hydrochloric acid (50 ml) and then with 96% ethanol (25–30 ml). The resulting mixture is poured into 5% ammonia solution (excess) containing ice; this precipitates bis-(*p*-nitrophenyl)stibinic acid (7 g, 97%), which is then converted into the trichloride by crystallization from 5N-hydrochloric acid.

Compounds of types Ar_2SbCl_3 and Ar_3SbCl_2 are obtained when double salts $ArN_2Cl \cdot SbCl_5$ are decomposed in acetone by iron powder[521] (the $SbCl_5$ double salts are obtained by treating the corresponding $FeCl_3$ double salt with $SbCl_5$ in chloroform or carbon tetrachloride and precipitating the new salt by ether):

$$2ArN_2Cl{\cdot}SbCl_5 + 3Fe \longrightarrow Ar_2SbCl_3 + 2N_2 + SbCl_3 + 3FeCl_2$$

$$3ArN_2Cl{\cdot}SbCl_5 + 5Fe \longrightarrow Ar_3SbCl_2 + 3N_2 + 2SbCl_3 + 5FeCl_2$$

Arenediazonium chloride–antimony pentachloride double salts decompose in the presence of cuprous chloride in acetone in the following manner:[527]

$$ArN_2Cl{\cdot}SbCl_5 + Cu_2Cl_2 \longrightarrow ArSbCl_4 + N_2 + 2CuCl_2$$

Mixed arylantimony halides can also be synthesized by the Nesmeyanov reaction. Compounds of type $ArAr'SbCl_3$, for instance, are obtained by decomposition of double salts $ArN_2Cl \cdot Ar'SbCl_4$ by iron powder in acetone,[528] as follows:

$$\begin{tikzcd}
ArN_2Cl{\cdot}Ar'SbCl_4 + Fe \arrow[r] & ArN_2Cl{\cdot}Ar'SbCl_2 + FeCl_2 \arrow[d] \\
& ArAr'SbCl_3 + N_2
\end{tikzcd}$$

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[521] O. A. Reutov and V. V. Kondrat'eva, *Zh. Obshch. Khim.*, **24**, 1259 (1954); O. A. Reutov, *Dokl. Akad. Nauk S.S.S.R.*, **87**, 991 (1952); *Chem. Abstr.*, **49**, 12,339 (1955); **48**, 143 (1954).

[522] O. A. Reutov, *Dokl. Akad. Nauk S.S.S.R.*, **87**, 73 (1952); *Chem. Abstr.*, **48**, 142 (1954).

[523] O. A. Reutov and A. G. Markovskaya, *Dokl. Akad. Nauk S.S.S.R.*, **98**, 979 (1954); *Chem. Abstr.*, **49**, 2926 (1955).

[524] O. A. Reutov, A. G. Markovskaya, and A. N. Lovtsova, *Dokl. Akad. Nauk S.S.S.R.*, **99**, 269 (1954); *Chem. Abstr.*, **49**, 15,767 (1955).

[525] A. N. Nesmeyanov and K. A. Kocheshkov, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1944**, 416; *Chem. Abstr.*, **39**, 4320 (1945).

[526] A. N. Nesmeyanov, O. A. Reutov, and O. A. Ptitsyna, *Dokl. Akad. Nauk S.S.S.R.*, **91**, 1341 (1953); *Chem. Abstr.*, **48**, 11,375 (1954).

[527] A. N. Nesmeyanov, O. A. Reutov, and P. G. Knol, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1954**, 410; *Chem. Abstr.*, **49**, 9651 (1955).

[528] O. A. Reutov and A. G. Markovskaya, *Dokl. Akad. Nauk S.S.S.R.*, **99**, 543 (1954); *Chem. Abstr.*, **49**, 15,767 (1955).

The stibine double salt shown above as intermediate can also be obtained, according to Reutov, as follows:[23]

$$\mathrm{Ar'SbCl_2 + ArN_2Cl{\cdot}FeCl_3 \longrightarrow ArN_2Cl{\cdot}Ar'SbCl_2 + FeCl_3}$$

and, of course, decomposes to $\mathrm{ArAr'SbCl_3}$ as above.

When arenediazonium salts are decomposed by elemental antimony powder in acetone or ethyl acetate containing calcium carbonate, the products are triarylstibine dichloride ($\mathrm{Ar_3SbCl_2}$), triarylstibine, and diarylchlorostibine ($\mathrm{Ar_2SbCl}$) in amounts that vary according to the nature of the aryl group.[27,28]

A further very interesting reaction, that affords arylantimony compounds from diarylhalonium salts, has been studied by Reutov and his co-workers.[529] They found that when double salts of diaryliodonium chloride and an antimony halide, specifically compounds of composition $\mathrm{(Ar_2ICl)_2 \cdot SbCl_3}$, $\mathrm{Ar_2ICl \cdot SbCl_3}$, or $\mathrm{Ar_2ICl \cdot SbCl_5}$, are decomposed by antimony powder in acetone or ethyl acetate at temperatures up to 120°, then products of composition $\mathrm{Ar_3SbCl_2}$, $\mathrm{Ar_2SbCl_3}$, and $\mathrm{Ar_2SbCl}$ are formed.[529]

Organobismuth compounds have been reviewed by Gilman and Yale.[530]

Alkyl and aryl derivatives of bismuth can be prepared with the metal in the valence state +3 and +5. The most important methods are those used also for arsenic and antimony compounds, as discussed above.

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[529] O. A. Reutov, O. A. Ptitsina, and G. Ertel, *Chem. Techn.*, **10**, 201 (1958); O. A. Ptitsina, A. N. Koslova, and O. A. Reutov, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1962**, 634; *Chem. Abstr.*, **57**, 15,148 (1962).

[530] H. Gilman and H. L. Yale, *Chem. Rev.*, **30**, 281 (1942).

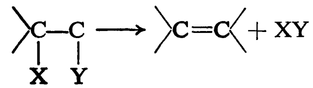
CHAPTER 11

Formation of Carbon–Carbon Multiple Bonds

Compiled by
I. Eichhorn

11.1. Ethylenic compounds

Carbon–carbon double bonds are introduced into a pre-existing carbon skeleton by β-elimination reactions, in which two groups are removed, one from each of two neighboring carbon atoms:



Here it is necessary to differentiate newly formed double bonds according to whether they are conjugated — in an aliphatic or aromatic carbocyclic or heterocyclic system — or isolated.

I. Isolated ethylenic bonds*

1. Removal of water from alcohols

Dehydration of alcohols is an extremely important method of introducing double bonds. It can be effected either by means of dehydrating agents or catalytically. The most important dehydrating agents include concentrated sulfuric acid, potassium hydrogen sulfate, zinc chloride, phosphorus(v) oxide, boric oxide, oxalic acid, *p*-toluenesulfonic acid, formic acid, acetyl chloride, the Grignard reagent, and iodine.

Water is not always split off in one direction only, and dehydration is often accompanied by isomerization, rearrangement, or even cleavage of the carbon chain. Thus heating 1-butanol with 85% phosphoric acid or 60% sulfuric acid leads to mixtures of 1- and 2-butene.[1] In several cases the individual olefins can be isolated from the mixture of isomers by fractional distillation, as F. C. Whitmore and his colleagues found for the isomeric octenes.[2] An isomerization that was actually desired occurs when cyclohexene or its homologs are heated over alumina at 470–480°, this affording alkylcyclopentenes.[3]

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* For a review of elimination reactions affording olefins in solution see W. H. Saunders, Jr., in S. Patai's "The Chemistry of Alkenes," Interscience Publishers, London–New York–Sydney, 1964, p. 149.

[1] W. G. Young and H. J. Lucas, *J. Amer. Chem. Soc.*, **52**, 1964 (1930).

[2] F. C. Whitmore, H. E. Whitmore, and N. C. Cook, *J. Amer. Chem. Soc.*, **72**, 51 (1950).

[3] H. Adkins and A. K. Roebuck, *J. Amer. Chem. Soc.*, **70**, 4041 (1948).

Alcohols that are branched at the α-position to the hydroxyl group, such as 3,3-dimethyl-2-butanol, rearrange readily on dehydration[4,5] (the retropinacol rearrangement[6]):

$$2C(CH_3)_3CH(OH)CH_3 \xrightarrow{-H_2O} (CH_3)_2C{=}C(CH_3)_2 + CH(CH_3)_2C(CH_3){=}CH_2$$

The carbon chain is cleaved when, *e.g.*, 2,2,4,4-tetramethyl-3-pentanol is heated with chloronaphthalenesulfonic acid at 180°:[7]

$$C(CH_3)_3CH(OH)C(CH_3)_3 \xrightarrow{-H_2O} (CH_3)_2C{=}CHCH_3 + (CH_3)_2C{=}CH_2$$

The direction in which water is removed generally follows Saytzeff's rule, according to which the hydrogen atom is removed from the β-carbon atom carrying the smallest number of hydrogen atoms or largest number of alkyl groups.[8]

This leads to the olefin with the largest number of alkyl groups on doubly bonded carbon. For instance, 3-methyl-2-butanol in concentrated sulfuric acid affords 2-methyl-2-butene and not 3-methyl-1-butene:

$$CH(CH_3)_2CH(OH)CH_3 \xrightarrow{-H_2O} (CH_3)_2{=}CHCH_3$$

As mentioned elsewhere (page 280), addition of water to an olefin occurs so that hydrogen is added to the carbon atom already carrying the larger number of hydrogen atoms; readdition of water to 2-methyl-2-butene thus affords 2-methyl-2-butanol, $(CH_3)_2C(OH)CH_2CH_3$, and not 3-methyl-2-butanol.

The ease of dehydration depends largely on the reaction conditions and still more on the structure of the alcohol in question. Increasing substitution by alkyl groups increases the rate of olefin formation. Also, the ease of dehydration increases in the order primary > secondary > tertiary alcohols; for the preparation of olefins it often suffices to warm a tertiary alcohol with a trace of iodine or in no more than 15% sulfuric acid.[9] For example, 2-methyl-2-hexene is formed merely by distilling 2-methyl-2-hexanol containing a trace of iodine,[10] and refluxing 2-methyl-2-butanol with 15% sulfuric acid affords 2-methyl-2-butene with a little 2-methyl-1-butene:[11]

$$CH_3CH_2C(CH_3)_2OH \xrightarrow{-H_2O} CH_3CH{=}C(CH_3)_2[+ CH_3CH_2C(CH_3){=}CH_2]$$

When a tertiary alcohol is formed by a Grignard reaction, the derived olefin is often easily obtained by warming the Grignard addition compound without isolation of the alcohol: after treatment of the alkyl- or aryl-magnesium halide with the carbonyl compound and removal of the solvent, the residue is heated for a short time, whereupon the olefin distils off.[12] In this way, for instance,

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[4] F. C. Whitmore and P. L. Meunier, *J. Amer. Chem. Soc.*, **55**, 3721 (1933).

[5] P. L. Cramer and A. L. Glasebrook, *J. Amer. Chem. Soc.*, **61**, 230 (1939).

[6] R. B. Scott, Jr., and J. B. Gayle, *J. Org. Chem.*, **18**, 740 (1953).

[7] F. C. Whitmore and E. E. Stahly, *J. Amer. Chem. Soc.*, **55**, 4153 (1933).

[8] A. Saytzeff, *Ann. Chem.*, **179**, 300 (1875).

[9] J. M. Church and F. C. Whitmore, *J. Amer. Chem. Soc.*, **56**, 182 (1934).

[10] G. Edgar, G. Calingaert, and R. E. Marker, *J. Amer. Chem. Soc.*, **51**, 1483 (1929).

[11] F. C. Whitmore, C. S. Rowland, S. N. Wrenn, and G. W. Kilmer, *J. Amer. Chem. Soc.*, **64**, 2970 (1942).

[12] J. M. Church and F. C. Whitmore, *J. Amer. Chem. Soc.*, **56**, 183 (1934).

diphenylethylene can be prepared from ethyl acetate and phenylmagnesium bromide;[13] and **α-methylstyrene** $C_6H_5C(CH_3) = CH_2$ is prepared from acetophenone and two equivalents of methylmagnesium iodide as follows:[14]

Methylmagnesium iodide (2 moles) and acetophenone (1 mole) are brought into reaction in the usual way, the ether is distilled off, and the residue is heated for 6 h at 100°. Decomposition with ice-water, extraction with ether, drying, and distillation then afford the unsaturated hydrocarbon, b.p. 162° (5–6 g from each 10 g of acetophenone).

Since secondary and primary alcohols are by no means readily dehydrated, high-boiling mineral acids such as sulfuric or phosphoric acid, or powerful dehydrating salts such as potassium hydrogen sulfate or zinc chloride, must be used.

The use of concentrated sulfuric acid is preparatively simple but is limited by a variety of circumstances. At the higher temperatures there are disturbances due to the oxidizing, carbonizing, and isomerizing action of sulfuric acid and the formation of ethers which occurs under the same conditions. Thus phosphoric is often preferred to sulfuric acid for such dehydrations. For instance, it is not advisable on a laboratory scale to prepare ethylene from ethanol by means of sulfuric acid, and this is done by phosphoric acid or, better, catalytically, by passing ethanol vapor over a heated catalyst.[15] For the preparation of cyclohexene from cyclohexanol it is better to use potassium hydrogen sulfate than concentrated sulfuric acid, since the latter readily causes carbonization and presence of sulfur dioxide as impurity in the product;[16] **cyclohexene** is, however, obtained rapidly and in good yield by dehydrating cyclohexanol with phosphoric acid as follows:[17]

Cyclohexanol (1 kg, 10 moles) is dropped during 4–5 h into 85% phosphoric acid (200 g) at a bath-temperature of 165–170°, cyclohexene and water distilling off through a column and attached condenser; during this operation the temperature at the head of the column should not exceed 90°. After the addition the bath-temperature is raised to 200° and kept thereat for 0.5 h. The distillate separates into two layers. The upper layer is separated, dried over magnesium sulfate, and distilled through a column, affording a 79–84% yield of cyclohexene, b.p. 81–82°. The residue consists mainly of unchanged cyclohexanol.

Oxalic acid has been preferred for dehydration of terpene alcohols and generally for compounds that rearrange readily.[18] According to Wallach,[19] boiling terpineol with aqueous oxalic acid gives mainly terpinolene, whereas isomerization to terpinene occurs when sulfuric acid is used.

2,3-Dimethyl-2-butene:[20] 2,3-Dimethyl-2-butanol (408 g) is heated with anhydrous oxalic acid (1200 g) for 8 h at 100°, then the mixture is distilled and the distillate is washed several times with ice-water, dried over calcium chloride, and distilled from sodium. Careful fractionation separates the product into two fractions, of which the higher-boiling (b.p. 72.9 to 73.2°/760 mm; 80% yield) consists of 2,3-dimethyl-2-butene. About 20% of the unsymmetrical

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[13] C. F. H. Allen and S. Converse, *Org. Syn.*, Coll. Vol. I, 219.

[14] A. Klages, *Ber. Deut. Chem. Ges.*, **35**, 2640 (1920).

[15] P. K. Ssakmin, *Ber. Deut. Chem. Ges.*, **67**, 392 (1934).

[16] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Verlag Walter de Gruyter & Co., Berlin, 36th ed, 1954, p. 100.

[17] B. B. Corson and V. N. Ipatieff, *Org. Syn.*, Coll. Vol. II, 152 (1955); E. Levas, *Ann. Chim.* (*Paris*), [xii], **3**, 149 (1948).

[18] N. Zelinsky and J. Zelikow, *Ber. Deut. Chem. Ges.*, **34**, 3249 (1901).

[19] O. Wallach, *Ann. Chem.*, **275**, 106 (1893).

[20] I. Schurman and C. E. Boord, *J. Amer. Chem. Soc.*, **55**, 4932 (1933).

2,3-dimethyl-1-butene is formed as by-product:

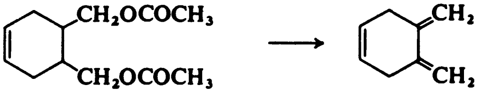
$$(CH_3)_2C(OH)CH(CH_3)_2 \longrightarrow \left[\begin{array}{ll} \longrightarrow CH_3)_2C{=}C(CH_3)_2 & 80\% \\ \longrightarrow CH_2{=}C(CH_3)CH(CH_3)_2 & 20\% \end{array}\right.$$

Phthalic anhydride has also been used for dehydration of terpene alcohols.[21] However, Waldmann and Petru[22] found that the dehydrating action of phthalic anhydride is appreciably increased by addition of a little benzenesulfonic acid; 2-propanol, 2-methyl-1-propanol, and cyclohexanol, *inter alia* are readily dehydrated by boiling phthalic anhydride containing a little benzenesulfonic acid.

Unsaturated compounds are obtained in good yield and often without isomerization by pyrolysis of esters of the requisite alcohol. These pyrolyses generally proceed with considerable stereoselectivity, yielding mostly the *cis*-olefin. A review of pyrolytic *cis*-eliminations has been provided by DePuy and King.[23] The experimental technique is very simple: the ester is heated as liquid or vapor at 300–500°. Working up of the product is also simple since neither a solvent nor another reactant is present. Pyrolysis of 1,2-dimethylpropyl acetate at 500° gives pure 3-methyl-1-butene in 72% yield; pyrolysis of 1,3-dimethylbutyl acetate also proceeds only in one direction, yielding 4-methyl-1-butene,[24] and it is to be noted that in these cases olefin formation does not follow Saytzeff's rule:

$$(CH_3)_2CHCH_2CH(CH_3)OCOCH_3 \xrightarrow{450^\circ} (CH_3)_2CHCH_2CH{=}CH_2$$

Even **4,5-di(methylene)cyclohexene**, which isomerizes extremely readily, can be prepared by pyrolysis of the corresponding diacetate:[25]



Nitrogen is passed through a vertical borosilicate combustion tube (20 × 300 mm) that is filled with solid masses and heated at 500°. 4,5-Cyclohexenedi(methyl acetate) (300 g, 1.33 moles) is added in portions at 1.5-min intervals. The product is condensed, washed with water, and dried over potassium carbonate. Thorough fractionation provides 4,5-di(methylene)cyclohexene (68.1 g) together with starting material and the (2-methylene-4-cyclohexenyl)methylacetate that results from partial pyrolysis.

Esters of higher fatty acids are pyrolysed with particular ease. According to Krafft,[26] distilling dodecyl palmitate at 600 mm affords 1-dodecene and palmitic acid very smoothly.

Further, instead of a preformed ester, a mixture of acetic anhydride and the alcohol may be pyrolysed directly, and this method is suitable for preparation of higher 1-alkenes.[27]

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[21] J. Zelikow, *Ber. Deut. Chem. Ges.*, **37**, 1376 (1904); S. Nametkin, *Ann. Chem.*, **440**, 66 (1924); G. Komppa and G. A. Nyman, *Ann. Chem.*, **535**, 252 (1938).

[22] H. Waldmann and F. Petru, *Chem. Ber.*, **83**, 287 (1950).

[23] C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

[24] W. J. Bailey and C. King, *J. Amer. Chem. Soc.*, **77**, 75 (1955).

[25] W. J. Bailey and J. Rosenberg, *J. Amer. Chem. Soc.*, **77**, 73 (1955).

[26] F. Krafft, *Ber. Deut. Chem. Ges.*, **16**, 3020 (1883).

[27] D. W. Aubrey, A. Barnatt, and W. Gerrard, *Chem. & Ind. (London)*, **1965**, 681.

As in the pyrolysis of carboxylic esters, thermal decomposition of xanthic esters[28,29] (the Tschugaeff reaction) provides unsaturated compounds free from impurities that would be due to isomerization:

$$CHR_2CR_2—O—C(S)SCH_3 \longrightarrow CR_2{=}CR_2 + COS + CH_3SH$$

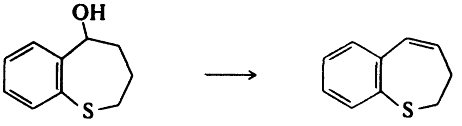
This decomposition occurs already at 110–180°, that is, under considerably milder conditions than are required for carboxylic ester pyrolysis. The method is applicable when low temperatures and basic conditions are necessary, but there is the disadvantage that the resulting olefins usually contain sulfur impurities.

The xanthates are obtained by warming the requisite alcohols with carbon disulfide and an alkali hydroxide,[30] alkali metal,[31] or sodium hydroxide,[32] and treating the resulting ester with an alkyl iodide. The xanthates most used are *S*-methyl derivatives.

Pyrolysis of readily available phosphinates affords olefins at relatively low temperatures (195–260°), in great purity, and without rearrangement.[33]

Di-*tert*-alkyl oxalates decompose to olefins (80–100% yield) at 140–160°.[34]

Secondary and tertiary alcohols derived from benzyl alcohol, and also tertiary aliphatic alcohols, afford olefins when heated for 9–10 hours in dimethyl sulfoxide. For example, 2,3-dihydrobenzo[*b*]thiepin is formed in 81% yield from 2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-ol in 4–8 molar equivalents of dimethyl sulfoxide:[35]



Boric acid is a mild dehydrating agent suitable for removal of water from some primary, secondary, or tertiary alcohols. Since the acid and the alcohol form first a trimeric metaboric ester, which then regenerates the boric acid when it decomposes to the olefin,[36] the reaction is somewhat similar to pyrolysis of carboxylic esters; but the boric acid dehydration occurs at appreciably lower temperatures (250–300°). Olefins are readily obtained by heating approximately molar equivalents of boric acid and 1-octanol, 1-heptanol, 1-hexanol, (—)-menthol, cyclohexanol, or 5α-cholestan-3β-ol;[36,37] but rearrangements may occur, as has been shown for 3,3-dimethyl-2-butanol, borneol, cyclohexanemethanol, and cyclobutanemethanol.[38]

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[28] H. R. Nace, *Org. Reactions*, **12**, 57 (1962).

[29] L. Tschugaeff, *Ber. Deut. Chem. Ges.*, **32**, 3332 (1899).

[30] F. C. Whitmore and C. T. Simpson, *J. Amer. Chem. Soc.*, **55**, 3809 (1933).

[31] D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3887 (1949); E. R. Alexander and A. Mudrak, *J. Amer. Chem. Soc.*, **72**, 1810 (1950).

[32] G. L. O'Connor and H. R. Nace, *J. Amer. Chem. Soc.*, **74**, 5454 (1952).

[33] K. D. Berlin and T. H. Austin, *J. Org. Chem.*, **30**, 2745 (1965).

[34] G. J. Karabatsos, J. M. Corbett, and K. L. Krumel, *J. Org. Chem.*, **30**, 689 (1965).

[35] V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).

[36] G. L. O'Connor and H. R. Nace, *J. Amer. Chem. Soc.*, **77**, 1578 (1955); S. Dev, *J. Indian. Chem. Soc.*, **33**, 769 (1956).

[37] W. Brandenberg and A. Galat, *J. Amer. Chem. Soc.*, **72**, 3275 (1950).

[38] O. L. Chapman and G. W. Borden, *J. Org. Chem.*, **26**, 4193 (1961).

Water is removed with especial ease from alcohols whose hydroxyl group is in a β-position to an oxo, alkoxycarbonyl, nitrile, or nitro group. For example, on aldolization of acetaldehyde the acid present in the reaction medium suffices for dehydration of the product to the unsaturated carbonyl compound, *i.e.*, to crotonaldehyde. One hour's boiling with dilute sulfuric acid suffices for preparation of 3-hepten-2-one from 4-hydroxy-2-heptanone:[39]

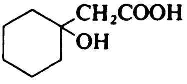
$$C_3H_7CH(OH)CH_2COCH_3 \xrightarrow{-H_2O} C_3H_7CH{=}CHCOCH_3$$

Diacetone alcohol $(CH_3)_2C(OH)CH_2COCH_3$ is dehydrated to **mesityl oxide** $(CH_3)_2C{=}CHCOCH_3$ in the presence of a trace of iodine, as follows:[40]

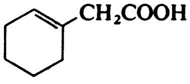
Iodine (0.5 g) is added to diacetone alcohol (700 g), and the mixture is distilled through a small column. After about two-thirds have distilled, the remaining one-third of the distillate of b.p. 125–130° (pure mesityl oxide) is collected separately. The first two-thirds form two layers, of which the lower, aqueous phase is discarded. The upper layer is dried over calcium chloride and fractionated, affording an acetone fraction (b.p. 60–80°), a middle fraction (b.p. 80–125°), and a mesityl oxide fraction (b.p. 126–130°). Saturating the aqueous layer with potassium carbonate affords a further small amount (11 g) of an oil that consists of equal parts of acetone and mesityl oxide. The total yield of crude mesityl oxide is 578 g (97.8%). According to Conant and Tuttle,[41] 0.1 g of iodine suffices for 1100 g of crude diacetone alcohol.

β-Hydroxy acids also readily lose water, yielding unsaturated acids; but the process is important only in isolated cases; one such was the preparation of *trans*-10-hydroxy-2-decenoic acid, a main constituent of royal jelly, for which purpose 3,10-dihydroxydecanoic acid was dehydrated in the presence of acetic anhydride.[42] In most cases, however, other methods make the unsaturated carboxylic acids more readily available than the hydroxy acids that would be used for their preparation.

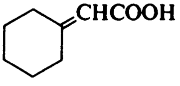
The β-hydroxy esters obtained by Reformatzki syntheses are very readily dehydrated, so that water is often lost on distillation and hydrolysis; then dehydration is completed by heating with acetic anhydride, acetyl chloride, potassium hydrogen sulfate, formic acid, or sulfuric acid. Depending on the nature of the substituents present on the β-carbon atom, the products are α,β- or β,γ-unsaturated acids or mixtures of both.[43] In a few exceptional cases α,β- or β,γ-unsaturated acids can be obtained at will from β-hydroxy acids by choice of a suitable dehydrating agent; an example of this is (1-hydroxycyclohexyl)acetic acid (**1**) which, according to Wallach,[44] is converted by potassium hydrogen sulfate or phosphorus(v) oxide into (1-cyclohexenyl)-acetic acid (**2**) but by acetic anhydride into the isomer, cyclohexylideneacetic acid (**3**):



(1)



(2)



(3)

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[39] M. Smith, B. Chase, and R. Rhodes, *J. Amer. Chem. Soc.*, **66**, 1548 (1944).

[40] H. Hibbert, *J. Amer. Chem. Soc.*, **37**, 1755 (1915).

[41] B. Conant and N. Tuttle, *Org. Syn.*, Coll. Vol. I, 345 (1941).

[42] E. E. Smissman, J. F. Muren, and N. A. Dahle, *J. Org. Chem.*, **29**, 3517 (1964).

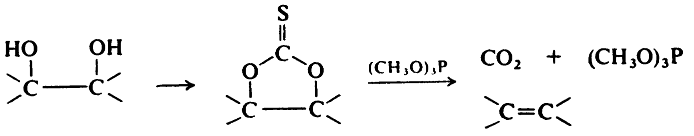
[43] R. L. Shriner, *Org. Reactions*, **1**, 11 (1942).

[44] O. Wallach, *Ann. Chem.*, **365**, 257 (1909).

α,β-Unsaturated acids are rarely formed from α-hydroxy acids by means of dehydrating agents, which, instead, afford lactides and anhydrides or, with loss of formic acid, aldehydes. However, α,β-unsaturated nitriles can be obtained from α-hydroxy nitriles (cyanohydrins) by means of thionyl chloride[45] or phosphorus(v) oxide,[46] and are readily hydrolysed to the corresponding α,β-unsaturated acids.

2-Methylacrylonitrile, $CH_2{=}C(CH_3)CN$:[46] Phosphorus(v) oxide (75 g) is weighed rapidly into a flask (500 ml) that is then fitted with a reflux condenser, dropping funnel, and drying tube and warmed in a water-bath at 10–15°. Acetone cyanohydrin (42.5 g) is dropped in with vigorous shaking during 0.5 h, after which the nitrile is removed by distillation from the viscous mass. A second distillation affords a 34.3% (11.5 g) yield of 2-methylacrylonitrile, b.p. 89–91°.

Complete control of the position and stereochemistry of the double bond is achieved when glycols are converted into olefins by way of thiocarbonic *O*-esters which are then cleaved by trimethyl or triethyl phosphite:[47]



The first stage of the process consists of refluxing the glycol with 1,1′-thiocarbonyldiimidazole for 30 min;[48] the resulting cyclic thiocarbonate is converted into the olefin by 70–80 hours' refluxing with an excess of trimethyl phosphite. In this way, for example, *cis*-stilbene was obtained in 92% yield from *meso*-hydrobenzoin, and *trans*-cyclodecene in 81% yield from *trans*-1,2-cyclodecanediol.

It is mainly on the industrial scale that catalytic dehydration of alcohols becomes important, but it has been used in the laboratory particularly for preparation of the lower alkenes such as ethylene, propene, and butene. The most suitable catalysts are γ-alumina, thorium dioxide, and blue tungsten oxide. Primary and secondary alcohols are usually dehydrated in the gas phase at 250–450°; high-boiling tertiary alcohols are dehydrated without need for a catalyst when they are heated at 150–200° (see page 814).

2. Removal of hydrogen halide

Two methods of dehydrohalogenation come up for discussion, namely, thermal-catalytic cleavage and cleavage by inorganic or organic bases.

Thermal removal of hydrogen halide, which is generally a radical process, requires rather high temperatures and is usually effected by use of a catalyst; this may be a material with a large surface, such as kaolin or kieselgur, or a metal such as aluminum, nickel, copper, or zinc or an anhydrous oxide thereof. For example, heating 1,2-dichloroethane at 600°/20 atm gives vinyl

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[45] A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, **1934**, 956; W. S. Rapson and R. Robinson, *J. Chem. Soc.*, **1935**, 1538; L. E. King and R. Robinson, *J. Chem. Soc.*, **1941**, 467.

[46] D. Gotkis and J. B. Cloke, *J. Amer. Chem. Soc.*, **56**, 2711 (1934).

[47] E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963).

[48] H. A. Staab and G. Walther, *Ann. Chem.*, **657**, 98 (1962).

chloride in good yield,[49] and the same reaction occurs at 500° in the presence of tin(IV) oxide/iron(II) oxide on charcoal.[50]

β-Chloro-α-fluorostyrene;[51] $C_6H_5CF_2CHCl_2 \rightarrow C_6H_5CF{=}CHCl$. A mixture of (2,2-dichloro-1,1-difluoroethyl)benzene (25.5 g, 0.12 mole), acetamide (40 g), copper dust (0.3 g), and zinc dust (11.8 g) is heated for 2 h at 150°. After cooling, the product is dissolved in water. Acidification with sulfuric acid, extraction with ether, drying and evaporation of the extract, and two distillations of the residue give β-chloro-α-fluorostyrene, b.p. 86–87°/14 mm, n_D^{20} 1.5531, in 81% yield (15.4 g).

Fluorinated olefins can be prepared in good yield by dehydrohalogenation of 1,1,1-trihaloethanes on metal oxides or active charcoal, *e.g.*:[52]

$$\mathrm{CH_3CF_2Cl} \longrightarrow \left\{ \begin{array}{l} \xrightarrow{\mathrm{Al_2O_3}} \mathrm{CH_2{=}CFCl}\quad 91\% \\ \xrightarrow[\mathrm{C}]{} \mathrm{CH_2{=}CF_2}\quad 93.5\% \end{array}\right.$$

Dehydrohalogenation by inorganic or organic bases can occur by different mechanisms according to the reaction conditions applied (*E*1 for solvolysis of secondary or tertiary alkyl halides, *E*2 in the presence of strong bases), and this sometimes makes dehydrohalogenation more advantageous than dehydration. In general, dehydrohalogenation is a diversionary route since the halides are themselves prepared from the corresponding hydroxy compounds. Whereas little stereospecificity attaches to acid dehydration by the *E*1 mechanism, the use of strong bases leads preferentially to *trans*-elimination (*E*2). Monomolecular eliminations occur in solvolytic dehydrohalogenation of secondary and tertiary alkyl halides.

As with alcohols, the ease of removal of HX from halides is greater the less hydrogen is attached to the carbon atom carrying the halogen, so that the ease of removal increases from primary through secondary to tertiary halides. It also increases with increasing atomic weight of the halogen.

As in dehydration of alcohols, the direction of removal of HHal is governed by Saytzeff's rule,[53] according to which the proton is split off preferentially from the carbon atom carrying the smallest number of hydrogen atoms. A typical example is *tert*-pentyl bromide, $CH_3CH_2C(CH_3)_2Br$;[54] when this is solvolysed in 80% ethanol, the olefins produced consist as to about four-fifths of 2-methyl-2-butene (three alkyl groups attached to doubly bonded carbon) and about one-fifth of 2-methyl-1-butene (two alkyl groups attached to doubly bonded carbon). Thus in some cases a desired shift of double bond can be effected by addition and subsequent removal of hydrogen halide, *e.g.*:

$$(\mathrm{CH(CH_3)_2CH{=}CH_2 + HI \longrightarrow CH(CH_3)_2CHICH_3 \longrightarrow (CH_3)_2C{=}CHCH_3 + HI}$$

Preparation of 2-methyl-2-butene in this way has, however, no practical importance since this compound is obtained more easily from pentyl alcohols.

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[49] Ger. Pat. 899,191; *Chem. Zentralbl.*, **1954**, 7288.

[50] J. C. Ghosh and S. R. Das Guha, *Petroleum* (*London*), **14**, 261 (1951).

[51] M. M. Nad, T. V. Talalaeva, G. V. Kazennikova, and K. A. Kocheshkov, *Izv. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1959**, 272.

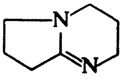
[52] F. H. Walker and A. E. Pavlath, *J. Org. Chem.*, **30**, 3284 (1965).

[53] A. Saytzeff, *Ann. Chem.*, **179**, 296 (1875).

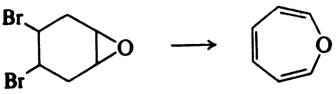
[54] M. L. Dhar, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, **1948**, 2065.

Dehydrohalogenating agents range from anhydrous alkali alkoxides and solid alkali hydroxides through solutions of alkali hydroxides in water or organic solvents, then through alkali salts of weak acids, to organic bases such as pyridine, aniline, dimethylaniline, and quinoline.

1,5-Diazabicyclo[4.3.0]non-5-ene (**4**) is a new reagent[55] which is more effective for dehydrohalogenation of secondary halides than are the bases usually applied. This superiority was first demonstrated in a new synthesis of vitamin A;[56] and use of this base permitted the first preparation of oxepin, by dehydrobromination of 1,2-dibromo-4,5-epoxycyclohexane:[57]



(**4**)



Removal of hydrogen halide is often accompanied by side reactions in which the halide is hydrolysed by the inorganic base:

$$\text{RHal} + \text{KOH} \longrightarrow \text{ROH} + \text{KHal}$$

or in which an ether is formed by the action of an alkali alkoxide:

$$\text{RHal} + \text{KOCH}_3 \longrightarrow \text{ROCH}_3 + \text{KHal}$$

Further, formation of quaternary salts can interfere in the ready removal of hydrogen halide by tertiary amines such as dimethylaniline, pyridine, or quinoline.[58] To overcome this, Hünig and Kiessel[59] successfully applied sterically hindered tertiary amines, *e.g.*, ethyldiisopropylamine and *N*-ethyldi(cyclohexyl)amine; for instance, removing hydrogen bromide from 1,2-dibromo-2-methylpropane by potassium hydroxide in ethylene glycol[60] gave unsatisfactory yields of **1-bromo-2-methyl-1-propene**:

$$\text{C(CH}_3\text{)}_2\text{BrCH}_2\text{Br} \longrightarrow \text{(CH}_3\text{)}_2\text{C{=}CHBr}$$

whereas good results were obtained by using *N*-ethyldi(cyclohexyl)amine, as follows:

N-Ethyldi(cyclohexyl)amine (47 g, 0.225 mole) is heated to 140° in a three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel, and 1,2-dibromo-2-methylpropane (32.3 g, 0.15 mole) is then dropped in rapidly. After 5.5 h, the mixture is distilled (bath-temperature 140°) through a short Vigreux column with vigorous stirring (distillate 15.5 g). Treating the residue with water (50 ml) and then steam-distilling it affords a further amount (about 1 g) of an oil. Redistillation of the main distillate and this additional material affords a 77% yield (15.5 g) of the monobromide, b.p. 91°, n_D^{20} 1.4623.

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[55] H. Oedinger, H.-J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

[56] Ger. Pat. 1,158,606; *Chem. Abstr.*, **60**, 5569 (1964).

[57] E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem. Int. Ed., Engl.*, **3**, 510 (1964).

[58] C. R. Noller and R. Dinsmore, *J. Amer. Chem. Soc.*, **54**, 1025 (1932).

[59] S. Hünig and M. Kiessel, *Chem. Ber.*, **91**, 381 (1958).

[60] E. A. Braude and E. A. Evans, *J. Chem. Soc.*, **1955**, 3328.

α-Halogenated ethers can be equally well dehydrohalogenated by *N*-ethyldi(cyclohexyl)amine or ethyldiisopropylamine; ethyl vinyl ether and butyl 2-chlorovinyl ether have been prepared in 80–86% yield in this way.[59]

α,β-Dihalo carbonyl compounds are readily dehydrohalogenated to α-halo carbonyl compounds, *e.g.*, 2,3-dibromobutyric acid is converted into 2-bromocrotonic acid in 90% yield by aqueous potassium hydroxide.[61]

Ethyl 2,3-dibromopropionate and sodium ethoxide in ice-cold anhydrous ethanol afford ethyl 2-bromoacrylate in 80% yield.[62]

Dicarboxylic acids of maleic–fumaric acid type are almost always obtained from halogenated succinic acids; fumaric acid is easily formed from monobromosuccinic acid, which loses 1 equivalent of hydrogen bromide when merely boiled with water[63] or heated above its melting point.[64]

3. Removal of halogen

Introduction of an ethylenic linkage by removal of two halogen atoms from a vicinal dihalide has little synthetic importance since the requisite dihalides are almost always obtained by addition of halogen to the double bond that is to be formed. However, the process is valuable because the halogen adducts can be useful for isolation or separation of a product.

The dehalogenating agent may be a metal such as copper, magnesium, zinc, aluminum, iron, or an alkali metal, etc., or may be an alkali hydroxide or alkali iodide in ethanol or acetone. The removal of halogen generally liberates a considerable amount of heat, so that presence of a solvent is advisable.[65]

Zinc dust in alcohol is usually applicable for removing two halogen atoms from vicinal carbon atoms, as is illustrated in the preparation of **4,4,4-trifluoro-1-butene:**[66]

1-Chloro-4,4,4-trifluoro-2-iodobutane (2.80 g) in ethanol (3 ml) is added slowly to zinc dust (10 g) in boiling ethanol (20 ml). The volatile product is washed with water and redistilled. This affords 80% (0.92 g) of 4,4,4-trifluoro-1-butene, b.p. 10.5°.

$$CF_3CH_2CHICH_2Cl \xrightarrow{Zn} CF_3CH_2CH{=}CH_2$$

Isolated halogen is not attacked by zinc under these conditions.[67]

There is no isomerization or rearrangement during such dehalogenations. However, cyclization cannot be entirely avoided on dehalogenation of 1,3-dihalo compounds[68] or some polyhalo compounds by, *e.g.*, zinc or aluminum. Roedig and his co-workers[69] used alcoholic potassium hydroxide in acetone

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[61] N. H. Cromwell and F. Pelletier, *J. Org. Chem.*, **15**, 881 (1950).

[62] H. Bretschneider, N. Karbitschka, and G. Piekarski, *Monatsh. Chem.*, **84**, 1084 (1953).

[63] R. Fittig and L. Dorn, *Ann. Chem.*, **188**, 90 (1877); J. Volhard, *Ann. Chem.*, **268**, 256 (1892); W. J. Müller and F. Suckert, *Ber. Deut. Chem. Ges.*, **37**, 2598 (1904).

[64] A. Kekulé, *Ann. Chem.*, **130**, 22 (1864); J. Volhard, *Ann. Chem.*, **242**, 158 (1887).

[65] Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1960, Vol. 5, Part 4, p. 720.

[66] R. N. Haszeldine, K. Leedham, and B. R. Steele, *J. Chem. Soc.*, **1954**, 2040.

[67] C. L. Wilson, *J. Chem. Soc.*, **1945**, 48.

[68] R. C. Fuson and H. Gilman, "Organic Chemistry," John Wiley and Sons, New York, 2nd ed, 1943, Vol. 1, p. 74.

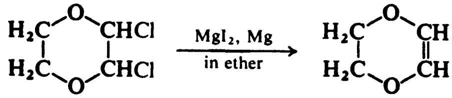
[69] A. Roedig, G. Voss, and E. Kuchinke, *Ann. Chem.*, **580**, 24 (1953).

for dechlorination of polychloro compounds; the cyclization that otherwise occurs readily is thus circumvented, an example being an 84% yield of α-perchloro-1,3,5-hexatriene:

$$CCl_2{=}CClCCl_2CCl_2CCl{=}CCl_2 \xrightarrow[\text{acetone}]{\text{KOH in}} CCl_2{=}CClCCl{=}CClCCl{=}CCl_2$$

According to Finkelstein,[70] dehalogenation can be effected by the action of alkali iodides in acetone or some other solvents on vicinal dihalo compounds; the iodides that are first formed are unstable, losing iodine, particularly if the compound contains a carbonyl or a carboxylic acid group.

A mixture of magnesium iodide and magnesium in anhydrous ether can also be applied for dehalogenation; for example, Summerbell and Umhoefer[71] obtained **dioxen** in this way from 2,3-dichlorodioxan:



Magnesium turnings (82.6 g, 3.4 moles) and anhydrous ether (1200 ml) are placed in a 5-l flask fitted with a dropping funnel, stirrer, and condenser closed by a calcium chloride tube. Iodine (91.5 g, 0.4 mole) is added, but only in small portions since the formation of magnesium iodide is markedly exothermic. To the resulting colorless solution is added, dropwise and with good stirring, a mixture of 2,3-dichlorodioxan (314 g, 2 moles) and ether (200 ml) at such a rate that the solution never becomes darker than pale brown (duration about 9 h). The mixture becomes colorless after final stirring for 0.5 h and is then poured into ice-water. The ethereal layer is separated, dried over sodium sulfate, and fractionated, affording a 49% yield (84.3 g) of dioxen, b.p. 93–95°.

When the usual dehalogenating agents are applied to dihalides in which the halogen is flanked by a carbonyl group, they cause reduction of the double bond or resinification. However, such compounds are converted into olefins readily and in good yield by treatment with an equivalent amount of a trialkyl phosphite:[72]

$$C_6H_5COCHBrCHBrCOC_6H_5 \xrightarrow{(RO)_3P} C_6H_5COCH{=}CHCOC_6H_5$$

trans-1,4-Diphenyl-2-butene-1,4-dione: *trans*-2,3-Dibromo-1,4-diphenylbutane-1,4-dione (20 g) and trimethyl phosphite (5.5 ml) are dissolved in dry toluene (150 ml) and heated under reflux for 20 h. The solvent is then removed and the residue is recrystallized from ethanol, affording the butenedione (10.7 g, 92%), m.p. 108–110°.

Perchloro ketones can be similarly dehalogenated by trialkyl phosphites or triphenylphosphine.[73]

Dehalogenation is sometimes used during preparation of derivatives of sensitive ethylenic compounds: halogen is first added to the olefin, the derivative is prepared, and the halogen finally removed.

For example, methyl and ethyl acrylate can be prepared by adding bromine to acrylic acid, esterifying the dibromide, and boiling the resulting 2,3-dibromopropionic ester with pieces of zinc in alcohol.[74]

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[70] H. Finkelstein, *Ber. Deut. Chem. Ges.*, **43**, 1528 (1910).

[71] R. K. Summerbell and R. R. Umhoefer, *J. Amer. Chem. Soc.*, **61**, 3019 (1939).

[72] S. Dershowitz and S. Proskauer, *J. Org. Chem.*, **26**, 3595 (1961).

[73] K. Pilgram and H. Ohse, *Angew. Chem. Int. Ed., Engl.*, **5**, 837 (1966).

[74] Ger. Pat. 555,933; *Chem. Abstr.*, **26**, 5964 (1932).

4. Cleavage of nitrogenous compounds

Water can be removed from alcohols by dehydrating agents either directly or indirectly, but the analogous removal of ammonia or an amine from primary, secondary, or tertiary amines is not generally feasible. The latter type of reaction succeeds only in individual cases when, occasionally, an olefin is formed by loss of, *e.g.*, ammonium chloride from the salt of an amine with a hydrohalogen acid:

$$RCH_2CH_2NH_3^+Cl^- \longrightarrow RCH{=}CH_2 + NH_4Cl$$

This reaction has been applied for preparative purposes mainly in the hydroaromatic series. For instance, according to Wallach,[75] the thujone obtained from thuja oil gives with ammonium formate an aminothujone whose hydrochloric acid salt affords thujene on dry distillation; and Harries and Antoni[76] obtained 2,3-dihydrotoluene analogously from 1-methyl-1-3-cyclohexanediamine.

Mannich bases are often valuable intermediates for preparation of unsaturated compounds. They are obtained by the action of formaldehyde and ammonia or a primary or secondary amine on compounds containing active hydrogen.[77,78] When a Mannich base or its salt is heated, the amino group is split off and the unsaturated compound is formed. Unsaturated ketones,[79] aldehydes,[80] acids,[77] and nitro compounds[81] can all be thus prepared.

According to Hagemeyer,[79] the tertiary amine obtained by boiling acetone, diethylamine hydrochloride, and paraformaldehyde for 6 h in isopropyl alcohol is treated with dry hydrogen chloride, and the resulting amine hydrochloride is deaminated by heating it at 150°; this gives **methyl vinyl ketone:**

$$\begin{tikzcd}[column sep=small]
CH_3COCH_3 + CH_2O + (C_2H_5)_2NH_2^+Cl^- \arrow[r] & CH_3COCH_2CH_2N(C_2H_5)_2{\cdot}HCl + H_2O \arrow[d] \\
& CH_3COCH{=}CH_2 + (C_2H_5)_2NH{\cdot}HCl
\end{tikzcd}$$

Amines can also be converted into olefins by thermal treatment (100–200°) of their quaternary hydroxides (Hofmann degradation).[82] Of the possible olefins the main product is that containing the smallest number of alkyl substituents; *i.e.*, the proton is removed from the β-carbon atom carrying the smallest number of alkyl groups:[83]

$$[(C_3H_7)(C_2H_5)(CH_3)_2N]^+OH^- \longrightarrow C_3H_7N(CH_3)_2 + CH_2{=}CH_2 + H_2O$$

To prepare olefins from quaternary bases it is usual to obtain first the qua-

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[75] O. Wallach, *Ann. Chem.*, **286**, 99 (1895).

[76] C. Harries and W. Antoni, *Ann. Chem.*, **328**, 88 (1903).

[77] F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

[78] Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, 1957, Vol. 11, Part 1, p. 731.

[79] H. J. Hagemeyer, Jr., *J. Amer. Chem. Soc.*, **71**, 1119 (1949).

[80] C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Amer. Chem. Soc.*, **70**, 147 (1948).

[81] A. T. Blomquist and T. H. Shelley, *J. Amer. Chem. Soc.*, **70**, 147 (1948).

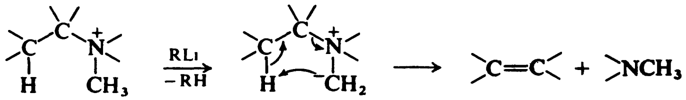
[82] A. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

[83] A. W. Hofmann, *Ann. Chem.*, **78**, 253 (1851); **79**, 11 (1851); M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mordour, G. A. Maw, and L. I. Woolf, *J. Chem. Soc.*, **1948**, 2097.

ternary iodide, to convert this into the hydroxide by silver oxide, and to decompose the hydroxide thermally or by the action of strong bases.

Cyclobutene:[84] Methyl iodide (16.5 g, 0.11 mole) is added to *N,N*-dimethylcyclobutylamine (10 g, 0.1 mole) in ether (100 ml). The quaternary iodide crystallizes at once, with evolution of heat, and is collected only after storage overnight in a refrigerator. The iodide (25 g, 0.1 mole) is shaken for 2 h with freshly prepared silver oxide (0.30 mole) in water (100 ml). The mixture is filtered and evaporated in a vacuum. The syrupy quaternary hydroxide is added dropwise to a flask heated at 140° and evacuated to 50 mm. The gas evolved is led through N-hydrochloric acid and that part which is not absorbed is collected in a trap cooled in Dry Ice. The yield of cyclobutene is 73% (0.073 mole).

Hofmann degradation usually occurs with *trans*-elimination (*E*2 reaction). Wittig and Polster[85,86] discovered a variant in which quaternary ammonium compounds are converted by strong bases such as phenyl- or butyl-lithium into olefins, by way of ylides, with intramolecular *cis*-elimination:[87]



They demonstrated the possibility of effecting Hofmann degradation under mild conditions — below 0° — by converting *N,N,N*-trimethylcyclooctylammonium bromide into ***trans*-cyclooctene** by potassium amide in liquid ammonia:[86]

N,N,N-Trimethylcyclooctylammonium bromide (15 g, 60 mmoles) was added in portions to a solution of potassium amide (60 mmoles) in liquid ammonia. The ammonia was kept boiling gently for 4 h, the precipitate being stirred up from time to time. The anhydrous ether (20 ml) was added and the ammonia was distilled off slowly through a cold trap (−20°). The residue was treated, with cooling, first with a few drops of ethanol and then with a little water. The resulting solution was made slightly acid with N-hydrochloric acid and worked up in the usual way, to give a 68% yield (4.5 g) of *trans*-cyclooctene, b.p. 31–32°/12 mm, whose identity was proved by a mixed melting point determination of the phenyl azide adduct, m.p. 106–107°.

Sulfonium[88] and phosphonium salts can be converted into olefins by methods analogous to Hofmann degradation of quaternary ammonium salts. For example, substituted styrenes are obtained in good yield by the slightly exothermic reaction of appropriate sulfonium bromides with 10% sodium hydroxide solution.[89]

In the presence of hydroxyl ions phosphonium salts decompose preferentially into the phosphine oxide and a hydrocarbon or into the alkylidenephosphorane.[90] However, (alkoxycarbonylalkyl)phosphonium salts (readily obtained from α-halo esters and tributyl- or triphenyl-phosphine) decompose when

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[84] J. D. Roberts and C. W. Sauer, *J. Amer. Chem. Soc.*, **71**, 3925 (1949).

[85] G. Wittig and R. Polster, *Ann. Chem.*, **599**, 13 (1956).

[86] G. Wittig and R. Polster, *Ann. Chem.*, **612**, 104 (1958).

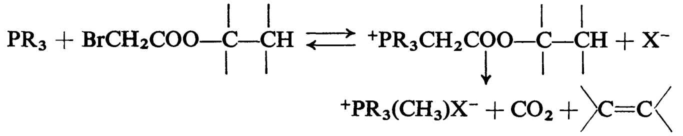
[87] G. Köbrich, *Angew. Chem.*, **74**, 461 (1962).

[88] K. A. Cooper, E. D. Hughes, C. K. Ingold, and B. J. MacNulty, *J. Chem. Soc.*, **1948**, 2038, 2043, 2049.

[89] W. H. Saunders and R. A. Williams, *J. Amer. Chem. Soc.*, **79**, 3712 (1957).

[90] H. J. Bestmann, *Angew. Chem. Int. Ed., Engl.*, **4**, 645 (1965).

heated at 130–225° into carbon dioxide, a phosphonium halide, and a (usually terminal) olefin:[91]



$$PR_3 + BrCH_2COO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}H \rightleftarrows {}^+PR_3CH_2COO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}H + X^-$$
$$\downarrow$$
$${}^+PR_3(CH_3)X^- + CO_2 + \rangle C=C\langle$$

However, rearrangements limit the utility of this method.

A mild method for introducing double bonds is by pyrolysis of amine oxides (the Cope–Mamlock–Wolffenstein reaction[92,93]); it occurs at low temperatures (85–115°) and gives high yields and *cis*-elimination.[94,95] When heated at 120° the amine oxide from optically pure *N*,*N*-dimethyl-(3-phenylbutyl)amine gives optically pure 3-phenyl-1-butene:[96]

$$C_6H_5CH(CH_3)CH_2CH_2N(O)(CH_3)_2 \longrightarrow C_6H_5CH(CH_3)CH{=}CH_2 + (CH_3)_2NOH$$

Hydrolysis of sulfoxides can also be used for preparation of olefins.[97]

Chloroolefins are formed in good yield by the action of sodium methoxide on vicinal chloronitro compounds whose nitro group is attached to tertiary carbon:[98]

$$CH_2ClC(CH_3)_2NO_2 \xrightarrow{-HNO_2} CHCl{=}C(CH_3)_2$$

1-Methoxyvinyl phenyl ketone is similarly prepared by removal of nitrous acid from the nitro ketone:[99]

$$C_6H_5COCH(OCH_3)CH_2NO_2 \;\text{——}\; C_6H_5COC(OCH_3){=}CH_2$$

Piperidine (4.9 g) in anhydrous ether (30 ml) is added, with ice-cooling, during 40 min to 2-methoxy-3-nitro-1-phenyl-1-propanone (12 g) in anhydrous ether (130 ml). The mixture is kept for 20 h, then the precipitate is filtered off, and the ethereal solution is washed with 2% hydrochloric acid and with water, dried over sodium sulfate, and evaporated. Distillation of the residue at 50–60° (bath-temperature)/0.01–0.03 mm gives the unsaturated ketone (7.7 g, 83%).

Nitriles having active hydrogen on a β-carbon atom can pass into olefins with loss of hydrogen cyanide under the influence of potassium amide in liquid ammonia.[100] Triphenylethylene, for instance, is accessible in this way in 94% yield:

$$C_6H_5CH_2(C_2H_5)_2CN \xrightarrow[\text{liq. }NH_3]{KNH_2\text{ in}} C_6H_5CH{=}C(C_6H_5)_2 + HCN$$

1,1,2-Triphenyl-1-propene and tetraphenylethylene can also be obtained in good yield in this way.

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[91] D. B. Denney, C. J. Rossi, and J. J. Vill, *J. Org. Chem.*, **29**, 1003 (1964).

[92] A. C. Cope, T. T. Foster, and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3929 (1943).

[93] L. Mamlock and R. Wolffenstein, *Ber. Deut. Chem. Ges.*, **33**, 159 (1900).

[94] D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.*, **76**, 5740 (1954).

[95] A. C. Cope and C. L. Bumgardner, *J. Amer. Chem. Soc.*, **79**, 960 (1957).

[96] D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2137 (1952).

[97] C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960).

[98] A. Dornow and A. Müller, *Chem. Ber.*, **93**, 41 (1960).

[99] M. I. Rybinskaya, L. V. Rybin, and A. N. Nesmeyanov, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1963**, 899; *Chem. Abstr.*, **59**, 7413 (1963).

[100] C. R. Hauser and W. R. Brasen, *J. Amer. Chem. Soc.*, **78**, 82 (1956).

II. Conjugated ethylenic bonds

1. Dienes[101]

The methods available for introduction of isolated double bonds can often be applied, in principle, also for introduction of conjugated double bonds, and the latter process is often easier than the former since conjugated double bonds are more favored energetically. The most important methods are: catalytic dehydrogenation of olefins; dehydration of glycols; pyrolysis of diol esters; removal of hydrogen halide from unsaturated halides; removal of hydrogen halide from dihalides; partial hydrogenation of vinylacetylenic hydrocarbons; and decomposition of quaternary ammonium hydroxides (from unsaturated diamines by exhaustive methylation).

Catalytic dehydrogenation of butenes is an important industrial process for preparation of butadiene.[102]

Dehydration of glycols is effected in the presence of phosphoric, silicic, phosphotungstic, or boric acid. The dehydrations leading to butadiene have been reviewed by Egloff and Hulla.[103]

Dehydration of unsaturated alcohols is important only in special cases, since such starting materials are difficultly accessible. According to Scheiber,[104] octadecadienoic acid can be prepared by dehydration of ricinoleic acid; owing to its conjugated double bonds it is a valuable starting material for synthetic drying oils of tung oil type.

1,2-, 1,3-, and 1,4-Diols are also amenable to dehydration. Allen and Bell[105] have reported that pinacol, $HOC(CH_3)_2C(CH_3)_2OH$, can be dehydrated to 2,3-dimethyl-1,3-butadiene in 60% yield by 48% hydrobromic acid; still better yields (86%) are obtained by passing pinacol vapor over alumina at 420–470°.

1,3-Butadiene is formed in good yield (up to 85%) from 1-chloro-2-butene and alcoholic potassium hydroxide solution, which afford the derived ether whence alcohol is removed by means of potassium hydroxide at 160–170°:[106]

$$CH_3CH{=}CHCH_2OR \xrightarrow{KOH} CH_2{=}CHCH{=}CH_2 + ROH$$

Pyrolysis of esters can be used with success for synthesis of dienes that are difficult to obtain by other methods. 1,3-Cyclohexadiene, for instance, is formed in 84% yield by pyrolysis of a mixture of *cis*- and *trans*-1,2-cyclohexylene diacetate.[107]

Removal of hydrogen halide from an unsaturated halide finds application, for instance, in the preparation of **2-phenyl-1,3-butadiene:**[108]

$$CH_2{=}C(C_6H_5)CHClCH_3 \longrightarrow CH_2{=}C(C_6H_5)CH{=}CH_2$$

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[101] M. Cais in S. Patai, "The Chemistry of the Alkenes," Interscience Publ., London–New York–Sydney, 1964, p. 957.

[102] G. Egloff and G. Hulla, *Chem. Rev.*, **35**, 279 (1941).

[103] G. Egloff and G. Hulla, *Chem. Rev.*, **36**, 63 (1945).

[104] J. Scheiber, *Farbe Lack*, **1929**, 153; *Angew. Chem.*, **46**, 643 (1933).

[105] C. F. H. Allen and A. Bell, *Org. Syn.*, **22**, 39, 40 (1942).

[106] G. M. Mkryan, N. A. Papasyan, and A. A. Pogosyan, *Zh. Org. Khim.*, **3**, 1160 (1967); *Chem. Abstr.*, **67**, 90,350 (1967).

[107] W. J. Bailey and W. B. Lawson, *J. Amer. Chem. Soc.*, **79**, 1444 (1957).

[108] K. Alder and J. Haydn, *Ann. Chem.*, **570**, 208 (1950).

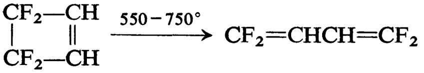
3-Chloro-2-phenyl-1-butene is dissolved in a three-fold volume of pyridine and heated on a boiling water-bath for 1 h. After cooling, the mixture is stirred into ice-cold ca. 30% sulfuric acid and treated at once with a little hydroquinone. The hydrocarbon is taken up in ether, washed, dried, and distilled in a vacuum; it has b.p. 66–67°/13 mm; the yield is about 50%.

Hydrogen halide is also removed when an unsaturated halide is distilled from its mixture with a solid alkali hydroxide; 4-methyl-1,3-hexadiene, for example, was prepared in this way from 4-bromo-4-methyl-1-hexene.[109]

1,4-Diphenyl-1,3-butadiene is easily prepared by removal of hydrogen halide from a dihalide; it suffices to heat 2,3-dibromo-1,4-diphenylbutane with quinoline for 0.5 hour at 160°.[110]

Hydrogenation of the triple bond in vinylacetylenes in methanol in the presence of palladium can be used for synthesis of substituted or unsubstituted conjugated dienes.[111]

Fluorinated butadienes can be obtained by pyrolysis of cyclobutenes or cyclobutyl acetates,[112] *e.g.*:



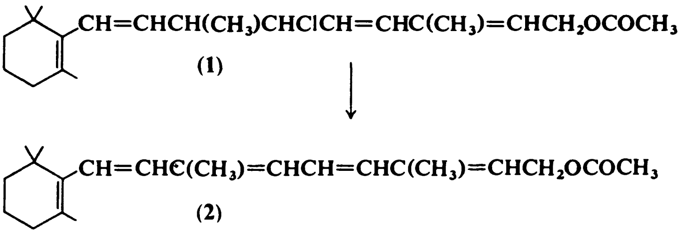
$$\begin{array}{l} CF_2\text{—}CH \\ |\quad\;\; \| \\ CF_2\text{—}CH \end{array} \xrightarrow{550-750^\circ} CF_2\text{=}CHCH\text{=}CF_2$$

and cyanobutadienes can be prepared by cleavage of 3-substituted 1,1,2,2-tetracyanocyclobutanes.[112]

2. Polyenes

Polyenes are important because they constitute widely distributed types of natural products, *e.g.*, carotenoids and vitamin A.[113]

A recent synthesis of vitamin A (**2**) employed dehydrohalogenation of the secondary halide (**1**) by 1,5-diazabicyclo[4,3,0]non-5-ene,[56] the new double bond being largely *cis*-oriented:



When cumulenes are more readily accessible than the corresponding polyenes, *e.g.*, the higher bisdiphenylene- and tetraaryl-cumulenes, the polyenes can be prepared by catalytic hydrogenation of the cumulenes in a Lindlar catalyst. For example, tetraphenylhexapentaene absorbs two equivalents of

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[109] N. A. Milas and A. McAlevy, *J. Amer. Chem. Soc.*, **57**, 581 (1935).

[110] A. V. Dombrovski and A. P. Terent'ev, *Zh. Obshch. Khim.*, **26**, 2780 (1956); *Chem. Abstr.*, **51**, 7337 (1957).

[111] Kh. V. Bal'yan, A. A. Petrov, and Yu. I. Pofir'eva, *Zh. Obshch. Khim.*, **27**, 365 (1957); *Chem. Abstr.*, **51**, 15,394 (1957).

[112] J. L. Anderson, R. E. Putnam, and W. H. Sharkey, *J. Amer. Chem. Soc.*, **83**, 382 (1961).

[113] H. Pommer, *Angew. Chem.*, **72**, 911 (1960).

hydrogen to afford *cis*-1,1,6,6-tetraphenyl-1,3,5-hexatriene; this passes into the *trans*-isomer when exposed to light.[114]

1,3,5-Hexatriene has been prepared in a four-stage process starting from sodium acetylide and crotonaldehyde; the first product, 4-hexen-1-yn-3-ol (**3**), is reduced to 1,4-hexadien-3-ol (**4**), whence the triene (**5**) is obtained in 60% yield by vapor-phase dehydration on alumina:[115]

$$\underset{\textbf{(3)}}{CH_3CH{=}CHCH(OH)C{\equiv}CH} \xrightarrow[H_2]{Pd-} \underset{\textbf{(4)}}{CH_3CH{=}CHCH(OH)CH{=}CH_2}$$

$$\xrightarrow[300^\circ]{Al} \underset{\textbf{(5)}}{CH_2{=}CHCH{=}CHCH{=}CH_2}$$

Diarylpolyene hydrocarbons are obtained by treating benzylmagnesium chloride with an aldehyde or acetal, the alkoxy compounds formed being then treated in alcoholic solution with aqueous 45% hydrobromic acid:[116]

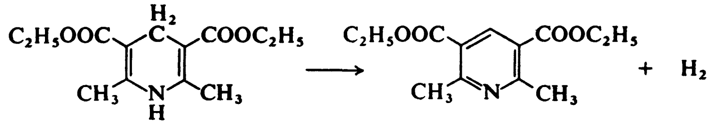
$$C_6H_5[CH(OC_2H_5)CH_2]_2CH(OC_2H_5)_2 + C_6H_5CH_2MgCl \longrightarrow$$

$$C_6H_5[CH(OC_2H_5)CH_2]_2CH(OC_2H_5)CH_2C_6H_5 \longrightarrow$$

$$C_6H_5CH{=}CHCH{=}CHCH{=}CHC_6H_5$$

3. Aromatic and heterocyclic double bonds

The most important methods of producing aromatic and heterocyclic "double bonds" involve dehydrogenations. Such reactions occur under relatively mild conditions since aromatic carboxylic and heterocyclic systems are particularly favored energetically. Dehydrogenation is easier the nearer the compound is to the aromatic state, *i.e.*, the greater is the number of double bonds already present. Thus, for instance, the aromatic pyridine ring is formed, with evolution of hydrogen, when diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinecarboxylate is warmed with palladium black even at 90°:[117]



Zelinsky[118] found that the three isomeric methylcyclohexenes are dehydrogenated to toluene when passed over a palladium catalyst at the relatively low temperature of 116–118°, with simultaneous formation of methylcyclohexane. This phenomenon, that unsaturated compounds give aromatic and perhydrogenated systems at relatively low temperatures, *i.e.*, disproportionation, is often observed during catalytic dehydrogenation, so that the theoretical

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[114] R. Kuhn and H. Fischer, *Chem. Ber.*, **93**, 2285 (1960).

[115] J. M. Shackelford, W. A. Michalowicz, and L. H. Schwartzman, *J. Org. Chem.*, **27** 1631 (1962).

[116] B. M. Mikhailov and L. S. Povarov, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1959**, 314; *Chem. Abstr.*, **53**, 19,925 (1959); B. M. Mikhailov and G. S. Ter-Sarkisyan, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1960**, 1267; *Chem. Abstr.*, **55**, 542 (1961).

[117] E. Knoevenagel and J. Fuchs, *Ber. Deut. Chem. Ges.*, **36**, 2848 (1903).

[118] N. D. Zelinsky, *Ber. Deut. Chem. Ges.*, **57**, 2055 (1924).

amount of hydrogen is rarely evolved as such. Raising the temperature depresses the disproportionation in favor of simple dehydrogenation.

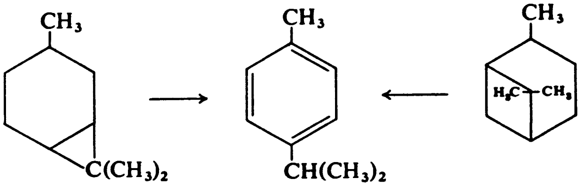
Considerably more energetic conditions are required for dehydrogenation of perhydrogenated compounds. Thus, whereas tetralin is dehydrogenated in the liquid phase in the presence of platinum or palladium catalysts at 185°, a temperature of at least 300° is necessary for dehydrogenation of decalin.[119]

Dehydrogenation, like hydrogenation, is temperature-dependent; at any given temperature there exists an equilibrium and this is shifted by a decrease in temperature in favor of hydrogenation and by an increase in favor of dehydrogenation. Thus hydrogenation catalysts will often also effect dehydrogenation.

The catalysts most often used for dehydrogenation are those from platinum or palladium.[120] Nickel catalysts are less useful for dehydrogenation because carbonization may readily occur at the necessary high temperatures. Osmium can also be used as dehydrogenation catalyst in some cases.[121]

High-boiling substances can be dehydrogenated by simple heating with the catalyst in the liquid phase. More volatile compounds are dehydrogenated in a sealed tube or are passed as vapor over the catalyst.[119]

Dehydrogenation is usually accompanied by a variety of side reactions: among such are loss of substituents, migration of side chains, ring contraction or expansion, ring fission, and ring closure. Perhydrogenated cyclic compounds that cannot yield aromatic systems directly, *e.g.*, cyclopentane and cycloheptane, are generally not susceptible to dehydrogenation; dehydrogenation has been used with great success for determination of the structure of terpenes and camphor derivatives, as in the degradation of carane and pinane to *p*-cymene, but this occurs only because cleavage of a three- or a four-membered ring produces an aromatic system:[122]



Oxides and sulfides such as Cr_2O_3 and MoS_2 also catalyse dehydrogenation, although only at rather high temperatures;[123] they also catalyse cyclization of saturated and unsaturated aliphatic to aromatic compounds.[124]

Chemical methods of dehydrogenation are applicable in a large number of

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[119] R. P. Linstead and K. O. A. Michaelis, *J. Chem. Soc.*, **1940**, 1127, 1134; R. P. Linstead, A. F. Millidge, S. L. S. Thomas, and A. L. Walpole, *J. Chem. Soc.*, **1937**, 1146.

[120] N. D. Zelinsky, *Ber. Deut. Chem. Ges.*, **44**, 3121 (1911).

[121] A. A. Balandin, *Z. Phys. Chem.*, *B*, **9**, 49 (1930).

[122] N. D. Zelinsky and R. J. Lewina, *Ann. Chem.*, **476**, 60 (1929).

[123] S. Goldwasser and H. S. Taylor, *J. Amer. Chem. Soc.*, **61**, 1766 (1939); B. Moldavski, G. Kamusher, and S. Livshitz, *Zh. Obshch. Khim.*, **7**, 131 (1937); *Chem. Abstr.*, **31**, 4282 (1937).

[124] B. Moldavski, G. Kamusher, and M. V. Kobylskaya, *Zh. Obshch. Khim.*, **7**, 169 (1947).

cases. Much success has been achieved in dehydrogenation of partially unsaturated compounds by sulfur or selenium. Dehydrogenation by sulfur is usually effected by methods worked out by Ruzicka:[125] the substance to be dehydrogenated is mixed with the calculated amount of sulfur and heated in a metal bath; evolution of hydrogen sulfide begins at about 180°, is allowed to proceed at 200–220°, and is completed, when necessary, at 260°; the reaction requires a few hours; working up is by vacuum-distillation, when possible. The preparation of **1-phenylnaphthalene** from its 3,4-dihydro compound will serve as example:[126]

Powdered sulfur (6 g, 0.18 mole) and 3,4-dihydro-1-phenylnaphthalene (35 g, 0.17 mole) are placed in a Claisen flask (200 ml) and heated in a metal-bath at 250–270°; evolution of hydrogen sulfide is complete in 0.5 h. The viscous residue distils at 134–135°/2 mm or 189 to 190°/12 mm. The yield is 91–94% (32–33 g).

Selenium was first used as dehydrogenation catalyst by Diels,[127] when by this method he established cyclopenta[*a*]phenanthrene as the parent skeleton of steroids, bile acids, steroid hormones, and other natural products. Dehydrogenation by selenium requires the use of higher temperatures and is thus often accompanied by side reactions.

The substance to be dehydrogenated is mixed with the calculated amount of selenium and heated at 250–280° in a flask fitted with an air-condenser. The temperature is slowly raised further, but generally not to above 350°. The reaction requires 20–100 h. Working up is by extraction with ether or benzene and fractionation of the residues from the extracts.

Caution: The experiment must be conducted in a very efficient fume-cupboard, as hydrogen selenide is exceedingly poisonous, even more so than hydrogen sulfide.

Chloranil is a mild dehydrogenating agent.[128] Xylene (b.p. 140°) is used as solvent, so that dehydrogenation occurs at a relatively low temperature.

2-Phenylnaphthalene, for example, is obtained in 90% yield when 3,4-dihydro-2-phenylnaphthalene is boiled for 15 h with chloranil in xylene.[129]

Pentaphenylbenzene is formed in 99% yield when a mixture of 1,2,3,4,5-pentaphenyl-1,3-hexadiene and chloranil in benzene is irradiated under nitrogen for 2.5 h by a mercury vapor lamp.[130]

Chloranil is particularly suitable for dehydrogenation of tetrahydrocarbazole derivatives. By its use Barclay and Campbell[131] obtained twenty different carbazoles, nitro and carboxyl groups being unaffected in the process. Other quinones, besides chloranil, can be used for such dehydrogenations, *e.g.*, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and tetrachloro-1,2-benzoquinone.[132] In especially favorable cases atmospheric oxygen,[133] selenium dioxide,[134] and sulfuric acid act as dehydrogenating agents. A reaction of

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[125] L. Ruzicka, *Fortschr. Chem. Phys., Phys. Chem.*, **19**, 1 (1928); L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, **4**, 505 (1921).

[126] R. Weiss, *Org. Syn.*, **24**, 84 (1944).

[127] O. Diels, *Ber. Deut. Chem. Ges.*, **69**, *A*, 195 (1936).

[128] R. T. Arnold and C. J. Collins, *J. Amer. Chem. Soc.*, **61**, 1407 (1939).

[129] N. Campbell and D. Kidd, *J. Chem. Soc.*, **1954**, 2154.

[130] G. R. Evanega, W. Bergmann, and J. English, *J. Org. Chem.*, **27**, 13 (1962).

[131] B. M. Barclay and N. Campbell, *J. Chem. Soc.*, **1945**, 530.

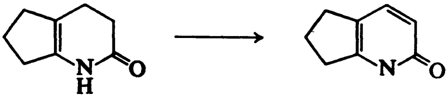
[132] E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, **1954**, 3569.

[133] H. Lewis, G. Ramage, and R. Robinson, *J. Chem. Soc.*, **1935**, 1412.

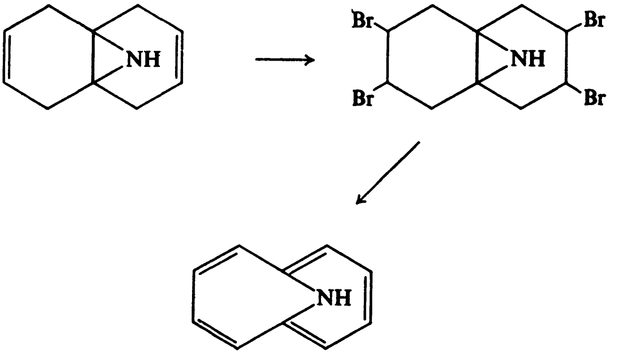
[134] E. Borgwardt and E. Schwenk, *J. Amer. Chem. Soc.*, **56**, 1185 (1934); G. Stein, *Angew. Chem.*, **54**, 146 (1941).

this type that proceeded rapidly and completely was described by Becke and Würtele:[135] hexachloro- and hexabromo-cyclohexane were dehydrogenated to the hexahalobenzene by sulfur trioxide as such or as an adduct, *e.g.*, chlorosulfuric acid.

6,7-Dihydro-1*H*-cyclopenta[*b*]pyrid-2(5*H*)-one is formed in 71% yield when the 3,4-saturated ketone is stirred in cold 96% sulfuric acid for 3 h.[136]



Aromatizations have also been achieved by adding bromine to partly unsaturated compounds and subsequently removing hydrogen bromide.[137–139] From 1,4,5,8-tetrahydro-5a,8a-epiminonaphthalene and bromine at −75°, Vogel *et al.*[137] obtained a tetrabromide which, when treated with sodium methoxide in tetrahydrofuran at 0–10°, lost hydrogen bromide to give a 75% yield of a compound formulated as 11-azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene.



III. Cumulated double bonds[140,141]

1. Allenes

Allenic compounds can in principle be prepared by methods similar to those used for formation of olefins, namely, dehalogenation, dehydrohalogenation, and dehydration of an unsaturated compound. Specific allene syn-

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[135] F. Becke and L. Würtele, *Ber. Deut. Chem. Ges.*, **91**, 1011 (1958).

[136] A. I. Meyers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964).

[137] E. Vogel, W. Pretzer, and S. Korte, *Tetrahedron Lett.*, **1965**, 3613.

[138] H. Paul and A. Weise, *Tetrahedron Lett.*, **1963**, 163.

[139] O. W. Webster and W. H. Sharkey, *J. Org. Chem.*, **27**, 3354 (1962).

[140] D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967).

[141] H. Fischer in S. Patai, "The Chemistry of the Alkenes," Interscience Publ., London–New York–Sydney, 1964, p. 1025.

theses are dehalogenation of *gem*-dihalocyclopropanes, acetylene rearrangements, and 1,4-additions to vinylacetylenes. The parent allene has been prepared in 80% yield by refluxing 2,3-dichloropropene in ethanolic solution with zinc dust:[142,143]

$$CH_2ClCCl{=}CH_2 \xrightarrow{Zn,\ C_2H_5OH} CH_2{=}C{=}CH_2 + CH_3CCl{=}CH_2$$

Pure allene, uncontaminated with 2-haloprene, can be obtained by dehydrobrominating 2,3-dibromopropene with zinc in butyl or isopentyl acetate.[144]

1,2-Butadiene is formed when 2,3-dibromo-1-butene is boiled with zinc and ethanol:[145]

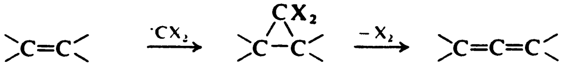
$$CH_3CHBrCHBrCH_2Br \longrightarrow CH_3CHBrCBr{=}CH_2 \longrightarrow CH_3CH{=}C{=}CH_2$$

2,3-Dibromo-1-butene: 1,2,3-Tribromobutane (419 g), water (20 ml), and sodium hydroxide (100 g) are placed in a flask (1 l) fitted with a distillation head and descending condenser. When this mixture is warmed with occasional shaking, a vigorous reaction soon sets in and distillation commences. The receiver is cooled in ice-water. When the initial vigorous reaction is over, the mixture is further heated until no more distillate collects. The distillate is washed with water and redistilled at reduced pressure, which separates the dibromobutene from unchanged tribromobutane. One more distillation affords the dibromo-1-butene (261 g), b.p. 75°/20 mm (86%).

1,2-Butadiene: A three-necked flask (1 l) is fitted with a dropping funnel, a glass inlet tube reaching nearly to the bottom of the flask (for passage of carbon dioxide), and a condenser; the condenser is connected *via* an exit tube to a smaller flask (100 ml) (placed in a water-bath at 30°) that serves as liquid trap, thence to a wider condenser, and finally to a receiver cooled in ice-salt (−12°). Ethanol (300 ml) and zinc dust (160 g) are placed in the reaction flask, and 2,3-dibromo-1-butene (131 g) is dropped in slowly; this causes the alcohol to boil vigorously. The 1,2-butadiene evolved collects in the cooled receiver. When all the dibromobutene has been added the mixture is boiled for a further few minutes, then the remainder of the butadiene is driven over by passing in carbon dioxide. The crude product is redistilled, then having b.p. 10.3° (yield 33.6 g, 72%).

Higher homologs can also be prepared by dehalogenation, the requisite dihaloalkenes being obtained either from the appropriately substituted allyl alcohols[146] or from the conjugated alkenynes and concentrated hydrobromic acid.[147]

Allenes can be synthesized simply and in good yield by treating 1,1-dihalocyclopropanes with methyl- or butyl-lithium in diethyl ether at −10° to −30°;[148] these dihalides are obtained by addition of dichloro- or dibromocarbene to an olefinic double bond:[149]



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[142] H. N. Cripps and E. F. Kiefer, *Org. Syn.*, **42**, 12 (1962).

[143] G. Gustavson and N. Demjanoff, *J. Prakt. Chem.*, **38**, 201 (1888).

[144] Ya. M. Slobodin and A. P. Khitrov, *Zh. Obshch. Khim.*, **31**, 3945 (1961); *Chem. Abstr.*, **57**, 8410 (1962).

[145] C. D. Hurd and R. N. Meinert, *J. Amer. Chem. Soc.*, **53**, 292 (1931).

[146] M. Bois, *Ann. Chim.* (*Paris*), [x], **9**, 402 (1928).

[147] M. Bertrand, Y. Pasternak, J. C. Traynard, J. LeGras, and A. Guillemonat, *Ann. Fac. Sci. Univ. Marseille*, **35**, 85 (1964).

[148] W. R. Moore and H. R. Ward, *J. Org. Chem.*, **27**, 4179 (1296).

[149] W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

Allene: 1,1-Dibromocyclopropane is dissolved in ether under nitrogen, and the solution is cooled to −10°. An excess of an ethereal solution of freshly prepared butyllithium is dropped in with stirring, after which the solution is kept for a further 10 min at −10° and then treated cautiously with water. The ethereal layer is separated, washed several times with water, and dried over magnesium sulfate. The solvent is distilled off and the allene is isolated from the residue by preparative gas chromatography.

A one-stage reaction is also possible, without isolation of the dihalocyclopropane, in which the olefin is treated with carbon tetrachloride and methyllithium. 1,2,6-Cyclononatriene and 1,2-cyclononadiene have been prepared in that way.[150]

Cyclic allenes with nine and ten carbon atoms,[151] polyhaloallenes,[152] and arylallenes[153,154] have been prepared by dehydrohalogenation reactions. Tetraphenylallene has been obtained in quantitative yield from diphenylethylene and diphenylmethyl bromide through various intermediates, thus:[153]

$$(C_6H_5)_2C{=}CH_2 \xrightarrow[\text{reflux in } C_6H_6]{(C_6H_5)_2CHBr} (C_6H_5)_2CBrCH_2CH(C_6H_5)_2 \longrightarrow$$

$$(C_6H_5)_2C{=}CHCH(C_6H_5)_2 \longrightarrow (C_6H_5)_2CBrCHBrCH(C_6H_5)_2 \longrightarrow$$

$$(C_6H_5)_2C{=}CBrCH(C_6H_5)_2 \longrightarrow (C_6H_5)_2C{=}C{=}C(C_6H_5)_2$$

Dehydration of α,β-unsaturated alcohols is of only minor importance for synthesis of allenes.[140]

Since acetylenes are usually more easily prepared than allenes, syntheses of the latter from the former have significance. Di- and tri-arylallenes can be obtained in good yields by isomerization of arylacetylenes on activated basic alumina.[155,156]

Triphenylallene:[155] A solution of 1,3,3-triphenylpropyne (m.p. 78–78.5°; 2.06 g) in heptane (75 ml) and light petroleum (b.p. 20–40°; 25 ml) is placed rapidly on a column (1.7 × 10 cm) filled with activated alumina (previously dried for 5 days at 160–175°). The product is at once eluted with heptane. The eluate is filtered and the solvent is removed under reduced pressure. This affords triphenylallene (1.72 g, 83.5%), m.p. 77.5–79°.

Allenes can be obtained from propargyl halides[157,158] or propargyl alcohols[159] by treatment with zinc and copper,[157] lithium tetrahydroaluminate,[158] or copper(I) halides:[159]

$$(CH_3)_2CClC{\equiv}CH \xrightarrow[C_2H_5OH]{Zn/Cu} (CH_3)_2C{=}C{=}CH_2$$

$$RR'C(OH)C{\equiv}CH \xrightarrow[CuCl]{\text{aq. HCl}} RR'C{=}C{=}CHCl$$

When allenes are prepared from propargyl halides there are fewer by-products when zinc and copper are used rather than lithium tetrahydroaluminate.[160]

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[150] K. G. Untch, D. J. Martin, and N. T. Castellucci, *J. Org. Chem.*, **30**, 3572 (1965).

[151] W. R. Moore and R. C. Bertelson, *J. Org. Chem.*, **27**, 4182 (1962).

[152] A. Roedig, N. Detzer, and H. J. Friedrich, *Angew. Chem. Int. Ed., Engl.*, **3**, 382 (1964).

[153] W. Tadros, A. B. Sakla, and A. A. A. Helmy, *J. Chem. Soc.*, **1961**, 2687.

[154] F. B. Kirby, W. G. Kofron, and C. R. Hauser, *J. Org. Chem.*, **28**, 2176 (1963).

[155] T. L. Jacobs, D. Dankner, and S. Singer, *Tetrahedron*, **1964**, 2177.

[156] T. L. Jacobs and D. Dankner, *J. Org. Chem.*, **22**, 1424 (1957).

[157] J. I. Ginsbburg, *Zh. Obshch. Khim.*, **15**, 442 (1945); *Chem. Abstr.*, **40**, 4655 (1946).

[158] W. J. Bailey and C. R. Pfeifer, *J. Org. Chem.*, **20**, 95 (1955).

[159] T. L. Jacobs and W. L. Petty, *J. Org. Chem.*, **28**, 1360 (1963).

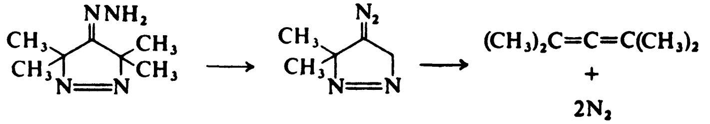
[160] T. L. Jacobs and R. D. Wilcox, *J. Amer. Chem. Soc.*, **86**, 2240 (1963).

Additions to vinylacetylenes open up a variety of possibilities for synthesis of allenes.[140] When alkyllithiums are added to a vinylacetylene subsequent hydrolysis affords allenic hydrocarbons:[161]

$$RC{\equiv}CCH{=}CH_2 \xrightarrow[\text{then } H_3O^+]{R'Li,} RCH{=}C{=}CH_2R'$$

If, however, the allenyllithium formed as intermediate is made to react with an aldehyde or a ketone, the product is an allenic alcohol.[162]

A novel method of preparing tetramethylallene is by cycloelimination from 3,3,5,5-tetramethyl-1-pyrazolin-4-one hydrazone, which occurs on treatment of this compound with an excess of nickel peroxide at room temperature, yielding nitrogen and 87–91% of the allene:[163]



The chemistry of cumulenes has been elucidated largely by R. Kuhn.[164] For synthesis of cumulenes, a diacetylene is converted into its di-Grignard reagent, which on treatment with a ketone (fluorenone, benzophenone, di-*p*-tolylketone, etc.) affords a diacetylenic glycol, whence reduction by chromium(II) chloride and hydrochloric acid gives the cumulene(III):

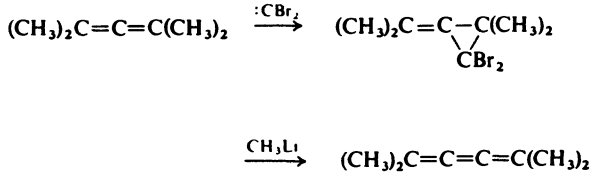
$$\underset{\text{(I)}}{BrMgC{\equiv}C{-}C{\equiv}CMgBr} \longrightarrow \underset{\text{(II)}}{(R)_2C(OH){-}C{\equiv}C{-}C{\equiv}C{-}C(OH)(R)_2}$$

$$\longrightarrow \underset{\text{(III)}}{(R)_2C{=}C{=}C{=}C{=}C(R)_2}$$

Pentatetraenes are formed from dibromopentadienes and potassium hydroxide in dimethylformamide:[165]

$$(C_6H_5)_2C{=}CBrCH_2CBr{=}C(C_6H_5)_2 \longrightarrow (C_6H_5)_2C{=}C{=}C{=}C{=}C(C_6H_5)_2$$

Addition of a dihalocarbene to an allene gives a cyclopropane derivative which, on treatment with methyllithium at −78°, affords the alkyl-substituted cumulene:[166]



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[161] A. A. Petrov and V. A. Kormer, *Dokl. Akad. Nauk S.S.S.R.*, **125**, 1041 (1959); *Chem. Abstr.*, **53**, 21,610 (1959).

[162] O. V. Perepelkin, L. N. Cherkasov, V. A. Kormer, and Kh. V. Bal'yan, *Zh. Obsch. Khim.*, **35**, 574 (1965); L. N. Cherkasov, V. A. Kormer, and Kh. V. Bal'yan, *Zh. Obshch. Khim.*, **35**, 616 (1965); O. V. Perepelkin, V. A. Kormer, and Kh. V. Bal'yan, *Zh. Obshch. Khim.*, **35**, 957 (1965); *Chem. Abstr.*, **63**, 1721, 2915, 9797 (1965).

[163] R. Kalish and W. H. Pirkle, *J. Amer. Chem. Soc.*, **89**, 2781 (1967).

[164] R. Kuhn and co-workers, *Ber. Deut. Chem. Ges.*, **71**, 783, 1510 (1938); **73**, 1410 (1940); **84**, 566 (1951); **86**, 759 (1953).

[165] R. Kuhn, H. Fischer, and H. Fischer, *Chem. Ber.*, **97**, 1760 (1964).

[166] L. Skattebøl, *Tetrahedron Lett.*, **1965**, 2175.

2. Ketenes

Of the various methods of preparing ketenes,[167] only those that involve introduction of the C=C double bond have their place in this Section. The oldest of these methods is dehalogenation of α-halo carbonyl chlorides by zinc in boiling ether or boiling ethyl acetate;[168] but this gives only poor yields, except for some oxoketenes, which are obtained in 90–95% yield,[169] and carbon suboxide.

Carbon suboxide, $O=C=C=C=O$:[170] A solution of dibromomalonic dichloride (30 g) in anhydrous ether (300 ml) is dropped on to zinc turnings (20 g) placed in a 1-l flask, the rate of addition being such that the liquid remains boiling. The carbon suboxide vapor escaping with the ether is passed through a condenser and trapped in vessels cooled in a freezing mixture. The yield of the suboxide is 80% (4.8 g).

Carbon suboxide is a poisonous gas that strongly irritates the eyes and respiratory organs. It condenses at +7°.

An alternative method of preparing ketenes is to dehydrohalogenate acid chlorides by tertiary amines.

However, tertiary amines catalyse the dimerization of ketenes, so that only those with little tendency to dimerize can be obtained by this route. Diphenylketene is formed almost quantitatively by removing hydrogen chloride from diphenylacetyl chloride with tripropylamine.[171]

Trimethylamine is the best base to use for preparation of oxoketenes.[172]

Sodium in liquid ammonia is a suitable dehydrohalogenating agent for synthesis of di-*tert*-butylketene from di-*tert*-acetyl chloride (2-*tert*-butyl-3,3-dimethylbutyryl chloride).[173]

Diphenylketene is accessible by thermal fission of α-azobenzyl phenyl ketone, $N_2C(C_6H_5)COC_6H_5$.[174]

Benzil monohydrazone is converted by yellow mercuric oxide into α-azobenzyl phenyl ketone, which affords diphenylketene and nitrogen when heated at 100–110°:[175]

$$\begin{tikzcd}
NH_2N{=}C(C_6H_5)COC_6H_5 + HgO \arrow[r] & N_2C(C_6H_5)COC_6H_5 + Hg + H_2O \arrow[d] \\
& N_2 + (C_6H_5)_2C{=}C{=}O
\end{tikzcd}$$

Other ketenes can also be obtained by this method.

Because many ketenes have a great tendency to dimerize, fission of the dimers is an important method for their preparation. The dimers are cleaved when heated at 500–600°, giving the monomers free from by-products, so that formation of and regeneration from the dimers can be used for purification of the monomers.[176]

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[167] R. N. Lacey in S. Patai, "The Chemistry of the Alkenes," Interscience Publ., London–New York–Sydney, 1964, p. 1161.

[168] H. Staudinger, *Ber. Deut. Chem. Ges.*, **38**, 1735 (1905).

[169] H. Staudinger, *Ann. Chem.*, **356**, 51 (1908).

[170] H. Staudinger and S. Bereza, *Ber. Deut. Chem. Ges.*, **41**, 4465 (1908).

[171] H. Staudinger, *Ber. Deut. Chem. Ges.*, **44**, 1619 (1911).

[172] U.S. Pat. 2,268,169; *Chem. Abstr.*, **36**, 2737 (1942).

[173] M. S. Newman, A. Arkell, and T. Fukunaga, *J. Amer. Chem. Soc.*, **82**, 2498 (1960).

[174] G. Schroeter, *Ber. Deut. Chem. Ges.*, **42**, 2346 (1909).

[175] L. I. Smith and H. H. Hoehn, *Org. Syn.*, Coll. Vol. 3, 356 (1955).

[176] A. B. Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).

11.2. Acetylenic bonds

Introduction of a triple bond into a pre-existing carbon skeleton is almost always effected by a method that starts from compounds containing an ethylenic bond or proceeds through such compounds as intermediates.[177] The reaction most commonly used is dehydrohalogenation of appropriate halogen compounds, namely, either of chloro- or bromo-alkenes (**1** or **2**) or of dichloro- or dibromo-alkenes (**3**, **4**, or **5**) carrying the two halogen atoms on vicinal or the same carbon atom.

$$\underset{(1)}{\mathrm{HalCR{=}CHR'}} \qquad \underset{(2)}{\mathrm{RCH{=}CHHal}} \qquad \underset{(3)}{\mathrm{HalCHRCH_2Hal}}$$

$$\underset{(4)}{\mathrm{RCH_2CH(Hal)_2}} \qquad \underset{(5)}{\mathrm{RC(Hal)_2CH_3}}$$

An acetylenic bond may, however, be introduced also by dehalogenation of vicinal dihaloalkenes, occasionally by cleavage of nitrogenous compounds, or from enol esters by elimination reactions.[178]

1. Dehydrohalogenation of dihalides or haloalkenes

The most important dehydrohalogenating agents for introducing triple bonds are potassium hydroxide and sodamide, but other basic reagents may also be used, *e.g.*, alkali alkoxides, hydrides, and carbonates, alkaline-earth hydroxides and carbonates, and occasionally organometallic compounds.

From saturated halogen compounds removal of the first molecule of hydrogen halide, to form an ethylenic linkage, is considerably easier than removal of the second, to form the triple bond. For example, in the preparation of ethoxyacetylene $CH{\equiv}COC_2H_5$ from 1,2-dibromoethyl ethyl ether the first molecule of hydrogen bromide can be removed by diethylaniline, but the second only by potassium hydroxide in a vacuum.[179]

Alkali hydroxides are most commonly used, with or without a solvent. Suitable solvents, in order of importance, are ethanol, methanol, butanol, ethanol–water mixtures, ethylene glycols and its ethers, glycerol, and hydrocarbons. The usual reagent is saturated ethanolic potassium hydroxide (*ca.* 4N, *ca.* 20) at room temperature, but always more than the theoretical amount. For dehydrohalogenation of arylalkenyl halides it often suffices to reflux the compound for some time in a suitable solvent, but preparation of purely aliphatic acetylenes sometimes requires heating in an autoclave at temperatures around 170°.[180] Reaction times vary, from a few minutes to several hours.

***p*-Tolylacetylene:**[181] β-Chloro-4-methylstyrene (85 g) is boiled under reflux for 24 h with potassium hydroxide (50 g) in anhydrous ethanol (100 ml). The mixture is then poured into

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[177] G. Köbrich, *Angew. Chem. Int. Ed., Engl.*, **4**, 49 (1965).

[178] J. C. Craig, M. D. Bergenthal, I. Fleming, and J. Harley-Mason, *Angew. Chem. Int. Ed., Engl.*, **8**, 429 (1969).

[179] Ya. N. Nazarov, Zh. A. Krasnaya, and V. P. Vinogradov, *Zh. Obshch. Khim.*, **28**, 460 (1958); *Chem. Abstr.*, **52**, 13611 (1958).

[180] L. Pauling, H. D. Springall, and K. J. Palmer, *J. Amer. Chem. Soc.*, **61**, 928 (1939).

[181] L. J. Smith and H. H. Hoehn, *J. Amer. Chem. Soc.*, **63**, 1175 (1941).

ice-water (1 l), the oil is separated, and the aqueous layer is extracted with ether. The oil and the ethereal extract are united and dried over potassium hydroxide. Removing the ether and distilling the residue affords the acetylene (31 g, 65%), b.p. 79–82°/31–33 mm.

Phenylacetylene:[182] Bromine (410 g) is added during 2 h, with cooling and stirring, to a mixture of chloroform (200 ml) and styrene (312 g), and the whole is stirred for a further 0.5 h at 30°. Removing the chloroform and drying the residue in the air gives pure, white styrene dibromide (653 g), m.p. 73°.

Potassium hydroxide (240 g) in methanol (240 ml) is heated to boiling and styrene dibromide (264 g) is stirred in portionwise during 1.5 h. The whole is heated under reflux for a further 0.5 h, then cooled and treated with water (400 ml). The oil that separates is removed and dried over potassium carbonate. Distillation at 10 mm affords an oil (*ca.* 75 g) boiling up to 100°, which on redistillation at atmospheric pressure gives phenylacetylene (67 g, 66%), b.p. 141–143°.

Acetylenic carboxylic acids are relatively easily accessible. Acetylenedicarboxylic acid is prepared from dibromosuccinic acid by reaction with methanolic potassium hydroxide solution.[183] Phenylpropiolic acid can be prepared by the action of the same reagent on ethyl α,β-dibromocinnamate and treatment of the resulting potassium salt with dilute sulfuric acid:[184]

$$C_6H_5CHBrCHBrCOOC_2H_5 + 3KOH \longrightarrow$$
$$C_6H_5C{\equiv}CCOOK + C_2H_5OH + 2KBr + 2H_2O$$

Smaller amounts of **phenylpropiolic acid** can be obtained from α,β-dibromocinnamic acid, itself obtained in 95% yield from cinnamic acid and bromine in boiling carbon tetrachloride.[185]

Cinnamic acid dibromide (25 g) is placed in an evaporating dish and treated with a 25% solution (100 ml) of potassium hydroxide in methanol. The mixture is heated on a vigorously boiling water-bath until the methanol is wholly removed. Further methanol (75 ml) is added to the viscous residue and again evaporated off, so as to complete the reaction. When the mass cools, adhering methanol is removed from the pale yellow, granular product by suction. This solid, dry product is washed with a small amount of cold methanol and dissolved in ice-water (500 ml). Ice-cold hydrochloric acid is stirred in slowly until an acid reaction is obtained. The precipitated oil solidifies overnight in an ice-bath. An 80% yield of phenylpropiolic acid, m.p. 136–138°, is obtained.

Alkali hydroxides are used without a solvent[186] for preparation of acetylenic ethers from alkoxy- or aryloxy-bromoethylenes, *e.g.*, of phenoxyacetylene from 1-bromo-2-phenoxyethylene:[187]

$$CHBr{=}CHOC_6H_5 \xrightarrow{KOH} CH{\equiv}COC_6H_5$$

Temperatures around 200° are customary for work with alkali hydroxide melts. Pure potassium hydroxide melts at 360°, so that recourse is had to mixtures of two parts of potassium hydroxide plus one of sodium hydroxide (m.p. 200°) or to addition of a little water to potassium hydroxide. However, commercial potassium hydroxide usually contains enough water to allow it to melt around 200°.

Phenylacetylene:[188] Potassium hydroxide (80 g) is placed in a flask fitted with a dropping funnel and a descending condenser and heated in an oil-bath at 200–215°. β-Bromostyrene (25 g) is added at about one drop per second. The phenylacetylene formed distils off continu-

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[182] Chem. Werke Hüls AG, cited by W. Franke, W. Ziegenbein, ad H. Meister, *Angew. Chem.*, **72**, 400 (1960).

[183] T. W. Abbott, R. T. Arnold, and R. B. Thompson, *Org. Syn.*, Coll. Vol. 2, 10 (1943).

[184] T. W. Abbott, *Org. Syn.*, Coll. Vol. 2, 515 (1943).

[185] M. Reimer, *J. Amer. Chem. Soc.*, **64**, 2510 (1942).

[186] F. Kraft and L. Reuter, *Ber. Deut. Chem. Ges.*, **25**, 2244 (1982).

[187] T. L. Jacobs, R. Cramer, and F. F. Weiss, *J. Amer. Chem. Soc.*, **62**, 1849 (1940); T. L. Jacobs, R. Cramer, and J. E. Hanson, *J. Amer. Chem. Soc.*, **64**, 223 (1942).

[188] J. Hessler, *J. Amer. Chem. Soc.*, **44**, 425 (1922); *Org. Syn.*, Coll. Vol. 1, 438 (1941).

ously. Towards the end of the reaction the temperature is raised slowly to 235°. The distillate contains two layers, which are separated. The upper layer of phenylacetylene is dried over potassium hydroxide and fractionated, affording an 80% yield (11 g) of material boiling at 142–144°.

The use of alkali hydroxides for such reactions is limited when substituents sensitive to alkali hydroxides are present and by the possibility of rearrangements at high alkali concentrations and high temperatures.

Sodamide in an inert solvent at 110–160° may also be used for dehydrohalogenation. It must be finely powdered and used in excess (precautions against possible explosion must be taken during its pulverization). 3-Cyclohexylpropyne can be prepared from 2-bromo-3-cyclohexylpropyne in this way.[189]

Unusually mild conditions are applied when sodamide in liquid ammonia is used for removing the hydrogen halide.[190] The reaction is carried out in an open vessel at the boiling point of ammonia or in a pressure vessel at room temperature.[191]

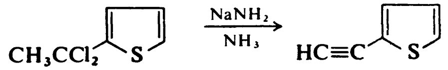
Moisture must be completely excluded because sodamide readily becomes coated with sodium hydroxide; it is thus advisable to prepare the reagent shortly before use by reaction of sodium with anhydrous liquid ammonia[192] in the presence of iron(III) chloride or nitrate.[190] 2-Butyn-1-ol (**7**) is then obtained in 80% from 3-chloro-2-buten-1-ol (**6**) by way of its sodium salt, the original starting material being 1,3-dichloro-2-butene:[193]

$$\begin{tikzcd} \underset{\textbf{(6)}}{\mathrm{CH_3CCl{=}CHCH_2OH}} \arrow[r, "\mathrm{NaNH_2}", "\mathrm{NH_3}"'] & \mathrm{CH_3C{\equiv}CCH_2ONa} \arrow[d, "\mathrm{NH_4Cl}"] \\ & \mathrm{CH_3C{\equiv}CCH_2OH}\quad \textbf{(7)} \end{tikzcd}$$

Sodamide in liquid ammonia is a particularly suitable reagent for preparation of alkoxyacetylenes, *e.g.*, methoxy-, ethoxy-, and butoxy-acetylene, from dialkyl chloroacetals;[194] both hydrogen halide and the alcohol are split off in this process:

$$\mathrm{ClCH_2CH(OR)_2} \xrightarrow[\mathrm{NH_3}]{\mathrm{NaNH_2}} \mathrm{CH{\equiv}COR}$$

Good yields of acetylenic derivatives in the heterocyclic series, *e.g.*, 2-ethynylthiophene, can also be obtained by means of sodamide in liquid ammonia:[195]



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[189] R. Lespieu and M. Bourguel, *Org. Syn.*, Coll. Vol. 1, 191 (1941).

[190] T. H. Vaughn, R. R. Vogt, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 2120 (1934); A. T. Bottini, B. J. King, and J. M. Lucas, *J. Org. Chem.*, **27**, 3688 (1962).

[191] W. Franke, W. Ziegenbein, and H. Meister, *Angew. Chem.*, **72**, 394 (1960).

[192] K. W. Greenlee and A. L. Henne, *Inorg. Syn.*, **2**, 75, 70 (1946).

[193] P. J. Ashworth, G. H. Mansfield, and M. C. Whiting, *Org. Syn.*, **35**, 20 (1955).

[194] G. Eglinton, E. R. H. Jones, B. L. Shaw, and M. C. Whiting, *J. Chem. Soc.*, **1954**, 1860.

[195] A. Vaitiekunas and F. F. Nord, *J. Org. Chem.*, **19**, 902 (1954).

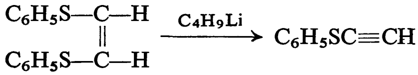
Of the other dehydrohalogenating agents, sodium hydride deserves a special mention. It is valuable chiefly for the preparation of arylpropiolic esters (*o*-, *m*-, and *p*-chloro-, -methoxy-, and -nitro-phenylpropiolic esters): the aryl-2,3-dibromopropionic ester, in solution in benzene containing a little anhydrous ethanol, is brought into reaction with the sodium hydride;[196] the hydride and the ethanol form sodium ethoxide, which is the actual agent for removal of hydrogen bromide and which by reaction with the hydrogen bromide generated re-forms ethanol, so it suffices to use only a small amount of ethanol:

$$C_2H_5OH + NaH \longrightarrow C_2H_5ONa + H_2$$

$$C_2H_5ONa + HBr \longrightarrow C_2H_5OH + NaBr$$

Therein lies the advantage of the method, for it avoids the ether formation that occurs readily if alkali alkoxides or alcoholic alkali hydroxide solutions are used.

A few organometallic compounds, *e.g.*, butyl- and phenyl-lithium can also be used to introduce a triple bond.[197] Phenylthioacetylene is formed when *cis*- or *trans*-bis(phenylthio)ethylene is treated with butyllithium:[198]



$$\begin{array}{c} C_6H_5S\text{—}C\text{—}H \\ \| \\ C_6H_5S\text{—}C\text{—}H \end{array} \xrightarrow{C_4H_9Li} C_6H_5SC{\equiv}CH$$

Phenylacetylene is formed in 70% yield when β-chlorostyrene reacts with phenyllithium.[199]

2. Dehalogenation

Dehalogenation is not important for preparation of acetylenic compounds. A few vicinal dibromoalkenes have been dehalogenated by metals — usually finely divided metals in an appropriate solvent. For example, diphenylacetylene may be made by treating 1,2-dibromo-1,2-diphenylethylene with zinc in acetone (yield 85%);[200] and about 80% of fluoroacetylene is formed on removal of bromine from 1,2-dibromo-1-fluoroethylene with magnesium in tetrahydrofuran:[201]

$$CFBr{=}CHBr \xrightarrow{Mg} CF{\equiv}CH + MgBr_2$$

1,1,2-Trichloro-3,3,3-trifluoropropene, zinc dust, and a little zinc chloride in solvents such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, and 1-methyl-2-pyrrolidone give a 75% yield of 3,3,3-trifluoropropyne.[202]

3. Cleavage of nitrogenous compounds

Certain diquaternary ammonium compounds generate acetylenes on decomposition, in reactions closely analogous to the Hofmann degradation. One such is that of the ethylenediamine derivative: on a laboratory scale the

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[196] M. S. Newman and S. H. Merrill, *J. Amer. Chem. Soc.*, **77**, 5549 (1955).

[197] M. Schlosser, *Angew. Chem. Int. Ed., Engl.*, **3**, 287 (1964).

[198] W. E. Parham and P. L. Stright, *J. Amer. Chem. Soc.*, **78**, 4783 (1956).

[199] G. Wittig and H. Witt, *Ber. Deut. Chem. Ges.*, **74**, 1474 (1941).

[200] F. Strauss, *Ann. Chem.*, **342**, 190 (1905).

[201] H. G. Viehe and E. Franchimont, *Chem. Ber.*, **95**, 319 (1962).

[202] W. G. Finnegan and W. P. Norris, *J. Org. Chem.*, **28**, 1139 (1963).

diquaternary ammonium salt obtained from ethylene dibromide and an excess of trimethylamine gives an 80% yield of acetylene when heated with 40% aqueous potassium hydroxide solution:[203]

$$(CH_3)_3\overset{+}{N}CH_2CH_2\overset{+}{N}(CH_3)_3\ 2OH^- \longrightarrow CH{\equiv}CH + 2N(CH_3)_3 + 2H_2O$$

Propyne and 2-hexen-4-yne can be obtained similarly in good yields.

Diacetylenes can be prepared by the same method from the 1,4-diquaternary ammonium salt derivatives of 2-chloro-2-butene and 2-butyne:[204]

$$R_3\overset{+}{N}CH_2CH{=}CClCH_2\overset{+}{N}R_3\ 2Br^- \xrightarrow{NaOH} HC{\equiv}CC{\equiv}CH$$

$$R_3\overset{+}{N}CH_2C{\equiv}CCH_2\overset{+}{N}R_3\ 2Br^- \xrightarrow{NaOH} HC{\equiv}CC{\equiv}CH$$

In a noteworthy reaction sequence reported by Babayan and Grigoryan[205] tetrolic acid (2-butynoic acid) (**11**) is formed from *N*,*N*-dimethyl-2-butynylamine through the intermediates (**9**) and (**10**):

$$\underset{\textbf{(8)}}{(CH_3)_2NCH_2C{\equiv}CCH_3} \xrightarrow{Cl_2} \underset{\textbf{(9)}}{(CH_3)_2NCH_2CCl_2CCl_2CH_3} \xrightarrow{CH_3I}$$

$$\underset{\textbf{(10)}}{I^-(CH_3)_3\overset{+}{N}CH_2CCl_2CCl_2CH_3} \xrightarrow{NaOH} \underset{\textbf{(11)}}{CH_3C{\equiv}CCOOH}$$

***N*,*N*-Dimethyl-(2,2,3,3-tetrachlorobutyl)amine** (**9**): Chlorine (75 g) is passed into a solution of *N*,*N*-dimethyl-2-butynylamine (**8**) (48.5 g) in 34% hydrochloric acid (100 ml). The mixture is then neutralized with concentrated potassium carbonate solution and the precipitated crystalline amine is collected, washed several times with water, and dried. The yield is 90.3% (108 g), and the m.p. is 46–47°.

***N*,*N*,*N*-Trimethyl-(2,2,3,3-tetrachlorobutyl)ammonium iodide** (**10**): The amine (**9**) (23.9 g) and methyl iodide (21.3 g) in acetone (60 ml) are heated on a water-bath for 3 h, then the crystalline iodide is filtered off and washed with alcohol. The yield is almost quantitative; after recrystallization from methanol the m.p. is 187°.

Tetrolic acid (**11**): A solution of sodium hydroxide (48 g) in water (40 ml) is dropped during 20 min into a solution of the iodide (**10**) (76.2 g) in water (40 ml) at −10°. The exothermic reaction is complete in about 1 h. The trimethylamine evolved may be collected by passage through a wash-bottle containing hydrochloric acid. The residual reaction mixture is washed with ether, and the aqueous layer is then acidified cautiously with hydrochloric acid and extracted several times with ether. The ethereal extracts are united and dried over sodium sulfate. The residue obtained on removal of the ether crystallizes completely (yield 11.8 g, 70.2%) and after recrystallization from light petroleum melts at 78–78.5°.

Curtius *et al.*[206] showed that acetylenes can also be prepared by oxidizing vicinal dihydrazones with yellow mercuric oxide. Diphenylacetylene, for example, is thus obtained in 75% yield from benzil dihydrazone.[207] In a variant of the Curtius procedure diacetylenes can be prepared in 80–85% yield by oxi-

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[203] Ya. M. Slobodin and N. A. Selezneva, *Zh. Obshch. Khim.*, **26**, 691 (1956); *Chem. Abstr.*, **50**, 14502 (1956); *Zh. Obshch. Khim.*, **27**, 2473 (1957).

[204] A. T. Babayan, G. M. Mrkyan, and Sh. L. Mndzkoyan, *Zh. Obshch. Khim.*, **27**, 604 (1957); *Chem. Abstr.*, **51**, 16278 (1957).

[205] A. T. Babayan and A. A. Grigoryan, *Zh. Obshch. Khim.*, **26**, 1945 (1956); *Chem. Abstr.*, **51**, 4940 (1957).

[206] T. Curtius, *Ber. Deut. Chem. Ges.*, **22**, 2161 (1889); T. Curtius and K. Thun, *J. Prakt. Chem.*, **44**, 168 (1891).

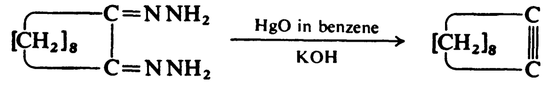
[207] W. Schlenk and E. Bergmann, *Ann. Chem.*, **463**, 76 (1928); A. C. Cope, D. S. Smith, and R. J. Cotter, *Org. Syn.*, **34**, 42 (1954).

dizing vicinal dihydrazones with silver trifluoroacetate and triethylamine with acetonitrile or ethanol as solvent:[208]

$$\begin{matrix} C_6H_5C\text{—}CC_6H_5 \\ \| \quad \| \\ NH_2\text{—}N \quad N\text{—}NH_2 \end{matrix} + 4CF_3COOAg + 4N(C_2H_5)_3 \longrightarrow$$

$$C_6H_5C{\equiv}CC_6H_5 + 4(C_2H_5)_3NH^+[CF_3COO]^- + 4Ag + 2N_2$$

Certain cyclic acetylenic compounds can also be synthesized by this method, *e.g.*, cyclodecyne[209] in 36% yield by oxidation of 1,2-cyclodecanedione dihydrazone with yellow mercuric oxide in benzene containing ethanolic potassium hydroxide solution and anhydrous sodium sulfate; and cyclodecyne has been obtained similarly.[210]



Several reviews[211] are available for consultation regarding the preparation of acetylenes.

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[208] M. S. Nemwan and D. E. Reid, *J. Org. Chem.*, **23**, 665 (1958).

[209] A. T. Blomquist, R. E. Burge, and A. C. Sucsy, *J. Amer. Chem. Soc.*, **74**, 3636 (1952).

[210] V. Prelog and M. Speck, *Helv. Chim. Acta*, **38**, 1790 (1952).

[211] T. L. Jacobs, *Org. Reactions*, **5**, 1 (1949); W. Franke, W. Ziegenbein, and H. Meister, *Angew. Chem.*, **72**, 392 (1960); J. F. Arens, *Advan. Org. Chem.*, **2**, 121 (1960).

PART B

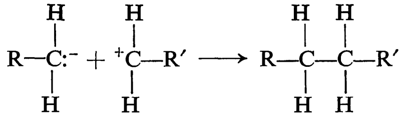
Formation of new carbon–carbon bonds

PART B

Formation of new carbon-carbon bonds

Compiled by
H. Gross, C. Bischoff, E. Höft, and E. Gründemann

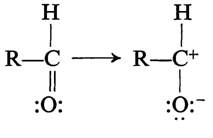
Carbon bonds can be formed by addition or replacement. In general it is a requirement that the carbon atoms to be bonded together shall be oppositely polarized, *i.e.*, that one shall be cationic (a carbonium ion) and the other an anion (a carbanion). The new bond is formed by addition of the lone pair of electrons of the carbanion at the site of the electron deficiency of the carbonium ion, in a reaction that is analogous to neutralization:



$$R{-}\overset{H}{\underset{H}{C}}{:}^- + {}^+\overset{H}{\underset{H}{C}}{-}R' \longrightarrow R{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}R'$$

1.1. Formation of new carbon–carbon bonds by addition

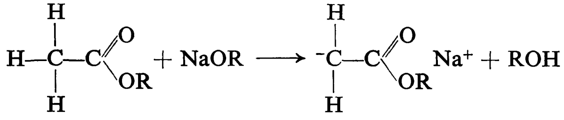
This Section deals with addition to multiple bonds such as those in C=C, C=O, and C≡N groups. Very often, and particularly in additions to carbonyl or nitrile groups, this occurs by anionoid addition; here the addend functions as carbanion, and the acceptor containing the double bond functions as carbanion, the π-electron pair of the double bond being shifted towards the atom having the greater electron affinity, *e.g.*:



$$R{-}\overset{H}{\underset{\overset{\|}{:O:}}{C}} \longrightarrow R{-}\overset{H}{\underset{:\ddot{O}:^-}{C^+}}$$

This type of anionoid addition also occurs at a C=C bond when the latter is conjugated to a carbonyl or a nitrile group.

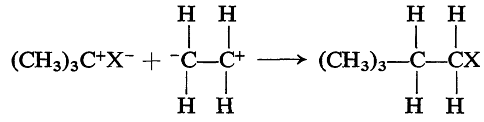
The carbanion of the addend is usually formed by loss of a proton, but in many cases only under the influence of a base (NaOH or NaOR), *e.g.*:



$$H{-}\overset{H}{\underset{H}{C}}{-}C\begin{smallmatrix}{/\!\!/}O\\ \backslash OR\end{smallmatrix} + NaOR \longrightarrow {}^-\overset{H}{\underset{H}{C}}{-}C\begin{smallmatrix}{/\!\!/}O\\ \backslash OR\end{smallmatrix}\; Na^+ + ROH$$

The proton is lost more easily when there is a neighboring atom of high electron affinity, such as the carbonyl oxygen atom in the above reaction. Aromatic and aliphatic hydrocarbons rarely react in this way, since their C–H acidity is too low; they yield carbanions only when forced to do so by conversion into an organometallic compound, *e.g.*, by a Grignard reaction.

C=C bonds that are not activated by neighboring groups usually undergo only cationoid addition; here the carbanion of the acceptor forms the new bond with the carbonium ion of the addend. All the additions of alkyl halides, acyl halides, and saturated hydrocarbons to olefins in the presence of strongly acidic catalysts occur by the cationoid addition mechanism:



$$(CH_3)_3C^+X^- + {}^-\overset{H}{\underset{H}{C}}—\overset{H}{\underset{H}{C}}{}^+ \longrightarrow (CH_3)_3—\overset{H}{\underset{H}{C}}—\overset{H}{\underset{H}{C}}X$$

In addition to these anionoid and cationoid additions, there is, especially for addition to a C=C bond, the possibility of addition by a radical mechanism. This can be set in motion by a radical-forming agent such as a peroxide or azo compound. C–C bonding then occurs by coupling of the double bond of the acceptor with the addend containing the two single electrons derived by homolytic cleavage of the π-electron pair:

$$\cdot CHR—CH_2\cdot + CCl_4 \longrightarrow ClCHR—CH_2CCl_3$$

I. Addition to C=C bonds

1. Addition to ethylenic bonds

Addition of aliphatic hydrocarbons to ethylenic compounds occurs under the influence of catalysts such as sulfuric acid, phosphoric acid, and aluminum chloride.[1] For instance, isobutane and propene afford the three isomeric heptanes. This reaction is not of particular importance in laboratory practice. However, addition of aromatic compounds to olefins is often a practicable method of alkylation.[2] Thus ethylbenzene is formed from ethylene and benzene under the influence of aluminum chloride or when the hydrocarbon mixture is passed over a silica–alumina catalyst; and Brochet[3] obtained 2-phenylhexane from benzene and 1-hexene. The C–C bond is always formed to the doubly bonded carbon atom carrying the smaller number of hydrogen atoms; benzene and propene, for instance, give cumene, which is important as intermediate in the preparation of phenol. Corson and Ipatieff[4] report that benzene reacts especially readily with cyclohexene, yielding **cyclohexylbenzene**:

Adding cyclohexene (164 g) during 2 h, with stirring, to an ice-cold mixture of benzene (400 g) and concentrated sulfuric acid (92 g) affords cyclohexylbenzene (200 g), b.p. 239–245°. When the reaction mixture is worked up, it is important that before distillation the oily layer must be washed twice with cold concentrated sulfuric acid (50-ml portions) and then successively with water, dilute alkali hydroxide solution, and water.

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[1] V. N. Ipatieff, A. V. Grosse, H. Pines, and V. I. Komarewski, *J. Amer. Chem. Soc.*, **58**, 913 (1936).

[2] A. A. D'Kelly, J. Kellet, and J. Plucker, *Ind. Eng. Chem.*, **39**, 154 (1947).

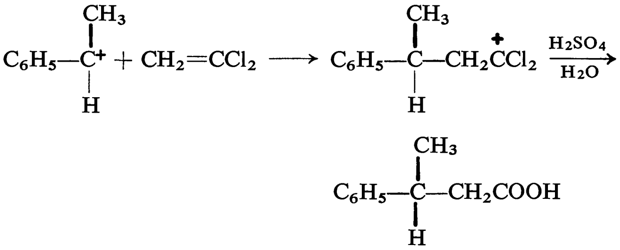
[3] A. Brochet, *C. R. Hebd. Séances Acad, Sci.*, **117**, 115 (1893).

[4] B. B. Corson and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **59**, 645 (1937).

Under the above conditions allyl chloride converts benzene into ω-chlorocumene, thus providing a key atom in the side chain for further reactions:

$$C_6C_6 + CH_2{=}CHCH_2Cl \longrightarrow C_6H_5CH(CH_3)CH_2Cl$$

Addition of tertiary or secondary carbonium ions to 1,1-dichloroethylene in sulfuric acid at 0–15° leads to substituted acetic acids,[5] the yield being considerably increased, when necessary, if the acid contains 8% by weight of boron trifluoride. Olefins, alcohols, chlorides, and esters can be used to provide the cation.



$$C_6H_5\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C^+}} + CH_2{=}CCl_2 \longrightarrow C_6H_5\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C}}\text{—}CH_2\overset{+}{C}Cl_2 \xrightarrow[H_2O]{H_2SO_4} C_6H_5\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle H}{C}}\text{—}CH_2COOH$$

3-Phenylbutyric acid:[6] A mixture of α-methylbenzyl alcohol (122 g) and 1,1-dichloroethylene (291 g) is dropped into 90% sulfuric acid (200 ml) with stirring at 5–7°. Addition and subsequent stirring each occupy 2 h. The mixture is then hydrolysed with ice, and the precipitated product is taken up in ether. The carboxylic acid is purified by dissolution in aqueous sodium hydroxide solution and reprecipitation by dilute hydrochloric acid. This gives a product (85 g,) m.p. 38–40°, b.p. 113–115°/2 mm.

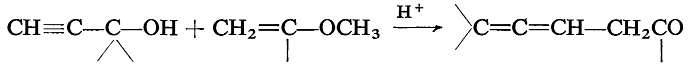
Stroh and his co-workers[7] alkylated phenols and aromatic amines by olefins in the presence of metallic aluminum as catalyst at high temperatures, substitution occurring preferentially in the *ortho*-position.

Alkali salts of carboxylic acids that have a C–H bond at the α-position to the carboxyl group can be alkylated by olefins at 150–200° and 60–200 atm in the presence of sodium potassium, sodium hydride, or sodamide:[8]

$$CHRR'COO^- + CH_2{=}CH_2 \longrightarrow CH_3CH_2CRR'COO^-$$

Yields are between 30 and 80%. The reactivity increases along the series $CH_3COO^- < RCH_2COO^- < R_2CHCOO^-$, so that formation of the fully alkylated compounds is favored.

Tertiary acetylenic alcohols react with isopropenyl ethers in the presence of a small amount of acid to yield 2-oxoalkyl allenes:[9]



$$CH{\equiv}C\text{—}\underset{/\backslash}{C}\text{—}OH + CH_2{=}\underset{|}{C}\text{—}OCH_3 \xrightarrow{H^+} \rangle C{=}C{=}CH\text{—}CH_2\underset{|}{C}O$$

6-Methyl-4,5-heptadien-2-one:[9] 2-Methyl-3-butyn-2-ol (172 g), light petroleum (b.p. 60 to 90°; 800 ml), hydroquinone (0.4 g), and isopropenyl methyl ether (432 g) are treated with *p*-toluenesulfonic acid (0.2 g). There is an exothermic reaction, after which the mixture is

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[5] K. Bott, *Chem. Ber.*, **100**, 978 (1967).

[6] K. Bott, *Chem. Ber.*, **100**, 2791 (1967).

[7] R. Stroh, J. Eibersberger, H. Haberland, and W. Hahn, *Angew. Chem.*, **69**, 124 (1957); R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.*, **69**, 699 (1957).

[8] L. Schmerling and W. G. Toekelt, *J. Amer. Chem. Soc.*, **84**, 3694 (1962).

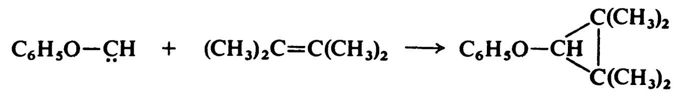
[9] G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 1158 (1967).

stirred for 15–24 h in an oil-bath kept at 80°; the internal temperature, initially about 55°, is thus raised gradually to about 65°. Next the mixture is cooled and treated with a solution of anhydrous sodium acetate (0.2 g) in methanol (20 ml), and a forerun is distilled off through a Vigreux column at 15 mm. The residue is distilled at 0.1 mm, the fraction of b.p. 35–50° being collected. This affords about 95% (233–239 g) of crude oxoalkyl allene. The pure product boils at 70°/19 mm.

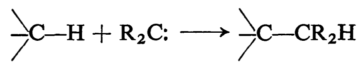
Ethylenic compounds add carbenes, to form cyclopropane derivatives.[10] Carbenes can be prepared by treating appropriate halogen compounds with an organometallic compound (*e.g.*, butyllithium), α-elimination of lithium chloride resulting:

$$C_6H_5OCH_2Cl \xrightarrow{+C_4H_9Li} C_6H_5OCHClLi \xrightarrow{-LiCl} C_6H_5O\underset{\cdot\cdot}{C}H$$

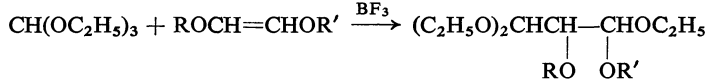
For example, adding phenoxycarbene to 2,3-dimethyl-2-butene gives a 70% yield of 1,1,2,2-tetramethyl-3-phenoxycyclopropane:[11]



The original literature should be consulted for other methods of preparing carbenes and for the stereochemistry of addition of singlet and triplet carbene.[10–12] Besides adding to carbon-carbon double bonds, carbenes can become inserted into C–H bonds:[10]



Boron trifluoride catalyzes addition of orthoesters or acetals to 1,2-dialkoxyethylenes, *e.g.*:[13]



$$CH(OC_2H_5)_3 + ROCH{=}CHOR' \xrightarrow{BF_3} (C_2H_5O)_2CH\underset{RO}{CH}{-}\underset{OR'}{C}HOC_2H_5$$

2. Polymerization of ethylene derivatives

The polymerization of ethylene derivatives has recently become extremely important for the manufacture of plastics. Certain substituents in ethylene — those that increase the polarization — increase both the extent and the rate of polymerization. Such substituents are aromatic groups (as in styrene), oxygen-containing groups (as in acrolein, acrylic esters, and vinyl esters and ethers), and halogens (as in vinyl chloride). Multiplication of these substituents, however, depresses or completely suppresses the tendency to polymerize; for instance, stilbene gives only a dimer when illuminated in benzene.[14]

Polymerization can be accelerated by ultraviolet irradiation or by peroxides, and also by acid or basic catalysts.

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[10] W. Kirmse, "Carbene Chemistry," Academic Press, New York, London, 1964.

[11] U. Schöllkopf, A. Lerch, and J. Paust, *Chem. Ber.*, **96**, 2266 (1963).

[12] U. Schöllkopf and P. Hilbert, *Angew. Chem. Int. Ed., Engl.*, **1**, 401 (1962).

[13] H. Baganz and K. Praefcke, *Chem. Ber.*, **96**, 2661, 2666 (1963).

[14] G. Ciamician and P. Silber, *Ber. Deut. Chem. Ges.*, **35**, 4129 (1902).

A radical chain mechanism must be assumed for polymerization on irradiation or in presence of peroxides:

$$\mathrm{R\cdot + CH_2{=}CHCl \longrightarrow RCH_2{-}\underset{\cdot}{C}HCl + CH_2{=}CHCl \longrightarrow}$$
$$\mathrm{{}^{\cdot}CH_2{-}CHCl{-}CH_2{-}\underset{\cdot}{C}HCl,\ etc.}$$

When the starting reaction has formed an activated monomer in the above manner, the latter acts as seed for polymer growth. Short chains are formed when many such seeds are present, and a small number of seeds leads to longer chains. Antioxidants such as hydroquinone and thiophenols hinder radical-chain polymerization; and many inorganic reducing agents, *e.g.*, sodium hydrogen sulfate and sodium sulfite, also break the chain reactions. Thus the course of polymerization can be directed as desired by using an appropriate redox system, *i.e.*, a combination of oxidizing (peroxide) and reducing agent. Growth of the chain ceases if the energy of a growing chain is transferred to a monomer molecule, *e.g.*, by loss of a hydrogen atom, a new polymerization seed being formed in the process:

$$\mathrm{R{-}[CH_2CHCl]_{\mathit{n}}{-}CH_2CHCl\cdot + CH_2{=}CHCl \longrightarrow}$$
$$\mathrm{R{-}[CH_2CHCl]_{\mathit{n}}{-}CH{=}CHCl + CH_3CHCl\cdot}$$

Peroxides also initiate telomerization, which is a process also occurring by way of radicals.[15] In this reaction compounds such as halomethanes participate to form short-chain polymers with both ends of the chain defined. In the overall reaction the taxogen (*e.g.*, ethylene) combines with the telogen (*e.g.*, carbon tetrachloride) to afford a **telomer**:

$$x\mathrm{CH_2{=}CH_2 + CCl_4 \longrightarrow Cl{-}[CH_2CH_2]_{\mathit{x}}{-}CCl_3}$$

Joyce and his co-workers[16] carried out this reaction as follows:

Freshly distilled carbon tetrachloride (210 g, 1.36 moles), water (35 g), and benzoyl peroxide (0.47 g, 0.00194 mole) are placed in a stainless steel autoclave (capacity about 350 ml) fitted with a gas-inlet tube and a thermoelement for temperature measurement. Air is removed from the autoclave, and ethylene is pressed in to 35 atm. The autoclave is then shaken in a horizontal position and heated; when the temperature of the mixture reaches 70°, more ethylene is pressed in, to give a pressure of about 100 atm. The mixture is then kept at 95° for 5 h, more ethylene being pressed in to keep the pressure at 85–100 atm. Finally the autoclave is cooled and the product is removed, separated from the water, and dried over anhydrous magnesium sulfate. After unchanged carbon tetrachloride has been distilled off, fractionation of the telomer gives the following yields:

x	B.p. (mm)	Yield (g)	B.p. of pure substance (mm)
1	90°/12	11.7	159°/760
2	90–115°/11	97.0	112°/24
3	115–145°/11	36.0	143°/24
4	145–175°/11	12.5	168°/20
>4	Residue	5.0	—

The higher the pressure of the taxogen (ethylene in the above case) the greater is the molecular weight of the telomer. x may be 1 at low pressures.

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[15] F. Asinger, "Chemie und Technologie der Monoolefine," Akademie-Verlag, Berlin, 1957, p. 731; E. Müller, *Angew. Chem.*, **64**, 246 (1952).

[16] R. M. Joyce, W. E. Hanford, and J. Harmon, *J. Amer. Chem. Soc.*, **70**, 2529 (1948).

Addition ($x = 1$), and not telomerization, occurs when a large excess of telogen (100 : 1) is used (see also page 856).

Carbon tetrabromide undergoes almost wholly addition at a molar ratio of 4 : 1 to 2 : 1, polymerization being almost non-existent.

The role of telogen can be assumed, not merely by the above-mentioned halomethanes,[15] but also by alcohols,[17] aldehydes or ketones,[18] esters,[19] amines,[20] or formamide,[21] as in:

$$x\text{CH}_2\text{=CH}_2 + \text{RCH}_2\text{OH} \longrightarrow \text{H—[CH}_2\text{CH}_2]_x\text{—CHROH}$$

When aldehydes are used, an acyl radical and a hydrogen atom are added, and ketones are formed.[22]

In the presence of acidic catalysts (aluminum trichloride, boron trifluoride, acids) polymerization of olefins is a cationoid ionic chain reaction. On an industrial scale polymerization of isobutene is carried out in solution in, *e.g.*, ethane at −70° to −100° with the aid of 0.05% of boron trifluoride and then affords a quantitative yield within a few minutes; the product is a solid polymerisate resembling caoutchouc.[23] The reaction temperature is very important as determining the molecular weight of the polymerisate; lower temperatures lead to higher molecular weights, *e.g.*, using α-methylstyrene in ethyl chloride containing aluminum chloride at 23° affords a polymerisate of molecular weight around 1000 but at −130° the molecular weight of the product is 84,000. The choice of solvent also affects the molecular weight: Pepper[24] found that the molecular weight of the polymer formed from α-methylstyrene and tin tetrachloride to be greater the greater is the dielectric constant of the solvent used.

Weaker catalysts (*e.g.*, tin tetrachloride or titanium tetrachloride[25]) require the presence of a co-catalyst such as water, *tert*-butyl alcohol, acetic acid, trichloroacetic acid, or sulfuric acid. The actual polymerization catalyst is then probably the Lewis acid formed. As an example, isobutene reacts only slowly at −80° in hexane containing titanium tetrachloride, but a violent reaction occurs if moist air is led slowly through the mixture. Evans and Meadows[26] similarly found that no reaction occurs when completely anhydrous isobutene is kept with anhydrous boron trifluoride for 2 hours at −80° in a flask that was previously dried in a high vacuum at 400° but that immediate reaction occurs if the vessel is dried without being heated in a high vacuum. From the last experiment it can be concluded that a co-catalyst is necessary even with power-

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[17] Ger. Pat. 1,058,981; *Chem. Abstr.*, **55**, 9279 (1961); J. D. Lazerte and R. J. Koshar, *J. Amer. Chem. Soc.*, **77**, 910 (1955); W. H. Urry, F. W. Stacey, E. S. Huyser, and O. O. Juveland, *J. Amer. Chem. Soc.*, **76**, 540 (1954).

[18] M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1948); M. S. Kharasch, J. Kuderna, and W. Nudenberg, *J. Org. Chem.*, **18**, 1225 (1953).

[19] W. H. Urry and E. S. Huyser, *J. Amer. Chem. Soc.*, **75**, 4876 (1953).

[20] W. H. Urry, O. O. Juveland, and F. W. Stacey, *J. Amer. Chem. Soc.*, **74**, 6155 (1952); W. H. Urry and O. O. Juveland, *J. Amer. Chem. Soc.*, **80**, 3322 (1958).

[21] A. Rieche, E. Schmitz, and E. Gründemann, *Angew. Chem.*, **73**, 621 (1961).

[22] H. Stockmann, *J. Org. Chem.*, **29**, 245 (1964).

[23] K. Hamann, *Angew. Chem.*, **63**, 234 (1951).

[24] D. Pepper, *Nature (London)*, **158**, 789 (1946); *Trans. Faraday Soc.*, **45**, 397 (1949).

[25] P. H. Plesch, *Nature (London)*, **160**, 868 (1947).

[26] A. G. Evans and G. W. Meadows, *Trans. Faraday Soc.*, **46**, 327 (1950).

ful catalysts but that minute amounts of water suffice to initiate the polymerization. The reaction can be formalized as follows:

$$BF_3 + HX \longrightarrow H^+[BF_3X]^-$$

$$H^+[BF_3X]^- + CH_2{=}C(CH_3)_2 \longrightarrow (CH_3)_3C^+[BF_3X)]^-$$

$$\xrightarrow{CH_2=C(CH_3)_2} (CH_3)_3CCH_2\overset{+}{C}(CH_3)_2[BF_3X]^-$$

Chain termination occurs by addition of an anion or loss of a proton:

$$(CH_3)_3C[CH_2C(CH_3)_2]_nCH_2\overset{+}{C}(CH_3)_2[BF_3X]^- \begin{cases} \longrightarrow (CH_3)_3C[CH_2C(CH_3)_2{}_nCH_2]C(CH_3)_2X + BF_3 \\ \longrightarrow (CH_3)_3C[CH_2C(CH_3)_2]_nCH{=}C(CH_3)_2 + H^+[BF_3X]^- \end{cases}$$

Until recently ethylene itself could be polymerized only at high pressure and high temperatures. Ziegler and his colleagues[27] have, however, shown that ethylene, which is otherwise so inert, can be polymerized at atmospheric pressure by use of a triethylaluminum–titanium tetrachloride catalyst in a suitable solvent; details for the laboratory preparation of this interesting and technically important variety of polyethylene have been given by Ziegler and Martin.[28]

Although the low-pressure polymerization of ethylene in the presence of a Ziegler catalyst is a catalytic process, the growth reaction of aluminum hydride or a corresponding alkylaluminum with ethylene occurs as an organometallic synthesis:[29] at 60–80° aluminum hydride reacts with ethylene to yield triethylaluminum:

$$\text{al—H} + C_2H_5 \longrightarrow \text{al—}C_2H_5$$

this is followed at 100–120° by the growth reaction with further ethylene:

$$\text{al—}C_2H_5 \xrightarrow{+C_2H_4} \text{al—}CH_2CH_2C_2H_5 \xrightarrow{+C_2H_4} \text{al—}[CH_2CH_2]_2C_2H_5, \text{etc.}$$

The structure of the products is governed by purely statistical laws, so that the final products consist of mixtures of trialkylaluminums of various chain lengths. Treating the trialkylaluminums with water affords the alkyl chains in the form of saturated hydrocarbons.

If the growth reaction is carried out at about 200°, the trialkylaluminums decompose to olefins and aluminum hydride (or its partly alkylated derivatives), which at once reacts with more ethylene:

$$\text{al—}CH_2CH_2\text{—}[CH_2CH_2]_n\text{—}C_2H_5 \longrightarrow \text{al—H} + CH_2{=}CH\text{—}[CH_2CH_2]_n\text{—}C_2H_5$$

Anionoid chain polymerization occurs under the influence of alkaline catalysts. In the polymerization of styrene by sodamide in liquid ammonia the starting reaction consists of addition of an amide anion to the double bond, yielding a carbanion:

$$NH_2^- + C_6H_5CH{=}CH_2 \longrightarrow NH_2CH(C_6H_5)CH_2^- \xrightarrow{+C_6H_5CH=CH_2}$$
$$NH_2CH(C_6H_5)CH_2CH(C_6H_5)CH_2^-$$

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[27] K. Ziegler, E. Holzkamp, H. Breil, and H. Martin, *Angew. Chem.*, **67**, 541 (1955); K. Ziegler, *Angew. Chem.*, **76**, 545 (1964).

[28] K. Ziegler and H. Martin, *Makromol. Chem.*, **18/19**, 186 (1956).

[29] K. Ziegler, *Angew. Chem.*, **64**, 323 (1952).

As follows from this mechanism, the polystyrene molecules then contain amino groups. Styrene is not polymerized by sodamide in ether.

Not every ethylene derivative can be polymerized by each of the three mechanisms. The cationoid mechanism is favored when the doubly bonded atom carries a substituent that shifts the π-electron pair of the double bond away from it, as in a vinyl ether:

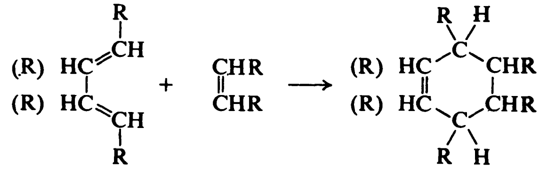
$$CH_2{=}CH{-}OR \longrightarrow \overset{-}{C}H_2{-}\overset{+}{C}H{-}OR \longrightarrow \overset{-}{C}H_2{-}CH{=}\overset{+}{O}R$$

In compounds that can be polymerized by the anionoid mechanism a doubly bonded atom carries a strongly polar group that attracts the π-electrons of the double bond, as in acrylonitrile:

$$CH_2{=}CH{-}CN \longrightarrow \overset{+}{C}H_2{-}\overset{-}{C}H{-}CN$$

3. Diene syntheses[30]

The term "diene synthesis", introduced by Diels[31] and Alder,[32f] denotes addition of an ethylenic compound (the philodiene) to a compound containing a system of conjugated bonds (the diene). All such reactions occur in accord with the scheme:



The reaction thus always leads to a six-membered ring, by 1,4-addition. Of the three double bonds concerned in the reaction, only one is retained in the product, and that at a different position. Rearrangements rarely occur in these reactions. Moreover, they are stereospecific: on addition of maleic acid to a diene the adduct produced is a *cis*-dicarboxylic acid, and on addition of fumaric acid it is a *trans*-dicarboxylic acid. Substituents on the diene or philodiene are not wholly without effect on the course of the addition; for example, 1,2,3,4-tetramethylbutadiene (3,4-dimethyl-2,4-hexadiene) reacts smoothly,[33] but the tetraphenyl analog shows no tendency to add a philodiene. Bulky substituents at the 2,3-positions can completely suppress the addition, presumably because they prevent free rotation and thus disfavor formation of the con-

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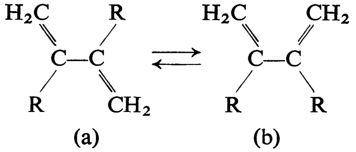
[30] J. Sauer, *Angew. Chem. Int. Ed., Engl.*, **5**, 211 (1966); J. Hamer, "Organic Chemistry," Vol. 8, Academic Press, New York, London, 1967.

[31] O. Diels, *Angew. Chem.*, **42**, 911 (1929).

[32] "Neuere Methoden der präparativen organischen Chemie," ed. W. Foerst, Verlag Chemie, Weinheim/Bergstraße, Vol. 1, 1949, (a) pp. 413, 432 (D. Kästner), (b) 469 (G. Wittig); Vol. 2, 1960, (c) p. 190; Vol. 4, (d) p. 1 (I. Ugi); English translation, "Newer Methods of Preparative Organic Chemistry," Interscience, New York, 1948, pp. (e) 359 (B. Eistert, translated by F. W. Spangler), (f) 381 (K. Alder, translated by C. V. Wilson and J. A. Van Allan).

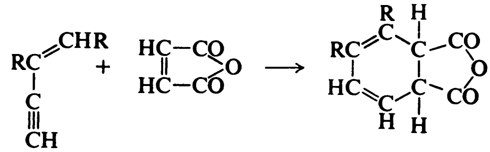
[33] H. Backer, J. Strating, and L. Huisman, *Rec. Trav. Chim.*, **53**, 525 (1934); **58**, 761 (1939); **60**, 557 (1941).

formation (b) that is necessary for the addition:[34]

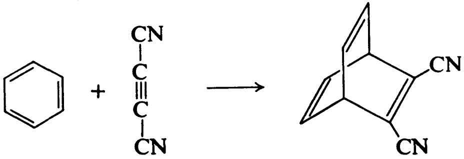


Thus, whereas 2,3-di-*tert*-butylbutadiene does not react with a philodiene,[35] normal addition occurs to 1,3-di-*tert*-butylbutadiene.[36] Cyclopentadiene is particularly reactive because in it free rotation is prevented and the molecule is fixed in a particularly favorable conformation.

The acetylenic bond of enynes and dienynes of types C=C—C≡C and C=C—C≡C—C=C can also participate. As always in the Diels–Alder reaction, there is 1,4-addition, but in such cases with shift of hydrogen:

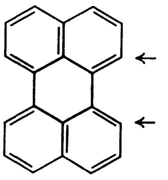


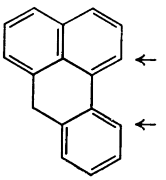
Not only acyclic 1,3-dienes but also alicyclic and certain aromatic compounds can be used in diene syntheses. Benzene itself has little tendency to add olefins, but presence of aluminum chloride leads to a 63% yield of the adduct of benzene and dicyanoacetylene:[37]



However, addition of dicyanoacetylene to hexamethylbenzene occurs in 83% yield in benzene at 130° even without presence of a catalyst.

There is normal diene reactivity in highly condensed aromatic systems such as perylene and benzanthrene; here the "conjugated double bonds" belong to different rings, the positions at which the philodiene is added being indicated by arrows in the following formulae:





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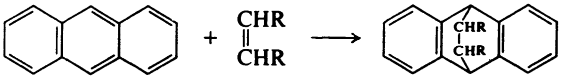
[34] K. Alder and M. Schumacher, *Ann. Chem.*, **571**, 87 (1951); P. D. Bartlett and K. Schueler, *J. Amer. Chem. Soc.*, **90**, 6071, 6077 (1968).

[35] H. Backer, *Rec. Trav. Chim.*, **58**, 643 (1939).

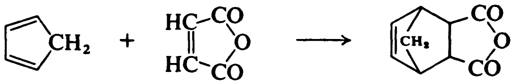
[36] H. Backer and J. Strating, *Rec. Trav. Chim.*, **56**, 1069 (1937).

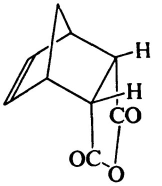
[37] E. Ciganek, *Tetrahedron Lett.*, **1967**, 3321; W. M. Hardham and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 3200 (1967).

In anthracene it is the bonds in the middle ring that react, so that a carbon bridge is formed:

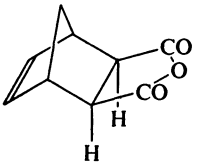


Ring compounds containing carbon bridges are also formed by addition of, *e.g.*, maleic anhydride to alicyclic dienes such as cyclopentadiene and cycloheptadiene; of the two possible stereoisomers it is always the *endo*-compound that is produced (Woodward–Hoffmann rules[38]). Such reactions, however, fail when the product would break Bredt's rule.



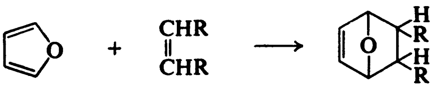


endo-cis

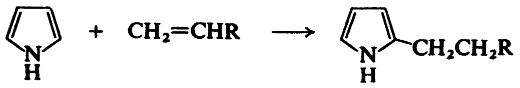


exo-cis

Epoxy compounds are formed if furan is used instead of cyclopentadiene:



However, with less active philodienes furan undergoes substitutive addition, and for pyrrole this entirely replaces the diene synthesis:[39]



Thiophen is totally inert, undergoing neither 1,4-addition nor substitutive addition; but, like benzene, it does react as a diene component when present as part of a highly condensed system.

The ability to react with dienes is not restricted to the ethylenic double bond. Compounds containing a hetero atom as part of the reactive group, whether of the diene or of the philodiene, cyclize to yield heterocycles.[40]

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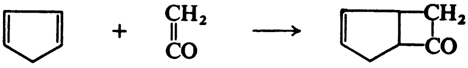
[38] D. Seebach, *Fortschr. Chem. Forsch.*, **11**, 177 (1969).

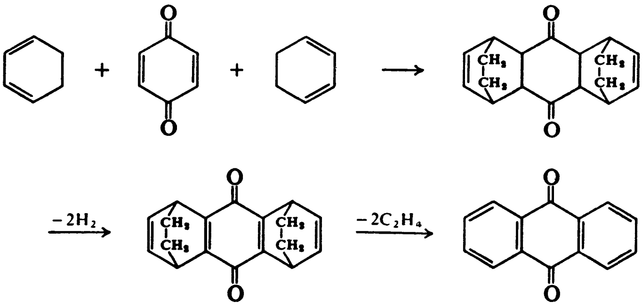
[39] I. D. Webb and G. T. Borcherdt, *J. Amer. Chem. Soc.*, **73**, 752 (1951); K. Alder and C. H. Schmidt, *Ber. Deut. Chem. Ges.*, **76**, 183 (1943).

[40] S. Needleman and M. Chang Kuo, *Chem. Rev.*, **62**, 405 (1962); R. Schulz and H. Hartmann, *Chem. Ber.*, **95**, 2739 (1962).

Nitrile, azo, and nitroso groups, and even the oxygen molecule, take part in such reactions, and acetylenic triple bonds in particular confer reactivity as philodiene. As for dienes, so for philodienes the reactivity depends on the constitution. Activating groups particularly favor addition. The most reactive components include α,β-unsaturated carbonyl compounds such as acrolein, acrylic acid, maleic acid and its anhydride, acetylenedicarboxylic acid, *p*-benzoquinone and cinnamaldehyde, as well as saturated nitriles and α,β-unsaturated nitro compounds. Tetracyanoethylene also reacts with dienes.[41,42] Conjugation of the double bond to an active group is not absolutely essential for a philodiene, for dienes add under certain conditions also to philodienes with isolated double bonds; examples of the latter type are vinyl esters and vinylacetic acid. Ketenes do not undergo the Diels–Alder reaction with dienes, but instead yield cyclobutanone derivatives:[43,44]



A double diene synthesis occurs with benzoquinone. With 2 molecules of cyclohexadiene, for instance, this affords the 1,4,5,8-diethanoanthracene ring system; the resulting 1,4,4a,5,8,8a,9a,10a-octahydro-1,4,5,8-diethanoanthraquinone readily loses four hydrogen atoms, to give the 1,4,5,8-tetrahydro compound and, when that is heated, it spits off ethylene to afford anthraquinone:



Anthracene homologs can also be prepared in this way, by using derivatives of cyclohexadiene. Further, 1,4-naphthoquinone can be used as starting material (for a single diene synthesis); and the ethylene bridge may be substituted without destroying the ability of the product to split off the ethylene derivative.

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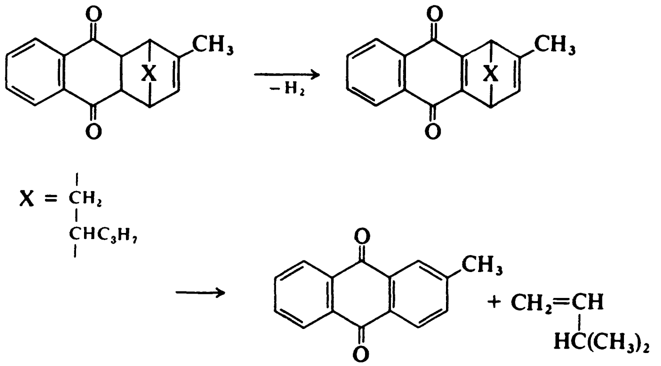
[41] C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963); G. Smith, C. L. Warren, and W. R. Vaughan, *J. Org. Chem.*, **28**, 3323 (1963).

[42] G. Wittig and E. Benz, *Tetrahedron*, **10**, 37 (1960).

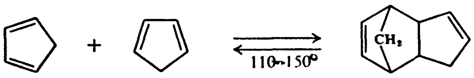
[43] H. Staudinger and E. Suter, *Ber. Deut. Chem. Ges.*, **53**, 1092 (1920).

[44] B. T. Brooks and G. Wilbert, *J. Amer. Chem. Soc.*, **63**, 870 (1941); K. Alder and H. F. Rickert, *Ann. Chem.*, **543**, 15 (1940).

Thus reaction of 1,4-naphthoquinone with phellandrene leads finally to 2-methylanthraquinone:



Compounds such as cyclopentadiene often function as both diene and philodiene at the same time, *i.e.*, they dimerize:



The technique for effecting diene syntheses is extremely simple. In favorable cases it suffices to mix calculated amounts of the diene and philodiene in an organic solvent, the reaction then occurring exothermally (17–19 kcal/mole). More sluggish reactions may be carried out at elevated temperatures, *e.g.*, in a pressure vessel or in the melt. However, the exothermal Diels–Alder reaction is an equilibrium reaction and at high temperatures the product may readily redissociate to the reactants; nevertheless, a large excess of one of the two components can shift the equilibrium in the desired direction of synthesis.

The following are some examples of the techniques.

As described by Diels and Alder,[45] cyclopentadiene (1 mole) is added gradually, with cooling, to a suspension of maleic anhydride (1 mole) in benzene (5 parts), whereupon the maleic anhydride dissolves with evolution of much heat. **cis-1,2,3,6-tetrahydro-3,6-methanophthalic anhydride** separates in almost theoretical yield and after recrystallization from light petroleum melts at 164–165°.

Butadiene reacts somewhat less readily with maleic anhydride:[46]

Butadiene (2.0–2.5 g) is dissolved in benzene (10 ml), mixed with maleic anhydride (4 g), sealed in a bomb tube, set aside for 12 h, and then heated for 5 h at 100°. **cis-1,2,3,6-tetrahydrophthalic anhydride** is formed quantitatively and after recrystallization from light petroleum has m.p. 103-104°.

Norcantharidin:[47] Maleic anhydride (2 g) is suspended in ether and treated with the calculated amount of furan. Reaction occurs gradually with slight evolution of heat. After several hours, cooling the mixture causes separation of the adduct, *cis*-1,2,3,6-tetrahydro-

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[45] O. Diels and K. Alder, *Ann. Chem.*, **460**, 111 (1928).

[46] O. Diels and K. Alder, *Ann. Chem.*, **460**, 113 (1928).

[47] O. Diels and K. Alder, *Ber. Deut. Chem. Ges.*, **62**, 557 (1929).

3,6-epoxyphthalic anhydride, mostly in crystalline form. The theoretical amount is obtained on removal of the ether. This product melts at 125° with foaming and decomposition into the reactants. Finally it is hydrogenated in sodium carbonate solution in the presence of colloidal palladium, thus affording norcantharidin.

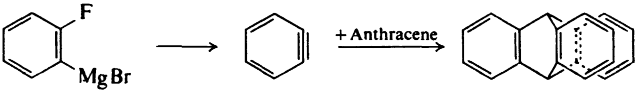
1,2,5,6-Tetrahydro-2,5-ethanobenzaldehyde:[48] Cyclohexadiene (7 g) and acrolein (10 g) are heated in a sealed tube for 3.5 h at 100°, whereafter fractionation affords the product (3 g), b.p. 84–85°/12 mm (semicarbazone, m.p. 176–177°).

When anthracene is used as diene with maleic anhydride, addition occurs at positions 9 and 10, yielding **9,10-dihydro-9,10-ethanoanthracene-cis-11,12-dicarboxylic anhydride:**[49]

Anthracene (12 g) and maleic anhydride (8 g) are heated together by a paraffin bath until reaction sets in. This reaction then progresses rapidly from the outside inwards. The mixture is heated for a further 15–20 min, the bath-temperature not being allowed to exceed 260°; then, after cooling, the product is finely powdered and the excess of maleic anhydride is extracted in ether. Recrystallization from ethyl malonate affords colorless crystals, which melt at 262–263° when rapidly heated.

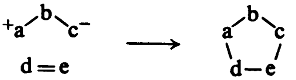
Dehydrobenzene also functions as a philodiene, as may be illustrated by the synthesis of **tryptycene** described by Wittig and his co-workers:[42,50]

Reaction of anthracene (42 mmoles) and *o*-bromofluorobenzene (30 mmoles) with magnesium in tetrahydrofuran affords a mixture of hydrocarbons. This is first freed from unchanged anthracene by treatment with maleic anhydride. Chromatography then affords 11 % of triphenylene (m.p. 194–195°) and 28 % of tryptycene (m.p. 255–256.5°). Formation of the latter occurs as follows:



4. 1,3-Dipolar cycloaddition[51]

As described by Huisgen, 1,3-dipolar cycloaddition consists of reaction of a 1,3-dipole with a multiple-bond system (the dipolarophile) with formation of a five-membered ring. The formal charges are removed by cyclic electron shift:



The dipolarophile may contain any type of double or triple bond, *e.g.*, an ethylenic, acetylenic, carbonyl, thiocarbonyl, or nitrile group. Compounds used as 1,3-dipoles in this reaction include nitrilylides $\left(-C\equiv\overset{+}{N}-\overset{-}{C}\langle \longleftrightarrow -\overset{+}{C}=N-\overset{-}{C}\langle\right)$, nitrile imines $\left(-\overset{+}{C}=N-\overset{-}{N}- \longleftrightarrow -C\equiv\overset{+}{N}-\overset{-}{N}-\right)$, nitrile oxides $\left(-\overset{+}{C}=N-\overset{-}{O} \longleftrightarrow -C\equiv\overset{+}{N}-\overset{-}{O}\right)$, diazoalkanes, hydrogen azide and its

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[48] O. Diels and K. Alder, *Ann. Chem.*, **478**, 144 (1930).

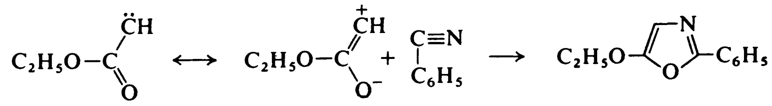
[49] O. Diels and K. Alder, *Ann. Chem.*, **486**, 196 (1931).

[50] G. Wittig and R. Ludwig, *Angew. Chem.*, **68**, 40 (1956).

[51] R. Huisgen, *Angew. Chem. Int. Ed., Engl.*, **2**, 565 (1963).

esters, azomethinylides $\left(\rangle\overset{+}{C}-\underset{|}{N}-\overset{-}{C}\langle \longleftrightarrow \rangle C=\underset{|}{\overset{+}{N}}-\overset{-}{C}\langle\right)$, azomethine oxides (nitrones) $\left(\rangle\overset{+}{C}-\underset{|}{N}-\overset{-}{O} \longleftrightarrow \rangle C=\underset{|}{\overset{+}{N}}-\overset{-}{O}\right)$, and azomethine imines $\left(\rangle\overset{+}{C}-\underset{|}{N}-\overset{-}{N}- \longleftrightarrow \rangle C=\underset{|}{\overset{+}{N}}-\overset{-}{N}-\right)$. A large number of five-membered heterocyclic systems can be built in this way. For addition of diazomethane to the C=C double bond see page 866.

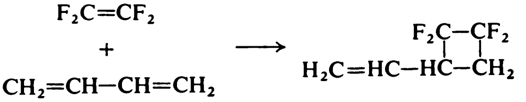
1,3-Dipolar addition may be exemplified by the formation of **5-ethoxy-2-phenyloxazole**[52] from ethoxycarbonylcarbene and benzonitrile:



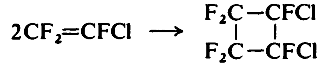
A solution of ethyl diazoacetate (2.28 g) in benzonitrile (100 ml) is stirred during 3 h into benzonitrile (300 ml) that has been pre-heated to 145°. The theoretical amount of nitrogen is evolved after a further one hour's heating at 145°. The excess of benzonitrile is distilled off at 12 mm and the residue is distilled in a high vacuum. A fraction boiling at 90–100° (bath)/0.01 mm (1.74 g) and one boiling at 140–200° (bath)/0.01 mm (1.05 g) are collected. Rubbing the first fraction with ice-cold light petroleum and working up the mother-liquors give a total of 42% (1.60 g) of 5-ethoxy-2-phenyloxazole, m.p. 38–39° (after recrystallization from light petroleum).

5. Syntheses of cyclobutane derivatives[53]

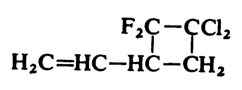
In contrast to ethylene and tetracyanoethylene, tetrafluoroethylene does not undergo a Diels–Alder reaction with 1,3-butadiene; instead of this 1,4-addition, it reacts by 1,2-addition to give a cyclobutane derivative:[54]



This reaction takes place at 125° and gives a 90% yield. In the absence of the diene, tetrafluoroethylene dimerizes, but this dimerization is slower than reaction with butadiene to form the cyclobutane ring. Unsymmetrically substituted chlorofluoroethylenes cyclize by head-to-head addition:[55]



Treatment of 1,1-dichloro-2,2-difluoroethylene with butadiene affords only one product:[56]



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[52] R. Huisgen, H. J. Sturm, and G. Binsch, *Chem. Ber.*, **97**, 2864 (1964).

[53] J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 1 (1962); O. L. Chapman, "Organic Photochemistry," Vol. 1, M. Dekker, Inc., New York, 1967, p. 283.

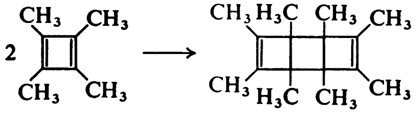
[54] D. D. Coffman, P. L. Barnick, R. D. Cramer, and M. S. Raasch, *J. Amer. Chem. Soc.*, **71**, 490 (1949).

[55] J. R. Lacher, G. W. Tompkin, and J. D. Park, *J. Amer. Chem. Soc.*, **74**, 1693 (1952).

[56] P. D. Bartlett, L. K. Montgomery, and B. Seidel, *J. Amer. Chem. Soc.*, **86**, 616 (1964).

Stereochemical investigation of the reactions of 1,1-dichloro-2,2-difluoroethylene with the geometrical isomers of 2,4-hexadiene has indicated a radical addition mechanism involving intermediate formation of an open-chain diradical addition compound.[57]

Thermal cycloaddition, to form a cyclobutane ring, is not confined to fluorinated ethylenes. Cyclobutadiene derivatives are formed as intermediates and dimerize to yield a cyclobutane ring:[48]



A number of allenes, ketenes, and olefins also react with formation of cyclobutane derivatives.[43,53,59] For example, diphenylketene and styrene yield **2,2,3-triphenylcyclobutanone:**[60]

Diphenylketene (8.0 g) and styrene (4.5 g) are heated in a bomb-tube at 60° for 24 h. The mixture solidifies to a white crystalline mass, which after recrystallization from ethanol has m.p. 135–136° (11.5 g, 93%). This product dissociates to the reactants when heated at about 200° in a vacuum.

Unsaturated compounds also yield cyclobutane derivatives in cycloaddition photoreactions sensitized by benzophenone,[61,62] examples being cycloaddition of maleic anhydride and various alkyl and halo maleic anhydrides and maleimides.[63–65]

Symmetrical cycloaddition (*i.e.*, the two reactants are identical) of 2 molecules of dimethylmaleic anhydride gives **1,2,3,4-tetramethyl-1,2,3,4-cyclobutanetetracarboxylic dianhydride:**[65]

A mixture of dimethylmaleic anhydride (3.15 g) and benzophenone (1.5 g) in benzene (150 ml) is irradiated for 6 h at 8°. Irradiation is carried out by a high-pressure Philips mercury lamp HPK 125 W, under argon, in an apparatus[66] incorporating a water-cooled glass tube, and the solution is stirred magnetically. The tetramethylcyclobutanetetracarboxylic anhydride (1.92 g) is precipitated by the reaction; after sublimation at 230°/0.3 mm, it melts from 380° with re-formation of the reactants.

As an example of mixed cycloaddition (the two reactants being different) the reaction of 2-butyne with maleic anhydride to form **3,4-dimethyl-3-cyclobutene-1,2-dicarboxylic anhydride**[62] may be described:

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[57] L. K. Montgomery, K. Schueller, and P. D. Bartlett, *J. Amer. Chem. Soc.*, **86**, 622 (1964).

[58] R. Criegee and G. Louis, *Chem. Ber.*, **90**, 417 (1957).

[59] A. Roedig and H. Niedenbrück, *Chem. Ber.*, **90**, 673 (1957).

[60] C. S. Marvel and M. J. Kohan, *J. Org. Chem.*, **16**, 741 (1951).

[61] G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.*, **96**, 498 (1963).

[62] R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *Chem. Ber.*, **97**, 2942 (1964).

[63] H. D. Scharf and F. Korte, *Chem. Ber.*, **98**, 764 (1965).

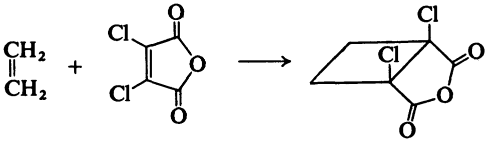
[64] R. Askani, *Chem. Ber.*, **98**, 2322 (1965).

[65] G. O. Schenck, W. Hartmann, S.-P. Mannsfeld, W. Metzner, and C. H. Krauch, *Chem. Ber.*, **95**, 1642 (1962).

[66] G. O. Schenck, Dechema Monographien, **24**, 105 (1955).

Freshly distilled maleic anhydride (5.6 g), benzophenone (2.0 g), and pure butyne (150 ml) are irradiated for 60 h under nitrogen in an apparatus[67d] embodying water-cooling and a magnetic stirrer. The light source is a Philips mercury high-pressure lamp HOQ 400 W with a water-cooled Pyrex or Jena glass mantle. Removing the residual butyne from the resulting yellowish-brown solution left a residue (10.8 g) from which sublimation at 60°/1 mm gave 95% (8.25 g) of crude cyclobutene derivative. After alternate recrystallization from hexane and sublimation this melts at 80°.

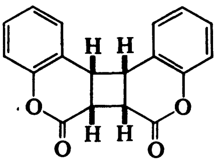
Dichloro- and dibromo-maleimide react with ethylene without the necessity for presence of benzophenone; but reaction of dichloromaleic anhydride with ethylene gives only a 7% yield of the cycloadduct in absence of benzophenone whereas it is almost quantitative in its presence:[63]



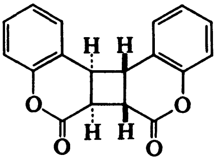
In these reactions the products are the 1,2-*cis*-dihalo-1,2-cyclobutanedicarboxylic anhydrides or the corresponding maleimides.

The rate of reaction of dichloromaleimide with ethylene in various solvents decreases in the order diethoxyethane > dioxan > diisopropyl ether > tetrahydrofuran. No ethylene is consumed in benzene or cyclohexane.

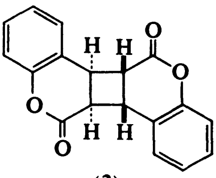
Unsensitized photocyclodimerization of coumarin gives the *cis*-head-to-head adduct (**1**), but the sensitized reaction gives the *trans*-head-to-head adduct (**2**) with a small amount of the *trans*-head-to-tail adduct (**3**).[68]



(**1**)



(**2**)



(**3**)

Photocyclodimerization to afford cyclobutane derivatives has also been observed for a large number of other compounds, including stilbenes, α,β-unsaturated acids, α,β-unsaturated ketones, and 1,4-naphthoquinones.[67a]

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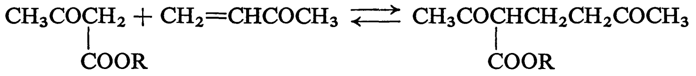
[67] (a) "Präparative organische Photochemie," ed. A. Schönberg, Springer-Verlag, Berlin–Göttingen–Heidelberg, 1958, (b) p. 42, (c) p. 111, (d) Fig. 8, p. 222.

[68] G. O. Schenck, J. von Wilucki, and C. H. Krauch, *Chem. Ber.*, **95**, 1409 (1962).

6. Addition of CH-acidic compounds (Michael addition)

In a reaction originating with Michael[69] and Claisen,[70] compounds containing active hydrogen add to α,β-unsaturated aldehydes, ketones, esters, nitriles, sulfones, or nitro compounds, the C–C bond being formed to the vinyl carbon atom that is β to the carbonyl (or analogous) group:

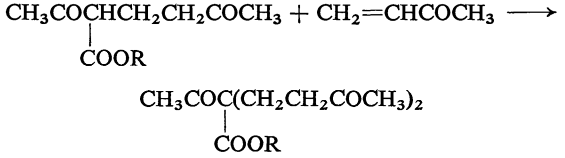


$$\mathrm{CH_3CO\underset{\substack{|\\ \mathrm{COOR}}}{C}H_2 + CH_2{=}CHCOCH_3 \rightleftarrows CH_3CO\underset{\substack{|\\ \mathrm{COOR}}}{C}HCH_2CH_2COCH_3}$$

Henecka,[71] for instance obtained **ethyl 2-acetyl-5-oxohexanoate** from ethyl acetoacetate and methyl vinyl ketone as follows:

Ethyl acetoacetate (780 g) is treated with a solution (10 ml) of sodium methoxide (from 23 g of sodium in 400 ml of methanol), and then freshly distilled methyl vinyl ketone (210 g) is dropped in at 30–35° with stirring and occasional cooling. The mixture is then set aside overnight, dissolved in methylene chloride, and neutralized with a little dilute acetic acid. The methylene chloride is evaporated and the residue is distilled in a vacuum, affording a pale yellow oil, b.p. 127–129°/4.5 mm, in 85–88% yield.

Since the ester obtained in this way still contains one active hydrogen atom, it can be condensed with a second molecule of methyl vinyl ketone, which yields ethyl 2-acetyl-5-oxo-2-(3-oxobutyl)hexanoate:



$$\mathrm{CH_3CO\underset{\substack{|\\ \mathrm{COOR}}}{C}HCH_2CH_2COCH_3 + CH_2{=}CHCOCH_3 \longrightarrow CH_3CO\underset{\substack{|\\ \mathrm{COOR}}}{C}(CH_2CH_2COCH_3)_2}$$

This product, b.p. 160°/1.3 mm, can be obtained in one step if the preceding directions are modified so that twice the proportion of methyl vinyl ketone reacts with ethyl acetoacetate, the yield being 92%.

Vorländer and Knötzsch[72] prepared diethyl 2-acetylglutarate from ethyl acetoacetate and ethyl acrylate.

The ease of reaction depends both on the CH acidity of the addend and on the polarizability of the ethylenic double bond of the acceptor. Thus, in general, only such compounds function as addend in which a methylene or methine group is activated by two neighboring carbonyl or nitrile groups, as, for example, in malonic esters, malonodinitrile, cyanoacetic esters, 1,3-dioxo compounds and 3-oxo carboxylic esters, and their monoalkyl substitution products. The ethylenic double bond of the acceptor is polarized by conjugation with a polar multiple bond, so that the olefinic component is usually an α,β-unsaturated ketone, an α,β-unsaturated ester, or an α,β-unsaturated nitrile. The addition is catalysed by bases such as potassium hydroxide solution, sodium ethoxide, and amines.

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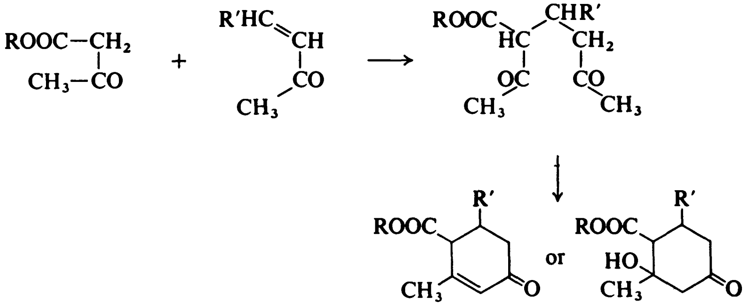
[69] A. Michael, *J. Prakt. Chem.*, [ii], **35**, 349 (1887).

[70] See T. Komnenos, *Ann. Chem.*, **218**, 161 (1883).

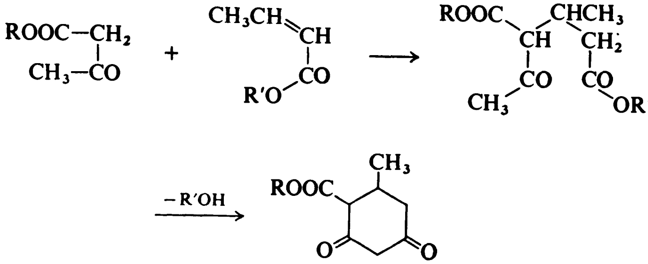
[71] H. Henecka, *Chem. Ber.*, **81**, 189 (1948).

[72] D. Vorländer and A. Knötzsch, *Ann. Chem.*, **294**, 317 (1897).

If a molar amount of the catalyst is used, the resulting adduct can cyclize. If the adduct is a 1,5-diketone, crotonaldehyde or aldol condensation leads to a cyclohexanone or hydroxycyclohexanone derivative, respectively:



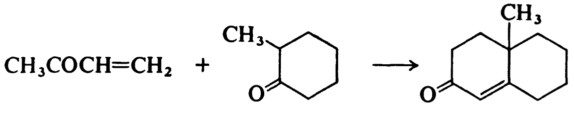
If the adduct is a 5-oxohexanoic ester, rather than a 1,5-diketone, ester condensation occurs giving a substituted dihydroresorcinol:



Ethyl dihydromethylresorcinolcarboxylate (ethyl 2-methyl-4,6-dioxocyclohexanecarboxylate) is prepared as follows:[73] Ethyl acetoacetate (42 g), followed by ethyl crotonate (34 g), are added to a solution of sodium (6.9 g) in anhydrous ethanol (100 ml). After the mixture has been heated on a water-bath for 2 h a thick slurry of the sodium salt of the above esters has separated. Acidifying an aqueous solution of this salt by dilute sulfuric acid precipitates the ester as an oil, which soon solidifies. It has m.p. 89–90° after crystallization from hot water.

Quaternary Mannich bases react like α,β-unsaturated ketones under the conditions of a Michael addition. The vinyl ketone is formed from the Mannich base in a sufficiently reactive state to add to simple ketones under the influence of sodamide and not to require the usual 1,3-dicarbonyl compound; then ring closure follows immediately:

$$[CH_3COCH_2CH_2N(CH_3)_3]^+ + NaNH_2 \longrightarrow CH_3COCH{=}CH_2 + N(CH_3)_3 + H^+$$



This Robinson–Mannich procedure[74] has been used with particular success in steroid syntheses.

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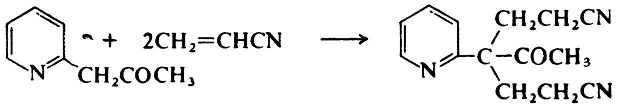
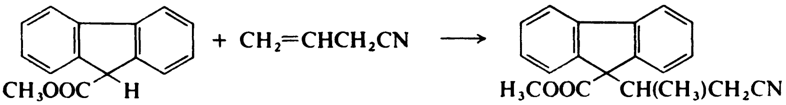
[73] R. von Schilling and D. Vorländer, *Ann. Chem.*, **308**, 195 (1899).

[74] A. Mondon, *Angew. Chem.*, **64**, 123 (1952).

In this connexion cyanoethylation by unsaturated nitriles may also be noted;[75] for instance, 2-pyridylmethyl ketones were added to acrylonitrile by Beyer and his co-workers:[76]

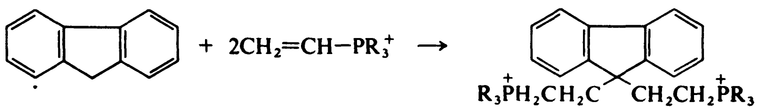


Tucker[77] has described the addition of methyl fluorene-9-carboxylate to allyl cyanide:



Although allyl cyanide is a β,γ-unsaturated compound, the new C–C bond is formed at the β-position; and addition of the above ester to acrylonitrile also occurs at the β-position.[78]

Vinylphosphonium salts also react with reactive methylene groups under basic catalysis (phosphonethylation), as in the reaction:[79]



Fishman and Zuffanti[80] reported the addition of 2-nitropropane to benzylideneacetophenone in methanol in the presence of calcium hydride:

$$C_6H_5COCH{=}CHC_6H_5 + (CH_3)_2CHNO_2 \longrightarrow C_6H_5COCH_2CH(C_6H_5)C(CH_3)_2NO_2$$

Also ethyl 4-nitro-3-phenylbutyrate is obtained in 76% yield from nitromethane and ethyl cinnamate when benzyltrimethylammonium hydroxide (Triton B) is used as catalyst.[81]

In the presence of Triton B, reaction of nitromethane with acrylonitrile affords tris-(2-cyanoethyl)nitromethane [4-(2-cyanoethyl)-4-nitroheptanedinitrile].[82] Nitroalkanes can also be added to acrylonitrile, ethyl acrylate, and acrylamide in liquid ammonia without addition of a catalyst;[83] when

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[75] H. A. Bruson, *Org. Reactions*, **5**, 79 (1949).

[76] H. Beyer, W. Lässig, and G. Schudy, *Chem. Ber.*, **90**, 592 (1957).

[77] S. H. Tucker, *J. Chem. Soc.*, **1949**, 2182.

[78] A. Campbell and S. H. Tucker, *J. Chem. Soc.*, **1949**, 2623; T. Holbo and E. Tagman, *Helv. Chim. Acta*, **33**, 2187 (1950); M. C. Kloetzel and F. L. Chubb, *J. Amer. Chem. Soc.*, **72**, 150 (1950).

[79] P. T. Keough and M. Grayson, *J. Org. Chem.*, **29**, 631 (1964); E. E. Schweizer and L. D. Smucker, *J. Org. Chem.*, **31**, 3146 (1966).

[80] N. Fishman and S. Zuffanti, *J. Amer. Chem. Soc.*, **73**, 4466 (1951); T. Rogers, *J. Chem. Soc.*, **1943**, 590; W. C. Kloetzel, *J. Amer. Chem. Soc.*, **72**, 4786 (1950).

[81] N. J. Leonhard, A. B. Simon, and D. L. Felley, *J. Amer. Chem. Soc.*, **73**, 857 (1951); R. B. Moffett, *Org. Syn.*, **32**, 86 (1952).

[82] C. Caldo, *Chim. Ind. (Milan)*, **44**, 258 (1962); V. I. Isagulyants and Z. Poredda, *Zh. Obshch. Khim.*, **33**, 318 (1963); *Chem. Abstr.*, **58**, 13789 (1963).

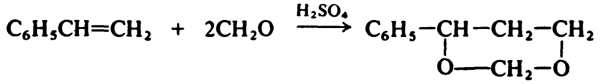
[83] S. Wakamutsu and K. Shimo, *J. Org. Chem.*, **27**, 1609 (1962).

potassium trinitromethanide is added to these compounds in anhydrous methanol the products may undergo further reaction involving elimination of nitrite.[84] 5-Methyl-1,4-hexadien-3-one adds trinitromethane, dinitromethane, 1,1-dinitroethane, nitroacetic acid, and dinitroacetic acid.[85]

Chloroform adds to acrylonitrile or ethyl acrylate with formation of 4,4,4-trichlorobutyronitrile or the derived ester, respectively.[86]

7. Addition of formaldehyde (Prins reaction)[87]

Formaldehyde can be added at an ethylenic bond under the influence of acidic reagents.[88] Reaction of styrene with formaldehyde in sulfuric acid yields **4-phenyl-*m*-dioxan** as follows:[89]



$$C_6H_5CH{=}CH_2 + 2CH_2O \xrightarrow{H_2SO_4} \begin{array}{l} C_6H_5-CH-CH_2-CH_2 \\ \qquad\quad | \qquad\qquad\quad | \\ \qquad\quad O-CH_2-O \end{array}$$

A mixture of 37% aqueous formaldehyde solution (675 g), sulfuric acid (*d* 1.84; 48 g), and styrene (312 g) is heated cautiously for 7 h with stirring and refluxing. After this has cooled, benzene (500 ml) is stirred in, the layers are separated, and the aqueous layer is extracted with benzene (500 ml). The benzene layers are united, washed twice with water (750-ml portions), and freed from benzene by distillation. Fractionation of the residue gives the product, b.p. 96–103°/2 mm (353–436 g, 70–88%).

In acetic acid the product is mainly 1-phenyltrimethylene diacetate:[90]

$$C_6H_5CH{=}CH_2 + H_2O \xrightarrow{H_2SO_4} C_6H_5CH(OH)CH_2CH_2OH \xrightarrow{CH_3COOH}$$

$$CH_3COOCH(C_6H_5)CH_2CH_2OCOCH_3$$

Other olefins can also be used in such reactions, but arylalkenes give the best yields.[89,91]

The stereochemistry of the Prins reaction has been discussed by Bernadi and Leone.[92]

8. Addition of organic halogen compounds

Halo-substituted unsaturated hydrocarbons behave like aromatic hydrocarbons towards saturated halides in the presence of aluminum chloride.[93] Suitable acceptors are the halogen substitution products of ethylene; in particular, chloromethanes, and best of all chloroform and methylene chloride

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[84] M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **28**, 2128 (1963).

[85] S. S. Novikov, I. S. Korsakova, and N. N. Bulatova, *Izvest. Visshikh Ucheb. Zavedenii Khim. i Khim. Tekhnol.*, **3**, No. 1, 132 (1960); *Chem. Abstr.*, **54**, 17258 (1960).

[86] H. Viehe, E. Franchimont, and P. Valange, *Chem. Ber.*, **96**, 426 (1963).

[87] E. Arundale and L. A. Mikeska, *Chem. Rev.*, **51**, 505 (1952); N. C. Yang, D. D. H. Yang, and C. B. Ross, *J. Amer. Chem. Soc.*, **81**, 133 (1959).

[88] H. J. Prins, *Chem. Weekbl.*, **16**, 1072, 1510 (1919).

[89] R. L. Shriner and P. R. Ruby, *Org. Syn.*, **33**, 72 (1953).

[90] R. W. Shortridge, *J. Amer. Chem. Soc.*, **70**, 873 (1948).

[91] E. Drukker and M. Beets, *Rec. Trav. Chim.*, **70**, 29 (1951); M. Hellin, M. Davidson, D. Lumbroso, and F. Coussemant, *Bull. Soc. Chim. France*, **1964**, 800; L. J. Dolby, *J. Org. Chem.*, **27**, 2971 (1962).

[92] L. Bernadi and A. Leone, *Tetrahedron Lett.*, **1964**, 499.

[93] H. J. Prins and F. Engelhard, *Rec. Trav. Chim.*, **54**, 307 (1935); **57**, 659 (1938).

are added. Chloroethanes behave similarly but the reaction is slower. An example of this addition is the preparation of **1,1,2,3,3-pentachloropropane** from chloroform and 1,2-dichloroethylene:[94]

$$CHCl_3 + CHClCHCl \longrightarrow CHCl_2CHClCHCl_2$$

Pure chloroform (120 g) is boiled for a few minutes with 1% of aluminum chloride; the same treatment is given to dichloroethylene (97 g) but in this case not above 40°. The two components, thus saturated with aluminum chloride, are cooled, mixed, and heated at 50° for 5–10 min, *i.e.*, until the temperature begins to rise spontaneously. The mixture is then cooled in running water so that the temperature remains at 50–55° — at higher temperatures the reaction goes out of control. After 30 min the temperature begins to fall, then the mixture is warmed at 55–60° for a further ca. 10 min. Unchanged reactants are then removed in steam, the amount of oil in the distillate being continuously observed. When the amount of oil in 10 ml of total distillate falls to 3 ml, the receiver is changed; at this point the pentachloropropane distils almost constantly at the rate of 2.5 ml per 10 ml of distillate. Distillation is stopped when 10 ml contain only 0.5 ml of oil. The yield is 70–75%. The original paper should be consulted for unfavorable influences of unknown origin.

The reaction of isopropyl chloride with trichloroethylene has been described by Schmerling[95] who gives also other examples. The halogen atom adds to the carbon atom carrying the smaller number of hydrogen atoms; iron(III) chloride can be used as catalyst as well as aluminum chloride;[96] Schmerling also added variously branched alkyl halides to ethylene, obtaining, *e.g.*, a 75% yield of 1-chloro-3,3-dimethylbutane from *tert*-butyl chloride and ethylene:[97]

$$(CH_3)_3CCl + CH_2{=}CH_2 \xrightarrow{AlCl_3} (CH_3)_3CCH_2CH_2Cl$$

Radical addition of halo methanes to olefins was achieved by Kharasch and his co-workers[98,99] when they warmed a mixture of an olefin with, *e.g.*, carbon tetrabromide or an excess of carbon tetrachloride in the presence of 1–5 mole % of a diacyl peroxide at 70–90°:

$$CH_3{-}[CH_2]_5{-}CH{=}CH_2 + CBr_4 \longrightarrow CH_3{-}[CH_2]_5{-}CHBrCH_2CBr_3$$

Carbon tetrabromide adds when irradiated even without addition of a peroxide catalyst.[100]

Kharasch *et al.* also achieved peroxide-catalysed addition of α-bromo fatty acid esters, thus obtaining γ-bromo fatty acid esters:[99,101]

$$C_6H_{13}CH{=}CH_2 + CH_3CHBrCOOC_2H_5 \longrightarrow C_6H_{13}CHBrCH_2CH(CH_3)COOC_2H_5$$

According to Straus and Thiel,[102] addition of α-halo ethers occurs especially readily in the presence of zinc chloride:

$$CH_3OCH_2Cl + CHR{=}CHR' \longrightarrow CH_3OCH_2CHRCHClR'$$

The resulting γ-halo ethers do not react further in the above manner since the mobility of the halogen decreases with increasing distance from the ether-oxygen atom.

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[94] H. J. Prins and F. Engelhard, *Rec. Trav. Chim.*, **54**, 309 (1935).

[95] L. Schmerling, *J. Amer. Chem. Soc.*, **68**, 1655 (1946).

[96] L. Schmerling, *J. Amer. Chem. Soc.*, **71**, 701 (1949).

[97] L. Schmerling, *J. Amer. Chem. Soc.*, **67**, 1152 (1945).

[98] M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Amer. Chem. Soc.*, **69**, 1105 (1947).

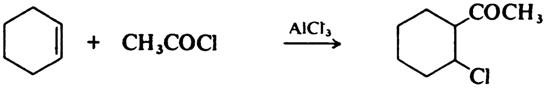
[99] C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, 1957.

[100] M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Amer. Chem. Soc.*, **68**, 154 (1946).

[101] M. S. Kharasch, P. S. Skell, and P. Fisher, *J. Amer. Chem. Soc.*, **70**, 1055 (1948).

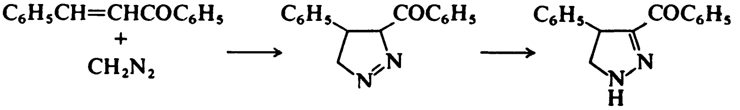
[102] F. Straus and W. Thiel, *Ann. Chem.*, **525**, 151 (1936).

Acid chlorides can also be added at double bonds by the action of aluminum chloride, β-halo ketones being thus obtained:[103,104]



9. Addition of diazomethane or hydrogen cyanide[32e,105,106l]

Pyrazole can be prepared by addition of diazomethane to acetylene, and ethylene analogously gives pyrazoline. Substituted ethylenes, cyclenes, 1,3-dienes, and α,β-unsaturated carbonyl compounds can also add diazomethane.[107] In these reactions 1-pyrazolines are the primary products, but these are converted by basic or acidic reagents or by light into the 2-pyrazolines:[108]



(4)

Smith and Pings[109] report the formation of 3-benzoyl-4-phenyl-2-pyrazoline (**4**) from benzylideneacetophenone and diazomethane.

The reaction of acrylic esters with diazomethane is analogous; the CH_2 group of the diazomethane always adds in these reactions to the β-carbon atom of an α,β-unsaturated ester or ketone, although addition to the α-carbon atom has also been observed.[110]

When heated, 1-pyrazolines generally decompose with evolution of nitrogen, often yielding cyclopropane derivatives;[111] in some cases the cyclopropane derivative is obtained directly in the addition reaction.

Phenylcyclopropane:[112] Freshly distilled styrene (20.8 g, 0.2 mole) is added to a distilled solution of diazomethane (about 0.3 mole) in ether (from 35 g of recrystallized methylnitrosourea), and the mixture is kept for 2–5 days in a fume cupboard in the dark at room temperature. The solvent is then distilled off in a vacuum. At 35°/14 mm distillation of a very small

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[103] H. Wieland and L. Bettag, *Ber. Deut. Chem. Ges.*, **55**, 2246 (1922).

[104] A. Bremer and H. Schinz, *Helv. Chim. Acta*, **35**, 1621 (1952); U.S. Pat., 1,737,203; *Chem. Abstr.*, **24**, 626 (1930).

[105] L. Summers, *Chem. Rev.*, **55**, 301 (1955).

[106] Houben–Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, Vol. 4, Part 2, 1955, pp. (a) 435, (b) 453 (H. Koch), (c) 758 (K. Ziegler; Vol. 7, Part 1, 1952, pp. (e) 16, (f) 20, (g) 29, (h) 36 (O. Bayer); Vol. 8, 1952, pp. (i) 267, (j) 274, (k) 293 (P. Kurtz), (l) 377, (m) 563 (H. Hemecka); Vol. 11, Part 1, 1957, pp. (n) 795, (o) 5731 (R. Schröter).

[107] H. Paul, I. Lange, and A. Kausmann, *Z. Chem.*, **3**, 61 (1963); A. Kost and V. V. Ershov, *Usp. Khim.*, **17**, 431 (1958); *Chem. Abstr.*, **52**, 16357 (1958); M. Mühlstädt, *Z. Chem.*, **2**, 336 (1962); D. McGreer, N. Chiu, M. Vinje, and K. Wong, *Can. J. Chem.*, **43**, 1407 (1965).

[108] H. Paul, I. Lange, and A. Kausmann, *Chem. Ber.*, **98**, 1789 (1965).

[109] L. I. Smith and W. P. Pings, *J. Org. Chem.*, **2**, 23 (1937).

[110] R. Huisgen, *Angew. Chem.*, **75**, 742 (1963); B. Eistert and A. Langbein, *Ann. Chem.*, **678**, 78 (1964).

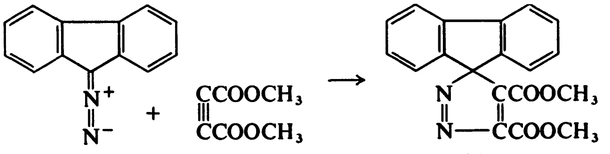
[111] C. Overberger, and J. Anselme, *J. Amer. Chem. Soc.*, **86**, 658 (1964); R. Crawford and co-workers, *J. Amer. Chem. Soc.*, **88**, 3959 (1966); H. Wieland and O. Probst, *Ann. Chem.*, **530**, 277 (1937).

[112] H. Paul and J. Schulze, unpublished work.

amount of unchanged styrene begins. At 150–160° (metal-bath) evolution of nitrogen begins and phenylcyclopropane distils (b.p. 64°/14 mm). Finally a little 3-phenyl-2-pyrazoline passes over at 155°/14 mm. The yield of redistilled phenylcyclopropane (b.p. 174°) is 81.5% (18.7 g) calculated on the amount of styrene used.

Derivatives with substituents in the phenyl ring can be prepared with similar good yields.

Other diazo compounds also undergo addition: van Alphen[113] obtained the spiran (**5**) in quantitative yield after keeping the components in anhydrous ether for 1 day; and the formation of ethyl 3-indoleacetate from indole and ethyl diazoacetate[114] may also be noted.



(**5**)

Hydrogen cyanide adds to acetylene to give acrylonitrile. Simple olefins rarely add hydrogen cyanide, but yields are often good if the ethylenic bond is activated by a neighboring atom; thus α-alkoxy nitriles are formed from vinyl ethers and hydrogen cyanide:[1061,115]

$$CH_2{=}CHOC_2H_5 + HCN \longrightarrow CH_3CH(CN)OC_2H_5$$

This addition occurs under the influence of alkaline catalysts (alkali cyanides, pyridine); methyl, ethyl, butyl, cyclohexyl, and decahydronaphthyl vinyl ether have been used.

2-Butoxypropionitrile: Butyl vinyl ether (200 g), tetrahydrofuran (200 g), and hydrogen cyanide (54 g) are heated in a rotating autoclave at 250° for 6 h. Distillation of the product affords 2-butoxypropionitrile (145 g).

Addition of vinyl esters occurs still more readily. 2-(Acyloxy)propionitriles are obtained in more than 80% yield. Also, hydrogen cyanide can be added to esters of α,β-unsaturated acids,[116,117] *e.g.*, ethyl crotonate and alkylidenemalonate):

$$CHR{=}C(COOC_2H_5)_2 + KCN + HCl \longrightarrow RCH(CN)CH(COOC_2H_5)_2$$

However, presence of alkyl or aryl groups attached to the vinyl group disfavor the capacity for addition.

Diethyl (α-cyanobenzyl)malonate:[118] Diethyl benzylidenemalonate (24.5 g) is dissolved in ethanol (250 ml), and a solution of potassium cyanide (6.5 g) in water (100 ml) is added. To the resulting clear liquid, 30% hydrochloric acid (11 g), diluted with water (50 ml), is added gradually and with cooling. The mixture is set aside for some days. Then the weakly acidic liquid, which barely smells of hydrogen cyanide, is treated with sufficient water to cause incipient turbidity. After 24 h a considerable yield of condensation product has separated as needles, which, when collected and washed with ethanol, melt at 48.5°.

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[113] J. van Alphen, *Rec. Trav. Chim.*, **62**, 491 (1943).

[114] R. W. Jackson and R. H. Manske, *Can. J. Res.*, **13**, *B*, 170 (1935).

[115] French Pat. 892,870; *Chem. Zentralbl.*, **1948**, I, 170.

[116] L. Higginbotham and A. Lapworth, *J. Chem. Soc.*, **121**, 51 (1922).

[117] G. B. Brown, *Org. Syn.*, **26**, 54 (1947).

[118] J. Bredt and J. Kallen, *Ann. Chem.*, **293**, 343 (1896).

Although hydrogen cyanide does not add to the double bond of all α,β-unsaturated acids and esters, it does so to α,β-unsaturated ketones in most cases. This affords γ-oxo carbonitriles, and a second molecule of hydrogen cyanide can then add to the carbonyl group. Unsaturated aldehydes, however, add only one mole of hydrogen cyanide. As example may be quoted the preparation of α-phenacylbenzyl cyanide in 90% yield from benzylideneacetophenone and hydrogen cyanide:[119]

$$C_6H_5CH{=}CHCOC_6H_5 + HCN \longrightarrow C_6H_5CH(CN)CH_2COC_6H_5$$

Hydrogen cyanide can equally be added to α,β-unsaturated nitriles, sulfones, and nitro compounds.[120]

II. Addition to the C=O bond

1. Addition of CH-acidic compounds (aldol condensation; Darzens condensation)

Under the influence of alkali aldehydes form aldols and ketones form ketols. In this way acetaldol (3-hydroxybutyraldehyde) is obtained by condensation of two molecules of acetaldehyde:

$$CH_3CHO + CH_3CHO \longrightarrow CH_3CH(OH)CH_2CHO$$

Acetaldol:[121,122] Acetaldehyde (100 g), freshly prepared from paraldehyde, is added slowly to ice-cold water (200 ml); the solution is cooled to −12° and an ice-cold solution of potassium cyanide (2.5 g) in water (100 ml) is added cautiously at such a rate that the temperature does not exceed −8°. The mixture is kept for a further 2 h in the freezing mixture and then for 30 h at 0°, after which it is saturated with sodium chloride and extracted several times with ether. When dried and fractionated, the extracts afford 40–45% of the aldol at 80–90°/20 mm. The pure product boils at 83°/20 mm.

Higher aliphatic aldehydes give their aldols similarly, it being always the α-methylene group that reacts:

$$RCH_2CHO + RCH_2CHO \longrightarrow RCH_2CH(OH)CHRCHO$$

An example of reaction of an aldehyde with a ketone is provided by formation of **4-hydroxy-2-pentanone** from acetaldehyde and acetone:[121]

$$CH_3CHO + CH_3COCH_3 \longrightarrow CH_3CH(OH)CH_2COCH_3$$

Acetone (105 g) is cooled to −12° and treated with a solution of potassium cyanide (5 g) in water (100 ml), followed, under continued cooling, by freshly prepared acetaldehyde (40 g). The mixture is kept cold for a further 8 h and then extracted with ether. The extracts are shaken with saturated sodium chloride solution, dried, and evaporated. Distillation of the residue gives the product, b.p. 77–78°/19 mm.

Diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) is obtained from two molecules of acetone by the action of barium hydroxide[123] or an anion exchange resin:[124a]

$$CH_3COCH_3 + CH_3COCH_3 \longrightarrow (CH_3)_2C(OH)CH_2COCH_3$$

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[119] A. Hann, A. Lapworth, and E. Wechsler, *J. Chem. Soc.*, **85**, 1358 (1904); **97**, 41 (1910); C. F. H. Allen and R. K. Kimball, *Org. Syn.*, Coll. Vol. II, 498 (1943).

[120] P. Kurtz, *Ann. Chem.*, **572**, 35 (1951).

[121] L. Claisen, *Ann. Chem.*, **306**, 324 (1899).

[122] L.-P. Kyriakides, *J. Amer. Chem. Soc.*, **36**, 532 (1914).

[123] J. B. Conant and N. Tuttle, *Org. Syn.*, **1**, 45 (1921).

[124] C. J. Schmidle and R. C. Mansfield, *Ind. Eng. Chem.*, **44**, (a) 1389, (b) 1388 (1952).

Such aldol condensations involve nucleophilic addition of a methylene component to the carbonyl group:

$$\mathrm{CH_3{-}\overset{+}{C}H{-}\overset{-}{O}} + [^{-}\mathrm{CH_2CHO}]\mathrm{M^+} \longrightarrow [^{-}\mathrm{OCH(CH_3)CH_2CHO}]\mathrm{M^+}$$

$$\xrightarrow[-\mathrm{MOH}]{\mathrm{H_2O}} \mathrm{CH_3CH(OH)CH_2CHO}$$

(M = alkali or alkaline earth)

An essential feature of the reaction is presence of an active hydrogen atom, and other compounds besides aldehydes and ketones can function as the methylene component.

Thus propionaldehyde and nitromethane afford **1-nitro-2-butanol,** as described by Schmidle and Mansfield:[124b]

$$\mathrm{CH_3CH_2CHO + CH_3NO_2 \longrightarrow CH_3CH_2CH(OH)CH_2NO_2}$$

A mixture of propionaldehyde (58 g), nitromethane (91 g), and ethanol (50 g) is passed during 3 h through a column (18 mm in diameter and 40 cm in length) filled with Amberlite IRA-400 and cooled by a jacket to 27–30°. The nitro alcohol, b.p. 107–115°/25 mm, n_D^{25} 1.4432, is obtained in 70% yield.

In general the reaction of nitroalkanes with aldehydes can be carried out by one of three processes:[125] (1) Just sufficient alkali may be added to provide a sufficiently rapid reaction without dehydration or polymerization; the reaction is slow and with the more complex reactants yields are also much lowered. (2) An equimolar amount of 10N-sodium hydroxide solution may be added at not more than 10°, but this method gives good yields only with nitromethane and straight-chain aldehydes and it fails with secondary nitroalkanes. (3) A solution of the aldehyde bisulfite compound may be treated with a warm solution of the sodium salt of the nitroalkane, primary nitro compounds then giving 70–80% yields.

According to a patent,[126] 2-nitro-1-phenyl-1-propanol is obtained by adding a solution of nitroethane gradually, with stirring, to the benzaldehyde bisulfite compound at room temperature.

Carrara and his colleagues[127] prepared 3-(*p*-nitrophenyl)serine ethyl ester from glycine ethyl ester and *p*-nitrobenzaldehyde:

$$p\text{-}\mathrm{NO_2C_6H_4CHO + NH_2CH_2COOC_2H_5 \longrightarrow} p\text{-}\mathrm{NO_2C_6H_4CH(OH)CH(NH_2)COOC_2H_5}$$

3-(2-Thienyl)serine is formed analogously from 2-thiophenecarbaldehyde and glycine.[128]

Adding benzyl cyanide to phenylglyoxylic acid in piperidine affords 3-cyano-2-hydroxy-2,3-diphenylpropionic acid in 40% yield:[129]

$$\mathrm{C_6H_5COCOOH + C_6H_5CH_2CN \longrightarrow C_6H_5CH(CN)C(OH)(C_6H_5)COOH}$$

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[125] C. A. Sprang and E. F. Degering, *J. Amer. Chem. Soc.*, **64**, 1063 (1942).

[126] U.S. Pat. 2,151,517; *Chem. Abstr.*, **32**, 5003 (1938).

[127] G. Carrara, G. Cristiani, V. D'Amato, E. Pace, and R. Pagani, *Gazz. Chim. Ital.*, **82**, 325 (1952).

[128] G. Weitnauer, *Gazz. Chim. Ital.*, **81**, 162 (1951).

[129] P. Cardier and J. Moreau, *C. R. Hebd. Séances Acad. Sci.*, **214**, 621 (1942).

Acetylene can also be added to carbonyl groups, *e.g.*:

$$(CH_3)_2CO + CH{\equiv}CH \longrightarrow HO(CH_3)_2C{-}C{\equiv}CH$$

According to Hurd and McPhee[130] **2-methyl-3-butyn-2-ol** is obtained as follows: Sodium (4.6 g) is added in small portions to liquid ammonia (300 ml) at −50° and then dry acetylene is passed in at a rate of 15–20 l/h until the blue color disappears. Anhydrous acetone (0.042% of water; 14.6 ml, 11.6 g) is added, with stirring, during 1 h to the resulting suspension of the sodioacetylene, and the whole is stirred for a further 4 h at −50°, after which the ammonia is allowed to evaporate. The white residue is dissolved in water (120 ml) and acidified with 50% acetic acid (90 ml). The clear solution is extracted six times with ether, and the extracts are united and dried over sodium sulfate. Fractionation through a Vigreux column then affords an 86% yield of the product, b.p. 100–102°, n_D^{20} 1.4202.

To prevent deterioration of the yield, water must be rigidly excluded. Carrying out the reaction with sodamide in ether leads to yields of only 40–46%.[131]

Under the influence of potassium hydroxide, chloroform can also be added to carbonyl groups; this affords trichloromethyl alcohols, *e.g.*:

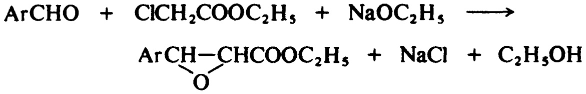
$$(CH_3)_2CO + CHCl_3 \longrightarrow CCl_3C(CH_3)_2OH$$

Weizmann, Bergmann, and Sulzbacher[132] prepared this **2-(trichloromethyl)-2-propanol** according to the following procedure: Freshly molten and powdered potassium hydroxide (102 g) was added to anhydrous methylal (formaldehyde dimethyl acetal; 500 ml) at −4°; a mixture of chloroform (215 g) and acetone (116 g) was next run in at the same temperature during 2 h. The mixture was stirred for a further 2 h, after which it was poured into dilute sulfuric acid and ice. The upper layer was separated and the aqueous layer was shaken with methylal. The solvent was distilled off from the united organic layers, and the crystalline residue was distilled in steam, affording the product as needles, m.p. 91°.

Aldehydes react in accordance with the preceding scheme only if branched at the α-position. According to Rapson *et al.*[133], benzaldehyde reacts with an aqueous-alcoholic solution of chloroform containing sodium hydroxide. Straight-chain aliphatic and nitrated aromatic aldehydes react with chloroform in an anhydrous mixture of tetrahydrofuran and *tert*-butyl alcohol containing potassium *tert*-butoxide at 0° to −20°, yields being good.[134]

Viehe and his co-workers[86] carried out the addition of chloroform to carbonyl groups in liquid ammonia; the yield depended on the structure of the acceptor; their condensing agents were sodamide, sodium hydroxide, and sodium alkoxides; acetone, ethyl methyl ketone, diethyl ketone, cyclopentanone, cyclohexanone, and benzaldehyde were treated in this way. It is also possible to add tribromomethane, but not fluorinated methanes.

Darzens[135] and Claisen[136] described the preparation of glycidic esters (oxiranecarboxylic esters) according to the scheme:



$$\mathrm{ArCHO + ClCH_2COOC_2H_5 + NaOC_2H_5 \longrightarrow Ar\underset{\searrow O \swarrow}{CH{-}CH}COOC_2H_5 + NaCl + C_2H_5OH}$$

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[130] C. D. Hurd and W. D. McPhee, *J. Amer. Chem. Soc.*, **69**, 239 (1947).

[131] D. D. Coffman, *Org. Syn.*, **20**, 40 (1940).

[132] C. Weizmann, E. D. Bergmann, and M. Sulzbacher, *J. Amer. Chem. Soc.*, **70**, 1189 (1948); E. Bergmann, D. Ginsburg, and D. Lavie, *J. Amer. Chem. Soc.*, **72**, 5012 (1950).

[133] W. S. Rapson, D. H. Saunder, and E. T. Stewart, *J. Chem. Soc.*, **1944**, 74.

[134] E. Kaspar and R. Wiechert, *Chem. Ber.*, **91**, 2664 (1958).

[135] G. Darzens, *C. R. Hebd. Séances Acad. Sci.*, **139**, 1214 (1904).

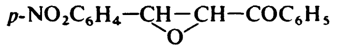
[136] L. Claisen, *Ber. Deut. Chem. Ges.*, **38**, 693, 699 (1905).

Such condensations can be carried out with the dry ethoxide in absence of a solvent or with sodamide in ether or another solvent.

Anhydrous conditions are essential for this reaction, and it has been further recommended to use an inert-gas atmosphere in certain cases. It is advisable to use 1.6 moles each of the chloro ester and alkoxide per mole of carbonyl compound.[137] The temperature should be low at the beginning of the reaction (temperatures down to −80° have been recommended[138]), but the mixture is warmed for a short time on the water-bath for completion. Working up is by treatment with dilute acid and fractionation in a vacuum.

Aliphatic or aromatic ketones can be used with success in place of the aromatic aldehydes, but, unlike aromatic aldehydes, aliphatic aldehydes give only poor yields. Further, other α-chloro esters may replace the chloroacetic ester.

Aromatic halo ketones can also be condensed with aromatic aldehydes; for example, ω-bromoacetophenone and *p*-nitrobenzaldehyde afford 2-benzoyl-3-(*p*-nitrophenyl)oxirane in 88% yield:[139]



$$p\text{-NO}_2\text{C}_6\text{H}_4\text{—}\underset{\diagdown\,\text{O}\,\diagup}{\text{CH—CH}}\text{—COC}_6\text{H}_5$$

Two examples of the procedure are as follows:

Ethyl 3-methyl-3-phenyloxirane-2-carboxylate:[140] Finely powdered sodamide (47.2 g, 1.2 moles) is added during 2 h to a mixture of acetophenone (120 g, 118.5 ml, 1.0 mole), ethyl chloroacetate (123 g, 109 ml, 1.0 mole), and anhydrous benzene (200 ml) placed in a three-necked flask (1-l capacity) fitted with a stirrer and a low-temperature thermometer, while the temperature is kept at 15–20° by cooling. The mixture is stirred for a further 2 h at room temperature and then poured with shaking on crushed ice (700 g). The organic layer is separated, and the aqueous layer is re-extracted with benzene (200 ml). The benzene solutions are united, dried over sodium sulfate (25 g), and freed from solvent. Fractionation of the residue in a vacuum affords the product, b.p. 107–113°/3 mm, which after a second distillation boils at 111–114°/3 mm, the yield being 62–64% (128–132 g).

Ethyl 1-oxaspiro[2.5]octane-2-carboxylate:[141] The reaction is carried out in a three-necked flask (500-ml capacity) fitted with a stirrer, a thermometer, and a pressure equalization device on a dropping funnel. The funnel is fitted for evacuation and for introduction of nitrogen. The apparatus is evacuated and dried over a flame. Freshly distilled cyclohexanone (14.5 g, 0.148 mole) and freshly distilled ethyl chloroacetate (18.15 g, 0.148 mole) are placed in the flask. A solution of potassium (6 g, 0.153 mole) in anhydrous *tert*-butyl alcohol (125 ml) is placed in the dropping funnel. Then the air is pumped out and replaced by nitrogen. The flask is cooled in ice, and the potassium *tert*-butoxide is dropped in, with stirring, during 1.5 h, the temperature of the mixture being maintained at 10–15°. Thereafter the mixture is stirred for a further 1.0–1.5 h at about 10°. Then most of the *tert*-butyl alcohol is removed by distillation at water-pump vacuum with a bath at 100°. The oily residue is taken up in ether, washed with water and saturated sodium chloride solution, and dried over sodium sulfate. Removal of the ether and distillation of the residue through a Vigreux column afford 83–95% (22.5–26 g) of the colorless glycidic ester, b.p. 134–137°/21 mm, n_D^{25} 1.4568–1.4577

Cyanooxiranes can be obtained by using chloroacetonitrile; *e.g.*, with benzophenone this reaction gives an 81% yield of 3-cyano-2,2-diphenyloxirane.[142]

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[137] M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949).

[138] W. A. Yarnall and E. S. Wallis, *J. Org. Chem.*, **4**, 270 (1939).

[139] H. H. Wasserman and N. E. Aubrey, *J. Amer. Chem. Soc.*, **77**, 590 (1955).

[140] C. F. H. Allen and J. van Allan, *Org. Syn.*, Coll. Vol. III, 727 (1955).

[141] R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Syn.*, **34**, 54 (1954); for apparatus see W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1950).

[142] G. Storck, W. S. Worrall, and I. J. Pappas, *J. Amer. Chem. Soc.*, **82**, 4315 (1960).

2. Acyloin condensation

The acyloin condensation is a reaction according to the scheme:

$$\mathrm{RCHO + RCHO \longrightarrow HOCHRCOR}$$

For this reaction in its simplest form the greatest importance for preparative purposes lies in the aromatic series, where for benzaldehyde and its substitution products it is known as the benzoin condensation. It is rarely successful in the aliphatic series. Phenylglyoxal reacts as follows:[143]

$$\mathrm{2C_6H_5COCHO \longrightarrow C_6H_5COCH(OH)COCOC_6H_5}$$

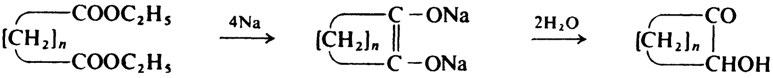
In the benzoin condensation an alcoholic solution of the aldehyde, *e.g.*, benzaldehyde, is heated under reflux with about one-tenth of its weight of potassium cyanide, usually with addition of water; the product, *e.g.*, **benzoin,** $C_6H_5CH(OH)COC_6H_5$, separates in crystalline form on cooling. The benzoin obtained is usually pale yellow and is difficult to separate from the colored impurities, but Weissberger and his co-workers[144] state that this can be done by crystallization from diisopentyl ether, the melting point then being 137°.

The potassium cyanide may be replaced by sodium or barium cyanide, but not by free hydrocyanic acid or complex cyanides; thus the catalytic action is ascribed to the cyanide ion, which is not available in sufficient amount from free hydrocyanic acid or cyano complexes owing to their slighter dissociation.

The acyloin (benzoin) condensation is applicable, not merely to benzaldehyde itself, but also to its homologs, to its alkoxy derivatives, and to furfuraldehyde. It fails, however, with free hydroxybenzaldehydes and with halogenated nitro and amino benzaldehydes; and cinnamaldehyde gives diminutive yields.

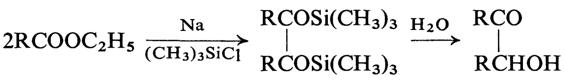
Mixed acyloins, such as the *Ar*-substituted ω-hydroxy-ω-(3-pyridyl)acetophenones, can be prepared by reaction of 3-pyridinecarbaldehyde with *p*-hydroxy- or *p*-(dimethylamino)-benzaldehyde in the presence of cyanide ion.[145]

Macrocyclic acyloins are obtained by the Hansley–Prelog–Stoll technique[146a] from dicarboxylic esters and finely divided liquid sodium in boiling xylene. When the dilution method is used, *i.e.*, gradual addition of the ester in very small successive amounts to a large volume of xylene, this reductive cyclization leads to excellent yields of the ten-membered ring compound; but yields of the seven-, eight-, and nine-membered ring analogs are only 30–40%. The reaction must be effected under pure nitrogen.



$$[\mathrm{CH_2}]_n\begin{cases}\mathrm{COOC_2H_5}\\ \mathrm{COOC_2H_5}\end{cases} \xrightarrow{\mathrm{4Na}} [\mathrm{CH_2}]_n\begin{cases}\mathrm{C-ONa}\\ \| \\ \mathrm{C-ONa}\end{cases} \xrightarrow{\mathrm{2H_2O}} [\mathrm{CH_2}]_n\begin{cases}\mathrm{CO}\\ | \\ \mathrm{CHOH}\end{cases}$$

When chloro(trimethyl)silane is added, the five- and six-membered ring acyloins can be prepared, as can also open-chain acyloins from monocarboxylic esters:[147]



$$\mathrm{2RCOOC_2H_5} \xrightarrow[\mathrm{(CH_3)_3SiCl}]{\mathrm{Na}} \begin{array}{c}\mathrm{RCOSi(CH_3)_3}\\ | \\ \mathrm{RCOSi(CH_3)_3}\end{array} \xrightarrow{\mathrm{H_2O}} \begin{array}{c}\mathrm{RCO}\\ | \\ \mathrm{RCHOH}\end{array}$$

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[143] G. Söderbaum and P. W. Abenius, *Ber. Deut. Chem. Ges.*, **25**, 3468 (1892).

[144] A. Weissberger, H. Mainz, and E. Strasser, *Ber. Deut. Chem. Ges.*, **62**, 1952 (1929).

[145] P. Bergmann and H. Paul, *Z. Chem.*, **6**, 339 (1966).

[146] Review: H. Krauch and W. Kunz, "Reaktionen der organischen Chemie," Dr. A. Hüthig-Verlag, Heidelberg, 3rd ed., 1966, pp. (a) 279, (b) 439, (c) 587.

[147] U. Schräpler and K. Rühlmann, *Chem. Ber.*, **97**, 1383 (1964); **96**, 2780 (1963).

3. Formation of pinacols

Pinacols can be obtained from ketones by using reducing agents of very varied type:

$$2RCOR' \xrightarrow{+2H} HOCRR'CRR'OH$$

The preparation of **benzopinacol** may be given as example of pinacol formation by zinc in acid solution:[148]

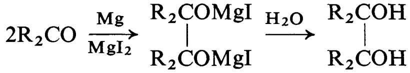
Benzophenone (1 part), zinc (2 parts), and 80% acetic acid (10 parts) are boiled for 15 min with effective shaking. After cooling, the crystals that have separated are collected and the filtrate is boiled again several times with zinc, the crystals being collected as above each time. The benzopinacol produced is washed with dilute acetic acid and recrystallized from boiling glacial acetic acid. It then melts at 185–186° with decomposition to benzophenone and benzhydrol (diphenylmethanol).

Bachmann[149,67c] described the preparation of benzopinacol in 95% yield by photoreduction of benzophenone in 2-propanol in sunlight.

Gomberg and Bachmann[150,151] obtained a large number of aromatic pinacols in good yield by reduction with the binary mixture magnesium–magnesium bromide or iodide. For example, ***di*-(2-naphthyl)-1,2-diphenyl-1,2-ethanediol** can be prepared as follows:[151]

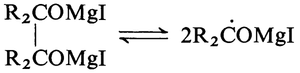
2-Naphthyl phenyl ketone (2.32 g) is shaken with magnesium (1 g) and magnesium iodide (3 g) in a 1 : 1 mixture (30 ml) of ether and benzene with exclusion of air and moisture. The solution becomes reddish-brown. Access of air causes immediate decoloration, but the color returns when air is later excluded. The excess of magnesium is filtered off, the mixture is decomposed with ice and ammonium chloride, the organic layer is washed with water and dried over sodium sulfate, and its solvent is removed in a vacuum. The crude product, when recrystallized from chloroform–ethanol, melts at 175° (yield 91%). An anhydrous magnesium–magnesium iodide reducing mixture can be prepared from magnesium powder (4 g) and iodine (12 g) in anhydrous ether (75 ml) and anhydrous benzene (75 ml).[150]

The reaction mechanism can be rendered as:



$$2R_2CO \xrightarrow[MgI_2]{Mg} \begin{array}{c} R_2COMgI \\ | \\ R_2COMgI \end{array} \xrightarrow{H_2O} \begin{array}{c} R_2COH \\ | \\ R_2COH \end{array}$$

However, the metal ketyl is formed as intermediate that exists in equilibrium with the pinacolate:



$$\begin{array}{c} R_2COMgI \\ | \\ R_2COMgI \end{array} \rightleftharpoons 2R_2\dot{C}OMgI$$

Reduction of unsaturated aldehydes to pinacols by zinc–copper alloy has been described by Kuhn and Rebel;[152] this reaction occurs at 0° in dilute

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[148] A. Zagumenny, *Ber. Deut. Chem. Ges.*, **14**, 1402 (1991); *Russ. Phys. Chem. Ges.*, **12**, 429 (1880); L. Vanino, "Handbuch der präparativen organischen Chemie," Vol. 2, Enke Verlag, Stuttgart, 1937, 3rd ed., p. 560.

[149] W. E. Bachmann, *Org. Syn.*, Coll. Vol. II, 71 (1943); J. W. Lynn and J. English, *J. Org. Chem.*, **16**, 1547 (1951); M. R. Kegelmann and E. V. Brown, *J. Amer. Chem. Soc.*, **75**, 4649, 5961 (1953).

[150] M. Gomberg, and W. E. Bachmann, *J. Amer. Chem. Soc.*, **49**, 236 (1927); J. E. Hodgkins and J. A. King, *J. Amer. Chem. Soc.*, **85**, 2679 (1963).

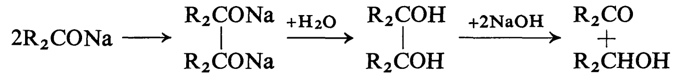
[151] W. E. Bachmann and R. V. Shankland, *J. Amer. Chem. Soc.*, **51**, 306 (1929).

[152] R. Kuhn and O. Rebel, *Ber. Deut. Chem. Ges.*, **60**, 1565 (1927).

acetic acid. Young, Levanas, and Jesaitis[153] obtained 2,6-hexadiene-4,5-diol in 67% yield from crotonaldehyde by means of the zinc–copper couple.[154]

Laude and Wiemann[155] reported the reduction of mixtures of ketones to unsymmetrical pinacols.

Alkyl aryl ketones can be reduced by aluminum foil and a little mercuric chloride in benzene–ethanol.[156] Davis and Marvel[157] reduced ethyl methyl ketone to 3,4-dimethyl-3,4-hexanediol by magnesium amalgam (prepared from magnesium and mercuric chloride). In reductions by sodium or sodium amalgam[158] care must be taken that the alkali hydroxide liberated on hydrolysis of the pinacol–alkali compound does not cleave the pinacol to ketone and alcohol, wherefore it is advisable to effect the hydrolysis by acetic acid:[158]

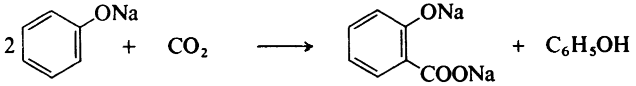


$$2R_2CONa \longrightarrow \begin{array}{c}R_2CONa\\|\\R_2CONa\end{array} \xrightarrow{+H_2O} \begin{array}{c}R_2COH\\|\\R_2COH\end{array} \xrightarrow{+2NaOH} \begin{array}{c}R_2CO\\+\\R_2CHOH\end{array}$$

Electrolytic reductions have been reported by Allen[159] and by Pearl;[160] and Sisido and Nozaki[161] carried out the reduction by aluminum amalgam.

4. Carbonylation (Kolbe–Schmitt reaction, etc.)

Kolbe and Schmitt[162] showed that salicyclic acid could be obtained by passing dry carbon dioxide over dry sodium phenoxide, the temperature being raised gradually to 110–200° during the reaction:



In that reaction part of the sodium phenoxide is converted into free phenol which does not react with carbon dioxide; so, in order to obtain complete reaction, as required in an industrial process, Schmitt caused carbon dioxide to react with sodium phenoxide in a pressure vessel, heating in that case being to 120–150°.

If the reaction is carried out with potassium phenoxide, the isomer, *p*-hydroxybenzoic acid is obtained; between 100° and 150° dipotassium salicylate is formed in this case also, but it rearranges, completely at 200°, to *p*-hydroxybenzoic acid. Addition of carbon dioxide to polyhydric phenols or aminophenols occurs even in aqueous solution. 1-Naphthol is also amenable to the reaction.

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[153] W. G. Young, L. Levanas, and Z. Jesaitis, *J. Amer. Chem. Soc.*, **58**, 2274 (1936).

[154] J. Gladstone and A. Tribe, *J. Chem. Soc.*, **31**, 561 (1877).

[155] G. Laude and J. Wiemann, *Bull. Soc. Chim. France*, [v], **13**, 256 (1946).

[156] M. S. Newman, *J. Org. Chem.*, **26**, 582 (1961).

[157] D. W. Davis and C. S. Marvel, *J. Amer. Chem. Soc.*, **53**, 3843 (1931).

[158] W. B. Bachmann, *J. Amer. Chem. Soc.*, **55**, 1183, 2829 (1933).

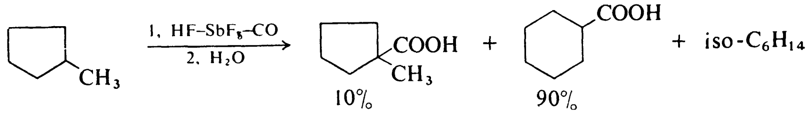
[159] M. I. Allen, *J. Amer. Chem. Soc.*, **72**, 3797 (1950); **73**, 3503 (1951).

[160] I. A. Pearl, *J. Amer. Chem. Soc.*, **74**, 4260 (1952).

[161] K. Sisido and H. Nozaki, *J. Amer. Chem. Soc.*, **70**, 776 (1948).

[162] H. Kolbe and R. Schmitt, *J. Prakt. Chem.*, [ii], **10**, 89 (1874); **31**, 397 (1885); A. S. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).

In hydrogen fluoride containing antimony pentafluoride, aliphatic hydrocarbons are converted by carbon monoxide at atmospheric pressure and 0–20° into carboxylic acids or ketones:[163]



If after the absorption of carbon monoxide by methylcyclohexane the mixed products are treated with benzene, a 63% yield of cyclohexyl phenyl ketone is obtained, together with 10% of dicyclohexyl ketone and other by-products.

Open-chain alkanes behave similarly, but then no hydrocarbon of low molecular weight is formed as by-product; instead, surprisingly, hydrogen is liberated:

$$\text{iso-C}_5\text{H}_{12} \xrightarrow[2,\text{H}_2\text{O}]{1,\text{HF}-\text{SbCl}_5-\text{CO}} \text{iso-C}_5\text{H}_{11}\text{COOH} + \text{H}_2$$

5. Cyanohydrin synthesis[106j]

Cyanohydrin synthesis consists of addition of hydrogen cyanide to a carbonyl compound according to the scheme:

$$\text{R}_2\text{CO} + \text{HCN} \rightleftarrows \text{HOCR}_2\text{CN}$$

Aldehydes generally undergo this reaction faster and more completely than ketones. Alkyl aryl ketones give only poor yields of cyanohydrin, and diaryl ketones give none at all.

Cyanohydrin formation is an equilibrium reaction, and equilibration is very slow in the absence of a catalyst. Effective catalysts are substances with an alkaline reaction, such as potassium cyanide,[164] potassium carbonate,[165] and ammonia.[166]

Cyanohydrins are thermally unstable, reverting to the starting materials at higher temperatures.

For a **cyanohydrin synthesis** the carbonyl compound is treated with a concentrated solution of hydrogen cyanide, or sometimes with anhydrous hydrogen cyanide, or with an alkali cyanide and an acid.

The procedure with hydrogen cyanide is as follows: A few drops of concentrated potassium cyanide solution are added cautiously to an equimolar mixture of the aldehyde or ketone and hydrogen cyanide (10% excess of the acid for ketones). The mixture soon begins to boil, and an efficient condenser and on occasions cooling are required. When the reaction ceases, the mixture is made distinctly acid by sulfuric acid, with good cooling. Then unchanged hydrogen cyanide and aldehyde or ketone are distilled off and the residue is fractionated in a vacuum.

For preparation of large amounts of cyanohydrin it is preferable to add the hydrogen cyanide to a mixture of the carbonyl compound and catalyst. For the lower-boiling acetaldehyde a mixture of hydrogen cyanide and the aldehyde is dropped into a mixture of the catalyst with some cyanohydrin derived from a preliminary experiment.

Cyclodecanone cyanohydrin[167] can be prepared in ether; it is then precipitated and thus removed from the equilibrium mixture. Hydrogen cyanide (270 ml) is dropped, with stirring

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[163] R. Paatz and G. Weisgerber, *Chem. Ber.*, **100**, 984 (1967).

[164] A. Lapworth, *J. Chem. Soc.*, **85**, 1206 (1904).

[165] M. von Romburgh, cited by M. Ultee, *Rec. Trav. Chim.*, **28**, 2 (1909).

[166] H. Kiliani, *Ber. Deut. Chem. Ges.*, **21**, 916 (1888).

[167] W. Kirchhof, W. Stumpf, and W. Franke, *Ann. Chem.*, **681**, 32 (1965).

during 45 m in into a mixture of cyclodecanone (500 g) and triethylamine (5 g) in ether (400 ml); the temperature is kept at 32° for 6 h, then the mixture is boiled for 1 h. The crystalline cyanohydrin begins to separate after the first hour, and further ether is added as necessary to facilitate stirring. Finally the mixture is kept at 0° for some time, before being acidified with acetic acid (10 ml). The product is then filtered off and dried in the air and for 2 h in a vacuum at room temperature; after recrystallization from acidified methanol it melts at 115–116.5°.

Diethylaluminum cyanide is an efficient reagent for use in cyanohydrin synthesis; 6-methoxy-1-tetralone can be converted into its cyanohydrin only by use of that compound.[168]

Spiegel[169] recommended the use of potassium cyanide and hydrogen chloride for preparation of **mandelonitrile:** somewhat more than 1 mole of pure potassium cyanide is moistened with a little water, covered with a layer of 1 mole of benzaldehyde, and treated dropwise, with repeated shaking and with cooling, with 1 mole of hydrogen chloride in the form of fuming hydrochloric acid. The resulting brown oil is then decanted from the slurry of salts.

According to Bucherer and Grolee,[170] it is sometimes possible to treat the bisulfite compound of a ketone or aldehyde with aqueous potassium cyanide solution, and it is often unnecessary to isolate the bisulfite compound. This is exemplified as follows:

Acetone (1 mole) is shaken with a concentrated aqueous solution of sodium hydrogen sulfite (1 mole). The mixture becomes warm and is allowed to cool, then a concentrated aqueous solution of potassium cyanide (1 mole) is dropped in with good shaking, whereupon the solution again becomes warm. The mixture is cooled again and the oily layer of acetone cyanohydrin is separated from the aqueous layer, which is then extracted several times with ether. The cyanohydrin layer and ether extracts are united, washed with sodium hydrogen sulfite solution to remove acetone, and then with saturated sodium chloride solution, and freed from ether. Completely alkali-free **acetone cyanohydrin** boils at 82°/23 mm and melts at −19°.

So as to be able to distil completely alkali-free cyanohydrins, Ultee[171] recommended stabilizing them by addition of traces of acid; 1–2% of an organic acid (mercaptoacetic or chloroacetic acid) that distils together with the cyanohydrin have proved valuable. However, sulfuric acid, phosphoric acid, and iodine have also been used.

Another method of preparing a cyanohydrin is to treat one cyanohydrin (usually a ketone cyanohydrin) with a different carbonyl compound (usually an aldehyde) in the presence of a small amount of an alkaline catalyst;[172] an equilibrium is set up in which the cyanohydrin with the smaller decomposition constant preponderates:

$$\mathrm{HOCRR'CN} + \mathrm{R''CHO} \rightleftarrows \mathrm{HOCHR''CN} + \mathrm{RCOR'}$$

The cyanohydrin synthesis is particularly important in the carbohydrate series; Fischer thus converted, *e.g.*, pentoses into hexoses by way of the lactones of the aldonic acids which he later reduced. Admittedly, the nitriles produced as intermediates (best obtained in other cases by dehydration of the corresponding oximes) are generally not isolated. On the other hand, the corresponding amides can often be separated in a pure state, as shown, *e.g.*, by Kiliani[166] for **heptonamide**:

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[168] W. Nagata and M. Yoshioka, *Tetrahedron Lett.*, **1966**, 1913.

[169] A. Spiegel, *Ber. Deut. Chem. Ges.*, **14**, 235 (1881).

[170] H. Bucherer and A. Grolee, *Ber. Deut. Chem. Ges.*, **39**, 1225 (1906).

[171] M. Ultee, *Rec. Trav. Chim.*, **28**, 1 (1909).

[172] I. N. Nazarov, A. Akhrem, and A. V. Kamernitzkii, *Zh. Obshch. Khim.*, **25**, 1345 (1955); *Chem. Abstr.*, **50**, 4950 (1956).

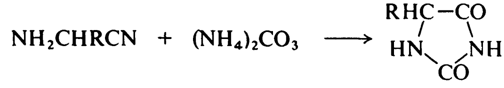
Finely powdered galactose (30 g) is treated with water (5 ml) and the calculated amount of ca. 50% hydrogen cyanide solution and then with a few drops of ammonia. The flask is tightly stoppered and thoroughly shaken. When the mixture is set aside, the galactose becomes yellow and gradually liquefies, and after 6–8 h colorless needles separate, sometimes with considerable evolution of heat. After a further 12 h, an equal volume of water is added, and the mixture is shaken and filtered or poured on a porous plate. A 40–50% yield of crude heptonamide is thus obtained.

A modification of the cyanohydrin synthesis is provided by Strecker's amino acid synthesis, in which an α-amino nitrile is obtained by the action of hydrogen cyanide and ammonia on an aldehyde or ketone:

$$\mathrm{RCHO + NH_3 + HCN \longrightarrow NH_2CHRCN + H_2O}$$

Treatment with a mineral acid then hydrolyses the nitrile and provides the α-amino acid.

Bucherer[173] varied this procedure by treating the bisulfite compound of the aldehyde in hot alcoholic solution with hydrogen cyanide and ammonium carbonate; this gives hydantoins, which crystallize well and on hydrolysis by hot mineral acid also afford the amino acids:



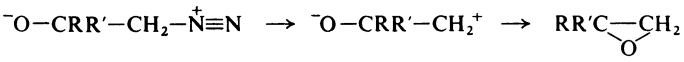
6. Addition of diazomethane to carbonyl groups[32e]

The first step in the reaction of diazomethane with an aldehyde or a ketone, known as the Arndt–Eistert reaction, is addition of the diazomethane to the carbonyl group:

$$\mathrm{RR'\overset{+}{C}{-}O^- + {}^-CH_2{-}\overset{+}{N}{\equiv}N \longrightarrow {}^-O{-}CRR'{-}CH_2{-}\overset{+}{N}{\equiv}N}$$

$$\mathrm{(R, R' = H, alkyl, or\ aryl)}$$

The diazonium betaines formed are sometimes reasonably stable. The rearrangements which occur with evolution of nitrogen and formation of homologous ketones or aldehydes are described in detail on page 1092; it suffices in this Section to mention the formation of oxiranes (epoxides), which can also occur on evolution of nitrogen:



This epoxide formation takes place almost exclusively when R is an electron-attracting group; *e.g.*, 2-(trichloromethyl)oxirane is obtained from chloral and diazomethane,[174] and **2-(*o*-nitrophenyl)oxirane** from *o*-nitrobenzaldehyde.[175,176]

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[173] H. Bucherer, *J. Prakt. Chem.*, **140**, 291 (1934); **141**, 5 (1934).

[174] F. Arndt and B. Eistert, *Ber. Deut. Chem. Ges.*, **61**, 1118 (1928).

[175] F. Arndt, B. Eistert, and W. Partale, *Ber. Deut.Chem. Ges.*, **61**, 1107 (1928).

[176] F. Arndt, B. Eistert, and W. Partale, *Ber. Deut. Chem. Ges.*, **60**, 446 (1927).

o-Nitrobenzaldehyde (10 g) is added to 1.5 equivalents of diazomethane in ethereal solution at −10°. When the aldehyde has dissolved and the lively evolution of nitrogen has ceased, the solution is allowed gradually to assume room temperature and kept thereat for a further 2 h. Removing the ether, finally in a vacuum, leaves an oil that solidifies almost completely when cold. For purification the crude product is liquefied and mixed with about twice its volume of warm methanol, whereafter gradual cooling to −10° causes most of the product to crystallize in a fairly pure state. After filtration, the mother-liquor is evaporated and the residue is distilled in steam, whereupon the remainder of the product slowly distils, usually crystallizing in the condenser. The total yield at this stage is 6–8 g. For complete purification, the oxirane is recrystallized from methanol until a sample dissolved in alcohol no longer gives a color with alkali hydroxide; it then forms odorless, almost colorless crystals, m.p. 65°, b.p. 144°/10 mm.

If R is an electron-repelling group, oxirane formation is less evident and the rearrangements discussed on page 1092 provide the products.

7. Addition of Grignard reagents and other organometallic compounds[177]

Interaction of Grignard reagents and carbonyl groups leads to formation of a new carbon–carbon bond and hydrogenation; formally, the parent hydrocarbon RH of a Grignard reagent RMgX adds to the carbonyl group:

$$\mathrm{RR'RR''\overset{+}{C}{—}O^- + \overset{-}{R}{—}\overset{+}{M}gBr \longrightarrow RR'R''C{—}OMgBr \xrightarrow{+H_2O}}$$
$$\mathrm{RR'R''COH + MgBr(OH)}$$

The great majority of Grignard reactions are carried out in diethyl ether, but in some special cases recourse is had to dibutyl or diisopentyl ether. Methylene dichloride can also be used as solvent for Grignard reactions;[178] acetylenic Grignard reagents are more soluble in methylene dichloride than in ether.

Although working with small quantities of organomagnesium compounds in ethereal solution presents no difficulty, it must be remembered that with larger batches a clumsy technique can be a source of serious **danger**: to add water to a Grignard solution that has reacted only partially is as inadvisable as to add water to concentrated sulfuric acid.

Ethereal solutions of organomagnesium compounds are sensitive to moisture, carbon dioxide, and air. Gilman and Hewlett[179] have described an apparatus by means of which access of air can be prevented completely.

The concentration of a Grignard solution can be determined satisfactorily by a procedure due to Gilman and his co-workers[180] (see also page 766).

Grignard solutions, once prepared, are almost always immediately used for further reactions.

This further reaction does not, however, always at once proceed to the stage shown in the above formal equation. For instance, it appears that oxiranes and aliphatic organomagnesium compounds give first an oxonium compound.[181]

For the subsequent reaction the Grignard solution must be brought to the temperature appropriate for each case; usually it is a matter of cooling, but

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[177] M. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice Hall, Inc., New York, 1954.

[178] H. Viehe and M. Reinstein, *Chem. Ber.*, **95**, 2557 (1962).

[179] H. Gilman and P. Hewlett, *Rec. Trav. Chim.*, **48**, 1124 (1929).

[180] H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Amer. Chem. Soc.*, **45**, 150 (1923).

[181] E. E. Dreger, *Org. Syn.*, **6**, 56 (1926), note 5.

the temperature must be adjusted to be optimal for a reasonable time of reaction. In any case it is advisable to provide a means of measuring the temperature of the reacting mixture.

Although ethereal solutions of the Grignard reagents usually present a homogeneous phase, solid precipitates can be formed readily in the subsequent reactions, and this must be taken into account if the other reactant is provided as a gas (carbon dioxide, oxirane, formaldehyde, etc.); in such cases it is better not to pass the gas into the solution, which can lead to blocked inlet tubes, but merely to pass it over the surface of the solution.

Finally, it is often necessary to warm the mixture for complete reaction. The end of the reaction can be recognized by absence of Grignard reagent in the solution.

Gilman, Schulze, and Heck[182] have described a generally applicable **color reaction for Grignard reagents:** The solution (0.5 ml) to be tested for presence of an organomagnesium compound is added to a 1% solution (0.5 ml) of Michler's ketone in anhydrous benzene. Water (1 ml) is then added for hydrolysis, followed by a few drops of a 0.2% solution of iodine in glacial acetic acid. Formation of a bluish-green color indicates presence of a Grignard reagent; its absence denotes complete consumption of the organomagnesium compound.

After preparation of the Grignard reagent and its addition to a reactive substance the last operation consists of **decomposition of the primary product.** This process also is always exothermic, and incautious procedure can not merely endanger success of the experiment but can also, even at this stage, be dangerous.

The reagent for hydrolysis may be hydrochloric acid, sulfuric acid, or ammonium chloride solution. Water alone leads to magnesium hydroxide, which makes further working up more difficult.

If the reaction mixture can be removed readily from the reaction vessel, it is best to pour it first on to ice and then, if necessary, after addition of more ice, to run in a suitable acid to the desired concentration. When acid may lead to polymerization or other undesirable reactions, ammonium chloride solution is used.

If, because of its consistency, the reaction mixture cannot be removed readily from the flask, it is then necessary to add the hydrolysing agent to the mixture. In such cases considerable amounts of ice and water must also be added, to provide rapid dilution and cooling, as local overheating may lead to evaporation of the ether, loss of the product, or fires. The final working up procedure must be adapted to each case.

a. Treatment of Grignard reagents with ketones

Tertiary alcohols are usually formed on treatment of ketones with Grignard reagents, as exemplified by the reaction:[183]

$$\mathrm{CH_2FCOC_6H_5 + C_6H_5MgBr \longrightarrow CH_2FC(C_6H_5)_2OMgBr \longrightarrow CH_2FC(C_6H_5)_2OH}$$

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[182] H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925); H. Gilman and L. L. Heck, *J. Amer. Chem. Soc.*, **52**, 4949 (1930).

[183] E. C. Ashby and M. B. Smith, *J. Amer. Chem. Soc.*, **86**, 4363 (1964).

Bergmann and Kalmus[184] prepared 2-fluoro-1,1-diphenylethanol from ω-fluoroacetophenone and phenylmagnesium bromide in just that manner.

A solution of phenylmagnesium bromide is prepared from bromobenzene (20 g), magnesium (2.5 g), and ether (50 ml) and is then treated dropwise during 15 min at 0° with a solution of ω-fluoroacetophenone (14 g) in ether (25 ml). Finally a solution of ammonium chloride in ice-water is slowly added. The layers are separated and the aqueous solution is extracted three times with ether. The united ethereal solutions are dried over sodium sulfate and fractionated in a vacuum. The distillate of b.p. 70–75°/0.2 mm crystallizes rapidly and forms prisms, m.p. 71–72°, from light petroleum (yield 65%).

Grignard reagents do not add to sterically hindered compounds; instead, reduction of the carbonyl to a secondary alcohol group occurs[184] provided that the Grignard organic radical has a hydrogen atom on the β-carbon atom:

$$[(CH_3)_2CH]_2CO + (CH_3)_2CHMgBr \longrightarrow [(CH_3)_2CH]_2CHOMgBr + CH_3CH{=}CH_2$$

In such reactions an olefin is formed from the Grignard reagent. When, however, propylmagnesium bromide is allowed to react with diisopropyl ketone, reduction to the secondary alcohol (63%) is accompanied by normal addition of the Grignard reagent to the carbonyl group with formation of the tertiary alcohol (30%);[185] and if magnesium bromide is added to the reaction mixture the yield of tertiary alcohol is considerably increased (to 65%).[185]

The cause of this behavior has been assigned[186] to formation, before the reaction proper, of a cyclic complex constituted from two molecules of Grignard reagent and one of the ketone with participation of the solvent. This complex formation enhances the heteropolar character of the Grignard reagent and the polarization of the carbonyl group, so that the reaction can proceed. Such a complex cannot, however, be formed from sterically hindered ketones, so that the carbonyl group is reduced to a secondary alcoholic group, as described above. On the other hand, when magnesium bromide is added, a similar cyclic complex constituted from one molecule each of ketone, magnesium bromide, and Grignard reagent is obtained, so that the Grignard reaction can proceed, at least in part, along its normal course.

The Grignard reagent adds to ketenes at the carbonyl double bond, the carbon–carbon bond being indifferent; trimesitylvinyl alcohol is thus obtained from dimesityl ketone and mesitylmagnesium bromide:[187]

$$\begin{gathered}[(CH_3)_3C_6H_2]_2C{=}C{=}O + (CH_3)_3C_6H_2MgBr \longrightarrow \\ [(CH_3)_3C_6H_2]_2C{=}C(OH)C_6H_2(CH_3)_3\end{gathered}$$

Kohler showed[188] that α,β-unsaturated ketones undergo both 1,2-addition of Grignard reagents to the carbonyl group and 1,4-addition to the conjugated system; thus ω,ω-diphenylpropiophenone is obtained from benzylideneacetophenone and phenylmagnesium bromide:

$$\begin{gathered}C_6H_5CH{=}CHCOC_6H_5 + C_6H_5MgBr \longrightarrow (C_6H_5)_2CHCH{=}C(C_6H_5)OMgBr \longrightarrow \\ (C_6H_5)_2CHCH{=}C(C_6H_5)OH \longrightarrow (C_6H_5)_2CHCH_2COC_6H_5\end{gathered}$$

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[184] F. Bergmann and A. Kalmus, *J. Amer. Chem. Soc.*, **76**, 4137 (1954).

[185] A. H. Blatt and J. F. Stone, *J. Amer. Chem. Soc.*, **54**, 1495 (1932); C. G. Swain and H. B. Boyles, *J. Amer. Chem. Soc.*, **73**, 870 (1951).

[186] V. Franzen and H. Krauch, *Chem.-Ztg.*, **79**, 137 (1955).

[187] R. C. Fuson, R. H. Chadwick, and M. L. Ward, *J. Amer. Chem. Soc.*, **68**, 389 (1946).

[188] E. P. Kohler, *Amer. Chem. J.*, **31**, 642 (1904); **29**, 352 (1903).

A Grignard solution prepared in the usual way from bromobenzene (80 g) and magnesium (12 g) in ether (750 ml) is treated gradually with benzylideneacetophenone (54 g), and the mixture obtained is poured into cold dilute sulfuric acid. **ω,ω-Diphenylpropiophenone** then separates and after recrystallization from ethanol forms colorless needles, m.p. 96° (yield 90%).

The diphenylpropiophenone reacts normally with further phenylmagnesium bromide, giving 1,1,3,3-tetraphenyl-1-propanol, m.p. 95–96°:[189]

$$(C_6H_5)_2CHCH_2COC_6H_5 + C_6H_5MgBr \longrightarrow (C_6H_5)_2CHCH_2C(C_6H_5)_2OH$$

Some aliphatic ketones are known that do not add methylmagnesium halides but react like compounds containing active hydrogen, as in the following example:[190]

$$(C_2H_5)_3CCOCH_3 + CH_3MgI \longrightarrow (C_2H_5)_3CC(OMgI){=}CH_2 + CH_4$$

b. Treatment of Grignard reagents with esters

Tertiary alcohols are also formed by treatment of carboxylic esters with Grignard reagents:

$$RCOOR' + R''MgX \longrightarrow R'OCRR''OMgX \xrightarrow[-R'OMgX]{+R''MgX}$$
$$RR''R''COMgX \longrightarrow RR''R''COH$$

Fewer synthetic variations are possible than with ketones because the two groups introduced by the Grignard reagent must be identical, but the method is nevertheless sometimes preferable as esters are often cheaper and more accessible than ketones or aldehydes. Side reactions seldom occur and yields tend to be satisfactory.

Bachmann and Hetzner[191] obtained **triphenylmethanol**, m.p. 161–162°, in 90% yield by adding ethyl benzoate in dry benzene during 1 h to phenylmagnesium bromide in anhydrous ether, cooled in water, in such a way that the mixture boils gently. After a final 1 hour's heating on a steam-bath the solution is cooled and hydrolysed by ice and sulfuric acid.

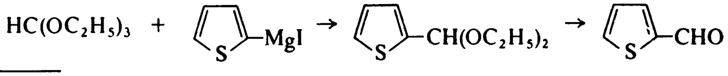
With formic esters, but only with these esters, the reaction can be stopped at the first stage. Hydrolysis of the adducts then leads to aldehydes, *e.g.*:

$$HCOOC_2H_5 + RMgX \longrightarrow RCH(OC_2H_5)OMgX \xrightarrow{H_2SO_4}$$
$$RCH(OC_2H_5)OH \longrightarrow RCHO$$

Orthoesters react very smoothly with Grignard reagents, yielding ketones:

$$RC(OC_2H_5)_3 + R'MgX \xrightarrow{-C_2H_5OMgX} RR'C(OC_2H_5)_2 \xrightarrow{+H_2O} RR'CO$$

In accord with this, orthoformic esters afford aldehydes, *e.g.*, **2-thiophenecarbaldehyde:**[192]



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[189] E. P. Kohler, *Amer. Chem. J.*, **31**, 651 (1904).

[190] F. C. Whitmore and C. E. Lewis, *J. Amer. Chem. Soc.*, **64**, 2964 (1942).

[191] W. E. Bachmann and H. P. Hetzner, *Org. Syn.*, **23**, 98 (1943).

[192] E. Grishkevich-Trochimovski, *J. Russ. Phys. Chem. Soc.*, **43**, 204 (1911); E. Grishkevich-Trochimovski and I. Matzurevich, *J. Russ. Phys. Chem. Soc.*, **44**, 570 (1912); *Chem. Abstr.*, **6**, 223, 2406 (1912).

Ethyl orthoformate (38 g) is added with cooling to a Grignard solution prepared from 2-iodothiophene (53 g) and magnesium (6.6 g) in anhydrous ether (65 ml), and the mixture is heated under reflux for 6 h, cooled, and added to ammonium chloride solution in a separatory funnel. After thorough shaking, the layers are separated, and the ethereal solution is shaken again with ammonium chloride solution and then with water and dried over calcium chloride. Distillation in a vacuum affords a forerun of unchanged orthoester and then 2-thiophenecarbaldehyde diethyl acetal as a colorless oil (24 g, 51 %), boiling at 97–102°/15 mm.

The acetal is hydrolysed by boiling dilute hydrochloric acid; distillation in steam, extraction of the distillate with ether, washing of the extract with water, drying, and fractionation then give 2-thiophenecarbaldehyde, b.p. 192°.

Carbonic esters constitute a special case: they give tertiary alcohols containing three identical groups, *e.g.*:

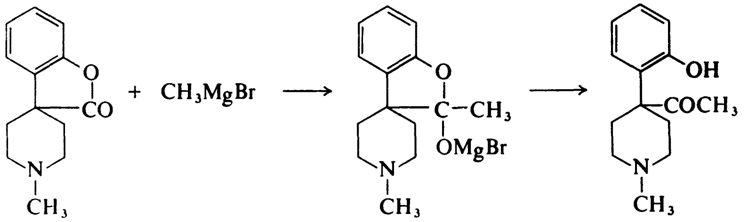
$$CO(OC_2H_5)_2 + 3C_2H_5MgBr \xrightarrow[\substack{-2C_2H_5OMgBr \\ -MgBr(OH)}]{+H_2O} (C_2H_5)_3COH$$

1,1-Diethyl-1-propanol (triethylcarbinol) can also be prepared conveniently from a propionic ester and ethylmagnesium bromide, but pure propionic esters, free from homologs, are by no means cheap, so that **1,1-diethyl-1-propanol** is at least as well obtained by the above reaction:[193]

Magnesium turnings (107 g) and anhydrous ether (800 ml) are placed in a three-necked flask (3-l capacity) fitted with a dropping funnel, stirrer, and reflux condenser, then a little (5 ml) ethyl bromide is added without stirring. When the reaction has started, a mixture of ethyl bromide (480 g) and ether (1 l) is run in at a rate such that the mixture boils continuously (this requires about 2 h). The whole is stirred for a further 15 min, diethyl carbonate (156 g) in ether (200 ml) is run in with vigorous stirring during about 3 h, so that again the mixture boils continuously. Finally the whole is stirred for a further hour on the water-bath, after which it is added with frequent shaking to ice (1500 g) and a solution of ammonium chloride (300 g) in water (600 ml) placed in a large flask (5 l). The ether layer is separated and the salt solution is extracted with two portions (each 500 ml) of ether (recovered ether may be used). The solvent is removed from the ethereal solutions, and the crude product is dried over potassium carbonate (10 g) and distilled. The fraction boiling at 139–142° contains the product and is collected separately. Treatment of the forerun with anhydrous potassium carbonate and redistillation gives a further fraction (25 g) boiling at 139–142°, and repetition of the process gives a third fraction (20 g). The total yield then amounts to 125–135 g (82–88 %).

Higher homologs, up to triheptylcarbinol, can be obtained in the same way in similarly good yields.

Reaction of lactones with the Grignard reagent proceeds as follows:



For further details see Kägi and Miescher.[194]
Phthalic anhydride affords dimethylphthalide.

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[193] W. W. Moyer and C. S. Marvel, *Org. Syn.*, Coll. Vol. 2, 602 (1943).

[194] H. Kägi and K. Miescher, *Helv. Chim. Acta*, **32**, 2489 (1949).

c. Treatment of Grignard reagents with aldehydes

Treatment of aldehydes with Grignard reagents affords secondary alcohols in accord with the following scheme of addition:

$$RCHO + R'MgX \longrightarrow RR'CHOMgX \longrightarrow RR'CHOH$$

For example, Coburn[195] describes the preparation of 3-penten-2-ol[196] in 85% yield on addition of an ethereal solution of crotonaldehyde dropwise with stirring and cooling to an ethereal solution of methylmagnesium chloride (from magnesium and methyl chloride):

$$CH_3MgCl + CH_3CH{=}CHCHO \longrightarrow CH_3CH{=}CHCH(CH_3)OH$$

Correspondingly, primary alcohols are formed from formaldehyde and a Grignard reagent:

$$CH_2O + RMgX \longrightarrow RCH_2OH$$

Newman and Wotiz[196] used this reaction to synthesize 2-heptyn-1-ol, the requisite Grignard reagent being obtained from 1-hexyne and ethylmagnesium bromide:

$$CH_3[CH_2]_3C{\equiv}CH + C_2H_5MgBr \longrightarrow CH_3[CH_2]_3C{\equiv}CMgBr + C_2H_6$$

Reaction of Grignard reagents with compounds containing active hydrogen, as with 1-hexyne in the preceding case, is quite general. As one equivalent of hydrocarbon is formed per active hydrogen atom, the amount of methane evolved on treatment with methylmagnesium iodide has been used to determine the number of active hydrogen atoms in a compound (the Zerevitinov method), although this has now been superceded by nmr spectroscopy that gives so much additional information.

$$ROH + CH_3MgI \longrightarrow ROMgI + CH_4$$

The 2-heptynylmagnesium bromide obtained in this way affords the 2-heptyn-1-ol on reaction with formaldehyde:

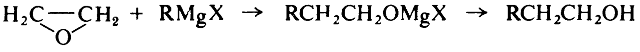
$$CH_3[CH_2]_3C{\equiv}CMgBr + CH_2O \longrightarrow CH_3[CH_2]_3C{\equiv}CCH_2OH$$

1-Hexyne (82 g, 1 mole) in anhydrous ether (300 ml) is added slowly to ethylmagnesium bromide (1.1 moles) in ether (300 ml). The mixture is heated under reflux for 6 h, then cooled in an atmosphere of nitrogen, after which gaseous formaldehyde is led in with nitrogen at a rate such that the mixture boils gently. The exothermal reaction ceases when one equivalent of formaldehyde has reacted. The usual working up affords **2-heptyn-1-ol,** b.p. 93.6°/22 mm, in 82% yield (92 g).

The formaldehyde for this reaction is prepared from paraformaldehyde: dry nitrogen is passed into a flask containing paraformaldehyde (dried for at least 2 weeks over phosphoric oxide) and heated at 180° (bath). This method is preferable to the older method of Grignard and Tissier[197] in which trioxymethylene was brought into reaction with the Grignard reagent; the latter is slow, usually requiring several days, and yields are not particularly satisfactory. Paraldehyde cannot be used for Grignard syntheses in the same way as trioxymethylene, and it is depolymerized by distillation with 5% of N-sulfuric acid shortly before use.

d. Treatment of Grignard compounds with oxirane (ethylene oxide) or carbon dioxide

Grignard reagents react with oxirane (ethylene oxide) as follows:



$$\underset{O}{H_2C{-}CH_2} + RMgX \rightarrow RCH_2CH_2OMgX \rightarrow RCH_2CH_2OH$$

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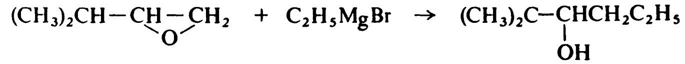
[195] E. R. Coburn, *Org. Syn.*, **27**, 65 (1947).

[196] M. S. Newman and J. H. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1294 (1949).

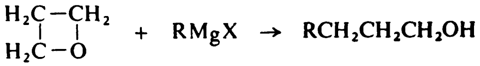
[197] V. Grignard and L. Tissier, *C. R. Hebd. Séances Acad. Sci.*, **134**, 107 (1902).

The reaction thus affords primary alcohols with the chain lengthened by two carbon atoms; for example, hexyl alcohol has been prepared in 60% yield from butylmagnesium bromide and oxirane.[198] Malinovski and Konevichev[199] treated 2-isopropyloxirane with ethylmagnesium bromide and obtained 2-methyl-3-hexanol:



$$(CH_3)_2CH-\underset{O}{CH-CH_2} + C_2H_5MgBr \rightarrow (CH_3)_2C-\underset{OH}{C}HCH_2C_2H_5$$

Oxetane can be used quite analogously for synthesis of primary alcohols in which the chain has been lengthened by three carbon atoms:



Searles[200] gives general directions for this reaction: A solution of oxetane in three times its quantity of anhydrous ether is added with stirring to a cold ethereal solution of the Grignard reagent. At the end of the initial weakly exothermic reaction, during which a white precipitate is formed, the mixture is heated for an hour under reflux. Then benzene is added, the ether is distilled off through a Vigreux column, and the residue is heated for 4 h, then cooled and immediately hydrolysed by saturated ammonium chloride solution.

Reaction of Grignard reagents with carbon dioxide, in which low temperatures and thorough mixing are important, leads to the derived carboxylic acids:

$$RMgX + CO_2 \longrightarrow RCOOH$$

The ethereal solution of the Grignard reagent may be treated at 10° to −10° with gaseous carbon dioxide[201] or it may be poured on an excess of powdered solid carbon dioxide.[202] Gaseous carbon dioxide under pressure must be used with certain tertiary Grignard reagents.[203]

8. Syntheses by means of organo-lithium[204] or -zinc compounds (the Reformatsky synthesis[205])

Organolithium compounds react with ketones in the same way as Grignard reagents do, but are more reactive than the latter. Thus organolithium compounds can be used when Grignard reactions fail. For example, ketones that are too hindered sterically to react with the Grignard reagent can be treated with organolithium compounds,[206,207] as, for instance, diisopropyl ketone with isopropyllithium:

$$[(CH_3)_2CH]_2CO + (CH_3)_2CHLi \longrightarrow [(CH_3)_2CH]_3COLi$$

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[198] E. E. Dreger, *Org. Syn.*, **6**, 54 (1926).

[199] M. S. Malinovskii and B. N. Konevichev, *Zh. Obshch. Khim.*, **18**, 1833 (1948); *Chem. Abstr.*, **43**, 3776 (1949).

[200] S. Searles, *J. Amer. Chem. Soc.*, **73**, 124 (1951); L. Bemejo and V. G. Aranda, *An. Soc. Espan. Fis. Quim.*, **27**, 798 (1929).

[201] H. Gilman, N. John, and F. Schulze, *Org. Syn.*, Coll. Vol. 2, 425 (1943).

[202] T. L. Jacobs, S. Winstein, R. Henderson, J. Bond, J. Ralls, D. Seymour, and W. Florsheim, *J. Org. Chem.*, **11**, 233 (1946).

[203] C. T. Lester and J. R. Proffitt, Jr., *J. Amer. Chem. Soc.*, **71**, 1878 (1949).

[204] G. Wittig, *Angew. Chem.*, **53**, 241 (1940).

[205] R. L. Shriner, *Org. Reactions*, **1**, 1 (1942).

[206] G. Vavan and H. Colin, *C. R. Hebd. Séances Acad. Sci.*, **222**, 801 (1946).

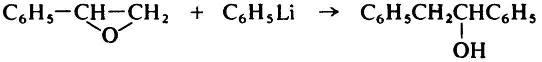
[207] E. Müller and E. Hertel, *Ann. Chem.*, **555**, 157 (1944).

The disadvantage attaching to the lithium compounds is their great sensitivity to oxygen, so that their reactions must be effected under nitrogen. Alkyl and aryl derivatives of lithium are usually prepared by treating the organic halide with the metal in an inert solvent,[208] as described in detail on page 755. The ethereal solutions can rarely be kept unchanged for a long time and must thus be used immediately after preparation; they soon decompose with formation of lithium alkoxides. Solutions in benzene or cyclohexane, however, can be used months later. Oxygen, moisture, and carbon dioxide must be excluded. The concentration of a solution is determined by running an aliquot part into water and titrating the lithium hydroxide with 0.1N-hydrochloric acid to Methyl Orange. The following examples illustrate the technique used for adding an organolithium compound to a carbonyl group.

Braude and Coles[209] described the preparation of **cyclohexenyldiphenylmethanol:** Freshly distilled, pure 1-chlorocyclohexene is added slowly, with stirring, to a suspension of lithium pieces in anhydrous ether under nitrogen, and the mixture is stirred overnight. Then an ethereal solution of benzophenone is added at 0°, the whole is stirred for 18 h, and the product is hydrolysed by saturated ammonium chloride solution.

2,6-Dimethoxybenzaldehyde was prepared by Wittig as follows:[210] When a mixture of resorcinol dimethyl ether (13.8 g, 0.1 mole) and phenyllithium (0.1 mole) in anhydrous ether (100 ml) is kept at room temperature for 60 h, the lithio derivative separates as large transparent crystals. Then *N*-methylformamide (13.5 g), dissolved in anhydrous ether (100 ml), is dropped in, which causes the mixture to boil. When the main reaction has ceased, the mixture is set aside for 0.5 h, then poured into an excess of dilute sulfuric acid. The ether layer is separated, dried, and freed from solvent. The residue is distilled at 13 mm until the vapor temperature reaches 130°. The residue in the distillation flask crystallizes from cyclohexane or much water in needles, m.p. 98–99°. The yield is 55%.

Cristol, Douglass, and Meek[211] treated 2-phenyloxirane (styrene oxide) with phenyllithium and obtained α-phenylphenethyl alcohol (1,2-diphenylethanol):



$$C_6H_5-\underset{\diagdown O \diagup}{CH-CH_2} + C_6H_5Li \rightarrow C_6H_5CH_2\underset{\displaystyle OH}{\underset{|}{C}}HC_6H_5$$

As for a Grignard reaction the Gilman test (page 879) can be used to determine the conclusion of the reaction.

A reaction of preparative importance, involving zinc, is the Reformatsky synthesis,[212] in which this metal causes an α-halo ester to react with a carbonyl compound. It is analogous to the Grignard reaction:

$$RCOCH_3 + Zn + BrCH_2COOC_2H_5 \longrightarrow BrZnOCR(CH_3)CH_2COOC_2H_5$$
$$\longrightarrow HOCR(CH_3)CH_2COOC_2H_5$$

The organozinc compound first formed is unstable; therefore the reaction is carried out in such a way that the carbonyl compound to be added to the ester is present during formation of the organozinc derivative. The primary products are the β-hydroxy esters, as illustrated (a hydracrylic ester from

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[208] K. Ziegler, H. Colonius, and H. Zeiser, *Ann. Chem.*, **479**, 147 (1930); **485**, 185 (1931); L. Gattermann, "Die Praxis des organischen Chemikers," 35th ed, Verlag de Gruyter & Co, Berlin, 1953, p. 320.

[209] E. A. Braude and J. A. Coles, *J. Chem. Soc.*, **1950**, 2014.

[210] G. Wittig, *Angew. Chem.*, **53**, 243 (1940).

[211] S. J. Cristol, J. R. Douglass, and J. S. Meek, *J. Amer. Chem. Soc.*, **73**, 816 (1951).

[212] S. Reformatsky, *Ber. Deut. Chem. Ges.*, **20**, 1210 (1887).

bromoacetic ester), but these lose water to give α,β-unsaturated esters, often spontaneously. Thus reaction of ethyl bromoacetate with a ketone gives a product of type $CRR'{=}CHCOOC_2H_5$ and with an aldehyde gives one of type $CHR{=}CHCOOC_2H_5$, whilst higher α-bromo esters give products of type $CRR'{=}CR''COOC_2H_5$.[213]

Reformatsky syntheses are best carried out at 90–105°. The zinc may be in the form of foil that has been scratched with sandpaper. Some authors recommend granulated zinc that has been activated by hydrochloric acid[214] or heated in a round-bottomed flask with 1 part per thousand of iodine until the surface is no longer shiny.[215] Other authors recommend coppering the surface by immersion in copper sulfate solution or amalgamating the zinc.[216] (The reaction can also be carried out with amalgamated magnesium, for Colonge and Joly[217] obtained a 3-hydroxy-2-methyl-3-propylhexanoic ester in 70% yield from 4-heptanone and an α-bromopropionic ester.) If the bromoacetic ester is replaced by the cheaper chloroacetic ester, the reaction should be initiated by a little copper powder.[216]

The following two examples illustrate the procedure.

Ethyl 3-hydroxy-3-phenylpropionate:[205,218] Purified zinc dust or granulated zinc (40 g, 0.62 mole) is placed in a three-necked flask (500-ml capacity) fitted with a stirrer, dropping funnel, drying tube, and reflux condenser. A small amount (15 ml) of a solution of ethyl bromoacetate (83.5 g, 0.5 mole) and benzaldehyde (65 g, 0.61 mole) in anhydrous benzene (80 ml) and ether (20 ml) is added to the zinc, and the flask is warmed until reaction sets in. The mixture is then stirred and the remainder of the ester–aldehyde solution is added at a rate sufficient to keep the solution refluxing gently (about 1 h is required). The mixture is next boiled for a further 0.5 h, then cooled in ice and poured into ice-cold 10% sulfuric acid (300 ml) with vigorous stirring. The organic layer is separated and washed successively with ice-cold 5% sulfuric acid (two 50-ml portions), cold 10% sodium carbonate solution (25 ml), cold 5% sulfuric acid (25 ml), and water (two 25-ml portions). The acid extracts are united and shaken with ether (two 50-ml portions). Then the ether–benzene solutions are united, dried over anhydrous magnesium sulfate (5 g) or Drierite, and the solvents are evaporated. Fractionation of the residue affords ethyl 3-hydroxy-3-phenylpropionate, b.p. 151–154°/11–12 mm, 128–132°/5–7 mm, in 61–64% yield (59–62 g).

Ethyl 1-hydroxy-1-cyclohexaneacetate:[205,219] Benzene (800 ml) and toluene (700 ml) are mixed with ethyl bromoacetate (334 g, 2 moles) and cyclohexanone (196 g, 2 moles). A part (300 ml) of this solution is placed in a three-necked flask (capacity 5 l) fitted with a stirrer, dropping funnel, and reflux condenser attached to a drying tube; zinc foil (130 g, 2 moles), cleaned with sandpaper and cut into strips, is added to this batch, followed by a few crystals of iodine, and this mixture is stirred on a boiling water-bath. A vigorous reaction sets in, after which the remainder of the reaction mixture is run in at a rate sufficing to maintain refluxing. After his addition the whole is stirred for a further 2 h, the zinc dissolving almost completely. After cooling, the product is worked up by means of dilute sulfuric acid. When dried over sodium sulfate and distilled, the benzene–toluene layer affords ethyl 1-hydroxy-1-cyclohexaneacetate, b.p. 86–89°/2 mm (219–278 g, 56–71%).

A further example, the preparation of ethyl 3-hydroxy-3-phenylbutyrate from acetophenone, ethyl bromoacetate, and zinc has been described by Lindenbaum.[220]

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[213] H. Rupe and co-workers, *Ber. Deut. Chem. Ges.*, **47**, 68 (1914); J. von Braun, *Ann. Chem.*, **451**, 1, 47 (1927).

[214] E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **67**, 1432 (1945).

[215] A. Lewinsohn, *Perfum. Essent. Oil Rec.*, **15**, 45 (1924).

[216] J. A. Nieuwland and S. F. Daly, *J. Amer. Chem. Soc.*, **53**, 1842 (1931); G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, **1932**, 2461.

[217] J. Colonge and D. Joly, *Ann. Chim. (Paris)*, [11], **18**, 306 (1943).

[218] C. R. Hauser and D. S. Breslow, *Org. Syn.*, **21**, 51 (1941).

[219] S. Natelson and S. P. Gottfried, *J. Amer. Chem. Soc.*, **61**, 970 (1939).

[220] S. Lindenbaum, *Ber. Deut. Chem. Ges.*, **50**, 1270 (1917).

The objective of most Reformatsky syntheses is, however, not the hydroxy ester but the unsaturated ester. If the latter is not formed spontaneously during the synthesis, the hydroxy ester can be dehydrated by one of the methods described on pages 818-19; if so, it is often unnecessary to isolate the hydroxy ester; it suffices to heat the crude product with phosphorus oxychloride or to distil it from phosphoric oxide.

For example, after acetophenone (72 g) has been allowed to react with ethyl bromoacetate (100 g), and zinc turnings (41 g) in benzene (250 ml), the solvent is distilled off and the residue is treated with phosphorus oxychloride (20 drops). Distillation then gives **ethyl β-methylcinnamate** (80 g) as the fraction boiling at 155–165°/28 mm.[221]

The poor yields often obtained in Reformatsky syntheses are due to side reactions: for instance, the basic zinc salts may cause aldol condensation of aldehydes; and coupling of 2 molecules of the bromo ester has been observed to give the succinic ester. An indication of how to avoid these side reactions has been provided by Lipkin and Stewart.[222]

Other halides may be used in place of the bromo ester. Reaction of a propargyl halide, for example, with various carbonyl compounds gives γ,δ-acetylenic alcohols of type (6) in good yield.[223] Also the carbonyl component may be replaced by an orthoformic ester, which leads to a malonic monoester monoaldehyde acetal of type (7) in 44–58% yield.[224]

$$\underset{(6)}{\mathrm{HOCRR'CH_2C{\equiv}CH}} \qquad \underset{(7)}{\mathrm{C_2H_5OOCCHRCH(OC_2H_5)_2}}$$

Reformatsky reactions have been used in the total synthesis of various important natural products such as phytol,[225] naturally occurring polyenes,[226] and vitamin A (from β-ionylideneacetaldehyde).[227]

A note by Epstein and Sonntag[228] should be consulted for information on the steric course and stereospecificity of the Reformatsky reaction.

III. Addition to C–N multiple bonds

1. Addition of Grignard reagents[177]

Grignard reagents add to nitriles in the following manner:

$$\mathrm{RC{\equiv}N + R'MgX \longrightarrow RR'C{=}N{-}MgX}$$

Acid hydrolysis of such adducts usually leads to the corresponding ketones:

$$\mathrm{RR'C{=}N{-}MgX + H_2O \longrightarrow RR'CO + NH_3 + MgX(OH)}$$

In some cases the intermediate ketimines can be obtained[229] by hydrolysis under sufficiently mild conditions, *e.g.*, by aqueous ammonium chloride at

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[221] R. Stoermer, F. Grimm, and E. Laage, *Ber. Deut. Chem. Ges.*, **50**, 959 (1917).

[222] D. Lipkin and T. D. Stewart, *J. Amer. Chem. Soc.*, **61**, 3295 (1939).

[223] H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, **1949**, 2696.

[224] N. C. Deno, *J. Amer. Chem. Soc.*, **69**, 2233 (1947).

[225] F. G. Fischer, *Ann. Chem.*, **475**, 183 (1929).

[226] R. Kuhn and M. Hoffer, *Ber. Deut. Chem. Ges.*, **65**, 651 (1932).

[227] P. Karrer and co-workers, *Helv. Chim. Acta*, **15**, 883 (1932).

[228] W. W. Epstein and A. C. Sonntag, *Tetrahedron Lett.*, **1966**, 791.

[229] C. Moureau and G. Mignonac, *C. R. Hebd. Séances Acad. Sci.*, **156**, 1801 (1913).

a low temperature. The ketimines are then isolated as the hydrochlorides after treatment of their dry ethereal solution with dry gaseous hydrogen chloride. If the ketimine is very susceptible to hydrolysis it is advisable to use liquid ammonia for the hydrolysis.[230]

Ethereal ethylmagnesium bromide is prepared from ethyl bromide (42.3 g) and magnesium (9 g) in anhydrous ether (150 ml) and is treated slowly with a solution of cyclopropyl cyanide (10.35 g) in three times its volume of ether. The mixture is heated under gentle reflux for 12 h, then dropped slowly from a dropping funnel into liquid ammonia (300 ml) that is protected from moisture by a basic drying agent. The whole is shaken occasionally during the next 20 h. Anhydrous ether (200 ml) is next added and the mixture is filtered through a Büchner funnel protected from moisture. The ammonia is removed from the filtrate in a stream of dry air. The residue is diluted somewhat with ether, and dry gaseous hydrogen chloride is led in. The precipitated **cyclopropyl ethyl ketimine hydrochloride** is purified by dissolution in glacial acetic acid (50 ml) containing acetic anhydride (5 ml) and reprecipitation by anhydrous ether. The yield is 48% (10 g).

Fieser and Seligman[231] describe the preparation of a very stable ketimine. The Grignard reagent prepared from 1-bromo-8-methylnaphthalene (66 g) and the equivalent of magnesium is mixed with *o*-chlorobenzonitrile (26 g) in benzene and heated with stirring for 16 h under reflux. Then dilute hydrochloric acid is added and the ***o*-chlorophenyl 8-methyl-1-naphthyl ketimine hydrochloride** is filtered off and washed successively with cold water, alcohol, and ether. The yield amounts to 60 g. This ketimine is stable to hot hydrochloric acid of various concentrations.

In general it is more difficult to add Grignard reagents to nitriles than to the analogous oxygen-containing compounds, so that long heating or use of a high-boiling solvent is required. Shriner and Turner[232] described the preparation of **alkyl phenyl ketones** from aliphatic nitriles and phenylmagnesium bromide in which it proved advisable to use a four-fold excess of the Grignard reagent.

A solution of an aliphatic nitrile (0.25 mole) in anhydrous ether (100 ml) is run during 15 min into a stirred phenylmagnesium bromide solution prepared from magnesium (25 g) and bromobenzene (160 g) in anhydrous ether (300 g), and the whole is stirred for 1 h and then set aside overnight. The solution is next poured on ice (500 g) and concentrated hydrochloric acid (300 ml). The aqueous layer is separated and heated under vigorous reflux for 1 h; after cooling, it is extracted four times with ether (200-ml portions). These extracts are dried over calcium chloride and are worked up by removal of the ether and distillation of the residue in a vacuum. The product is the ketone.

Secondary amines are obtained on adding a Grignard reagent to an aldimine (*i.e.*, to a Schiff's base):

$$\text{RMgX} + \text{R'N}{=}\text{CHR''} \longrightarrow \text{XMg—NR'—CHRR''} \longrightarrow \text{R'NH—CHRR''}$$

The preparation of ***N*-ethyl-(1-phenylbutyl)amine** by Campbell and his co-workers[233] illustrates this type of reaction: *N*-Benzylideneethylamine (66.5 g, 0.5 mole) in anhydrous ether (50 ml) is added during 1.5–2 h to propylmagnesium bromide (1 mole) in anhydrous ether (250 ml). The mixture is heated under reflux for some hours, set aside overnight, and poured, for hydrolysis, on ice and hydrochloric acid.

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[230] E. F. Cornell, *J. Amer. Chem. Soc.*, **50**, 3311 (1928); J. B. Cloke, L. H. Baer, J. M. Robbins, and G. E. Smith, *J. Amer. Chem. Soc.*, **67**, 2155 (1945); J. B. Cloke, *J. Amer. Chem. Soc.*, **62**, 117 (1940).

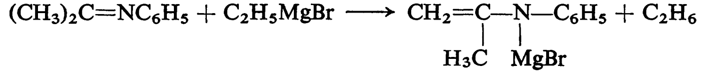
[231] L. F. Fieser and A. M. Seligman, *J. Amer. Chem. Soc.*, **61**, 141 (1939).

[232] R. L. Shriner and T. A. Turner, *J. Amer. Chem. Soc.*, **52**, 1267 (1930).

[233] K. N. Campbell, C. H. Helbing, M. D. Florowski, and B. K. Campbell, *J. Amer. Chem. Soc.*, **70**, 3868 (1948); H. Gilman and J. Mortin, *J. Amer. Chem. Soc.*, **70**, 2514 (1948); R. B. Moffett and W. M. Hoehn, *J. Amer. Chem. Soc.*, **69**, 1792 (1947).

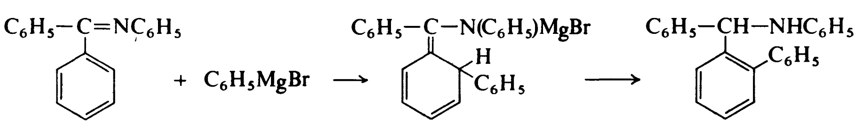
Only for the simplest azomethines, such as *N*-benzylidenemethylamine, and very reactive Grignard reagents, such as methylmagnesium bromide, do equimolar amounts of the reactants give yields as high as 60–90%. In other cases a two-fold excess of the Grignard reagent is preferable, as in the experiment just described.

Grignard reagents do not add to ketimines in the manner described above.[234] Aliphatic and alkyl aryl ketone anils react as if they existed in the tautomeric enamine form:



$$(CH_3)_2C{=}NC_6H_5 + C_2H_5MgBr \longrightarrow CH_2{=}\underset{H_3C}{C}{-}\underset{MgBr}{N}{-}C_6H_5 + C_2H_6$$

With benzophenone anil and phenylmagnesium bromide 1,4-addition occurs (yield 42%):[235]

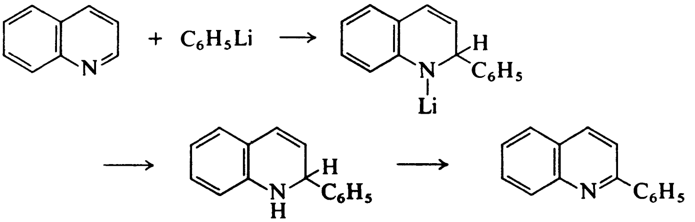


Isocyanates[236] and thioisocyanates[237] add Grignard reagents smoothly (80–90% yields) as follows:

$$RMgX + R'NCO \longrightarrow XMgOCR{=}NR' \longrightarrow RCONHR'$$

The products are the derived amides or thioamides.

Organolithium compounds can also be added at a C=N double bond. According to Ziegler and his co-workers[208] phenyllithium and quinoline give 1,2-dihydro-2-phenylquinoline, which can be dehydrogenated by nitrobenzene to 2-phenylquinoline:



2. Addition of CH-acidic compounds

Nitromethane adds to *N*-benzylideneaniline by formation of a carbon–carbon bond to the doubly bonded atom:[238]

$$C_6H_5CH{=}NC_6H_5 + CH_3NO_2 \longrightarrow O_2NCH_2CH(C_6H_5)NHC_5H_5$$

and other 1-nitroalkanes add analogously at the 1-carbon atom.

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[234] W. F. Short and J. S. Watt, *J. Chem. Soc.*, **1930**, 2293.

[235] H. Gilman, J. E. Kirby, and C. R. Kinney, *J. Amer. Chem. Soc.*, **51**, 2252 (1929).

[236] R. B. Carlin and L. O. Smith, Jr., *J. Amer. Chem. Soc.*, **69**, 2007 (1947).

[237] G. Alliger, G. E. P. Smith, Jr., E. L. Carr, and H. P. Stevens, *J. Org. Chem.*, **14**, 962 (1949).

[238] N. J. Leonhard, G. W. Leubner, and E. H. Burk, *J. Org. Chem.*, **15**, 979 (1950); C. D. Hurd and J. S. Strong, *J. Amer. Chem. Soc.*, **72**, 4813 (1950).

***N*-Phenyl-α-(nitromethyl)benzylamine:** *N*-Benzylideneaniline (100 g, 0.55 mole) and nitromethane (100 g, 1.64 moles) are heated together in anhydrous ethanol (50 ml) under reflux for 6 h. The solvent and excess of nitromethane are then removed in a vacuum by a current of air at room temperature. The residue is digested with 95% ethanol and collected. Washing it with cold alcohol several times leaves a 79% yield (106 g) of air-dry material, m.p. 85–87°. When recrystallized from 95% ethanol this forms yellow prisms, m.p. 86–87.5°.

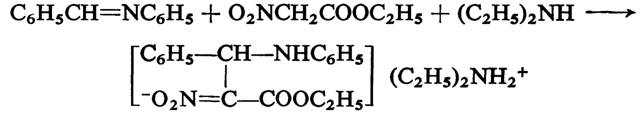
***N*-Phenyl-α-(1-nitroethyl)benzylamine:** *N*-Benzylideneaniline (5 g, 27.6 mmoles), nitroethane (6.2 g, 82.6 mmoles), 95% ethanol (5 ml), and diethylamine (0.6 g, 8.2 mmoles) are heated together under reflux for 15 min. Working up as in the preceding example affords yellow prisms, m.p. 100–102° (2.1 g, 30%).

Use of nitropropane as above, but for 2 h under reflux, affords ***N*-phenyl-α-(1-nitropropyl)-benzylamine** as yellow prisms, m.p. 128–130° (55% yield).

***N*-Phenyl-β-nitro-α-phenylphenethylamines:**[239] When *N*-benzylideneaniline (9.1 g), ω-nitrotoluene (10.3 g), and diethylamine (0.5 ml) are kept for 10 days in a refrigerator, this product separates in 91% yield; after two recrystallizations from light petroleum it has m.p. 124° (dec.).

ω-Nitrotoluene has also been added to *N*-benzylidene- and *m*-nitrobenzylidene-*p*-toluidine and to *N*-(*o*-nitrobenzylidene)- and *N*-(*p*-nitrobenzylidene)-aniline.

Dornow and Frese[240] studied the addition of ethyl nitroacetate to Schiff's bases and, adding an equimolar amount of diethylamine, obtained reactions of the following type:

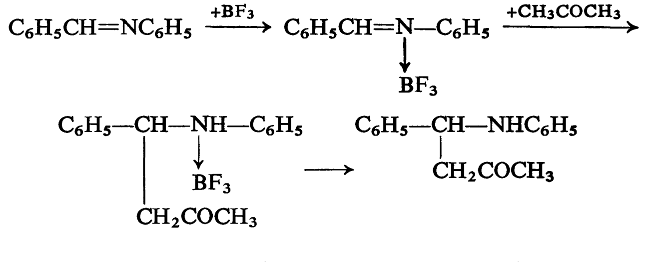


$$C_6H_5CH{=}NC_6H_5 + O_2NCH_2COOC_2H_5 + (C_2H_5)_2NH \longrightarrow$$

$$\left[\begin{array}{c} C_6H_5\text{—}CH\text{—}NHC_6H_5 \\ | \\ {}^-O_2N{=}C\text{—}COOC_2H_5 \end{array}\right] (C_2H_5)_2NH_2^+$$

These adducts are, however, very unstable and even in the solid state can be kept only for a short time; two molecules of the adduct very readily form the 3-aryl-2,4-dinitroglutaric ester.

Ketones can be added to *N*-benzylideneaniline under the influence of boron trifluoride. Snyder, Kornberg, and Romig[241] formulated the reaction as follows:



$$C_6H_5CH{=}NC_6H_5 \xrightarrow{+BF_3} \begin{array}{c} C_6H_5CH{=}N\text{—}C_6H_5 \\ \downarrow \\ BF_3 \end{array} \xrightarrow{+CH_3COCH_3}$$

$$\begin{array}{l} C_6H_5\text{—}CH\text{—}NH\text{—}C_6H_5 \\ \quad\;\; | \qquad\;\; \downarrow \\ \quad\;\; | \qquad BF_3 \\ \quad CH_2COCH_3 \end{array} \longrightarrow \begin{array}{c} C_6H_5\text{—}CH\text{—}NHC_6H_5 \\ | \\ CH_2COCH_3 \end{array}$$

Boron trifluoride etherate (2 ml) is added to *N*-benzylideneaniline (2.86 g) in anhydrous ether (155 ml), and the resulting precipitate is filtered off. When the filtrate is kept for several hours in a closed vessel yellow needles, m.p. 135–145° (dec.), separate and these are collected. This adduct (1.5 g) is dissolved in acetone (25 ml), which causes the mixture to become slightly warm. After a few minutes water is added and the mixture is cooled. **4-Phenyl-4-(phenylamino)-2-butanone** then crystallizes as colorless needles and after three recrystallizations from aqueous ethanol melts at 87–88° (yield 0.5 g).

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[239] A. Dornow and F. Boberg, *Ann. Chem.*, **578**, 94 (1952).

[240] A. Dornow and A. Frese, *Ann. Chem.*, **578**, 112 (1952).

[241] H. R. Snyder, H. A. Kornberg, and J. R. Romig, *J. Amer. Chem. Soc.*, **61**, 3556 (1939).

It is unnecessary to isolate the boron trifluoride complex, for the following procedure can also be used. A solution of *N*-benzylideneaniline (3.6 g) in four equivalents of acetone is cooled in ice, and then boron trifluoride etherate (2.8 g) is added. After being kept for 5 min in ice, this mixture is at once poured on to ice + water (100 ml). The oil that separates soon crystallizes.

Not only acetone, but also ethyl methyl ketone, isobutyl methyl ketone, methyl pentyl ketone, 4-methyl-2-hexanone, acetophenone, or cyclopentanone may be added to the base.

Heating a Schiff's base with diethyl malonate for 0.5 h in the presence of catalytic amounts of piperidine (or acetic acid, hydrochloric acid, or ammonium chloride) in closed ampoules affords the diethyl [(arylamino)benzyl]malonate in 50% yield.[242]

When *N*-benzylidenealkylamines are treated with cyanoacetic esters the reaction proceeds beyond addition and yields monoester monoamide of 1,3-dicyano-2,4-diphenyl-1,3-cyclo butanedicarboxylic acid.[243]

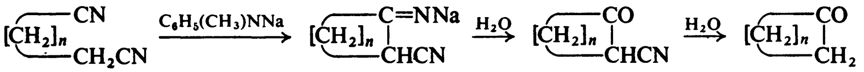
Boyd and Leshin[244] treated a number of aromatic isocyanates with nitromethane and with ethyl nitroacetate and obtained the derived amides:

$$\mathrm{ArN{=}CO + O_2NCH_2COOC_2H_5 \longrightarrow ArNH{-}CO{-}CH(NO_2)COOC_2H_5}$$

The reaction of ethyl nitroacetate is effected in the presence of an equimolar amount of potassium carbonate. For the reaction of nitromethane with *o*-chlorophenyl or *o*-tolyl isocyanate the nitromethane must be converted by metallic sodium into its sodio derivative.

3. Addition of nitriles (Thorpe reaction)[146]

The method for cyclization of nitriles introduced by Ziegler, Eberle, and Ohlinger[106c] is suitable particularly for the synthesis of large-ring systems. It involves treatment of dinitriles with sodio-*N*-methylaniline in an atmosphere of nitrogen:



The reaction is carried out in solution in an ether (diethyl, diisopropyl, or di-*n*-propyl ether), at a temperature that must not exceed 100°. To induce intramolecular cyclization at the expense of intermolecular polymerization, the dinitrile is added in a continuous but slow stream to the stirred reaction medium (the Ruggli–Ziegler dilution principle). The decisive factors are the stationary concentration and thus the rate of reaction of the reactants; high dilution favours intramolecular cyclization and disfavors intermolecular chain formation, and this dilution is achieved by adding the cyclizing material gradually into a relatively small reaction space.

According to Ziegler and his co-workers,[245] the condensing agent is best prepared by the reaction:

$$\mathrm{2C_6H_5NHCH_3 + C_6H_5CH{=}CH_2 + 2Na \longrightarrow 2C_2H_5NNaCH_3 + C_6H_5CH_2CH_3}$$

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[242] N. S. Koslov and A. D. Nikolaev, *Zh. Obshch. Khim.*, **33**, 2387 (1963); *Chem. Abstr.*, **59**, 8642 (1963).

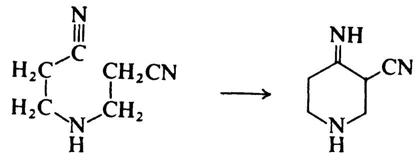
[243] H. Böhme and S. Ebel, *Chem. Ber.*, **98**, 1819 (1965).

[244] R. N. Boyd and R. Leshin, *J. Amer. Chem. Soc.*, **75**, 2762 (1953).

[245] K. Ziegler, L. Jakob, H. Wollthan, and A. Wenz, *Ann. Chem.*, **511**, 69 (1934).

The ethylbenzene formed does not interference with subsequent reactions. The condensing agent is sensitive to air, so that all operations must be conducted with an atmosphere of pure nitrogen. For each 0.1 mole of the dinitrile, 1.5 l of a 0.60–0.67 molar solution of sodio-*N*-methylaniline containing a 25% excess of *N*-methylaniline is used;[246] the solution is heated and stirred under reflux in a nitrogen atmosphere while the dinitrile is run in continuously during 72 h. The subsequent hydrolysis to the cyclic ketone is carried out as indicated in the scheme above.

Bachman and Barker[247] cyclized bis-(2-cyanoethyl)amine in a simple reaction, obtaining a 70% yield of **4-iminopiperidine-3-carbonitrile:**



Dioxan (400 ml), distilled over sodium, is placed in a three-necked flask fitted with a gas inlet tube, a reflux condenser carrying a calcium chloride tube, and an efficient stirrer. Naphthalene (25 g), sodium (2 g), and bis-(2-cyanoethyl)amine (50 g) are added and the air is replaced by nitrogen. The mixture is heated, with stirring, on a water-bath for several hours, then poured whilst hot into benzene (1 l), in which the cyclic compound is insoluble. After recrystallization from ethanol, the 4-iminopiperidine-3-carbonitrile melts at 187–188° with decomposition.

4. Addition of hydrogen cyanide or diazomethane

Von Miller and Plöchl[248] found that hydrogen cyanide added to anils thus:

$$HCN + C_6H_5N{=}CHR \longrightarrow C_6H_5NHCHRCN$$

For this purpose an aldehyde, *e.g.*, propionaldehyde, is added to aniline in an excess of ether, the water that separates in the ensuing very vigorous reaction being later separated. When pure hydrogen cyanide is added to the ethereal solution an extremely vigorous reaction sets in. The mixture is set aside for a short time, then the ether and the excess of hydrogen cyanide are evaporated. This leaves the amino nitrile as a thick oil, which crystallizes in a few days, or faster if cooled.

Alternatively, hydrogen cyanide and then, dropwise, the aldehyde are added to the aniline in ether, whereupon water separates in a resulting vigorous reaction. Or, if the anil is available in advance, it is simply treated with hydrogen cyanide in ether.

Hydrolysis of the amino nitrile produced affords the α-(phenylamino)alkanoic acid.

A series of Schiff's bases from various 1,2-diamines and aromatic or heterocyclic aldehydes add hydrogen cyanide at both C=N bonds.[249]

Hydrogen cyanide adds to hydrazones in a similar reaction.[248] Moreover, it adds analogously to oximes, for Hurd and Longfellow[250] found that propionaldehyde or butyraldehyde react with hydroxylamine hydrochloride, sodium cyanide, and sodium dihydrogen phosphate in aqueous solution to afford

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[246] K. Ziegler and R. Aurnhammer, *Ann. Chem.*, **513**, 55 (1934).

[247] G. B. Bachman and R. S. Barker, *J. Amer. Chem. Soc.*, **69**, 1535 (1947).

[248] W. von Miller and J. Plöchl, *Ber. Deut. Chem. Ges.*, **25**, 2020 (1892); **26**, 1545 (1893); **27**, 1281 (1894); H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Amer. Chem. Soc.*, **75**, 1933 (1953).

[249] A. E. Frost and H. H. Freedman, *J. Org. Chem.*, **24**, 1905 (1959).

[250] C. D. Hurd and J. M. Longfellow, *J. Org. Chem.*, **16**, 761 (1951).

good yields of, respectively, 2-(hydroxyamino)butyronitrile and 2-(hydroxyamino)valeronitrile.

$$CH_3CH_2CH{=}NOH + HCN \longrightarrow CH_3CH_2CH(CN)NHOH$$

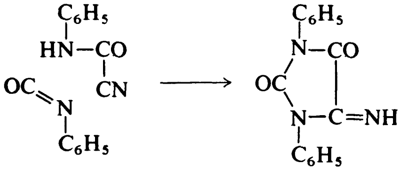
This reaction is, however, not generally applicable.

According to Hurd and Longfellow,[250] the best treatment for acetaldoxime and heptanal oxime is to treat the oxime with an excess of hydrogen cyanide in the presence of a molar amount of pyridine.

A trace of an alkaline condensing agent, best pyridine, suffices for addition of hydrogen cyanide to isocyanates:

$$C_6H_5NCO + HCN \longrightarrow C_6H_5NHCOCN$$

The resulting cyanoformanilide reacts with a second molecule of phenyl isocyanate, affording 1,3-diphenylparabanic acid 4-imide (5-imino-1,3-diphenylimidazolidine-2,4-dione):[251]



Petersen[252] added hydrogen cyanide to diisocyanates but found that the bisycanoformamides produced were cleaved with great ease to regenerate the components, even at temperatures as low as 120–130°. He describes the reaction of hexamethylene diisocyanate to give ***N*,*N*′-bis(cyanoformyl)hexamethylenediamine** as follows:[252]

$$OCN[CH_2]_6NCO + 2HCN \rightleftarrows NCCONH[CH_2]_6NHCOCN$$

Hexamethylene diisocyanate (252 g) in toluene (660 ml) is treated with anhydrous hydrogen cyanide (120 ml). The mixture is thoroughly cooled, pyridine (10 ml) is added, and the whole is set aside. The temperature rises, slowly at first, but as soon as the product separates, then instantaneously to 45°. Next day the slurry that has been formed is washed from the flask in toluene and filtered. The crystals are washed free from hydrogen cyanide by toluene and, for purification, dissolved in warm ethyl acetate (750 ml), to which toluene (1500 ml) is added. This affords white needles (290 g), m.p. 102°.

A number of anils add diazomethane, yielding 1,2,3-triazolines.[253]

5. Reactions of isocyanides[32d]

With certain reactants isocyanides undergo three-component condensation and with others four-component condensation.[32d]

Three-component addition occurs when isocyanides react with the combinations carboxylic acid–carbonyl compound, hydrogen azide–carbonyl compound, tropylium salt–water, or two molecules of hydrogen thiocyanate.

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[251] W. Dieckmann and H. Kämmerer, *Ber. Deut. Chem. Ges.*, **40**, 3737 (1907).

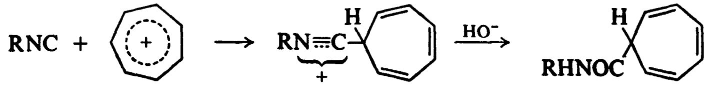
[252] S. Petersen, *Ann. Chem.*, **562**, 211, 220 (1949).

[253] P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **26**, 2331 (1961).

When aldehydes or ketones react with aryl isocyanides in the presence of a carboxylic acid, α-acyloxy carboxanilides are formed (the Passerini reaction);[146b]

$$\mathrm{RR'CO + ArNC + R''COOH \longrightarrow R''COOCRR'CONHAr}$$

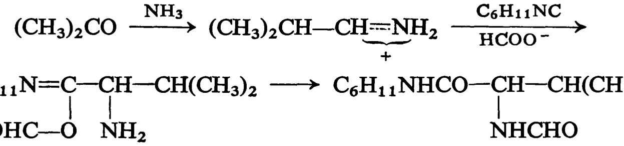
Tropylium ions unite with isocyanides to form nitrilium ions, which with water yield *N*-substituted 1*H*-cycloheptatrienecarboxamides:



Among four-component condensations is that of amines, carbonyl compounds, certain acids (HO^-, HSe^-, $S_2O_3^{2-}$, N_3^-, NCO^-, NCS^-, and $RCOO^-$), and isocyanides, which leads to α-amino acid derivatives:

$$\mathrm{R^1R^2CO + R^3R^4NH \longrightarrow R^1R^2\overset{+}{C{=}N}R^3R^4 \xrightarrow{RNC,\ HO^-} RNHCOCR^1R^2NR^3R^4}$$

Four-component condensation with carboxylic acids is accompanied by intramolecular acyl migration and formation of α-(acylamino) carboxamides:[32d]



$$\mathrm{(CH_3)_2CO \xrightarrow{NH_3} (CH_3)_2CH{-}\underset{+}{CH{=}NH_2} \xrightarrow[HCOO^-]{C_6H_{11}NC}}$$

$$\mathrm{C_6H_{11}N{=}\underset{OHC-O}{C}{-}\underset{NH_2}{CH}{-}CH(CH_3)_2 \longrightarrow C_6H_{11}NHCO{-}\underset{NHCHO}{CH}{-}CH(CH_3)_2}$$

***N*-Formylvaline cyclohexylamide:**[254] Ammonium formate (3.15 g), isobutyraldehyde (2.16 g), and cyclohexyl isocyanide (2.73 g) in 80% aqueous methanol (25 ml) are heated under reflux for 8 h. On concentration of the solution to one-third of its original volume, a mass of colorless crystals (3.04 g; m.p. 190–193°) separates. Recrystallization from methanol affords needles (2.76 g, 49%), m.p. 199–200°.

1.2. Formation of new carbon–carbon single bonds by exchange

I. C–C linkage by removal of hydrogen

1. Pyrochemical reactions

Although pyrochemical reactions are very important in the chemical industry (coking, cracking, etc.), reactions of this type are seldom used nowadays in preparative organic chemistry in the laboratory.[106a]

One of the oldest pyrochemical reactions is the formation of biphenyl from benzene. The older prescriptions require that benzene vapor be passed through a red-hot iron tube, whereby biphenyl is accompanied by hydrogen, carbon, and terphenyls as pyrolysis products. Zanetti and Egloff[255] give 750° as the optimum temperature for production of biphenyl, larger proportions of by-

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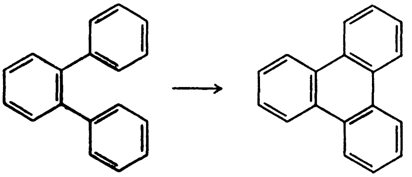
[254] I. Ugi and C. Steinbrückner, *Chem. Ber.*, **94**, 2802 (1961).

[255] J. E. Zanetti and G. Egloff, *Ind. Eng. Chem.*, **9**, 350 (1917).

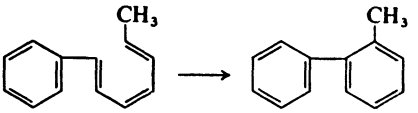
products being obtained at higher temperatures. Smith and Lewcock[256] varied, not only the temperature, but also the rate of passage of benzene and the length and diameter of the iron tube, and also studied the effect of adding barium peroxide, alumina, zinc oxide, and red lead. Grant and James[257] describe the use of red-hot metal wires for this reaction, and Lowe and James[258] describe a laboratory apparatus for the preparation of biphenyl based on that work. Hixson and his co-workers[106b,259] describe an apparatus for conducting the reaction directly in a heated metal-bath.

Wibaut and his colleagues[260] studied the pyrochemical formation of biphenyl from benzene under pressure and in presence of catalysts (nickel or iodine), which permit the use of lower temperatures. However, the proportion of side reactions then increases, *e.g.*, formation of methane when nickel is used as catalyst.

Noble metals also catalyse the formation of carbon–carbon bonds in the aromatic series. For example, if *o*-terphenyl is dissolved in decalin and passed with hydrogen over charcoal coated with palladium and platinumat 490°, there is 77% conversion into a product containing 82.5% of triphenylene:[261]



Mattox and Grosse[262] report the formation of biphenyl, anthracene, and naphthalene from benzene, toluene, or butylbenzene in presence of a chromium–aluminum dehydrogenation catalyst; and if 1-phenyl-*trans*-1,*cis*-3, *trans*-5-heptatriene is heated for 15 min with palladized charcoal in an evacuated tube at 180°, a very good yield of 2-methylbiphenyl is obtained:[263]



The pyrochemical conversion of diphenylmethane into fluorene and of bibenzyl into phenanthrene, first effected by Graebe,[264] is fully analogous to that of biphenyl from benzene. These reactions, as well as the preparation of carbazole from diphenylamine, were carried out by Zelinsky and his co-wor-

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[256] C. Smith and W. Lewcock, *J. Chem. Soc.*, **101**, 1453 (1912).

[257] A. J. Grant and C. James, *J. Amer. Chem. Soc.*, **39**, 934 (1917).

[258] C. H. Lowe and C. James, *J. Amer. Chem. Soc.*, **45**, 2666 (1923).

[259] A. W. Hixson, L. T. Work, H. V. Allessandroni, G. E. Clifford, and G. A. Wilkens, *Ind. Eng. Chem., Anal. Ed.*, **3**, 289 (1931).

[260] J. P. Wibaut, H. M. Romijn, and H. D. T. Willink, *Rec. Trav. Chim.*, **53**, 584 (1934).

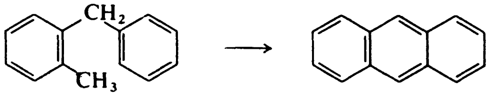
[261] P. G. Copeland, R. E. Dean, and D. McNeil, *J. Chem. Soc.*, **1960**, 1687.

[262] W. J. Mattox and A. V. Grosse, *J. Amer. Chem. Soc.*, **67**, 84 (1945).

[263] F. S. Edmunds and R. A. W. Johnson, *J. Chem. Soc.*, **1965**, 2998.

[264] C. Graebe, *Ann. Chem.*, **174**, 194, 177 (1874); *Ber. Deut. Chem. Ges.*, **7**, 48 (1874).

kers[265] at 300° in the presence of platinized charcoal and with much greater success. If *o*-benzyltoluene is passed through a quartz tube at 970°/1 mm, with residence time 0.03 sec, a 91% yield of anthracene is obtained:[266]

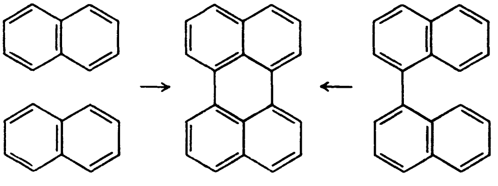


The formation of fluorene and 4-methylfluorene by repeated passage of 2-methyl- and 2,2′-dimethyl-fluorene, respectively, over palladized charcoal at 450° was reported by Orchin.[267]

More recently there have been detailed studies of the pyrolysis of pure hydrocarbons and of hydrocarbon mixtures, mainly by Badger and by Lang, who have reviewed their work.[268]

2. Removal of hydrogen catalysed by aluminum chloride

It is possible to remove hydrogen catalytically, with formation of new carbon–carbon bonds, especially by means of aluminum chloride. The main importance of this process lies in the preparation of condensed ring systems in the aromatic series. It is convenient to differentiate an intermolecular reaction such as the formation of perylene from naphthalene from an intramolecular reaction such as formation of the same product from 1,1′-binaphthalene:[269]



Scholl and his colleagues have investigated this reaction, which is accordingly known as the Scholl reaction.[270,271c]

Intramolecular reactions starting from hydrocarbons, as, for example, the formation of perylene from 1,1′-binaphthalene mentioned above, mostly give only moderate yields. Results are better if there is a possibility for the hydrogen that is split off to be added, at least temporarily, at another situation in the

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[265] N. D. Zelinsky, I. Titz and M. Gaverdowskaja, *Ber. Deut. Chem. Ges.*, **59**, 2591 (1926).

[266] L. A. Errede and J. P. Cassidy, *J. Amer. Chem. Soc.*, **82**, 3653 (1960).

[267] M. Orchin, *J. Amer. Chem. Soc.*, **67**, 499 (1945); M. Orchin and E. O. Woolfolk, *J. Amer. Chem. Soc.*, **67**, 122 (1945).

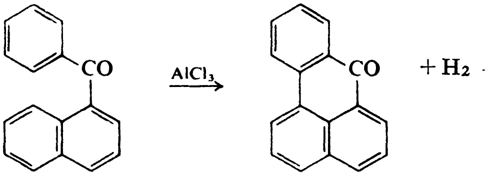
[268] G. M. Badger, *Progr. Phys. Org. Chem.*, **3**, 1 (1965); K. F. Lang, H. Buffleb, and M. Zander, *Erdöl Kohle*, **16**, 944 (1963).

[269] R. Scholl, C. Seer, and R. Weitzenböck, *Ber. Deut. Chem. Ges.*, **43**, 2202 (1910).

[270] C. A. Thomas, (a) "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, 1941, (b) p. 649, (c) pp. 690, 712.

[271] G. A. Olah, (a) "Friedel–Crafts and Related Reactions," Intersience Publ., New York, 1964, (b) Vol. 1, p. 659; Vol. 2, pp. (c) 979, (d) 1257.

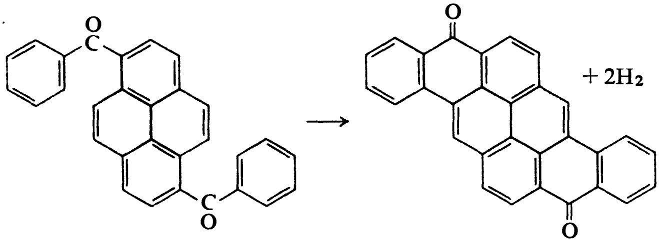
molecule. Such a position is, for instance, on a ketone or quinone-carbonyl group. Later the hydrogen may be removed by oxidative working up. Thus 7-benz[*de*]anthrone is obtained by "baking" 1-benzoylnaphthalene:[272]



The reaction is a general one and can be carried out with any aromatic mono- or poly-ketone that has at least one position free *peri* to the ketone group.

7-Benz[de]anthrone:[272] A finely divided mixture of 1-naphthyl phenyl ketone (1 part) and anhydrous aluminum chloride (5 parts) is heated, with protection by a calcium chloride tube, during 0.5 h from 60° to 115°, during a further 1 h from 115° to 130°, and during a final 1 h from 130° to 150°. The cake is decomposed by dilute hydrochloric acid, and the resulting solid is filtered off and washed with alcohol and ether; it then consists of moderately pure benzanthrone (yield 76%). Recrystallization from glacial acetic acid, with charcoal, affords the pure compound as pale brown needles, m.p. 167–168° (uncorr.).

Yields are better if air or oxygen is led through the melt; and they are appreciably better still if a non-viscous melt of aluminum chloride plus an alkali chloride is used and a stream of dry air or oxygen is led through this. An example of the last method is provided by the preparation of pyranthrone from 1,6-dibenzoylpyrene by Vollmann and his co-workers:[273]



Pyranthrone:[273] 1,6-Dibenzoylpyrene (50 g; m.p. 239°) is stirred into a melt of aluminum chloride–sodium chloride (500 g; composed of 266 parts of $AlCl_3$ per 56 parts of NaCl) at about 120°. Whilst the temperature is gradually raised to 140–160° a stream of dry oxygen is led in at a rate of ca. 60 l per h, being very finely divided in the melt by the stirrer. The color of the melt, originally magenta, changes in 0.5–0.75 h (depending on the efficiency of the stirring) through violet to pure blue. Pouring the melt into water gives pale brownish-orange flocks of almost pure pyranthrone, which can be recrystallized from 1-chloronaphthalene (yield 140 g, 80%).

Since the polycyclic ketones required for the Scholl reaction are generally prepared by the Friedel–Crafts synthesis, the two reactions can be combined; thus, passing a stream of oxygen into an aluminum chloride–sodium chloride melt containing 1-benzoylpyrene and *p*-toluoyl chloride yields 3-methyl-8,16-

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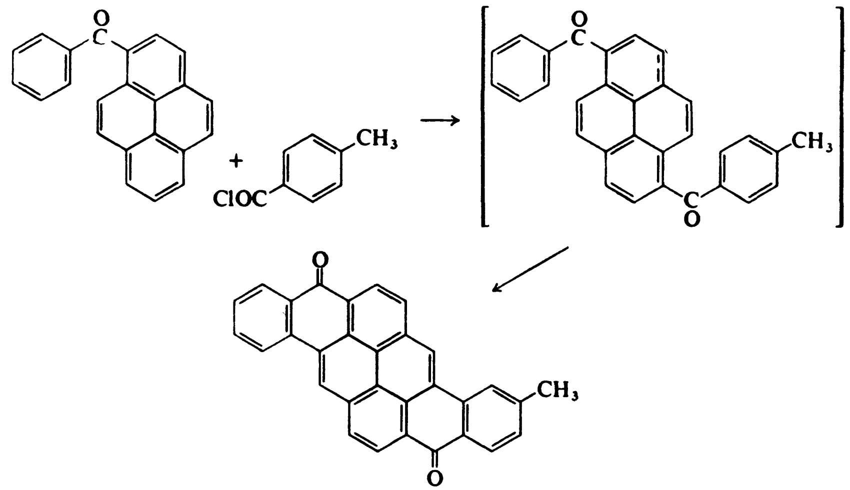
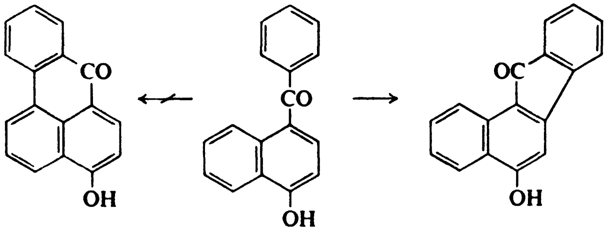
[272] R. Scholl and C. Seer, *Ann. Chem.*, **394**, 111 (1912).

[273] H. Vollmann, H. Becker, M. Corell, and H. Streeck, *Ann. Chem.*, **531**, 118 (1937).

pyranthrenedione:[274]

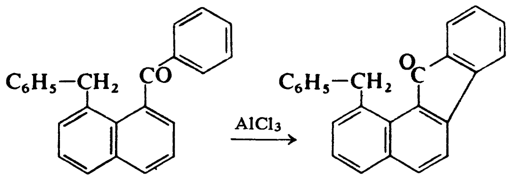


Scholl reactions generally lead to six-membered rings; but a few cases have been reported where five-membered rings were formed, particularly from ketones that carried a hydroxyl or an alkoxyl group *para* to the carbonyl group, such a case was reported by Fierz-David and Jaccard[275] who found that 4-hydroxy-1-naphthyl phenyl ketone (and its methyl ether) gave 5-hydroxybenzo[*a*]fluoren-11-one and not 4-hydroxybenz[*de*]anthrone:



This result was confirmed by Cook and Preston,[276] who moreover improved the technique for preparation of the fluorenone.

If there is a substituent in the *peri*-position to the carbonyl group, then also a five-membered ring may be formed, as Dziewoński and Moszew[277] found in the conversion of 8-benzyl-1-naphthyl phenyl ketone into 1-benzylbenzo[*a*]-fluoren-11-one:



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[274] R. Scholl, K. Meyer, and J. Donat, *Ber. Deut. Chem. Ges.*, **70**, 2180 (1937).

[275] H. E. Fierz-David and G. Jaccard, *Helv. Chim. Acta*, **11**, 1046 (1928).

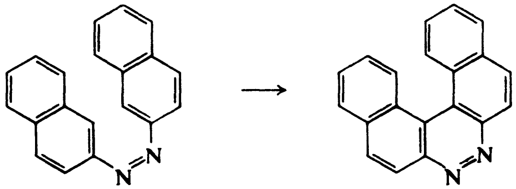
[276] J. W. Cook and R. W. G. Preston, *J. Chem. Soc.*,, **1944**, 553.

[277] K. Dziewoński and J. Moszew, *Rocz. Chem.*, **11**, 169 (1931).

Intermolecular union of two aromatic nuclei can be effected by means of aluminum chloride in the same way as in the pyrochemical reactions discussed above except that presence of a catalyst permits reaction at lower temperatures.

When aromatic hydrocarbons are treated with aluminum chloride the autocondensation is accompanied by side reactions (ring contraction, partial hydrogenation, etc.); reactions of phenyl and naphthyl ethers are, however, smoother, and Scholl and Seer[278] obtained good yields of 4,4'-diethoxy-1,1'-binaphthalene from 1-ethoxynaphthalene and aluminum chloride in nitrobenzene.

Condensed heterocyclic systems can also be obtained in this way: when 2,2'-azonaphthalene is heated with aluminum chloride in methylene dichloride under reflux for 1 h, a 90% yield of benzo[*f*]naphtho[2,1-*c*]cinnoline is produced:[279]



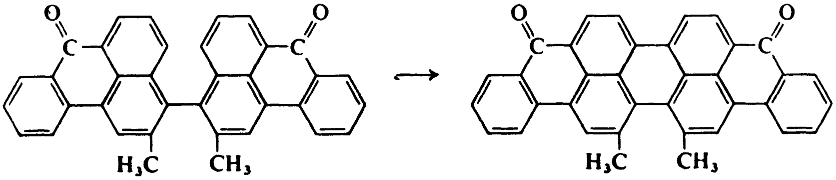
3. Oxidative removal of hydrogen

The use of oxidizing agents can lead to the union, not only of aromatic nuclei, but also of aliphatic methyl, methylene, or methine groups, with elimination of hydrogen. Such a reaction is an oxidative dimerization.

It has long been known[280,281] that **1,1'-binaphthalene** is formed when naphthalene is oxidized by manganese dioxide and sulfuric acid:

Naphthalene is boiled with manganese dioxide and ca. 50% sulfuric acid and then diluted with boiling water. The mixture is filtered and the solids are exhaustively extracted with ethanol. The filtrates are distilled. The distillate above 360° is collected separately and, when crystallized several times from ethanol and light petroleum, gives 1,1'-binaphthalene, m.p. 160.5°.

Hey and his co-workers[282] used this method successfully with a polycyclic ketone: 2-methylbenz[*de*]anthrone is converted by manganese dioxide in 80% sulfuric acid at 0–5° into 2,2'-dimethyl-3,3'-bibenz[*de*]anthrone (78% yield), which affords 16,17-dimethyl-5,10-violanthrenedione only when treated with potassium hydroxide and a little ethanol at 120–130°:



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[278] R. Scholl and C. Seer, *Ber. Deut. Chem. Ges.*, **55**, 330 (1922).

[279] P. F. Holt and C. W. Went, *J. Chem. Soc.*, **1963**, 4099.

[280] F. Lossen, *Ann. Chem.*, **144**, 78 (1867).

[281] W. Smith, *J. Chem. Soc.*, **35**, 225 (1879).

[282] D. H. Hey, R. J. Nicholls, and C. W. Pritchett, *J. Chem. Soc.*, **1944**, 97.

Oxidative dimerization of 2-methyl-1-naphthylamine to 3,3′-dimethyl-1,1′-binaphthalene-4,4′-diamine has also been effected by iron(III) oxide and by mercury(II) sulfate.[283]

When potassium permanganate is used as oxidizing agent the alkali concentration that builds up in the mixture as reaction proceeds is often a hindrance; it can be avoided by buffering with salts or by use of, *e.g.*, acetic anhydride as solvent.

Oxidative removal of hydrogen has been satisfactory more frequently with phenols and their ethers; examples are the conversion of 6-methyl-2-naphthol by iron(III)[284] and of 1-naphthol methyl ether by peroxyformic acid[285] into the derived 1,1′-binaphthalene derivatives.

Oxidation of 1-naphthol methyl ether: A mixture of hydrogen peroxide solution (1.65 ml, containing 0.0165 mole of the peroxide) and formic acid (25 ml) is added during 90 min to a stirred solution of the ether (2.37 g, 0.015 mole) in 98–100% formic acid (75 ml) at 40°. After a few minutes the solution becomes red, and precipitation of crystals begins within 30 min. The mixture is stirred for 15 min after addition of the peroxide–formic acid solution and is then set aside at room temperature for 12 h. The crystals of **4,4′-dimethoxy-1,1′-binaphthalene** are collected and washed with a little ethanol, then having m.p. 256–257° (1.35 g). Concentrating the mother-liquor gives a small further batch (0.3 g). The total yield is 70%.

However, oxidation of 2-naphthol methyl ether (nerolin) leads to a quinone, namely, 4-(2′-methoxy-1′-naphthyl)-1,2-naphthoquinone.

Oxidative dimerization of anthrone and its derivatives can be effected by oxygen,[286] aromatic nitro compounds,[287] diazomethane,[288] or oxygen in the presence of palladium.[289] The following procedure is for the use of nitrobenzene:[287]

A solution of anthrone (5 g) and nitrobenzene (3 ml) in anhydrous xylene (30 ml) containin a little hydrogen chloride is heated under reflux for 5 h. Leaflets of aniline hydrochloride and droplets of water appear in the condenser and the solution becomes orange. Cooling then affords **10,10′-bianthrone** in an almost pure state (4.2 g, 86%). (For alternative nomenclature see Kortüm *et al.*[290])

Synthesis of biaryl compounds is not the only use for oxidative dimerization; it can lead to formation of new carbon–carbon bonds also in the aliphatic series. These reactions have been carried out with peroxides, especially diacetyl peroxide, for example, the formation of 2,3-dichlorosuccinic acid from chloroacetic acid and of 2,3-dimethyl-2,3-diphenylbutane from isopropylbenzene;[291] and hydrogen peroxide[292] and a mixture of ammonium persulfate and sodium

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[283] H. E. Fierz-David, L. Blangey, and H. Dübendorfer, *Helv. Chim. Acta*, **29**, 1661 (1946).

[284] R. Royer, *Ann. Chim. (Paris)*, [12], **1**, 429 (1946).

[285] H. Fernholz and G. Piazolo, *Chem. Ber.*, **87**, 578 (1954).

[286] V. V. Koslov and K. I. Kudelina, *Zh. Obshch. Khim.*, **17**, 302 (1947); *Chem. Abstr.*, **42**, 551 (1948).

[287] V. M. Ingram, *J. Chem. Soc.*, **1950**, 2246.

[288] F. Arndt and J. M. Schlatter, *Chem. Ber.*, **87**, 1336 (1954).

[289] A. Stoll, B. Becker, and A. Helfenstein, *Helv. Chim. Acta*, **33**, 313 (1950).

[290] G. Kortüm, W. Theilacker, H. Zeininger, and H. Elliehausen, *Chem. Ber.*, **86**, 294 (1953).

[291] M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Org. Chem.*, **10**, 386 (1945); M. S. Kharasch, H. C. McBay, and W. H. Urry, *J. Org. Chem.*, **10**, 394 (1945).

[292] H. J. Barber and R. Slack, *J. Chem. Soc.*, **1944**, 612.

acetate[293] have been recommended for similar reactions; treating *tert*-butyl alcohol, for instance, with hydrogen peroxide and ferrous sulfate solution in an acid medium gives 2,5-dimethyl-2,5-hexanediol under very mild conditions.[294]

In some cases oxidative union of two carbon atoms can be used for preparation of diphenylethane derivatives: House[295] describes a simple synthesis of 4,4′-dinitrobibenzyl from *p*-nitrotoluene:

4,4′-Dinitrobibenzyl:[295] 30% Methanolic potassium hydroxide solution (2 l) is placed in a three-necked flask (capacity 3 l) fitted with a stirrer and a gas inlet tube reaching to the bottom of the flask. The mixture is cooled externally by ice to 10° and then *p*-nitrotoluene (100 g, 0.729 mole) is added. The mixture is then stirred vigorously while a rapid stream of air is led through it. After 3 h the ice-bath is removed and the passage of air and the stirring are continued for a further 5 h. The mixture is then filtered without delay, and the filter cake is washed with boiling water (2 l) and then with 95% ethanol (300 ml). The product is dried in the air and recrystallized from benzene; the yield is 74–76% (73–75 g), and the m.p. is 179–180°.

Aerial oxidation of acetylene derivatives to diacetylenes in the presence of copper salts is a method that is also often used. As an example, passing air for 6.5 h through an aqueous-alcoholic solution of 3-butyn-2-ol containing copper(I) chloride, ammonium chloride, and hydrogen chloride gives a very good yield of the mixed stereoisomers of 3,5-octadiyne-2,7-diol:[296]

$$2HOCH(CH_3)C{\equiv}CH \longrightarrow HOCH(CH_3)C{\equiv}C{-}C{\equiv}CCH(CH_3)OH$$

Similar techniques have been tested by various authors[297] for a variety of substituted and also for long-chain acetylenes. The reaction is particularly smooth in the presence of a copper(I)-amine complex in an organic solvent; pyridine and *N,N,N′,N′*-tetramethylethylenediamine have been used as the amine.[298] Detailed directions for the preparation of 1,4-diphenylbutadiyne by oxidative dimerization of phenylacetylene have been given by Campbell and Eglington.[299]

Heterocyclic compounds are also amenable to oxidative dimerization. For example, oxidizing pyridine by potassium persulfate in alkaline solution gives a mixture of various bi- and ter-pyridines from which pure **2,2′-bipyridine** can easily be isolated:[300]

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[293] H. Shechter and R. B. Kaplan, *J. Amer. Chem. Soc.*, **75**, 3980 (1953).

[294] E. L. Jenner, *Org. Syn.*, **40**, 90 (1960).

[295] H. O. House, *Org. Syn.*, **34**, 35 (1954).

[296] K. Bowden, Sir Ian Heilbron, E. R. H. Jones, and K. H. Sargent, *J. Chem. Soc.*, **1947**, 1579.

[297] Yu. S. Zal'kind and N. Iremadze, *Zh. Obshch. Khim.*, **18**, 1554 (1948); *Chem. Abstr.*, **43**, 1368 (1949); Ju. S. Salkind and Fr. B. Fundyler, *Ber. Deut. Chem. Ges.*, **69**, 128 (1936); J. D. Rose and B. C. L. Weedon, *J. Chem. Soc.*, **1949**, 782; H. K. Black and B. C. L. Weedow, *J. Chem. Soc.*, **1953**, 1785; R. Ahmad and B. C. L. Weedow, *J. Chem. Soc.*, **1933**, 3286; A. W. Nineham, *J. Chem. Soc.*, **1953**, 2601; B. L. Shaw and M. C. Whiting, *J. Chem. Soc.*, **1954**, 3217; A. I. Nogaideli and R. Shvangiradze, *Zh. Obshch. Khim.*, **24**, 1025 (1954); *Chem. Abstr.*, **49**, 8799 (1955).

[298] A. S. Hay, *J. Org. Chem.*, **25**, 1275 (1960); **27**, 3320 (1962); H. Stansbury, Jr., and W. R. Proops, *J. Org. Chem.*, **27**, 320 (1962).

[299] I. D. Campbell and G. Eglinton, *Org. Syn.*, **45**, 39 (1965).

[300] P. Möckel and G. Stärk, *Z. Chem.*, **7**, 21 (1967).

Pyridine (200 ml) and anhydrous sodium carbonate (70 g) are placed in a flask fitted with a reflux condenser and are then heated in an oil-bath to about 90° and treated with potassium persulfate (150 g) that is added in 2–3 portions during 0.5 h. The mixture is heated for some hours, after which the pyridine solution is filtered from the salts, which are then washed with pyridine. The pyridine solutions are united and distilled in a vacuum. After recovery of unchanged pyridine there remains a dark oil (about 40 g) containing bi- and ter-pyridines. The 2,2′-bipyridine can be isolated from this mixture by distillation in steam or, particularly from large batches, by distillation in a vacuum (air-condenser), the 2,2′-isomer passing over at 150–165°/12 mm. This product solidifies in a refrigerator to large, colorless crystals, which, when collected, washed with cold water, dissolved in *ca.* 20% acetic acid and reprecipitated by ammonia, are pure and melt at 71°. The yield is 20% calculated on unrecovered pyridine.

In more recent work, pyridine, quinoline, and their derivatives have been dimerized with the aid of specially prepared Raney nickel catalyst.[301]

4. Photochemical dehydrodimerization[67b] and cyclodehydrogenation

Two carbon atoms can also be bonded together, with elimination of hydrogen, by photochemical methods. Such reactions are generally carried out in the presence of a hydrogen acceptor such as oxygen or a carbonyl compound (a ketone or a quinone) or of a dye that is thereby converted into its leuco compound.

The formation of 9,9′-bianthracene from 9,10-dihydroanthracene with loss of hydrogen has been described by Meyer and Eckert;[302] Schönberg and Mustafa[303] found that in sunlight, thioxanthene and anthrone, *inter alia*, are converted into 10,10′-bi(thioxanthene) and 10,10′-bianthrone, respectively, by air; Hooker[304] reported the photo-dehydrodimerization of 2-hydroxy-1,4-naphthoquinone to a quinonoid dimer; and Schönberg and Mustafa[303,305] converted a number of diarylmethanes into the corresponding tetraarylethanes with exclusion of air but in presence of a quinone or a ketone.

10.10′-Bi(thioxanthene):[303,305] A benzene solution (15 ml) of thioxanthene (1 g) and an equivalent amount of xanthone was exposed for 6 h to the July sunlight in Cairo. The benzene was free from thiophene: The reaction was carried out in a Monax glass tube that had been filled with dry carbon dioxide and then sealed. The dimer produced was filtered off, washed with benzene, and recrystallized from xylene, then having m.p. 325° (yield 80%).

Various 2,2′- and 4,4′-biphenyldiols can be obtained in good yield by passing oxygen into boiling ethanolic solutions of the appropriate phenol that is illuminated by a mercury-arc lamp.[306]

Photochemical methods can also be used to effect cyclodehydrogenation under mild conditions. Thus, irradiating a cyclohexane solution of a stilbene at 22–23° in presence of oxygen and a little iodine, by means of a mercury-arc lamp

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[301] G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.*, **1956**, 616; W. H. F. Sasse, *Org. Syn.*, **46**, 5 (1966).

[302] H. Meyer and A. Eckert, *Monatsh. Chem.*, **39**, 243 (1918).

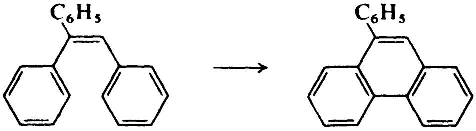
[303] A. Schönberg and A. Mustafa, *J. Chem. Soc.*, **1945**, 657.

[304] S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1212 (1936).

[305] A. Schönberg and A. Mustafa, *J. Chem. Soc.*, **1944**, 67.

[306] A. W. Johnson and S. W. Tam, *Chem. & Ind. (London)*, **1964**, 1425.

leads to good yields of the corresponding phenanthrene derivative,[307] *e.g.*:



in these reactions it is helpful to add copper(I) chloride, particularly for α,α'-disubstituted stilbenes.[308]

Although for steric reasons this reaction cannot be applied to *N*-benzylideneaniline, it suceeds with, *e.g.*, *N*-(diphenylmethylene)aniline, which is thus converted into 6-phenylphenanthridine.[309]

II. C–C linkage by replacement of halogen by carbon

1. Reaction with basic condensing agents

a. C–C linkage between two halides

i, Syntheses of Wurtz type

A Wurtz synthesis consists of removal of halogen from an alkyl halide by means of an alkali metal, with linkage of two alkyl groups to form a longer alkyl chain, thus:

$$\mathrm{RHal} + 2\mathrm{Na} \longrightarrow \mathrm{RNa} + \mathrm{NaHal}$$

$$\mathrm{RNa} + \mathrm{R'Hal} \longrightarrow \mathrm{R{-}R'} + \mathrm{NaHal}$$

Fittig applied this reaction to the aromatic series, combining an alkyl with an aryl halide.

In the aliphatic series the results are useful only for linkage of two identical halides, *i.e.*, when $R = R'$; the smooth course of the Fittig reaction (see below) depends on the facts that aromatic halides react much faster than alkyl halides with the metal and, further, that arylsodiums react faster than alkylsodiums with an alkyl halide (for justification of these statements see the elementary textbooks).

Nowadays the Wurtz synthesis is seldom used, but it still provides a method for preparing very long-chain carbon compounds of defined molecular weight.

Hell and Hägele[310] prepared **hexacontane** as follows: When triacontyl iodide (10 parts) is heated with potassium (1 part) at 130–140°, the reaction appears to be complete after 2 h. Working up is very laborious: the product is boiled successively with water, ethanol, light petroleum, and glacial acetic acid, then recrystallized from benzene, and again boiled with light petroleum until finally hexacontane remains as an indistinctly crystalline, colorless powder of m.p. 101–102°.

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[307] C. S. Wood and F. B. Mallory, *J. Org. Chem.*, **29**, 3373 (1964); F. B. Mallory and C. S. Wood, *Org. Syn.*, **45**, 91 (1965); cf. R. H. Martin, M. Flammag–Barbieux, J. P. Cosyn, and M. Gelbcke, *Tetrahedron Lett.*, **1968**, 3507.

[308] D. J. Collins and J. J. Hobbs, *Chem. & Ind.* (*London*), **1965**, 1725.

[309] F. B. Mallory and C. S. Wood, *Tetrahedron Lett.*, **1965**, 2643.

[310] C. Hell and C. Hägele, *Ber. Deut. Chem. Ges.*, **22**, 502 (1889).

Morton and his colleagues[311] as well as Ziegler and his colleagues[312] studied the Wurtz reaction in detail and give important general advice on the technique of the operation.

Morton's school used an excess of the metal in a finely divided state as well as high-speed stirring.

Ziegler's school found iodides more satisfactory than bromides, and sodium more satisfactory than potassium. Anhydrous diethyl ether or, for sparingly soluble compounds, dibutyl ether was used as solvent. The reaction temperature should be as low as possible and the concentration of halide as high as possible, although yields up to 80% can be forthcoming even when the solubility in boiling ether is only about 0.1 mole per liter.

16-(*p*-Methoxyphenoxy)hexadecyl iodide (11.9 g) is boiled for 10 h with sodium (1.8 g) in a mixture of diethyl ether (40 ml) and dibutyl ether (20 ml). When reaction is complete the ether is evaporated, unchanged sodium is removed by treatment with methanol, and the insoluble material is filtered off. This material is rubbed successively with methanol, water, methanol, and ether and again collected. The ether washing removes the easily soluble by-products of the Wurtz synthesis. The final residue is almost pure **dotriacontamethylene bis-(*p*-methoxyphenyl) ether** (6.3 g), m.p. 124°.

Güsten and Horner[313] found it advantageous for the Wurtz synthesis to replace the metallic sodium by the sodionaphthalene that is obtained from sodium and naphthalene in anhydrous tetrahydrofuran, 1,2-diarylethanes being then obtained from benzyl halides in crude yields of about 90%.

For Fittig syntheses the halide and the diluent must be quite rigidly dried. The sodium is used as wire or slices but, when reaction is sluggish, it is best to use sodium or potassium powder. A 0.05-molar excess of the metal is preferable.

Powdered sodium: Sodium (100 g) is covered with anhydrous xylene (400 ml) in a sulfonation flask (1.5-l capacity) and the air in the flask is replaced by nitrogen. The whole is heated to 120°, whereupon the sodium melts. Then, without further heating, the whole is stirred as fast as possible by a high-speed motor. The stirrer is best made from a KPG rod, one end of which is drawn into a fine wire that is twisted into loops of 3–5 cm diameter; the bundle of loops is strengthened by cross-wires and diagonals and is twisted so as to be arranged as symmetrically as possible around the axis of the rod. The period of stirring should be quite short as otherwise at the melting point of sodium the sodium balls into large lumps. Finally the xylene is decanted from the sodium powder, and ether or some other solvent is added.

The preparation of very finely divided sodium has been described by Morton and his colleagues[311] and by other authors.[314,315]

Ether is the diluent of choice, but benzene and light petroleum may also be used.

Reaction is sometimes preceded by an induction period of several hours, after which it sets in with great violence; when necessary, therefore, reaction is started by addition of a little ethyl acetate which provides clean sodium surfaces.

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[311] A. A. Morton, J. B. Davidson, and H. A. Newey, *J. Amer. Chem. Soc.*, **64**, 2240 (1942), and previous papers.

[312] K. Ziegler, H. Weber, and H. G. Gellert, *Ber. Deut. Chem. Ges.*, **75**, 1715 (1942).

[313] H. Güsten and L. Horner, *Angew. Chem. Int. Ed., Engl.*, **1**, 455 (1962).

[314] E. B. Hershberg and L. F. Fieser, *Org. Syn.*, Coll. Vol. 2, 194 (1943).

[315] C. S. Marvel and W. B. King, *Org. Syn.*, Coll. Vol., **1**, 252 (1941).

The resulting ethyl sodioacetoacetate is easily removed. Acetonitrile also often acts as accelerator.

It is customary to add the halide mixture at such a rate that reaction remains in process and to apply heat when spontaneous boiling ceases and for some time thereafter. The progress of the reaction can be followed from the appearance of the sodium: as reaction begins, the metal becomes covered with bluish-grey flecks; later the pieces of metal swell as they are converted into a sodium halide that contains free sodium in the lattice and is therefore colored. Also an individual piece of metal can be examined for residual inclusions of metal. Some batches require 2–3 days for complete reaction.

To remove the last traces of halide, subsequent careful fractionation of the product is always followed by addition of a small amount of sodium.

A practical example is provided by the preparation of **propylbenzene**, as described by Fittig[316] and reworked by C. Weygand: Fine slices of sodium (44 g) and anhydrous ether (300 ml) are placed in a round-bottomed flask fitted with a reflux condenser and a dropping funnel. The mixture is cooled to 0° and a mixture (also cooled to 0°) of freshly distilled bromobenzene (b.p. 156–157°; 100 g) and propyl bromide (washed with sodium carbonate solution, dried, and freshly distilled; b.p. 70–71°; 98 g) is run in during 5 min. The cooling is then removed. Reaction begins after 45 min and, with occasional external cooling, proceeds to completion within 3 h. The product is set aside overnight, then the ether is distilled off from a water-bath and distillation is continued from an oil-bath until the residue in the flask appears externally to be dry. This residue is extracted several times with portions of the recovered ether, and the main distillate and these extracts are fractionated through a Vigreux column. This provides a 79% yield (calculated on propyl bromide; 60 g) of propylbenzene, b.p. 157–158°, which is completely free from bromine so that distillation over sodium is in this case unnecessary. The yield is almost the same if at the end of the reaction ethanol and water are added until the residual sodium has dissolved and the product is washed, dried, and fractionated.

Butylbenzene can be obtained similarly in 65—70% yield from butyl bromide and bromobenzene.[317] For preparation of hexadecylbenzene Wibaut and his co-workers[318] boiled bromobenzene and cetyl bromide with sodium for 6 h without presence of a solvent, the yield being 40%.

The alkyl halide may be replaced by an alkyl sulfate. For example, 1,2-dimethylnaphthalene is formed in 76% yield when 1-bromo-2-methylnaphthalene is treated with lithium in ether and the product of this reaction is treated with dimethyl sulfate.[319]

In some cases metal–halogen exchange competes with the Wurtz–Fittig reaction.[320,321] Wittig and Witt, for example, obtained bromobenzene and bibenzyl instead of diphenylmethane from phenyllithium and benzyl bromide (for details see the original paper[322]).

Hall, Lesslie, and Turner[323] obtained 9,10-dihydrophenanthrene in 86% yield from 2,2′-bis(bromomethyl)biphenyl and phenyllithium.

According to Hugel and Lerer[324] the organosodium compounds obtained from polycyclic aromatic compounds such as naphthalene and anthracene in liquid ammonia or other media also react with alkyl halides, and especially with isopentyl and isobutyl chloride; they yield doubly substituted hydrocarbons. The experimental conditions are briefly illustrated as follows:

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[316] R. Fittig, *Ann. Chem.*, **149**, 324 (1869).

[317] R. R. Read, L. S. Foster, A. Russell, and V. L. Simril, *Org. Syn.*, Coll. Vol. 3, 157 1955).

[318] J. P. Wibaut, J. Overhoff, and E. W. Jonker, *Rec. Trav. Chim.*, **62**, 31 (1943).

[319] P. A. Plattner and A. Ronco, *Helv. Chim. Acta*, **27**, 400 (1944).

[320] G. Wittig and U. Pockels, *Ber. Deut. Chem. Ges.*, **72**, 89 (1939).

[321] R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).

[322] G. Wittig and H. Witt, *Ber. Deut. Chem. Ges.*, **74**, 1474 (1941).

[323] D. M. Hall, S. M. Lesslie, and E. E. Turner, *J. Chem. Soc.*, **1950**, 711.

[324] G. Hugel and M. Lerer, *C. R. Hebd. Séances Acad. Sci.*, **195**, 249 (1932).

1,4-Diisobutyltetralin: Sodium (45 g), naphthalene (30 g), and isobutyl chloride (160 g) are dissolved in liquid ammonia (1 l). After evaporation of the ammonia, exhaustive extraction of the residue with benzene and fractionation afford a little tetralin, unchanged naphthalene (10 g), and 1,4-diisobutyltetralin, b.p. 170–175°/12 mm.

9,10-Dihydro-9,10-diisopentylanthracene: This was prepared also in ether. Sodium (60 g) is shaken with anthracene (200 g) in ether (2 l) under nitrogen for 48 h. The resulting violet-red solution is cooled in ice and nitrogen is led in while isopentyl chloride (239 g) is added cautiously. Lastly, after decolorization, a little water is added to remove the excess of sodium. The ether is removed from the solution, and the residue is taken up in a little light petroleum; fractionation of this solution in a high vacuum affords a small forerun of anthracene and then at 134–138° the dihydrodiisopentylanthracene as a viscous liquid (75%); a little diisopentylanthracene crystallizes from the last portions of the distillate.

Other metals such as magnesium and zinc can be used for reactions that can formally be regarded as of Wurtz–Fittig type.

Hydrocarbons may be prepared by Grignard synthesis (cf. pages 762 *et seq.*) according to the general scheme:

$$\text{RMgX} + \text{R'X} \longrightarrow \text{R—R'} + \text{MgX}_2$$

this is not often preferable but it is advantageous for introduction of unsaturated side chains into aromatic compounds, as, for example, in the reaction of arylmagnesium halides with allyl halides. This reaction is exothermic and occurs rapidly at room temperature; it is, however, advisable to add the allyl chloride gradually to the Grignard reagent at temperatures around 0° and to warm the mixture finally for a short time to complete the reaction. Care must be taken to prevent the allylbenzenes from being converted into propenylbenzenes by alkali.

The following directions, given by Hershberg[325] and re-worked by H. Bredereck, are for synthesis of **allylbenzene:** A phenylmagnesium bromide solution is prepared in the usual way from magnesium (50.3 g), bromobenzene (324 g), and ether (800 ml). It is cooled in ice-water while allyl bromide (250 ml) in ether (300 ml) is dropped in during 1.5 h. The mixture is heated for 2 h on a water-bath. Two layers are formed. The whole is cooled in ice-water, and water (500 ml) is added. The resulting two phases are separated, the aqueous phase is extracted twice with ether, and the united ether layers are dried over sodium sulfate, freed from ether, and distilled over sodium. This gives 87% (213 g) of a product of b.p. 150–170°, from which fractionation over sodium through a Widmer column affords pure allylbenzene (153 g, 62.7%), b.p. 158–160°.

Allyl ethers may replace the allyl bromide in this preparation, the yield then being 85%.[326]

This process of treating arylmagnesium halides with unsaturated compounds is not confined to introducing olefinic side chains into aromatic compounds. Alkyl Grignard reagents also react, yielding olefins, with β,γ-unsaturated alkyl halides; the solvent recommended for the Grignard reagent in such cases is dibutyl ether.[327] In this way, for example, 1-pentene is obtained from ethylmagnesium bromide and allyl bromide in 54% yield; and diallyl (1,5-hexadiene) is obtained from allyl bromide and magnesium in 55–65% yield.[328]

α,β-Unsaturated alkyl halides are also admissible in this reaction: reaction of phenylmagnesium bromide with propenyl bromide in the presence of cobalt chloride gives propenylbenzene in 51% yield,[329] and with dichloro-

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[325] E. B. Hershberg, *Helv. Chim. Acta*, **17**, 352 (1934).

[326] A. Lüttringhaus and co-workers, *Ann. Chem.*, **557**, 46 (1947).

[327] C. D. Hurd, G. H. Goodyear, and A. R. Goldsby, *J. Amer. Chem. Soc.*, **58**, 235 (1936).

[328] A. Turk and H. Chanan, *Org. Syn.*, **27**, 7 (1947).

[329] M. S. Kharasch and C. F. Fuchs, *J. Amer. Chem. Soc.*, **65**, 504 (1943).

acetylene gives 1-chloro-2-phenylacetylene in 70% yield.[330] However, it is the allyl halogen of 2,3-dibromo-1-propene that reacts preferentially, for with 3-methoxybenzyl bromide and magnesium this compound gives *m*-(3-bromo-3-butenyl)anisole in 74% yield.[331]

Acetylenic hydrocarbons can be prepared in good yield from the Grignard reagent and substituted propargyl halides $RC{\equiv}CCH_2X$.[332]

Saturated hydrocarbons can be prepared by treatment of Grignard reagents with *p*-toluenesulfonates, thus:[333]

A benzylmagnesium chloride solution is prepared from magnesium (24.3 g), benzyl chloride (126.5 g), and ether (500 ml), heated for a further 15 min, and then cooled. A solution of butyl *p*-toluenesulfonate (456 g) in double its volume of ether is then run in during 2 h at a rate such that the ether remains gently boiling. Whilst still hot, the mixture is stirred for a further 2 h, then the thick slurry is poured on ice and treated with concentrated hydrochloric acid (about 125 ml). The magnesium *p*-toluenesulfonate is brought into solution by adding water (about 2 l). Then the ether layer is separated, the aqueous layer is extracted with ether (200 ml), and the united ethereal solutions are washed with water (100 ml), dried by shaking with potassium carbonate (10 g), and filtered. The ether is distilled off and the residue is boiled for about 2 h with freshly cut sodium (5 g) (this removes the small amount of benzyl alcohol formed from the benzylmagnesium chloride by atmospheric oxygen). Decanting the liquid from the sodium and then fractionating it through an efficient column gives 50–60% (74–88 g) of **pentylbenzene**, b.p. 198–202° (mostly 199–201°).

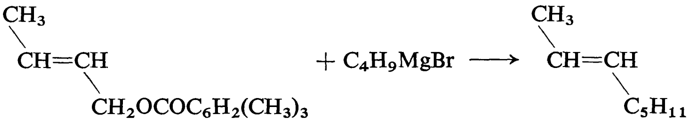
For lengthening the carbon chain of a halide RX by three CH_2 groups it has been recommended[334] to treat the corresponding Grignard reagent RMgX with 3-chloropropyl *p*-toluenesulfonate (yield 50–60%):

$$RMgX + p\text{-}CH_3C_6H_4SO_2O[CH_2]_3Cl \longrightarrow R[CH_2]_3Cl + p\text{-}CH_3C_6H_4SO_2OMgX$$

A similar reaction can be effected with, *e.g.*, 2-chloroethyl *p*-toluenesulfonate (71% yield), the chain lengthening then being by two CH_2 units.[335]

Dialkyl sulfates react analogously to sulfonic esters with aryl or benzyl Grignard reagents, giving alkylated aromatic compounds.[336,337]

A selective synthesis of the otherwise difficultly accessible *trans*-alkenes is by treatment of the appropriate substituted allyl mesitoate with a Grignard reagent; the latter does not react with the carbonyl group of the ester owing to steric hindrance, but instead acts as alkylating agent; an example is the formation of *trans*-2-octene as follows:[338]



$$\begin{array}{l}CH_3\\ \quad\diagdown\\ \quad CH{=}CH\\ \qquad\quad\diagdown\\ \qquad\quad CH_2OCOC_6H_2(CH_3)_3\end{array} + C_4H_9MgBr \longrightarrow \begin{array}{l}CH_3\\ \quad\diagdown\\ \quad CH{=}CH\\ \qquad\quad\diagdown\\ \qquad\quad C_5H_{11}\end{array}$$

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[330] E. Ott and W. Bossaller, *Ber. Deut. Chem. Ges.*, **76**, 88 (1943).

[331] N. A. Nelson and J. C. Wollensak, *J. Amer. Chem. Soc.*, **80**, 6626 (1958).

[332] K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, **62**, 1798 (1940).

[333] H. Gilman and L. L. Heck, *J. Amer. Chem. Soc.*, **50**, 2223 (1928); H. Gilman and J. Robinson, *Org. Syn.*, Coll. Vol. 2, 47 (1943).

[334] S. S. Rossander and C. S. Marvel, *J. Amer. Chem. Soc.*, **50**, 1491 (1928); J. Harmon and C. S. Marvel, *J. Amer. Chem. Soc.*, **54**, 2515 (1932).

[335] F. F. Blicke and F. Leonard, *J. Amer. Chem. Soc.*, **68**, 1934 (1946).

[336] H. Gilman and R. E. Hoyle, *J. Amer. Chem. Soc.*, **44**, 2621 (1922).

[337] C. E. Boord and co-workers, *Ind. Eng. Chem.*, **41**, 609, 613 (1949).

[338] G. M. C. Higgins, B. Saville, and M. B. Evans, *J. Chem. Soc.*, **1965**, 702.

Just as the Wurtz synthesis generally fails with tertiary halides, so are yields often unsatisfactory when a Grignard reagent is applied to preparation of highly branched alkanes (for the preparation of 2,2,3,3-tetramethylbutane see Whitmore *et al.*[339] and Calingaert *et al.*[340]). Nevertheless, coupling of Grignard reagents from tertiary halides or aryl halides can be effected by their reaction with copper(II) bromide or silver bromide, thus:[341]

$$2\mathrm{RMgBr} + 2\mathrm{AgBr} \longrightarrow \mathrm{R{-}R} + 2\mathrm{MgBr_2} + 2\mathrm{Ag}$$

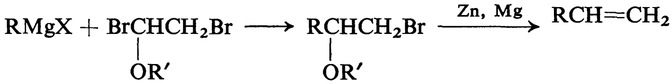
The following exemplifies this:

1,1′-Binaphthalene:[342] A mixture of magnesium turnings (2.4 g, 0.1 mole), anhydrous ether (18 ml), 1-bromonaphthalene (20.7 g, 0.1 mole), and a crystal of iodine is gently warmed until reaction begins (about 30 min), then the heating bath is removed. A precipitate that is soon formed is redissolved by addition of benzene (25 ml; dried over sodium). Heating is then continued until nearly all the magnesium has dissolved. The 1-naphthyl-magnesium bromide solution is then poured slowly, with cooling and exclusion of moisture, into a suspension of anhydrous copper(II) chloride (13.5 g, 0.1 mole) in ether (50 ml). The whole is boiled under reflux for 1 h and is then shaken with water and dilute hydrochloric acid until the copper chloride has dissolved. The organic layer is separated, washed successively with dilute hydrochloric acid, aqueous ammonia, and water, dried over calcium chloride, and freed from ether. This procedure affords an 80% yield (10 g) of 1,1′-binaphthalene, m.p. 154°.

A smooth Grignard reaction is observed with 1-alkoxy-alkyl halides (α-halo ethers), which affords branched-chain ethers, generally in good yield:[343,344]

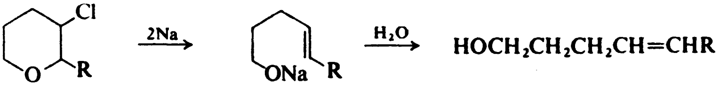
$$\mathrm{ROCHR'Cl} + \mathrm{R''MgX} \longrightarrow \mathrm{R'R''CHOR}$$

Only the α-halogen atom of α,β-dihalo ethers is replaced, and the resulting branched-chain β-halo ethers are intermediates for the prolific Boord synthesis of 1-alkenes:[344]



$$\mathrm{RMgX} + \underset{\mathrm{OR'}}{\mathrm{Br\underset{|}{C}HCH_2Br}} \longrightarrow \underset{\mathrm{OR'}}{\mathrm{R\underset{|}{C}HCH_2Br}} \xrightarrow{\mathrm{Zn,\ Mg}} \mathrm{RCH{=}CH_2}$$

Cyclic halo ethers also undergo reaction with Grignard reagents. 3-Chlorotetrahydro-2-propylpyran is formed in 73% yield from 2,3-dichlorotetrahydropyran and propylmagnesium bromide.[345] In a reaction analogous to the Boord synthesis, compounds of this structure are readily cleaved by sodium to the unsaturated alkanols:[345,346]



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[339] F. C. Whitmore and co-workers, *J. Amer. Chem. Soc.*, **55**, 1561, 3807 (1933).

[340] G. Calingaert and co-workers, *J. Amer. Chem. Soc.*, **66**, 1389 (1944).

[341] J. B. Conant and A. H. Blatt, *J. Amer. Chem. Soc.*, **50**, 551 (1928); J. H. Gardner and P. Borgstrom, *J. Amer. Chem. Soc.*, **51**, 3375 (1929).

[342] E. Sakellarios and T. Kyrimis, *Ber. Deut. Chem. Ges.*, **57**, 322 (1924); J. L. Hamonet, *Bull. Soc. Chim. France*, [iv], **3**, 254 (1908); *C. R. Hebd. Séances Acad. Sci.*, **138**, 813 (1904).

[343] H. I. Waterman and co-workers, *Rec. Trav. Chim.*, **56**, 437 (1937); C. D. Hurd and M. A. Pollack, *J. Amer. Chem. Soc.*, **60**, 1905 (1938); L. Malm and L. Summers, *J. Amer. Chem. Soc.*, **73**, 362 (1951).

[344] L. C. Swallen and C. E. Boord, *J. Amer. Chem. Soc.*, **52**, 651 (1930); H. B. Dykstra, J. F. Lewis, and C. E. Boord, *J. Amer. Chem. Soc.*, **52**, 3396 (1930); B. H. Shoemaker and C. E. Boord, *J. Amer. Chem. Soc.*, **53**, 1505 (1931).

[345] M. Jacobson, *J. Amer. Chem. Soc.*, **72**, 1489 (1950).

[346] L. Crombie and S. H. Harper. *J. Chem. Soc.*, **1950**, 1707, 1714; R. C. Brandon, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **72**, 2120 (1950).

The following details for the above-mentioned reaction of dichlorotetrahydropyran with propylmagnesium bromide illustrate the technique:

3-Chlorotetrahydro-2-propylpyran:[345] An ethereal solution of propylmagnesium bromide is prepared from dry, freshly distilled propyl bromide (600 g, 4.96 moles) and magnesium turnings (127 g, 5.22 moles) in a three-necked flask (capacity 5 l) fitted with a stirrer, dropping funnel, and reflux condenser carrying a calcium chloride tube. This solution is stirred while 2,3-dichlorotetrahydropyran (482 g, 3.11 moles) in anhydrous ether (1 l) is added so that, with occasional cooling, the ether boils gently. As the reaction proceeds, the mixture becomes grey and stirring becomes difficult, to ease which further amounts of ether are added periodically. When addition is complete (4.5 h) the mixture is cooled in ice and cautiously hydrolysed with ice and hydrochloric acid (18%). The ether layer is separated, washed with water, and dried over sodium sulfate. The ether is distilled off and the residue is fractionated in a vacuum, yielding the product (367.6 g, 73%) as a colorless liquid, b.p. 72–80°/13 mm, n_D^{25} 1.4550, with a menthol odor.

Zinc has a specific role to play in some special cases for removal of halogen in a Wurtz-like reaction.[347] It is used especially for the synthesis of small-ring compounds, *e.g.*, of cyclopropanes from 1,3-dihalogen compounds.[348] Shortridge[348] describes the preparation of **1,1-dimethylcyclopropane** as follows:

95% Ethanol (900 ml), distilled water (90 ml), and zinc dust (628 g, 9.6 moles) are placed in a three-necked flask (capacity 2 l) fitted with a dropping funnel, stirrer, and reflux condenser (attached ot a receiver that is cooled in acetone–Dry Ice). The mixture is stirred vigorously to prevent agglomeration of the zinc. The whole is warmed until it boils gently while 1,3-dibromo-2,2-dimethylpropane (562 g, 2.4 moles) is dropped in, and boiling and stirring are continued for 24 h thereafter. Most of the hydrocarbon collects in the receiver during these operations; the remainder is distilled over with a little alcohol into the receiver by a final heating. The crude product (162 g) is washed with ice-water and dried. For further purification it is distilled through a cooled column (for details see the original paper[348]); it has b.p. 19.9–20.6°.

Phenylcyclopropane has been obtained in 75–85% yield from 1,3-dibromo-1-phenylpropane and a zinc–copper alloy in dimethylformamide.[349]

Halogenated aromatic compounds can be condensed with alkyl or aryl halides by using copper to remove the halogen; Zincke[350] prepared ethyl phenylacetate in this way from bromobenzene and ethyl chloroacetate; and Ullmann and his co-workers[351] prepared biaryls from 2 moles of aryl halide and copper (for a review see Fanta[352]).

Iodides react best with copper; chlorides react only when a substituent such as a benzoyl[207] or a nitro group eases removal of the halogen from the ring; for example, 2,2′-dinitrobiphenyl is readily obtained from *o*-chloronitrobenzene.[353] At the opposite extreme, the reaction with copper may become explosive when the halogen atom is particularly activated and in such cases a diluent must be used.[353] The following exemplifies the technique:

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[347] M. Gomberg, *Ber. Deut. Chem. Ges.*, **33**, 3150 (1900).

[348] F. C. Whitmore and co-workers, *J. Amer. Chem. Soc.*, **63**, 124 (1941); R. W. Shortridge and co-workers, *J. Amer. Chem. Soc.*, **70**, 946 (1948).

[349] T. F. Corbin, R. C. Hahn, and H. Shechter, *Org. Syn.*, **44**, 30 (1964).

[350] T. Zincke, *Ber. Deut. Chem. Ges.*, **2**, 738 (1869).

[351] F. Ullmann, G. M. Meyer, O. Loewenthal, and E. Gilli, *Ann. Chem.*, **332**, 38 (1904).

[352] P. E. Fanta, *Chem. Rev.*, **38**, 139 (1946).

[353] F. Ullmann and J. Bielecki, *Ber. Deut. Chem. Ges.*, **34**, 2174 (1901).

2,2′-Dinitrobiphenyl:[353,354] A mixture of *o*-chloronitrobenzene (30 g) and dry sand (50 g) is heated at 200–210° and stirred with the thermometer while copper powder (30 g) is added gradually. The temperature should not be allowed to exceed 250°, and after each addition there should be a pause until the temperature falls to 220°. After the addition, the mixture is heated for 30 min at 240–245°, then cooled and extracted exhaustively with benzene. Concentrating the extracts affords 2,2′-dinitrobiphenyl (60%), m.p. 124°.

ii, Ketone syntheses by means of organometallic compounds

Interaction of carbonyl halides and Grignard reagents normally leads to tertiary alcohols, but it stops at the ketone stage if formation of this alcohol is hindered by, *e.g.*, steric hindrance:

$$\mathrm{RCOCl + R'MgCl \longrightarrow RCOR' + MgCl_2}$$

For this reason Cook and Percival[355] obtained di-*tert* butyl ketone from *tert*-butylmagnesium chloride and pivaloyl chloride in the presence of copper chloride (yield 71.6%). However, reaction between an acid chloride and a Grignard reagent can also be stopped at the ketone stage by using the so-called "inverse addition," *i.e.*, adding the Grignard reagent to the chloride and not, as usual, the halide to the Grignard reagent.[356] The rate of addition of the Grignard reagent and the temperature have no influence on the yield, which, however, is usually not very high. The method provides a general method of preparing mixed ketones, RCOR′.

Yields are appreciably better if the Grignard reagent is first converted in an organozinc compound: zinc chloride in ether is dropped into the Grignard solution at a rate sufficing to keep the solution at the boiling point:

$$\mathrm{RMgCl + ZnCl_2 \longrightarrow RZnCl + MgCl_2}$$

The resulting organozinc chloride is then treated with the acid chloride, giving up to 93% yields of ketone.[357] For ketone syntheses by means of ethylzinc iodide see Morton, Davidson, and Newey.[311]

Klein and Neff[358] prepared mono- and di-ketones as well as oxo esters in excellent yield by treating alkylzinc iodides with carbonyl chlorides, dicarbonyl dichlorides, or monoester monochlorides of dicarboxylic acids. The alkylzinc iodides were obtained directly from the alkyl iodides and a zinc–copper alloy in toluene–ethyl acetate, as in the following example.

6-Dodecanone:[358] Pure pentyl iodide (148 parts, 0.75 mole), pure anhydrous ethyl acetate (22 parts), anhydrous toluene (44 parts), zinc–copper alloy (98 parts, 1.4 moles of zinc), and a crystal of iodine are vigorously stirred together in a large flask (1000 ml). Reaction is started by infrared heating, and then proceeds without heating for 10–15 min. The mixture is next stirred and heated for a further hour, then stirring and heating are discontinued and the mixture is cooled by ice–salt, further toluene (44 parts) being added at this stage. When the excess of zinc alloy has settled nicely, the supernatant solution of pentylzinc iodide is decanted, by means of a syphon and without contact with the air, into a flask containing further cold toluene (44 parts); no metallic zinc must be transferred. If cooling is efficient and the apparatus is flushed with nitrogen, the very hygroscopic and air-sensitive solution does not become warm. A solution of heptanoyl chloride (74.2 parts, 0.5 mole) in toluene (74.2 parts) is at once added to the decanted solution, the temperature being not allowed

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[354] R. C. Fuson and E. A. Cleveland, *Org. Syn.*, Coll. Vol. 3, 339 (1955).

[355] N. C. Cook and W. C. Percival, *J. Amer. Chem. Soc.*, **71**, 4141 (1949).

[356] H. Gilman and M. L. Mayhue, *Rec. Trav. Chim.*, **51**, 47 (1932).

[357] G. A. Schmidt and D. A. Shirley, *L. Amer. Chem. Soc.*, **71**, 3804 (1949).

[358] H. Klein and H. Neff, *Angew. Chem.*, **68**, 681 (1956).

to rise above +8°. This mixture is then stirred for 1 h, after which the addition compound is decomposed by cautious addition of water (375 parts), followed by 20% sulfuric acid (75 parts). The liberated ketone is taken up in toluene (1000 parts), and the toluene layer is separated, washed, dried, and chromatographed on an aluminum oxide column. Removal of the solvent affords the liquid 6-dodecanone (90 g, 98% calculated on heptanoyl chloride).

Cadmium alkyls, obtainable from Grignard reagents and cadmium chloride,[329] also lead to ketones when treated with acid chlorides:

$$2RMgX + CdCl_2 \longrightarrow CdR_2 + 2MgXCl$$

Yields are normally 50–84% but are lower if the two groups R are secondary alkyl cadmium compounds.[360] Aryl and alkyl bromides are more suitable than the iodides for this reaction.[361] Alkylcadmiums are usually preferred to alkylzincs because of their less ready reaction with carbonyl groups. The preparation of **1-phenyl-3-eicosanone**[362] from stearoyl chloride and bisphenethylcadmium provides an example:

$$2CH_3[CH_2]_{16}COCl + Cd(CH_2CH_2C_6H_5)_2 \longrightarrow 2CH_3[CH_2]_{16}COCH_2CH_2C_6H_5$$

A solution of phenethylmagnesium bromide is prepared from magnesium (1.78 moles, 42.7 g) and phenethyl bromide (1.755 moles, 325 g) in anhydrous ether and is cooled in ice and rapidly stirred while cadmium chloride (0.936 mole, 171.5 g) is added during 10 min. The mixture is allowed to warm to room temperature, then the solvent is distilled off on a water-bath until the residue can no longer be stirred. Next anhydrous benzene (1.5 l) is added and the concentration process is repeated. A second batch of anhydrous benzene is added and this mixture is heated under reflux with vigorous stirring until the hard solid is thoroughly subdivided. The suspension is then well stirred while a solution of stearoyl chloride (1.405 moles, 400 g) in anhydrous benzene (1 l) is added during 2 h. The whole is boiled under reflux for 5 h and then treated with ice and hydrochloric acid. The organic layer is separated and shaken with sodium carbonate solution, and the benzene distilled off. The residue is hydrolysed with alcoholic potassium hydroxide solution in the usual way, and the desired product is isolated as non-saponifiable fraction by extraction with benzene. The benzene extract is well washed with water and then saturated sodium chloride solution and dried over magnesium sulfate, and the solvent is removed. Distillation of the residue in a vacuum affords the ketone (65.5%), m.p. 56°, b.p. 219°/1 mm.

This method of preparing ketones has been reviewed by Shirley[363] and by Cason.[364]

Carboxylic anhydrides and alkylcadmiums give ketones in 50–70% yield;[359] this reaction is also smooth with Grignard reagents, especially at low temperatures (−70°).[365] Oxo carboxylic acids are obtained when alkylcadmiums or alkylzincs are treated with cyclic acid anhydrides[359,366,367] or when a monoester monochloride of a dicarboxylic acid reacts with an isoalkylmagnesium bromide.[368] (The oxo group can be reduced by Clemmensen's

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[359] P. L. de Benneville, *J. Org. Chem.*, **6**, 462 (1941); G. W. Stacy and R. M. McCurdy, *J. Amer. Chem. Soc.*, **76**, 1914 (1954).

[360] J. Cason, *J. Amer. Chem. Soc.*, **68**, 2078 (1946); W. G. Dauben, *J. Org. Chem.*, **13**, 313 (1948).

[361] W. G. Dauben and H. Tilles, *J. Org. Chem.*, **15**, 785 (1950); R. P. Jacobsen, *J. Amer. Chem. Soc.*, **73**, 3463 (1951).

[362] K. W. Sherk, M. V. Augur, and M. D. Soffer, *J. Amer. Chem. Soc.*, **67**, 2239 (1945).

[363] D. A. Shirley, *Org. Reactions*, **8**, 28 (1954).

[364] J. Cason, *Chem. Rev.*, **40**, 15 (1947); J. Cason and F. S. Prout, *Org. Syn.*, **28**, 75 (1948).

[365] M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

[366] L. F. Fieser and F. C. Novello, *J. Amer. Chem. Soc.*, **64**, 802 (1942).

[367] G. Komppa and W. Rohrmann, *Ann. Chem.*, **509**, 259 (1934).

[368] C. R. Fordyce and J. R. Johnson, *J. Amer. Chem. Soc.*, **55**, 3368 (1933).

method, so that this synthesis provides a method for chain extension of carboxylic acids.) **o-Tolyl glyoxalate** can be obtained in 50% yield by reaction of ethoxalyl chloride with di-*o*-tolylcadmium, as follows:[359]

A Grignard solution is prepared in the usual way from *o*-bromotoluene (45 g, 0.26 mole), magnesium powder (5.75 g, 0.24 mole), and ether (in total about 150 ml), decanted from residual magnesium, and dropped into a stirred suspension of anhydrous cadmium chloride (22 g, 0.12 mole) in ether (150 ml) at such a rate that the ether refluxes gently. After the addition, the mixture is stirred until the Gilman test is negative. To remove the magnesium salts, the solution is filtered through a glass frit with exclusion of moisture and then added to a solution, very rapidly stirred and cooled in Dry Ice and acetone, of ethoxalyl chloride (54.4 g, 0.40 mole) in ether (70 ml) at such a rate that the temperature remains between −30° and −40°. After this addition the mixture is allowed to reach room temperature and then poured on a mixture of ice (70 g) and water (70 ml). The whole is shaken vigorously until the odor of ethoxalyl chloride can no longer be detected. The ether layer is separated and washed twice with 10% sodium hydrogen carbonate solution (70-ml portions) and once with water (35 ml), then dried over anhydrous sodium sulfate. Removal of the ether and fractionation of the residue through a 15-cm column give the product (23.4 g, 50%), b.p. 136–137°/8 mm, n_D^{20} 1.5178, d_4^{20} 1.1016.

Methyl ketones are formed in excellent yield when acyl chlorides react with methylaluminum dichloride.[369]

b. C–C linkage between halides and compounds containing active protons

i, *Alkylation of active-methylene compounds*

Alkylation or acylation of ethyl malonate, ethyl acetoacetate, or other compounds containing methylene groups activated by strongly electron-attracting groups are very fruitful preparative methods. Reactions according to the schemes:

$$\mathrm{RHal} + \mathrm{CH_2X_2} \xrightarrow[-\mathrm{NaHal}]{\mathrm{NaOC_2H_5}} \mathrm{RCHX_2}$$

$$\mathrm{RHal} + \mathrm{R'CHX_2} \xrightarrow[-\mathrm{NaHal}]{\mathrm{NaOC_2H_5}} \mathrm{RR'CX_2}$$

$$(\mathrm{X} = \mathrm{CN}, \mathrm{COR''}, \mathrm{COOR''}, \mathrm{NO_2}, \text{etc.})$$

provide a great variety of intermediates that can be used in many types of further reaction.

The alkylation is generally effected by bringing together a solution or suspension of the sodio derivative of the compound to be alkylated and the alkylating agent, usually an alkyl halide, at any suitable temperature, and it is rarely necessary to isolate the sodio derivative in substance. The sodio derivatives are obtained by reaction of the active methylene compound with sodium, sodamine or sodium hydride in an inert solvent, *e.g.*, ether; alcoholic solutions of the sodio compounds are obtained by treating the methylene components with the calculated amount of sodium alkoxide solution.

Sodamide in liquid ammonia is often used. Compounds containing reactive methylene groups can be treated with very reactive halides (*e.g.*, allyl or benzyl

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[369] H. Adkins and C. Scanley, *J. Amer. Chem. Soc.*, **73**, 2854 (1951).

halides) in liquid ammonia without the need for sodium. Yields of over 90% of alkylation product have been achieved in this way.[370]

Recently anion-exchange resins have been used successfully as bases for such reactions.[371,372]

Monoalkylation of malonic esters by primary and some secondary alkyl halides usually gives yields of 75–90%; on occasions using an excess of the malonic ester has a very favorable effect on the yield.[373] Yields are usually somewhat lower for replacement of the second hydrogen atom. It should be noted that in monoalkylation by alkyl halides of low molecular weight the products always contain some of the dialkylated products,[374] and these are very difficult to separate by distillation. Equally, dialkylated products prepared in one step always contain monoalkylated products as impurity;[375] for separating the monoalkylated products Norris and Tucker[376] recommend two hours' boiling with 50% potassium hydroxide solution, which hydrolyses only the monoalkyl derivatives. Specific advice has been given by various authors on alkylation of malonic esters by diethyl sulfate,[377] ethyl *p*-toluenesulfonate,[378] and other *p*-toluenesulfonic esters.[379]

The preparation of **diethyl butylmalonate**[380] is an example of alkylation by an alkyl halide: A cooled and stirred solution of sodium alkoxide (from 115 g of sodium and 2.5 l of anhydrous ethanol) is treated gradually with refractionated ethyl malonate (b.p. within 5°; 825 g); with further cooling as necessary, this ester is followed by butyl bromide (685 g) during 1 h. Then the solution is heated on a water-bath until neutral to litmus (2–3 h), after which alcohol (2 l) is distilled off from a water-bath, the residue is treated with its own volume of water, and the organic phase is separated and distilled in a vacuum. A forerun of unchanged malonic ester is followed by the diethyl butylmalonate (89–92%, 960–990 g), b.p. 144–145°/40 mm.

Preparation of cycloheptatrienylmalonic acid from tropylium bromide, ethyl malonate, and sodium ethoxide in 71% yield has been described by Korte, Büchel, and Wiese.[381]

It has also been recommended[382] that an alkyl carbonate should be added during alkylation of β-oxo, malonic, and α-cyano esters. According to this method a solution of the methylene compound in an alkyl carbonate is treated with an equivalent amount of the sodium alkoxide and the alcohol liberated is distilled off, thereby completing formation of the sodio derivative of the methylene compound; subsequent alkylation gives good yields of alkyl derivatives even when other methods give unsatisfactory results, as in the alkylation of malonic esters already carrying a secondary alkyl substituent. A further advantage of this procedure is that it avoids the alcoholysis and loss of carb-

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[370] D. Hartley, *J. Chem. Soc.*, **1962**, 4722.

[371] K. Shimo and S. Wakamatsu, *J. Org. Chem.*, **28**, 504 (1963).

[372] B. G. Chatterjee, V. V. Rao, and B. N. G. Mazumdar, *J. Org. Chem.*, **30**, 4101 (1965).

[373] J. B. Cohen and co-workers, *J. Chem. Soc.*, **107**, 887 (1915).

[374] L. T. C. Schey, *Rec. Trav. Chim.*, **16**, 332 (1897).

[375] E. Fischer and A. Dilthey, *Ber. Deut. Chem. Ges.*, **35**, 844 (1902).

[376] J. F. Norris and H. F. Tucker, *J. Amer. Chem. Soc.*, **55**, 4697 (1933).

[377] C. D. Hurd, R. N. Jones, and F. H. Blunck, *J. Amer. Chem. Soc.*, **57**, 2033 (1935).

[378] D. H. Peacock and P. Tha, *J. Chem. Soc.*, **1928**, 2303.

[379] W. Braker, E. J. Pribyl, and W. A. Lott, *J. Amer. Chem. Soc.*, **69**, 866 (1947).

[380] R. Adams and C. S. Marvel, *J. Amer. Chem. Soc.*, **42**, 310, 316 (1920).

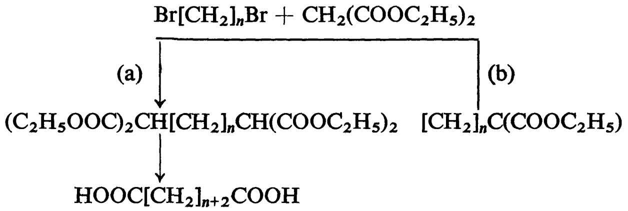
[381] F. Korte, K.-H. Büchel, and F. F. Wiese, *Ann. Chem.*, **664**, 114 (1963).

[382] V. H. Wallingford, M. A. Thorpe, and A. H. Homeyer, *J. Amer. Chem. Soc.*, **64**, 580 (1942).

oxyl groups that occasionally complicate reaction in pure alcohol. Alkylation of diethyl *sec*-butylmalonate[382] illustrates the technique:

Sodium ethoxide is prepared by evaporating completely to dryness, in a vacuum, a solution of sodium in an excess of ethanol. To the solid residue are added, with cooling, an equimolar amount of diethyl *sec*-butylmalonate and an excess of diethyl carbonate (4–6 moles), and the whole is stirred at room temperature until the alkoxide has dissolved. The alcohol is then completely removed by distillation, finally in a vacuum, through an electrically heated column (internal diameter 13 mm, length 44 cm) filled with glass spirals and fitted for total condensation and variable take-off. A reflux condenser, stirrer, and dropping funnel are then placed on the flask, and a 10–15% excess of ethyl bromide is run in during 15–20 min. The mixture is then well stirred, heated cautiously to 95–105°, and kept at that temperature until it no longer reacts alkaline to phenolphthalein (54 h). It is cooled, added to the same volume of cold water, neutralized with acetic acid, and extracted with diisopropyl ether. The ether solution is dried and distilled, affording **diethyl *sec*-butylethylmalonate** (95%), b.p. 69–72°/1 mm, n_D^{21} 1.4331.

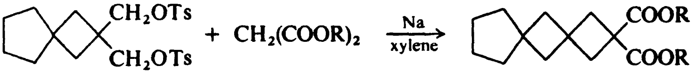
α,ω-Dicarboxylic acids can be prepared by interaction of an α,ω-dibromoalkane and an excess of ethyl malonate, an example being the conversion of 1,10-dibromodecane into tetradecanedioic acid (reaction a, $n = 10$; yield 64%):[383]



$$\begin{tikzcd}
 & Br[CH_2]_nBr + CH_2(COOC_2H_5)_2 \arrow[dl, "(a)"'] \arrow[dr, "(b)"] & \\
(C_2H_5OOC)_2CH[CH_2]_nCH(COOC_2H_5)_2 \arrow[d] & & [CH_2]_nC(COOC_2H_5) \\
HOOC[CH_2]_{n+2}COOH & &
\end{tikzcd}$$

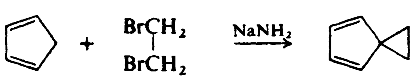
Reaction of ethylene dibromide or trimethylene dibromide with an insufficiency of sodiomalonic ester can lead to ring closure to cyclopropane[384] or cyclobutane derivatives,[385] respectively (reaction b).

High yields of cyclobutane derivatives are obtained from the bis-*p*-toluenesulfonates of 1,3-diols, as is shown by the synthesis of diethyl dispiro[3.1.4.1]-undecane-2,2-dicarboxylate from 2,2-spiro[3,4]octanebis(methyl *p*-toluenesulfonate) and ethyl malonate (warming with sodium in xylene):[386]



[Ts = p-$C_6H_4(CH_3)SO_2$]

Ring closure also occurs on reaction of cyclopentadiene with ethylene dibromide and sodium in liquid ammonia, the product being spiro[2.4]-hepta-4,6-diene (75% yield):[387]



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[383] R. G. Jones, *J. Amer. Chem. Soc.*, **69**, 2350 (1947).

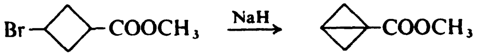
[384] A. W. Dox and L. Yoder, *J. Amer. Chem. Soc.*, **43**, 2097 (1921).

[385] G. B. Heisig and F. H. Stodola, *Org. Syn.*, **23**, 16 (1943); A. W. Dox and L. Yoder, *J. Amer. Soc.*, **43**, 680 (1921).

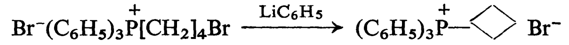
[386] E. Buchta, K. Geibel, and W. Theuer, *Ann. Chem.*, **648**, 36 (1961); **666**, 81 (1963).

[387] K. Alder, H.-J. Ache, and F. H. Flock, *Chem. Ber.*, **93**, 1888 (1960).

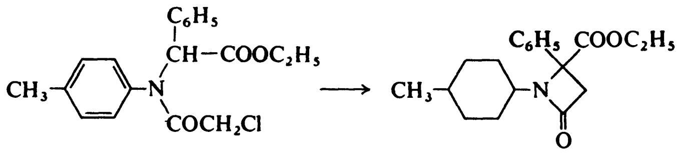
Within certain structural requirements alkyl halides may cause intramolecular alkylation to give three- and four-membered ring systems. For example, methyl bicyclo[1.1.0]butane-1-carboxylate is obtained in 77% yield from methyl 3-bromocyclobutanecarboxylate and sodium hydride:[388]



and (4-bromobutyl)triphenylphosphonium bromide and phenyllithium afford cyclobutyl(triphenyl)phosphonium bromide:[389]

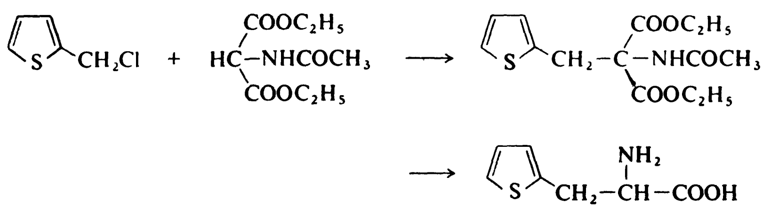


Finally, β-lactams can be formed analogously, *e.g.*, "Acetidinone" [ethyl-4-oxo-2-phenyl-1-(*p*-tolyl)acetane-2-carboxylate] from ethyl α-[*N*-(chloroacetyl)-*N*-(*p*-tolyl)-amino]-α-phenylacetate:[372]



In this case the base used was the anion-exchange resin Amberlite IRA-400.

Amino acids are accessible by use of ethyl (acetylamino)malonate. Dittmer, Hert, and Chambers treated 2-(chloromethyl)thiophene with ethyl (acetylamino)malonate in the presence of sodium ethoxide, obtaining an 87% yield of α-(acetylamino)-α-(2-thienyl)malonate which was converted into β-(2-thienyl)alanine in 78% yield by boiling hydrobromic acid:[390]



Phenylacetic acid, benzyl chloride, and sodamide in liquid ammonia give more than 80% of 2,3-diphenylpropionic acid:[391]

$$C_6H_5CH_2COOH \longrightarrow C_6H_5CHNaCOONa \xrightarrow{C_6H_5CH_2Cl} C_6H_5CH_2CH(C_6H_5)COOH$$

Dialkyl[392] and alkyl aryl ketones[393] can be alkylated under similar conditions; and here too all the α-hydrogen atoms can under certain circum-

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[388] K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965); E. P. Blanchard, Jr., and A. Cairncross, *J. Amer. Chem. Soc.*, **88**, 498 (1966).

[389] K. V. Scherer, Jr., and R. S. Lunt, *J. Org. Chem.*, **30**, 3215 (1965).

[390] K. Dittmer, W. Hert, and J. S. Chambers, *J. Biol. Chem.*, **166**, 541 (1946).

[391] C. R. Hauser and W. R. Dunnavant, *Org. Syn.*, **40**, 38 (1960).

[392] I. N. Nasarow, *Ber. Deut. Chem. Ges.*, **70**, 594 (1937).

[393] A. Haller, *Bull. Soc. Chim. France*, [iv], **31**, 1073 (1922).

stances be replaced by alkyl groups; thus Vavon and Conia[394] found that triallylacetophenone (2,2-diallyl-1-phenyl-4-penten-1-one) was formed in 70% yield on reaction of acetophenone with three equivalents of allyl bromide in the presence of sodium *tert*-pentyl oxide. The composition of the alkylation products of ketones sometimes depends markedly on the reaction temperature.[395] Sodamide has been recommended specifically as condensing agent for ketones:[396] a benzene solution of the ketone is heated under reflux with the calculated amount of finely powdered sodamide until evolution of ammonia ceases. Sodium isopropoxide is also useful for monoalkylations. Use of sodium *tert*-pentyl oxide is indicated when sodamide gives poor yields;[397] sodium hydride can also be used with advantage.

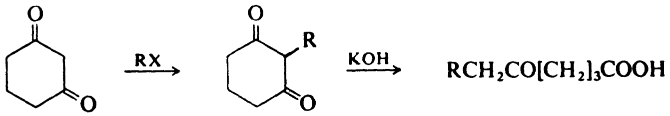
Formaldehyde diethyl dithioacetal can also be metalated by sodamide in liquid ammonia. Reaction of butyl bromide leads to an 84% yield of pentanal diethyl bisthioacetal:[398,399]

$$C_4H_9Br + CH_2(SC_2H_5)_2 \xrightarrow[\text{liquid } NH_3]{NaNH_2} C_4H_9CH(SC_2H_5)_2$$

Diketones can be treated in ethereal solution directly with sodium,[400,401] alkylation being later effected in acetone or dioxan. Potassium has been used successfully in some cases when use of sodium failed.[402]

Methylbenzoylacetone (2-methyl-1-phenyl-1,3-butanedione):[400,401] The calculated amount of sodium wire is added to benzoylacetone dissolved in six times its amount of anhydrous ether. This precipitates the sodio derivative as a sulfur-yellow powder. For further reaction[402] a portion (3 g) of this derivative is dried over phosphoric oxide and heated for 4 h under reflux with methyl iodide (1.9 g) in anhydrous acetone (50 ml). The acetone is then distilled off and the residue is taken up in ether, shaken with water, dried, and fractionated, giving 88% of the product, b.p. 130–134°/11 mm.

1,3-Cyclohexanedione is also readily alkylated at position 2, and the alkyl derivatives formed can be cleaved hydrolytically to δ-oxo carboxylic acids by alkali. Stetter has reviewed[403] the syntheses carried out by himself and his colleagues by this method.



The method of alkylating β-oxo esters is very similar, and the condensing agents noted for alkylation of ketones can also be applied to these esters. Renfrow and Renfrow[404] have studied the results obtained with various condensing

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[394] G. Vavon and J. Conia, *C. R. Hebd. Séances Acad. Sci.*, **223**, 157, 245 (1946).
[395] G. Wash, B. Shive, and H. L. Lochte, *J. Amer. Chem. Soc.*, **63**, 2975 (1941).
[396] A. Haller and E. Bauer, *C. R. Hebd. Séances Acad. Sci.*, **148**, 70 (1909).
[397] M. J. Conia, *Bull. Soc. Chim. France*, [v], **17**, 537 (1950).
[398] W. E. Truce and F. E. Roberts, *J. Org. Chem.*, **28**, 961 (1963).
[399] A. Fröling and J. F. Arens, *Rec. Trav. Chim.*, **81**, 1009 (1962).
[400] E. Fischer and C. Bülow, *Ber. Deut. Chem. Ges.*, **18**, 2131 (1885).
[401] C. Weygand, *J. Prakt. Chem.*, [ii], **116**, 293, 297, 306 (1927).
[402] C. Weygand, H. Forkel, and C. Bischoff, *Ber. Deut. Chem. Ges.*, **61**, 687 (1928).
[403] H. Stetter, *Angew. Chem.*, **67**, 769 (1955).
[404] W. B. Renfrow and A. Renfrow, *J. Amer. Chem. Soc.*, **68**, 1801 (1946).

agents and particularly recommend potassium *tert*-butoxide for introducing secondary alkyl groups into α-substituted ethyl acetoacetate, which can be thus effected with yields of up to 80%.

Hunsdiecker[405] reports the intramolecular alkylation of ω-halo β-oxo esters to yield β-oxo cyclic esters.

A third alkyl group can be introduced into α,α-dialkyl-substituted acetic esters by metallation with (triphenylmethyl)sodium or (triphenylmethyl)-potassium and subsequent treatment with an alkyl halide:[406]

$$R_2CHCOOC_2H_5 \xrightarrow[-(C_6H_5)_3CH]{(C_6H_5)_3CNa} R_2CNaCOOC_2H_5 \xrightarrow{R'X} R_2R'CCOOC_2H_5$$

Barbituric acid derivatives have been alkylated with yields of more than 90%,[407] and cyanoacetic esters with yields of 60–78%.[382]

The following synthesis of **2-cyano-2-ethyl-3-methylbutyramide**[371] from 2-cyano-3-methylbutyramide and ethyl bromide exemplifies the use of an anion-exchange resin as condensing agent:

Ethyl iodide (1.6 g, 0.01 mole) is added to a mixture of 2-cyano-3-methylbutyramide (1.26 g, 0.01 mole) and Amberlite IRA-400 (3.7 g, 0.01 mole; OH^- form with a capacity of 2.7 milliequiv. per g) in 50% aqueous ethanol (25 ml). The mixture is shaken for 2 h at room temperature, then the resin is filtered off and washed with aqueous ethanol. The filtrate and washings are evaporated to dryness in a vacuum and the residual solid is digested with hot light petroleum (b.p. 78–108°; 25 ml). Unchanged 2-cyano-3-methylbutyramide (0.3 g, 24%) is insoluble and is recovered. The alkylation product (0.74 g, 48%), m.p. 110–111°, is obtained from the petroleum solution by cooling.

Finkbeiner[408] has described the alkylation of hydantoins on the way to a synthesis of α-amino acids. The methylene group is first activated by introducing an alkoxycarbonyl group by means of methoxymagnesium methyl carbonate; then the amino acid is obtained by alkylation and subsequent hydrolysis with decarboxylation. The original paper should be consulted for details.

The procedures described above can also be used to alkylate nitriles that contain α-hydrogen atoms.[409,410] Sodamide is the usual condensing agent in this case, and the reaction is carried out in an inert solvent (ether or benzene) or in liquid ammonia.

Cyclohexylphenylacetonitrile:[411] A three-necked flask (capacity 1 l) is fitted with a stirrer, inlet tube, and reflux condenser that is connected by way of a soda-lime tower to a gas-absorption vessel; the flask is carefully dried and protected from moisture and then cooled in a Dry Ice–trichloroethylene bath. Anhydrous ammonia (200 ml) is introduced, the cooling-bath is removed, the inlet tube replaced by a stopper, and a crystal (about 0.2 g) of hydrated iron nitrate is added. A small piece (ca. 5 mm) of sodium is added next without delay, and the liquid ammonia is stirred until the blue color disappears, whereupon the remainder of the sodium (total 8.1 g, 0.35 mole) is added in small pieces with continued vigorous stirring. When the color of the solution has faded from blue to grey, the contents of the flask are swirled so as

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[405] H. Hunsdiecker, *Ber. Deut. Chem. Ges.*, **76**, 142 (1943).

[406] R. Lebine, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1230 (1944), and earlier papers.

[407] O. Rosen and F. Sandberg, *Acta Chem. Scand.*, **4**, 675 (1950).

[408] H. Finkbeiner, *J. Amer. Chem. Soc.*, **86**, 961 (1964).

[409] F. W. Bergstrom and W. C. Fernelius, *Chem. Rev.*, **12**, 135 (1933); **20**, 451 (1937).

[410] A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 107 (1957).

[411] E. M. Hancock and A. C. Cope, *Org. Syn.*, Coll. Vol. 3, 219 (1955).

to bring down the particles of sodium adhering to the surface of the glass. The freezing-bath is then replaced and benzyl cyanide (41 g, 0.35 mole) is run in during 10 min from a dropping funnel. The freezing-bath is removed again and the liquid is stirred for 15 min, after which sulfur-free toluene (200 ml; dried over sodium) and anhydrous ether (25 ml) are added dropwise as the ammonia evaporates. The remainder of the ammonia is then removed by warming with hot water, and in this process most of the ether also escapes through the uncooled reflux condenser. A fresh drying tube is placed on the condenser, the cooling is reinstated, and dry bromocyclohexane (65.2 g, 0.4 mole) is added to the still warm solution during about 20 min. The initial violent reaction may require moderation by cooling, but later the mixture is heated under reflux for 2 h by means of an oil-bath. Then the mixture is cooled and washed with water (300 ml). The aqueous layer is extracted twice with benzene (50-ml portions), and the benzene and toluene layers are united, washed twice with water (50-ml portions), and distilled in a vacuum, giving cyclohexylphenylacetonitrile (45–53 g, 65–77%), b.p. 174–176°/13 mm, m.p. 50–53.5°. When recrystallized from pentane (15% loss), the product has m.p. 56–58°.

For alkylation of malonodinitrile, dimethyl sulfoxide is recommended as solvent and sodium hydride as base, the reaction then occurring faster, under milder conditions, and in better yield than by other procedures. **Dibenzylmalonodinitrile,** for instance, is thus obtained in 64–76% yield:[412]

Malonodinitrile (16.5 g, 0.25 mole) is dissolved in dimethyl sulfoxide (45 ml) and then stirred while sodium hydride (12.0 g, 0.5 mole) in dimethyl sulfoxide (75 ml) is added during 15 min. The mixture is stirred for a further 15 min with occasional cooling, then benzyl chloride (63.2 g, 0.5 mole) is run in during 20 min with occasional cooling. The whole is then stirred for 8.5 h at room temperature, next poured into water (500 ml), and filtered from the voluminous precipitate which is repeatedly washed with cold water and finally dried in the air. This solid is recrystallized, with charcoal, from hot 95% ethanol (400 ml), giving dibenzylmalonodinitrile (39.0 g, 64.5%) as white needles, m.p. 131.8–132.5°. Concentration of the mother-liquor affords a further fraction (7 g, 11.4%), m.p. 122°.

The above technique is also suitable for alkylation of diketones. Stereospecific alkylation of cyclic α-oxo nitriles has been discussed by Kuehne.[413]

Alicyclic nitriles may be formed by intramolecular alkylation of halo nitriles, *e.g.*, cyclopropyl cyanide from 4-chlorobutyronitrile (yields 74–79%).[414]

Henrich[415] reported that on alkylation cyclopentadiene reacted like acetoacetic ester, and glutaconic ester $C_2H_5OOCCH{=}CHCH_2COOC_2H_5$ like malonic ester, of which it can be considered a vinolog.

The literature[416] should be consulted for side-chain alkylation of picolines.

Organolithium compounds, generally phenyl- or butyllithium, can be used, in the same way as (triphenylmethyl)sodium (see page 917), as base for *C*-alkylation, since in certain cases they react by metal exchange with activated hydrocarbons. For instance, the 2-lithio derivative of resorcinol dimethyl ether is formed in 70% yield on reaction with phenyllithium. The organolithium compounds thus obtained react readily with alkyl halides or sulfates, forming a carbon–carbon bond;[32b] for example, 2,6-dimethoxytoluene is formed by

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[412] J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).

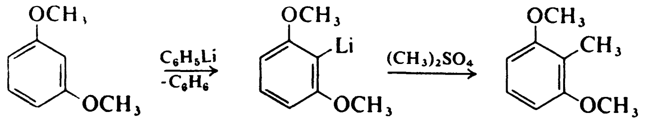
[413] M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).

[414] C. M. McCloskey and G. H. Coleman, *Org. Syn.*, **24**, 36 (1944).

[415] F. Henrich, *Ber. Deut. Chem. Ges.*, **31**, 2103 (1898).

[416] G. A. Knight and B. D. Shaw, *J. Chem. Soc.*, **1938**, 682; F. Brody and M. T. Bogert, *J. Amer. Chem. Soc.*, **65**, 1075 (1943).

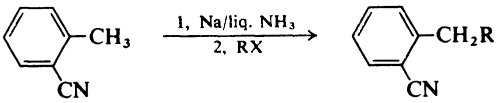
treating the 2-lithioresorcinol dimethyl ether with dimethyl sulfate:[417]



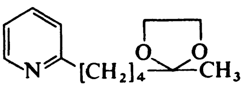
For the preparation of phenyllithium and metallation of resorcinol dimethyl ether by Wittig's method see pages 756 and 758.[326,418]

The synthesis of hexylbenzene in 76% yield from toluene, pentyl chloride, and sodium in the presence of potassium isopropoxide[419] probably also involves direct metallation of the hydrocarbon as an intermediate stage.

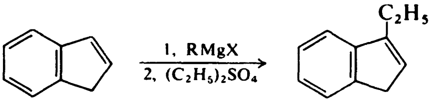
An analogous reaction is that of *o*-tolunitrile with sodium in liquid ammonia and then with alkyl or aryl halides, which gives the derived alkylbenzonitriles in 63–86% yield:[420]



α-Picoline (2-methylpyridine) gives a lithio derivative that with 5-bromo-2-pentanone ethylene ketal affords 6-(2-pyridyl)-2-hexanone ethylene ketal in 80% yield:[421]



Finally, 3-ethylindene is obtained in 92% yield by converting indene by isopropylmagnesium chloride into its magnesio derivative and treating this with diethyl sulfate in hexamethylphosphoramide:[422]



It is not only simple alkyl halides that can be used with reactive methylene compounds: halo ketones, halo carboxylic esters, and analogous compounds such as *N*,*N*-dimethyl-2-chloroethylamine[423] react equally smoothly.

Aminoalkylation of compounds containing active methylene groups by means of α-halo amines is discussed on page 958.

1,4-Diketones of acetonylacetone type can be obtained by treating a sodioacetoacetic ester with iodine;[424] it seems probable that the iodoacetoacetic

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[417] J. P. Lambooy, *J. Amer. Chem. Soc.*, **78**, 771 (1956).

[418] H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 258 (1954).

[419] A. A. Morton and A. E. Brachman, *J. Amer. Chem. Soc.*, **73**, 4363 (1951).

[420] F. H. Rash, S. Boatman, and C. R. Hauser, *J. Org. Chem.*, **32**, 372 (1967).

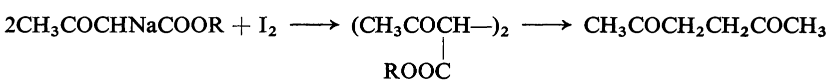
[421] G. Jones, *J. Chem. Soc.*, **1962**, 1129.

[422] T. Cuvigny and H. Normant, *Bull. Soc. Chim. France*, **1964**, 2000.

[423] J. A. Barltrop, *J. Chem. Soc.*, **1946**, 958; O. Eisleb, *Ber. Deut. Chem. Ges.*, **74**, 1433 (1941).

[424] L. Knorr and F. Haber, *Ber. Deut. Chem. Ges.*, **27**, 1155 (1894); E. Fischer. *Ann. Chem.*, **306**, 356, note (1899); "Anleitung zur Darstellung organischer Präparate," Verlag Vieweg, Brunswick, 1930, p. 54.

ester is first formed, then reacting further in the usual way:



$$2\mathrm{CH_3COCHNaCOOR} + \mathrm{I_2} \longrightarrow (\mathrm{CH_3CO}\underset{\substack{|\\ \mathrm{ROOC}}}{\mathrm{C}}\mathrm{H}\text{—})_2 \longrightarrow \mathrm{CH_3COCH_2CH_2COCH_3}$$

Bischoff and Rach[425] have described the preparation of tetraethyl 1,1,2,2-ethanetetracarboxylate in quantitative yield by the analogous reaction with iodine.

ii, Acylation of active-methylene compounds

Complications often arise when an acyl group is introduced into a compound containing an active methylene group; this is because the acylated products are more acidic than the starting materials so that their further reaction is easier than that of the starting materials; this problem has been discussed by Claisen.[426]

The following procedure for preparation of **ethyl α-benzoylacetoacetate** illustrates Claisen's technique:[426]

Sodium (35.4 g) is dissolved in ethanol and the solution is made up to a known volume (600 ml). Half of this sodium ethoxide solution is mixed in the cold with ethyl acetoacetate (100 g); this mixture is cooled to 5° and stirred while benzoyl chloride (45 ml) is then added during about 15 min and the temperature is not allowed to exceed 10°. The solution is next set aside for 30 min, after which half of the residual sodium ethoxide solution (*i.e.*, 150 ml) is added in one portion, followed, gradually this time, by benzoyl chloride (22.5 ml), and again the mixture is set aside for a short time. This procedure is repeated, each time with half the previous amounts of ethoxide and benzoyl chloride, until all the material has been added. Meanwhile a mixture of sodium chloride and ethyl sodiobenzoylacetoacetate has separated from the alcoholic solution. The final mixture is set aside for a further *ca.* 12 h in the cold, then the solids are filtered off and washed with ether. The wash-ether precipitates a further amount of sodium enolate from the filtrate and this is added to the main fraction of solids. The crude sodium enolate is briefly dried, then dissolved in a three-fold amount of water and treated, with ice-cooling, with acetic acid until no more oil is precipitated. This oily product is taken up in ether, dried over calcium chloride, and fractionated; the desired ester has b.p. 175–176°/12 mm.

Benzoylacetone can also be benzoylated by the method just detailed; but the product, acetyldibenzoylmethane, is more conveniently obtained by another method due to Claisen;[426] this second method can also be used for benzoylation of acetoacetic and malonic esters though the yields are there not as good; the procedure is to treat a mixture of benzoyl chloride and benzoylacetone in boiling ether with anhydrous sodium carbonate, as follows:

Acetyldibenzoylmethane (2-benzoyl-1-phenyl-1,3-butanedione): Benzoylacetone (16.2 g) and benzoyl chloride (14 g) are dissolved in anhydrous ether (100 ml), finely powdered anhydrous sodium carbonate (32 g) is added, and the mixture is set aside in a flask fitted with a reflux condenser and protected from moisture. The ether begins to boil in a short time. The mixture is set aside at room temperature for about 16 h, then the mixture of sodium chloride,sodium carbonate, and sodium enolate is filtered off, washed with ether, and whilst still moist with ether is dissolved in water. The ether is removed in a current of air, and precipitation by acetic acid then affords very pure acetyldibenzoylmethane (10 g). A further amount of enolate can be extracted from the ethereal mother-liquor by 10% sodium carbonate solution, the total yield amounting to 87% (14 g). The pure product melts at about 110°.[427]

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[425] C. A. Bischoff and C. Rach, *Ber. Deut. Chem. Ges.*, **17**, 2781 (1884).

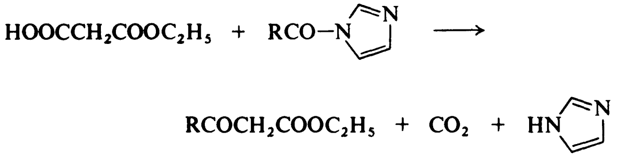
[426] L. Claisen, *Ann. Chem.*, **277**, 196 (1893); **291**, 53, 67 (1896).

[427] W. Dieckmann, *Ber. Deut. Chem. Ges.*, **49**, 2203 (1916); C. Weygand, *Z. Anorg. Allg. Chem.*, **205**, 414 (1932).

Weygand and Forkel[402] treated sodiodibenzoylmethane in acetone with benzoyl chloride, obtaining tribenzoylmethane in 45% yield.

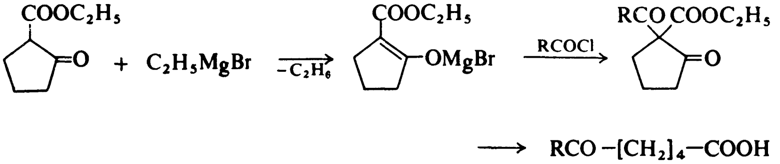
The ethoxymagnesium derivatives of malonic esters are excellent intermediates for selective introduction of different acyl groups into the esters;[428] oxo esters can be acylated by boiling them with the acyl chloride and magnesium in benzene (46–52% yields).[429]

The bisacylation of methylene-active compounds mentioned above can be avoided by using acylimidazoles in place of acyl halides (acylimidazoles are obtained from the carboxylic acid and sulfinyldiimidazole); for example, reaction of the magnesium enolate of ethyl hydrogen malonate and an acylimidazole, with concomitant decarboxylation, gives the corresponding β-oxo ester:[430]



α,α-Dialkyl-substituted β-oxo esters are obtained free from monoalkylated products by acylating the sodio derivatives of α,α-dialkylated acetic esters, the latter being accessible as described above (page 917) from a disubstituted acetic ester and (triphenylmethyl)sodium.[431]

Plešek[432] has described a method, giving high yields, of lengthening a carbon chain by five carbon atoms; it is sufficiently indicated by the following scheme, the overall yield being 79% in this case:



The reaction of nitroalkanes with methoxymagnesium methyl carbonate represents an acylation by carbonic acid; it affords good yields of α-nitro carboxylic acids by way of a chelate-like intermediate:[433]

$$RCH_2NO_2 \xrightarrow[2,\ H_2O]{1,\ CH_3OCOOMgCH_3} NO_2\text{—}CHRCOOH$$

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[428] G. W. Anderson and co-workers, *J. Amer. Chem. Soc.*, **67**, 2197 (1945); B. Riegel and W. M. Lilienfeld, *J. Amer. Chem. Soc.*, **67**, 1273 (1945); H. Lund and A. Voigt, *Org. Syn.*, Coll. Vol. 2, 594 (1953); E. C. Taylor and A. McKillop, *Tetrahedron*, **23**, 898 (1967).

[429] A. Spassow, *Org. Syn.*, **21**, 46 (1941); J. H. Hunter and J. A. Hogg, *J. Amer. Chem. Soc.*, **71**, 1922 (1949).

[430] G. Bram and M. Vilkas, *Bull. Soc. Chim. France.* **1964**, 945.

[431] C. R. Hauser and W. B. Renfrew, Jr., *Org. Syn.*, Coll. Vol. 2, 268 (1943).

[432] J. Plešek, *Collect. Czech. Chem. Commun.*, **21**, 1312 (1956); **22**, 49, 1661 (1957).

[433] H. L. Finkbeiner and M. Stiles, *J. Amer. Chem. Soc.*, **85**, 616 (1963); H. Finkbeiner, *J. Amer. Chem. Soc.*, **87**, 4588 (1965).

iii, Synthesis of alkyl, aryl, and acyl cyanides[434]

Cyanides (nitriles) can be obtained by reaction of alkyl halides with alkali cyanides:

$$\text{RHal} + \text{NaCN} \longrightarrow \text{RCH} + \text{NaHal}$$

Good yields are produced by primary alkyl halides in aqueous ethanol; secondary alkyl halides react well in dimethyl sulfoxide;[435] tertiary alkyl halides apparently do not react at all.

The preparation of **undecanenitrile**[106k,430] is an example of such reactions:

Decyl bromide (475 g) and potassium cyanide (150 g) are heated under reflux on a water-bath for about 10 h in 96% ethanol (1.5 l) and water (250 ml). After cooling, the potassium bromide is filtered off, the ethanol is distilled off on a water-bath, and the residual oil is distilled under diminished pressure. The crude nitrile is purified by hydrolysis with concentrated hydrochloric acid in the cold, recrystallization of the resulting amide from ethanol, and removal of water therefrom by phosphoric oxide to give the nitrile (for details of these procedures see ref. [106], Vol. 8, pages 293, 330). The pure nitrile, b.p. 139.6–139.8°, is then obtained in 84% yield.

Sodium cyanide is less reactive than potassium cyanide but can be used with success in many cases; for example, glutarodinitrile, $NC[CH_2]_3CN$ has been prepared in 80% yield from 1,3-dibromopropane and sodium cyanide.[437]

The reactivity increases, as usual, along the series chloride < bromide < iodide, so that halogens can be replaced selectively: 1-bromo-3-chloropropane and somewhat less than the theoretical amount of potassium cyanide give exclusively 4-chlorobutyronitrile (70%).[438]

Benzyl halides are very smoothly convertible into nitriles; mesitylacetonitrile is obtained in 89–93% yield from (chloromethyl)mesitylene.[439]

Using dimethyl sulfoxide as solvent leads to excellent results; even secondary halides give yields of up to 80% therein,[435] as shown in the following case:

***sec.*-Butyl cyanide:** Sodium cyanide (30 g) is warmed in dimethyl sulfoxide (150 ml) to 90° and treated with *sec*-butyl chloride (0.5 mole) during 30 min. An exothermic reaction occurs. The mixture is boiled under reflux for 3 h, the final temperature being 150°. After cooling, the mixture is poured into water, and the product is extracted in ether or chloroform. The extracts are washed several times with sodium chloride solution, dried over calcium chloride, and distilled, affording 79% of *sec*-butyl cyanide, b.p. 125–126°.

α,ω-Dicyanides can be similarly obtained from the corresponding dihalides in dimethyl sulfoxide in yields of over 95%:

2,2-Bis-(3-cyanopropyl)-1,3-dioxalane: The procedure was analogous to that in the preceding example: addition during 10 min; subsequent stirring for 30 min; the sulfoxide had been dried over calcium hydride, and the sodium cyanide at 100°/16 mm overnight. Yield 96%. M.p. 42–42.5°, b.p. 151–152°/0.2 mm.

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[434] H. Brintzinger and A. Scholz, *Ber. Deut. Chem. Ges.*, **83**, 141 (1950); D. T. Mowry, *Chem. Rev.*, **42**, 189 (1948); V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., New York, 1947.

[435] R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960); L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

[436] R. Merckx, J. Verhulst, and P. Bryulants, *Bull. Soc. Chim. Belg.*, **42**, 180 (1933).

[437] C. S. Marvel and E. M. McColm, *Org. Syn.*, **5**, 103 (1925).

[438] C. F. H. Allen, *Org. Syn.*, **8**, 52 (1928).

[439] R. C. Fuson and N. Rabjohn, *Org. Syn.*, Coll. Vol., 3,557 (1955).

Alkyl sulfates or sulfonates may also be used, in place of alkyl halides.[436,440] For example, in the steroid field replacement of a *p*-toluenesulfonyloxy group is effected by calcium cyanide in 1-methyl-2-pyrrolidone (81% yield); 5α-cholestane-3α-carbonitrile is thus formed from 5α-cholestan-3α-yl *p*-toluenesulfonate.[441]

A simple synthesis of cyanides that can be effected in an aqueous medium consists of treating the alkyl halides with benzyltrimethylammonium cyanide (prepared *in situ* from benzyltrimethylammonium chloride and sodium cyanide):[442]

$$C_6H_5CH_2\overset{+}{N}(CH_3)_3Cl^- + NaCN \longrightarrow C_6H_5CH_2\overset{+}{N}(CH_3)_3CN^-$$

$$\xrightarrow{C_6H_5CH_2CH_2Br} C_6H_5CH_2CH_2CN$$

This synthesis of 3-phenylpropionitrile is achieved in 91–93% yield.

Anion-exchange resins such as Amberlite IRA 400 in the cyanide form can also be used for direct synthesis of nitriles; benzyl bromide in 95% ethanol gave 53% of phenylacetonitrile in this way.[443]

For the preparation of aromatic cyanides from aromatic halides Rosenmund and von Braun introduced copper cyanide in place of the alkali cyanide: the halide is warmed with copper cyanide, if necessary with addition of a little pyridine, at 150–250°. The reaction can be accelerated by small amounts of a nitrile or of copper sulfate.[444]

1-Naphthonitrile:[445] 1-Bromonaphthalene (66 g, 0.32 mole), dry powdered copper(I) cyanide (35 g, 0.39 mole), and pyridine (dried over barium oxide; 30 ml) are placed in a dry flask (200-ml capacity) fitted with a reflux condenser and a calcium chloride tube. The mixture becomes warm; later it is heated at 215–220° for 15 h. Whilst still hot (about 100°), the resulting dark brown solution is poured into a flask containing aqueous ammonia (*d* 0.90; 150 ml) and water (150 ml); benzene (about 140 ml) is added and the flask is closed and shaken until complete solution is obtained. The solution is cooled to room temperature, ether (100 ml) is added, and the whole is filtered through a glass frit (the solution destroys paper). The ether–benzene layer is washed four times with dilute aqueous ammonia (100-ml portions); if the last of these washings is still colored, another ammonia wash (100 ml) is given. Then the solution is washed twice with 6N-hydrochloric acid. Any precipitate formed is filtered off, and the solution is finally washed twice with water (100-ml portions) and twice with saturated sodium chloride solution. The ether and benzene are distilled off and the residue is distilled at 173–174°/27 mm or 166–169°/18 mm, the yield of nitrile being 40–44 g (82–90%).

Similar yields are obtained from 1-chloronaphthalene on 24 hours' heating at 245–250°.

For the preparation of *p*-(benzyloxy)benzonitrile containing nitrile-^{14}C from $Cu^{14}CN$ and the aryl iodide in dimethylformamide see Grisebach and Patschke.[446]

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[440] M. Zief, H. G. Fletcher, Jr., and H. R. Kirshen, *J. Amer. Chem. Soc.*, **68**, 2743 (1946); V. C. Sekera and C. S. Marvel, *J. Amer. Chem. Soc.*, **55**, 345 (1933).

[441] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, **1962**, 954.

[442] N. Sugimoto and co-workers, *Chem. Pharm. Bull.*, **10**, 427 (1962).

[443] M. Gordon and C. E. Griffin, *Chem. & Ind. (London)*, **1962**, 1019.

[444] C. F. Koelsch and A. G. Whitney, *J. Org. Chem.*, **6**, 795 (1941); C. F. Koelsch, *J. Amer. Chem. Soc.*, **58**, 1328 (1936).

[445] M. S. Newman, *Org. Syn.*, **21**, 89 (1941).

[446] H. Grisebach and L. Patschke, *Chem. Ber.*, **95**, 2098 (1962).

Because of the solubility of copper cyanide in 1-methyl-2-pyrrolidone the latter has been recommended[447] as solvent for the reaction with alkyl halides.

When an alkali cyanide is melted with an alkali arenesulfonate the aromatic nitrile is formed by replacement of the sulfo group; this reaction has been applied mainly in the naphthalene series.[448]

It is preferable to use copper cyanide rather than alkali cyanide also for the preparation of unsaturated nitriles, *e.g.*, of allyl cyanide from allyl chloride; seven hours' refluxing in the presence of potassium iodide, with exclusion of water, affords a 79–84% yield of allyl cyanide.[449]

Vinyl halides can be brought into reaction under the same conditions as aryl halides: fumarodinitrile, for example, is formed in 74% yield from 1,2-diiodoethylene;[450] and ethynyl nitriles are obtained from ethynyl iodides and either an alkali cyanide in acetone or copper cyanide in xylene.[451]

This method of reaction is also applicable to the preparation of hydroxy nitriles (from chlorohydrins, yields about 80%)[452] and α-alkoxy nitriles (from α-halo ethers and copper cyanide, yields 55–80%).[453]

Acyl cyanides are best (yields 60–87%[454]) obtained from acyl halides by heating the latter with copper cyanide in absence of a solvent; the reaction of bromides is more satisfactory than that of chlorides.

Acetyl cyanide:[455] Copper(I) cyanide is prepared by adding potassium cyanide in portions to copper(II) sulfate with cooling and vigorous shaking. The copper cyanide is filtered off, washed thoroughly, and dried in a thermostat at 60–70°. Acetyl bromide (1 mole) is added to copper cyanide (1 mole), which causes ebullition; no solvent is used. The mixture is heated under reflux for 1.5–2 h, then the nitrile formed is separated from the copper(I) bromide formed by distillation from an oil-bath; the nitrile boils at 93°; the yield is 85–87%.

iv, Acylation and alkylation of unsaturated compounds

(α) Reactions of phosphine alkylenes (alkylidenephosphoranes). Acylation and alkylation have greater preparative importance when they involve replacement of hydrogen on an unsaturated carbon atom. Preeminent among such reactions are Friedel–Crafts syntheses, which, however, are treated in a later Section of this book. The present Section deals with the acylation and alkylation of alkylidenetriphenylphosphoranes, and of enamines and acetylenes, that occur directly or indirectly under the influence of basic reagents.

Alkylidenephosphoranes have recently achieved great importance by their use in Wittig olefination. The manifold applications of that reaction are supplemented by the reactions involving introduction of acyl or alkyl groups; the latter have been reviewed by Bestmann.[455-457] It should be noted that,

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[447] M. S. Newman and D. K. Phillips, *J. Amer. Chem. Soc.*, **81**, 3667 (1959).

[448] F. C. Whitmore and A. L. Fox, *J. Amer. Chem. Soc.*, **51**, 3363 (1929).

[449] E. Rietz, *Org. Syn.*, **24**, 96 (1944).

[450] U.S. Pat. 2,399,349; *Chem. Abstr.*, **40**, 4744 (1946).

[451] M. S. Newman and J. H. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1292 (1949).

[452] E. C. Kendall and B. McKenzie, *Org. Syn.*, **3**, 57 (1923); C. H. G. Hands and B. Y. Walker, *J. Soc. Chem. Ind. (London)*, **67**, 458 (1948).

[453] H. R. Henze, G. W. Benz, and G. L. Sutherland, *J. Amer. Chem. Soc.*, **71**, 2122 (1949).

[454] W. Tschelinzeff and W. Schmidt, *Ber. Deut. Chem. Ges.*, **62**, 2210 (1929); T. S. Oakwood and C. H. Weisgerber, *Org. Syn.*, **24**, 14 (1944).

[455] H. J. Bestmann, *Angew. Chem. Int. Ed., Engl.*, **4**, 583 (1965).

[456] H. J. Bestmann, *Angew. Chem. Int. Ed., Engl.*, **4**, 645 (1965).

[457] H. J. Bestmann, *Angew. Chem. Int. Ed., Engl.*, **4**, 830 (1965).

although formulated here as alkylidenephosphoranes, the reagents can also be regarded as ylides.

The procedures for acylation, mainly due to Bestmann and his collaborators, consist in their simplest form of treatment of an alkylidenephosphorane with an acid halide, normally a chloride:[456,458]

$$(C_6H_5)_3P{=}CHR + R'COHal \longrightarrow (C_6H_5)_3P{=}CRCOR' + HHal \qquad (1)$$

A second molecule of the ylide is consumed in binding of the halogen acid formed (transylidation); instead of this, another base, such as triethylamine, may be added, but this must then be a stronger base than the ylide used. The following details describe the general synthetical technique:

Acylation of alkylidenetriphenylphosphoranes by acid chlorides:[456] A salt-free solution of an alkylidenetriphenylphosphorane (0.022 mole) in anhydrous benzene (100 ml) is heated under nitrogen to the boiling point in a Schlenk tube fitted with a Claisen distillation head that carries a dropping funnel and a reflux condenser closed by a mercury valve. Into this boiling, colored solution is dropped a solution of the acid chloride (0.01 mole) in benzene (50 ml); the phosphonium chloride is thereupon precipitated; addition of the acid chloride must be stopped as soon as the ylide is all consumed, this being recognizable by decoloration of the solution (an excess of acid chloride must on all accounts be avoided as it attacks the acylated ylide). The protecting nitrogen is no longer needed after this reaction. The phosphonium chloride is filtered off and washed with benzene, and the solution and washings are evaporated in a vacuum. The evaporation residue, consisting of the acylalkylidenetriphenylphosphorane is treated with ethyl acetate (20 ml) and, after brief cooling of the mixture in ice–salt, is collected again. A second fraction can be obtained by evaporating the mother-liquors. Occasionally the evaporation residue is oily, but this usually then crystallizes when dissolved in ethyl acetate and kept in a refrigerator for 24 h.

Most of the acylalkylidenetriphenylphosphoranes can be recrystallized from ethyl acetate. The solubility in this solvent increases with increasing number of methyl groups in the molecule. A small amount of ether often hastens a slow crystallization. Many acylalkylidenetriphenylphosphoranes retain the solvent tenaciously.

It is not essential to isolate the acylated product before using it in further reactions; the residue obtained on evaporating the benzene solution may be used directly; or, if the further reaction is to be effected in benzene, the acylation solution itself may be used after removal of the phosphonium salt.

The phosphonium chlorides are obtained in 80–100% yield and can be used for further ylide formation after one precipitation from chloroform by ether and rigorous drying. Occasionally the chlorides are precipitated as oils, but these crystallize when rubbed.

The acid chlorides specified in reaction (1) may be replaced by *S*-esters of thiocarboxylic acids [*i.e.*, $RC(O)SC_6H_5$ or $RC(O)SC_2H_5$ in place of RCOCl];[458] their reaction leads to separation of a thiophenol or an alkanethiol, and these products do not consume a second molecule of the alkylidenephosphorane. The last statement is true also for the reaction with 1-acylimidazoles described by Bestmann, Sommer, and Staab.[459]

Acylation of alkylidenetriphenylphosphoranes by thiocarboxylic *S*-ethyl esters:[456] The reactions are carried out in a Schlenk tube, as above. To a boiling solution (which need not be filtered) of a salt-free alkylidenephosphorane (0.022 mole) in anhydrous toluene is added an *S*-ethyl thiocarboxylate (0.02 mole), and the mixture is boiled for 18 h. The phosphonium thiolate, that is initially precipitated as an oil, gradually redissolves. If an unfiltered ylide solution was used, the reaction solution must be filtered hot at this stage to remove sodium

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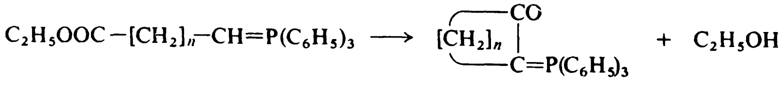
[458] H. J. Bestmann, *Tetrahedron Lett.*, **1960**, 7; H. J. Bestmann and B. Arnason, *Tetrahedron Lett.*, **1961**, 455; *Chem. Ber.*, **95**, 1513 (1962).

[459] H. Bestmann, N. Sommer, and H. A. Staab, *Angew. Chem.*, **74**, 293 (1962).

halide, but nitrogen protection is unnecessary in this operation. Evaporation of the reaction solution in a vacuum leaves the acylalkylidenetriphenylphosphorane as an oil that crystallizes when rubbed; it can be recrystallized from ethyl acetate. The excess of phosphonium salt needed increases with increasing length of the group R in the alkyltriphenylphosphonium salt $[R{-}CH_2P^+(C_6H_5)_3]X^-$.

Alkyl esters cannot be used for these acylations in place of the carbonyl compounds mentioned above unless an intramolecular cyclization (somewhat analogous to a Dieckmann cyclization) can occur, as, for instance:[460]



$$C_2H_5OOC{-}[CH_2]_n{-}CH{=}P(C_6H_5)_3 \longrightarrow [CH_2]_n \begin{cases} CO \\ C{=}P(C_6H_5)_3 \end{cases} + C_2H_5OH$$

(2-Oxocyclohexylidene)triphenylphosphorane:[456] [5-(Ethoxycarbonyl)pentyl]triphenyl-phosphonium iodide (42 g) is added to a solution of potassium (3.4 g) in *tert*-butyl alcohol (300ml), and the mixture is heated under reflux for 12 h and then evaporated in a vacuum. The residue is shaken with chloroform and water. The chloroform layer is separated and dried, and the ylide is precipitated by ethyl acetate; it has m.p. 243–245° (22.1 g, 79%).

Reaction (1) does, however, take place when phenyl esters $R'COOC_6H_5$ are used.[456,458]

Finally, alkoxycarbonyl groups can be introduced by treatment of alkylidenetriphenylphosphoranes with ethyl chloroformate $ClCOOC_2H_5$;[461] in these cases the hydrogen chloride formed must be bound, as discussed above.

Alkylation of alkylidenetriphenylphosphoranes can be effected in the same way as acylation:[456,462]

$$(C_6H_5)_3P{=}CHCOOCH_3 + RHal \longrightarrow (C_6H_5)_3P{=}CRCOOCH_3 + HHal$$

The halogen acid can be bound by a second molecule of ylide, as above. R may be an alkyl, allyl, or arylalkyl group, but α-bromo ketones, bromoacetic esters, and chloroacetonitrile have also becen used.[456,462]

Alkylation of [(methoxycarbonyl)methylene]triphenylphosphorane: An alkyl halide (0.2 mole) is added to a boiling solution of [(methoxycarbonyl)methylidene]triphenylphosphorane (0.4 mole) in anhydrous ethyl acetate, and the mixture is boiled under reflux for 2 h. The precipitated [(methoxycarbonyl)methyl]triphenylphosphonium halide is filtered off (yield 80–95%) and the filtrate is evaporated. The residue consists of the alkylated ylide; it is often obtained as an oil, but this generally crystallizes when rubbed and can be recrystallized from ethyl acetate.

The original literature[456,463] should be consulted for alkylation by pyrylium salts and the subsequent reactions then observed (formation of aromatic compounds and azulenes). Cyclizations that occur on intramolecular alkylation have been reviewed by Bestmann.[456]

Finally, mention should be made of the formylation of ylides by dimethylformamide and carbonyl chloride, which is analogous to the Vilsmeier reaction.[456,464]

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[460] H. O. House and H. Babad, *J. Org. Chem.*, **28**, 90 (1963); L. D. Bergelson, V. A. Vaver, L. I. Barsukov, and M. M. Shemyakin, *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, **1963**, 1134; *Chem. Abstr.*, **59**, 8607 (1963).

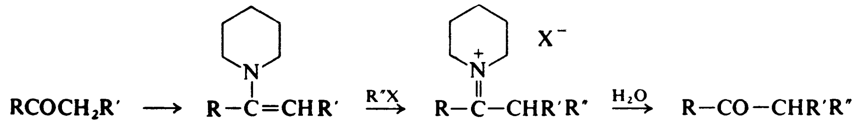
[461] H. J. Bestmann and H. Schulz, *Ann. Chem.*, **674**, 11 (1964).

[462] H. J. Bestmann and H. Schulz, *Chem. Ber.*, **95**, 2921 (1962); H. J. Bestmann, F. Seng, and H. Schulz, *Chem. Ber.*, **96**, 465 (1963).

[463] G. Märkl, *Angew. Chem. Int. Ed., Engl.*, **1**, 511 (1962).

[464] G. Märkl, *Tetrahedron Lett.*, **1962**, 1027.

(*β*) **Reactions of enamines.** Stork and his co-workers[465,466] found a new and generally applicable method of acylating and alkylating carbonyl compounds that has received wide use; it has been reviewed by Stork and his colleagues[467] and by Szmuszkowicz.[468] The carbonyl compound is first converted by reaction with a secondary amine into an enamine (see page 516), which can then be smoothly acylated or alkylated in good yield; the resulting immonium salt can then be hydrolysed to the α-substituted carbonyl compound:



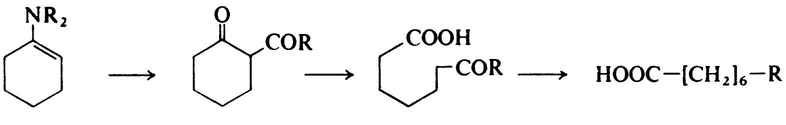
Both aldehydes (R = H) and ketones (R = alkyl or aryl) can be used as the carbonyl compound.

Acyl groups are introduced by reaction of the enamine with an acid chloride (R'' = acyl).[465,467] The products of hydrolysis are then β-diketones or, if R = H, β-oxo aldehydes.[469]

Reaction of the enamines with ethyl chloroformate gives good yields of ethyl β-oxo carboxylates (R'' = $COOC_2H_5$),[465,467] and cyanogen chloride affords β-oxo nitriles (R'' = CN) smoothly.[470]

Further, enamines can be formylated by treatment with formic acid and acetic anhydride[467] or with dimethylformamide and carbonyl chloride, the latter process being analogous to the Vilsmeier reaction and sometimes giving very good yields.[471]

Some of the β-dicarbonyl compounds and substituted ketones obtained in the above-mentioned ways can be used without isolation for a wide variety of further reactions. For instance, Hünig and his co-workers[472] used such compounds for preparation of long-chain acids: the 2-acylcyclohexanones obtained from *N*,*N*-dialkyl-1-cyclohexenylamine and an acyl chloride were cleaved by acid to ω-acyl hexanoic acids, whose oxo groups were then reduced by the Wolff–Kishner method:



Moreover, they acylated enamines from cyclododecane by dicarbonyl dichlorides and then by ring expansion of the C_{12} system and acid fission obtained dicarboxylic acids of precisely predetermined chain length up to C_{56}.[472]

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[465] G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **76**, 2099 (1954).

[466] G. Stork and H. Landesman, *J. Amer. Chem. Soc.*, **78**, 5128 (1956).

[467] G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

[468] J. Smuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

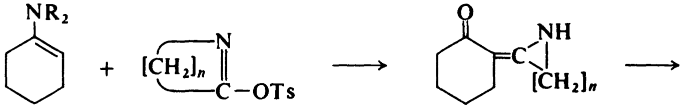
[469] T. Inukai and R. Yoshizawa, *J. Org. Chem.*, **32**, 404 (1967).

[470] M. E. Kuehne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959).

[471] W. Ziegenbein, *Angew. Chem. Int. Ed., Engl.*, **4**, 358 (1965).

[472] S. Hünig, E. Lücke, and E. Benzig, *Chem. Ber.*, **91**, 129 (1958); S. Hünig and H. J. Buysch, *Chem. Ber.*, **100**, 4017 (1967), and earlier papers.

Still further, by using lactim *O*-sulfonates for the acylation and an analogous series of further reactions they achieved long-chain ω-amino acids:[473]



$$NH_2{-}[CH_2]_n{-}CO{-}[CH_2]_5{-}COOH \rightarrow NH_2{-}[CH_2]_{n+6}{-}COOH$$

($Ts = p\text{-}CH_3C_6H_4SO_2$)

The original literature and the reviews[467,468] make interesting reading on these and other applications. Here we give only two examples of the technique:[467]

2-Hexanoylcyclohexanone: Hexanoyl chloride (13.0 g, 0.096 mole) is added to a well stirred solution of 4-(1-cyclohexenyl)morpholine (28.0 g, 0.17 mole) in anhydrous benzene (150 ml) under nitrogen and the mixture is boiled under reflux for 20 h, then cooled and filtered. The precipitated enamine hydrochloride is washed with dry ether, and the combined filtrates are treated with 10% aqueous hydrochloric acid (60 ml) and boiled under reflux for 4–6 h with vigorous stirring. The layers are separated and the aqueous phase is extracted with benzene. The benzene layers are united and as much as possible of the solvent is removed in a vacuum. Fractionating the residue gives the 2-hexanoylcyclohexanone (11.41 g), b.p. 132–155°/0.25 mm. A further amount (1.5 g) of the product is obtained by boiling the residue with dioxan (20 ml) and 10% aqueous hydrochloric acid (10 ml) for 3 h. The total yield amounts to 65–70%.

Ethyl 2-oxocyclohexanecarboxylate: Ethyl chloroformate (7.2 g, 0.066 mole) is added to a well stirred solution of 4-(1-cyclohexenyl)morpholine (20.0 g, 0.12 mole) in anhydrous benzene (100 ml) under nitrogen, and the mixture is boiled under reflux for 10 h, then cooled and filtered. The precipitate of enamine hydrochloride is washed with anhydrous ether. The united filtrates are treated with 10% aqueous hydrochloric acid (22 ml) and the mixture is stirred vigorously for 15–30 min. The layers are separated, the aqueous phase is extracted with benzene, the organic phases are united, and the solvent is distilled off under reduced pressure. Fractionation of the residue gives 62% (6.2 g) of the β-oxo ester, b.p. 112–115°/10 mm.

Alkylation (R'' = alkyl or substituted alkyl) is most satisfactorily accomplished with active halogen compounds such as allyl, benzyl, and propargyl halides, but α-halo ketones, esters, and nitriles can also be used.[467,474] Treating 1-(1-cyclohexenyl)pyrrolidine with allyl bromide in the presence of *N*-ethyldicyclohexylamine as base leads to introduction of two allyl groups, *i.e.*, formation of 2,6-diallylcyclohexanone.[475] Arylation can be effected by, for example, 1-chloro-2,4-dinitrobenzene (R'' = 2,4-dinitrophenyl).[476] *N*-Isobutyl-*n*-butylamine[477] and pyrrolidine[478] have been recommended as amine components for *C*-alkylation by simple alkyl halides such as ethyl and methyl iodides. The following two examples are illustrative:

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[473] S. Hünig, W. Grässmann, V. Meurer, E. Lücke, and W. Brenninger, *Chem. Ber.*, **100**, 3039 (1967).

[474] G. Opitz and H. Mildenberger, *Angew. Chem.*, **72**, 169 (1960).

[475] G. Opitz, H. Mildenberger, and H. Suhr, *Ann. Chem.*, **649**, 47 (1961).

[476] M. E. Kuehne, *J. Amer. Chem. Soc.*, **84**, 837 (1962).

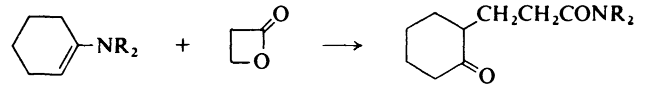
[477] T. J. Curphey and J. Chao–Yu Hung, *Chem. Commun.*, **1967**, 510.

[478] G. Stork and J. W. Schulenberg, *J. Amer. Chem. Soc.*, **84**, 284 (1962).

2-Benzylcyclohexanone:[467] Benzyl chloride (6 g) is added to a solution of 1-(1-cyclohexyl)-pyrrolidine (5 g) in dioxan (25 ml) and the mixture is boiled under reflux for 12 h. Then water (5 ml) is added and the whole is boiled for a further 3 h. The solvent is removed under diminished pressure, the residue is extracted with ether, and the ethereal phase is washed successively with 5% hydrochloric acid, 5% sodium carbonate solution, and water, dried, and evaporated. Distillation then gives 2-benzylcyclohexanone (3.3 g, 55%), b.p. 165–167°/18 mm. The residue from the distillation crystallizes when rubbed with light petroleum and on recrystallization from methanol provides 2,6-dibenzylcyclohexanone (0.5 g, 5.4%) as colorless, glittering plates, m.p. 122–123°.

2-Allyl-2-ethylhexanal:[475] A solution of 1-(2-ethyl-1-hexenyl)pyrrolidine (13.95 g, 0.08 mole) in acetonitrile (30 ml) is treated, slowly and with stirring, with an equimolar amount (9.3 g, 0.08 mole) of allyl bromide. The mixture is then boiled under reflux for 1 h and set aside at room temperature for 12 h. Most of the solvent is removed and the residue is hydrolysed with cold dilute hydrochloric acid (25 ml). The product is then removed in ether, washed with sodium hydrogen carbonate solution, dried, and distilled, giving 2-allyl-2-ethylhexanal (9.75 g, 75%), b.p. 83–85°/10 mm.

Alkylation is also achieved smoothly by lactones: 4-(1-cyclohexenyl)morpholine and β-propiolactone, when simply warmed together, give 3-(2-oxocyclohexyl)propionylmorpholide in 83% yield:[479]



A further method of α-alkylation, discovered by Stork, is to treat the Schiff base *N*-isobutylidene-*tert*-butylamine with a Grignard reagent, affording the magnesio enamine which can be alkylated in the same way as the above-mentioned enamines, *e.g.*;[480]

$$(CH_3)_2CH{-}CH{=}N{-}C_4H_9\text{-}t + C_2H_5MgBr \xrightarrow[-C_2H_6]{} (CH_3)_2C{=}C{-}N(MgBr)C_4H_9\text{-}t$$

$$\xrightarrow{C_6H_5CH_2Cl} C_6H_5CH_2C(CH_3)_2CH{=}N{-}C_4H_9\text{-}t \longrightarrow C_6H_5CH_2C(CH_3)_2CHO$$

(γ) Reactions of acetylenes. Acetylenes having hydrogen attached to the triply bonded atoms are acidic. They can thus be readily acylated and alkylated if presented as alkali or halomagnesium salts (acetylenic Grignard compounds).[481a]

Acetylenic Grignard reagents are formed when ethylmagnesium bromide reacts with acetylene or alkyl or aryl-acetylenes:

$$RC{\equiv}CH + C_2H_5MgBr \longrightarrow RC{\equiv}CMgBr + C_2H_6$$

They then yield acetylenic ketones when treated with acid anhydrides:

$$RC{\equiv}CH \xrightarrow{(R'CO)_2O} RC{\equiv}CCOR'$$

3-Octyn-2-one:[483] Ethyl chloride in twice its quantity of ether is converted into ethylmagnesium chloride by reaction with the metal. The solution is then stirred in an atmosphere of nitrogen while the calculated amount of an alkylacetylene is introduced. The mixture is

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[479] G. Schroll, P. Klemmensen, and S.-O. Lawesson, *Acta Chem. Scand.*, **18**, 2201 (1964)

[480] G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

[481] W. Ziegenbein, (a) "Äthinylierung und Alkinylierung," Verlag Chemie, Weinheim Bergstraße, 1963, (b) p. 9.

[482] J. W. Kroeger and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **58**, 1861 (1936).

[483] T. F. Rutledge, *J. Org. Chem.*, **22**, 649 (1957).

boiled under reflux until ethane is no longer evolved. With 0.25-molar batches the reaction requires about 2 h. Then the nitrogen atmosphere is restored.

Hexinylmagnesium chloride solution (0.25 mole), prepared as above, is cooled to −30° and stirred vigorously while acetic anhydride (0.5 mole) in ether is added at a rate such that the temperature does not exceed −25° (2.5 h). The mixture is stirred for a further 2 h at −30°, then for 2 h at −5° (ice–salt bath), the product is decomposed by ice-water, and the ethereal layer is fractionated. This affords some 1-hexyne (8 g) and the product, 3-octyn-2-one (18 g, 98% calculated on hexyne consumed), b.p. 76–77°/15 mm.

Similar procedures are used with alkali acetylides, which are obtained from acetylenes and either sodium in ether or alkali in liquid ammonia.[483–486]

Sodium acetylide:[483,484] A flask is fitted with a KPG stirrer, a gas-inlet tube, and an inlet for admission of reactants, and is placed in a Dewar beaker and cooled with methanol–carbon dioxide. Ammonia (200 ml) is added to the flask and is then saturated at −70° with pure acetylene. Introduction of acetylene is continued while sodium (6 g) is dropped in in small pieces. This gives a suspension of sodium acetylide that is generally used as such.

In another procedure a mixture of toluene and tetrahydrofuran is used as medium:[481b] Sodium (3 parts by weight) is stirred and heated under reflux in toluene (4 parts by weight) until the temperature reaches 105–110°. The mixture of molten sodium and toluene is then stirred with a high-speed stirrer for some minutes; the resulting suspension is cooled to room temperature as soon as stirring is stopped. Next, tetrahydrofuran (9 parts by weight) is added and a lively stream of acetylene is passed through the suspension. There is a slow rise in temperature, which is kept below 50° by cooling; it falls again after 3–4 h. The yield of monosodium acetylide is quantitative.

Potassium and lithium acetylide can be prepared analogously.

Finally, a convenient method of obtaining sodium acetylide is by reaction of acetylene or an alkylacetylene with the calculated amount of sodium (methylsulfinylmethyl)sodium (dimsyl sodium).[487]

For the synthesis of arylacetylenic ketones an alkali acetylide may be treated either with an acyl chloride[488] or with an acid anhydride.[489]

Benzoylphenylacetylene (1,3-diphenyl-2-propyn-1-one):[490] Phenylacetylene is dissolved in the five- to ten-fold amount of anhydrous ether and brought into contact with the calculated amount of sodium wire under ether. Hydrogen is at once evolved and a granular coating of sodium phenylacetylide is formed on the surface of the metal. The reaction is allowed to proceed with occasional shaking. The ether may then be cautiously distilled off, with exclusion of moisture, but that is unnecessary for synthesis of most acetylenic ketones.

The ethereal suspension of sodium phenylacetylide is treated with the calculated amount of benzoyl chloride and set aside for several hours. Then ice-water is added, and the ethereal layer is separated, dried over calcium chloride, and fractionated in a vacuum. Benzoylphenylacetylene is a moderately sensitive material and should be distilled at the lowest available pressures. The yield in the above synthesis is 74% of material boiling at 200–202°/15 mm.

Acetylphenylacetylene (4-phenyl-3-butyn-2-one):[489] Phenylacetylene (76 g, 0.75 mole) in ether (50 ml) is converted into sodium phenylacetylide by sodium (16.8 g) in ether (100 ml) as described by Gilman and Young.[491] More ether (100 ml) is added and the suspension is stirred slowly into a solution of acetic anhydride (76 g, 0.75 mole) in ether (200 ml) that is cooled in ice. The mixture is stirred for some hours more, then cold dilute hydrochloric acid is added, and the whole is set aside until the anhydride is hydrolysed. The ethereal layer is then washed thoroughly with sodium carbonate solution, dried over magnesium sulfate, and distilled in a vacuum. The product (58 g, 55%) boils at 120–125°/14 mm.

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[484] O. Neunhoeffer and V. Georgi, *Ber. Deut. Chem. Ges.*, **92**, 791 (1959).

[485] T. L. Jacobs, *Org. Reactions*, **5**, 1 25 (1949).

[486] K. N. Campbell and M. J. O'Connor, *J. Amer. Chem. Soc.*, **61**, 2897 (1939).

[487] J. Kříž, M. J. Beneš, and J. Peske, *Collect. Czech. Chem. Commun.*, **32**, 398 (1967).

[488] C. D. Heid and F. L. Cohen, *J. Amer. Chem. Soc.*, **53**, 1068 (1931).

[489] D. Nightingale and F. Wadsworth, *J. Amer. Chem. Soc.*, **67**, 416 (1945).

[490] J. U. Nef, *Ann. Chem.*, **308**, 275 (1899).

[491] H. Gilman and R. V. Young, *J. Org. Chem.*, **1**, 315 (1936).

For acylation by sensitive carboxylic acids it has been recommended[492] to treat lithium acetylides with mixed anhydrides of the carboxylic acid and a monoalkyl carbonate (prepared *in situ* from the carboxylic acid and ethyl chloroformate):

$$\mathrm{RCOOH + ClCOOC_2H_5 \longrightarrow RCO{-}O{-}COOC_2H_5 \xrightarrow{LiC\equiv CC_4H_9} RCOC{\equiv}CC_4H_9}$$

Silylated acetylenes can also be acylated: bis(trimethylsilyl)acetylene reacts with acetyl chloride in the presence of aluminum chloride in carbon disulfide, giving 4-(trimethylsilyl)-3-butyn-2-one in 90% yield:[493]

$$\mathrm{CH_3COCl + (CH_3)_3Si{-}C{\equiv}C{-}Si(CH_3)_3 \longrightarrow CH_3CO{-}C{\equiv}C{-}Si(CH_3)_3}$$

Sodium acetylides and chloroformic esters give the α-acetylenic carboxylic esters.[494]

When an alkali acetylide is allowed to react with an alkylating agent such as an alkyl halide or sulfate, the derived mono- or di-alkylacetylene is formed:

$$\mathrm{HC{\equiv}CNa + RX \longrightarrow HC{\equiv}CR}$$

$$\mathrm{R'C{\equiv}C{-}MgBr + (RO)_2SO_2 \longrightarrow R'C{\equiv}CR}$$

Using an alkyl bromide gives yields of 70–90% of monoalkylacetylene[495] and 30–70% of dialkylacetylene,[486] these yields being lower the longer the chain of the alkyl bromide. Alkyl sulfates[496] and sulfonates[487] give 60–85% yields of the mono- or di-alkylacetylene.

Acetylenic Grignard reagents can also be smoothly alkylated by alkyl halides, sulfates, or sulfonates:[485,498–500]

$$\mathrm{RC{\equiv}C{-}MgX + (R'O)_2SO_2 \longrightarrow RC{\equiv}CR'}$$

1,3-Diphenylpropyne:[498,499] An ethereal solution of (phenylethynyl)magnesium bromide is prepared by refluxing phenylacetylene (63 g, 0.6 mole) with an approximately molar solution of ethylmagnesium bromide in slight excess and is then added dropwise during 2.5 h to a stirred, gently boiling solution of benzyl *p*-toluenesulfonate (330 g, 1.25 moles) in anhydrous ether (900 ml). The mixture is then refluxed for a further 6 h, after which the product is hydrolysed by dilute, cold hydrochloric acid. The ethereal layer is separated, washed successively with water, sodium carbonate solution, and water, and evaporated. The residue is treated with 15% potassium hydroxide solution and distilled in steam. The distillate contains benzyl bromide and benzyl alcohol and is discarded. The involatile oil is taken up in ether, washed thoroughly with water, dried over anhydrous potassium carbonate, and distilled in a current of nitrogen. This affords 72% (84 g) of 1,3-diphenylpropyne, b.p. 150–160°/4 mm. A second distillation affords a pale yellow, highly refractive liquid, b.p. 128–129°/1–2 mm, d_4^{20} 1.0273, n_D^{20} 1.5946.

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[492] U. Schmidt and M. Schwochau, *Chem. Ber.*, **97**, 1649 (1964).

[493] L. Birkofer, A. Ritter, and H. Uhlenbrauck, *Chem. Ber.*, **96**, 3280 (1963).

[494] C. Moureau and R. Delange, *C. R. Hebd. Séances Acad. Sci.*, **136**, 552 (1903).

[495] K. N. Campbell and B. K. Campbell, *Org. Syn.*, **30**, 15 (1950); A. L. Henne and K. W. Greenlee, *J. Amer. Chem. Soc.*, **67**, 484 (1945).

[496] T. F. Rutledge, *J. Org. Chem.*, **24**, 840 (1959).

[497] A. L. Kranzfelder and F. J. Sowa, *J. Amer. Chem. Soc.*, **59**, 1490 (1937).

[498] J. R. Johnson, A. M. Schwartz, and T. L. Jacobs, *J. Amer. Chem. Soc.*, **60**, 1882 (1938).

[499] J. R. Johnson, T. L. Jacobs, and A. M. Schwartz, *J. Amer. Chem. Soc.*, **60**, 1885 (1938).

[500] I. A. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene," Reinhold Publ. Corp., New York, 1945, pp. 74–81; T. L. Jacobs and S. Singer, *J. Org. Chem.*, **17**, 475 (1952).

6-Chloro-1-hexyne:[451] 1-Bromo-4-chlorobutane (858 g, 5 moles) is added during 4 h to a mixture of sodium acetylide (5 moles) and liquid ammonia (3 l); the suspension is stirred for a further 7 h under reflux. After most of the ammonia has evaporated (8 h), water (2 l) is added. The organic layer is taken up in ether, washed with dilute hydrochloric acid and then water, and dried. Distillation affords 6-chloro-1-hexyne (430 g, 74%), b.p. 143–144°.

Alkylation of sodium acetylides by alkyl halides or sulfates also occurs smoothly and under mild conditions when dimethyl sulfoxide is used as solvent;[487] and, as mentioned above, sodium acetylides can be prepared simply in this medium.

Acetylenic amines are obtained by reaction of sodium acetylides with ω-bromo amine hydrobromides in dimethylformamide and liquid ammonia;[501] 7-octyn-1-amine has been prepared in 90% yield in this way.[501]

p-Iodoanisole and copper phenylacetylide give 4-methoxytolane in 83% yield.[502]

Bohlmann and his co-workers have described the synthesis of polyacetylenes from 1-bromo-2-phenylacetylene and butadiyne in the presence of copper(I) chloride[503] and by a multi-step method from bromopropiolic acid.[504]

2. Reactions with acidic condensing agents

a. Friedel–Crafts synthesis[270,271,505]

i, General

A Friedel–Crafts synthesis occurs according to the scheme:

$$\mathrm{ArH} + \mathrm{RX} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArR} + \mathrm{HX}$$

where R is, for instance, an alkyl or an acyl group. Such reactions have great preparative importance as they permit extremely varied types of carbon-containing groups to be introduced into aromatic compounds.

The recommended solvent is usually carbon disulfide, less often light petroleum or nitromethane. A mixture of nitromethane and carbon disulfide has been introduced more recently and has the practical advantages of providing a homogeneous medium to the end of the reaction and of moderating the action of the aluminum chloride.[506]

An excess of the aromatic hydrocarbon is generally used when it is cheap.

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[501] J.-L. Dumont, J. Tohier, and P. Cadiot, *C. R. Hebd. Séances Acad. Sci.*, **256**, 3146 (1963).

[502] C. E. Castro and R. D. Stephens, *J. Org. Chem.*, **28**, 2163, 3313 (1963).

[503] F. Bohlmann, P. Herbst, and H. Gleinig, *Chem. Ber.*, **94**, 948 (1961).

[504] F. Bohlmann, W. Sucrow, and I. Queck, *Chem. Ber.*, **97**, 2586 (1964).

[505] "Unit Processes in Organic Synthesis," P. H. Groggins, ed., McGraw–Hill Book Co., New York, 3rd ed., 1947, p. 759; G. Kränzlein, "Aluminiumchlorid in der organischen Chemie," Verlag Chemie, Berlin, 3rd ed., 1939; C. C. Price, *Org. Reactions*, **3**, 1 (1946); E. Berliner, *Org. Reactions*, **5**, 229 (1949); A. Schaarschmidt, *Angew. Chem.*, **37**, 286 (1924); W. Borsche and co-workers, *Ann. Chem.*, **553**, 260 (1942); **549**, 238 (1941).

[506] I. Reichel and R. Vilceanu, *Rev. Chim. (Bucharest)*, **11**, 206 (1960).

When the condensation can lead to position isomers the relative amounts produced may be influenced by the nature of the solvent (*e.g.*, for naphthalene, β-derivatives in nitrobenzene, α-derivatives in carbon disulfide, mixtures in light petroleum[507]). Aluminum chloride is the usual condensing agent.

A great deal of study has been devoted to determining the most suitable physical state of aluminum chloride used in Friedel–Crafts syntheses.[508-512] Pure aluminum chloride often gives different results from those obtained with material containing basic chlorides: benzene, trichloroacetyl chloride, and pure aluminum chloride give good yields of triphenylvinyl alcohol or ω,ω-diphenylacetophenone, but ω,ω,ω-trichloroacetophenone is the sole product when the aluminum chloride is moist and already slightly sticky.[513]

Care is needed when opening ampoules of aluminum chloride as there is usually an overpressure of hydrogen chloride inside. The coarse commercial material can generally be used without being powdered, since the reaction is usually of sufficient violence to require moderation and the coarse pieces still react smoothly. A finely powdered aluminum chloride should be used when the double compound formed in the reaction is first to be isolated or when the sluggishness of certain reactions necessitates stirring.

Titanium tetrachloride and tin tetrachloride are milder catalysts and have the important advantage of solubility in organic media such as carbon disulfide, so that reaction in a homogeneous phase becomes possible. Cullinane and Leyshon[514] recommend titanium tetrachloride particularly for alkylations since polyalkylation is then not observed. When the aromatic reactant carries an *ortho-para*-directing substituent, alkylation under the influence of titanium tetrachloride usually occurs only at the *para*-position.

Tin tetrachloride has often been recommended for the preparation of cyclic ketones;[515] it is also advantageous to use it with furan derivatives.

According to Meerwein and others,[32a,516] use of boron trifluoride may be valuable, since it forms well-defined molecular compounds with simple aliphatic carboxylic acids: for example, aromatic and heterocyclic hydrocarbons and aryl ethers can be acetylated smoothly and in good yield by acetic anhydride and boron trifluoride.[32a] The preparation of boron trifluoride has been described by Krause and Nitsche and by Booth and Willson.[517]

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[507] G. Baddeley, *J. Chem. Soc.*, **1949**, Suppl., 99; Ng P. Buu-Hoï and P. Cagniant, *Bull. Soc. Chim. France*, [v], **12**, 307 (1945); M. Chopin, *Bull. Soc. Chim. France*, [iv], **35**, 613 (1924).

[508] F. Stockhausen and L. Gattermann, *Ber. Deut. Chem. Ges.*, **25**, 3521 (1892).

[509] M. Gomberg, *Ber. Deut. Chem. Ges.*, **33**, 3144 (1900).

[510] V. Meyer, *Ber. Deut. Chem. Ges.*, **29**, 847 (1896).

[511] H. Biltz, *Ber. Deut. Chem. Ges.*, **26**, 1960 (1893).

[512] R. Scholl, *Ber. Deut. Chem. Ges.*, **32**, 3492 (1899).

[513] H. Biltz, *J. Prakt. Chem.*, **142**, 196 (1935).

[514] N. M. Cullinane and D. M. Leyshon, *J. Chem. Soc.*, **1954**, 2942.

[515] W. E. Bachmann and co-workers, *J. Amer. Chem. Soc.*, **64**, 94 (1942); **62**, 824 (1940); *J. Org. Chem.*, **6**, 36 (1941).

[516] H. Meerwein, *Ber. Deut. Chem. Ges.*, **66**, 411 (1933); H. Meerwein and D. Vossen, *J. Prakt. Chem.*, [ii], **141**, 149, 156 (1934); H. D. Hartough and A. I. Kosak, *J. Amer. Chem. Soc.*, **70**, 867 (1948); H. G. Walker, Jr., J. J. Sanderson, and C. R. Hauser, *J. Amer. Chem. Soc.*, **75**, 4109 (1953).

[517] E. Krause and R. Nitsche, *Ber. Deut. Chem. Ges.*, **54**, 2784 (1921); H. S. Booth and K. S. Willson, *J. Amer. Chem. Soc.*, **57**, 2273 (1935).

Ferric chloride can be applied with advantage for introduction of two acyl groups into polyhydric phenols,[518] and has been recommended for introduction of a *tert*-butyl group into *o*-xylene (73% yield).[519]

Zinc chloride is an efficient catalyst for acetylation of polyhydric phenols.[520]

Dermer and his colleagues[521] have made a study of the comparative efficiencies of various metal halides as catalysts.[521]

Naphthalene reacts well (90% yield) with benzoyl chloride in the presence of catalytic amounts of phosphoric oxide at 180–200°.[522] This method can also be usefully employed in the thiophene series,[523] where moreover excellent results (yields of more than 90%) have been obtained with phosphoric acid.[524,525]

Phosphoryl chloride catalyzes the reaction of polyhydric phenols with acetyl chloride,[526] particular success having been achieved in the phenol series with a mixture of phosphoryl chloride and zinc chloride.[527,528]

Hydrogen fluoride has occasionally been used for alkylation,[529] as has amalgamated aluminum.[530]

The Friedel–Crafts synthesis with acyl chlorides and anhydrides can be applied to all aromatic hydrocarbons and to many heterocyclic compounds, in particular to thiophene, furan, and pyrrol derivatives. Pyridine does not react,[531,532] and hydrocarbons carrying electron-attracting substituents react with difficulty or not at all.

However, the reaction gives good results with aromatic compounds carrying electron-donating substituents, *e.g.*, with alkyl derivatives, halides, aryl ethers, substituted amines, and phenols. In the absence of a condensing agent phenols give first the aryl esters (see pages 374 and 378), which can be rearranged to acyl phenols by a Fries reaction (see page 1068). The inhibiting effect of electron-attracting substituents may be removed by further substitution: unlike their analogs that do not contain an alkoxy group, *p*-nitroanisole[270,271a,505] and anisic esters can be both acylated and alkylated. 2-Furoic acid[533] and 1-naphthoic esters are also susceptible to Friedel–Crafts reactions.

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[518] M. Nencki, *Ber. Deut. Chem. Ges.*, **30**, 1766 (1897); **32**, 2414 (1899).

[519] B. W. Larner and A. T. Peters, *J. Chem. Soc.*, **1953**, 680; E. Illingworth and A. T. Peters, *J. Chem. Soc.*, **1952**, 2730.

[520] S. R. Cooper, *Org. Syn.*, **21**, 103 (1941).

[521] O. C. Dermer and co-workers, *J. Amer. Chem. Soc.*, **63**, 2881 (1941).

[522] S. Grucarevic and V. Merz, *Ber. Deut. Chem. Ges.*, **6**, 1240 (1873).

[523] W. Steinkopf and co-workers, *Ann. Chem.*, **413**, 343 (1917); **424**, 1 (1921).

[524] H. D. Hartough, A. I. Kosak, and L. G. Conley, *J. Amer. Chem. Soc.*, **69**, 3096, 3098 (1947).

[525] A. I. Kosak and H. D. Hartough, *Org. Syn.*, **28**, 1 (1948).

[526] H. von Euler, H. Hasselquist, and B. Högberg, *Ark. Kemi*, **20A**, No. 20 (1945).

[527] J. L. Bose and R. C. Shah, *J. Indian Chem. Soc.*, **38**, 701 (1961).

[528] P. K. Grover, G. D. Shah, and R. C. Shah, *Chem. & Ind. (London)*, **1955**, 62; S. R. Dolal and R. C. Shah, *Chem. & Ind. (London)*, **1957**, 140.

[529] J. H. Simons and S. Archer, *J. Amer. Chem. Soc.*, **60**, 2952, 2953 (1938).

[530] L. I. Diuguid, *J. Amer. Chem. Soc.*, **63**, 3527 (1941); W. W. Hartman and R. Phillips, *Org. Syn.*, Coll. Vol. 2, 232 (1955).

[531] C. M. Jephcott, *J. Amer. Chem. Soc.*, **50**, 1189 (1928).

[532] K. Thomas and D. Jerchel, *Angew. Chem.*, **70**, 719 (1958).

[533] H. Gilman and N. O. Calloway, *J. Amer. Chem. Soc.*, **55**, 4197 (1933).

Acetylation of aromatic compounds containing electron-donating substituents gives *ortho*- and *para*-compounds almost exclusively, but *meta*-derivatives are also formed in alkylations. Details concerning orientation should be sought in standard works and the literature.[270,271a,505,507]

Reactants with longer aliphatic chains give products containing branched-chain substituents, even when the starting material is a straight-chain alkyl halide; pure compounds are obtained only when the alkyl group of the halide is maximally branched, as in the production of *tert*-pentylbenzene from benzene and *tert*-pentyl chloride.

To carry out a reaction the aluminum chloride is added to one of the organic components and the solvent, and the other component is run in alone or in a solvent. If the catalyst is added first to the halogen compound, then — particularly with acyl chlorides — formation of a double compound must be expected, and this reacts less violently with the second component (the hydrocarbon);[534] this is known as the Perrier modification. On the other hand, it is better to add the catalyst to the hydrocarbon when the latter serves also as solvent, *e.g.*, benzene.

The optimal amount of condensing agent cannot be given as a generally applicable figure. In ketone syntheses it is never less than one equivalent, and a 30% excess usually does no harm.

For work with inert solvents the condensing agent is suspended or dissolved in the diluent, and the mixture or solution is added to the two reactants gradually in any suitable manner. This procedure is particularly valuable when one of the reactants is resinified by aluminum chloride, for, once formed, the acyl derivative or its molecular compound with aluminum chloride is generally stable.

When a reaction is undertaken for the first time, it is started with cooling (ice or a freezing mixture); incipient reaction is recognized by evolution of hydrogen chloride or a rise in temperature on removal of the cooling. If reaction is delayed its beginning is sometimes sudden and very violent. It is also possible to start the reaction at a higher temperature and to use a lower temperature for its continuation. Progress of the reaction is best followed by the evolution of hydrogen chloride. In some cases the mixture can finally be warmed, as overheating is impossible with carbon disulfide because of its low boiling point; in other cases no warming is permissible. If there is no final warming, stirring should be continued after apparent end of the reaction, but in case of doubt this period should not be too extensive and certainly not overnight. However, evolution of hydrogen chloride never ceases completely, particularly at elevated temperatures. As reported by Calloway and Green,[535] undesirable further reactions may occur if the reaction time is too prolonged.

For working up, the reaction mixture is poured on crushed ice and acidified with hydrochloric acid — until all the aluminum hydroxide has dissolved; or the reaction mixture may be poured into a mixture of fuming hydrochloric acid and ice, best contained in a wide-necked separatory funnel. Adding ice and hydrochloric acid to the reaction mixture may cause local overheating and decomposition; when, however, this procedure is unavoidable because of

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[534] D. T. Mowry, M. Renoll, and W. F. Huber, *J. Amer. Chem. Soc.*, **68**, 1105 (1946).

[535] N. O. Calloway and L. D. Green, *J. Amer. Chem. Soc.*, **59**, 809 (1937).

the viscosity of the reaction mixture, the latter must first be cooled and the ice then added all at once so as to moderate the violence of the decomposition.

ii, Alkylation of aromatic compounds[270,271a,505,536]

Friedel–Crafts alkylation has not the preparative importance of acylation by this method. For alkylation, titanium tetrachloride is recommended[514] as condensing agent in place of aluminum chloride which usually has too violent a reaction for this purpose (see Thomas[270c]). Titanium chloride dissolves well in organic solvents, does not cause polyalkylation and places the alkyl group only at the *para*-position to substituents already present. Alkyl chlorides or olefins can be used as alkylating agent, but alcohols are also effective (see page 950). When an alcohol is used an equivalent of titanium chloride must be added, but with alkyl chlorides and olefins traces suffice. Some authors recommend ferric chloride as catalyst, *e.g.*, for introducing a *tert*-butyl group into *o*-xylene which can be achieved with 73% yield.[519] *p*-Toluenesulfonic esters can also be used as alkylating agent.[537] The olefins which can often be used in place of alkyl halides react as if addition of hydrogen chloride had already taken place: thus propene reacts like isopropyl chloride, and isobutene like *tert*-butyl chloride.

Alkylation with compounds containing more than two carbon atoms almost always gives products containing branched chains: thus with benzene *n*-propyl chloride gives isopropylbenzene and not *n*-propylbenzene. The occasional exceptions — alkylation without isomerization — occur when the reaction takes place at low temperatures or involves long-chain alkyl groups.[537,538]

The following preparation of **octadecylbenzene**[537] illustrates the technique:

To procure dry solvent, 39 g are distilled off from 156 g of benzene. To the residue are added octadecyl *p*-toluenesulfonate (42.5 g, 0.1 mole) and aluminum chloride (13.3 g, 0.1 mole) and the mixture is stirred for 15 h at room temperature, then for 10 h at 50–55°, and finally again at room temperature for 14 h. The deep orange mixture is added to an excess of ice and hydrochloric acid; the organic layer is separated, washed with warm dilute hydrochloric acid, and dried over calcium chloride, then the benzene is distilled off. The residue is distilled once at water-pump vacuum and again at 0.25 mm, giving octadecylbenzene (24.2 g, 73%), b.p. 155–160°/0.25 mm.

Aromatic compounds containing straight-chain alkyl groups can also be synthesized by the Wurtz–Fittig reaction; the two methods are complementary.

Friedel–Crafts syntheses of alkylbenzenes and alkylnaphthalenes can also be effected with amalgamated aluminum as catalyst if this is activated by an alkyl chloride immediately before the main reaction.[530] Yields are on occasions very good and side reactions such as resinification are avoided.

Interaction of methyl 2-chloro-2-methoxyacetate and a benzene derivative gives the corresponding *O*-methylmandelic ester in yields of up to 90%, and

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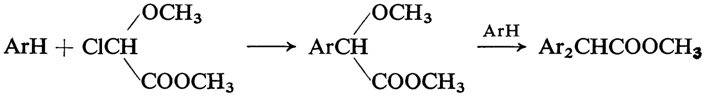
[536] C. C. Price, *Org. Reactions*, **3**, 1 (1946); *Chem. Rev.*, **29**, 44 (1941); A. W. Francis, *Chem. Rev.*, **43**, 257 (1948); O. Calloway, *Chem. Rev.*, **17**, 327 (1935).

[537] D. A. Shirley and J. R. Zietz, Jr., *J. Amer. Chem. Soc.*, **75**, 6333 (1953); W. J. Hickinbottom and N. W. Rogers, *J. Chem. Soc.*, **1957**, 4124.

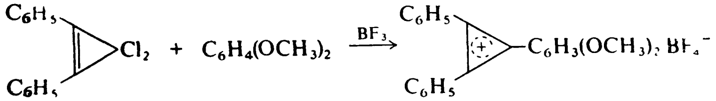
[538] H. Gilman and J. A. V. Turck, Jr., *J. Amer. Chem. Soc.*, **61**, 478 (1939).

if an excess of the aromatic component is used the diarylacetic ester is obtained in one step.[539]

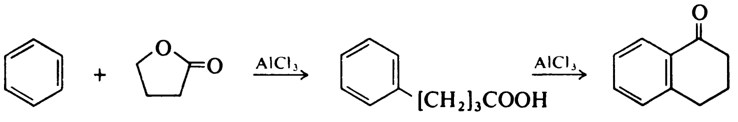


$$\mathrm{ArH} + \mathrm{ClCH}(\mathrm{OCH_3})\mathrm{COOCH_3} \longrightarrow \mathrm{ArCH}(\mathrm{OCH_3})\mathrm{COOCH_3} \xrightarrow{\mathrm{ArH}} \mathrm{Ar_2CHCOOCH_3}$$

Activated aromatic compounds are also alkylated by 3,3-dichloro-1,2-diphenylcyclopropene in a less usual type of reaction: in the presence of boron trifluoride etherate, resorcinol dimethyl ether, for instance, gives 1-(2,4-dimethoxyphenyl)-2,3-diphenylpropylium fluoroborate:[540]

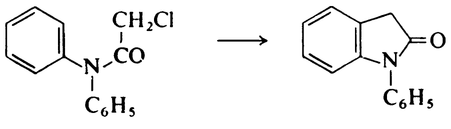


Strained cyclic ethers react with aromatic compounds with formation of hydroxyalkyl derivatives: with ethylene oxide (oxirane) and aluminum chloride, benzene gives phenethyl alcohol in 70% yield,[541] and with oxetane gives 3-phenyl-1-propanol.[542] Lactones undergo a similar reaction: in the presence of 0.3 equivalent of aluminum chloride, butyrolactone and benzene affords 4-phenylbutyric acid (73%), but when 0.6 equivalent of aluminum chloride is used the product is 1-tetralone (66%):[543]



For reaction of β-lactones with substituted propionic acids papers by Harley-Mason[544] should be consulted.

Cyclic compounds can be formed by intramolecular alkylation: when warmed with aluminum chloride, *N*-(chloroacetyl)diphenylamine gives 1-phenyloxindole in 90% yield:[546]



According to Rieche and Schmitz[545] isochroman is formed smoothly in more than 90% yield when phenethyl alcohol is treated with formaldehyde and hydro-

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[539] H. Gross and J. Freiberg, *Chem. Ber.*, **99**, 3260 (1966); *Z. Chem.*, **7**, 148 (1967).

[540] H. Föhlisch and P. Bürgle, *Ann. Chem.*, **701**, 67 (1967).

[541] H. Hopff and K. Koulen, *Ber. Deut. Chem. Ges.*, **85**, 897 (1952).

[542] S. Searles, *J. Amer. Chem. Soc.*, **76**, 2313 (1954).

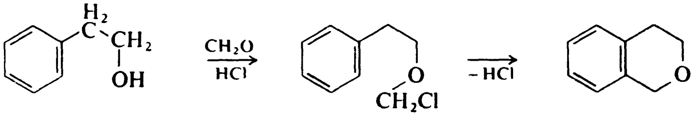
[543] W. E. Truce and C. E. Olson, *J. Amer. Chem. Soc.*, **74**, 4721 (1952); C. E. Olson and A. R. Bader, *Org. Syn.*, **35**, 95 (1955); W. L. Mosby, *J. Org. Chem.*, **18**, 964 (1953).

[544] J. Harley-Mason, *Chem. & Ind.* (*London*), **1951**, 886; *J. Chem. Soc.*, **1952**, 2433; T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick, and W. L. Bears, *J. Amer. Chem. Soc.*, **73**, 2345 (1951).

[545] P. Chovin and J. Gunthart, *Bull. Soc. Chim. France*, [v], **12**, 100 (1945).

[546] A. Rieche and E. Schmitz, *Ber. Deut. Chem. Ges.*, **89**, 1254 (1956).

gen chloride; the chloromethyl phenethyl ether formed as intermediate cyclizes with loss of hydrogen chloride even in the absence of a catalyst:



iii, Acylation of aromatic compounds

(α) Acylation by carbonyl chlorides. Since Friedel–Crafts acylation is treated in detail in elementary textbooks, two examples will suffice here.

***p*-Pentylacetophenone:** Aluminum chloride (20 g) is placed in a flask fitted with a stirrer and dropping funnel, carbon disulfide (100 ml) is added, and a mixture of pentylbenzene (15 g) and acetyl chloride (10.5 g) is dropped in with stirring and cooling in ice. Immediately after this addition, and in spite of any further evolution of hydrogen chloride, the resulting clear yellow solution is added to a mixture of ice and concentrated hydrochloric acid, and ether is added until the oily layer is lighter than water. This layer is then separated, washed with water until neutral, and dried over calcium chloride. The solvent mixture is distilled off and the residue is fractionated. *p*-Pentylacetophenone (16 g, 83%) distils at 132–133°/4 mm. Yields are appreciably lower if the reaction mixture is set aside for any length of time after mixing of the reactants.

***trans*-Dibenzoylethylene (*trans*-1,4-diphenyl-2-butene-1,4-dione):**[547] Fumaroyl chloride (18 g) is added slowly, with stirring under a reflux condenser, to a mixture of finely powdered aluminum chloride (31 g) and benzene (250 ml). After 1 hour's stirring at room temperature the mixture is poured on ice, and the benzene layer is separated, washed with sodium carbonate solution, dried, and concentrated. From the concentrated solution dibenzoylethylene separates as pale yellow needles; further evaporation yields a product that is colored red by an impurity. The crystals are recrystallized with charcoal from ethanol (yield 20.5 g, 74%) and then melt at 111°.

Boiling chloroacetyl chloride with pyrocatechol and phosphoryl chloride in benzene gives ω-chloro-3,4-dihydroxyacetophenone in 85% yield.[526] *para*-Acylation of acetanilide in 79–83% yield has been effected by chloroacetyl chloride and aluminum chloride in carbon disulfide.[548]

Diketones can be obtained by use of dicarbonyl dichlorides, *e.g.*, 1,6-diphenyl-1,6-hexanedione in 81% yield from adipoyl dichloride.[549] For the use of oxalyl bromide see page 980.

Ester chlorides of dicarboxylic acids, *e.g.*, ethoxalyl chloride afford arylglyoxalic esters:[550,551]

$$\mathrm{ArH} + \mathrm{ClCOCOOC_2H_5} \longrightarrow \mathrm{ArCOCOOC_2H_{25}} + \mathrm{HCl}$$

and these can be converted in various ways into other products such as arylacetic acids[551] and aldehydes (see page 1017).

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[547] J. B. Conant and R. E. Lutz, *J. Amer. Chem. Soc.*, **45**, 1303 (1923); N. Campbell and N. M. Khanna, *J. Chem. Soc.*, **1949**, Suppl. 33.

[548] J. L. Leiserson and A. Weissgerber, *Org. Syn.*, **28**, 26 (1948); N. J. Leonard and A. M. Hyson, *J. Amer. Chem. Soc.*, **71**, 1961 (1949).

[549] R. C. Fuson and J. T. Walker, *Org. Syn.*, Coll. Vol. 2, 169 (1955).

[550] L. Roser, *Ber. Deut. Chem. Ges.*, **14**, 940, 1750 (1881); L. Bouveault, *C. R. Hebd. Séances Acad. Sci.* **122**, 1062, 1207 (1896); *Bull. Soc. Chim. France*, [iii], **15**, 1014 (1896).

[551] K. Kindler, W. Metzendorf, and Dschi-yin-Kwok, *Ber. Deut. Chem. Ges.*, **76**, 308 (1943).

Because it appears as a "neutral" product, the methyl ester chloride of phthalic acid has various advantages over the anhydride for preparation of aroylbenzoic acids and esters:[552] reaction times are shorter, the required temperatures are lower, yields are good, and the products are more easily isolated.

(β) Acylation by carboxylic anhydrides or acids. Carboxylic anhydrides can be used in place of acyl chlorides, the reaction being:

$$\mathrm{ArH} + (\mathrm{RCO})_2\mathrm{O} \longrightarrow \mathrm{ArCOR} + \mathrm{RCOOH}$$

This often gives better yields than are obtained from the corresponding acyl chloride, *e.g.*, in the case of acetophenone. Boron trifluoride is particularly useful in these reactions as a mild condensing agent.[32a,516]

Perchloric acid has also been recommended as condensing agent, as, for example, in the case of **acetylthiophen:**[553]

A mixture of acetic anhydride (15.5 g) and 60% perchloric acid (*d* 1.535; 6 drops) is added to thiophen (8.5 g) with stirring, and the mixture is set aside for 30 min and then poured into a mixture of ice and water (50 ml). The organic layer is separated, and the aqueous layer is extracted with ether. The united organic phases are washed with water and then with sodium carbonate solution, dried over sodium sulfate, and distilled, affording 2-acetylthiophene, b.p. 209–212°, in 95% yield.

2-Acetylthiophen can also be prepared from thiophen and acetic anhydride with boron trifluoride (70% yield),[32a,516] 85% phosphoric acid,[554] "concentrated" phosphoric acid,[525] or sulfuric acid.[555]

2,5-Dimethylfuran is acetylated in 87% yield at position 3 by acetic anhydride and tin tetrachloride at room temperature.[556]

Indole is acetylated at position 3 by acetic anhydride without a catalyst when vinyl acetate is used as reaction medium.[557] Heating benzanilide and benzoic anhydride with polyphosphoric acid for 3 hours at 150° leads, after hydrolysis, to an 84% yield of *p*-aminobenzophenone.[558] Trifluoroacetylation of azulenes has been reported by Anderson and Anderson.[559]

Cyclic anhydrides react in the same sense; their use in Friedel–Crafts syntheses has been reviewed by Berliner.[505] For example, phthalic anhydride and benzene give *o*-benzoylbenzoic acid in yields exceeding 90%;[560] succinic anhydride with benzene gives 4-oxo-4-phenylbutyric acid,[561] and with anisole in the presence of aluminum chloride gives 4-(*p*-methoxyphenyl)-4-oxobutyric

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[552] C. Dufraisse and A. Allais, *Bull. Soc. Chim. France*, [v], **11**, 531 (1944).

[553] G. N. Dorofeenko, *Zh. Vsesoyuz. Khim. Obshchestva im. D. I. Mendeleeva*, **5**, 354 (1960); *Chem. Abstr.*, **54**, 22 563 (1960).

[554] J. Kellett and H. E. Rasmussen, *Ind. Eng. Chem.*, **40**, 384 (1948).

[555] S. S. Israelstam and H. Stephen, *J. S. Afr. Chem. Inst.*, **26**, 41, 49 (1943); **27**, 15 (1944).

[556] P. H. Williams, G. B. Payne, W. J. Sullivan, and P. R. Van Ess, *J. Amer. Chem. Soc.*, **82**, 4883 (1960).

[557] G. Hart, D. R. Liljegren, and K. T. Potts, *J. Chem. Soc.*, **1961**, 4267.

[558] D. A. Denton and H. Suschitzky, *J. Chem. Soc.*, **1963**, 4741; J. D. Edwards, Jr., S. E. McGuire, and C. Hignite, *J. Org. Chem.*, **29**, 3028 (1964).

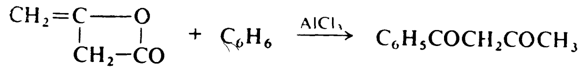
[559] A. G. Anderson, Jr., and R. G. Anderson, *J. Org. Chem.*, **27**, 3578 (1962).

[560] C. Friedel and J. M. Crafts, *Ann. Chim. (Paris)*, [vi], **14**, 433 (see p. 446) (1888); G. Heller and co-workers, *Angew. Chem.*, **19**, 669 (1906); *Ber. Deut. Chem. Ges.*, **41**, 3631 (1908).

[561] S. Gabriel and J. Colman, *Ber. Deut. Chem. Ges.*, **32**, 395 (1899).

acid in 93% yield;[562] maleic anhydride and *m*-xylene in tetrachloroethane containing aluminum chloride as catalyst at 0° gives 4-(2,4-dimethylphenyl)-4-oxo-2-butenoic acid smoothly in 91% yield.[563]

Diketene affords diketones in reactions such as:[564]



$$\begin{array}{l}CH_2{=}C{-}O\\ \quad\ |\qquad |\\ CH_2{-}CO\end{array} + C_6H_6 \xrightarrow{AlCl_3} C_6H_5COCH_2COCH_3$$

Carboxylic acids themselves can also be used for acylation. **Acetophenone** can be obtained as follows:[565]

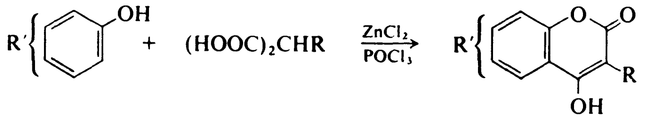
Heating benzene (390 g, 5 moles), glacial acetic acid (60 g, 1 mole), and aluminum chloride (400 g, 3 moles) for 5.5 h at 86° (b.p. benzene) gives a 64% yield (77 g) of acetophenone.

This procedure can be extended to aromatic carboxylic acids.[565]

The following are some further examples. Acetomesitylene is obtained from mesitylene and glacial acetic acid in the presence of phosphoric oxide and kieselguhr, yields reaching 82.5%.[525,566] (*o*-Nitrobenzoyl)mesitylene is obtained (75%) from mesitylene and *o*-nitrobenzoic acid in the presence of boron trifluoride and trifluoroacetic anhydride.[567] Toluene and benzoic acid in the presence of molybdenum pentafluoride give a 70% yield of 4-methylbenzophenone, but with aluminum chloride give a mixture of the 2- and the 4-methyl derivative.[568]

The relatively high temperature sometimes used in these reactions may lead to formation of by-products; thus, for example, binaphthyl is formed during acetylation of naphthalene.

Polyhydric phenols react with carboxylic acids even in the presence of zinc chloride[520] or boron trifluoride and hydrogen fluoride.[569] A mixture of zinc chloride and phosphoryl chloride has been recommended[527,528] as a very efficient and mild agent for condensation of variously substituted phenols with malonic acid derivatives; this leads to 4-hydroxycoumarins without isolation of the intermediates:[527,528]



Hydroxy-benzophenones and -propiophenones can be obtained in the same way; substituted salicylic acid ethers and phenols lead to xanthones by way

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[562] D. G. Thomas and A. H. Nathan, *J. Amer. Chem. Soc.*, **70**, 331 (1948).

[563] D. Papa and co-workers, *J. Amer. Chem. Soc.*, **70**, 3356 (1948); O. Grummitt, E. I. Becker, and C. Miesse, *Org. Syn.*, **29**, 11 (1949).

[564] A. B. Boese, Jr., *Ind. Eng. Chem.*, **32**, 16 (1940).

[565] P. H. Groggins, R. H. Nagel, and A. J. Stirton, *Ind. Eng. Chem.*, **26**, 1313, 1317 (1934).

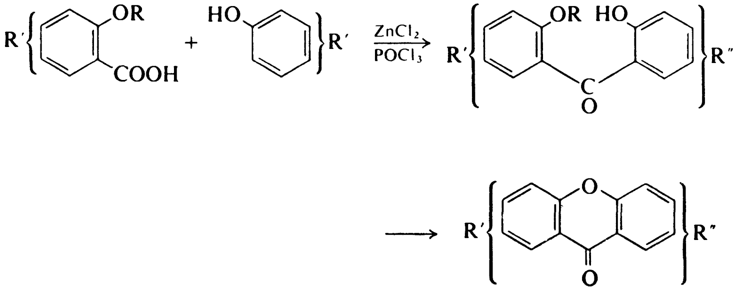
[566] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 1651 (1947).

[567] H. H. Szmant and C. M. Harmuth, *J. Amer. Chem. Soc.*, **81**, 962 (1959).

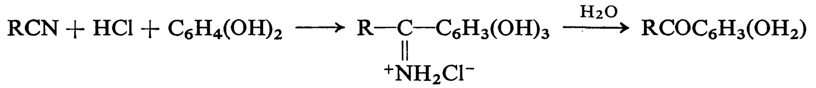
[568] M. L. Larson, *J. Amer. Chem. Soc.*, **82**, 1223 (1960).

[569] Ng. P. Buu-Hoi, and Ng. D. Yuong, *J. Org. Chem.*, **26**, 2401 (1961).

of the derived hydroxybenzophenones:[527,528]



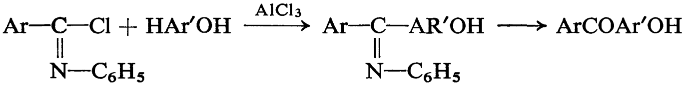
(γ) Houben–Hoesch synthesis. The Houben–Hoesch synthesis[570] is a method of introducing an acyl group into a phenol or aryl ether: nitriles are treated with phenols in the presence of hydrochloric acid, the reaction being exemplified as:



$$RCN + HCl + C_6H_4(OH)_2 \longrightarrow \underset{\underset{{}^+NH_2Cl^-}{\|}}{R{-}C{-}C_6H_3(OH)_3} \xrightarrow{H_2O} RCOC_6H_3(OH_2)$$

Ketimine hydrochlorides are formed as intermediates and give the phenolic ketones on hydrolysis. Ether is generally the solvent chosen. The use of zinc chloride as catalyst has been recommended for special cases.

Reaction of imidoyl chlorides with phenols in the presence of aluminum chloride and subsequent hydrolysis also give phenolic ketones:[571]



$$\underset{\underset{N-C_6H_5}{\|}}{Ar{-}C{-}Cl} + HAr'OH \xrightarrow{AlCl_3} \underset{\underset{N-C_6H_5}{\|}}{Ar{-}C{-}AR'OH} \longrightarrow ArCOAr'OH$$

(δ) Preparation of cyclic ketones.[270,271a,505,572] Ring closure at the *ortho*-position occurs easily and often in excellent yield provided that the new ring is five- or six-membered. Moreover, the new ring may contain hetero atoms. Some cases have been cited on the preceding pages; the following is a selection from the numerous other examples in the literature:

1-Naphthylacetyl chloride ⟶ 1-acenaphthenone[573]
(Phenylthio)acetyl chloride ⟶ thioindoxyl[573]
4-Phenylheptanedioyl dichloride ⟶ 3-(1,2,3,4-tetrahydro-4-oxo-1-naphthyl)-propionic acid[574]
3-Chloropropionanilide ⟶ 3,4-dihydro-2(1*H*)-quinolone[575]
o-(4-Methylbenzyl)benzoic acid ⟶ 2-methyl-9-anthrone[576]

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[570] K. Hoesch, *Ber. Deut. Chem. Ges.*, **48**, 1122 (1915); K. Hoesch and T. von Zarzecki, *Ber. Deut. Chem. Ges.*, **50**, 462 (1917); J. Houben, *Ber. Deut. Chem. Ges.*, **59**, 2878 (1926); P. E. Spoerri and A. S. Du Bois, *Org. Reactions*, **5**, 387 (1949).

[571] R. Phadke and R. C. Shah, *J. Indian Chem. Soc.*, **27**, 349 (1950).

[572] W. S. Johnson, *Org. Reactions*, **2**, 114 [1944).

[573] Ger. Pat. 197,162; 230,237; *Chem. Abstr.*, **2**, 2454 (1908); **5**, 2699 (1911).

[574] R. H. Manske, *J. Amer. Chem. Soc.*, **53**, 1104 (1931).

[575] F. Mayer and co-workers, *Ber. Deut. Chem. Ges.*, **60**, 858 (1927).

[576] L. F. Fieser and H. Heymann, *J. Amer. Chem. Soc.*, **64**, 376 (1942).

o-(Bromomethyl)benzoyl bromide + benzene ⟶ anthrone[577]
3-(2-Bromo-5-methoxyphenyl)propionic acid ⟶ 4-bromo-7-methoxy-1-indanone[578]
p-Thiocresol + oxalyl chloride ⟶ 5-methyl-1-benzothiophene-2,3-dione[579]

The preparation of **7,8,9,10-tetrahydro-5(*6H*)benzocyclooctenone**[580] illustrates both such cylizations and the dilution principle:

Finely powdered aluminum chloride (100 g, 0.75 mole) and carbon disulfide (1750 ml; distilled from aluminum chloride) are placed in a flask (capacity 4 l) fitted with a stirrer and reflux condenser. Whilst this mixture is stirred and refluxed vigorously, 6-phenyloctanoyl chloride (45.6 g, 0.216 mole) in carbon disulfide (1250 ml) is added during 40 h through the condenser, this arrangement ensuring that the chloride solution is further diluted by the refluxing solvent. The reaction mixture soon becomes colored, and a dark brown solid encrusts the walls of the flask. The mixture is refluxed for a further 2 h after the addition is complete, then the solvent is distilled off and the residue is hydrolysed by ice and water (about 1 kg). The product is next distilled off in much steam, and the distillate (about 5 l) is saturated with sodium chloride and extracted with ether. After removal of the ether, the tetrahydrobenzocyclooctenone distils at 146–148° in a vacuum, the yield at this stage being 68% (25.9 g). Careful redistillation gives a colorless liquid, b.p. 148–148.5°/12 mm.

Other condensing agents used for such ring closures include hydrogen fluoride,[576] polyphosphoric acid,[578] phosphoryl chloride,[581] zinc chloride,[582] and mixtures of phosphoryl chloride and zinc chloride.[527,528]

iv, *Synthesis of aromatic aldehydes*[106e,347,583]

When an aromatic compound is treated with a mixture of carbon monoxide and hydrogen chloride in the presence of aluminum chloride and copper(I) chloride, the derived aromatic aldehyde is obtained. Presumably formyl chloride is formed from the carbon monoxide and hydrogen chloride, although it is stable only as the adduct with aluminum chloride.

$$\mathrm{ArH} + [\mathrm{HCOCl}] \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCHO} + \mathrm{HCl}$$

This is known as the Gattermann–Koch synthesis. It is used industrially in special cases but is less suitable for laboratory work because it is preparatively inconvenient and tedious and must often be conducted under pressure. Its use is mainly restricted to treatment of alkylbenzenes.

The reaction is carried out by passing a stream of dry hydrogen chloride plus carbon monoxide (generated from chlorosulfuric and formic acid[584]) into a solution of the hydrocarbon in ether or nitrobenzene containing aluminum chloride and copper(I) chloride. Yields then range from 30% to 50% but are increased to 80–90% by working under pressure without the copper

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[577] F. Mayer and W. Fischbach, *Ber. Deut. Chem. Ges.*, **58**, 1251 (1925).

[578] H. R. Snyder and F. X. Werber, *J. Amer. Chem. Soc.*, **72**, 2965 (1950).

[579] D. Papa, E. Schwenk, and H. F. Ginsberg, *J. Org. Chem.*, **14**, 723 (1949).

[580] R. Huisgen and W. Rapp, *Ber. Deut. Chem. Ges.*, **85**, 826 (1952).

[581] L. Goldberg and R. Robinson, *J. Chem. Soc.*, **1941**, 575.

[582] A. T. Marchevskii and M. I. Ushakov, *Zh. Obshch. Khim.*, **10**, 1369 (1940); *Chem. Abstr.*, **35**, 3626 (1941).

[583] N. N. Crounse, *Org. Reactions*, **5**, 290 (1952).

[584] L. Bert, *C. R. Hebd. Séances Acad. Sci.*, **221**, 77 (1945).

chloride.[585] There is a prescription[586] for preparation of *p*-tolualdehyde in 46–51% yield; and on a laboratory scale 2-(chloromethyl)-5-hydroxy-4-pyrone is almost quantitatively formylated at position 3 by carbon monoxide and hydrogen chloride in trifluoroacetic acid.[587]

More recently, Oláh and Kuhn[588] have performed such formylations by the relatively stable formyl fluoride at 0–10° in carbon disulfide with boron trifluoride as catalyst; yields of 56–78% were obtained from various aromatic hydrocarbons.

The Gattermann–Koch synthesis fails with phenols and aryl ethers. However, Gattermann showed[106f,589] that good results were obtained if such compounds were treated with hydrogen chloride and hydrogen cyanide in the presence of zinc chloride; the aldimine hydrochloride is first formed and gives the aldehyde on hydrolysis:

$$\mathrm{ArH + HCN + HCl \xrightarrow{ZnCl_2} ArCH{=}NH_2^+Cl^- \longrightarrow ArCHO}$$

An improvement by Adams and his collaborators[590] makes this into a convenient laboratory method; they replaced the hydrogen cyanide-hydrogen chloride by zinc cyanide and hydrogen chloride, then obtaining yields of more than 90%.

2,4-Dihydroxybenzaldehyde:[590] A reaction flask (500-ml capacity) is fitted with an efficient stirrer, a reflux condenser, and a wide gas-inlet tube; the end of the condenser is connected to, successively, a wash-bottle containing sulfuric acid, an empty safety flask, and a tube that passes over the surface of a sodium hydroxide solution. Resorcinol (20 g) and anhydrous ether (150–200 ml) are placed in the reaction flask, and anhydrous zinc cyanide (1.5 equivalents) is added. Then a rapid stream of dry gaseous hydrogen chloride is passed in. The zinc cyanide disappears as a milky mixture is formed; and as the hydrogen chloride dissolves, the imide hydrochloride condensation product separates as a thick oil which solidifies in 10–30 min. The ether is usually saturated in 1.5 h, after which hydrogen chloride is passed in slowly for a further 0.5 h. Then the ether is decanted, water (100 ml) is added to the imide hydrochloride, and the solution is heated to the boiling point, filtered and allowed to cool. About half the aldehyde separates. After this has been collected the remainder of the aldehyde crystallizes in 10–15 h. The total yield is about 95%, and the m.p. is 135–136° after recrystallization with charcoal from water.

The preparation of anhydrous zinc chloride is described in the original paper.[590]

Aromatic hydrocarbons can also be submitted to this reaction, particularly if Hinkel's modification[591] is used in which an aluminum chloride–hydrogen cyanide adduct forms the reactant.

Fuson and his co-workers[592] further improved the Adams modification: they raised the reaction temperature to 70°, using tetrachloroethane as solvent, and thus obtained particularly good yields from aromatic compounds.

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[585] J. H. Holloway and N. W. Krase, *Ind. Eng. Chem.*, **25**, 497 (1933).

[586] G. H. Coleman and D. Craig, *Org. Syn., Coll. Vol.* 2, 583 (1943).

[587] L. L. Woods and P. A. Dix, *J. Org. Chem.*, **26**, 1028 (1961).

[588] G. A. Oláh and S. J. Kuhn, *J. Amer. Chem. Soc.*, **82**, 2380 (1960).

[589] W. E. Truce, *Org. Reactions*, **9**, 37 (1957).

[590] R. Adams and I. Levine, *J. Amer. Chem. Soc.*, **45**, 2373 (1923); R. Adams and E. Montgomery, *J. Amer. Chem. Soc.*, **46**, 1518 (1924).

[591] L. E. Hinkel, E. E. Ayling, and W. H. Morgan, *J. Chem. Soc.*, **1932**, 2793; L. E. Hinkel, E. E. Ayling, and J. H. Beynon, *J. Chem. Soc.*, **1936**, 339.

[592] R. C. Fuson and co-workers, *J. Amer. Chem. Soc.*, **64**, 30 (1942); *Org. Syn.*, **23**, 57 (1943).

McDonald[593] reported very good yields in the formylation of pyrrol derivatives by hydrogen cyanide and hydrogen chloride in ether–chloroform mixtures, the method being due to Fischer and Zerweck.

A variant of the Gattermann–Koch reaction due to Rieche, Gross, and Höft[594] and applicable to aromatic hydrocarbons, phenols and their ethers, and heterocyclic compounds consists of the reaction of these compounds with alkyl dichloromethyl ethers in the presence of tin tetrachloride or aluminum chloride:

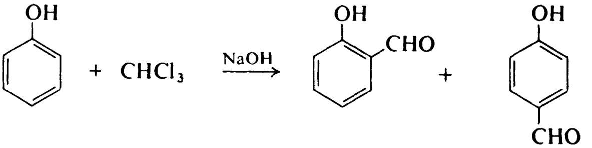
$$\mathrm{ArH} + \mathrm{ROCHCl_2} \xrightarrow{\mathrm{AlCl_3}} [\mathrm{ArCHClOR}] \xrightarrow{\mathrm{H_2O}} \mathrm{ArCHO}$$

This method is very convenient, requires relatively little time, and gives yields of 70–90%. It can be applied to condensed aromatic systems such as pyrene[594] and coronene[595] and to ferrocene[596] and colchicine.[597] Results are equally good when the alkyl dichloromethyl ether is replaced by dichloromethyl methyl sulfide.[598] An example is the formylation of veratrole described below, and the same procedure can be used for preparation of mesitylenecarbaldehyde from mesitylene:

3,4-Dimethoxybenzaldehyde:[599] Veratrole (83 g, 0.6 mole) and anhydrous methylene dichloride (350 ml) are placed in a three-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. Tin tetrachloride (260 g, 117 ml, 1 mole) is added during 3 min with stirring and ice-cooling, followed within 30 min under the same conditions by dichloromethyl methyl ether (total 57.5 g, 0.5 mole); when about a quarter of the ether has been added the ice-bath is removed until the reaction, recognizable by evolution of hydrogen chloride, has begun. After addition of all the ether, the mixture is stirred for a further 10 min in the ice-bath, then for 1 h without cooling, and finally at 35° for 15 min. The mixture is finally poured on crushed ice (about 0.5 kg) in a separatory funnel and the whole is well shaken. After separation of the organic phase the aqueous phase is washed twice with methylene dichloride (50-ml portions), and the organic solutions are united and washed three times with water (75-ml portions). The methylene dichloride solution is treated with a few crystals of hydroquinone and dried over sodium sulfate, the solvent is removed, and the residue is distilled in a vacuum. The fraction distilling at 105–115°/0.01 mm is redistilled, giving the aldehyde (58–63 g, 70–76%), b.p. 108–112°/0.01 mm, m.p. 40–42°.

Treatment with ethyl orthoformate and aluminum chloride is particularly suitable for formylation of polyhydric phenols;[594] and guaiazulene is converted analogously into the 3-carbaldehyde in 89% yield by the orthoester in ethanol and perchloric acid.[600]

The Reimer–Tiemann reaction[106h,601] – treatment of a phenol with chloroform in an alkaline medium — also leads to aldehydes:



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[593] S. F. McDonald, *J. Chem. Soc.*, **1952**, 4184.

[594] A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, **92**, 88 (1960); H. Gross, A. Rieche, and G. Matthey, *Chem. Ber.*, **96**, 308 (1963).

[595] H. Reimlinger, J.-P. Golstein, J. Jadot, and P. Jung, *Chem. Ber.*, **97**, 349 (1964).

[596] P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, **1962**, 3880.

[597] G. Müller, A. B. Font, and R. Bardoneschi, *Ann. Chem.*, **662**, 105 (1962).

[598] H. Gross and G. Matthey, *Chem. Ber.*, **97**, 2606 (1964).

[599] A. Rieche, H. Gross, and E. Höft, *Org. Syn.*, **47**, 1 (1967).

[600] E. C. Kirby and D. H. Reid, *J. Chem. Soc.*, **1961**, 1724.

[601] H. Wynberg, *Chem. Rev.*, **60**, 169 (1960).

This reaction is not of Friedel–Crafts type. It was much used in early work but has nowadays been replaced by more efficient methods; nevertheless, it gives good yields in some cases, *e.g.*, 38–48% of 2-hydroxy-1-naphthaldehyde from 2-naphthol.[602]

v, Synthesis of aromatic carboxylic acids[1061,271d]

Various methods analogous to the Friedel–Crafts synthesis are available for introduction of a carboxyl group into aromatic compounds.

In a Friedel–Crafts type of reaction phosgene leads to carboxylic acids or their chlorides or to ketones;[603] *p*-(dimethylamino)benzoic acid, for instance, is obtained in 50% yield from dimethylaniline and phosgene without a catalyst:[604]

$$\mathrm{ArH} + \mathrm{COCl_2} \longrightarrow \mathrm{ArCOCl} + \mathrm{HCl}$$

When azulene is kept with phosgene at room temperature, again without a catalyst, the first product is presumably 1-azulenecarbonyl chloride; ethanolysis gives the ester (93%), hydrolysis the free acid (95%), and aminolysis the amide (89%).[605]

Oxalyl chloride affords diketones (benzene gives benzil); but under the reaction conditions oxalyl chloride decomposes partly to phosgene, so that the acid chloride or monoketone may also be formed.[606] The method thus has value also for preparation of carboxylic acids; as examples, carboxylation of mesitylene in 65–70% yield by oxalyl chloride is recorded in *Organic Syntheses*,[607] and 1,1-di-(*p*-tolyl)ethylene gives 3,3-di-(*p*-tolyl)acrylic acid in 80% yield.[608]

Further, oxalyl bromide (or the chloride), at low temperature in the absence of a catalyst, gives very good yields of the very reactive α-oxo carbonyl bromides:

$$\mathrm{RH} + (\mathrm{COBr})_2 \xrightarrow{-20^\circ} \mathrm{RCOCOBr} + \mathrm{HBr}$$

These bromides may be isolated in substance or worked up to give the free acid or the ester. Azulenes (*e.g.*, isoguaiazulene) and olefins[609] react in this way. Indoles react with oxalyl chloride by substitution at position 3.[610]

A convenient laboratory method for direct carboxylation of aromatic compounds is treatment with 2,2-dichloro-1,3-benzodioxole (pyrocatechol dichloromethylene ether) in the presence of aluminum chloride or tin tetrachloride.[611] The procedure is applicable to aromatic hydrocarbons, including fused hydro-

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[602] A. Russell and L. B. Lockhart, *Org. Syn.*, Coll. Vol. 3, 463 (1955).

[603] C. Liebermann and M. Zsuffa, *Ber. Deut. Chem. Ges.*, **44**, 202 (1911); **45**, 1186 (1912); H. Staudinger, *Ber. Deut. Chem. Ges.*, **41**, 3558 (1908).

[604] D. S. Breslow, *J. Amer. Chem. Soc.*, **72**, 4244 (1950).

[605] W. Treibs, H.-J. Neupert, and J. Hiebsch, *Chem. Ber.*, **92**, 1216 (1959).

[606] H. G. Latham, Jr., E. L. May, and E. Mosettig, *J. Amer. Chem. Soc.*, **70**, 1079 (1948).

[607] P. E. Sokol, *Org. Syn.*, **44**, 69 (1964).

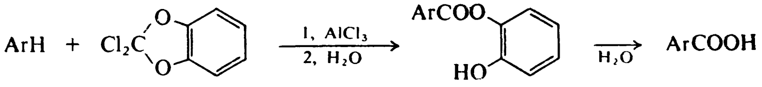
[608] F. Bergmann and co-workers, *J. Amer. Chem. Soc.*, **70**, 1612 (1948).

[609] W. Treibs and H. Orttmann, *Naturwissenschaften*, **45**, 85 (1958); *Chem. Ber.*, **93**, 545 (1960); W. Treibs, *Chem. Ber.*, **92**, 2152 (1959).

[610] G. Domschke and H. Fürst, *Chem. Ber.*, **94**, 2353 (1961).

[611] H. Gross, J. Rusche, and M. Mirsch, *Chem. Ber.*, **96**, 1382 (1963).

carbons, phenols, aryl ethers, and aromatic heterocycles; yields are usually between 80% and 96%.



Aromatic carboxylic acids or their thiol-esters can also be prepared in good yield by use of trichloromethyl methyl sulfide and aluminum chloride:[612]

$$ArH + CH_3SCCl_3 \xrightarrow[2,\ H_2O]{1,\ AlCl_3} ArCO{-}SCH_3 \xrightarrow{H_2O} ArCOOH$$

Nitriles are formed in good yields in reactions with cyanogen halides,[613,614] and dicyanogen has been used by Janz[615] for the same purpose. As its addition compound with aluminum chloride, carbamoyl chloride has found application for introduction of a carbamoyl group:[616]

$$ArH + ClCONH_2 \xrightarrow{AlCl_3} ArCONH_2 + HCl$$

In the same way biphenyl and carbamoyl chloride give 4′-biphenylcarboxamide in 83% yield.[617]

A *N,N*-dimethylcarbamoyl group can be introduced directly by treating aromatic compounds with dimethylcarbamoyl chloride in the presence of aluminum chloride; *e.g.*, tetra-*N*-methyl-4,4-oxydibenzamide is formed in 85% yield from diphenyl ether.[618]

A rational procedure, very simple to carry out, for converting an aromatic compound into its carboxamide was discovered by Effenberger and Gleiter;[619] it is to treat the compound with an isocyanate and aluminum chloride:

$$ArH + RNCO \xrightarrow[2,\ H_2O]{1,\ AlCl_3} ArCONHR$$

R may be alkyl or aryl; and yields are generally very good.

vi, Acylation of alkanes, cycloalkanes, and alkenes

Extensive investigations of the Friedel–Crafts reaction between cycloalkanes and acetyl chloride have been reported by Zelinsky and Tarassowa;[620] they found that, according to the reaction conditions, either saturated or unsaturated ketones were formed and that cyclohexane derivatives may rearrange to methylcyclopentane derivatives (cf. Nenitzescu and Hopff[621-623]).

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[612] H. Gross and G. Matthey, *Chem. Ber.*, **97**, 2606 (1964).

[613] P. Karrer, A. Rebmann, and E. Zeller, *Helv. Chim. Acta*, **3**, 267 (1920); **2**, 482 (1919).

[614] G. W. Gray and B. Jones, *J. Chem. Soc.*, **1954**, 678.

[615] G. J. Janz, *J. Amer. Chem. Soc.*, **74**, 4529 (1952).

[616] L. Gattermann, *Ann. Chem.*, **244**, 50 (1888).

[617] H. Hopff and H. Ohlinger, *Angew. Chem.*, **61**, 183 (1949).

[618] V. M. Ivanova, S. A. Nemleva, Z. N. Seina, E. G. Kaminskaya, S. S. Gitis, and A. Ya. Kaminskii, *Zh. Org. Khim.*, **3**, 46 (1967); *Chem. Abstr.*, **66**, 94780 (1967).

[619] F. Effenberger and R. Gleiter, *Chem. Ber.*, **97**, 472, 480 (1964).

[620] N. D. Zelinsky and E. M. Tarassowa, *Ann. Chem.*, **508**, 115 (1934).

[621] C. D. Nenitzescu and co-workers, *Ann. Chem.*, **491**, 189 (1931); *Ber. Deut. Chem. Ges.*, **66**, 1097 (1933).

[622] C. D. Nenitzescu and I. P. Cantuniari, *Ber. Deut. Chem. Ges.*, **65**, 1449 (1932).

[623] H. Hopff, *Ber. Deut. Chem. Ges.*, **65**, 482 (1932).

Such reactions have very little importance for alkanes. However, if the aliphatic compound has active centers it can be acylated with good results by an acyl chloride and aluminum chloride; *e.g.*, ethyl 3-methyl-2-butenoate, acetyl chloride and aluminum chloride afford ethyl 3-methyl-5-oxo-2-hexenoate in 72% yield:[624]

$$(CH_3)_2C{=}CHCOOC_2H_5 + CH_3COCl \xrightarrow{AlCl_3} CH_3COCH_2C(CH_3){=}CHCOOC_2H_5$$

γ- and δ-Oxo carboxylic acids can be cyclized by an acylating agent, *e.g.*, acetyl chloride in the presence of aluminum chloride to 2-alkyl-1,3-cyclopentanediones or 2-alkyl-1,3-cyclohexanediones:[625]

$$\begin{array}{l} CH_2COOH \\ | \\ [CH_2]_nCOCH_2R \end{array} + CH_3COCl \xrightarrow{AlCl_3} \begin{array}{l} CH_2\text{—}CO \\ | \qquad\quad >CHR \\ [CH_2]_n\text{—}CO \end{array}$$

(n = 1 or 2)

The preparation of **2-methyl-1,3-cyclopentanedione**[625] forms an example of the general procedure:

A sulfonation flask (capacity 350 ml) is fitted with a stirrer, reflux condenser, dropping funnel, and thermometer. Sublimed aluminum chloride (0.24 mole) is placed in this flask with exclusion of moisture and dissolved or suspended in nitromethane or nitrobenzene, respectively (1 ml per g of the chloride). The temperature rises to 50–60°. When these components have cooled to 20° the oxo carboxylic acid (0.05 mole) is added; this is followed by the acylating agent (0,1 mde) with cooling by running water. Rapid but brief evolution of gas sets in. The mixture is heated for 3 h at 80°, then cooled to about 10° and poured on ice (2 g per g of the chloride). Crude 2-alkyl-1,3-cycloalkanedione separates; it is collected, washed with cold water (10 ml), and recrystallized with charcoal from water.

In the preparation of 2-methyl-1,3-cyclopentanedione from 4-oxohexanoic acid and propionyl chloride a second fraction of the product is obtained by boiling the aqueous phase of the filtrate with charcoal, filtering, and extracting the filtrate continuously with ether. When the solvent is nitrobenzene the dione is obtained in 70% yield with m.p. 214–216°.

Acetylation of cyclohexanone affords 2-chloro-2-cyclohexenyl methyl ketone in 82% yield.[626]

Cycloalkenes can also be acylated with aluminum chloride or tin tetrachloride as catalyst;[627,628] cycloheptene, acetyl chloride, and aluminum chloride give 70% of 1-cycloheptenyl methyl ketone.[629] The yield from cyclohexene and phenylacetyl chloride is, however, below 30%; but better yields are obtained with acetyl chloride and zinc chloride (60% of 1-cyclohexenyl methyl ketone[630,631]) or acetic anhydride and tin tetrachloride.[632]

1-Cyclohexenyl methyl ketone: Cyclohexene (123 g, 1.5 moles) and tin tetrachloride (260.5 g, 1 mole) are placed in a flask fitted with a Hershberg stirrer, a reflux condenser, a dropping funnel, and a thermometer dipping into the reaction mixture and with all openings

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[624] I. Alkonyi, *Chem. Ber.*, **98**, 3099 (1965).

[625] H. Schick, G. Lehmann, and G. Hilgetag, *Chem. Ber.*, **100**, 2973 (1967).

[626] N. K. Kochekov, E. E. Nifan'tev, and V. N. Shibaev, *Khim. Nauka i Prom.*, **4**, 808 (1959); *Zh. Obshch. Khim.*, **30**, 2275 (1960); *Chem. Abstr.*, **54**, 10980 (1960); **55**, 8366 (1961).

[627] H. Bergs, *Ber. Deut. Chem. Ges.*, **67**, 238 (1934).

[628] W. Cook and L. Hewett, *J. Chem. Soc.*, **1933**, 1098.

[629] N. Jones, H. T. Taylor, and E. Rudd, *J. Chem. Soc.*, **1961**, 1342; **1959**, 4017.

[630] R. E. Christ and R. C. Fuson, *J. Amer. Chem. Soc.*, **59**, 893 (1937).

[631] L. Ruzicka, D. R. Koolhaas, and A. H. Wind, *Helv. Chim. Acta*, **14**, 1157 (1931).

[632] E. E. Royals and C. M. Hendry, *J. Org. Chem.*, **15**, 1147 (1950).

closed by calcium chloride tubes. The flask is cooled in ice, and 99–100% acetic anhydride (102 g, 1 mole) is dropped in during 30 min; the temperature of the mixture varies between 25° and 35°. Stirring is continued for a further 15 min with ice-cooling, then the mixture is poured on crushed ice (300–400 g), and the whole is extracted with ether. The ethereal solution is washed with sodium hydrogen carbonate solution, then with water, dried over calcium chloride and evaporated. Fractionation of the residue in a vacuum affords the ketone (67 g, 54%, calculated on acetic anhydride), b.p. 65–69°/5 mm, 202.5°/760 mm [semicarbazone, m.p. 220°; oxime (recrystallized from aqueous ethanol), m.p. 58–59°]. By-products are chlorocyclohexane, b.p. 142°, and cyclohexyl acetate, b.p. 174–175°.

Acetylenes also react with acid chlorides, giving 2-chlorovinyl ketones in 62–80% yield:[633]

$$\mathrm{RCOCl + CH{\equiv}CH \longrightarrow RCOCH{=}CHCl}$$

b. Formation of diazo ketones by acylation of diazo-alkanes and -esters

Diazo ketones, which are used in very widely differing types of synthesis, are usually prepared by reaction of diazomethane with carbonyl chlorides in ether or methylene dichloride:

$$\mathrm{RCOCl + 2CH_2N_2 \longrightarrow RCOCHN_2 + CH_3Cl + N_2}$$

The preparation and applications of diazo ketones have been reviewed repeatedly;[32e,634,635] accordingly, it suffices here to note that addition of a base has been recommended[636] (this obviates use of the second molecule of diazomethane) and to give a general method of preparing diazo ketones:[32e]

Preparation of diazo ketones: The acid chloride may be added in undiluted form if liquid, or as a fine powder if solid, to a solution of 2.2–3.0 moles of diazomethane with stirring at 0–10°; alternatively the chloride may be added as a solution. Reaction is very rapid even in the cold and is usually complete in about 1 h at room temperature. Because of their betaine character, diazo ketones are mostly sparingly soluble in ether and crystallize when ether solutions are cooled to about −20°; but they may also be obtained with advantage by concentration of their solutions under reduced pressure. In some cases the diazo ketone solution can be used directly for further reactions. Crude diazo ketones mostly contain a few percent of the chloro ketone.

When the starting material is a basic carboxylic acid such as a pyridine- or quinoline-carboxylic acid, and this is converted into its acid chloride by thionyl chloride, it must be remembered that the product is then not the pure acid chloride but its hydrochloride; in such cases a large excess of diazomethane must be used, so as to convert the hydrochloric acid into methyl chloride.

Some more recent work may repay attention in special cases.[637,638] Acid anhydrides may be used analogously in place of acid chlorides.[32e,634]

Diazoalkanes in general can be acylated in the same way as diazomethane;[639] and α-diazo β-oxo esters are obtained from acid chlorides and diazoacetic

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[633] C. C. Price and J. A. Pappalardo, *J. Amer. Chem. Soc.*, **72**, 2613 (1950).

[634] F. Weygand and H. J. Bestmann, *Angew. Chem.* **72**, 535 (1960).

[635] W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 38 (1942).

[636] M. S. Newman and P. Beal, *J. Amer. Chem. Soc.*, **71**, 1506 (1949); M. Berenbom and W. S. Fones, *J. Amer. Chem. Soc.*, **71**, 1629 (1949).

[637] E. D. Bergmann and E. Hoffmann, *J. Org. Chem.*, **26**, 3555 (1961).

[638] N. Ried, G. Deuschel, and A. Kotelko, *Ann. Chem.*, **642**, 121 (1961).

[639] A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948).

esters:[634,640,641]

$$\mathrm{RCOCl} + \mathrm{CHN_2COOC_2H_5} \longrightarrow \mathrm{RCOC(N)_2COOC_2H_5}$$

Other ω-diazoalkanoic esters undergo reactions similar to the last-mentioned, being acylated to ω-acyl-ω-diazoalkanoic esters.[642] The reaction with carbylic anhydrides has been recommended[634] for the preparation of 3-oxo-4,4,4-trifluorobutyric esters.[634]

Ethyl 2-diazo-3-oxo-4,4,4-trifluorobutyrate:[634] A solution of trifluorvacetic anhydride (131g) in methylene dichloride (75 ml) is dropped, during 1 h, into a stirred solution of ethyl diazoacetate (73.5 g) and pure, anhydrous pyridine (51 g) in methylene dichloride (100 ml). The precipitated pyridinium trifluoroacetate is filtered off and the filtrate is washed with sodium carbonate solution and then with an oxalic acid solution and dried over magnesium sulfate. Subsequent fractionation in a vacuum affords the product (109 g; 83%), b.p. 75–77°/10 mm.

III. C–C linkage by replacement of hydroxyl by carbon*

1. Alkylation by alcohols+

Compounds containing active methylene groups can be alkylated by alcohols with loss of hydrogen from that position. For example, in the presence of boron trifluoride, isopropyl alcohol and ethyl acetoacetate give ethyl 2-isopropylacetoacetate in 60–70% yield;[643] the isopropyl group can be introduced in the same way into acetylacetone (2,4-pentanedione);[644] and reactions of xanthhydrol with malonic esters have also been recorded in the literature.[645]

The loss of the elements of water between an alcohol and an aromatic hydrocarbon is a smooth reaction, particularly when the alcohol is of benzyl type or an alkanol with a chain length of at least three carbon atoms (see also page 970).

Benzyl alcohol and benzene in a mixture of glacial acetic acid and sulfuric acid give diphenylmethane even at room temperature,[646] and diphenylmethanol gives an almost theoretical yield of diphenyl-*p*-tolylmethane when boiled with toluene and phosphoric oxide;[647] diphenylacetic acid is formed in yields up to 96% on reaction of mandelic acid with benzene in the presence of aluminum chloride.[648]

In such reactions aliphatic alcohols do not give straight-chain products: branched-chain compounds are always produced, as in Friedel–Crafts syntheses with alkyl chlorides. Various alkylaromatic compounds are produced

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* For acylation of aromatic compounds by carboxylic acids see page 939.

\+ For alkylation of aromatic compounds by alcohols see page 936.

[640] H. Staudinger, J. Becker, and H. Hirzel, *Ber. Deut. Chem. Ges.*, **49**, 1978 (1916).

[641] J. H. Looker and C. H. Hayes, *J. Org. Chem.*, **28**, 1342 (1963).

[642] S. Hauptmann and K. Hirschberg, *J. Prakt. Chem.*, [iv], **34**, 262 (1966).

[643] J. T. Adams, R. Levine, and C. R. Hauser, *Org. Syn.*, **27**, 35 (1947).

[644] T. F. Crimmins and C. R. Hauser, *J. Org. Chem.*, **32**, 2615 (1967).

[645] R. G. Jones and co-workers, *J. Amer. Chem. Soc.*, **70**, 2843 (1948); K. Ziegler, *Ann. Chem.*, **434**, 40 (1923).

[646] V. Meyer and C. Wurster, *Ber. Deut. Chem. Ges.*, **6**, 964 (1873).

[647] W. Hemilian, *Ber. Deut. Chem. Ges.*, **7**, 1203 (1874).

[648] M.-L. Hsu, H.-G. Jen, and H.-H. Lei, *Yao Hsueh Hsueh Pao*, **8**, 105 (1960); *Chem. Abstr.*, **56**, 7201 (1962).

industrially by nuclear alkylation with alcohols, *e.g.*, cumene from benzene and isopropyl alcohol, and thymol from *m*-cresol and isopropyl alcohol.[649] Normally the condensing agent is sulfuric acid,[650] but other agents such as tin tetrachloride, zinc chloride,[651] *p*-toluenesulfonic acid,[652] and aluminum chloride[653,654] can also be used; boron trifluoride and phosphoric oxide give yields of up to 80% in alkylations by alcohols of chain length C_4 to C_{12};[655,656] phosphoric acid is particularly suitable for alkylation of phenols and their ethers.[657]

Cumene: Benzene (50 g) is heated with isopropyl alcohol (19 g) and 80% sulfuric acid (400 ml) for 3–4 h at 65°. The usual working up then gives a 65% yield of cumene.

Toluene, xylenes, phenols, cresols, resorcinol, *o*-nitrotoluene, chlorobenzene and naphthalene have been condensed in the same way with isopropyl alcohol, *sec*-butyl alcohol, isobutyl alcohol, and cyclohexanol.

p-Cymene can be obtained from toluene and isopropyl alcohol in the presence of phosphoric acid, the yield then being 80%.[658] The use of boron trifluoride and phosphoric oxide is illustrated in the following preparation of ***sec*-butylbenzene**:[655]

A mixture of benzene (156 g, 2 moles) and 1-butanol (37 g, 0.5 mole) is stirred and cooled in running water under a hood while boron trifluoride is led in until 0.5 mole (34 g) has been absorbed. Phosphoric oxide (17.7 g, 0.125 mole) is then added rapidly and the mixture is slowly raised to the boiling point whilst stirring is continued. The solution becomes turbid and separates into two layers, whereupon stirring is stopped; but heating is continued for a further 3 h. The upper layer is then separated, washed with aqueous alkali, and fractionally distilled, giving *sec*-butylbenzene (50 g, 75%), b.p. 170–172°/744 mm.

The following synthesis of ***tert*-butylbenzene** is an example of the condensation effected by aluminum chloride:[654]

A suspension of aluminum chloride (66.5 g, 0.5 mole) in benzene (390 g, 5 moles) is rapidly stirred at 20–30° while *tert*-butyl alcohol (74 g, 1 mole) is added dropwise. The mixture is set aside overnight and then poured on crushed ice and hydrochloric acid. The benzene layer is separated and the aqueous layer is washed with ether. The united benzene–ether solutions are evaporated and the residue is fractionated through a 30-cm column, giving *tert*-butylbenzene (65–70%), b.p. 168–170°/740 mm.

Phenols are alkylated mainly in the *para*-position;[659] for example *p-tert*-butylphenol is formed in 95% yield from phenol and isobutyl alcohol; in this case a cation-exchange resin KU-2 was used, with 4 hours' heating at 130°.[660]

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[649] Brit. Pat. 288,122; *Chem. Abstr.*, **23**, 395 (1929).

[650] H. Meyer and K. Bernhauer, *Monatsh. Chem.*, **53/54**, 721 (1929).

[651] I. P. Tsukervanik, *Zh. Obsch. Khim.*, **17**, 1005 (1947); I. P. Tsukervanik and V. Sergeeva, *Zh. Obshch. Khim.*, **17**, 1009; *Chem. Abstr.*, **42**, 4541 (1948).

[652] E. P. Pratt, R. K. Preston, and J. D. Draper, *J. Amer. Chem. Soc.*, **72**, 1367 (1950).

[653] R. C. Huston and I. A. Kaye, *J. Amer. Chem. Soc.*, **64**, 1576 (1942).

[654] R. C. Huston, W. B. Fox, and M. N. Binder, *J. Org. Chem.*, **3**, 251 (1939).

[655] N. F. Toussaint and G. F. Hennion, *J. Amer. Chem. Soc.*, **62**, 1145 (1940).

[656] C. E. Welsh and G. F. Hennion, *J. Amer. Chem. Soc.*, **63**, 2603 (1941).

[657] A. E. Tschitschibabin, *Bull. Soc. Chim. France*, [v], **2**, 497 (1935).

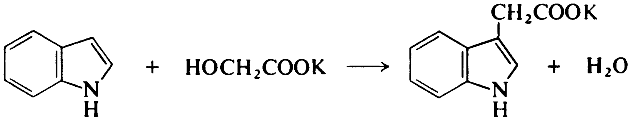
[658] I. P. Tsukervanik and V. Tambovtseva, *Zh. Obshch. Khim.*, **15**, 699, 820 (1945); *Chem. Abstr.*, **40**, 5707 (1946); **41**, 732 (1947).

[659] R. C. Huston and co-workers, *J. Amer. Chem. Soc.*, **58**, 439 (1936); **59**, 2001 (1937).

[660] V. I. Isagulyants and E. V. Panidi, *Zh. Prikl. Khim.*, **34**, 1849 (1961); P. S. Belov, Ch'ao-Ch'i Lu, and V. I. Isaguljants, *Khim. Prom.*, **1962**, 480; *Chem. Abstr.*, **56**, 371 (1962); **58**, 2392 (1963).

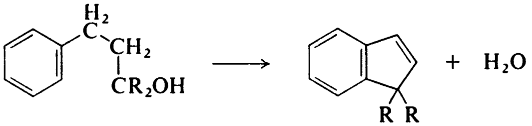
Toluidine is methylated in the ring by methanol and hydrogen chloride under pressure;[661] aniline can also be alkylated in the ring by alcohols;[662] and so can indoles by alcohols containing alkoxides at 220° under pressure.[663]

In a high-yielding synthesis of indole-3-acetic acids the heterocycle is heated with potassium glycolate at 250°, *e.g.*:[664]



and other α-hydroxy acids react analogously.[664]

Indane and tetralin derivatives can be obtained by cyclodehydration of 3-aryl-1-alkanols and 4-aryl-1-alkanols, respectively.[665] Isomerization does not occur in such reactions; thus 4-phenyl-1-butanol gives tetralin and not 1-methylindane, and only 1,1-dialkylindanes are formed from the corresponding tertiary alcohols, *e.g.*:



however, neither primary nor secondary alcohols of this type cyclize, owing to polymerization.

An interesting case is the preparation of ionene (1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene).[666]

1,1-Dimethylindane:[665] 85% Sulfuric acid (1.2 parts by volume) is added slowly to vigorously stirred 2-methyl-4-phenyl-2-butanol (1 part by volume) at 10°. Reaction appears to be instantaneous, but for certainty stirring is continued for another hour at room temperature. Then the mixture is diluted with water (10–15 parts by volume) and distilled. An oil separates in the distillate and is separated; the aqueous distillate is returned to the distillation flask, and the mixture is redistilled. The oil is redistilled from aqueous alkali, separated from that distillate, dried over calcium chloride, and fractionated, giving 1,1-dimethylindane (65%), b.p. 191°.

The same process has been employed for preparation of 1,1,2-trimethylindane (90%), b.p. 208°, tetralin (55%), and 1,1,4-trimethyltetralin (86%).[667]

2-(1-Cyclohexenyl)benzyl alcohol cyclizes when warmed for a short time in formic acid, giving a 53% yield of 1,2,3,4-tetrahydrofluorene.[668]

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[661] R. W. Cripps and D. H. Hey, *J. Chem. Soc.*, **1943**, 14.

[662] I. J. Rinkes, *Rec. Trav. Chim.*, **62**, 557 (1943).

[663] R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, **1942**, 680.

[664] H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 1246 (1963); N. A. Preobrazhenskii, M. E. Maurit, G. I. Bazilevskaya, G. V. Smirnova, M. M. El'manovich, A. I. Valakhanovich, and E. Persiyanova, *Zh. Obshch. Khim.*, **30**, 2250 (1960); *Chem. Abstr.*, **55**, 9367 (1961).

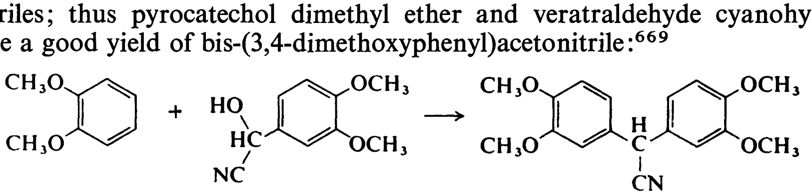
[665] M. T. Bogert and D. Davidson, *J. Amer. Chem. Soc.*, **56**, 185 (1934).

[666] M. T. Bogert, D. Davidson, and P. M. Apfelbaum, *J. Amer. Chem. Soc.*, **56**, 959 (1934).

[667] M. C. Kloetzel, *J. Amer. Chem. Soc.*, **62**, 3405 (1940).

[668] W. E. Parham, C. D. Wright, and D. A. Bolon, *J. Amer. Chem. Soc.*, **83**, 1751 (1961).

Cyanohydrins react with hydrocarbons with loss of water and formation of nitriles; thus pyrocatechol dimethyl ether and veratraldehyde cyanohydrin give a good yield of bis-(3,4-dimethoxyphenyl)acetonitrile:[669]



Ethyl cyanoacetate is converted by acetaldehyde cyanohydrin in the presence of sodium alkoxide into ethyl 2,3-dicyanobutyrate in 80% yield.[670]

2. Alkylation by aldehydes

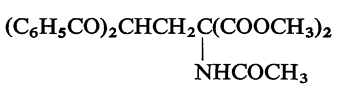
Only one new carbon–carbon bond is formed by the methods described above: two new carbon–carbon bonds are formed simultaneously if in such condensations the alcohol is replaced by a carbonyl compound, *e.g.*:

$$2RH + R'CHO \longrightarrow CHR_2R' + H_2O$$

Such reactions, which will not be discussed further here, include the formation of diarylmethanes from an aldehyde and two molecules of an aromatic hydrocarbon, of triphenylmethane derivatives from an aldehyde and two molecules of an aromatic amine, and of phthaleins from phthalic anhydride and two molecules of phenol or resorcinol.

This type of reaction includes also the formation of diarylacetic esters from glyoxalic esters and aromatic compounds, yields again being good.[671]

Preparative importance attaches further to Hellmann and Dietrich's so-called asymmetric three-carbon condensation, in which, within certain limitations, two different compounds containing active methylene groups are linked together by formaldehyde with formation of two new carbon–carbon bonds. For example, dibenzoylmethane, dimethyl (acetylamino)malonate, and formaldehyde afford an 88% yield of dimethyl α-(acetylamino)-α-(2,2-dibenzoylethyl)malonate [1-(acetylamino-3-benzoyl-4-oxo-4-phenyl-1,1-butanedicarboxylate].[672]



$$(C_6H_5CO)_2CHCH_2\underset{\displaystyle NHCOCH_3}{\underset{|}{C}}(COOCH_3)_2$$

A series of otherwise inaccessible compounds can be prepared in this way.[672,673]

3. Chloromethylation[271b,674]

A reaction:

$$ArH + HCl + CH_2O \longrightarrow RCH_2Cl + H_2O$$

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[669] A. Müller and M. Vajda, *J. Org. Chem.*, **17**, 800 (1952).

[670] A. Higson and F. J. Thorpe, *J. Chem. Soc.*, **89**, 1455 (1906); R. P. Linstead and M. Whalley, *J. Chem. Soc.*, **1954**, 3722.

[671] G. Werber, M. Ruccia, and A. Sabahni, *Ann. Chim. (Rome)*, **50**, 1438 (1960); G. Werber and M. Riccia, *Ann. Chim. (Rome)*, **50**, 1368 (1960); G. Werber and F. Maggio, *Atti Accad. Sci. Lett. Arti Palermo*, [4], **20**, 15 (1961).

[672] H. Hellmann and D. Dietrich, *Ann. Chem.*, **632**, 73 (1960).

[673] H. Hellmann, D. Dietrich, and K. Müller, *Ann. Chem.*, **656**, 70 (1962) and earlier papers.

[674] R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).

can be used to introduce a chloromethyl group directly into an aromatic system. On an industrial scale this reaction is effected without a solvent,[675] but in preparations on a laboratory scale chloroform, carbon tetrachloride, light petroleum, or acetic acid saturated with hydrogen chloride is employed as solvent. Zinc chloride is usually prescribed as condensing agent or catalyst.

Adding phosphoric acid sometimes improves the yield. According to Weygand a mixture of benzyl chloride and ω,ω-dichloroxylene is obtained as follows:

Zinc chloride (84 g), trioxymethylene (90 g), chloroform or carbon tetrachloride (200 ml), and benzene (78 g) are placed in a sulfonation flask (1 l) fitted with a gas-inlet tube, reflux condenser, and stirrer and are stirred while a rapid stream of hydrogen chloride is led in. The mixture becomes warm and is cooled at the beginning of the reaction but is warmed to 50–60° towards the end. After 2 h the mixture is washed successively with water (several times), dilute sodium carbonate solution, and water; it is then dried over calcium chloride, and most of the chloroform is distilled off. Distillation of the residue in a vacuum affords benzyl chloride (84 g, 66%) and **ω,ω-dichloroxylene** (55 g, 30%), the latter consisting mainly of the *para*-compound.

The dichloroxylene can also be obtained analogously from benzyl chloride (127 g) by means of zinc chloride (42 g), trioxymethylene (45 g), and carbon tetrachloride (100 ml). After the reaction the product is taken up in ether, washed with water and dilute sodium carbonate solution, and worked up as above. 83% (145 g) of the dichloroxylenes are obtained, from which the *para*-compound (100 g) crystallizes.

Naphthalene can be chloromethylated at position 1 in 74–77% yield.[676]

Chloromethyl methyl ether may be used in place of the formaldehyde and hydrogen chloride:

$$\mathrm{ArH + CH_3OCH_2Cl \longrightarrow ArCH_2Cl + CH_3OH + H_2O}$$

for example, 1,3,5-triisopropylbenzene is converted by this chloro ether in carbon disulfide with tin tetrachloride as catalyst into 2,4,6-triisopropylbenzyl chloride in 85% yield.[592] Less reactive aromatic compounds can also be chloromethylated — by longer heating with the chloro ether in the presence of aluminum chloride; 2-hydroxy-5-nitrobenzaldehyde, for instance, is chloromethylated at position 3 in 90% yield after reaction for 80 hours.[677] Monochloro ethers have been used also for chloromethylation of a considerable range of styrene–divinylbenzene polymers[678] (for the literature see Gross and Höft[679]); and the preparation of the chloromethyl derivative of polystyrene for use in peptide synthesis has been described by Merrifield.[680] A review of halomethylation by mono- and symmetrical di-halo ethers has been given by Gross and Höft[679] and others.[271b]

ω-Chloromethylation of styrene has been reported by Wichterle and Černy.[681]

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[675] Ger. Pat. 508,890; *Chem. Abstr.*, **25**, 716 (1931).

[676] O. Grummitt and A. Buck, *Org. Syn.*, **24**, 30 (1944).

[677] L. D. Taylor and R. B. Davis, *J. Org. Chem.*, **28**, 1713 (1963).

[678] U.S. Pat. 2,694,702; *Chem. Abstr.*, **49**, 6551 (1955).

[679] H. Gross and E. Höft, *Angew. Chem. Int. Ed., Engl.*, **6**, 335 (1967).

[680] R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963); *Biochemistry*, **3**, 1385 (1964); *Science*, **150**, 178 (1965); G. R. Marshall and R. B. Merrifield, *Biochemistry*, **4**, 2394 (1965).

[681] O. Wichterle and J. Černy, *Collect, Czech. Chem. Commun.*, **20**, 1288 (1955).

A 1-chloroethyl group can be introduced into aromatic compounds by the reaction:[682]

$$\mathrm{ArH + CH_3CHO + HCl \longrightarrow ArCHClCH_3 + H_2O}$$

Thus salicylic acid, chloral, and hydrogen chloride in concentrated sulfuric acid afford 2-hydroxy-5-(1,2,2,2-tetrachloroethyl)benzoic acid in very good yield.[683]

Bromomethylation is also possible, *e.g.*, the preparation of benzyl bromide in 86.5% yield from benzene, formaldehyde, and hydrogen bromide in acetic plus sulfuric acid.[684,685] So is iodomethylation of aromatic compounds, by reaction of bis(chloromethyl) ether and hydrogen iodide in glacial acetic acid.[686]

4. Hydroxymethylation

In an alkaline medium formaldehyde reacts with reactive hydrogen atoms, providing a hydroxymethylation:

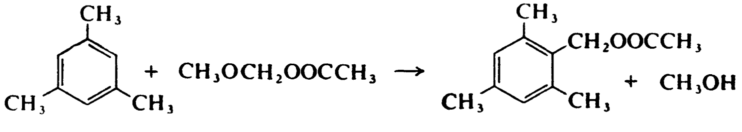
$$\mathrm{RH + CH_2O \longrightarrow RCH_2OH}$$

Thus an almost quantitative yield of ethyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate is obtained from ethyl 2-oxocyclohexanecarboxylate and aqueous formaldehyde in the presence of calcium oxide;[687] and 2-butanone and formaldehyde in sodium hydroxide solution give a 70% yield of 4-hydroxy-3-methyl-2-butanone, whence 3-methyl-3-buten-2-one is formed in 74% yield by removal of water.[688] Hydroxymethylation of acetone[689] and of ω-nitrotoluene (phenylnitromethane)[690] have also been reported.

A weakly alkaline medium suffices for satisfactory introduction of a hydroxymethyl group into phenols; *e.g.*, 2,6-bis(hydroxymethyl)phenols have been prepared in 50–96% yield.[691] This reaction is of fundamental importance in condensation of phenols with formaldehyde.[691]

The Prins reaction has been described elsewhere in this book (page 864).

Acetoxymethylation is observed when a hydrocarbon is treated with methoxymethyl acetate: 2,4,6-trimethylbenzyl acetate is produced in 53% from mesitylene:[692]



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[682] R. L. Frank, C. E. Adams, R. E. Allen, R. Gander, and P. V. Smith, *J. Amer. Chem. Soc.*, **68**, 1365 (1946); R. Quelet and J. Ducasse, *C. R. Hebd. Séances Acad. Sci.*, **208**, 1317 (1939); *Bull. Soc. Chim. France*, [v], **7**, 196, 205 (1940).

[683] R. Chalaust and G. Quesnel, *C. R. Hebd. Séances Acad. Sci.*, **256**, 5154 (1963).

[684] G. Kubiczek and L. Neugebauer, *Monatsh. Chem.*, **81**, 917 (1950).

[685] G. Darzens, *C. R. Hébd. Séances Acad. Sci.*, **208**, 818 (1939).

[686] E. Matarasso–Tchiroukhine, *Bull. Soc. Chim. France*, **1962**, 851.

[687] Ki-Wei Hiong, *Ann. Chim. (Paris)*, [xi], **17**, 269 (1942).

[688] J. Colonge and L. Cumet, *Bull. Soc. Chim. Frαnce*, [v], **14**, 838 (1947).

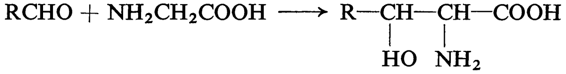
[689] S. Olsen, *Chem. Ber.*, **88**, 205 (1955).

[690] L. F. Fieser and co-workers, *J. Amer. Chem. Soc.*, **68**, 2248, 2249 (1946).

[691] J. Strating and H. J. Backer, *Rec. Trav. Chim.*, **62**, 57 (1943).

[692] L. Summers, *J. Amer. Chem. Soc.*, **76**, 3481 (1954).

Hydroxyalkylation occurs when certain compounds containing active protons are treated with higher aldehydes: *e.g.*, the copper chelate of glycine reacting with aldehydes affords α-amino-β-hydroxy acids:[693,694]



$$\mathrm{RCHO + NH_2CH_2COOH \longrightarrow R{-}\underset{HO}{\underset{|}{C}H}{-}\underset{NH_2}{\underset{|}{C}H}{-}COOH}$$

Diethyl chloromalonate and acetaldehyde give diethyl α-chloro-α-(1-hydroxyethyl)malonate analogously.[695]

5. Aminomethylation (Mannich reaction)[1060,696,697a]

A mixture of formaldehyde with ammonia or a primary or secondary amine can be used to replace mobile hydrogen by an aminomethyl or (substituted amino)methyl group. This reaction, which was systematically explored by Mannich,[698] can be formulated as:

$$\mathrm{RH + CH_2O + R'_2NH_2{}^+Cl^- \longrightarrow RCH_2NHR'_2{}^+Cl^- + H_2O}$$

It has been widely employed in synthesis. Many groups of workers have devoted an extremely large number of papers to its application to the most varied types of compound containing acidic CH groups. The frequent use of this reaction is due to the simplicity of the technique and the far-ranging applicability of the so-called Mannich bases in syntheses of very varied type. Several reviewers have collected the available material;[696] an excellent oversight, including the synthetic applications of Mannich bases, is given in a book by Hellmann and Opitz.[697a] The CH-acidic compounds used include acetylenes, nitriles, ketones, both cyclic and open-chain, alkyl aryl and diaryl ketones, oxo acids, dicarboxylic acids, aldehydes, *N*,*N*-dialkylarylamines, phenols, aromatic compounds with activated side chains, ψ-aromatic compounds such as azulenes, aliphatic nitro compounds, and heterocycles such as furan, pyrrole, indole, and pyrazolone. For the reaction with hydrogen cyanide see page 519.

The carbonyl component has been almost exclusively formaldehyde, in aqueous solution or as paraformaldehyde, and only rarely other aldehydes such as acetaldehyde.[699]

The amine component may be ammonia or a primary or secondary amine, generally presented as hydrochloride. In reactions of ammonia or a primary amine, further condensation has been observed as a side reaction:

$$\mathrm{NH_3 \longrightarrow RCH_2NH_2 \longrightarrow (RCH_2)NH \longrightarrow (RCH_2)_3N}$$

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[693] T. T. Otani and M. Winitz, *Arch. Biochem. Biophys.*, **102**, 464 (1963); H. Mix and F. W. Wilcke, *Z. Physiol. Chem.*, **337**, 40 (1964).

[694] H. Mix, *Z. Physiol. Chem.*, **327**, 41 (1961).

[695] H. Gault and P. Bouvier, *C. R. Hebd. Séances Acad. Sci.*, **254**, 2179 (1962).

[696] F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); B. Reichert, "Die Mannich-Reaktion," Springer-Verlag, Berlin, 1959.

[697] H. Hellmann and G. Opitz, (a) "A-Aminoalkylierung," Verlag Chemie, Weinheim/Bergstraße, 1960, (b) p. 218, (c) pp. 251, 256, 263.

[698] C. Mannich and co-workers, *Arch. Pharm.*, **250**, 647 (1912); **264**, 65, 164 (1926); **265**, 684 (1927); *Ber. Deut. Chem. Ges.*, **55**, 3510 (1922); **53**, 1874 (1920).

[699] C. Mannich and P. Mohs, *Ber. Deut. Chem. Ges.*, **63**, 608 (1930), P. Petrenko-Kritschenko, *Ber. Deut. Chem. Ges.*, **42**, 3683 (1909).

For the preparation of primary amines by Mannich reaction it is useful to start from dibenzylamine as the two benzyl groups can be removed later by catalytic hydrogenation.

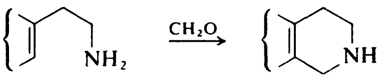
A further side reaction is occasionally the introduction of a second aminomethyl group, *e.g.*:

$$C_6H_5COCH_3 \xrightarrow[R_2NH]{CH_2O} C_6H_5COCH_2CH_2NR_2 \xrightarrow[R_2NH]{CH_2O} C_6H_5COCH(CH_2NR_2)_2$$

The annexed Table gives a few examples of the application of Mannich reactions to compounds of the types mentioned above.

RH	C=O cpd	Amine	Yield (%)	Ref.
Acetylene	CH$_2$O	Diethylamine	76	700
(Ethylthio)acetylene	CH$_2$O	Diethylamine	100	701
Phenylacetonitrile	CH$_2$O	Morpholine	51	702
m-Nitroacetophenone	CH$_2$O	Diethylamine	80–90	703
Tetralone	CH$_2$O	Tetrahydroisoquinoline	66	704
Isobutyraldehyde	CH$_2$O	Methylamine	70	705
Phenol	CH$_2$O	Ammonia	92	706
N,*N*-Diethylaniline	CH$_2$O	Piperidine	74	707
2,4,6-Trinitrotoluene	CH$_2$O	Diethanolamine	95	708
2-Nitropropane	CH$_2$O	Diallylamine	89	709
Azulene	CH$_2$O	[(CH$_3$)$_2$N]$_2$CH$_2$	66	710
2-Methylfuran	CH$_2$O	Morpholine	78	711
Indole	CH$_2$O	Dimethylamine	80	712
Indole	CH$_3$CHO	Isopropylamine	39–60	713
Naphthol	CHOCOOH	Morpholine	85–90	714

In structurally suitable cases the Mannich condensation may be intramolecular, leading to heterocycles, notably when the CH-acidic component group is suitably placed in the same molecule:



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[700] J. C. Sauer, B. W. Howk, and R. T. Stiehl, *J. Amer. Chem. Soc.*, **81**, 693 (1959).

[701] H. J. Boonstra and J. F. Arens, *Rec. Trav. Chim.*, **79**, 866 (1960).

[702] H. E. Zaugg, B. W. Horrom, and M. R. Vernsten, *J. Amer. Chem. Soc.*, **75**, 288 (1953).

[703] C. Mannich and M. Dannehl, *Arch. Pharm.*, **276**, 206 (1938).

[704] E. Mosettig and E. L. May, *J. Org. Chem.*, **5**, 528 (1940).

[705] C. Mannich and H. Wieder, *Ber. Deut. Chem. Ges.*, **65**, 385 (1932).

[706] G. K. Abdullaev and A. S. Arabova, *Uch. Zap., Azerb. Gos. Univ., Ser. Fiz.-Mat. i Khim. Nauk*, **1962**, 43; *Chem. Abstr.*, **60**, 1627 (1964).

[707] H. Böhme, E. Mundlos, W. Lehners, and O. E. Herboth, *Chem. Ber.*, **90**, 2008 (1957).

[708] H. A. Bruson and G. B. Butler, *J. Amer. Chem. Soc.*, **68**, 2348 (1946).

[709] G. B. Butler, *J. Amer. Chem. Soc.*, **78**, 482 (1956).

[710] K. Hafner, *Angew. Chem.*, **70**, 419 (1958).

[711] R. F. Holdren and R. M. Hixon, *J. Amer. Chem. Soc.*, **68**, 1198 (1946).

[712] H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Amer. Chem. Soc.*, **66**, 200 (1944).

[713] H. R. Snyder and D. S. Matteson, *J. Amer. Chem. Soc.*, **79**, 2217 (1957).

[714] E. Biekert and T. Funck, *Chem. Ber.*, **97**, 363 (1964).

These ring-closures often occur in excellent yield; they are included in the book cited above.[697a]

General experimental details are as follows.[697b] It is usual first to mix the carbonyl component with the amine, which is presented as, *e.g.*, hydrochloride or acetate. An appropriate hydrogen ion concentration must be maintained. For the preparation of aminoalkyl compounds that are liable to hydrolysis it is recommended that the water produced be removed by a drying agent or by azeotropic distillation. Dioxan is a suitable solvent, but it is often recommended that acetic acid be added to it. Ketones react better in alcohol with paraformaldehyde. Copper chloride or iron chloride is said to be a useful addition in reactions of acetylenes. Reactions of amines, phenols, and furans, even under mild conditions, may be accompanied by multiple condensation or resinification. 4-Hydroxybenzylamine is reported[706] to be obtained in 92% yield when ammonia is led into a mixture of phenol and formaldehyde.

Two detailed examples must suffice.

3-(Dimethylamino)propiophenone hydrochloride:[715] Acetophenone (60 g, 58.5 ml, 0.5 mole), dimethylammonium chloride (52.7 g, 0.65 mole), and paraformaldehyde (19.8 g, 0.66 mole) are placed in a round-bottomed flask (capacity 500 ml). A mixture of concentrated hydrochloric acid (*d* 1.19; 1 ml) and 95% ethanol (80 ml) is added and the whole is boiled under reflux for 2 h. If the yellowish solution produced is turbid it is filtered through a heated filter and, whilst still hot, diluted with acetone (400 ml). The solution is allowed to cool slowly to room temperature and placed in a refrigerator overnight. The crystals formed are filtered off, washed with acetone (25 ml), and dried for 2.5 h at 40–50°; this crude product is obtained in 68–72% yield (72–77 g) and melts at 138–141°. It is somewhat hygroscopic and if dried for a further 4 h melts at 152–153°. It can be recrystallized by dissolution in 95% ethanol (85–90 ml) and slow addition of acetone (450 ml); recovery is then about 90%, the m.p. being 155–156°.

2,4,6-Tris[(dimethylamino)methyl]phenol:[716] A mixture of phenol (94 g, 1 mole) with 25% aqueous dimethylamine solution (720 g, 4 moles) is cooled to 20° in a three-necked flask (capacity 2 l) fitted with a stirrer, thermometer, and dropping funnel. 30% Aqueous formaldehyde solution (350 g) is dropped in with stirring, at a rate such that the temperature remains at 25–30° (about 0.5 h). Stirring is then continued for a further hour at that temperature, after which the dropping funnel is replaced by a reflux condenser and the mixture is heated, still with stirring, for 2 h on a water-bath. Sodium chloride (200 g) is then added to the hot solution, and heating and stirring are continued for about 20 min. The organic layer is separated from the hot solution, transferred to a Claisen flask (capacity 500 ml), and distilled in a vacuum, the fraction boiling at 130–150°/1–2 mm (228 g, 86%) being collected. Its pale red color can be removed by a second distillation (b.p. 130–135°/1 mm).

In some cases, *e.g.*, if water is to be excluded, it is advisable to use the very reactive *O*,*N*- or *N*,*N*-acetals.[717] This method makes it possible to use carbonyl compounds that do not otherwise undergo the Mannich reaction. (For examples of the reaction with *N*,*N*-acetals see page 973.)

$$\mathrm{RH + NR'_2CHR''NR'_2 \longrightarrow CHRR''NR'_2 + NHR'_2}$$

$$\mathrm{RH + R'OCHR''NR'_2 \longrightarrow CHRR''NR'_2 + R'OH}$$

$$\mathrm{RH + HOCH_2NR'COCH_3 \longrightarrow CH_2RNR'COCH_3 + H_2O}$$

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[715] C. E. Maxwell, *Org. Syn.*, **23**, 30 (1943).

[716] G. F. Grillot and W. T. Gormley, Jr., *J. Amer. Chem. Soc.*, **67**, 1968 (1945); H. A. Bruson and C. W. McMullen, *J. Amer. Chem. Soc.*, **63**, 270 (1941).

[717] H. Böhme, H. J. Bohn, E. Köhler, and J. Roehr, *Ann. Chem.*, **664**, 130 (1963).

N-Semiacetals of formaldehyde, $HOCH_2NR_2$,[718] and their esters[719] have also been recommended for aminoalkylations; their use has given good results even when side reactions otherwise occur, *e.g.*, with naphthols.

Böhme and his co-workers[720] showed that reaction of α-halo alkylamines (R = alkyl below) with compounds containing reactive methylene groups amounts to aminoalkylation and affords Mannich bases that can be obtained only with difficulty or not at all by other methods:

$$RR'\overset{+}{N}{=}CH_2Cl^- + CH_2XY \longrightarrow NRR'CH_2CHXY + HCl$$

Such is the case also for *N*-(halomethyl) carboxamides (R = H or alkyl, R′ = acyl)[721] and *N*-(halomethyl) diacylamides (R and R′ = acyl), which are specific for amidomethylation of β-diketones, a reaction that cannot be effected otherwise); for a review of these reactions see Gross and Höft[679]). Amino- and amido-methylation of aromatic carbocyclic and heterocyclic compounds by α-halo amines and amides have also been reported.[707,722,723]

Tscherniac–Einhorn condensation of reactive aromatic compounds with (hydroxymethyl)-acyl- or -diacyl-amines also constitutes an amidoalkylation and has been reviewed:[32c,106n,724]

$$ArH + C_6H_5CONHCH_2OH \longrightarrow ArCH_2NHCOC_6H_5$$

Formaldehyde plus a nitrile may replace the (hydroxymethyl) amides; the resulting reaction:

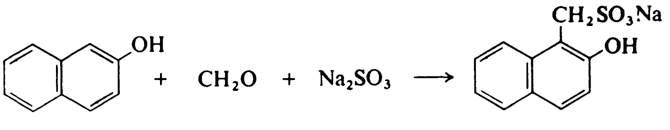
$$ArH + CH_2O + RCN \longrightarrow ArCH_2NHCOR$$

provides *N*-acylbenzylamines in one step directly from the aromatic compound.[725]

For alkylation by Mannich bases see page 970.

6. Sulfomethylation

Suter, Bair, and Bordwell[726] have described a reaction in which a hydrogen atom is replaced by a sulfomethyl group. From 2-naphthol, formaldehyde, and sodium sulfite they obtained sodium (2-hydroxy-1-naphthyl)methyl sulfate in 95% yield:



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[718] H. Böhme, A. Dick, and G. Driesen, *Chem. Ber.*, **94**, 1879 (1961).

[719] S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, **31**, 133 (1966).

[720] H. Böhme, E. Mundlos, and G. Keitzer, *Chem. Ber.*, **91**, 656 (1958).

[721] H. Böhme, R. Broese, A. Dick, F. Eiden, and D. Schünemann, *Chem. Ber.*, **92**, 1599 (1959); H. Böhme, A. Dick, and G. Driesen, *Arch. Pharm.*, **294**, 312 (1961).

[722] H. Böhme and A. Müller, *Arch. Pharm.*, **296**, 65 (1963).

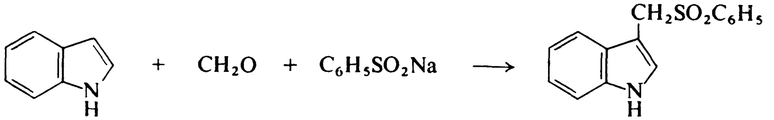
[723] Ger. Pat. 134979; *Friedländer*, **6**, 143 (1902); A. Einhorn, *Ann. Chem.*, **343**, 207 (1905).

[724] H. Hellmann, *Angew. Chem.*, **69**, 463 (1957).

[725] C. L. Parris and R. M. Christenson, *J. Org. Chem.*, **25**, 1888 (1960).

[726] C. M. Suter, R. K. Bair, and F. G. Bordwell, *J. Org. Chem.*, **10**, 470 (1945).

If a compound containing an acidic CH group is treated with formaldehyde and sodium benzenesulfinate the derived (phenylsulfonyl)methyl derivative is formed; *e.g.*, indole gives a 93% yield in the following reaction:[727]



IV. C–C linkage by replacement of OR by carbon

1. Ester condensation[106m,728]

The designation "ester condensations" includes all reactions of carboxylic or carbonic esters with compounds that contain an activated methylene or methine group. These reactions occur in an alkaline medium, with loss of an alcohol and formation of a new carbon–carbon bond, and can be formulated generally as:

$$RCOOR' + CH_2R''R''' \xrightarrow{NaOR'} RCOCHR''R''' + R'OH$$

A few of the many possible condensations are: that of two molecules of an ester to give a β-oxo ester, of an ester with a ketone to give a 1,3-diketone, of a formic ester with a ketone to give a 3-oxo aldehyde, of an oxalic ester with a ketone to give a dioxo ester, and of an alkyl carbonate with a nitrile to give an α-cyano carboxylic ester.

The condensing agent may be an alkali metal (usually sodium), sodamide, a sodium alkoxide, or sodium hydride.[729] Sodium metal is used in the form of wire or slices. If a group in one of the reactants is liable to alteration by "nascent" hydrogen the use of a sodium alkoxide is indicated.

For some unknown reason, large batches often give better yields in ester condensations than do small batches.

Care is essential when working with sodamide because it may detonate violently for no visible reason; old samples, not entirely free from suspicion, must without qualification be rejected. The following is a convenient and safe method for **preparation of sodamide:**[730]

Powdered iron(III) nitrate hexahydrate is added to liquid ammonia (500 ml, placed in a 2-l flask). The mixture is stirred and sodium (about 1 g) is added. Stirring is continued until the blue color changes to grey, then further small pieces of sodium are introduced seriatim as the color changes each time to grey, until all the sodium (26 g, 1.13 moles) has been added. The mixture is finally stirred for a further 15 min after all the sodium has been added and the

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[727] H. Hellmann and K. Müller, *Chem. Ber.*, **98**, 638 (1965).

[728] C. R. Hauser and B. E. Hudson, Jr., *Org. Reactions*, **1**, 266 (1942); C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 59 (1954).

[729] F. B. La Forge and S. B. Soloway, *J. Amer. Chem. Soc.*, **69**, 2932, 2677 (1947); N. Green and F. B. La Forge, *J. Amer. Soc.*, **70**, 2287 (1948).

[730] T. H. Vaughn, R. R. Vogt, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 2120 (1934); A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **60**, 2644 (1938); D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, 1951, p. 267; E. M. Hancock and A. C. Cope, *Org. Syn.*, **25**, 25 (1945); K. N. Campbell and B. C. Campbell, *Org. Syn.*, **30**, 72 (1950).

solution has become grey again. For additional details about apparatus see the description of the preparation of cyclohexylphenylacetonitrile on page 917.

Sodamide prepared in this way should not be stored as a solid (obtainable by evaporation of the ammonia) as it can form explosive compounds.

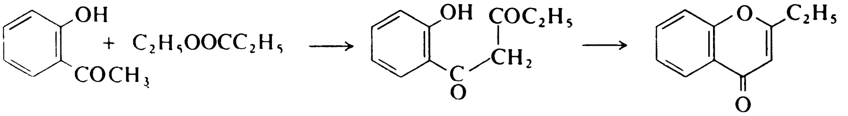
Hauser and Walker record the use of (diethylamino)magnesium bromide as condensing agent.[731]

The presence of alcohol, even if only in traces, is essential if ester condensations are to proceed normally, so a little dry alcohol is specially added when necessary.

In ester condensations it is sometimes necessary to warm the mixture gently to overcome an induction period, but cooling is often required as the reaction proceeds, otherwise side reactions may occur, *e.g.*, Bouveault–Blanc reduction (see page 76). It is not always easy or possible to determine the end of the reaction from the appearance of precipitated solids, because the sodium may become coated mechanically and withdrawn from the reaction. **Care** is thus needed during working up, which usually begins with acidification of the reaction mixture; when possible, the acetic acid used for acidification should not be added to the reaction flask, but the reaction mixture should be poured into a wide, open porcelain dish and the larger pieces of sodium should be then removed by hand.

The **ethyl acetate** often used for ester condensations should be purified as follows: If it gives an acid reaction, it should be washed with sodium carbonate solution, followed by water until the alkaline reaction disappears; in other cases two washings with water suffice. It is then dried provisionally with a little calcium chloride; after that, it should be set aside over a large amount of calcium chloride for 24 h, though losses due to formation of an addition compound are unavoidable. Inglis and Roberts[732] washed the ethyl acetate only with water and dried it over solid potassium hydroxide. The ester thus obtained still contains alcohol and boils over a range of 2–3°. The dry ethyl acetate need not be distilled. Since it is very hygroscopic it should be poured carefully away from the drying agent and not filtered.

Scheibler[733] has described a laboratory method of preparing acetoacetic ester that is convenient and gives very good yields. In industry it is obtained by use of sodium dust in autoclaves, quantitative yields being claimed[734] for this process. Occasionally acetoacetic ester is prepared by condensation of ethyl acetate and used, without isolation, for further reactions, whereby excellent yields of the final products are obtained.[735] Ethyl benzoate and acetophenone give dibenzoylmethane in about 70% yield.[736] *o*-Hydroxyacetophenone, condensed with ethyl propionate and sodium in ether, afford 1-(*o*-hydroxyphenyl)-1,3-pentanedione which is cyclized to 2-ethylchromone in 70–75% yield by hydrochloric and acetic acid.[737]



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[731] C. R. Hauser and H. G. Walker, Jr., *J. Amer. Chem. Soc.*, **69**, 295 (1947).

[732] J. K. H. Inglis and K. C. Roberts, *Org. Syn.*, **6**, 36 (1926).

[733] H. Scheibler, *Ann. Chem.*, **565**, 176 (1949).

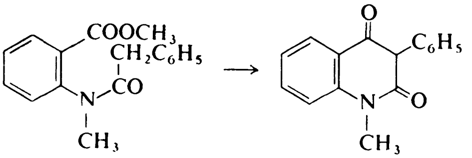
[734] O. D. Frampton and J. F. Nobis, *Ind. Eng. Chem.*, **45**, 404 (1953).

[735] F. Kuiban, S. Chilyanu, and F. Shcherbesku, *Med. Prom. S.S.S.R.* 12, No. 10, 36 (1958); *Chem. Abstr.*, **53**, 16139 (1959).

[736] A. Magnani and S. M. McElvain, *Org. Syn.*, **20**, 32 (1940).

[737] R. Mozingo, *Org. Syn.*, **21**, 42 (1941).

Cyclization by ester condensation is involved in the formation of 1-methyl-3-phenyl-2,4(1*H*,3*H*)-quinolinedione (86%) from methyl *o*-(*N*-methyl-*N*-phenylacetylamino)benzoate:[738]

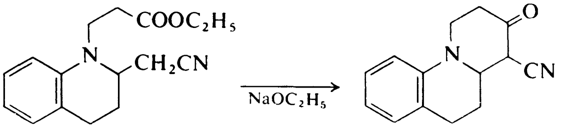


β-Oxo nitriles are obtained by treating nitriles with esters in the presence of sodium ethoxide:[739]

$$RCH_2CN + R'COOC_2H_5 \longrightarrow RCH(CN)COR' + C_2H_5OH$$

For example, phenylacetonitrile, esters, and sodamide in ether give *α*-acylphenylacetonitriles in 60–80% yield.[740]

When the structure is favorable, intramolecular acylation becomes possible, as in the synthesis in 82% yield of 4-cyano-4,4a,5,6-tetrahydro-1*H*-benzo[*c*]-quinolizin-3(2*H*)-one from ethyl 2-(cyanomethyl)-1,2,3,4-tetrahydro-1-quinolinepropionate:[741]



Ester condensation with formic esters leads to formyl derivatives. Thus a formic ester substitutes the free methylene group of diethyl (*p*-methoxyphenyl)succinate by an aldehyde group, the yield being about 50%.[664,742] The *β*-oxo aldehydes formed from ketones and formic esters usually exist as their tautomers, the hydroxymethylene compounds. 2-(Hydroxymethylene)-cyclopentadecanone is obtained from cyclopentadecanone with sodium ethoxide as condensing agent[743] (yield 66%); formylation of acetophenone has been described by Panizzi,[744] and other examples are recorded by Snyder and his co-workers.[745] Phthaloylglycine containing a ^{14}C-labelled carboxyl-carbon atom, with ethyl formate, gave a product which, on reduction of the formyl group, yielded a 1-labelled serine derivative.[746]

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[738] O. Märtensson and E. Nilsson, *Acta Chem. Scand.*, **14**, 1129 (1960).

[739] J. B. Dorsch and S. M. McElvain, *J. Amer. Chem. Soc.*, **54**, 2960 (1932); R. S. Long, *J. Amer. Chem. Soc.*, **69**, 990 (1947).

[740] R. Levine and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 760 (1946).

[741] G. Jones and J. Wood, *Tetrahedron*, **21**, 2961 (1965).

[742] G. Swain, A. R. Todd, and W. S. Waring, *J. Chem. Soc.*, **1944**, 548.

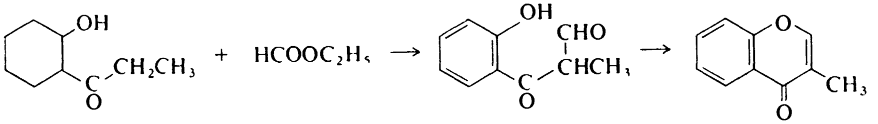
[743] V. Prelog and U. Geyer, *Helv. Chim. Acta*, **28**, 1677 (1945).

[744] L. Panizzi, *Gazz. Chim. Ital.*, **77**, 549 (1947).

[745] R. J. Tuite, A. D. Josey, and H. R. Snyder, *J. Amer. Chem. Soc.*, **82**, 4360 (1960).

[746] A. Schöberl, and C.-V. Pape, *Chem. Ber.*, **98**, 1688 (1965).

A generally applicable chromone synthesis also utilizes condensation with a formic ester, yields being about 80%:[747]



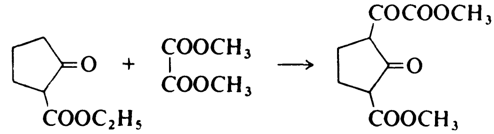
3-Methylchromone:[747] A mixture of *o*-hydroxypropiophenone (20 g) and ethyl formate (300 g) is cooled to 0° and sodium (16 g) is added in small portions with shaking. When the reaction abates, the mixture is set aside at room temperature for 3 days, atmospheric moisture being excluded by a mercury valve. Vigorous and long shaking is necessary during the reaction. At the end of the 3 days the mixture is poured on ice and ether. The aqueous layer is separated and washed several times with ether in order to remove entirely the colored products. The ethereal solutions are then united, washed a few times with saturated ammonium sulfate solution, and dried over sodium sulfate. The ether is evaporated and the residue, which contains much water, is distilled in a vacuum, giving the chromone (18 g), b.p. 156°/15 to 16 mm, m.p. 68° (after recrystallization from benzene and light petroleum).

An aldehyde group can also be introduced by use of orthoformic esters:[748]

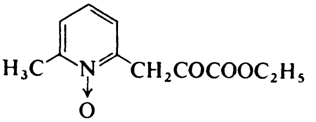
$$\mathrm{XYCH_2 + HC(OC_2H_5)_3 \xrightarrow{Ac_2O} XYC{=}CHOC_2H_5 \longrightarrow XYCHCHO}$$

This reaction, discovered long ago by Claisen, often gives excellent yields; the ethoxymethylene compounds are formed in 98% yield.[749]

Using an oxalic ester replaces a reactive hydrogen atom by an oxo ester (alkoxalyl) group.[750] Thus diethyl 3-methyl-2-oxoglutarate is obtained in 70% yield from ethyl propionate and diethyl oxalate;[751] and dimethyl dioxohomonorcamphorate [methyl(3-methoxycarbonyl-2-oxocyclopentyl)glyoxalate] can be prepared in 90% yield from ethyl 2-oxocyclopentanecarboxylate and methyl oxalate:[752]



An oxo ester group can be introduced similarly (96% yield) in the 2-position of 1-tetralone;[753] under mild conditions, with sodium hydride as base, 2,6-lutidine *N*-oxide gives a 91% yield of ethyl 3-(6-methyl-1-oxido-2-pyridyl)-pyruvate:[754]



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[747] C. Mentzner and P. Meunier, *Bull. Soc. Chim. France*, [v], **11**, 302 (1944).

[748] L. Claisen, *Ber. Deut. Chem. Ges.*, **26**, 2729 (1893); *Ann. Chem.*, **297**, 1 (1897).

[749] R. G. Jones, *J. Amer. Chem. Soc.*, **74**, 4889 (1952).

[750] L. Claisen and N. Stylos, *Ber. Deut. Chem. Ges.*, **20**, 2188 (1887); C. S. Marvel and E. E. Dreger, *Org. Syn.*, Coll. Vol. 1, 238 (1943).

[751] R. F. B. Cox and S. M. McElvain, *Org. Syn.*, Coll. Vol. 2, 272 (1943); E. A. Steck, L. L. Hallock, and A. J. Holland, *J. Amer. Chem. Soc.*, **68**, 131 (1946).

[752] P. S. Pinkney, *Org. Syn.*, Coll. Vol. 2, 116 (1955); G. Konppa and A. Talvitie, *Ann. Acad. Sci. Fenn.*, Ser. A, **57**, No. 15, 2 (1941).

[753] I. Ugi, R. Huisgen, and D. Pawellek, *Ann. Chem.*, **641**, 63 (1961).

[754] V. Boekelheide and R. J. Windgassen, Jr., *J. Amer. Chem. Soc.*, **81**, 1456 (1959).

ethyl 3-(diethoxyphosphinyl)propionate and diethyl oxalate is substituted at position 2, giving a 90% yield of the product:[755]

$$(C_2H_5O)_2P(O)CH_2CH(COOC_2H_5)COCOOC_2H_5$$

Two equivalents of acetophenone and one of diethyl oxalate yield 62–74% of 1,6-diphenyl-1,3,4,6-hexanetetraone;[756] and ethyl crotonate, as a vinylogous ethyl acetate, also undergoes ester condensation, giving with diethyl oxalate and sodium ethoxide diethyl 5-oxo-2-hexenedioate:[757]

$$(COOC_2H_5)_2 + CH_3CH{=}CHCOOC_2H_5 \longrightarrow C_2H_5OOCCOCH_2CH{=}CHCOOC_2H_5$$

The similar condensation of ethyl sorbate is detailed below as an example of the procedure:[758]

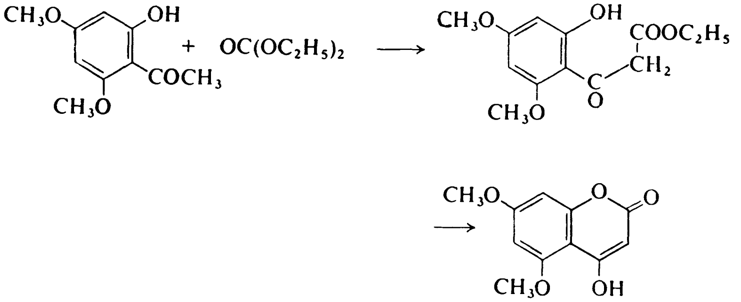
Diethyl 7-oxo-2,4-octadienedioate: Potassium (13 g), under ether (85 ml), is treated with ethanol (58 ml). Then a mixture of diethyl oxalete (24.3 g) and ether (10 ml) is added with cooling in ice and shaking, followed 15 min later by a mixture of ethyl sorbate (23.3 g) and ether (10 ml), whereupon the mixture at once becomes deep red. The flask is then securely stoppered and set aside for 24 h, after which the potassium enolate that has separated is filtered off as fast as possible, washed with cold water, and dried on porous plate in a desiccator. This enolate (27–28 g) is dissolved in water, and the solution is acidified with 2N-acetic acid; the precipitated free ester soon solidifies and after recrystallization from ethyl acetate or light petroleum melts at 100°.

Treatment of a carboxylic ester with diethyl oxalate and potassium ethoxide in pyridine at 70° and subsequent decarboxylation to yield an α-oxo carboxylic ester are described by Adickes and Andresen.[759]

Ester condensation with diethyl carbonate introduces an alkoxycarbonyl group.[760] Diethyl carbonate and 2-octanone in the presence of sodamide give ethyl 3-oxononanoate in 52% yield;[761] and in a similar reaction nitriles afford α-cyano esters in yields up to 87%,[762] *e.g.*:

$$RCH_2CN + OC(OC_2H_5)_2 \longrightarrow RCH(CN)COOC_2H_5$$

Boyd and Robertson[763] describe a synthesis providing a good yield of 4-hydroxycoumarins from *o*-hydroxyacetophenone derivatives and diethyl carbonate:



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[755] N. Kreutzkamp and W. Mengel, *Chem. Ber.*, **100**, 709 (1967).

[756] I. L. Finar, *J. Chem. Soc.*, **1955**, 1205.

[757] A. Lapworth, *Proc. Chem. Soc.*, **16**, 132 (1900).

[758] W. Borsche and R. Manteuffel, *Ber. Deut. Chem. Ges.*, **65**, 868 (1932).

[759] F. Adickes and G. Andresen, *Ann. Chem.*, **555**, 41 (1944).

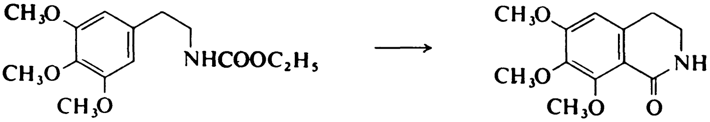
[760] J. C. Hessler, *Amer. Chem. J.*, **32**, 120 (1904); W. L. Nelson and L. H. Cretcher, *J. Amer. Chem. Soc.*, **50**, 2758 (1928).

[761] R. Levine and C. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1768 (1944); G. W. Anderson and co-workers, *J. Amer. Chem. Soc.*, **67**, 2197 (1945).

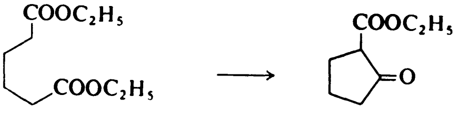
[762] V. H. Wallingford, D. M. Jones, and A. H. Homeyer, *J. Amer. Chem. Soc.*, **64**, 576 (1942).

[763] J. Boyd and A. Robertson, *J. Chem. Soc.*, **1948**, 174.

Intramolecular condensation of urethanes with particularly reactive aromatic groups can be achieved, and may be exemplified by the following preparation of 3,4-dihydro-6,7,8-trimethoxy-1(2*H*)-quinolone in 38% yield[764] by means of polyphosphoric acid:



An important variation of the ester condensation is due to Dieckmann.[765] It consists of a cyclization when two ester groups are attached to the same chain. For example, **ethyl 2-oxocyclopentanecarboxylate** is obtained from diethyl adipate in this way:[752]



A three-necked flask (capacity 3 l) is fitted with a stirrer, dropping funnel (250-ml capacity) and reflux condenser carrying a calcium chloride tube. In it are placed dry toluene (250 ml) and sodium (23 g, 1 mole). This mixture is stirred and diethyl adipate (202 g, 1 mole) is dropped in over a period of about 2 h while the reaction mixture is heated in an oil-bath at 100–115°. This temperature is then maintained for a further 5 h. Dry toluene is added from time to time through the condenser so as to keep the mixture sufficiently fluid (750–1000 ml are needed for this purpose). After cooling, the product is poured slowly into 10% acetic acid (1 l), pre-cooled to 0° (ice–salt bath), and the toluene layer is separated and washed with, successively, water, cold 7% sodium carbonate solution (twice), and water. The toluene is distilled off at atmospheric pressure and the residue is distilled in a vacuum. This affords a cyclic ester (115–127 g, 74–81%), b.p. 83–88°/5 mm, 79–84°/3 mm.

The Dieckmann condensation has been employed with success, for total synthesis of some alkaloids, *e.g.*, that of tropinone by Willstätter and Bommer,[766] and also by various authors[767] for synthesis of large-ring ketones.

2. Simple reactions involving loss of ROH

Alongside ester condensations ranks a series of simple condensations that involve formation of a new carbon–carbon bond with loss of an alcohol but that can be applied only in isolated cases. One such is the condensation of acetals with aromatic compounds with loss of alcohol, as when ethyl diethoxyacetate and nerolin (methyl 1-naphthyl ether) in glacial acetic plus sulfuric

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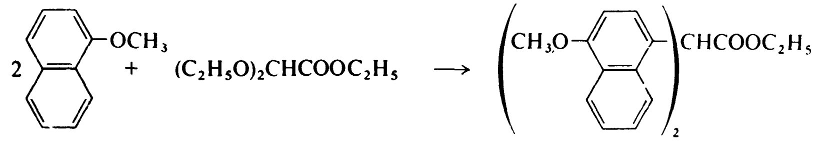
[764] A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).

[765] W. Dieckmann, *Ann. Chem.*, **317**, 27 (1901).

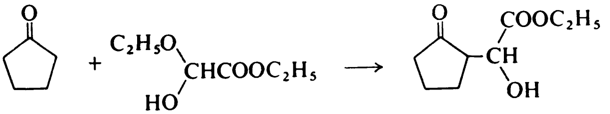
[766] R. Willstätter and M. Bommer, *Ann. Chem.*, **422**, 15 (1921).

[767] M. Stoll, *Chimia* (*Aarau*), **2**, 223 and note 31 (1948); E. A. Prill and S. M. McElvain, *J. Amer. Chem. Soc.*, **55**, 1233 (1933); N. J. Leonard and co-workers, *J. Amer. Chem. Soc.*, **71**, 3098 (1949); **74**, 1704, 4620, 6251 (1952).

acid give ethyl bis-(4-methoxy-1-naphthyl)acetate in 80% yield:[768]

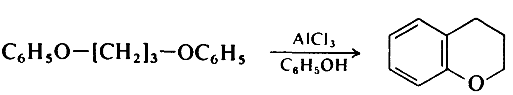


Also the ethyl semiacetal of glyoxalic ester gives α-hydroxy-γ-oxo carboxylic esters when heated with ketones in an autoclave at 200°, again with loss of alcohol,[769] *e.g.*:



The Friedel–Crafts synthesis with cyclic ethers such as oxirane has been discussed on page 937.

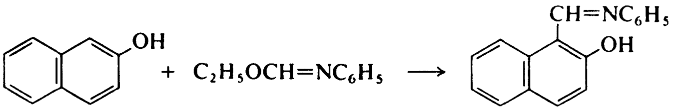
Chroman can be obtained in 72% yield by simply boiling 1,3-diphenoxypropane with aluminum chloride:[770]



The reaction between orthoesters and hydrogen cyanide in the presence of zinc chloride proceeds with loss of alcohol and gives very good yields of α,α-dialkoxy nitriles:[771]

$$RC(OR')_3 + HCN \longrightarrow RC(OR')_2CN + R'OH$$

Azomethines are formed in 80% yield when ethoxyisoformanilide [*N*-(ethoxymethylene)aniline is used as the ester component:[772]



V. C–C linkage by replacement of O–acyl by carbon

1. Acylation by carboxylic anhydrides

As mentioned above, β-diketones can be obtained by condensation of esters with ketones, but they can also be prepared in another way, namely, by reaction of methyl ketones with acid anhydrides in the presence of boron

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[768] C. Broquet–Borgel and R. Quelet, *C. R. Hebd. Séances Acad. Sci.*, **249**, 1761 (1959).
[769] A. W. Noltes and F. Kögl, *Rec. Trav. Chim.*, **80**, 1334 (1961).
[770] L. W. Deady, R. D. Topsom, and J. Vaughan, *J. Chem. Soc.*, **1963**, 2094.
[771] J. G. Erickson, *J. Amer. Chem. Soc.*, **73**, 1338 (1951).
[772] E. B. Knott, *J. Chem. Soc.*, **1947**, 976.

trifluoride:

$$RCOCH_3 + (CH_3CO)_2O \xrightarrow{BF_3} RCOCH_2COCH_3 + CH_3COOH$$

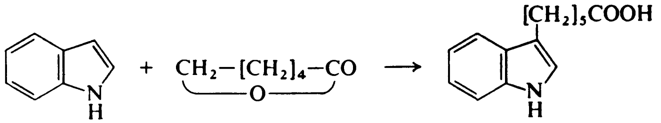
For example, Meerwein and Vossen[773] describe the preparation of **benzoylacetone (1-phenyl-1,3-butanedione)** as follows:

Acetophenone (20 g) and acetic anhydride (34 g, 2 moles) are mixed and boron trifluoride is led in, with ice-cooling, to saturation. The mixture becomes almost filled with yellowish crystals and is poured into a solution of crystalline sodium acetate (45 g) in water (100 ml) and distilled in steam. A small amount of oil first distils and is followed by the benzoylacetone which tends to solidify in the condenser. This product is taken up in ether, washed with sodium hydrogen carbonate solution, dried over sodium sulfate, and distilled in a vacuum. The yield is 83.3% (22.5 g).

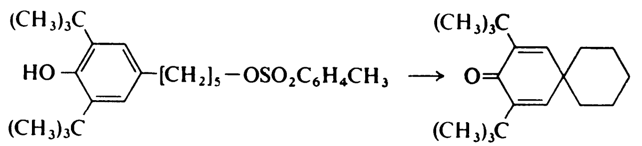
Other examples are recorded by Hauser and Adams.[774] Other acylations by acetic anhydride recorded on previous pages are those of aromatic compounds on page 939, of acetylides on page 931, of alkylcadmiums on page 911, and of diazo compounds on page 948.

2. Alkylation by esters, lactones, alkyl sulfates, or alkyl sulfonates

When indole is heated with 6-hexanolide in the presence of potassium hydroxide, cleavage of the lactone leads to alkylation and formation of 3-indolehexanoic acid in 95% yield:[775]



p-Toluenesulfonic acid is eliminated when 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)pentyl *p*-toluenesulfonate is heated with potassium *tert*-butoxide, the product (98%) being 2,4-di-*tert*-butylspiro[5.5]undeca-1.4-dien-3-one:[776]



The heading of this Section covers formally many reactions involving alkylation that were more conveniently treated in earlier Sections. These are: alkylation of Grignard reagents by allyl esters of mesitylenecarboxylic acid (see page 907); acylation of alkylidenephosphoranes by alkyl or aryl carboxylates (page 925); use of lactones (page 937) or enamines (page 929) for alkylation of aromatic compounds by Friedel–Crafts methods (page 936); acylation of enamines by lactim *p*-toluenesulfonates (page 962); use of sulfonates for alkylation of Grignard reagents (page 967), compounds containing reactive methylene groups (pages 912–914), cyanides (page 923), acetylides (pages 931, 932), and aromatic compounds by Friedel–Crafts methods

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[773] H. Meerwein and D. Vossen, *J. Prakt. Chem.*, **141**, 157 (1934).

[774] C. R. Hauser and J. T. Adams, *J. Amer. Chem. Soc.*, **66**, 345 (1944); **67**, 284 (1945).

[775] H. E. Fritz, *J. Org. Chem.*, **28**, 1384 (1963).

[776] J. D. McClure, *J. Org. Chem.*, **27**, 2365 (1962).

(page 936); and use of dialkyl sulfates for alkylation by the Fittig reaction (page 938) and for alkylation of Grignard reagents (page 940), of compounds containing reactive methylene groups (pages 913, 920) of cyanides (page 923), and of acetylides (page 931).

VI. C–C linkage by replacement of nitrogen by carbon

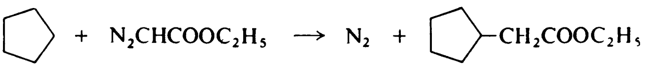
1. Removal of elemental nitrogen

a. Reactions of diazo esters

There are various methods of forming new carbon–carbon bonds that involve loss of nitrogen. Some have been described in preceding Sections, *e.g.*, the reaction of aldehydes and ketones with diazomethane (page 907); the original literature should be consulted for others, such as the reaction for diazomethane with compounds containing reactive methylene groups (formation of methyl derivatives);[777,778] yet others have now only historical interest (see, *e.g.*, Gomberg and Berger[779]). The following are some of the more important of the remainder.

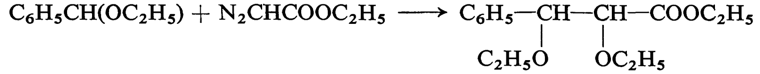
Ethyl diazoacetate reacts with benzene with loss of nitrogen and formation of ethyl norcara-2,4-diene-7-carboxylate.[780]

Substituted acetic acids are formed on irradiation of ethyl diazoacetate in admixture with cycloalkanes:[781]



Alkyl halides and ethyl diazoacetate give higher α-halo aliphatic acids, *e.g.*, ethyl 2-bromo-4-pentenoate from allyl bromide in 68–74% yield.[782]

Acetals react with ethyl diazoacetate in the presence of boron trifluoride; benzaldehyde diethyl acetal affords ethyl 2,3-diethoxy-3-phenylpropionate:[783]



$$C_6H_5CH(OC_2H_5) + N_2CHCOOC_2H_5 \longrightarrow C_6H_5{-}\underset{C_2H_5O}{\underset{|}{CH}}{-}\underset{OC_2H_5}{\underset{|}{CH}}{-}COOC_2H_5$$

An analogous reaction occurs with dithioacetals, giving bis(methylthio) compounds.[783,784]

b. Reactions of diazo ketones

Diazo ketones can cyclize with loss of nitrogen: 2-[*o*-(diazoacetyl)phenyl]-naphthalene is converted in chrysenol when treated with glacial acetic and sulfuric acid.[785]

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[777] R. Daniels and O. L. Salerni, *Proc. Chem. Soc.*, **1960**, 286; K. Syhora, *Collect. Czech. Chem. Commun.*, **26**, 107 (1961).

[778] A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie, and P. A. Wilkinson, *J. Chem. Soc.*, **1961**, 4547.

[779] M. Gomberg and H. W. Berger, *Ber. Deut. Chem. Ges.*, **36**, 1090 (1903); **30**, 2043 (1897).

[780] N. Braren and E. Buchner, *Ber. Deut. Chem. Ges.*, **34**, 989 (1901).

[781] W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **78**, 4947 (1956).

[782] I. A. Dyakonov and N. B. Vinogradova, *Zh. Obshch. Khim.*, **21**, 851 (1951); *Chem. Abstr.*, **46**, 440 (1952).

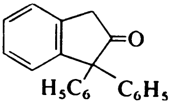
[783] A. Schönberg and K. Praefcke, *Tetrahedron Lett.*, **1964**, 2043.

[784] A. Schönberg and K. Praefcke, *Chem. Ber.*, **100**, 778 (1967).

[785] J. W. Cook and R. Schoental, *J. Chem. Soc.*, **1945**, 288.

When treated with boron trifluoride in ether, 3-diazo-1,1,1-triphenylacetone cyclizes almost quantitatively to 1,1-diphenyl-2-indanone with loss of nitrogen:[786]

$(C_6H_5)_3CCOCHN_2 \longrightarrow N_2 +$



c. Reactions of diazonium salts

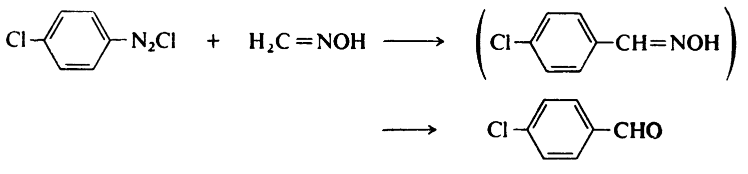
Carbon–carbon bonds can be formed in very varied ways in reactions of diazonium compounds. For example, 1-chloro-4-(*p*-nitrophenyl)-2-butene (88% yield) is formed from diazotized *p*-nitroaniline and butadiene in aqueous acetone containing copper chloride and sodium acetate,[787] whereas in the same conditions 5-phenyl-2,4-pentadienoic acid gives 1-(*p*-nitrophenyl)-4-phenyl-1,3-butadiene.[788] The latter reaction is a special case of Meerwein arylation, by which stilbenes are formed in good yields from diazonium salts and cinnamic acids:[789]

$$ArN_2Cl + HOOCCH{=}CHAr' \longrightarrow ArCH{=}CHAr' + HCl + CO_2 + N_2$$

Synthesis of **4-chlorostilbene**[790] is an example:

A solution of *p*-chloroaniline in water (100 ml) and hydrochloric acid (80 ml) is diazotized at 0° by a solution of sodium nitrite (15 g) in water (30 ml). The clear (filtered, if necessary) diazonium solution is added to a cold solution of cinnamic acid (30 g) in acetone (250 ml). Then sodium acetate (44 g), followed by a solution of copper(II) chloride (8.5 g) in water (20 ml), are added. The temperature may rise slowly to 16° when gas evolution has begun. The mixture is stirred at 14–16° for 3 h. By the end of the coupling reaction two layers will have been formed — an upper layer of dark green oil and a lower layer of pale green aqueous acetone. The whole is distilled in steam. The residue is extracted in benzene and washed several times with 3N-ammonia solution and then with water. Distilling off the benzene leaves a crystalline residue of 4-chloro-stilbene which recrystallizes from 2-propanol in shiny leaflets, m.p. 129° (40%).

Diazonium salts and acrylonitrile react by addition and loss of nitrogen, yielding 1-chloro-2-arylpropionitriles in *ca.* 80% yield;[790] but use of formaldoxime leads to an aldehyde synthesis:[792]



Nitriles can be obtained from diazonium salts by the Sandmeyer method, which involves treatment with copper(I) in the hot.[793] An example of this valuable reaction is the preparation of **o-nitrobenzonitrile** from *o*-nitroaniline:[794]

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[786] A. L. Wilds, J. van der Berghe, C. H. Winestock, R. L. von Trebra, and N. F. Woolsey *J. Amer. Chem. Soc.*, **84**, 1503 (1962).

[787] E. C. Coyner and G. A. Ropp, *J. Amer. Chem. Soc.*, **70**, 2283 (1948).

[788] F. Bergmann and Z. Weinberg, *J. Org. Chem.*, **6**, 134 (1941).

[789] H. Meerwein, E. Büchner, and K. van Emster, *J. Prakt. Chem.*, **152**, 237 (1939).

[790] F. Bergmann, J. Weizman, and D. Schapiro, *J. Org. Chem.*, **9**, 408 (1944).

[791] W. H. Brunner and co-workers, *Monatsh. Chem.*, **79**, 187 (1948); **82**, 100 (1951).

[792] W. F. Beech, *J. Chem. Soc.*, **1954**, 1297.

[793] T. Sandmeyer, *Ber. Deut. Chem. Ges.*, **17**, 2650 (1884).

[794] M. T. Bogert and W. F. Hand, *J. Amer. Chem. Soc.*, **24**, 1035 (1902).

A mixture of powdered *o*-nitroaniline (13.8 g, 0.1 mole) and concentrated hydrochloric acid (17.5 ml) is stirred until the base is converted into its hydrochloride. Then water (500 ml) is added rapidly and the suspension is stirred while a solution of sodium nitrite (7 g, 0.1 mole) in water (40 ml) is dropped in during 1 h — cooling is not necessary. The whole is stirred for a further hour, after which the solution is decanted from the unchanged *o*-nitroaniline and allowed to flow very slowly into a stirred solution (prepared in a fume cupboard) of potassium copper(I) cyanide (from 25 g of copper sulfate hydrate, 150 ml of water, and 28 g of 96% potassium cyanide) at 90°. The mixture is kept at 90–100°, then boiled for a few minutes and filtered hot. The work with cyanide must be done in a fume cupboard because dicyanogen is formed. Crystals separate as the filtrate cools. The residue on the filter is extracted with boiling water until these extracts no longer deposit crystals on cooling. All the crystals are collected, washed with water, dried, and extracted with boiling carbon tetrachloride which leaves inorganic salts undissolved. The carbon tetrachloride solution is cooled. The nitrile which separates is recrystallized twice from dilute acetic acid, then having m.p. 109.5° (9.7 g, 65%).

Clarke and Read[795] have given further directions for carrying out the Sandmeyer reaction.

An interesting alternative to the Sandmeyer reaction is to treat a diazonium with tetracarbonylnickel in acetic acid, which yields the carboxylic acid directly:[796]

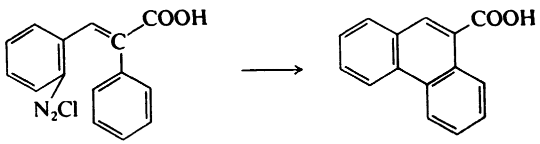
$$ArN_2^+BF_4^- + Ni(CO)_4 \xrightarrow{CH_3COOH} ArCOOH$$

p-Anisic acid, for instance, is obtained in 74% yield and this method may well be of interest when the compound contains functional groups that will not withstand hydrolysis of the nitrile.

Diazonium compounds decompose when copper powder and alcohol are added to their aqueous solutions, biphenyl derivatives being formed,[797] but this reaction is of importance only in special cases. A variant which gives up to 84% of the biaryl is to treat the diazonium salt with a solution of tetraaminocopper sulfate and hydroxylamine.[798]

Reaction of diazotized *p*-aminoacetophenone with *p*-benzoquinone gives an almost quantitative yield of 2-(*p*-acetylphenyl)-1,4-benzoquinone.[799]

A very fruitful reaction is the intramolecular condensation of diazotized α-aryl *o*-aminocinnamic acids to phenanthrene derivatives.[800,801] This is known as the Pschorr phenanthrene synthesis[802] and occurs in the presence of copper:



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[795] H. T. Clarke and R. R. Read, *J. Amer. Chem. Soc.*, **46**, 1001 (1924); *Org. Syn.*, **4**, 69 (1925).

[796] J. C. Clark and R. C. Cookson, *J. Chem. Soc.*, **1962**, 686.

[797] L. Gattermann and R. Ehrhardt, *Ber. Deut. Chem. Ges.*, **23**, 1226 (1890).

[798] L. Chardonnens and A. Würmli, *Helv. Chim. Acta*, **29**, 922 (1946); E. R. Atkinson and co-workers, *J. Amer. Chem. Soc.*, **63**, 730 (1941); **67**, 1513 (1945).

[799] G. A. Reynolds and J. A. Van Allan, *Org. Syn.*, **34**, 1 (1954).

[800] De Los F. de Tar, *Org. Reactions*, **9**, 409 (1957).

[801] P. H. Leake, *Chem. Rev.*, **56**, 27 (1956).

[802] R. Pschorr, *Ber. Deut. Chem. Ges.*, **29**, 496 (1896); **39**, 3106 (1906).

Substituted phenanthrenecarboxylic acids can be obtained in this way and yield the phenanthrene hydrocarbons on decarboxylation. Weisbach and his co-workers[803] applied this reaction to synthesis of aporphine.

Analogous ring closure to give fluorenones is also possible: 2-amino-4′-methyl-5-nitrobenzophenone gives 6-methyl-2-nitrofluorenone in 75% yield on diazotization and three hours' warming at 50°.[798,804]

2. Removal of amines[805]

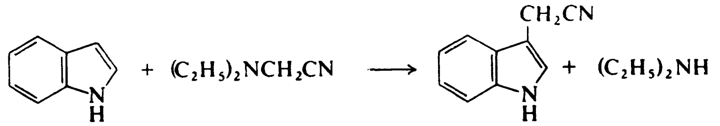
a. Alkylation by Mannich bases

A number of very successful preparative methods involve removal of an amino group and depend on treatment of a Mannich base or its hydrochloride or methiodide with a compound containing an acidic CH group. Relatively few examples can be given here, but others can be found in the excellent review by Hellmann and Opitz.[697c]

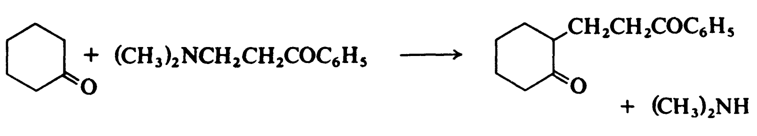
When 3-(dimethylamino)propiophenone hydrochloride is boiled for 0.5 hour with aqueous potassium cyanide solution, 4-oxo-4-phenylbutyronitrile is formed in 67% yield, dimethylamine being split off:[806]

$$C_6H_5COCH_2CH_2N(CH_3)_2{\cdot}HCl + KCN \longrightarrow C_6H_5COCH_2CH_2CN + NH(CH_3)_2$$

Analogously N^{α}-methylgraminium iodide and potassium cyanide yield 3-indoleacetic acid in 76% yield by way of the nitrile.[807,808] This nitrile can also be obtained, in 33–44% yield, from indole and (diethylamino)acetonitrile:[809]



Heating 3-(dimethylamino)propiophenone with a ketone at 160° for 20 minutes affords a 1,5-diketone, as in the following example (95% yield):[810]



and the same amine gives 4-methyl-4-nitro-1-phenyl-1-pentanone in 82% yield when boiled for 6.5 hours with 2-nitropropane in aqueous sodium hydroxide solution.[810] Gramine and triethyl methanetricarboxylate at 115°

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[803] J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963).

[804] L. Chardonnens and C. Perriard, *Helv. Chim. Acta*, **28**, 593 (1945).

[805] H. Hellmann, *Angew. Chem.*, **65**, 473 (1953); J. H. Brewster and E. L. Eliel, *Org. Reactions*, **7**, 99 (1953).

[806] E B. Knott, *J. Chem. Soc.*, **1947**, 1190; E. Haggett and S. Archer, *J. Amer. Chem. Soc.*, **71**, 2255 (1949).

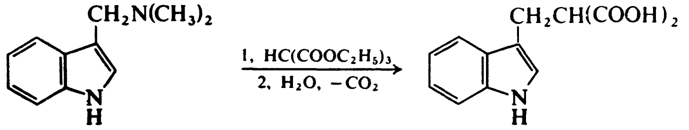
[807] T. A. Geissman and A. Armen, *J. Amer. Chem. Soc.*, **74**, 3916 (1952).

[808] H. R. Snyder and F. J. Pilgrim, *J. Amer. Chem. Soc.*, **70**, 3770 (1948).

[809] E. L. Eliel and N. J. Murphy, *J. Amer. Chem. Soc.*, **75**, 3589 (1953).

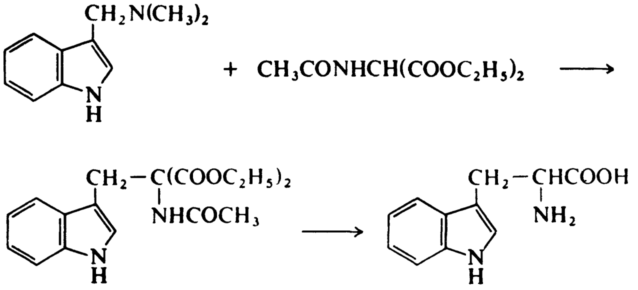
[810] N. S. Gill and co-workers, *J. Amer. Chem. Soc.*, **74**, 4923 (1952).

afford a condensation product which affords (3-indolylmethyl)malonic acid in 67% yield when, without isolation, it is hydrolysed by alkali and partially decarboxylated:[811]



When gramine reacts with diethyl nitromalonate, the primary product obtained is diethyl α-(3-indolylmethyl)-α-nitromalonate (96.5%), which is converted into tryptophan by partial hydrolysis and decarboxylation, followed by reduction and further hydrolysis.[812]

Acylated aminomalonic esters have been used with particular success for synthesis of various amino acids.[712,813] Thus, for example, tryptophan is also obtained by reaction of diethyl (acetylamino)malonate with gramine, the yield then being 73% referred to gramine:[814]



DL-Triptophan: Powdered sodium hydroxide (17 g) and toluene (or xylene) (1200 ml) are heated to boiling in a three-necked flask (capacity 5 l) fitted with a stirrer, reflux condenser, and gas-inlet tube, and gramine (250 g, 1.43 moles) and diethyl (acetylamino)malonate (311 g, 1.43 moles) are added. Nitrogen is led in while this mixture is rapidly stirred for a further 5 h under reflux. Evolution of dimethylamine is rapid at first but slackens later. The reaction mixture is then filtered through a heated filter, and the filtrate is cooled to room temperature, then kept for several hours at 5°. The ester formed as primary product is then filtered off and washed with cold toluene followed by light petroleum; the yield is 90% (446 g), and the m.p. is 158–159°.

This ester product (33.62 g, 0.097 mole) is boiled under reflux for 4 h with sodium hydroxide (19.2 g, 0.48 mole) in water (192 ml). The solution is treated with charcoal, filtered, and cooled in ice, then cold concentrated hydrochloric acid (50 ml, 0.6 mole) is added without allowing the temperature to rise above 25°. This solution is cooled for 4 h, whereafter the pale pink precipitate is collected and dried over calcium chloride in an evacuated desiccator for 15 h. The crude product (32 g), containing a little sodium chloride, melts at 136–139°.

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[811] H. R. Snyder and E. L. Eliel, *J. Amer. Chem. Soc.*, **71**, 663 (1949).

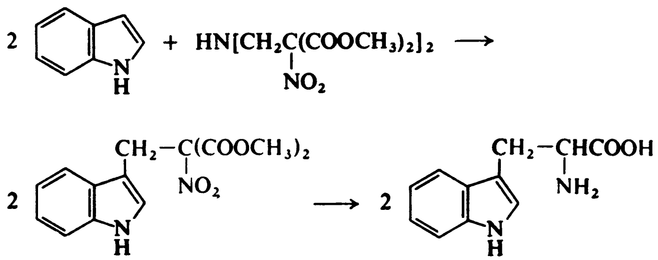
[812] D. I. Weisblat and D. A. Lyttle, *J. Amer. Chem. Soc.*, **71**, 3079 (1949).

[813] A. Galat, *J. Amer. Chem. Soc.*, **69**, 965 (1947); C. Schöpf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951); A. Butenandt, W. Weidel, and W. von Derjugin, *Naturwissenschaften*, **30**, 51 (1942); N. F. Albertson and B. F. Tullar, *J. Amer. Chem. Soc.*, **67**, 502 (1945); H. Hellmann and E. Brendle, *Z. Physiol. Chem.*, **287**, 235 (1951).

[814] E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Amer. Chem. Soc.*, **67**, 38 (1945); H. R. Snyder and C. W. Smith, *J. Amer. Chem. Soc.*, **66**, 350 (1944); H. Hellmann, *Z. Physiol. Chem.*, **284**, 163 (1949).

This crude acid (28 g) is heated in water (120 ml) for 2.5 h under reflux. The resulting *N*-acetyltryptophan is less soluble that the starting acid and gradually crystallizes from the reaction mixture. Sodium hydroxide (16 g, 0.4 mole) in water (40 ml) is next added and the solution is boiled for 20 h under reflux. It is then treated with charcoal, filtered, and acidified with glacial acetic acid (24 g, 0.4 mole), this causing immediate formation of a white precipitate. The mixture is kept for 12 h in a refrigerator, after which the precipitate is collected and dissolved in aqueous sodium hydroxide (5 g in 200 ml). This solution is treated with charcoal and filtered. 95% ethanol (100 ml) is added to the filtrate which is then warmed to 70°, acidified with glacial acetic acid (7.5 ml), and cooled slowly. Tryptophan, which separates as plate-like crystals, is filtered off, washed successively with water (2 × 40 ml), ethanol (2 × 40 ml), and ether (2 × 30 ml). The yield is 81% calculated on the ester product (14 g), and the m.p. is 272–280° (dec.) after recrystallization from 33% ethanol.

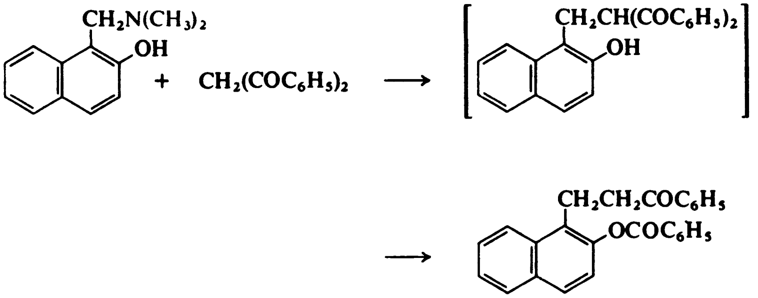
Conversely, indole can be condensed with the Mannich base from nitromalonic ester, formaldehyde, and ammonium acetate, giving an intermediate that can be worked up to give an overall yield of tryptophan of 77%:[815]



Alkylation of phenylacetylene by (ferrocenylmethyl)trimethylammonium iodide proceeds analogously:[816]

$$C_5H_5FeC_5H_4{-}CH_2\overset{+}{N}(CH_3)_3I^- + HC{\equiv}CC_6H_5 \longrightarrow C_5H_5FeC_5H_4{-}CH_2C{\equiv}CC_6H_5$$

and reaction of *N,N*-dimethyl-(2-hydroxy-1-naphthylmethyl)amine with dibenzoylmethane gives the expected *gem*-dibenzoyl derivative which, however, rearranges to 2-(2-benzoyloxy-1-naphthyl)ethyl phenyl ketone (89%):[817]



Loss of an amine also occurs in acylaminomethylation of (acetylamino)-malonic ester, which proceeds, for example, in accord with the following reac-

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[815] T. Okuda, *Bull. Chem. Soc. Japan*, **32**, 1165 (1959).

[816] P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, **1963**, 2990.

[817] H. Hellmann and J. L. W. Pohlmann, *Ann. Chem.*, **642**, 28 (1961); **643**, 43 (1961).

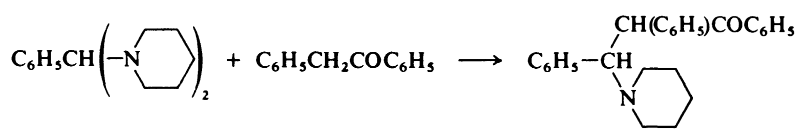
tions (see also page 957):

$$C_6H_5CONHCH_2N(CH_3)_2 + CH_3CONHCH(COOC_2H_5)_2 \longrightarrow$$

$$C_6H_5CONHCH_2C(COOC_2H_5)_2NHCOCH_3 \longrightarrow NH_2CH_2CH(NH_2)COOH$$

Hellmann and Haas[818] obtained a 94% yield of the 2,3-diaminopropionic acid on hydrolysis of the primary condensation product, itself obtained in 87% yield from *N*-[(dimethylamino)methyl]benzamide and diethyl (acetylamino)malonate.

N,N-Acetals (geminal diamines) react with compounds containing reactive CH groups also with loss of an amine and production of aminoalkylation products (see page 957). Thus 1,1′-benzylidenedipiperidine with, for instance, deoxybenzoin in ethanol affords 1,2,3-triphenyl-3-piperidino-1-propanone in 90% yield within 10 minutes at room temperature:[819]

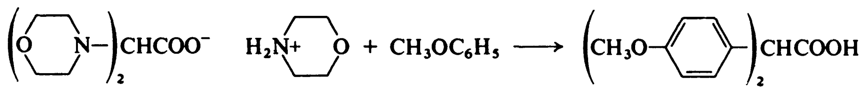


A reaction of the same type is that of *N,N′*-benzylidenediacetamide in acetic anhydride with compounds containing a reactive CH group, which gives α-(acetylamino)benzyl derivatives with removal of acetamide:

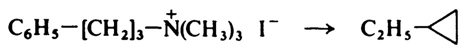
$$RH + C_6H_5CH(NHCOCH_3)_2 \longrightarrow RCH(C_6H_5)NHCOCH_3 + CH_3CONH_2$$

for example, 5-methylrhodanine affords 5-[β-(acetylamino)benzyl]-5-methyl-2-thiothiazolidin-4-one in almost quantitative yield.[820]

However, both amino groups of *N,N*-acetals may be replaced in other cases: morpholinium dimorpholinoacetate and anisole give di-(*p*-methoxyphenyl)-acetic acid in 74% yield:[821]



In suitable circumstances loss of the amine may also occur intramolecularly phenylcyclopropane is formed from *N,N,N*-trimethyl-3-phenylpropylammo: nium iodide:[822]



b. Acylation by carboxamide derivatives

If an aromatic carboxamide is used instead of an amide, an acyl group is introduced in a similar type of reaction. Thus, for example, pyridine and

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[818] H. Hellmann and G. Haas, *Chem. Ber.*, **90**, 1357 (1957).

[819] F. Fischer, F. Schmutzler, and E. Haak, *J. Prakt. Chem.*, **24**, 216 (1964).

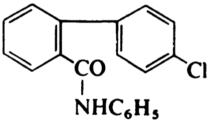
[820] G. Stefanovic, A. Stojiljković, and M. Stefanovic, *Tetrahedron*, **18**, 413 (1962).

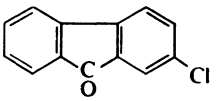
[821] A. Brault and M. Kerfanto, *C. R. Hebd. Séances Acad. Sci.*, **258**, 5465 (1964).

[822] C. L. Bumgardner, *J. Amer. Chem. Soc.*, **83**, 4420 (1961).

N,*N*-methylbenzamide give a mixture containing mostly 2- and a little 4-benzoylpyridine.[823]

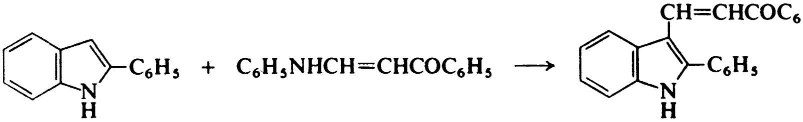
2-Chlorofluorenone is obtained analogously when *o*-(*p*-chlorophenyl)-benzanilide is heated for 2 hours in phosphoric acid, the yield being almost quantitative:[824]





For *C*-acylation of 1-acylimidazoles see page 921.

Unsaturated side chains may be introduced by means of vinylogous amides: 2-anilinovinyl phenyl ketone and 1-methyl-2-phenylindole give the 3-(2-benzoylvinyl) derivative:[825]



Finally, *N*,*N*-dimethylacetamide may undergo self-condensation: boiling it for 6–7 hours with phosphoryl chloride in benzene affords *N*,*N*-dimethylacetoacetamide in 75% yield:[826]

$$2CH_3CON(CH_3)_2 \xrightarrow{POCl_3} CH_3COCH_2CON(CH_3)_2$$

c. Formylation by formamide derivatives (Vilsmeier reaction)

The Vilsmeier reaction is similar in principle to the Mannich reaction: it consists of introduction of a formyl group by means of an alkylated formamide and thus constitutes a synthesis of aldehydes:[106g,827–829]

$$NR_2CHO + POCl_3 \longrightarrow {}^{+}NR_2{=}CHOPOCl_2Cl^{-} \xrightarrow{ArH}$$

$$[ArCH(NR_2)OPOCl_2] \xrightarrow{H_2O} ArCHO$$

The reaction is widely applicable: when treated with phosphoryl chloride and, *e.g.*, *N*-methylformanilide, aromatic hydrocarbons, aryl ethers,[829] condensed aromatic carbocyclic,[830] and heterocyclic compounds such as thiophen[831]

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[823] G. B. Bachman and R. M. Schisla, *J. Org. Chem.*, **22**, 858, 1302 (1957).

[824] D. H. Hey and T. M. Moynehan, *J. Chem. Soc.*, **1959**, 1563.

[825] M. Colonna, P. Bruni, and A. Monti, *Gazz. Chim. Ital.*, **95**, 868 (1965).

[826] M. Bredereck, R. Gompper, and K. Klemm, *Chem. Ber.*, **92**, 1456 (1959).

[827] A. van Darmael, *Ind. Chim. Belge*, **16**, 433 (1951); A. Vilsmeier, *Chemiker-Ztg.*, **75**, 133 (1951).

[828] H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959).

[829] A. Vilsmeier and A. Haack, *Ber. Deut. Chem. Ges.*, **60**, 119 (1927).

[830] L. F. Fieser, J. L. Hartwell, J. E. Jones, J. H. Wood, and R. W. Bost, *Org. Syn.*, Coll. Vol. 3, 98 (1955).

[831] A. W. Weston and R. J. Michaels, Jr., *J. Amer. Chem. Soc.*, **72**, 1422 (1950); *Org. Syn.*, **31**, 108 (1951).

and pyrrole derivatives[832] give carboxaldehydes, some of them in excellent yield. It is advisable to use a solvent such as dichlorobenzene with high-melting condensed aromatic compounds.

The following exemplifies practice of the Vilsmeier reaction:

2-Ethoxy-1-naphthaldehyde:[830] A mixture of *N*-methylformanilide[833] (45 g, 0.33 mole), phosphoryl chloride (51 g, 0.33 mole), and ethyl 2-naphthyl ether (43 g, 0.25 mole) is heated for 6 h on a water-bath in a round-bottomed flask (500-ml capacity) carrying an air-condenser. The hot solution is then poured in a thin stream into cold water (700 ml) with vigorous stirring to prevent formation of lumps. The aldehyde should then separate in granular form. It is filtered off, washed thoroughly with water (1 l) and, without being dried, is dissolved in ethanol (450 ml). This solution is boiled for 15 min with Norite (4 g), filtered hot through a doubled paper in a heated funnel, and cooled. The aldehyde is then collected and washed with cold ethanol (40 ml). It crystallizes in pale yellow needles, m.p. 111–112° (37–42 g, 74–84%).

Other formamide derivatives may be used in place of *N*-methylformamide,[834] and the phosphoryl chloride may be replaced by phosgene or thionyl chloride.[835]

More recently it has almost always been recommended to use the combination dimethylformamide–phosgene (*e.g.*, for formylation of *N*,*N*-dimethylaniline[828]) or dimethylformamide–phosphoryl chloride: derivatives of 1,2-methylenedioxybenzene[836] and of thiophen,[837] as well as azulene[838] and ferrocene,[839] have been formylated in this way, some of them in excellent yield. *Organic Syntheses* contains directions for formylation of indole (97% yield of the 3-carbaldehyde)[840] and *N*,*N*-dimethylaniline (80–84% yield of the *para*-aldehyde).[841] The following is a further example in detail:

2-Pyrrolecarbaldehyde:[842] The reaction vessel is a three-necked flask (3-l capacity) fitted with a stirrer, a dropping funnel, and a reflux condenser. Phosphoryl chloride (169 g, 1.1 moles) is added dropwise during 15 min to ice-cooled dimethylformamide (80 g, 1.1 moles); the reaction is exothermic and the temperature is kept at 10–20° during the addition. Then the mixture is stirred for 15 min without cooling. Next the ice-bath is restored and ethylene dichloride (250 ml) is added, followed over a period of 1 h by freshly distilled pyrrole (67 g, 1 mole) in ethylene dichloride (250 ml), dropwise, with stirring, while the internal temperature is 5°. Finally the mixture is boiled under reflux for 15 min, hydrogen chloride being evolved. The mixture is then cooled to 25–30° and a solution of sodium acetate trihydrate (750 g, 5.5 moles) in water (1 l) is dropped in from a dropping funnel, at first slowly, later rapidly. This mixture is heated for 15 min under reflux with vigorous stirring. After cooling, the two layers are separated, and the aqueous phase is extracted three times with ether (500-ml portions). The ethereal and ethylene dichloride solutions are united and washed three times with saturated aqueous sodium carbonate solution (100-ml portions), care being required because carbon dioxide is evolved. The organic phase is dried over anhydrous sodium car-

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[832] A. C. Shabica, E. E. Howe, J. B. Ziegler, and M. Tishler, *J. Amer. Chem. Soc.*, **68**, 1156 (1946).

[833] L. F. Fieser and J. E. Jones, *Org. Syn.*, Coll. Vol. 3, 590 (1955).

[834] E. Campaigne and W. L. Archer, *J. Amer. Chem. Soc.*, **75**, 989 (1953); S. Akabori and Y. Senoh, *Bull. Chem. Soc., Japan*, **14**, 166 (1939).

[835] Ger. Pat. 677,207; *Chem. Abstr.*, **33**, 6880 (1939).

[836] F. Dallacker and F.-E. Eschenbach, *Ann. Chem.*, **689**, 171 (1965).

[837] P. Friedmann and P. Allen, Jr., *J. Org. Chem.*, **30**, 780 (1965).

[838] K. Hafner and J. Schneider, *Ann. Chem.*, **624**, 37 (1959).

[839] H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **29**, 97 (1964).

[840] G. Domschke and G. Müller, *J. Prakt. Chem.*, [iv], **21**, 85 (1963); P. N. James and H. R. Snyder, *Org. Syn.*, **39**, 30 (1959).

[841] E. Campaigne and W. L. Archer, *Org. Syn.*, **33**, 27 (1953).

[842] R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syn.*, **36**, 74 (1956).

bonate, the solvents are distilled off, and the residue is distilled in a vacuum from an oil-bath. The crude 2-pyrrolecarbaldehyde (85–90 g, 89–95%) forms an almost water-white liquid, b.p. 78°/2 mm, which soon crystallizes; a sample dried on a porous plate melts at 35–40°; it recrystallizes from boiling light petroleum (b.p. 40–60°; 25 ml per g) that is cooled slowly to room temperature and then kept for some hours in a refrigerator. The pure aldehyde (yield 78–79%) melts at 44–45°.

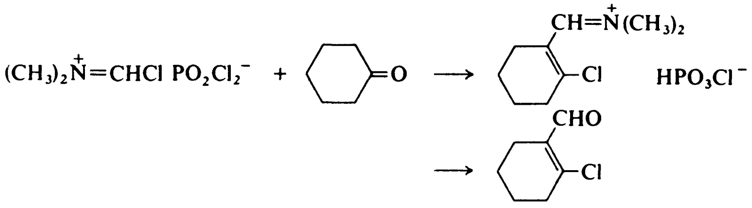
Two formyl groups can be introduced into 3,5,*N*,*N*-tetramethylaniline by dimethylformamide and phosphoryl chloride.[843]

Arnold and his colleagues have applied the combination of dimethylformamide with phosgene or phosphoryl chloride also to formylation of aliphatic compounds such as acetals,[844,845] ketals,[846] vinyl ethers,[844,845,847] and ketones[848,849] (see also Ziegenbein and his co-workers[850]). Vinyl ethers afford 2-alkyl-3-(dialkylamino) derivatives of acrylaldehyde:[844]

$$\mathrm{RCH{=}CHOC_2H_5 \xrightarrow[2,\ H_2O]{1,\ (CH_3)_2NCHO\text{-}COCl_2} (CH_3)_2NCH{=}CRCHO}$$

These are potential sources of malondialdehyde. Similar unsaturated aldehydes are obtained also from acetals and are useful for conversion into other products. Formylation of ketones has found wider application in synthesis because the β-chloro-α-unsaturated aldehydes produced are interesting starting materials for further elaboration:[850]

$$\mathrm{(CH_3)_2NCHO + POCl_3 \longrightarrow (CH_3)_2\overset{+}{N}{=}CHCl\ PO_2Cl_2^-}$$



Details of this synthesis of 2-chloro-1-cyclohexenecarbaldehyde are given in *Organic Syntheses*.[851] For further details of this type of synthesis the original literature may be consulted, but the formylation of enamines and of alkylidenephosphoranes is described on page 927 above.

Compounds containing activated double bonds can also be formylated by dimethylformamide and phosphoryl chloride; styrene thus gives cinnamaldehyde,[852] and chloroformylation to give β-chloro-α-unsaturated aldehydes occurs with acetylenes, *e.g.*:[853]

$$\mathrm{C_6H_5C{\equiv}CH \longrightarrow C_6H_5CCl{=}CHCHO}$$

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[843] C. Grundmann and J. M. Dean, *Angew. Chem. Int. Ed., Engl.*, **4**, 955 (1965).

[844] Z. Arnold and F. Šorm, *Collect. Czech. Chem. Commun.*, **23**, 452 (1958).

[845] Z. Arnold, *Collect. Czech. Chem. Commun.*, **24**, 760 (1959).

[846] Z. Arnold and J. Žemlička, *Collect. Czech. Chem. Commun.*, **24**, 786 (1959).

[847] Z. Arnold and J. Žemlička, *Collect. Czech. Chem. Commun.*, **24**, 2378 (1959).

[848] Z. Arnold and J. Žemlička, *Collect. Czech. Chem. Commun.*, **24**, 2385 (1959).

[849] Z. Arnold and J. Žemlička, *Proc. Chem. Soc.*, **1958**, 227.

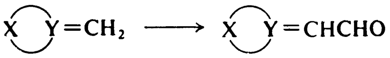
[850] W. Ziegenbein and W. Lang, *Chem. Ber.*, **93**, 2743 (1960); W. Ziegenbein and W. Franke, *Angew. Chem.*, **71**, 628 (1959).

[851] L. A. Paquette, B. A. Johnson, and F. M. Hinga, *Org. Syn.*, **46**, 18 (1966).

[852] C. J. Schmidle and P. G. Barnett, *J. Amer. Chem. Soc.*, **78**, 3209 (1956).

[853] W. Ziegenbein and W. Franke, *Angew. Chem.*, **71**, 573 (1959).

exo-Methylene derivatives in the cyclic terpene series also give α,β-unsaturated aldehydes when formylated by the above reagents:[854]



Furthermore, reactions analogous to Vilsmeier formylation can be carried out with vinylogs of dimethylformamide, *e.g.*, with 3-(*N*-methyl-*N*-phenylamino)acraldehyde, thus:

$$C_6H_5N(CH_3)CH{=}CHCHO + RH + POCl_3 \longrightarrow$$

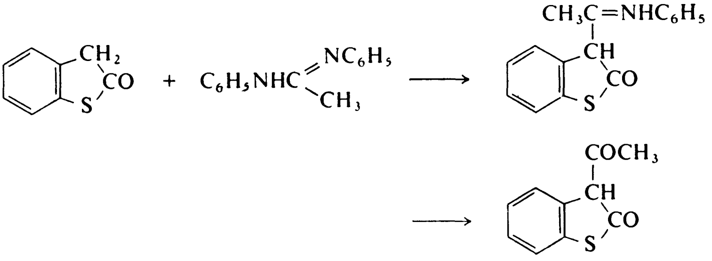
$$RCH{=}CHCH{=}\overset{+}{N}(CH_3)C_6H_5\ PO_2Cl_2^- + HCl$$

the derivatives of the unsaturated aldehydes thus formed can react further in a variety of ways.[838]

Benzanilide and phosgene have been used to introduce a benzoyl group into dimethylaniline (85% yield);[828] and other acylations can be effected analogously, as when ethyl 8-(1-azulenyl)-8-oxooctanoate is obtained in 80% yield from azulene, ethyl 7-(*N*,*N*-dimethylcarbamoyl)heptanoate, and phosphoryl chloride.[855]

d. Various reactions involving C–N cleavage

Ketone and aldehyde groups can also be introduced by use of amidines. Glauert and Mann[856] treated thiooxindole with *N*,*N*′-diphenylacetamidine, obtaining 3-[1-(phenylimino)ethyl]thiooxindole (64%) which was converted in yields of over 90% into 3-acetylthiooxindole. Using *N*,*N*′-diphenylformamidine gives the anil of thiooxindole-3-carbaldehyde (70–78%) analogously, and this may be hydrolysed to the free aldehyde (72).



Phenolic aldehydes can be obtained by the Duff reaction, in which the phenol is heated with urotropine, boric acid, and glycerol for 30 minutes at 150–160°;[857] the yields are not high (15–20%), but the procedure is simpler and less time -consuming than the Reimer–Tiemann synthesis; the products are the *ortho*-derivatives. Dialkylanilines can be formylated in the same way,[858] but here the products are the *para*-aldehydes.

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[854] G. Walter, F. Wolf, and E. Günther, *Z. Chem.*, **7**, 347 (1967).

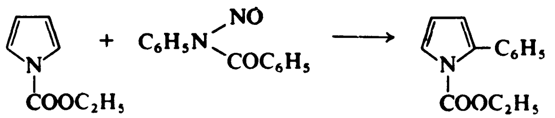
[855] K. Hafner and C. Bernhard, *Ann. Chem.*, **625**, 108 (1959).

[856] R. H Glauert and F. G. Mann, *J. Chem. Soc.*, **1952**, 2127.

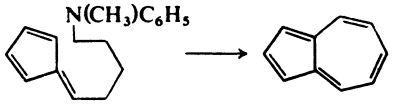
[857] J. C. Duff, *J. Chem. Soc.*, **1941**, 547; L. M. Ligget and H. Diehl, *Proc. Iowa Acad. Sci.*, **52**, 191 (1945).

[858] J. C. Duff, *J. Chem. Soc.*, **1945**, 276.

Besides the methods described above for forming new carbon–carbon bonds with elimination of elemental nitrogen or an amine there are other processes in which other nitrogenous compounds are eliminated. For example, Rinkes[859] obtained ethyl 2-phenyl-1-pyrrolecarboxylate by treating ethyl 1-pyrrolecarboxylate with *N*-nitrosoacetanilide:



Also, a synthesis of azulene that gives good yields starts from the fulvene derivative[860] that is formed quantitatively from cyclopentadiene and pentanedial *N*-methyl-*N*-phenylmonoimide:



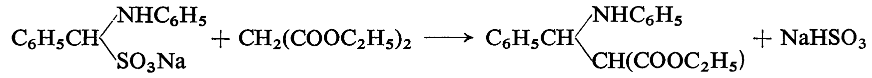
Finally there is the reaction of tetramethylformamidinium chloride with hydrogen cyanide at 0–10° which gradually yields (dimethylamino)malondinitrile in 92% yield:[861]

$$(CH_3)_2NCH{=}\overset{+}{N}(CH_3)_2\ Cl^- + HCN \longrightarrow (CH_3)_2NCH(CN)_2 + HCl$$

VII. C–C linkage by replacement of sulfur by carbon

There are only a few examples of this type of reaction. When 2-naphthol is heated with mercaptoacetic acid in ethylene glycol at 145–150°, hydrogen sulfide is eliminated and 2-hydroxy-1-naphthaleneacetic acid is formed in 89% yield.[862] When thiophenol reacts with *tert*-butyl phenyl sulfide under catalysis by boron trifluoride, *p*-(*tert*-butyl)thiophenol is formed in yields of up to 81% and a different molecule of thiophenol is eliminated (it is an apparent rearrangement).[863]

Finally, sodium α-(phenylamino)-α-toluenesulfonate and diethylmalonate give an 85% yield of diethyl [α-(phenylamino)benzyl]malonate with elimination of the sulfonate group:[864]



$$C_6H_5CH\begin{cases}NHC_6H_5\\ SO_3Na\end{cases} + CH_2(COOC_2H_5)_2 \longrightarrow C_6H_5CH\begin{cases}NHC_6H_5\\ CH(COOC_2H_5)\end{cases} + NaHSO_3$$

For the acylation of thiol esters see page 925.

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[859] I. J. Rinkes, *Rec. Trav. Chim.*, **62**, 116 (1943); E. Bamberger, *Ber. Deut. Chem. Ges.*, **30**, 366 (1897).

[860] K. Ziegler and K. Hafner, *Angew. Chem.*, **67**, 301 (1955).

[861] H. Gold and O. Bayer, *Chem. Ber.*, **94**, 2594 (1961).

[862] F. M. Furman, J. H. Thelin, D. W. Hein, and W. B. Hardy, *J. Amer. Chem. Soc.*, **82**, 1450 (1960).

[863] E. A. Bartkus, E. B. Hotelling, and M. B. Neuworth, *J. Org. Chem.*, **25**, 232 (1960).

[864] L. Neelakatan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959).

1.3. Formation of new carbon–carbon double bonds by exchange

I. Removal of hydrogen with formation of a new ethylenic bond

The formation of an ethylenic bond linking two reactants with elimination of hydrogen has been known since the classical synthesis of indigo. Although oxygen suffices as dehydrogenating agent in this case, such reactions proceed more readily in the presence of an oxidizing agent; for example, stilbene derivatives are obtained when a substituted toluene is oxidized by iodine.

Weizmann and Patai[865] mixed an ethereal solution of iodine with an alcoholic solution of 4-bromobenzyl cyanide, and an ethanolic sodium ethoxide solution is then dropped in with cooling; **4,4′-dibromo-α,α′-dicyanostilbene** was formed in 78–82% yield. This experiment is derived from work by Chalanay and Knoevenagel.[866]

An alternative method is to use sulfur as dehydrogenating agent. As early as 1888 Ziegler[867] prepared tetraphenylethylene by heating diphenylmethane with sulfur at 240–250°; much more recently Toland, Wilkes, and Brutschy[868] obtained 4,4′-stilbenedicarboxylic acid from *p*-toluic acid and sulfur in 57% yield.

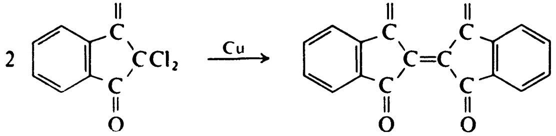
Further, disulfur dichloride was used by Chovin[545,869] with success in similar syntheses: in that way he obtained *N*,*N*-diphenylisoindigo in 78% yield from 1-phenyloxindole, and isoindigo itself in 90% yield from oxindole.

II. Removal of halogen with formation of a new ethylenic bond

1. Removal of halogen by means of metals

The removal of halogen with intermolecular formation of a new carbon–carbon double bond may be regarded as an extension of the Wurtz–Fittig reaction; it has been applied almost exclusively to the preparation of hydrocarbons but its importance is mainly in the stilbene series. Buckles and Matlack[870] prepared tetraphenylethylene in 70% yield by treating diphenylmethylene dibromide with copper powder; and tetrakis-(*p*-nitrophenyl)ethylene has been obtained in 47% yield from bis-(*p*-nitrophenyl)methylene dibromide by means of pentacarbonyliron.[871]

Noteworthy also is the synthesis of **$\Delta^{2,2'}$-bi-(1,3-indanedione)**, the carbon analog of indigo, by Schönberg and Moubasher:[872]



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[865] M. Weizmann and S. Patai, *J. Amer. Chem. Soc.*, **71**, 2587 (1949).

[866] L. Chalanay and E. Knoevenagel, *Ber. Deut. Chem. Ges.*, **25**, 285 (1892).

[867] J. H. Ziegler, *Ber. Deut. Chem. Ges.*, **21**, 779 (1888).

[868] W. G. Toland, Jr., J. B. Wilkes, and F.-J. Brutschy, *J. Amer. Chem. Soc.*, **75**, 2263 (1953); **76**, 307 (1954).

[869] P. Chovin, *Bull. Soc. Chim. France*, [v], **11**, 82 (1944).

[870] R. E. Buckles and G. M. Matlack, *Org. Syn.*, **31**, 104 (1951).

[871] C. Coffey, *J. Amer. Chem. Soc.*, **83**, 1623 (1961).

[872] A. Schönberg and R. Moubasher, *J. Chem. Soc.*, **1949**, 212.

2,2-Dichloro-1,3-indanedione (2 g) was boiled with copper bronze in dry benzene for 6 h; this gave 1.2 g of the bi-compound.

In a similar reaction dibromomalononitrile and copper powder gave tetracyanomethylene.[873]

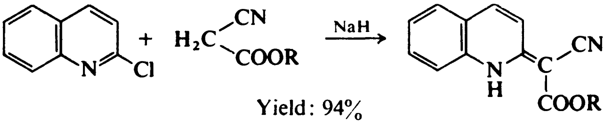
2. Removal of halogen by means of alkalis

Removal of hydrogen halide by means of alkali with concomitant intermolecular formation of a double bond gives good results only when the carbon–halogen bond is weakened by some other substituents. In the aliphatic series this activation may be effected by a nitro group: for instance, Bisgrove, Brown, and Clapp[874] obtained 3,4-dinitro-3-hexene from 1-chloro-1-nitropropane and aqueous potassium hydroxide. The reaction is, however, much more often used with arylalkyl compounds where the carbon–halogen bond is loosened by one or more aryl groups. Nevertheless it has been found that alkali hydroxides often give unsatisfactory results and that yields are better when organic bases are used. The nature of the solvent in which removal of hydrogen halide is to occur has also been observed to be important: Pinck and Hilbert[875] obtained 2,2′,7,7′-tetrabromo-$\Delta^{9,9'}$-bifluorene in 67% yield from 2,7-dibromo-9-chlorofluorene and triethylamine in nitromethane although use of alcoholic sodium hydroxide or triethylamine in diisopentyl ether gave only poor yields.

Choline[876] and potassium amide[877] have also given good results as dehydrohalogenating agents. Nitro- and cyano-benzyl chlorides are mostly converted very smoothly into stilbene derivatives when treated with alcoholic alkali hydroxide, as exemplified by Walden and Kernbaum for **4,4′-dinitrostilbene:**[878]

4-Nitrobenzyl chloride (50 g) is dissolved in warm ethanol (150 g) and, after cooling, is treated slowly with a solution of potassium hydroxide (17.5 g) in ethanol (60 g) and water (15 ml). When the first few drops are added the solution becomes green but this color changes through bluish-red to yellow. Yellowish crystals separate during the addition and, after final cooling, are collected and washed with hot water and with warm undiluted ethanol until free from chloride. The crude product (36 g, 90%) is a mixture of stereoisomeric 4,4′-dinitrostilbenes of unsharp melting point. Extraction with acetone removes the lower-melting isomer; the higher-melting isomer can be obtained pure, with m.p. 280–285°, by recrystallization from glacial acetic acid, acetone, or nitrobenzene.

Borror and Haeberer[879] obtained 2-alkylidene-1,2-dihydroquinolines by reaction of 2-chloroquinolines with compounds containing reactive methylene groups in the presence of sodium hydride, *e.g.*:



Yield: 94%

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[873] R. A. Carboni, *Org. Syn.*, Coll. Vol. 4, 877 (1963).

[874] D. E. Bisgrove, J. F. Brown, Jr., and L. B. Clapp, *Org. Syn.*, **37**, 23 (1957).

[875] L. A. Pinck and G. E. Hilbert, *J. Amer. Chem. Soc.*, **68**, 2014 (1946).

[876] F. Bergmann, *Bull. Soc. Chim. France*, **1952**, 78.

[877] C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

[878] P. Walden and A. Kernbaum, *Ber. Deut. Chem. Ges.*, **23**, 1959 (1890).

[879] A. L. Borror and A. F. Haeberer, *J. Org. Chem.*, **30**, 243 (1965).

III. Formation of a new C=C bond by removal of halogen and oxygen

The recently discovered reaction[880] of methylene dibromide or diiodide with carbonyl compounds in the presence of magnesium amalgam provides an extremely simple synthesis of terminal olefins:

$$R_2CO + CH_2X_2 \xrightarrow{Mg} R_2C{=}CH_2$$

In this way Cainelli and his colleagues[880] obtained styrene from benzaldehyde in about 70% yield, and also 1-tridecene from dodecanal, and the methylene derivatives from steroidal ketones.

General procedure: A solution of the carbonyl compound (0.25 mole) and methylene dibromide (or diiodide) (0.26 mole) in ether (100 ml) is added during 2 h to a stirred suspension of magnesium amalgam (from 0.5 mole of magnesium in 400 g of mercury) in ether (100 ml) under dry argon. The whole is boiled for 30 min under reflux and then worked up.

IV. Formation of a new C=C bond by removal of water

Two main types of reaction are available for intermolecular formation of a carbon–carbon double bond on loss of water, namely:

$$2R_2CHOH \longrightarrow R_2C{=}CR_2 + 2H_2O$$

$$R_2CO + H_2CR'_2 \longrightarrow R_2C{=}CR'_2 + H_2O$$

The first of these has only rarely been applied in laboratory practice; Bischoff and Walden[881] obtained diphenylmaleic anhydride on heating mandelic acid at 500 mm.

Many very important methods of condensation belong to the second class. However, methyl and methylene groups can be involved in elimination of water only if the carbon–hydrogen bonds are weakened by activating groups such as neighboring carbonyl, carboxyl, nitrile, or nitro groups or by suitably substituted aromatic groups. These reactions have different names according to the nature of these functional groups.

1. Synthesis of α,β- and β,γ-unsaturated carboxylic acids

a. Perkin synthesis

In 1868 W. H. Perkin, Sen., discovered that heating the sodium derivative of salicylaldehyde with acetic anhydride led to coumarin,[882] and this reaction has gained great importance as a method of synthesizing α,β-unsaturated acids. The method consists of heating an aromatic aldehyde with the anhydride of an aliphatic acid and the sodium or potassium salt of the same acid. This reaction, the Perkin synthesis, can also be carried out with cinnamaldehyde but not with purely aliphatic aldehydes.

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[880] G. Cainelli, F. Bertini, P. Grasselli, and G. Zubiani, *Tetrahedron Lett.*, **1967**, 5153.

[881] C. Bischoff and P. Walden, *Ann. Chem.*, **279**, 120 (1894).

[882] W. H. Perkin, Sen., *J. Chem., Soc.*, **21**, 53, 181 (1868).

Cinnamic acid:[883] Freshly distilled benzaldehyde (20 g), acetic anhydride (30 g), and freshly molten sodium acetate (10 g) are heated under reflux for 16 h. When cold, the product is stirred into water, the unchanged benzaldehyde and some of the acetic acid are removed in steam, the residue is neutralized with dilute alkali, and the solution is filtered hot. Acidification with hydrochloric acid then precipitates cinnamic acid (15–17 g, 57%). Longer heating (24 h) raises the yield to 70–75%.[879]

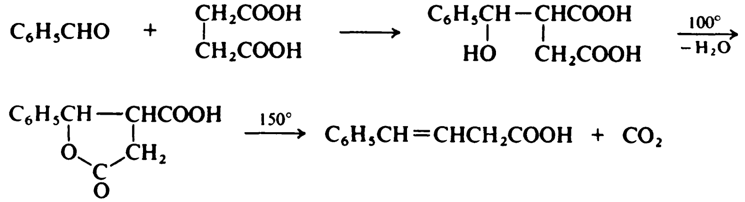
Yields vary considerably according to any ring substituents present in the benzaldehyde: nitro- and halo-benzaldehydes give very good yields of substituted cinnamic acids;[884,885] even *p*-hydroxybenzaldehyde gives a somewhat better yield (62%) of 4-hydroxycinnamic acid than that of cinnamic acid from benzaldehyde itself; alkyl- and hydroxyalkyl-benzaldehydes give poor yields, and (dimethylamino)benzaldehyde does not react at all.[886] Heterocyclic carbaldehydes can also be used with success in the Perkin synthesis: Biedermann[887] obtained 3-(2-thienyl)acrylic acid from 2-thiophenecarbaldehyde, and the synthesis of 3-(2-furyl)acrylic acid is described in *Organic Syntheses*.[888]

α-Substituted cinnamic acids are obtained by condensing higher aliphatic anhydrides with aromatic aldehydes in the presence of the alkali salts of the corresponding aliphatic acid.

α-Methylcinnamic acid:[889] This is formed in 82% yield when benzaldehyde, propionic anhydride, and sodium propionate are heated in a sealed tube for 24 h at 150°.

Under the usual conditions of the Perkin reaction, cinnamaldehyde gives an excellent yield of 5-phenyl-2,4-pentadienoic acid;[890] but decarboxylation occurs when it is heated with phenylacetic acid and acetic anhydride in the presence of lead(II) oxide, 1,4-diphenyl-1,3-butadiene being formed in 30% yield,[891] and under these conditions two equivalents of cinnamaldehyde and one of succinic acid give 1,8-diphenyl-1,3,5,7-octatetraene.[892]

A Perkin-type reaction gives a different result when an aromatic — or an aliphatic — aldehyde reacts with succinic acid in the molar ratio 1 : 1; the products then are γ-aryl- or γ-alkyl-paraconic acids and, when heated, these lose carbon dioxide and give the β,γ-unsaturated acids together with small amounts of the corresponding butyrolactone:



$$C_6H_5CHO + \begin{matrix} CH_2COOH \\ | \\ CH_2COOH \end{matrix} \longrightarrow \begin{matrix} C_6H_5CH{-}CHCOOH \\ |\quad\quad | \\ HO\quad CH_2COOH \end{matrix} \xrightarrow[-H_2O]{100^\circ}$$

$$\begin{matrix} C_6H_5CH{-}CHCOOH \\ |\quad\quad | \\ O \diagdown_{C} \diagup CH_2 \\ \| \\ O \end{matrix} \xrightarrow{150^\circ} C_6H_5CH{=}CHCH_2COOH + CO_2$$

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[883] W. H. Perkin, Sen., *J. Chem. Soc.*, **31**, 389 (1877); *Ber. Deut. Chem. Ges.*, **10**, 299 (1877).

[884] F. Böck, G. Lock, and K. Schmidt, *Monatsh. Chem.*, **64**, 401 (1934).

[885] F. K. Thayer, *Org. Syn.*, **5**, 83 (1925).

[886] H. Meyer and R. Beer, *Monatsh. Chem.*, **34**, 649 (1913).

[887] A. Biedermann, *Ber. Deut. Chem. Ges.*, **19**, 1855 (1886).

[888] S. Rajagopalan and P. V. A. Raman, *Org. Syn.*, Coll. Vol. 3, 426 (1955).

[889] M. Conrad and C. A. Bischoff, *Ann. Chem.*, **204**, 187 (1880); R. Fittig, *Ber. Deut. Chem. Ges.*, **16**, 1436 (1883).

[890] W. H. Perkin, Sen., *J. Chem. Soc.*, **31**, 388 (1877).

[891] B. B. Corson, *Org. Syn.*, Coll. Vol. 2, 229 (1943).

[892] R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **11**, 103 (1928).

Phenylparaconic acid:[893] Benzaldehyde, sodium succinate, and acetic anhydride are heated together at 100° for 15–20 h. The mixture is taken up in hot water and, when cold, this solution is extracted with ether. The phenylparaconic acid is extracted from the ether by shaking with sodium carbonate solution and precipitated therefrom by hydrochloric acid. A small amount of phenylisocrotonic acid can be isolated by digestion with carbon disulfide.

Phenylisocrotonic acid:[894] This acid is obtained in greater yield if the above condensation is effected at 125–130° or if the phenylparaconic acid is heated at 300°.

The Fittig paraconic acid synthesis can also be carried out with monosubstituted succinic acids: phenylsuccinic acid and benzaldehyde at 125° afford diphenylisocrotonic acid, $C_6H_5CH{=}C(C_6H_5)CH_2COOH$.[895,896]

On thermal decarboxylation of paraconic acids the isocrotonic acids produced are accompanied by the anhydrides of the itaconic (alkylidene- or arylidene-succinic) and citraconic (substituted maleic) acids.

b. Knoevenagel reaction[897]

The methylene group of malonic or cyanoacetic acid is sufficiently reactive to condense under mild conditions with aliphatic or aromatic aldehydes or with ketones. Initially such reactions were carried out in the same way as the Perkin reaction, in acetic acid solution or in the presence of acetic anhydride; however, use of acetic anhydride is unnecessary.

Claisen and Chrismer[898] prepared **benzylidenemalonic acid** by heating malonic acid (1 part), freshly distilled benzaldehyde (1 part), and glacial acetic acid (0.5 part by weight) on a boiling water-bath for 8–10 h. On cooling, benzylidenemalonic acid crystallizes in 55% yield and is filtered off and washed with chloroform.

Decarboxylation occurs if the reaction is carried out in boiling glacial acetic acid.

For the preparation of **crotonic acid,**[899] equimolar amounts of malonic acid and glacial acetic acid are boiled with an excess of paraldehyde for 3 days under an efficient reflux condenser and are then fractionated.

Knoevenagel[900] applied weak bases (ammonia or an amine) as catalysts for this type of reaction, thereby enabling the condensation and the decarboxylation of the intermediate arylidene- or alkylidene-malonic acids to be effected at lower temperatures and thus achieving higher yields.

4-Methoxycinnamic acid:[901] An 8% solution (21 g) of ammonia in 95% ethanol is poured on a solution of *p*-anisaldehyde (13.6 g) and malonic acid (12.6 g) in a small amount of 95% ethanol, and the mixture is heated on a steam-bath. The alcohol is distilled off and the oily residue is heated on a boiling water-bath until evolution of carbon dioxide is completed and the residue has become solid. The product is treated with warm water and dissolved by addition of a small amount of sodium carbonate. This solution is boiled for a few minutes with charcoal (1–2 g) and then filtered. The warm filtrate is stirred into an excess of ice-cold 20% sulfuric acid, from which the free acid crystallizes.

The introduction of pyridine as solvent was important because it enabled multiply unsaturated acids to be synthesized. In this way Doebner[902] prepared

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[893] R. Fittig and H. W. Jayne, *Ann. Chem.*, **216**, 99 (1883).

[894] R. Fittig, *Ann. Chem.*, **216**, 113 (1883).

[895] F. Fichter and W. Latzko, *J. Prakt. Chem.*, [ii], **74**, 330 (1906).

[896] E. Buckles and J. Cooper, *J. Org. Chem.*, **30**, 1588 (1965).

[897] G. Jones, *Org. Reactions*, **15**, 204 (1967).

[898] L. Claisen and L. Chrismer, *Ann. Chem.*, **218**, 135 (1883).

[899] T. Kommenos, *Ann. Chem.*, **218**, 149 (1883); **283**, 82 (1894); J. von Braun, *Monatsh. Chem.*, **17**, 213 (1896).

[900] E. Knoevenagel, *Ber. Deut. Chem. Ges.*, **31**, 2604 (1898).

[901] J. R. Johnson, *Org. Reactions*, **1**, 249 (1942).

[902] O. Doebner, *Ber. Deut. Chem. Ges.*, **33**, 2140 (1900); **35**, 1137 (1902); C. F. H. Allen and J. Van Allan, *Org. Syn.*, **24**, 92 (1944).

sorbic acid (2,4-hexadienoic acid) from crotonaldehyde and malonic acid, and 3-(2-furyl)acrylic acid[903] can also be obtained in good yield from furfuraldehyde and malonic acid. Piperidine was also often added when the Doebner technique was used: 4-methyl-2,4-pentadienoic acid,[904] 2,3-dimethoxycinnamic acid,[905] and 4,5-methylenedioxy-2-nitrocinnamic acid[906] have thus been obtained. *p*-(Dimethylamino)benzaldehyde, which does not react under the conditions of the Perkin synthesis, gives an 80% yield of the cinnamic acid by the Doebner technique,[907] and by the same method Kuhn and Grundmann[908] synthesized 1,3,5,7,9,11-tridecahexaene-1,1-dicarboxylic acid, which afforded 2,4,6,8,10,12-tetradecahexaenoic acid in good yield when boiled with a 1 : 1 mixture of glacial acetic acid and acetic anhydride.

Ketones can also be condensed with malonic acid by the Knoevenagel method: for example, 3-methyl-2-butenoic acid is formed in 60% yield when malonic acid is heated with acetone in pyridine containing a little piperidine;[909] when diethyl ketone is used in this synthesis the yield falls to 35%, and the reaction fails (yield 5%) with cyclohexanone. However, in such cases condensation of ketones with malonic acid is successful if piperidine acetate is used as catalyst.

Kuhn *et al.*[910] prepared octatrienal by condensation of two molecules of crotonaldehyde:

$$2CH_3CH{=}CHCHO \longrightarrow CH_3[CH{=}CH]_3CHO$$

showing that only the salts of secondary amines were effective catalysts for this reaction, and he concluded from his own observations and those of others that the progress of a Knoevenagel reaction depends less on the catalytic effect of the amine than on that of its salts.

For the condensation of aldehydes with ethyl cyanoacetate Cope[911] also used piperidine acetate and he treated ketones with this ester in the presence of ammonium acetate as catalyst; he used benzene as solvent, removing the water produced through a water-separator. When this process is applied to acetone the benzene must be replaced by chloroform as entraining agent.[912]

Ethyl 2-cyano-2-alkenoates: Ethyl cyanoacetate (0.5 mole), a ketone (0.6 mole), ammonium acetate (3.85 g, 0.05 mole), glacial acetic acid (6 g, 0.1 mole), and benzene (50 ml) are boiled under a water-separator (oil-bath at about 130–160°). An aqueous layer is collected gradually that contains small amounts of ammonium acetate or acetamide. When separation of water ceases, the mixture is boiled for a further 1 h.

The reaction is equally successful when isopropylidene malonate is used in place of malonic acid or diethyl malonate.[913] The isopropylidene ester contains an unusually acidic methylene group as well as an ester group that can be

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[903] S. Rajagopalan and P. V. A. Raman, *Org. Syn.*, Coll. Vol. 3, 425 (1955).

[904] T. Lennartz, *Ber. Deut. Chem. Ges.*, **76**, 1009 (1943).

[905] J. Koo, M. S. Fish, G. N. Walker, and J. Blake, *Org. Syn.*, **31**, 35 (1951).

[906] K. Schofield and J. C. Simpson, *J. Chem. Soc.*, **1945**, 512.

[907] C. W. Shoppee, *J. Chem. Soc.*, **1930**, 968.

[908] R. Kuhn and C. Grundmann, *Ber. Deut. Chem. Ges.*, **70**, 1326 (1937).

[909] S. Dutt, *Quart. J. Indian Chem. Soc.*, **1**, 297 (1924–25).

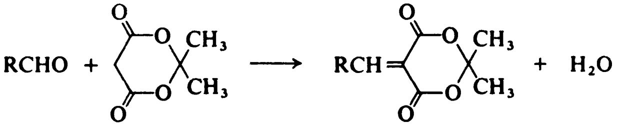
[910] R. Kuhn, W. Badstübner, and C. Grundmann, *Ber. Deut. Chem. Ges.*, **69**, 98 (1936).

[911] A. C. Cope, *J. Amer. Chem. Soc.*, **59**, 2327 (1937); **63**, 733, 3452 (1941).

[912] S. Wiedequist, *Acta Chem. Scand.*, **3**, 304 (1949).

[913] J. A. Hedge, C. Kruse, and H. R. Snyder, *J. Org. Chem.*, **26**, 3166 (1961).

hydrolysed under extremely mild conditions. Thus it reacts with cinnamaldehyde in dimethylformamide in absence of a catalyst during 10 hours at room temperature to give an 82% yield of 5-cinnamylidene-2,2-dimethyl-*m*-dioxan-4,6-dione:



Use of this reagent thus appears advantageous when a compound carries functional groups that will not withstand the conditions of the normal diethyl malonate synthesis.

Amino acids may also be applied as catalysts in the Knoevenagel reaction;[914,915] thus ethyl 2-cyano-4-methyl-2-pentenoate has been prepared in 87% yield from 2-butanone and ethyl cyanoacetate in the presence of *β*-alanine.[916] Other catalysts that have been recommended are benzylamine (additional to the salt of a secondary amine), [917] ion-exchangers,[918] and alkali fluorides.[919]

Further, *β*-oxo carboxylic esters can be used as carbonyl components.[920] If, however, aldehydes are to be condensed with *β*-oxo carboxylic esters, the technique of Knoevenagel or the frequently successful Cope method[921] is used:

Alkylideneacetoacetic esters: Ethyl acetoacetate (0.5 mole) and an aldehyde (0.55 mole) are cooled to −5°. Piperidine (0.5 g) in alcohol (1 g) is then added in 5–10 min at a rate such that the temperature does not rise above +5° to +10°. The mixture is cooled to 0°, kept for 12–20 h in a refrigerator, and then washed three times with water (100-ml portions) containing a few drops of glacial acetic acid. The aqueous washings are extracted with ether, and the ethereal solution is united with the ester and fractionated in a vacuum through a Widmer spiral column. Yields are 80%.

Galat[922] described a similar reaction that led to an *α*,*β*-unsaturated ester in one stage: he used the acid ester of malonic acid as the methylene component:

Ethyl *p*-(dimethylamino)cinnamate:[922] *p*-(Dimethylamino)benzaldehyde (3 g, 0.02 mole), methyl hydrogen malonate (4.8 ml, *ca.* 0.04 mole), piperidine (0.25 ml), and dry pyridine (10 ml) are heated on a steam-bath for 4 h under reflux. The pyridine is then distilled off in a vacuum and the crystalline residue is taken up in hot acetone (10–15 ml). Water is added gradually to this solution until precipitation is complete. The crystals are collected, washed with acetone, and dried at 90–100°. The yield is 95% (3.9 g).

Acetals can also be used as carbonyl component in the Knoevenagel reaction: Klein and Meyer[923] obtained *α*-cyanocinnamic acids from benzaldehyde diethyl acetal and cyanoacetic acid in boiling benzene in the absence of a catalyst.

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[914] F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953).

[915] F. S. Prout, A. Abdel-Latif, and M. Kamal, *J. Chem. Eng. Data.*, **8**, 597 (1963).

[916] F. S. Prout, R. J. Hartman, E. P.-Y. Huang, C. J. Korpics, and G. R. Tichelaar, *Org. Syn.*, **35**, 6 (1955).

[917] S. Deo, *J. Indian Chem. Soc.*, **30**, 665 (1953).

[918] M. J. Astle and W. C. Gergel, *J. Org. Chem.*, **21**, 493 (1956).

[919] L. Rand, J. Swisher, and C. Cronin, *J. Org. Chem.*, **27**, 3505 (1962).

[920] R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 283 (1948).

[921] A. C. Cope and C. M. Hofmann, *J. Amer. Chem. Soc.*, **63**, 3457 (1941).

[922] A. Galat, *J. Amer. Chem. Soc.*, **68**, 376 (1946).

[923] J. Klein and A. Meyer, *J. Org. Chem.*, **29**, 1035 (1964).

c. Claisen synthesis of cinnamic esters

The Claisen condensation is little used for the preparation of α,β-unsaturated carboxylic acids since the methods given above are usually preferable. Cinnamic esters have, however, been obtained by Claisen's method from aromatic aldehydes, alkanoic esters, and metallic sodium, *e.g.*, methyl 4-methoxycinnamate[924] and ethyl 5-(2-furyl)-2,4-pentadienoate[925] in yields between 70% and 80%. α-Substituted cinnamic esters can also be obtained by this method, from higher alkanoic esters.[926]

d. Stobbe condensation

The synthesis of paraconic acids described above starts from succinic acid; the Stobbe condensation uses succinic esters and their substitution products:

$$R_2CO + ROOCCH_2CH_2COOR + NaOR \longrightarrow R_2C{=}C(COOR)CH_2CH_2COONa + 2ROH$$

The carbonyl compounds that can undergo this condensation include aliphatic, aromatic, and α,β-unsaturated aldehydes, aliphatic, saturated carbocyclic, and aromatic ketones, diketones, oxo esters, and cyano ketones. Sodium ethoxide and potassium *tert*-butoxide are the condensing agents generally used.

3-(Ethoxycarbonyl)-4,4-diphenyl-3-butenoic acid:[927] Benzophenone (9.11 g, 0.05 mole) and diethyl succinate (13.05 g, 0.075 mole) are added to a solution of potassium (2.15 g, 0.055 mole) in dry *tert*-butyl alcohol (45 ml) with cooling. The air is replaced by dry nitrogen, and the mixture is boiled gently for 0.5 h and then cooled and acidified with dilute hydrochloric acid. The *tert*-butyl alcohol and ethanol are then removed in a vacuum and the residue is treated with water and extracted with ether. The acid ester is extracted from the ethereal solution into 20% sodium hydroxide solution whence it is obtained (13.94 g, 90%; m.p. 119–123°) by acidification. After recrystallization from benzene–light petroleum it melts at 125–126°.

Further examples are given in *Organic Reactions*.[928]

2. Synthesis of α,β-unsaturated aldehydes and ketones

Reaction between two carbonyl compounds (aldehydes or ketones) in which at least one of these components has an α-methyl or α-methylene group give aldols (β-hydroxy carbonyl compounds) usually under very mild conditions, and these products lose water either spontaneously or at temperatures between 60° and 100° to give α,β-unsaturated aldehydes or ketones.

Suitable catalysts are alcoholic or aqueous alkali solutions, aluminum alkoxides, piperidine acetate, mineral acids, and ion-exchangers.

A mixed aldol condensation between an aldehyde and a ketone can theoretically lead to four products. In practice, however, it proceeds in only one direction which is determined by the greater reactivity of the aldehyde than of the ketone as methylene component. For methyl ketones such as ethyl

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[924] A. Horeau, *Bull. Soc. Chim. France*, [v], **15**, 414 (1948).

[925] A. Hinz, G. Meyer, and G. Schücking, *Ber. Deut. Chem. Ges.*, **76**, 683 (1943).

[926] L. Claisen, *Ber. Deut. Chem. Ges.*, **23**, 978 (1890); T. Possner, *J. Prakt. Chem.*, [ii], **82**, 435 (1910).

[927] W. S. Johnson, J. Petersen, and W. P. Schneider, *J. Amer. Chem. Soc.*, **69**, 76 (1947).

[928] W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

methyl ketone it is the experimental conditions that determine whether the α-methyl group or the α'-methylene group reacts. Harries and Müller[929] obtained 1-phenyl-1-penten-3-one from ethyl methyl ketone and benzaldehyde when 10% sodium hydroxide was used but 3-methyl-4-phenyl-3-buten-2-one when gaseous hydrogen chloride was used.

When acetone is used as methylene component care must be taken to have the acetone in excess, otherwise two molecules of aldehyde react with one of acetone.[930]

Benzylideneacetone:[931] Acetone (635 g, *ca.* 11 moles) is mixed with freshly distilled, acid-free benzaldehyde (420 g, 4 moles) and water (400 ml) in a round-bottomed flask (capacity 2 l) fitted with a stirrer. 10% Sodium hydroxide solution (100 ml) is then added, with stirring and water-cooling, at a rate such that the temperature in the flask remains between 25° and 31°; this requires about 0.5–1 h. The mixture is stirred at room temperature for a further 2.25 h, then made acid to litmus by dilute hydrochloric acid. The heavier aqueous layer is separated and extracted with benzene (100 ml), and the benzene extract is united with the benzylideneacetone layer and shaken with water (100 ml). The organic layer therefrom is separated, the benzene is removed by distillation from a water-bath, and the residue is distilled in a vacuum, the water contaminant distilling almost completely in a forerun. The fraction boiling at 148–160°/25 mm is collected and on redistillation gives the product (375 to 450 g, 65–78%), b.p. 137–142°/16 mm.

Furfurylideneacetone[932] and benzylideneacetophenone[933] have been prepared similarly in good yields.

Condensation of hydroxyacetophenones with hydroxybenzaldehydes is important as it leads to substituted chalcones[934] which are readily converted into the corresponding flavanones by mineral acids.

The aldol condensation has also been used successfully to introduce side chains into the cyclopentanone ring of steroids.[935]

Heterocyclic aldehydes such as 6-quinolinecarbaldehyde[936] and 2-quinolinecarbaldehyde[937] can also be condensed with ketones and esters.

Pseudoionone, which is an important starting material for the synthesis of vitamin A, can be prepared in 50% yield from citral and acetone in the presence of sodium ethoxide in ethanol.[938]

Aldol condensation between purely aliphatic aldehydes is unidirectional only between two molecules of the same aldehyde, one of which acts as the component with acidic CH whilst the other acts as proton acceptor, *e.g.*:

$$C_2H_5CH_2CHO + CH_2(C_2H_5)CHO \xrightarrow{NaOH} C_2H_5CH_2CH{=}C(C_2H_5)CHO$$

2-Ethyl-2-hexenal:[939] N-Sodium hydroxide solution (750 ml) is warmed to 80° and vigorously stirred while freshly distilled butyraldehyde (2520 g) is added during 1.5 h (the rate of addition depends on the efficiency of the reflux condenser and should be as fast as possible).

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[929] C. Harries and G. H. Müller, *Ber. Deut. Chem. Ges.*, **35**, 966 (1902).

[930] C. R. Conard and M. A. Dolliver, *Org. Syn.*, Coll. Vol. 2, 167 (1943).

[931] N. L. Drake and P. Allen, Jr., *Org. Syn.*, **3**, 17 (1923).

[932] G. J. Leuck and L. Cejka, *Org. Syn.*, **7**, 42 (1927).

[933] E. P. Kohler and H. M. Chadwell, *Org. Syn.*, **2**, 1 (1922).

[934] L. Reichel, W. Burkart, and K. Müller, *Ann. Chem.*, **550**, 146 (1942).

[935] W. C. J. Ross, *J. Chem. Soc.*, **1945**, 25.

[936] B. P. Lugovkin, *Zh. Obshch. Khim.*, **28**, 1007 (1958); *Chem. Abstr.*, **52**, 17 273 (1958).

[937] S. V. Tsukerman, K.-S. Chang, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **34**, 832 (1964); *Chem. Abstr.*, **60**, 15 826 (1964).

[938] A. Russell and R. L. Kenyon, *Org. Syn.*, Coll. Vol. 3, 747 (1955).

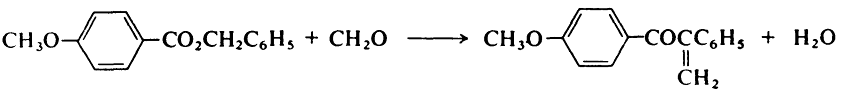
[939] M. Häusermann, *Helv. Chim. Acta*, **34**, 1487 (1951).

The temperature rises to 93° during the addition. The mixture is then boiled for a further 1 h. After cooling, the upper layer is separated and, without further treatment, is distilled through a Vigreux column (150 cm). This affords pure 2-ethyl-2-hexenal (1880 g, 86%), b.p. 59.5–60°/10 mm, n_D^{18} 1.4556.

Diketones can also be used with success in the aldol condensation. Tetraphenylcyclopentadienone is formed in 95% yield from benzil and dibenzyl ketone in the presence of potassium hydroxide;[940] and Hunsdiecker[941] obtained cyclopentenone derivatives from suitable 1,4-diketones by means of aqueous sodium hydroxide solution. If one of the two carbonyl groups is vicinal to a methyl group, as in $CH_3COCH_2CH_2COCH_2R$, that carbonyl group does not take part in the condensation, and acetonylacetone itself does not undergo this condensation at all. 1,5-Diketones give analogously the substituted cyclohexenones;[942] and these can also be obtained from ethyl acetoacetate and aldehydes.[943] Diketones can further be used for synthesis of macrocyclic ketones: muscone, for instance, was obtained by condensation of 2,15-hexadecanedione under the influence of the Grignard reagent from *N*-methylaniline and subsequent hydrogenation.[944]

An important synthesis of polyene aldehydes due to Kuhn and Winterstein[945] is vinylogous to the above reactions. They obtained 7-phenylheptatrienal in 50% yield by condensing cinnamaldehyde with crotonaldehyde in 70% ethanol containing piperidine acetate; and 11-phenylundecapentaenal and 15-phenylpentadecaheptaenal are formed in the same way.

Use of piperidine acetate was also successful in the condensation of 4-methoxydeoxybenzoin with formaldehyde, which gave 1-(*p*-methoxyphenyl)-2-phenyl-2-propen-1-one:[946]



α-Methylene aldehydes are also readily accessible by way of the Mannich bases: thus 2-ethylacraldehyde is easily obtained from butyraldehyde, dimethylamine hydrochloride, and aqueous formaldehyde.[947]

An exchange resin sulfonic acid has also been used as catalyst in a very elegant ketone condensation: Lorette[948] obtained mesityl oxide in almost 80% yield by passing acetone vapors over Dowex 50; ethyl methyl ketone gives a mixture of the two isomers (5-methyl-4-hepten-3-one and 3,4-dimethyl-3-hexen-2-one); diethyl ketone gives 5-ethyl-4-methyl-4-hepten-3-one, and cyclohexanone gives 2-(1-cyclohexenyl)cyclohexanone. Dypnone is the main product, with a little 1,3,5-triphenylbenzene, from such a condensation of acetophenone.

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[940] J. R. Johnson and O. Grummitt, *Org. Syn.*, **23**, 92 (1943).

[941] H. Hunsdiecker, *Ber. Deut. Chem. Ges.*, **75**, 455 (1942).

[942] V. Prelog, L. Ruzicka, P. Barman, and J. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948).

[943] E. C. Horning, M. O. Denekas, and R. E. Field, *J. Org. Chem.*, **9**, 547 (1944); *Org. Syn.*, **27**, 24 (1947).

[944] M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **20**, 525 (1937); **30**, 2019 (1947).

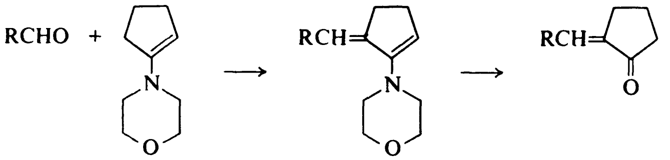
[945] R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **12**, 493 (1929).

[946] H. Fiesselmann and J. Ribka, *Chem. Ber.*, **89**, 27 (1956).

[947] C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Amer. Chem. Soc.*, **70**, 1694 (1948).

[948] N. B. Lorette, *J. Org. Chem.*, **22**, 347 (1957).

In their reactions with aldehydes in the presence of alkali cyclic ketones such as cyclopentanone and cyclohexanone generally give only the dialkylidene or diarylidene compounds, and not the monosubstituted derivatives, since the two methylene groups vicinal to the carbonyl group are equally activated. Monosubstituted cyclanones can be obtained in this way only when about a six-fold excess of the ketone and special precautions are used.[949] On the other hand, Birkofer and his co-workers showed monoalkylidenecycloalkanones to be easily obtained starting from enamines;[950] yields are between 30% and 90%:



R = CH_3, C_2H_5, n-or iso-C_3H_7, iso-C_4H_9, furyl, or benzyl.

Letsinger and Jamison[951] describe a simple route to 4-pyrones: they treated dibenzyl ketone with acetic acid in the presence of polyphosphoric acid.

3. Other condensations

a. Condensation with nuclear methyl groups

Nuclear methyl groups are reactive if attached to an aromatic ring carrying other substituents in certain positions or if attached to a heterocyclic ring.

One substituent is usually insufficient to facilitate condensation: mononitrotoluenes react poorly with benzaldehyde, but condensation between the dinitrotoluenes and benzaldehyde leads to the corresponding stilbene derivatives.[952] However, methyl groups attached to heterocyclic systems have been much more often used for such condensations: Ladenburg[953] showed that 2-methylpyridine and acetaldehyde at 250° give 2-propenylpyridine; and 4-methylpyridine reacts similarly.[954]

In their porphyrin syntheses Fischer and his co-workers[955] made great use of the condensation of methylpyrroles with pyrrolecarbaldehyde. Methyl groups attached to aromatic condensed heterocycles can also be condensed with aldehydes in this way: in the presence of zinc chloride, quinaldine hydrochloride and 2-ethylhexanal give 2-(3-ethyl-1-heptenyl)quinoline in 87% yield;[956] and 9-methylacridine condenses with *m*- or *p*-nitrobenzaldehyde, giving the 9-styryl derivatives in good yield.[957]

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[949] R. Mayer, *Chem. Ber.*, **88**, 1853 (1955).

[950] L. Birkofer, S. Kim, and H. Engels, *Chem. Ber.*, **95**, 1495 (1962).

[951] R. Letsinger and J. Jamison, *J. Amer. Chem. Soc.*, **83**, 193 (1961).

[952] J. Thiele and R. Escales, *Ber. Deut. Chem. Ges.*, **34**, 2843 (1901).

[953] A. Ladenburg, *Ann. Chem.*, **247**, 26 (1888).

[954] K. Friedländer, *Ber. Deut. Chem. Ges.*, **38**, 2838 (1905).

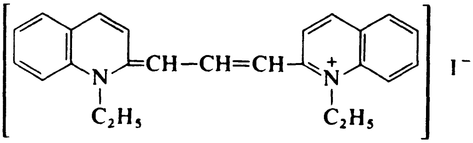
[955] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Akademischer Verlag, Leipzig, 1934.

[956] E. Graef, J. M. Fredericksen, and A. Burger, *J. Org. Chem.*, **11**, 261 (1946).

[957] W. Sharp, M. M. J. Sutherland, and F. J. Wilson, *J. Chem. Soc.*, **1943**, 5, 344.

b. Methine condensations

Several methods have been developed for the synthesis of the methine dyes that are of such importance in photography. König[958] introduced the orthoester process in which, for instance, two molecules of quinaldine ethiodide are condensed with one of ethyl orthoformate, giving the product:

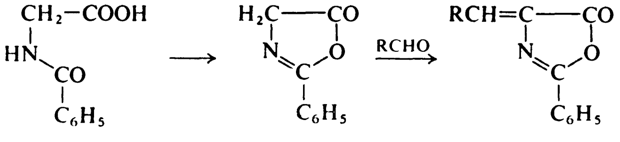


Pinacyanine iodide:[958] *N*-Ethylquinaldinium iodide (6 g) and acetic anhydride (50 ml) are heated to the b.p. in a Claisen distillation flask fitted with a dropping funnel and a thermometer, and ethyl orthoformate (2 g) is added to the gently boiling solution during 5 min. The mixture, initially yellow, soon changes to green and finally to deep blue, while crystals separate and a mixture of ethyl acetate, ethyl iodide, and a little acetic anhydride distil off. Towards the end of the reaction the temperature is raised and about half of the acetic anhydride used is distilled off. As the residual solution cools, a slurry of fairly pure pinacyanine iodide separates; on recrystallization the dye forms small prisms with a magnificent green sheen and, after drying at 140°, these decompose at 278° (yield 2.4 g, 50%).

When orthoesters of other carboxylic acids are used, alkyl groups are present in the side chain of the cyanine. In this form the procedure affords only symmetrical dyes, but many variations are possible: of practical importance is the replacement of the orthoformate by formamide,[959] an *N*-(alkoxymethylene)aniline,[960] *N*,*N'*-diphenylformamidine,[960] or *s*-triazine[961] (see also page 955), as these reagents permit the same reaction to be carried out in two stages so that it can be applied to synthesis also of unsymmetrical dyes.

c. Erlenmeyer amino acid synthesis

The Erlenmeyer amino acid synthesis[962] depends on condensation of an aldehyde with hippuric acid; this gives an alkylidene azlactone, which is an intermediate in the synthesis, being converted into an α-amino acid by reduction and hydrolysis.



The alkylidene azlactones are prepared by boiling hippuric acid, the aldehyde, glacial acetic acid, and sodium acetate under reflux. As a class they are amenable to many types of reaction: by hydrolysis with alkali they afford α-oxo acids, and on oxidation by hydrogen peroxide in alkali they yields the

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[958] W. König, *Ber. Deut. Chem. Ges.*, **55**, 3293 (1922).

[959] S. Hünig, *Ann. Chem.*, **574**, 99, 106, 112 (1951).

[960] E. B. Knott, *J. Chem. Soc.*, **1946**, 120.

[961] A. Kreuzberger, *Angew. Chem. Int. Ed., Engl.*, **4**, 1090 (1965).

[962] E. Erlenmeyer, Jr., *Ann. Chem.* **271**, 164 (1894); **307**, 138 (1899); **337**, 265 (1904).

carboxylic acid containing one carbon atom more than the aldehyde. Hudson and Walton[963] prepared 4-methoxy-2-methylphenylacetic acid in this way from the benzaldehyde.

Hippuric acid has often been replaced in these reactions by *N*-acetylglycine; Herbst and Shemin,[964] for example, used it with benzaldehyde when preparing 4-benzylidene-2-methyl-5-oxazolone in 75% yield.

Creatinine has also been applied as methylene component; Nicolet and Campbell[965] thus prepared β-substituted *N*-methylalanine derivatives; and the condensation of vanillin with creatinine (95% yield) is described in *Organic Syntheses*.[966]

Further, hydantoin,[967] thiohydantoin, dioxopiperazine, and rhodanine have all been used in similar condensation, yielding the derived α,β-unsaturated compounds.

d. Preparation of enamines

Meerwein and his collaborators[968] showed that the acetals derived from amides or lactams, *e.g.*, the diethyl acetals of dimethylformamide, dimethylacetamide, 1-methyl-2-pyrrolidone, and 1-methyl-2(1*H*)-quinolone, react with compounds containing a reactive methylene group to give enamines in good yield without the need for addition of a catalyst. The compounds shown in the attached Table have been prepared by using dimethylformamide diethyl acetal.

Preparation of dimethylaminomethylene compounds $(CH_3)_2N—CH=R$

Condensation with	R in the product	Reaction temp.	Yield (%)
Acetophenone	$=CHCOC_6H_5$	185°	65
Benzylideneacetone	$=CHCOCH=CHC_6H_5$	200°	90
Cyanoacetic ester	$=C(CN)COOR$	20°	76
Malonodinitrile	$=C(CN)_2$	20°	83
Acetoacetic ester	$=C(COCH_3)COOR$	200°	77
Nitromethane	$=CHNO_2$	70°	85
2,4-Dinitrotoluene	$=CH—C_6H_3(NO_2)_2$	100°	50
Cyclopentadiene	Cyclopentadienylidene	B.p.	32

Bredereck and Bredereck,[969] however, found that it was unnecessary to start with acetals, and that enamines are formed in about 80% yield when compounds containing reactive methylene groups are treated with dimethylformamide or other amides in the presence of phosphoryl chloride. Eiden[970] used acetic anhydride instead of phosphoryl chloride, but the yields then sank to 25–40%.

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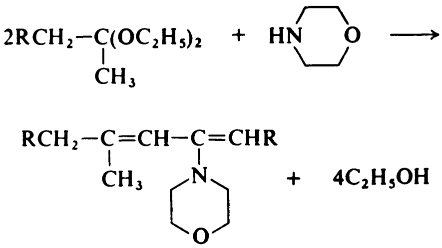
[963] B. J. Hudson and E. Walton, *J. Chem. Soc.*, **1946**, 86.
[964] R. M. Herbst and D. Shemin, *Org. Syn.*, Coll. Vol. 2, 1 (1943).
[965] B. H. Nicolet and E. D. Campbell, *J. Amer. Chem. Soc.*, **50**, 1158 (1928).
[966] V. Deulofeu and T. J. Guerrero, *Org. Syn.*, **22**, 89 (1942).
[967] G. Billek, *Monatsh. Chem.*, **92**, 352 (1961).
[968] H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann. Chem.*, **641**, 1 (1961).
[969] H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).
[970] F. Eiden, *Arch. Pharm.*, **295**, 516 (1962).

4-(2-Alkylidene-2-alkenyl)morpholines[971] are formed when equivalent amounts of morpholine and a *n*-alkyl methyl ketal are heated together for 36–48 hours, yields being 55–80%:



($R = CH_3$, C_2H_5, n-C_3H_7, or n-C_4H_9)

4. Preparation of unsaturated nitro compounds

Primary aliphatic nitro compounds condense smoothly with aldehydes or ketones. The primary product is usually the nitro compound, whence an unsaturated nitro compound can be obtained by esterification and subsequent removal of the elements of the esterifying acid:

$$ArCH(OH)CHRNO_2 \longrightarrow ArCH{=}CRNO_2$$

The double bond may, however, be formed during the condensation when aromatic aldehydes are used.

Dinitro compounds arising by addition of the nitroalkane to the nitroalkene are sometimes formed as by-products.

Condensing agents are basic catalysts such as alkali carbonates, hydrogen carbonates, hydroxides, or alkoxides, or primary aliphatic amines or calcium hydroxide; zinc chloride may also be used with aromatic aldehydes. Ethylenediamine was introduced by Lerner[972] for use in the synthesis of unsaturated nitriles in the aromatic series and he gave a large number of examples in which yields were around 95%.

Although interaction of an aromatic aldehyde and a primary nitro compound with a primary amine as catalyst leads to the nitro olefin in one step, this need not be the case with other catalysts.

1-Phenyl-2-nitropropene:[973] Benzaldehyde (1 mole), nitroethane (1 mole), butylamine (5 ml), and anhydrous ethanol (100 ml) are boiled in a 1-l flask for 8 h under reflux. On cooling, a yellow crystalline mass is formed, which on recrystallization from anhydrous ethanol provides the product (105 g, 60%), m.p. 65°.

Similarly to the nitropropene, 4-hydroxy-3-methoxy-ω-nitrostyrene is prepared from the appropriately substituted benzaldehyde and nitromethane in the presence of methylamine as catalyst.[974] The following illustrates a slight variant of the technique:

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[971] G. Bianchetti, P. D. Croce, and D. Pocar, *Tetrahedron Lett.*, **1965**, 2039.

[972] O. M. Lerner, *Zh. Prikl. Khim.*, **31**, 663 (1958); *Chem. Abstr.*, **52**, 18 271 (1958).

[973] H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

[974] F. A. Ramirez and A. Burger, *J. Amer. Chem. Soc.*, **72**, 2781 (1950).

2,3-Dimethoxybenzaldehyde, nitromethane, and alcoholic potassium hydroxide solution give the derived α-nitro alcohol if the reaction mixture is later acidified with 50% acetic acid; however, acidification with N-sulfuric acid affords **2,3-dimethoxy-ω-nitrostyrene** (93% yield) directly.[975]

Purely aliphatic nitro olefins can rarely be obtained in one step, as the condensation then leads only to the nitro alcohol; but these products afford the nitro olefin when they are esterified with acetic acid and the esters are cleaved with potassium hydrogen carbonate.[976]

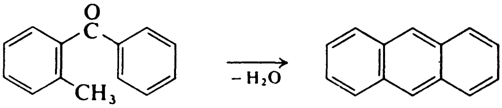
5. Preparation of aromatic systems

Removal of water from certain compounds is often used for synthesis of aromatic rings. Adams and Hufferd[977] obtained mesitylene from acetone by treatment with sulfuric acid, and Lyle *et al.*[978] give the following generalized procedure for preparation of **1,3,5-triarylbenzenes:**

A substituted acetophenone (10 g) is added to anhydrous ethanol (50 ml) previously saturated with gaseous hydrogen chloride. After storage for 30 days the mixture is filtered and the solid triarylbenzene is washed with cold ethanol. The yield is improved if the mother-liquors are poured into water, and the solid product is then collected; this material is somewhat impure and must be washed several times with ethanol. Depending on the substituent in the acetophenone, the yield varies between 20% and 85%.

The Knoevenagel reaction can also be applied to synthesis of aromatic rings: thus 2,3-dimethyl-1,4-naphthalenedicarbonitrile is obtained in 65% yield when biacetyl and *o*-phenylenediacetonitrile are condensed in anhydrous piperidine with initial cooling and later 3 hours' storage.[979]

Diaryl ketones carrying a methyl or a methylene group in the *ortho*-position to the carbonyl group often cyclize with loss of water on pyrolysis (the Elbs reaction), *e.g.*:



This reaction has some importance for the preparation of derivatives of anthracene,[980] dibenz[*a*,*h*]anthracene,[981] benz[*a*]anthracene,[982] and cholanthrene.[983]

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[975] E. Späth, K. Riedl, and G. Kubiczek, *Monatsh. Chem.*, **79**, 72 (1948); L. Canonica, *Gazz. Chim. Ital.*, **79**, 192 (1949).

[976] E. Schmidt and G. Rutz, *Ber. Deut. Chem. Ges.*, **61**, 2142. (1928).

[977] R. Adams and R. W. Hufferd, *Org. Syn.*, **2**, 41 (1922).

[978] R. E. Lyle, E. J. DeWitt, N. M. Nichols, and W. Cleland, *J. Amer. Chem. Soc.*, **75**, 5959 (1953).

[979] H. Moureu, P. Chovin, and G. Rivoal, *Bull. Soc. Chim. France*, [v], **13**, 106 (1946).

[980] G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, **1929**, 2203.

[981] J. W. Cook, *J. Chem. Soc.*, **1931**, 489; E. Clar, *Ber. Deut. Chem. Ges.*, **62**, 1574 (1929); W. E. Bachmann and L. H. Pence, *J. Amer. Chem. Soc.*, **59**, 2339 (1937).

[982] J. W. Cook, *J. Chem. Soc.*, **1932**, 432; L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **59**, 2502 (1937).

[983] L. F. Fieser and A. M. Seligman, *J. Amer. Chem. Soc.*, **57**, 942, 2174 (1935); W. E. Bachmann, *J. Org. Chem.*, **3**, 434 (1939).

This reaction is usually carried out by heating the ketone with neither a catalyst nor a solvent at its boiling point or at a temperature around 400–450° until no more water distils. Yields are seldom above 50%.

The Elbs reaction is treated in detail in *Organic Reactions*.[984]

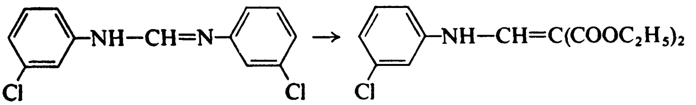
V. Removal of nitrogen with formation of a C=C bond

Decomposition of diazo compounds. It is well known that diethyl fumarate is formed when ethyl diazoacetate is decomposed catalytically by copper powder.[985] Grundmann applied this reaction to diazo ketones,[986] obtaining a moderate yield of 3-hexene-2,5-dione from diazoacetone, and analogous products from ω-diazoacetophenone and 1-diazo-2-nonadecanone.

Schönberg and Frese[987] report that reaction of ethyl diazoacetate or a diazo ketone with an aromatic thioketone in the presence of copper powder gives the β,β-disubstituted acrylic ester or the α,β-unsaturated ketone, respectively, in 80–90% yield.

Cleavage of Schiff bases and analogous compounds. In the condensation of aldehydes with compounds containing reactive methylene groups, as described on page 986, the aldehydes can often be replaced by their Schiff bases. This can be a real advantage since some of these compounds, *e.g.*, *o*-aminobenzaldehyde, are not readily accessible. Borsche and his co-workers,[988] for instance, replaced the *o*-aminobenzaldehyde required for a Friedländer quinoline synthesis by *N*-(*o*-aminobenzylidene)-*p*-toluidine and obtained ethyl 2-methyl-3-quinolinecarboxylate in good yield.

ω-Nitrotoluene (phenylnitromethane)[989] and phenyl *p*-tolyl sulfone[990] react analogously with azomethines. Also, formamidines and their vinylogs react with compounds containing reactive methylene groups: N^1,N^2-bis-(*m*-chlorophenyl)formamidine and diethyl malonate afford diethyl [*N*-(*m*-chlorophenyl)aminomethylene]malonate:[991]



Arnold and Zemlicka[992] used tetramethylformamidinium perchlorate and *N*,*N*-dimethyl-α-cyanoacetamide and obtained 2-cyano-3-(dimethylamino)-*N*,*N*-dimethylacrylamide in 94% yield by means of sodium in liquid ammonia. Phenalene condenses with azacyanine perchlorates in pyridine containing so-

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[984] L. F. Fieser, *Org. Reactions*, **1**, 129 (1942).

[985] A. Loose, *J. Prakt. Chem.*, [ii], **79**, 507 (1909).

[986] C. Grundmann, *Ann. Chem.*, **536**, 30 (1938).

[987] A. Schönberg and E. Frese, *Chem. Ber.*, **96**, 2420 (1963).

[988] W. Borsche, W. Doeller, and M. Wagner-Roemmich, *Ber. Deut. Chem. Ges.*, **76**, 1099 (1943); W. Borsche and J. Barthenheier, *Ann. Chem.*, **548**, 50 (1941).

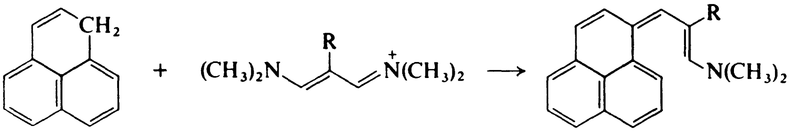
[989] D. Robertson, *J. Org. Chem.*, **25**, 47 (1960).

[990] H. D. Becker, *J. Org. Chem.*, **29**, 2891 (1964).

[991] C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1255 (1946).

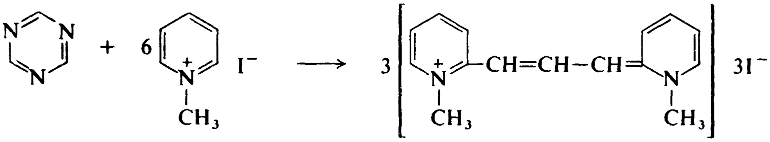
[992] Z. Arnold and J. Zemlicka, *Collect. Czech. Chem. Commun.*, **25**, 1302 (1960).

dium methoxide under nitrogen, yielding more than 90% of the substituted phenafulvenes:[993]



Kreutzberger[994] showed that *s*-triazine reacts as a formamidine derivative with compounds containing reactive methylene groups: thus its reaction with the activated methyl or methylene groups of heterocyclic compounds such as 1-methyl-2- and -4-picolinium iodide, 1-ethyllepidinium iodide, 1-ethylquinaldinium iodide, 2,3-dimethylbenzooxazolium iodide, and 2,3-dimethylbenzoselenazolium iodide leads to trimethinecyanines. This reaction occurs under relatively mild conditions with such compounds — conditions under which the orthoester process fails (see page 990):

Bis-(1-methyl-2-pyridine)trimethinecyanine iodide: The yellowish solution obtained by heating 1-methyl-2-picolinium iodide (14.1 g) in anhydrous ethanol (60 ml) becomes intensely red as soon as *s*-triazine (1.6 g) and 22.4% ethanolic potassium hydroxide solution (40 g) are added. After 5 minutes' boiling on a water-bath, the dark blue trimethinecyanine iodide crystallizes in quantitative yield (10.7 g).



VI. Removal of sulfur with formation of a C=C bond

Under the same conditions as for triethyl orthoformate, interaction of triethyl orthotrithioformate and diethyl malonate leads analogously to **diethyl [(ethylthio)methylene] malonate:**[995]

$$CH(SC_2H_5)_3 + CH_2(COOC_2H_5)_2 \longrightarrow C_2H_5SCH{=}C(COOC_2H_5) + 2C_2H_5SH$$

Triethyl orthotrithioformate (30 g, 0.15 mole), diethyl malonate (24.8 g), acetic anhydride (31.5 g), and anhydrous zinc chloride (2.5 g) are boiled under reflux (oil-bath at 130–140°) for 10 h. After cooling, the liquid is decanted from a small amount of dark resin and is fractionated in a vacuum; a little decomposition occurs toward the end of the distillation. Diethyl [(ethylthio)methylene]malonate distils at 170–172°/19 mm as a pale yellow oil (17.67 g, 49%).

Triethyl orthotrithioformate has been used in analogous condensations for the synthesis of cyanine dyes.[996]

A reaction analogous to the Knoevenagel reaction is that of 5-aryl-1,2-dithiol-

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[993] C. Lutz and R. Kirchlechner, *Angew. Chem. Int. Ed., Engl.*, **5**, 516 (1966).
[994] A. Kreutzberger, *Arch. Pharm.*, **299**, 897, 984 (1966).
[995] K. D. Gundermann, *Ann. Chem.*, **578**, 48 (1952).
[996] J. D. Cendall and J. R. Maier, *J. Chem. Soc.*, **1948**, 687.

3-ones with compounds containing activated methylene groups, such as ethyl cyanoacetate, rhodanine, barbituric acid, and dimedone, in glacial acetic acid containing pyridine; this gives 3-alkylidene-5-aryl-1,2-dithioles.[997]

VII. Removal of phosphorus with formation of a C=C bond (Wittig reaction)[455–457, 998]

The Wittig reaction is a very elegant method of converting a carbonyl group into a C=C bond. It was first used by Wittig and Geissler[999] who treated methylenetriphenylphosphorane (triphenylphosphine methylene) with benzophenone and obtained 1,1-diphenylethylene in 84% yield:

$$(C_6H_5)_3P{=}CH_2 + CO(C_6H_5)_2 \longrightarrow (C_6H_5)_3PO + CH_2{=}C(C_6H_5)_2$$

Since that time, very many phosphorus ylides have been treated with compounds containing carbonyl groups.

Of the various methods of preparing phosphorus ylides, that much preferred — apart from a few exceptions — is the action of bases on phosphonium salts. The strength of the base is adjusted to the acidity of the phosphonium salt; bases used have been carbon bases such as butyl- and phenyllithium, nitrogen bases such as sodamide, lithium diethylamide, and 1,5-diazabicyclo-[4.3.0]non-5-ene, and oxygen bases such as sodium hydroxide and potassium alkoxides. The pairs dimethylsulfoxide–sodium hydride[1000] and dimethyl sulfoxide–potassium *tert*-butoxide[1001] have proved particularly valuable.

Methylenetriphenylphosphorane:[1002] First, anhydrous ether (200 ml) and then, with stirring, during 5 min, methyltriphenylphosphonium bromide (0.1 mole) are added to an ethereal solution of butyllithium (0.1 mole) under nitrogen. After 4 hours' stirring at room temperature the solution can be used for further reactions.

Reactions with more than 100 ylides have been described, and in accord with theoretical considerations these have shown that the reactivity of an ylide of the formula:

$$R_3P{=}CR'_2 \longleftrightarrow R_3\overset{+}{P}{-}\overset{-}{C}R'_2$$

is weaker the more powerfully electron-attracting is the substituent R′.

The range of applicability of the Wittig reaction has in recent years become extremely extensive and there have been reports of its use for the preparation of alkyl- and aryl-substituted alkenes, unsaturated aldehydes, ketones, and carboxylic acid derivatives, vinyl halides, and vinyl ethers. In the preparation of these compounds there is often the possibility of *cis–trans* isomerism; Bestmann and Kratzer[1003] state that the *trans*-olefin is always obtained when an alkylidenetricyclohexylphosphorane is used, and Schlosser and Christ-

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[997] Y. Mollier, N. Lozac'h, and F. Terrier, *Bull. Soc. Chim. France*, **1963**, 157.

[998] A. Maercker, *Org. Reactions*, **14**, 270 (1965); S. Trippett, *Advan. Org. Chem.*, **1**, 83 (1960); *Quart. Rev.*, **17**, 406 (1963); L. D. Bergel'son, V. A. Vaver, and M. M. Shemyakin, *Angew. Chem. Int. Ed., Engl.*, **3**, 125 (1964); A. W. Johnson, "Ylid Chemistry," Academic Press, New York, 1966; H. Bestmann, *Angew. Chem. Int. Ed., Engl.*, **4**, 583, 645, 850 (1965).

[999] G. Wittig and G. Geissler, *Ann. Chem.*, **580**, 44 (1953).

[1000] B. Greenwald, M. Chaykovsky, and E. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

[1001] D. Denney and J. Song, *J. Org. Chem.*, **29**, 495 (1965).

[1002] G. Wittig and U. Schöllkopf, *Org. Syn.*, **40**, 66 (1960).

[1003] H. Bestmann and O. Kratzer, *Chem. Ber.*, **95**, 1894 (1962).

mann[1004] have described a method that gives preponderatingly the *trans*-product; the latter authors[1005] also found that using an alkylidenetriphenylphosphorane generally tends to give the *cis*-olefin. The proportion of *cis*-olefin in the olefin mixture produced is highest when the ylide was salt-free.[106] Lithium salts favor formation of the *trans*-isomer the more the greater is the radius of the anion. Ylides containing α-substituents that are capable of mesomerism, such as benzylidenetriphenylphosphorane, are not suitable for *cis*-selective olefination.

The reaction of ylides with alicyclic ketones has achieved especial significance since it is the only method of converting ketones into olefins with the double bond in the exocyclic position. Cyclohexanone and methylenetriphenylphosphorane give methylenecyclohexane free from its isomers,[1002] and benzylidenetriphenylphosphorane gives analogously benzylidenecyclohexane.[1007]

Methylenecyclohexane: Cyclohexanone (9.8 g, 0.1 mole) is added to a solution of methylenetriphenylphosphorane (0.1 mole) in anhydrous ether (200 ml). A white precipitate is at once formed. The whole is warmed for 3 h at 65°, then the precipitate is centrifuged off and washed several times with ether. The ethereal solutions are washed with water and evaporated. Fractionation of the residual oil through a Vigreux column (30 cm) affords methylenecyclohexane (5.4 g, 52%), b.p. 100–103°/744 mm.

It is advisable to use 1,5-diazabicyclo[4.3.0]non-5-ene[1008] in dimethyl sulfoxide for Wittig reactions with alkali-sensitive aldehydes.

The preparation of **o-divinylbenzene**[1009] exemplifies the technique for an aromatic aldehyde:

Sodamide (60 mmoles) in liquid ammonia (300 ml) is mixed with methyltriphenylammonium bromide (55 mmoles), and the ammonia is evaporated. The residue is boiled in ether (200 ml) under reflux. *o*-Phthalaldehyde (28 mmoles) in ether (100 ml) is stirred during 15 min into the orange-yellow solution of methylenetriphenylphosphorane, and the mixture is boiled for 2 h. After removal of the triphenylphosphine oxide, concentration of the filtrate to 50 ml, and then removal of further oxide, the filtrate affords *o*-divinylbenzene, b.p. 75–78°/14 mm, in 75% yield (2.7 g).

There are also many examples of the synthesis of α,β- and β,γ-unsaturated carbonyl compounds. By reaction of (formylmethylene)triphenylphosphorane with benzaldehyde or heptanal Trippett and Walker[1010] obtained, respectively, cinnamaldehyde in 60% yield and 2-nonenal in 81% yield. Reaction of the ylide with ketones does not, however, succeed: α,β-unsaturated ketones are obtained by treating acetonylidenetriphenylphosphorane[1011] with aldehydes. Further, the action of (ethoxycarbonylmethylene)triphenylphosphorane on

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[1004] M. Schlosser and K. Christmann, *Angew. Chem. Int. Ed., Engl.*, **5**, 126 (1966); *Ann. Chem.*, **708**, 1 (1967).

[1005] M. Schlosser, G. Müller, and K. Christmann, *Angew. Chem. Int. Ed., Engl.*, **5**, 667 (1966).

[1006] G. Wittig, H. Eggers, and P. Duffner, *Ann. Chem.*, **619**, 10 (1958).

[1007] G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).

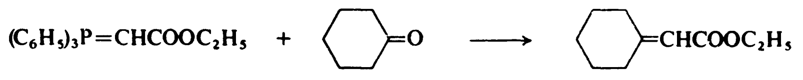
[1008] H. Oediger, H. J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

[1009] G. Wittig, H. Eggers, and P. Duffner, *Ann. Chem.*, **619**, 22 (1958).

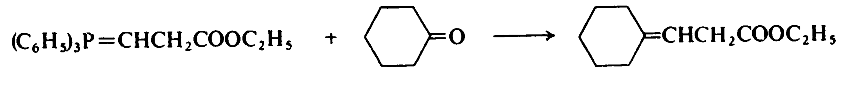
[1010] S. Trippett and D. Walker, *J. Chem. Soc.*, **1961**, 1266.

[1011] F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

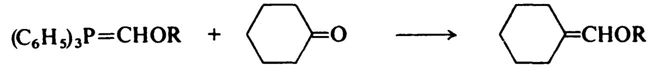
cyclohexanone in boiling benzene affords ethyl cyclohexylideneacetete in 25% yield:[1012]



The same ylide was used by Isler and his collaborators[1013] for synthesis of polyene carboxylic acids. *β,γ*-Unsaturated carboxylic acids are accessible by starting from (2-ethoxycarbonylethyl)triphenylphosphonium chloride[1014] and, *e.g.*, cyclohexanone[1015] in dimethyl sulfoxide–tetrahydrofuran containing sodium hydride:



Vinyl halides and ethers can also be prepared if the proper ylide is chosen for the Wittig reaction. Vinyl chlorides, for example, are obtained from aliphatic ketones and (chloromethylene)triphenylphosphorane,[1016] and vinyl ethers by reaction of (alkyoxymethylene) — or (aryloxymethylene) — triphenylphosphorane with aldehydes or ketones. (Alkoxymethylene)triphenylphosphoranes are not very stable at room temperature, so it is advisable to use a low temperature for their reactions with aldehydes or ketones; By treatment of (methoxymethylene)triphenylphosphorane or the butoxymethylene analog with cyclohexanone Wittig, Böll, and Krück[1017] obtained, respectively, cyclohexylidenemethyl methyl ether in 71% yield and the analogous butyl ether in 74% yield:



($R = CH_3$ or n-C_4H_9)

A synthesis relared to the Wittig reaction is the "PO-activated olefination" described by Horner and his collaborators.[1018] In this a phosphonic ester, *e.g.*, $(RO_2P(O)CH_2C_6H_5$, or a phosphine oxide, *e.g.*, $(C_6H_5)_2P(O)CH_2C_6H_5$, is converted into an olefin by treatment with an aldehyde or a ketone in the presence of a base; **general directions for PO-activated olefination** are:

The phosphonic ester or phosphine oxide (0.01 mole) is shaken for 5 min with potassium *tert*-butoxide (0.02 mole) in dimethylformamide (15 ml) in a closed vessel; metallation occurs exothermally and is recognizable by appearence of an orange or a red color. Then the aldehyde or ketone (0.01 mole) in toluene or dimethylformamide (20 ml) is added and the whole is shaken until evolution of heat ceases (about 5 min). When a phosphonic ester was used, 15% acetic acid (10 ml) is then added, the two phases are separated and the olefin is isolated

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[1012] S. Trippett and D. Walker, *Chem. & Ind.* (*London*), **1961**, 990.

[1013] O. Isler, H. Gutmann, M. Montavon, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

[1014] D. Denney and L. Smith, *J. Org. Chem.*, **27**, 3404 (1962).

[1015] H. Corey, J. McCormick, and W. Swensen, *J. Amer. Chem. Soc.*, **86**, 1884 (1964).

[1016] D. Seyferth, S. Grim, and T. Read, *J. Amer. Chem. Soc.*, **82**, 1510 (1960); **83**, 1617 (1961).

[1017] G. Wittig, W. Böll, and K. H. Krück, *Chem. Ber.*, **95**, 2514 (1962).

[1018] L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. Toscano, *Chem. Ber.*, **95**, 581 (1962).

from the organic phase. When a phosphine oxide was used, the deposited potassium diphenylphosphinate is filtered off, water is added, and the olefin is worked up.

New applications of the Wittig reaction continue to be reported. Some recent examples are the synthesis of α,β-unsaturated carboxylic acids by Wadsworth and Emmons,[1019] of α,β-unsaturated ketones by Normant and Sturtz,[1020] and of acrylonitrile derivatives in the steroid field by Drefahl, Ponsold and Schick.[1021] It has, however, transpired that in some cases PO-activated olefination is to be preferred to the Wittig reaction.[1012]

[1019] W. Wadsworth and W. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

[1020] N. Normant and G. Sturtz, *C. R. Hebd. Séances Acad. Sci.*, **256**, 1800 (1963).

[1021] G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **97**, 2011 (1964).

PART C

Cleavage of Carbon–Carbon Bonds

PART C

Cleavage of Carbon-Carbon Bonds

Compiled by
G. Hilgetag

Reactions leading to cleavage of carbon–carbon bonds have a certain degree of preparative importance although, as a whole, less than that of reactions leading to formation of such bonds. In addition, however, the various degradative reactions have especial value in the classical methods of determining the constitution of organic compounds.

In this Section the methods of cleaving carbon–carbon bonds are considered under the headings: thermal decomposition, oxidative degradation, and hydrolysis.

1.1. Thermal decomposition

I. Removal of carbon dioxide

In the majority of cases thermal cleavage of carbon–carbon bonds consists of decarboxylation of a carboxylic acid RCOOH; the tenacity with which the carboxyl group is retained varies within wide limits. Aliphatic acids can normally be decarboxylated only under rather extreme conditions, and the same applies to simple aromatic carboxylic acids unless the attachment of the carboxyl group is weakened by, *e.g.*, *ortho-* or *para*-hydroxyl groups or by a hetero-ring atom (at a suitable distance from the carboxyl group). On the other hand, many carboxylic acids are known that lose carbon dioxide at or relatively little above room temperature either spontaneously or under the influence of acidic or basic catalysts. In most cases, the decarboxylation occurs by a polar mechanism, in an S_E reaction:

$$\mathrm{RCOOH} \longrightarrow \mathrm{R^- + CO_2 + H^+}$$
$$\mathrm{R^- + H^+} \longrightarrow \mathrm{RH}$$

In such heterolytic decarboxylations the electron pair binding the carboxyl-carbon atom to the organic group R thus remains attached to the group R, with the consequence that the electronic nature of R and, in particular, of its α- or β-carbon atom may contribute appreciably to the conditions required for the reaction. Three possibilities can be distinguished in respect of the contribution of R to cleavage of a carboxyl group:

1. The group R has almost no influence on the ease of fission of the acid, which is then difficult to decarboxylate.

2. Decarboxylation is relatively easy and smooth; this occurs when the electron density at the carbon atom in the α-position to the carboxyl group is relatively low so that the electron affinity of the group R is high (type 1).

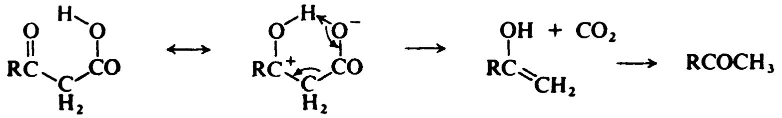
3. Heterolysis is also made easier when a cationoid centre can be formed at the carbon atom in the β-position to the carboxyl group, as such a centre can take up the electron pair binding the carboxyl group, thus forming a double bond (type 2).

The last two, extreme, cases can be illustrated by the following examples:

Case 1:

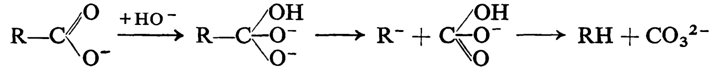
$$CCl_3COOH \longrightarrow Cl_3C^- + CO_2 + H^+ \longrightarrow CHCl_3 + CO_2$$

Case 2:



1. Carboxylic acids that are not easily decarboxylated

Carboxylic acids that are difficult to decarboxylate comprise in particular the aliphatic acids and simple aromatic carboxylic acids. They can be decarboxylated only by pyrogenic decomposition of their salts in admixture with an alkali hydroxide or lime. In such mixtures an additional charge produced on the carboxyl group makes it possible, by induction, to remove the group R as an anion:



$$R{-}C\begin{matrix}{\scriptstyle /\!/O}\\{\scriptstyle \backslash O^-}\end{matrix} \xrightarrow{+HO^-} R{-}C\begin{matrix}{\scriptstyle /OH}\\{\scriptstyle -O^-}\\{\scriptstyle \backslash O^-}\end{matrix} \longrightarrow R^- + C\begin{matrix}{\scriptstyle /OH}\\{\scriptstyle -O^-}\\{\scriptstyle \backslash\!\backslash O}\end{matrix} \longrightarrow RH + CO_3^{2-}$$

Alkali or alkaline earth salts of the carboxylic acids are generally used, but other salts such as the silver, mercury, or copper salts may be used with advantage. Occasionally such decarboxylations can be effected in high-boiling solvents, *e.g.*, ethylene glycol. This method of decarboxylation has been aplied principally to aromatic and heterocyclic carboxylic acids whose carboxyl groups have not been loosened by suitable *ortho-* or *para*-substituents or by a neighboring hetero-ring atom.

For example, **collidine** is obtained from collidine-3,5-dicarboxylic acid by mixing its dry potassium salt with twice its weight of calcium hydroxide, heating the mixture to red heat in a combustion tube, and collecting the collidine that distils.[1]

With other carboxylic acids, in particular cycloalkanecarboxylic acids, side reactions often occur. Thus barium cyclohexanecarboxylate gives, not cyclohexane, but a mixture of cyclohexene and cyclohexadiene.[2]

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[1] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," 33rd ed., Walter de Gruyter & Co., Berlin, 1947, p. 329.

[2] N. Zelinsky and J. Gutt, *Ber. Deut. Chem. Ges.*, **41**, 2074 (1908).

Only moderate yields of hydrocarbon are obtained in this way from salts of aliphatic acids; here the main side reaction is formation of the ketone by only partial decarboxylation. This ketone formation becomes the main reaction if the calcium salt is not mixed with an excess of lime but is submitted alone to dry distillation:

$$\text{RCOOCaOCOR} \longrightarrow \text{RCOR} + \text{CaCO}_3$$

Ketonic decarboxylation of the less volatile acids can also be carried out by distilling the free acid in admixture with a small amount of a suitable metal oxide, hydroxide, or carbonate. When, for instance, barium carbonate is used, the small amount of barium salt of the organic acid first formed yields ketone plus barium carbonate, the latter reacts with the excess of acid to give carbon dioxide and the barium salt which again decomposes, and so on until all the acid is consumed. Such distillation of calcium salts is particularly successful in formation of cyclic ketones from certain dicarboxylic acids; thus alkaline earth salts of adipic acid afford cyclopentanone,[3] and those of pimelic acid afford cyclohexanone.[4] These cyclic ketones are also formed from the free 1,6- and 1,7-dicarboxylic acids either by heating them with a mere 5% of calcium oxide at 280–290° or, as shown by Blanc,[5] by heating them in acetic anhydride at about 240°; this behavior differentiates them from 1,4- and 1,5-dicarboxylic acids, which are merely converted into their anhydrides under these conditions; it provides Blanc's rule which has often been applied as a diagnostic tool for determination of ring size, particularly in steroid chemistry — although there are occasional exceptions where anhydrides are obtained instead of cyclic ketones from 1,6-dicarboxylic acids under the conditions stated above.[6]

A method used in industry for ketonization of aliphatic acids is to pass the carboxylic acid vapors at about 300° over calcium, barium, or thorium oxide catalysts, and this is in principle also a calcium salt distillation.

Neunhoeffer[7] has shown that the mechanism of most of these reactions probably involves intermediate formation of a β-oxocarboxylic acid, *e.g.*:

$$(\text{CH}_3\text{COO})_2\text{Ca} \longrightarrow \text{CH}_3\text{COCH}_2\text{COOCaOH} \longrightarrow \text{CH}_3\text{COCH}_3 + \text{CaCO}_3$$

Decarboxylation of an aliphatic acid to the hydrocarbon is best effected by the so-called "salt degradation" method. That method is to treat the silver or mercury salt of, preferably, an aliphatic or alicyclic carboxylic acid with bromine in an inert solvent; a halogenated hydrocarbon is then formed, together with carbon dioxide and the metal bromide, usually in an exothermic reaction, and the bromine can then usually be readily removed either catalytically or by means of a Grignard reagent (the Hunsdiecker reaction):

$$\text{RCOOAg} + \text{Br}_2 \longrightarrow \text{RBr} + \text{CO}_2 + \text{AgBr}$$

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[3] J. F. Thorpe and G. A. R. Kon, *Org. Syn.*, **5**, 37 (1925).

[4] L. Ruzicka and co-workers, *Helv. Chim. Acta*, **9**, 515 (1926).

[5] H. G. Blanc, *C. R. Hebd. Séances Acad. Sci.*, **144**, 1356 (1907); A. Windaus, *Z. Physiol. Chem.*, **130**, 116 (1923).

[6] E. H. Farmer and J. Kracovsky, *J. Chem. Soc.*, **1927**, 680; F. Vocke, *Ann. Chem.*, **508**, 1 (1934).

[7] O. Neunhoeffer, *Ber. Deut. Chem. Ges.*, **72**, 919 (1939).

Small amounts of esters are formed as by-products in these reactions as a result of alkylation of the silver salt by the halide already formed:

$$\mathrm{RCOOAg + RBr \longrightarrow RCOOR + AgBr}$$

Ester formation even becomes the main reaction if equimolar amounts of silver salt and iodine are used.[8]

The primary products of the Hunsdiecker reaction are probably the hypothetical acyl hypohalites that later undergo radical decomposition:

$$\mathrm{C_6H_5COOAg + Br_2 \longrightarrow AgBr + C_6H_5COOBr \longrightarrow}$$
$$\mathrm{CO_2 + Br^{\bullet} + C_6H_5{}^{\bullet} \longrightarrow C_6H_5Br}$$

Lüttringhaus[9] described the preparation of **undecyl bromide** from dodecanoic acid as follows:

Hot solutions of silver nitrate (50 g) in water (100 ml) and of dodecanoic acid (59 g) in 1.45N-potassium hydroxide solution (200 ml) are poured simultaneously, with stirring, into hot water (100 ml). After cooling in the dark, the precipitated silver dodecanoate is filtered off, washed with water and then acetone, and dried in the dark, first in the air and then in a high vacuum over phosphoric oxide at 60° (yield 85 g). This silver salt (46 g) and carbon tetrachloride (200 ml) are placed in a three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel and are cooled and stirred vigorously while a solution of bromine (7.5 ml) in carbon tetrachloride (20 ml) is added slowly. The mixture is then heated gradually and evolution of carbon dioxide is completed by boiling for a short time. The mixture is filtered through a Soxhlet extraction thimble, and the solid is extracted for 1–2 h by the filtrate, leaving the silver bromide in the thimble. Unchanged dodecanoic acid (5.5 g, 18%) is removed from the extract by shaking with dilute sodium hydroxide solution and then with water. After removal of the carbon tetrachloride distillation in a vacuum affords 67% (24 g) of undecyl bromide, b.p. 131–134°/15 mm.

2. Decarboxylation of carboxylic acids with increased electron affinity at the α-carbon atom

Decarboxylations of the type described above as type 1 may be exemplified by those in the following Subsections.

a. Halogenated fatty acids and their salts

For α-halo aliphatic acids it is the rule that the ease of loss of carbon dioxide increases with the atomic weight of the halogen. For example, trichloroacetic acid can be distilled unchanged and decomposes only at temperatures above 200°, and then slowly; triiodoacetic acid, however, is decarboxylated at its melting point, 150°.

Trichloroacetic acid is stable in toluene, carbon disulfide, or 6N-sulfuric acid, *i.e.*, in solvents having little or no proton-acceptor properties. The situation is different in basic solvents, *e.g.*, in water: in aqueous solution trichloroacetic acid decomposes to chloroform and carbon dioxide when warmed to 70°. Thus the undissociated acid is moderately stable, but the anion is not. Cor-

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[8] J. W. H. Oldham, *J. Chem. Soc.*, **1950**, 100.

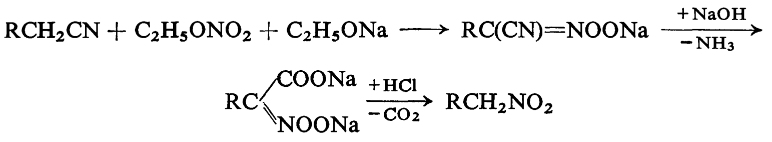
[9] A. Lüttringhaus, *Ber. Deut. Chem. Ges.*, **74**, 1565 (1941); J. Kleinberg, *Chem. Rev.*, **40**, 381 (1947); R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 219 (1956); C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).

respondingly salts of α-halo aliphatic acids are much less stable than the free acids. This explains why, in non-aqueous solvents where the acid is not or only slightly ionized, the rate of decarboxylation is proportional to the anion concentration that can be achieved by addition of a base: in hot benzene solution trichloroacetic acid is decarboxylated only on addition of, *e.g.*, aniline. Similarly salts of triiodoacetic acid generally are unstable. The ready decarboxylation of salts of trichloro- and tribromo-acetic acid has recently been utilized for preparation of dihalo carbenes in aprotic media,[10] a reaction applied, for instance, to the preparation of **dichloronorcarane** as follows:

Sodium trichloroacetate (40 g) and cyclohexene (105 g) are heated in 1,2-dimethoxyethane (70 ml) for 22 h under reflux, after which they afford dichloronorcarane in 65% yield (23.1 g) calculated on the trichloroacetate.

b. α-Nitro carboxylic acids

α-Nitro carboxylic acids behave analogously to α-halo acids. For instance, nitroacetic acid is very unstable, being converted into nitromethane when merely boiled with water or when dilute sulfuric acid is poured over its sodium or potassium salt. The importance of such reactions for the preparation of nitro alkanes has been mentioned above (page 476). The following scheme illustrates a general method for preparation of primary nitro compounds from nitriles,[11,12] leading through the sodium salt of the *aci*-nitro nitrile to the α-nitro carboxylic acid from which the nitro alkane is obtained by loss of carbon dioxide:



$$RCH_2CN + C_2H_5ONO_2 + C_2H_5ONa \longrightarrow RC(CN){=}NOONa \xrightarrow[-NH_3]{+NaOH}$$

$$RC\begin{cases}COONa\\NOONa\end{cases} \xrightarrow[-CO_2]{+HCl} RCH_2NO_2$$

α-Nitro carboxylic acids are relatively stable as undissociated acid and also as dianion in strongly alkaline solution: only the univalent anion is readily decarboxylated.

c. α-Amino carboxylic acids

It is characteristic of α-amino acids that their anions are relatively stable while they can be readily decarboxylated as free acids. It is to be assumed that carbon dioxide is split off from the zwitterion since it is only this form of an amino acid that has a substituent exerting effective electron attraction at the α-carbon position. α-Amino carboxylic acids often afford the next lower amine when heated at 200–250° in an inert solvent such as glycerol, diphenylmethane, or diphenylamine; tyramine, for example, has been obtained from tyrosine in this way.[13]

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[10] W. H. Wagner, *Proc. Chem. Soc.*, **1959**, 229.

[11] W. Wislicenus and A. Endres, *Ber. Deut. Chem. Ges.*, **35**, 1757 (1902).

[12] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," 33rd ed., Walter de Gruyter & Co., Berlin, 1947, p. 231.

[13] E. Abderhalden and E. Gebelem, *Z. Physiol. Chem.*, **152**, 126 (1926).

Wada[14] claimed that it was advantageous first to convert the α-amino acid by, *e.g.*, urea into the hydantoin and to boil this with aqueous acid or alkali, thus obtaining the next lower amine by simultaneous hydrolysis and elimination of carbon dioxide. However, the process has been tested by several authors who failed to reproduce it under the conditions given by Wada.

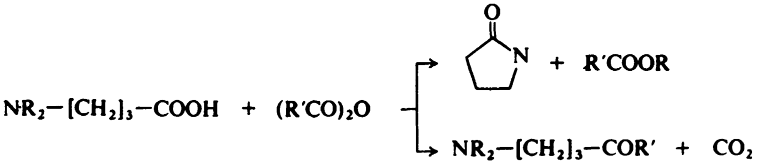
Such decarboxylations are occasionally of industrial importance: for example, primary amines may be monomethylated by converting them by chloroacetic acid into *N*-substituted glycines which can then be decarboxylated;[15] *p*-(methylamino)phenol (Metol) is prepared industrially in this way.

d. Dakin–West and related reactions

The Dakin–West synthesis of α-acylamino ketones[16] is closely related to the decarboxylation of α-amino carboxylic acids. Interaction of a carboxylic acid anhydride, *e.g.*, acetic or benzoic anhydride, and an α-amino acid in the presence of pyridine or some similar base affords the derived α-acylamino ketone by decarboxylation.

3-(Acetylamino)-4-phenyl-2-butanone:[17] A mixture of DL-phenylalanine (0.075 mole), pyridine (0.5 mole), and acetic anhydride (0.64 mole) is heated on a steam-bath for 5 h, and is then freed from pyridine by steam-distillation. The residue is treated with an excess of sodium hydrogen carbonate solution and extracted exhaustively with ether. Removal of the ether and recrystallization of the residue from xylene gives a 79% yield of the product as colorless needles, m.p. 98–99°.

Related to the Dakin–West reaction is the finding that reaction of a carboxylic acid anhydride with simple γ- or δ-(dialkylamino) carboxylic acids having an α-CH_2 group and a primary alkyl group as substitutent on the nitrogen affords a 47–65% yield of the γ- or δ-(dialkylamino) ketone.[18] If the nitrogen carries a secondary alkyl group or a benzyl group the reaction takes a different course, leading namely to the lactam and alkyl ester in 65–85% yield.



General procedure: The dialkylamino acid (1 part) is dissolved in acetic anhydride (4 parts) or in a mixture of propionic anhydride and xylene and heated under reflux for 15 min in an atmosphere of nitrogen. The gas evolved is led into barium hydroxide solution where precipitation of barium carbonate shows that the ketone has been formed. The excess of anhydride (and solvent) are then distilled off at atmospheric pressure until finally a bath-temperature of 180–200° is recorded. The product is obtained pure by a final vacuum-distillation.

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[14] M. Wada, *Biochem. Z.*, **260**, 47 (1933); F. Möller in Houben–Weyl, "Methoden der organischen Chemie," 4th ed., Georg Thieme Verlag, Stuttgart, Vol. 11, Part 1, 1957, p. 992.

[15] H. Henecka in Houben–Weyl, "Methoden der organischen Chemie," 4th ed., Georg Thieme Verlag, Stuttgart, Vol. 8, 1952, p. 489.

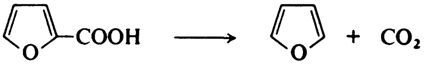
[16] H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91, 745, 757 (1928).

[17] G. H. Cleland and C. Niemann, *J. Amer. Chem. Soc.*, **71**, 841 (1949).

[18] P. A. Cruickshank and J. C. Sheehan, *J. Amer. Chem. Soc.*, **83**, 2891 (1961).

e. N- and O-Heterocyclic α-carboxylic acids

As in the case of α-amino carboxylic acids, the zwitterions of N- and O-heterocyclic α-carboxylic acids can be decarboxylated; thus α-picolinic, thiazole-2-carboxylic, quinaldic, and chelidonic acid afford, respectively, pyridine, thiazole, quinoline, and 4-pyrone. Furan is best prepared by removal of carbon dioxide from pyromucic acid (2-furoic acid) by heat; in early work this was effected by heating the acid in a sealed tube or with soda-lime, but Wilson[19] has described a convenient method that involves only simple apparatus and affords the very good yields of 72–78%:



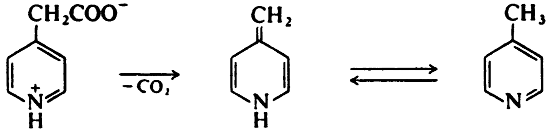
However, a still better yield (85–91%) is obtained as follows:

Furan: 2-Furoic acid is heated at 170° with high-boiling pyridine bases (about 3.5 parts by weight) containing a little copper oxide. This procedure uses the facts that such decarboxylations are effected particularly smoothly in the presence of high-boiling tertiary bases and are catalysed by copper powder or copper oxide.

3. Decarboxylation of carboxylic acids with a cationoid centre at the β-carbon atom

a. Pyridineacetic acids

Pyridineacetic and thiazoleacetic acid can also be decarboxylated by way of the zwitterions or analogous cyclic intermediates.[20] In these cases the formation of the zwitterion does not lead to electron attraction by the β-carbon atom but, instead, produces a cationoid centre at the β-position. 2-Ethyl-2-methyl-2-(2′-pyridyl)acetic acid, for instance, is stable in boiling concentrated hydrochloric acid or boiling sodium carbonate solution but is readily decarboxylated in neutral solution. 4-Pyridineacetic acid behaves similarly. Decarboxylation of optically active pyridineacetic acid derivatives having an asymmetric α-carbon atom leads to completely racemic products, and as the racemization is simultaneous with, and not subsequent to, the decarboxylation it is assumed that an enamine is formed as intermediate, *e.g.*:



b. Malonic acids and anhydrides; decarboxylating acylation of arylacetic acids

Malonic acids are decarboxylated preferentially by way of the transition state formulated as type 2 in the introduction to this Chapter (page 1004). Thus they react readily as undissociated molecules but are decarboxylated

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[19] W. C. Wilson, *Org. Syn.*, 7, 40 (1927).

[20] B. R. Brown and D. Phil, *Quart. Rev.* (*London*), 5, 131 (1951).

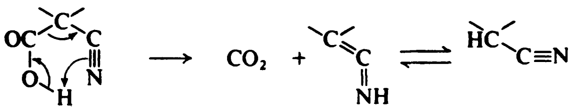
less easily as univalent anions and are almost completely stable as divalent anions ($v = k$[dicarboxylic acid] + k'[dicarboxylic acid monoanion] with $k > k'$).[21]

This must not be confused with the behavior of dibromomalonic acid.[22] Here the inductive effect of the bromine substituents predominates, so that in aqueous solution, where the acid exists mainly as univalent anion, decarboxylation occurs even at room temperature, whereas the acid is stable for months if its dissociation is strongly repressed.

The decarboxylation affords dibromoacetic acid, but in the presence of bromine the end-product is tribromoacetic acid; since bromine has no effect on the rate of reaction, and since dibromoacetic acid is not brominated under the reaction conditions, the carbanion mechanism is conclusively proved for this case.

Among other studies of the decarboxylation of malonic acids is the interesting discovery that racemic methyl propionate is obtained from methyl hydrogen ethylmalonate; this racemization is most simply interpreted as arising through formation of an enol or enolate as intermediate.

Racemization also occurs on decarboxylation of optically active disubstituted cyanoacetic acids (which can be regarded as half nitriles of malonic acids), the reaction yielding disubstituted acetonitriles:



The principal application of the decarboxylation of malonic acids is to the preparation of substituted acetic acids:

$$RR'C(COOH)_2 \longrightarrow RR'CHCOOH + CO_2$$

Some examples have been given above (page 983). Here it suffices to draw attention to the preparation of hexanoic acid by Adams and Marvel;[23] these workers studied the removal of carbon dioxide under various conditions and obtained the best results when the decarboxylation was carried out in one step alongside the hydrolysis of the butylmalonic ester.

Hexanoic acid: A solution of potassium hydroxide (500 g) in water (500 ml) is heated in a round-bottomed flask (5-l capacity) fitted with a reflux condenser and a dropping funnel, then diethyl butylmalonate (500 g) is added gradually with repeated shaking; hydrolysis is rapid, the main reaction being over and the solution clear by the end of the addition. To complete the hydrolysis and to remove most of the alcohol produced the flask is heated without its attachments for 1–2 h on a water-bath, whereafter the reflux condenser and dropping funnel are replaced in position and the solution is acidified with hydrochloric acid (*d* 1.19; 1500 ml), care being taken to avoid excessive foaming. Next the solution is boiled for 4–5 h, whereafter it is distilled with a descending condenser until almost all the hexanoic acid (which separates as an oil) has passed over. This acid is separated from the aqueous portion of the distillate, and part (about 400 ml) of the distillate is returned to the 5-l reaction flask; renewed distillation gives more hexanoic acid. Finally the residual acid is salted out from the united aqueous layers by calcium chloride. The fractions of the product are united, dried over calcium chloride, and distilled, this gives a 74% yield (200 g) of hexanoic acid, b.p. 200–205°.

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[21] G. A. Hall, *J. Amer. Chem. Soc.*, **71**, 2691 (1949).

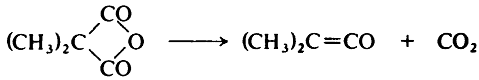
[22] J. Muus, *J. Phys. Chem.*, **39**, 343 (1935); **40**, 121 (1936).

[23] R. Adams and C. S. Marvel, *J. Amer. Chem. Soc.*, **42**, 317 (1920).

Hydrolysis and decarboxylation of acylmalonic esters, which also react as β-oxo acids, affords methyl ketones:

$$RCOCH(COOR')_2 + 2H_2O \xrightarrow{H^+} RCOCH_3 + 2CO_2 + 2R'OH$$

Dialkylmalonic anhydrides can be converted into dialkylketenes by heating them under diminished pressure at 100–200°:[24]



Dimethylketene: Acetic anhydride (25 g), dimethylmalonic acid (6.5 g), and concentrated sulfuric acid (1 drop) are placed in a dry Claisen flask; dissolution occurs when the mixture is shaken. The solution is set aside at room temperature for 2 days, then a little powdered barium carbonate is added and the acetic acid and anhydride are removed by gentle heating in a vacuum. A new receiver is then attached and this is cooled in ice. The temperature is then gradually raised to about 100°, whereupon the dimethylmalonic anhydride decomposes with evolution of carbon dioxide and distillation of the dimethylketene produced. The yield is 65% (2.3 g) and the b.p. 34°.

Only the simpler dialkylketenes such as the dimethyl-, diethyl-, dipropyl-, and diisopropylketene can, however, be obtained by this method.

Because malonic anhydrides are difficultly accessible, Staudinger recommended the decomposition of mixed anhydrides as a generally applicable method; these mixed anhydrides can be obtained by the action of, *e.g.*, diphenylketene on disubstituted malonic acids in ethereal solution.[25]

The mixed anhydrides are insoluble in ether and can be isolated almost quantitatively, and the desired ketenes are obtained by heating the anhydrides under diminished pressure until no more carbon dioxide is evolved:

$$RR'C[COOCOCH(C_6H_5)_2]_2 \longrightarrow RR'C{=}CO + [(C_6H_5)_2CHCO]_2O + CO_2$$

Compounds prepared in this way include dibenzyl- (73% yield), diallyl- (80% yield), and methylphenyl-ketene (75% yield).

The decarboxylation of mixed anhydrides of malonic acids with phenylacetic acid is related to the decarboxylating acylation of arylacetic acids,[26] of which the following is an example:

A mixture of phenylacetic acid (13.6 g), acetic anhydride (50 ml), and pyridine (50 ml) is boiled under reflux for 6 h, evolution of carbon dioxide being initially lively. The pyridine and the excess of anhydride are then distilled off and the residue is taken up in benzene and shaken with 10% sodium hydroxide solution. Removal of the benzene, followed by fractionation of the residue (12 g), afford **phenylacetone** (7.5 g, 56%), b.p. 30–64°/0.1 mm, and, after a small intermediate fraction, **dibenzyl ketone** (2.5 g, 24%), b.p. 112–125°/0.1 mm.

Under the same conditions 3-phenylpropionic acid reacts only so far as to give the anhydride, the CH-acidity at the α-carbon atom being in this case insufficient to lead to formation of the ketone.

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[24] H. Staudinger, *Helv. Chim. Acta*, **8**, 306 (1925).

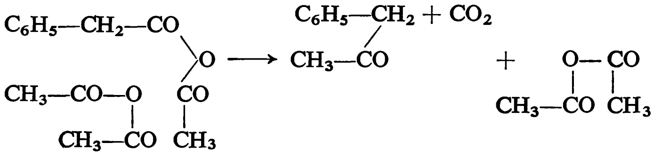
[25] H. Staudinger, H. Schneider, P. Schotz, and P. M. Strong, *Helv. Chim. Acta*, **6**, 291 (1923); W. E. Hanford and J. C. Sauer, *Org. Reactions*, **3**, 116 (1946).

[26] J. A. King and I. H. McMillan, *J. Amer. Chem. Soc.*, **73**, 49 11 (1951).

It has been found that the decarboxylating acylation probably begins with the equilibrations:

$$\begin{array}{c} 2C_6H_5CH_2COOH + (CH_3CO)_2O \\ \updownarrows \\ C_6H_5CH_2COOCOCH_3 + C_6H_5CH_2COOH + CH_3COOH \\ \updownarrows \\ (C_6H_5CH_2CO)_2O + 2CH_3COOH \end{array}$$

The formation of phenylacetone can then be formulated as:



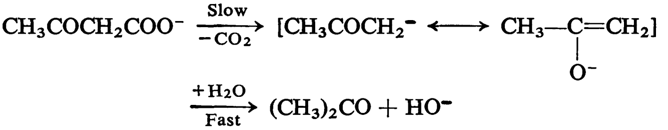
c. β-Oxo acids

Like malonic acids, acetoacetic acid and analogous β-oxo acids are more readily decarboxylated as undissociated acids than as their anions. The rate equation for the two types of acid is the same:

$$v = k\,[\text{oxo acid}] + k'\,[\text{oxo acid anion}] \qquad k > k'$$

Thence it can be concluded that such decarboxylations can occur in either of two ways; neither of these two routes involves the enol form of the acid or its salt since dimethylacetoacetic acid behaves in the same way. The two terms in the rate equation thus correspond simply to the monomolecular decomposition of the oxo acid or its anion, respectively. Here too decomposition of the oxo acid[27] must be assumed to proceed by way of a cyclic intermediate containing an intramolecular hydrogen bridge, as formulated in the introduction (page 1004) for a type 2 reaction.

Alongside that reaction there is decomposition of the anion by way of an anionic intermediate that becomes stabilized as the ketone:



$$CH_3COCH_2COO^- \xrightarrow[-CO_2]{\text{Slow}} [CH_3COCH_2^- \longleftrightarrow CH_3{-}\underset{\displaystyle O^-}{\underset{|}{C}}{=}CH_2] \xrightarrow[\text{Fast}]{+H_2O} (CH_3)_2CO + HO^-$$

The intermediate carbanion or ketone enol can be trapped by carrying out the decarboxylation in the presence of bromine or iodine,[28] which leads to the formation of the bromo or iodo ketone; the rate of this reaction is unaffected by the concentration of oxo acid, whence it follows that the halogenation does not precede the decarboxylation; also halogenation is not subsequent to formation of the ketone, since the ketone is not halogenated under the conditions used for the decarboxylation. If then halogenation follows decarboxylation and precedes ketone formation, the only possibility is reaction of the short-lived intermediate carbanion or enol.

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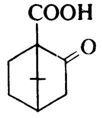
[27] F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, **63**, 3283 (1941).

[28] K. J. Pederson, *J. Amer. Chem. Soc.*, **51**, 2098 (1929); **58**, 240 (1936).

This further provides an explanation of the fact that it is very difficult to decarboxylate bicyclic β-oxo acids whose carboxyl group is attached at a bridgehead, as in ketopinic acid:



in such cases, steric grounds prevent formation of an enolic form of the decarboxylation product, in accord with Bredt's rule.

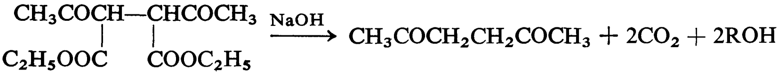
Decarboxylation of β-oxo acids is catalysed in particular by small amounts of a weak base. Thus, oxaloacetic acid, which is only slowly decarboxylated to pyruvic acid in boiling alcoholic solution, evolves carbon dioxide at room temperature on addition of a small amount of pyridine.

However, in strongly alkaline solution, β-oxo acids are not decarboxylated but undergo acid fission (see page 1047).

Preparative use can be made of both methods of catalytically influencing the reaction: either (a) dilute aqueous or alcoholic alkali hydroxide or dilute aqueous alkali carbonate solution or (b) dilute acid can be used.

It should also be noted that decarboxylation of β-oxo acids is subject to specific catalysis by primary amines as well as to general catalysis. For example, the very smooth decarboxylation of 2,2-dimethylacetoacetic acid in water is uninfluenced by addition of a secondary or tertiary amine but its rate is increased by a factor of 10 on addition of aniline. The explanation lies in the fact that primary amines can react to form β-imino acids, whose imino-nitrogen atom, being considerably more strongly basic than the ketonic oxygen atom, causes almost complete transfer of the proton from the carboxyl group, and it is this transfer that initiates the decomposition. A further example is the violent decomposition to acetone and carbon dioxide that occurs when a small amount of aniline is added to acetonedicarboxylic acid.

The ketone fission of β-oxo acids has great practical importance for the synthesis or ketones of the general type RCOCHR'R''. Starting materials are suitably substituted β-oxo esters, which are first hydrolysed and then decarboxylated. For example, Knorr prepared 2,5-hexanedione from diethyl 2,3-diacetylsuccinate as follows:[29]



$$\begin{array}{ll}\mathrm{CH_3COCH{-}} & \mathrm{CHCOCH_3} \\ \quad\,| & \quad| \\ \mathrm{C_2H_5OOC} & \mathrm{COOC_2H_5}\end{array} \xrightarrow{\mathrm{NaOH}} \mathrm{CH_3COCH_2CH_2COCH_3} + 2\mathrm{CO_2} + 2\mathrm{ROH}$$

2,5-Hexanedione (acetonylacetone): Exactly 3% (titrated) sodium hydroxide solution (100 ml) is poured over diethyl 2,3-diacetylsuccinate (10 g), a soda-lime tube is attached to the flask, and the whole is heated on a water-bath until after 2–3 h no diacetylsuccinate is precipitated on acidification of a sample. The mixture is allowed to cool, then saturated with potassium carbonate. Oily diketone separates and is removed. The alkaline layer is extracted twice with ether, and these extracts are united with the separated diketone and the mixture is dried and distilled. Much diketone distils with the ether, but if the foreruns are worked up a total yield of 90% (4 g) of 2,5-hexanedione, b.p. 194°, is obtained.

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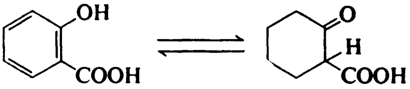
[29] L. Knorr, *Ber. Deut. Chem. Ges.*, **22**, 2100 (1889).

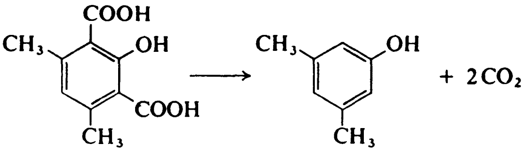
d. Aromatic hydroxy and amino carboxylic acids

Aromatic *o*-hydroxy carboxylic acids behave very similarly to *β*-oxo carboxylic acids; they sometimes lose carbon dioxide when merely boiled with water, but this is a general reaction when they are heated with pyridine, quinoline, aniline, or dimethylaniline. This behavior can certainly be ascribed to reaction of aromatic *o*-hydroxy acids as the keto tautomer:



As examples, *β*- and *γ*-resorcylic acid afford resorcinol readily when boiled with water.[30]

When there are two carboxyl groups in *ortho*-position to a hydroxyl group, both are split off at the same time; thus 3,5-xylenol is obtained in 90% yield when 2-hydroxy-4,6-dimethylisophthalic acid is heated in quinoline at 160 to 210° until gas evolution ceases:[31]

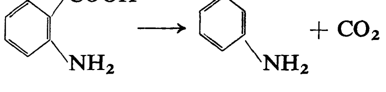


Pyridonecarboxylic and *o*-hydroxyquinolinecarboxylic acids can be similarly decarboxylated. 4-Hydroxy-3-quinolinecarboxylic acid, for example, can be converted into **4-quinolinol** by either of the two following methods:[32]

(1) The dry powdered acid is heated at its melting point in a metal-bath until evolution of carbon dioxide ceases. The crude 4-quinolinol is dissolved in ethanol and decolorized by charcoal. The product obtained on evaporation of the alcohol is further purified by recrystallization.

(2) The acid is added to five times its amount of "Dowtherm," and the mixture is heated until all the acid has dissolved (about 30 min). After cooling, the solution is diluted with twice its volume of hexane, and the precipitated product is purified as above.

o-Amino carboxylic acids show a similar tendency to decarboxylation. For instance, anthranilic acid decomposes completely to aniline and carbon dioxide when heated rapidly to about 210°; and the same decomposition occurs when the acid is boiled with water:[33]



Analogous *p*-hydroxy and *p*-amino carboxylic acids can be decarboxylated under similar conditions, as in their keto and imino forms they can be regarded

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[30] F. von Hemmelmayer, *Monatsh. Chem.*, **46**, 144 (1925).

[31] V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 675 (1947).

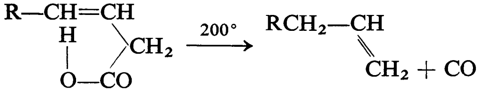
[32] B. Riegel, *J. Amer. Chem. Soc.*, **68**, 1264 (1946).

[33] L. McMaster and R. L. Shriner, *J. Amer. Chem. Soc.*, **45**, 751 (1923).

as vinylogous β-oxo acids. The corresponding *m*-hydroxy and *m*-amino carboxylic acids, however, are largely stable on thermal treatment, as is benzoic acid.

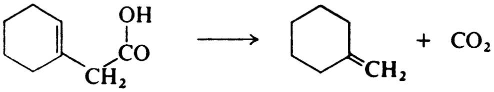
e. β,γ-Unsaturated acids

Decarboxylation of β,γ-unsaturated acids closely resembles that of β-oxo acids; here too a cyclic transition state can be assumed, this being guaranteed by the similar behavior of an olefinic double bond and a NH_3^+ group. It is in agreement with this formulation that a double bond shift occurs during the decarboxylation:



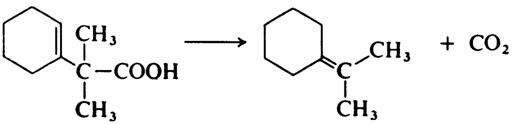
For such decarboxylations, however, the reaction conditions must be rather rigidly controlled because neither can true zwitterions be formed nor can appreciable proton transfer to the γ-carbon atom be induced by intramolecular hydrogen bonding.

As an example, methylenecyclohexane is obtained as decarboxylation product on distillation of 1-cyclohexeneacetic acid:[34]



The reaction mechanism proposed requires that migration of the double bond accompanies the decarboxylation.

Moreover, it is quite certain that the double bond does not migrate before the decarboxylation by three-carbon tautomerism $—CH{=}CH—CH_2— \rightleftharpoons —CH_2—CH{=}CH—$ (this usually requires base catalysis but can also occur without a catalyst at temperatures above 200°); the migration occurs only when allied to elimination of carbon dioxide, as is shown by the fact that it takes place also when α,α-dimethyl-1-cyclohexeneacetic and 2,2-dimethyl-3-butenoic acid are decarboxylated although neither of these acids possesses a vinylic hydrogen atom:



$$CH_2{=}CH—C(CH_3)_2COOH \longrightarrow CH_3CH{=}C(CH_3)_2 + CO_2$$

Analogous carboxylic acids containing conjugated double bonds can also often be decarboxylated, the conjugation being no longer present in the product:

$$C{=}C—C{=}C—C—COOH \xrightarrow[-CO_2]{} C{=}C—C—C{=}CH$$

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[34] F. Šorm and J. Beranek, *Chem. Listy*, **47**, 708 (1953); *Chem. Abstr.*, **49**, 194 (1955).

On the other hand, 4-phenyl- and 2,2-dimethyl-4-phenyl-3-butenoic acid are very stable thermally, the reason being that in these cases the loss of conjugation that would result from decarboxylation would be energetically a very unfavorable process.

f. α,β-Unsaturated acids

In many cases the decarboxylation of α,β-unsaturated acids probably takes the same course as that of β,γ-unsaturated carboxylic acids.[35] This would require that these α,β-unsaturated acids first rearrange to the β,γ-unsaturated isomers and that the latter are then decarboxylated in the manner described above. Indeed it could be shown that various α,β-unsaturated acids are in dynamic equilibrium with the corresponding β,γ-unsaturated acids at the temperatures required for decarboxylation provided that the interconversion requires only a shift of a vinylic proton:[36]

$$RCH_2CH{=}CR'COOH \overset{200°}{\rightleftarrows} RCH{=}CHCHR'COOH \longrightarrow RCH_2CH{=}CHR' + CO_2$$

The decarboxylation, which appears to occur without migration of the double bond, actually involves two migrations, of which the second is the reverse of the first. It would then be expected that an α,β-unsaturated acid that is unable to rearrange to the β,γ-unsaturated isomer by a proton shift would be difficult to decarboxylate, and in fact *tert*-butylacrylic acid (4,4-dimethyl-2-pentenoic acid) remains unchanged when heated for 2 hours at 200° because it does not contain allylic hydrogen:[35]

$$(CH_3)_3CCH{=}CHCOOH$$

However, there are other α,β-unsaturated acids that cannot undergo three-carbon tautomerism and yet can be very easily decarboxylated; the commonest examples are acids of cinnamic acid type — they can be converted into styrenes:[37]

$$C_6H_5CH{=}CHCOOH \longrightarrow C_6H_5CH{=}CH_2 + CO_2$$

Styrene: Dry cinnamic acid, together with a little hydroquinone as antioxidant, is vigorously boiled in a round-bottomed flask carrying a fractionating column attached to a descending condenser, the dimensions of the assembly being such that the temperature at the head of the column reaches 120°. Styrene collects in a receiver to which also a little hydroquinone has been added as stabilizer; this material is distilled in steam, and the colorless oil obtained is dried over calcium chloride and distilled under diminished pressure (b.p. 44–46°/40 mm; yield 38–41%).

Recent studies have made it very probable that such decarboxylations are bimolecular and not unimolecular.[38] S_E2 reactions of this type occur preferably in acid solution, where the α-carbon atom of α,β-unsaturated acids are protonated before the original carbon–carbon bond between the carboxyl group and the α-carbon atom is broken. Decarboxylations of this type thus involve, not carbanion intermediates, but carbonium intermediates having the

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[35] R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Amer. Chem. Soc.*, **72**, 4359 (1950).

[36] R. P. Linstead and co-workers, *J. Chem. Soc.*, **1925**, 616; **1929**, 2153; **1930**, 1603.

[37] T. W. Abbott and J. R. Johnson, *Org. Syn.*, **8**, 84 (1928).

[38] W. S. Johnson and W. E. Heinz, *J. Amer. Chem. Soc.*, **71**, 2913 (1949); H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 514 (1948).

charge on the β-carbon atom; the reaction is then favored by electron-donating substituents or aryl groups at the β-position, as these will tend to stabilize the carbonium intermediate. An example is 3,3-diphenylacrylic acid:

$$(C_6H_5)_2C{=}CHCOOH + H^+ \longrightarrow (C_6H_5)_2C^+{-}CH_2COOH \longrightarrow$$
$$(C_6H_5)_2C{=}CH_2 + CO_2 + H^+$$

g. α-Oxo acids

The decarboxylation of α-oxo acids is often of greater preparative importance than the decarboxylations discussed above.

Decomposition of α-oxo acids at elevated temperatures does not, however, give only the aldehyde and carbon dioxide: there is a competing reaction in which carbon monoxide is eliminated with formation of the carboxylic acid containing one fewer carbon atoms than are in the starting acid.

$$CO + RCOOH \longleftarrow RCOCOOH \longrightarrow RCHO + CO_2$$

In the aliphatic series no other useful route has yet been found for the synthesis of aldehydes which is the outcome usually desired from this reaction. Results are, however, more favorable with aromatic oxo carboxylic acids: their thermal decomposition results in elimination of both carbon monoxide and carbon dioxide, but it can be directed towards formation of the aldehyde by decarboxylating the anils of the oxo acid;[39] these yield Schiff bases in the first place:

$$RCOCOOH \longrightarrow R'N{=}CRCOOH \longrightarrow RCH{=}NR' \longrightarrow RCHO$$

The usual procedure in practice is to boil the α-oxo acid with aniline until loss of water is complete; then the water and aniline are distilled off, the residue is taken up in mineral acids, which hydrolyse the Schiff base, and the aldehyde produced is then isolated. This can be exemplified by directions for preparation of **p-propylbenzaldehyde:**[40]

Ethyl (*p*-propylphenyl)glyoxylate (44 g), accessible in good yield from propylbenzene and ethoxalyl chloride by a Friedel–Crafts reaction, is hydrolysed to the acid by aqueous sodium hydroxide solution. Freshly distilled aniline (about 20 g, a slight excess) is poured over the crude acid in a Claisen flask, whereupon the solid anilinium salt is formed exothermally. When this salt is heated, water and carbon dioxide are split off with slight foaming. The residual yellowish liquid is then at once distilled in a vacuum, yielding a forerun at 205°/12 mm, followed by the Schiff base (32 g, *ca.* 72%). This base is next heated for 15 min on a water-bath with 25% sulfuric acid (150 ml). After cooling, the solution is extracted three times with ether, and the extracts are washed with sodium carbonate solution and with water, dried over sodium sulfate, and distilled, affording *p*-propylbenzaldehyde (14 g, 65%), b.p. 112–114°/13 mm. A higher-boiling fraction contains a considerable further amount of the aldehyde.

Another method of decarboxylating α-oxo acids makes use of the bisulfite compounds, the conversion of phthalonic acid into phthaldehyde described on page 1045 being an example of this.

The general picture is that α-oxo acids can be converted into aldehydes only if their keto groups are not enolizable. Most of the available starting materials

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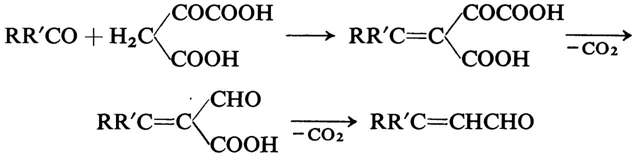
[39] L. Bouveault, *Bull. Soc. Chim. France*, [iii], **15**, 1020 (1896); **17**, 363 (1897).

[40] T. Siebenmark, Dissertation, Leipzig, 1940.

are thus aromatic oxo acids and others in which the carbonyl group is attached to an α,β-unsaturated group or to a tertiary carbon atom. The requisite excludes the preparation of aldehydes by decarboxylation of most of the α-oxo acids obtained by oxalic ester condensation, since the methylene components (esters, ketones, or nitriles) used in the ester condensation must contain at least two hydrogen atoms on the α-carbon atom. Decarbonylations of preparative interest are, for instance, the preparation of 2-oxocyclohexane carboxylic esters and monosubstituted malonic esters (see page 1023).

β,γ-Unsaturated α-oxo acids are not enolizable and can therefore be decarboxylated; they are mostly accessible by condensation of an aldehyde or ketone with oxaloacetic acid,[41] and this provides a route from a carbonyl compound to the α,β-unsaturated aldehyde containing two more carbon atoms:

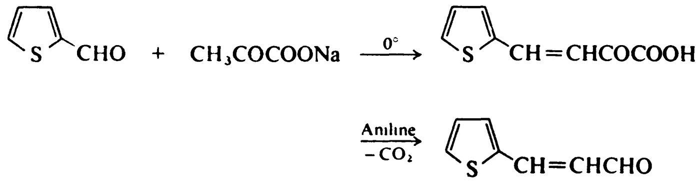


$$RR'CO + H_2C\begin{matrix}\diagup COCOOH\\ \diagdown COOH\end{matrix} \longrightarrow RR'C{=}C\begin{matrix}\diagup COCOOH\\ \diagdown COOH\end{matrix} \xrightarrow[-CO_2]{}$$

$$RR'C{=}C\begin{matrix}\diagup CHO\\ \diagdown COOH\end{matrix} \xrightarrow[-CO_2]{} RR'C{=}CHCHO$$

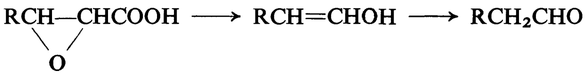
For example, β-methylcinnamaldehyde has been obtained in this way from acetophenone, and β-ionylideneacetaldehyde from β-ionone.[41]

Equally effective syntheses can be achieved by condensing, especially, aromatic aldehydes with sodium pyruvate, *e.g.*, 3-(2-thienyl)acrylaldehyde from 2-thiophencarbaldehyde:[42]

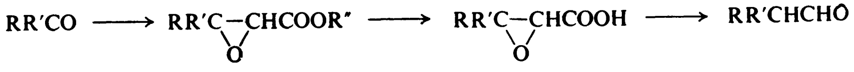


h. Glycidic acids

Glycidic acids (which are isomeric with α-oxo acids) can also be cleaved to an aldehyde and carbon dioxide either thermally or by the action of acids:



Since glycidic esters can usually be prepared from carbonyl compounds and chloroacetic esters, hydrolysis of the ester group and decarboxylation of the resulting glycidic acid gives as end-product the aldehyde containing one carbon atom more than those in the aldehyde or ketone:



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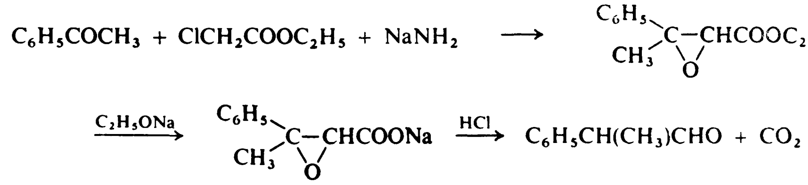
[41] D. A. Van Dorp and F. F. Arens, *Rec. Trav. Chim.*, **67**, 459 (1948).

[42] R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 1720 (1951).

Conversion of the glycidic ester into the aldehyde is usually performed in two steps: the ester is first hydrolysed by aqueous or alcoholic alkali, and the glycidic acid is then cleaved by heating with dilute hydrochloric acid or thermally in a vacuum in the presence of copper or copper chromite.

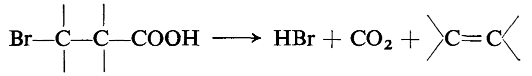
2-Phenylpropionaldehyde:[43] Ethyl methylphenylglycidate,[44] which is readily obtained from acetophenone and ethyl chloroacetate, is hydrolysed by sodium ethoxide. The resulting sodium methylphenylglycidate solution is then added to dilute hydrochloric acid, and the whole is warmed cautiously. Carbon dioxide is evolved and the aldehyde is precipitated.



A variation that is preparatively useful is to treat a glycidic acid with pyridine tribromide and semicarbazide, which on decarboxylation leads to the α,β-unsaturated aldehyde.[45]

i. Grob fragmentation

Decarboxylating elimination has been observed with β-bromo carboxylic acids:



$$\mathrm{Br{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}COOH} \longrightarrow \mathrm{HBr} + \mathrm{CO_2} + {>}\mathrm{C{=}C}{<}$$

Insofar as such decarboxylations with β-elimination occur by an *E*2 mechanism they are very highly stereospecific. Thus *trans*-2,3-dibromo-3-phenylpropionic acid is decarboxylated in acetone homogeneously to *cis*-bromostyrene. If this reaction is carried out in water, *E*1 elimination preponderates and *trans*-bromostyrene is the main product (78%) along with 22% of the *cis*-isomer. Bulky substituents on the two carbon atoms participating in the β-elimination occasionally hinder such decarboxylating eliminations.

All decarboxylations occurring with β-elimination can be considered as Grob fragmentations.[46]

α,β-Unsaturated β-halo carboxylic acids can also be decarboxylated and afford acetylene derivatives.[47] When studying the decarboxylation of these acids Grob found that the *cis*-acids reacted faster and more homogeneously than their *trans*-isomers: the latter formed methyl ketones as well as the acetylene derivative. Grob therefore proposed two mechanisms: for the *cis*-series a one-stage fragmentation in which removal of carbon dioxide is synchronous with that of the halide ion; for the *trans*-series a two-stage mechanism in which the bromide ion is first eliminated, giving a zwitterion that either

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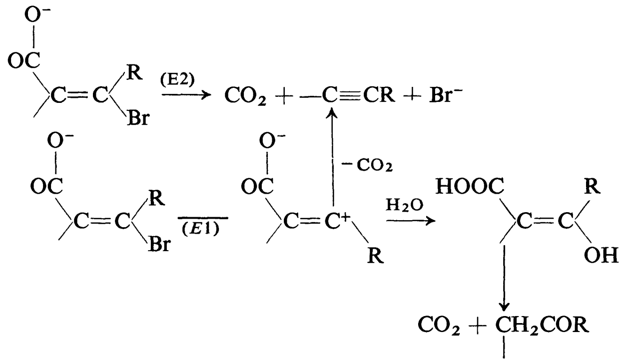
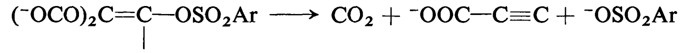
[43] C. Allan and J. van Allan, *Org. Syn.*, **24**, 87 (1944).
[44] C. Allan and J. van Allan, *Org. Syn.*, **24**, 82 (1944).
[45] R. B. Woodward and co-workers, *J. Amer. Chem. Soc.*, **78**, 3087 (1956).
[46] C. A. Grob, *Helv. Chim. Acta*, **38**, 594 (1955).
[47] C. A. Grob, J. Csapilla, and G. Csech, *Helv. Chim. Acta*, **47**, 1590 (1964).

generates an acetylene derivative by loss of carbon dioxide or adds water to form a β-oxo acid, the latter product then being decarboxylated to the methyl ketone under the reaction conditions used.



Fleming and Harley-Mason[48] showed that enol arenesulfonates fragment with decarboxylation to afford acetylenic carboxylic acids even under "physiological" conditions:



$$({}^-OCO)_2C{=}\underset{|}{C}{-}OSO_2Ar \longrightarrow CO_2 + {}^-OOC{-}C{\equiv}C + {}^-OSO_2Ar$$

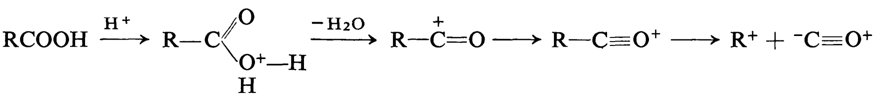
The decarboxylation of diazotized anthranilic acid carried out by Stiles and Miller[49] is also a fragmentation reaction; it affords dehydrobenzene (benzyne), which reacts at once as a dienophile with, *e.g.*, furan, giving 1-naphthol by way of an epoxide.

II. Removal of carbon monoxide

Decarbonylations can occur by either an ionic or a radical mechanism. The former mechanism is involved in reactions catalysed by acids, Lewis acids, or bases, and the latter in chain reactions induced thermally, photolytically, or by some other radical-forming process.

1. Heterolytic decarbonylation

Heterolytic decarbonylation is undergone by various carboxylic acids and carboxylic acid derivatives such as acid chlorides and esters provided that they are convertible by, *e.g.*, very strong acids into acyl cations; the cations then eliminate carbon monoxide provided that the group R is such that it can be stabilized by loss of a proton or that the electron deficiency resulting from elimination of carbon monoxide can be made good in some way:



$$RCOOH \xrightarrow{H^+} R{-}C\begin{matrix}{\nearrow O}\\{\searrow \underset{H}{O^+}{-}H}\end{matrix} \xrightarrow{-H_2O} R{-}\overset{+}{C}{=}O \longrightarrow R{-}C{\equiv}O^+ \longrightarrow R^+ + {}^-C{\equiv}O^+$$

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[48] I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, **1963**, 4771; *Proc. Chem. Soc.*, **1961**, 245.

[49] M. Stiles and R. G. Miller, *J. Amer. Chem. Soc.*, **82**, 3802 (1960).

This decarbonylation mechanism is involved in the following reactions:

Oxalic acid decomposes to carbon monoxide, carbon dioxide, and water when heated alone above 100° or when treated with concentrated sulfuric acid.

Oxalyl chloride decomposes to carbon monoxide and phosgene when gently warmed with aluminum chloride:[50]

$$(COCl)_2 + AlCl_3 \longrightarrow [^{+}O{\equiv}C{-}COCl]\,[AlCl_4^{-}] \longrightarrow$$

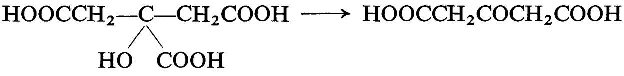
$$CO + [O{=}\overset{+}{C}{-}Cl]\,[AlCl_4^{-}] \longrightarrow AlCl_3 + COCl_2$$

Intermediates analogous to the carboxonium salt formulated in the preceding example are also formed during Friedel–Crafts acylations and these can undergo decarbonylation, so that reaction of an aromatic compound with an acid chloride may result in alkylation instead of acylation; for example, 2,2-dimethylpropionyl chloride reacts with aromatic compounds in the presence of aluminum chloride to some extent in accord with the formulation:

$$(CH_3)_3CCOCl \xrightarrow[-CO]{AlCl_3} (CH_3)_3C^{+} \xrightarrow{ArH} ArC(CH_3)_3$$

This side reaction is very largely repressed if the aromatic compound is very reactive, since the greater its reactivity the more likely it is to react with the acyl cation before decarbonylation of the latter can occur. Thus, reaction of 2,2-dimethylpropionyl chloride and aluminum chloride under the same conditions with benzene, toluene, and anisole gives about 90%, 50%, and 10%, respectively, of carbon monoxide.[51]

α-Hydroxy acids sometimes lose carbon monoxide and water when heated alone or in presence of concentrated sulfuric acid, yielding an aldehyde or ketone. Yields are often high (up to 90%), especially in the aliphatic series from C_5 upwards. Acetonedicarboxylic acid can be prepared from citric acid by this method:[52]



$$HOOCCH_2{-}\underset{HO\quad COOH}{C}{-}CH_2COOH \longrightarrow HOOCCH_2COCH_2COOH$$

Acetonedicarboxylic acid: Finely powdered citric acid is added in portions to 20% oleum at 0–10°. It dissolves rapidly and completely. When the solution is warmed slowly to 30°, carbon monoxide is evolved; when this evolution ceases, the liquid is cooled again to 0° and crushed ice is added, the temperature being allowed to rise slowly to 25–30°. The mixture is then cooled again to 0° and filtered through a fritted filter. The solid is moistened several times with a little ethyl acetate, being sucked dry after each addition. This affords 92–97% of acetonedicarboxylic acid. The acid is stable only for a few hours and further reactions with it should be carried out immediately.

When the degradation of an α-hydroxy acid to the aldehyde containing one fewer carbon atoms is unsatisfactory, the acetoxy acid or, better, according to Darzens[53] the α-alkoxy carboxylic acid may be used. This procedure was used, for instance, for preparation of heptadecanal: 2-bromostearic acid,

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[50] H. Staudinger, *Ber. Deut. Chem. Ges.*, **41**, 3566 (1908).

[51] E. Rothstein and R. W. Saville, *J. Chem. Soc.*, **1949**, (1946).

[52] R. Adams, H. M. Chiles, and C. F. Rassweller, *Org. Syn.*, **5**, 5 (1925).

[53] G. Darzens, *C. R. Hebd. Séances Acad. Sci.*, **196**, 348 (1933).

obtained by bromination of stearic acid, was converted by treatment with sodium methoxide into 2-methoxystearic acid, which afforded the desired aldehyde in almost quantitative yield when heated at 300°:

$$\mathrm{RCHBrCOOH} \longrightarrow \mathrm{RCH(OCH_3)COOH} \longrightarrow \mathrm{RCHO} + \mathrm{CO} + \mathrm{CH_3OH}$$

The α-bromo carboxylic acid required for preparation of the α-alkoxy acid is often obtained by a malonic ester synthesis: the malonic ester is treated with an alkyl halide, the alkylmalonic acid obtained by hydrolysis of the product is brominated by elemental bromine at a low temperature, and the resulting α-bromo dicarboxylic acid is decarboxylated.[54] This has led to a particularly important synthesis of aldehydes which utilizes the decarbonylation of α-hydroxy or α-alkoxy acids for conversion of an alkyl halide RX into the aldehyde RCHO containing one more carbon atom:

$$\mathrm{RX} + \mathrm{CH_2(COOR')_2} \longrightarrow \mathrm{CHR(COOR')_2} \longrightarrow \mathrm{CHR(COOH)_2} \longrightarrow$$
$$\mathrm{CRBr(COOH)_2} \xrightarrow[-\mathrm{CO_2}]{} \mathrm{CHRBrCOOH} \longrightarrow \mathrm{R''OCHRCOOH} \longrightarrow$$
$$\mathrm{RCHO} + \mathrm{CO} + \mathrm{R''OH}$$

The same objective can be achieved by treating an alkoxymalonic ester with the alkyl halide:[55]

$$\mathrm{C_2H_5OCH(COOR')_2} \xrightarrow{+\mathrm{RX}} \mathrm{C_2H_5OCR(COOR')_2} \longrightarrow$$
$$\mathrm{C_2H_5OCR(COOH)_2} \longrightarrow \mathrm{C_2H_5OCHRCOOH} \longrightarrow \mathrm{RCHO} + \mathrm{CO} + \mathrm{C_2H_5OH}$$

Very closely related to decarbonylation of an α-hydroxy acid is the Wohl degradation, in which an α-hydroxy aldehyde is degraded to the aldehyde with one fewer carbon atoms. This starts from the oxime, which is converted by removal of water into the hydroxy nitrile, whence elimination of hydrogen cyanide — analogous to that of carbon monoxide and water from an α-hydroxy acid — affords the lower aldehyde:

$$\mathrm{HOCHRCHO} \xrightarrow{\mathrm{NH_2OH}} \mathrm{HOCHRCH{=}NOH} \xrightarrow[-\mathrm{H_2O}]{}$$
$$\mathrm{HOCHRCN} \longrightarrow \mathrm{RCHO} + \mathrm{HCN}$$

This method of degradation has proved particularly valuable in the carbohydrate series. For example, glucose oxime, when heated with acetic anhydride and sodium acetate, gives penta-*O*-acetylgluconitrile whence hydrogen cyanide is removed either by silver oxide and ammonia according to the old method of Wohl[56] or more simply by sodium methoxide in a stirred chloroform solution at −12°; a final hydrolysis by dilute sulfuric acid gives about 65% of arabinose.[57]

Oxalo derivatives of aliphatic esters and ketones undergo decarbonylation similarly. These derivatives, readily obtained by ester condensation of ethyl oxalate with the appropriate methylene component (see page 962), are thermo-

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[54] E. Fischer and W. Schmitz, *Ber. Deut. Chem. Ges.*, **39**, 2208 (1906).

[55] G. Darzens, and M. Meyer, *C. R. Hebd. Séances Acad. Sci.*, **196**, 489 (1933).

[56] A. Wohl, *Ber. Deut. Chem. Ges.*, **26**, 734 (1893).

[57] G. Braun, *Org. Syn.*, **20**, 4 (1940).

labile and form monosubstituted malonic esters, with elimination of carbon monoxide, when heated above about 120°:

$$\mathrm{R'OOCCOCHRCOOR'} \longrightarrow \mathrm{CO} + \mathrm{CHR(COOR')_2}$$

Diethyl methylmalonate, for instance, is formed in 97% yield when diethyl 3-methyl-2-oxosuccinate is heated at 130° until evolution of carbon monoxide ceases.[58]

As mentioned above (page 1018), thermal decarbonylation of non-enolizable α-oxo carboxylic acids is preferably carried out with their anils, but it can also be effected by concentrated sulfuric acid. For example, phenylglyoxylic acid is cleaved to benzoic acid and carbon monoxide when gently warmed in concentrated sulfuric acid. Such decarbonylations catalysed by protonic acids are known also for normal carboxylic acids such as triphenylacetic[59] and 2,2-diarylpropionic acid;[60] in the first of these examples the triphenylmethyl cation formed on decarbonylation is stabilized as the alcohol when the mixture is poured into water or as an ether when the mixture is poured into an alcohol, but it was found that 1,1-diarylethylenes were also formed from the 2,2-diarylpropionic acids so that in this case stabilization by deprotonation also occurred.

Base-catalysed loss of carbon monoxide has occasionally been observed as well as the acid-catalysed decarbonylation. Such reactions include the decomposition of formic esters to carbon monoxide and alcohols under the influence of alkali alkoxides,[61] *e.g.*:

$$\mathrm{HCOOC_2H_5} \longrightarrow \mathrm{CO} + \mathrm{C_2H_5OH}$$

They include also the degradation of α-amino acid chlorides by aqueous alkali, an example of which is the conversion of *N*-(benzenesulfonyl)-α-phenylglycyl chloride by sodium hydroxide into benzenesulfonamide, benzaldehyde, and carbon monoxide:

$$\mathrm{ArSO_2NHCH(C_6H_5)COCl} \xrightarrow[-\mathrm{H_2O}]{\mathrm{HO^-}} \mathrm{ArSO_2N^-{-}CH(C_6H_5)\overset{+}{C}O} + \mathrm{Cl^-}$$

$$\longrightarrow \mathrm{ArSO_2N{=}CHC_6H_5} + \mathrm{CO} \longrightarrow \mathrm{ArSO_2NH_2} + \mathrm{C_6H_5CHO}$$

Only those arenesulfonylamino acid chlorides undergo this reaction that carry at least one alkyl or aryl group at the α-position to the carbonyl group,[62] and tosylglycyl chloride cannot be degraded in this way.

The corresponding azides react similarly but with evolution of nitrogen in place of carbon monoxide:

$$\mathrm{ArSO_2NHCHRCON_3} \xrightarrow{\mathrm{HO^-}} \mathrm{ArSO_2NH_2} + \mathrm{RCHO} + \mathrm{N_2} + \mathrm{NCO^-}$$

α,α,*N*-Triphenylglycine is converted by *p*-toluenesulfonyl chloride and pyridine into benzophenone anil, carbon monoxide, and pyridinium *p*-toluene-

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[58] R. Cox and S. M. McElvain, *Org. Syn.*, **17**, 56 (1937).

[59] H. D. Dittmar, *J. Chem. Phys.*, **33**, 533 (1929).

[60] C. M. Welch and H. A. Smith, *J. Amer. Chem. Soc.*, **75**, 1412 (1953).

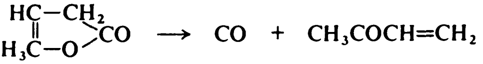
[61] F. A. Dickens and G. Schäfer, *Chem. Ber.*, **65**, 950 (1932); J. A. Christiansen and J. C. Gjaldbaek, *Kgl. Danske Videnskab. Selskab., Math.-fys. Medd.*, **20**, No. 3 (1942); *Chem. Abstr.*, **38**, 38 986 (1944).

[62] A. F. Beecham, *J. Amer. Chem. Soc.*, **79**, 3257 (1957).

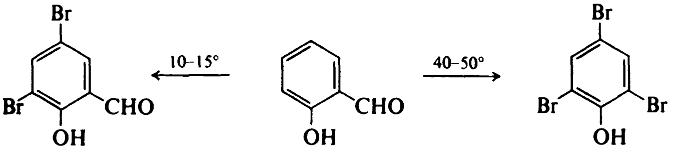
sulfonate, a reaction that is comparable with the degradation of acylamino acid chlorides and probably occurs by way of an unusual mixed anhydride.[63]

The following observations should also be included among the heterolytic decarbonylations:

The enol lactone of levulic acid is cleaved to carbon monoxide and an unsaturated ketone when heated with pieces of silica at 570°:[64]



When *o*- or *p*-hydroxy (or amino)benzaldehyde is titrated with bromine in aqueous solution at 40–45° 2,4,6-tribromophenol or -aniline is obtained almost quantitatively; the aldehyde group is not oxidized to carboxyl but replaced by bromine; it is eliminated as carbon monoxide which originates from decomposition of formyl bromide that is formed as intermediate.[65] At 10° and 15°, respectively, these hydroxy and amino aldehydes are, however, merely converted into the dibromo aldehydes with retention of the CHO group, *e.g.*:



2. Radical decarbonylation

Although not of much real preparative interest, radical decarbonylation has been observed with a large number of aldehydes and ketones at high temperatures and/or under ultraviolet irradiation or in the presence of peroxides. For example, carbon monoxide is eliminated in 90% yield when 3-methyl-3-phenylbutanal is heated for five hours at 130° in the presence of di-*tert*-butyl peroxide; fractionation of the residue then affords 70% of a 1 : 1 mixture of *tert*-butyl- and isobutyl-benzene, so that the *β*,*β*-dimethylphenethyl radical formed on elimination of carbon monoxide from the $C_6H_5C(CH_3)_2CH_2CO$— radical must be assumed to have partially rearranged.[66]

When this experiment is carried out at 80° under otherwise identical conditions no carbon monoxide or butylbenzene is formed; the acyl radical is stable at this temperature and reacts with carbon tetrachloride to give the acid chloride or with an olefin to give a ketone.

Aromatic aldehydes can be decarbonylated even at the boiling point in the presence of palladium–charcoal; although the products are almost always accessible more easily by other routes, the high yields (61–94%) of the decarbonylation are remarkable.[67]

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[63] J. C. Sheehan and J. W. Frankenfeld, *J. Org. Chem.*, **27**, 628 (1962).

[64] Brit. Pat. 601,922; *Chem. Abstr.*, **42**, 7319 (1948).

[65] A. W. Francis and A. J. Hill, *J. Amer. Chem. Soc.*, **46**, 2498 (1924).

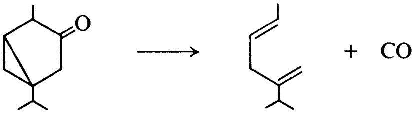
[66] S. Winstein and F. H. Seubold, Jr., *J. Amer. Chem. Soc.*, **69**, 2917 (1949).

[67] J. O. Hawthorne and M. H. Wilt, *J. Org. Chem.*, **25**, 2215 (1960).

It has proved useful to carry out radical decarbonylation of aldehydes in the presence of small amounts of toluene-α-thiol, which apparently represses chain cleavage.[68] For instance, it has been found that in the absence of toluene-α-thiol 2-ethylhexanal gives only 9% of heptane after ultraviolet irradiation for 20 hours at 140°, whereas in presence of the thiol it affords 55% of heptane in 7 hours under otherwise similar conditions.

Analogous decarbonylations have been observed for ketones under ultraviolet irradiation at elevated temperatures. From a preparative point of view the behavior of α,α-diphenyl-substituted and α,α-divinyl-substituted ketones is interesting, as they are decarbonylated when their benzene solutions are subjected to ultraviolet irradiation.[69] This favorable effect of phenyl substitutents on decarbonylation has been noted also for cyclic ketones: for example, under suitable conditions 1-phenyl-2-indanone eliminates carbon monoxide and yields 90% of 5,6,11,12-tetrahydro-5,6-diphenyldibenzo[*a*,*e*]cyclooctene as a mixture of *cis*- and *trans*-forms,[70] whereas 2-indanone itself is hardly decarbonylated at all in benzene solution. That in other cases decarbonylation is usually more profitable in the gas than in the liquid phase is shown by studies of the photolysis of tetramethyl-1,3-cyclobutanedione which in the gas phase gives 2 equivalents of carbon monoxide and a quantitative yield of 2,3-dimethyl-2-butene.[71]

In some quite special cases decarbonylation of ketones assumes real preparative importance; *e.g.*, ultraviolet irradiation converts thujone into carbon monoxide and 2-isopropyl-1,4-hexadiene readily and unusually rapidly:[72]



Photolysis of α-oxo carboxylic esters takes an unusual course:[73] in contrast to the result of heterolytic decarbonylation, this type of compound yields, alongside carbon monoxide, a ketone and an aldehyde, and not the carboxylic ester containing one fewer carbon atoms; the reaction can be generalized as follows, where R = alkyl or aryl and R′ and R″ = alkyl and/or H:

$$\mathrm{RCOCOOCHR'R''} \longrightarrow \mathrm{CO + RCHO + COR'R''}$$

Diene syntheses in which cyclopentadienone is the diene component give, as primary products, ketones whose decarbonylation is a radical reaction similar to those discussed above; these Diels–Alder adducts contain a bridging carbonyl group which is readily eliminated as carbon monoxide when the

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[68] S. G. Cohen, J. D. Berman, and S. Orman, *Tetrahedron Lett.*, **1962**, 43.

[69] G. Quinkert, K. Opitz, W. W. Wiersdorf, and J. Weinlich, *Tetrahedron Lett.*, **1963**, 1863.

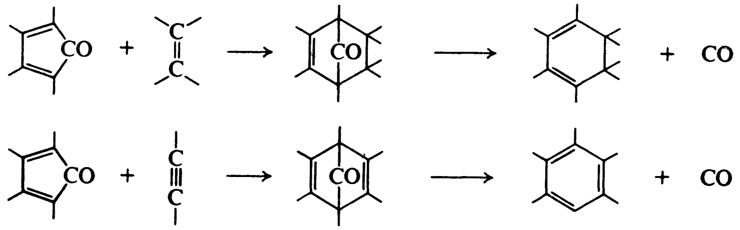
[70] G. Quinkert, K. Opitz, and J. Weinlich, *Angew. Chem.*, **74**, 507 (1962).

[71] N. J. Turro, G. W. Byers, and P. A. Leermakers, *J. Amer. Chem. Soc.*, **86**, 955 (1964).

[72] R. H. Eastman, J. E. Starr, R. S. Martin, and M. K. Sakata, *J. Org. Chem.*, **28**, 2162 (1963).

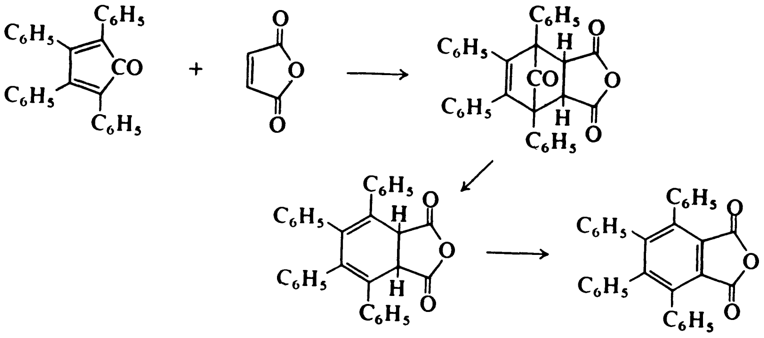
[73] P. A. Leermakers, P. C. Warren, and G. T. Vesley, *J. Amer. Chem. Soc.*, **86**, 1768 (1964); G. S. Hammond, P. A. Leermakers, and N. J. Turro, *J. Amer. Chem. Soc.*, **83**, 2395 (1961).

products are heated; derivatives of dihydrobenzene or of benzene are thus obtained according as the diene synthesis was effected with an olefinic or an acetylenic component:[74]



If the olefinic component contains hydrogen on each of the doubly bonded carbon atoms, then loss of carbon monoxide is frequently accompanied by dehydrogenation to an aromatic system.

Tetraphenylphthalic anhydride: Tetraphenylcyclopentadienone (tetracyclone) and maleic anhydride in boiling benzene give an almost quantitative yield of the normal adduct, 7-oxobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride. If this primary adduct is heated in chlorobenzene it loses carbon monoxide, passing into 1,2-dihydro-3,4,5,6-tetraphenylphthalic anhydride. If, finally, the condensation is carried out in boiling nitrobenzene the solvent acts as dehydrogenating agent and tetraphenylphthalic anhydride is produced directly. Thus this diene synthesis affords three different products according to the nature of the solvent used.



Hexaphenylbenzene can be obtained analogously from tetraphenylcyclopentadienone and tolane.

III. Removal of other fragments

Thermal cleavage of a carbon–carbon bond with formation of fragments other than carbon monoxide or carbon dioxide is relatively rarely of value on a laboratory scale. The examples described in the succeeding Subsections constitute cases that are worth noting.

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[74] W. Foerst, "Neuere Methoden der präparativen Chemie," Verlag Chemie, Weinheim, 1949, Vol. 1, p. 311.

1. Cleavage of ricinoleic acid

10-Undecenoic esters and heptanal are formed in good yield when ricinoleic esters are cleaved pyrolytically:

$$CH_3{-}[CH_2]_5{-}CH(OH)CH_2CH{=}CH{-}[CH_2]_7COOR \longrightarrow$$

$$CH_3{-}[CH_2]_5CHO + CH_2{=}CH{-}[CH_2]_8{-}COOR$$

This reaction is reminiscent of the decarboxylation of β,γ-unsaturated acids. Experimentally, the process is carried out by transesterifying castor oil by methanol and sulfuric acid, dropping the crude methyl ester into a heat-transfer reagent at 500–600°, and fractionating the resulting distillate in a vacuum.[75]

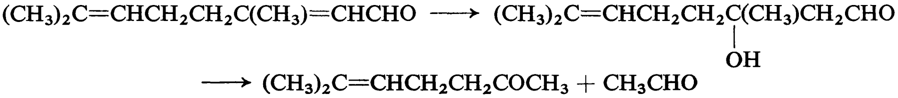
2. Alkoxide cleavage

Behavior similar to that of methyl ricinoleate (see the preceding paragraph) is observed also with other alcohols exposed to high temperatures in the presence of alkali alkoxides. However, for this to occur, the molecule must contain, near the alcoholic hydroxyl group, features ensuring that the polarity induced by the negative charge of the alkoxide ion leads to removal, as a carbon anion, of one of the groups attached to the carbon atom carrying the hydroxyl group.

This constitutional demand is met by β-oxo alcohols containing tertiary alcohol groups, for instance, diacetone alcohol which, when treated with an alkali under energetic conditions, is cleaved into two molecules of acetone:[76]

$$HOC(CH_3)_2CH_2COCH_3 \longrightarrow 2CO(CH_3)_2$$

This is a reversal of the aldol (or ketol) condensation; it assumes preparative importance in the fission of citral which, as an α,β-unsaturated aldehyde, is cleaved by boiling potassium carbonate solution into methylheptenone and acetaldehyde,[77] a reaction in which addition of water to give a tertiary alcohol must be assumed:



$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO \longrightarrow (CH_3)_2C{=}CHCH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}(CH_3)CH_2CHO$$

$$\longrightarrow (CH_3)_2C{=}CHCH_2CH_2COCH_3 + CH_3CHO$$

Under such conditions secondary alcohols rarely afford homogeneous products, as the aldehydes expected as primary products too readily undergo further reactions. Exceptionally, a preparatively useful application has been found in the degradation of aldose diethyl dithioacetals: these are oxidized by organic peracids or by hydrogen peroxide in the presence of ammonium molybdate to the disulfones which are cleaved at secondary alcohol groups by dilute ammonia solution.[78,79] This method has been applied to acetyl-

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[75] French Pat. 952,985; *Chem. Abstr.*, **45**, 7586 (1951).

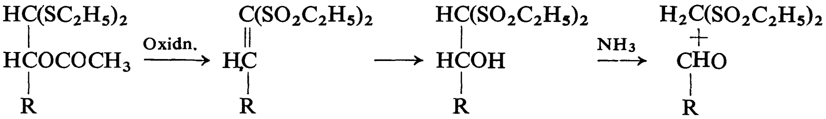
[76] L. Bouveault and R. Locquin, *Ann. Chim.* (*Paris*), [viii], **21**, 415 (1910); C. C. French, *J. Amer. Chem. Soc.*, **51**, 3215 (1929).

[77] M. A. Verley, *Bull. Soc. Chim. France*, [iii], **17**, 176 (1897); F. Tiemann, *Ber. Deut. Chem. Ges.*, **32**, 107 (1899).

[78] D. L. MacDonald and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **74**, 2087 (1952).

[79] J. Staněk, M. Cerny, J. Kocourek, and J. Pacák, "The Monosaccharides," Publishing House of the Czechoslovak Academy of Sciences, Prague, 1963, p. 128.

ated[78] and to non-acetylated[80] diethyl dithioacetals of hexoses,[80-82] pentoses,[83,84] and L-rhamnose,[85,86] as well as to fructose.[87]



$$\begin{array}{c} HC(SC_2H_5)_2 \\ | \\ HCOCOCH_3 \\ | \\ R \end{array} \xrightarrow{\text{Oxidn.}} \begin{array}{c} C(SO_2C_2H_5)_2 \\ \| \\ HC \\ | \\ R \end{array} \longrightarrow \begin{array}{c} HC(SO_2C_2H_5)_2 \\ | \\ HCOH \\ | \\ R \end{array} \xrightarrow{NH_3} \begin{array}{c} H_2C(SO_2C_2H_5)_2 \\ + \\ CHO \\ | \\ R \end{array}$$

β-D-Arabinose:[88] 1-Deoxy-1,1-bis(ethylsulfonyl)-D-mannitol (1 g) (prepared by oxidation of D-mannose diethyl dithioacetal with peroxypropionic acid in dioxan) is made into a slurry with water (10 ml), and then concentrated aqueous ammonia solution (1 drop) is added. The sulfone dissolves rapidly and after 30 min the precipitated diethyl methylene disulfone is filtered off. The filtrate is extracted four times with chloroform (10-ml portions), and the aqueous phase is evaporated in a vacuum at 40°. The residue is treated with hot methanol (5 ml) and after being kept for 24 h at 4° affords β-D-arabinose (0.32 g, 86%), $[\alpha]_D^{20}$ $-102°$ (*c* 3.5; at equilibrium in water).

α,β-Acetylenic alcohols are similarly cleaved to acetylene and a carbonyl compound, in a reversal of the Reppe synthesis, when heated with concentrated alkali hydroxide solutions. Propargyl alcohol, which can be prepared by addition of formaldehyde to acetylene, is cleaved by hot concentrated alkali hydroxide solutions into these components, although the formaldehyde produced reacts further at once to give alkali formate or carbonate:

$$HC{\equiv}C{-}CH_2OH \rightleftarrows CH{\equiv}CH + CH_2O$$

β-Hydroxy acids and α,β-unsaturated acids undergo a similar fission, the latter acids presumably being first converted into the former. The reaction affords, besides acetic acid, the carbonyl compound containing two fewer carbon atoms, and this product, if an aldehyde, is immediately converted into the derived acid by the dehydrating action of the alkali melt. The end effect is thus oxidative cleavage by concentrated alkali solution at an olefinic double bond, and the reaction is therefore treated on page 1037 as an oxidative cleavage of a carbon–carbon bond.

Heterolytic fragmentation affords a further cleavage reaction of hydroxylic compounds.[89] In this type of reaction a molecule of, *e.g.*, the general formula HO—C—C—C—X where X is an electron-attracting group, breaks up to three fragments $OC\langle$, $\rangle C{=}C\langle$, and X under the influence of a base. The degradation of 3-mesyl-D-glucose to 2-deoxy-D-ribose by sodium hydroxide

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[80] D. L. MacDonald and H. O. L. Fischer, *Biochim. Biophys. Acta*, **12**, 203 (1953).

[81] L. Hough and T. J. Taylor, *J. Chem. Soc.*, **1956**, 970.

[82] R. Barker and D. L. MacDonald, *J. Amer. Chem. Soc.*, **82**, 2297 (1960).

[83] L. Hough and T. J. Taylor, *J. Chem. Soc.*, **1955**, 1212.

[84] C. E. Ballou, H. O. L. Fischer, and D. L. MacDonald, *J. Amer. Chem. Soc.*, **77**, 5967 (1955).

[85] L. Hough and T. J. Taylor, *J. Chem. Soc.*, **1955**, 3544.

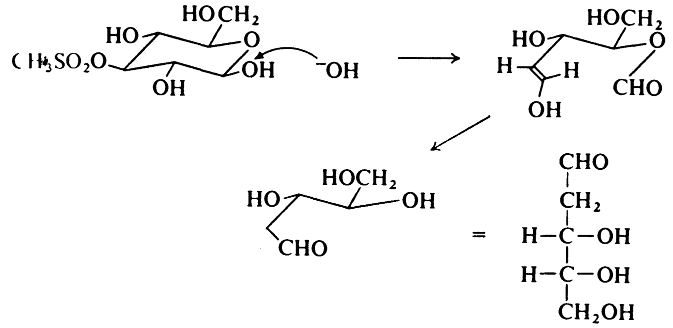
[86] E. L. Patterson, R. Milstrey, and E. L. R. Stokstad, *J. Amer. Chem. Soc.*, **78**, 5868 (1956).

[87] E. J. Bourne and R. Stephens, *J. Chem. Soc.*, **1954**, 4004.

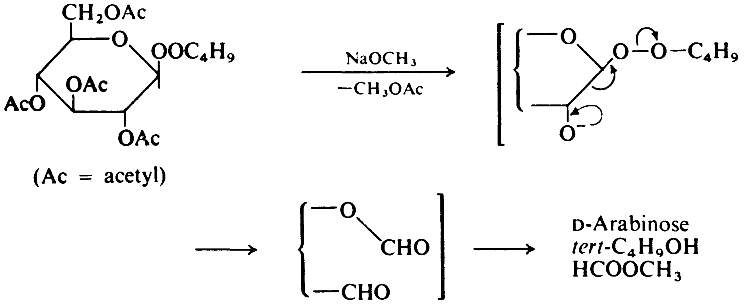
[88] D. L. MacDonald in R. L. Whistler and M. L. Wolfrom, "Methods in Carbohydrate Chemistry," Academic Press, New York, London, 1962, Vol. 1, p. 73.

[89] C. A. Grob and P. W. Schiers, *Angew. Chem. Int. Ed., Engl.*, **6**, 1 (1967).

solution[90,91] has been claimed as an interesting preparatively useful fragmentation reaction:



Particular preparative interest attaches to the somewhat similar carbohydrate degradation described by Schulz and his co-workers,[92] in which, for example, *tert*-butyloxy tetra-*O*-acetyl-β-D-glucopyranoside (a peroxyglycoside) is converted quantitatively into D-arabinose in a five-centre fragmentation initiated by catalytic amounts of sodium methoxide:



General procedure: An acylated *tert*-butyl peroxyglycoside (4 mmoles) is left in 0.005 to 0.01N-methanolic sodium methoxide solution (50 ml) at room temperature until paper chromatography shows complete degradation of the peroxyglycoside (about 24 h). Warming to 40–50° accelerates the reaction considerably. The solution is then treated with the cation-exchanger Wofatit F, whereafter all the volatile materials (methanol, methyl acetate and formate, and *tert*-butyl alcohol) are removed in a vacuum. The residue is a paper-chromatographically pure carbohydrate containing one fewer carbon atoms than the starting material.

The Haller–Bauer reaction is mechanistically related to alkoxide fissions. In this reaction a non-enolizable ketone is cleaved by sodamide into an amide and a hydrocarbon:[93]

$$\mathrm{CORR'} + \mathrm{NH_2^-} \rightleftarrows \mathrm{RR'C(NH_2)O^-} \rightleftarrows \mathrm{R^-} + \mathrm{R'CONH_2} \longrightarrow \mathrm{RH} + \mathrm{R'CONH^-}$$

This type of reaction has some preparative value, especially for the preparation of trisubstituted acetamides and the amines derivable from them by Hofmann

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[90] D. C. C. Smith, *Chem. & Ind. (London)*, **1955**, 92.

[91] E. Hardegger, M. Schellenbaum, R. Huwyler, and A. Züst, *Helv. Chim. Acta*, **40**, 1816 (1957).

[92] M. Schulz, H.-F. Boeden, and P. Berlin, *Ann. Chem.*, **703**, 190 (1967).

[93] K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 2 (1957).

or Curtius degradation. However, its most important application is for cleavage of aliphatic or alicyclic phenyl ketones; for example, pivalamide can be obtained quantitatively from *tert*-butyl phenyl ketone by means of sodamide in boiling benzene; and 1-methylcyclohexanecarboxamide is obtained analogously in 88% yield from 1-methylcyclohexyl phenyl ketone.

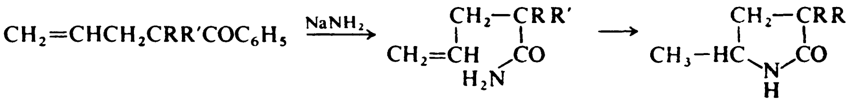
For the cleavage of trialkylacetophenones $CR^1R^2R^3COC_6H_5$ it has transpired that the reaction always proceeds normally when $R^1 = R^2 =$ methyl, even if R^3 is very large, *e.g.*, C_{18}, but that it does not give homogeneous products if only R^1 is a small alkyl group (CH_3 or C_2H_5) unless the sum $R^1 + R^2 + R^3$ is not less than C_{10}. This rule holds also for 1-alkyl-substituted alicyclic phenyl ketones.

On fission by sodamide, diketones of the type:

$$C_6H_5COCRR—[CH_2]_n—CRRCOC_6H_5$$

give α,α,α′,α′-tetraalkyl-α,ω-alkanedicarboxamides.

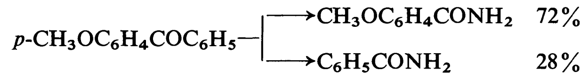
An interesting subsequent reaction has been observed for a series of 1,1-dialkyl-3-butenyl phenyl ketones: the resulting unsaturated carboxamides cyclize to pyrrolidone derivatives:



Various 3,3-dialkyl-5-methyl-2-pyrrolidones have been prepared in this way.

Non-enolizable aliphatic ketones are cleaved analogously. For example, pivalamide and isobutane are formed in good yield from hexamethylacetone (2,2,4,4-tetramethyl-3-pentanone). Most unsymmetrically substituted ketones afford the four possible products (2 amides and 2 hydrocarbons), but often in unequal amounts, *e.g.*, pivalamide and 2,2-diethylbutyramide in 5 : 1 proportions from 4,4-diethyl-2,2-dimethyl-3-hexanone. Hexaalkyl-substituted acetone derivatives containing branched alkyl groups generally do not react.

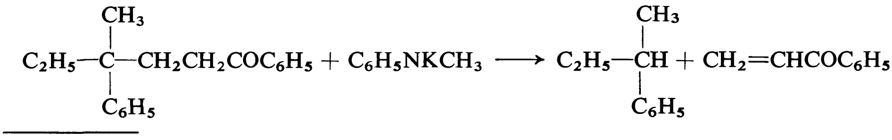
Diaryl ketones are also readily cleaved by sodamide. Benzophenone gives benzamide and benzene. Unsymmetrical diaryl ketones give mixtures, in which, however, the influence of the substituents is distinctly noticeable:



$$p\text{-}CH_3OC_6H_4COC_6H_5 — \begin{cases} \longrightarrow CH_3OC_6H_4CONH_2 & 72\% \\ \longrightarrow C_6H_5CONH_2 & 28\% \end{cases}$$

Of ditertiary cyclic ketones, substituted cyclopentanones are most readily cleaved: 2,2,5,5-tetramethylcyclopentanone affords 2,2,5-trimethylhexanamide when treated with sodamide, but the corresponding cyclohexanone is very resistant to this reagent.

For enolizable ketones, Cram and his co-workers[94] have shown that compounds of the type of 4-methyl-1,4-diphenyl-1-hexanone are cleaved by alkali *N*-alkylanilides at a carbon–carbon bond in the following way:



$$C_2H_5—\overset{\displaystyle CH_3}{\underset{\displaystyle C_6H_5}{C}}—CH_2CH_2COC_6H_5 + C_6H_5NKCH_3 \longrightarrow C_2H_5—\overset{\displaystyle CH_3}{\underset{\displaystyle C_6H_5}{CH}} + CH_2{=}CHCOC_6H_5$$

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[94] D. J. Cram, A. Langemann, J. Allinger, and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 5740 (1959).

The same reagent is even more successful for synthesis of a series of secondary and tertiary alcohols containing a 2-phenylbutyl group in a reaction involving electrophilic substitution on a saturated carbon atom:[94]

$$\text{HOCRR}'\text{R}'' + \text{C}_6\text{H}_5\text{NKCH}_3 \longrightarrow \text{RH} + \text{COR}'\text{R}''$$

$$(\text{R} = \text{2-phenylbutyl; R}' \text{ and R}'' = \text{alkyl, aryl, or H})$$

3. Ketene from acetone

Ketene and methane are obtained by pyrolytic decomposition of acetone. Quadbeck[95] has described an apparatus suitable for use in the laboratory (see Figures 5 and 6).

$$\text{CH}_3\text{COCH}_3 \longrightarrow \text{CH}_2\text{=CO} + \text{CH}_4$$

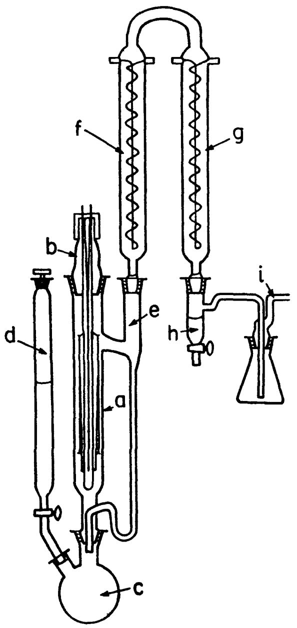

Figure 5. Apparatus for preparation of ketene from acetone (the ketene lamp).

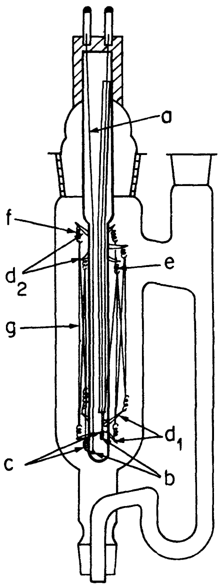

Figure 6. Detail of the ketene lamp (the pyrogenic chamber).

Acetone is boiled in a 1-l flask (*c*) (Figure 5), being introduced from a dropping funnel (*d*). The vapors pass into a reaction vessel (*a*) in which heating elements are suspended from a head (*b*). The vapors then pass into a condenser (*f*) where unchanged acetone condenses and returns through an adaptor (*e*) to the reaction flask (*c*). Ketene passes through a second condenser (*g*) and a separator (*h*) into a receiver (*i*), where it is either condensed (b.p. −41°) or used directly for further reaction.

The improvement introduced in this apparatus over previous proposals consists mainly in the elaboration of an efficient, durable heating element, details of which are illustrated in Figure 6. This element consists of ordinary chromium–nickel resistance wire (diameter

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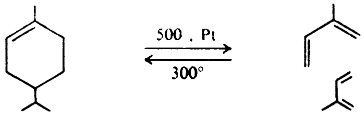
[95] G. Quadbeck, *Chem.-Ing.-Technol.*, **24**, 210 (1952); *Angew. Chem.*, **68**, 361 (1956).

0.4 mm), which is stretched over glass hooks and whose thermal expansion is taken up by V_2A (stainless) steel spiral springs. Current reaches these wires from the bottom, the leads coming from the head of the vessel; it is this arrangement which is said to prevent the undesirable deposition of carbon. The current is regulated by a resistance of about 30 ohms or by a transformer. The performance of this generator is strongly dependent on the current, and the optimum current must be maintained to prevent deposition of carbon. Details of the ketene generator in Figure 6 are: (*a*) copper leads, of which one is enclosed in a glass tube up to the point where it is sealed into glass; (*b*) short pieces of Kovar I wire soldered onto the copper wires for passage through glass; (*c*) V_2A steel clamps; (d_1), (d_2) glass hooks on which the heating wire is fastened; (*e*) V_2A steel springs to keep the heating wire under tension; (*f*) V_2A steel hooks.

Caution is necessary in work with ketene: it is an extremely **poisonous** gas which about equals phosgene in toxicity and causes approximately the same symptoms (edema of the lungs).

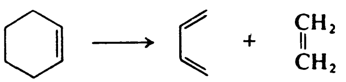
4. Cleavage of cyclohexene derivatives

A number of cyclohexene derivatives can be cleaved thermally to an olefin and a diene, preferably by passage in the vapor phase over red-hot metal wires. This is the reverse of the Diels–Alder diene synthesis. The oldest example is the formation of isoprene from dipentene described by Harries and Gottlob:[96]



They gave details of the apparatus, called an isoprene lamp and later used it for other purposes, in which dipentene vapors pass over an electrically heated platinum wire wound on a glass spindle in the same way as in old-fashioned metal wire lamps.

According to Harries,[97] butadiene can be obtained from cyclohexene[98] in a very similar way:



Using an apparatus constructed on the same principles, Ott and Schmidt[99] prepared carbon suboxide C_3O_2 by thermal decomposition of diacetyltartaric anhydride on a feebly glowing platinum catalyst — the nature of chemical reaction is obscure.

5. Conversion of lumisterol into tachysterol

Labile carbon–carbon bonds are sometimes cleaved, not merely at high temperatures, but on irradiation of the compound by ultraviolet light; thus, for instance, in the course of the photochemical conversion of ergosterol into

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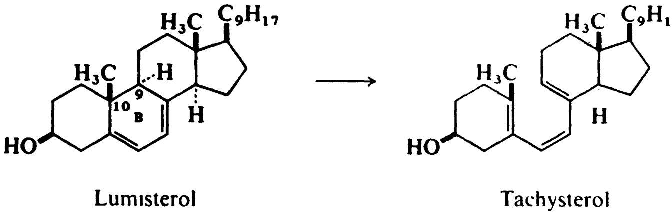
[96] C. D. Harries and K. Gottlob, *Ann. Chem.*, **383**, 228 (1911).

[97] C. D. Harries, "Untersuchungen über die natürlichen und künstlichen Kautschukarten," Springer-Verlag, Berlin, 1919, p. 142.

[98] F. B. Hershberg and J. R. Ruhoff, *Org. Syn.*, **17**, 25 (1937).

[99] E. Ott and K. Schmidt, *Ber. Deut. Chem. Ges.*, **55**, 2126 (1922).

vitamin D_2 the tetracyclic compound lumisterol is converted into the tricyclic compound tachysterol by fission of the 9,10-bond and introduction of a new double bond:



Various other steroids containing the same arrangement of double bonds in ring B undergo the same photochemical fission.[100]

1.2. Oxidative cleavage of carbon–carbon bonds

I. Oxidative cleavage of C–C bonds in alkenes and cycloalkanes

1. Manufacture of fatty acids for soaps by the Fischer–Tropsch–Gatsch process

Oxidative fission of a carbon–carbon bond of aliphatic hydrocarbons is generally devoid of preparative interest because the chain may be broken at various places and mixtures of carboxylic, dicarboxylic, and hydroxy carboxylic acids with other oxidation products are formed. If, however, certain experimental conditions are precisely maintained, alkanes of high molecular weight can be oxidized catalytically by air, *e.g.*, by the Fischer–Tropsch–Gatsch process, reasonably homogeneously to fatty acids of medium chain length (C_{10}–C_{18}), and this has assumed much industrial importance for the manufacture of soap.

Manufacture is carried out by blowing finely divided air into the paraffin containing, *e.g.*, a manganese salt as catalyst at about 100° and breaking off the reaction when about one-third of the hydrocarbon has been oxidized.

2. Oxidation of cyclohexane to adipic acid by nitric acid

Cycloalkanes are generally oxidized to straight-chain dicarboxylic acids only with great difficulty and then in poor yield. For example, on oxidation by nitric acid cyclohexane gives a mixture of 29% of adipic acid and 36% of nitrocyclohexane.[101]

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[100] H. Lettré, H. H. Inhoffen, and R. Tschesche, "Über Sterine, Gallensäuren, and verwandte Naturstoffe," 2nd ed., Ferdinand Enke Verlag, Stuttgart, 1954, Vol. 1, p. 184.

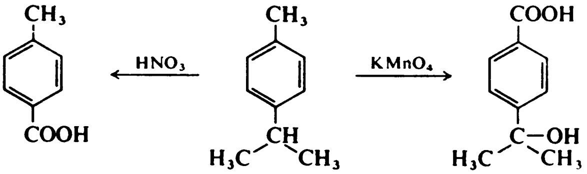
[101] U.S. Pat. 2,343,534; *Chem. Abstr.*, **38**, II, 2971 (1944).

II. Oxidative degradation of side chains on aromatic and heterocyclic rings

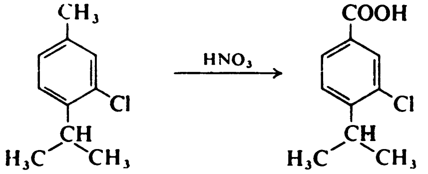
1. Oxidative degradation of long aliphatic side chains on aromatic or heterocyclic systems

Since an aromatic ring can be cleaved only under special conditions, it is relatively easy to oxidize an aliphatic side chain on an aromatic ring to a carboxyl group. The conversion of methyl groups attached to a ring into carboxyl groups has been treated in detail on page 317. Longer alkyl side chains, both branched and unbranched, are generally degraded by oxidation down to the carboxyl group attached directly to the ring. If several side chains are attached to an aromatic ring, oxidation is governed by the rules that longer chains are usually degraded first and that branched chains containing tertiary carbon atoms are attacked more easily than unbranched chains. On the other hand, side chains containing quaternary carbon atoms, such as *tert*-butyl groups, are extraordinarily resistant to oxidizing agents.

The reagents most used for oxidation of side chains in aromatic compounds are dilute nitric acid, chromic acid, and potassium permanganate. The course of the oxidation of multiply substituted aromatic compounds may depend on the nature of the oxidizing agent used: for example, with dilute nitric acid *p*-cymene gives *p*-toluic acid but with potassium permanganate gives *p*-(1-hydroxy-1-methylethyl)benzoic acid:[102]



The nitric acid used for side chain oxidation must usually be diluted 1 : 3 with water, so as to avoid nitration of the ring. Only with nitroarenes, *e.g.*, 2-chloro-6-nitrotoluene, can concentrated acid be used.[103] Halogen in the *ortho*-position to an alkyl group usually greatly reduces the ease of oxidation of the side chain; thus, in contrast to the conversion of *p*-cymene into *p*-toluic acid described above, 3-chloro-4-isopropylbenzoic acid is obtained from 3-chlorocymene:[104]



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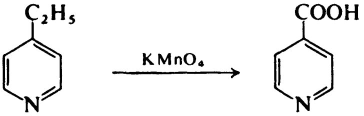
[102] A. R. Leeds, *Ber. Deut. Chem. Ges.*, **14**, 484 (1881).

[103] A. W. Singer and S. M. McElvain, *Org. Syn.*, **20**, 79 (1940).

[104] E. von Gerichten, *Ber. Deut. Chem. Ges.*, **11**, 364 (1878).

To remove halogen-containing side chains by means of nitric acid it is necessary to add silver nitrate, which binds the halogen that causes the difficulty.

Chromic acid and potassium permanganate are more powerful oxidizing agents than nitric acid; they usually convert all side chains into carboxyl groups. Like benzene homologs, alkylpyridines can also be oxidized, yielding pyridinecarboxylic acids, *e.g.*, **isonicotinic acid** from 4-ethylpyridine:



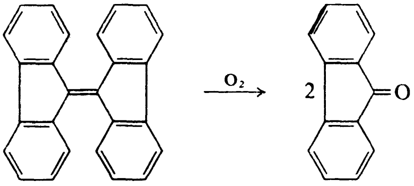
4-Ethylpyridine (160 g) and water (300 ml) are warmed to 80°; then a solution of potassium permanganate (960 g) in water (4 l), prewarmed to 80°, is added at such a rate that the mixture boils continuously. Then the whole is boiled for a further 15 min after which the manganese oxides are filtered from the hot mixture. These oxides are well washed with water, and the filtrate is evaporated (to 1 l) in a vacuum. The solution of potassium isonicotinate obtained is acidified at 60° to pH 3–4 by concentrated hydrochloric acid and then cooled to 20°. Isonicotinic acid (165 g, 90%) separates and is collected.

2. Degradation of phenol homologs to phenolic carboxylic acids by an oxidative alkali melt

The oxidants named above degrade phenol homologs to phenolic carboxylic acids only if the hydroxy group is protected, *e.g.*, as alkoxy group. However, the free phenolic carboxylic acids can be obtained directly from phenol homologs if the side chains are oxidized away by air in an alkali melt; *e.g.*, in an alkali melt thymol affords 2-hydroxy-4-methylbenzoic acid, among other products.[105]

III. Oxidative degradation of olefins

Most compounds containing an olefinic double bond can be readily cleaved into two fragments by oxidizing agents. However, it is only rarely that atmospheric oxygen can effect this reaction; one such case is the oxidation of Gräbe's $\Delta^{9,9'}$-bifluorene in alcoholic or ethereal solution to two molecules of fluorenone:[106,107]



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[105] L. Barth, *Ber. Deut. Chem. Ges.*, **11**, 1571 (1878).

[106] A. Hantzsch and W. H. Glover, *Ber. Deut. Chem. Ges.*, **39**, 4156 (1906).

[107] C. Gräbe, *Ber. Deut. Chem. Ges.*, **25**, 3146 (1892).

More powerful oxidants are almost always needed. Those commonly used for cleavage of olefins — and for other degradations — include nitric acid, hydrogen peroxide, permanganate, chromic acid, very concentrated alkali hydroxides, and in particular ozone. The products to be expected from oxidative fission of an ethylenic carbon–carbon double bond are carbonyl compounds — an aldehyde or a ketone or both according as the doubly bonded carbon atoms do or do not carry a hydrogen atom — but it often happens that 1,2-glycols are obtained as intermediates.

$$R^1R^2C{=}CHR^3 \longrightarrow R^1R^2CO + R^3CHO$$

If the doubly bonded olefinic carbon atom carries no hydrogen, the product is always unambiguously a ketone; but if the carbon atom carries one or more hydrogen atoms, the aldehyde first formed by the oxidation may react further to give an acid. Aldehydes can only be obtained with certainty by use of ozone and special techniques for cleavage of the ozonide; when other oxidants are used, olefins actually give aldehydes only when specific constitutional requirements are fulfilled.

In exceptional cases, oxidation of olefins even under energetic conditions does not lead to cleavage of the carbon–carbon bond: Hurd, McNamee, and Green[108] report the ready accessibility of benzoylformic acid by permanganate oxidation of styrene.

1. Oxidative cleavage of unsaturated carbonyl compounds by alkali melts

Oxidative cleavage of an olefinic double bond is useful, not merely for preparation of the product, but also for determination of the site of a double bond in structural studies. For the latter purpose it should be noted that cleavage of an unsaturated carbonyl compound may be preceded in an alkali melt by migration of the double bond to the immediate neighborhood of the carbonyl group (see page 1057); for example, when melted with alkali oleic acid gives palmitic acid smoothly and in very good yield:

$$CH_3{-}[CH_2]_7{-}CH{=}CH{-}[CH_2]_7{-}COOH \longrightarrow C_{15}H_{31}COOH + CH_3COOH$$

This method of oxidative cleavage is thus useless for determining the structure of olefins. Preparatively, however, it is often very valuable, as when nonanoic acid is obtained from the readily accessible 10-undecenoic acid:

$$CH_2{=}CH{-}[CH_2]_8{-}COOH \xrightarrow{KOH} [CH_3{=}[CH_2]_7{-}CH{=}CHCOOH] \longrightarrow$$
$$C_8H_{17}COOH + CH_3COOH$$

Nonanoic acid:[109] 10-Undecenoic acid (1 part) and potassium hydroxide (3–4 parts) are heated in an iron vessel with a little water, the solids dissolving. Heating is continued with stirring until no more steam is evolved, then the temperature is raised so that the mixture becomes wholly fluid; appreciable amounts of hydrogen are then evolved during 2–3 h. After cooling, the melt is dissolved in water, solids are filtered off, and the filtrate is acidified warm with hydrochloric acid. The precipitated oil is washed with water, then this crude acid is distilled in a vacuum, affording a moist forerun and then quite pure nonanoic acid, b.p. 186°/100 mm, m.p. 12.5°.

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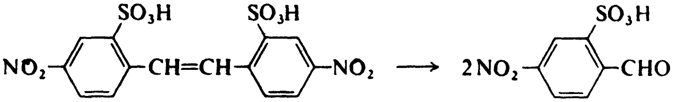
[108] C. D. Hurd, R. W. McNamee, and F. O. Green, *J. Amer. Chem. Soc.*, **61**, 2979 (1939).

[109] F. Krafft, *Ber. Deut. Chem. Ges.*, **15**, 1691 (1882).

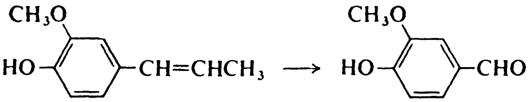
2. Oxidative cleavage of olefins to aldehydes by the usual oxidants

Cleavage of olefins by permanganate (the reagent that has been most often used) proceeds by way of 1,2-glycols which can be isolated under suitable experimental conditions. If an aldehyde is desired as product of oxidation of an olefin, the permanganate oxidation should be stopped at the glycol stage and this product should be treated with an oxidant known specifically to yield aldehydes (see page 1044). Specific constitutional requirements must be fulfilled if permanganate oxidation of an olefin is to afford an efficient preparation of the aldehyde through the glycol stage; for instance, degradation of arylethylene derivatives stops at the aldehyde only — or at least best — when the aldehyde is quasi-protected by negative *ortho*-substituents; in this way permanganate oxidation of 4,4′-dinitro-2,2′-stilbenedisulfonic acid affords 2-formyl-4-nitrobenzenesulfonic acid in very good yield:[110]



Aldehydes can also sometimes be obtained from olefins by oxidation with chromic acid or nitric acid, *e.g.*, acetylvanillin from isoeugenol.[111]

A special case is the formation of *o*- and *p*-hydroxybenzaldehydes from the appropriate arylethylene derivatives by means of nitrobenzene and alkali, *e.g.*, the production of vanillin from isoeugenol by two hours' heating with nitrobenzene and 2N-sodium hydroxide solution at 180° under pressure:[112]



3. Oxidative cleavage of olefins to ketones and carboxylic acids by the usual oxidants

From a preparative point of view the commonest use of oxidative cleavage of olefins by the usual oxidizing agents is for preparation of ketones and, even more so, of carboxylic acids. **Azelaic acid** is obtained by permanganate oxidation of ricinoleic acid as follows:[113]

Ricinoleic acid (240 g), dissolved in water (1600 ml) containing potassium hydroxide (64 g), is added in one portion to a solution of potassium permanganate (625 g) in water (7.5 l) at 35°. The temperature rises to 75°. After 0.5 hour's stirring the permanganate color has disappeared and the solution is then acidified with sulfuric acid and filtered hot from manganese oxides. These oxides are boiled with water, and the resulting extracts and the original filtrate are evaporated to 4 l. Azelaic acid crystallizes from the cooled solution and can be recrystallized from water; it has m.p. 104–106° and the yield is 32–36% (48–56 g).

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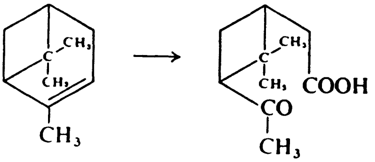
[110] Ger. Pat. 115,410; *Friedlander*, **6**, 128 (1900–1902).

[111] J. Schwyzer, *Chemiker-Ztg.*, **1930**, 840

[112] B. Leopold, *Acta Chem. Scand.*, **4**, 1523 (1950).

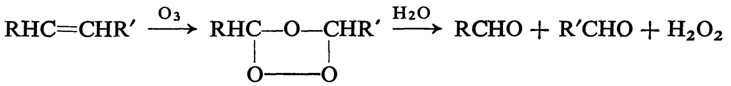
[113] J. W. Hill and W. L. McEwen, *Org. Syn.*, **13**, 4 (1933).

Oxidative cleavage of cycloalkenes is an important reaction, usually affording ω,ω'-dicarboxylic acids; *e.g.*, adipic acid is formed on oxidation of cyclohexene by permanganate.[114] If there is no hydrogen on one of the doubly bonded carbon atoms, the product is an oxo carboxylic acid, *e.g.*, α-pinonic acid from α-pinene:[115]



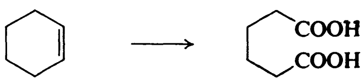
4. Oxidative cleavage of olefins by ozone

Better yields are often obtained when ozone is used for oxidative cleavage of olefins to carboxylic acids or of cycloalkenes to dicarboxylic acids. Olefinic double bonds are very much more easily attacked by ozone than are aromatic systems, so that arylethylene derivatives can be successfully treated with ozone without appreciable effect on the ring. If the ozonide which is formed initially is decomposed with water, the aldehyde is obtained together with hydrogen peroxide and other products:



$$RHC{=}CHR' \xrightarrow{O_3} \underset{\text{O———O}}{RHC\text{—}O\text{—}CHR'} \xrightarrow{H_2O} RCHO + R'CHO + H_2O_2$$

To convert olefins into carboxylic acids in this way it is preferable to oxidize the primary fission products of the ozonide in a subsidiary reaction. Particularly good results were obtained by Asinger using a hot suspension of silver oxide[116] and by Wilms using peracetic acid;[117] Wilms thus obtained **adipic acid** in yields of about 90% from cyclohexene:



Solutions in methyl or ethyl acetate, chloroform, or methylene dichloride at −50° to −20°, or in somewhat diluted acetic acid at 0°, are used for ozonization. When ozonization is complete, a 1:1 (vol/vol) mixture of glacial acetic and peroxyacetic acid is added to provide one equivalent of active oxygen per double bond. If at this stage the mixture still contains appreciable amounts of precipitated ozonide, it is warmed cautiously to 50° until dissolution occurs. Lower-boiling solvents are distilled off in a vacuum at 50°, and the residual glacial acetic acid solution is treated with peroxyacetic acid containing two equivalents of active oxygen. This mixture is kept at 50–60° for 12 h and then boiled under reflux for a further hour to complete destruction of any residual ozonide and of the peroxyacetic acid. Evaporation of the acetic acid in a vacuum then leaves the products as a residue which generally crystallizes.

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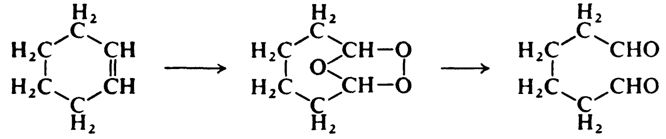
[114] K. Vogt, *Mitt. Schlesischen Kohlenforschungsinst.*, **2**, 69 (1925); *Chem. Abstr.*, **21**, 3890 (1927).

[115] A. Baeyer, *Ber. Deut. Chem. Ges.*, **29**, 22 (1896).

[116] F. Asinger, *Ber. Deut. Chem. Ges.*, **75**, 656 (1942).

[117] H. Wilms, *Ann. Chem.*, **567**, 96 (1950).

Aldehydes can be obtained homogeneously from ozonides by reductive cleavage, which can be effected either by zinc in glacial acetic acid or by catalytic hydrogenation of the ozonide[118,119] in the presence of a 1 : 19 palladium–calcium carbonate catalyst.[120] Adipdialdehyde has thus been obtained from cyclohexene in 60–70% yield:[121]



5. Wieland degradation of side chains

A special case of oxidative cleavage of olefins is involved in Wieland's method of degrading certain side chains. This method permits side chains containing terminal carboxyl groups to be degraded from the carboxyl end by one carbon atom at a time. Using a method due originally to Barbier and Locquin,[122] Wieland, Jacobi and Schlichting[123], carried out a systematic degradation of the carboxyalkyl side chain of cholic acid: the cholic ester was converted by a Grignard reaction into a tertiary alcohol, loss of water from which gave an olefin, which was degraded by oxidation with, *e.g.*, chromic acid to the 24-norcholic acid containing one less carbon atom than the starting acid:

$$C_{19}H_{31}\text{—}CH(CH_3)CH_2CH_2COOCH_3 \xrightarrow{2CH_3MgX}$$

Methyl cholate

$$C_{19}H_{31}\text{—}CH(CH_3)CH_2CH_2C(CH_3)_2OH \xrightarrow[-H_2O]{}$$

$$C_{19}H_{31}\text{—}CH(CH_3)CH_2CH{=}C(CH_3)_2 \xrightarrow{CrO_3}$$

$$C_{19}H_{31}\text{—}CH(CH_3)CH_2COOH + (CH_3)_2CO$$

24-Norcholic acid

This process could be repeated twice more, degrading the side chain to a compound in which a carbonyl group was attached directly to the ring system. This stepwise degradation afforded unquestionable proof of the structure of the side chain and of its point of attachment to the ring system of the cholic acids. A modification of it is also of preparative importance today: the modification consists of using *N*-bromosuccinimide for a simplified degradation. The ester is converted, as before, by a Grignard reaction and loss of water into the olefin, and this is now treated with bromosuccinimide (NBS) which introduces bromine primarily into the allyl position; the product loses hydrogen bromide spontaneously, yielding a diene

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[118] F. G. Fischer, H. Dull, and L. Ertel, *Ber. Deut. Chem. Ges.*, **65**, 1467 (1932).

[119] A. L. Henne and W. L. Perilstein, *J. Amer. Chem. Soc.*, **65**, 2183 (1943).

[120] M. Busch and H. Stöwe, *Ber. Deut. Chem. Ges.*, **49**, 1064 (1916).

[121] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," 35th ed., Walter de Gruyter & Co., Berlin, p. 335.

[122] P. Barbier and R. Locquin, *C. R. Hebd. Séances Acad. Sci.*, **156**, 1443 (1913).

[123] H. Wieland, R. Jacobi, and O. Schlichting, *Z. Physiol. Chem.*, **161**, 80 (1926).

which is converted by oxidation in one stage into the ketone that is so often required in partial synthesis of steroid hormones.[124]

$$\begin{aligned} &\mathrm{C_{19}H_{31}{-}CH(CH_3)CH_2CH{=}C(CH_3)_2} \xrightarrow{\mathrm{NBS}} \\ &\mathrm{C_{19}H_{31}{-}CH(CH_3)CHBrCH{=}C(CH_3)_2} \xrightarrow[-\mathrm{HBr}]{} \\ &\mathrm{C_{19}H_{31}{-}C(CH_3){=}CHCH{=}C(CH_3)_2} \xrightarrow{\mathrm{CrO_3}} \\ &\qquad\qquad\qquad \mathrm{C_{19}H_{31}{-}COCH_3} \end{aligned}$$

IV. Oxidative cleavage of carbon–carbon bonds where a functional group is at the position of cleavage

Of the many methods of oxidative cleavage of carbon–carbon bonds that could be included in this Section, the only ones of general preparative application concern secondary alcohols, ketones (especially methyl ketones), and 1,2-glycols; the usual or specific oxidants may be used.

1. Oxidative cleavage of secondary alcohols and ketones

Cleavage of secondary alcohols and ketones containing methylene or methine groups at the α-position does not usually proceed in one direction only: it affords mixtures of carboxylic acids or of carboxylic acids and ketones, because the oxidation can attack both of the carbon atoms immediately neighboring the functional group, Thus symmetrical ketones with two α-methylene groups give two carboxylic acids differing in composition by one carbon atom; and such unsymmetrical ketones give mixtures of up to four carboxylic acids whose separation may be very difficult:

$$\mathrm{RCH_2COCH_2R'} \xrightarrow{\mathrm{O}} \begin{cases} \longrightarrow \mathrm{RCH_2COOH + R'COOH} \\ \longrightarrow \mathrm{RCOOH + R'CH_2COOH} \end{cases}$$

Oxidative cleavage is clearer-cut when one of the carbon atoms in α-position to the carbonyl group is that of a methyl group (see below) or carries no hydrogen (as in alkyl aryl ketones); the oxidant then attacks only at the side where the α-methylene or methine group lies. Ditertiary ketones such as benzophenone are therefore almost completely stable against oxidation.

Greater preparative importance attaches to oxidative ring opening of cycloalkanols and cycloalkanones, which then afford alkanedioic acids containing an unchanged number of carbon atoms. Thus, for instance, **adipic acid** is obtained in up to 90% yield from cyclohexanol or cyclohexanone by means of about 60% nitric acid containing vanadium and copper salts as catalyst:[125]

Ammonium vanadate (0.32 part) and copper turnings (0.4 part) are warmed with 60% nitric acid (301 parts) at 55°, then cyclohexanol (100 parts) is added gradually at 55–60°

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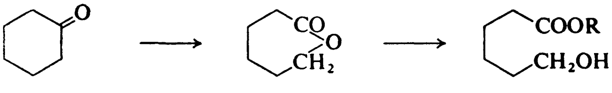
[124] F. Bohlmann, *Arzneimittel-Forsch.*, **4**, 28 (1954).

[125] French. Pat. 919,755; *Chem. Zentralbl.*, **1947**, II, 745.

during 5 h. The mixture is kept at the stated temperature for a further hour, then cooled to 17° and filtered. The precipitated adipic acid is washed twice on the filter funnel at 17° with a saturated aqueous solution (100 parts) of adipic acid and is then dried at 90–95°. The yield is 89% (130 parts).

The action of peroxyacids, such as Caro's acid, on cyclic ketones affords ω-hydroxy carboxylic acids or their lactones, the latter being convertible into ω-hydroxy carboxylic esters by the action of an alcohol and an acid; cyclohexanone, for instance, gives a 6-hydroxyhexanoic ester in this way:[126,127]



2. Oxidative cleavage of methyl ketones

Frequent use is made in the laboratory of oxidative degradation of methyl ketones. With alkyl ketones the resistance of the methyl group to attack by the usual oxidants is so great that reaction occurs only at one point; thus an unbranched alkyl methyl ketone, for instance, on oxidation by chromic and sulfuric acid in glacial acetic acid affords, besides acetic acid, the alkanoic acid containing two fewer carbon atoms than the ketone; *e.g.*, palmitic acid from 2-octadecanone:[128]

$$C_{16}H_{33}COCH_3 \longrightarrow C_{15}H_{31}COOH + CH_3COOH$$

Oxidative degradation of methyl ketones was used by Krafft[129] to determine the structure of stearic acid: he first submitted it to "calcium salt distillation" by heating its barium salt with barium acetate (see page 1005), thus obtaining the methyl ketone which on oxidative cleavage gave acetic acid and the alkanoic acid containing one less carbon atom than stearic acid; he repeated these operations until the stearic acid had been degraded to decanoic acid, which was by that time already available synthetically.

If, however, there is no hydrogen attached to the carbon atom carrying the acetyl group, then the ketone is converted into the acid containing only one fewer carbon atoms; *e.g.*, chromic–sulfuric acid converts pinacone into 2,2-dimethylpropionic acid:[130]

$$(CH_3)_3CCOCH_3 \xrightarrow{O} (CH_3)_3CCOOH + CO_2$$

Pinacone can, however, be converted into the α-oxo acid, 3,3-dimethyl-2-oxobutyric acid, under other conditions — by alkaline permanganate — and this product can then yield 2,2-dimethylpropionic acid on oxidative decarboxylation by hydrogen peroxide in alkali:[131]

$$(CH_3)_3CCOCH_3 \xrightarrow[NaOH]{KMnO_4} (CH_3)_3CCOCOOH \xrightarrow[NaOH]{H_2O_2} (CH_3)_3CCOOH$$

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[126] A. Baeyer and V. Villiger, *Ber. Deut. Chem. Ges.*, **32**, 3625 (1899); C. H. Hassall, *Org. Reactions*, **9**, 73 (1957).

[127] S. L. Friess, *J. Amer. Chem. Soc.*, **71**, 2571 (1949).

[128] F. Krafft, *Ber. Deut. Chem. Ges.*, **15**, 1707 (1882).

[129] F. Krafft, *Ber. Deut. Chem. Ges.*, **12**, 1672 (1879).

[130] S. Reformatzky, *Ber. Deut. Chem. Ges.*, **23**, 1596 (1890).

[131] M. J. Böseken, *Rec. Trav. Chim.*, **30**, 142 (1911).

This two-stage degradation of methyl ketones to carboxylic acids containing one fewer carbon atoms cannot be realized in all cases, but only when the acetyl group is attached to a quaternary carbon as in pinacone and a series of aryl methyl ketones of the acetophenone type.

Alkyl and aryl ketones are degraded to the carboxylic acid containing one fewer carbon atoms more easily and generally under milder conditions by the haloform reaction, in which a hypohalite is used as oxidant. Pinacone thus gives a 70% yield of 2,2-dimethylpropionic acid.[132] The hypohalite converts the terminal methyl group into a trihalomethyl group, and that product is readily hydrolysed in the alkaline medium used into the next lower carboxylic acid (see page 1004):

$$\begin{tikzcd}
\mathrm{RCOCH_3 + 3NaOCl} \arrow[r] & \mathrm{[RCOCCl_3 + 3NaOH]} \arrow[d] \\
 & \mathrm{RCOONa + CHCl_3}
\end{tikzcd}$$

In the case of 2,4,6-trichloroacetophenone Fuson, Bertetti, and Ross[133] succeeded in isolating the intermediate formulated in the above sense, namely, **α,α,α-tribromo-2,4,6-trichloroacetophenone:**

2,4,6-Trichloroacetophenone (5 g) was prepared in 50% yield from 2,4,6-trichlorobenzoyl chloride and methylmagnesium bromide, and a hypobromite solution by dissolving bromine (50 g) in 10% sodium hydroxide solution (500 ml) at 0°. The ketone (5 g) was stirred with this hypobromite solution for 30 h at about 50° and then for 50 h at 70°, whereupon the tribromo ketone (8 g, 80%), m.p. 126–127°, separated. On prolonged boiling with 50% sodium hydroxide solution this product was hydrolysed almost quantitatively to 2,4,6-trichlorobenzoic acid.

For the haloform reaction to be smooth the group R of the ketone $RCOCH_3$ should not contain hydrogen that is easily replaceable by halogen. However, under the reaction conditions used, methylene groups in R are not so easily substituted, as is shown by the smooth formation of 3-methyl-3-phenylbutyric acid in 84% yield from 4-methyl-4-phenyl-2-pentanone:[134]

$$\mathrm{C_6H_5C(CH_3)_2CH_2COCH_3} \longrightarrow \mathrm{C_6H_5C(CH_3)_2CH_2COOH}$$

Levine and Stephens[135] showed that ethyl and propyl ketones $RCOC_2H_5$ and $RCOC_3H_7$ in which R is an aryl or heterocyclic group undergo this reaction smoothly in the same sense as methyl ketones do; *e.g.*, benzoic acid is obtained in 64% yield from propiophenone:

$$\mathrm{C_6H_5COC_2H_5} \longrightarrow \mathrm{C_6H_5COOH}$$

Unsaturated acids can also be obtained in this way, by hypohalite oxidation of α,β-unsaturated methyl ketones: 3-methyl-2-butenoic acid has thus been obtained from mesityl oxide,[136] and 5-phenyl-2,4-pentadienoic acid in 70% yield from cinnamylideneacetone:[137]

$$\mathrm{C_6H_5CH{=}CHCH{=}CHCOCH_3} \longrightarrow \mathrm{C_6H_5CH{=}CHCH{=}CHCOOH}$$

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[132] L. T. Sandborn and E. W. Bousquet, *Org. Syn.*, **8**, 108 (1928).

[133] R. C. Fuson, J. W. Bertetti, and W. E. Ross, *J. Amer. Chem. Soc.*, **54**, 4380 (1932).

[134] J. Colonge and L. Pichat, *Bull. Soc. Chim. France*, [v], **16**, 180 (1949).

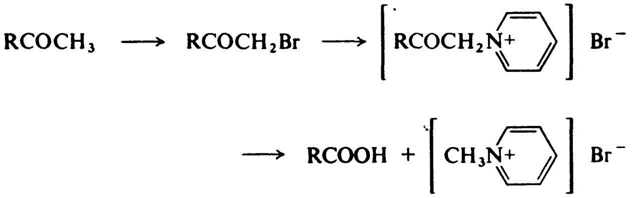
[135] R. Levine and J. R. Stephens, *J. Amer. Chem. Soc.*, **72**, 1642 (1950).

[136] L. J. Smith, W. Richard, and L. J. Spillane, *Org. Syn.*, **23**, 27 (1943).

[137] J. T. Plati, W. H. Strain, and S. L. Warren, *J. Amer. Chem. Soc.*, **65**, 1273 (1943).

A disadvantage of this method is that the ketone is usually only suspended in the aqueous medium, it being advisable in such cases to add an emulsifier that is unaffected by the oxidant. Nevertheless it has been found useful to add certain solvents such as dioxan to the hypochlorite or hypobromite solution.

Kröhnke[138] has described a different, very smooth degradation of methyl ketones to the carboxylic acid containing one fewer carbon atoms. The principle of his method is to convert the methyl ketone by bromine into its monobromo derivative and to bring this into reaction with pyridine; this forms the pyridinium bromide which usually crystallizes nicely and, when treated with sodium hydroxide in aqueous-alcoholic solution is hydrolysed to the carboxylic acid and methylpyridinium bromide:



The complete reaction sequence can be carried out without special purification of the intermediates and gives the desired carboxylic acids in good yields. The following is an example:

1-Naphthoic acid: Methyl 1-naphthyl ketone is dissolved in glacial acetic acid (5–10 parts) and treated with the calculated amount of bromine in the cold. The mixture is warmed gently on a water-bath and then poured into water containing a little sulfur dioxide; the precipitated crystals of bromomethyl 1-naphthyl ketone are filtered off and pressed on porous plate; they are then treated with an excess of pyridine and, when reaction has set in, the mixture is heated for a short time on the water-bath, after which the whole is dissolved in alcohol and the 1-(1-naphthoylmethyl)pyridinium bromide is precipitated by ether. If recrystallized from water (10 parts), this salt melts at 170°. For hydrolysis, the bromide (0.5 g) is dissolved in water (40 g) and ethanol (12 ml), 10% sodium hydroxide solution (2 ml) is added, and the whole is heated for 12 min on a water-bath. Acidification then precipitates the 1-naphthoic acid.

2-Naphthoic acid has been prepared similarly, 0.25 g being obtained from 0.5 g of the pyridinium bromide.

An elegant simplification has been introduced by King,[139] which also increases the utility of the method: the methyl or methylene ketone is heated on the water-bath for about an hour with iodine in anhydrous pyridine, being thus converted directly into the pyridinium iodide under very mild conditions; this salt is hydrolysed as before by aqueous-alcoholic sodium hydroxide solution; overall yields of 60–83% have been obtained.

3. Cleavage by lead tetraacetate

Compounds containing functional groups on neighboring carbon atoms are particularly amenable to oxidative cleavage between these atoms. Such com-

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[138] F. Kröhnke, *Ber. Deut. Chem. Ges.*, **66**, 604 (1933); *Angew. Chem.*, **65**, 605 (1953).

[139] L. C. King, *J. Amer. Chem. Soc.*, **66**, 894, 1612 (1944).

pounds include 1,2-diols, ketols, α-hydroxy acids, α-hydroxy amines, 1,2-diamines, α-amino acids, and oxalic acid. They are all cleaved smoothly between the carbon atoms carrying the functional groups either by lead tetraacetate in Criegee's method[140] or by periodic acid in Malaprade's method.[141] The fission products are carbonyl compounds or imines, though the latter are usually further dehydrogenated to nitriles:

$$\rangle C(OH){-}C\langle(OH) \longrightarrow \rangle CO + \rangle CO$$

$$CHR(OH){-}COOH \longrightarrow RCHO + CO_2$$

$$RR'C(OH){-}COOH \longrightarrow RR'CO + CO_2$$

$$CHR(NH_2){-}COOH \longrightarrow CO_2 + CHR{=}NH \longrightarrow RCN$$

Lead tetraacetate is the reagent most used in such reactions because it is soluble in organic solvents. Baer, Grossheintz, and Fischer[142] have, however, shown that it can be applied as an emulsion in water or in mixtures of water and other solvents. Periodic acid is used in an aqueous medium, often with addition of another solvent such as dioxan or acetic acid or with an emulsifier. Osmium tetraoxide has also proved a valuable oxidant in special cases.[143]

Although, in general, the two oxidants lead tetraacetate and periodic acid give the same results[144] and the former has usually been preferred because it is cheaper, it should be noted that periodic acid has the virtue of being more selective. For instance, lead tetraacetate but not periodic acid attacks ditertiary glycols and α-hydroxy acids; thus only lead tetraacetate, as shown by Oeda,[145] converts 2-hydroxy-3-phenylpropionic acid into **phenylacetaldehyde:**

$$C_6H_5CH_2CH(OH)COOH \longrightarrow C_6H_5CH_2CHO$$

2-Hydroxy-3-phenylpropionic acid (10 g; prepared from phenylalanine) is boiled in benzene (150 ml) until most of it has dissolved and then lead tetraacetate (26 g) is added gradually with stirring. The lead(II) acetate that separates is filtered off and washed with benzene. Distillation of the benzene solutions in a vacuum affords phenylacetaldehyde (4.2 g, 58%), b.p. 84–86°/17 mm.

Tartaric acid, however, can be converted into glyoxylic acid only by periodic acid since lead tetraacetate attacks all four carbon atoms of tartaric acid.[146] Weygand nevertheless worked out a method of obtaining glyoxylic esters from tartaric esters by means of lead tetraacetate because α-hydroxy esters are as resistant to cleavage as are esterified or etherified glycols.

$$ROOCCH(OH)CH(OH)COOR \longrightarrow 2OHCCOOR$$

Ethyl glyoxylate: Diethyl tartrate (232 g) is dissolved in benzene (1200 ml; dried over sodium) and cooled in ice, then lead tetraacetate (500 g) is added with stirring during 1 h, the temperature being kept at not more than 10°. Reaction is completed by a further 12 hours'

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[140] R. Criegee, *Angew. Chem.*, **53**, 324 (1940).

[141] L. Malaprade, *C. R. Hebd. Séances Acad. Sci.*, **186**, 382 (1928).

[142] E. Baer, J. M. Grossheintz, and H. O. Fischer, *J. Amer. Chem. Soc.*, **61**, 2607, 3379 (1939).

[143] R. Criegee, *Ann. Chem.*, **522**, 75 (1936).

[144] P. Caro and R. Hirohata, *Helv. Chim. Acta*, **16**, 959 (1933).

[145] H. Oeda, *Bull. Chem. Soc. Japan*, **9**, 13 (1934).

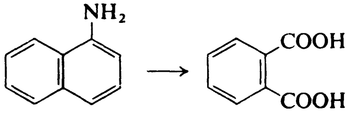
[146] Freury and Bon-Bernatets, *J. Pharm. Chim.*, [viii], **23**, 85 (1936).

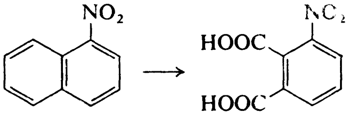
stirring, then the precipitate is filtered off and washed with benzene, and the benzene is removed from the filtrates under reduced pressure. After a considerable amount (500 ml) of benzene has distilled, the receiver is changed, and a sample of further distillate is tested for glyoxylic ester by warming with an equal amount of 2N-ammonia solution; if glyoxylic ester is present, the solution becomes yellow deepening to bluish-red. In the above case, distillation is continued until the residue amounts to 300 ml. This residue is diluted with anhydrous ethanol (900 g) and then fractionated through a column. After the alcohol has been removed, a fraction of b.p. 40–48°/17 mm consists mainly of benzene, and this is followed at 54–55°/16 mm by the ethyl glyoxylate ethanolate (146 g, 43 %).

V. Oxidative degradation of aromatic and heterocyclic ring systems

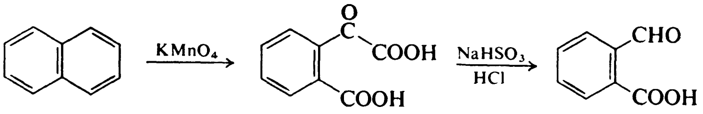
1. Oxidative cleavage of fused aromatic ring systems

It is often possible to break individual rings of fused aromatic ring systems by oxidation. The best known example is the preparation of phthalic acid from naphthalene; good yields are obtained by the classical method[147] of oxidation by oleum in the presence of mercury(II) sulfate at 250–300°, but the modern method is oxidation by air at 400–500° in the presence of vanadium oxide or molybdenum oxide catalysts (which gives the anhydride).[148] The presence of certain substituents, such as hydroxyl or amino groups, in an aromatic compound usually makes that ring easier to break. Thus phthalic anhydride is obtained relatively easily from naphthols or naphthylamines. "Negative" substituents such as a nitro group or a halogen atom, however, increase the resistance to oxidation of rings containing them, so that chromic acid oxidizes 1-nitronaphthalene cleanly to 3-nitrophthalic acid:[149]





When naphthalene is degraded by permanganate under precisely defined conditions, phthalonic acid can be isolated instead of the usual phthalic acid, and this intermediate can be decarboxylated to phthalaldehydic acid (see page 1007):[150]



2. Oxidative cleavage of fused heterocyclic ring systems

Oxidative cleavage of fused heterocyclic systems is often of preparative value. The benzene ring of quinoline, for instance, can be oxidized away,

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[147] Ger. Pat. 91,202; *Friedlander*, **4**, 164 (1894–97).

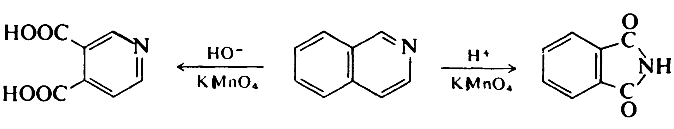
[148] Ger. Pat. 347,610, 349,089; *Friedlander*, **14**, 450, 838 (1926).

[149] F. Beilstein and A. Kurbatow, *Ann. Chem.*, **202**, 217 (1880).

[150] J. H. Cardner and C. A. Naylor, *Org. Syn.*, **16**, 68 (1936).

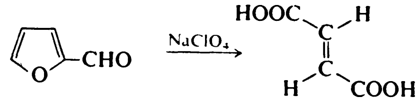
[151] W. von Müller, *Ber. Deut. Chem. Ges.*, **24**, 1900 (1891).

affording 2,3-pyridinedicarboxylic acid,[151] and under the same conditions isoquinoline gives 3,4-pyridinedicarboxylic acid. However, under other conditions it may be possible to open the heterocyclic ring of such systems: on oxidation by acid permanganate isoquinoline yields phthalimide:[152]

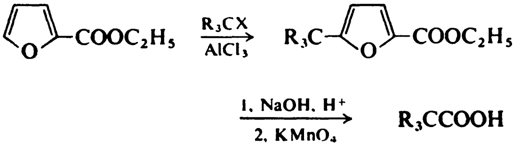


3. Fumaric acid from furfuraldehyde

An example of oxidative cleavage of a monocyclic hetero system is the conversion of furfuraldehyde into fumaric acid, a reaction that has been widely used:[153]



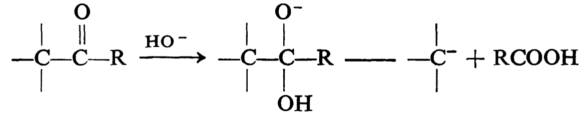
The ability to open the furan ring by oxidation has also been utilized for synthesis of trialkylacetic acids: A 2-furoic ester is first subjected to a Friedel–Crafts reaction with a tertiary alkyl halide, and the 5-alkyl-2-furoic acid obtained from the product by hydrolysis is then oxidized by alkaline permanganate to the trialkylacetic acid:[154]



1.3. Hydrolytic cleavage

1. Fencholic acid from fenchone

Cleavage of carbon–carbon bonds in hydrolytic reactions is relatively rare, but those reactions that occur are important. The reagent is usually a concentrated solution of an alkali, and the starting material must contain a carbonyl group; the first stage is addition of a hydroxyl anion to this group, and the resulting intermediate splits to a carbon anion and a carboxylic acid:



$$-\overset{|}{\underset{|}{C}}-\overset{\overset{O}{\|}}{C}-R \xrightarrow{HO^-} -\overset{|}{\underset{|}{C}}-\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}-R \longrightarrow -\overset{|}{\underset{|}{C}}{}^- + RCOOH$$

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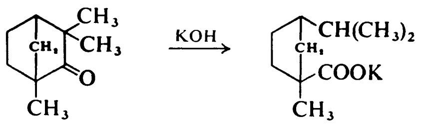
[152] G. Goldschmied, *Monatsh. Chem.*, **9**, 676 (1888).

[153] N. A. Milas, *J. Amer. Chem. Soc.*, **49**, 2007 (1927); *Org. Syn.*, **11**, 46 (1931).

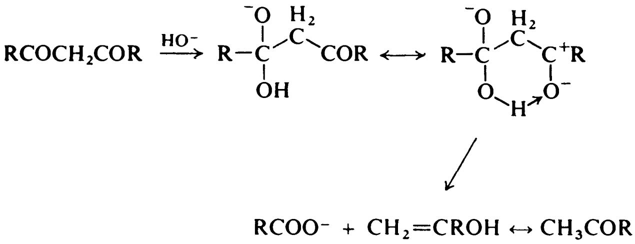
[154] T. Reichstein and co-workers, *Helv. Chim. Acta*, **18**, 721 (1935).

Cleavage by hydrolysis in this way requires relatively vigorous conditions and so is not to be expected with simple aldehydes and ketones; such compounds usually undergo other reactions before the fission is reached, and only those simple ketones that cannot undergo the various side reactions are amenable to hydrolysis by alkali at elevated temperatures. An example of this last type is fenchone whose carbonyl group is flanked by carbon atoms neither of which carries hydrogen; with potassium hydroxide solution at 220° it yields fencholic acid in a smooth hydrolysis:[155]



2. Acid fission of *β*-diketones and *β*-oxo esters

Only relatively mild conditions are needed for hydrolysis of a carbon–carbon bond in *β*-diketones and *β*-oxo esters. In these cases a cationic centre formed at the *β*-position to the carbonyl group aids fission of the carbon–carbon bond from the carbonyl group:



$$RCOCH_2COR \xrightarrow{HO^-} R{-}\overset{O^-}{\underset{OH}{C}}{-}CH_2{-}COR \longleftrightarrow R{-}\overset{O^-}{\underset{O}{C}}{-}CH_2{-}\overset{}{\underset{O^-}{C^+}}R$$

$$RCOO^- + CH_2{=}CROH \leftrightarrow CH_3COR$$

One molecule of acid and one of ketone is thus obtained on hydrolysis of a *β*-diketone in this way; but unsymmetrical *β*-diketones may be expected often to give two different acids and two different ketones because cleavage may occur at two different places, viz.:

$$RCOCH_3 + R'COOH \xleftarrow{a} RCOCH_2COR' \xrightarrow{b} RCOOH + CH_3COR'$$

If, however, R is an aryl and R′ an alkyl group, then cleavage affords almost exclusively the alkyl aryl ketone by reaction (*a*), *e.g.*, acetophenone from benzoylacetone:

$$C_6H_5COCH_2COCH_3 \longrightarrow C_6H_5COCH_3 + CH_3COOH$$

From *β*-oxo esters hydrolysis of this type affords two molecules of (different) carboxylic acids:

$$R^1COR^2R^3COOR^4 \longrightarrow R^1COOH + CHR^2R^3COOH + R^4OH$$

These fissions, which are usually carried out by concentrated alkali solutions, are therefore known as "acid fission" of *β*-oxo esters, in contrast with the "ketone fission" which occurs with decarboxylation under the influence of

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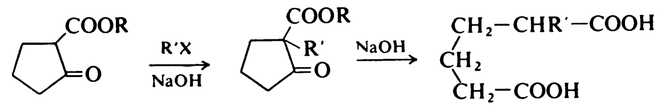
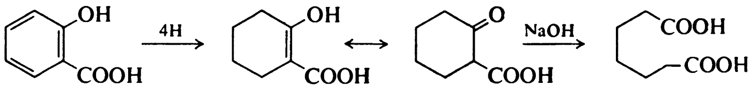
[155] O. Wallach and H. Wienhaus, *Ann. Chem.*, **369**, 72 (1909).

acid or dilute alkali (see page 1013). Ketone fission is often smoother than acid fission, whose success depends largely on the correct choice of alkali concentration. The acid fission has not been applied very widely in preparative chemistry, partly because the acids obtained can mostly be prepared more elegantly and more conveniently by malonic ester syntheses. It has, however, proved useful for preparation of α-substituted adipic acids and of pimelic acid. For the former purpose a 2-oxocyclopentanecarboxylic ester obtained from the adipic diester by a Dieckmann condensation (see page 964)[156] is first alkylated at the α-position by treatment of its enol salt with an alkyl halide, and this product is subjected to acid fission; the α-substituted adipic acid is then obtained in almost quantitative yield:



The preparation of pimelic acid from a 2-oxocyclohexanecarboxylic ester by an excess of boiling methanolic potassium hydroxide solution is an equally smooth reaction.[157] Pimelic acid is also obtained readily by reduction of salicylic acid with sodium and 1-pentanol, doubtless because 2-oxocyclohexanecarboxylic acid is formed as intermediate in the reducing medium:[158]



Birkofer and Storch[159] mention that 4-aminosalicylic acid (COOH = 1) cannot be cleaved to 3-aminopimelic acid in an analogous reduction.

Acylated β-oxo esters undergo acid fission particularly readily. Any desired β-oxo ester can be thus prepared from acetoacetic ester with comparative ease, by subjecting the acylacetoacetic ester to hydrolysis or alcoholysis: the acetyl group of the acetoacetic ester, and not the new acyl group, is then generally split off, so that, for instance, 2-benzoylpropionic ester is obtained by gently warming 2-benzoyl-2-methylacetoacetic ester with a small amount of sodium methoxide in methanol:

$$CH_3CO\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle COC_6H_5}{C}}\text{—}COOR \xrightarrow{ROH} CH_3COOR + C_6H_5COCH(CH_3)COOR$$

Shriner and Schmidt[161] have described the following similar procedure for preparation of benzoylacetic ester from benzoylacetoacetic ester by gentle warming with an aqueous solution of ammonia and ammonium chloride:

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[156] P. S. Pinkney, *Org. Syn.*, **17**, 30 (1937).

[157] W. Dieckmann, *Ann. Chem.*, **317**, 100 (1901); A. Müller and E. Rolz, *Org. Syn.* **11**, 42 (1931).

[158] A. Müller and E. Rölz, *Monatsh. Chem.*, **48**, 734 (1927).

[159] L. Birkofer, and I. Storch, *Ber. Deut. Chem. Ges.*, **86**, 749 (1953).

[160] W. Dieckmann and A. Wittmann, *Ber. Deut. Chem. Ges.*, **55**, 3344 (1922).

[161] R. L. Shriner and A. G. Schmidt, *J. Amer. Chem. Soc.*, **51**, 3636 (1929).

Ethyl acetoacetate (260 g) and sodium (46 g) in anhydrous benzene (4.5 l) are boiled under reflux for 24 h in a flask (5-l capacity) fitted with a stirrer and a reflux condenser. Benzoyl chloride (350 g) is then dropped in during 3 h and the whole is boiled for a further 8 h. The solution is then poured on crushed ice (500 g), the benzene phase is separated, the benzene is distilled off, and the residue is fractionated in a vacuum, giving **ethyl benzoylacetoacetate** (350 g, 74.8%), b.p. 177–181°/20 mm.

For hydrolysis, ethyl benzoylacetoacetate (58.5 g) is added to a mixture of concentrated ammonia solution (10 ml) and ammonium chloride (32 g) in water (150 ml) at 40°. After being kept at 40° for 10 min, this mixture is rapidly cooled and extracted with ether (100 ml). The ethereal solution is dried over anhydrous magnesium sulfate, the ether is removed, and the residue is distilled in a vacuum, giving **ethyl benzoylacetate** (37.5 g, 78.1%), b.p. 165–169°/20 mm.

α,α-Disubstituted β-oxo esters are sometimes also amenable to alcoholysis under catalysis by alkali, giving two molecules of (different) aliphatic esters, *e.g.*, ethyl acetate and ethyl isobutyrate from ethyl 2,2-dimethylacetoacetate:[162]

$$CH_3COC(CH_3)_2COOR \xrightarrow{C_2H_5OH} CH_3COOC_2H_5 + (CH_3)_2CHCOOC_2H_5$$

The mechanism for acid fission of β-oxo esters applies also to the hydrolysis of trichloroacetaldehyde to chloroform and formic acid that occurs under the influence of alkali:

$$CCl_3CHO \xrightarrow{HO^-} CCl_3CH(OH)O^- \longrightarrow CHCl_3 + HCOO^-$$

Trichloromethyl ketones undergo a similar degradation to chloroform and a carboxylic acid:

$$RCOCCl_3 \xrightarrow{NaOH} RCOONa + CHCl_3$$

Since, however, trichloromethyl ketones are generally formed by treating the corresponding methyl ketones with a hypohalite and form non-isolable intermediates in the haloform reaction, this method of cleavage by hydrolysis has been treated above (page 1042) among the oxidative degradations.

When chloral is cleaved by treatment with a primary or secondary amine, the substituted formamide is obtained in good yield (cf. page 545):

$$^+NR_2H—CH(CCl_3)—O^- \longrightarrow NR_2CHO + CHCl_3$$

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[162] W. Dieckmann, *Ber. Deut. Chem. Ges.*, **33**, 2672 (1900).

PART D

Rearrangements of Carbon Compounds

PART D

Rearrangements of Carbon Compounds

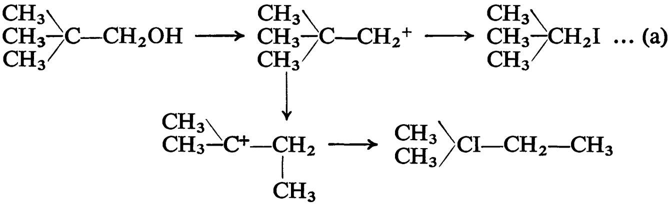
Compiled by
E. Schmitz

The reactions treated in the preceding Chapters were those that involved addition, removal, or exchange of atoms or groups of atoms. Their common characteristic is that the only bonds broken, formed, or rearranged were those between the main part of the molecule on the one hand and the atoms or groups added or removed on the other.

There is, however, another group of reactions in which not only are leaving groups removed and new groups introduced but also bonds within the molecule are regrouped. Such changes lead to migration of substituents, to migration or formation of double bonds, or to ring closure. Such reactions are termed rearrangements.

Rearrangements in which the molecular formula of the compound is unchanged may also be termed isomerizations.

For example, neopentyl alcohol may react normally with replacement of the hydroxyl group by iodine in such a way that the new substituent (I) enters at the position from which the previous one (OH) left (reaction a); alternatively, when the hydroxyl group has been lost, a methyl group may migrate to the neighboring carbon atom, the new substituent entering at the original site of the methyl group. The two reactions, in fact, occur side by side.[1]



The definition of a rearrangement given above covers almost all the reactions to be discussed under the heading Rearrangements in this Chapter; but it also includes all ring closures. Nevertheless it is neither useful nor customary to consider all ring closures as rearrangements, because many ring closures don ot differ in principle from other reactions that occur without ring closure. For example, intramolecular cyclization of phenethylcyclohexene to octa-

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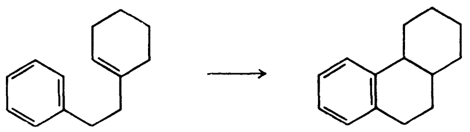
[1] F. C. Whitmore, E. L. Wittle, and B. R. Harriman, *J. Amer. Chem. Soc.*, **61**, 1585 (1939).

hydrophenanthrene[2] corresponds to the reaction of benzene with cyclohexene:



Most such ring closures have therefore been treated in the preceding Chapters. On the other hand, cyclization of phthaloyl dichloride to dichlorophthalide (page 1067) has no analogy in the acyclic series and is therefore treated in the present Chapter.

For the purpose of this book, rearrangements have been divided into four types:

1. Rearrangement with retention of the carbon skeleton
2. Rearrangement with extension of the carbon skeleton
3. Rearrangement with degradation of the carbon skeleton
4. Rearrangement with reorganization of the carbon skeleton

Within each section, rearrangements of hydrocarbons are treated before those of compounds containing oxygen, nitrogen, halogen, or sulfur.

In accord with the general principle laid down for this book, attention is focussed on the bonds that are broken or newly constituted on formal passage from a starting material to an end product. The material is arranged without regard to whether the reactions are intra- or inter-molecular and of whether they are of ionic or radical type. Specialist literature should be consulted on questions of reaction mechanism.[3a]

1.1. Rearrangement with retention of the carbon skeleton

I. Migration of a multiple bond

1. Migration of a double bond

Double bonds may be caused to migrate within unsaturated compounds with a readiness that varies according to the nature of the compound but is always easier in the presence of an acidic or basic substance as catalyst. The danger of such migration should be taken into account even during introduction of the double bond into the molecule. For example, heating 1-dodecanol with anhydrous phosphoric acid at 210–220° gives a dodecene mixture in which the double bond is widely distributed through the molecule;[4] and, if the conditions leading to isomerization are sufficiently prolonged, an equilibrium

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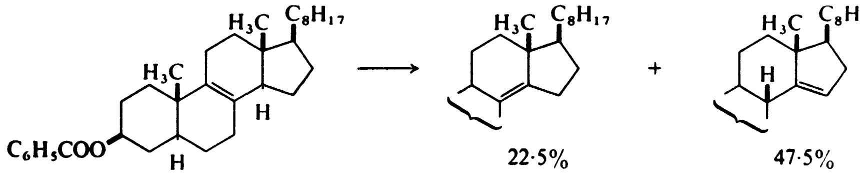
[2] D. Perlman, D. Davidson, and M. T. Bogert, *J. Org. Chem.*, **1**, 288 (1936).

[3] (a) P. de Mayo, "Molecular Rearrangements," Interscience Publ., New York–London, 1963, (b–e) Vol. 1, pp. (b) 1–25 (Y. Pocker), (c) 528 (P. A. S. Smith), (d) 660–684 (S. J. Rhoads), (e) 684–696 (S. J. Rhoads).

[4] F. Asinger, *Ber. Deut. Chem. Ges.*, **75**, 1247 (1942).

is often set up in which the double bond is randomized statistically throughout the whole molecule. This has been proved by, for instance, Asinger's careful studies[4] of the preparation of, and double-bond migration in, long-chain alkenes; he obtained a mixture of all the possible position isomers in isomerization of dodecene by cobalt carbonyl at 150°,[5] and the same mixture was formed on removal of hydrogen chloride from 1-dodecyl chloride. Similar mixtures were also obtained on dehydration of other higher 1-alkanols.

Wieland and Görnhardt[6] allowed hydrogen chloride to react with dihydrozymosteryl benzoate [5α-cholest-8(9)-en-3β-yl benzoate] in chloroform for 8 hours at room temperature and then isolated the cholest-8(13)-ene and -13(16)-ene derivatives from the reaction mixture.



Hünig and Eckardt[7] found that the double bond wanders away from the end of the chain when 10-undecenoic acid is heated in 2N-potassium hydroxide solution in diethylene glycol at 200°, 50% of the acid being isomerized in 4.5 hours and 70% in 15 hours.

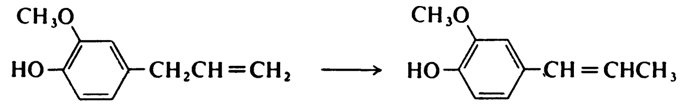
1-Butene is isomerized within minutes when treated with potassium *tert*-butoxide in dimethyl sulfoxide at 55°;[8] in this and other cases it has been observed that the isomerization leads preferentially to the thermodynamically less stable *cis*-isomer.

A reasonably unambiguous and complete shift of a double bond to a desired position can be expected only if in its new position this bond is conjugated to a carbon–carbon, carbon–oxygen, or carbon–nitrogen multiple bond. There are many examples of such unambiguous rearrangements; they are brought about by the action of alkali or acid or simply by heat.

The preparation of nonanoic acid from 10-undecenoic acid in an alkali melt described on page 1036 involves migration of the double bond over eight atoms, as well as loss of the two terminal carbon atoms:

$$CH_2{=}CH{-}[CH_2]_8{-}COOH \longrightarrow CH_3{-}[CH_2]_7{-}CH{=}CH{-}COOH$$

Tiemann[9] described the conversion of eugenol into isoeugenol as follows:



Conversion of eugenol into isoeugenol: Potassium hydroxide (12.5 parts) is boiled in pentyl alcohol (18 parts), then the solution is decanted from carbonate, mixed with eugenol (5 parts), and heated at 140° for 16–20 h. Then the pentyl alcohol is removed in steam, the residual

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[5] F. Asinger, *Chem. Ber.*, **88**, 445 (1955).
[6] H. Wieland and L. Görnhardt, *Ann. Chem.*, **557**, 248 (1947).
[7] S. Hünig and W. Eckardt, *Chem. Ber.*, **95**, 2498 (1962).
[8] S. Bank, A. Schriesheim, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **87**, 3244 (1965).
[9] F. Tiemann, *Ber. Deut. Chem. Ges.*, **24**, 2870 (1891).

solution is acidified with sulfuric acid, and the oil that separates is washed with sodium carbonate solution and distilled in steam. Working up gives isoeugenol as a colorless, viscous oil, b.p. 261°.

Wagner[10] describes the isomerization of 3-methyl-3-butenoic acid:

$$CH_2{=}C(CH_3)CH_2COOH \longrightarrow (CH_3)_2C{=}CHCOOH$$

A mixture of 3-methyl-3-butenoic acid (10 g), anhydrous ether (20 ml), and 90% sulfuric acid (10 g) is set aside at room temperature for 24 h. Then dilution with water and the usual working up gives **3-methyl-2-butenoic acid** (9.7 g, 97%), m.p. 68–70°.

On the other hand a conjugated double bond can be shifted into an isolated position if the small amount of non-conjugated material present at equilibrium can be removed continuously from the equilibrating mixture. Isomesityl oxide (4-methyl-4-penten-2-one), for instance, can be thus prepared from mesityl oxide:[11,12]

$$(CH_3)_2C{=}CHCOCH_3 \longrightarrow CH_2{=}C(CH_3)CH_2COCH_3$$

Commercial mesityl oxide (which contains about 9% of the non-conjugated isomer) is purified as described in the literature,[11,12] treated with 0.2% of *p*-toluenesulfonic acid, and distilled at atmospheric pressure through a column of 85 theoretical plates. The acid causes equilibration, and the lower-boiling **4-methyl-4-penten-2-one** becomes enriched in the distillate. The fractions of refractive index 1.4210–1.4230 are redistilled through the same column at a reflux ratio of 1 : 40. The new product boils at 121.5°, the conjugated material at 129.8°.

2. Allylic rearrangement[13]

The allylic rearrangement can be expressed in the generalized form:

$$R{-}CH{=}CH{-}CHX{-}R' \rightleftarrows R{-}CHX{-}CH{=}CH{-}R'$$

The substituent X moves two atoms along the chain, and the double bond moves in the opposite direction to the position where X is still an allylic group. This migration can occur so readily that it is reasonable to regard the isomerization of allyl halides as true tautomerism. For example, equilibrium between 2-butenyl bromide and 1-methylallyl bromide is set up in a few hours at 75°:[14]

$$CH_3CH{=}CHCH_2Br \rightleftarrows CH_3CHBrCH{=}CH_2$$

It is not thus permissible to assign a structure to an allylic halide on the basis of its method of formation.

The possibility of rearrangement must be borne in mind particularly when considering reactions of allylic compounds. Substitution of S_N1 type, which dominates in polar solvents, always leads to mixtures of isomeric rearrangement products: bimolecular substitution occurs without rearrangement. Thus choice of strongly nucleophilic reactants and, particularly, repression of S_N1 reaction by selection of an apolar solvent such as acetone permit reactions of allylic compounds to be undertaken without rearrangement.[13]

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[10] R. B. Wagner, *J. Amer. Chem. Soc.*, **71**, 3214 (1949).

[11] F. H. Stross, J. M. Monger, and H. De V. Finck, *J. Amer. Chem. Soc.*, **69**, 1627 (1947).

[12] G. Hesse, R. Hatz, and U. Dutt, *Chem. Ber.*, **100**, 923 (1967).

[13] R. H. De Wolfe and W. G. Young, *Chem. Rev.*, **56**, 753 (1956).

[14] W. G. Young and S. Winstein, *J. Amer. Chem. Soc.*, **57**, 2013 (1935).

Allylic rearrangement has enormously increased the difficulty of determining the structure of many compounds of allylic type, but on the other hand there is a whole series of cases in which it has been put to preparative use. For example, Heilbron and his co-workers[15] prepared the dienynediol (**1**) from crotonaldehyde and the Grignard derivative of acetylene and converted it into the isomeric diol (**2**) by a double allylic rearrangement:

$$\mathrm{CH_3CH{=}CHCH(OH)C{\equiv}CCH(OH)CH{=}CHCH_3} \qquad \textbf{(1)}$$
$$\downarrow$$
$$\mathrm{CH_3CH(OH)CH{=}CHC{\equiv}CCH{=}CHCH(OH)CH_3} \qquad \textbf{(2)}$$

A solution of 2,8-decadien-5-yne-4,7-diol (5 g) (**1**) in ether (20 ml) was shaken with 10% sulfuric acid (30 ml) under nitrogen for 24 h at 20°. The ether phase was separated, washed, and dried, and then afforded **3,7-decadien-5-yne-2,9-diol** (4.3 g) as a viscous liquid that distilled at 65–70° (bath temperature)/10^{-4} mm.

Conversion of tertiary into primary alcohols by way of the acetates in accord with the scheme:

$$\underset{\textbf{(3)}}{\mathrm{RCH_2C(CH_3)(OH)CH{=}CH_2}} \longrightarrow \underset{\textbf{(4)}}{\mathrm{RCH_2C(CH_3){=}CHCH_2OH}}$$

has played a part in synthesis of the natural products geraniol, farnesol, and phytol.

Farnesol (**4**; R = $C_{10}H_{17}$):[16] Nerolidol (**3**; R = $C_{10}H_{17}$) (1 part) is heated with acetic anhydride (1.5 parts) under an atmosphere of carbon dioxide for 20 h at 120–140°. The acetic acid formed and the excess of acetic anhydride are removed below 100° in a vacuum and the residue is hydrolysed by alcoholic potassium hydroxide solution under a stream of hydrogen. Subsequent vacuum-distillation gave a forerun containing farnesene (formed by removal of water) and unchanged nerolidol, followed by crude farnesol at 115–130°/0.5 mm. After purification through the hydrogen phthalate the farnesol had b.p. 120–121°/0.3 mm.

The allylic rearrangement is an example of a very widespread type of rearrangement, in which a 1,3 migration is accompanied by shift of a double bond. These isomerizations can be represented formally as:

$$\mathrm{A{=}B{-}C{-}X} \longrightarrow \mathrm{X{-}A{-}B{=}C}$$

where A, B, and C may be carbon, nitrogen, or oxygen, and X is the group that migrates in the rearrangement. For example, if A = B = C = carbon and X = H, the result of this simplest case is the allylic rearrangement:

$\mathrm{{-}CH{=}CH{-}CH_2{-}} \rightleftarrows \mathrm{{-}CH_2{-}CH{=}CH{-}}$ (three-carbon tautomerism)

Other examples are:

$\mathrm{{-}C{=}C{-}O{-}H} \rightleftarrows \mathrm{{-}CH{-}C{=}O}$	Keto–enol tautomerism
$\mathrm{{-}N{=}N{-}C{-}H} \longrightarrow \mathrm{{-}NH{-}N{=}C}$	Conversion of azo compounds into hydrazones
$\mathrm{{-}CH{-}N{=}O} \longrightarrow \mathrm{{-}C{=}N{-}O{-}H}$	Conversion of nitroso compounds into oximes
$\mathrm{{-}C{=}N(O){-}O{-}H} \rightleftarrows \mathrm{{-}CH{-}N(O){=}O}$	Tautomerism of nitro and *aci*-nitro compounds

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[15] J. M. Heilbron, E. R. H. Jones, and R. A. Raphael, *J. Chem. Soc.*, **1943**, 268.

[16] L. Ruzicka, *Helv. Chim. Acta*, **6**, 489 (1923).

3. Migration of a triple bond[17]

Migration of a triple bond was discovered by Favorskii[18] when he found that ethanolic potassium hydroxide solution at 170° converted 1-pentyne into 2-pentyne, but 3-methyl-1-butyne into 3-methyl-1,2-butadiene (1,1-dimethylallene):

$$\mathrm{CH{\equiv}CCH_2CH_2CH_3 \longrightarrow CH_3C{\equiv}CC_2H_5}$$

$$\mathrm{CH{\equiv}CCH(CH_3)_2 \longrightarrow CH_2{=}C{=}C(CH_3)_2}$$

However, according to Jacobs, Akawie, and Cooper,[19] treating either 1- or 2-pentyne with this reagent at 175° for 3 hours affords the same equilibrium mixture of 2-pentyne 95.4%, 1-pentyne 1.3%, and 1,2-pentadiene 3.3%. The equilibrium thus lies almost completely towards the disubstituted acetylene.

The reverse rearrangement, namely, conversion of a disubstituted into a monosubstituted acetylene, can, however, be achieved if the latter can yield salts by means of which it can be continuously removed from the mixture. Thus disubstituted acetylenes pass into monosubstituted acetylenes when heated with sodium at 100°; however, as sodium always reduces the triple bond to some extent, it is preferable to use sodamide as rearrangement agent.

Successive methylation of a sodioacetylene and rearrangement by sodamide provide an elegant method of chain extension:

$$\mathrm{NaC{\equiv}CR \longrightarrow CH_3C{\equiv}CR \text{ —— } NaC{\equiv}CCH_2R}$$

This sequence can be repeated several times, and Bourguel[20] converted 3-cyclohexyl-1-propyne into 6-cyclohexyl-1-hexyne by three-fold chain extension in this way. The following are details for the penultimate rearrangement step:

5-Cyclohexyl-2-pentyne (107 g), sodamide (39 g), and a petroleum fraction of b.p. 125 to 140°/15 mm (300 ml) are mixed and heated at 160°. Evolution of ammonia is complete after 2.5 h. Then part of the solvent is distilled off in a vacuum, unchanged starting material being removed with it. The residue is decomposed by ice, whereafter working up affords **5-cyclohexyl-1-pentyne** (81 g, 89%), b.p. 84–85.5°/16 mm.

Migration of a triple bond over several positions has also been observed and has been utilized for preparative purposes.[21]

II. Rearrangement with change of an oxygen group

1. Conversion of epoxides into carbonyl compounds[22]

The conversion of epoxides into carbonyl compounds is an irreversible reaction. At 400° ethylene oxide (oxirane) passes into acetaldehyde, and at 500° propylene oxide (1-methyloxirane) gives a 2 : 1 mixture of propion-

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[17] T. L. Jacobs, *Org. Reactions*, **5**, 13 (1949).

[18] A. Favorski, *J. Prakt. Chem.*, **44**, 208 (1891).

[19] T. L. Jacobs, R. Akawie, and R. G. Cooper, *J. Amer. Chem. Soc.*, **73**, 1273 (1951).

[20] M. Bourguel, *Ann. Chim. (Paris)*, [10], **3**, 363 (1925).

[21] T. H. Vaughn, *J. Amer. Chem. Soc.*, **55**, 3453 (1933).

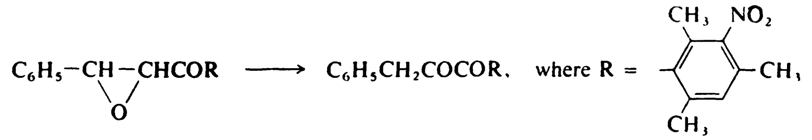
[22] A. Rosowsky in A. Weissberger, "Heterocyclic Compounds with Three- and Four-membered Rings," Interscience Publ., New York–London, 1964, Vol. 19, Part 1, pp. 230 to 270.

aldehyde and acetone.[23] In laboratory practice such changes are generally effected by Lewis acids such as zinc chloride, magnesium bromide, and boron trifluoride.[24]

Studies of the direction of ring opening have often been made more difficult by competition between hydride shift and alkyl shift; this occurs particularly with epoxides derived from multiply branched olefins. Reactions involving hydride shift are the transformation of *cis*-2,3-epoxybutane into butanone,[25] of 1-oxospiro[2.7]decane (the epoxide from methylenecyclooctane) into cyclooctanecarbaldehyde,[26] and that of 1,2-epoxy-1-phenethylcyclohexane into **2-phenethylcyclohexanone** described by Grewe[27] as follows:

The epoxide (10 g), concentrated hydrochloric acid (10 g), and methanol (50 ml) are heated together under reflux for several hours, whereafter the ketonic product is precipitated by water, taken up in ether, and purified by distillation in a vacuum (yield 60%; b.p. 174°/12 mm).

In more recent work alkaline catalysts have been applied for rearrangement of epoxides, *e.g.*:[28,29]



2,3-Epoxy-1-(3-nitromesityl)-3-phenyl-1-propanone (1 mole) and N-aqueous potassium hydroxide solution (1.5 moles) are boiled together in ethanolic solution for 1.5 h, thus affording a 75% yield of **1-(3-nitromesityl)-3-phenyl-1,2-propanedione.**[28]

2. Willgerodt reaction[30,31]

Straight-chain alkyl aryl ketones are converted into amides when heated with ammonium polysulfide above 200°:[32]

$$C_6H_5COCH_3 \xrightarrow{(NH_4)_2S_x} C_6H_5CH_2CONH_2$$

In this reaction it is not the aryl group that migrates, as it does in the Wolff rearrangement (page 1090); on the contrary, the oxygen moves to the end of the chain and the carbon skeleton is unaffected. The reaction is not confined to aryl methyl ketones. For example, propiophenone gives 3-phenylpropionamide:[33]

$$C_6H_5COCH_2CH_3 \longrightarrow C_6H_5CH_2CH_2CONH_2$$

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[23] J. U. Nef, *Ann. Chem.*, **335**, 201 (1904).

[24] H. O. House, *J. Amer. Chem. Soc.*, **77**, 5083 (1955).

[25] E. R. Alexander and D. C. Dittmer, *J. Amer. Chem. Soc.*, **73**, 1665 (1951).

[26] A. C. Cope and P. E. Burton, *J. Amer. Chem. Soc.*, **82**, 5439 (1960).

[27] R. Grewe, *Ber. Deut. Chem. Ges.*, **72**, 1314 (1939).

[28] R. P. Barnes and L. A. Gist, Jr., *J. Amer. Chem. Soc.*, **72**, 2509 (1950).

[29] A. C. Cope and B. D. Tiffany, *J. Amer. Chem. Soc.*, **73**, 4158 (1951).

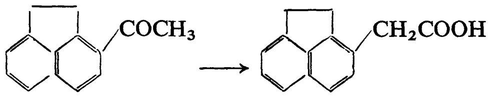
[30] M. Carmack and M. A. Spielman, *Org. Reactions*, **3**, 83 (1949); H. Kaltwasser, *Chem. Tech.* (*Berlin*), **9**, 392 (1957).

[31] W. Foerst, "Neuere Methoden der präparativen organischen Chemie," Verlag Chemie, Weinheim, 1949, pp. (a) 366 (B. Eistert), (b) 378–388 (B. Eistert), (c) 444–448 (D. Kästner); Vol. 3, 1961, pp. (d) 1–8 (R. Wegler, E. Kühle, and W. Schäfer), (e) 136–163 (F. Korte and K. H. Büchel).

[32] C. Willgerodt, *Ber. Deut. Chem. Ges.*, **21**, 534 (1888).

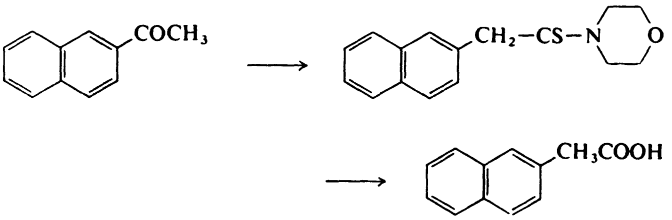
[33] C. Willgerodt and F. H. Merk, *J. Prakt. Chem.*, [ii], **80**, 192 (1909).

Epoxides, acetylenes derivatives, olefins, and alcohols of the alkylaryl series containing unbranched chains can also be used in the Willgerodt reaction. Results are especially good with methyl ketones derived from multifused aromatic compounds such as phenanthrene and pyrene. Fieser and Kilmer[34] give the following directions for converting 1-acenaphthenyl methyl ketone into **1-acenaphtheneacetic acid:**



1-Acenaphthenyl methyl ketone (2 g) is heated with purified dioxan (8 g) and a solution of sulfur (1 g) in ammonium sulfide solution [10 g; prepared by saturating ammonia solution (*d* 0.88) with hydrogen sulfide] in a sealed tube at 160° for 12 h. The crude 1-acenaphthene-acetamide produced is hydrolysed by 4 hours' boiling with 15% sodium hydroxide solution (50 ml), giving a 57% overall yield of the acid.

A reaction temperature of 160–170° can be taken as standard for this technique, but lower temperatures can be used in variants described by Kindler.[35] He described, for example, how a methyl ketone can be converted by an approximately equivalent amount of sulfur and an amine (usually morpholine) into the thioamide which is then hydrolysed to the acid; this reaction is sufficiently fast at the boiling point of morpholine (128°).[36]



A mixture of 2-acetonaphthone (373 g, 2.2 moles), sulfur (105 g, 3.3 moles), and morpholine (290 g, 3.3 moles) are heated together, at first gently to prevent too great foaming and evolution of hydrogen sulfide; the temperature is increased after 1 h and finally the mixture is boiled under reflux for 10–15 h. The hot mixture, which has formed two phases, is then poured into hot ethanol (1200 ml) and set aside for crystallization. This gives **4-[2-naphthyl-(thioacetyl)]morpholine** (534 g, 90%), m.p. 102–108°, which is sufficiently pure for further reactions. It is hydrolysed to the acid by 5 hours' boiling with a mixture of glacial acetic and dilute sulfuric acid.

3. Keto–enol tautomerism

Carbonyl compounds and derivatives of vinyl alcohol exist together in an equilibrium that involves change of position of a proton and a shift of a double bond. Although the amount of enol form is immeasurably small in most aldehydes and ketones, these two forms coexist in comparable amounts when

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[34] L. F. Fieser and G. W. Kilmer, *J. Amer. Chem. Soc.*, **62**, 1354 (1940).

[35] K. Kindler, *Ann. Chem.*, **431**, 193, 222 (1923).

[36] M. Carmack and M. A. Spielman, *Org. Reactions*, **3**, 97 (1949).

the carbon–carbon double bond formed on the enolization is conjugated to another carbonyl group, as in 1,3-diketones and β-oxo esters:

$$\mathrm{RCOCH_2COR'} \rightleftarrows \mathrm{RC(OH){=}CHCOR'}$$

where R′ = alkyl or alkoxyl.

This phenomenon is generally described as tautomerism when rapid and reversible interchange leads to amounts of the two components of the same order of magnitude.

Equilibrium mixtures can be converted wholly into the enolic form through the enolate, but there is no actual chemical method of bringing ketonization about—of shifting the equilibrium completely in that direction—although it can be accelerated catalytically.

Weygand and Koch[37] isolated a pure **enolic form of 2-methyl-1-phenyl-1,3-butanedione** as follows:

$$\mathrm{C_6H_5COCH(CH_3)COCH_3} \longrightarrow \mathrm{C_6H_5C(OH){=}C(CH_3COCH_3}$$

or

$$\mathrm{C_6H_5COC(CH_3){=}C(OH)CH_3}$$

The oily 3-methyl-1-phenyl-1,3-butanedione (1 g) is added to a solution of sodium (0.15 g) in methanol (3 ml), and the deep yellow solution is at once filtered and dropped into 5N-sulfuric acid (30 ml) cooled in ice–salt. The emulsion that is thus first formed must be whipped vigorously with a glass rod to cause solidification, so that most of the material becomes finely powdered and readily filterable; if the oil globules once become large the product does not crystallize well and is unstable. The solid precipitate is at once filtered off, washed with very dilute hydrochloric acid, followed by ice-cold ethanol and then light petroleum, and is finally recrystallized from low-boiling light petroleum in a quartz vessel. The m.p. is 51° and the yield almost quantitative.

4. Isomerization of ketols (acyloins)

von Auwers, Ludewig, and Müller[38] have reported rearrangements of α-ketols (acyloins) in accord with the scheme:

$$\mathrm{RCOCH(OH)R'} \rightleftarrows \mathrm{RCH(OH)COR'}$$

Whereas keto and enol tautomers can be isolated only in the crystalline form and when in solution or melted pass rapidly one into the other, 2-hydroxy-1-phenyl-1-propanone $\mathrm{CH_3CH(OH)COC_6H_5}$ and 1-hydroxy-1-phenyl-2-propanone $\mathrm{CH_3COCH(OH)C_6H_5}$ have not merely been isolated in pure form but also their different chemical properties have been demonstrated. Their interconversion is catalysed by alkali.

The terminal situation of this grouping presents a special case: the equilibrium lies completely on the side of the hydroxy ketone:

$$\mathrm{RCH(OH)CHO} \longrightarrow \mathrm{RCOCH_2OH}$$

For example, mandelaldehyde ($\mathrm{R{=}C_6H_5}$) passes at once into ω-hydroxyacetophenone when liberated from its acetal.[39] Moreover, a partial synthesis

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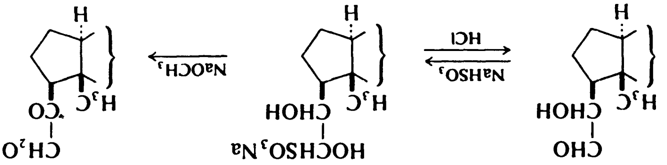
[37] C. Weygand and P. Koch, *Ber. Deut. Chem. Ges.*, **68**, 237 (1935).

[38] K. von Auwers, H. Ludewig, and A. Müller, *Ann. Chem.*, **526**, 143 (1936).

[39] W. G. Dauben, W. L. Evans, and R. I. Meltzer, *J. Amer. Chem. Soc.*, **63**, 1883 (1941).

of corticosterone[40] depended upon this ready transformation:



Corticosterone: 11β,20β-Dihydroxy-3-oxo-4-pregnen-21-al, when treated in aqueous-methanolic solution with sodium hydrogen sulfite, gives the bisulfite compound that is derived from the aldehyde form since the aldehyde is regenerated by decomposition with acid. However, sodium methoxide solution decomposes the bisulfite compound with isomerization to afford the hydroxy ketone, corticosterone, in 60% yield.

5. Cannizzaro rearrangement

α-Oxo aldehydes usually rearrange to α-hydroxy acids under the influence of alkali, *e.g.*, mandelic acid is formed quantitatively from phenylglyoxal:[41]

$$\mathrm{RCOCHO} \xrightarrow{\mathrm{HO}^-} \mathrm{RCH(OH)COOH}$$

This reaction is, however, only of preparative use if the glyoxal derivative is itself obtained in a reaction carried out in alkaline solution, *i.e.*, in the same batch. An example of this is provided by the preparation of **p-bromomandelic acid** from *p*,ω,ω-tribromoacetophenone recorded in *Organic Syntheses*:[42]

$$p\text{-}\mathrm{BrC_6H_4COCHBr_2} \xrightarrow{\mathrm{HO}^-} p\text{-}\mathrm{BrC_6H_4CH(OH)COOH}$$

The hydroxy acid is obtained in 69–83% yield when the tribromo derivative is set aside in aqueous sodium hydroxide solution for several days at 5°.

An elegant synthesis of α-hydroxy acids from the next-lower (non-hydroxylated) carboxylic acids has been described by Weygand and Bestmann.[43] They converted the acid chloride into the diazo ketone by means of diazomethane, treated the diazo ketone with ethanesulfenyl chloride, and decomposed the resulting α-chloro-α-(ethylthio) ketone with aqueous alkali, *e.g.*:

$$\mathrm{C_6H_5COCHN_2} + \mathrm{C_2H_5SCl} \longrightarrow \mathrm{C_6H_5COCHClSC_2H_5} \longrightarrow \mathrm{C_6H_5CH(OH)COOH}$$

Ethanesulfenyl chloride (7.9 g) is added slowly to a solution of diazoacetophenone (12 g) in anhydrous ether (75 ml) at 0–5°. Nitrogen is evolved vigorously. After 2 h at room temperature the ether is removed in a vacuum. The ω-chloro-ω-(ethylthio)acetophenone that is produced almost quantitatively must be at once used for further reaction. The crude product (3 g) is shaken with N-potassium hydroxide solution for 2 h, then warmed for 1 h on a water-bath. After cooling, by-products are removed by extraction with ether; finally **mandelic acid** (formed in 65% yield) is liberated by acidification and is isolated by means of ether.

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[40] D. Taub and co-workers, *J. Amer. Chem. Soc.*, **76**, 4094 (1954).

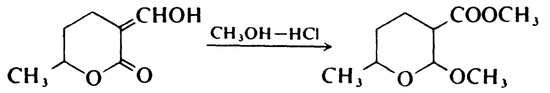
[41] H. von Pechmann, *Ber. Deut. Chem. Ges.*, **20**, 2904 (1887); **22**, 2558 (1889).

[42] J. J. Klingenberg, *Org. Syn.*, **35**, 11 (1955).

[43] F. Weygand and H. J. Bestmann, *Chem. Ber.*, **88**, 1991 (1955).

6. Acyl-lactone rearrangement

The presence of acid causes acyl lactones to undergo ring fission and recyclization to yield carboxylic acid derivatives of cyclic acetals. For example, 2-(hydroxymethylene)-5-hexanolactone can be converted into **methyl tetrahydro-2-methoxy-6-methyl-3-pyrancarboxylate,**[44] as follows:



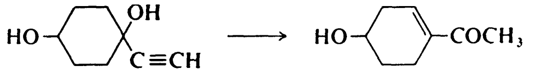
2-(Hydroxymethylene)-5-hexanolactone (118 g) is dissolved in anhydrous methanol (1.2 l) containing 3.4% of hydrogen chloride and is set aside for 48 h at room temperature. The mixture is then stirred into an excess of potassium carbonate solution. Extraction with ether and distillation of the extract affords the ester (125 g, 80%) as a colorless oil, b.p. 43–44°/0.05 mm.

The reaction has been the subject of reviews,[31e,45] from which it will be seen that the reaction can be applied to synthesis of five- and six-membered oxygen-heterocycles, sulfur-heterocycles, bicyclic compounds, and compounds containing an additional heteroatom in the ring.

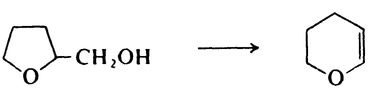
7. Other rearrangements

The rearrangement of α-alkynyl alcohols to vinyl ketones, which occurs when the former are heated with concentrated formic acid, oxalic acid, or phosphoric oxide, is called the Rupe rearrangement after its discoverer.[46]

According to Jones and Sondheimer,[47] 1-ethynyl-1,4-cyclohexanediol is boiled for 2.5 h in 85% formic acid, after which the acid is distilled off in a vacuum, and the residue is heated with water for 30 min (to hydrolyse any formic ester). **4-Hydroxy-1-cyclohexenyl methyl ketone** is thus obtained in 62% yield.



Paul[48] observed that tetrahydrofurfuryl alcohol is converted by dehydration and ring expansion into 3,4-dihydro-2*H*-pyran when passed over alumina at 370–380°; experimental details are given in *Organic Syntheses*.[48]



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[44] F. Korte and H. Machleidt, *Chem. Ber.*, **88**, 1676 (1955).

[45] F. Korte and K. H. Büchel, *Angew. Chem.*, **71**, 709 (1959).

[46] H. Rupe, *Helv. Chim. Acta*, **11**, 454 (1928).

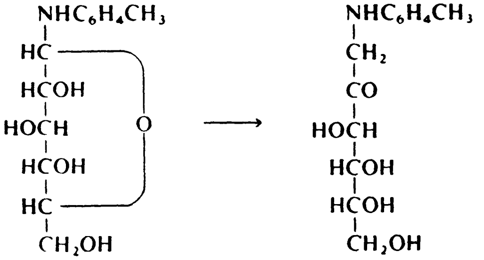
[47] E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, **1949**, 615.

[48] R. Paul, *Compt. rend. Hebd. Séances Acad. Sci.*, **196**, 1409 (1933); R. L. Sawyer and D. W. Andrus, *Org. Syn.*, **23**, 25 (1943).

III. Rearrangement of nitrogen compounds

1. Amadori rearrangement

By condensation of D-glucose with arylamines, Amadori[49] obtained, alongside the glycosylamines, rearrangement products thereof which he considered to be Schiff bases. Kuhn and Weygand,[50] however, showed that these products were 1-arylamino-1-deoxy-2-ketoses, but the rearrangement is nevertheless termed the Amadori rearrangement. As an example, *N*-*p*-tolyl-D-glucosylamine affords 1-deoxo-1-(*p*-tolylamino)-D-fructose:



D-Aldoses are thus converted into D-ketoses. The reaction is analogous to the ketol isomerization described on page 1061.

According to Weygand,[51] the Amadori rearrangement is catalysed by hydrogen ions, but Hodge and Rist achieved this catalysis by means of sodium salts of CH-acidic compounds.[52]

α-D-Glucose (5 g) and dibenzylamine (8.1 g) are mixed and added to a 10% solution (150 ml) of ethyl sodiomalonate in anhydrous ethanol. This mixture is heated on a steam-bath for 2 h, the sugar dissolving during the first 0.5 h. The resulting golden-yellow solution is cooled, filtered, and set aside for 20 h at 0°, then affording **1-deoxy-1-(dibenzylamino)-D-fructose** (8.9 g, 89%), m.p. 161–162°.

2. Chapman rearrangement[53]

The Chapman rearrangement provides an elegant synthesis of unsymmetrical diarylamines that are otherwise difficult of access. When aryl *N*-arylbenzimidoates are heated, the *O*-aryl group migrates to nitrogen while the double bond moves from the N=C to the C=O position. For example, 2,4,6-trichlorophenyl *N*-(*o*-chlorophenyl)benzimidoate is converted quantitatively into *N*-(*o*-chlorophenyl)-*N*-(2,4,6-trichlorophenyl)benzamide when heated for

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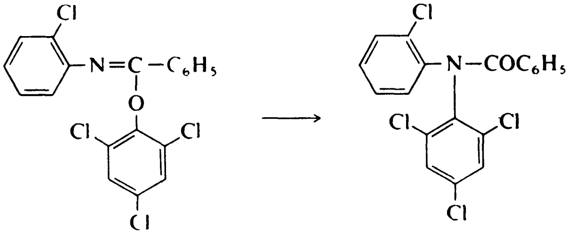
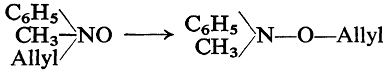
[49] M. Amadori, *Atti Reale Accad. Lincei Roma*, [vi], **2**, 337 (1925).
[50] R. Kuhn and F. Weygand, *Ber. Deut. Chem. Ges.*, **70**, 769 (1937).
[51] F. Weygand, *Ber. Deut. Chem. Ges.*, **73**, 1259 (1940).
[52] J. E. Hodge and C. E. Rist, *J. Amer. Chem. Soc.*, **75**, 316 (1953).
[53] J. W. Schulenberg and S. Archer, *Org. Reactions*, **14**, 1 (1965).

2 hours at 250–270°, thus:[54]



3. Rearrangement of amine oxides

Meisenheimer found that when oxides of tertiary derivatives of arylamines are heated at 100° allyl and benzyl groups can migrate from nitrogen to oxygen whereby *O*-substituted hydroxylamines are formed:[55]

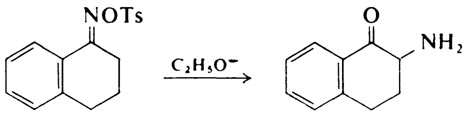


$$\left.\begin{array}{l}C_6H_5\\CH_3\\\text{Allyl}\end{array}\right\rangle NO \longrightarrow \left.\begin{array}{l}C_6H_5\\CH_3\end{array}\right\rangle N{-}O{-}\text{Allyl}$$

Cope and his co-workers[56] later showed that allyl and benzyl groups migrate also within aliphatic amine oxides; *e.g.*, *N*,*N*-dimethylbenzylamine oxide at 160° isomerizes to afford *O*-benzyl-*N*,*N*-dimethylhydroxylamine in 51% yield.[57]

4. Neber rearrangement[58]

The Neber rearrangement is the transition of an oxime *p*-toluenesulfonate into an amino ketone under the influence of an alkoxide, *e.g.*:



(Ts = p-$CH_3C_6H_4SO_2-$)

1,2,3,4-Tetrahydro-1-oxo-2-naphthylammonium chloride: 2-Tetralone oxime *p*-toluenesulfonate (10 g) is suspended in anhydrous ethanol (30 ml) and treated with a solution of potassium (1.3 g) in anhydrous ethanol (15 ml). Reaction is complete in 0.5 h and the solution has become green. Potassium *p*-toluenesulfonate is filtered off and the amino ketone is isolated from the filtrate as the hydrochloride (72%), m.p. 117° (dec.).[59]

A methylene group adjacent to the oxime group is essential for occurrence of the Neber rearrangement. In oximes of unsymmetrical ketones it is the

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[54] A. W. Chapman, *J. Chem. Soc.*, **1929**, 569.

[55] J. Meisenheimer, *Ber. Deut. Chem. Ges.*, **52**, 1667 (1919); **55**, 513 (1922).

[56] A. C. Cope and co-workers, *J. Amer. Chem. Soc.*, **71**, 3423 (1949); **72**, 4896 (1950).

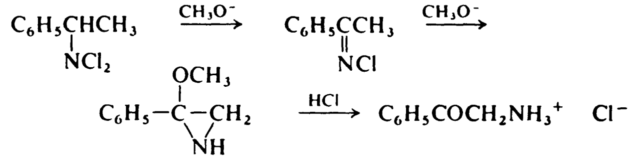
[57] U. Schöllkopf and H. Schäfer, *Ann. Chem.*, **683**, 42 (1965).

[58] C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).

[59] P. W. Neber, A. Burgard, and W. Thier, *Ann. Chem.*, **526**, 277 (1936).

more acidic methylene group that takes part preferentially in the rearrangement. This reaction leads to α-amino ketones even when other methods of preparation such as reduction of hydroxyimino ketones fail, and it has therefore been used to an increasing extent in recent years.

The scope of this rearrangement has been expanded by observations of Baumgarten and his colleagues, who found that *N*,*N*-dichloro amines give amino ketones under the influence of sodium methoxide; *N*-chloro imides are formed as intermediates and are analogous to the oxime toluenesulfonates. The following scheme illustrates these reactions:[60]



IV. Rearrangement of halogen compounds

1. Isomerization

Lucas and Jameson[61] showed that at 248° 1-bromobutane is converted slowly but completely into 2-bromobutane; but this reaction has no preparative importance.

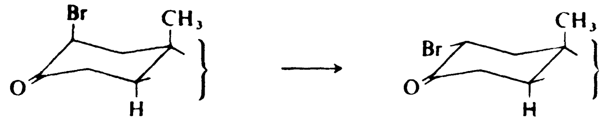
Very much milder conditions suffice for the conversion of α-bromo β-oxo esters into γ-bromo β-oxo esters:[62]

$$CH_3COCHBrCOOR \longrightarrow CH_2BrCOCH_2COOR$$

and the reaction is catalysed by hydrogen bromide.

According to Reid and Fortenbauch,[63] bromination of ethyl 2,5-dimethyl-3-oxohexanoate in chloroform and storage overnight leads to production of the 4-bromo derivative from the 2-bromo derivative that is formed initially.

Such rearrangements are particularly common among brominated steroidal ketones.[64a] Bromination of a steroidal ketone usually affords first the axial bromo ketone which can pass into the stable equatorial isomer in a reaction catalysed by hydrogen bromide:[65]



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[60] H. E. Baumgarten and J. M. Petersen, *Org. Syn.*, **41**, 82 (1961).

[61] H. Lucas and A. Jameson, *J. Amer. Chem. Soc.*, **46**, 2476 (1924).

[62] A. Hantzsch, *Ber. Deut. Chem. Ges.*, **27**, 3168 (1894).

[63] E. B. Reid and N. B. Fortenbauch, *J. Org. Chem.*, **16**, 33 (1951).

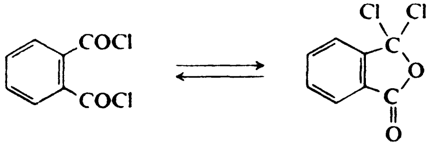
[64] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, pp. (a) 280–294, (b) 283.

[65] E. J. Corey, *J. Amer. Chem. Soc.*, **76**, 175 (1954).

For example, 2β(*ax*)-bromo-5α-cholestan-3-one is so unstable that it cannot be obtained pure and passes into the equatorial isomer even on filtration of its benzene solution over aluminum oxide.[66]

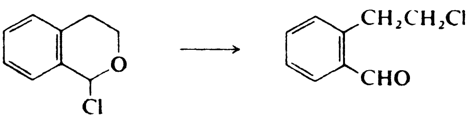
Analogously, the diaxial dibromides formed preferentially from unsaturated steroids in kinetically controlled reactions rearrange to the diequatorial dibromides.[66]

Interconversion of phthaloyl dichloride and its isomer, 3,3-dichlorophthalide, has been studied in especial detail:[67]



At the boiling point the equilibrium lies completely towards the symmetrical phthaloyl dichloride; however, this chloride can be rearranged by aluminum chloride to the unsymmetrical dichlorophthalide since that compound can be withdrawn as its stable complex with the metal salt. Detailed experimentation has been described in *Organic Syntheses*.[68]

α-Halobenzyl ethers rearrange analogously. Thus, Rieche and Schmitz found 1-chloroisochroman to rearrange to **o-(2-chloroethyl)benzaldehyde** when heated, as follows:[69]



Chlorine (71 g) is passed during 4 h into isochroman (134 g, 1 mole) that is placed in a freezing mixture and protected from moisture. The dosage of chlorine was controlled by condensing the gas in a trap cooled in methanol and Dry Ice, weighing it, and passing it to the reaction in a stream of nitrogen. At the start of the reaction care must be taken that the isochroman does not crystallize (m.p. 3°). At the end of the stated time, the product is placed in a vacuum for 1 h, then heated in an oil-bath to 180° and kept at that temperature for 10 min. Finally fractionation through a 50-cm Vigreux column gave first unchanged isochroman (28 g), b.p. 49–51°/0.5 mm, and then *o*-(2-chloroethyl)benzaldehyde (118.4g), b.p. 80–85°/ 0.8 mm (89% based on isochroman that reacted).[70]

2. Rearrangement during reaction of halogen compounds

Rearrangement often occurs when attempts are made to replace a halogen atom by a different group. This applies particularly to reactions of halo carbonyl compounds, which will be illustrated by a few examples in which the carbon skeleton remains unchanged.

When 3-chloro-2,4-pentanedione is treated with an alkali formate, the formyloxy group does not appear at the site of the chlorine atom but at the

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[66] G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, **1954**, 4284.

[67] E. Ott, *Ann. Chem.*, **392**, 245 (1912).

[68] E. Ott, *Org. Syn.*, **11**, 88 (1931).

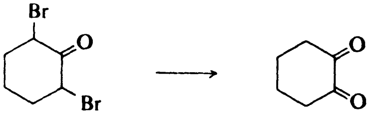
[69] A. Rieche and E. Schmitz, *Chem. Ber.*, **89**, 1254 (1956).

[70] E. Schmitz, *Chem. Ber.*, **91**, 1133 (1958).

neighboring position, the product being 1-methyl-2,3-dioxobutyl formate owing to the rearrangement:[71]

$$CH_3COCHClCOCH_3 \xrightarrow{HCOO^-} CH_3COCOCH(CH_3)OCHO$$

Hydrolysis of 2,6-dibromocyclohexanone gives 1,2-cyclohexanedione:[72]



Similarly, on reaction with *o*-phenylenediamine, 2β,4β-dibromo-5β-cholestan-3-one gives the quinoxaline derived from the 3,4-diketone.[64b]

Thus considerable care is needed when attempting to deduce the structure from reactions of halo carbonyl compounds.

A rearrangement that sometimes has preparative use occurs on hydrolysis of an 1,2-alkylene dibromide where one bromine atom is attached to a tertiary carbon atom. The dibromide may be obtained from the alkene or by bromination of the corresponding tertiary alcohol. Production of **isobutyraldehyde** is a particularly smooth reaction:[73]

$$(CH_3)_3COH \xrightarrow{Br_2} (CH_3)_2CBrCH_2Br \longrightarrow (CH_3)_2CHCHO$$

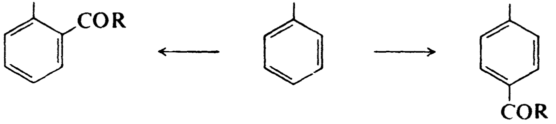
2-Methylpropylene dibromide (2 moles) is heated with water (2 l) in a flask fitted with a fractionating column (90 cm in length). Heating is arranged so that at first the column acts only as a reflux condenser, but later the temperature is increased. When the temperature at the column head reaches 59–64° it is isobutyraldehyde that distils. After 50 h the dibromide layer in the reaction flask has disappeared and much distillate (185 g) has collected. Redistillation gives isobutyraldehyde (108 g, 75%), b.p. 58–65°. The hydrolysis can be accelerated considerably by stirring.

1.2. Rearrangement with extension of the carbon skeleton

I. Migration from oxygen to carbon

1. Fries rearrangement[74]

The Fries rearrangement is the name for the very widespread rearrangement of aryl esters to hydroxyaryl ketones,[75] thus:



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[71] G. Hesse and H. Stahl, *Chem. Ber.*, **2414** (1956), where previous references are cited.

[72] O. Wallach, *Ann. Chem.*, **437**, 173 (1924).

[73] F. C. Whitmore and co-workers, *J. Amer. Chem. Soc.*, **55**, 1136 (1933).

[74] A. H. Blatt, *Org. Reactions*, **1**, 342 (1947).

[75] K. Fries and G. Fink, *Ber. Deut. Chem. Ges.*, **41**, 4271 (1908).

Experimentally this is a very important reaction, for on it are based many syntheses of hydroxyaryl ketones of great practical importance. The reason for this, as Fries himself remarked, is that direct introduction of an acetyl group — and particularly of a substituted acetyl group — is by no means as smooth a route as the by-way through the aryl ester since reaction of phenols with aluminum chloride sometimes leads to most unsatisfactory products. Moreover, the technique used for a Fries rearrangement requires very little modification to be suitable for a large number of esters.

The Fries rearrangement is carried out under conditions similar to those used for Friedel–Crafts acylation, except that higher temperatures are usually required. The solvent used is almost always nitrobenzene, more rarely carbon disulfide, light petroleum, or chlorobenzene. Aluminum chloride in stoichiometric proportions is the usual catalyst, but it should be noted that this reagent sometimes causes a shift or loss of nuclear alkyl groups. Meerwein and Kastner[31c] studied the application of boron trifluoride as catalyst, and Dann and Mylius[76] investigated carrying out the rearrangement in anhydrous hydrogen fluoride.

Migration of the acyl group may be to the *ortho-* or to the *para*-position. The ratio of *ortho-* to *para*-isomer formed depends on the structure of the aryl ester used, but can be influenced within limits by variation of the temperature, the solvent, and the nature and amount of the catalyst. Low temperatures (below 60°) favor migration to the *para*-position, higher temperatures favor *ortho*-migration. This influence is particularly developed in the case of *m*-tolyl acetate, which at 25° gives 80% of 4-hydroxy-2-methylacetophenone (the *para*-product) but at 165° gives 95% of 2-hydroxy-4-methylacetophenone.[77] However, formation of a desired product cannot always be achieved in such ways; then the mixture of isomeric hydroxy ketones can often be separated by steam-distillation, the *ortho*-hydroxy ketone being volatile in steam and the *para*-isomer involatile.

Freudenberg and Orthner have described the rearrangement of phenyl acetate to **o-hydroxyacetophenone** as follows:[78]

Aluminum chloride (200 g), is added in portions to phenyl acetate (100 g), initially with cooling, and when the violent reaction has moderated the mixture is heated for 5 h at 120°, then decomposed with ice, and distilled in steam superheated to 150°. Working up the distillate affords *o*-hydroxyacetophenone (37 g), b.p. 91–92°/13 mm.

Dann and Mylius[76] obtained **p-hydroxyacetophenone** in good yield by working in anhydrous hydrogen fluoride, as follows:

Phenyl acetate (10 g) and technical anhydrous hydrogen fluoride (20 ml) are mixed in a cast-steel bomb at 0° and then heated at 100° for 3 h with occasional shaking. After cooling, most of the hydrogen fluoride is removed on a water-bath, and the residue is nearly neutralized by concentrated sodium hydroxide solution and then extracted with ether. After removal of the ether, steam-volatile portions of the residue are removed; the material involatile in steam crystallizes on cooling, to afford an 80% yield of *p*-hydroxyacetophenone, m.p. 105–107°.

The Fries rearrangement can be applied to acyl derivatives of heterocycles

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[76] O. Dann and G. Mylius, *Ann. Chem.*, **587**, 1 (1954).

[77] K. Rosenmund and W. Schnurr, *Ann. Chem.*, **460**, 56 (1928).

[78] K. Freudenberg and L. Orthner, *Ber. Deut. Chem. Ges.*, **55**, 1748 (1922).

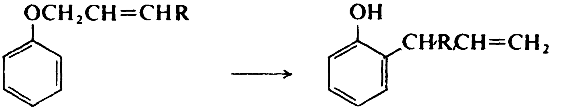
that contain an acid imino group. For example, 3- and a little 1-acetylcarbazole are obtained from 9-acetylcarbazole.[79]

2. Claisen rearrangement[3d,80]

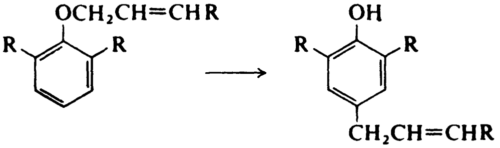
In 1912 Claisen observed the rearrangement of enol allyl ethers to *C*-allyl compounds, *e.g.*, with acetoacetic ester and acetylacetone:[81]

$$CH_3COCH{=}C(CH_3)OCH_2CH{=}CH_2 \longrightarrow (CH_3CO)_2CHCH_2CH{=}CH_2$$

Of greater preparative value is the rearrangement of allyl aryl ethers to allylphenols, also discovered by Claisen:



If at least one *ortho*-position is free, *ortho*-migration always occurs, and the allyl group reappears after suffering an allylic rearrangement. If neither *ortho*-position is free, the allyl group moves to the *para*-position but now usually without the allylic rearrangement:



The reaction occurs without the need for a catalyst and is a typical multicenter reaction that is little dependent on the solvent. The usual reaction temperature is around 200° and oxygen is preferably excluded. The aryl ether is heated either alone or in boiling dimethylaniline (b.p. 193°) or diethylaniline (b.p. 215°). Ring substituents have little influence on the reaction, Claisen rearrangements having been effected both with a nitro group and with an acetylamino group in the ring.

Claisen[82] heated allyl phenyl ether in a carbon dioxide atmosphere at the boiling point until a thermometer in the liquid showed a rise from 190° to around 220°. This usually requires about 6 h; if the temperature does not quite reach 220°, further heating has no purpose since this will be due to formation of rather more than usual of the by-product 2,3-dihydro-2-methylbenzofuran which depresses the boiling point of *o*-allylphenol. To remove the 4–6% of 2,3-dihydro-2-methylbenzofuran that is always present, the product is dissolved in twice its volume of 20% sodium hydroxide solution and extracted twice with light petroleum. Acidification of the aqueous phase, removing the organic material in ether, drying this extract over calcium chloride, and distilling it affords **o-allylphenol**, b.p. 99°/12 mm in more

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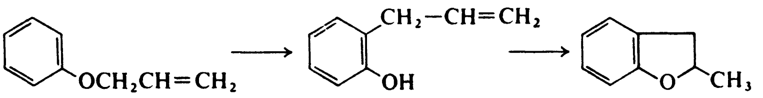
[79] E. Meitzner, *J. Amer. Chem. Soc.*, **57**, 2327 (1935).

[80] D. S. Tarbell, *Org. Reactions*, **2**, 1 (1948); D. L. Dalrymple, T. L. Kruger, and W. N. White in S. Patai, "The Chemistry of the Ether Linkage," Interscience Publ., London, 1967, p. 635.

[81] L. Claisen, *Ber. Deut. Chem. Ges.*, **45**, 3157 (1912).

[82] L. Claisen, *Ann. Chem.*, **418**, 79 (1919).

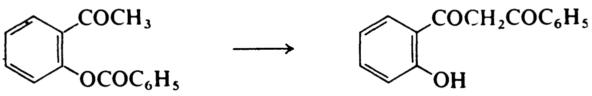
than 80% yield. Addition of pyridine hydrochloride increases the yield of 2,3-dihydro-2-methylbenzofuran to 60%.



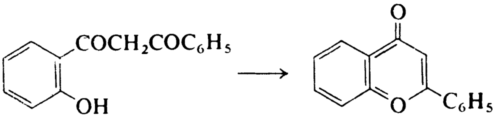
The allyl group has such a strong tendency to move into the ring that repetition of the above process, *i.e.*, etherification of the *o*-allylphenol and a second rearrangement, leads first to 2,6-diallylphenol, and by a further repetition to 2,4,6-triallylphenol. When 3,5-diallyl-2-allyloxybenzoic acid is rearranged, the migrating allyl group even expels the carboxyl group, affording 2,4,6-triallylphenol and carbon dioxide:

3. Baker–Venkataraman rearrangement

The rearrangement of 2-aroyloxyacetophenones to 2-hydroxy derivatives of dibenzoylmethanes, thus:



was reported simultaneously by Baker[83] and Venkataraman.[84] It occurs in the presence of basic catalysts such as potassium carbonate, sodamide, or sodium ethoxide. The rearrangement can be regarded as an intramolecular Claisen condensation. It has considerable preparative importance because the rearrangement products can be easily cyclized to flavones by, *e.g.*, hydrogen bromide in glacial acetic acid:



According to Cramer and Elschnig,[85] sodium ethoxide (10 g) is added to 2-(*o*-toluyloxy)-acetophenone (10 g) in anhydrous benzene (200 ml), and the mixture is boiled on a water-bath for 20 min, then cooled and extracted with dilute hydrochloric acid. The benzene layer is dried and evaporated and the residue is recrystallized from methanol with charcoal, affording **1-(*o*-hydroxyphenyl)-3-(*o*-tolyl)-1,3-propanedione** (4.2 g, 42%) as pale yellow crystals, m.p. 96–97°.

4. Benzyl ether rearrangement

In 1925 Schorigin obtained 1,2-diphenylethanol on heating dibenzyl ether with metallic sodium for a long time at 100°:[86]

$$C_6H_5CH_2\text{—}O\text{—}CH_2C_6H_5 \longrightarrow C_6H_5CH_2CH(C_6H_5)OH$$

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[83] W. Baker, *J. Chem. Soc.*, **1933**, 1381.

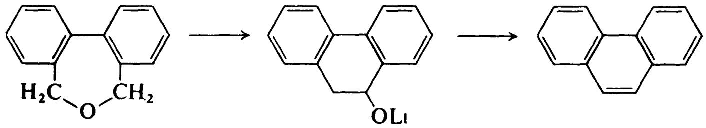
[84] K. Venkataraman, *Curr. Sci.*, **2**, 214 (1933).

[85] F. Cramer and G. H. Elschnig, *Chem. Ber.*, **89**, 8 (1956).

[86] P. Schorigin, *Ber. Deut. Chem. Ges.*, **58**, 2031 (1925).

At first the reaction found no preparative application because the energetic conditions needed did not allow use of complex compounds whereas the simple phenylalkanols are more easily accessible by other routes.

Later, however, Wittig, by introducing phenyllithium as metalating agent, was able to isomerize benzyl ethers at room temperature. The preparative uses of the benzyl ether rearrangement that this made possible may be exemplified by a synthesis of **phenanthrene**, as follows:[87]

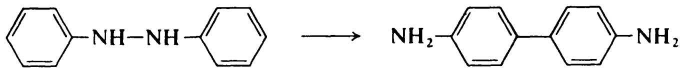


A 1.3N-solution (2 ml) of phenyllithium is added to a solution of 2,7-dihydrodibenz[*c*,*e*]-oxepin (0.4 g, 2 mmoles) in anhydrous ether (15 ml), and the mixture is set aside for a week. A pale red color is formed gradually but fades again, and colorless crystals separate during this time. Addition of water and evaporation of the ether leave 9.10-dihydro-9-phenanthrol (0.3 g, 77%). Removal of water by sulfuric acid in glacial acetic acid leads smoothly to phenanthrene.

II. Migration from nitrogen to carbon

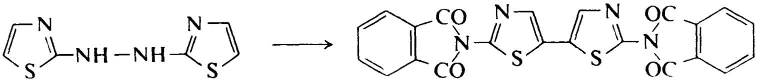
1. Benzidine rearrangement

The rearrangement of hydrazobenzene to benzidine under the influence of strong acids is the prototype of numerous similar reactions which are therefore called benzidine rearrangements. Benzidines are intermediates in the production of substantive wool dyes.



When a solution of hydrazobenzene in the minimum of ether is dropped into ice-cold 18% hydrochloric acid, crystalline **benzidine hydrochloride** separates.[88b]

Benzidine rearrangements in the thiazole series have been described by Beyer and Kreutzberger,[89] but they are successfull only if the diamine produced is trapped by conversion into the phthaloylamino compound by reaction with phthalic anhydride:



2,2′-Hydrazothiazole dihydrochloride (10.9 g) is intimately ground with phthalic anhydride (11.9 g), and the mixture is heated in an oil-bath, beginning to sinter above 100°. Phthalic anhydride that sublimes is returned to the reacting mixture from time to time. The mixture is kept at 180–200° for 1 h with periodic stirring. Then dark decomposition products are

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[87] G. Wittig, P. Davis, and G. König, *Chem. Ber.*, **84**, 630 (1951).

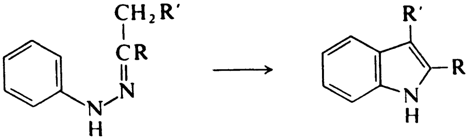
[88] L. Gattermann and H. Wieland, "Die Praxis des organischen Chemikers," Walter Gruyter and Co., Verlin, 33rd ed., 1947, pp. (a) 138, (b) 172, (c) 204.

[89] H. Beyer and A. Kreutzberger, *Chem. Ber.*, **84**, 518 (1951).

removed by extraction with boiling pyridine and sodium carbonate solution. **2,2′-Di(phthalimido)-5,5′-bithiazole** is left as a yellowish-grey powder insoluble in all solvents. The phthaloyl groups are removed by hot fuming hydrochloric acid.

2. Emil Fischer indole synthesis[90]

The mechanism of the Fischer indole synthesis is related to that of the benzidine rearrangement.[91] This synthesis consists of the preparation of indole and substituted indoles by heating the phenylhydrazones or substituted phenylhydrazones of aldehydes, ketones, or oxo acids with reagents such as zinc chloride, or mineral acids that lead to elimination of ammonia, thus:[92]



The reaction has acquired great importance for the synthesis of natural products: *e.g.*, the total synthesis of strychnine[93] begins with the preparation of 2-(3,4-dimethoxyphenyl)indole from acetoveratrone and phenylhydrazine.

Detailed directions for the preparation of **2-phenylindole** from acetophenone phenylhydrazone are given in *Organic Syntheses*:[94]

A mixture of freshly prepared acetophenone phenylhydrazone (53 g) and powdered anhydrous zinc chloride (250 g) is stirred manually while heated in an oil-bath at 170°. After 3–4 min the mass liquefies and white fumes are evolved. The oil-bath is then removed and stirring continued for a further 5 min, after which working up affords a 72–80% yield of 2-phenylindole, m.p. 188–189°.

This method is a particularly good one for the preparation of tetrahydrocarbazoles from cyclohexanone and phenylhydrazine or its derivatives; in this case glacial acetic acid suffices as condensing agent.

As described by Rogers *et al.* in *Organic Syntheses*,[95] phenylhydrazine (108 g) is added during 1 h to a stirred, boiling mixture of cyclohexanone (98 g) and glacial acetic acid (360 g), then the whole is boiled for a further 1 h. After cooling, with stirring, to 5°, the crystalline **1,2,3,4-tetrahydrocarbazole** is filtered off, washed with water and then with 75% ethanol, and recrystallized from methanol. The yield is 75–85%, and the m.p. 115–116°.

3. Stevens rearrangement

A substituent migrates from nitrogen to the α-carbon atom of certain quaternary ammonium salts under the influence of strong bases; the reaction may be exemplified as follows when R is, for instance, phenyl:[96]

$$RCH_2\overset{+}{N}(CH_3)_2CH_2C_6H_5 \longrightarrow R{-}\overset{-}{C}H{-}\overset{+}{N}(CH_3)_2CH_6C_6H_5 \longrightarrow$$
$$C_6H_5CH_2{-}CHR{-}N(CH_3)_2$$

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[90] B. Robinson, *Chem. Rev.*, **63**, 373 (1963).

[91] G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **1918**, 639.

[92] Ger. Pat. 38,784; *Friedländer*, **1**, 151 (1886); E. Fischer and O. Hess, *Ber. Deut. Chem. Ges.*, **17**, 559 (1884).

[93] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).

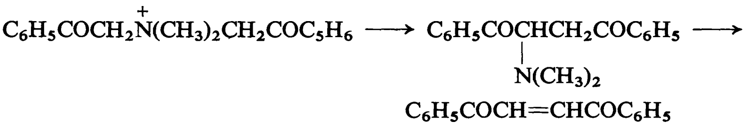
[94] R. L. Shriner, W. C. Ashley, and H. Coonradt, *Org. Syn.*, **22**, 98 (1942).

[95] C. U. Rogers and B. B. Corson, *Org. Syn.*, **30**, 90 (1950).

[96] T. Thomsen and T. S. Stevens, *J. Chem. Soc.*, **1932**, 1932.

According to Wittig,[97] the base (sodium alkoxide, phenyllithium, or sodamide) removes a proton from the α-carbon atom, yielding the unstable ylide in which the benzyl group then migrates from nitrogen to carbon.

As a preparative example we reproduce the directions of Heffe and Kröhnke[98] for conversion of diphenacylammonium bromides into dibenzoylethylene; it is brought about by even relatively weak bases such as aqueous dimethylamine or dilute sodium hydroxide solution:



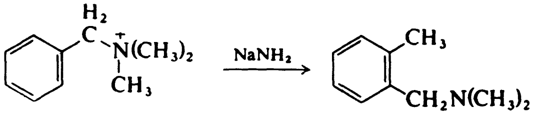
$$C_6H_5COCH_2\overset{+}{N}(CH_3)_2CH_2COC_5H_6 \longrightarrow C_6H_5CO\underset{\underset{N(CH_3)_2}{|}}{C}HCH_2COC_6H_5 \longrightarrow C_6H_5COCH{=}CHCOC_6H_5$$

N,*N*-Dimethyldiphenacylammonium bromide is stirred in aqueous 33% dimethylamine solution (10 parts) at room temperature. After a short time the yellow color fades and the solution becomes milky. The mixture is cooled to 0° and crystallization is brought about by seeding. After being kept for 8 h at 0°, the *N*,*N*-dimethyl-1-benzoyl-3-oxo-3-phenylpropylamine is filtered off (yield 78%), washed with water, and recrystallized from methanol, forming crystals of m.p. 65°.

Warming this amine in neutral or weakly acidic solution leads to loss of dimethylamine and formation of **dibenzoylethylene.**

4. Sommelet rearrangement

The Stevens rearrangement is often accompanied by a side reaction in which the benzene ring is alkylated in the *ortho*-position,[99] and this can be made into the main reaction by working at a low temperature. It receives its name from Sommelet who first observed a rearrangement of this type,[100] but it derives its preparative importance from work by Cantor and Hauser.[101] The rearrangement occurs almost instantaneously at the boiling point of ammonia (−33°) if sodamide is used as metallating agent. Directions for the preparation *N*,*N*,2-trimethylbenzylamine from *N*,*N*,*N*-trimethylbenzylammonium iodide in 90–95% yield is described in *Organic Syntheses.*[102]



By replication of alternate quaternization and Sommelet rearrangement of *N*,*N*-dimethylbenzylamine Cantor and Hauser[101] reached finally the fully methylated benzylamine $(CH_3)_5C—CH_2N(CH_3)_2$.

III. Migration from sulfur to carbon

The Stevens and the Sommelet rearrangement have their analogs in rearrangement of sulfonium salts by strong bases.

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[97] G. Wittig, *Angew. Chem.*, **66**, 10 (1954).

[98] W. Heffe and F. Kröhnke, *Chem. Ber.*, **89**, 835 (1956).

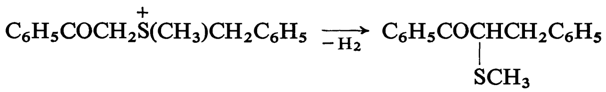
[99] G. Wittig, *Ann. Chem.*, **560**, 116 (1948).

[100] M. Sommelet, *Compt. rend. Hebd. Séances Acad. Sci.*, **205**, 56 (1937).

[101] S. W. Cantor and C. R. Hauser, *J. Amer. Chem. Soc.*, **73**, 4122 (1951).

[102] W. R. Brasen and C. R. Hauser, *Org. Syn.*, **34**, 61 (1954).

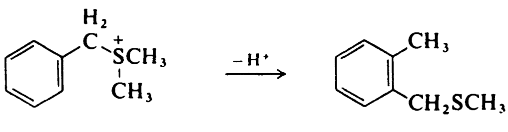
Rearrangement of benzylmethylphenacylsulfonium bromide to 2-(methylthio)-3-phenylpropiophenone occurs analogously to the former in a reaction also described by Stevens and a collaborator:[103]



$$C_6H_5COCH_2\overset{+}{S}(CH_3)CH_2C_6H_5 \xrightarrow[-H_2]{} C_6H_5CO\underset{\substack{|\\ SCH_3}}{C}HCH_2C_6H_5$$

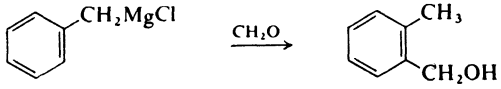
Krollpfeifer and Hartmann[104] describe this reaction as follows: The sulfonium bromide (40 g) is added to a solution prepared from sodium (8 g) and methanol (580 ml), and the mixture is heated for 1 h on the water-bath. The methanol is then removed in steam, and the residual oily **2-(methylthio)-3-phenylpropiophenone** is taken up in ether, dried over calcium chloride, and recovered by evaporation. It crystallizes when rubbed and after recrystallization from ethanol has m.p. 55–56° (yield 81%).

Rearrangements of Sommelet type have been described for sulfonium salts by Hauser, Cantor, and Brasen.[105] For example, sodamide converts *S*,*S*-dimethylbenzylsulfonium bromide in boiling ether into methyl 2-methylbenzyl sulfide:



IV. Benzyl-*o*-tolyl rearrangement

Treatment of benzylmagnesium chloride with formaldehyde leads, not to phenethyl alcohol, but to 2-methylbenzyl alcohol:[106]



Smith and Spillane[107] describe this reaction as follows:

Paraformaldehyde (165 g; dried for several days over phosphoric oxide in a vacuum) is added to a filtered ethereal solution of benzylmagnesium chloride (from 3.4 moles of benzyl chloride). The mixture is boiled, with stirring, for 18 h, then poured on ice and acidified with dilute sulfuric acid. The organic layer is washed successively with water, 5% sodium carbonate solution and water. The aqueous phases are extracted with ether, and these extracts are washed as before. Fractionation of the united ethereal layers through a filled column afford **2-methylbenzyl alcohol** (248–263 g, 59–63%), b.p. 106–109°/12 mm.

The alcohol thus obtained can be converted into its chloride and subjected to similar reaction. By three successive such rearrangements, Reichstein and his co-workers[108] obtained 2,3,4-trimethylbenzyl alcohol, but the yields in the later stages were unsatisfactory.

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[103] T. Thomsen and T. S. Stevens, *J. Chem. Soc.*, **1932**, 69.

[104] F. Krollpfeifer and H. Hartmann, *Chem. Ber.*, **83**, 97 (1950).

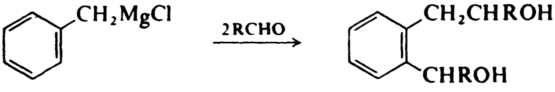
[105] C. R. Hauser, S. W. Cantor, and W. R. Brasen, *J. Amer. Chem. Soc.*, **75**, 2660 (1953).

[106] M. Tiffeneau and R. Delange, *Compt. rend. Hebd. Séances Acad. Sci.*, **137**, 573 (1903).

[107] L. I. Smith and L. J. Spillane, *J. Amer. Chem. Soc.*, **62**, 2639 (1940).

[108] T. Reichstein and co-workers, *Helv. Chim. Acta*, **19**, 412 (1936).

Higher aldehydes react with benzylmagnesium chloride partially with formation of diols, thus:[109]

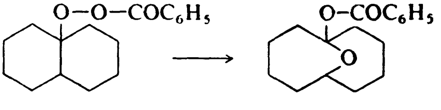


1.3. Rearrangement with degradation of the carbon skeleton

I. Migration from carbon to oxygen

1. Criegee rearrangement

In 1944 Criegee[110] observed that benzoyl 4a-decalyl peroxide was rearranged by heat to an isomer for which the structure of a benzoylated hemiacetal was proved:



Benzoyl 4a-decalyl peroxide (m.p. 67–68°; 0.28 g) was boiled for 1 min with pyridine hydrochloride (0.2 g) in pyridine (2 ml). After cooling, the mixture was poured into dilute sulfuric acid, and the precipitated oil was placed in a refrigerator for crystallization. This afforded **11-oxabicyclo[4.4.1]undecan-1-yl benzoate** (0.15 g) which after recrystallization from aqueous methanol had m.p. 96–97°.

This reaction is an example of the fission of a carbon–carbon bond that had been known for some time previously to occur with many organic peroxides. This occurs, for instance, in the industrially important acid fission of "cumyl hydroperoxide" (α,α-dimethylbenzyl hydroperoxide) to phenol and acetone, as follows:[111]

$$C_6H_5C(CH_3)_2OOH \xrightarrow{H^+} C_6H_5\overset{+}{O}C(CH_3)_2 \xrightarrow{H_2O} C_6H_5O{-}C(CH_3)_2OH$$

The protonated hydroperoxide undergoes heterolysis of the oxygen–oxygen bond which is coupled with migration of the phenyl group; the carbenium ion thus formed takes up water to yield an unstable hemiketal which at once breaks down to phenol and acetone. This acid fission is carried out with advantage in glacial acetic acid containing a catalytic amount of perchloric acid.[112]

A systematic investigation by Hedaya and Winstein[113] has shown that the rate of rearrangement depends especially strongly on the nature of the migrating group; for *p*-nitrobenzoic esters of *tert*-alkyl hydroperoxides the rates of migration of methyl, ethyl, isopropyl, and *tert*-butyl groups are in the ratios 1 : 45 : 2940 : 22,800.

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[109] *E.g.*, S. Siegel, S. K. Coburn, and D. R. Levering, *J. Amer. Chem. Soc.*, **73**, 3163 (1951).

[110] R. Criegee, *Ber. Deut. Chem. Ges.*, **77**, 724 (1944).

[111] H. Hock and S. Lang, *Ber. Deut. Chem. Ges.*, **77**, 257 (1944).

[112] M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **15**, 748 (1950).

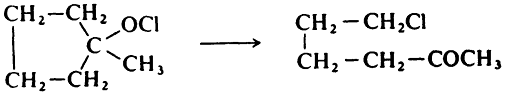
[113] E. Hedaya and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1661 (1967).

The insertion of peroxidic oxygen between the α- and the β-carbon atom is also responsible for the abnormal course often observed in ozonization of olefins:[114] many examples are known in which ozonization of olefins having a functional group next to the double bond causes, not only cleavage at the double bond, but also cleavage of the single bond leading to that functional group; formaldehyde, for instance, is formed when crotonaldehyde is ozonized, thus:[115]

$$\mathrm{CH_3{-}CH{=}\,\vdots\,{=}CH{-}\,\vdots\,{-}CHO}$$

2. Hypochlorite rearrangement

On attempted vacuum-distillation of the 1-methylcyclopentyl hypochlorite obtained by chlorination of 1-methylcyclopentanol in alkaline solution, Cairns and Englund[116] observed quantitative rearrangement of this material to 6-chloro-2-hexanone:

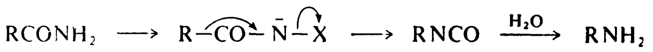


This reaction opens a route to ω-halo ketones that are otherwise difficultly accessible. It has been recognized as a radical chain reaction.[117]

II. Migration from carbon to nitrogen

1. Hofmann amide degradation[118]

In the Hofmann degradation an amide is *N*-halogenated in alkaline solution, and then removal of the halogen from the nitrogen triggers off migration of a group from the neighboring carbon atom. When the reaction is effected in aqueous solution the isocyanate formed decomposes hydrolytically to carbon dioxide and an amine that contains one fewer carbon atoms than were in the starting material. Migration of an optically active group occurs with retention of configuration.[3]



$$\mathrm{RCONH_2 \longrightarrow R{-}CO{-}\overset{-}{N}{-}X \longrightarrow RNCO \xrightarrow{H_2O} RNH_2}$$

The reaction is generally carried out by warming the amide in aqueous hypohalite solution rapidly to about 70°. Allen and Wolf give the following directions in *Organic Syntheses*[119] for conversion of nicotinamide into **3-pyridinamine:**

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[114] J. E. Leffler, *Chem. Rev.*, **45**, 385 (1949).

[115] W. G. Young and co-workers, *J. Amer. Chem. Soc.*, **68**, 293 (1946).

[116] T. L. Cairns and B. E. Englund, *J. Org. Chem.*, **21**, 140 (1956).

[117] F. D. Greene, M. L. Saritz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963).

[118] E. S. Wallis and S. F. Lane, *Org. Reactions*, **3**, 267 (1949).

[119] C. F. H. Allen and C. N. Wolf, *Org. Syn.*, **30**, 3 (1950).

A solution of sodium hypobromite is prepared under cooling by ice and salt from bromine (95.8 g) and a solution of sodium hydroxide (75 g) in water (800 ml). To this solution at 0° is added finely powdered nicotinamide (60 g) in one portion; with rapid stirring the amide dissolves within 15 min. The mixture is then placed in a water-bath at 75° and is kept at 70–75° for 45 min. Working up (see *Organic Syntheses*[119] for details) yields 3-pyridinamine (60–65%).

When the reaction is carried out in aqueous solution, aliphatic acid amides having six or more carbon atoms tend to give the *N*-acyl-*N'*-alkylurea, whose formation can be interpreted as being from the alkali salt of the *N*-halo amide and the isocyanate formed as intermediate. For such cases Jeffreys[120] prefers to use alcoholic solutions and to hydrolyse the resulting urethane to the amine.

Palmitamide (25.5 g) is dissolved in methanol (65 g) by gentle warming, mixed with a solution from sodium (4.6 g) in methanol (115 g), and treated at once with bromine (16 g) dropwise; however, the order of mixing is unimportant, as the bromine may be added to the amide before the methoxide solution. The mixture is next warmed for 10 min on a water-bath, after which it is neutralized with acetic acid. The methanol is distilled off, the residue is taken up in water, and the urethane (**methyl *N*-pentadecylcarbamate**) is filtered off, washed, dried, and taken up in warm light petroleum (b.p. 70–80°) in which unchanged amide is insoluble. The urethane, m.p. 60–62°, is then recovered from the petroleum (84–93%).

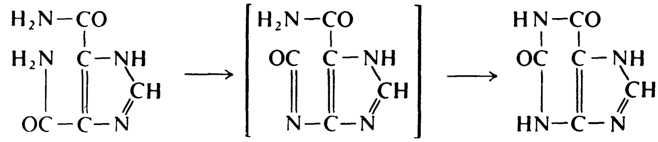
The urethane is thoroughly mixed with a four-fold amount of calcium hydroxide and the mixture is distilled. The **pentadecylamine** formed passes over quantitatively. It is taken up in light petroleum, dried over potassium hydroxide, and distilled from sodium. It melts at 36.5° and boils at 298–301°.

For larger batches the expensive sodium hypobromite may be replaced by hypochlorite.

Hofmann degradation of α-hydroxy acids and α,β-unsaturated acids gives aldehydes containing one fewer carbon atoms, a reaction that can be used for preparation of phenylacetaldehyde, thus:

$$C_6H_5CH{=}CHCOOH \longrightarrow [C_6H_5CH{=}CHNH_2] \longrightarrow C_6H_5CH_2CHO$$

When the reaction is applied to dicarboxamides of suitable chain length, reaction of one amide group may be followed by ring closure to yield the acylurea. For example, 4,5-imidazoledicarboxamide gives xanthine:[121]



2. Curtius degradation[122]

The synthetic purpose of a Hofmann degradation may also be achieved by thermal decomposition of an acid azide, a reaction that is known as the Curtius degradation:

$$RCON_3 \longrightarrow RNCO + N_2$$

In contrast to the Hofmann reaction, the isocyanate can be isolated by using an inert solvent such as benzene.

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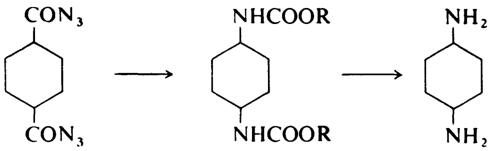
[120] E. Jeffreys, *Ber. Deut. Chem. Ges.*, **30**, 898 (1897).

[121] R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, **1945**, 232.

[122] P. A. S. Smith, *Org. Reactions*, **3**, 337 (1949).

Phenyl isocyanate:[88a] Completely dry benzazide (12 g) is heated in benzene (40 ml; dried over sodium) cautiously and slowly to 60–70°, whereupon lively evolution of nitrogen sets in. When the main reaction is over, the temperature is raised to 80° and the benzene is distilled off at atmospheric pressure, followed by the phenyl isocyanate (7–8 g) at 60°/20 mm.

Decomposing the azide in alcoholic solution affords the urethane, which can then be hydrolysed to the amine by concentrated hydrochloric acid, *e.g.*:



1,4-Cyclohexanediamine:[123] *trans*-1,4-Cyclohexanedicarbonyl diazide (5 g) is heated under reflux in anhydrous ethanol (200 ml) for 2 h. The solution is filtered and concentrated in a vacuum. On cooling, **diethyl *N,N'*-1,4-cyclohexylenedicarbamate,** m.p. 236° (5.2–5.5 g, 90–95%), crystallizes.

A mixture of this urethane (4.8 g) and concentrated hydrochloric acid (50 ml) is heated in a sealed tube at 120° for 7 h or under reflux for 24 h and then evaporated to dryness, which affords **1,4-cyclohexanediamine dihydrochloride** in 95–98% yield.

It is not always necessary for the Curtius reaction that the azide be isolated in substance. It is often possible to treat an acyl halide with sodium azide and reach the isocyanate in one stage. This variant may be exemplified by the preparation of **methyl isocyanate** as follows:[124]

Sodium azide (14.5 g) in dipentyl ether (100 ml) is treated with acetyl chloride (15.5 g) with cooling. Reaction begins when the mixture is warmed to 60–70° and soon becomes very vigorous. The methyl isocyanate distils off through a reflux condenser and is condensed in a receiver cooled in a freezing mixture; collection of the isocyanate is completed by letting the water out of the condenser and increasing the heating. Fractionation of the distillate (10 g) gives pure methyl isocyanate (8 g), b.p. 42–43°.

According to von Braun,[125] Curtius degradation of α-bromo carboxylic acids provides a practical synthesis of aldehydes or ketones containing one fewer carbon atoms. The reaction from the α-bromo carbonyl chloride runs through the following steps:

$$\mathrm{RCHBrCOCl} \xrightarrow{\mathrm{NaN_3}} \mathrm{RCHBrCON_3} \longrightarrow \mathrm{RCHBrNCO} \xrightarrow{\mathrm{KOH}}$$

$$\mathrm{RCHBrNH_2} \longrightarrow \mathrm{RCHO}$$

None of these intermediates need be isolated. Yields of carbonyl compound are around 60%.

For example, a solution of 2-bromo-5-phenylvaleryl chloride in benzene is treated with sodium azide (1.5 equivalents) that has preferably been activated by hydrazine as described by Nelles.[126] Brief warming on the water-bath initiates the reaction. For hydrolysis of the isocyanate produced, the solution is cooled, treated with a cold solution of potassium hydroxide (2.5 equivalents) in ethanol, set aside for a short time, then acidified and subjected to steam-distillation. The **4-phenylbutyraldehyde** that passes over redistils at 120–122°/16 mm in 58% yield.

$$\mathrm{C_6H_5{-}[CH_2]_3{-}CHBrCOCl} \longrightarrow \mathrm{C_6H_5{-}[CH_2]_3{-}CHO}$$

---

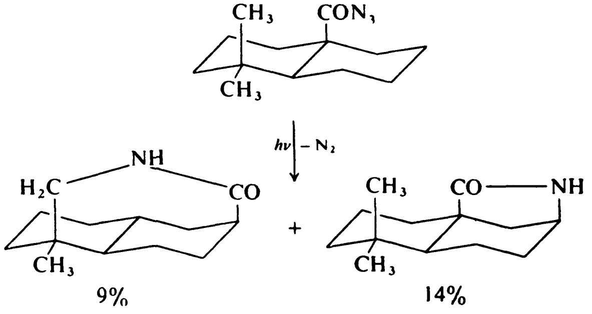
[123] T. Curtius, E. Darmstädter, and H. Pringsheim, *J. Prakt. Chem.*, [ii], **91**, 1 (1915).

[124] G. Schröter, *Ber. Deut. Chem. Ges.*, **42**, 3356 (1909).

[125] J. von Braun, *Ber. Deut. Chem. Ges.*, **67**, 218 (1934).

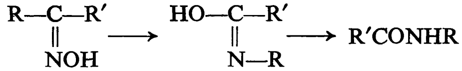
[126] J. Nelles, *Ber. Deut. Chem. Ges.*, **66**, 1345 (1933).

In the thermal decomposition of azides the evolution of nitrogen and migration of the group R are synchronous. In a recent investigation of the photolysis of acyl azides[127] it was shown that loss of nitrogen may be accompanied by insertion into favorably situated carbon–hydrogen bonds:



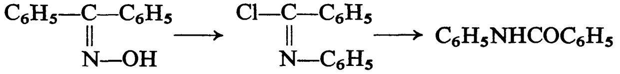
3. Beckmann rearrangement[128]

When treated with phosphorus pentachloride, sulfuric acid, or a pyridine solution of a sulfonyl chloride, ketoximes are converted into amides; it is the *trans*-group that migrates, thus:[129]



$$\mathrm{R{-}\underset{\underset{\displaystyle NOH}{\|}}{C}{-}R'} \longrightarrow \mathrm{HO{-}\underset{\underset{\displaystyle N{-}R}{\|}}{C}{-}R'} \longrightarrow \mathrm{R'CONHR}$$

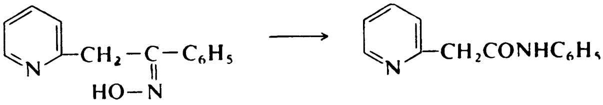
Beckmann[130] treated benzophenone oxime in phosphoryl chloride with phosphorus pentachloride and isolated the imidoyl chloride, which he hydrolysed to benzanilide by aqueous alcohol:



$$\mathrm{C_6H_5{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}C_6H_5} \longrightarrow \mathrm{Cl{-}\underset{\underset{\displaystyle N{-}C_6H_5}{\|}}{C}{-}C_6H_5} \longrightarrow \mathrm{C_6H_5NHCOC_6H_5}$$

In more recent work this reaction was carried out in ether or benzene.

α-(2-Pyridyl)acetanilide:[131] A solution of phenacylpyridine oxime (3 g) in anhydrous ether is treated gradually, with stirring, with phosphorus pentachloride (3 g) and shaking is continued for a further 3 h. The mixture is then made weakly alkaline with potassium carbonate solution and worked up. This gives the pyridylacetanilide in 90% yield.



According to Horning and Stromberg,[132] the Beckmann rearrangement gives particularly good results when carried out by means of polyphosphoric acid:

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[127] W. L. Meyer and A. S. Lavinson, *J. Org. Chem.*, **28**, 2859 (1963); cf. J. W. Apsimon and O. E. Edwards, *Proc. Chem. Soc.*, **1961**, 461; R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 171 (1964).

[128] L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

[129] J. Meisenheimer, *Ann. Chem.*, **468**, 202 (1929); **495**, 249 (1932).

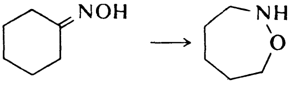
[130] E. Beckmann, *Ber. Deut. Chem. Ges.*, **19**, 988 (1886).

[131] F. Galinowski and G. Kainz, *Monatsh. Chem.*, **77**, 137 (1947).

[132] E. C. Horning and V. L. Stromberg, *J. Amer. Chem. Soc.*, **74**, 2681 (1952).

A mixture of 4,4′-dimethoxybenzophenone oxime (2 g) and polyphosphoric acid (60 g) is heated, with stirring, to 130° and kept at that temperature for 10 min, then poured into water and extracted with 1 : 1 ether–ethyl acetate. After being washed with water and then saturated salt solution and dried over sodium sulfate, the organic phase affords **N-*p*-anisoylanisidine**, m.p. 199–203°, in 91% yield.

An industrially important application is the ring expansion of cyclohexanone oxime to 6-hexanolactam:[133]



The following details have been given by Ziegenbein, Schäffler, and Kaufhold[134] for the rearrangement of 4-ethylcyclohexanone to 4-ethyl-6-hexanolactam:

4-Ethylcyclohexanone oxime (19 g) is dropped with stirring into concentrated sulfuric acid (30 g), the temperature not being raised above 125°. The mixture is then allowed to cool to 90° and further amounts (150 g each) of the oxime and 25% oleum are slowly added. The rearrangement is complete in 45–60 min but the mixture is finally briefly heated at 130°. In the working up, the mixture is dropped into dilute ammonia for neutralization, and the product is taken up in much methylene dichloride and distilled in a vacuum. A 90% yield of crude **4-ethyl-6-hexanolactam,** b.p. 160–165°/15 mm, is obtained.

The quite stringent conditions of the reaction described last are less necessary for the actual rearrangement step than for conversion of the hydroxyl group into the sulfonate group that is the necessary leaving group, and the reaction can be effected under considerably milder conditions if the esterification that precedes the rearrangement is carried out with a sulfonyl chloride.

The following steroid example was described by Kaufmann:[135]

o-(Acetylamino)benzenesulfonyl chloride (10 g) in pyridine (50 ml) is added to a solution of 3β-acetoxy-5-androsten-17-one oxime (10 g) in pyridine (100 ml), and the mixture is kept for 3 h at room temperature, then poured on ice and neutralized with dilute hydrochloric acid. The precipitate is taken up in chloroform, washed with water, and dried over sodium sulfate. Evaporation of the solvent and recrystallization of the residue from methanol gave a 50% yield of 3β-acetoxy-17a-aza-D-homo-5-androsten-17-one, m.p. 295–298°.

4. Schmidt reaction[136]

The Schmidt reaction comprises all reactions of carbonyl compounds with hydrogen azide in the presence of a strong mineral acid.[137]

The reaction of carboxylic acids with hydrogen azide, as follows:

$$\mathrm{RCOOH + HN_3 \longrightarrow RNH_2 + CO_2 + N_2}$$

leading to an amine containing one fewer carbon atoms, is analogous in result to the Hofmann and Curtius degradations. It has the advantage that the amine is obtained in a one-step reaction, whereas the Hofmann and Curtius reactions require preliminary formation of acid derivatives. Disadvantages of the Schmidt reaction are the very poisonous nature of hydrogen azide and the

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[133] J. J. Donleavy and M. A. Kise, *Org. Syn.*, **17**, 63 (1937).

[134] W. Ziegenbein, A. Schäffler, and R. Kaufhold, *Chem. Ber.*, **88**, 1906 (1955).

[135] S. Kaufman, *J. Amer. Chem. Soc.*, **73**, 1779 (1951).

[136] H. Wolff, *Org. Reactions*, **3**, 307 (1949).

[137] K. F. Schmidt, *Ber. Deut. Chem. Ges.*, **57**, 704 (1924).

necessity to catalyse the reaction by concentrated sulfuric acid, the latter feature restricting application of this method to compounds that are resistant to this concentrated acid. However, good yields are obtained from long-chain aliphatic carboxylic acids and from cycloalkanecarboxylic acids.

As described by von Braun,[138] 2-methyl-3-phenylpropionic acid (5.5 g) is dissolved in concentrated sulfuric acid (8 ml) and treated, dropwise at 40°, with a 10% chloroform solution of hydrogen azide (1.3 moles). When evolution of nitrogen ceases, the mixture is poured on ice, the chloroform is distilled off, and the amine is carried over in steam. Neutralizing the distillate with hydrochloric acid and evaporation give pure **α-methylphenethylamine hydrochloride** (4 g, 73%), m.p. 146°.

The reaction of ketones with hydrogen azide is formally the insertion of an NH group between the carbonyl-carbon and a neighboring carbon atom, thus:

$$RCOR + HN_3 \longrightarrow RCONHR + N_2$$

A symmetrical ketone gives in this way the same amide as it does by way of the oxime and a Beckmann rearrangement.

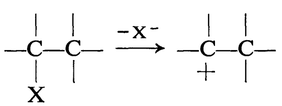
1.4. Rearrangement with reorganization of the carbon skeleton

I. Wagner–Meerwein rearrangement and related reactions

1. Wagner–Meerwein rearrangement[3b]

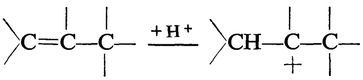
Wagner–Meerwein rearrangements comprise reorganization of the carbon skeleton in eliminations that lead to olefins, in additions to multiple bonds, and in nucleophilic substitutions. Their common characteristic is that after or during formation of an electron deficiency on a carbon atom an alkyl or aryl group moves to that site from a neighboring carbon atom. The electron deficiency can occur as follows:

(*a*) by removal of a hydroxyl ion or the anion of a strong acid:



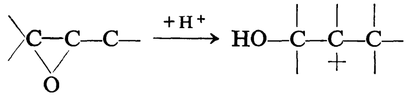
$$-\overset{|}{\underset{\underset{X}{|}}{C}}-\overset{|}{\underset{|}{C}}- \xrightarrow{-X^-} -\overset{|}{\underset{+}{C}}-\overset{|}{\underset{|}{C}}-$$

(*b*) by addition of a proton to a carbon–carbon double bond:



$$>C=\overset{|}{C}-\overset{|}{\underset{|}{C}}- \xrightarrow{+H^+} >CH-\overset{|}{\underset{+}{C}}-\overset{|}{\underset{|}{C}}-$$

(*c*) by opening of an epoxide ring:



$$>\underset{\diagdown O \diagup}{C-C}-C- \xrightarrow{+H^+} HO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{+}{C}}-\overset{|}{\underset{|}{C}}-$$

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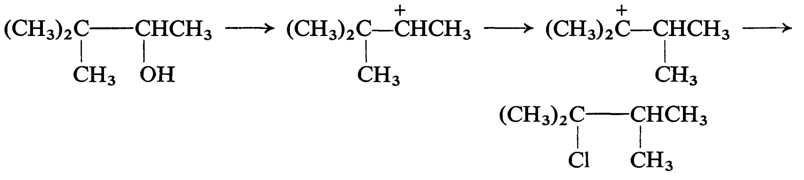
[138] J. von Braun, *Ber. Deut. Chem. Ges.*, **66**, 684 (1933).

After a substituent has moved from a neighboring carbon atom to the site of the electron deficiency, the rearranged cation becomes stabilized by addition of an anion or loss of a proton, *e.g.*:



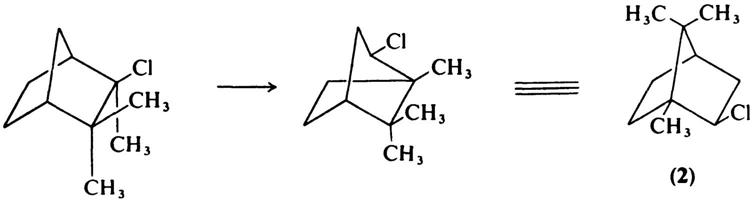
$$(\mathrm{CH_3})_2\underset{\mathrm{CH_3}}{\mathrm{C}}-\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{HCH_3} \longrightarrow (\mathrm{CH_3})_2\underset{\mathrm{CH_3}}{\mathrm{C}}-\overset{+}{\mathrm{C}}\mathrm{HCH_3} \longrightarrow (\mathrm{CH_3})_2\overset{+}{\mathrm{C}}-\underset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{HCH_3} \longrightarrow (\mathrm{CH_3})_2\underset{\mathrm{Cl}}{\mathrm{C}}-\underset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{HCH_3}$$

Formally there has been an interchange of positions between alkyl and halogen or hydroxyl groups.

The steric course at the carbon atom from which the leaving group departs is between the extremes of complete Walden inversion and complete racemization; the same is true for the carbon atom from which the migrating group departs; but the migrating group always retains its configuration.[139]

The tendency to migration of individual groups increases with the electron density of the bond that is broken by the migration.[140] In bicyclic compounds, however, the electronic effects are often surpassed by stereoelectronic effects: an antiparallel arrangement of the two bonds to be broken favors the rearrangement.

Wagner-Meerwein rearrangements occur extremely frequently among branched-chain aliphatic and alkylaryl compounds, and are particularly important in the terpene and camphor series. An example of rearrangement of type (*a*) is that of camphene hydrochloride (**1**) into isobornyl chloride (**2**), for which Meerwein and van Emster[141] give the following directions:



(**1**)

(**2**)

A solution of camphene (300 g) in ethyl bromide (150 g) is saturated with hydrogen chloride at 10–20° and heated under reflux for 6 days at 55°. Most of the ethyl bromide is then removed in a current of dry air, and the isobornyl chloride is filtered off and dried in a vacuum over potassium hydroxide (yield 271 g; m.p. 145°). Recrystallization from pentyl alcohol gives material of m.p. 161.5°.

An example of the rearrangement of an olefin [type (*b*)] was described by Criegee and Riebel:[142] in a two-fold Wagner–Meerwein rearrangement,

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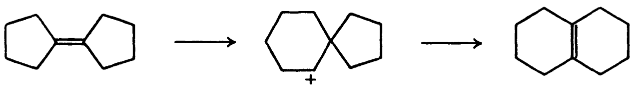
[139] D. J. Cram in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons Inc., New York, 1956, p. 249.

[140] C. K. Ingold, *J. Chem. Soc.*, **1954**, 2845.

[141] H. Meerwein and K. van Emster, *Ber. Deut. Chem. Ges.*, **55**, 2526 (1922).

[142] R. Criegee and A. Riebel, *Angew. Chem.*, **65**, 136 (1953).

$\Delta^{1,1'}$-bicyclopentane (3) passes into 1,2,3,4,5,6,7,8-octahydronaphthalene (5) by way of the cation (4):



(3) (4) (5)

$\Delta^{1,1'}$-Bicyclopentane (2.5 g) is stirred with phosphoric oxide (1 g) at 140° for 3 h. The product is extracted from the cooled solution by ether, washed with dilute sodium carbonate solution and then with water, dried, and distilled; the **octalin** (1.2 g, 50%) has b.p. 190°.

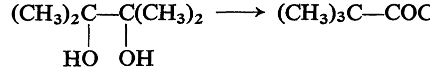
House[143] has described the rearrangement of an epoxide, effected by boron trifluoride:

$$C_6H_5CO-\underbrace{CH-CH}_{O}-C_6H_5 \longrightarrow C_6H_5COCH(C_6H_5)CHO$$

A solution of *trans*-chalcone oxide (*trans*-1-benzoyl-2-phenyloxirane) (0.5 g) in anhydrous ether (25 ml) is heated at the b.p. with boron trifluoride etherate (5 ml) for 30 min. The mixture is then shaken with water and the **α-formyldeoxybenzoin** that is formed quantitatively is precipitated as copper salt.

2. Pinacolin and retropinacolin rearrangements

The first recorded case of migration of an alkyl group in a saturated system is the rearrangement of 2,3-dimethyl-2,3-butanediol into 3,3-dimethyl-2-butanone (pinacolin) discovered by Fittig.[144] As a result of the old trivial name of this ketone, this and similar rearrangements of glycols are termed pinacolin rearrangements. Their differentiation from the Wagner–Meerwein rearrangement has a historical basis but they are similar in formal course, mechanism, and experimental conditions.

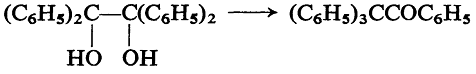


$$\underset{HO}{(CH_3)_2C}-\underset{OH}{C(CH_3)_2} \longrightarrow (CH_3)_3C-COCH_3$$

The preparative importance of the pinacolin rearrangement is considerable; it leads not only to ketones that are hard to prepare in other ways but also from them to triply substituted acetic acids. The reagent effecting the rearrangement is always acidic, either a moderately strong organic acid or a mineral acid.

Hill and Flosdorf[145] have given details for conversion of 2,3-dimethyl-2,3-butanediol into pinacolin in 65–72% yield by hot 6N-sulfuric acid.

Aromatic ditertiary glycols can be rearranged to the corresponding ketones in essentially the same way; Gomberg and Bachmann[146] give instructions for conversion of tetraphenyl-1,2-ethanediol into phenyl triphenylmethyl ketone in 95–96% yield by 1% of iodine in five parts of boiling glacial acetic acid:



$$\underset{HO}{(C_6H_5)_2C}-\underset{OH}{C(C_6H_5)_2} \longrightarrow (C_6H_5)_3CCOC_6H_5$$

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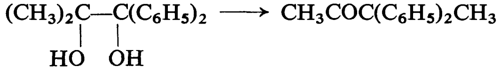
[143] H. O. House, *J. Amer. Chem. Soc.*, **76**, 1235 (1954).

[144] R. Fittig, *Ann. Chem.*, **114**, 56 (1860).

[145] G. A. Hill and E. W. Flosdorf, *Org. Syn.*, **5**, 91 (1925).

[146] M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.*, **49**, 246 (1927); cf. *Org. Syn.*, **14**, 2 (1934).

Zaugg and his co-workers[147] described the rearrangement of a mixed alkyl aryl glycol:



$$\underset{\text{HO}}{(CH_3)_2C}-\underset{\text{OH}}{C(C_6H_5)_2} \longrightarrow CH_3COC(C_6H_5)_2CH_3$$

2-Methyl-1,1-diphenyl-1,2-propanediol (50 g) is added with stirring to concentrated sulfuric acid (300 ml) at 5°. The mixture is left at room temperature for 2 h, then poured on ice and diluted with water (to 3 l); the precipitated **3,3-diphenyl-2-butanone** is distilled in a vacuum, then having b.p. 101–103°/0.3 mm and m.p. 40–41° (38 g).

Disecondary glycols can also be rearranged; they give aldehydes.[148]

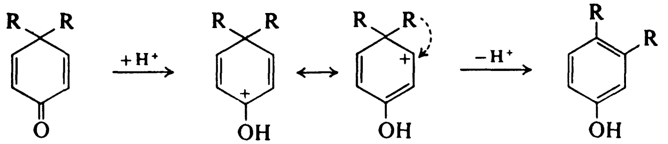
Wagner–Meerwein rearrangement of open-chain branched systems is occasionally termed the retropinacolin rearrangement. The classical example is the loss of water from 3,3-dimethyl-2-butanol, to give 2,3-dimethyl-2-butene:

$$(CH_3)_3CCH(OH)CH_3 \longrightarrow (CH_3)_2C{=}C(CH_3)_2$$

but the product is never pure: it consists of a mixture of isomers.[149]

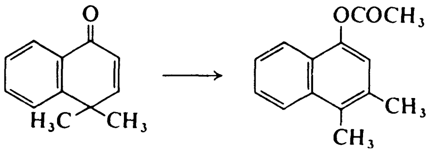
3. Dienone–phenol rearrangement

When treated with acid, 4,4-dialkylcyclohexadienones are converted into substituted phenols by migration of an alkyl group:



The reaction may be regarded as a vinylogous retropinacolin rearrangement that occurs by way of a mesomeric allyl cation.

The conversion of 4,4-dimethyl-1(4*H*)-naphthalenone into **3,4-dimethyl-1-naphthyl acetate** has been described by Arnold, Buckley, and Richter[150] as follows:



Rearrangement occurred when the ketone (1.72 g) was kept for 5 h at room temperature in acetic anhydride (35 ml) containing sulfuric acid (0.5 g). Carefully pouring the solution into cold water (250 ml) then gave colorless crystals (2.01 g), m.p. 88–90°.

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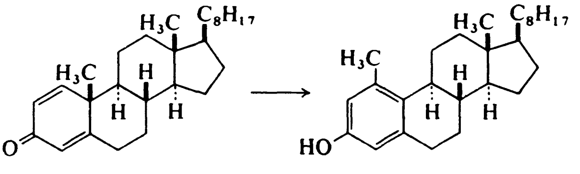
[147] H. E. Zaugg, M. Freifelder, and B. W. Horron, *J. Org. Chem.*, **15**, 1191 (1950).

[148] H. Krauch and W. Kunz, "Reaktionen der organischen Chemie," Dr. A. Huthig-Verlag, Heidelberg, 1966 p. 463.

[149] F. C. Whitmore and P. L. Meunier, *J. Amer. Chem. Soc.*, **55**, 3721 (1933).

[150] R. T. Arnold, J. S. Buckley, and J. Richter, *J. Amer. Chem. Soc.*, **69**, 2322 (1947).

Inhoffen[151] achieved the aromatization of ring A of 1,4-cholestadien-3-one under similar conditions:



4. Isomerization of hydrocarbons[152]

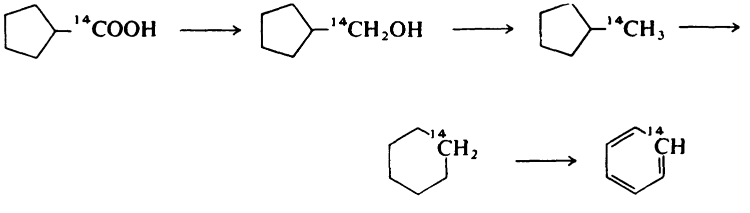
The action of aluminum chloride on aliphatic hydrocarbons has been investigated by Nenitzescu and Drăgan.[153] Even at the boiling point hexane is largely isomerized to a mixture of methylpentanes but a small proportion is dehydrogenated to cyclohexane. These reactions proceed by way of cations.

Nenitzescu and Cantuniari[154] cleared up contradicatory statements in the literature. They showed that pure anhydrous aluminum chloride is almost without action on cyclohexane, but that isomerization occurs if water is present:

Cyclohexane (1500 ml) is boiled for 3 h with freshly sublimed aluminum chloride (500 g) and water (13.6 ml). The supernatant liquid is then washed and dried. Fractionation gave material (330 ml), b.p. 71.3–72.3°, that was almost pure **methylcyclopentane.**

On the other hand, a mixture of cyclohexane and methylcyclopentane is obtained from methylcyclopentane under the same conditions. Thus an equilibrium is established between the two ring systems; it was shown by measurement of the refractive index of the product mixture to contain 23% of methylcyclopentane.

The conversion of methylcyclopentane into cyclohexane has been used by Turner and Werne[155] for the preparation of [$^{14}C_1$]**benzene**, as follows:



Dehydration of cyclopentanemethanol over aluminum oxide at 320° gave an olefin mixture whence hydrogenation afforded a mixture (94%) of [^{14}C]methylcyclopentane with about 34% of [^{14}C]cyclohexane. The mixed cycloalkanes were transformed into [^{14}C]cyclohexane by Nenitzescu and Cantuniari's method,[154] and dehydrogenation on a platinum–charcoal catalyst at 360° then yielded [$^{14}C_1$]benzene.

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[151] H. H. Inhoffen, *Angew. Chem.*, **53**, 471 (1940).

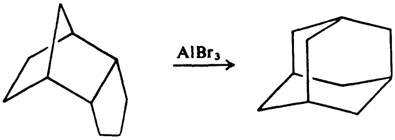
[152] L. Schmerling, *Ind. Eng. Chem.*, **45**, 1447 (1953) (review).

[153] C. D. Nenitzescu and A. Drăgan, *Ber. Deut. Chem. Ges.*, **66**, 1892 (1933).

[154] C. D. Nenitzescu and P. Cantuniari, *Ber. Deut. Chem. Ges.*, **66**, 1097 (1933).

[155] H. S. Turner and R. J. Werne, *J. Chem. Soc.*, **1953**, 789.

The isomerization of hydrocarbons by Lewis acids found a surprising use in the hands of Schleyer and Donaldson:[156] The action of aluminum halides on bicyclo[5.2.1.0^{2,6}]decane (the hydrogenation product of the dimer of cyclopentadiene) afforded adamantane by a series of isomerizations:

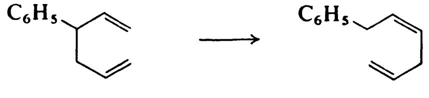


A mixture of aluminum bromide (39.2 g), *endo*-bicyclo[5.2.1.0^{2,6}]decane (100 g), and *sec*-butyl bromide (2.5 g) is stirred at room temperature for 48 h. During the first 6 h hydrogen bromide is led in. Cautious hydrolysis and then cooling of the organic phase in Dry Ice gave crude **adamantane** (26.4 g), which on sublimation gave a pure product (18.8 g), m.p. 269.6 to 270.8°.

II. Cope rearrangement; valence isomerization

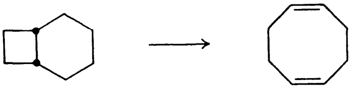
1. Cope rearrangement[3e]

The Cope rearrangement is a term applied to conversion of a 1,5-hexadiene derivative into an isomer that also has the 1,5-hexadiene structure: a bond is formed between C-1 and C-6, the bond between C-3 and C-4 is broken, and the double bonds alter their positions, *e.g.*:



3-Phenyl-1,5-hexadiene (25 g) is heated under nitrogen at 176–178° for 26 h. Distillation through a Widmer column then gives almost pure **1-phenyl-1,5-hexadiene** (18 g, 72%), b.p. 102.5–103.5°/8 mm.[157]

The Cope rearrangement, like the Claisen rearrangement, is a "no mechanism reaction" and thus does not involve ionic or radical intermediates. For practical purposes the result is that Cope rearrangements are independent of catalysts and of the nature of the solvent, and that substituent effects are slight. Steric influences, however, are considerable: *cis*-1,2-divinylcyclobutane rearranges to 1,5-cyclooctadiene within a few minutes at 120°:



but the *trans*-isomer decomposes to two molecules of butadiene at 240°.[158] According to Doering and Roth,[159] *meso*-3,4-dimethyl-1,5-hexadiene re-

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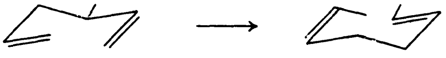
[156] P. von R. Schleyer and M. M. Donaldson, *J. Amer. Chem. Soc.*, **82**, 4645 (1960).

[157] H. Levy and A. C. Cope, *J. Amer. Chem. Soc.*, **66**, 1684 (1944).

[158] E. Vogel, *Ann. Chem.*, **615**, 1 (1958).

[159] W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

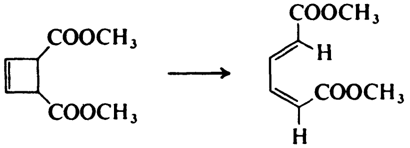
arranges stereospecifically to *cis-trans*-2,6-octadiene to the extent of 97% within 24 h at 280°, but only 0.3% of the *trans-trans*-isomer is formed:



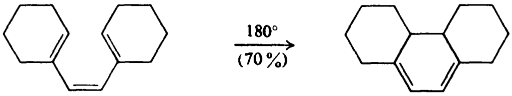
2. Valence isomerization

The Cope rearrangement is an example of valence isomerization, which has been extensively studied in recent years. Valence isomerizations are isomerizations in which only single bonds are broken and formed whilst double bonds change their site. They have a high degree of stereospecificity, the steric result depending on the number of double bonds and on whether the reaction is initiated thermally or photochemically.[160]

According to Vogel,[161] heating dimethyl *cis*-3-cyclobutene-1,2-dicarboxylate at 120° for 10 min and recrystallizing the product from methanol and then from hexane gives dimethyl *cis-trans*-muconate (m.p. 75°):



Similar interconversions between conjugated hexatriene and cyclohexadiene systems have been observed in both directions, and both thermally and photochemically, *e.g.*:[162]



3. Benzilic acid rearrangement[163]

One of the first rearrangements to be discovered was the conversion of benzil into benzilic acid under the influence of strong alkali:

$$C_6H_5COCOC_6H_5 + NaOH \longrightarrow HOC(C_6H_5)_2COONa$$

According to Gattermann and Wieland,[88c] solutions of benzil (5 g) in ethanol (15 ml) and of potassium hydroxide (5 g) in water (10 ml) are mixed and heated under reflux on a water-bath for 10 min. When the solution has cooled, the crystal mass of potassium benzilate is filtered off with good suction, washed with ethanol, and dissolved in water (20–30 ml). After filtration, the **benzilic acid** (4 g) is precipitated from the boiling aqueous solution by dilute sulfuric acid.

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[160] R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 395 (1965).

[161] E. Vogel, *Ann. Chem.*, **615**, 14 (1958).

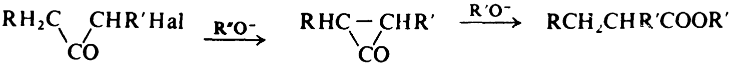
[162] N. Marvell, cited in P. de Mayo, "Molecular Rearrangements," Interscience Publ., New York-London, 1963, p. 698.

[163] O. K. Neville and co-workers, *J. Amer. Chem. Soc.*, **77**, 3280 (1955), where previous references are cited.

The reaction is applicable to almost all aromatic diketones, but in the aliphatic series it is restricted to isolated cases.[164] When carrying out the benzilic acid rearrangement it is necessary to ensure that the diketone is free from cyanide, because Dilthey and Scheidt[165] have shown that in the presence of cyanide ions benzil is cleaved hydrolytically to benzaldehyde and benzoic acid.

4. Favorski rearrangement[166]

Favorski[167] noted the formation of acid derivatives when strong bases act on α-halo ketones. The structure of the acid formed can be derived by postulating as intermediate a cyclopropanone derivative whose ring is opened by the base, thus:

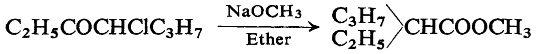


$$\underset{\diagdown CO \diagup}{RH_2C \quad CHR'Hal} \xrightarrow{R'O^-} \underset{\diagdown CO \diagup}{RHC-CHR'} \xrightarrow{R'O^-} RCH_2CHR'COOR'$$

This formulation leads one to expect that the configuration shall be inverted at the point of attachment of the halogen, and this is observed experimentally.[168] Of the two possible products of cleavage of the ring, that obtained is usually the one that is more highly substituted at the α-position to the carboxyl group.

The Favorski rearrangement is widely applicable. In the aliphatic series it leads to branched-chain carboxylic acids and in the cycloalkane series to ring contraction. The latter feature has been made use of in conversion of a six-membered into a five-membered steroid ring D and in the synthesis of cubane.

The reaction is effected by potassium hydroxide in ethanol, by an alkoxide in the corresponding alcohol, or often in two phases by sodium methoxide and diethyl ether. It usually occurs at room temperature.

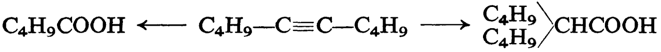


$$C_2H_5COCHClC_3H_7 \xrightarrow[\text{Ether}]{NaOCH_3} \begin{matrix}C_3H_7\\C_2H_5\end{matrix}\!>\!CHCOOCH_3$$

4-Chloro-3-heptanone (200 g) is stirred with a suspension of sodium methoxide (73.5 g) in anhydrous ether (400 ml) for 75 min, the temperature being kept below 10°. Thereafter the mixture is boiled for 40 min and then treated with water. **Methyl 2-ethylvalerate** (147 g, 77%) is obtained from the ethereal layer.[169]

5. Rearrangement on oxidation of dialkylacetylenes

Franzen[170] observed that when dialkylacetylenes are oxidized by peracetic acid a rearrangement to give dialkylacetic acids accompanies cleavage of the triple bonds, *e.g*:



$$C_4H_9COOH \longleftarrow C_4H_9-C\equiv C-C_4H_9 \longrightarrow \begin{matrix}C_4H_9\\C_4H_9\end{matrix}\!>\!CHCOOH$$

This reaction is somewhat analogous to the Wolff–Schröter rearrangement (see below).

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[164] W. Hückel, "Theoretische Grundlagen der organischen Chemie," 7th ed., Akad. VerlagsGes. Geest and Portig K.-G., Leipzig, 1952, Vol. 1, p. 369.

[165] W. Dilthey and P. Scheidt, *J. Prakt. Chem.*, **142**, 125 (1935).

[166] A. S. Kende, *Org. Reactions*, **11**, 261 (1960).

[167] A. Favorski, *J. Prakt. Chem.*, [ii], **51**, 533 (1895).

[168] G. Stork and I. J. Borowitz, *J. Amer. Chem. Soc.*, **82**, 4307 (1960).

[169] J. G. Aston and J. D. Newkirk, *J. Amer. Chem. Soc.*, **73**, 3900 (1951).

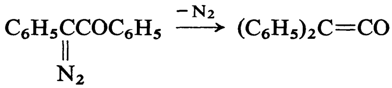
[170] V. Franzen, *Chem. Ber.*, **87**, 1223 (1954).

5-Decyne (20 g) is treated with a 12% solution of peracetic acid (3 molar equivalents) in glacial acetic acid. The mixture is set aside for 10 days, initially with cooling. After removal of the acetic acid in a vacuum, the residue is esterified with methanol and hydrogen chloride. Fractionation then affords a fraction, b.p. 90°/9 mm, which on alkaline hydrolysis gives **2-butylhexanoic acid** (12 g, 54%), b.p. 137°/12 mm.

III. Rearrangement on decomposition of diazo compounds

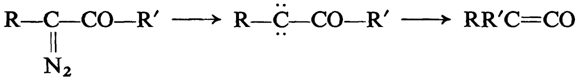
1. Wolff–Schröter rearrangement[171]

Schröter[172] in 1909 found that azideoxybenzoin loses nitrogen when warmed, yielding diphenylketene:



$$C_6H_5\underset{\overset{\|}{N_2}}{C}COC_6H_5 \xrightarrow{-N_2} (C_6H_5)_2C{=}CO$$

In generalized form the reaction is:



$$R{-}\underset{\overset{\|}{N_2}}{C}{-}CO{-}R' \longrightarrow R{-}\underset{\cdot\cdot}{\ddot{C}}{-}CO{-}R' \longrightarrow RR'C{=}CO$$

after removal of the nitrogen the group R′ next to the carbonyl group migrates to the neighboring carbon atom.

According to Smith and Hoehn,[173] **diphenylketene** is obtained in 64% yield when a benzene solution of azideoxybenzoin is dropped slowly into a Claisen flask placed in an oil-bath at 110°; at this temperature the benzene distils off and the residual azideoxybenzoin loses nitrogen and rearranges.

According to Horner, Spietschka, and Gross,[174] the decomposition can be effected under very mild conditions, namely by UV-irradiation at 0°, yields then being around 90%.

The light source used was an S81 lamp from Quarzlampengesellschaft Hanau and was placed in a quartz vessel cooled in ice-water. The reaction vessel (capacity 170 ml) was placed in a Dewar vessel with ice or a freezing mixture.

Azideoxybenzoin (4.4 g) was dissolved in anhydrous ether (170 ml) and illuminated for 3 h while a slow stream of nitrogen was passed in. At the end of the reaction the ether was removed under nitrogen, and the **diphenylketene** was distilled in a vacuum (yield 3.5 g).

In most cases the monomeric ketene is unstable, and the importance of the reaction is that the diazo ketone can be decomposed in presence of water, alcohol, or ammonia, which traps the ketene as acid, ester, or amide.

Wolff[175] early showed that heating ω-diazoacetophenone in the presence of a suitable catalyst and ammonia afforded phenylacetamide.

After Arndt and his collaborators[30b,176] had made ω-diazo ketones readily accessible, their rearrangement to acid derivatives assumed great preparative importance. The process elaborated by Arndt and Eistert[177] permits carboxylic

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[171] L. L. Rodina and I. K. Korobitsina, *Usp. Khim.*, **36**, 611 (1967); *Chem. Abstr.*, **67**, 116 250a (1967).

[172] G. Schröter, *Ber. Deut. Chem. Ges.*, **42**, 2346 (1909).

[173] L. I. Smith and H. H. Hoehn, *Org. Syn.*, **20**, 47 (1940).

[174] L. Horner, E. Spietschka, and A. Gross, *Ann. Chem.*, **573**, 17 (1951).

[175] L. Wolff, *Ann. Chem.*, **394**, 43 (1912).

[176] W. E. Bachmann and W. S. Struwe, *Org. Reactions*, **1**, 38 (1947).

[177] F. Arndt and B. Eistert, *Ber. Deut. Chem. Ges.*, **68**, 204 (1935); **69**, 1805 (1936).

acids quite generally to be converted by way of their chlorides into ω-diazo ketones which can be rearranged to carboxylic acids homologous with the starting acid:

$$\mathrm{RCOCl} \xrightarrow{\mathrm{CH_2N_2}} \mathrm{RCO{-}CHN_2} \longrightarrow \mathrm{RCH_2COOH}$$

According to Arndt and Eistert,[177] the diazo ketone is heated in the presence of finely divided silver, copper, or platinum in water, alcohol, ammonia, or an amine until evolution of nitrogen is complete, this affording the derivative of the homologous acid. It is usually preferable to prepare first the ester or amide of the homologous acid and then to hydrolyse this product to the acid.

The process is generally applicable provided that the molecule contains no functional group such as phenolic hydroxyl or carbonyl that reacts with diazomethane.

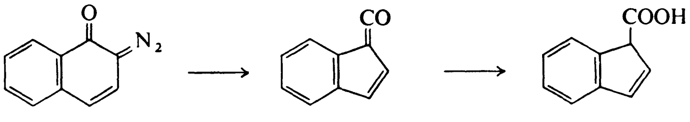
Arndt and Eistert[177] record the following example:

o-Nitrobenzoyldiazomethane (16 g) is dissolved in ethanol (150 ml) at 50–60°, 2N-ammonia solution (150 ml) is added, followed by 10% aqueous silver nitrate solution (10 ml), and the mixture is stirred at 70° until, after 2–3 h, evolution of nitrogen ceases. The solution is then diluted with water and cooled, and the **o-nitrophenylacetamide** produced is filtered off. After recrystallization from ethanol this has m.p. 160–161°. The yield is 10 g (66%).

Direct conversion into the acid, without isolation of a derivative, can be effected with 1-naphthoyldiazomethane, but the yield is mediocre:[178]

A solution of 2-naphthoyldiazomethane (3 g) in dioxan (25 ml) is added to a solution of silver oxide (2 g) and sodium thiosulfate (3 g) in water (100 ml) at 50–60°. The mixture is stirred until evolution of nitrogen ceases (1 h), then cooled and acidified with dilute nitric acid. After recrystallization from water, **1-naphthaleneacetic acid,** m.p. 130°, is obtained in 49% yield (1.4 g).

Süs and his co-workers[179] have applied the Wolff–Schröter rearrangement to *o*-quinone diazides, which are accessible by diazotization of *o*-aminophenols and subsequent treatment with alkali. When irradiated, the quinone diazides lose nitrogen and pass into ketenes by ring contraction; the ketenes are isolated as acids since the reaction is always effected in water.



5-Nitroindene-1-carboxylic acid:[180] 6-Nitro-1,2-naphthoquinone 2-diazide [2-diazi-6-nitro-1(2*H*)-naphthalenone] (15 g) is dissolved in glacial acetic acid (4.5 l) and water (240 ml), treated with charcoal, and filtered. It is then irradiated by sunlight or an arc lamp in ice-cooled, closed, glass fermentation flasks. When no more diazo compound is detectable (after 4 h), the solution is again treated with charcoal, filtered, and at once concentrated (to 500ml) in a bath at 35–40°. The indole acid, which is precipitated in crystalline form, is filtered off and washed with petrol; the yield is 6.5 g, but a further 2 g can be obtained from the filtrate. After recrystallization from glacial acetic acid the product melts at 188–189° (dec.).

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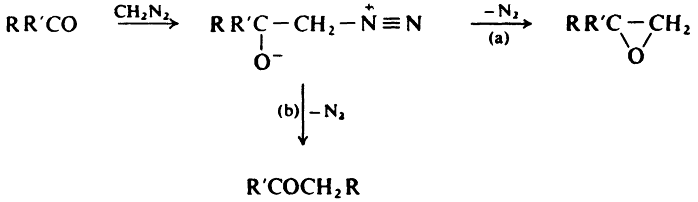
[178] F. Arndt and B. Eistert, *Ber. Deut. Chem. Ges.*, **68**, 200 (1935).

[179] O. Süs and co-workers, *Ann. Chem.*, **556**, 65, 85 (1944); **579**, 133 (1953); **583**, 150 (1953); **593**, 91 (1955).

[180] O. Süs, *Ann. Chem.*, **579**, 133 (1953).

2. Rearrangement on treatment of carbonyl compounds with diazomethane[30a]

Aldehydes and ketones react with diazomethane with evolution of nitrogen. Diazonium betaines are assumed to be intermediates, and in them electron-attracting groups R such as trichloromethyl or *p*-nitrophenyl favor intramolecular substitution which affords epoxides; in other cases, however, the removal of nitrogen is coupled with 1,2-shifts of hydrogen or alkyl or aryl groups:



In extensive investigations Müller and his co-workers[181] showed that appreciably better yields are obtained in this homologation of cyclic ketones on catalysis by boron trifluoride etherate. For example, cyclooctanone affords 44% of the nine-membered ring ketone in this way, compared with 15–20% in the uncatalysed reaction.[181]

Boron trifluoride etherate (1 ml) is added to cyclooctanone (18.9 g, 150 mmoles) in anhydrous ether (150 ml), and then a ca. 0.6M-ethereal diazomethane solution (240 mmoles) is dropped in rapidly with stirring and ice-cooling. The reaction is rapid at first but slower later, and it can be accelerated by addition of further boron trifluoride etherate (1 ml). Working up (after combination of three batches of the above size) and distillation through a spinning band column afford cyclooctanone (15%), **cyclononanone** (27.7 g, 44%), b.p. 90–93°/11 mm, and cyclodecanone (17%).

Interaction of cyclohexanone and diazomethane leads to cycloheptanone by ring expansion; details for this have been given by de Boer and Backer,[182] who produced the diazomethane *in situ* from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, thus:

A mixture of cyclohexanone (49 g) and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (125 g), 95% ethanol (150 ml), and water (10 ml) is cooled to 0° with stirring, and a solution of potassium hydroxide (15 g) in 50% ethanol (50 ml) is dropped in slowly, the rate of addition being adjusted so that the temperature does not rise above 20°. Evolution of nitrogen ceases after 2 h. The mixture is then neutralized to litmus with 2N-hydrochloric acid, and the **cycloheptanone** formed (33–36%) is isolated by way of the hydrogen sulfite compound.

3. Rearrangement of alkylcarbenes[183]

Alkylcarbenes react preferentially so as to achieve stabilization intramolecularly, the intervention of reactants being without effect in almost all cases. Alongside isomerization to afford olefins are observed insertions into *β*-C–H bonds, which yield cyclopropanes,[184] and with cyclic carbenes of

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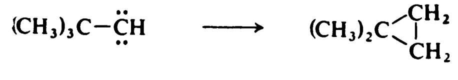
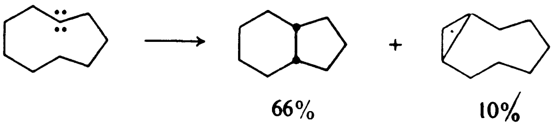
[181] E. Müller and M. Bauer, *Ann. Chem.*, **654**, 92 (1962).
[182] T. J. de Boer and H. J. Backer, *Org. Syn.*, **34**, 24 (1954).
[183] W. Kirmse, "Carbene Chemistry," Academic Press, New York, 1964.
[184] L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **81**, 5512 (1959).

suitable ring size also transannular insertions that yield *cis*-fused bicyclic systems:[185]

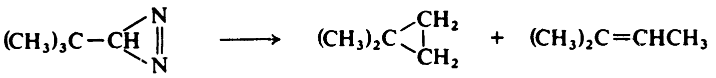




Carbenes are best produced by thermal decomposition of diazo compounds that are formed *in situ*: for example, the sodium salt of a *p*-toluenesulfonylhydrazone is decomposed at 130–150°; it is best to effect this decomposition in a proton-free solvent, usually "Diethylcarbitol," which avoids a competing reaction that involves carbonium ions:

$$\mathrm{RR'C{=}NNNaTos} \longrightarrow \mathrm{RR'C{=}\overset{+}{N}{=}\overset{-}{N}} \xrightarrow{-\mathrm{N_2}} \mathrm{RR'\overset{\bullet}{\underset{\bullet}{C}}}:$$

Diazirines are particularly favorable carbene precursors:[186]

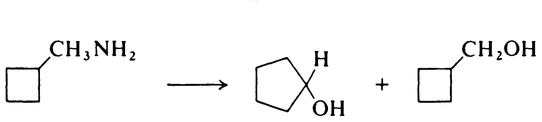


tert-Butyldiazirine (1 g) in nitrobenzene (5 ml) is dropped in 15 min into nitrobenzene (10 ml) kept at 210°. The products pass through a bulb condenser warmed to 50° and are collected in a cold trap at −70°. When the addition is complete, a slow stream of nitrogen is passed through the reaction flask for 5 min so as to sweep the rest of the products into the receiver. Gas chromatography shows the products (0.62 g, 93%) to consist of **1,1-dimethylcyclopropane** (80%) and 2-methyl-2-butene (20%).

4. Rearrangement on treatment of amines with nitrous acid[187]

Reaction of primary amines with nitrous acid usually leads to rearrangements; for example, propylamine and nitrous acid give a mixture of 1- and 2-propanol.

The reactions frequently involve rearrangement of the carbon skeleton. For example, cyclobutanemethylamine, on treatment with nitrous acid, gives cyclopentanol (Demjanow ring expansion[188]), one of the β-carbon atoms migrating to the carbon carrying the functional group; this product is accompanied by varying amounts of the primary alcohol formed by the normal reaction:



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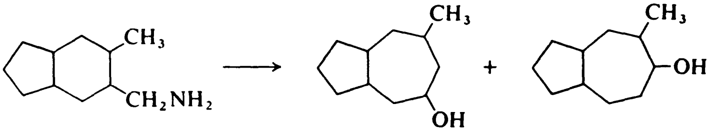
[185] L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **83**, 3159 (1961).

[186] E. Schmitz, D. Habisch, and A. Stark, *Angew. Chem. Int. Ed., Engl.*, **2**, 548 (1963); D. Habisch, Dissertation, Humboldt University, Berlin, 1966.

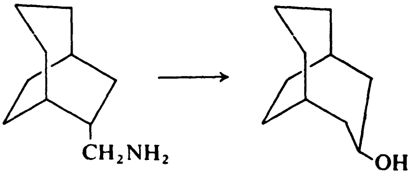
[187] P. A. S. Smith and D. R. Baer, *Org. Reactions*, **11**, 157 (1960).

[188] D. Demjanow and M. Luschnikow, *J. Russ. Phys.-Chem. Soc.*, **35**, 26 (1903).

The preparative value of the reaction is further limited by the fact that two isomers may be formed when another substituent is present in the cycloalkane ring, *e.g.*:[189]

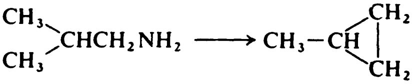


Nevertheless, the reaction was put to good use by Alder and his co-workers, who prepared a bicyclo[3.3.2]decan-3-ol of unspecified configuration in this way:[190]



Aqueous solutions of sodium nitrite (4.5) and of acetic acid (4 g) are added successively to one of bicyclo[3.2.2]nonane-6-methylamine hydrochloride (13 g) in water (50 ml) while a rapid stream of steam is passed through the solution. When this reaction ceases, further sodium nitrite (2 g) and acetic acid (1.8 g) are added and distillation is continued. The distillate is extracted with ether, and the extracts are washed with dilute hydrochloric acid until free from amine, neutralized with sodium hydrogen carbonate, and evaporated. The residue is mixed with 10% sodium hydroxide solution (10 ml) and distilled in steam. The **bicyclo[3.3.2]decan-3-ol** that solidifies in the distillate is collected (7.5 g, 71%).

Friedman and his co-workers[191] have been responsible for a new development: on diazotization by an alkyl nitrite and an equivalent amount of acetic acid in an aprotic solvent such as chloroform or benzene, a primary amine gives a weakly solvated cation whose reactions resemble those of carbenes. For example, isobutylamine in this way affords about 30% of mixed hydrocarbons containing about 15% of methylcyclopropane:



$$(CH_3)_2CHCH_2NH_2 \longrightarrow CH_3{-}CH\begin{smallmatrix}CH_2\\|\\CH_2\end{smallmatrix}$$

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[189] H. Arnold, *Ber. Deut. Chem. Ges.*, **76**, 777 (1943).

[190] K. Alder, S. Hartung, and G. Hausman, *Chem. Ber.*, **89**, 1972 (1956).

[191] J. H. Bayless, F. D. Mendicino, and L. Friedman, *J. Amer. Chem. Soc.*, **87**, 5790 (1965).

Appendix I

Purification and drying of organic solvents

Compiled by
H. Schick

The most varied requirements attach to organic solvents used in preparative work. For some experiments water must be rigidly excluded, for others the absence of acids, alcohols, or reducing substances is absolutely essential. The following paragraphs describe, for the most important solvents, methods of purification and drying that suffice for preparative chemistry. Methods necessary for analytical or spectroscopic work or for physical measurements are purposely omitted, since the requirements are often highly specific in individual cases; they have been reviewed by Bunge.[1c]

Aliphatic hydrocarbons

The light petroleum of various boiling ranges is generally sufficiently pure for most purposes. Unsaturated hydrocarbons can be removed by treatment with fuming sulfuric acid (oleum).

Purification of aliphatic hydrocarbons by concentrated sulfuric acid:[1b] The petroleum or hexane to be purified is repeatedly shaken with small portions of weakly fuming sulfuric acid (5% sulfur trioxide content), until the acid phase remains colorless or at most becomes pale yellow. It is then washed successively with concentrated sulfuric acid, distilled water, 2% sodium hydroxide solution, and distilled water, dried over sodium sulfate, shaken with fuller's earth, filtered, and distilled.

Phosphoric oxide or sodium can be used for drying. It is best to use the sodium as a fine wire from a press and to add successive portions at intervals of time as, contrary to its behavior in ether, the metal becomes coated with a tenaciously adhering layer of oxide and thus rapidly becomes ineffective.

Aromatic hydrocarbons

Benzene, toluene, and xylene are sufficiently pure for most purposes as supplied. They can be freed from water by a simple distillation since water passes over with the first portions. They can also be dried by calcium chloride, phosphoric oxide, or sodium. Thiophen-free benzene is obtained as follows:

Removal of thiophen from benzene:[2] Benzene (1 l) is stirred with concentrated sulfuric acid (80 ml) for 1.5 h at room temperature. The sulfuric acid is separated and these operations

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[1] Houben-Weyl, "Methoden der organischen Chemie," 4th ed., Georg Thieme Verlag, Stuttgart, 1952–1959, Vol. 1, (a) Part 1, p. 901, (b) Part 2, p. 775, (c), Part 2, p. 769, (d) Part 2, p. 831, (e) Vol. 2, p. 73.

[2] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, New York, 1941.

are repeated until the indophenin reaction becomes negative. [If thiophen is present a bluish-green color develops when a solulion of isatin (10 mg) in concentrated sulfuric acid (1 ml) is shaken with benzene (3 ml).]

Chlorinated hydrocarbons

Because of the danger of **explosions**, chlorinated hydrocarbons must never be dried by sodium. They generally undergo slow decomposition by atmospheric oxygen and light; 4-methylmorpholine has been recommended as stabilizer, being added in amounts of 0.002–0.01% of the amount of solvent.[3]

Methylene dichloride is prepared by chlorination of methane and thus contains chloroform and carbon tetrachloride as impurities. Water can be removed by drying over sodium sulfate, calcium chloride, potassium carbonate, or phosphoric oxide. Further purification can be achieved by prior washing with, successively, water, concentrated sulfuric acid, water, sodium hydroxide solution, and again water.

Chloroform is also prepared by chlorination of methane but also by treatment of ethanol with bleaching powder. Because of its tendency to decompose, chloroform contains phosgene, hydrogen chloride, and chlorine as well as other chlorination products of methane; it is usually stabilized by addition of 0.5–1.0% of ethanol. The impurities formed by decomposition are removed by washing with water or dilute potassium hydroxide solution. Further purification, which is usually superfluous, can be effected as for methylene dichloride. The same drying agents as in that case may be used; of these, calcium chloride and phosphoric oxide are most efficient in removing also the ethanol.

Carbon tetrachloride is prepared by chlorinating methane or carbon disulfide. In the latter case the solvent always contains traces of disulfur dichloride or carbon disulfide as impurity; it cannot be freed from these contaminants by distillation, but they are removed by vigorous shaking with dilute sodium hydroxide solution.[4] Further purification, if necessary, can be effected as for methylene dichloride. All higher chloroalkanes can be purified by essentially the above methods.

Alcohols

Methanol, which nowadays is prepared by hydrogenation of carbon monoxide, contains traces of formaldehyde, formic acid, and water as impurities. The water content can be reduced to below 1% by fractional distillation; treatment with magnesium turnings has become established for complete removal of water and formic acid:

Drying of methanol by magnesium turnings:[5] Methanol (50 ml) is heated with magnesium turnings (5 g) until lively evolution of hydrogen sets in. If this does not occur, the metal is activated by addition of iodine (0.5 g). When the magnesium begins to dissolve, further methanol (950 ml), which must contain less than 1% of water, is added and the mixture is boiled under reflux until after 2–3 h the magnesium is all in solution, whereafter the methanol is distilled off.

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[3] U.S. Pat. 2,721,883; *Chem. Abstr.*, **50**, 7879 (1956).

[4] K. A. Klein, *J. Ass. Offic. Agr. Chem.*, **32**, 349 (1949).

[5] H. Lund and J. Bjerrum, *Ber. Deut. Chem. Ges.*, **64**, 210 (1931).

If necessary, the formaldehyde may be removed by treatment with hypoiodite (iodine and sodium hydroxide solution) before the above purification.[6]

As obtained synthetically, ethanol contains 4 wt.-% of water, as well as acetaldehyde and acetone. Alcohol obtained by fermentation contains also higher alcohols. Further "impurities" are the denaturing agents that are usually added (methanol, pyridine bases, petroleum). Absolute alcohol obtained commercially by azeotropic distillation may contain also traces of benzene or trichloroethylene.

If ethanol is to be rendered anhydrous by means of magnesium its water content must not exceed 1%, and this excellent method can thus be applied only to commercial "absolute" alcohol. 96% Alcohol must be pre-dried as follows:

Drying of ethanol by calcium oxide:[7] 92% Ethanol (2 l) is boiled under reflux for 24 h with roasted lime (400 g) and then distilled off therefrom. The resulting ca. 99% ethanol is again treated with lime (70 g), yielding ethanol of more than 99.7% purity.

Because of the unfavorable position of the equilibrium, drying by sodium cannot be recommended.

Drying of ethanol by magnesium turnings:[5] Magnesium (5 g), iodine (0.5 g), and at least 99% ethanol (50 ml) are boiled under reflux until the iodine color has disappeared. If a lively gas evolution has not set in by that time, further iodine (0.5 g) is added. The mixture is heated until all the magnesium is converted into ethoxide, then the remainder (900 ml) of the ethanol, containing less than 1% of water, is added and the whole is heated under reflux for a further 5 h, whereafter the ethanol is distilled off.

Ethyl bromide (1 ml) may be used in place of iodine for activation of the magnesium.

Treatment with zinc dust and sodium hydroxide solution has been recommended[8] for removal of acetaldehyde from ethanol. Aldehyde-free ethanol remains colorless on prolonged boiling with concentrated potassium hydroxide solution and is advisable for preparation of stable ethanolic solutions of alkali hydroxides.

Removal of acetaldehyde from ethanol:[8] Ethanol (1 l) is heated under reflux with water (2.5 ml), sodium hydroxide (2.5 g), and zinc dust (5 g) for 30 min and then distilled off.

2-Propanol is prepared industrially by addition of water to propene or by hydrogenation of acetone. The commercial azeotropic mixture contains 87.4 wt.-% of 2-propanol. Major amounts of water can be removed by drying anhydrous sodium carbonate or potassium carbonate. 87% 2-Propanol can be salted out from dilute aqueous solutions by saturation with sodium chloride.[9] The following procedure has been recommended[9] for preparation of anhydrous 2-propanol from the azeotrope:

Preparation of anhydrous 2-propanol by means of sodium hydroxide:[9] The azeotrope (1 l) is shaken with solid sodium hydroxide (80 g), the aqueous phase formed is removed, and the alcohol is shaken with further sodium hydroxide (100 g), decanted therefrom, and distilled.

No trace of turbidity appears when this product is mixed with eight times its volume of carbon disulfide, xylene, or light petroleum.

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[6] L. Light, *Z. Phys. Chem.*, **122**, 414 (1926).

[7] C. D. Smyth and W. N. Stoops, *J. Amer. Chem. Soc.*, **51**, 3312, 3330 (1929).

[8] H. Dubovitz, *Chem.-Ztg.*, **46**, 654 (1922).

[9] L. E. Gilson, *J. Amer. Chem. Soc.*, **54**, 1445 (1932).

tert-Butyl alcohol, prepared by addition of water to isobutene, is available commercially as a fine chemical of high purity; the water content of this material, which remains completely solid at a temperature of 22–23°, should not exceed 1%. For drying it is boiled with sodium[10] or roasted lime[11] and fractionally distilled; it may then also be fractionally crystallized.[10,11]

Drying of *tert*-butyl alcohol by distillation from sodium: Sodium wire (12 g) is pressed into the alcohol containing 1% of water, and the mixture is boiled under reflux until the metal is dissolved, whereafter the alcohol is distilled off. Since sodium dissolves only very slowly in *tert*-butyl alcohol even at the boiling point, the metal should not be added in large pieces.

Ethylene glycol is obtained commercially by addition of water to ethylene oxide (oxirane). Its most important impurities are propylene glycol and di- and tri-ethylene glycol, which, however, are rarely detrimental to its use as a solvent. It is extremely hygroscopic and thus almost always contains water. For purification and removal of water it is dried over sodium sulfate[12] and then fractionated in a vacuum; but it may also be distilled in a vacuum without pre-drying — the water passes over in a forerun since the glycol does not form an azeotrope with water.

Diethylene glycol and triethylene glycol are also formed by addition of water to ethylene oxide. Impurities are ethylene glycol, propylene glycol, and polyethylene glycols. Purification is by vacuum-distillation, as for ethylene glycol. These two glycols do not form azeotropes with water. Ethylene glycol and its derivatives are not physiologically harmless; their toxicity is generally underestimated.

Ethers

Diethyl ether, diisopropyl ether, tetrahydrofuran, and dioxan, as well as the hydrocarbons decalin and tetralin and even petroleum fractions and xylene, usually contain peroxides. Owing to their involatility, peroxides become enriched in distillation residues and have often given rise to very severe **explosions.**[13] To avoid accidents when working with these solvents it is essential to test for the presence of peroxides and, if they are present, to take steps to remove them. Then, to suppress formation of further peroxides in these solvents, they must be stored in dark flasks and access of atmospheric oxygen must be very rigidly excluded.

Detection of peroxides by sodium iodide: Sodium iodide (0.1 g) is dissolved in glacial acetic acid (1 ml), and this reagent is mixed with the solvent (10 ml) to be tested for peroxide. Formation of iodine indicates the presence of peroxide.

Hydroperoxides liberate iodine instantaneously, other peroxides do so more or less slowly.

Difficultly reducible peroxides are hydrolysed by 50% sulfuric acid and give a yellow or orange color with titanium sulfate.[1e]

The removal of peroxides is described below for each solvent individually.

Besides peroxides, diethyl ether contains ethanol, acetaldehyde, and water. Pressing sodium wire into ether that has been pre-dried over calcium chloride removes all these impurities, including peroxides, and distillation is then usually unnecessary.

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[10] A. A. Maryott, *J. Amer. Chem. Soc.*, **63**, 3079 (1941).

[11] G. S. Parks and C. T. Anderson, *J. Amer. Chem. Soc.*, **48**, 1506 (1926).

[12] C. P. Smyth and W. S. Walls, *J. Amer. Chem. Soc.*, **58**, 813 (1936).

[13] H. Rein, *Angew. Chem.*, **62**, 120 (1950).

If only the peroxides are to be removed, the ether is filtered through aluminum oxide, a method that is recommended also for tetrahydrofuran, dioxan, and other solvents:[14]

Purification of diethyl ether by aluminum oxide:[14] Peroxidized ether is filtered through an upright column filled with activated aluminum oxide. This removes peroxides completely and reduces the water and aldehyde content of the ether. Filtration through a column 1.9 cm in diameter and 33 cm long, containing 82 g of aluminum oxide, removes peroxides completely from more than 700 ml of ether that contained 127 mmoles of oxygen per liter.

Ether that is stored over a clean sodium wire can be considered as peroxide-free. Formation of further peroxide or aldehyde is claimed[15] as prevented by addition of 0,05% of sodium *N*,*N*-diethyldithiocarbamate.

Diisopropyl ether, which is occasionally used in the laboratory as a higher-boiling ether, is especially liable to peroxide-formation.[16] It is advisable to purify it by filtration through aluminum oxide, as for diethyl ether, and to store it over sodium wire or to stabilize it by addition of 0.001% of pyrocatechol, resorcinol, or hydroquinone.[17]

Tetrahydrofuran is prepared industrially by removal of water from 1,4-butanediol or by hydrogenation of furan. Water and peroxides are the most important impurities. It is customary to remove the water by treatment with solid potassium hydroxide, but this has occasionally led to serious **explosions** due to the presence of peroxides;[18] it is therefore urgently recommended not to dry peroxide-containing tetrahydrofuran by solid potassium hydroxide before removal of the peroxides by boiling the solvent with copper(I) chloride.

Removal of peroxides from tetrahydrofuran by copper(I) chloride:[19] Tetrahydrofuran (1000 g) containing 0.4% of active oxygen is boiled with copper(I) chloride (4 g) for 1 h, and the peroxide-free tetrahydrofuran is then distilled off. Addition of 0.1% of copper(I) chloride to the distillate has been recommended in order to repress formation of fresh peroxide.

Drying of tetrahydrofuran by potassium hydroxide and sodium:[20] After test-tube experiments have shown that the tetrahydrofuran is peroxide-free and that no violent reaction ensues on shaking with solid potassium peroxide, the solvent (1 l) is treated with sufficient potassium hydroxide (about 100 g) to ensure that some solid hydroxide remains after formation of the aqueous layer. The liquid solvent is decanted after one day and, for further purification, is boiled for 1 h under reflux with potassium hydroxide (100 g) and then fractionated. If completely anhydrous tetrahydrofuran is required, sodium wire is pressed into this distillate.

Peroxide-free tetrahydrofuran containing only a little water can be dried by treatment with lithium aluminum hydride and distillation under nitrogen.[21]

Dioxan is obtained industrially by the action of sulfuric acid on ethylene glycol. It contains acetaldehyde ethylene acetal (2-methyl-1,3-dioxolane), acetic acid, water, and peroxides as impurities. Because of the danger of peroxide explosions, considerable residues should be left on distillation of dioxan.

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[14] W. Dasler and C. D. Bauer, *Ind. Eng. Chem., Anal. Ed.*, **18**, 52 (1946).

[15] E. Mallinckrodt, R. D. Rands, and A. E. Ruehle, *Chem. Eng. News*, **33**, 3194 (1955).

[16] G. T. Morgan and R. H. Pickard, *Chem. & Ind. (London)*, **55**, 421 (1936).

[17] M. Katsuno, *J. Soc. Chem. Ind. Japan*, **44**, 903 (1941).

[18] Anon., *Org. Syn.*, **46**, 105 (1966).

[19] Ger. Pat. 948,506; *Chem. Abstr.*, **53**, 2252 (1959).

[20] M. Pestemer, *Angew. Chem.*, **63**, 118 (specifically 122) (1951).

[21] K. Heusler, P. Wieland, and C. Meystre, *Org. Syn.*, **45**, 57 (1965).

Peroxides are removed from dioxan by shaking it with zinc(II) chloride[22] or by filtration through activated aluminum oxide (as for diethyl ether),[14] the acetal by hydrolysis with concentrated hydrochloric acid, and the acetic acid and water by treatment with potassium hydroxide and sodium.

Purification of dioxan:[23] Dioxan (1 l) is boiled under reflux for 7–12 h with 37% hydrochloric acid (13 ml) and water (100 ml) under a stream of inert gas. To remove water and acid, this material is then shaken with solid potassium hydroxide, further quantities of this being added until no more dissolves in the aqueous phase. The organic layer is separated from the aqueous phase and shaken with further solid potassium hydroxide and again separated. This dioxan is boiled under reflux, with exclusion of moisture, with an amount of sodium wire such that some sodium remains clean even after prolonged boiling; finally it is fractionally distilled.

Methods of purifying dioxan have been described in detail by Stumpf.[24]

Ketones

Condensation reactions usually occur when ketones are dried by the usual drying agents, so that distillation is necessary after all drying operations.

Acetone is prepared by fission of cumene hydroperoxide (α,α-dimethylbenzyl hydroperoxide) or by dehydrogenation of 2-propanol. Since acetone does not form an azeotrope with water, the water content of the industrial material is less than 0.4%. Organic impurities such as acetaldehyde and methanol amount to less than 1%.

Removal of reducing substances from acetone:[25,26] Acetone (2–3 l) is stirred for 30 min with a solution of potassium permanganate (2 g) in water (80 ml) and concentrated sulfuric acid (20 ml) and is then set aside for several hours. The acetone is then distilled off through a long column. Additionally it may be treated with silver nitrate in an alkaline medium.[27]

Drying of acetone:[28] Acetone is treated with calcium chloride or potassium carbonate[26] for some hours and then distilled. Phosphoric oxide is added to the distillate which is then fractionated (water content 0.01–0.02%); a second distillation reduces the water content to 0.001%.

If still higher purity is necessary, the acetone is purified by way of its bisulfite compound[26] or its sodium iodide compound.[29]

Ethyl methyl ketone (2-butanone) is purified in the same ways as for acetone, but it should be noted that it yields an azeotrope containing 11.3% of water.

Carboxylic acids

Acetic acid is the most important carboxylic acid used as solvent. It is prepared by oxidation of acetaldehyde or of ethanol and is one of the purest industrial products.

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[22] F. R. Fischer and R. A. Baxter, *Mines Mag.*, **30**, 447, 448, 460 (1940).

[23] E. Eigenberger, *J. Prakt. Chem.*, [ii], **130**, 75 (1931).

[24] W. Stumpf, "Chemie und Anwendung des Dioxans," Verlag Chemie, Weinheim/Bergstraße, 1956, p. 15.

[25] R. F. Hudson and J. E. Wardill, *J. Chem. Soc.*, **1950**, 1731.

[26] G. Scheibe, F. May, and H. Fischer, *Ber. Deut. Chem. Ges.*, **57**, 1330 (1924).

[27] E. A. Werner, *Analyst*, **58**, 335 (1933).

[28] J. Timmermans and L. Gillo, *Rocz. Chem.*, **18**, 812 (1938).

[29] R. Livingston, *J. Amer. Chem. Soc.*, **69**, 1220 (1947).

For removal of reducing substances, acetic acid is boiled for several hours with 2% of potassium permanganate[30] or with 2% of chromium(VI) oxide[31] and then distilled.

Phosphoric oxide is suitable as drying agent for acetic acid.[32] If a small content of acetic anhydride is not deleterious for a particular use, it has been recommended to boil the acid with 5–10% of acetic anhydride under reflux for 2h and to fractionate the product through a column.

Carboxylic anhydrides

Acetic acid is the main impurity in acetic anhydride, which is prepared industrially from acetaldehyde or from acetic acid and ketene. The acid can be removed by fractionation, and residual amounts thereof by prolonged boiling with magnesium turnings.[33]

Carboxylic esters

The esters preferred as solvents are those of acetic acid, in particular ethyl acetate.

Ethyl acetate, prepared industrially from acetaldehyde and catalytic amounts of aluminum ethoxide, contains acetic acid, ethanol, and water as impurities. 100 g of ethyl acetate dissolves 3.3 g of water at 25°; the azeotrope contains 8.5% of water.

Purification of ethyl acetate:[34] The ester (1 l) is heated under reflux for 6 h with acetic anhydride (85 ml), then distilled through a Vigreux column. The distillate is shaken with anhydrous potassium carbonate and redistilled.

The preceding method removes water, ethanol, and acetic acid. Drying over calcium chloride is not recommended. Ethyl acetate containing abnormal amounts of ethanol should be shaken with saturated sodium chloride solution and dried over magnesium sulfate before being treated with acetic anhydride.[35] The ester can be dried by phosphoric oxide if it is decanted from the drying agent before distillation.

Carboxamides

Dimethylformamide has become the most important amide for use as solvent. Its most important impurities are dimethylamine, formaldehyde, and water.

Purification of *N,N*-dimethylformamide:[1d] Benzene (115 ml) and water (40 ml) are added to dimethylformamide (900 ml), and the mixture is fractionated; a mixture of benzene and water passes over, together with the amine, as a forerun. A final distillation in a vacuum yields very pure dimethylformamide.

A simple distillation in a vacuum does not ensure total removal of basic constituents.

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[30] A. I. Vogel, *J. Chem. Soc.*, **1948**, 1814.

[31] K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, **1927**, 983.

[32] M. Rabinowitsch, *Z. Phys. Chem.*, **119**, 59, 70 (1926).

[33] W. S. Callott, F. L. English, and O. C. Wilbur, *Ind. Eng. Chem.*, **17**, 942 (1925).

[34] C. D. Hurd and J. S. Strong, *Anal. Chem.*, **23**, 542 (1951).

[35] A. I. Vogel, *J. Chem. Soc.*, **1948**, 624.

Nitriles

Acetonitrile contains water, ammonia, hydrogen cyanide, and acetic acid as impurities. Water is removed by sodium sulfate,[36] basic constituents by phosphoric oxide,[37] and acidic impurities by distillation from potassium carbonate.

Sulfur compounds

Carbon disulfide is obtained industrially from carbon and sulfur and is contaminated by sulfides and other sulfur-containing substances. It can be dried by calcium chloride or phosphoric oxide. Sulfur-containing contaminants can be removed by shaking with mercury and mercury(II) chloride[38] or by treatment with concentrated nitric acid[38] or potassium permanganate solution.[39]

Carbon disulfide is extremely **flammable** and stringent precautions must be taken when using it; in fact, it should only be used when essential; for Friedel–Crafts reactions it should, if at all possible, be replaced by some other solvent.

Dimethyl sulfoxide is obtained industrially by oxidation of dimethyl sulfide. It contains small amounts of dimethyl sulfide and dimethyl sulfone as well as about 0.5% of water.

Purification and drying of dimethyl sulfoxide: Dimethyl sulfoxide (1 l) containing 0.5% of water is stirred for a day with calcium hydride (20 g), then decanted and fractionated in a vacuum, if necessary under nitrogen. It boils at 72.5°/12 mm.

Drying of dimethyl sulfoxide has also been effectively carried out by means of molecular sieves[40] and by sodium hydride.[41]

Nitrogen bases

Pyridine, obtained from coal tar by distillation, contains alkylpyridines and traces of aniline and phenol. It forms an azeotrope, b.p. 94°, containing 43% of water; a material of low water content can thus be obtained by fractional distillation. To obtain anhydrous pyridine, the commercial material is allowed to stand over solid potassium hydroxide, then decanted and fractionated after a further addition of 5% of potassium hydroxide. Alkylpyridines can, if necessary, be removed by oxidation with potassium permanganate[42] or selenium dioxide.[43]

Nitro compounds

Nitromethane is prepared industrially by gas-phase nitration of aliphatic hydrocarbons of low molecular weight. It contains small amounts of aldehydes, alcohols, and water. Because of its reactivity it must not be dried by

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[36] J. Timmermans and F. Hennant–Roland, *J. Chim. Phys.*, **27**, 401 (1930).

[37] G. L. Lewis and C. P. Smyth, *J. Chem. Phys.*, **7**, 1085 (1939).

[38] M. Pestemer, *Angew. Chem.*, **63**, 118 (specifically 121) (1951).

[39] H. Wieland and L. Bettag, *Ber. Deut. Chem. Ges.*, **38**, 3612 (1905).

[40] D. Martin, A. Weise, and H.-J. Niclas, *Angew. Chem. Int. Ed., Engl.*, **6**, 318 (1967).

[41] C. Agami, *Bull. Soc. Chim. France*, **1967**, 1391.

[42] H. Goldschmidt and E. J. Constam, *Ber. Deut. Chem. Ges.*, **16**, 2978 (1883).

[43] D. Jerchel and E. Bauer, *Angew. Chem.*, **68**, 61 (1956).

alkali or by sodium. The recommended method of purification is careful fractional distillation, which may be preceded by drying with sodium sulfate, calcium chloride,[44] or phosphoric oxide.[44]

Reactions in nitromethane should be carried out at temperatures below 100°, in order to avoid the **explosions** that have been reported from time to time.[45] Noteworthy is that nitromethane is an excellent solvent for aluminum chloride and has given excellent service in Friedel–Crafts alkylations[46] and acylations;[47] it is to be preferred to carbon disulfide for such reactions because of its greater safety.

Nitrobenzene, obtained by nitration of benzene, may contain very small amounts of the nitration products of the toluene or thiophen present in the benzene.

Purification and drying of nitrobenzene: Nitrobenzene (1 l) is dried by periodic shaking with sodium hydroxide (50 g), decantation, and fractionation in a vacuum.

Water may be removed by drying over calcium chloride or phosphoric oxide. Anhydrous nitrobenzene can also be obtained by fractional distillation if the forerun is discarded.

For safety, mixtures of nitrobenzene with aluminum chloride or alkali hydroxide should not be heated above 100°.

Appendix II

Preparation and purification of gases

Compiled by
H. Schick

The following paragraphs describe methods of purifying gases that generally meet the requirements of the preparative chemist. The preparation of gases on a commercial scale is only briefly mentioned. Detailed directions for the preparation and purification of gases are to be found in specialist monographs.[48a,49,50a]

Hydrogen

Hydrogen is prepared industrially by electrolysis or from water gas and is marketed in steel bottles. Electrolytic hydrogen contains about 99.7–99.8% of hydrogen, 0.1% of oxygen, and 0.2% of nitrogen. Since the 0.2% of nitrogen

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[44] C. P. Smyth and K. B. McAlpine, *J. Amer. Chem. Soc.*, **56**, 1697 (1934).

[45] Anon., *Nachr. Chem. Technik*, **7**, 233 (1959).

[46] L. Schmerling, *Ind. Eng. Chem.*, **40**, 2072 (1948).

[47] H. Schick, G. Lehmann, and G. Hilgetag, *Angew. Chem. Int. Ed., Engl.*, **6**, 80 (1967).

[48] (a) A. Klemenc, "Die Behandlung und Reindarstellung von Gasen," 2nd ed., Springer-Verlag, Vienna, 1948, pp. (b) 177, (c) 190.

[49] G. Müller and G. Gnauck, "Reinste Gase," VEB Deutscher Verlag der Wissenschaften, Berlin, 1965.

[50] (a) G. Brauer, "Handbuch der präparativen anorganischen Chemie," 2nd ed., Ferdinand Enke Verlag, Stuttgart, 1960, Vol. 1, pp. (b) 305, (c) 412, (d) 436, 437, (e) 572, (f) 112.

is rarely a disturbing factor in laboratory work, the commercial hydrogen can usually be used after passage through a combustion tube filled with reduced copper(II) oxide wire at 400° and subsequent drying by calcium chloride or phosphoric oxide.

Hydrogen obtained from water gas contains appreciable amounts of carbon monoxide and dioxide, oxygen, and nitrogen, and sometimes also arsine, hydrogen sulfide, and pentacarbonyliron.[50f] Carbon dioxide is adsorbed by potassium hydroxide solution or by soda lime, arsine and hydrogen sulfide by saturated potassium permanganate solution. For removal of oxygen, the gas is led over hot copper or red-hot platinized asbestos, which also decomposes the pentacarbonyliron thermally. Removal of carbon monoxide is most fool-proof when effected by freezing out in liquid air.

Hydrogen can be prepared in the laboratory from zinc and 50% sulfuric acid in a Kipp apparatus.

Oxygen

Oxygen is prepared industrially by electrolysis or by liquefaction of air and is marketed in steel bottles. Electrolytic oxygen contains up to 3% of hydrogen, which is removed by passage of the gas over red-hot copper oxide or platinized asbestos. Oxygen obtained by liquefaction can be freed from any nitrogen or noble gases present by fractional condensation or fractional evaporation.

Oxygen can be dried by sulfuric acid, calcium chloride, or phosphoric oxide; it can be purified by prior washing with potassium permanganate and potassium hydroxide solution.

If steel bottles of oxygen are not available or if nitrogen-free oxygen is required, it may be obtained by decomposition of hydrogen peroxide under catalysis by platinum; apparatus for this purpose has been described in the literature.[50b,51]

Nitrogen

Nitrogen obtained by liquefaction of air is marketed in steel bottles. The purest nitrogen (electric lamp quality) contains only traces of oxygen and is sufficiently pure for most purposes.

Water, carbon dioxide, and other impurities are removed by passing the nitrogen over phosphoric oxide and potassium hydroxide or soda lime.

Oxygen can be removed from small amounts of nitrogen by the following procedure:

Purification of nitrogen by alkaline pyrogallol solution: The nitrogen to be purified is passed through a frit immersed in a solution of pyrogallol (2 g) and potassium hydroxide (6 g) in water (50 ml), contained in a wash bottle. The effluent gas must then be dried.

Oxygen is best removed from larger amounts of nitrogen by passage through a "copper tower" in which the oxygen is bound on copper that is precipitated on kieselguhr and heated at 170°.[50c,52]

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[51] H. von Wartenberg, *Z. Anorg. Allg. Chem.*, **238**, 297 (1938).

[52] F. R. Meyer and G. Ronge, *Angew. Chem.*, **52**, 637 (1939).

Ammonia

Ammonia, which is prepared industrially from nitrogen and hydrogen, is marketed in steel bottles. This material contains traces of water and carbon dioxide. It is dried by passage through a tube containing soda lime, solid potassium hydroxide, and sodium wire; when dried in this way, nitrogen no longer reacts even with phosphoric oxide.

If no steel bottles of ammonia are available, the gas can be driven out of concentrated ammonia solution by heat and dried by calcium oxide.

Nitric oxide (NO)

Preparation of nitric oxide from nitric acid and copper:[53] Nitric acid of density 1.1–1.2 is run onto pieces of copper foil, with water-cooling to moderate the reaction if necessary. The nitric oxide evolved is contaminated with nitrogen, dinitrogen monoxide, dinitrogen tetroxide, and oxygen. Dinitrogen tetroxide is removed by washing with 4N-potassium hydroxide solution. Drying is by 90% sulfuric acid and phosphoric oxide. Dinitrogen monoxide and oxygen can be eliminated by freezing the nitric oxide in liquid air and subsequent fractional distillation.

Preparation of nitric oxide from nitrites and sulfuric acid:[50d] 50% Sulfuric acid is dropped into a solution of potassium nitrite (30 g) and potassium iodide (15 g) in water (100 ml). The gas evolved is washed consecutively with 4N-potassium hydroxide solution and 90% sulfuric acid. Water is removed from the gas by freezing with Dry Ice, then the gas is condensed by liquid air and fractionally distilled.

It is, however, simpler to cover the sodium nitrite with 2–3 times its weight of water and to drop in dilute sulfuric acid, the gas produced being then purified as described above.

Dinitrogen tetroxide (N_2O_4)

Preparation of dinitrogen tetroxide from lead nitrate: Powdered lead nitrate is dried at 110–120°, mixed with its own volume of sand, and heated in a hard-glass tube until evolution of gas begins. If the dinitrogen tetroxide evolved is not sufficiently pure it can be condensed by an ice–salt mixture and then fractionally distilled.

Carbon monoxide

If carbon monoxide is unavailable in steel bottles, it may be prepared by the following method:

Preparation of carbon monoxide from formic acid:[50e] A round-bottomed flask (capacity 1 l) is fitted by ground-glass joints with a dropping funnel and a gas-outlet tube, filled two-thirds full with concentrated phosphoric acid, and heated in a water-bath to 80°; then formic acid is dropped in slowly. For removal of impurities (carbon dioxide, air, acid vapors, water vapor), the carbon monoxide evolved is passed successively through 50% potassium hydroxide solution and an alkaline solution of sodium dithionate (25 g of dithionate in 125 ml of water containing also 20 ml of 70% potassium hydroxide solution) and over potassium hydroxide, calcium chloride, and phosphoric oxide.

Carbon monoxide from steel flasks contains also carbon dioxide, oxygen, hydrogen, methane, nitrogen, and pentacarbonyliron. It can be freed from oxygen and pentacarbonyliron by being passed slowly over reduced copper wire heated at 600° and from carbon dioxide by passage over potassium hydroxide. Very pure carbon monoxide is obtained by liquefaction and fractional distillation.

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[53] L. Moser, "Die Reindarstellung von Gasen," Ferdinand Enke Verlag, Stuttgart, 1920.

Carbon dioxide

Commercial carbon dioxide, marketed in pressure flasks, contains water vapor, carbon monoxide, oxygen, and nitrogen, and more rarely traces of hydrogen sulfide and sulfur dioxide as impurities.

Purification of carbon dioxide from pressure flasks:[54] Normal demands of purity are met by passing the gas successively through two wash-bottles containing chromium(II) acetate solution (to remove most of the oxygen), an U-tube containing pieces of potassium hydrogen carbonate (to absorb acid vapors), a wash-bottle containing M-potassium permanganate or dichromate solution (to remove hydrogen sulfide), and a wash-bottle containing concentrated sulfuric acid (for drying), and finally over active copper and copper(I) oxide heated at 200° (to remove residual carbon monoxide and oxygen).

Carbon dioxide of the highest quality is obtained by fractional distillation.[55]

For preparation of carbon dioxide in the laboratory, marble is decomposed by 18% hydrochloric acid in a Kipp apparatus.

Phosgene

Liquid phosgene is marketed in pressure bottles.

For its preparation in the laboratory, carbon tetrachloride is dropped into 45% oleum at 78°; the phosgene evolved is almost pure but is preferably washed with sulfuric acid.[48c]

The same method of purification is advisable for phosgene from steel bottles.

Hydrogen cyanide

Hydrogen cyanide is evolved when potassium or sodium cyanide is treated with sulfuric acid. Ziegler[56] describes a method in which concentrated aqueous sodium cyanide solution and a mixture of equal parts of concentrated sulfuric acid and water are admitted simultaneously from separate dropping funnels into a not too small flask; under the outlets of the dropping funnels hangs a small filter funnel whose tip is drawn into a siphon, so that the reaction takes place in the funnel and the sulfate solution flows away. Since hydrogen cyanide boils at 26.5°, drying tubes (containing calcium chloride) are placed in warm water. Steinkopf[57] described an apparatus for dosage with liquid hydrogen cyanide.

Sulfur dioxide

For the preparation of sulfur dioxide in the laboratory, sulfuric acid is dropped into a concentrated solution of sodium hydrogen sulfite; the sulfur dioxide evolved is dried by sulfuric acid and phosphoric oxide and is purified by condensation and distillation.

Industrial sulfur dioxide, contained in pressure vessels, contains only traces of air, carbon dioxide, and moisture as impurities, and these, being volatile,

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[54] L. Moser, *Z. Anorg. Allg. Chem.*, **110**, 125 (1921).

[55] A. Klemenc and O. Bankowski, *Z. Anorg. Allg. Chem.*, **208**, 348 (1932); **209**, 225 (1932).

[56] K. Ziegler, *Ber. Deut. Chem. Ges.*, **54**. 110 (1921).

[57] W. Steinkopf, *Chem.-Ztg.*, **34**, 1319 (1910).

escape from the pressure vessel with the first portions of sulfur dioxide removed. If desired, the product can be further purified as just described.

Chlorine

The preparation and purification of chlorine were described on page 103 together with methods for other halogens.

Hydrogen halides

The preparation and purification of hydrogen chloride, bromide, and iodide were reported on pages 119–121.

Ethylene

Ethylene, supplied in steel bottles, is purified by cold sulfuric acid and dried by phosphoric oxide. It can be prepared in the laboratory as follows:

Preparation of ethylene from ethanol and phosphoric acid:[58] Syrupy phosphoric acid (50–60 ml) is warmed in a round-bottomed flask to 200–230° and anhydrous ethanol is dropped in from a dropping funnel. The rate of addition determines the rate of evolution of the ethylene. The product is washed with potassium hydroxide solution contained in two wash-bottles at 0° and with concentrated sulfuric acid.

Ethylene can also be obtained by removing the bromine from ethylene dibromide by means of zinc.[59]

Acetylene

Purified acetylene is supplied commercially for chemical work as a solution in acetone contained in steel bottles. Acetone carried over in the gas from the bottle can be separated in a cold trap at −78°. The gas can be dried by passage through sulfuric acid.

Preparation of acetylene from calcium carbide in the laboratory gives a product that is difficult to purify. The literature[48b] should be consulted for methods of purifying this material.

Appendix III

Preparative organic work with small quantities

Compiled by
Ö. Kovács

General

The modern organic chemist very often has only a small amount of material available for identification, determination of structure, or synthesis and thus requires to carry out his chemical manipulations on a micro scale. In many cases satisfactory results can be obtained merely by reducing the size of the

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[58] K. Stahrfoss, *J. Chim. Phys.*, **16**, 187 (1918).

[59] J. H. Gladstone and A. Tribe, *Ber. Deut. Chem .Ges.*, **7**, 364 (1874).

apparatus and using the customary methods on a reduced scale. However, it has often been necessary for the chemist to develop new processes and new apparatus and to discover how to use them. Further indeed, after a little practice, microchemical methods have the advantage of saving time, space, and material.

It will not be possible to record here all the methods available: the following Sections describe only the simplest of the procedures that have proved their worth, are readily carried out in any laboratory, and are not — at least not in the form described below — part of ordinary experimental practice.

Definition of dimensions: The absolute values attaching to the terms macro, semimicro, micro, and ultramicro are not the same in analytical as in preparative chemistry. In analytical chemistry the designation macro applies to an investigation with 100 mg of material, semimicro to 10–100 mg, micro to 0.1–10 mg, and ultramicro to less than 0.1 mg: in preparative chemistry the term macro is applied when the amount of substance used exceeds 1000 mg, semimicro when it is 100–1000 mg, and micro when it is 20–100 mg. In preparative organic chemistry the phrase "small amount of substance" implies a micro or semimicro method.

Batch size: When only a small amount of substance is available the amount to be used in a single experiment is determined mainly by the nature of the reaction and the expected result. For instance, 10–20 mg suffice for a microhydrogenation and 30–50 mg for oxidation by chromic acid, whereas 100 to 500 mg may be essential for a condensation reaction or for some other complicated reaction involving more than one phase.

It simplifies calculation and interpretation of results if the quantities of material used are in simple fractions of the molecular weights.

The volume of a reaction mixture may sometimes be increased by use of additional solvent, so that certain operations such as filtration can be carried out on a macro scale.

Equipment: For microchemical work a few pieces of special apparatus and tools should be always on hand. The vessels needed for individual operations will be described below in connexion with each technique, but the following should be prepared in readiness for general use.

An important part of the general equipment is a spatula, usefully of stainless steel (diameter 3.5 mm, length 15–20 cm), one end being ground to a gradually tapering point, the other flattened to make a little shovel; careful tooling and good polishing are extremely important, and flat portions should be knife-blade thin.

Both soft and hard wires of various diameters and lengths will often be used. Hardened-steel wires should be bent into hooks at the end (for, *e.g.*, removal of cotton wool plugs), others should be flattened (for, *e.g.*, pressing), yet others partly coiled, with cotton wool round the coils (for, *e.g.*, cleaning of tubes and tap bores).

Micro stirring rods are prepared by sealing capillaries or drawing out glass rods; one end of the rod can be melted to form a small ball.

A good supply of capillary tubes, suction balls (see page 1113), and capillary pipettes of various sizes should also be prepared in advance in considerable numbers.

Measuring vessels (diameter 3–8 mm), prepared from test tubes, with flattened bases, are suitable for weighing out materials and for introducing liquids into an apparatus.

A variety of plastic-covered pincers and tongs, a knife, steel needles, platinum loops, a carborundum glass-cutter, and a lens with ten-fold magnification will also be required.

Solutions of defined normality or molarity that are frequently used should be stored in advance in reagent bottles.

It should be particularly noted that the nature of microtechniques requires all reagents and solvents to be purer than is necessary for most work on a larger scale, and that scrupulously clean working is essential.

Weighing and measuring

Weighing on an analytical or semimicro balance usually suffices for micropreparative work. Solids should, whenever possible, be weighed into the vessel to be used for the experiment. For simple weighing, the substance is placed in a plastic, glass, or porcelain boat or on a plate of cellophane or a sheet of cerate or black glazed paper. Liquids of known specific weight should always be measured out by volume; in other cases they may be weighed by use of a suction ball, a capillary fitted with a small rubber cap, or in an open capillary. A platinum loop can be used to advantage when weighing out very viscous liquids such as ointments and gels.

Liquids are measured out for a reaction by means of capillaries fitted with a rubber cap, a suction ball, a dropping tube, or a pipette.

It is useful to store solvents and liquid reagents in 20–50 ml testtubes closed by a ground-glass stopper that carries a capillary fitted with a rubber cap. Each testtube, dropping tube, and liquid should then be tared as a set and labelled with the number of drops required to give 1 ml or 1 gram. The weight of a drop depends on the diameter, the area of the open end of the dropping tube, and the surface tension or density of the liquid; thus, with a dropping tube of 2.4 mm internal diameter, 25 drops = 1 g of water, 50 drops = 1 g of chloroform, and 100 drops = 1 g of ether.

Acids, bases, and other reagents should be kept as solutions of various known concentrations; in this way they can be used in units of volume, making work more precise and faster.

Micropreparative techniques require that liquids shall be measured from pipettes or, more rarely, from burettes. 1-ml and 2-ml pipettes with divisions in hundredths, and also 0.1-ml and 0.2-ml micropipettes with divisions in hundredths (error ±3–5%), are used. Pipettes as used in blood-cell counts are useful for very small volumes, but each must be previously tared. Microburettes can be used for series experiments. A large number of precision microburettes with limits of error of only 0.01–0.1% have been described in the literature.

For very precise measurement of volume Pregl pipettes[60] of 0.1–5.0 ml, tared for output, are used, but it should be noted that they are only wholly exact for liquids of d_4^{20} 1.0.

Small amounts of solution of definite concentration can be prepared in small measuring flasks. An improved form of these measuring flasks, with 0.1–1.0 ml capacity and an error of only 0.5–1.0% has been described by Kirk.[61] According to Gorbach,[62] calibrated Pregl pipettes can also be used for this purpose.

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[60] F. Pregl, "Die quantitative organische Mikroanalyse," 3rd ed., Springer-Verlag, Berlin, 1930.

[61] P. L. Kirk, "Quantitative Ultramicroanalysis," 1942.

[62] G. Gorbach, "Mikrochemisches Praktikum," Springer-Verlag, Berlin, 1956.

A more difficult task is to add small amounts of liquid in small portions at definite time intervals. A simple method, but one requiring great patience, is to draw out the ends of a suction ball so finely that a definite amount drops out at certain time intervals. More reliable is the use of a pipette provided either with a rubber cap and screw clip at the top[62] or with a precision tap at the bottom. Other possibilites involve 1–5 ml medical syringes or 1 ml tuberculin syringes; the injection needles are introduced through a rubber stopper, and sinking of the flask is regulated by an attached thread; for corrosive solutions the injection needles can be replaced by glass capillaries connected to the syringe head by narrow plastic tubing. Dosage can also be effected by means of the hydraulic dosage and dropping apparatus shown in Figure 7: adding the auxiliary liquid (water, mercury, etc.) gradually raises the level of liquid and thus forces the liquid to be dosed over into the reaction.tube.

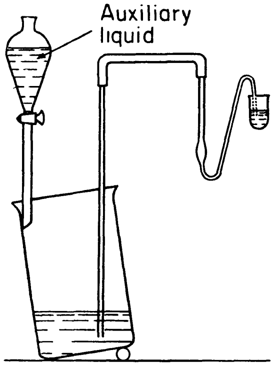

Figure 7. Hydraulic dosage and dropping apparatus.

Powdering, shaking, and stirring

Powdering of small amounts of solid before reaction, extraction, or drying, etc., should, whenever possible, be carried out in the vessel to be used for the later operations. It is effected with a glass rod whose end has been rounded or flattened by melting. Finer powdering can be achieved in the usual agate mortar but losses may then amount to 10–25%.

Because of the small dimensions of the apparatus no special mechanical apparatus is required for discontinuous shaking in micro chemistry. For continuous shaking, any of the usual laboratory shaking machines can be used, vibratory shakers being particularly suitable for micro work.[63]

Small amounts of materials are usually mixed by hand-shaking or stirring with a glass rod. When continuous stirring is required, a smaller version of the usual laboratory stirrer can be used if the shape and size of the vessel permit, or the very useful magnetic stirrers can be inserted.[64]

A vibratory stirrer with controllable amplitude is a very simple and effective tool; the stirring rod is made of acid-resistant steel or glass and ends in a

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[63] V. Herout, B. Keil, M. Protiva, M. Hudlický, I. Ernest, and J. Gut, "Laboratoriumstechnik der organischen Chemie," Akademie-Verlag, Berlin, 1961.

[64] R. L. Clements, *Chemist-Analyst*, **48**, 20 (1959).

perforated sheet of the desired size. For work in a closed vessel, the stirring rod is passed through a hole in a rubber plate.[65]

For substances with high-boiling points and for reactions in the cold, stirring may be by means of a stream of dry and pure gas.

Viscous mixtures can be stirred only by the classical method, in a round-bottomed cylindrical vessel by means of an anchor stirrer and an electric motor.[66]

Cooling and heating

When reactions with small amounts of material require cooling or heating it is always necessary to bear in mind the low heat capacity of the apparatus and contained substances. The small dimensions confer the advantage that heat transfer is very rapid, but they also have the disadvantage that the temperature of the tiny amounts of material can be controlled only through that of its surroundings. Thus there are, for instance, the danger that reaction may begin too violently and the difficulty that low-temperature filtration involves also the cooling bath or the use of defined conditions.

The techniques of cooling are the same as in work on a larger scale except that particular care must be taken to secure the small vessels firmly.

The simplest method of warming is by a micro flame or by a water-bath or oil-bath. Conditions are more certain if the bath is stirred mechanically and heated electrically while the temperature is controlled by a thermostat. A good heat-transfer agent, such as tritolyl phosphate, should be used.[67]

Electrically heated, standardized metal blocks can also be used conveniently for warming reaction mixtures, for distillation, sublimation, and extraction, and for approximate determination of melting points.

Open or closed infrared lamps are also very good for heat transfer.

Recrystallization

a. Preparation of the solution

Recrystallization is usually effected in short, wide testtubes of various dimensions (*e.g.*, 7 × 50, 15 × 50, or 15 × 90 mm; see Figures 8a, b, and c). Operations are sometimes easier if a lip for pouring is provided and a glass side-arm (40–60 mm long) is sealed on (Figure 8b). Centrifuge tubes with conical ends (Figure 8d), 5–25 ml Erlenmeyer flasks, and pear-shaped flasks can also be used.

Before recrystallizing a small amount of material it is advisable to carry out a few trials in a micro testtube to find a suitable solvent and the optimal concentration. The general rules for choice of a solvent apply also for microtechniques, except that hot-saturated solutions should not be used. Solvent mixtures, such as ethanol–ether, benzene–light petroleum, and ethanol–water are favored; if the substance has different solubilities in the two components of the solvent mixture, it can be dissolved in one in the cold, that solution can be clarified or filtered, and crystals then obtained by adding the second solvent.

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[65] R. Morris, *Nature*, **183**, 201 (1959).

[66] S. Kasman, *J. Chem. Educ.*, **37**, 150 (1960).

[67] G. Rosendahl, *Chemist-Analyst*, **48**, 20 (1959).

The solutions are warmed in a water-bath or in an electrically regulated heating block[61,68] in which holes of various sizes are bored, or simply heated cautiously over a micro flame. The testtube or flask may be provided with a condenser (Figure 9), but this is only required with solvents of very low boiling point. If the solution is to be heated for a long time, a cold finger may be attached to the tube (Figure 9b). To accelerate dissolution the mixture may be stirred or swirled by means of a small glass rod drawn out at one end to finish in a little ball.

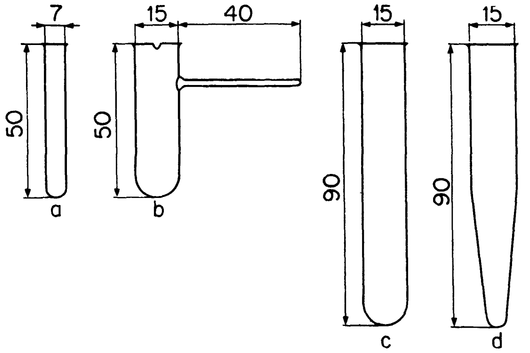

Figure 8. Testtubes adapted for small amounts of substance; (*d*) a centrifuge tube.

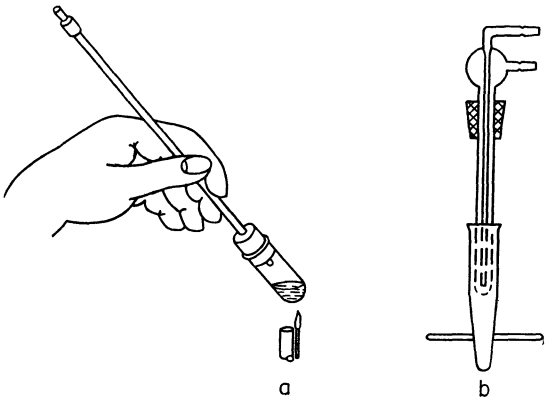

Figure 9. Testtubes fitted with (*a*) a condenser and (*b*) a cold finger.

In general work on a micro scale, hot-saturated solutions are used only when filtration and clarification are unnecessary or when the substance has little tendency to crystallize. However, to prevent crystallization during filtration, it is better to use solutions that are less than saturated even at room temperature; after clarification and filtration, the dilute solution is concentrated until saturated hot or, alternatively, the dilute solution is evaporated to dryness and the residue is dissolved in a fresh small amount of the solvent.

It sometimes happens that recovery of very small amounts of a substance by evaporation of a dilute solution in a relatively large flask yields the material as a thin film on the wall of the vessel; in such cases quantitative recovery of the substance can be achieved by means of a suction ball.

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[68] R. T. Schenk and T. S. Ma, *Mikrochemie*, **40**, 245 (1952); H. P. Schulz, *J. Chem. Educ.*, **35**, 564 (1958).

This suction ball is a plum-shaped 0.5–20 mm glass ball with capillaries of medium internal diameter (length 100–350 mm, diameter 0.3–2.5 mm) attached at diametrically opposite sides.[62] The principle of operating a suction ball is to seal one capillary, warm the ball so that air or solvent vapor is driven out of the other end, and then to dip the open end into the liquid which is then sucked into the ball as the latter cools. The suction ball can be emptied either analogously by warming or by cutting off the sealed end of the capillary. The suction ball has many advantages over the micropipette with rubber cap used for similar purposes.

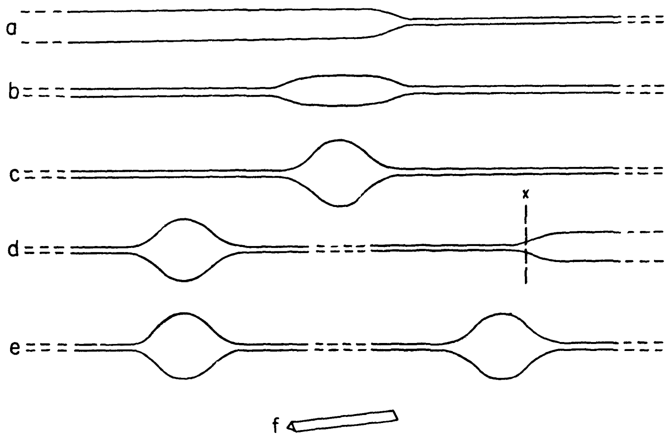

Figure 10. Preparation of a suction ball. For a description of the steps *a–f* see the text.

Preparation of a suction ball is very simple: two capillaries are drawn, about 10–40 mm apart, from a soft glass tube of 5–10 mm diameter, by means of a wide blow-pipe flame (Figures 10a and b), then a plum-shaped ball is blown in the straight part with slow rotation (Figure 10c); one capillary is sealed before storage. A carborundum prism is used for the glass-cutting so as to ensure straight ends (Figure 10f). A properly made suction ball has uniform wall thickness and does not break if dropped on a laboratory bench.

The suction ball can be used to transfer small amounts of liquid from large to small vessels. About 2 ml of solvent are added to the liquid in the large flask and most of this solvent is evaporated by gentle warming; the vapors condense on the walls of the flask and wash the adhering substance to the bottom of the flask. Repeating this operation two or three times collects all the substance at the lowest part of the flask. One capillary of a suction ball of suitable size is then sealed and a few drops of solvent are introduced into the ball through the open capillary; for this operation with low-boiling solvents the ball is not heated but the liquid is made to enter the ball by cooling the ball externally (by a stream of cold air or by cotton wool wetted with ethyl chloride). Next the pure solvent in the ball is evaporated by gentle warming and the open capillary is placed in the liquid that is to be transferred; as the vapors in the ball condense, this liquid is sucked up. Finally the contents of the suction ball are transferred to the small vessel by cautious warming or by cutting the sealed capillary. These operations may, if desired, be repeated once or twice.

It is also possible to repeat several times the evaporation and condensation of the solvent added to the larger vessel, before introducing this solution into the suction ball; in this way the lower part of the vessel is washed by the condensed solvent that runs down the walls.

If the solution is to be preserved in the suction ball, all the fractions are introduced into one ball, which is then turned so that the open capillary is on top; the solution in this capillary is allowed to run back completely into the ball, the ball is then warmed and quickly reversed and the open capillary is dipped in pure solvent, which washes the capillary as it is sucked up; these operations are then repeated for a second and a third washing. It is inadvisable to carry out this repeated suction into the ball with solvents boiling below 50–60°. When all the materials are in the ball the two capillaries, one after the other, are shortened and sealed.

b. Filtration and clarification

When small amounts of liquid are used for recrystallization they may be filtered or clarified by use of a suction ball. In clarifications it must be remembered that too large an amount of adsorbent may cause considerable loss of material. A suction ball suitable for filtration is prepared by making the second capillary shorter and of larger internal diameter than the other and cutting it from the original tube in such a way that its open end is conically expanded (see Figure 10d). Before filtration, a twisted cotton wool plug, preferably in two parts, is introduced into the conical end, a little solvent is sucked into the ball and then cautiously evaporated — too rapid warming ejects the plug; this prepared end is then introduced into the solution to be filtered; so that this may be sucked up completely the end of the conical portion must be uniformly circular.

The vessel and suction ball must be firmly clamped (see Figure 11) until filtration is complete. If necessary, the wall of the vessel may be washed down with a little solvent from a micropipette, even before filtration is complete.

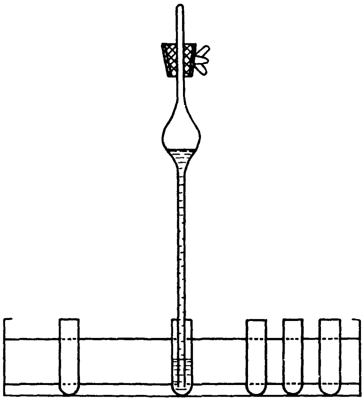

Figure 11. Filtration by means of a suction ball.

After the filtration, the filter end is cut off and, after being emptied, the suction ball is washed with solvent in the usual way. When dilution of the solution must be avoided, some of the solvent may be evaporated by heat, provided, of course, that further heating does not decompose the solute; the solvent vapor above the solution is sucked up into the empty suction ball, where it condenses and washes the walls of the ball; this condensate is then removed from the ball in the usual way; two or three repetitions of this process provide quantitative filtration.

The classical use of a micro filter funnel and folded paper or cotton wool always leads to loss of material; and when a suction ball is used, the filtrate contains neither threads from the paper nor colloidal portions of the clarifying agent. If the solute crystallizes in the suction ball during or after filtration, then, when filtration is complete and the filter end has been cut off, the suction ball is heated in a bath with the open capillary upwards until the crystals have redissolved.

For filtration of opalescent solutions containing colloidal impurities, the conical part of the filtration capillary is made longer (20–30 mm) and there are introduced into it, first, a well tamped cotton wool plug, then iron-free charcoal for polar solvents or alumina (chromatographic quality) for apolar solvents, and finally a second cotton wool plug. Since this filter is only slowly permeable, it is wetted only with the solvent, and the solvent necessary for the suction process is introduced from the other capillary; after evaporation of the solvent through this free capillary end the latter is at once sealed.

This type of filtration is usually slow but causes no particular delay. To accelerate it, the solution may be pretreated with a small amount of the adsorbent, which is then allowed to settle, and the end of the filter capillary is inserted into this sediment; during filtration the surface is thus increased and the process speeded up.

Hot-saturated solutions can also be filtered if this process is modified:[69] A normal testtube of appropriate size is drawn out to a filter capillary at its open end (see Figure 12); a cotton wool plug is introduced and filtration is carried out as usual. If the solute crystallizes in the capillary or in the testtube, the latter is warmed cautiously in a water-bath. After the recrystallization, the drawn out portion is cut off from the remainder of the testtube.

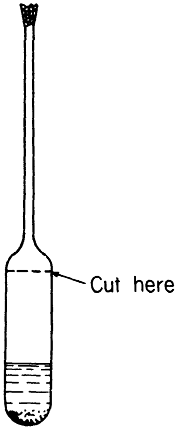

Figure 12. Apparatus for filtration of hot-saturated solutions.

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[69] M. Svoboda, *Chem. Listy*, **53**, 31 (1959).

The filtration apparatus described by Cockburn[70] (Figure 13a) and its modified form (Figure 13b) are also very useful. The substance to be recrystallized is dissolved in the flask-shaped part of the apparatus, after which the whole is set up in the position illustrated and filtration is effected under pressure. Jena glass micro filters (12 G 3 and 30 G 3) or Pregl micro filter tubes (154 G 1) can also be used.

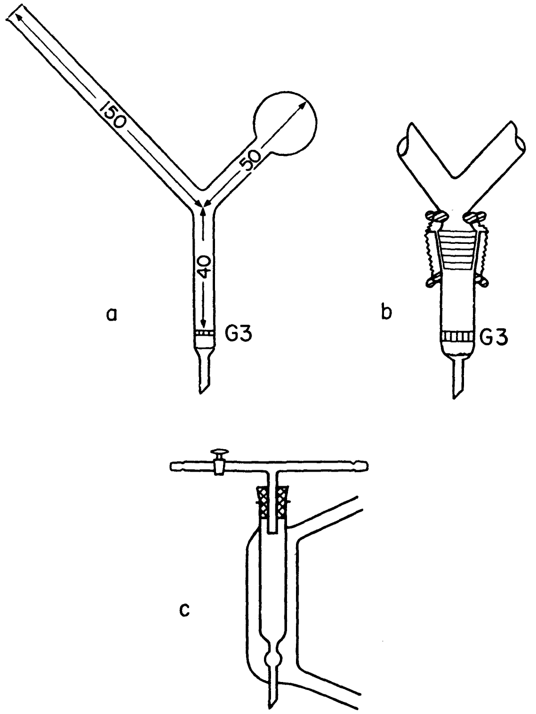

Figure 13. Various filtration apparatus.

Apparatus involving a heating mantle (Figure 13c) may also be used for hot-saturated solutions. The bulb near the bottom of the apparatus is filled with cotton wool or asbestos; vapors of the solvent used for the recrystallization wash the walls of the mantle. Filtration is carried out under pressure.

Suction must not be used during filtration on a micro scale since evaporation then becomes a disturbing factor owing to the small amounts of solution and the relatively large surfaces.

Solid can be separated from liquid materials also by means of the vessels illustrated in Figures 14a and b; they are centrifuged.[71-75]

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[70] W. F. Cockburn, *Can. J. Chem.*, **29**, 715 (1951).

[71] H. Lieb and W. Schöniger, "Anleitung zur Darstellung organischer Präparate mit kleinen Substanzmengen," Springer-Verlag, Vienna, 1950.

[72] N. D. Cheronis, "Micro and Semimicro Methods," Vol. 6 in A. Weissberger's series "Technique of Organic Chemistry," Interscience Publishers, New York, 1954.

[73] D. A. Forss, *Chemist-Analyst*, **46**, 11 (1957).

[74] V. Horák, *Chemie*, **10**, 588 (1958).

[75] M. Martin-Smith, *Lab. Practice*, **7**, 572 (1958).

After clarification and filtration a dilute solution can be concentrated by heating it in a water-bath (see Figure 15a) or on a controllable electric hotplate, a capillary being placed 1.0–1.5 cm above the surface of the solution and attached at its other end to a water-pump; regular boiling is achieved by means of a micro boiling capillary. With this arrangement the material obtained on concentration does not creep up the walls of the testtube.[63,76,77] If it is necessary to ensure absence of moisture or carbon dioxide, or to use a stream of inert gas, the apparatus shown in Figure 15b can be used, but care must be taken that the capillary attached to the pump dips sufficiently close to the surface of the liquid and is sufficiently far from the under side of the stopper.

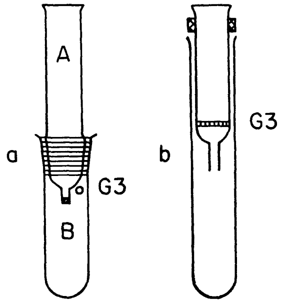

Figure 14. Apparatus used for filtration on a centrifuge.

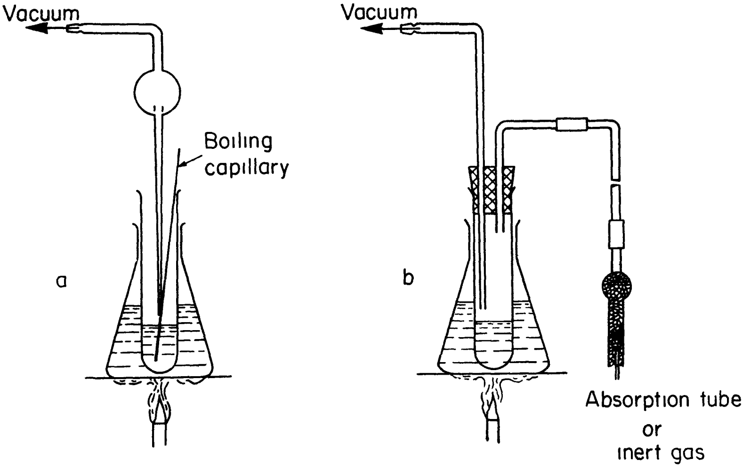

Figure 15. Apparatus for concentration of solutions.

c. Isolation of the crystallizate

In preparative microchemistry the method and apparatus used for isolation of crystals depend on the nature of the substance. To prevent loss of material, the method should, when possible, be so chosen that it is unnecessary to pour the suspension of crystals and mother

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[76] M. T. Bush, *Microchem. J.*, **1**, 109 (1957).

[77] G. W. Perold, *Mikrochim. Acta*, **1959**, 251.

liquor from the vessel in which crystallization has taken place: the larger the surface with which the suspension comes into contact, the higher are the losses.

In rapid orienting experiments and crystallization trials, the crystals can be separated from the mother liquor by pouring the whole on an unglazed porcelain plate (porous plate); when the mother liquor has been absorbed by the porous plate, the crystals are scratched together by a microspatula and washed with a few drops of solvent on another part of the plate. The mother liquor can be recovered by smashing the plate into small pieces and extracting these. The suction apparatus developed by Weygand (see Figure 17c) can be used instead of porous plate.

Various methods have been described in the literature[72,78,79] for recrystallization of very small amounts of material on a microscope carrier glass or in a capillary tube; the former method is suitable only for orienting experiments, and the latter is rather wearisome. In our experience it is, however, possible to recrystallize even very small amounts of material very nicely by means of testtubes of suitable size and a suction ball.

When recrystallization is effected in testtubes or pear-shaped flasks, the method used to separate the mother liquor must be adapted to the nature of the crystals produced. For well developed crystals a suction ball is used whose capillary end is drawn out to a fine capillary; if the end of the capillary becomes blocked with crystals during the filtration, these can be removed by cautiously rotating the ball — but no air must be allowed to penetrate into the ball; when the supernatant mother liquor has been sucked up, the crystals are washed with a few drops of solvent, which is again removed by means of the suction ball.

When strong cooling and a low-boiling solvent are used, it is advisable to use a double suction ball, as illustrated in Figure 10e, one ball being warmed and the other used for sucking up the mother liquor.

Medium-sized crystals that filter easily can best be collected on an Emich filter stick (micro filter rod 91 G 3, diameter of the plate 3–10 mm). This stick is passed through a stopper through which two holes have been bored and which is placed directly in the flask or testtube; or the apparatus suggested by Gut and Šedivý (Figure 16a) may be used.[80] In the latter the inner tube *B* can be raised and lowered, so that receivers *A* of various sizes can be inserted; for ease of handling, the Emich stick is attached to the apparatus by a small piece of plastic tubing.

It is advisable to use only a feeble vacuum when filtering, otherwise solvent may be lost and filters blocked. The Emich stick should be lowered slowly into the solution, so that the crystals collect at the bottom of the testtube and can be well pressed together. After release of the vacuum, the walls of the testtube and the crystals are washed with a few drops of cold solvent, which is then sucked off. Finally the filter stick is lifted carefully out of the tube, and the crystals adhering to its surface are removed by a micro spatula.

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[78] F. Schneider, "Qualitative Organic Microanalysis," John Wiley and Sons, New York, 1946.

[79] N. D. Cheronis, J. B. Entrikin, and E. M. Hodnett, "Semimicro Qualitative Organic Analysis," 3rd ed., Interscience Publishers, N,ew York, 1960.

[80] J. Gut and L. Šedivý, *Chem. Listy*, **46** 284 (1951); *Chem. Abstr.*, **46**, 293 (1952).

This procedure has the advantages that several successive recrystallizations can be carried out in the same testtube, which can then be used for drying and eventually for storage of the product. Further, the vessel containing the crystals and mother liquor can, if necessary, be cooled in a freezing mixture during the filtration.[81]

If the amount of solid is small in relation to the amount of liquid and the crystals do not settle readily, the apparatus shown in Figure 16b may be used; a disc of hardened filter paper is wetted with the solvent and then placed in the upper part of the filtration capillary. Jena glass frits (12 G 3, 15 G 3,

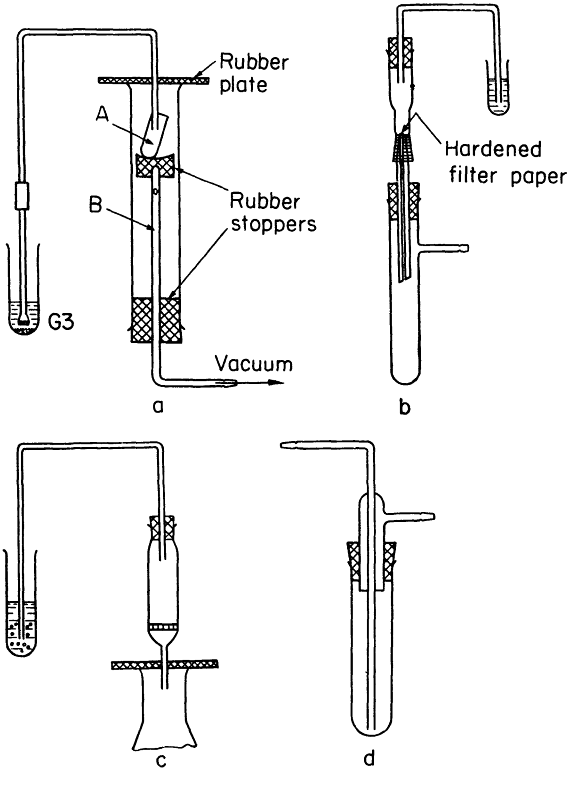

Figure 16. Apparatus for collection of crystals.

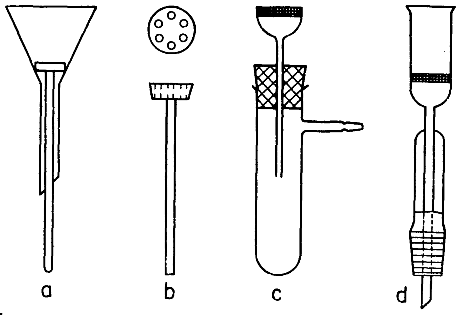

Figure 17. Micro filters.

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[81] A. L. Bluhm, *J. Chem. Educ.*, **35**, 200 (1958).

and 3 G 3) can also be used with similar arrangements (see Figure 16c). By use of a stopper with two holes, it is also possible (see Figure 16d) to carry out the filtration with exclusion of moisture or in a stream of inert gas.

Filtration can also be carried out with a Jena micro filter frit (12 G 3 or 30 G 3), a glass "nail" (Figure 17a), an acid-resistant steel "nail" (Figure 17b), a Weygand suction filtration apparatus (Figure 17c), or a filter head fitted with a standard ground glass joint (Figure 17d). Mother liquor remaining in the last-mentioned filter head can be recovered, after removal of the crystals, by extraction and evaporation.

Substances that separate in a very finely divided state and cannot be filtered by the methods described above must be centrifuged. The liquid lying above the sediment can then be removed by a suction ball, after which the precipitate should be stirred with fresh solvent and again centrifuged. The paste resulting from these operations is freed from residual solvent on a porous plate or in the centrifuge vessel itself.

d. Drying of crystals

Crystals can be dried in any of the usual types of apparatus, such as the Abderhalden drying pistol or the variant described by Smith,[82] or on a Benedetti–Pichler drying block. However, simpler apparatus also suffices: 100-ml or 250-ml wide-necked flasks with well-fitting ground glass joints can be used as, *e.g.*, micro desiccators; and a wide glass tube closed by a stopper and tap (Figure 18) can serve as a vacuum-desiccator that can be heated.

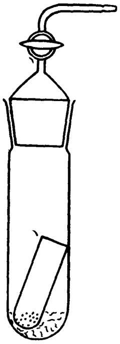

Figure 18. A "vacuum desiccator" that can be heated.

Distillation

Selection of a suitable apparatus for distillation of small amounts of a substance is the hardest part of the operation, for the surface becomes relatively larger as the dimensions of the apparatus decrease and this can cause considerable loss of material. For micro work the most suitable apparatus is generally one in which the surface for evaporation is large but the surface for condensation is small and in which continuous fractionation can be carried out. For high-boiling or sensitive substances the mean free path for distillation should be as short as possible.

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[82] G. F. Smith, *Anal. Chim. Acta*, **17**, 192 (1957).

Micro preparations are often carried out by the customary distillation at atmospheric or reduced pressure. Quite different methods should, however, be sought for separation of two or more substances, and fractional distillation is therefore often replaced by chromatography, which is a milder method, gives better yields, and permits isolation of a larger number of fractions.

Naturally, fractional distillation can also prove successful in certain cases, particularly on a semimicro scale. Yet, although the literature contains numerous claims of favorable results by this method, it has been repeatedly found that use of microfractionation apparatus for distillation of substances with similar boiling points gives pure fractions only by very great sacrifice of yields.

Emich microfractionation capillaries can be used for distillation of 0.1 to 0.2 ml of liquid.

These capillaries (Figure 19a) are 60 mm long and 5–8 mm in diameter. For ease of handling they are closed by a glass rod (*A*) 50 mm in length. A little asbestos or thin-fibre glass wool (*B*) is placed in this capillary, and a constriction (*C*) is formed in the neck. The substance to be distilled is sucked up into a thin capillary, which is then placed in the microfractionation tube, and the liquid is transferred to the surface of the asbestos or glass wool by centrifugation. The thin capillary is next removed, and the distillation tube is slowly rotated in a sloping position while its lower end is heated over a micro flame. As soon as the first distillation ring reaches the constriction, the tube is removed from the flame and place dhorizontally. The distillate is removed by means of a thin capillary, the residual liquid is returned to the bottom of the tube by centrifugation, and distillation is continued as above. In this way several fractions can be obtained.

Emich's method has been developed further by Morton and Mahomey.[83] They put forward the use of a capillary, 130 mm in length and 1.5–2.0 mm in diameter and filled this to its constriction with glass wool cut into small pieces (Figure 19b). The substance to be distilled is transferred by centrifugation to the capillary, which is then placed up to the neck in a metal block

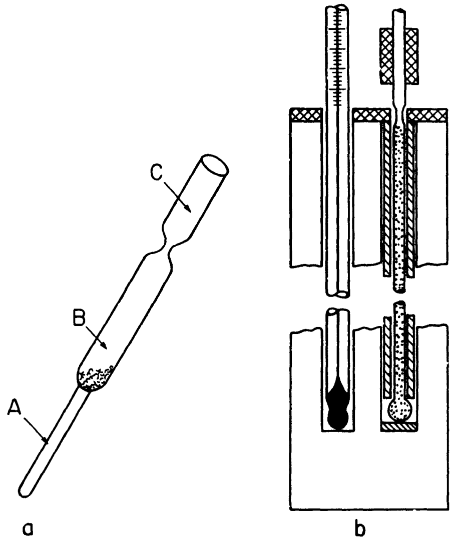

Figure 19. Emich fractionation capillaries.

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[83] A. A. Morton and J. F. Mahomey, *Ind. Eng. Chem., Anal. Ed.*, **13**, 494 (1941).

and packed round with glass wool or asbestos; a piece of wet filter paper is placed round the part of the tube projecting through the block. The block is warmed cautiously and the first distillate is returned by centrifugation to the tube, this process being repeated several times; only after that are the various fractions isolated. In this way these workers obtained, for instance, 70 fractions from no more than 23 mg of material.[72]

The Weygand–Ellis apparatus shown in Figure 20 is also often used. It is one of the best microdistillation arrangements because the surface is relatively small and because it provides for continuous fractionation and use of a vacuum. The condensate drops from the condenser into a cup whence it is transferred, through the capillary tube, into the receiver by the action of the applied vacuum.

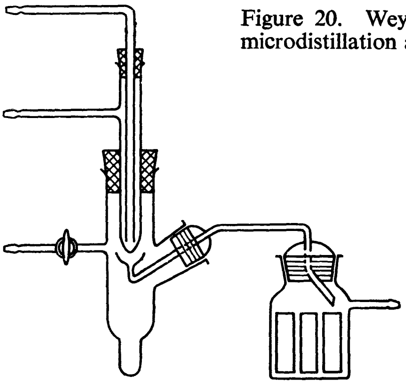

Figure 20. Weygand–Ellis microdistillation apparatus.

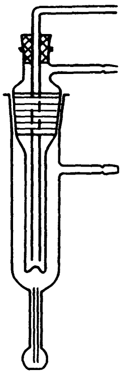

Figure 21. Craig microdistillation apparatus.

An apparatus (Figure 21) proposed by Craig[84] is similar but operates discontinuously. The distillate collects in the spherical lower end of the cold finger and can be removed therefrom by means of a capillary.[85,86]

The so-called collar flasks (Figure 22)[63] are remarkable for their simplicity. The very short neck of the boiling flask presents very little hindrance to the passage of vapor from the evaporation surface in this flask to the condensation surface of the condenser, so that use of such flasks comes very close to short-path distillation proper.

Various types of collar flask permit distillation of any amount of liquid between 50 mg and 5 g. For 50–1000 mg quantities the flask (Figures 22a and 22b) is filled with thin-fibre glass wool, preferably by use of a glass tube that is thin enough to pass through the narrow neck of the flask, and the substance to be distilled is placed on the glass wool by means of a suction ball. Any solvent present is removed at room temperature by application of a slight vacuum, then the apparatus is immersed up to the vacuum tube in a water-bath and is warmed; later it is immersed to half-way up the neck in a paraffin

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[84] L. C. Craig, *Ind. Eng. Chem., Anal. Ed.*, **8**, 219 (1936); **9**, 441 (1937).

[85] L. Erdös, *Mikrochemie*, **24**, 278 (1938).

[86] F. Neumann and K. Hess, *Ber. Deut. Chem. Ges.*, **70**, 721 (1937).

or silicone bath; it is advisable to place a piece of card under the neck to stop radiation of heat from the bath. The rate of distillation is controlled by the bath temperature. The distillate is removed by means of a suction ball after the apparatus has been placed in a sloping position. For low-boiling substances, the thermometer is replaced by a cold finger (Figure 22b).

It should be added that for small amounts of liquid distillation can be followed easily if the thermometer is placed in the heating bath but near the distillation flask. The results are well reproducible if the vacuum, level of the heating bath, position of the thermometer, rate of heating, etc., are the same in replicate distillations.

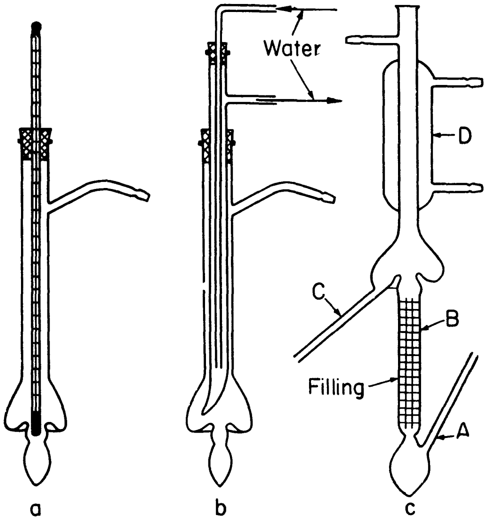

Figure 22. Distillation apparatus involving collar flasks.

1–5 g quantities of liquid are distilled from a flask (Figure 22c) with an attached side arm (*A*) through which a microcapillary is inserted to ensure regular boiling. This apparatus can be combined with a side arm (*C*) through which the distillate is led for receipt in testtubes. A substantially similar apparatus has been described for distillation of solid substances.[87] Separations can be made more efficient by insertion of columns (*B*) of various lengths containing one of the usual fillings. When high-boiling substances are to be distilled the evaporatory part of the apparatus and the column are heated in an electrical heating body set to the desired temperature.

Gorbach[62] distilled small amounts of material by vaporization in a slow gas stream. The distillation apparatus described by Shrader and Ritzer[88] also appears to provide efficient separation (Figure 23), and the apparatus described by Klenk and Schumwirth[89] can give good results for high-boiling substances. Semiautomatic apparatus is provided by many firms for fractionation of semimicro quantities. Columns with rotating fillings are particularly efficient.[90,91]

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[87] K. Bernhauer, P. Müller, and F. Neisper, *J. Prakt. Chem.*, [ii], **145**, 306 (1936).
[88] S. A. Shrader and J. E. Ritzer, *Ind. Eng. Chem., Anal. Ed.*, **11**, 54 (1939).
[89] E. Klenk and K. Schumwirth, *Z. Physiol. Chem.*, **267**, 260 (1941); **277**, 147 (1943).
[90] S. D. Lesedne and H. L. Lochte, *Ind. Eng. Chem., Anal. Ed.*, **10**, 450 (1938).
[91] H. Koch, F. Hilberath, and F. Weinrotter, *Chem. Fabrik*, **14**, 387 (1941).

A new area of microtechnique was opened up when Conway and Byrne[92,93] introduced a simple apparatus for diffusion-distillation or isothermal distillation.

Molecular distillation (free-path distillation) and freeze-drying are often very useful in work with small amounts of material.[1a]

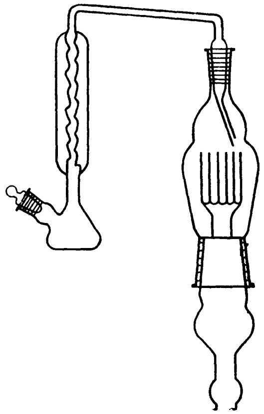

Figure 23. Shrader and Ritzer's distillation apparatus.

Distillation in steam

Steam-distillation is also often applied in micro work. The apparatus described by Pozzi-Escot[94] (Figure 24a) or that described by Erdös and László[95] (Figure 24b) is usually used.

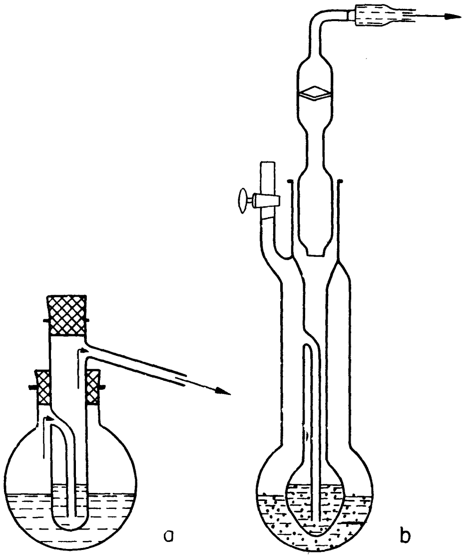

Figure 24. Steam-distillation apparatus described by (a) Pozzi-Escot and (b) Erdös and Lázló.

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[92] E. J. Conway and A. Byrne, *Biochem. J.*, **27**, 419 (1933).

[93] E. J. Conway, "Microdiffusion Analysis and Volumetric Error," 2nd ed., Crosby-Lockwood, London, 1947.

[94] M. E. Pozzi-Escot, *Bull. Soc. Chim. France*, [iii], **31**, 932 (1904).

[95] J. Erdös and B. Lázló, *Mikrochim. Acta*, **3**, 304 (1938).

Sublimation

Sublimation plays an important role in the purification of organic compounds on a micro scale since it involves little loss of material, is convenient and fast, and provides very efficient purification. An essential condition for its application is, however, that the substance has sufficient vapor pressure at the temperature to be used.

Sublimation in a vacuum is often advantageous.

For successful sublimation particular attention must be paid to the rate of evaporation because, if this is too fast, involatile impurities may be carried over; further, the sublimate then forms a hard microcrystalline layer on the condenser and readily falls off when the apparatus is taken apart.

The bath temperature should, whenever possible, be lower than the melting point of the substance – about 10° lower for substances melting between 40° and 100°, about 50–80° lower for those melting between 100° and 200°, and 100–150° lower for those melting above 200°. The crystal size of the sublimate depends largely on the temperature of the condenser.

Attention must also be paid to the distance between the condenser and the evaporator when subliming substances that have low vapor pressures. Apparatus that has a variable condenser position is thus extremely useful because this position can then be varied to suit the substance and the pressure to be used. The distance from the substance to the condenser is usually 7–25 mm in micro apparatus.

Microsublimation is less often complicated by inclusion of involatile impurities in the film formed on sublimation. If formed, this film coats the surface of the solid, thus hindering vaporization of the material in the interior of the crystals; thus it is always advisable to add the substance in solution and then to evaporate the solvent slowly, so that the substance forms a thin layer in the lower part of the apparatus.

Microsublimation is used principally for the first step of purification and again immediately before analysis. The former use removes involatile impurities with relatively little loss of material and provides a crystalline product that can be further purified by other methods. Analytical samples obtained by sublimation are completely dry and, further, can be removed selectively from the condenser surface.

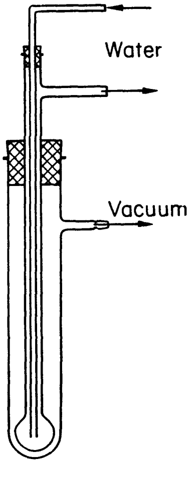

Figure 25. Microsublimation apparatus.

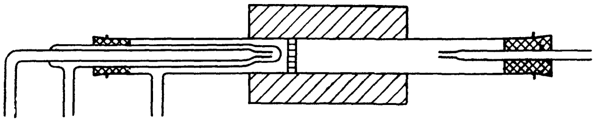

Figure 26. Electrically heated microsublimation apparatus.[100]

Various types of apparatus for microsublimation have been described in the literature; for instance, a simple arrangement of suction tube and cold finger illustrated in Figure 25 may be conveniently used; here, too, the distance between the evaporator and the condenser can be regulated. When sublimation is complete, the apparatus is carefully taken apart and the sublimate is removed from the surface of the condenser by means of a spatula or by use of a solvent.

The literature also contains descriptions[96,97] of numerous types of apparatus similar to the above but comprising ground glass joints.

Metal blocks with borings of various diameters and controllable electrical heating are often used for microsublimation;[98,99] a horizontal type with a glass filter is illustrated in Figure 26. Microsublimation of very small samples can be effected advantageously at atmospheric or reduced pressure on a Kofler block.[101] A vacuum-sublimation arrangement described by Schmidt[102] affords excellent fractionation.

Extraction

Extraction of solid substances: For substances that are readily extracted it often suffices merely to digest or boil them with an appropriate amount of a suitable solvent. The solvent is then removed by centrifugation or by means of a suction ball adapted for filtration. Specialized apparatus[103-107] is preferably used for substances that are difficult to extract or sparingly soluble.

Extraction of liquids: Discontinuous extraction of small amounts of liquid can be carried out in testtubes fitted with ground glass stoppers; after separa-

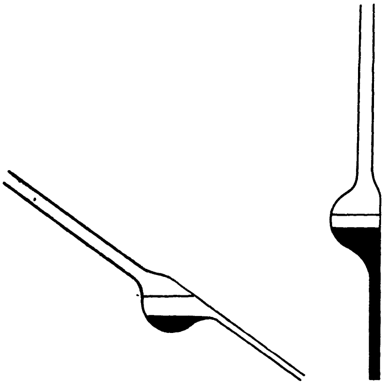

Figure 27. "Stork beaks".

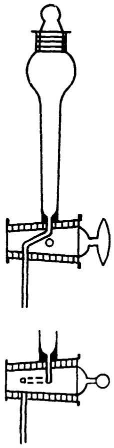

Figure 28. Micro separatory funnels.

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[96] C. M. Marberg, *J. Amer. Chem. Soc.*, **60**, 1509 (1938).

[97] G. Klein and O. Werner, *Z. Physiol. Chem.*, **143**, 141 (1925).

[98] M. Hubmacher, *Ind. Eng. Chem., Anal. Ed.*, **15**, 448 (1943).

[99] B. Löw, *Acta Chem. Scand.*, **4**, 294 (1950).

[100] A. Soltys, *Mikrochem., Emich-Festschrift*, 275 (1930).

[101] L. Kofler and A. Kofler, "Thermo-Mikromethoden zur Kennzeichnung organischer Stoffe," 3rd ed., Verlag Chemie, Berlin, 1954.

[102] G. Schmidt, *Mikrochim. Acta*, **1959**, 406.

[103] R. Gagarin, *Chem.-Ztg.*, **57**, 204 (1933).

[104] L. Titus and V. W. Meloche, *Ind. Eng. Chem., Anal. Ed.*, **5**, 286 (1933).

[105] A. Wasitzky, *Mikrochemie*, **11**, 1 (1932).

[106] J. M. Connoly, *Analyst*, **76**, 495 (1951).

[107] B. K. Blount, *Mikrochemie*, **19**, 162 (1935/1936).

tion of the two phases, the upper is removed by means of a suction ball. Extraction can, however, also be effected in a suction ball open at both ends or in a Gorbach "stork beak" (Figure 27). Various small separatory funnels with a capacity of 5 ml are also useful (see Figure 28).[61,108,109]

20–200 μl amounts of liquid can be extracted in a capillary of length 10–12 cm.[110] The liquid to be extracted and the solvent are, for instance, placed by means of a micropipette into a tube sealed at one end. The capillary is then sealed also at the other end and centrifuged. After centrifugation for some minutes, the tube is reversed so that the heavier phase becomes uppermost, and centrifugation is repeated. These procedures are repeated several times, then the capillary is opened and the two phases are separated by means of a microcapillary.

After the extraction, the solutions must usually be dried, and this is advantageously carried out in the separatory funnel but only after any water that separates from the united extracts has been removed.

If only a small amount of substance is present in a large amount of solvent, the quantity of drying agent used must be carefully judged, lest adsorption cause substantial loss of material. Filtration should then be through a cotton wool plug placed in the lower tube from the tap and, best, directly into the flask in which evaporation is subsequently to be effected.

Small amounts of solution are dried in small testtubes fitted with stoppers, and the drying agent is removed by transferring the solution to a suction ball fitted with a cotton wool filter.

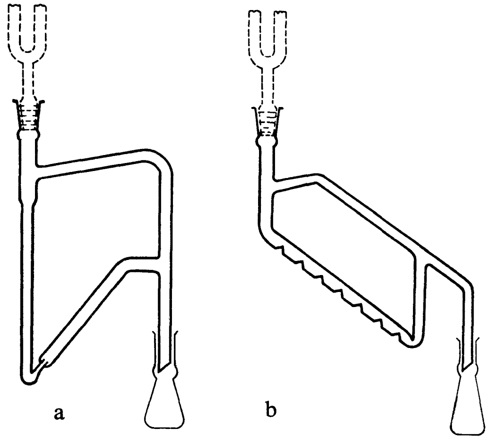

Figure 29. Extractors for use with liquids (*a*) lighter and (*b*) heavier than the solution.

Scaled-down types of the customary continuous liquid extraction apparatus are also useful in micro work. As proposed by Wayman and Wright,[111] the arrangement shown in Figure 29a is convenient for extraction of about 8 ml of an aqueous phase with a solvent of specific gravity less than 1.0, and that in Figure 29b for extraction of 25 ml of aqueous solution with a solvent of specific gravity above 1.0.[112]

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[108] K. H. Alber, *Ind. Eng. Chem., Anal. Ed.*, **13**, 656 (1941).

[109] B. L. Browning, *Mikrochemie*, **26**, 54 (1939).

[110] J. Niederl, *J. Amer. Chem. Soc.*, **51**, 474 (1929).

[111] M. Wayman and G. F. Wright, *Ind. Eng. Chem., Anal. Ed.*, **17**, 55 (1945).

[112] R. Antoszewski, *Naturwissenschaften*, **45**, 42 (1958).

Reaction under pressure

Micro bomb tubes are used for reactions in a homogeneous phase at pressures up to 15–20 atm. Microautoclaves fitted with a heating mantle and temperature control are also available for small quantities; when placed in a shaker, these can be used also for reaction of heterogeneous phases. Reactions of a few milligrams of material can be carried out in thick-walled capillaries under high pressure.

Addition of glass inserts permits autoclaves of greater capacity to be used. For example, a 20-ml glass "duck" may be placed in a 1-l shaking autoclave for hydrogenation of small amounts of material under pressure.

Flasks fitted with a magnetic stirrer and a manometer are available for hydrogenation at atmospheric pressure on a semimicro scale. Before hydrogenation is begun, the air is removed from the apparatus by repeated evacuation. Special apparatus can be obtained commercially for analytical microhydrogenation of a few miligrams of material.

SUBJECT INDEX

This index deals primarily with the preparation of the compounds named, but in many cases also with their principal reactions; sub-entries beginning "by" or "from" indicate methods of preparation; on pages denoted by bold type experimental details will be found. Starting materials are not normally listed but some important reagents and name reactions are included. General reactions will be found under class names such as Amines, Ketones, but individual members of the classes are listed as their own chemical names. Inverted entries, e.g. Benzene, nitro-, are used. Esters are normally given as sub-entries under the acids.

Errata

48,	line 3	read	(see page 322).
86,	line 22	read	. . . of the Chapter.
86,	line 26	read	. . . of the same element. Advantage is
90,	line 8	read	deuteride, $LiAlD_4$,
272,	line 13	read	well as in the present Chapter, page 197.
272,	line 14	read	C–C bonds (page 1005)
436,	line 21	read	. . . formazans (see page 437).
496,	line 3	read	$CH(NHAcyl)_3$, can be prepared from ethyl ortho-
645,	line 13	read	previously (pages 202, 213)
998,	line 1	read	. . . affords ethyl cyclohexylideneacetate . . .
998,	line 19	read	A synthesis related . . .