CHAPTER VI

MONOHYDRIC ALCOHOLS

An alcohol is a compound that contains one or more *hydroxyl* groups, *i.e.*, alcohols are hydroxy-derivatives of the paraffins. They are classified according to the number of hydroxyl groups present. Monohydric alcohols contain one hydroxyl group; dihydric, two; trihydric, three; etc. When the alcohols contain four or more hydroxyl groups, they are usually called polyhydric alcohols.

The monohydric alcohols form an homologous series with the general formula $C_nH_{2n+2}O$, but, since their functional group is the hydroxyl group, their general formula is more satisfactorily written as $C_nH_{2n+1}OH$ or ROH.

Nomenclature. The simpler alcohols are commonly known by their trivial names, which are obtained by naming the alcohol as a derivative of the alkyl radical attached to the hydroxyl group, *e.g.*, CH_3OH, methyl alcohol; $CH_3{\cdot}CH_2{\cdot}CH_2OH$. *n*-propyl alcohol; $CH_3{\cdot}CH(OH){\cdot}CH_3$, *iso*-propyl alcohol; $(CH_3)_3COH$, *tert.*-butyl alcohol.

Another system of nomenclature considers the alcohols as derivatives of methyl alcohol, which is named *carbinol*, *e.g.*, $CH_3{\cdot}CH_2OH$, methylcarbinol. The *Chemical Society*, however, now proposes to use *methanol* instead of carbinol, *e.g.*, $CH_3{\cdot}CH_2{\cdot}CHOH{\cdot}CH_3$, ethylmethylmethanol (both methods have been used in this book).

In the I.U.P.A.C. system of nomenclature, the longest carbon chain containing the hydroxyl group is chosen as the parent hydrocarbon. The class suffix is *-ol*, and the positions of side-chains and the hydroxyl group are indicated by numbers, the lowest possible number being given to the hydroxyl group (p. 63), *e.g.*, CH_3OH, methanol; C_2H_5OH, ethanol; $CH_3{\cdot}CH_2{\cdot}CH_2OH$, propan-1-ol; $(CH_3)_2CH{\cdot}CHOH{\cdot}CH_3$, 3-methylbutan-2-ol.

Monohydric alcohols are subdivided into primary, secondary and tertiary alcohols according as the alkyl group attached to the hydroxyl group is a primary, secondary or tertiary group, respectively. Primary alcohols contain the *primary alcoholic group* $—CH_2OH$, *e.g.*, ethanol, $CH_3{\cdot}CH_2OH$; secondary alcohols, the *secondary alcoholic group* $\cdot CH(OH)\cdot$, *e.g.*, *iso*propanol, $(CH_3)_2CHOH$; and tertiary alcohols the *tertiary alcoholic group* $\equiv C(OH)$, *e.g.*, *tert.*-butanol, $(CH_3)_3COH$.

General methods of preparation. 1. By the hydrolysis of an alkyl halide with aqueous alkali or silver oxide suspended in water:

$$RX + \text{“}AgOH\text{”} \longrightarrow ROH + AgX$$

2. By the hydrolysis of esters with alkali:

$$R{\cdot}CO_2R' + KOH \longrightarrow R{\cdot}CO_2K + R'OH$$

This method is important industrially for preparing certain alcohols that occur naturally as esters.

As pointed out previously (p. 113), tertiary halides do not give a good yield of alcohol on hydrolysis. A good yield of alcohol can, however, be obtained by first heating the tertiary halide with silver acetate in ethanolic solution, and then hydrolysing the ester so formed with alkali. Under these conditions the tertiary alkyl radical shows little tendency to form olefin:

$$R_3CX + CH_3{\cdot}CO_2Ag \longrightarrow CH_3{\cdot}CO_2CR_3 + AgX$$
$$CH_3{\cdot}CO_2CR_3 + NaOH \longrightarrow CH_3{\cdot}CO_2Na + R_3COH$$

3. By heating ethers with dilute sulphuric acid under pressure, *e.g.*, diethyl ether forms ethanol:

$$(C_2H_5)_2O + H_2O \xrightarrow{H_2SO_4} 2C_2H_5OH$$

This method is important industrially, since ethers are formed as by-products in the preparation of certain alcohols (see ethanol and propanols).

4. By the reduction of aldehydes, ketones or esters by means of excess sodium and ethanol as the reducing agent (*Bouveault–Blanc reduction*, 1903), *e.g.*,

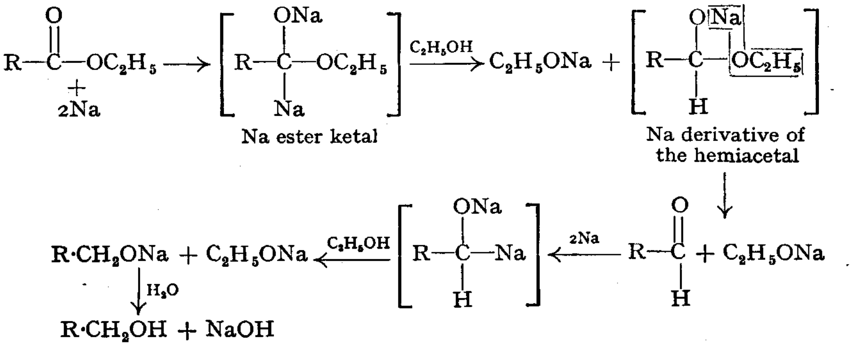
(i) *Aldehydes*: $R{\cdot}CHO + 2[H] \longrightarrow R{\cdot}CH_2OH$ (*g.–v.g.*)

(ii) *Esters*: $R{\cdot}CO_2R' + 4[H] \longrightarrow R{\cdot}CH_2OH + R'OH$ (*g.*)

(iii) *Ketones*: $R_2CO + 2[H] \longrightarrow R_2CHOH$ (*g.*)

Hansley (1947) has improved the Bouveault–Blanc method by using the *theoretical* quantity of sodium and ethanol (see below), and carrying out the reaction in an inert solvent such as toluene or xylene. The yields are usually 85–90 per cent.

The mechanism of the reaction is uncertain. Hansley has proposed the following:



According to these equations, the theoretical amount of sodium is *four* atoms per molecule of ester and *two* molecules of the reducing alcohol.

Darzens (1947) found that sodium hydride, NaH, gives a better yield of alcohol than does sodium by the Bouveault–Blanc reduction of aldehydes, ketones and esters. Nystrom and Brown (1947) have found that lithium aluminium hydride, $LiAlH_4$, also gives very good yields of alcohols from aldehydes, ketones, esters, acids, acid chlorides and acid anhydrides, and one advantage of this reagent is that it does not normally reduce the olefinic bond, and hence an unsaturated aldehyde, ketone, etc., can be reduced to an unsaturated alcohol. The most remarkable feature of this reagent is the reduction of an *acid* to an alcohol, *e.g.*, stearic acid is reduced to octadecan-1-ol:

$$CH_3{\cdot}(CH_2)_{16}{\cdot}CO_2H \xrightarrow{LiAlH_4} CH_3{\cdot}(CH_2)_{16}{\cdot}CH_2OH \quad (91\%)$$

Reductions with lithium aluminium hydride are usually carried out in ethereal solutions, the compound in ether being added to the lithium aluminium hydride solution. In certain cases the reverse addition is necessary, *i.e.*, the hydride solution is added to the solution of the compound to be reduced.

The reactions for the various compounds have been formulated as follows:

(i) $4R{\cdot}CO{\cdot}R + LiAlH_4 \longrightarrow (R_2CHO)_4LiAl \xrightarrow{H_2O} 4R_2CHOH + LiOH + Al(OH)_3$

(ii) $2R{\cdot}CO_2R' + LiAlH_4 \longrightarrow (R{\cdot}CH_2O)_2(OR')_2LiAl \xrightarrow{H_2O} 2R{\cdot}CH_2OH + 2R'OH$

(iii) $4R{\cdot}CO_2H + 3LiAlH_4 \longrightarrow (R{\cdot}CH_2O)_4LiAl + 2LiAlO_2 + 4H_2 \xrightarrow{H_2O} 4R{\cdot}CH_2OH$

(iv) $2R{\cdot}COCl + LiAlH_4 \longrightarrow (R{\cdot}CH_2O)_2LiAlCl_2 \xrightarrow{H_2O} 2R{\cdot}CH_2OH$

(v) $(R{\cdot}CO)_2O + LiAlH_4 \longrightarrow (R{\cdot}CH_2O)_2LiAlO \xrightarrow{H_2O} 2R{\cdot}CH_2OH$

Aluminium trialkyls and dialuminium hydrides appear to be similar in their reducing properties to lithium aluminium hydride (*inter alia*, Miller *et al.*, 1959).

Sodium borohydride, $NaBH_4$, which is insoluble in ether but soluble in water without decomposition, also reduces carbonyl compounds to alcohols, but does not reduce acids. On the other hand, lithium borohydride, which is soluble in ether and is decomposed by water, behaves like lithium aluminium hydride but is not so vigorous and hence may be used to reduce a more reactive group when the molecule contains two or more reducible groups, *e.g.*, when the compound contains both a carbonyl and a carboxyl group, the former is reduced preferentially:

$$R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \xrightarrow{LiBH_4} R{\cdot}CHOH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

Aldehydes, ketones, esters, acid chlorides and acid anhydrides can be reduced catalytically to alcohols in very good yields, *e.g.*,

acid chloride: $R{\cdot}COCl + 2H_2 \xrightarrow{cat.} R{\cdot}CH_2OH + HCl$

acid anhydride: $(R{\cdot}CO)_2O + 4H_2 \xrightarrow{cat.} 2R{\cdot}CH_2OH + H_2O$

Catalytic reduction is particularly useful for preparing the higher alcohols from esters. The ester is hydrogenated at 200° and at 150–200 atm. using a copper catalyst, whereupon alcohols free from hydrocarbons are produced. If a nickel catalyst is used and the temperature is above 250°, hydrocarbons are the main product. Cadmium–nickel salts of acids may also be hydrogenated under pressure in the presence of copper chromite to alcohols, the lower members (C_1 to C_5) giving 70–95 per cent. yields (Adams *et al.*, 1952). On the other hand, carboxylic acids can be hydrogenated to primary alcohols in the presence of a ruthenium or copper chromite catalyst (Guyer *et al.*, 1955). Aldehydes, ketones, carboxylic acids, acid chlorides, and esters are readily reduced to alcohols by diborane (Brown *et al.*, 1957).

5. Primary, secondary and tertiary alcohols may be prepared by means of a Grignard reagent and the appropriate carbonyl compound (see p. 352).

6. A number of alcohols are obtained by fermentation processes (see later).

7. In recent years synthetic methods have become very important for preparing various alcohols:

(i) By the hydration of olefins, *e.g.*, ethanol, *iso*propanol, etc.

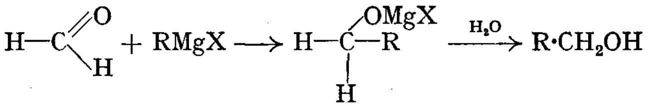
(ii) By heating a mixture of carbon monoxide and hydrogen under pressure in the presence of a catalyst, *e.g.*, zinc chromite plus small amounts of alkali metal or iron salts. A mixture of alcohols containing methyl, ethyl, *n*-

propyl, *iso*butyl and higher-branched alcohols is obtained, the individuals being separated by fractional distillation (see below).

(iii) By the " *oxo* " process, which is the process whereby carbon monoxide and hydrogen are added to olefins to yield aldehydes and alcohols (which are separated by fractional distillation). Carbon monoxide, hydrogen and the olefin are compressed to 200 atm. at 125–145°, and passed over a catalyst. One catalyst consists of cobalt, thoria, magnesia and kieselguhr in the proportions of 100 : 5 : 8 : 200—this catalyst is also used in the Fischer–Tropsch synthesis (p. 60); *e.g.*, propylene, CO and H_2 give a mixture of the two straight-chain butanols. The oxo-process is also known as the oxo-synthesis and the carbonylation or hydroformylation reaction.

(iv) Methanol, ethanol, propanols and butanols are prepared industrially by the oxidation of natural gas (p. 60).

Most of the methods given above can be used for the preparation of any particular class of alcohol: it is only a question of starting with the appropriate compound. *Primary* alcohols may be prepared by the hydrolysis of *primary* alkyl halides; by the reduction of aldehydes, esters, acids, acid chlorides and acid anhydrides; and by means of a Grignard reagent and formaldehyde:



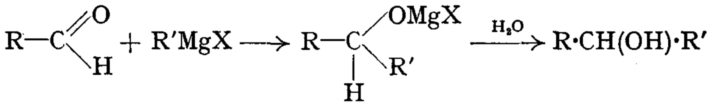
$$H{-}C{\overset{\displaystyle /\!\!/O}{\underset{\displaystyle \backslash H}{}}} + RMgX \longrightarrow H{-}\underset{\displaystyle H}{\overset{\displaystyle OMgX}{C}}{-}R \xrightarrow{H_2O} R{\cdot}CH_2OH$$

In addition to these, primary alcohols may be prepared, in variable yields, by the action of nitrous acid on primary amines of the type $R{\cdot}CH_2{\cdot}NH_2$:

$$R{\cdot}CH_2{\cdot}NH_2 + HNO_2 \longrightarrow R{\cdot}CH_2OH + N_2 + H_2O$$

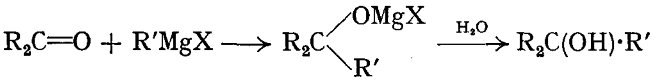
Primary alcohols may also be prepared by the oxidation of primary trialkylborons (p. 76).

Secondary alcohols may be prepared by the hydrolysis of *secondary* alkyl halides, or better, via the ester (see above); by the reduction of ketones; and by means of a Grignard reagent and any aldehyde other than formaldehyde:



$$R{-}C{\overset{\displaystyle /\!\!/O}{\underset{\displaystyle \backslash H}{}}} + R'MgX \longrightarrow R{-}\underset{\displaystyle H}{C}{\overset{\displaystyle OMgX}{\underset{\displaystyle R'}{}}} \xrightarrow{H_2O} R{\cdot}CH(OH){\cdot}R'$$

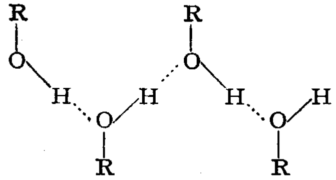
Tertiary alcohols may be prepared by the *indirect* hydrolysis of *tertiary* alkyl halides, *viz.*, via the ester; and by means of a Grignard reagent and a ketone (or an ester):



$$R_2C{=}O + R'MgX \longrightarrow R_2C{\overset{\displaystyle OMgX}{\underset{\displaystyle R'}{}}} \xrightarrow{H_2O} R_2C(OH){\cdot}R'$$

General properties of the alcohols. The alcohols are neutral substances: the lower members are liquids, and have a distinctive smell and a burning taste; the higher members are solids and are almost odourless.

In a group of isomeric alcohols, the primary alcohol has the highest boiling point and the tertiary the lowest, with the secondary having an intermediate value. The lower members are far less volatile than is to be expected from their molecular weight, and this is believed to be due to association through hydrogen bonding *extending over a chain of molecules,* thus giving rise to a " large molecule " the volatility of which would be expected to be low:



The lower alcohols are very soluble in water, and the solubility diminishes as the molecular weight increases. Their solubility in water is to be expected, since the oxygen atom of the hydroxyl group in alcohols can form hydrogen bonds with the water molecules. In the lower alcohols the hydroxyl group constitutes a large part of the molecule, whereas as the molecular weight of the alcohol increases the hydrocarbon character of the molecule increases, and hence the solubility in water decreases. This, however, is not the complete story; the structure of the carbon chain also plays a part, *e.g.*, *n*-butanol is fairly soluble in water, but *tert.*-butanol is miscible with water in all proportions.

General reactions of the alcohols. 1. Alcohols react with organic and inorganic acids to form *esters*:

$$R{\cdot}CO_2H + R'OH \longrightarrow R{\cdot}CO_2R' + H_2O$$

Esters of the halogen acids are, as we have seen (p. 100), the alkyl halides.

Alcohols, when heated with concentrated hydriodic acid and red phosphorus, are converted into paraffins.

The order of reactivity of an alcohol with a given organic acid is primary alcohol>secondary>tertiary, but with a given halogen acid the order is reversed. This implies that the mechanism of *esterification* (p. 187) of organic acids is different from that of halogen acids. It has also been observed that for a given alcohol the order of reactivity of the halogen acids is HI>HBr>HCl. An explanation of all these observations is offered later when the mechanism of esterification is discussed in detail.

2. Alcohols react with phosphorus halides to form alkyl halides (p. 103). Treatment of alcohols with chlorine or bromine results in the formation of halogen-substituted oxidised products (see also p. 168), *e.g.*, chlorination of ethanol gives trichloroacetaldehyde (*cf.* chloroform):

$$CH_3{\cdot}CH_2OH \xrightarrow{Cl_2} CCl_3{\cdot}CHO$$

On the other hand, when chlorine is passed into an alcohol (primary or secondary) in the presence of alkali, an organic hypochlorite is formed:

$$R_2CHOH + Cl_2 \xrightarrow{NaOH} R_2CHOCl + HCl$$

These hypochlorites are unstable, and when heated or exposed to light, eliminate hydrogen chloride:

$$R_2CHOCl \longrightarrow R_2CO + HCl$$

3. Alcohols combine with phenyl *iso*cyanate to form phenyl-substituted urethans:

$$C_6H_5{\cdot}NCO + ROH \longrightarrow C_6H_5{\cdot}NH{\cdot}CO_2R$$

Urethans are well-defined crystalline solids, and so may be used to characterise the alcohols.

Readily dehydrated alcohols, particularly tertiary alcohols, do not form urethans but produce olefins and diphenylurea as follows:

$$R_2C(OH)\cdot CH_2\cdot CH_3 \longrightarrow R_2C{=}CH\cdot CH_3 + H_2O$$
$$C_6H_5\cdot NCO + H_2O \longrightarrow C_6H_5\cdot NH_2 + CO_2$$
$$C_6H_5\cdot NCO + C_6H_5\cdot NH_2 \longrightarrow C_6H_5\cdot NH\cdot CO\cdot NH\cdot C_6H_5$$

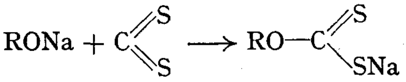
4. Alcohols are attacked by strongly electropositive metals, *e.g.*, sodium and potassium; hydrogen is liberated and the *alkoxide* is formed; *e.g.*, ethanol reacts with sodium to form sodium ethoxide:

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5ONa + H_2$$

Sodium and potassium alkoxides are electrovalent compounds, *i.e.*, their formulæ should be written, *e.g.*, RO^-Na^+; they are white deliquescent solids, readily soluble in water with decomposition:

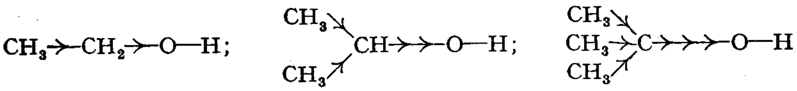
$$RONa + H_2O \rightleftharpoons ROH + NaOH$$

Alkoxides react with carbon disulphide to form xanthates:



$$RONa + C\begin{smallmatrix}\nearrow\!\!\!\!\!\nearrow S\\ \searrow\!\!\!\!\!\searrow S\end{smallmatrix} \longrightarrow RO{-}C\begin{smallmatrix}\nearrow\!\!\!\!\!\nearrow S\\ \searrow SNa\end{smallmatrix}$$

The order of ease of formation of an alkoxide with sodium or potassium is primary alcohol> secondary> tertiary. This may be explained as follows. There are two possible ways in which the group COH may undergo fission: C|—O—H and C—O—|H. Since oxygen has a higher electron-affinity than either carbon or hydrogen, the shared electron pairs are displaced towards the oxygen, *i.e.*, we have $\overset{\delta+}{C} \rightarrow \overset{\delta-}{O} \leftarrow \overset{\delta+}{H}$. The greater the displacement of the shared pair towards the oxygen atom in the C—O bond, the larger is the negative charge on the oxygen atom, and consequently the weaker is the attraction of the oxygen atom for the shared pair of the O—H bond. Since alkyl groups are electron-releasing, the larger the number of alkyl groups attached to the carbon atom of the COH group, the greater will be the negative charge on the oxygen atom. This may be represented as follows:



$$CH_3 \rightarrow CH_2 \rightarrow O{-}H; \quad \begin{matrix}CH_3\searrow & \\ & CH \rightarrow\rightarrow O{-}H;\\ CH_3\nearrow & \end{matrix} \quad \begin{matrix}CH_3\searrow & \\ CH_3\rightarrow & C \rightarrow\rightarrow\rightarrow O{-}H\\ CH_3\nearrow & \end{matrix}$$

Thus the displacement of the bonding pair of electrons in the C—O bond towards the O atom is least in primary alcohols and greatest in tertiary, and consequently the tendency of the COH group to break as C|—OH is greatest in tertiary alcohols and least in primary; conversely, the tendency of the COH group to break as C—O—|H is greatest in primary alcohols and least in tertiary. Hence reactions involving the breaking of the C—O bond will take place most readily with tertiary alcohols and least readily with primary; but those reactions which involve the breaking of the O—H bond will take place most readily with primary alcohols and least readily with tertiary. When sodium attacks an alcohol, hydrogen is evolved, and since this involves the breaking of the O—H bond, we can now understand why the order of ease of formation of alkoxides is primary alcohol> secondary> tertiary.

A number of alkoxides are important as synthetic reagents; *e.g.*, sodium ethoxide, C_2H_5ONa; aluminium ethoxide, $(C_2H_5O)_3Al$; aluminium *tert.*-butoxide $[(CH_3)_3CO]_3Al$ (see text for their uses). The aluminium alkoxides may be conveniently prepared by the action of aluminium amalgam or aluminium shavings on the alcohol.

5. Primary and secondary alcohols may be acetylated with acetyl chloride, *e.g.*, ethanol gives ethyl acetate:

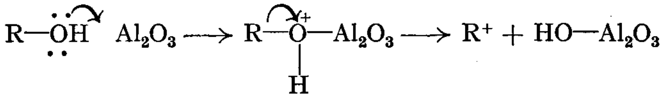
$$CH_3{\cdot}COCl + C_2H_5OH \longrightarrow CH_3{\cdot}CO_2C_2H_5 + HCl$$

With tertiary alcohols the reaction is often accompanied by dehydration of the alcohol to olefin, or by the formation of a tertiary alkyl chloride; *e.g.*, *tert.*-butanol gives a good yield of *tert.*-butyl chloride:

$$(CH_3)_3COH + CH_3{\cdot}COCl \longrightarrow (CH_3)_3{\cdot}CCl + CH_3{\cdot}CO_2H$$

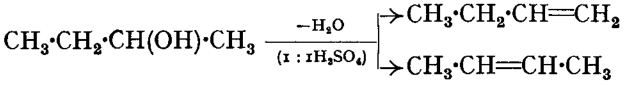
6. Alcohols may be oxidised, and the products of oxidation depend on the class of the alcohol (see below).

7. Alcohols may be dehydrated to olefins by heat alone, but the temperature must be high (400–800°). Dehydration, however, can be effected at lower temperatures in the presence of catalysts, *e.g.*, all three classes of alcohols are dehydrated by passing over alumina at 350°; primary alcohols are dehydrated by concentrated sulphuric acid at about 170°, and secondary and tertiary alcohols by boiling dilute sulphuric acid (this is used to avoid polymerisation of the olefin). The mechanism when sulphuric acid is used is described on p. 80. The mechanism with alumina is uncertain; a possibility is:



$$R{-}\ddot{O}H \quad Al_2O_3 \longrightarrow R{-}\overset{+}{\underset{H}{O}}{-}Al_2O_3 \longrightarrow R^+ + HO{-}Al_2O_3$$

With secondary and tertiary alcohols, dehydration may occur in two ways, *e.g.*,



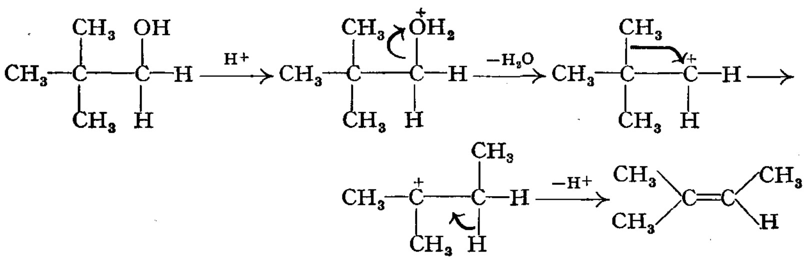
$$CH_3{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_3 \xrightarrow[(1\,:\,1H_2SO_4)]{-H_2O} \begin{cases} CH_3{\cdot}CH_2{\cdot}CH{=}CH_2 \\ CH_3{\cdot}CH{=}CH{\cdot}CH_3 \end{cases}$$

Experiment shows that hydrogen attached to the adjacent carbon atom joined to the least number of hydrogen atoms is eliminated most easily. Thus, in the above reaction, the main product is but-2-ene (65–80 per cent.). This elimination thus occurs in accordance with Saytzeff's rule for the dehydrohalogenation of alkyl halides, and the reason is the same (see p. 112).

When alcohols containing no hydrogen atoms on the carbon atom adjacent to the COH group are dehydrated, dehydration and molecular rearrangement occur together, *e.g.*, *neo*pentyl alcohol gives 2-methylbut-2-ene:

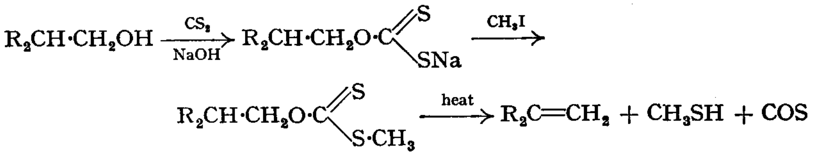
$$(CH_3)_3C{\cdot}CH_2OH \xrightarrow{-H_2O} (CH_3)_2C{=}CH{\cdot}CH_3$$

This is an example of the 1,2-shift, and the mechanism may be formulated as follows (see also p. 101):



When a double bond is produced in the product and is accompanied by a 1,2-shift, the reaction is said to be a *retropinacol rearrangement*. This type of rearrangement, when occurring in *open-chain* compounds, is also sometimes called the *Wagner rearrangement.*

Alcohols may also be converted into olefins via their methyl xanthates (*Tschugaev reaction,* 1899):



$$R_2CH{\cdot}CH_2OH \xrightarrow[NaOH]{CS_2} R_2CH{\cdot}CH_2O{\cdot}C\begin{smallmatrix}\nearrow S\\ \searrow SNa\end{smallmatrix} \xrightarrow{CH_3I}$$

$$R_2CH{\cdot}CH_2O{\cdot}C\begin{smallmatrix}\nearrow S\\ \searrow S{\cdot}CH_3\end{smallmatrix} \xrightarrow{heat} R_2C{=}CH_2 + CH_3SH + COS$$

A very important feature of this reaction is that no rearrangement occurs in the formation of the olefin from alcohols which undergo rearrangement when dehydrated by the usual dehydrating agents.

By means of dehydration, it is possible to convert a primary alcohol into a secondary or tertiary, according to the structure of the primary alcohol, *e.g.*,

$$\text{(i)}\ CH_3{\cdot}CH_2{\cdot}CH_2OH \xrightarrow[350^\circ]{Al_2O_3} CH_3{\cdot}CH{=}CH_2 \xrightarrow{HI}$$

$$CH_3{\cdot}CHI{\cdot}CH_3 \xrightarrow{\text{“AgOH”}} CH_3{\cdot}CH(OH){\cdot}CH_3$$

$$\text{(ii)}\ (CH_3)_2CH{\cdot}CH_2OH \xrightarrow[350^\circ]{Al_2O_3} (CH_3)_2C{=}CH_2 \xrightarrow{HI}$$

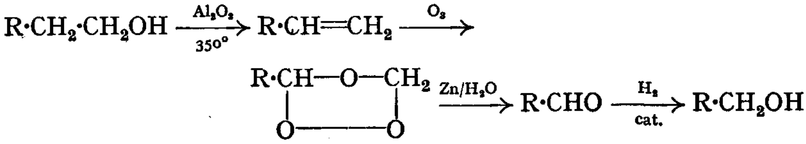
$$(CH_3)_2CI{\cdot}CH_3 \xrightarrow{\text{“AgOH”}} (CH_3)_2C(OH){\cdot}CH_3$$

In the same way, a secondary alcohol of suitable structure can be converted into a tertiary alcohol, *e.g.*,

$$(CH_3)_2CH{\cdot}CH(OH){\cdot}CH_3 \xrightarrow[350^\circ]{Al_2O_3} (CH_3)_2C{=}CH{\cdot}CH_3 \xrightarrow{HI}$$

$$(CH_3)_2CI{\cdot}CH_2{\cdot}CH_3 \xrightarrow{\text{“AgOH”}} (CH_3)_2C(OH){\cdot}CH_2{\cdot}CH_3$$

It is also possible to step down the alcohol series by means of dehydration, *e.g.*,



$$R{\cdot}CH_2{\cdot}CH_2OH \xrightarrow[350^\circ]{Al_2O_3} R{\cdot}CH{=}CH_2 \xrightarrow{O_3}$$

$$\begin{array}{l} R{\cdot}CH{-}O{-}CH_2 \\ \ \ \ |\qquad\quad\ | \\ \ \ \ O{-}{-}{-}{-}O \end{array} \xrightarrow{Zn/H_2O} R{\cdot}CHO \xrightarrow[cat.]{H_2} R{\cdot}CH_2OH$$

8. Alcohols also combine with acetylene in the presence of mercury compounds as catalyst to form acetals:

$$2ROH + CH{\equiv}CH \xrightarrow{Hg^{++}} CH_3{\cdot}CH(OR)_2$$

If, however, the reaction is carried out in the presence of potassium alkoxides at high temperature and under pressure, vinyl ethers are obtained (p. 94).

9. Alcohols can be made to undergo self-condensation in the presence of sodium alkoxide at elevated temperatures:

$$2RCH_2{\cdot}CH_2OH \longrightarrow RCH_2{\cdot}CH_2{\cdot}CHR{\cdot}CH_2OH$$

This is known as the **Guerbet reaction** (1899), and can be used for primary and secondary alcohols and also for mixed condensations.

Methods of Distinguishing between the Three Classes of Alcohols. 1. By means of *oxidation.* The nature of the oxidation products of an alcohol depends on whether the alcohol is primary, secondary or tertiary.

(i) A *primary* alcohol on oxidation first gives an *aldehyde,* and this, on further oxidation, gives an acid. *Both the aldehyde and acid contain the same number of carbon atoms as the original alcohol, e.g.*:

$$CH_3{\cdot}CH_2OH \xrightarrow{[O]} CH_3{\cdot}CHO \xrightarrow{[O]} CH_3{\cdot}CO_2H$$

(ii) A *secondary* alcohol, on oxidation, first gives a *ketone with the same number of carbon atoms as the original alcohol.* Ketones are fairly difficult to oxidise, but prolonged action of the oxidising agents produces a mixture of acids, each containing *fewer* carbon atoms than the original alcohol, *e.g.*, methyl-*n*-propylmethanol gives first pentan-2-one, and then a mixture of acetic and propionic acids:

$$CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \xrightarrow{[O]} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \xrightarrow{[O]} CH_3{\cdot}CO_2H + CH_3{\cdot}CH_2{\cdot}CO_2H$$

(iii) *Tertiary* alcohols are resistant to oxidation in neutral or alkaline solution, but are readily oxidised by acid oxidising agents to a mixture of *ketone and acid, each containing fewer carbon atoms than the original alcohol.*

$$(CH_3)_2C(OH){\cdot}CH_2{\cdot}CH_3 \xrightarrow{[O]} (CH_3)_2CO + CH_3{\cdot}CO_2H$$

The oxidising agents usually used for oxidising alcohols are: acid dichromate, acid or alkaline potassium permanganate, and dilute nitric acid.

The mechanism of oxidation of alcohols is still uncertain. There is, however, evidence to show, at least in the case of primary and secondary alcohols, that the first step is dehydrogenation at the carbon of the C—OH group. Westheimer *et al.* (1949) found that there is a kinetic isotope effect (p. 36) when 2-deutero*iso*propanol, $CH_3{\cdot}CDOH{\cdot}CH_3$, is oxidised with chromic acid; the rate of oxidation of this compound was found to be about one-sixth the rate of oxidation of *iso*propanol. Thus the rate-determining step is the fission of the C—H bond in the group H—C—OH. This is supported by the fact that these authors found no kinetic isotope effect in the oxidations of $(CH_3)_2CHOH$ and $(CD_3)_2CHOH$. In tertiary alcohols, which are very resistant to oxidation, there is no H—C—OH group. Consequently it is logical to conclude that tertiary alcohols are oxidised by a different mechanism. Since tertiary alcohols are very readily dehydrated, their oxidation may therefore proceed via the oxidation of an intermediate olefin.

2. The three classes of alcohols differ in their behaviour when the vapour is passed over copper at 300°:

(i) A primary alcohol is dehydrogenated to an aldehyde, *e.g.*,

$$CH_3{\cdot}CH_2OH \xrightarrow[300^\circ]{Cu} CH_3{\cdot}CHO + H_2$$

(ii) A secondary alcohol is dehydrogenated to a ketone, *e.g.*,

$$CH_3{\cdot}CH(OH){\cdot}CH_3 \xrightarrow[300^\circ]{Cu} CH_3{\cdot}CO{\cdot}CH_3 + H_2$$

(iii) A tertiary alcohol is dehydrated to an olefin, *e.g.*,

$$(CH_3)_2C(OH){\cdot}CH_2{\cdot}CH_3 \xrightarrow[300^\circ]{Cu} (CH_3)_2C{=}CH{\cdot}CH_3 + H_2O$$

3. The alcohol is converted by phosphorus tri-iodide into its corresponding iodide, which is then heated with silver nitrite, and the resulting nitroparaffin is treated with nitrous acid and alkali. Characteristic colours are obtained according as the alkyl group is primary, secondary or tertiary (see p. 305).

Methyl alcohol, methanol (*carbinol*), CH_3OH, is prepared industrially by several methods. The earliest method was by the destructive distillation of wood, whereby tar and an aqueous fraction known as *pyroligneous acid* are obtained. Pyroligneous acid contains methanol, acetone and acetic acid, and all three compounds may be obtained by suitable treatment (see acetic acid, p. 181). It was this method which gave rise to the name "wood spirit" for methanol. The modern methods are synthetic.

(i) Water gas mixed with half its volume of hydrogen—synthesis gas—is passed at a pressure of 200 atmospheres over a catalyst containing the oxides of copper, zinc and chromium at 300°:

$$CO + 2H_2 \longrightarrow CH_3OH$$

If the proper precautions are taken, the yield of methanol is almost 100 per cent., and its purity is above 99 per cent. By changing the catalyst and the ratio of carbon monoxide to hydrogen, methanol and a variety of higher alcohols are produced (p. 126). Another commercial method uses carbon dioxide instead of the monoxide; again a catalyst is required:

$$CO_2 + 3H_2 \longrightarrow CH_3OH + H_2O$$

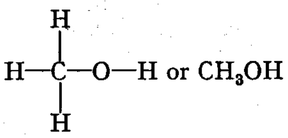
(ii) By the catalytic oxidation of methane. A mixture of methane and oxygen (ratio by volume of 9 : 1) at a pressure of 100 atmospheres is passed through a copper tube at 200°:

$$CH_4 + \tfrac{1}{2}O_2 \longrightarrow CH_3OH$$

Methanol is a colourless, inflammable liquid, b.p. 64°, and is poisonous. It is miscible with water in all proportions, and is also miscible with most organic solvents. It burns with a faintly luminous flame, and its vapour forms explosive mixtures with air or oxygen when ignited. It combines with calcium chloride to form $CaCl_2{\cdot}4CH_3OH$, and hence cannot be dried this way (*cf.* ethanol).

Methanol is used as a solvent for paints, varnishes, shellac, celluloid cements, etc.; in the manufacture of dyes, perfumes, formaldehyde, etc. It is also used for making methylated spirit and automobile antifreeze mixtures.

Structure of methanol. Analysis and molecular-weight determinations show that the molecular formula of methanol is CH_4O. Assuming that carbon is quadrivalent, oxygen bivalent and hydrogen univalent, only one structure is possible:



$$H-\overset{\displaystyle H}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-O-H \text{ or } CH_3OH$$

This is supported by all the chemical reactions of methanol, *e.g.*, (i) only one hydrogen atom in methanol is replaceable by sodium; this suggests that one hydrogen atom is in a different state of combination from the other three.

(ii) Methanol is formed from methyl chloride by hydrolysis with sodium hydroxide. Methyl chloride can have only the structure CH_3Cl. It is reasonable to suppose that the methyl group in methyl chloride is unchanged by the action of dilute alkali, and that the reaction takes place by the replacement of the chlorine atom by a hydroxyl group.

(iii) The presence of the hydroxyl group is confirmed, for example, by the reaction between methanol and phosphorus pentachloride, when methyl chloride, hydrogen chloride and phosphoryl chloride are formed. Thus one oxygen atom (bivalent) and one hydrogen atom (univalent) have been replaced by one chlorine atom (univalent). This implies that the oxygen and hydrogen atoms exist as a univalent radical in methanol: the only possibility is as a hydroxyl group, OH. It is the hydrogen of the hydroxyl group which is displaced by sodium.

All these reactions indicate that the structure of methanol is CH_3OH.

Ethyl alcohol, ethanol (*methylcarbinol*), C_2H_5OH, is prepared industrially by several methods: (i) Ethylene (from cracked petroleum) is absorbed in concentrated sulphuric acid (98 per cent.) at 75–80°, under pressure (250–500 lb./per sq. in.). Ethyl hydrogen sulphate and ethyl sulphate are formed:

$$C_2H_4 + (HO)_2SO_2 \longrightarrow C_2H_5O\cdot SO_2\cdot OH$$
$$C_2H_5O\cdot SO_2\cdot OH + C_2H_4 \longrightarrow (C_2H_5O)_2SO_2$$

The reaction mixture is then diluted with about an equal volume of water, and warmed. Hydrolysis takes place and ethanol together with some diethyl ether is formed:

$$C_2H_5O\cdot SO_2\cdot OH + H_2O \longrightarrow C_2H_5OH + H_2SO_4$$
$$(C_2H_5O)_2SO_2 + 2H_2O \longrightarrow 2C_2H_5OH + H_2SO_4$$
$$(C_2H_5O)_2SO_2 + C_2H_5OH \longrightarrow (C_2H_5)_2O + C_2H_5O\cdot SO_2\cdot OH$$

The ether is kept to a minimum by separating the ethyl sulphate from the reaction products, and hydrolysing it separately.

The hydrolysed liquids are distilled, and the aqueous ethanol distillate is concentrated by fractional distillation (see also below).

Ethanol is also manufactured by the *direct* hydration of ethylene with steam under pressure in the presence of a suitable catalyst:

$$C_2H_4 + H_2O \longrightarrow C_2H_5OH$$

(ii) Acetaldehyde (from acetylene) is catalytically reduced to ethanol by passing its vapour, mixed with hydrogen, over finely divided nickel at 100–140°:

$$CH_3\cdot CHO + H_2 \longrightarrow CH_3\cdot CH_2OH$$

(iii) The earliest method of preparing ethanol is by fermentation, and this is still used for the manufacture of beer, wine, brandy, etc., and also as a source of ethanol. The starting material is starch, which is obtained from sources depending on the particular country: common sources of starch are wheat, barley, potato, etc. Recently, molasses (p. 460) has also been used as the starting material for ethanol. The grain, *e.g.*, wheat or barley, is mashed with hot water, and then heated with malt (germinated barley) at 50° for 1 hour. Malt contains the enzyme *diastase* which, by hydrolysis, converts starch into the sugar, maltose (*q.v.*):

$$(C_6H_{10}O_5)_n + \frac{n}{2}H_2O \xrightarrow{\text{diastase}} \frac{n}{2}C_{12}H_{22}O_{11}$$

If molasses is used, then this step is unnecessary, since it contains carbohydrates already present as sugars which can be fermented.

The liquid is cooled to 30° and fermented with yeast for 1–3 days. Yeast contains various enzymes, among which are *maltase*, which converts the maltose into glucose, and *zymase*, which converts the glucose into ethanol:

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow{\text{maltase}} 2C_6H_{12}O_6$$

$$C_6H_{12}O_6 \xrightarrow{\text{zymase}} 2C_2H_5OH + 2CO_2$$

The carbon dioxide is recovered and sold as a by-product. The fermented liquor or " wort ", which contains 6–10 per cent. ethanol and some other compounds, is fractionated into three fractions:

(i) *First runnings*, which consists mainly of acetaldehyde.
(ii) *Rectified spirit*, which is 93–95% w/w ethanol.
(iii) *Final runnings* or *fusel oil*, which contains *n*-propyl, *n*-butyl, *iso*butyl, *n*-amyl, *iso*amyl and " active " amyl alcohol.

Industrial alcohol is ordinary rectified spirit. *Methylated spirit* is of two kinds: (*a*) *Mineralised methylated spirit* is 90 per cent. rectified spirit, 9 per cent. methanol and 1 per cent. petroleum oil, and a purple dye. (*b*) *Industrial methylated spirit* is 95 per cent. rectified spirit and 5 per cent. methanol, whose purpose is to " *denature* " the rectified spirit, *i.e.*, make it unfit for drinking purposes.

Absolute alcohol is 99·5 per cent. ethanol, and is obtained from rectified spirit. When an aqueous solution of ethanol is fractionated, it forms a constant-boiling mixture containing 96 per cent. ethanol from which 100 per cent. ethanol may be obtained by adding a small amount of benzene, and then distilling. The first fraction is the ternary azeotrope, *i.e.*, a constant-boiling mixture containing three constituents, b.p. 64·8° (water, 7·4 per cent.; ethanol, 18·5 per cent.; benzene, 74·1 per cent.). After all the water has been removed, the second fraction that distils over is the binary azeotrope, b.p. 68·2° (ethanol, 32·4 per cent.; benzene, 67·6 per cent.). After all the benzene has been removed, pure ethanol, b.p. 78·1°, distils over.

Ethanol cannot be dried by means of calcium chloride, since a compound (an *alcoholate*) is formed, *e.g.*, $CaCl_2{\cdot}3C_2H_5OH$ (*cf.* methanol). Distillation of rectified spirit over calcium oxide, and then over calcium, gives absolute alcohol. This method is often used in the laboratory, and was formerly used industrially.

Ethanol is a colourless, inflammable liquid, b.p. 78·1°. It is miscible with water in all proportions, and is also miscible with most organic solvents. Ethanol and methanol resemble each other very closely, but they may be distinguished (i) by the fact that ethanol gives the haloform reaction (*q.v.*), whereas methanol does not; and (ii) ethanol gives acetic acid on oxidation; methanol gives formic acid. These two acids are readily distinguished from each other (p. 181).

Ethanol is used for the preparation of esters, ether, chloral, chloroform, etc. It is also used as a solvent for gums, resins, paints, varnishes, etc., and as a fuel.

Structure of ethanol. Analysis and molecular-weight determinations show that the molecular formula of ethanol is C_2H_6O. Assuming that carbon is quadrivalent, oxygen bivalent, and hydrogen univalent, two structures are possible:

$$\underset{\text{(I)}}{CH_3{-}CH_2{-}OH} \qquad \underset{\text{(II)}}{CH_3{-}O{-}CH_3}$$

(i) Only one hydrogen atom in ethanol is replaceable by sodium or potassium. This indicates that one hydrogen atom is in a different state of combination from the other five. In (I), one hydrogen atom differs from the other five, but in (II) all the hydrogen atoms are equivalent.

(ii) When ethanol is treated with hydrochloric acid or phosphorus pentachloride, one oxygen atom (bivalent) and one hydrogen atom (univalent) are replaced by one chlorine atom (univalent) to give ethyl chloride, C_2H_5Cl. This implies the presence of a hydroxyl group (*cf.* methanol).

(iii) When ethyl chloride is hydrolysed with dilute alkali, ethanol is obtained. This reaction also indicates the presence of a hydroxyl group in ethanol.

(iv) Ethanol may be prepared as follows:

$$C_2H_6 \xrightarrow{Cl_2} C_2H_5Cl \xrightarrow{NaOH} C_2H_5OH$$

The arrangement of the six hydrogen atoms in ethane is known, and it is reasonable to suppose that five retain their original arrangement in ethyl chloride and ethanol, since these five hydrogen atoms do not enter (presumably) into the above reactions. Thus there is an ethyl radical C_2H_5— in ethanol. This is so in (I), but not in (II).

(v) Structure (II) is definitely eliminated, since it can be shown that it is the structure of dimethyl ether (*q.v.*), a compound that has very little resemblance, physically or chemically, to ethanol.

Thus (I) is accepted as the structure of ethanol, and it accounts for all the known properties of ethanol.

It can be seen from the various examples given on structure determination, *e.g.*, ethane, propane, ethylene, methanol and ethanol, that the method of approach follows certain definite lines. First the molecular formula is obtained. Then, if the compound is simple—in the sense that it contains a small number of unlike atoms, and that the total number of atoms is also small—the valencies of the atoms present are assumed, and various possible structures are written down. If the compound is " simple " the number of possible structures will not be large (four or five at the most). Then by considering the chemical properties of the compound in question, the structure which best fits the observed facts is accepted as the correct one. If the compound is not " simple ", the procedure is to detect the presence of as many functional groups as possible; to degrade the compound into simpler substances whose structures are already known or which may be determined by further degradation; to build up structural formulæ based on the facts obtained; and then to choose that structure which best fits the facts. Finally a synthesis is attempted, and if successful, will usually give proof of the correctness of the structure suggested.

It can be seen from the above arguments that it is necessary to have methods, preferably simple ones, for detecting the presence of functional groups. The reader will become familiar with these methods as he reads the text. At this stage we shall confine our attentions to detecting the presence of a hydroxyl group. The usual tests are: (i) Treatment with sodium; if hydrogen is evolved, a hydroxyl group is present. (ii) Treatment with phosphorus pentachloride or acetyl chloride; the evolution of hydrochloric acid fumes indicates the presence of a hydroxyl group.

Acetyl chloride is usually the most satisfactory (remember, however, alcohols of the type R_3COH, p. 130).

Propyl alcohols, C_3H_7OH. Two isomeric propyl alcohols are possible, and both are known.

n-*Propyl alcohol, propan*-1-*ol,* n-*propanol,* $CH_3{\cdot}CH_2{\cdot}CH_2OH$, was originally obtained from fusel oil (see above), but it is now also produced by the hydrogenation of carbon monoxide. A more recent method is by the catalytic reduction of propargyl alcohol (from acetylene and formaldehyde):

$$CH{\equiv}C{\cdot}CH_2OH + 2H_2 \xrightarrow{Ni} 2CH_3{\cdot}CH_2{\cdot}CH_2OH$$

n-Propanol is a colourless liquid, b.p. 97·4°, and is miscible with water, ethanol and ether. It is used in the preparation of propionic acid, toilet preparations such as lotions, etc.

iso*Propyl alcohol, propan-2-ol,* iso*propanol,* $CH_3{\cdot}CH(OH){\cdot}CH_3$, is prepared industrially:

(i) By the catalytic hydrogenation of acetone under pressure:

$$CH_3{\cdot}CO{\cdot}CH_3 + H_2 \xrightarrow{Ni} CH_3{\cdot}CH(OH){\cdot}CH_3$$

(ii) By passing propylene (from cracked petroleum) into concentrated sulphuric acid, then diluting with water, and distilling off the *iso*propanol. *iso*Propyl ether is obtained as a by-product (*cf.* ethanol):

$$CH_3{\cdot}CH{=}CH_2 + (HO)_2SO_2 \longrightarrow (CH_3)_2CHO{\cdot}SO_2{\cdot}OH$$

$$(CH_3)_2CHO{\cdot}SO_2{\cdot}OH + CH_3{\cdot}CH{=}CH_2 \longrightarrow [(CH_3)_2CHO]_2SO_2$$

$$(CH_3)_2CHO{\cdot}SO_2{\cdot}OH + H_2O \longrightarrow (CH_3)_2CHOH + H_2SO_4$$

$$[(CH_3)_2CHO]_2SO_2 + 2H_2O \longrightarrow 2(CH_3)_2CHOH + H_2SO_4$$

$$[(CH_3)_2CHO]_2SO_2 + (CH_3)_2CHOH \longrightarrow [(CH_3)_2CH]_2O + (CH_3)_2CHO{\cdot}SO_2{\cdot}OH$$

*iso*Propanol can also be prepared by *direct* hydration, and this can be effected by passing a mixture of propylene and steam at 220–250°, and under pressure (220 atm.), over a catalyst of tungsten oxide plus zinc oxide, on a silica carrier.

*iso*Propanol is a colourless liquid, b.p. 82·4°, and is soluble in water, ethanol and ether. It is used for preparing esters, acetone, keten, as a solvent, and for high-octane fuel.

Butyl alcohols, C_4H_9OH. Four isomers are possible, and all are known.

n-*Butyl alcohol, butan-1-ol,* n-*butanol,* $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH$, b.p. 117·4°, is prepared industrially:

(i) By the *Weizmann process* (1911). Starch or molasses is fermented with the micro-organism, *Clostridium acetobutylicum,* whereupon acetone and *n*-butanol are obtained.

(ii) Synthetically from acetaldehyde:

$$2CH_3{\cdot}CHO \xrightarrow{NaOH} \underset{\text{aldol}}{CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CHO} \xrightarrow[-H_2O]{heat}$$

$$\underset{\text{crotonaldehyde}}{CH_3{\cdot}CH{=}CH{\cdot}CHO} \xrightarrow{H_2/Ni} CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH$$

(iii) From propylene by the Oxo process (p. 127).

n-Butanol is widely used as a solvent.

iso*Butyl alcohol, 2-methylpropan-1-ol,* iso*butanol,* $(CH_3)_2CH{\cdot}CH_2OH$, b.p. 108°, is obtained as a by-product in the preparation of methanol from synthesis gas (p. 133). It behaves as a primary alcohol, but it readily rearranges due to the presence of a branched chain near the COH group, *e.g.*, when it is treated with hydrochloric acid, *iso*butyl chloride and *tert.*-butyl chloride are obtained (*cf.* p. 101):

$$(CH_3)_2CH{\cdot}CH_2OH \xrightarrow{HCl} (CH_3)_2CH{\cdot}CH_2Cl + (CH_3)_3CCl$$

sec.-*Butyl alcohol, butan-2-ol,* sec.-*butanol,* $CH_3{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_3$, b.p. 100°, is prepared industrially by the hydration of 1- or 2-butene (from cracked petroleum) by means of concentrated sulphuric acid (*cf.* ethanol and *iso*propanol).

sec.-Butanol is used for the preparation of butanone, esters, and as a lacquer solvent.

tert.-*Butyl alcohol,* tert.-*butanol* (*trimethylmethanol*), $(CH_3)_3COH$, m.p. 25·5°, b.p. 83°, is prepared synthetically by the hydration of *iso*butene (from cracked petroleum). It is mainly used as an alkylating agent.

Amyl alcohols, $C_5H_{11}OH$. Eight isomers are possible, and all are known:

1. $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH$, *n*-amyl alcohol, pentan-1-ol, *n*-pentanol, b.p. 138°.
2. $(CH_3)_2CH{\cdot}CH_2{\cdot}CH_2OH$, *iso*amyl alcohol, *iso*pentanol, b.p. 130°.
3. $CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CH_2OH$, "active" amyl alcohol, 2-methylbutan-1-ol, b.p. 128°.
4. $(CH_3)_3C{\cdot}CH_2OH$, *neo*pentyl alcohol, *tert.*-butylcarbinol, b.p. 113°.
5. $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_3$, pentan-2-ol, methyl-*n*-propylcarbinol, b.p. 120°.
6. $CH_3{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_3$, pentan-3-ol, diethylcarbinol, b.p. 117°.
7. $(CH_3)_2CH{\cdot}CH(OH){\cdot}CH_3$, 3-methylbutan-2-ol, methyl*iso*propylcarbinol, b.p. 114°.
8. $(CH_3)_2C(OH){\cdot}CH_2{\cdot}CH_3$, 2-methylbutan-2-ol, *tert.*-amyl alcohol, *tert.*-pentanol, ethyldimethylcarbinol, b.p. 102°.

Three amyl alcohols, *viz.*, *n*-pentanol, *iso*pentanol and "active" amyl alcohol, have been isolated from fusel oil (*q.v.*). The last two are the chief constituents of fusel oil, and all three are produced by the fermentation of protein matter associated with the carbohydrates in starch. This mixture of amyl alcohols (from fusel oil) is used for the preparation of esters (for artificial essences), scents, and as a laboratory reducing agent with sodium it is better than ethanol owing to its higher boiling point (this mixture of amyl alcohols will be referred to in future as *iso*pentanol).

A mixture of amyl alcohols, known as *pentasol*, is prepared industrially by chlorinating at 200°, and in the dark, a mixture of *n*- and *iso*pentanes (from petroleum) to the amyl chlorides which are hydrolysed with dilute sodium hydroxide solution plus a little sodium oleate for emulsification, to the amyl alcohols. Seven isomeric amyl chlorides are theoretically possible by the chlorination of *n*- and *iso*pentanes, but in practice six are obtained—no 2-chloro-3-methylbutane is produced. Pentasol (the mixture of six amyl alcohols) finds great use as a solvent in the lacquer industry.

Commercial "*sec.*-amyl alcohol" (80 per cent. 2- and 20 per cent. 3-pentanol) is made by hydrating 1- and 2-pentenes (from cracked petroleum).

A number of higher alcohols occur as esters in waxes, *e.g.*, cetyl (palmityl) alcohol (hexadecan-1-ol), $C_{16}H_{33}OH$, m.p. 49°, occurs as the palmitate in spermaceti (obtained from the oil of the sperm whale); carnaubyl alcohol (tetracosan-1-ol), $C_{24}H_{49}OH$, m.p. 69°, as esters in wool-grease; ceryl alcohol (hexacosan-1-ol), $C_{26}H_{53}OH$, m.p. 79°, as the cerotate in chinese wax; myricyl (melissyl) alcohol (triacontan-1-ol), $C_{30}H_{61}OH$, m.p. 88°, as esters in bees-wax.

A number of higher alcohols are now prepared industrially by the catalytic reduction of the ethyl (or glyceryl) esters of the higher fatty acids, particularly the alcohols lauryl (dodecan-1-ol), $C_{12}H_{25}OH$, m.p. 24°; myristyl (tetradecan-1-ol), $C_{14}H_{29}OH$, m.p. 38°; palmityl (hexadecan-1-ol), $C_{16}H_{33}OH$, m.p. 49°; and stearyl (octadecan-1-ol), $C_{18}H_{37}OH$, m.p. 59°. These alcohols are used in the form of sodium alkyl sulphates, $RO{\cdot}SO_2{\cdot}ONa$, as detergents, emulsifying agents, wetting agents, insecticides, fungicides, etc. These sodium salts lather well, and are not affected by hard water, and hence can be used as a soap substitute.

QUESTIONS

1. Write out the structures and names (three methods) of the isomeric amyl alcohols. Indicate the class of each alcohol.

2. By means of equations show how you would convert: (*a*) *n*-butanol, (*b*) *n*-pentanol, (*c*) hexan-2-ol, into butan-2-ol.

3. Give as many methods as you can for distinguishing between the three classes of alcohols.

4. Define and give examples of:—(*a*) primary alcohol, (*b*) secondary alcohol, (*c*) tertiary alcohol, (*d*) the Bouveault-Blanc reduction, (*e*) association, (*f*) dehydrogenation, (*g*) fermentation, (*h*) the oxo process, (*i*) dehydration, (*j*) hydration, (*k*) Tschugaev reaction, (*l*) Wagner rearrangement.

5. Name the products and indicate the conditions under which they are formed when ethanol is treated with:—(*a*) AcOH, (*b*) HI, (*c*) PCl_3, (*d*) PBr_5, (*e*) PI_3, (*f*) Na, (*g*) AcCl, (*h*) H_2SO_4, (*i*) $C_6H_5{\cdot}NCO$, (*j*) Br_2.

6. Give an account of the evidence for the structure of (*a*) EtOH, (*b*) Pr^iOH.

7. Starting from acetylene, how would you prepare:—(*a*) EtOH, (*b*) C_2H_6, (*c*) CH_4, (*d*) $EtNO_2$, (*e*) Et_2O?

8. Starting with the following compounds, name the alcohol formed and indicate the necessary conditions:—(*a*) acetaldehyde, (*b*) butan-2-one, (*c*) ethyl propionate, (*d*) palmitic acid, (*e*) acetyl chloride, (*f*) propionic anhydride, (*g*) *n*-propylamine, (*h*) EtMgI and HCHO, (*i*) MeMgI and $CH_3{\cdot}CHO$, (*j*) MeMgI and Me_2CO.

9. Write brief notes on the industrial preparation of:—(*a*) MeOH, (*b*) EtOH, (*c*) PrOH, (*d*) the four butyl alcohols, (*e*) *iso*PrOH, (*f*) pentasol, (*g*) lauryl alcohol.

10. Suggest why the tertiary alcohols may be dehydrated or converted into alkyl chlorides by AcCl.

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CHAPTER VII

ETHERS

THE general formula of the ethers is $C_nH_{2n+2}O$ (which is the same as that for the monohydric alcohols), and since their general structure is R—O—R′, they may be regarded as alkyl oxides or the anhydrides of the alcohols (see below).

When the two alkyl groups in an ether are the same, the ether is said to be symmetrical or simple, *e.g.*, diethyl ether, $C_2H_5—O—C_2H_5$, is a simple ether. When the two alkyl groups are different, the ether is said to be unsymmetrical or mixed, *e.g.*, ethyl methyl ether, $CH_3—O—C_2H_5$, is a mixed ether.

Nomenclature. 1. In this system of nomenclature all the members are known as ethers, and the individuals are named according to the alkyl groups attached to the oxygen atom, *e.g.*, $CH_3—O—CH_3$, dimethyl ether; $C_2H_5—O—CH(CH_3)_2$, ethyl *iso*propyl ether.

2. According to the I.U.P.A.C. system of nomenclature, the ethers are regarded as hydrocarbons in which a hydrogen atom is replaced by an alkoxyl group, —OR, the larger radical being chosen as the alkane. For symmetrical ethers, method 1 is to be used, *e.g.*, $C_2H_5{\cdot}O{\cdot}C_2H_5$, diethyl ether; $CH_3{\cdot}O{\cdot}C_2H_5$, methoxyethane.

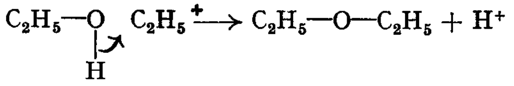
General methods of preparation. 1. By heating excess of alcohol with concentrated sulphuric acid or glacial phosphoric acid. One molecule of water is removed from two molecules of alcohol—hence the reason for regarding ethers as the anhydrides of alcohols:

$$2ROH \xrightarrow[-H_2O]{H_2SO_4} R_2O$$

According to Van Alphen (1930), ether is formed from ethanol as follows (*cf.* ethylene):

$$C_2H_5OH + H_2SO_4 \longrightarrow [C_2H_5\overset{\curvearrowright}{—}OH_2]^+HSO_4^- \longrightarrow C_2H_5^+ + H_2O + HSO_4^-$$

The ethyl carbonium ion may eliminate a proton to form ethylene (which is obtained as a by-product), or react with a molecule of ethanol (which is in excess) to form ether:



$$C_2H_5—\underset{\displaystyle H}{\underset{|}{O}}\ C_2H_5^+ \longrightarrow C_2H_5—O—C_2H_5 + H^+$$

On the other hand, Brooks (1935) believes that ethyl sulphate is formed first, and this then reacts with the excess of alcohol to form ether (*cf.* ethanol):

$$2C_2H_5OH + H_2SO_4 \longrightarrow (C_2H_5O)_2SO_2 + 2H_2O$$
$$(C_2H_5O)_2SO_2 + C_2H_5OH \longrightarrow (C_2H_5)_2O + C_2H_5O{\cdot}SO_2{\cdot}OH$$

The yields of ether are good from primary alcohols and fairly good from secondary. Mixed ethers may also be prepared by this method, *e.g.*, addition of *tert.*-butyl alcohol to a boiling mixture of ethanol and aqueous sulphuric acid gives *tert.*-butyl ethyl ether in excellent yield.

2. By **Williamson's synthesis,** in which the sodium of potassium alkoxide is heated with an alkyl halide:

$$RONa + R'X \longrightarrow R{\cdot}O{\cdot}R' + NaX \quad (g.)$$

The mechanism is probably:

$$RO^{-}\overset{\curvearrowright}{}R'{-}X \longrightarrow \overset{\delta-}{RO}{-}{-}R'{-}\overset{\delta-}{X} \longrightarrow R{\cdot}O{\cdot}R' + X^{-}$$

This method is particularly useful for preparing mixed ethers, and it is best to use the alkoxide of the secondary or tertiary alcohol, and primary alkyl halide because secondary and tertiary alkyl halides readily decompose into olefins.

Williamson's synthesis proves the structure of the ethers.

When R′ is a methyl or ethyl radical, methyl or ethyl sulphate, respectively, can be used instead of the corresponding alkyl halide, *e.g.*,

$$C_2H_5ONa + (CH_3)_2SO_4 \longrightarrow CH_3{\cdot}O{\cdot}C_2H_5 + CH_3NaSO_4$$

3. By heating alkyl halides with *dry* silver oxide:

$$2RX + Ag_2O \longrightarrow R_2O + 2AgX \quad (v.p.)$$

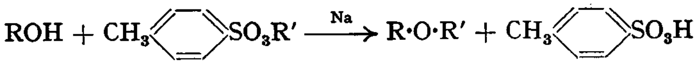
4. By passing the alcohol vapour over a catalyst such as alumina, thoria, etc., at 250° and under pressure:

$$2ROH \longrightarrow R_2O + H_2O$$

5. By passing an olefin into concentrated sulphuric acid, etc. (see ethanol and *iso*propanol).

6. From halogeno-ethers and Grignard reagents (p. 354).

7. Ethers may also be obtained by refluxing alcohols with esters of toluene-*p*-sulphonic acid in the presence of sodium (Drahowzal *et al.*, 1951).



General properties of the ethers. The lower members are gases or volatile liquids, and their vapours are highly inflammable. Their boiling points are much lower than those of the alcohols containing the same number of carbon atoms, and this is probably due to the fact that ethers cannot associate through hydrogen bonding. All the ethers are less dense than water in which they are not very soluble, but their solubility is very much increased in the presence of small amounts of alcohol.

The solubility of ethers is not as high as might have been expected in view of the fact that the oxygen in ethers can form hydrogen bonds with water. This low solubility may possibly be due to steric effects of the alkyl groups in the ether.

General reactions. 1. Ethers form stable salts (oxonium compounds) with strong inorganic acids, *e.g.*, $[(C_2H_5)_2OH]^{+}Cl^{-}$, $[(C_2H_5)_2OH]^{+}HSO_4^{-}$. Because of this, ethers can be separated from paraffins and alkyl halides, *e.g.*, by shaking with concentrated sulphuric acid, ether is removed from a mixture of ether and ethyl bromide.

2. When heated with dilute sulphuric acid under pressure, ethers form the corresponding alcohols:

$$R_2O + H_2O \xrightarrow{H_2SO_4} 2ROH$$

3. When warmed with concentrated sulphuric acid, ethers form alkyl hydrogen sulphates:

$$R_2O + H_2SO_4 \longrightarrow RHSO_4 + ROH$$
$$ROH + H_2SO_4 \longrightarrow RHSO_4 + H_2O$$

4. Ethers are readily attacked by concentrated hydriodic or hydrobromic acid, the final products depending on the temperature of the reaction.

(i) *in the cold*:

$$R_2O + HI \longrightarrow RI + ROH$$

In the case of a mixed ether the iodine atom attaches itself to the *smaller* alkyl radical:

$$CH_3{\cdot}O{\cdot}C_2H_5 + HI \longrightarrow CH_3I + C_2H_5OH$$

If both alkyl radicals contain the same number of carbon atoms, the iodine atom attaches itself to the *less complex* group. Propyl *iso*propyl ether, however, is an exception:

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH(CH_3)_2 + HI \longrightarrow (CH_3)_2CHI + CH_3{\cdot}CH_2{\cdot}CH_2OH$$

(ii) *When heated*:

$$R_2O + 2HI \longrightarrow 2RI + H_2O$$

Reactions (i) and (ii) are very useful for identifying the groups present in an ether. Furthermore, since (i) occurs very easily, it is possible to "protect" a hydroxyl group in a polyfunctional compound by converting the hydroxyl group into an ether, which is later treated with concentrated hydriodic acid to regenerate the hydroxyl group (see, *e.g.*, p. 236).

Decomposition of ethers by concentrated hydriodic acid is the basis of the *Zeisel* method for estimating methoxyl and ethoxyl groups (p. 314).

Although heating ethers with hydriodic acid results mainly in the formation of alkyl iodides, some reduction products are also formed (p. 49). This reduction may be avoided by heating the ether with potassium iodide and phosphoric acid (Stone *et al.*, 1950):

$$R{\cdot}O{\cdot}R + 2KI + 2H_3PO_4 \longrightarrow 2RI + 2KH_2PO_4 + H_2O$$

Birch (1951) has shown that ethers are converted into paraffin and alcohol when treated with sodium in liquid ammonia.

$$R{\cdot}O{\cdot}R' + 2[H] \longrightarrow \left[\begin{array}{l} \longrightarrow RH + R'OH \\ \longrightarrow R'H + ROH \end{array}\right.$$

Which of these two directions occurs is decided by which transition state has the lower energy.

5. When treated with chlorine or bromine, ethers undergo substitution, the extent of which depends on the conditions. Hydrogen joined to the carbon directly attached to the oxygen atom is most readily replaced, *e.g.*, diethyl ether reacts with chlorine in the dark to form 1 : 1′-dichlorodiethyl ether:

$$CH_3{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_3 \xrightarrow{Cl_2} CH_3{\cdot}CHCl{\cdot}O{\cdot}CH_2{\cdot}CH_3 \xrightarrow{Cl_2} CH_3{\cdot}CHCl{\cdot}O{\cdot}CHCl{\cdot}CH_3$$

In the presence of light, perchlorodiethyl ether is obtained:

$$(C_2H_5)_2O \xrightarrow{Cl_2} (C_2Cl_5)_2O$$

Halogeno-ethers may also be prepared in other ways (see, *e.g.*, p. 354).

6. Acid chlorides react with ethers when heated in the presence of anhydrous zinc chloride, aluminium chloride, etc.; *e.g.*,

$$R_2O + CH_3{\cdot}COCl \xrightarrow{ZnCl_2} RCl + CH_3{\cdot}CO_2R$$

Acid anhydrides also split ethers to form esters:

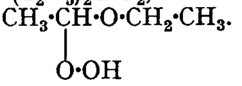
$$R_2O + (CH_3{\cdot}CO)_2O \xrightarrow{ZnCl_2} 2CH_3{\cdot}CO_2R$$

7. Ethers react with carbon monoxide at 125–180° and at a pressure of 500 atmospheres, in the presence of boron trifluoride plus a little water:

$$R_2O + CO \longrightarrow R{\cdot}CO_2R$$

Dimethyl ether (*methyl ether*) is prepared industrially by passing methanol vapour at 350–400°, and at a pressure of 15 atmospheres, over aluminium phosphate as catalyst (p. 141). It is a gas, b.p. $-23{\cdot}6°$, and is used as a refrigerating agent.

Diethyl ether (*ether,* "*sulphuric ether*") is prepared in the laboratory and industrially by the "*continuous etherification process*", *i.e.*, heating excess ethanol with concentrated sulphuric acid. It is also obtained industrially: (i) as a by-product in the preparation of ethanol from ethylene and sulphuric acid (p. 134); (ii) by passing ethanol vapour, under pressure, over heated alumina or aluminium phosphate (*cf.* dimethyl ether).

Diethyl ether is a colourless liquid, b.p. 34·5°. It is fairly soluble in water, and is miscible with ethanol in all proportions. It is highly inflammable and forms explosive mixtures with air; this is a great disadvantage in its use as an industrial solvent for oils, fats, gums, resins, etc., and as an extracting solvent. It is also used in surgery as an anæsthetic, and is the usual solvent for carrying out Grignard reactions. In the presence of air and light, ether forms ether peroxide $(C_2H_5)_2O{\cdot}O_2$, whose structure, according to Rieche and Meister (1936), is  $CH_3{\cdot}CH(O{\cdot}OH){\cdot}O{\cdot}CH_2{\cdot}CH_3$. Ether peroxide is a heavy, pungent, oily liquid, and is explosive. Since its boiling point is higher than that of ether, it is left in the residue after ether distillations, and may cause explosions. Addition of a small amount of a cuprous compound, *e.g.*, cuprous oxide, has been recommended for avoiding the formation of ether peroxide. The chief impurity in ether is ethanol, and this has the property of preventing the formation of ether peroxide.

An important derivative of ether is 2 : 2′-dichlorodiethyl ether, which is prepared by heating ethylene chlorohydrin with concentrated sulphuric acid at 100°:

$$2ClCH_2{\cdot}CH_2OH \xrightarrow[-H_2O]{H_2SO_4} ClCH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2Cl$$

It may also be prepared by passing a mixture of ethylene and chlorine into ethylene chlorohydrin at 80°:

$$CH_2OH{\cdot}CH_2Cl + C_2H_4 + Cl_2 \longrightarrow (CH_2Cl{\cdot}CH_2)_2O + HCl$$

2 : 2′-Dichlorodiethyl ether is used as a solvent, as a soil fumigant and also as the starting point of many chemicals.

2 : 2′-Dichlorodiethyl ether is also named as bis-(2-chloroethyl) ether. The prefix bis (Latin, twice) indicates that there are *two identical groups* attached to a given atom; it is generally used for complex groups.

Di-*iso*propyl ether is obtained industrially as a by-product in the preparation of *iso*propanol from propylene and sulphuric acid (p. 137). It is also prepared by passing propylene into 75 per cent. sulphuric acid at 75–125° under a pressure of 3–7 atmospheres; very little *iso*propanol is formed under these conditions.

Di-*iso*propyl ether is a colourless liquid, b.p. 69°. It is used as an industrial solvent for extraction operations, and for decreasing the knocking properties of petrol which, mixed with di-*iso*propyl ether, acquires a high octane number.

Di-*iso*amyl ether, $[(CH_3)_2CH{\cdot}CH_2{\cdot}CH_2{-}]_2O$, is prepared by the action of concentrated sulphuric acid on *iso*pentanol. It is a colourless liquid, b.p. 172°, and has a pear-like odour. It is used as an industrial solvent, and as a solvent in Grignard reactions in which higher temperatures are required than can be obtained by using ether.

Mixed ethers of the following types have been prepared: primary–primary; primary–secondary; primary–tertiary; secondary–secondary; secondary–tertiary; tertiary–tertiary.

Isomerism within the ether series, and any other series in which the isomers differ by the nature of the groups attached to a given atom, *e.g.*, the amines (*q.v.*), is sometimes known as *metamerism*: thus there are three *metamers* of formula $C_4H_{10}O$, *viz.*, diethyl ether, $C_2H_5{\cdot}O{\cdot}C_2H_5$; methyl propyl ether, $CH_3{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$; methyl *iso*propyl ether, $CH_3{\cdot}O{\cdot}CH(CH_3)_2$.

The term metamerism was introduced by Berzelius, but he gave it a wider meaning than that which is accepted today (see p. 399).

QUESTIONS

1. Write out the structures and names of the isomeric ethers having the molecular formula $C_5H_{12}O$.
2. Name the compounds and state under what conditions they are formed when ether is treated with:—(*a*) H_2SO_4, (*b*) HBr, (*c*) Br_2, (*d*) PCl_5, (*e*) Na, (*f*) AcCl, (*g*) CO, (*h*) NaOH, (*i*) O_2.
3. Define and give examples of:—(*a*) Williamson's synthesis, (*b*) the Zeisel determination, (*c*) metamerism.
4. A compound has the molecular formula $C_4H_{10}O$. How would you show whether it was an alcohol or an ether? If it is an ether, how would you determine its structure?

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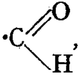
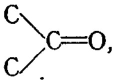
Norris and Rigby, Preparation and Properties of Mixed Aliphatic Ethers, *J. Amer. Chem. Soc.*, 1932, **54**, 2088.
Evans and Edlund, Tertiary Alkyl Ethers, *Ind. Eng. Chem.*, 1936, **28**, 1186.

CHAPTER VIII

ALDEHYDES AND KETONES

ALDEHYDES and ketones both have the general formula $C_nH_{2n}O$.

Aldehydes are the first oxidation products of *primary* alcohols, and their functional group is the *aldehyde* group •CHO or  $\cdot C\begin{smallmatrix}\nearrow O \\ \searrow H\end{smallmatrix}$, which can only occur at the *end* of a chain, since the carbon atom of the group has only one available valency. **Ketones** are the first oxidation products of *secondary* alcohols, and their functional group is the *ketonic* group  $\begin{smallmatrix}C \\ C\end{smallmatrix}\!\!>\!C{=}O$, which cannot occur at the end of a chain, since in ketones the CO group has two available valencies, each of which is joined to a carbon atom (*cf.*, however, ketens, p. 287).

The C=O group is known as the *carbonyl* group, but when it occurs in ketones, it is referred to as the ketonic group.

Nomenclature. *Aldehydes.* The lower members are commonly named after the acids that they form on oxidation. The suffix of the names of acids is *-ic* (the names of the trivial system are used, see p. 174); this suffix is deleted and replaced by *aldehyde*, *e.g.*,

$$\underset{\text{form}\textit{aldehyde}}{H\cdot CHO} \xrightarrow{[O]} \underset{\text{form}\textit{ic}\text{ acid}}{H\cdot CO_2H}$$

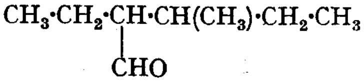
$$\underset{\textit{iso}\text{butyr}\textit{aldehyde}}{(CH_3)_2CH\cdot CHO} \xrightarrow{[O]} \underset{\textit{iso}\text{butyr}\textit{ic}\text{ acid}}{(CH_3)_2CH\cdot CO_2H}$$

The positions of side-chains or substituents are indicated by Greek letters, the α carbon atom being the one *adjacent* to the aldehyde group, *e.g.*,

$$\overset{\gamma}{C}H_3\cdot\overset{\beta}{C}H(OH)\cdot\overset{\alpha}{C}H_2\cdot CHO \quad \beta\text{-hydroxybutyraldehyde}$$

According to the I.U.P.A.C. system of nomenclature, aldehydes are designated by the suffix *-al*, which is added to the name of the hydrocarbon from which they are derived. The longest carbon chain containing the aldehyde group is chosen as the parent hydrocarbon; the positions of side-chains or substituents are indicated by numbers, and the aldehyde group is given the number 1, which may be omitted from the name if the aldehyde group is the only functional group present in the compound (see p. 63), *e.g.*,

$CH_3\cdot CHO$ ethanal



$CH_3\cdot CH_2\cdot\underset{\displaystyle CHO}{\underset{|}{C}H}\cdot CH(CH_3)\cdot CH_2\cdot CH_3$ 2-ethyl-3-methylpentanal

Ketones. The lower members are commonly named according to the alkyl groups attached to the ketonic group, *e.g.*,

$CH_3\cdot CO\cdot CH_3$ dimethyl ketone

$CH_3\cdot CH_2\cdot CO\cdot CH(CH_3)_2$ ethyl *iso*propyl ketone

The positions of side-chains or substituents are indicated by Greek letters, the α carbon atom being the one *adjacent* to the ketonic group, *e.g.*,

$$\overset{\beta}{CH_3}\cdot\overset{\alpha}{C}HCl\cdot CO\cdot\overset{\alpha'}{C}H_2\cdot\overset{\beta'}{C}H_2Cl \quad \alpha : \beta'\text{-dichlorodiethyl ketone}$$

If the two alkyl groups in a ketone are the same, the ketone is said to be simple or symmetrical; if unlike, mixed or unsymmetrical (*cf.* ethers).

According to the I.U.P.A.C. system of nomenclature, ketones are designated by the suffix *-one*, which is added to the name of the hydrocarbons from which they are derived. The longest carbon chain containing the ketonic group is chosen as the parent hydrocarbon; the positions of side-chains or substituents are indicated by numbers, and the ketonic group is given the lowest number possible, *e.g.*,

$CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot CH_3$ pentan-2-one

$(CH_3)_2CH\cdot CO\cdot CH(CH_3)\cdot CH_2\cdot CH_3$ 2 : 4-dimethylhexan-3-one

Since aldehydes and ketones both contain the carbonyl group, it might be expected that they would resemble one another. It is therefore instructive to compare their general methods of preparation and their general properties.

General methods of preparation of aldehydes and ketones

1. *Aldehydes.* By the oxidation of a *primary* alcohol:

$$R\cdot CH_2OH \xrightarrow{[O]} R\cdot CHO$$

Oxidation may be effected by acid dichromate (yield: *f.g.–g.*); or by passing the alcohol vapour mixed with air over heated silver (250°) as catalyst (yield: *g.*). Alternatively, the alcohol may be *dehydrogenated* by passing the alcohol vapour over heated copper (300°) as catalyst:

$$R\cdot CH_2OH \xrightarrow[300^\circ]{Cu} R\cdot CHO + H_2 \quad (ex.)$$

tert.-Butyl chromate (prepared by adding chromium trioxide to *tert.*-butanol) oxidises primary alcohols to aldehydes almost quantitatively (Oppenauer *et al.*, 1949).

Ketones. By the oxidation of a *secondary* alcohol (using the same oxidising agents as for aldehydes), or by dehydrogenation over heated copper:

$$R\cdot CH(OH)\cdot R' \xrightarrow{[O]} R\cdot CO\cdot R' \quad (g.\text{–}ex.)$$

$$R\cdot CH(OH)\cdot R' \xrightarrow[300^\circ]{Cu} R\cdot CO\cdot R' + H_2 \quad (ex.)$$

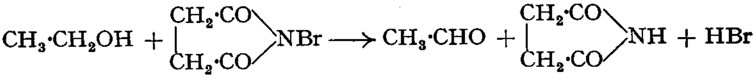
There is, however, a specific reagent for oxidising secondary alcohols to ketones, *viz.*, aluminium *tert.*-butoxide, $[(CH_3)_3CO]_3Al$ (the **Oppenauer oxidation.** 1937). The secondary alcohol is refluxed with the reagent in excess acetone solution; *it is the acetone which is reduced*:

$$R\cdot CH(OH)\cdot R' + CH_3\cdot CO\cdot CH_3 \longrightarrow R\cdot CO\cdot R' + CH_3\cdot CH(OH)\cdot CH_3 \quad (g.\text{–}v.g.)$$

This reagent is particularly useful for oxidising *unsaturated* secondary alcohols because it does not affect the double bond. On the other hand, *primary* alcohols (particularly unsaturated alcohols) may also be oxidised to aldehydes if acetone is replaced by *p*-benzoquinone. In general, quinones and aromatic ketones are better hydrogen acceptors than acetone.

The mechanism of the Oppenauer oxidation is probably the reverse of that of the Meerwein–Ponndorf–Verley reduction (p. 150).

N-Bromosuccinimide (p. 375) oxidises primary and secondary alcohols to aldehydes and ketones, respectively (Barakat *et al.*, 1952), *e.g.*,



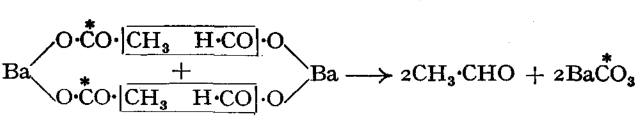
Primary and secondary alcohols, both saturated and unsaturated, may be oxidised to the corresponding carbonyl compound by means of manganese dioxide in acetone solution (*inter alia*, Bharucha, 1956). Ruthenium tetroxide also oxidises saturated primary and secondary alcohols to the corresponding carbonyl compound (Berkowitz *et al.*, 1958).

2. *Aldehydes.* By heating a mixture of the calcium salts of formic acid and any one of its homologues:

$$(R{\cdot}CO_2)_2Ca + (H{\cdot}CO_2)_2Ca \longrightarrow 2R{\cdot}CHO + 2CaCO_3$$

The yields are poor on account of many side reactions.

The mechanism of this decomposition has been studied by Bell *et al.* (1952), who prepared acetaldehyde by heating a mixture of barium acetate containing ^{13}C and barium formate, and obtained acetaldehyde containing no ^{13}C.



Ketones. By heating the calcium salt of any fatty acid other than formic acid (yield: variable due to many side reactions):

$$(R{\cdot}CO_2)_2Ca \longrightarrow R_2CO + CaCO_3$$

If a mixture of calcium salts is used, mixed ketones are obtained:

$$(R{\cdot}CO_2)_2Ca + (R'{\cdot}CO_2)_2Ca \longrightarrow 2R{\cdot}CO{\cdot}R' + 2CaCO_3$$

Apparently only methyl ketones have actually been prepared this way, *i.e.*, calcium acetate is one of the salts used. This method of pyrolysis of calcium salts as a *general* method seems to be of no value.

3. *Aldehydes.* By passing a mixture of the vapours of formic acid and any one of its homologues over manganous oxide as catalyst at 300°:

$$R{\cdot}CO_2H + H{\cdot}CO_2H \xrightarrow{MnO} R{\cdot}CHO + CO_2 + H_2O \quad (\textit{f.g.–g.})$$

R_2CO and R·CHO are obtained as by-products, and the reaction probably proceeds via the manganous salt, the manganous carbonate which is formed decomposing at 300°.

$$MnCO_3 \longrightarrow MnO + CO_2$$

This mechanism postulating the decomposition of the intermediate manganous salt is supported by experiments using isotopically enriched acid (Reed, 1955).

Ketones. By passing the vapour of any fatty acid other than formic acid over manganous oxide at 300°:

$$2R{\cdot}CO_2H \xrightarrow{MnO} R_2CO + CO_2 + H_2O \quad (\textit{g.})$$

A mixture of fatty acids gives mixed ketones:

$$R{\cdot}CO_2H + R'{\cdot}CO_2H \longrightarrow R{\cdot}CO{\cdot}R' + CO_2 + H_2O$$

R_2CO and R'_2CO are obtained as by-products.

4. *Aldehydes.* By the reduction of an acid chloride with hydrogen in boiling xylene using a palladium catalyst suspended on barium sulphate (**Rosenmund's reduction,** 1918):

$$\mathrm{R{\cdot}COCl + H_2 \longrightarrow R{\cdot}CHO + HCl} \quad (g.\text{–}v.g.)$$

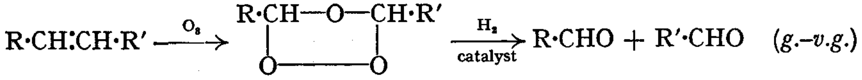
Aldehydes are more readily reduced than are acid chlorides, and therefore one would expect to obtain the alcohol as the final product. It is the barium sulphate that prevents the aldehyde from being reduced, acting as a poison (to the palladium catalyst) in this reaction. Generally, when the Rosenmund reduction is carried out, a small amount of quinoline and sulphur is added; these are very effective in poisoning the catalyst in the aldehyde reduction. Sakurai *et al.* (1944) have improved the Rosenmund reduction by using $BaSO_4$—$Pd(OH)_2$ as catalyst, and anhydrous acetone or ethyl acetate as solvent (yield: 80–90 per cent.). On the other hand, Davies *et al.* (1943) have shown that aliphatic acid chlorides may be reduced to aldehydes in reasonable yield by means of sodium amalgam.

Brandt (1949) has shown that lithium hydride reduces acid chlorides, anhydrides and thiolesters to the corresponding aldehyde, the yield being best with thiolesters (70 per cent.).

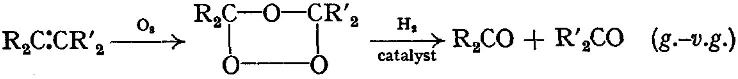
When *t*-butanol is added to lithium aluminium hydride in ether, lithium tri-*t*-butoxyaluminium hydride is precipitated. This, in diethylene glycol dimethyl ether solution at −78°, readily reduces acid chlorides to the corresponding aldehydes (Brown *et al.*, 1958). The yields are comparable with those obtained by the Rosenmund reduction. Kuivila (1960) has also shown that tri-*n*-butyltin reduces acid chlorides to aldehydes in good yield.

Ketones. There is no analogous method for the preparation of ketones.

5. *Aldehydes.* By the ozonolysis of olefins of the type $\mathrm{R{\cdot}CH{:}CH{\cdot}R'}$:



Ketones. By the ozonolysis of olefins of the type $\mathrm{R_2C{:}CR'_2}$:



6. *Aldehydes.* By the oxidation of 1 : 2-glycols of the type $\mathrm{R{\cdot}CH(OH){\cdot}CH(OH){\cdot}R'}$ with lead tetra-acetate or periodic acid (see p. 73):

$$\mathrm{R{\cdot}CH(OH){\cdot}CH(OH){\cdot}R' \xrightarrow{[O]} R{\cdot}CHO + R'{\cdot}CHO} \quad (g.\text{–}v.g.)$$

Ketones. By the oxidation of 1 : 2 glycols of the type $\mathrm{R_2C(OH){\cdot}C(OH)R'_2}$ with lead tetra-acetate or periodic acid:

$$\mathrm{R_2C(OH){\cdot}C(OH)R'_2 \xrightarrow{[O]} R_2CO + R'_2CO} \quad (g.\text{–}v.g.)$$

7. *Aldehydes.* Acetylene, when passed into hot dilute sulphuric acid in the presence of mercuric sulphate as catalyst, is converted into acetaldehyde:

$$\mathrm{CH{\vdots}CH + H_2O \longrightarrow [CH_2{:}CHOH] \longrightarrow CH_3{\cdot}CHO} \quad (v.g.)$$

Ketones. All homologues of acetylene, treated in the same way as acetylene, form ketones, *e.g.*,

$$\mathrm{RC{\vdots}CH + H_2O \longrightarrow [R{\cdot}C(OH){:}CH_2 \longrightarrow R{\cdot}CO{\cdot}CH_3} \quad (g.)$$

8. *Aldehydes.* By **Stephen's method** (1925). An alkyl cyanide is dissolved in ether, or better, in ethyl formate or ethyl acetate (Stephen *et al.*,

1956), and reduced with stannous chloride and hydrochloric acid, and then steam distilled. Turner (1956), who has modified Stephen's method, also showed that the yield of aldehyde from *normal*-cyanides increases with increase in chain-length, and that branching in the α-position lowers the yield.

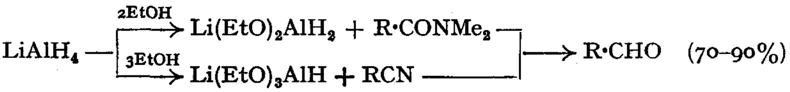
According to Hantzsch (1931), Stephen's reaction proceeds via the iminochloride or aldimine hydrochloride (which is present as the stannichloride):

$$\text{R·C}{\equiv}\text{N} \xrightarrow{\text{HCl}} [\text{R·C}{\equiv}\text{NH}]^{+}\text{Cl}^{-} \xrightarrow[\text{HCl}]{\text{SnCl}_4} [\text{R·CH}{=}\text{NH}_2]_2{}^{+}\text{SnCl}_6{}^{--} \xrightarrow{\text{H}_2\text{O}} \text{R·CHO}$$

Alkyl cyanides may also be reduced to aldehydes by means of the reverse addition of the calculated amount of lithium aluminium hydride at low temperature (see also p. 125).

$$4\text{R·CN} + \text{LiAlH}_4 \longrightarrow (\text{R·CH}{=}\text{N}{-})_4\text{LiAl} \xrightarrow{\text{H}_2\text{O}} 4\text{R·CHO}$$

Brown *et al.* (1959) have reduced amides and cyanides to aldehydes using ethoxyaluminium hydrides:



$$\text{LiAlH}_4 \begin{cases} \xrightarrow{2\text{EtOH}} \text{Li(EtO)}_2\text{AlH}_2 + \text{R·CONMe}_2 \\ \xrightarrow{3\text{EtOH}} \text{Li(EtO)}_3\text{AlH} + \text{RCN} \end{cases} \longrightarrow \text{R·CHO} \quad (70\text{–}90\%)$$

Khuri (1960) has used lithium trimethylborohydride to reduce cyanides to aldehydes.

Ketones. There is no analogous method for the preparation of ketones.

9. *Aldehydes.* By means of a Grignard reagent and formic ester (see p. 354).

Ketones. By means of a Grignard reagent and, for example, an alkyl cyanide (see p. 355). Ketones are also formed by reaction between an alkyl cyanide and lithium-alkyls (p. 361).

10. *Ketones.* By the ketonic hydrolysis of the alkyl derivatives of acetoacetic ester (see p. 228), and also from ethyl malonate derivatives (p. 234).

Aldehydes. There is no analogous method for the preparation of aldehydes.

11. *Aldehydes.* Many aldehydes may be prepared by the *oxo* process (p. 127), *e.g.*, propionaldehyde (*q.v.*).

Ketones. There is no analogous method for the preparation of ketones.

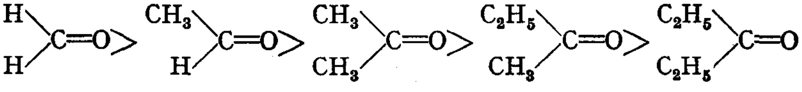
12. *Aldehydes.* Aldehydes may be prepared (in yields up to 50 per cent.) by means of the modified *Sommelet reaction* (Angyal *et al.*, 1953; see benzaldehyde, p. 647); *e.g.*, *n*-hexanal is produced by adding an aqueous solution of *n*-hexylamine hydrochloride to a solution of hexamine in acetic acid through which steam is passed.

$$\text{CH}_3\text{·(CH}_2)_5\text{·NH}_2\text{·HCl} + (\text{CH}_2)_6\text{N}_4 \longrightarrow \text{CH}_3\text{·(CH}_2)_4\text{·CHO} \quad (17\%)$$

Ketones. There is no analogous method for the preparation of ketones.

Reactions common to aldehydes and ketones

It has been found that the reactivity of the carbonyl group depends on the nature of the alkyl groups attached to it; the smaller the alkyl group, the more reactive is the carbonyl group. Thus the order of reactivity is:



If the alkyl groups are very large, *e.g.*, *tert.*-butyl, the carbonyl group shows very little reactivity. One contributing factor to this decreasing reactivity with increasing size of the attached groups is steric hindrance (p. 107).

The carbonyl compounds undergo many nucleophilic addition reactions. An important point in this connection is that the attack at a *carbon atom* is always considered to be the factor that decides whether the attack is electrophilic or nucleophilic; *i.e.*, a negatively charged carbon atom is attacked by an electrophilic reagent and a positively charged carbon atom by a nucleophilic reagent. It is not necessarily the *order* in which the fragments of the addendum add on that decides electrophilic or nucleophilic addition; it is whether the *first carbon atom* atom attacked is negative or positive, respectively (see below).

1. Aldehydes and ketones are reduced catalytically or by nascent hydrogen, aldehydes producing primary, and ketones secondary, alcohols, *e.g.*,

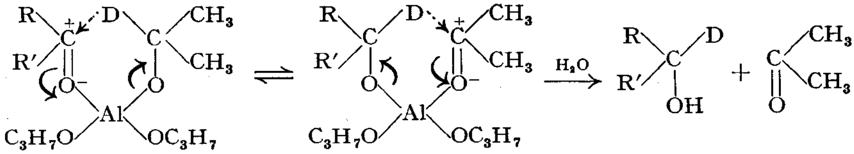
$$>C{=}O + 2[H] \xrightarrow{\text{metal/acid}} >CHOH \quad (g.\text{–}v.g.)$$

Aldehydes and ketones are conveniently reduced by Raney nickel in aqueous or ethanolic solution (yield: *g.–v.g.*). Reduction may also be effected by means of the **Meerwein–Ponndorf–Verley reduction** (1925, 1926). The carbonyl compound is heated with aluminium *iso*propoxide in *iso*propanol solution; the *iso*propoxide is oxidised to acetone, which is removed from the equilibrium mixture by slow distillation:

$$R_2CO + (CH_3)_2CHOAl/_3 \rightleftharpoons R_2CHOAl/_3 + CH_3{\cdot}CO{\cdot}CH_3 \xrightarrow[H_2SO_4]{\text{dilute}} R_2CHOH \ (g.)$$

This reducing agent is specific for the carbonyl group, and so may be used for reducing aldehydes and ketones containing some other functional group that is reducible, *e.g.*, a double bond or a nitro-group. The Meerwein–Ponndorf–Verley reduction has been improved by Truett *et al.* (1951). Aldehydes and ketones are also reduced to alcohols by lithium aluminium hydride, lithium borohydride and sodium borohydride (p. 126).

Williams *et al.* (1953) used aluminium *iso*propoxide containing deuterium to reduce *cyclo*hexanone, and concluded that the mechanism involves the formation of a cyclic complex:



When carbonyl compounds are heated with concentrated hydriodic acid and red phosphorus, the carbonyl group is reduced to a methylene group $—CH_2—$. This may also be effected by means of the **Clemmensen reduction** (1913): the carbonyl compound is reduced with *amalgamated zinc* and concentrated hydrochloric acid:

$$R{\cdot}CHO + 4[H] \xrightarrow[HCl]{Zn/Hg} R{\cdot}CH_3 + H_2O$$

$$R{\cdot}CO{\cdot}R' + 4[H] \xrightarrow[HCl]{Zn/Hg} R{\cdot}CH_2{\cdot}R' + H_2O$$

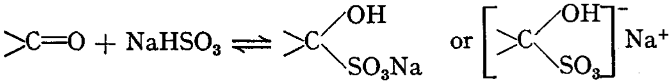
The Clemmensen reduction does not appear to work well for aldehydes, but is reasonably good for many ketones.

The mechanism of the Clemmensen reduction is uncertain. Poutsma *et al.* (1959) have shown, by gas chromatography, that the reduction of acetophenone proceeds as follows ($Ph = C_6H_5$):

$$\mathrm{PhCOMe} \longrightarrow \mathrm{PhCHOHMe} \longrightarrow \mathrm{PhCHClMe} \longrightarrow \mathrm{PhCH_2Me}$$

It was also shown that the alcohol, phenylmethylmethanol, was reduced to ethylbenzene under the same conditions.

2. Aldehydes and ketones add on sodium hydrogen sulphite to form *bisulphite* compounds:



$$>C{=}O + NaHSO_3 \rightleftharpoons >C\begin{matrix}OH\\SO_3Na\end{matrix} \quad \text{or} \quad \left[>C\begin{matrix}OH\\SO_3\end{matrix}\right]^- Na^+$$

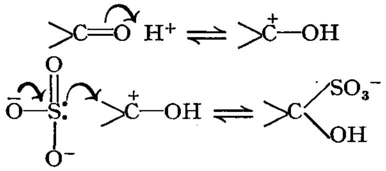
These bisulphite compounds are *hydroxysulphonic acid salts*, since the sulphur atom is *directly* attached to the carbon atom. This structure is supported by work with isotope ^{34}S (Sheppard *et al.*, 1954).

Most aldehydes form bisulphite compounds. Ketones of the type $CH_3{\cdot}CO{\cdot}R$, where R is a *primary* alkyl group, form bisulphite compounds fairly readily; but where R is a secondary or tertiary alkyl group, the bisulphite compound is formed very slowly. If the ketone is of the type $R{\cdot}CO{\cdot}R'$ where R and R′ are ethyl or higher alkyl groups, the bisulphite compound is not formed at all (*cf.* reactivity of carbonyl compounds, above).

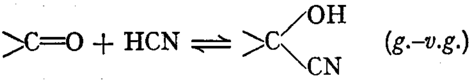
Bisulphite compounds are usually crystalline solids, insoluble in sodium hydrogen sulphite solution. Since they regenerate the carbonyl compound when heated with dilute acid or sodium carbonate solution, their formation affords a convenient means of separating carbonyl compounds from non-carbonyl compounds.

The mechanism of bisulphite formation is uncertain. Kinetic studies have shown that it is probably sulphite ions which are the active species; thus a possibility is:

$$NaHSO_3 \rightleftharpoons Na^+ + H^+ + SO_3^{2-}$$



3. Aldehydes and ketones add on hydrogen cyanide to form *cyanohydrins*. The carbonyl compound is treated with sodium cyanide and dilute sulphuric acid:



$$>C{=}O + HCN \rightleftharpoons >C\begin{matrix}OH\\CN\end{matrix} \qquad (g.\text{–}v.g.)$$

Cyanohydrins are important compounds in organic synthesis since they are readily hydrolysed to α-hydroxy-acids:

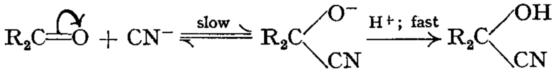
$$R{\cdot}CH(OH){\cdot}CN \xrightarrow{H_2O} R{\cdot}CH(OH){\cdot}CO_2H$$

All aldehydes form cyanohydrins; only the ketones acetone, butanone, pentan-3-one, and pinacolone form cyanohydrins.

Cyanohydrins are also prepared, if possible, indirectly from the bisulphite compound, which is treated with sodium (or potassium) cyanide solution:

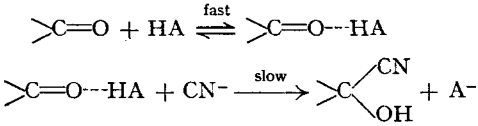
$$>\!C(OH){\cdot}SO_3Na + NaCN \longrightarrow\, >\!C(OH){\cdot}CN + Na_2SO_2 \quad (v.g.)$$

Lapworth (1903, 1904) showed that the addition of hydrogen cyanide to carbonyl compounds is accelerated by bases and retarded by acids, and he concluded that the addendum was the cyanide ion, and proposed the following mechanism:



$$R_2C{=}O + CN^- \underset{}{\overset{\text{slow}}{\rightleftharpoons}} R_2C(O^-)(CN) \xrightarrow{H^+;\ \text{fast}} R_2C(OH)(CN)$$

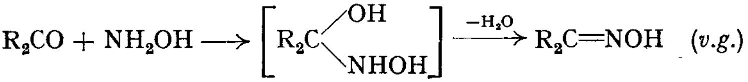
Svirbeley *et al.* (1955), however, have found that the addition of cyanide ion to, *e.g.*, propionaldehyde, is slightly subject to general acid catalysis (*cf.* p. 168). In this respect, the reaction is similar to semicarbazone formation (p. 153), and so the following mechanism has been proposed:



$$>\!C{=}O + HA \overset{\text{fast}}{\rightleftharpoons}\, >\!C{=}O\text{---}HA$$

$$>\!C{=}O\text{---}HA + CN^- \xrightarrow{\text{slow}}\, >\!C(CN)(OH) + A^-$$

4. Aldehydes and ketones form *oximes* when treated with hydroxylamine:



$$R_2CO + NH_2OH \longrightarrow \left[R_2C(OH)(NHOH)\right] \xrightarrow{-H_2O} R_2C{=}NOH \quad (v.g.)$$

The mechanism of this reaction is discussed in connection with semicarbazones (see below).

Oximes are usually well-defined crystalline solids, and may be used to identify carbonyl compounds.

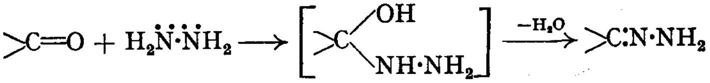
Aldoximes form cyanides when boiled with acetic anhydride, whereas ketoximes form the acetyl derivative of the oxime:

$$R{\cdot}CH{:}N{\cdot}OH \xrightarrow[-H_2O]{(CH_3{\cdot}CO)_2O} R{\cdot}CN$$

$$R_2C{:}N{\cdot}OH \xrightarrow{(CH_3{\cdot}CO)_2O} R_3C{:}N{\cdot}O{\cdot}CO{\cdot}CH_3$$

5. Aldehydes and ketones react with hydrazine to form *hydrazones* and *azines*. The mechanism of their formation is probably similar to that of oxime formation (see above):

Hydrazone:



$$>\!C{=}O + H_2\ddot{N}{\cdot}\ddot{N}H_2 \longrightarrow \left[>\!C(OH)(NH{\cdot}NH_2)\right] \xrightarrow{-H_2O}\, >\!C{:}N{\cdot}NH_2$$

Azine:

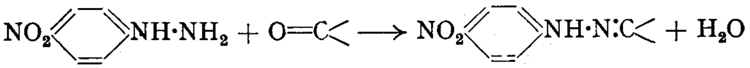
$$>\!C{:}N{\cdot}NH_2 + O{=}C\!< \longrightarrow H_2O\, +\, >\!C{:}N{-}N{:}C\!<$$

By using suitable derivatives of hydrazine, more well-defined crystalline products are obtained (and azine formation is avoided), *e.g.*,

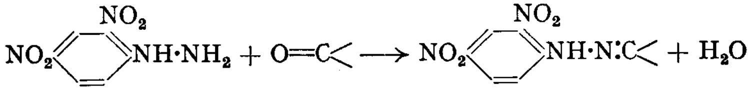
(i) Phenylhydrazine forms *phenylhydrazones*:

$$C_6H_5{\cdot}NH{\cdot}NH_2 + O{=}C\!< \longrightarrow H_2O + C_6H_5{\cdot}NH{\cdot}N{:}C\!<$$

(ii) *p*-Nitrophenylhydrazine forms *p*-nitrophenylhydrazones:



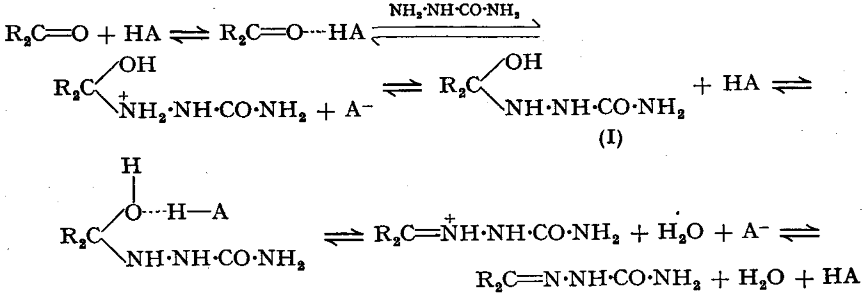
(iii) 2 : 4-Dinitrophenylhydrazine forms 2 : 4-dinitrophenylhydrazones:



(iv) Semicarbazide forms *semicarbazones*:

$$NH_2\cdot CO\cdot NH\cdot NH_2 + O{=}C\!< \longrightarrow NH_2\cdot CO\cdot NH\cdot N{:}C\!< + H_2O$$

The semicarbazone reaction has been studied in some detail by Conant *et al.* (1932) and Westheimer (1934), and has been shown to be a general acid-catalysed reaction. The following mechanism has been proposed by Bartlett (1953):


(I)

Since the first step is formation of the acid complex, the rate of its formation would be expected to increase with increasing pH. On the other hand, the greater the pH, the greater will be the concentration of the semicarbazide salt:

$$NH_2\cdot NH\cdot CO\cdot NH_2 + H_3O^+ \rightleftharpoons \overset{+}{N}H_3\cdot NH\cdot CO\cdot NH_2 + H_2O$$

This salt, however, no longer has a lone pair of electrons on the N atom, and so is no longer a nucleophilic reagent. Thus the second step will be retarded or may even be inhibited. It can therefore be expected that there will be an optimum pH for the reaction. Both Conant and Westheimer found this to be the case.

This mechanism is also believed to operate in the formation of oximes and phenylhydrazones. The addition compound (of type I) has been isolated in certain cases, *e.g.*, with chloral.

The carbonyl compound may be regenerated from the oxime, phenylhydrazone or semicarbazone by boiling with dilute acid (hydrochloric or sulphuric acid).

Wolff–Kishner reduction (1912). When hydrazones (or semicarbazones) are heated with sodium ethoxide at 180°, nitrogen is eliminated, and a hydrocarbon is obtained, *i.e.*, by this means the carbonyl group is converted into the methylene group:

$$>C{:}N\cdot NH_2 \longrightarrow\ >CH_2 + N_2 \quad (g.\text{–}v.g.)$$

An improved technique is to heat the carbonyl compound in ethylene or trimethylene glycol with 85 per cent. hydrazine hydrate in the presence of three equivalents of sodium, sodium hydroxide or potassium hydroxide, at 180–200°; the yield is usually above 65 per cent. (Huang–Minlon, 1946). The yield of hydrocarbon is better than that obtained by the Clemmensen reduction. Reduction of sterically hindered carbonyl groups by either the Clemmensen reduction or the Wolff–Kishner procedure is not easily effected. Barton *et al.*

(1954, 1955) have modified Huang–Minlon's method (by excluding water), and have thereby reduced sterically hindered carbonyl groups.

According to Szmant *et al.* (1952), the mechanism of the Wolff–Kishner reaction is (B is the base):

$$R_2C{=}N{\cdot}NH_2 + B \rightleftharpoons R_2C{=}N{\cdot}\bar{N}H + BH^+ \longrightarrow R_2\bar{C}H + N_2 \xrightarrow{BH^+} R_2CH_2$$

Weisberger *et al.* (1956) have suggested a free-radical mechanism.

Girard's reagents for carbonyl compounds (1934, 1936). Girard introduced two reagents for carbonyl compounds: Girard's reagents " T " and " P ", which are respectively trimethylaminoacetohydrazide chloride: $[(CH_3)_3N{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2]^+Cl^-$, and pyridinium-acetohydrazide chloride, $[C_5H_5N{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2]^+Cl^-$ (see p. 209). These reagents react with carbonyl compounds to form derivatives of the type $[(CH_3)_3N{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}N{:}C{<}]^+Cl^-$. These compounds are *soluble* in water, and have been found particularly useful for isolating certain ketonic hormones.

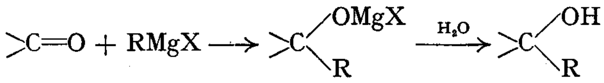
6. Aldehydes and ketones condense with thio-alcohols (mercaptans) to form *mercaptals* and *mercaptols*, respectively:

$$>C{=}O + 2RSH \longrightarrow >C(SR)_2 + H_2O$$

When mercaptols (dithioketals) are heated with hydrazine hydrate and Raney nickel at 90–135°, the compound undergoes desulphuration (Georgian *et al.*, 1959).

$$R_2C(SR')_2 \longrightarrow R_2CH_2$$

7. Aldehydes and ketones add on a molecule of a Grignard reagent, and the complex formed, when decomposed with water, gives a secondary alcohol from an aldehyde (except formaldehyde, which gives a primary alcohol), and a tertiary alcohol from a ketone (see p. 352):



$$>C{=}O + RMgX \longrightarrow >C\begin{matrix}OMgX\\ R\end{matrix} \xrightarrow{H_2O} >C\begin{matrix}OH\\ R\end{matrix}$$

8. Both aldehydes and ketones undergo the Wittig reaction to form olefins (p. 64).

9. Phosphorus pentachloride reacts with *simple* carbonyl compounds to form *gem*-dichlorides:

$$>C{=}O + PCl_5 \longrightarrow >CCl_2 + POCl_3$$

The yield of *gem*-dichloride is usually good with aldehydes, but with ketones it is poor. With more complicated carbonyl compounds chlorination also takes place, substitution occurring on the α-carbon atom only; *e.g.*, di-*iso*propyl ketone gives α-chlorodi*iso*propyl ketone when treated with one molecule of phosphorus pentachloride:

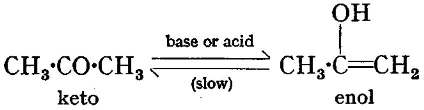
$$(CH_3)_2CH{\cdot}CO{\cdot}CH(CH_3)_2 + PCl_5 \longrightarrow (CH_3)_2CCl{\cdot}CO{\cdot}CH(CH_3)_2 + PCl_3 + HCl$$

Very little *gem*-dibromides are obtained with phosphorus pentabromide; the main product from any carbonyl compound is the α-bromo-derivative. Phosphorus pentabromide dissociates more readily than phosphorus pentachloride, and it is probable that the halogenation in the α-position is brought about by the free halogen (see below).

10. Chlorine or bromine replaces one or more α-hydrogen atoms in aldehydes and ketones, *e.g.*, acetone may be brominated in glacial acetic acid to give monobromoacetone:

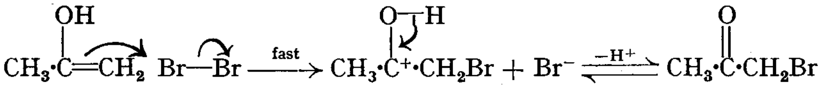
$$CH_3{\cdot}CO{\cdot}CH_3 + Br_2 \longrightarrow CH_3{\cdot}CO{\cdot}CH_2Br + HBr \quad (43\text{–}44\%)$$

The halogenation of carbonyl compounds is catalysed by bases and by acids, but the details of the mechanisms are not certain. Let us consider the case of acetone. Now it is known that both bases and acids catalyse enolisation of a ketone (see p. 221 for further details).



$$\underset{\text{keto}}{CH_3\cdot CO\cdot CH_3} \xrightleftharpoons[\text{(slow)}]{\text{base or acid}} \underset{\text{enol}}{CH_3\cdot\overset{OH}{\overset{|}{C}}=CH_2}$$

If the enol form is the one which is brominated, the bromination can be considered to occur as follows:

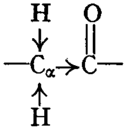


$$CH_3\cdot\overset{OH}{\overset{|}{C}}=CH_2\quad Br—Br \xrightarrow{\text{fast}} CH_3\cdot\overset{O—H}{\overset{|}{C^+}}\cdot CH_2Br + Br^- \xrightleftharpoons{-H^+} CH_3\cdot\overset{O}{\overset{\|}{C}}\cdot CH_2Br$$

In both base and acid catalysed reactions it has been shown that the rate of bromination (and of any other halogen) is independent of the concentration of the bromine but is proportional to the concentration of ketone and base or acid present. This is in agreement with at least a two-stage reaction, the first and slow stage being enolisation, and the second and fast stage being bromination.

A very interesting point about this mechanism is that if the change from keto to enol could be speeded up to such an extent that it is now faster than the halogenation, then the concentration of the halogen would enter into the rate equation. This has actually been observed in, *e.g.*, the iodination of acetophenone in the presence of sulphuric acid (Hammett *et al.*, 1939).

Another point that we shall discuss here is: How is it possible for a C—H bond to be broken so readily? This must occur whatever the mechanism of enolisation, and has been explained as follows. Owing to the inductive effect of the carbonyl group (caused by the high electron-affinity of the oxygen atom), the electrons of the C—H bonds on the α-carbon atom are displaced towards the carbon atom, thus giving rise to a condition for an *incipient* proton leaving C_α.



$$—\overset{\overset{H}{\downarrow}}{\underset{\underset{H}{\uparrow}}{C_\alpha}}\rightarrow\overset{\overset{O}{\|}}{C}—$$

Since the inductive effect falls off extremely rapidly from the source, only α-hydrogen atoms will be affected by the inductive effect of the carbonyl group. This offers an explanation for the unusual reactivity of hydrogen in a methyne group (=CH—) or in a methylene group (—CH_2—) when adjacent to a carbonyl group or any other strongly electron-attracting group. In such structures the incipient proton is readily removed, and the compound is said to possess an " active " methyne or methylene group.

Aldehydes and ketones with α-hydrogen atoms readily react with sulphuryl chloride at room temperature in the absence of a catalyst, to replace α-hydrogen atoms only, *e.g.*,

$$CH_3\cdot CO\cdot CH_3 \xrightarrow{SO_2Cl_2} CH_3\cdot CO\cdot CH_2Cl$$

The halogen atom in the group CX·CO is very reactive, far more so than the halogen atom in alkyl halides. It appears that the adjacent carbonyl group plays a part, but its mode of operation is still not clear.

11. Aldehydes and ketones with a methyl or methylene group adjacent to the carbonyl group are oxidised by selenium dioxide at room temperature to dicarbonyl compounds; *e.g.*, acetaldehyde forms glyoxal, and acetone forms methylglyoxal:

$$CH_3\cdot CHO + SeO_2 \longrightarrow CHO\cdot CHO + Se + H_2O$$
$$CH_3\cdot CO\cdot CH_3 + SeO_2 \longrightarrow CH_3\cdot CO\cdot CHO + Se + H_2O$$

12. Aldehydes and ketones are converted into the formyl derivative of the corresponding primary amine by excess ammonium formate or formamide (**Leuckart reaction.** 1885):

$$>C{=}O + 2H{\cdot}CO_2NH_4 \longrightarrow >CH{\cdot}NH{\cdot}CHO + 2H_2O + CO_2 + NH_3$$

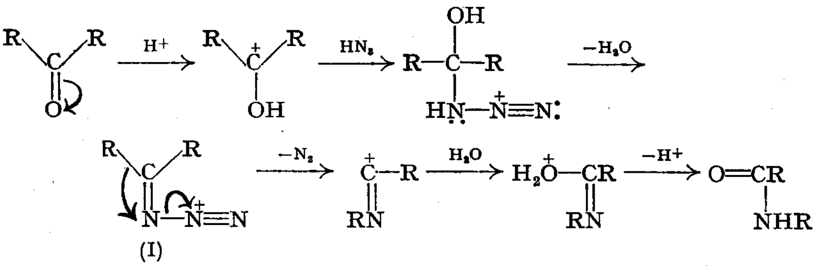
$$>C{=}O + 2H{\cdot}CO{\cdot}NH_2 \longrightarrow >CH{\cdot}NH{\cdot}CHO + CO_2 + NH_3$$

13. Aldehydes and ketones undergo the **Schmidt reaction** (1924). This is the reaction between a carbonyl compound and hydrazoic acid in the presence of, *e.g.*, concentrated sulphuric acid. Aldehydes give a mixture of cyanide and formyl derivatives of primary amines, whereas ketones give amides:

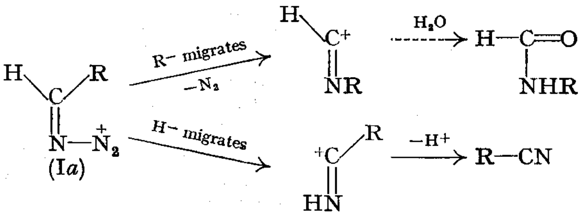
$$R{\cdot}CHO + HN_3 \xrightarrow{H_2SO_4} R{\cdot}CN + R{\cdot}NH{\cdot}CHO$$

$$R{\cdot}CO{\cdot}R + HN_3 \xrightarrow{H_2SO_4} R{\cdot}CO{\cdot}NH{\cdot}R + N_2$$

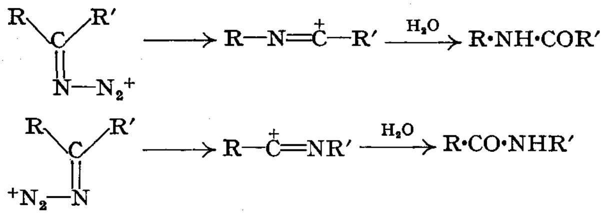
The mechanism of the reaction is uncertain. It has been shown to be intramolecular, and Smith (1948) has proposed the following mechanism, which is an example of the 1,2-shift (from carbon to nitrogen); for ketones:



For aldehydes the mechanism is the same, except that ion (I) is now (I*a*), and hence R *or* H can migrate:



In ketones, if the two radicals are not identical, then two geometrical isomers of (I) are possible. It is also reasonable to suppose that the *anti* group (to the diazonium nitrogen) is the group that migrates (*cf.* the Beckmann rearrangement, p. 667). In this way it is possible to explain how steric factors may influence the isomer ratio of amides formed:



14. Aldehydes and ketones undergo condensation reactions, *i.e.*, two or more (identical or different) molecules unite with, or without, the elimination

of water (or any other simple molecule). There is very little difference between the terms condensation and condensation polymerisation or polycondensation (p. 79); generally, condensation is used for those reactions in which the resulting compound is made up of a small number of the reacting molecules.

Aldol Condensation. Acetaldehyde, in the presence of dilute sodium hydroxide, potassium carbonate or hydrochloric acid, undergoes condensation to form a syrupy liquid known as *aldol*:

$$2CH_3\cdot CHO \xrightarrow{NaOH} CH_3\cdot CH(OH)\cdot CH_2\cdot CHO \quad (50\%)$$

On heating, aldols eliminate water to form unsaturated compounds, *e.g.*, aldol forms crotonaldehyde:

$$CH_3\cdot CH(OH)\cdot CH_2\cdot CHO \longrightarrow CH_3\cdot CH{:}CH\cdot CHO + H_2O$$

In many cases it is the unsaturated compound that is isolated, and not the aldol, *e.g.*, mesityl oxide and phorone (*q.v.*).

The aldol condensation can occur: (i) between two aldehydes (identical or different); (ii) between two ketones (identical or different); and (iii) between an aldehyde and a ketone. Whatever the nature of the carbonyl compound, *it is only the α-hydrogen atoms which are involved in the aldol condensation.*

(i) Generally, with two different aldehydes all four possible condensation products are obtained; but by using different catalysts one product may be made to predominate in the mixture, *e.g.*,

$$CH_3\cdot CHO + CH_3\cdot CH_2\cdot CHO \overset{NaOH}{\rightleftharpoons} CH_3\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CHO$$

$$CH_3\cdot CHO + CH_3\cdot CH_2\cdot CHO \overset{HCl}{\rightleftharpoons} CH_3\cdot CH(OH)\cdot CH(CH_3)\cdot CHO$$

(ii) Acetone, in the presence of barium hydroxide, gives diacetone alcohol:

$$2CH_3\cdot CO\cdot CH_3 \overset{Ba(OH)_2}{\rightleftharpoons} (CH_3)_2C(OH)\cdot CH_2\cdot COCH_3$$

This equilibrium lies almost completely on the left, but the yield of diacetone alcohol may be increased (71 per cent.) by boiling acetone in a Soxhlet with solid barium hydroxide in the thimble. The acetone in the flask gets richer and richer in diacetone alcohol, since the boiling point of the latter is 164°, and that of the former is 56°.

When acetone is treated with hydrochloric acid, mesityl oxide and phorone are formed:

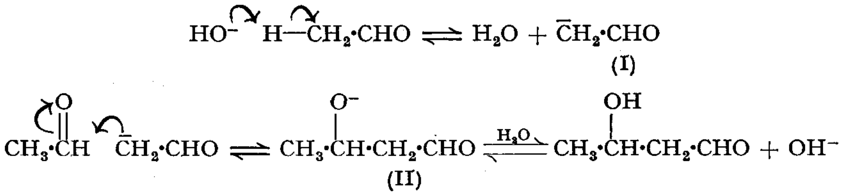
$$2CH_3\cdot CO\cdot CH_3 \overset{HCl}{\rightleftharpoons} (CH_3)_2C{:}CH\cdot CO\cdot CH_3 \overset{CH_3\cdot CO\cdot CH_3}{\rightleftharpoons} (CH_3)_2C{:}CH\cdot CO\cdot CH{:}C(CH_3)_2$$

(iii) When aldehydes condense with ketones, it is the α-hydrogen atom of the *ketone* which is involved in the condensation, *e.g.*,

$$CH_3\cdot CHO + CH_3\cdot CO\cdot CH_3 \overset{NaOH}{\rightleftharpoons} CH_3\cdot CH(OH)\cdot CH_2\cdot CO\cdot CH_3 \quad (25\%)$$

The yield of 4-hydroxypentan-2-one is low because aldol and diacetone alcohol are also formed.

It is generally accepted that the base-catalysed aldol condensation of acetaldehyde takes place in two steps, the first being the formation of the carbanion (I), and the second the combination of this anion with a second molecule of acetaldehyde to form the anion (II) of the aldol. The simplest mechanism that embraces these facts is:

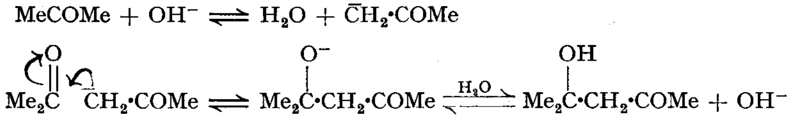


$$HO^- \; H{-}CH_2{\cdot}CHO \rightleftharpoons H_2O + \bar{C}H_2{\cdot}CHO \quad \text{(I)}$$

$$CH_3{\cdot}\overset{O}{\overset{\|}{C}}H \;\; \bar{C}H_2{\cdot}CHO \rightleftharpoons CH_3{\cdot}\overset{O^-}{\overset{|}{C}}H{\cdot}CH_2{\cdot}CHO \; \text{(II)} \xrightleftharpoons{H_2O} CH_3{\cdot}\overset{OH}{\overset{|}{C}}H{\cdot}CH_2{\cdot}CHO + OH^-$$

Bell's work (1937) suggested that the reaction in dilute sodium hydroxide solution was first-order with respect to the aldehyde, thereby indicating that the first step is the rate-determining one. Bell also found that the reaction was *not* exactly first-order in hydroxide ion. This is not in keeping with the mechanism given above. More recent kinetic work led to a reaction order between first and second, varying with the aldehyde concentration (Broche *et al.*, 1955). This suggests that the first and second steps of the reaction are of comparable rates, and this conclusion was supported by the work of Bell *et al.* (1958). Bell *et al.* (1960), however, have investigated the acidic properties of acetaldehyde in alkaline solutions, where it is converted into the ion (III), $CH_3{\cdot}CHOH{\cdot}O^-$. This produces considerable reduction of the hydroxide ion concentration and affects the apparent order of the reaction. Ion (III) is present in concentrations comparable to the hydroxide ion concentration and may well contribute to the formation of carbanion (I) in the first step given above. When the formation of (III) was taken into account, Bell found that the corrected results showed the aldol condensation is almost of the second-order in acetaldehyde. These results have been interpreted by assuming the ionisation and condensation steps have comparable rates (as already suggested above).

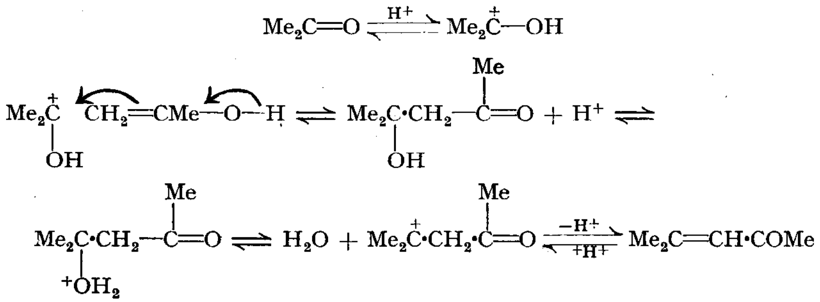
On the basis of analogy with acetaldehyde, the mechanism of the base-catalysed condensation of acetone will be:



$$MeCOMe + OH^- \rightleftharpoons H_2O + \bar{C}H_2{\cdot}COMe$$

$$Me_2\overset{O}{\overset{\|}{C}} \;\; \bar{C}H_2{\cdot}COMe \rightleftharpoons Me_2\overset{O^-}{\overset{|}{C}}{\cdot}CH_2{\cdot}COMe \xrightleftharpoons{H_2O} Me_2\overset{OH}{\overset{|}{C}}{\cdot}CH_2{\cdot}COMe + OH^-$$

There appear to be no detailed kinetic investigations on acid-catalysed aldol condensations, but it is generally assumed that the condensation proceeds by reaction between conjugate acid and the *enol form* of the carbonyl compound; *e.g.*, the formation of mesityl oxide:



$$Me_2C{=}O \xrightleftharpoons{H^+} Me_2\overset{+}{C}{-}OH$$

$$Me_2\underset{OH}{\underset{|}{\overset{+}{C}}} \;\; CH_2{=}CMe{-}O{-}H \rightleftharpoons Me_2\underset{OH}{\underset{|}{C}}{\cdot}CH_2{-}\overset{Me}{\overset{|}{C}}{=}O + H^+ \rightleftharpoons$$

$$Me_2\underset{^+OH_2}{\underset{|}{C}}{\cdot}CH_2{-}\overset{Me}{\overset{|}{C}}{=}O \rightleftharpoons H_2O + Me_2\overset{+}{C}{\cdot}CH_2{\cdot}\overset{Me}{\overset{|}{C}}{=}O \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} Me_2C{=}CH{\cdot}COMe$$

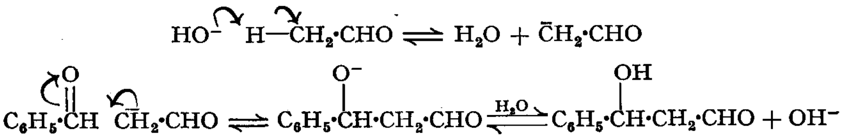
Claisen condensation (1881). This is the condensation between an ester and another molecule of an ester or ketone (see p. 224).

Claisen–Schmidt reaction (also known as the **Claisen reaction**) is the condensation between an *aromatic* aldehyde (or ketone) and an aldehyde or ketone, *in the presence of dilute alkali* to form an αβ-unsaturated compound.

This reaction is similar to the aldol condensation, and is illustrated by the formation of cinnamaldehyde from benzaldehyde and acetaldehyde:

$$C_6H_5{\cdot}CHO + CH_3{\cdot}CHO \xrightarrow{NaOH} C_6H_5{\cdot}CH{:}CH{\cdot}CHO + H_2O$$

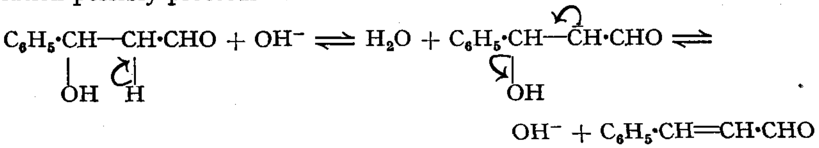
The mechanism of the Claisen–Schmidt reaction is probably that of the base-catalysed aldol condensation:



$$HO^- \; H{-}CH_2{\cdot}CHO \rightleftharpoons H_2O + \bar{C}H_2{\cdot}CHO$$

$$C_6H_5{\cdot}\overset{\overset{O}{\|}}{C}H \;\; \bar{C}H_2{\cdot}CHO \rightleftharpoons C_6H_5{\cdot}\overset{\overset{O^-}{|}}{C}H{\cdot}CH_2{\cdot}CHO \underset{}{\overset{H_2O}{\rightleftharpoons}} C_6H_5{\cdot}\overset{\overset{OH}{|}}{C}H{\cdot}CH_2{\cdot}CHO + OH^-$$

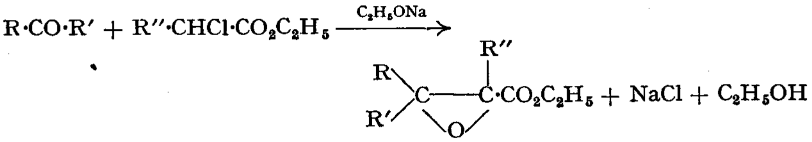
The elimination of a molecule of water from the condensation product in alkaline solution possibly proceeds as follows:



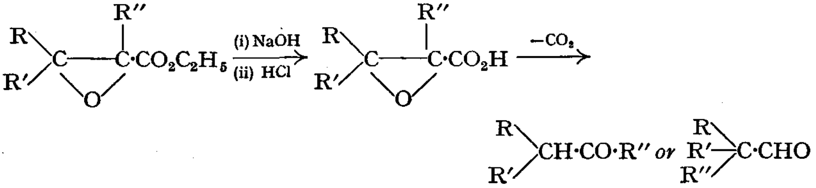
$$\underset{\underset{OH}{|}}{C_6H_5{\cdot}CH}{-}\underset{\underset{H}{|}}{CH}{\cdot}CHO + OH^- \rightleftharpoons H_2O + C_6H_5{\cdot}\underset{\underset{OH}{|}}{CH}{-}\bar{C}H{\cdot}CHO \rightleftharpoons OH^- + C_6H_5{\cdot}CH{=}CH{\cdot}CHO$$

Other condensations involving aldehydes or ketones are the *Knoevenagel* (p. 280) and *Perkin* (p. 651) reactions.

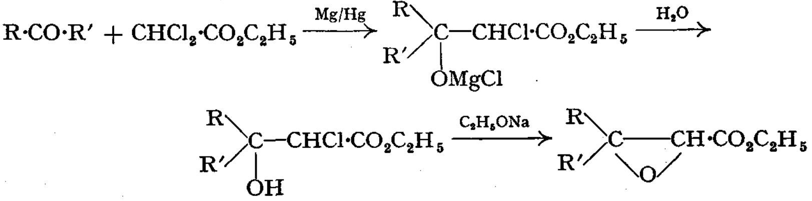
15. **Darzens Glycidic Ester Condensation** (1904). This reaction involves the condensation of an aldehyde or ketone with an α-halogeno-ester to produce an α : β-epoxy-ester (*glycidic ester*); the condensing agent is usually sodium ethoxide or sodamide:



These glycidic esters, on hydrolysis, give the epoxy-acid, and this, on decarboxylation, gives a ketone, or an aldehyde which is formed by rearrangement:

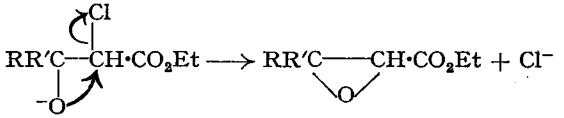


Darzens (1936, 1937) has also prepared glycidic esters by condensing α : α-dihalogeno-esters with an aldehyde or ketone in the presence of dilute magnesium amalgam:



According to Ballester *et al.* (1955), the mechanism of the reaction is:

$$CH_2Cl\cdot CO_2Et + B \rightleftharpoons \bar{C}HCl\cdot CO_2Et + BH^+ \xrightarrow{RR'CO}$$



This is an example of neighbouring group participation.

Reactions given by aldehydes only. 1. Aldehydes restore the magenta colour to Schiff's reagent (rosaniline hydrochloride is dissolved in water, and sulphur dioxide is passed in until the magenta colour is discharged). The mechanism of this reaction is obscure.

2. Aldehydes are very easily oxidised, and hence are powerful reducing agents. Aldehydes reduce Fehling's solution (an alkaline solution containing a complex of copper tartrate) to red cuprous oxide; and Tollens' reagent (ammoniacal silver nitrate solution) to metallic silver, which often appears as a silver mirror on the walls of the containing vessel. In both cases the aldehyde is oxidised to the corresponding acid:

$$R\cdot CHO + [O] \longrightarrow R\cdot CO_2H$$

It is worth noting that Fehling's solution and Tollens' reagent are both weak oxidising agents, and can be used to oxidise *readily oxidisable* groups, *e.g.*, they will oxidise unsaturated aldehydes to the corresponding unsaturated acids; they are not sufficiently strong oxidising agents to attack an ethylenic bond.

According to Veksler (1952), ketones with the structures $Ar\cdot CH_2\cdot CO\cdot CH_3$ and $Ar_2CH\cdot CO\cdot CH_3$ (Ar = aryl radical) reduce cold ammoniacal solutions of *silver oxide* to a silver mirror; it appears that ammoniacal *silver nitrate* is *not* reduced.

According to Daniels *et al.* (1960), some aliphatic aldehydes, *e.g.*, acetaldehyde, crotonaldehyde, etc., do *not* give a positive test with Fehling's solution. These authors suggest that Tollens' test is most satisfactory for distinguishing between aldehydes and ketones.

3. All aldehydes except formaldehyde form resinous products when warmed with concentrated sodium hydroxide solution. The resin is probably formed via a series of condensations, *e.g.*,

$$2CH_3\cdot CHO \longrightarrow CH_3\cdot CH(OH)\cdot CH_2\cdot CHO \xrightarrow{-H_2O} CH_3\cdot CH{:}CH\cdot CHO \xrightarrow{CH_3\cdot CHO}$$

$$CH_3\cdot CH{:}CH\cdot CH(OH)\cdot CH_2\cdot CHO \xrightarrow{-H_2O} CH_3\cdot CH{:}CH\cdot CH{:}CH\cdot CHO, \text{ etc.}$$

Aldehydes that have no α-hydrogen atoms undergo the **Cannizzaro reaction** (1853), in which two molecules of the aldehyde are involved, one molecule being converted into the corresponding alcohol, and the other into the acid. The usual reagent for bringing about the Cannizzaro reaction is 50 per cent. aqueous or ethanolic alkali, *e.g.*,

$$2H\cdot CHO + NaOH \longrightarrow H\cdot CO_2Na + CH_3OH$$

The Cannizzaro reaction is mainly applicable to aromatic aldehydes (see p. 649).

Although the Cannizzaro reaction is characteristic of aldehydes having no α-hydrogen atoms, it is not confined to them, *e.g.*, certain aliphatic α-monoalkylated aldehydes undergo quantitative disproportionation when heated with aqueous sodium hydroxide at 170–200° (Häusermann, 1951):

$$2(CH_3)_2CH{\cdot}CHO + NaOH \xrightarrow{200^\circ} (CH_3)_2CH{\cdot}CO_2Na + (CH_3)_2CH{\cdot}CH_2OH \ (100\%)$$

The Cannizzaro reaction can take place between two different aldehydes, and is then known as a " crossed " Cannizzaro reaction (see formaldehyde, p. 165).

All aldehydes can be made to undergo the Cannizzaro reaction by treatment with aluminium ethoxide. Under these conditions the acid and alcohol are combined as the ester, and the reaction is then known as the **Tischenko reaction** (1906); *e.g.*, acetaldehyde gives ethyl acetate, and propionaldehyde gives propyl propionate:

$$2CH_3{\cdot}CHO \xrightarrow{Al(OC_2H_5)_3} CH_3{\cdot}CO_2C_2H_5$$

$$2CH_3{\cdot}CH_2{\cdot}CHO \xrightarrow{Al(OC_2H_5)_3} CH_3{\cdot}CH_2{\cdot}CO_2CH_2{\cdot}CH_2{\cdot}CH_3$$

Aldehydes give simple esters with aluminium ethoxide, the aldol condensation with sodium ethoxide, and trimeric glycol esters with magnesium or calcium ethoxides (Villani and Nord, 1947):

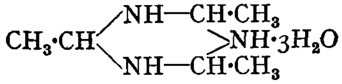
$$3R{\cdot}CH_2{\cdot}CHO \xrightarrow{Mg(OC_2H_5)_2} R{\cdot}CH_2{\cdot}CH(OH){\cdot}CHR{\cdot}CH_2O{\cdot}CO{\cdot}CH_2{\cdot}R$$

4. Aldehydes (except formaldehyde) react with ammonia in ethereal solution to give a precipitate of *aldehyde-ammonia, e.g.*,

$$CH_3{\cdot}CHO + NH_3 \longrightarrow CH_3{\cdot}CH(OH){\cdot}NH_2 \quad (50\%)$$

These aldehyde-ammonias are unstable and readily undergo cyclic polymerisation, and it has been suggested, from X-ray crystal analysis, that acetaldehyde-ammonia is the trihydrate of trimethylhexahydrotriazine * (Moerman, 1938):

$$CH_3{\cdot}CHO + NH_3 \longrightarrow CH_3{\cdot}CHO{\cdot}NH_3 \xrightarrow{\text{polymerises}} (CH_3{\cdot}CHO{\cdot}NH_3)_3 \longrightarrow$$



5. Aldehydes combine with alcohols in the presence of dry hydrogen chloride or calcium chloride to form first the *hemi-acetal*, and then the *acetal*:

$$R{\cdot}CHO + R'OH \xrightleftharpoons{HCl} R{\cdot}CH(OH){\cdot}OR' \xrightleftharpoons{R'OH} R{\cdot}CH(OR')_2 + H_2O \quad (g.)$$

The hemi-acetal is rarely isolated since it very readily forms the acetal. Acetals are diethers of the unstable 1 : 1-dihydroxyalcohols, and may be named as 1 : 1-dialkoxyalkanes. Unlike the parent dihydroxyalcohols these acetals are stable. They are also stable in the presence of alkali, but are converted into the aldehyde by acid. Thus acetal formation may be used to protect the aldehyde group against *alkaline* oxidising agents. On the other hand, the aldehyde group can be protected in *acid* solution by mecaptal formation (p. 334).

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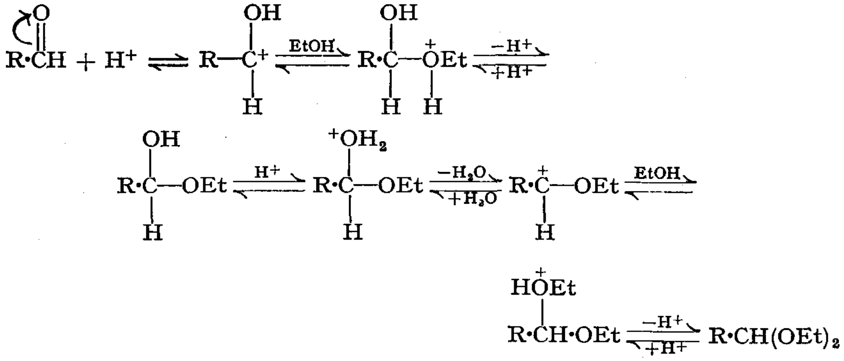
* The reaction between aldehydes and ammonia is usually quoted to be simple. Although the first product is simple, the final one is complicated, and so this reaction is not characteristic of aldehydes, since ketones also give complex products with ammonia. In the latter case, however, it is doubtful whether a simple addition product has ever been isolated.

A possible mechanism is:



6. Aldehydes react with aniline to form *anils* (azomethines):

$$R{\cdot}CHO + C_6H_5{\cdot}NH_2 \longrightarrow R{\cdot}CH{:}N{\cdot}C_6H_5 + H_2O$$

Aliphatic azomethines tend to polymerise; the aromatic analogues are stable.

7. The lower aldehydes polymerise with great ease (see formaldehyde and acetaldehyde, below).

Reactions given by ketones only. 1. Ketones do not give Schiff's reaction. Acetone, however, restores the magenta colour *very slowly*.

2. Ketones are not easily oxidised (*cf.* p. 132); they do not reduce Fehling's solution or ammoniacal silver nitrate (see p. 160).

α-Hydroxyketones, *i.e.*, compounds containing the group ·CH(OH)·CO·, readily reduce Fehling's solution and ammoniacal silver nitrate.

Strong oxidising agents, *e.g.*, acid dichromate, nitric acid, etc., oxidise ketones, only the carbon atoms adjacent to the carbonyl group being attacked, and the carbon atom joined to the smaller number of hydrogen atoms is preferentially oxidised:

$$CH_3{\cdot}CO{\cdot}|CH_2{\cdot}CH_3 \xrightarrow{[O]} 2CH_3{\cdot}CO_2H$$

If the adjacent carbon atoms have the same number of hydrogen atoms, the carbonyl group remains chiefly with the *smaller* alkyl group; *e.g.*, when hexan-3-one is oxidised, the main product is propionic acid, and this is accompanied by much smaller amounts of acetic and butyric acids:

$$CH_3{\cdot}CH_2{\cdot}CO{\cdot}|CH_2{\cdot}CH_2{\cdot}CH_3 \xrightarrow{[O]} 2CH_3{\cdot}CH_2{\cdot}CO_2H$$

$$CH_3{\cdot}CH_2|{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \xrightarrow{[O]} CH_3{\cdot}CO_2H + CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

All ketones containing the acetyl group, $CH_3{\cdot}CO$, undergo the **haloform reaction.** This reaction is best carried out by dissolving the compound in dioxan, adding dilute sodium hydroxide, then a slight excess of iodine in potassium iodide solution, warming, and finally adding water. If the compound contains the acetyl group, iodoform is precipitated (*cf.* iodoform, p. 118).

The haloform reaction is very useful in organic degradations. A positive iodoform test is given by all compounds containing the acetyl group attached to either carbon or hydrogen, or by compounds which are oxidised under the conditions of the test to derivatives containing the acetyl group, *e.g.*, ethanol, *iso*propanol, etc.

Booth and Saunders (1950) have shown that a number of other compounds besides those mentioned above also give the haloform reaction, *e.g.*, certain quinones, quinols and *m*-dihydric phenols.

In practice, the base-catalysed iodination of aliphatic methyl ketones does *not* occur quantitatively according to the equation:

$$CH_3\cdot CO\cdot R + 3I_2 + 4NaOH \longrightarrow CHI_3 + R\cdot CO_2Na + 3NaI + 3H_2O$$

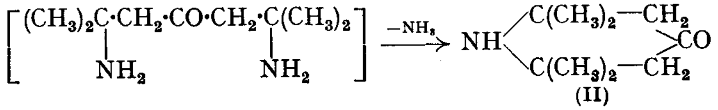
For example, acetone and butanone consume more than the theoretical amount of iodine, whereas, *e.g.*, methyl *iso*propyl ketone consumes less than this quantity (Cullis *et al.*, 1956). Thus methods based on this reaction for the quantitative estimation of methyl ketones are unsatisfactory.

3. Ketones react with ammonia to form complex condensation products, *e.g.*, if acetone is treated with ammonia and then followed by acidification of the reaction products, *diacetonamine* (I), and *triacetonamine* (II), are formed. If the reaction is carried out at room temperature (I) is the chief product; if heated, (II) is the chief product (Bradbury *et al.*, 1947).

The mechanism of the reactions is uncertain, but it may be as follows. Ammonia (base) causes acetone to undergo the aldol condensation to give mesityl oxide and phorone, which then combine with ammonia to form respectively (I) and (II) (see also p. 278):

$$(CH_3)_2C{:}CH\cdot CO\cdot CH_3 + NH_3 \longrightarrow \underset{\text{(I)}}{(CH_3)_2C(NH_2)\cdot CH_2\cdot CO\cdot CH_3}$$

$$(CH_3)_2C{:}CH\cdot CO\cdot CH{:}C(CH_3)_2 + 2NH_3 \longrightarrow$$



(II)

4. Ketones do not readily form *ketals* when treated with alcohols in the presence of hydrogen chloride or calcium chloride (*cf.* acetals, above). Ketals may, however, be prepared by treating the ketone with ethyl orthoformate (Helferich and Hauser, 1924):

$$R_2CO + H\cdot C(OC_2H_5)_3 \longrightarrow R_2C(OC_2H_5)_2 + H\cdot CO_2C_2H_5 \quad (g.)$$

5. When ketones are reduced catalytically or in acid solution, secondary alcohols are obtained in good yields, but when they are reduced in neutral or alkaline solution, *pinacols* are the main products; *e.g.*, acetone reduced with magnesium amalgam forms *pinacol*:

$$2CH_3\cdot CO\cdot CH_3 + 2[H] \xrightarrow[H_2O]{Mg/Hg} (CH_3)_2C(OH)\cdot C(OH)(CH_3)_2$$

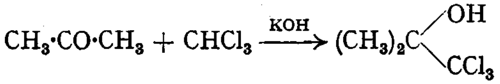
6. When ketones are treated with nitrous acid, the "half oxime" of the α-dicarbonyl compound is formed, *e.g.*, acetone gives oximinoacetone (*iso*nitrosoacetone; see p. 307):

$$CH_3\cdot CO\cdot CH_3 + HNO_2 \xrightarrow{C_2H_5\cdot O\cdot NO/HCl} CH_3\cdot CO\cdot CH{:}N\cdot OH + H_2O$$

All compounds containing the $\cdot CH_2\cdot CO\cdot$ group form the oximino-derivative with nitrous acid, and this has been used to detect the presence of the $\cdot CH_2\cdot CO\cdot$ group.

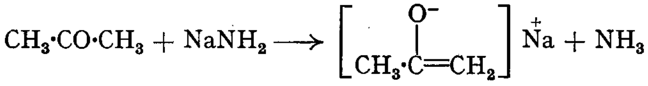
Benzaldehyde can also be used to detect the presence of the $\cdot CH_2\cdot CO\cdot$ group (p. 651):

7. Ketones condense with chloroform in the presence of potassium hydroxide to form chlorohydroxy-compounds.



$$CH_3\cdot CO\cdot CH_3 + CHCl_3 \xrightarrow{KOH} (CH_3)_2C\genfrac{}{}{0pt}{}{\diagup OH}{\diagdown CCl_3}$$

8. Ketones form *sodio-derivatives* when treated with sodium or sodamide in ethereal solution (see p. 230), *e.g.*,



$$CH_3\cdot CO\cdot CH_3 + NaNH_2 \longrightarrow \left[\begin{matrix} O^- \\ | \\ CH_3\cdot C{=}CH_2\end{matrix}\right]\overset{+}{Na} + NH_3$$

Formaldehyde (*methanal*), H·CHO, is prepared industrially:

(i) By passing methanol vapour over copper at 300°:

$$CH_3OH \longrightarrow H\cdot CHO + H_2$$

(ii) By passing methanol vapour mixed with air over a copper or silver catalyst at 250–360°:

$$CH_3OH + \tfrac{1}{2}O_2 \longrightarrow H\cdot CHO + H_2O$$

The amounts of methanol and air must be carefully controlled, otherwise formic acid will result due to the further oxidation of the formaldehyde:

$$H\cdot CHO + \tfrac{1}{2}O_2 \longrightarrow H\cdot CO_2H$$

The vapours are cooled, and the condensate obtained is a mixture of formaldehyde, methanol and water. It is freed from excess methanol by distillation, and the resulting mixture is known as *formalin* (40 per cent. formaldehyde, 8 per cent. methanol, 52 per cent. water).

(iii) By passing a mixture of methane and oxygen over certain catalysts, *e.g.*, molybdenum oxides:

$$CH_4 + O_2 \longrightarrow H\cdot CHO + H_2O$$

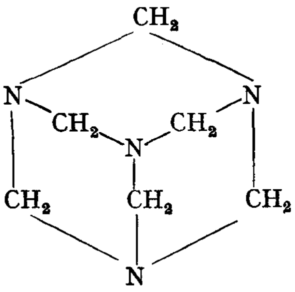
(iv) By the oxidation of natural gas.

Formaldehyde is a colourless, pungent-smelling gas, b.p. —21°, extremely soluble in water. The low boiling points of aldehydes (and ketones) compared with those of alcohols are probably due to the inability of carbonyl compounds to associate through hydrogen bonding. On the other hand, since the carbonyl oxygen atom is capable of forming hydrogen bonds with water, the solubility of aldehydes and ketones in water is to be expected for the lower members (*cf.* alcohols).

Formaldehyde is a powerful disinfectant and antiseptic, and so is used for preserving anatomical specimens. Its main uses are in the manufacture of dyes, the hardening of casein and gelatin, and for making plastics.

Formaldehyde undergoes many of the general reactions of aldehydes, but differs in certain respects. When treated with ammonia, it does not form an aldehyde-ammonia, but gives instead *hexamethylenetetramine*:

$$6H\cdot CHO + 4NH_3 \longrightarrow (CH_2)_6N_4 + 6H_2O\ (80\%)$$



The structure of hexamethylenetetramine appears to be a complicated ring compound. It is a crystalline solid, and has been used in medicine under the name of *urotropine* or *aminoform* as treatment for gout and rheumatism.

Formaldehyde, since it has no α-hydrogen atoms, readily undergoes the Cannizzaro reaction (see p. 160).

Formaldehyde is very useful for methylating primary and secondary amines, *e.g.*, it converts ethylamine into ethylmethylamine:

$$C_2H_5{\cdot}NH_2 + 2H{\cdot}CHO \longrightarrow C_2H_5{\cdot}NH{\cdot}CH_3 + H{\cdot}CO_2H$$

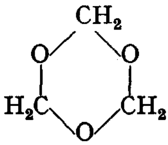
Polymers of formaldehyde. (i) In dilute aqueous solution, formaldehyde is almost 100 per cent. hydrated to form methylene glycol (Bieber *et al.*, 1947). This is believed to be the reason for the stability of dilute formaldehyde solutions (see also p. 168):

$$CH_2O + H_2O \rightleftharpoons CH_2(OH)_2$$

(ii) When a formaldehyde solution is evaporated to dryness, a white crystalline solid, m.p. 121–123°, is obtained. This is known as *paraformaldehyde*, $(CH_2O)_n{\cdot}H_2O$, and it appears to be a mixture of polymers, n having values between 6 and 50. Paraformaldehyde reforms formaldehyde when heated.

Formaldehyde cannot be separated from methanol (in formalin) by fractionation; pure aqueous formaldehyde may be obtained by refluxing paraformaldehyde with water until solution is complete.

(iii) When a formaldehyde solution is treated with concentrated sulphuric acid, *polyoxymethylenes*, $(CH_2O)_n{\cdot}H_2O$—n is greater than 100—are formed. Polyoxymethylenes are white solids, insoluble in water, and reform formaldehyde when heated.



(iv) When allowed to stand at room temperature, formaldehyde gas slowly polymerises to a white solid, *trioxymethylene* (*metaformaldehyde, trioxan*), $(CH_2O)_3$, m. p. 61–62°. This trimer is soluble in water, and does not show any reducing properties. Hence it is believed to have a cyclic structure (in which there is no free aldehyde group).

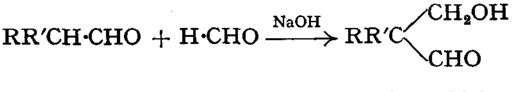
Trioxan is very useful for generating formaldehyde since: (*a*) it is an anhydrous form of formaldehyde; (*b*) the rate of depolymerisation can be controlled; and (*c*) it is soluble in organic solvents.

(v) Formaldehyde polymerises in the presence of weak alkalis, *e.g.*, calcium hydroxide, to a mixture of sugars of formula $C_6H_{12}O_6$, which is known as *formose* or *α-acrose*.

Condensation reactions of formaldehyde. Formaldehyde can participate in the " crossed " Cannizzaro reaction, and the nature of the final product depends on the structure of the other aldehyde. Aldehydes with *no* α-hydrogen atoms readily undergo the crossed Cannizzaro reaction; *e.g.*, benzaldehyde forms benzyl alcohol:

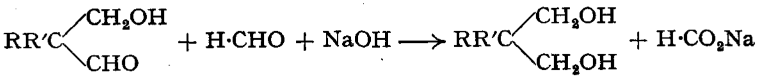
$$C_6H_5{\cdot}CHO + H{\cdot}CHO + NaOH \longrightarrow C_6H_5{\cdot}CH_2OH + H{\cdot}CO_2Na$$

Aldehydes with *one* α-hydrogen atom react as follows:



$$RR'CH{\cdot}CHO + H{\cdot}CHO \xrightarrow{NaOH} RR'C\begin{cases}CH_2OH\\CHO\end{cases}$$

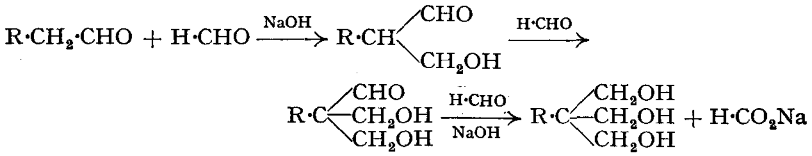
This β-hydroxyaldehyde in the presence of excess formaldehyde forms a substituted trimethylene glycol:



$$RR'C\begin{cases}CH_2OH\\CHO\end{cases} + H{\cdot}CHO + NaOH \longrightarrow RR'C\begin{cases}CH_2OH\\CH_2OH\end{cases} + H{\cdot}CO_2Na$$

Thus the first step in the above reaction is the replacement of the α-hydrogen atom by a *hydroxymethyl* group, $\cdot CH_2OH$, and the second step is the crossed Cannizzaro reaction.

In a similar manner, aldehydes with *two* α-hydrogen atoms are converted first into the hydroxymethyl, then into the bishydroxymethyl, and finally into the trishydroxymethyl compound:



$$R{\cdot}CH_2{\cdot}CHO + H{\cdot}CHO \xrightarrow{NaOH} R{\cdot}CH\left<\begin{array}{l}CHO\\ CH_2OH\end{array}\right. \xrightarrow{H\cdot CHO}$$

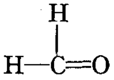
$$R{\cdot}C\left<\begin{array}{l}CHO\\ CH_2OH\\ CH_2OH\end{array}\right. \xrightarrow[NaOH]{H\cdot CHO} R{\cdot}C\left<\begin{array}{l}CH_2OH\\ CH_2OH\\ CH_2OH\end{array}\right. + H{\cdot}CO_2Na$$

A special case is acetaldehyde, which has *three* α-hydrogen atoms. This reaction is best carried out by adding powdered calcium oxide to a suspension of paraformaldehyde in water containing acetaldehyde. Tetrakishydroxymethylmethane (tetramethylolmethane) or *pentaerythritol* is formed:

$$CH_3{\cdot}CHO + 4H{\cdot}CHO \xrightarrow{Ca(OH)_2} C(CH_2OH)_4 + H{\cdot}CO_2Ca/2 \quad (55\text{–}57\%)$$

Pentaerythritol is important industrially since its tetra-nitrate is a powerful explosive.

Structure of formaldehyde, Analysis and molecular-weight determinations show that the molecular formula of formaldehyde is CH_2O. Assuming the quadrivalency of carbon, the bivalency of oxygen and the univalency of hydrogen, only one structure is possible:



$$\begin{array}{c}H\\ |\\ H{-}C{=}O\end{array}$$

This structure agrees with all the known properties of formaldehyde, and has been proved by both infra-red and ulta-violet spectra measurements.

Acetaldehyde (*ethanal*), $CH_3{\cdot}CHO$, is prepared industrially:

(i) By passing ethanol vapour over copper at 300°:

$$CH_3{\cdot}CH_2OH \longrightarrow CH_3{\cdot}CHO + H_2$$

(ii) By passing ethanol vapour mixed with air over a silver catalyst at 250°:

$$C_2H_5OH + \tfrac{1}{2}O_2 \longrightarrow CH_3{\cdot}CHO + H_2O$$

(iii) From acetylene:

$$C_2H_2 + H_2O \xrightarrow[HgSO_4]{H_2SO_4} CH_3{\cdot}CHO$$

(iv) By the hydrolysis of methyl vinyl ether (*q.v.*):

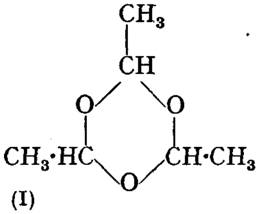
$$CH_3{\cdot}O{\cdot}CH{:}CH_2 + H_2O \longrightarrow CH_3{\cdot}CHO + CH_3OH$$

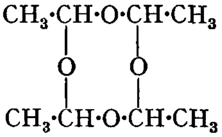
(v) By the oxidation of natural gas.

Acetaldehyde is a colourless, pungent-smelling liquid, b.p. 21°, miscible with water, ethanol and ether in all proportions. It is used in the preparation of acetic acid, ethanol, paraldehyde, rubber accelerators, phenolic resins, synthetic drugs, etc. Acetaldehyde is about 58 per cent. hydrated in aqueous solution to form ethylidene glycol (Bell *et al.*, 1952; see also p. 168):

$$CH_3{\cdot}CHO + H_2O \rightleftharpoons CH_3{\cdot}CH(OH)_2$$

Polymers of acetaldehyde. (i) When acetaldehyde is treated with a few drops of concentrated sulphuric acid, a vigorous reaction takes place and the trimer *paraldehyde*, $(CH_3{\cdot}CHO)_3$, is formed. This is pleasant-smelling liquid, b.p. 128°, and is used in medicine as an hypnotic. When paraldehyde is distilled with dilute sulphuric acid, acetaldehyde is regenerated. Paraldehyde has no reducing properties, and its structure is believed to be (I):


(I)

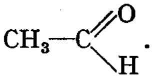

(II)

(ii) When acetaldehyde is treated with a few drops of concentrated sulphuric acid at 0°, the tetramer *metaldehyde*, $(CH_3{\cdot}CHO)_4$, is formed. This is a white solid, m.p. 246°, and regenerates acetaldehyde when distilled with dilute sulphuric acid. Its structure may be (II).

Structure of acetaldehyde. Analysis and molecular-weight determinations show that the molecular formula of acetaldehyde is C_2H_4O. Ethanol may be oxidised to acetaldehyde, which, in turn, may be oxidised to acetic acid. Both ethanol and acetic acid (*q.v.*) contain a methyl group, and it is therefore reasonable to suppose that this methyl group remains intact during the oxidation, and is therefore present in acetaldehyde:

$$\mathbf{CH_3}—CH_2OH \xrightarrow{[O]} \mathbf{CH_3}—CHO \xrightarrow{[O]} \mathbf{CH_3}—CO_2H$$

Phosphorus pentachloride reacts with acetaldehyde to form ethylidene chloride, $C_2H_4Cl_2$, and no hydrogen chloride is evolved in the reaction. This implies that there is no hydroxyl group present in acetaldehyde (*cf.* p. 136), and since two univalent chlorine atoms have replaced one bivalent oxygen atom, the inference is that there is a carbonyl group, $>C=O$, present.

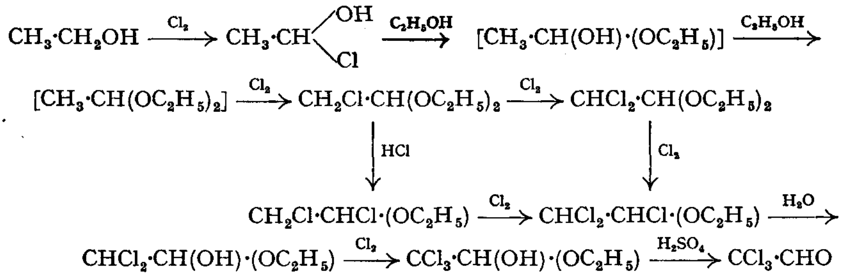
Thus the structure of acetaldehyde is  $CH_3—C\begin{matrix} /\!\!/ O \\ \diagdown H \end{matrix}$.

Study of the dipole moments of aldhydes and ketones, however, has presented some difficulty in elucidating the structure of carbonyl compounds. It has been suggested that the values of the dipole moments are larger than can be accounted for by the inductive effect of the oxygen atom, and it has therefore been proposed that aldehydes and ketones are resonance hybrids:

$$>C=O \longleftrightarrow >\overset{+}{C}—\overset{-}{O}$$

Chloral (*trichloroacetaldehyde*), $CCl_3{\cdot}CHO$, is prepared industrially by the chlorination of ethanol. Chlorine is passed into cooled ethanol, and then at 60°, until no further absorption of chlorine takes place. The final product is chloral alcoholate, $CCl_3{\cdot}CH(OH){\cdot}(OC_2H_5)$, which separates out as a crystalline solid which, on distillation with concentrated sulphuric acid, gives chloral.

The mechanism of the reaction is obscure. The following set of equations have been proposed (Fritsch, 1897):



$$CH_3\cdot CH_2OH \xrightarrow{Cl_2} CH_3\cdot CH\begin{matrix}OH\\ Cl\end{matrix} \xrightarrow{C_2H_5OH} [CH_3\cdot CH(OH)\cdot(OC_2H_5)] \xrightarrow{C_2H_5OH}$$

$$\begin{tikzcd} {[CH_3\cdot CH(OC_2H_5)_2]} \arrow[r, "Cl_2"] & CH_2Cl\cdot CH(OC_2H_5)_2 \arrow[r, "Cl_2"] \arrow[d, "HCl"] & CHCl_2\cdot CH(OC_2H_5)_2 \arrow[d, "Cl_2"] & \\ & CH_2Cl\cdot CHCl\cdot(OC_2H_5) \arrow[r, "Cl_2"] & CHCl_2\cdot CHCl\cdot(OC_2H_5) \arrow[r, "H_2O"] & {} \end{tikzcd}$$

$$CHCl_2\cdot CH(OH)\cdot(OC_2H_5) \xrightarrow{Cl_2} CCl_3\cdot CH(OH)\cdot(OC_2H_5) \xrightarrow{H_2SO_4} CCl_3\cdot CHO$$

Chloral is a colourless, oily, pungent-smelling liquid, b.p. 98°, soluble in water, ethanol and ether. When heated with concentrated potassium hydroxide, it yields pure chloroform:

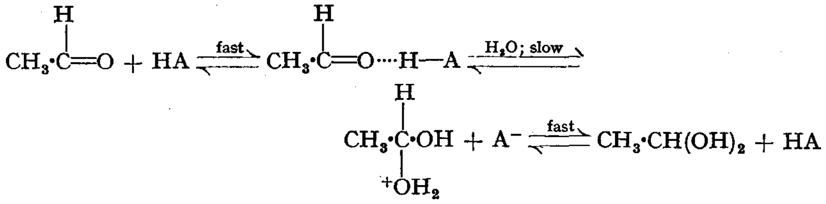
$$CCl_3\cdot CHO + KOH \longrightarrow CHCl_3 + H\cdot CO_2K$$

Chloral is oxidised by concentrated nitric acid to trichloroacetic acid (I), and is reduced by aluminium ethoxide to trichlorethanol (II).

$$\underset{(I)}{CCl_3CO_2H} \xleftarrow{HNO_3} CCl_3\cdot CHO \xrightarrow{Al(OC_2H_5)_3} \underset{(II)}{CCl_3\cdot CH_2OH}$$

Chloral undergoes the usual reactions of an aldehyde, but its behaviour towards water and ethanol is unusual. When chloral is treated with water or ethanol, combination takes place with the evolution of heat, and a crystalline solid is formed, chloral hydrate, m.p. 57°, or chloral alcoholate, m.p. 46°, respectively. *These compounds are stable,* and the water or ethanol can only be removed by treatment with concentrated sulphuric acid. It therefore seems likely that in chloral hydrate the water is present as *water of constitution, i.e.,* the structure of chloral hydrate is $CCl_3\cdot CH(OH)_2$; similarly, the structure of chloral alcoholate is $CCl_3\cdot CH(OH)\cdot(OC_2H_5)$. The stability of these compounds is remarkable in view of the fact that the group $>C(OH)_2$ in other compounds very readily eliminates water.

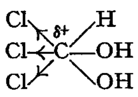
Bell *et al.* (1952) showed the forward and backward reactions in the hydration of acetaldehyde are subject to general acid and general base catalysis (*i.e.*, the catalytic effect is due to *all* of the acids or bases present). Bell proposed the following mechanism for general acid catalysis:



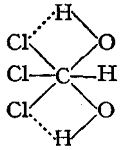
$$CH_3\cdot\overset{H}{C}{=}O + HA \overset{fast}{\rightleftharpoons} CH_3\cdot\overset{H}{C}{=}O\cdots H{-}A \overset{H_2O;\ slow}{\rightleftharpoons}$$

$$CH_3\cdot\underset{^+OH_2}{\overset{H}{C}}\cdot OH + A^- \overset{fast}{\rightleftharpoons} CH_3\cdot CH(OH)_2 + HA$$

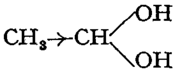
Since the reaction is reversible, the conversion of the hydrate into the aldehyde will involve the loss of a water molecule. If, however, the carbon atom of the C—$\overset{+}{O}H_2$ group has a positive charge, then fission of this bond is strongly opposed, and so the hydrate will be stabilised. In chloral, owing to the strong inductive effect of the chlorine atoms, the central carbon atom acquires a positive charge (III). On the other hand, Davies (1940) has shown from infrared studies



(III)



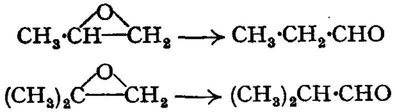
(IV)



(V)

that chloral hydrate (and related compounds) contain hydrogen bonds, and he suggests that this accounts for the stability of the hydrate (IV). Acetaldehyde hydrate (V) will be unstable because of the +I effect of the methyl group, and acetone hydrate still more unstable because of the +I effect of *two* methyl groups. In both of these hydrates the central carbon atom acquires a small negative charge and so facilitates fission of the $C—\overset{+}{O}H_2$ bond. In formaldehyde hydrate, there are no methyl groups, and so this compound would be expected to be more stable than the corresponding acetaldehyde hydrate.

Propionaldehyde, $CH_3{\cdot}CH_2{\cdot}CHO$, b.p. 49°, and ***iso*butyraldehyde,** $(CH_3)_2CH{\cdot}CHO$, b.p. 61°, are prepared industrially by the isomerisation of propylene oxide and *iso*butylene oxide, respectively, in the presence of steam and an alumina–silica catalyst.



Propionaldehyde is also prepared industrially by the *oxo process* by passing a compressed mixture of ethylene, carbon monoxide and hydrogen over the catalyst at 125–145° (p. 127).

Many higher aldehydes occur in nature, *e.g.*, *n*-octaldehyde, $C_8H_{16}O$, and *n*-nonaldehyde, $C_9H_{18}O$, in rose-oil; *n*-decaldehyde, $C_{10}H_{20}O$, in rose-oil and orange-peel oil.

Acetone (*dimethyl ketone, propan-2-one*), $CH_3{\cdot}CO{\cdot}CH_3$, is prepared industrially:

(i) By passing *iso*propanol vapour over copper at 300°:

$$CH_3{\cdot}CH(OH){\cdot}CH_3 \longrightarrow CH_3{\cdot}CO{\cdot}CH_3 + H_2$$

(ii) By passing acetic acid vapour over calcium oxide or manganous oxide at 300–400°:

$$2CH_3{\cdot}CO_2H \longrightarrow CH_3{\cdot}CO{\cdot}CH_3 + CO_2 + H_2O$$

(iii) By passing ethanol vapour mixed with steam over zinc chromite as catalyst, at 500°:

$$2C_2H_5OH + H_2O \longrightarrow CH_3{\cdot}CO{\cdot}CH_3 + CO_2 + 4H_2$$

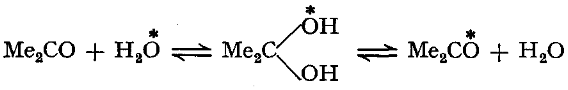
A newer process is to pass a mixture of acetylene and steam over heated pure zinc oxide as catalyst. Another new process is to heat a mixture of propylene and steam under pressure in the presence of a suitable catalyst (p. 137). Acetone is also manufactured by the oxidation of natural gas.

(iv) By fermentation (see *n*-butanol, p. 137), but this method is being replaced by the above synthetic methods.

Acetone is a colourless, pleasant-smelling liquid, b.p. 56°, miscible with water, ethanol and ether in all proportions. Pure acetone is best prepared by saturating acetone with sodium iodide at 25–30°. The solution is decanted off from the excess solid, cooled to −10°, and the precipitate, $NaI{\cdot}3CH_3{\cdot}CO{\cdot}CH_3$, is warmed to 30°, pure dry acetone thereby being produced. Acetone is used as a solvent for acetylene, cellulose acetate and nitrate, celluloid, lacquers, etc., and for the preparation of keten, sulphonal, etc. Acetone is hydrated to only a very slight extent in water:

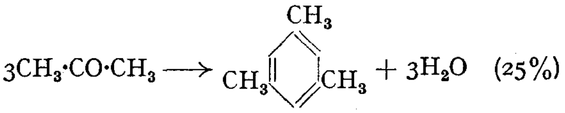
$$(CH_3)_2CO + H_2O \rightleftharpoons (CH_3)_2C(OH)_2$$

The fact that acetone *does* form a hydrate is shown by the isolation of acetone containing ^{18}O when dissolved in water enriched with ^{18}O (Urey *et al.*, 1938):



$$Me_2CO + H_2\overset{*}{O} \rightleftharpoons Me_2C(\overset{*}{O}H)(OH) \rightleftharpoons Me_2C\overset{*}{O} + H_2O$$

Ketones do not polymerise, but readily undergo condensation reactions. Acetone readily forms mesityl oxide, phorone and diacetone alcohol (p. 228). but in addition to these condensations, acetone forms mesitylene when distilled with concentrated sulphuric acid:



Structure of acetone. Analysis and molecular-weight determinations show that the molecular formula of acetone is C_3H_6O. Acetone reacts with phosphorus pentachloride to form *iso*propylidene chloride, $C_3H_6Cl_2$, and no hydrogen chloride is evolved. This indicates that there is no hydroxyl group present, and since a bivalent oxygen atom has been replaced by two univalent chlorine atoms, this implies that a carbonyl group is present. Assuming the quadrivalency of carbon, the bivalency of oxygen and the univalency of hydrogen, there are two structures possible for acetone:

$$\text{(I)}\quad CH_3{\cdot}CH_2{\cdot}CHO \qquad\qquad CH_3{\cdot}CO{\cdot}CH_3\quad \text{(II)}$$

(I) contains the aldehyde group, but since acetone does not behave like an aldehyde, (II) must be its structure. This is confirmed by all the known reactions of acetone (*cf.* acetaldehyde, for the structure of the carbonyl group).

Ethyl methyl ketone, butan-2-one, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3$, is prepared industrially:

(i) By passing *sec.*-butanol vapour over copper at 300°:

$$CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_3 \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3 + H_2$$

(ii) By the oxidation of *sec.*-butanol with air, using a silver catalyst at 250°:

$$CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_3 + \tfrac{1}{2}O_2 \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3 + H_2O$$

Butanone is a pleasant-smelling liquid, b.p. 80°. It is widely used as a solvent for vinyl resins, synthetic rubber, etc.

Methyl *iso*propyl ketone, 3-methylbutan-2-one, $CH_3{\cdot}CO{\cdot}CH(CH_3)_2$, b.p. 94°, may be prepared in several ways, but the best method is by treating *tert.*-pentanol with bromine and hydrolysing the dibromo-derivative, whereupon a molecular rearrangement takes place(see pinacone, below):

$$(CH_3)_2C(OH){\cdot}CH_2{\cdot}CH_3 \xrightarrow{Br_2} (CH_3)_2CBr{\cdot}CHBr{\cdot}CH_3 \xrightarrow{H_2O}$$
$$[(CH_3)_2C(OH){\cdot}CH(OH){\cdot}CH_3] \xrightarrow[\text{rearranges}]{-H_2O} (CH_3)_2CH{\cdot}CO{\cdot}CH_3$$

***tert.*-Butyl methyl ketone, pinacolone, pinacone,** $CH_3{\cdot}CO{\cdot}C(CH_3)_3$, may be prepared:

(i) By distilling pinacol or pinacol hydrate with sulphuric acid:

$$(CH_3)_2C(OH){\cdot}C(OH)(CH_3)_2 \xrightarrow{H_2O} CH_3{\cdot}CO{\cdot}C(CH_3)_3 \quad (65\text{–}72\%)$$

(ii) By passing pinacol dissolved in dioxan over a heated catalyst of silica-gel impregnated with phosphoric acid, a 94 per cent. yield of pinacolone being obtained (Emerson, 1947).

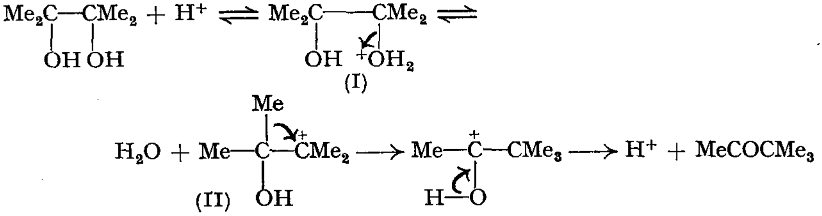
This conversion of pinacol into pinacone is an example of the 1,2-shift (p. 101), and is known as the *pinacol–pinacone rearrangement.*

Pinacolone is a colourless liquid, b.p. 119°, with a camphor-like odour. It is oxidised by alkaline sodium hypobromite to trimethylacetic acid:

$$CH_3{\cdot}CO{\cdot}C(CH_3)_3 \xrightarrow{Br_2/NaOH} (CH_3)_3C{\cdot}CO_2H \quad (71\text{–}74\%)$$

Many higher ketones occur in nature, *e.g.*, heptan-2-one, $CH_3{\cdot}CO{\cdot}C_5H_{11}$, in clove-oil, and undecan-2-one, $CH_3{\cdot}CO{\cdot}C_9H_{19}$, in oil of rue.

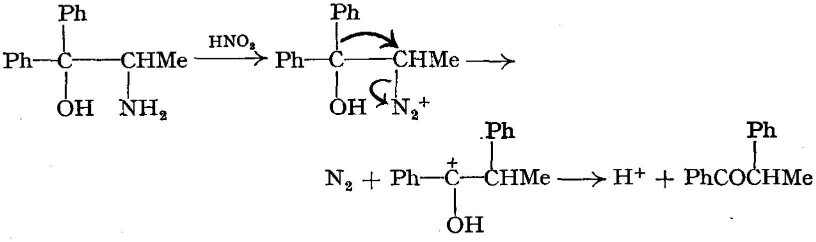
The pinacol–pinacone rearrangement is general for 1:2-glycols under acid conditions; the migrating group may be alkyl or aryl. The detailed mechanism of this rearrangement is not certain, but it is generally accepted that the first stage is the addition of a proton to one of the hydroxy-groups, followed by loss of this as water. This leaves a carbonium ion, and it is the nature of this ion and the steps leading to the product that are uncertain. According to Bunton *et al.* (1959), the mechanism for the rearrangement of pinacol itself is:



$$\underset{OH}{Me_2C}\text{—}\underset{OH}{CMe_2} + H^+ \rightleftharpoons \underset{OH}{Me_2C}\text{—}\underset{^+OH_2}{CMe_2} \ (I) \rightleftharpoons H_2O + Me\text{—}\overset{Me}{\underset{OH}{C}}\text{—}\overset{+}{C}Me_2 \ (II) \longrightarrow Me\text{—}\overset{+}{\underset{H\text{—}O}{C}}\text{—}CMe_3 \longrightarrow H^+ + MeCOCMe_3$$

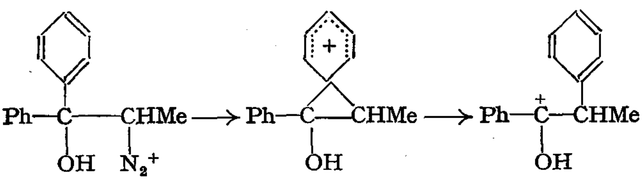
Kinetic measurements have shown that the conversion of (I) into (II) is the rate-determining step.

Whitmore *et al.* (1939), using a related pinacolic deamination, showed that when an optically active amine containing one asymmetric centre was used, this asymmetric centre was predominantly inverted in the product (*cf.* Walden inversion, p. 413; $Ph = C_6H_5$):



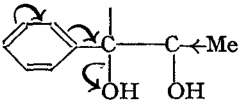
$$Ph\text{—}\overset{Ph}{\underset{OH}{C}}\text{—}\underset{NH_2}{CHMe} \xrightarrow{HNO_2} Ph\text{—}\overset{Ph}{\underset{OH}{C}}\text{—}\underset{N_2^+}{CHMe} \longrightarrow N_2 + Ph\text{—}\overset{+}{\underset{OH}{C}}\text{—}\overset{Ph}{C}HMe \longrightarrow H^+ + PhCO\overset{Ph}{C}HMe$$

These results mean that the classical carbonium ion, which is flat, if formed at all, must rearrange so fast that racemisation cannot occur (see p. 412). On the other hand, the inversion may be explained by a synchronous migration of a phenyl group and breaking of the C—N bond. In this case, the intermediate could be the ***phenonium ion***, *i.e.*, a bridged ion in which the configuration of the asymmetric carbon atom is held in the inverted position:



A pair of electrons of the benzene ring is used to form the bridge, and the rest of the benzene molecule is represented as a pentadienyl cation (see p. 516). The formation of this phenonium ion is supported by other experimental work, but whether a bridged ion is formed when an *alkyl* group migrates is very doubtful.

When dealing with unsymmetrical pinacols, there are several other points to be considered, *e.g.*, which hydroxyl group is removed. Since the OH group is removed as water, any polar effect in the molecule which weakens one C—O bond more than the other will facilitate the release of this OH group. Consider the two groups phenyl and methyl. The phenyl group has a powerful conjugative effect, whereas the methyl group has a weak inductive effect in comparison:



Therefore the OH group lost should be the one on the phenyl side, and consequently it will be the methyl group that migrates. This is borne out in practice, *e.g.*,

$$Ph_2C(OH){\cdot}C(OH)Me_2 \xrightarrow{H_2SO_4} Ph_2MeC{\cdot}COMe$$

Another problem is that of "migration aptitude", *i.e.*, which of the two groups migrates when the groups are different. A great deal of work has been done with pinacols of the type (Ar = aryl) ArAr′C(OH)C(OH)ArAr′, and it has been shown that the aryl group with the greater electron-releasing property is the one that migrates (Bachmann *et al.*, 1932–1934). This is understandable on the basis of the formation of an intermediate phenonium ion. Any polar factor that helps to release a pair of electrons from a benzene ring will therefore facilitate the formation of the bridged ion with *this* benzene ring. It has also been found that migration aptitudes depend on steric factors.

QUESTIONS

1. Write out the structures and names of the isomeric aldehydes and ketones having the molecular formula $C_5H_{10}O$.
2. What are all the possible oxidation products of: (*a*) *n*-pentanol, (*b*) hexan-2-ol, (*c*) *tert.*-butanol?
3. Give an analytical table to show how you could distinguish between the following alcohols: methanol, ethanol, *iso*propanol and pentan-3-ol.
4. Starting with ethanol, how would you synthesise: (*a*) *iso*butyraldehyde, (*b*) crotyl alcohol?
5. Show, by means of equations, how you would convert acetylene into isoprene.
6. Describe the industrial methods of preparation of:—(*a*) formaldehyde, (*b*) acetaldehyde, (*c*) chloral, (*d*) acetone, (*e*) butanone.
7. Give an account of the evidence for the structure of (*a*) propionaldehyde, (*b*) butanone.
8. Name the compounds and state the conditions under which they are formed when acetaldehyde or acetone, respectively, is treated with:—(*a*) "nascent" hydrogen, (*b*) molecular hydrogen, (*c*) aluminium *iso*propoxide, (*d*) aluminium ethoxide, (*e*) sodium ethoxide, (*f*) NH_3, (*g*) $NaHSO_3$, (*h*) HCN, (*i*) N_2H_4, (*j*) RSH, (*k*) Br_2, (*l*) PBr_5, (*m*) SeO_2, (*n*) NaOH, (*o*) HCl, (*p*) ammoniacal $AgNO_3$, (*q*) $C_6H_5{\cdot}NH_2$, (*r*) HN_3, (*s*) ROH, (*t*) HNO_2, (*u*) SO_2Cl_2, (*v*) Fehling's solution, (*w*) H·CHO.
9. Define and give examples of:—(*a*) the Oppenauer oxidation, (*b*) the Rosenmund reduction, (*c*) ozonolysis, (*d*) Stephen's aldehyde synthesis, (*e*) the Meerwein–Ponndorf–

Verley reduction, (*f*) the Wolff–Kishner reduction, (*g*) the Clemmensen reduction, (*h*) Girard's reagent, (*i*) the aldol condensation, (*j*) the Cannizzaro reaction, (*k*) the Claisen condensation, (*l*) the Claisen reaction, (*m*) the Knoevenagel reaction, (*n*) the Perkin reaction, (*o*) disproportionation, (*p*) the Tischenko reaction, (*q*) the haloform reaction, (*r*) the pinacol–pinacolone rearrangement, (*s*) the Schmidt reaction, (*t*) polymerisation, (*u*) condensation, (*v*) the crossed Cannizzaro reaction, (*w*) Darzens glycidic ester condensation.

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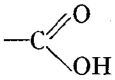
CHAPTER IX

FATTY ACIDS

THE fatty acid series was so named because some of the higher members, particularly palmitic and stearic acids, occur in natural fats. The general formula of the fatty acids is $C_nH_{2n}O_2$. As, however, their functional group is the carboxyl group, $—CO_2H$, they are more conveniently expressed as $C_nH_{2n+1}CO_2H$ or $R{\cdot}CO_2H$, since these show the nature of the functional group. Furthermore, since the fatty acids contain only one carboxyl group, they are also known as the *saturated monocarboxylic acids.*

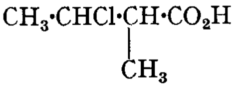
Only the hydrogen atom of the carboxyl group is replaceable by a metal; therefore the fatty acids are monobasic. The structure of the carboxyl group is written as  $—C\begin{smallmatrix}{\diagup\!\!\diagup}O\\ \diagdown OH\end{smallmatrix}$ (or —COOH), but, as we shall see later, it does not represent accurately the behaviour of the carboxyl group.

Nomenclature. The fatty acids are commonly known by the trivial names, which have been derived from the source of the particular acid; *e.g.*, formic acid, $H{\cdot}CO_2H$, was so named because it was first obtained by the distillation of ants; the Latin word for ant is *formica.* Acetic acid, $CH_3{\cdot}CO_2H$, is the chief constituent of vinegar, the Latin word for which is *acetum*; etc. (see below).

Another system of nomenclature considers the fatty acids, except formic acid, as derivatives of acetic acid, *e.g.*,

$CH_3{\cdot}CH_2{\cdot}CO_2H$	methylacetic acid
$(CH_3)_3C{\cdot}CO_2H$	trimethylacetic acid
$(CH_3)_2CH{\cdot}CH_2{\cdot}CO_2H$	*iso*propylacetic acid

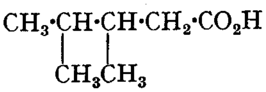
In the above two systems the positions of substituents in the chain are indicated by Greek letters, the α-carbon atom being the one joined to the carboxyl group, *e.g.*,

$CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$	γ-hydroxyvaleric acid
 $CH_3{\cdot}CHCl{\cdot}\underset{\displaystyle CH_3}{\underset{\mid}{C}H}{\cdot}CO_2H$	β-chloro-α-methylbutyric acid

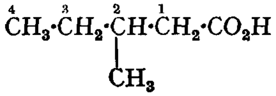
According to the I.U.P.A.C. system of nomenclature, the suffix of the mono-carboxylic acids is *-oic*, which is added to the name of the alkane corresponding to the longest carbon chain containing the carboxyl group, *e.g.*,

$H{\cdot}CO_2H$	methanoic acid
$CH_3{\cdot}CH_2{\cdot}CO_2H$	propanoic acid

The positions of side-chains (or substituents) are indicated by numbers, *the carboxyl group always being given number* 1 (see p. 63), *e.g.*,

 $CH_3{\cdot}\underset{\displaystyle CH_3}{\underset{\mid}{C}H}{\cdot}\underset{\displaystyle CH_3}{\underset{\mid}{C}H}{\cdot}CH_2{\cdot}CO_2H$	3 : 4-dimethylpentanoic acid

Alternatively, the carboxyl group is regarded as a substituent, and is denoted by the suffix carboxylic acid, *e.g.*,



$$\overset{4}{C}H_3\cdot\overset{3}{C}H_2\cdot\overset{2}{C}H(CH_3)\cdot\overset{1}{C}H_2\cdot CO_2H$$

2-methylbutane-1-carboxylic acid

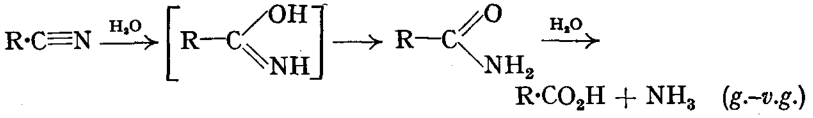
General methods of preparation. 1. Oxidation of alcohols, aldehydes or ketones with acid dichromate yields acids:

$$R\cdot CH_2OH \xrightarrow{[O]} R\cdot CHO \xrightarrow{[O]} R\cdot CO_2H \qquad (g.\text{–}v.g.)$$

$$R_2CHOH \xrightarrow{[O]} R_2CO \xrightarrow{[O]} R\cdot CO_2H + R'\cdot CO_2H \qquad (g.)$$

In certain cases the ester, and not the acid, is obtained by the oxidation of alcohols (see p. 190).

2. A very good synthetic method is the hydrolysis of cyanides with acid or alkali:



The amide, $R\cdot CO\cdot NH_2$, may be isolated if suitable precautions are taken (p. 203).

3. By the reaction between a Grignard reagent and carbon dioxide:

$$RMgX + CO_2 \longrightarrow R\cdot CO_2MgX \xrightarrow{H_2O} R\cdot CO_2H$$

4. Many fatty acids may be conveniently synthesised from alkyl halides and ethyl malonate or acetoacetic ester. These syntheses will be discussed in detail later (pp. 229, 233).

5. A number of higher fatty acids may be obtained by the hydrolysis of natural fats, but it is usually difficult to obtain the acids pure from these sources. On the other hand, higher fatty acids may be prepared by the electrolysis of a methanolic solution of a mixture of a monocarboxylic acid and a half-ester of a dicarboxylic acid (Linstead *et al.*, 1950; *cf.* p. 52):

$$R\cdot CO_2H + CO_2H\cdot(CH_2)_n\cdot CO_2CH_3 \longrightarrow H_2 + 2CO_2 + R\cdot(CH_2)_n\cdot CO_2CH_3$$

6. The sodium salt of a fatty acid may be obtained by heating a sodium alkoxide with carbon monoxide under pressure:

$$RONa + CO \longrightarrow R\cdot CO_2Na$$

It has also been found that the acid may be obtained by heating the alcohol with carbon monoxide at 125–180°, under a pressure of 500 atmospheres, in the presence of a catalyst of boron trifluoride and a little water:

$$ROH + CO \longrightarrow R\cdot CO_2H$$

The sodium salts of acetic and propionic acids are formed by the interaction of methylsodium or ethylsodium, respectively, and carbon dioxide, *e.g.*,

$$C_2\overset{-}{H}_5\overset{+}{Na} + CO_2 \longrightarrow C_2H_5\cdot CO_2Na$$

A recent method of preparing fatty acids is by the catalytic oxidation of long-chain hydrocarbons. The hydrocarbons are obtained from the wax fraction of the Fischer–Tropsch synthesis of hydrocarbons (p. 60), which are oxidised by the passage of air at 120° in the presence of manganous stearate as catalyst; or by oxidising with air in aluminium vessels, the aluminium acting as catalyst. A mixture of fatty acids is obtained, and this has been used for making fats. The actual composition of the mixture of acids has not yet been ascertained.

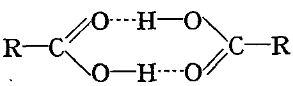
Another recent method for manufacturing fatty acids is to heat an olefin with carbon monoxide and steam under pressure at 300–400° in the presence of a catalyst, *e.g.*, phosphoric acid:

$$CH_2{=}CH_2 + CO + H_2O \longrightarrow CH_3{\cdot}CH_2{\cdot}CO_2H$$

$$CH_3{\cdot}CH{=}CH_2 + CO + H_2O \longrightarrow (CH_3)_2CH{\cdot}CO_2H$$

General properties of the fatty acids. The first three fatty acids are colourless, pungent-smelling liquids; the acids from butyric, $C_4H_8O_2$, to nonoic, $C_9H_{18}O_2$, are oils which smell like goats' butter; and those higher than decoic acid, $C_{10}H_{20}O_2$, are odourless solids.

The lower members are far less volatile than is to be expected from their molecular weight. Nash *et al.* (1957) have reported that formic, acetic, propionic, and *n*-butyric acid exist as dimers in aqueous solution. The existence of these dimers can be explained by hydrogen bonding, and electron diffraction studies (Pauling, 1934) have shown that an eight-membered ring is present. On the other hand, crystalline formic acid (Holtzberg *et al.*, 1953) and acetic acid (Jones *et al.*, 1958) exist as infinite chains in the extended form, whereas the long-chain fatty acids (von Sydow, 1956) consist of cyclic dimers.



The melting points of the *n*-fatty acids show alternation or oscillation from one member to the next, the melting point of an " even " acid being higher than that of the " odd " acid immediately below and above it in the series (see the physical constants of the individuals). A number of homologous series follow this oscillation or " saw-tooth " rule; some authors believe this to be connected with the zig-zag nature of the carbon chain.

The first four members are very soluble in water, and the solubility decreases as the molecular weight increases.

General reactions of the fatty acids. 1. The fatty acids are acted upon by the strongly electropositive metals with the liberation of hydrogen and formation of a salt:

$$R{\cdot}CO_2H + Na \longrightarrow R{\cdot}CO_2Na + \tfrac{1}{2}H_2$$

Salts are also formed by the reaction between an acid and an alkali:

$$R{\cdot}CO_2H + NaOH \longrightarrow R{\cdot}CO_2Na + H_2O$$

2. Fatty acids react with alcohols to form *esters*:

$$R{\cdot}CO_2H + R'OH \rightleftharpoons R{\cdot}CO_2R' + H_2O$$

3. Phosphorus trichloride, phosphorus pentachloride or thionyl chloride act upon the fatty acids to form *acid chlorides*:

$$3R{\cdot}CO_2H + PCl_3 \longrightarrow 3R{\cdot}COCl + H_3PO_3$$

$$R{\cdot}CO_2H + PCl_5 \longrightarrow R{\cdot}COCl + HCl + POCl_3$$

$$R{\cdot}CO_2H + SOCl_2 \longrightarrow R{\cdot}COCl + HCl + SO_2$$

The acid series may be " stepped up " via the acid chloride, but since the process involves many steps, the yield of the higher acid homologue is usually only *f.–f.g.*:

(*a*) $$R{\cdot}CO_2H \xrightarrow{PCl_5} R{\cdot}COCl \xrightarrow[\text{catalyst}]{H_2} R{\cdot}CHO \xrightarrow[\text{catalyst}]{H_2} R{\cdot}CH_2OH \xrightarrow{PBr_3}$$
$$R{\cdot}CH_2Br \xrightarrow{KCN} R{\cdot}CH_2{\cdot}CN \xrightarrow{H_2O} R{\cdot}CH_2{\cdot}CO_2H$$

(*b*) $$R{\cdot}CO_2H \xrightarrow{PCl_5} R{\cdot}COCl \xrightarrow{KCN} R{\cdot}CO{\cdot}CN \xrightarrow{H_2O}$$
$$R{\cdot}CO{\cdot}CO_2H \xrightarrow[\text{reduction}]{\text{Clemmensen}} R{\cdot}CH_2{\cdot}CO_2H$$

Although method (*b*) involves fewer steps than (*a*), the final yield of acid by route (*a*) is higher than that by (*b*), since the yields in each step of (*b*) are generally low.

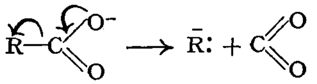
4. When the ammonium salts of the fatty acids are strongly heated, the *acid amide* is formed by the elimination of water:

$$R{\cdot}CO_2NH_4 \longrightarrow R{\cdot}CO{\cdot}NH_2 + H_2O$$

5. When the anhydrous sodium salt of a fatty acid is heated with soda-lime, a paraffin and other products are formed (p. 50).

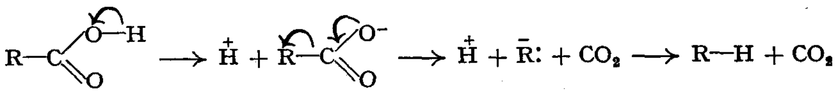
$$R{\cdot}CO_2Na + NaOH(CaO) \longrightarrow RH + Na_2CO_3$$

The mechanism of this decarboxylation is uncertain, but there is much evidence to show that *salts* decompose by an S_E1 reaction:



$$\bar{R}: + \overset{+}{H} \longrightarrow R{-}H$$

The decarboxylation of *free* acids may be:



The fatty acids may be " stepped down " by heating the calcium salt of the acid with calcium acetate (see p. 147), and the methyl ketone produced is oxidised with acid dichromate:

$$R{\cdot}CH_2{\cdot}CO_2Ca/_2 + CH_3{\cdot}CO_2{\cdot}Ca/_2 \longrightarrow R{\cdot}CH_2{\cdot}CO{\cdot}CH_3 \xrightarrow{[O]}$$
$$R{\cdot}CO_2H + CH_3{-}CO_2H$$

It should be noted that the second step is based on the general rule that when an unsymmetrical ketone is oxidised, the carbonyl group remains chiefly with the smaller alkyl group.

Since very few fatty acids containing an odd number of carbon atoms occur naturally, this method of descending the series affords a useful means of obtaining " odd " acids from "even ".

When a mixture of the calcium salt (or any of the others mentioned above) and calcium formate is heated, an aldehyde is obtained:

$$R{\cdot}CO_2Ca/_2 + H{\cdot}CO_2Ca/_2 \longrightarrow R{\cdot}CHO + CaCO_3$$

Metallic salts, particularly the silver salts, are converted by bromine into the alkyl bromide. This reaction may also be used to " step down " the acid series (p. 105).

6. When a concentrated aqueous solution of the sodium or potassium salt of a fatty acid is electrolysed, a paraffin is obtained:

$$2\mathrm{R{\cdot}CO_2K} + 2\mathrm{H_2O} \longrightarrow \mathrm{R{-}R} + 2\mathrm{CO_2} + 2\mathrm{KOH} + \mathrm{H_2}$$

7. Fatty acids react slowly with chlorine or bromine in the cold, but at higher temperatures and in the presence of a small amount of phosphorus, reaction proceeds smoothly to give α-halogeno-acids (see also p. 210); *e.g.*,

$$\mathrm{R{\cdot}CH_2{\cdot}CO_2H} \xrightarrow{\mathrm{P/Br_2}} \mathrm{R{\cdot}CHBr{\cdot}CO_2H} \xrightarrow{\mathrm{P/Br_2}} \mathrm{R{\cdot}CBr_2{\cdot}CO_2H}$$

8. All the fatty acids, except formic acid, are extremely resistant to oxidation, but prolonged heating with oxidising agents ultimately produces carbon dioxide and water.

9. All the fatty acids are resistant to reduction, but prolonged heating under pressure with concentrated hydriodic acid and a small amount of red phosphorus produces a paraffin. Paraffins are also produced when a fatty acid is heated with hydrogen at high temperature and under pressure, in the presence of a nickel catalyst.

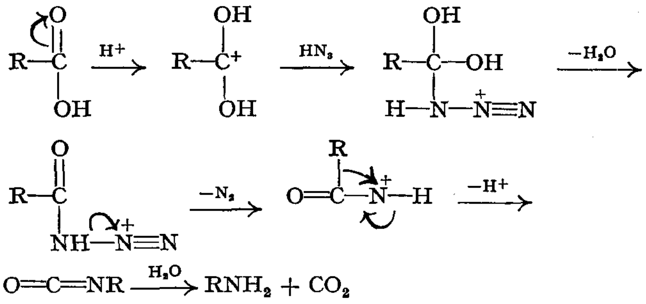
$$\mathrm{R{\cdot}CO_2H} + 3\mathrm{H_2} \xrightarrow{\mathrm{Ni}} \mathrm{R{\cdot}CH_3} + 2\mathrm{H_2O}$$

If the hydrogenation is carried out in the presence of a ruthenium or copper–chromium oxide catalyst, carboxylic acids are converted into primary alcohols (Guyer *et al.*, 1955). Lithium aluminium hydride also reduces acids to alcohols.

10. The fatty acids undergo the *Schmidt reaction* (p. 156) to form a primary amine:

$$\mathrm{R{\cdot}CO_2H} + \mathrm{HN_3} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{R{\cdot}NH_2} + \mathrm{CO_2} + \mathrm{N_2}$$

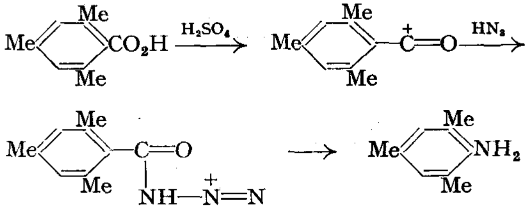
Schmidt's reaction with acids is a modification of the Curtius reaction (p. 209). Since sulphuric acid accelerates the decomposition of the acid azide, this implies that the conjugate acid of the azide decomposes more readily than the azide itself. The following mechanism has been proposed (*cf.* p. 156):



The rearrangement (1,2-shift) has been shown to be intramolecular, *e.g.*, Kenyon *et al.* (1939) showed retention of optical activity when α-phenylpropionic acid underwent the Schmidt reaction:

$$\mathrm{C_6H_5{\cdot}CH(CH_3){\cdot}CO_2H} \longrightarrow \mathrm{C_6H_5{\cdot}CH(CH_3){\cdot}NH_2}$$

This mechanism has been proposed for those acids which require warming to complete the reaction. Newman *et al.* (1948) showed that mesitoic acid underwent the Schmidt reaction at room temperature, whereas benzoic acid required heating at 25°. Mesitoic acid is a sterically hindered acid, and for such acids the reaction is believed to proceed through the acylium cation:



Formic acid (*methanoic acid*), $H{\cdot}CO_2H$, is prepared industrially by heating sodium hydroxide with carbon monoxide at 210°, and at a pressure of 6–10 atmospheres:

$$NaOH + CO \longrightarrow H{\cdot}CO_2Na$$

An aqueous solution of formic acid is obtained by distilling the sodium salt with dilute sulphuric acid:

$$2H{\cdot}CO_2Na + H_2SO_4 \longrightarrow 2H{\cdot}CO_2H + Na_2SO_4$$

Anhydrous formic acid is obtained by warming the sodium salt with concentrated sulphuric acid to which has been added some anhydrous formic acid. Concentrated sulphuric acid dehydrates formic acid to carbon monoxide:

$$H{\cdot}CO_2H \xrightarrow[H_2SO_4]{-H_2O} CO$$

On the other hand, concentrated sulphuric acid diluted with formic acid shows very little tendency to dehydrate formic acid.

Formic acid may be prepared in the laboratory in several ways. One method is to pass methanol vapour or formaldehyde mixed with air over a platinum-black catalyst:

$$CH_3OH + O_2 \xrightarrow{Pt} H{\cdot}CO_2H + H_2O$$

$$H{\cdot}CHO + \tfrac{1}{2}O_2 \xrightarrow{Pt} H{\cdot}CO_2H$$

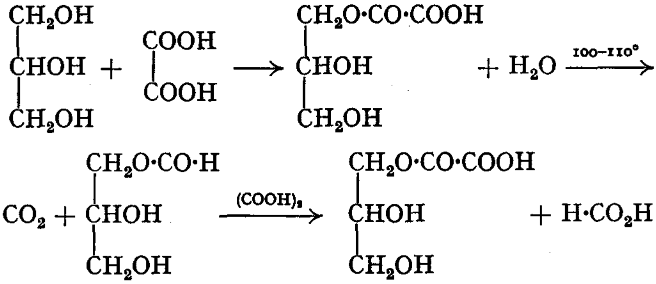
Another method, which is mainly of academic interest, is the hydrolysis of hydrogen cyanide:

$$HCN + 2H_2O \xrightarrow{acid} H{\cdot}CO_2H + NH_3$$

Carbon dioxide, when passed into an ethereal solution of lithium borohydride at 0°, is reduced to formic acid (Burr *et al.*, 1950):

$$2CO_2 + 2LiBH_4 \longrightarrow 2H{\cdot}CO_2Li + B_2H_6 \quad (69\text{–}88\%)$$

The most convenient laboratory preparation of formic acid is to heat glycerol with oxalic acid at 100–110°. Glyceryl monoxalate is produced, and decomposes into glyceryl monoformate (monoformin) and carbon dioxide. When the evolution of carbon dioxide ceases, more oxalic acid is added, whereupon formic acid is produced:



$$\begin{array}{l}\mathrm{CH_2OH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_2OH}\end{array} + \begin{array}{l}\mathrm{COOH}\\ |\\ \mathrm{COOH}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_2O{\cdot}CO{\cdot}COOH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_2OH}\end{array} + \mathrm{H_2O} \xrightarrow{100\text{–}110^\circ}$$

$$\mathrm{CO_2} + \begin{array}{l}\mathrm{CH_2O{\cdot}CO{\cdot}H}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_2OH}\end{array} \xrightarrow{\mathrm{(COOH)_2}} \begin{array}{l}\mathrm{CH_2O{\cdot}CO{\cdot}COOH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{CH_2OH}\end{array} + \mathrm{H{\cdot}CO_2H}$$

The distillate contains formic acid and water. The aqueous formic acid solution cannot be fractionated to give anhydrous formic acid because the boiling point of the acid is 100·5°. The procedure adopted is to neutralise the aqueous acid solution with lead carbonate, and concentrate the solution until lead formate crystallises out. The precipitate is then recrystallised, dried, and heated at 100° in a current of hydrogen sulphide:

$$\mathrm{(H{\cdot}CO_2)_2Pb} + \mathrm{H_2S} \longrightarrow \mathrm{2H{\cdot}CO_2H} + \mathrm{PbS}$$

The anhydrous formic acid which distils over contains a small amount of hydrogen sulphide, and may be freed from the latter by adding some dry lead formate and redistilling.

The above procedure for obtaining the anhydrous acid from its aqueous solution can only be used for volatile acids.

Formic acid is a pungent corrosive liquid, m.p. 8·4°, b.p. 100·5°, miscible in all proportions with water, ethanol and ether. It forms salts which, except for the lead and silver salts, are readily soluble in water (see p. 176). Formic acid is a stronger acid than any of its homologues (see Table III).

TABLE III

Acid	Dissociation Constant, *k* (at 25°)
Formic	$2{\cdot}4 \times 10^{-4}$
Acetic	$1{\cdot}845 \times 10^{-5}$
Propionic	$1{\cdot}22 \times 10^{-5}$
n-Butyric	$1{\cdot}5 \times 10^{-5}$
*iso*Butyric	$1{\cdot}4 \times 10^{-5}$
n-Valeric	$1{\cdot}56 \times 10^{-5}$
*iso*Valeric	$1{\cdot}68 \times 10^{-5}$
Trimethylacetic	$9{\cdot}6 \times 10^{-6}$
Caproic	$1{\cdot}4 \times 10^{-5}$
n-Heptoic	$1{\cdot}3 \times 10^{-5}$
Chloroacetic	$1{\cdot}55 \times 10^{-3}$
Bromoacetic	$1{\cdot}38 \times 10^{-3}$
Iodoacetic	$7{\cdot}3 \times 10^{-4}$
Dichloroacetic	$5{\cdot}14 \times 10^{-2}$
Trichloroacetic	$1{\cdot}2$

Formic acid is dehydrated to carbon monoxide by concentrated sulphuric acid (see above). When heated under pressure at 160°, formic acid is decomposed into carbon dioxide and hydrogen:

$$\mathrm{H{\cdot}CO_2H} \longrightarrow \mathrm{CO_2} + \mathrm{H_2}$$

The same decomposition takes place at room temperature in the presence of a catalyst such as iridium, rhodium, etc.

When metallic formates are heated with an alkali, hydrogen is evolved.

$$H{\cdot}CO_2Na + NaOH \longrightarrow H_2 + Na_2CO_3$$

When calcium or zinc formate is strongly heated, formaldehyde is produced:

$$(H{\cdot}CO_2)_2Ca \longrightarrow H{\cdot}CHO + CaCO_3$$

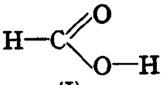
When sodium or potassium formate is rapidly heated to 360°, hydrogen is evolved and the oxalate is formed:

$$2H{\cdot}CO_2Na \longrightarrow (COONa)_2 + H_2$$

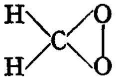
Formic acid forms esters, but since it is a relatively strong acid it is not necessary to use a catalyst; refluxing 90 per cent. formic acid with the alcohol is usually sufficient.

Formic acid differs from the rest of the members of the fatty acid series in being a powerful reducing agent; it reduces ammoniacal silver nitrate and the salts of many of the heavy metals, *e.g.*, it converts mercuric chloride into mercurous chloride.

Structure of formic acid. Analysis and molecular-weight determinations show that the molecular formula of formic acid is CH_2O_2. Assuming that carbon is quadrivalent, oxygen bivalent and hydrogen univalent, two structures are possible:



(I)



(II)

Only one of the two hydrogen atoms in formic acid is replaceable by a metal. This suggests that the two hydrogen atoms are not in the same state of combination. Moreover, since hydrogen is evolved when formic acid is treated with sodium, the implication is that a hydroxyl group is present. Structure (I), but not (II), satisfies the above observations, and also indicates the relationship of formic acid to aldehydes, thus accounting for its reducing properties (see also acetic acid, below).

Acetic acid (*ethanoic acid*), $CH_3{\cdot}CO_2H$, is prepared industrially by the oxidation of acetaldehyde with air in the presence of manganous acetate as catalyst:

$$CH_3{\cdot}CHO + \tfrac{1}{2}O_2 \longrightarrow CH_3{\cdot}CO_2H$$

The function of the catalyst appears to be to prevent the formation of peracetic acid (*q.v.*). Acetic acid is also manufactured by the oxidation of natural gas.

One of the earliest methods for preparing acetic acid was by the destructive distillation of wood to give pyroligneous acid. This contains about 10 per cent. acetic acid, and was originally treated by neutralising with lime and then distilling off the volatile compounds (these are mainly methanol and acetone). On distillation with dilute sulphuric acid, the residue gives dilute acetic acid. More recently, the acetic acid is extracted by means of solvents, *e.g.*, *iso*propyl ether.

Vinegar, which is a 6–10 per cent. aqueous solution of acetic acid, may be made in several ways. Malt vinegar is prepared by the oxidation of wort (p. 135) by means of the bacteria *Mycoderma aceti*:

$$CH_3{\cdot}CH_2OH + O_2 \longrightarrow CH_3{\cdot}CO_2H + H_2O$$

In the " quick vinegar process ", beech shavings, contained in barrels, are moistened with strong vinegar containing the bacteria. A 10 per cent. aqueous solution of ethanol containing phosphates and inorganic salts (which are necessary for the fermentation) is then poured through the barrels, and the ethanol is thereby oxidised to acetic acid. A plentiful supply of air is necessary, otherwise the oxidation is incomplete and acetaldehyde is produced.

It is only recently that vinegar has been used as a source of acetic acid, and this is entirely due to the introduction of highly efficient methods of fractionation.

Acetic acid is a pungent corrosive liquid, m.p. 16·6°, b.p. 118°, miscible in all proportions with water, ethanol and ether (see also p. 176). It is stable towards oxidising agents, and so is a useful solvent for chromium trioxide oxidations. Acetic acid is commonly used as a solvent, and in the preparation of acetates, acetone, acetic anhydride, etc.

Most of the normal acetates are soluble in water, whereas most of the basic acetates are insoluble. Calcium and manganese acetates are used in the preparation of acetone. Lead tetra-acetate is a very useful oxidising agent for 1:2 glycols. Aluminium acetate, which is known only in solution, is used for waterproofing cloth, and as a mordant.

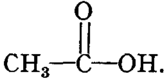
A solution of a neutral acetate gives a red coloration when treated with ferric chloride. The same coloration is also produced by neutral formates, but acetates and formates may be readily distinguished from one another by the fact that the latter are powerful reducing agents.

Structure of acetic acid. Analysis and molecular-weight determinations show that the molecular formula of acetic acid is $C_2H_4O_2$. The presence of a methyl group in acetic acid is indicated by the following considerations:

(i) Treatment of boiling acetic acid with chlorine gives halogen substituted acids. The highest halogenated acid that can be produced is trichloroacetic acid, $C_2HO_2Cl_3$. Of the four hydrogen atoms in the acetic acid molecule, three have been replaced by chlorine and are, therefore, in a different state of combination from the fourth. This suggests that acetic acid contains a methyl group.

(ii) Methyl chloride may be converted into methyl cyanide, which, on hydrolysis, gives acetic acid. Methyl chloride contains a methyl group, and when it is converted into methyl cyanide the chlorine atom is replaced by the cyano-group. Since there is no reason to suppose that the methyl group in methyl chloride is affected by the substitution, it follows that methyl cyanide contains a methyl group. Similarly, since the hydrolysis of a cyanide affects the cyano-group only, when methyl cyanide is hydrolysed to acetic acid, the methyl group remains intact. Thus the above reactions may be formulated:

$$\mathbf{CH_3}\text{—}Cl \xrightarrow{KCN} \mathbf{CH_3}\text{—}CN \xrightarrow{H_2O} \mathbf{CH_3}\text{—}CO_2H$$

When acetic acid is treated with phosphorus pentachloride, acetyl chloride, CH_3—COCl, is formed and hydrogen chloride is evolved. This indicates the presence of a hydroxyl group. Thus acetic acid contains a methyl group and a hydroxyl group. Assuming the quadrivalency of carbon, the bivalency of oxygen and univalency of hydrogen, only one structural formula is possible for acetic acid, *viz.*,  $CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-OH$. The presence of the carbonyl group is supported by the fact that acetyl chloride may be catalytically reduced to acetaldehyde, which has been shown to contain a carbonyl group (p. 167).

Kolbe's synthesis of acetic acid (1845) is interesting in connection with the vital force theory (p. 1). Carbon and sulphur were heated together, and the carbon disulphide produced chlorinated:

$$C + 2S \longrightarrow CS_2$$

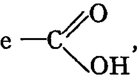
$$CS_2 \xrightarrow{Cl_2} CCl_4$$

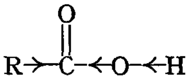
The carbon tetrachloride was then passed through a red-hot tube, whereupon chlorine and tetrachloroethylene were formed and these, on cooling, combined to form hexachloroethane; but in the presence of a little water and under the influence of direct sunlight, some of the tetrachloroethylene was converted into trichloroacetic acid:

$$CCl_2{=}CCl_2 + Cl_2 + 2H_2O \longrightarrow CCl_3{\cdot}CO_2H + 3HCl$$

Treatment of the trichloroacetic acid in aqueous solution with potassium amalgam, or the electrolysis of the aqueous solution of the trichloroacetic acid between electrodes of amalgamated zinc plates, produced acetic acid:

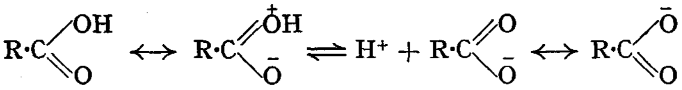
$$CCl_3{\cdot}CO_2H + 6[H] \longrightarrow CH_3{\cdot}CO_2H + 3HCl$$

The structure of the carboxyl group is still not known with certainty. If its structure were , then the acid strength should be greater than that of alcohols, due to the inductive effect of the carbonyl group which tends to facilitate the release of a proton:



$$R \rightarrow \overset{\overset{\displaystyle O}{\|}}{C} \leftarrow O \leftarrow H$$

The acid strength of the fatty acids is greater than that of alcohols, but it seems unlikely that the inductive effect alone would account for the large difference. It has therefore been suggested that the carboxyl group is a resonance hybrid:



Owing to the positive charge on the oxygen atom of the hydroxyl group, the electron pair of the O—H bond is displaced towards the oxygen atom, thereby facilitating the release of a proton. When the proton is released, the two *equivalent* resonating structures contribute to the carboxylate ion formed, and so the resonance energy of the ion will be greater than that of the undissociated acid. Thus the driving force for the dissociation is this tendency to achieve greater stabilisation. Since resonance is not possible in alcohols, proton release is much more difficult than in carboxylic acids.

If acids are resonance hybrids, the C═O bond will have some single-bond character, and its length should therefore be longer than that of a " pure " C═O double bond; similarly, the C—OH bond will have some double-bond character, and should be shorter than a " pure " C—OH single bond. Electron diffraction experiments (Schomaker and O'Gorman, 1947) have shown that the C═O bond length in formic acid monomer is a trifle greater than normal, and that the C—OH bond is considerably less than normal. These results are in keeping with a resonating structure of the carboxyl group.

The treatment of the carboxyl group and the carboxylate ion from the M.O. point of view also leads to the same results as those obtained by the V.B. method, the increased stability now being due to *delocalisation* (*cf.* p. 88). Let us first consider the *undissociated* carboxylic acid (Fig. 1*a*). The carbon atom is linked to the hydroxyl group by a σ-bond, and to the oxygen of the carbonyl group by one σ- and one π-bond. This is shown in (*b*). If the oxygen atom of the hydroxyl group has sp^2 hybridisation, this would leave a *p* orbital perpendicular to the plane of the carboxyl group, and it would contain a pair of electrons (*c*). This orbital could now overlap with both the *p* orbital of the carbon atom and that of the oxygen atom of the carbonyl group. The combination of these three orbitals would give rise to M.O.s embracing *three* nuclei (Fig. *d*). Since *four* electrons are involved, they must be accommodated, in the ground state, in the lowest two M.O.s. The M.O. with the lowest energy level has *one* node (Fig. *e*), and the next energy level has *two* nodes (Fig. *f*). Thus (*g*) represents the ground state of the undissociated carboxyl group. Because of delocalisation, this group has become more stable. Since a hydroxyl group is more electron-attracting than an oxygen atom, the delocalisation of the pair of electrons in the *p* orbital is not very large, *i.e.*, although this lone pair embraces three nuclei, this pair is far more likely to be found in the region of the donor atom than anywhere else. Since the oxygen atom of the hydroxyl group has lost " full-control " of this lone pair, it will acquire a small positive charge, and since the oxygen atom of the CO group has acquired a small share of this lone pair, this oxygen atom acquires a small negative charge (actually this oxygen atom already has a small negative charge due to the inductive effect). The greater electron-attracting power of oxygen in a hydroxyl group over that of an oxygen atom alone is due to the hydrogen atom sharing one pair of electrons in forming the bond, and thereby decreasing, to some extent, the electron density on that oxygen atom.

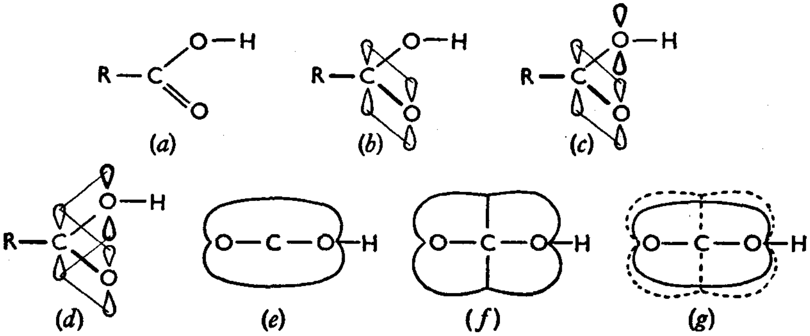


FIG. 9.1.

Now let us consider the *carboxylate ion* (Fig. 2*a*). The oxygen atom of the original hydroxyl group retains the σ-electrons when the hydrogen atom is removed as a proton. As in the case of the *carboxyl group*, one lone pair enters into conjugation with the π-bond of the C═O group (Fig. *b*). In the latter case, however, delocalisation is complete, *i.e.*, the lone pair is now likely to be found equally well on either oxygen atom (each atom will have a charge of $-\frac{1}{2}$). Since delocalisation is complete, the resonance (delocalisation) energy is much greater than in the case of the undissociated carboxyl group.

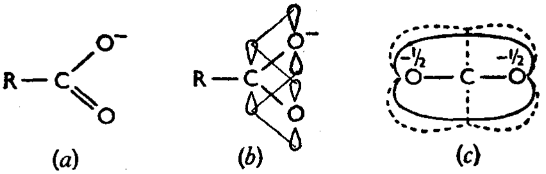
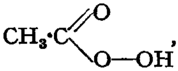
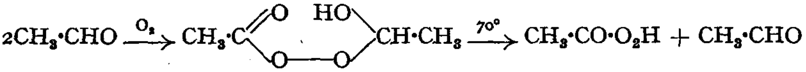


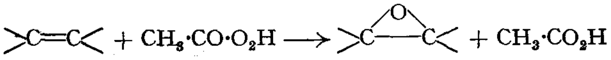
FIG. 9.2.

In Figs. 1 and 2, the orbitals drawn in thicker type indicate that the atoms concerned contain *two* electrons in these orbitals. This scheme has been used throughout the book.

Peracetic acid,  $CH_3{\cdot}C(=O){-}O{-}OH$, may be prepared by treating acetic anhydride with concentrated hydrogen peroxide, and then distilling under reduced pressure. It may also be prepared by adding 90 per cent. hydrogen peroxide to cooled glacial acetic acid in the presence of a small amount of sulphuric acid. Anhydrous peracetic acid may be prepared by autoxidation of acetaldehyde at 0° in the presence of cobaltous ion (Phillips *et al.*, 1957):



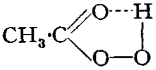
Peracetic acid is an unpleasant-smelling liquid, f.p. +0·1°, soluble in water, ethanol and ether. It explodes violently when heated above 110°. It is a powerful oxidising agent; it oxidises the olefinic bond to the oxide.



It also oxidises primary aromatic amines to nitroso-compounds, *e.g.*, aniline is converted into nitrosobenzene:

$$C_6H_5{\cdot}NH_2 + 2CH_3{\cdot}CO{\cdot}O_2H \longrightarrow C_6H_5{\cdot}NO + 2CH_3{\cdot}CO_2H + H_2O$$

Infrared absorption spectra measurements of per-acids show that these acids exist in solution very largely in the monomeric, intramolecularly hydrogen-bonded form (*inter alia*, Minkoff, 1954).



Propionic acid (*propanoic acid*), $CH_3{\cdot}CH_2{\cdot}CO_2H$, is prepared industrially by the oxidation of *n*-propanol:

$$CH_3{\cdot}CH_2{\cdot}CH_2OH \xrightarrow{[O]} CH_3{\cdot}CH_2{\cdot}CO_2H$$

It is a colourless liquid with an acrid odour, m.p. −22°, b.p. 141°, miscible with water, ethanol and ether in all proportions.

Butyric acids, $C_4H_8O_2$. There are two isomers possible, and both are known.

n-Butyric acid, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, occurs as the glyceryl ester in butter, and as the free acid in perspiration. It is prepared industrially by the oxidation of *n*-butanol, and by the *butyric* fermentation of carbohydrates by means of the micro-organism *Bacillus butyricus*.

n-Butyric acid is a viscous unpleasant-smelling liquid, m.p. −4·7°, b.p. 162°, miscible with water, ethanol and ether. It is the liberation of free *n*-butyric acid that gives stale butter its rancid odour.

***iso*Butyric acid,** $(CH_3)_2CH{\cdot}CO_2H$, occurs in the free state and as its esters in many plants. It is prepared industrially by the oxidation of *iso*butanol:

$$(CH_3)_2CH{\cdot}CH_2OH \xrightarrow{[O]} (CH_3)_2CH{\cdot}CO_2H$$

It may be prepared synthetically as follows:

$$(CH_3)_2CHOH \xrightarrow{PBr_3} (CH_3)_2CHBr \xrightarrow{KCN} (CH_3)_2CH{\cdot}CN \xrightarrow[\text{acid}]{H_2O} (CH_3)_2CH{\cdot}CO_2H$$

*iso*Butyric acid is a liquid, m.p. −47°, b.p. 154°. Its calcium salt is more soluble in hot water than in cold, whereas calcium butyrate is more soluble in cold water than in hot.

Valeric acids, $C_5H_{10}O_2$. There are four isomers possible, and all are known:

***n*-Valeric acid,** $CH_3\cdot CH_2\cdot CH_2\cdot CH_2\cdot CO_2H$, m.p. −34·5°, b.p. 187°.

***iso*Valeric acid,** $(CH_3)_2CH\cdot CH_2\cdot CO_2H$, m.p. −51°, b.p. 175°.

Ethylmethylacetic acid or **active valeric acid,** $CH_3\cdot CH_2\cdot CH(CH_3)\cdot CO_2H$, b.p. 175°.

Trimethylacetic acid or **pivalic acid,** $(CH_3)_3C\cdot CO_2H$, m.p. 35·5°, b.p. 164°.

The higher fatty acids which occur in nature usually have straight chains, and usually contain an *even* number of carbon atoms. **Caproic** (*hexoic*), $C_6H_{12}O_2$ (m.p. −9·5°, b.p. 205°), **caprylic** (*octoic*), $C_8H_{16}O_2$ (m.p. 16°, b.p. 237°), and **capric** (*decoic*) acid, $C_{10}H_{20}O_2$ (m.p. 31·5°, b.p. 270°), are present as glyceryl esters in goats' butter. **Lauric** (*dodecoic*), $C_{12}H_{24}O_2$ (m.p. 44°), and **myristic** (*tetradecoic*) acid, $C_{14}H_{28}O_2$ (m.p. 58°), occur as their glyceryl esters in certain vegetable oils. The most important higher fatty acids are **palmitic** (*hexadecoic*), $C_{16}H_{32}O_2$ (m.p. 64°), and **stearic** (*octadecoic*), $C_{18}H_{36}O_2$ (m.p. 72°), which are very widely distributed as their glyceryl esters (together with oleic acid) in most animal and vegetable oils and fats. The sodium and potassium salts of palmitic and stearic acids are the constituents of ordinary soaps.

Hansen *et al.* (1952, 1956) have shown the presence of branched-chain acids in a number of animal fats, *e.g.*, 13-methyltetradecanoic acid in butter fat, and 14-methylpentadecanoic acid (*iso*palmitic acid) in hydrogenated sheep fat.

Some still higher acids are found in waxes: **arachidic** (*eicosoic*), $C_{20}H_{40}O_2$ (m.p. 77°), **behenic** (*docosoic*), $C_{22}H_{44}O_2$ (m.p. 82°), **lignoceric** (*tetracosoic*), $C_{24}H_{48}O_2$ (m.p. 83·5°), **cerotic** (*hexacosoic*), $C_{26}H_{52}O_2$ (m.p. 87·7°), and **melissic** acid (*triacontoic*), $C_{30}H_{60}O_2$ (m.p. 90°).

The odd fatty acids may be obtained by degrading an even acid (see below). Two odd acids which may be prepared readily are ***n*-heptoic** or **œnanthylic acid,** $C_7H_{14}O_2$ (m.p. −10°, b.p. 223·5°), and **nonoic** or **pelargonic acid,** $C_9H_{18}O_2$ (m.p. 12°, b.p. 254°). *n*-Heptoic acid is prepared by the oxidation of *n*-heptaldehyde, which is obtained by destructively distilling castor oil which contains ricinoleic acid (*q.v.*):

$$CH_3\cdot(CH_2)_5\cdot CHO + [O] \xrightarrow[H_2SO_4]{KMnO_4} CH_3\cdot(CH_2)_5\cdot CO_2H \quad (68\text{–}70\%)$$

Nonoic acid is obtained by the oxidation of oleic acid (*q.v.*).

Margaric acid (heptadecanoic acid), $C_{16}H_{33}\cdot CO_2H$, m.p. 61°, is prepared by heating a mixture of the calcium salts of stearic and acetic acids, and then oxidising the heptadecyl methyl ketone so produced.

$$C_{17}H_{35}\cdot CO_2\mathit{ca} + CH_3\cdot CO_2\mathit{ca} \longrightarrow CaCO_3 + C_{17}H_{35}\cdot CO\cdot CH_3 \xrightarrow{[O]} C_{16}H_{33}\cdot CO_2H$$

Margaric acid has been used as a source of artificial fats for diabetics. Until recently, margaric acid was considered to be a synthetic compound. In 1954, however, Hansen *et al.* isolated *n*-heptadecanoic and *n*-pentadecanoic acids from mutton fat, and *n*-pentadecanoic and *n*-tridecanoic acids from butter fat, and in 1955 showed the presence of *n*-undecanoic acid in butter fat. Hansen *et al.* (1954) have also shown that ox perenephric fat contains the consecutive series of acids C_2 to C_{10}.

ESTERS

Esters are compounds which are formed when the hydroxylic hydrogen atom in oxygen acids is replaced by an alkyl group; the acid may be organic or inorganic. The most important esters are derived from the carboxylic acids. The general formula of the carboxylic esters is $C_nH_{2n}O_2$, which is the same as that of the carboxylic acids. The structural formula of the esters is $\mathrm{R}\overset{/\!\!/\mathrm{O}}{\mathrm{C}}\mathrm{—OR'}$, and they are named as the alkyl salts of the acid, *e.g.*,

$CH_3{\cdot}COOC_2H_5$	ethyl acetate
$(CH_3)_2CH{\cdot}COOCH(CH_3)_2$	*iso*propyl *iso*butyrate

Carboxylic esters are formed by the action of the acid on an alcohol:

$$\text{acid} + \text{alcohol} \rightleftharpoons \text{ester} + \text{water}$$

The reaction is reversible, the *forward* reaction being known as *esterification*, and the *backward* reaction as *hydrolysis*.

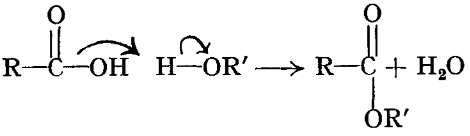
General methods of preparation of the carboxylic esters. 1. The usual method is *esterification*. The reaction is always slow, but is speeded up by the presence of small amounts of inorganic acids as catalysts, *e.g.*, when the acid is refluxed with the alcohol in the presence of 5–10 per cent. concentrated sulphuric acid:

$$R{\cdot}COOH + R'OH \xrightleftharpoons{H_2SO_4} R{\cdot}COOR' + H_2O \quad (v.g.)$$

Alternatively, hydrogen chloride is passed into the mixture of alcohol and acid until there is a 3 per cent. increase in weight, and the mixture is refluxed (the yields are very good). This is known as the *Fischer–Speier method* (1895), and is more satisfactory for secondary and tertiary alcohols than the sulphuric acid method, which tends to dehydrate the alcohol to olefin. Klosa (1956) has shown that phosphoryl chloride is a good catalyst in the esterification of acids with alcohols.

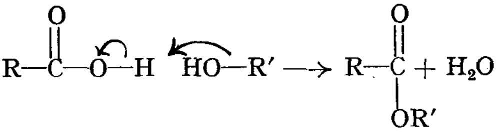
Esterification without the use of catalysts, and starting with one molecule of acid and one molecule of alcohol, gives rise to about $\frac{2}{3}$ molecule of ester. The yield of ester may be increased by using excess acid or alcohol, the cheaper usually being the one in excess. Increased yields may also be effected by dehydrating agents, *e.g.*, concentrated sulphuric acid behaves both as a catalyst and a dehydrating agent. The same effect may be obtained by removing the water or ester from the reaction mixture by distillation, which is particularly useful for high-boiling acids and alcohols. On the other hand, the water may be removed from the reaction mixture by the addition of benzene or carbon tetrachloride, each of which forms a binary mixture with water (and may form a ternary mixture with water and the alcohol), the azeotropic mixtures boiling at a lower temperature than any of the components.

The first point about esterification of a carboxylic acid is that it may be formulated in two ways:



$$R\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}OH \quad H\text{—}OR' \longrightarrow R\text{—}\underset{\underset{\displaystyle OR'}{|}}{\overset{\overset{\displaystyle O}{\|}}{C}} + H_2O$$

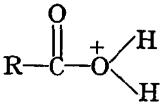
acyl–oxygen heterolysis

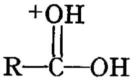


$$R\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}O\text{—}H \quad HO\text{—}R' \longrightarrow R\text{—}\underset{\underset{\displaystyle OR'}{|}}{\overset{\overset{\displaystyle O}{\|}}{C}} + H_2O$$

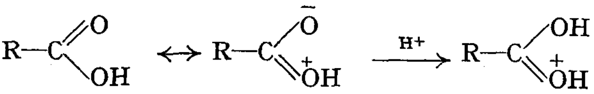
alkyl–oxygen heterolysis

The second point is that esterification is usually carried out in the presence of an acid catalyst (sulphuric or hydrochloric acid), and hence it is the conjugate acid of the carboxylic acid that is the substrate. The structure of this conjugate acid has been formulated in two ways:





Since carboxylic acids are resonance hybrids, it would appear more likely that protonation occurs on the carbonyl oxygen:



This is supported by the work of Fraenkel (1961), who examined the nuclear magnetic resonance spectrum of methyl formate in, *e.g.*, 100 per cent. sulphuric acid, and concluded from his results that the ester is protonated chiefly on the carbonyl oxygen.

Ingold (1941) has introduced the following notation: the letter *A* represents the substrate in the conjugate acid of the carboxylic acid, and the subscripts AO and AL respectively denote *acyl* and *alkyl* bond heterolysis. The numbers 1 and 2 represent the molecularity of the rate-determining step.

So far three different esterification mechanisms have been observed:

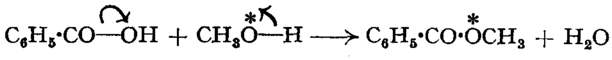
$$A_{\text{AO}}1,\ A_{\text{AO}}2,\ \text{and}\ A_{\text{AL}}1.$$

The most common esterification mechanism is $A_{\text{AO}}2$, *i.e.*, bimolecular acid esterification with acyl–oxygen heterolysis. It has long been known that the rates of hydrolysis of many esters are first-order both in ester and in hydrogen-ion concentration, *i.e.*,

$$\text{rate} \propto [\text{ester}]\,[\text{H}^+]$$

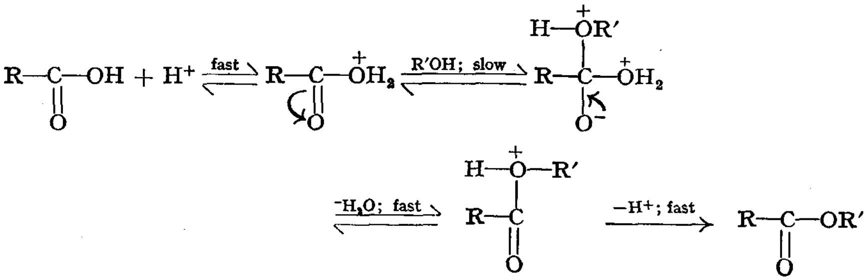
Since acid-catalysed hydrolysis of esters and esterification are the reverse of each other (and reversible), then according to the principle of microscopic reversibility (p. 32), the mechanism of acid-catalysed esterification will be that of acid-catalysed hydrolysis, but in reverse.

Evidence for acyl–oxygen fission in acid-catalysed esterification has been obtained in several ways, *e.g.*, Roberts *et al.* (1938) esterified benzoic acid with methanol enriched with ^{18}O and obtained water *not* enriched with ^{18}O. Therefore the oxygen in the water must have come from the benzoic acid; thus:

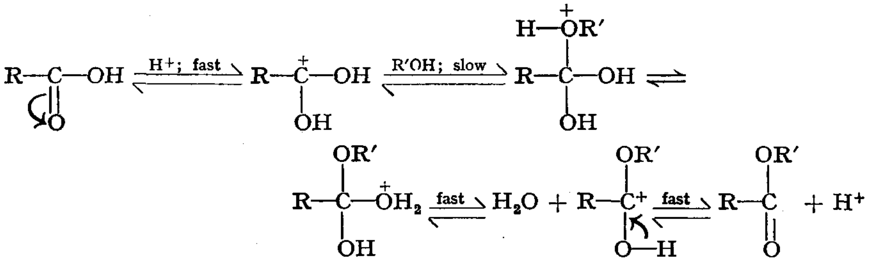


$$C_6H_5\cdot CO-OH + CH_3\overset{*}{O}-H \longrightarrow C_6H_5\cdot CO\cdot\overset{*}{O}CH_3 + H_2O$$

According to Ingold *et al.* (1939), the mechanism is:



However, if we assume that the carbonyl oxygen is protonated, then the mechanism is:

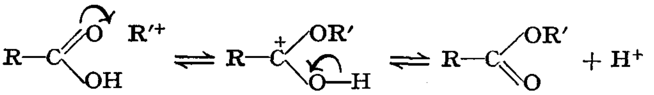


Since, in these mechanisms, the carbon atom which was originally joined to three groups becomes joined to four (hybridisation changes from sp^2 to sp^3), then one might anticipate steric retardation is possible in certain acids. The following results of Newman *et al.* (1952), who examined the relative rates of esterification of various acids with methanol, showed steric retardation was operating: *e.g.*,

Acid:	$MeCO_2H$	*n*-$PrCO_2H$	$Me_3C{\cdot}CO_2H$	$Et_3C{\cdot}CO_2H$
Relative rates:	1	0·51	0·037	0·00016

Now let us consider unimolecular acid-catalysed esterification with alkyl–oxygen heterolysis ($A_{AL}1$ mechanism). Definite evidence for this mechanism was obtained by Hughes, Ingold, *et al.* (1939), who showed that the esterification of acetic acid with optically active octan-2-ol in the presence of sulphuric acid gave a large amount of racemised ester. Thus a carbonium ion is produced which then racemises. The mechanism may therefore be formulated:

$$R'OH \underset{}{\overset{H^+}{\rightleftharpoons}} R'OH_2^+ \overset{slow}{\rightleftharpoons} H_2O + R'^+$$

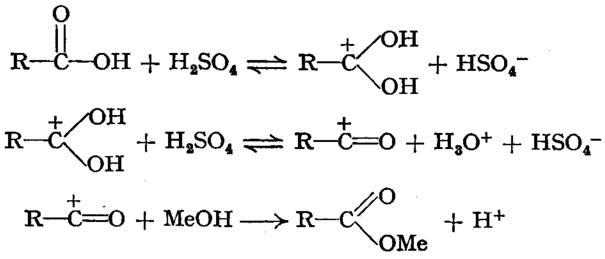


The $A_{AL}1$ mechanism is common for *t*-alcohols, and it is probably this type of mechanism which operates for halogen acids:

$$ROH + HX \rightleftharpoons ROH_2^+ + X^- \rightleftharpoons H_2O + R^+ + X^- \rightleftharpoons RX$$

This is in keeping with the fact that the rate of reaction is *t*-alcohol > *s*- > primary, since this is the order in which the OH group is removed (see p. 129).

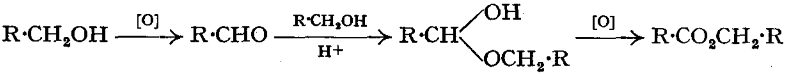
Unimolecular acid-catalysed esterification with acyl-oxygen fission ($A_{AC}1$ mechanism) occurs with highly sterically hindered acids, *e.g.*, mesitoic acid. Hammett *et al.* (1937) showed that when mesitoic acid is dissolved in concentrated sulphuric acid, the van't Hoff factor *i* is 4. When this solution is poured into methanol, methyl mesitoate is formed (Newman, 1941). A mechanism consistent with these facts is that the reaction proceeds via an acylium ion:



Many primary alcohols, on oxidation with chromic acid, form esters in addition to acids, *e.g.*, *n*-butanol gives *n*-butyl *n*-butyrate:

$$2C_3H_7{\cdot}CH_2OH \xrightarrow[H_2SO_4]{Na_2Cr_2O_7} C_3H_7{\cdot}CO_2C_4H_9 \quad (41\text{–}47\%)$$

Several mechanisms have been proposed for this reaction, *e.g.*, the direct esterification of unchanged alcohol with acid formed on oxidation, or hemiacetal formation followed by oxidation to ester. Mosher *et al.* (1953) have obtained evidence for the latter:



$$R{\cdot}CH_2OH \xrightarrow{[O]} R{\cdot}CHO \xrightarrow[H^+]{R{\cdot}CH_2OH} R{\cdot}CH\begin{cases}OH\\ OCH_2{\cdot}R\end{cases} \xrightarrow{[O]} R{\cdot}CO_2CH_2{\cdot}R$$

2. Acid chlorides or anhydrides react rapidly with alcohols to form esters:

$$R{\cdot}COCl + R'OH \longrightarrow R{\cdot}CO_2R' + HCl \qquad (v.g.\text{–}ex.)$$

$$(R{\cdot}CO)_2O + R'OH \longrightarrow R{\cdot}CO_2R' + R{\cdot}CO_2H \quad (v.g.\text{–}ex.)$$

The reaction with tertiary alcohols is very slow, and is often accompanied by the dehydration of the alcohol to olefin. When the acid chloride is used, there is also a tendency for a tertiary alcohol to form a tertiary alkyl chloride (p. 130). Esters of tertiary alcohols may be conveniently prepared by means of a Grignard reagent (see p. 356).

3. Esters may be prepared by refluxing the silver salt of an acid with an alkyl halide in ethanolic solution:

$$R{\cdot}CO_2Ag + R'Br \longrightarrow R{\cdot}CO_2R' + AgBr \quad (v.g.\text{–}ex.)$$

This method is useful where direct esterification is difficult (*cf.* 2 above).

4. Esters are formed when a mixture of the vapours of an acid and an alcohol is passed over a metallic oxide catalyst at 300°.

$$R{\cdot}CO_2H + R'OH \xrightarrow{ThO_2} R{\cdot}CO_2R' + H_2O$$

5. *Methyl* esters are very conveniently prepared by treating an acid with an ethereal solution of diazomethane (*q.v.*):

$$R{\cdot}CO_2H + CH_2N_2 \longrightarrow R{\cdot}CO_2CH_3 + N_2 \quad (ex.)$$

6. Esters are readily obtained when an acid is treated with an olefin in the presence of boron trifluoride as catalyst (Nieuwland *et al.*, 1934):

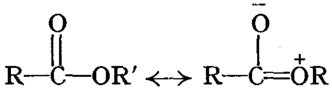
$$R{\cdot}CO_2H + C_2H_4 \xrightarrow{BF_3} R{\cdot}CO_2C_2H_5$$

It has been found that the complex $(CH_3{\cdot}CO_2H)_2{\cdot}BF_3$ is a very efficient catalyst in the preparation of esters from acids and alcohols (Smith *et al.*, 1940). Another example of the use of boron trifluoride as a catalyst in organic chemistry is the formation of esters by the interaction between an ether and carbon monoxide at 125–180°, under 500 atmospheres pressure, in the presence of boron trifluoride plus a little water:

$$R_2O + CO \longrightarrow R{\cdot}CO_2R$$

General properties of the esters. The carboxylic esters are pleasant-smelling liquids or solids. The boiling points of the straight-chain isomers are higher than those of the branched-chain isomers. The boiling points of the methyl and ethyl esters are lower than those of the corresponding acid, and this is probably due to the fact that the esters are not associated since they cannot form intermolecular hydrogen bonds. The esters of low molecular weight are fairly soluble in water—hydrogen bonding between ester and water is possible—and the solubility decreases as the series is ascended; all esters are soluble in most organic solvents.

The structure of the esters is usually written as $R\text{—}\overset{\overset{O}{\|}}{C}\text{—}OR'$, but, as in the case of the acids from which they are derived, there is a certain amount of evidence to show that esters are resonance hybrids (or conjugated, p. 184):



$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}OR' \longleftrightarrow R\text{—}\overset{\overset{\bar{O}}{|}}{C}\text{=}\overset{+}{O}R$$

General reactions of the esters. 1. Esters are hydrolysed by acids or alkalis:

$$R{\cdot}CO_2R' + H_2O \xrightarrow{\text{acid}} R{\cdot}CO_2H + R'OH$$
$$R{\cdot}CO_2R' + NaOH \longrightarrow R{\cdot}CO_2Na + R'OH$$

When hydrolysis is carried out with alkali, the salt of the acid is obtained, and since the alkali salts of the higher acids are soaps, alkaline hydrolysis is known as *saponification* (derived from Latin word meaning soap); saponification is far more rapid than acid hydrolysis.

Hydrolysis of secondary and particularly tertiary halides is accompanied by the formation of olefin (p. 108). In many cases a better yield of alcohol can be obtained by first converting the alkyl halide into the acetate ester by heating with silver acetate in ethanolic solution, and then saponifying the acetate ester:

$$CH_3{\cdot}CO_2Ag + RX \longrightarrow CH_3{\cdot}CO_2R \xrightarrow{NaOH} CH_3{\cdot}CO_2Na + ROH$$

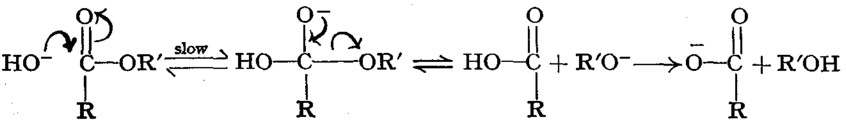
Under the above conditions, secondary and tertiary halides show far less tendency to form olefin than when hydrolysed directly by alkali.

In the case of hydrolysis of esters, not only can we have acid-catalysed reactions (as for esterification), but hydrolysis may be effected in alkaline solution (*i.e.*, saponification). Hydrolysis may also be effected in neutral solution, but since this is slow, it is not used. Using the symbols A, $_{AC}$, $_{AL}$, 1, and 2 as for esterification (p. 188) for the protonated ester (in *acid* solution), and using B for the unprotonated ester (in *alkaline* or *neutral* solution), then there are eight possible mechanisms ($B_{AC}1$, $B_{AC}2$, $B_{AL}1$, $B_{AL}2$; $A_{AC}1$, $A_{AC}2$, $A_{AL}1$, $A_{AL}2$). All except two, the first and last, have been observed.

The $B_{AC}2$ mechanism is a common one. Alkaline hydrolysis of esters has long been known to be a second-order reaction, *i.e.*, rate ∝ [ester][OH⁻]. Evidence for acyl–oxygen fission has been obtained in several ways, *e.g.*, Polanyi *et al.* (1934) showed that the alkaline hydrolysis of *n*-pentyl acetate in water enriched with ^{18}O gave *n*-pentyl alcohol containing *no* ^{18}O. Therefore acyl–oxygen fission must have occurred:

$$CH_3{\cdot}CO\overset{\curvearrowright}{\text{—}}OC_5H_{11} + \overset{*}{O}H^- \longrightarrow CH_3{\cdot}CO\overset{*}{O}H + C_5H_{11}O^- \xrightarrow{H_2O} C_5H_{11}OH$$

If the alcohol group R′ is optically active, then if acyl–oxygen fission occurs, the ion R′O⁻ will be liberated and will *retain* its optical activity, since the bond R′—O is never broken. Various examples of retention are known when the reaction is bimolecular. A mechanism consistent with these facts is:

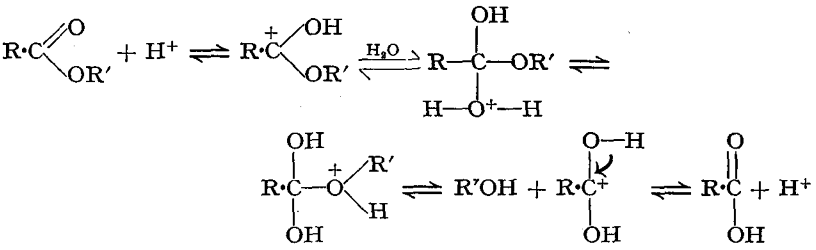


$$HO^- + \underset{\underset{R}{|}}{\overset{\overset{O}{\|}}{C}}\text{—}OR' \underset{}{\overset{\text{slow}}{\rightleftharpoons}} HO\text{—}\underset{\underset{R}{|}}{\overset{\overset{O^-}{|}}{C}}\text{—}OR' \rightleftharpoons HO\text{—}\underset{\underset{R}{|}}{\overset{\overset{O}{\|}}{C}} + R'O^- \longrightarrow \bar{O}\text{—}\underset{\underset{R}{|}}{\overset{\overset{O}{\|}}{C}} + R'OH$$

The $A_{AC}2$ mechanism is also a common one for the hydrolysis of esters; this is the reverse of the $A_{AC}2$ mechanism for esterification (p. 188). The order has been shown to be first in both ester and hydrogen-ion concentration, and evidence for acyl–oxygen heterolysis has been demonstrated in several ways, *e.g.*, Ingold *et al.* (1939) showed that the acid-catalysed hydrolysis of methyl hydrogen succinate in water enriched with ^{18}O gave methanol with *no* extra ^{18}O; therefore acyl–oxygen fission must have occurred:

$$HO_2C\cdot CH_2\cdot CH_2\cdot CO\overset{\curvearrowright}{-}OMe + H_2\overset{*}{O} \longrightarrow HO_2C\cdot CH_2\cdot CH_2\cdot CO\overset{*}{O}H + MeOH$$

A mechanism consistent with the facts is:



Ingold's mechanism is the reverse of the one given for esterification on p. 188.

The $A_{AL}1$ mechanism for the acid-catalysed hydrolysis of esters is the reverse of that for the $A_{AL}1$ mechanism for acid-catalysed esterification (p. 189). Evidence for alkyl–oxygen fission has been provided by, *e.g.*, Bunton *et al.* (1951), who hydrolysed *t*-butyl acetate with water enriched with ^{18}O and obtained *t*-butanol containing ^{18}O.

$$MeCO\cdot O\overset{\curvearrowleft}{-}Bu^t + H_2\overset{*}{O} \longrightarrow MeCO_2H + Bu^t\overset{*}{O}H$$

The $A_{AC}1$ mechanism for the acid-catalysed hydrolysis of esters is the reverse of that for esterification (p. 189).

The $B_{AL}1$ mechanism for the base-catalysed hydrolysis of esters has been shown to occur when the alkyl group of the alcohol is strongly electron-releasing, the solvent has a high dipole moment, and the hydroxide-ion concentration is very low. The mechanism is:

$$R\cdot CO\cdot O\overset{\curvearrowleft}{-}R' \rightleftharpoons R\cdot CO_2^- + R'^+$$
$$R'^+ + H_2O \rightleftharpoons R'OH_2^+$$
$$R\cdot CO_2^- + R'OH_2^+ \longrightarrow R'OH + R\cdot CO_2H$$

E.g., Kenyon *et al.* (1936) showed that the $B_{AL}1$ mechanism was operating when optically active 1-phenylethyl hydrogen phthalate was hydrolysed in faintly alkaline solution. The alcohol obtained, $C_6H_5\cdot CHOH\cdot CH_3$, was racemised, and this is in keeping with the intermediate formation of a carbonium ion.

The $B_{AL}2$ mechanism for the base-catalysed hydrolysis of esters is rare. Bunnett *et al.* (1951) have shown that dimethyl ether is formed when methyl benzoate is treated with methanolic sodium methoxide:

$$\overset{\curvearrowright}{MeO^-}\ Me\overset{\curvearrowright}{-}O\cdot CO\cdot C_6H_5 \longrightarrow Me_2O + C_6H_5\cdot CO_2^-$$

2. Esters are converted into alcohols by the Bouveault–Blanc reduction:

$$R\cdot CO_2R' + 4[H] \xrightarrow{C_2H_5OH/Na} R\cdot CH_2OH + R'OH \quad (g.)$$

The yield of alcohol from the acid portion of the ester increases with the molecular weight of the alkyl radical R′, *e.g.*, the amyl ester gives a higher yield of alcohol R·CH₂OH than does the ethyl ester. Esters which are difficult to reduce at the boiling point of ethanol are usually satisfactorily reduced in *n*-butanol, which has a higher boiling point than ethanol, and so permits the reduction to be carried out at a higher temperature. Lithium aluminium hydride also reduces esters to alcohols.

Esters may also be reduced by molecular hydrogen at 100–300 atmospheres in the presence of a copper chromite catalyst at 200–300° (the yields are almost quantitative).

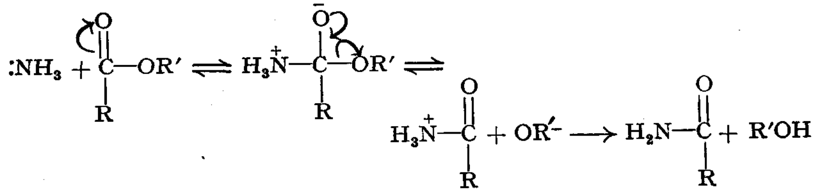
The formation of esters affords a convenient method of converting an acid into its corresponding alcohol, and stepping up the acid series:

$$R{\cdot}CO_2H \xrightarrow{R'OH} R{\cdot}CO_2R' \xrightarrow{[H]} R{\cdot}CH_2OH \xrightarrow{PBr_3} R{\cdot}CH_2Br \xrightarrow{KCN} R{\cdot}CH_2{\cdot}CN \xrightarrow[\text{acid}]{H_2O} R{\cdot}CH_2{\cdot}CO_2H$$

3. Esters react with ammonia to form amides. This reaction is an example of *ammonolysis* (which means, literally, splitting by ammonia):

$$R{\cdot}COOR' + NH_3 \longrightarrow R{\cdot}CO{\cdot}NH_2 + R'OH \quad (g.)$$

A possible mechanism for this reaction is:



With hydrazine, esters form acid hydrazides:

$$R{\cdot}COOR' + H_2N{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH_2 + R'OH$$

4. By means of *alcoholysis* (splitting by alcohol), an alcohol residue in an ester can be replaced by another alcohol residue. Alcoholysis is carried out by refluxing the ester with a large excess of alcohol, preferably in the presence of a small amount of acid or sodium alkoxide as catalyst. Alcoholysis is usually effective in replacing a higher alcohol by a lower one, *e.g.*,

$$CH_3{\cdot}CO_2C_4H_9 + C_2H_5OH \xrightleftharpoons{C_2H_5ONa} CH_3{\cdot}CO_2C_2H_5 + C_4H_9OH$$

Alcoholysis of esters is known as *transesterification*.

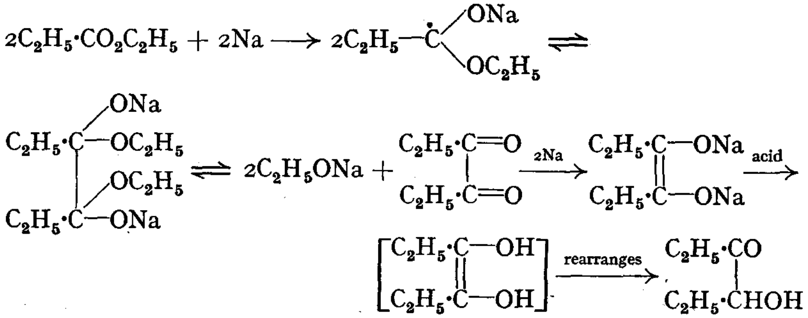
In *acidolysis*, the acid residue is displaced from its ester by another acid residue, *e.g.*,

$$CH_3{\cdot}CO_2C_2H_5 + C_5H_{11}{\cdot}CO_2H \rightleftharpoons C_5H_{11}{\cdot}CO_2C_2H_5 + CH_3{\cdot}CO_2H$$

Acidolysis is a useful reaction for converting the neutral ester of a dibasic acid into its acid ester.

5. When an ester—preferably the methyl or ethyl ester—is treated with sodium in an inert solvent, *e.g.*, ether, benzene or toluene, and subsequently with acid, an **acyloin** is formed (50–70 per cent. yield). It is important that the reaction be carried out *in the absence of any free alcohol.* Acyloins are *αβ-keto-alcohols*, and the mechanism of their formation is obscure.

According to Kharasch and his co-workers (1939), the formation of acyloins takes place via a free-radical mechanism, *e.g.*, propionin from ethyl propionate:



$$2C_2H_5\cdot CO_2C_2H_5 + 2Na \longrightarrow 2C_2H_5-\dot{C}\begin{matrix}\diagup ONa\\ \diagdown OC_2H_5\end{matrix} \rightleftharpoons$$

$$\begin{array}{l} \quad\diagup ONa \\ C_2H_5\cdot C-OC_2H_5 \\ \quad | \diagup OC_2H_5 \\ C_2H_5\cdot C-ONa \end{array} \rightleftharpoons 2C_2H_5ONa + \begin{array}{l} C_2H_5\cdot C=O \\ \quad | \\ C_2H_5\cdot C=O \end{array} \xrightarrow{2Na} \begin{array}{l} C_2H_5\cdot C-ONa \\ \quad \| \\ C_2H_5\cdot C-ONa \end{array} \xrightarrow{acid}$$

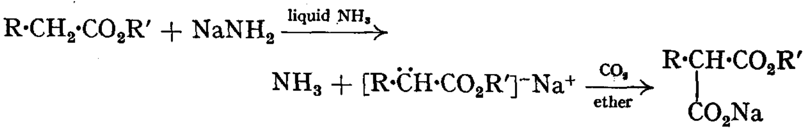
$$\left[\begin{array}{l} C_2H_5\cdot C-OH \\ \quad \| \\ C_2H_5\cdot C-OH \end{array}\right] \xrightarrow{rearranges} \begin{array}{l} C_2H_5\cdot CO \\ \quad | \\ C_2H_5\cdot CHOH \end{array}$$

6. Carboxylic esters which contain α-hydrogen atoms react with sodamide in liquid ammonia solution to form the acid amide and a condensation product involving two molecules of the ester, *e.g.*, ethyl acetate gives acetamide and acetoacetic ester (see also p. 224):

$$CH_3\cdot CO_2C_2H_5 + NaNH_2 \longrightarrow CH_3\cdot CO\cdot NH_2 + C_2H_5ONa$$

$$CH_3\cdot CO_2C_2H_5 + NaNH_2 \longrightarrow NH_3 + [\ddot{C}H_2\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{CH_3\cdot CO_2C_2H_5} CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + C_2H_5OH$$

Of particular interest is the *carbonation* of esters, *i.e.*, the introduction of the carboxyl group. The ester is treated with sodamide in liquid ammonia solution, the solvent is evaporated off, ether is added, and then solid carbon dioxide:

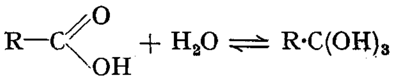


$$R\cdot CH_2\cdot CO_2R' + NaNH_2 \xrightarrow{liquid\ NH_3} NH_3 + [R\cdot\ddot{C}H\cdot CO_2R']^-Na^+ \xrightarrow[ether]{CO_2} \begin{array}{l} R\cdot CH\cdot CO_2R' \\ \quad | \\ \quad CO_2Na \end{array}$$

The yields of these *malonic acid derivatives* are 54–60 per cent. with acetates, and become progressively lower as the molecular weight of the acid increases.

Esters are used as solvents for cellulose, oils, gums, resins, etc., and as plasticisers. They are also used for making artificial flavours and essences, *e.g.*, *iso*amyl acetate—banana oil; amyl butyrate—apricot; *iso*amyl *iso*valerate—apple; methyl butyrate—pineapple; etc.

Ortho-esters are compounds of the type $R\cdot C(OR')_3$. They are derived from the ortho-acids, $R\cdot C(OH)_3$, which have not yet been isolated, but which are possibly present in aqueous solution (*cf.* ethylidene glycol, p. 168):

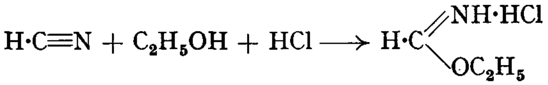


$$R-C\begin{matrix}\diagup\!\!\diagup O\\ \diagdown OH\end{matrix} + H_2O \rightleftharpoons R\cdot C(OH)_3$$

The most important ortho-esters are the orthoformic esters, particularly ethyl orthoformate. Ethyl orthoformate may be prepared by running ethanol and chloroform into sodium covered with ether:

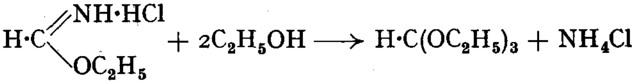
$$2CHCl_3 + 6C_2H_5OH + 6Na \longrightarrow 2H\cdot C(OC_2H_5)_3 + 6NaCl + 3H_2 \quad (70\%)$$

Another method is to pass dry hydrogen chloride into a solution of hydrogen cyanide and ethanol in ether:



$$H{\cdot}C{\equiv}N + C_2H_5OH + HCl \longrightarrow H{\cdot}C\begin{matrix}\nearrow NH{\cdot}HCl \\ \searrow OC_2H_5\end{matrix}$$

The formidic ester hydrochloride is then allowed to stand in ethanol, whereupon ethyl orthoformate is produced:



$$H{\cdot}C\begin{matrix}\nearrow NH{\cdot}HCl \\ \searrow OC_2H_5\end{matrix} + 2C_2H_5OH \longrightarrow H{\cdot}C(OC_2H_5)_3 + NH_4Cl$$

Ethyl orthoformate may be used for preparing ketals (p. 163), and for preparing aldehydes by means of a Grignard reagent (p. 355).

Esters of the Inorganic Acids

Alkyl halides, which can be prepared by the action of a halogen acid on an alcohol, may be regarded as esters, but are exceptional in that they do not contain oxygen.

Alkyl sulphates, $(RO)_2SO_2$. Only methanol and ethanol give a good yield of the alkyl sulphate by reaction with concentrated sulphuric acid; the higher alcohols give mainly olefins and ethers. On the other hand, all the alcohols give a fair yield of alkyl hydrogen sulphate when a mixture of alcohol and concentrated sulphuric acid is heated on a steam bath.

According to Barkenbus and Owen (1934), the most useful method for preparing alkyl sulphates is by the action of an alkyl chlorosulphonate on an alkyl sulphite:

$$(RO)_2SO + ClSO_2{\cdot}OR \longrightarrow (RO)_2SO_2 + HCl + SO_2 + R'{\cdot}CH{=}CH_2$$
$$(RO)_2SO + ClSO_2{\cdot}OR \longrightarrow (RO)_2SO_2 + SO_2 + RCl$$

Methyl sulphate may be prepared:

(i) By heating methyl iodide with silver sulphate:

$$2CH_3I + Ag_2SO_4 \longrightarrow (CH_3)_2SO_4 + 2AgI$$

(ii) By heating methanol with concentrated sulphuric acid, and then distilling the methyl hydrogen sulphate under reduced pressure:

$$CH_3OH + H_2SO_4 \longrightarrow CH_3HSO_4 + H_2O$$
$$2CH_3HSO_4 \longrightarrow (CH_3)_2SO_4 + H_2SO_4$$

(iii) By treating methanol with sulphur trioxide at low temperatures:

$$2SO_3 + 2CH_3OH \longrightarrow (CH_3)_2SO_4 + H_2SO_4$$

(ii) and (iii) are industrial methods.

Ethyl sulphate may be prepared by the same methods as methyl sulphate, but in addition, there is the industrial preparation by passing ethylene in excess into cold concentrated sulphuric acid:

$$2C_2H_4 + H_2SO_4 \longrightarrow (C_2H_5)_2SO_4$$

Methyl sulphate, b.p. 188°, and ethyl sulphate, b.p. 208°, are heavy poisonous liquids. They are largely used as alkylating agents since the alkyl group will replace the hydrogen atom of the groups —OH, ·NH· or —SH. The alkylation may be carried out by treating the compound with the alkyl sulphate in sodium hydroxide solution. Usually only one of the alkyl groups takes part in the reaction, *e.g.*, methylation of a primary amine:

$$R{\cdot}NH_2 + (CH_3)_2SO_4 + NaOH \longrightarrow R{\cdot}NH{\cdot}CH_3 + CH_3NaSO_4 + H_2O$$

The methyl and ethyl esters of the carboxylic acids may be conveniently prepared by treating the sodium salt of the acid with respectively methyl or ethyl sulphate:

$$R{\cdot}CO_2Na + (C_2H_5)_2SO_4 \longrightarrow R{\cdot}CO_2C_2H_5 + C_2H_5NaSO_4$$

The sodium alkyl sulphates of the higher alcohols are used as detergents, *e.g.*, sodium lauryl sulphate:

Alkyl nitrates, $R{\cdot}O{\cdot}NO_2$. The only important alkyl nitrate is ethyl nitrate, $C_2H_5{\cdot}O{\cdot}NO_2$. This may be prepared by heating ethyl iodide with silver nitrate in ethanolic solution:

$$C_2H_5I + AgNO_3 \longrightarrow C_2H_5{\cdot}O{\cdot}NO_2 + AgI$$

When concentrated nitric acid is added to ethanol, the reaction is usually violent; part of the ethanol is oxidised, and some of the nitric acid is reduced to nitrous acid. Apparently it is the presence of the nitrous acid which produces the violent oxidation of the alcohol by the nitric acid. This danger may be avoided by first boiling the nitric acid with urea, which destroys any nitrous acid present, and then adding this mixture to cool ethanol, any nitrous acid produced being immediately destroyed by the urea:

$$CO(NH_2)_2 + 2HNO_2 \longrightarrow CO_2 + 2N_2 + 3H_2O$$

Ethyl nitrate is a pleasant-smelling liquid, b.p. 87·5°. When reduced with tin and hydrochloric acid, it forms hydroxylamine and ethanol:

$$C_2H_5{\cdot}O{\cdot}NO_2 + 6[H] \xrightarrow{Sn/HCl} C_2H_5OH + NH_2{\cdot}OH + H_2O$$

Alkyl nitrites, $R{\cdot}O{\cdot}NO$. Alkyl nitrites are isomeric with the nitroparaffins (p. 301). The only important alkyl nitrites are the ethyl and amyl nitrites; the latter is actually mainly *iso*amyl nitrite, since the amyl alcohol used is the *iso*pentanol from fusel oil (p. 135). Ethyl and amyl nitrites are prepared by adding, concentrated hydrochloric acid or sulphuric acid to aqueous sodium nitrite and the alcohol, *e.g.*,

$$C_5H_{11}OH + HNO_2 \longrightarrow C_5H_{11}{\cdot}O{\cdot}NO + H_2O \quad (75\text{–}85\%)$$

Ethyl nitrite, b.p. 17°, and amyl nitrite, b.p. 99°, are pleasant-smelling liquids, and are used as a means of preparing nitrous acid in anhydrous media; *e.g.*, an ethanolic solution of nitrous acid may be prepared by passing dry hydrogen chloride into amyl nitrite dissolved in ethanol.

Trialkyl phosphates, $(RO)_3PO$, may be prepared by refluxing an alcohol with phosphoryl chloride in the presence of pyridine:

$$3ROH + POCl_3 + 3C_5H_5N \longrightarrow (RO)_3PO + 3C_5H_5N{\cdot}HCl \quad (g.)$$

Triethyl phosphate, tributyl phosphate and tricresyl phosphate are widely used as plasticisers.

Trialkyl borates, $(RO)_3B$, may be prepared by fractionally distilling a mixture of an alcohol and boric acid (Thomas, 1946):

$$3ROH + H_3BO_3 \longrightarrow (RO)_3B + 3H_2O \quad (ex.)$$

Trialkyl borates may be conveniently prepared in good yield by transesterification (alcoholysis) of methyl borate (which is readily available) with the appropriate alcohol (Brown *et al.*, 1956).

$$4(CH_3O)_3B + 3ROH \longrightarrow (RO)_3B + 3[CH_3OH,(CH_3O)_3B].$$

These authors have also shown that the following reaction readily occurs with primary and secondary alcohols:

$$3ROH + NaBH_4 + CH_3{\cdot}CO_2H \longrightarrow (RO)_3B + CH_3{\cdot}CO_2Na + 4H_2 .$$

With tertiary alcohols the reaction is:

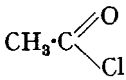
$$2ROH + NaBH_4 + CH_3{\cdot}CO_2H \longrightarrow (RO)_2BH + CH_3{\cdot}CO_2Na + 3H_2$$

Tributyl borate is mainly used as a plasticiser.

ACID OR ACYL CHLORIDES

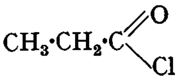
The general formula of the *acyl* radicals is $R{-}\overset{\diagup\!\!\diagup O}{C}{-}$. Acid chlorides, which may be prepared by the replacement of the hydroxyl in the carboxyl group by chlorine, are also known as *acyl chlorides* because they contain the acyl radical. Their general formula may therefore be written $R{-}C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown Cl\end{array}$.

Nomenclature. According to the I.U.P.A.C. system the class suffix of the acyl chlorides is *-oyl*, and the names may be illustrated by the following examples:



$$CH_3{\cdot}C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown Cl\end{array}$$

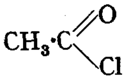
ethanoyl chloride



$$CH_3{\cdot}CH_2{\cdot}C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown Cl\end{array}$$

propanoyl chloride

This system is rarely used for naming the acyl chlorides. The more common names are formed by changing the suffix *-ic* of the *trivial* name of the acid into *-yl*, *e.g.*,



$$CH_3{\cdot}C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown Cl\end{array}$$

acetyl chloride

$(CH_3)_2CH{\cdot}COCl$

*iso*butyryl chloride

If the carboxyl group is considered as a substituent, then according to the I.U.P.A.C. system, the nomenclature of all substances containing acyl radicals is in all cases based on the name "carbonyl" for the CO group, *e.g.*,

$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}COCl$ propane-1-carbonyl chloride

When naming amides (see below), the "yl" is elided before the suffix amide, *e.g.*,

$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CONH_2$ propane-1-carbonamide

General methods of preparation. 1. The acid is heated with phosphorus trichloride or pentachloride, *e.g.*,

$$3R{\cdot}COOH + PCl_3 \longrightarrow 3R{\cdot}COCl + H_3PO_3 \qquad (g.)$$
$$R{\cdot}COOH + PCl_5 \longrightarrow R{\cdot}COCl + HCl + POCl_3 \qquad (v.g.)$$

The reaction with phosphorus trichloride is accompanied by the formation of small amounts of volatile phosphorus compounds, *e.g.*,

$$R\cdot CO_2H + PCl_3 \longrightarrow R\cdot CO_2PCl_2 + HCl$$

In some cases the acid anhydride is also formed due to the following reaction:

$$R\cdot CO_2H + R\cdot COCl \rightleftharpoons (R\cdot CO)_2O + HCl$$

Thionyl chloride may be used instead of the phosphorus chlorides:

$$R\cdot CO_2H + SOCl_2 \longrightarrow R\cdot COCl + SO_2 + HCl \quad (v.g.)$$

The inorganic chloride is chosen according to the boiling point of the acyl chloride formed. Phosphorous acid decomposes at 200°; the boiling point of phosphoryl chloride is 107°, and that of thionyl chloride is 76°. Since acetyl chloride boils at 52°, any of the three inorganic halides may be used, but it is difficult to separate acetyl chloride from thionyl chloride (which is generally used in excess) by fractionation. *n*-Butyryl chloride boils at 102°, and so phosphorus pentachloride cannot be used. Usually thionyl chloride is the most convenient, but although it may be used with all the monocarboxylic acids, it is not satisfactory for all dicarboxylic acids (p. 377).

2. By distilling the salt of the acid with either phosphorus trichloride, phosphoryl chloride or sulphuryl chloride, *e.g.*,

$$3CH_3\cdot CO_2Na + PCl_3 \longrightarrow 3CH_3\cdot COCl + Na_3PO_3$$
$$2CH_3\cdot CO_2Na + POCl_3 \longrightarrow 2CH_3\cdot COCl + NaCl + NaPO_3$$
$$(CH_3\cdot CO_2)_2Ca + SO_2Cl_2 \longrightarrow 2CH_3\cdot COCl + CaSO_4$$

This method is used industrially since the salts are cheaper than the acid.

Acyl bromides may be prepared by the action of phosphorus tribromide or pentabromide (red phosphorus and bromine) on the acid, or by the action of excess hydrogen bromide on the acyl chloride:

$$R\cdot COCl + HBr \longrightarrow R\cdot COBr + HCl$$

Acyl iodides are prepared in the same way as the bromides. *Acyl fluorides* are also known, and may be prepared by the action of hydrogen fluoride on acid anhydrides:

$$(R\cdot CO)_2O + HF \longrightarrow R\cdot COF + R\cdot CO_2H$$

General properties and reactions of the acyl chlorides. The lower acyl chlorides are colourless liquids with irritating odours; the higher members are colourless solids. The chlorine atom is very reactive and so the acid chlorides are important reagents.

1. The acyl chlorides are readily hydrolysed by water, the lower members reacting vigorously:

$$R\cdot COCl + H_2O \longrightarrow R\cdot CO_2H + HCl$$

Acyl chlorides usually react rapidly with compounds containing " active " hydrogen atoms, *i.e.*, hydrogen attached to oxygen, nitrogen or sulphur; *e.g.*, esters are formed with alcohols:

$$R\cdot COCl + R'OH \longrightarrow R\cdot COOR' + HCl$$

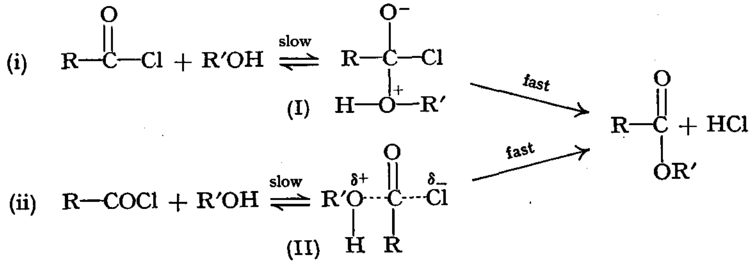
Amides are formed with ammonia, and *N*-substituted amides with primary and secondary amines:

$$R\cdot COCl + 2NH_3 \longrightarrow R\cdot CO\cdot NH_2 + NH_4Cl$$
$$R\cdot COCl + R'\cdot NH_2 \longrightarrow R\cdot CO\cdot NH\cdot R' + HCl$$

Hydrazides are formed with hydrazine, and hydroxamic acids with hydroxylamine:

$$R{\cdot}COCl + H_2N{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH_2 + HCl$$
$$R{\cdot}COCl + NH_2{\cdot}OH \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}OH + HCl$$

The mechanisms of all of these reactions are uncertain. Alcoholysis of acid chlorides has been studied in some detail, and some mechanisms that have been suggested are (i) and (ii), which differ in the nature of the intermediate (I) and the transition state (II).

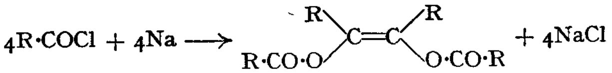


According to Hudson *et al.* (1955), the transition state is best represented as intermediate between (I) and (II), and is stabilised by solvation. It is possible that the other reactions—hydrolysis, ammonolysis, etc.—follow similar paths.

2. Acyl chlorides may be reduced catalytically to aldehydes or to alcohols:

$$R{\cdot}COCl \xrightarrow[Pd]{H_2} R{\cdot}CHO \xrightarrow{H_2} R{\cdot}CH_2OH$$

Acid chlorides are reduced to esters of an enediol by sodium amalgam in an inert solvent, *e.g.*, ether (*cf.* esters, p. 194):



$$4R{\cdot}COCl + 4Na \longrightarrow (R{\cdot}CO{\cdot}O)RC{=}CR(O{\cdot}CO{\cdot}R) + 4NaCl$$

Under suitable conditions, small yields of α-diketones have been obtained. Acid chlorides are reduced to alcohols by lithium aluminium hydride or sodium borohydride, and to aldehydes by lithium hydride or lithium tri-*t*-butoxyaluminium hydride (p. 148).

3. Acyl chlorides react with the sodium salt of the fatty acids to form *acid anhydrides* (*q.v.*):

$$R{\cdot}COCl + R'{\cdot}COONa \longrightarrow R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R' + NaCl$$

4. Acyl chlorides may be used in the Friedel–Crafts reaction to produce an aromatic ketone; *e.g.*, acetyl chloride reacts with benzene in the presence of anhydrous aluminium chloride to form acetophenone:

$$C_6H_6 + CH_3{\cdot}COCl \xrightarrow{AlCl_3} C_6H_5{\cdot}CO{\cdot}CH_3 + HCl$$

5. Acyl chlorides react with Grignard reagents to produce ketones or tertiary alcohols, according to the conditions (see p. 355); *e.g.*, acetyl chloride forms butanone with ethylmagnesium iodide:

$$CH_3{\cdot}COCl + C_2H_5{\cdot}Mg{\cdot}I \longrightarrow CH_3{\cdot}CO{\cdot}C_2H_5 + Mg{\cdot}ClI$$

6. Acyl chlorides react with carboxylic acids as follows:

$$R{\cdot}COCl + R'{\cdot}CO_2H \rightleftharpoons R{\cdot}CO_2H + R'{\cdot}COCl$$

If the acyl chloride, $R'\cdot COCl$, has the lowest boiling point, and the apparatus is arranged so as to allow only this to distil, all of $R\cdot COCl$ will be converted into $R'\cdot COCl$. This reaction may therefore be used to prepare a volatile acyl chloride.

A small amount of acid anhydride is formed as a by-product, due to the reaction:

$$R\cdot COCl + R'\cdot CO_2H \rightleftharpoons R\cdot CO\cdot O\cdot CO\cdot R' + HCl$$

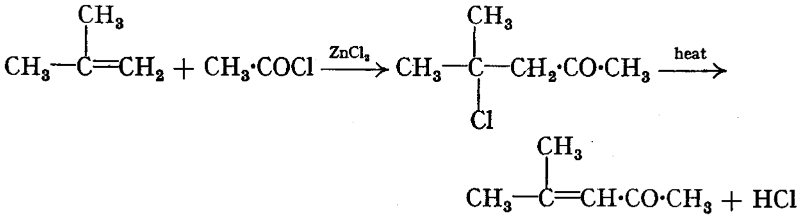
There will also be present the anhydrides $(R\cdot CO)_2O$ and $(R'\cdot CO)_2O$.

7. Acyl chlorides are readily halogenated in the α-position (see p. 210).

8. Acyl chlorides form esters (and other products) when heated with an ether in the presence of anhydrous zinc chloride as catalyst:

$$R\cdot COCl + R'_2O \xrightarrow{ZnCl_2} R\cdot CO_2R' + R'Cl$$

9. Acyl chlorides add on to the double bond of an olefin in the presence of a catalyst, *e.g.*, zinc chloride or aluminium chloride, to form a chloroketone which, on heating, eliminates a molecule of hydrogen chloride to form an unsaturated ketone:



$$CH_3-\overset{CH_3}{\overset{|}{C}}=CH_2 + CH_3\cdot COCl \xrightarrow{ZnCl_2} CH_3-\underset{\underset{Cl}{|}}{\overset{CH_3}{\overset{|}{C}}}-CH_2\cdot CO\cdot CH_3 \xrightarrow{heat}$$

$$CH_3-\overset{CH_3}{\overset{|}{C}}=CH\cdot CO\cdot CH_3 + HCl$$

Formyl chloride, $H\cdot COCl$, and **formyl fluoride,** $H\cdot COF$, are said to exist at low temperatures (—80°). There is no evidence of their existence at ordinary temperature, but a mixture of carbon monoxide and hydrogen chloride behaves as if it were formyl chloride in the Gattermann–Koch aldehyde synthesis (p. 646).

Acetyl chloride, $CH_3\cdot COCl$, is the most important acyl halide. It is a colourless fuming liquid, b.p. 52°, and is soluble in ether and chloroform. It is largely used as an *acetylating* agent, *i.e.*, as a means of introducing the acetyl group, into compounds containing " active " hydrogen atoms. It is also used to detect the presence of hydroxyl groups in organic compounds, and to estimate their number.

Acetyl chloride readily acetylates primary and secondary alcohols, but it tends to replace the hydroxyl group of a tertiary alcohol by chlorine (p. 130):

$$R_3COH + CH_3\cdot COCl \longrightarrow R_3CCl + CH_3\cdot CO_2H$$

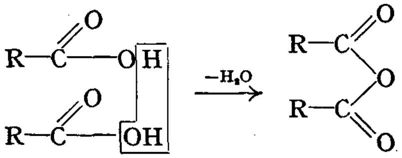
The acetate of a tertiary alcohol may, however, be obtained by carrying out the reaction in the presence of pyridine:

$$R_3COH + CH_3\cdot COCl \xrightarrow{pyridine} CH_3\cdot CO_2CR_3 + HCl$$

The accepted abbreviation for the acetyl group is Ac; *e.g.*, AcOH is acetic acid; Ac_2O, acetic anhydride; AcCl, acetyl chloride; $C_6H_5\cdot NH\cdot Ac$, acetanilide; etc.

ACID ANHYDRIDES

The acid anhydrides may be regarded theoretically as being derived from an acid by the removal of one molecule of water from two molecules of the acid:



It is possible in practice to prepare many acid anhydrides by the direct dehydration as indicated above, but this method is usually confined to the anhydrides of the higher members of the acid series (see below).

Nomenclature. The acid anhydrides are named as the anhydride of the acid radicals present, the *trivial* name of the acid being used, *e.g.*,

$(CH_3{\cdot}CO)_2O$	acetic anhydride
$(CH_3{\cdot}CH_2{\cdot}CO)_2O$	propionic anhydride

The most important acid anhydride is acetic anhydride, but propionic anhydride is increasing in importance due to its use in preparing cellulose propionate. Formic anhydride is unknown, but mixed anhydrides containing the formic acid radical have been prepared, *e.g.*, acetic formic anhydride, $H{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$.

Acetic anhydride, $(CH_3{\cdot}CO)_2O$, may be conveniently prepared by distilling a mixture of anhydrous sodium acetate and acetyl chloride:

$$CH_3{\cdot}CO_2Na + CH_3{\cdot}COCl \longrightarrow (CH_3{\cdot}CO)_2O + NaCl \quad (80\%)$$

Acetic anhydride is prepared industrially:

(i) By heating anhydrous sodium acetate with sufficient inorganic chloride —phosphoryl chloride, thionyl chloride or sulphuryl chloride—to convert half of the sodium salt into the acid chloride, which then reacts with unchanged sodium acetate to form acetic anhydride.

(ii) By passing chlorine into a mixture of sodium acetate and sulphur dichloride, and distilling:

$$8CH_3{\cdot}CO_2Na + SCl_2 + 2Cl_2 \longrightarrow 4(CH_3{\cdot}CO)_2O + 6NaCl + Na_2SO_4$$

(iii) By passing acetylene into glacial acetic acid in the presence of mercuric ions as catalyst, and distilling the resulting ethylidene acetate:

$$C_2H_2 + 2CH_3{\cdot}CO_2H \xrightarrow{Hg^{2+}} CH_3{\cdot}CH(O{\cdot}CO{\cdot}CH_3)_2 \xrightarrow{\text{heat}} (CH_3{\cdot}CO)_2O + CH_3{\cdot}CHO$$

(iv) By passing keten into glacial acetic acid:

$$CH_2{=}C{=}O + CH_3{\cdot}CO_2H \longrightarrow (CH_3{\cdot}CO)_2O$$

(v) By passing acetic acid vapour over a catalyst consisting of a mixture of sodium ammonium hydrogen phosphate and boron phosphate, at 600–620°:

$$2CH_3{\cdot}CO_2H \xrightarrow{-H_2O} (CH_3{\cdot}CO)_2O$$

Anhydrides of the higher acids may be prepared by heating, and then fractionating, a mixture of the acid and acetic anhydride:

$$2R{\cdot}CO_2H + (CH_3{\cdot}CO)_2O \rightleftharpoons (R{\cdot}CO)_2O + 2CH_3{\cdot}CO_2H$$

This method is only satisfactory for anhydrides which have higher boiling points than acetic acid. A much better method of preparation is to treat the acid chloride with pyridine and benzene, add the acid, and then heat:

$$R\cdot COCl + R\cdot CO_2H + C_5H_5N \longrightarrow (R\cdot CO)_2O + C_5H_5N\cdot HCl \quad (\textit{g.–ex.})$$

On the other hand, acid anhydrides may be prepared in very high yield by the action of thionyl chloride on an ethereal solution of a mixture of acid and pyridine (Gerrard *et al.*, 1952):

$$2R\cdot CO_2H + SOCl_2 + 2C_5H_5N \longrightarrow (R\cdot CO)_2O + C_5H_5N\cdot HCl + C_5H_5NH\cdot O\cdot SOCl$$

Properties of acetic anhydride. Acetic anhydride is a colourless liquid, b.p. 139·5°, with an irritating smell. It is neutral when pure, and is slighty soluble in water, but readily soluble in ether and benzene. It is hydrolysed slowly in water, but rapidly by alkali:

$$(CH_3\cdot CO)_2O + H_2O \longrightarrow 2CH_3\cdot CO_2H$$

It undergoes reactions similar to those of acetyl chloride, but with less vigour: only half of the acetic anhydride molecule is used in acetylation, the other half being converted into acetic acid:

$$(CH_3\cdot CO)_2O + C_2H_5OH \longrightarrow CH_3\cdot CO_2C_2H_5 + CH_3\cdot CO_2H$$
$$(CH_3\cdot CO)_2O + NH_3 \longrightarrow CH_3\cdot CO\cdot NH_2 + CH_3\cdot CO_2H$$

Acetylation with acetic anhydride is usually best carried out in the presence of a small amount of sodium acetate or concentrated sulphuric acid as catalyst. Acetic anhydride reacts with dry hydrogen chloride to form acetyl chloride:

$$(CH_3\cdot CO)_2O + HCl \longrightarrow CH_3\cdot COCl + CH_3\cdot CO_2H$$

It is readily halogenated, and may be used in the Friedel–Crafts reaction. It reacts with aldehydes to form alkylidene acetates; *e.g.*, with acetaldehyde it forms ethylidene acetate:

$$(CH_3\cdot CO)_2O + CH_3\cdot CHO \longrightarrow CH_3\cdot CH(O\cdot CO\cdot CH_3)_2$$

Acetic anhydride reacts with nitrogen pentoxide to form **acetyl nitrate,** $CH_3\cdot CO\cdot O\cdot NO_2$. This is a colourless fuming liquid, b.p. 22°/70 mm., which explodes violently if heated suddenly. It is hydrolysed by water to acetic and nitric acid:

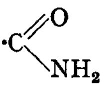
$$CH_3\cdot CO\cdot O\cdot NO_2 + H_2O \longrightarrow CH_3\cdot CO_2H + HNO_3$$

Acetyl nitrate is very useful for preparing certain aromatic nitro-compounds, but it is dangerous to handle (see p. 553).

Acetyl peroxide, $CH_3\cdot CO\cdot O\cdot O\cdot CO\cdot CH_3$, may be prepared by the action of barium peroxide on acetic anhydride. It is colourless, pungent-smelling liquid, b.p. 63°/21 mm., and tends to explode on warming. It is a powerful oxidising agent.

ACID AMIDES

Acid amides are compounds in which the hydroxyl of the carboxyl group has been replaced by the amino-group, $\cdot NH_2$, to form the *amido-group*:



There are three classes of amides: primary, $R{\cdot}CO{\cdot}NH_2$; secondary, $(R{\cdot}CO)_2NH$; and tertiary, $(R{\cdot}CO)_3N$. Only the primary amides are important, and it can be seen from their formulæ that all three classes may be regarded as the acyl derivatives of ammonia.

Nomenclature. According to the I.U.P.A.C. system of nomenclature, the suffix *-oic* of the parent acid is replaced by *amide* (see also acid chlorides, above):

$H{\cdot}CO{\cdot}NH_2$	methanamide
$CH_3{\cdot}CO{\cdot}NH_2$	ethanamide *or* methylcarbonamide

The amides, however, are commonly named by replacing the suffix *-ic* of the trivial name of the parent acid by *amide, e.g.*,

$H{\cdot}CO{\cdot}NH_2$	formamide
$CH_3{\cdot}CO{\cdot}NH_2$	acetamide

General methods of preparation of the amides. 1. By heating the ammonium salt of the acid:

$$R{\cdot}COONH_4 \longrightarrow R{\cdot}CO{\cdot}NH_2 + H_2O \quad (g.\text{–}v.g.)$$

Since the ammonium salts tend to dissociate on heating, the reaction is best carried out in the presence of some free acid $R{\cdot}CO_2H$ which represses the hydrolysis and the dissociation of the ammonium salt.

Amides may also be prepared by heating an acid with urea (Cherbuliez *et al.*, 1946):

$$R{\cdot}CO_2H + CO(NH_2)_2 \longrightarrow R{\cdot}CONH_2 + CO_2 + NH_3 \quad (g.\text{–}v.g.)$$

2. By *ammonolysis*, *i.e.*, the action of concentrated ammonia solution on acid chlorides, acid anhydrides or esters:

$$\begin{aligned} R{\cdot}COCl + 2NH_3 &\longrightarrow R{\cdot}CO{\cdot}NH_2 + NH_4Cl && (v.g.)\\ (R{\cdot}CO)_2O + 2NH_3 &\longrightarrow R{\cdot}CO{\cdot}NH_2 + R{\cdot}CO_2NH_4 && (v.g.)\\ R{\cdot}COOR' + NH_3 &\longrightarrow R{\cdot}CO{\cdot}NH_2 + R'OH && (g.) \end{aligned}$$

N-Substituted amides may be prepared by using primary or secondary amines instead of ammonia, *e.g.*,

$$R{\cdot}COCl + R'{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}R' + HCl$$

Philbrook (1954) has shown that amides may be readily prepared by adding a benzene solution of an acid chloride dropwise to benzene through which is passed a current of ammonia; for the lower aliphatic amides the yield is 65–95 per cent.

Meyer (1906) found that ammonolysis of esters occurs most readily with esters of strong acids and least readily with esters of weak acids or sterically hindered acids. It has been found that ammonia and aliphatic amines react, in general, more readily than aromatic amines. Stern (1956) has shown that acyl arylamides may be readily prepared as follows (Ar = aryl radical):

$$Ar{\cdot}NH_2 \xrightarrow[NaNH_2]{Na\ or} Ar{\cdot}NHNa$$

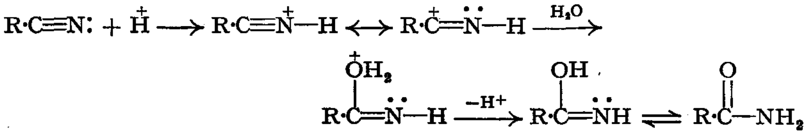
$$R{\cdot}CO_2C_2H_5 + Ar{\cdot}NHNa \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}Ar + C_2H_5ONa$$

3. By the *graded* hydrolysis of alkyl cyanides. The hydrolysis must be carried out carefully, since if taken too far, the acid is produced. The hydrolysis may be carried out satisfactorily by dissolving the alkyl cyanide

in concentrated sulphuric acid and then pouring the solution into cold water, or by shaking the alkyl cyanide with cold concentrated hydrochloric acid:

$$R\cdot C\equiv N + H_2O \longrightarrow R\cdot CO\cdot NH_2 \qquad (g.)$$

A possible mechanism for this hydrolysis is:



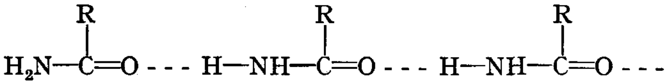
$$R\cdot C\equiv N\!: + \overset{+}{H} \longrightarrow R\cdot C\equiv\overset{+}{N}-H \longleftrightarrow R\cdot\overset{+}{C}=\overset{\cdot\cdot}{N}-H \xrightarrow{H_2O}$$

$$R\cdot\overset{\overset{+}{O}H_2}{\overset{|}{C}}=\overset{\cdot\cdot}{N}-H \xrightarrow{-H+} R\cdot\overset{OH}{\overset{|}{C}}=\overset{\cdot\cdot}{N}H \rightleftharpoons R\cdot\overset{O}{\overset{\|}{C}}-NH_2$$

Sometimes the conversion of an alkyl cyanide into the amide may be effected by means of alkaline hydrogen peroxide:

$$R\cdot CN + 2H_2O_2 \xrightarrow{NaOH} R\cdot CO\cdot NH_2 + O_2 + H_2O$$

General properties and reactions of the amides. Except for formamide, which is a liquid, all the amides are colourless crystalline solids, and those of low molecular weight are soluble in water (with which they can form hydrogen bonds). The lower amides have much higher melting points and boiling points than are to be expected from their molecular weights; this indicates association (through hydrogen bonding):



$$H_2N-\overset{R}{\overset{|}{C}}=O\;\text{- - -}\;H-NH-\overset{R}{\overset{|}{C}}=O\;\text{- - -}\;H-NH-\overset{R}{\overset{|}{C}}=O\;\text{- - -}$$

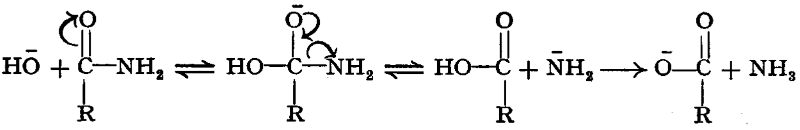
Infra-red spectroscopic studies indicate that in dilute solution (dioxan and chloroform) amides are monomeric; in concentrated solution (chloroform) and in the liquid state there is some association, and in the solid state association is complete. Furthermore, the spectroscopic evidence appears to indicate that amides are resonance hybrids (Richards and Thomson, 1947):

1. Amides are hydrolysed slowly by water, rapidly by acids, and far more rapidly by alkalis:

$$R\cdot CO\cdot NH_2 + H_2O \longrightarrow R\cdot CO_2H + NH_3$$

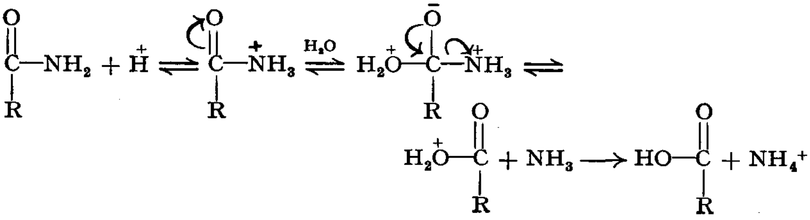
Possible mechanisms are:

Base hydrolysis



$$H\bar{O} + \underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}}-NH_2 \rightleftharpoons HO-\underset{\underset{R}{|}}{\overset{\bar{O}}{\overset{|}{C}}}-NH_2 \rightleftharpoons HO-\underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}} + \bar{N}H_2 \longrightarrow \bar{O}-\underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}} + NH_3$$

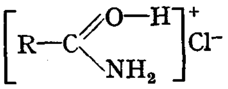
Acid hydrolysis

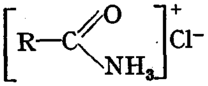


$$\underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}}-NH_2 + \overset{+}{H} \rightleftharpoons \underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}}-\overset{+}{N}H_3 \overset{H_2O}{\rightleftharpoons} H_2\overset{+}{O}-\underset{\underset{R}{|}}{\overset{\bar{O}}{\overset{|}{C}}}-\overset{+}{N}H_3 \rightleftharpoons$$

$$H_2\overset{+}{O}-\underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}} + NH_3 \longrightarrow HO-\underset{\underset{R}{|}}{\overset{O}{\overset{\|}{C}}} + NH_4^+$$

2. Amides are very feebly basic and form unstable salts with strong inorganic acids, *e.g.*, $R\cdot CO\cdot NH_2\cdot HCl$. The structure of these salts may be I or II:


(I)

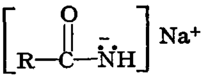

(II)

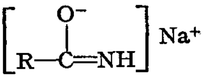
In the case of formamide (R=H), infra-red measurements have shown that II is the actual state. Addition of a proton to the NH_2 group inhibits resonance and consequently decreases stability, *i.e.*, the amide is more stable than the protonated molecule. Hence the weak basic properties of amides.

3. Amides are also feebly acidic; *e.g.*, they dissolve mercuric oxide to form covalent mercury compounds in which the mercury is probably linked to the nitrogen:

$$2R\cdot CO\cdot NH_2 + HgO \longrightarrow (R\cdot CO\cdot NH)_2Hg + H_2O$$

When amides are treated with sodium or sodamide in ethereal solution, the sodium *salt*, $[R\cdot CO\cdot NH]^-Na^+$, is formed, and the structure of these salts may be I or II:


(I)


(II)

When the dry sodium salt is heated with an alkyl iodide, the *N*-alkyl derivative is obtained; this corresponds to I. When, however, the silver salt is used, the *O*-alkyl derivative is obtained; this corresponds to II. It is possible that I and II are resonating structures.

4. Amides are reduced by sodium and ethanol, catalytically, or by lithium aluminium hydride to a primary amine:

$$R\cdot CO\cdot NH_2 + 4[H] \xrightarrow{Na/C_2H_5OH} R\cdot CH_2\cdot NH_2 + H_2O$$

5. When heated with phosphorus pentoxide, amides are dehydrated to alkyl cyanides:

$$R\cdot CO\cdot NH_2 \xrightarrow[-H_2O]{P_2O_5} R\cdot C\vdots N$$

Alkyl cyanides are also formed when the amides of the higher fatty acids are heated to a high temperature:

$$2R\cdot CO\cdot NH_2 \longrightarrow R\cdot CN + R\cdot CO_2H + NH_3$$

If this reaction is carried out in the presence of excess of ammonia, then all the amide is converted into alkyl cyanide:

$$R\cdot CO_2H + NH_3 \longrightarrow R\cdot CO_2NH_4 \xrightarrow{-H_2O} R\cdot CO\cdot NH_2 \xrightarrow{-H_2O} R\cdot CN$$

Amides may also be converted into cyanides by phosphorus pentachloride, and according to Wallach (1877), the reaction proceeds via the *amido-chloride* I and then the *imido-chloride* (*imino-chloride*) II.

$$R\cdot CO\cdot NH_2 \xrightarrow{PCl_5} \underset{(I)}{R\cdot CCl_2\cdot NH_2} \xrightarrow{-HCl} \underset{(II)}{R\cdot CCl{=}NH} \xrightarrow{-HCl} R\cdot CN$$

According to Kirsanov (1954), however, the reaction proceeds as follows, the intermediate III being decomposed by heat or by hydrogen chloride.

$$R\cdot CO\cdot NH_2 + PCl_5 \longrightarrow 2HCl + \underset{(III)}{R\cdot CO\cdot N{=}PCl_3} \longrightarrow R\cdot CN + POCl_3$$

Alkyl cyanides may be obtained from amides by treating the amide with the boron trifluoride-amide complex in the presence of a small amount of a carboxylic acid (Nieuwland, 1937), *e.g.*,

$$CH_3\cdot CONH_2\cdot BF_3 + CH_3\cdot CO\cdot NH_2 \xrightarrow{CH_3\cdot CO_2H} CH_3\cdot CN + CH_3\cdot CO_2H + NH_3\cdot BF_3$$

It is also interesting to note that the complex $CH_3\cdot CO\cdot NH_2\cdot BF_3$ has been found to be an effective acetylating agent for alcohols and phenols:

$$CH_3\cdot CO\cdot NH_2\cdot BF_3 + ROH \longrightarrow CH_3\cdot CO_2R + NH_3\cdot BF_3$$

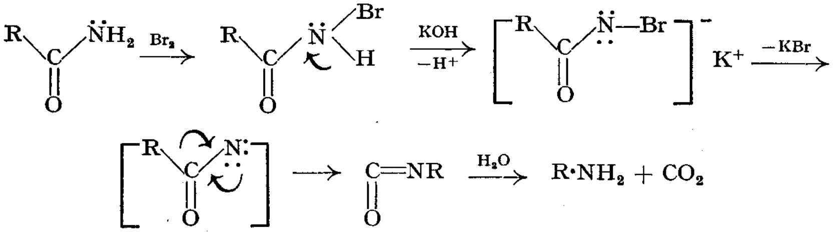
6. When amides are treated with nitrous acid, nitrogen is evolved and the acid is formed:

$$R\cdot CO\cdot NH_2 + HNO_2 \longrightarrow R\cdot CO_2H + N_2 + H_2O$$

7. **Hofmann reaction or Hofmann degradation** (1881). The Hofmann reaction is the conversion of an amide into a primary amine with one carbon atom less by means of bromine (or chlorine) and alkali. The overall equation for the reaction may be written:

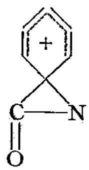
$$R\cdot CO\cdot NH_2 + Br_2 + 4KOH \longrightarrow R\cdot NH_2 + 2KBr + K_2CO_3 + 2H_2O$$

The mechanism of the Hofmann reaction has been the subject of a great deal of work. A number of intermediates have been isolated: *N*-bromamides, $R\cdot CO\cdot NHBr$; salts of these bromamides, $[R\cdot CO\cdot NBr]^-K^+$; *iso*cyanates, $R\cdot NCO$. On this basis, a possible mechanism is the following, which is an example of the 1,2-shift:

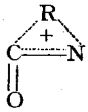


(I)

The uncertainty of this mechanism lies mainly in the formation of (I). Hauser *et al.* (1937) have shown that electron-releasing groups in the *para*-position of a migrating aryl group accelerate the reaction and electron-withdrawing groups retard the reaction. This supports the formation of a bridged ion (a phenonium ion), (I*a*), certainly when the migrating group is aromatic. Whether a bridged ion, (I*b*), is produced when the migrating group is an alkyl group, is uncertain (*cf.* p. 171). Furthermore, there is much recent work to show that the rearrangement is intramolecular, *e.g.*, Wallis *et al.* (1931), using the amide of optically active α-benzylpropionic acid, found that there was retention of configuration in the product, α-benzylethylamine; thus the migrating group is never free:



(I*a*)



(I*b*)

$$C_6H_5\cdot CH_2\cdot CHMe\cdot CO\cdot NH_2 \longrightarrow C_6H_5\cdot CH_2\cdot CHMe\cdot NH_2$$

The Hofmann reaction can be carried out on all monocarboxylic acids, and the yields are 70–90 per cent. for amides containing up to seven carbon atoms; amides with more than seven carbon atoms in the chain give mainly alkyl cyanide:

$$R\cdot CH_2\cdot CO\cdot NH_2 \xrightarrow{Br_2/KOH} R\cdot CN$$

The alkyl cyanide, however, may readily be reduced to the primary amine $R\cdot CH_2\cdot NH_2$.

It is possible to obtain the amine in good yield from the long-chain amides by modifying the procedure as follows. Bromine is added rapidly to a methanolic solution of the amide containing sodium methoxide:

$$R{\cdot}CO{\cdot}NH_2 + 2CH_3ONa + Br_2 \longrightarrow R{\cdot}NH{\cdot}CO_2CH_3 + 2NaBr + CH_3OH$$

The *N*-alkyl-urethan, on hydrolysis with alkali, gives the amine:

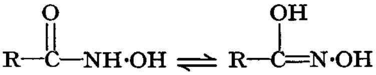
$$R{\cdot}NH{\cdot}CO_2CH_3 + 2NaOH \longrightarrow R{\cdot}NH_2 + Na_2CO_3 + CH_3OH$$

The Hofmann reaction offers an excellent method of preparing primary amines free from secondary and tertiary amines; it also affords a means of descending a series. A further interesting point about this reaction is that if the amide contains an electronegative group, the product is a bromide, *e.g.*, heptafluorobutyramide gives bromoheptafluoropropane (Haszeldine *et al.*, 1956):

$$C_3F_7{\cdot}CO{\cdot}NH_2 \xrightarrow[NaOH]{Br_2} C_3F_7Br \quad (85\%)$$

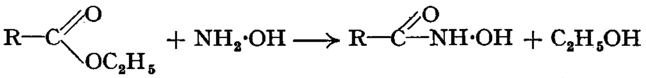
HYDROXAMIC ACIDS

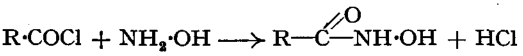
The hydroxamic acids exhibit tautomerism; the keto form I is known as the *hydroxamic* form, and the enol form II as the *hydroximic* form:

(I)  (II)

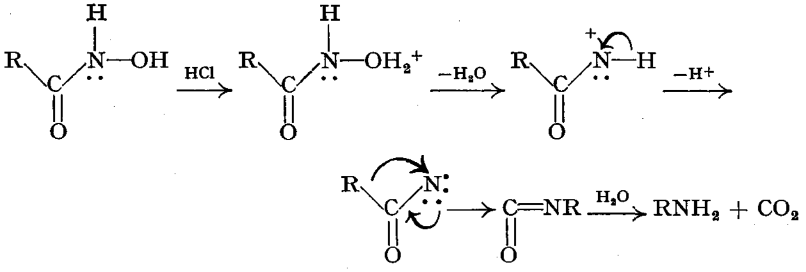
$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH{\cdot}OH \rightleftharpoons R{-}\overset{\overset{\displaystyle OH}{|}}{C}{=}N{\cdot}OH$$

Hydroxamic acids may be prepared by the action of hydroxylamine on esters or acid chlorides:



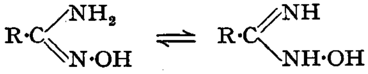


Hydroxamic acids give a red coloration with ferric chloride solution, a reaction which is characteristic of enols. When treated with a strong inorganic acid, hydroxamic acids undergo the **Lossen rearrangement** (1875), which results in the formation of a primary amine. The mechanism of the Lossen rearrangement is closely related to that of the Hofmann reaction, and so may be formulated:

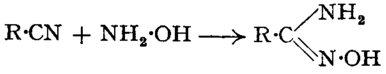


This rearrangement (1,2-shift) has been shown to be intramolecular, and electron-releasing groups in a migrating aryl group accelerate the reaction, thereby supporting the formation of a phenonium ion.

The amides of the hydroxamic acids are known as **amidoximes.** These are tautomeric substances:



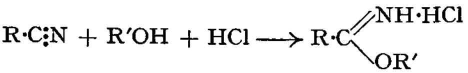
Aliphatic amidoximes are best obtained by the action of hydroxylamine on an alkyl cyanide:



$$R\cdot CN + NH_2\cdot OH \longrightarrow R\cdot C\begin{array}{l}\diagup NH_2\\ \diagdown\!\!\diagdown N\cdot OH\end{array}$$

IMIDIC ESTERS AND AMIDINES

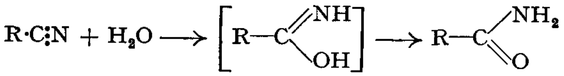
Imidic esters, which are also known as *imino-ethers,* are best prepared by passing dry hydrogen chloride into a solution of an alkyl cyanide in anhydrous alcohol; the imidic ester hydrochloride is slowly deposited (Pinner, 1877):



$$R\cdot C\vdots N + R'OH + HCl \longrightarrow R\cdot C\begin{array}{l}\diagup\!\!\diagup NH\cdot HCl\\ \diagdown OR'\end{array}$$

(*g.–v.g.*)

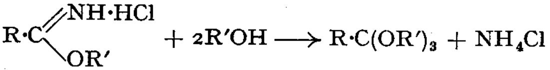
This reaction is believed to be analogous to the hydrolysis of cyanides to amides:



$$R\cdot C\vdots N + H_2O \longrightarrow \left[R-C\begin{array}{l}\diagup\!\!\diagup NH\\ \diagdown OH\end{array}\right] \longrightarrow R-C\begin{array}{l}\diagup NH_2\\ \diagdown\!\!\diagdown O\end{array}$$

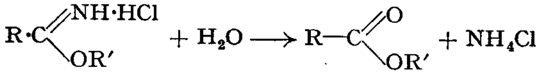
There is, however, no evidence for the existence of the enol form in unsubstituted amides.

Imidic esters form ortho-esters when allowed to stand in an alcohol:



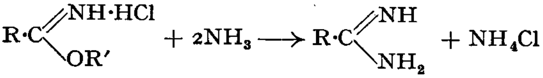
$$R\cdot C\begin{array}{l}\diagup\!\!\diagup NH\cdot HCl\\ \diagdown OR'\end{array} + 2R'OH \longrightarrow R\cdot C(OR')_3 + NH_4Cl$$

Imidic esters are readily hydrolysed to esters:



$$R\cdot C\begin{array}{l}\diagup\!\!\diagup NH\cdot HCl\\ \diagdown OR'\end{array} + H_2O \longrightarrow R-C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown OR'\end{array} + NH_4Cl$$

When an ethereal solution of an imidic ester hydrochloride is treated with potassium carbonate, the free ester $R\cdot C\begin{smallmatrix}\diagup\!\!\diagup NH\\ \diagdown OR'\end{smallmatrix}$, is obtained. When treated with an ethanolic solution of ammonia, the imidic ester hydrochloride forms the **amidine**:



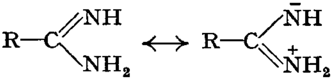
$$R\cdot C\begin{array}{l}\diagup\!\!\diagup NH\cdot HCl\\ \diagdown OR'\end{array} + 2NH_3 \longrightarrow R\cdot C\begin{array}{l}\diagup\!\!\diagup NH\\ \diagdown NH_2\end{array} + NH_4Cl$$

Formamidine acetate and acetamidine acetate may be prepared from ortho esters (R = H or Me) as follows (Taylor *et al.,* 1960):

$$R\cdot C(OEt)_3 + NH_3 + CH_3\cdot CO_2H \longrightarrow H_2N\cdot CR{=}NH_2{}^+CH_3\cdot CO_2{}^-$$

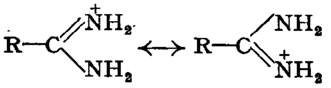
These acetates are better precursors of their respective amidines than are the corresponding hydrochlorides.

Amidines are strong monoacid bases, forming salts with strong acids. Their basic strength may be explained by resonance. In the amidine, two *different* resonating structures contribute to the actual state of the molecule:



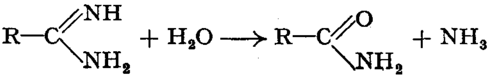
$$R-C\begin{array}{l}\diagup\!\!\diagup NH\\ \diagdown NH_2\end{array} \longleftrightarrow R-C\begin{array}{l}\diagup \bar{N}H\\ \diagdown\!\!\diagdown \overset{+}{N}H_2\end{array}$$

In the amidine *ion,* the resonating structures are *equivalent,* and hence the resonance energy is a maximum; the ion will therefore be stable:



$$R-C\begin{array}{l}\diagup\!\!\diagup \overset{+}{N}H_2\\ \diagdown NH_2\end{array} \longleftrightarrow R-C\begin{array}{l}\diagup NH_2\\ \diagdown\!\!\diagdown \overset{+}{N}H_2\end{array}$$

Amidines are readily hydrolysed to amides:



$$R-C\begin{array}{l}\diagup\!\!\diagup NH\\ \diagdown NH_2\end{array} + H_2O \longrightarrow R-C\begin{array}{l}\diagup\!\!\diagup O\\ \diagdown NH_2\end{array} + NH_3$$

Amidines or their salts may be reduced to aldehydes by sodium and ethanol in liquid ammonia, or by sodium and ethanol, but in the latter case the yields are lower (Birch *et al.*, 1954).

ACID HYDRAZIDES AND ACID AZIDES

Acid hydrazides may be prepared by the action of hydrazine on esters or acyl chlorides:

$$\begin{gathered}\mathrm{R{\cdot}COOC_2H_5 + N_2H_4 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH_2 + C_2H_5OH}\\ \mathrm{R{\cdot}COCl + N_2H_4 \longrightarrow R{\cdot}CO{\cdot}NH{\cdot}NH_2 + HCl}\end{gathered}$$

Girard's reagent " T " (p. 154) is trimethylaminoacetohydrazide, which may be prepared by interaction between trimethylamine, ethyl chloroacetate and hydrazine:

$$\begin{aligned}&\mathrm{(CH_3)_3N + ClCH_2{\cdot}CO_2C_2H_5 + N_2H_4 \longrightarrow}\\ &\qquad\qquad\mathrm{[(CH_3)_3N{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2]^+Cl^- + C_2H_5OH}\end{aligned}$$

Girard's reagent " P " is formed in a similar manner, except that pyridine is used instead of trimethylamine.

The acid hydrazides resemble the acid amides, but differ in the following ways:

(i) They are much more readily hydrolysed than the amides:

$$\mathrm{R{\cdot}CO{\cdot}NH{\cdot}NH_2 + H_2O \longrightarrow R{\cdot}CO_2H + N_2H_4}$$

(ii) They are reducing agents—hydrazine is a powerful reducing agent.

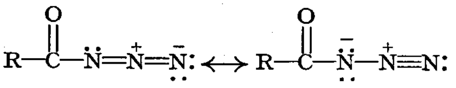
(iii) They form acid azides when treated with nitrous acid; no nitrogen is evolved:

$$\mathrm{R{\cdot}CO{\cdot}NH{\cdot}NH_2 + HNO_2 \longrightarrow R{\cdot}CO{\cdot}N_3 + 2H_2O}$$

Acid azides may also be prepared by the reaction between an acyl chloride and sodium azide:

$$\mathrm{R{\cdot}COCl + NaN_3 \longrightarrow R{\cdot}CO{\cdot}N_3 + NaCl}$$

The structure of the acid azides is best represented as a resonance hybrid:

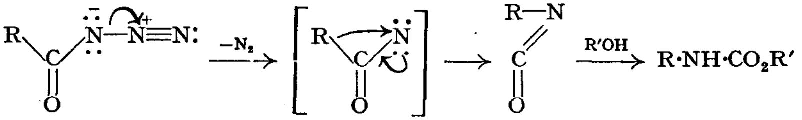


$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\ddot{N}{=}\overset{+}{N}{=}\overset{-}{N}\colon \longleftrightarrow R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\overset{-}{\ddot{N}}{-}\overset{+}{N}{\equiv}N\colon}$$

When boiled with an alcohol, acid azides undergo rearrangement to form *N*-alkyl-substituted urethans:

$$\mathrm{R{\cdot}CO{\cdot}N_3 + R'OH \longrightarrow R{\cdot}NH{\cdot}CO_2R' + N_2} \qquad (v.g.\text{–}ex.)$$

The mechanism of this rearrangement—the **Curtius rearrangement** (1894)—is similar to that of the Hofmann and Lossen rearrangements (see above), and so may be formulated:



This mechanism is supported by the fact that when the terminal nitrogen atom is ^{15}N in 3:5-dinitrobenzazide, all of this tracer is found in the nitrogen eliminated in the reaction (Bothner—By *et al.*, 1951).

The Curtius reaction may be used to step down a series (*cf.* the Hofmann reaction):

$$\begin{aligned}&\mathrm{R{\cdot}CO_2H \xrightarrow{C_2H_5OH} R{\cdot}CO_2C_2H_5 \xrightarrow{N_2H_4} R{\cdot}CO{\cdot}NH{\cdot}NH_2 \xrightarrow{HNO_2}}\\ &\qquad\qquad\mathrm{R{\cdot}CO{\cdot}N_3 \xrightarrow{CH_3OH} R{\cdot}NH{\cdot}CO_2CH_3 \xrightarrow{NaOH} R{\cdot}NH_2}\end{aligned}$$

The Curtius reactions offers a very good method for preparing primary amines free from secondary and tertiary amines, and may also be used for preparing *iso*cyanates and urethans; *e.g.*, when heated in benzene or chloroform solution, an acid azide rearranges to the alkyl *iso*cyanate which can be isolated. If the *iso*cyanate is warmed with an alcohol, an *N*-substituted urethan is formed:

$$R{\cdot}CO{\cdot}N_3 \xrightarrow[\text{solution}]{\text{benzene}} R{\cdot}NCO \xrightarrow{R'OH} R{\cdot}NH{\cdot}CO_2R'$$

HALOGEN DERIVATIVES OF THE FATTY ACIDS

The halogen derivatives of the fatty acids are compounds in which one or more hydrogen atoms in the *carbon chain* have been replaced by halogen.

Nomenclature. The usual method of naming the halogenated fatty acids is to use the trivial names of the acids, and to indicate the positions of the halogens atoms by Greek letters, *e.g.*,

$CH_2Cl{\cdot}CO_2H$	monochloroacetic acid
$CH_3{\cdot}CHCl{\cdot}CO_2H$	α-chloropropionic acid
$(CH_3)_2CCl{\cdot}CHBr{\cdot}CO_2H$	α-bromo-β-chloro*iso*valeric acid

Preparation of the halogenated acids. There are no general methods of preparing the various types of halogenated acids, *i.e.*, the α-, β-, γ-, etc., halogeno-acids; the method depends on the position of the halogen atom.

α-**Halogeno-acids.** Although the fatty acids themselves are not readily halogenated, their acid chlorides and anhydrides may be halogenated very easily. Bromination takes place only at the α-position, but chlorination, although it occurs mainly at the α-position, may also take place further in the chain; *e.g.*, chlorination of propionic acid results in the formation of the α- and β-chloro-derivatives:

$$CH_3{\cdot}CH_2{\cdot}CO_2H \xrightarrow{Cl_2} CH_3{\cdot}CHCl{\cdot}CO_2H + CH_2Cl{\cdot}CH_2{\cdot}CO_2H$$

Fluorination of the fatty acids has not yet been studied in great detail, but the work done so far seems to indicate that fluorine enters the chain somewhat indiscriminately; *e.g.*, fluorination of butyric acid in carbon tetrachloride solution gives the β- and γ-fluoro-derivatives (Bockemüller, 1933).

Iodo-derivatives are prepared from the chloro- or bromo-compound by the action of potassium iodide in methanolic or acetone solution (*cf.* alkyl iodides, p. 105).

The usual method for preparing α-chloro- or bromo-acids is by the **Hell–Volhard–Zelinsky reaction (H.V.Z. reaction)**, which is carried out by treating the acid with chlorine or bromine in the presence of a small amount of red phosphorus. The reaction possibly takes place as follows:

$$R{\cdot}CH_2{\cdot}CO_2H \xrightarrow{P + Br_2} R{\cdot}CH_2{\cdot}COBr \xrightarrow{Br_2} R{\cdot}CHBr{\cdot}COBr$$

$$R{\cdot}CHBr{\cdot}COBr + R{\cdot}CH_2{\cdot}CO_2H \rightleftharpoons R{\cdot}CHBr{\cdot}CO_2H + R{\cdot}CH_2{\cdot}COBr$$

$$R{\cdot}CH_2{\cdot}COBr \xrightarrow{Br_2} R{\cdot}CHBr{\cdot}COBr, \text{ etc.}$$

The second α-hydrogen atom may be replaced by chlorine or bromine by using excess of the halogen, but whereas bromination ceases when both α-hydrogen atoms have been replaced, chlorination proceeds further in the chain (see above). Since the H.V.Z. reaction with bromine is specific for α-hydrogen atoms, it can be used to detect the presence of α-hydrogen in an acid; *e.g.*, trimethylacetic acid does not undergo the H.V.Z. reaction with bromine.

The H.V.Z. reaction with bromine is applicable to dibasic and polybasic acids, all the α-positions being substituted if sufficient bromine is used.

Sulphuryl chloride, in the presence of a small amount of iodine, chlorinates aliphatic acids in the α-position; but in the presence of organic peroxides, the α-, β-, γ-, etc., positions are substituted.

Another convenient method of preparing α-bromo-acids is by brominating an alkyl-malonic acid and heating the bromo-acid, whereupon it is decarboxylated to the monobasic acid:

$$R{\cdot}CH(CO_2H)_2 \xrightarrow{Br_2} R{\cdot}CBr(CO_2H)_2 \xrightarrow{heat} R{\cdot}CHBr{\cdot}CO_2H + CO_2$$

β-Halogeno-acids may be prepared by treating an αβ-unsaturated acid with halogen acid; *e.g.*, acrylic acid forms β-bromopropionic acid when treated with hydrogen bromide in acetic acid solution:

$$CH_2{=}CH{\cdot}CO_2H + HBr \longrightarrow CH_2Br{\cdot}CH_2{\cdot}CO_2H$$

This addition takes place contrary to Markownikoff's rule, and may be explained by the inductive effect of the carboxyl group (see p. 282).

β-Halogeno-acids may also be prepared by treating an αβ-unsaturated aldehyde with halogen acid, and oxidising the β-chloroaldehyde produced; *e.g.*, acraldehyde gives β-chloropropionic acid when treated with concentrated hydrochloric acid, and the product then oxidised with concentrated nitric acid:

$$CH_2{=}CH{\cdot}CHO + HCl \longrightarrow CH_2Cl{\cdot}CH_2{\cdot}CHO \xrightarrow{[O]} CH_2Cl{\cdot}CH_2{\cdot}CO_2H \quad (60\text{–}65\%)$$

The addition of all the halogen acids to αβ-unsaturated carbonyl compounds takes place very readily, and in a direction contrary to Markownikoff's rule.

When an olefin cyanohydrin is refluxed with 40 per cent. hydrobromic acid, the β-bromoacid is obtained; *e.g.*, ethylene cyanohydrin gives β-bromopropionic acid:

$$CH_2(OH){\cdot}CH_2{\cdot}CN + 2HBr + H_2O \longrightarrow CH_2Br{\cdot}CH_2{\cdot}CO_2H + NH_4Br \quad (82\text{–}83\%)$$

Alternatively, when an olefin halohydrin is oxidised with concentrated nitric acid, the halogeno-acid is produced; *e.g.*, trimethylene chlorohydrin gives β-chloropropionic acid:

$$CH_2Cl{\cdot}CH_2{\cdot}CH_2OH \xrightarrow{[O]} CH_2Cl{\cdot}CH_2{\cdot}CO_2H \quad (78\text{–}79\%)$$

γ-Halogeno-acids may be prepared by the addition of halogen acid to a βγ-unsaturated acid; the addition occurs contrary to Markownikoff's rule (*cf.* above); *e.g.*, pent-3-enoic acid gives γ-bromo-*n*-valeric acid when treated with hydrobromic acid:

$$CH_3{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CO_2H + HBr \longrightarrow CH_3{\cdot}CHBr{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

γ-Halogeno-acids may also be prepared by heating a γ-hydroxyacid with concentrated halogen acid solution; *e.g.*, γ-hydroxybutyric acid gives γ-chlorobutyric acid when treated with concentrated hydrochloric acid:

$$CH_2OH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + HCl \longrightarrow CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + H_2O$$

δ-Halogeno-acids, etc., are prepared by methods which are usually specific for the particular acid.

Properties of the halogeno-acids. The α-halogeno-acids undergo most of the reactions of the alkyl halides, but the halogen atom in the acid is far more reactive than that in the alkyl halide; the enhanced reactivity is due to the adjacent carbonyl group. The reactions of the carboxyl group are unchanged. β-, γ- and δ-Halogeno-acids undergo some of the reactions of the alkyl halides, but tend to eliminate a molecule of hydrogen halide to form an unsaturated acid or a lactone (p. 396). They do not form Grignard reagents, but the halogeno-acid esters react with Grignard reagents to form halogen-substituted tertiary alcohols. The halogeno-acids are reduced to the corresponding fatty acids by sodium amalgam, but the reduction of acids of the type $RR'CCl{\cdot}CO_2H$ with lithium aluminium hydride gives chlorohydrins (I), alcohols (II), aldehydes (III) and glycols (IV).

$$\underset{\text{(I)}}{RR'CCl{\cdot}CH_2OH} \quad \underset{\text{(II)}}{RR'CH{\cdot}CH_2OH} \quad \underset{\text{(III)}}{RR'CH{\cdot}CHO} \quad \underset{\text{(IV)}}{RR'C(OH){\cdot}CH_2OH}$$

The amount of each depends on the nature of R and R′, *e.g.*, very little glycol is obtained unless at least one of these radicals is phenyl (Eliel *et al.*, 1956).

The behaviour of an halogeno-acid with alkali depends on the position of the halogen atom relative to the carboxyl group.

(*a*) α-Halogeno-acids are converted into the corresponding α-hydroxy-acid:

$$R{\cdot}CHX{\cdot}CO_2H + H_2O \xrightarrow{NaOH} R{\cdot}CH(OH){\cdot}CO_2H$$

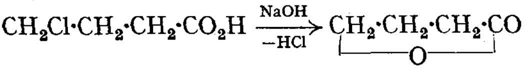
On the other hand, if the α-halogeno-acid ester is heated with a tertiary amine, the αβ-unsaturated acid ester is formed by the elimination of a molecule of hydrogen halide; *e.g.*, ethyl α-bromobutyrate gives ethyl crotonate when heated with dimethylaniline, $C_6H_5{\cdot}N(CH_3)_2$:

$$CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2C_2H_5 \xrightarrow{-HBr} CH_3{\cdot}CH{=}CH{\cdot}CO_2C_2H_5$$

(*b*) β-Halogeno-acids are converted into the corresponding β-hydroxyacid, which, on continued reflux with alkali, eliminates a molecule of water to form the αβ-unsaturated acid:

$$R{\cdot}CHBr{\cdot}CH_2{\cdot}CO_2H \xrightarrow{NaOH} R{\cdot}CH(OH){\cdot}CH_2{\cdot}CO_2H \xrightarrow[-H_2O]{NaOH} R{\cdot}CH{=}CH{\cdot}CO_2H$$

(*c*) γ- and δ-Halogeno-acids are converted into lactones; *e.g.*, γ-chlorobutyric acid gives γ-butyrolactone:



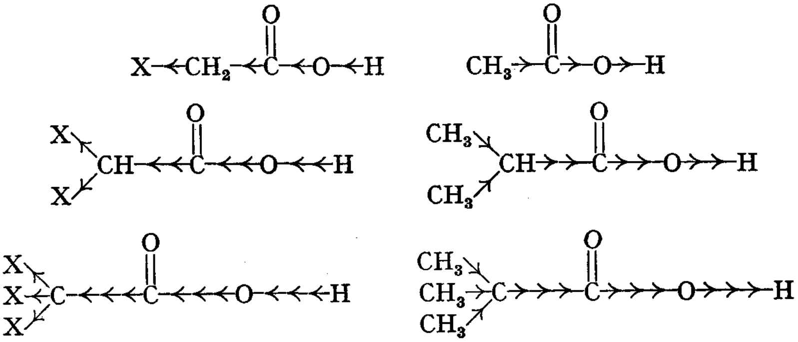
$$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \xrightarrow[-HCl]{NaOH} \underbrace{CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO}_{O}$$

(*d*) ε-Halogeno-acids, etc., give the corresponding hydroxyacid; *e.g.*, ε-bromocaproic acid gives ε-hydroxycaproic acid:

$$CH_2Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \xrightarrow{NaOH} CH_2OH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

The most characteristic reaction of the α-halogeno-acid esters is the *Reformatsky reaction* (p. 363).

The halogeno-acids are all stronger acids than the parent acid (see Table III, p. 180), and for a group of isomeric acids, the further the halogen is removed from the carboxyl group the weaker is the acid. The increase in acid strength may be explained by the high electron-affinity of the halogen atom which exerts a strong inductive effect, thereby facilitating the release of proton from the carboxyl group.



The larger the number of halogen atoms on the α-carbon atom, the stronger is the inductive effect, and consequently the stronger is the acid; also, the further removed the halogen atom is from the carboxyl group, the weaker is the inductive effect at the carboxyl group, and consequently the weaker is the acid. In the same way, since an alkyl group is electron-repelling, increasing their number on the α-carbon atom should *decrease* the strength of the acid since release of the proton will be hindered (see Table III). This explanation, based on the purely inductive effect through the chain of atoms, appears to be too simple. Work by Grob *et al.* (1955) has led them to conclude that the direct (or field) effect (p. 16) is the decisive factor in determining the strengths of the carboxylic acids.

Chloroacetic acid, $CH_2Cl{\cdot}CO_2H$, may be prepared by the H.V.Z. reaction; the reaction can be carried out in direct sunlight, and in the absence of phosphorus. Chloroacetic acid is prepared industrially: (i) by agitating trichloroethylene with 90 per cent. sulphuric acid:

$$CHCl{=}CCl_2 + 2H_2O \xrightarrow{H_2SO_4} CH_2Cl{\cdot}CO_2H + 2HCl$$

(ii) By the oxidation of ethylene chlorohydrin with nitric acid:

$$CH_2Cl{\cdot}CH_2OH \xrightarrow{HNO_3} CH_2Cl{\cdot}CO_2H \quad (84\%)$$

Chloroacetic acid is a deliquescent solid, m.p. 61°, soluble in water and ethanol. It finds many uses in organic syntheses, and is used in the industrial preparation of indigotin (*q.v.*).

Ethyl chloroacetate is converted into chloroacetamide when shaken with aqueous ammonia:

$$CH_2Cl{\cdot}COOC_2H_5 + NH_3 \longrightarrow CH_2Cl{\cdot}CO{\cdot}NH_2 + C_2H_5OH \quad (78\text{–}84\%)$$

Dichloroacetic acid, $CHCl_2{\cdot}CO_2H$, may be prepared in the laboratory and industrially by adding calcium carbonate to a warm aqueous solution of chloral hydrate, then adding an aqueous solution of sodium cyanide, and finally heating the mixture:

$$2CCl_3{\cdot}CH(OH)_2 + 2CaCO_3 \xrightarrow{NaCN} (CHCl_2{\cdot}CO_2)_2Ca + 2CO_2 + CaCl_2 + 2H_2O$$
$$\xrightarrow{HCl} CHCl_2{\cdot}CO_2H \quad (88\text{–}92\%)$$

The action of the sodium cyanide is not understood.

Dichloroacetic acid is a liquid, b.p. 194°. When carefully hydrolysed with dilute alkali, it gives glyoxylic acid (*q.v.*):

$$CHCl_2{\cdot}CO_2H + H_2O \xrightarrow{NaOH} CHO{\cdot}CO_2H + 2HCl$$

Vigorous hydrolysis with concentrated alkali gives oxalate and glycollate, due to the glyoxylic acid undergoing the Cannizzaro reaction (p. 160):

$$2CHO{\cdot}CO_2H + 3NaOH \longrightarrow (CO_2Na)_2 + CH_2(OH){\cdot}CO_2Na + 2H_2O$$

Trichloroacetic acid, $CCl_3{\cdot}CO_2H$, is best prepared by oxidising chloral hydrate with concentrated nitric acid:

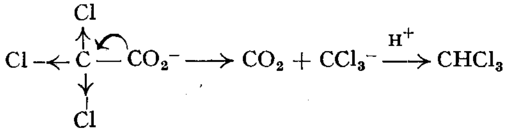
$$CCl_3{\cdot}CH(OH)_2 + [O] \xrightarrow{HNO_3} CCl_3{\cdot}CO_2H + H_2O$$

Trichloroacetic acid is a deliquescent solid, m.p. 58°, and is one of the strongest organic acids.

The presence of three chlorine atoms on a carbon atom adjacent to a carbonyl group causes the C—C bond to break very easily. Thus when trichloroacetic acid is boiled with dilute sodium hydroxide, or even water, chloroform is obtained:

$$CCl_3{\cdot}CO_2H \longrightarrow CHCl_3 + CO_2$$

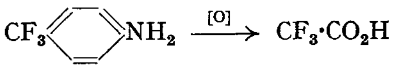
The ready fission of the C–Cl bond may be attributed to the strong inductive effect of the chlorine atoms, and a possible mechanism is:



$$\mathrm{Cl}\leftarrow\overset{\overset{\mathrm{Cl}}{\uparrow}}{\underset{\underset{\mathrm{Cl}}{\downarrow}}{\mathrm{C}}}-CO_2^- \longrightarrow CO_2 + CCl_3^- \xrightarrow{H^+} CHCl_3$$

When boiled with concentrated alkali, formates are produced, due to the hydrolysis of the chloroform which is formed first (see p. 117).

Trifluoroacetic acid, $CF_3{\cdot}CO_2H$, is conveniently prepared by the oxidation of *p*-trifluoromethyltoluidine with chromic acid:



Trifluoroacetic acid is a liquid that fumes in the air, and is one of the strongest organic acids known. It does not form fluoroform when heated with alkali, and is reduced to trifluoroacetaldehyde by lithium aluminium hydride. Peroxytrifluoroacetic acid, $CF_3{\cdot}CO_3H$, is a useful oxidising agent (Emmons, 1954; *cf.* peracetic acid).

Fluoroacetic acid may be prepared by heating a mixture of carbon monoxide, hydrogen fluoride and formaldehyde under pressure.

$$CO + HF + H{\cdot}CHO \longrightarrow CH_2F{\cdot}CO_2H$$

The simplest chloro-acid would be chloroformic acid, $Cl{\cdot}CO_2H$, but it is unknown; chlorination of formic acid results in the formation of hydrogen chloride and carbon dioxide:

$$H{\cdot}CO_2H \xrightarrow{Cl_2} 2HCl + CO_2$$

On the other hand, esters of chloroformic acid are known, and they may be prepared by the action of carbonyl chloride on an alcohol in the cold, *e.g.*, ethyl chloroformate from carbonyl chloride and ethanol:

$$COCl_2 + C_2H_5OH \longrightarrow Cl{\cdot}COOC_2H_5 + HCl$$

QUESTIONS

1. Write out the structures and the names of the isomeric acids having the molecular formula $C_6H_{12}O_2$.
2. Name the compounds and state the conditions under which they are formed when AcOH is treated with: (*a*) EtOH, (*b*) PCl_3, (*c*) PCl_5, (*d*) $SOCl_2$, (*e*) Br_2, (*f*) SO_2Cl_2, (*g*) $KMnO_4$, (*h*) HI/red P, (*i*) $LiAlH_4$, (*j*) H_2O_2, (*k*) CH_2N_2, (*l*) C_2H_4, (*m*) HN_3, (*n*) AcCl.
3. How would you determine the structures of *n*- and *iso*butyric acids?
4. Suggest a synthesis of each of the valeric acids, starting with compounds containing not more than three carbon atoms.
5. Name the compounds and state the conditions under which they are formed when EtOAc, AcCl and Ac_2O, respectively, are treated with:— (*a*) H_2O, (*b*) NaOH, (*c*) HCl, (*d*) nascent hydrogen, (*e*) molecular hydrogen, (*f*) NH_3, (*g*) *n*-BuOH, (*h*) PCl_5, (*i*) Br_2, (*j*) $NaNH_2$, (*k*) Na, (*l*) $NH_2{\cdot}OH$, (*m*) N_2H_4, (*o*) benzene, (*p*) Et_2O, (*q*) *iso*butene.
6. Name the compounds and state the conditions under which they are formed when $CH_3{\cdot}CO{\cdot}NH_2$ is treated with:—(*a*) NaOH, (*b*) HCl, (*c*) Na, (*d*) nascent hydrogen, (*e*) molecular hydrogen, (*f*) P_2O_5, (*g*) PCl_5, (*h*) HNO_2, (*i*) BF_3, (*j*) Br_2/KOH.
7. Define and give examples of:—(*a*) acetylation, (*b*) esterification, (*c*) saponification, (*d*) ammonolysis, (*e*) alcoholysis, (*f*) acidolysis, (*g*) acyloin condensation, (*h*) alkylation, (*i*) Hofmann degradation, (*j*) Curtius reaction, (*k*) Lossen rearrangement, (*l*) H.V.Z. reaction, (*m*) Rosenmund's reduction.
8. Describe the industrial preparations of:—(*a*) HCO_2H, (*b*) AcOH, (*c*) EtOAc, (*d*) AcCl, (*e*) Ac_2O, (*f*) Me_2SO_4, (*g*) Et_2SO_4, (*h*) $CH_2Cl{\cdot}CO_2H$, (*i*) $CHCl_2{\cdot}CO_2H$, (*j*) $CCl_3{\cdot}CO_2H$.
9. Show by means of equations how you would convert acetic acid into propionic acid and vice-versa.
10. Show how you would distinguish between:—(*a*) $CH_2Cl{\cdot}CO_2H$, $CH_3{\cdot}COCl$ and $CH_2Cl{\cdot}COCl$; (*b*) paraffin, olefin, alkyl halide, alcohol, ether, carboxylic acid, carboxylic ester, Ac_2O, AcCl and $AcNH_2$.
11. Discuss the mechanism of:—(*a*) esterification and hydrolysis, (*b*) the Hofmann, Curtius and Lossen rearrangements, (*c*) ammonolysis of esters and acid chlorides, (*d*) hydrolysis of cyanides and amides.
12. Discuss the methods of preparation and the properties of the halogeno-acids.

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CHAPTER X

TAUTOMERISM

Acetoacetic ester or **ethyl acetoacetate** (E.A.A.) is the ethyl ester of acetoacetic acid, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$, a β-ketonic acid. Acetoacetic ester was first discovered by Geuther (1863), who prepared it by the action of sodium on ethyl acetate, and suggested the formula, $CH_3{\cdot}C(OH){:}CH{\cdot}CO_2C_2H_5$ (β-hydroxycrotonic ester). In 1865, Frankland and Duppa, who, independently of Geuther, also prepared acetoacetic ester by the action of sodium on ethyl acetate, proposed the formula $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5$ (β-ketobutyric ester). These two formulæ immediately gave rise to two schools of thought, one upholding the Geuther formula, and the other the Frankland–Duppa formula, each school bringing forward evidence to prove its own claim, *e.g.*,

Evidence in favour of the Geuther formula (*reactions of an unsaturated alcohol*). (i) When acetoacetic ester is treated with sodium, hydrogen is evolved and the sodium derivative is formed. This indicates the presence of a hydroxyl group.

(ii) When acetoacetic ester is treated with an ethanolic solution of bromine, the colour of the latter is immediately discharged. This indicates the presence of an olefinic double bond.

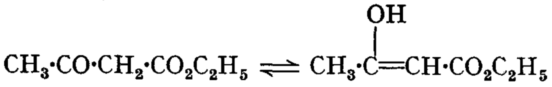
(iii) When acetoacetic ester is treated with ferric chloride, a reddish-violet colour is produced. This is characteristic of compounds containing the group $-C(OH){:}C<$ (*cf.* phenols).

Evidence in favour of the Frankland–Duppa formula (*reactions of a ketone*). (i) Acetoacetic ester forms a bisulphite compound with sodium hydrogen sulphite.

(ii) Acetoacetic ester forms a cyanohydrin with hydrogen cyanide.

(iii) Acetoacetic ester forms a phenylhydrazone with phenylhydrazine.

Thus the remarkable position arose where it was possible to show that a given compound had two different formulæ, each of which was based on a number of *particular* reactions. The controversy continued until about 1910, when chemists were coming to the conclusion that both formulæ were correct, and that the two compounds existed together in equilibrium in solution (or in the liquid state):



$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 \rightleftharpoons CH_3{\cdot}\overset{\overset{\displaystyle OH}{|}}{C}{=}CH{\cdot}CO_2C_2H_5$$

When a reagent which reacts with ketones is added to acetoacetic ester, the ketone form is removed. This upsets the equilibrium, and in order to restore the equilibrium mixture, the hydroxy-form of acetoacetic ester changes into the ketone form. Thus, provided sufficient reagent is added, acetoacetic ester reacts completely as the ketone form. Similarly, when a reagent which reacts with olefins or with hydroxy-compounds is added in sufficient quantity, acetoacetic ester reacts completely as the hydroxy-form.

The problem was finally settled by Knorr (1911), who succeeded in isolating both forms. He cooled a solution of acetoacetic ester in light petrol to −78°, and obtained crystals which melted at −39°. This substance gave no coloration with ferric chloride and did not combine with bromine, and was therefore the pure ketone form corresponding to the Frankland–Duppa formula. Knorr then suspended the sodium derivative of acetoacetic ester in light petrol cooled to −78°, and treated this suspension with just enough hydrogen chloride to decompose the sodium salt. He now obtained a product which did not crystallise, but set to a glassy solid when cooled. This substance gave an intense coloration with ferric chloride, and was therefore the pure hydroxy-form corresponding to the Geuther formula.

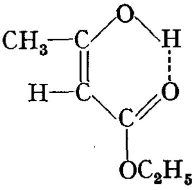
Thus acetoacetic ester is a substance that does the duty of two structural isomers, each isomer being capable of changing rapidly into the other when the equilibrium is disturbed, *e.g.*, by the addition of certain reagents. This is a case of *dynamic isomerism*, and the name *tautomerism* (Greek: *same parts*) was given to this phenomenon by Laar (1885). The two forms are known as *tautomers* or *tautomerides*, the ketone isomer being called the *keto* form, and the hydroxy isomer the *enol* form. Hence this type of tautomerism is known as *keto-enol* tautomerism. (In the I.U.P.A.C. system of nomenclature the suffix *-en* indicates the presence of a double bond, and the suffix *-ol*, a hydroxyl group. The word *enol* is a combination of these suffixes and indicates the structure of this form.)

A simplified version for the occurrence of tautomerism is as follows. Every structure has a certain amount of internal energy, and when dealing with two structural isomers, a definite amount of energy must be supplied in order to overcome the energy of transformation. If this amount of energy is small, then each isomer will change *spontaneously* into the other, resulting in an equilibrium mixture of the two forms. Calculations of the energy content of keto and enol tautomers on the basis of bond energies, show that the keto form is the more stable one. Thus, when the equilibrium mixture contains relatively large amounts of the enol form, then there must be present some stabilising factor for the enol form, *e.g.*, hydrogen bonding and resonance (see p. 223).

When one tautomer is more stable than the other under ordinary conditions, the former is known as the *stable* form, and the latter as the *labile* form. In practice, it is generally difficult to say which is the labile form, since very often a slight change in the conditions, *e.g.*, temperature, solvent, shifts the equilibrium from keto to enol or vice-versa (see below). Tautomerism in the solid state is rare, and hence, in the solid state, one or other tautomer is normally stable, but in the liquid or gaseous state, or in solution, the two forms usually exist as an equilibrium mixture.

It has been found that the enol form is more volatile than the keto, and that the change from enol to keto is extremely sensitive to catalysts. Meyer *et al.* (1920, 1921) found that traces of basic compounds were very effective catalysts. Thus they found that soft glass vessels were unsuitable for the separation of the keto and enol forms, since, when fractionated, the more volatile enol form rapidly changed into the original keto-enol mixture under the catalytic influence of the walls of the containing vessel. Meyer, however, succeeded in separating the enol form from the keto by carrying out the fractional distillation under reduced pressure in silica apparatus which had been thoroughly cleaned (freed from dust, moisture, etc.) Distillation under these conditions is known as *aseptic distillation.*

The greater volatility of the enol form is unexpected in view of the fact that alcohols are less volatile than ketones containing the same number of carbon atoms. This anomalous behaviour of the enol form may be explained by assuming that chelation takes place through hydrogen bonding. This is supported by various facts, *e.g.*, (i) the enol form is more soluble in *cyclo*hexane, and less soluble in water, than the keto form. The presence of the hydroxyl group should have made the enol form less soluble in *cyclo*hexane, and more soluble in water, than the keto (*cf.* alcohols). (ii) The formation of the hydrogen bond *intramolecularly* prevents the formation of the hydrogen bond *intermolecularly*, *i.e.*, prevents association which would have raised the boiling point of the enol form.



The vibrational spectrum of liquid ethyl acetoacetate shows *intermolecular* bonding between the enol and keto forms. In solvents such as carbon tetrachloride, and in dilute solution, *intramolecular* hydrogen bonding occurs in the enolic form, and the tautomeric equilibrium is displaced in the direction of the enol form (Shigorin, 1950).

In tautomerism in general there may be an equilibrium between two or more forms. One may predominate, or all may be present to about the same extent, the concentration of each form depending on the temperature and the solvent (if in solution). Although it may not be possible to separate tautomers owing to the ease and rapidity of their interconversion or, as in many cases, due to one form being almost completely absent, the presence of more than one compound may be shown by special properties of each isomer. The refractive index of the mixture may be observed directly, and the value obtained compared with those calculated for the various tautomeric structures. Spectral analysis may show the presence of more than one substance, since each structure will have its own characteristic absorption bands. Furthermore, the intensities of the bands change as the temperature changes, thus showing the displacement of the equilibrium. The Raman effect may also be used to show the presence of tautomers; *e.g.*, the equilibrium mixture of acetoacetic esters shows Raman shifts due to both the C=C and C=O groups. Experiments using deuterium exchange reactions have also shown the presence of keto-enol mixtures, *e.g.*, Klar (1934) showed that hydrogen is exchanged slowly by deuterium when acetaldehyde is dissolved in D_2O. Since the C—H bond in paraffins is stable under these conditions, the inference is that a hydroxyl group is present in acetaldehyde, *i.e.*, some enol form is present. Acetone was found to undergo this exchange more rapidly.

The methods used for the quantitative estimation of each form in any tautomeric equilibrium mixture, of which the keto-enol system is only one example, fall into two distinct groups, physical and chemical. Obviously, whatever the method used, it should be one that does not disturb the equilibrium of the mixture during the estimation.

Physical methods. Physical methods do not disturb the equilibrium, for they do not depend on the removal of one form, and they should therefore be used wherever possible.

(i) The refractive index of the equilibrium mixture is determined experimentally. The refractive indices of both the keto and enol forms are calculated (from a table of atomic refractions), and from these figures it is then possible to calculate the amount of each form present in the equilibrium mixture. In some cases, the refractive index of each form may be obtained directly by isolating it, *e.g.*, acetoacetic ester.

(ii) If *one* form is an electrolyte, the electrical conductivity of the mixture is determined experimentally, and the amount of this form present may be calculated from the results, *e.g.*, nitromethane (p. 304).

(iii) The composition of the equilibrium mixture may be determined by means of optical rotation measurements (*cf.* mutarotation, p. 451).

(iv) Joshi and Tuli (1951) have introduced a new physical constant which they have named the *refrachor*, and have used it to determine the percentage of tautomers in an equilibrium mixture, *e.g.*, they found that ethyl acetoacetate contains 7·7% enol, and acetylacetone 72·4% enol.

(v) Jarrett *et al.* (1953) have determined keto-enol equilibria in two β-diketones by measurement of proton resonance.

Chemical methods. Since chemical methods cause the removal of one form, it is necessary to use a reagent that reacts with this form faster than the rate of interconversion of the tautomers. Meyer (1911, 1912) found that in the case of keto-enol tautomerism, bromine reacts instantaneously with the enol form, and so slowly with the keto form in comparison with the enol, that the keto reaction may be ignored. Meyer introduced two procedures, the *direct* and the *indirect* method. In the *direct* method a weighed sample of the keto-enol mixture dissolved in ethanol is *rapidly* titrated with a dilute ethanolic solution of bromine at 0° (to slow down the interconversion of the tautomers). The first appearance of excess bromine indicates the end point (see also the bromination of acetone, p. 154).

The titration must be carried out rapidly; otherwise the keto form changes into the enol during the time taken for the titration. In any case, it has been found impossible to carry out the titration sufficiently rapidly to avoid the conversion of some keto into enol, and so this method always results in too high a value for the enol form.

More reliable results may be obtained by the *indirect* method. An *excess* of dilute ethanolic solution of bromine is added rapidly to the weighed sample dissolved in ethanol, and then an excess of 2-naphthol dissolved in ethanol is added *immediately*. By this means, the excess bromine is removed almost instantaneously, and so the keto-enol equilibrium is not given time to be disturbed. Potassium iodide solution and hydrochloric acid are now added, and the liberated iodine is titrated with standard thiosulphate:

$$KI + HCl \longrightarrow KCl + HI$$

$$CH_3{\cdot}CO{\cdot}CHBr{\cdot}CO_2C_2H_5 + KI \longrightarrow CH_3{\cdot}CO{\cdot}CHI{\cdot}CO_2C_2H_5 + KBr$$

$$CH_3{\cdot}CO{\cdot}CHI{\cdot}CO_2C_2H_5 + HI \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 + I_2$$

Cooper and Barnes (1938) have suggested an improved indirect method using methanol instead of ethanol, and di-*iso*butene instead of 2-naphthol (di-*iso*butene is a mixture of 2 : 4 : 4-trimethylpent-1-ene and 2 : 4 : 4-trimethylpent-2-ene).

Schwarzenbach and Wittwer (1947) have introduced a new technique, the *flow-method*, for the estimation of the enol content. The solution of the keto-enol mixture and an acidified bromide–bromate solution are simultaneously mixed and diluted in a mixing chamber, and the mixture made to flow past a platinum electrode. The relative amounts of the two solutions are adjusted so that the potential measured at the platinum electrode shows a sharp rise—this corresponds to the end-point in the titration of the enol form by the bromine. This method gives good results of enol contents as low as 10^{-5} per cent.; *e.g.*, the enol content of acetone in aqueous solution was found to be $2{\cdot}5 \times 10^{-4}$ per cent.

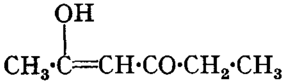
TABLE IV

Compound	Per cent. enol (in ethanol)
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2CH_3$	4·8
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5$	7·5
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$	76
$CH_3{\cdot}CO{\cdot}CH(CH_3){\cdot}CO{\cdot}CH_3$	31
$C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$	96
$CH_2(CO_2C_2H_5)_2$	trace
Aldehydes of type $R{\cdot}CH_2{\cdot}CHO$	trace
Ketones of type $R{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}R$	trace

The enol content in keto-enol mixtures (in dipropyl ether) has been determined by means of lithium aluminium hydride; the hydrogen liberated is estimated (Höfling *et al.*, 1952). The values obtained are about 10 per cent. higher than those obtained by the bromine titration or by physical methods.

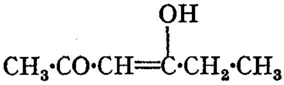
Enolisation. The phenomenon of enolisation is exhibited by compounds containing either a methylene group, $\cdot CH_2\cdot$, or a methyne group, $>CH-$, adjacent to a carbonyl group. The presence of one carbonyl group does not always give rise to an appreciable amount of enol form, *e.g.*, acetaldehyde, acetone (see Table IV, above). If the compound contains a methylene or methyne group attached to two carbonyl groups the percentage of enol form is usually high, *e.g.*, acetylacetone, $CH_3\cdot CO\cdot CH_2\cdot CO\cdot CH_3$. When a methyne group is attached to three carbonyl groups, the compound may exist almost completely as the enol form, *e.g.*, triacetylmethane, $(CH_3\cdot CO)_3CH$.

When the methylene or methyne group is attached to two or three carbonyl groups, the hydrogen atom might migrate equally well to one or other carbonyl group. This is not found to be so in practice for unsymmetrical compounds, one enol form being present exclusively, or largely predominating; *e.g.*, in acetoacetic ester the hydrogen atom migrates exclusively to the acetyl carbonyl group (see also below). When two or more enol forms are theoretically possible, ozonolysis may be used to ascertain the structure of the form present; *e.g.*, in hexane-2 : 4-dione, $CH_3\cdot CO\cdot CH_2\cdot CO\cdot CH_2\cdot CH_3$, the two possible enols are:



$$CH_3\cdot\overset{OH}{\overset{|}{C}}{=}CH\cdot CO\cdot CH_2\cdot CH_3$$

(I)



$$CH_3\cdot CO\cdot CH{=}\overset{OH}{\overset{|}{C}}\cdot CH_2\cdot CH_3$$

(II)

Ozonolysis of I will give $CH_3\cdot CO_2H$ and $CH_3\cdot CH_2\cdot CO\cdot CHO$; II will give $CH_3\cdot CO\cdot CHO$ and $CH_3\cdot CH_2\cdot CO_2H$. Identification of these compounds will decide whether the enol is I or II, or both.

The type of tautomerism discussed above is known as the **keto-enol triad system.** In this system a hydrogen atom migrates from atom 1 (*oxygen*) to atom 3 (*carbon*):

$$>\overset{3}{C}H-\overset{2}{C}{=}\overset{1}{O} \rightleftharpoons >\overset{3}{C}{=}\overset{2}{C}-\overset{1}{O}H$$

Enols resemble phenols in a number of ways; *e.g.*, both form soluble sodium salts; both give characteristic colorations with ferric chloride; and both couple with diazonium salts.

The keto-enol type of tautomerism is only one example of a triad system. The triad system is the most important class of tautomeric systems, and the following, which are exemplified in the text, are the commonest:

(i) *Three-carbon systems:*

$$CH-C{=}C \rightleftharpoons C{=}C-CH$$

(ii) *Nitro-acinitro* (*pseudonitro*) *system:*

$$CH-NO_2 \rightleftharpoons C{=}NO\cdot OH$$

(iii) *Nitroso-oximino system:*

$$CH-N{=}O \rightleftharpoons C{=}N\cdot OH$$

(iv) *Amidine system:*

$$NH-C{=}N \rightleftharpoons N{=}C-NH$$

(v) *Amido-imidol system:*

$$NH-C{=}O \rightleftharpoons N{=}C-OH$$

(vi) *Azo-hydrazone system:*

$$N{=}N{-}CH \rightleftharpoons HN{-}N{=}C$$

(vii) *Diazo-amino* (*triazen*) *system:*

$$N{=}N{-}NH \rightleftharpoons NH{-}N{=}N$$

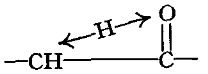
(viii) *Diazo-nitrosamine system:*

$$Ar{-}N{=}N{\cdot}OH \rightleftharpoons Ar{-}NH{-}N{=}O$$

In addition to the "open" systems of tautomerism, there are also, *e.g.*, *ring-chain tautomerism* (see, *e.g.*, aldol, p. 237; carbohydrates, p. 451, succinyl chloride, p. 377); and *valence tautomerism* (see p. 485).

Modern theories of tautomerism. Ingold (1927) suggested the name *cationotropy* for all those cases of tautomerism which involve the separation of a *cation*; and the name *anionotropy* for those cases which involve the separation of an *anion*. Lowry (1923) suggested the name *prototropy* for those cases in which a proton separates, and called such systems *prototropic* systems. Using Ingold's generalised classification of tautomeric systems, it can be seen that prototropy is a special case of cationotropy. Braude and Jones (1944) have proposed the term *oxotropy* for anionotropic rearrangements involving only the migration of a *hydroxyl* group (see allylic rearrangement, p. 272).

Laar (1885) attempted to account for keto-enol tautomerism by postulating that the hydrogen atom occupied a mean position with respect to the final positions it would occupy in the keto and enol forms, and that by a lateral movement in either direction the hydrogen atom formed the keto or enol form. Baly and Desch (1904) extended this theory into the *oscillation theory* (*isorropesis*), according to which the hydrogen atom oscillated continuously between the two positions as shown. This theory soon became untenable, since it did not agree with many of the experimental observations (see below).

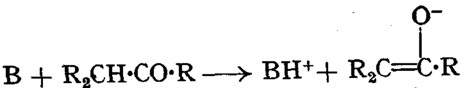


Jacobson (1887) objected to the use of the word tautomerism to describe the above phenomenon because it involved the view that tautomers have no definite structure, but are continually changing. Jacobson thought that *both* forms were present, and that the change from one into the other was caused by the presence of certain reagents. He therefore proposed the name *desmotropy* or *desmotropism* (Greek: change of bonds). Hantzsch and Hermann (1887) suggested that both the terms tautomerism and desmotropism should be used, the former to denote that a compound exhibited a dual nature, and the latter to indicate those cases of tautomerism where the two forms exist in different physical forms (*i.e.*, those cases of tautomerism in which both forms have been isolated).

Knorr (1896) introduced the term *allelotropic mixture* for equilibrium mixtures whose composition varied with changes in temperature, *i.e.*, an allelotropic mixture is a tautomeric mixture in the liquid state or in solution; a mixture of solid tautomers is not an allelotropic mixture.

The term *pseudomerism* has also been used for those cases of tautomerism in which only one form, the keto or enol, may be shown to be present.

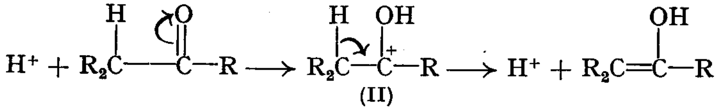
The actual steps involved in keto-enol tautomerism are still the subject of much discussion. According to Hughes and Ingold, base-catalysed enolisation of a ketone proceeds through an enolate anion I whose formation is controlled largely by the inductive effects of the alkyl groups.



$$B + R_2CH{\cdot}CO{\cdot}R \longrightarrow BH^+ + R_2C{=}\overset{\overset{\displaystyle O^-}{|}}{C}{\cdot}R$$

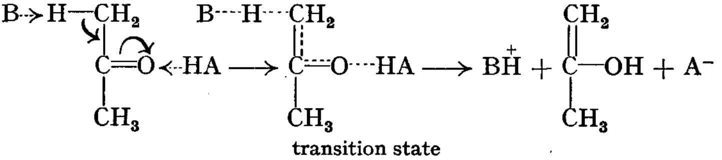
(I)

Acid-catalysed enolisation involves the removal of a proton from the conjugate acid of the ketone, II, and this process is dependent mainly on the hyperconjugation (p. 270) by the alkyl groups in the transition state for the formation of the carbon-carbon double bond.

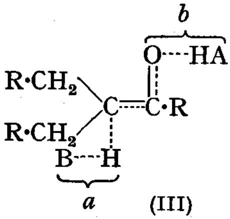

(II)

Evidence for these mechanisms is that alkyl groups depress base-catalysed reaction rates.

The mechanisms described above are step-wise mechanisms, and they appear to operate in certain cases. On the other hand, there is evidence that in other cases, acid and base catalysis of enolisation take place by a *concerted* or *push-pull* mechanism, *i.e.*, the molecule undergoing change is attacked simultaneously at two places. Thus the enolisation of, *e.g.*, acetone, proceeds by the simultaneous removal of a proton from an α-carbon and the addition of a proton to the oxygen of the carbonyl group. This may be represented as follows (B is a general base, and HA is a general acid):



In this type of mechanism, the solvent water molecules are believed to be involved, one acting as a proton acceptor and the other as a proton donor. Furthermore, the above mechanism is termolecular, and Swain (1950) has presented evidence to show that both the acid- and base-catalysed enolisation of acetone are termolecular reactions. Emmons *et al.* (1956) have obtained evidence supporting Swain's termolecular mechanism for ketone enolisation, but propose that the transition state for both acid- and base-catalysed enolisation may be represented by III.

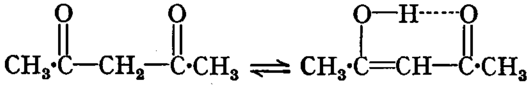

(III)

Under these conditions in either acid- or base-catalysed reactions, the transition state will be very close to the enol and hence will be stabilised by hyperconjugation. In the acid-catalysed reaction, bond *b* is relatively tight and bond *a* is relatively loose. Hence in acid-catalysed enolisation, steric hindrance around bond *a* is not observed in most cases, and hyperconjugation is therefore a dominating factor in the enolisation of a ketone. In the base-catalysed reaction, bond *a* is relatively tight and bond *b* is relatively loose. Under these conditions a steric factor becomes important and is probably the reason why alkyl groups depress base-catalysed reaction rates.

The tremendous increase in speed by acid and base catalysts is well illustrated by the fact that the pure keto and enol forms of ethyl acetoacetate change very slowly into the equilibrium mixture (several weeks), whereas the latter is obtained rapidly (several minutes) by the addition of acid or base catalysts (Lowry *et al.*, 1924).

It has been shown that in keto-enol equilibrium mixtures, the enol form reacts extremely rapidly with halogens, is acidic and produces an anion which is reactive both at the oxygen and α-carbon (to the hydroxyl group).

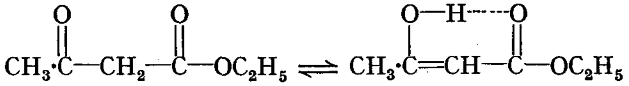
It has been pointed out above (see also Table IV, p. 219) that in keto-enol tautomerism the enol content of the equilibrium mixture varies from compound to compound; but the reason for this is still an open question. It appears to be quite certain that the solvent plays a part, but the nature of the other factors is uncertain. Some authors believe that resonance and hydrogen bonding are involved; *e.g.*, it has been suggested that the enol form of acetylacetone is stabilised by chelation through hydrogen bonding:



$$CH_3\cdot\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}\cdot CH_3 \rightleftharpoons CH_3\cdot\overset{\overset{O-H\cdots\cdots O}{|\qquad\qquad\|}}{C=CH-C}\cdot CH_3$$

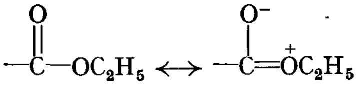
Hydrogen bond formation is not possible in acetaldehyde, acetone, etc., and therefore the enol forms of these compounds cannot be stabilised this way.

Now let us consider the case of ethyl acetoacetate:



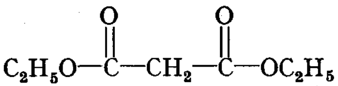
$$CH_3\cdot\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 \rightleftharpoons CH_3\cdot\overset{\overset{O-H\cdots\cdots O}{|\qquad\qquad\|}}{C=CH-C}-OC_2H_5$$

The enol form is stabilised by chelation; but ethyl acetoacetate contains 54 per cent. enol form in the vapour state, whereas acetylacetone contains 92 per cent. If chelation were the only factor involved, one might have expected that the enol content of the two compounds would have been about the same. A possible explanation for this difference may be due to the resonating structure of the carbethoxy group:



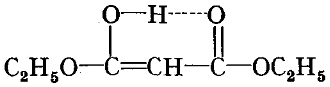
$$-\overset{\overset{O}{\|}}{C}-OC_2H_5 \longleftrightarrow -\overset{\overset{O^-}{|}}{C}=\overset{+}{O}C_2H_5$$

This effect will tend to stabilise the keto form, thereby reducing the tendency to enolise. The large part played by the resonance effect of the carbethoxy group in reducing the enol content may be inferred by considering ethyl malonate. This compound contains only a trace of the enol form. Its structure is IV, and its enol structure will be V.



$$C_2H_5O-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

(IV)



$$C_2H_5O-\overset{\overset{O-H\cdots\cdots O}{|\qquad\qquad\|}}{C=CH-C}-OC_2H_5$$

(V)

If both carbethoxy groups are affected by resonance, the *keto* form will be stabilised, *i.e.*, there will be very little tendency to enolise.

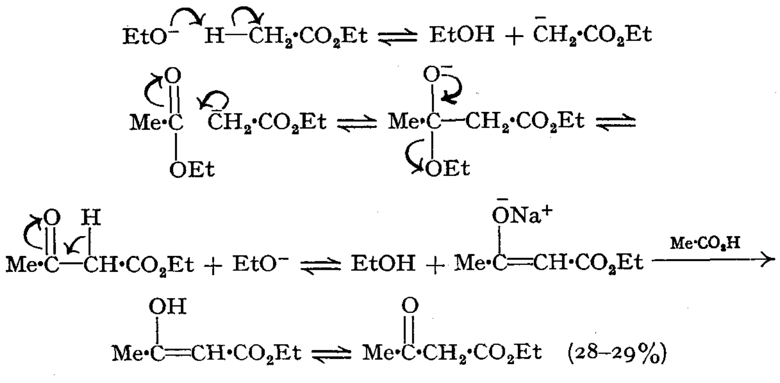
It was pointed out above that the nature of the solvent also affects the position of equilibrium in keto-enol tautomerism. If we assume (as we have above) that the enol form is, where possible, stabilised by chelation, then solvents that prevent chelation will reduce the enol content. Thus hydroxylic solvents such as water, methanol, ethanol, acetic acid, etc., in which the hydrogen atom of the hydroxyl group can form a hydrogen bond with the oxygen atom of the carbonyl group of the keto form, will tend to reduce the enol content; *e.g.*, ethyl acetoacetate contains 54 per cent. enol in the vapour phase; in ethanol, the enol content is 7·5 per cent. On the other hand, where hydrogen bond formation with the solvent is not possible, *e.g.*, in hexane, benzene, etc., the enol content will be large.

According to Arndt *et al.* (1946), the effect of the solvent on enol content is to be explained as follows. Hydrophilic solvents favour the keto form, whereas hydrophobic and lipophilic solvents favour the enol form. The above authors have shown that the more the hydrophobic groups predominate in a molecule of a tautomeric substance of a given structure, the greater is the enol content in the equilibrium mixture. Thus they found that the enol content of the esters of acetoacetic acid increased in the order methyl, ethyl, propyl, butyl, 2-octyl and benzyl; this is the order in which the whole molecule (ester) becomes more hydrophobic.

The preparation of ethyl acetoacetate. In the preparation of ethyl acetoacetate, condensation is effected between two molecules of the same ester. This is one example of the **Claisen condensation** (1887), in which a keto-ester is formed by the reaction between two molecules of an ester containing α-hydrogen atoms. In certain cases the second ester does not contain an α-hydrogen atom, *e.g.*, ethyl formate, ethyl benzoate and ethyl oxalate (see text for examples of their use). The Claisen condensation may also take place between an ester and a ketone to form a 1 : 3-diketone. The condensation is brought about by sodium ethoxide, sodamide, triphenylmethylsodium, etc. Sodium ethoxide is the reagent usually employed in the preparation of ethyl acetoacetate.

If sodium is added to ethyl acetate which has been very carefully freed from ethanol, very little action takes place. When a small amount of ethanol is added, a vigorous reaction sets in. This seems to indicate that it is probably sodium ethoxide, and not sodium, which is the effective reagent for the condensation (Snell and McElvain, 1931). The product is the sodium enolate of ethyl acetoacetate and this, on treatment with acid, liberates ethyl acetoacetate, which may be purified by distillation *in vacuo*.

Many mechanisms have been proposed for the formation of ethyl acetoacetate. The one most widely accepted at the moment is (*cf.* aldol condensation).



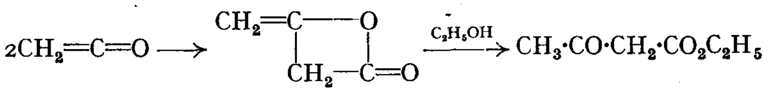
$$\mathrm{EtO^- \;\; H{-}CH_2{\cdot}CO_2Et \rightleftharpoons EtOH + \bar{C}H_2{\cdot}CO_2Et}$$

$$\mathrm{Me{\cdot}\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle OEt}{|}}{C}}}\;\; \bar{C}H_2{\cdot}CO_2Et \rightleftharpoons Me{\cdot}\overset{\displaystyle O^-}{\overset{|}{\underset{\underset{\displaystyle OEt}{|}}{C}}}{-}CH_2{\cdot}CO_2Et \rightleftharpoons}$$

$$\mathrm{Me{\cdot}\overset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\displaystyle H}{\overset{|}{C}}H{\cdot}CO_2Et + EtO^- \rightleftharpoons EtOH + Me{\cdot}\overset{\displaystyle \bar{O}Na^+}{\overset{|}{C}}{=}CH{\cdot}CO_2Et \xrightarrow{Me{\cdot}CO_2H}}$$

$$\mathrm{Me{\cdot}\overset{\displaystyle OH}{\overset{|}{C}}{=}CH{\cdot}CO_2Et \rightleftharpoons Me{\cdot}\overset{\displaystyle O}{\overset{\|}{C}}{\cdot}CH_2{\cdot}CO_2Et \quad (28\text{–}29\%)}$$

Ethyl acetoacetate is now also being prepared industrially by polymerising keten in acetone solution to diketen, which is then treated with ethanol.

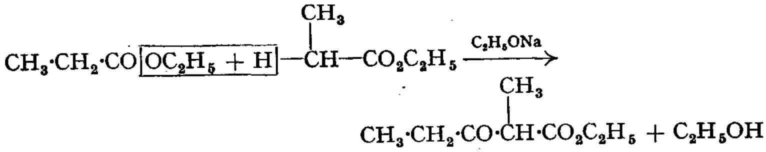


$$\mathrm{2CH_2{=}C{=}O \longrightarrow \begin{array}{c} CH_2{=}C{-}O \\ |\qquad | \\ CH_2{-}C{=}O \end{array} \xrightarrow{C_2H_5OH} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5}$$

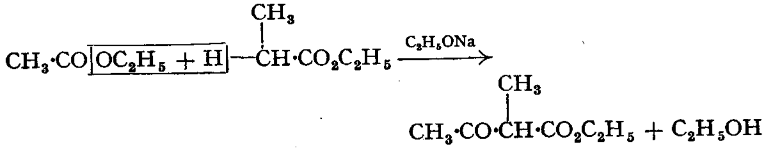
In " mixed ethyl acetoacetate condensations " between two different esters, a mixture of all four possible products is usually obtained; *e.g.*, with ethyl acetate and ethyl propionate:

(i) $\mathrm{CH_3{\cdot}CO\boxed{OC_2H_5 + H}{-}CH_2{\cdot}CO_2C_2H_5 \xrightarrow{C_2H_5ONa}}$

$\mathrm{CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 + C_2H_5OH}$

(ii) 

$$CH_3\cdot CH_2\cdot CO\boxed{OC_2H_5 + H}-\overset{CH_3}{\overset{|}{C}}H-CO_2C_2H_5 \xrightarrow{C_2H_5ONa} CH_3\cdot CH_2\cdot CO\cdot\overset{CH_3}{\overset{|}{C}}H\cdot CO_2C_2H_5 + C_2H_5OH$$

(iii) 

$$CH_3\cdot CO\boxed{OC_2H_5 + H}-\overset{CH_3}{\overset{|}{C}}H\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} CH_3\cdot CO\cdot\overset{CH_3}{\overset{|}{C}}H\cdot CO_2C_2H_5 + C_2H_5OH$$

(iv) $$CH_3\cdot CH_2\cdot CO\boxed{OC_2H_5 + H}-CH_2\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} CH_3\cdot CH_2\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + C_2H_5OH$$

These reactions clearly show that only α-hydrogen atoms are involved in the Claisen condensation.

Properties of ethyl acetoacetate. Ethyl acetoacetate is a colourless, pleasant-smelling liquid, b.p. 181° (with slight decomposition), sparingly soluble in water, but miscible with most organic solvents. It is readily reduced by sodium amalgam, or catalytically to β-hydroxybutyric ester:

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + 2[H] \longrightarrow CH_3\cdot CH(OH)\cdot CH_2\cdot CO_2C_2H_5$$

Lithium aluminium hydride reduces ethyl acetoacetate to butane-1 : 3-diol (Buchta *et al.*, 1951).

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 \xrightarrow{LiAlH_4} CH_3\cdot CHOH\cdot CH_2\cdot CH_2OH \quad (30\%)$$

On the other hand, ethyl acetoacetate may be reduced to ethyl butyrate by treating it with methyl mercaptan in the presence of zinc chloride and sodium sulphate, and then reducing the thioketal with Raney nickel in ethanolic solution (Newman *et al.*, 1950; *cf.* p. 334).

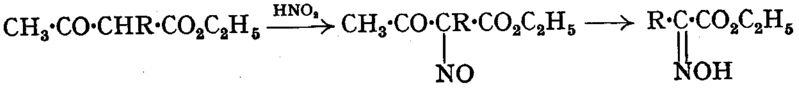
Ethyl acetoacetate is neutral to litmus, but is soluble in dilute sodium hydroxide solution: it is the enol form which dissolves to form the sodium salt. When ethyl acetoacetate is hydrolysed in the cold with dilute sodium hydroxide, the solution then acidified, extracted with ether and the ether removed in the cold under reduced pressure, free acetoacetic acid is obtained. Krueger (1952) has prepared acetoacetic acid as a crystalline solid, m.p. 36–37°. As prepared in the usual way it is unstable, readily decomposing into acetone and carbon dioxide:

$$CH_3\cdot CO\cdot CH_2\cdot CO_2H \longrightarrow CH_3\cdot CO\cdot CH_3 + CO_2$$

All β-ketonic acids readily decompose in this manner, but it is interesting to note that trifluoroacetoacetic acid, $CF_3\cdot CO\cdot CH_2\cdot CO_2H$, is quite stable and can be distilled without much decomposition. Ethyl acetoacetate forms α-oximinoacetoacetate when treated with nitrous acid:

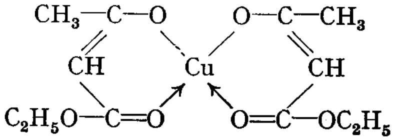
$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 \xrightarrow{HNO_2} CH_3\cdot CO\cdot C({=}NOH)\cdot CO_2C_2H_5$$

On the other hand, monosubstituted derivatives of ethyl acetoacetate are split by nitrous acid; the nitroso-compound is formed first and then rearranges to the oximino form with fission of the molecule.

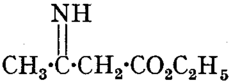


$$CH_3\cdot CO\cdot CHR\cdot CO_2C_2H_5 \xrightarrow{HNO_2} CH_3\cdot CO\cdot\underset{\underset{NO}{|}}{C}R\cdot CO_2C_2H_5 \longrightarrow R\cdot\underset{\underset{NOH}{\|}}{C}\cdot CO_2C_2H_5$$

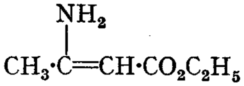
Ethyl acetoacetate forms a green copper compound which is soluble in organic solvents. This indicates that the copper compound is not an ionic but a chelate compound, and its structure is possibly:



Acetoacetic ester reacts with ammonia (and with primary amines), but the structure of the compound produced is uncertain, there being two possibilities, the *imine* form I, and the *amine* form II:

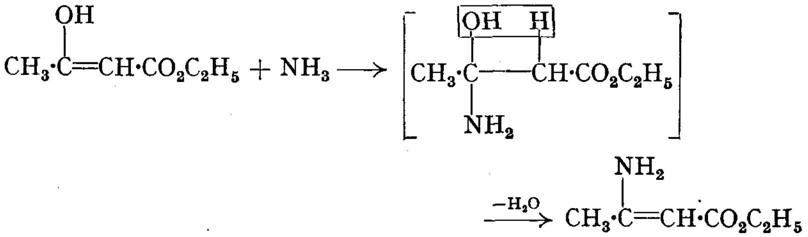
(I) 

$CH_3{\cdot}C(=NH){\cdot}CH_2{\cdot}CO_2C_2H_5$

 (II)

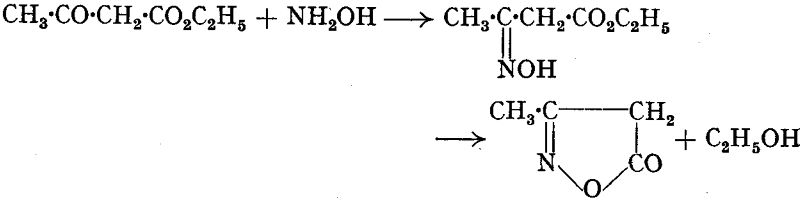
$CH_3{\cdot}C(NH_2){=}CH{\cdot}CO_2C_2H_5$

Most of the experimental work favours II. It is possible that the reaction takes places through the enol form:



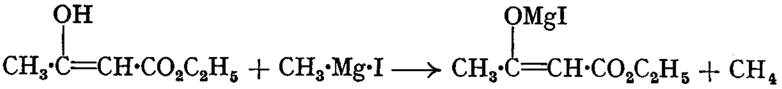
$$CH_3{\cdot}C(OH){=}CH{\cdot}CO_2C_2H_5 + NH_3 \longrightarrow \left[CH_3{\cdot}C(OH)(NH_2){-}CH(H){\cdot}CO_2C_2H_5\right] \xrightarrow{-H_2O} CH_3{\cdot}C(NH_2){=}CH{\cdot}CO_2C_2H_5$$

Monoalkyl derivatives of acetoacetic ester, $CH_3{\cdot}CO{\cdot}CHR{\cdot}CO_2C_2H_5$, react with ammonia in a similar manner but the dialkyl derivatives, $CH_3{\cdot}CO{\cdot}CR_2{\cdot}CO_2C_2H_5$, form the amide $CH_3{\cdot}CO{\cdot}CR_2{\cdot}CO{\cdot}NH_2$. This supports the mechanism given above, since the monoalkyl derivatives can enolise, whereas the dialkyl derivatives cannot. Ethyl acetoacetate also reacts with hydroxylamine to form an *iso*-oxazolone.



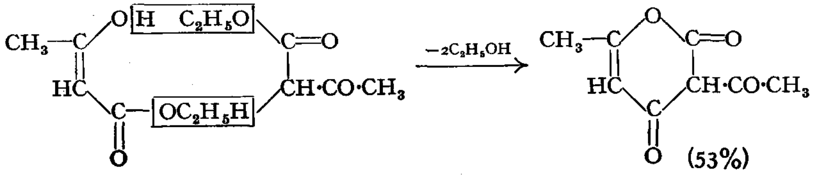
With phenylhydrazine, ethyl acetoacetate forms a pyrazolone (p. 755).

Acetoacetic ester undergoes the Knoevenagel reaction due to the presence of an "active" methylene group (p. 155), and also couples with diazonium salts. It reacts with Grignard reagents to form the hydrocarbon, which indicates that it reacts in the enol form, *e.g.*,

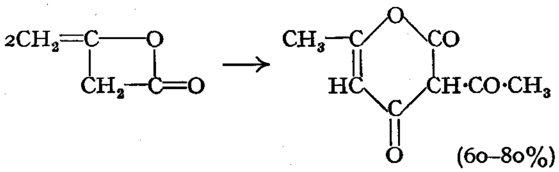


$$CH_3{\cdot}C(OH){=}CH{\cdot}CO_2C_2H_5 + CH_3{\cdot}Mg{\cdot}I \longrightarrow CH_3{\cdot}C(OMgI){=}CH{\cdot}CO_2C_2H_5 + CH_4$$

When acetoacetic ester is heated under reflux with a trace of sodium hydrogen carbonate, ethanol is eliminated and **dehydroacetic acid,** m.p. 180°, is obtained:



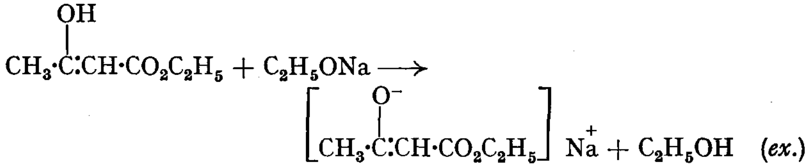
Dehydroacetic acid may also be prepared by the polymerisation of diketen:



THE USE OF ACETOACETIC ESTER IN THE SYNTHESIS OF KETONES AND FATTY ACIDS

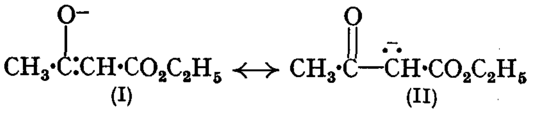
The synthetic use of acetoacetic ester depends on two chemical properties:

1. (*a*) When treated with sodium ethoxide, acetoacetic ester forms sodioacetoacetic ester, *i.e.*, the sodium derivative of the enolic form:



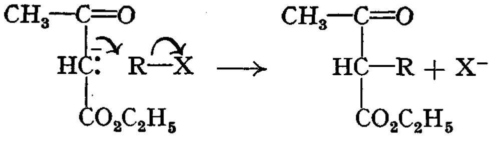
$$CH_3\cdot\overset{OH}{C}{:}CH\cdot CO_2C_2H_5 + C_2H_5ONa \longrightarrow \left[CH_3\cdot\overset{O^-}{C}{:}CH\cdot CO_2C_2H_5\right]\overset{+}{Na} + C_2H_5OH \quad (ex.)$$

(*b*) Sodioacetoacetic ester readily reacts with primary and secondary alkyl halides (vinyl and aryl halides do *not* react) to produce alkyl derivatives of acetoacetic ester in which the alkyl group is attached to carbon. This fact has given rise to considerable speculation regarding the mechanism of the alkylation process. The problem is still not settled, but a highly favoured theory is that the negative ion is a resonance hybrid:



$$\underset{(I)}{CH_3\cdot\overset{O^-}{C}{:}CH\cdot CO_2C_2H_5} \longleftrightarrow \underset{(II)}{CH_3\cdot\overset{O}{\overset{\|}{C}}-\overset{\cdot\cdot-}{C}H\cdot CO_2C_2H_5}$$

Thus in the actual state both the oxygen and carbon atoms have a negative charge; but since a negatively charged carbon atom is more reactive than a negatively charged oxygen atom, it is the carbon atom that is the point of attack. As the actual state of the molecule cannot be represented by a single formula, the process of alkylation may be regarded as involving structure II, *i.e.*, a carbanion. There is also evidence to show that the alkylation occurs by an S_N2 process. Thus:



For the sake of simplicity the alkylation of sodioacetoacetic ester will, in future, be represented as:

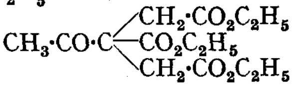
$$[CH_3{\cdot}CO{\cdot}CH{\cdot}CO_2C_2H_5]^-Na^+ + RX \longrightarrow CH_3{\cdot}CO{\cdot}CHR{\cdot}CO_2C_2H_5 + NaX \quad (v.g.)$$

After one alkyl group has been introduced, the whole process may then be repeated to give the dialkyl derivative of acetoacetic ester:

$$CH_3{\cdot}CO{\cdot}CHR{\cdot}CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3{\cdot}CO{\cdot}CR{\cdot}CO_2C_2H_5]^-Na^+ \xrightarrow{R'X} CH_3{\cdot}CO{\cdot}CRR'{\cdot}CO_2C_2H_5 \quad (g.\text{–}v.g.)$$

Until recently, it was not considered possible to prepare ***disubstituted*** derivatives of acetoacetic ester in *one* step. Sandberg (1957), however, has now carried out this one-step reaction in the preparation of ethyl β-acetotricarballylate from acetoacetic ester (0·5 mole), ethyl bromoacetate (1·2 mole) and sodium hydride (1·2 mole) in benzene solution.

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 + 2CH_2Br{\cdot}CO_2C_2H_5 \xrightarrow{2NaH}$$



$$CH_3{\cdot}CO{\cdot}C(CH_2{\cdot}CO_2C_2H_5)_2(CO_2C_2H_5) \quad (77\%)$$

Potassium *tert.*-butoxide is usually best for preparing the metallo-acetoacetic ester compounds, and generally alkyl iodides react faster than alkyl bromides (Renfrow and Renfrow, 1946).

2. Acetoacetic ester and its alkyl derivatives can undergo two types of hydrolysis with potassium hydroxide:

(*a*) **Ketonic hydrolysis.** Ketonic hydrolysis, so called because a ketone is the chief product, is carried out by boiling with ***dilute*** aqueous or ethanolic potassium hydroxide solution, *e.g.*,

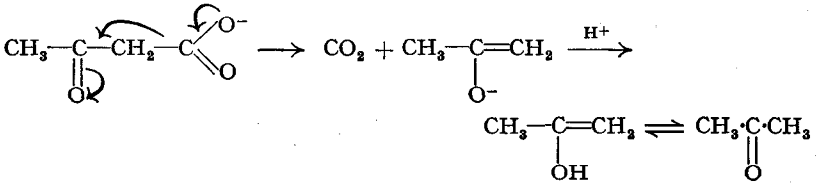
$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 + 2KOH \longrightarrow CH_3{\cdot}CO{\cdot}CH_3 + K_2CO_3 + C_2H_5OH \quad (g.)$$

$$CH_3{\cdot}CO{\cdot}CHR{\cdot}CO_2C_2H_5 + 2KOH \longrightarrow CH_3{\cdot}CO{\cdot}CH_2R + K_2CO_3 + C_2H_5OH \quad (g.)$$

The ketone obtained is acetone or its derivatives, and the latter *always contain the group* $CH_3{\cdot}CO$—.

Dehn and Jackson (1933) found that 85 per cent. phosphoric acid was a very good catalyst for the ketonic hydrolysis of acetoacetic ester and its alkyl derivatives, the yield of ketone reaching 95 per cent.

The mechanism of ketonic hydrolysis is uncertain; a possibility is:



It is the electron-attracting property of the carbonyl group that facilitates the elimination of carbon dioxide.

(*b*) **Acid hydrolysis.** Acid hydrolysis, so called because an acid is the chief product, is carried out by boiling with ***concentrated*** ethanolic potassium hydroxide solution, *e.g.*,

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + 2KOH \longrightarrow CH_3\cdot CO_2K + CH_3\cdot CO_2K + C_2H_5OH \quad (f.g.)$$

$$CH_3\cdot CO\cdot CR_2\cdot CO_2C_2H_5 + 2KOH \longrightarrow CH_3\cdot CO_2K + R_2CH\cdot CO_2K + C_2H_5OH \quad (f.g.)$$

The acid obtained is acetic acid or its derivatives as the potassium salt. From this the free acid is readily obtained by treatment with inorganic acid.

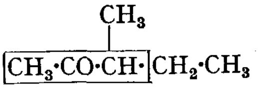
The mechanism of acid hydrolysis is possibly a reversal of the Claisen condensation. Only the ester of acetic acid undergoes condensation, and when the condensation is reversed, the ester is converted into the potassium salt which cannot recondense; hence the equilibrium is forced in the reverse direction to that of condensation.

Examples of the synthesis of ketones. The formula of the ketone is written down, and ***provided it contains the group*** $CH_3\cdot CO$—, the ketone can be synthesised via acetoacetic ester as follows. The acetone nucleus is picked out, and the alkyl groups attached to it are then introduced into acetoacetic ester one at a time; this is followed by ketonic hydrolysis. It is usually better to introduce the larger group before the smaller (steric effect):

(i) *Butanone.* $\boxed{CH_3\cdot CO\cdot CH_2\cdot}CH_3$

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{CH_3I} CH_3\cdot CO\cdot CH(CH_3)\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3\cdot CO\cdot CH_2\cdot CH_3$$

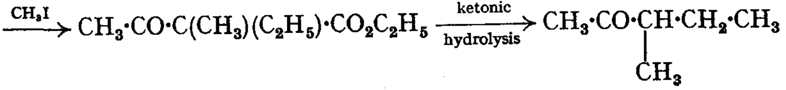
(ii) 3-*Methylpentan*-2-*one.*



$$\boxed{CH_3\cdot CO\cdot \overset{\displaystyle CH_3}{\overset{|}{C}H}\cdot}CH_2\cdot CH_3$$

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{C_2H_5I}$$

$$CH_3\cdot CO\cdot CH(C_2H_5)\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3\cdot CO\cdot C(C_2H_5)\cdot CO_2C_2H_5]^-Na^+$$



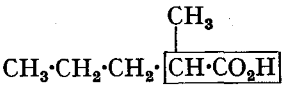
$$\xrightarrow{CH_3I} CH_3\cdot CO\cdot C(CH_3)(C_2H_5)\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3\cdot CO\cdot \underset{\displaystyle CH_3}{\underset{|}{C}H}\cdot CH_2\cdot CH_3$$

Examples of the synthesis of fatty acids. The approach is similar to that for ketones except that the acetic acid nucleus is picked out, and the acetoacetic ester derivative is subjected to acid hydrolysis. The acetoacetic ester acid synthesis is usually confined to the preparation of straight-chain acids or branched-chain acids where the branching occurs on the α-carbon atom:

(i) n-*Butyric acid.* $CH_3\cdot CH_2\cdot\boxed{CH_2\cdot CO_2H}$

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{C_2H_5I} CH_3\cdot CO\cdot CH(C_2H_5)\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{acid}} CH_3\cdot CH_2\cdot CH_2\cdot CO_2H$$

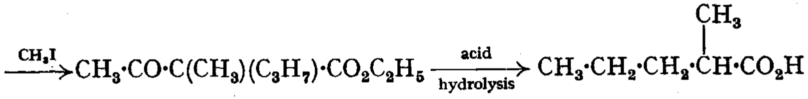
(ii) α-*Methyl*-n-*valeric acid.*



$$CH_3\cdot CH_2\cdot CH_2\cdot\boxed{\overset{\displaystyle CH_3}{\overset{|}{C}H}\cdot CO_2H}$$

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{C_3H_7Br}$$

$$CH_3\cdot CO\cdot CH(C_3H_7)\cdot CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [CH_3\cdot CO\cdot C(C_3H_7)\cdot CO_2C_2H_5]^-Na^+$$



$$\xrightarrow{CH_3I} CH_3\cdot CO\cdot C(CH_3)(C_3H_7)\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{acid}} CH_3\cdot CH_2\cdot CH_2\cdot \overset{\displaystyle CH_3}{\overset{|}{C}H}\cdot CO_2H$$

It has been found that ketonic hydrolysis and acid hydrolysis of acetoacetic ester *always take place simultaneously*, but one or the other can be made to predominate by adjusting the concentration of the potassium hydroxide. Thus, in the preparation of acids, there will always be some ketone formed as by-product; and vice-versa. For this reason it is better to use ethyl malonate to synthesise acids since the yields are greater.

Ritter *et al.* (1962) have improved the preparation of acids via E.A.A. by heating the mono-alkyl derivatives with catalytic amounts of alkoxide in excess of absolute ethanol:

$$MeCO\cdot CHR\cdot CO_2Et + EtOH \xrightarrow{OEt^-} MeCO_2Et + R\cdot CH_2\cdot CO_2Et \ (70\text{–}90\%)$$

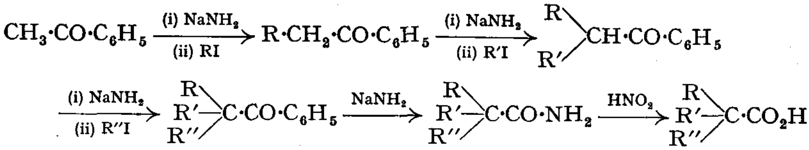
In addition to the acetoacetic ester ketone synthesis, ketones may be prepared in a somewhat analogous method as follows:

(i) From simpler ketones; *e.g.*, acetone in ether solution is treated with sodamide and the sodioacetone then treated with methyl iodide, whereupon ethyl methyl ketone is produced:

$$CH_3\cdot CO\cdot CH_3 \xrightarrow[\text{ether}]{NaNH_2} [CH_3\cdot CO\cdot CH_2]^-Na^+ \xrightarrow{CH_3I} CH_3\cdot CO\cdot CH_2\cdot CH_3$$

Repetition of the process on ethyl methyl ketone gives a mixture of methyl *iso*propyl ketone and diethyl ketone, which can be separated by fractional distillation. By repeating the process hexamethylacetone (di-*tert.*-butyl ketone), $(CH_3)_3C\cdot CO\cdot C(CH_3)_3$, can finally be obtained.

This synthesis has been modified to prepare *tert.*-carboxylic acids, acetophenone being the ketone used as starting material (Haller *et al.*, 1914). The yields are good for the simpler members of the series (Carter *et al.*, 1946).



$$CH_3\cdot CO\cdot C_6H_5 \xrightarrow[\text{(ii) }RI]{\text{(i) }NaNH_2} R\cdot CH_2\cdot CO\cdot C_6H_5 \xrightarrow[\text{(ii) }R'I]{\text{(i) }NaNH_2} \begin{matrix}R\\R'\end{matrix}\!\!>CH\cdot CO\cdot C_6H_5$$

$$\xrightarrow[\text{(ii) }R''I]{\text{(i) }NaNH_2} \begin{matrix}R\\R'\\R''\end{matrix}\!\!>C\cdot CO\cdot C_6H_5 \xrightarrow{NaNH_2} \begin{matrix}R\\R'\\R''\end{matrix}\!\!>C\cdot CO\cdot NH_2 \xrightarrow{HNO_2} \begin{matrix}R\\R'\\R''\end{matrix}\!\!>C\cdot CO_2H$$

(ii) Ketones may also be prepared from certain esters. It has been found that esters of the type $R_2CH\cdot CO_2C_2H_5$ do not undergo the normal Claisen condensation with sodium ethoxide. In the presence of triphenylmethylsodium, $(C_6H_5)_3C^-Na^+$, however, they readily form the sodio-salt (Schlenk *et al.*, 1931). These sodium salts react with acid chlorides, and the resulting compounds, which are β-keto-esters, yield ketones on ketonic hydrolysis:

$$R_2CH\cdot CO_2C_2H_5 \xrightarrow{(C_6H_5)_3CNa} [R_2C\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{R'\cdot COCl} R'\cdot CO\cdot CR_2\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} R'\cdot CO\cdot CHR_2$$

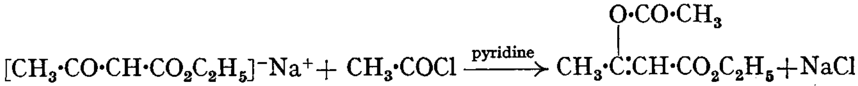
(iii) β-Keto-acids, $R\cdot CO\cdot CHR'\cdot CO_2H$, can be prepared by α-carboxylation of ketones, $R\cdot CO\cdot CH_2R'$, with magnesium methyl carbonate. The intermediate magnesium salt can be alkylated *in situ* and then decarboxylated to give ketones, $R\cdot CO\cdot CHR'R''$ (Stiles *et al.*, 1959).

Sodioacetoacetic ester reacts with many other halogen compounds besides alkyl halides, and so may be used to synthesise a variety of compounds.

(i) 1 : 3-*Diketones.* In the synthesis of 1 : 3-diketones the halogen compound used is an acid chloride. Since acid chlorides react with ethanol, the reaction cannot be carried out in this solvent in the usual way. The reaction, however, may conveniently be carried out by treating acetoacetic ester in benzene solution with magnesium and the acid chloride; *e.g.*, pentane-2:4-dione may be obtained by the ketonic hydrolysis of the intermediate product ethyl diacetylacetate:

$$CH_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + CH_3\cdot COCl \xrightarrow{Mg} (CH_3\cdot CO)_2CH\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3\cdot CO\cdot CH_2\cdot CO\cdot CH_3$$

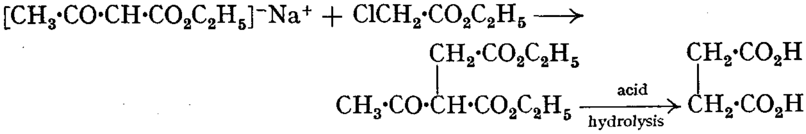
If sodioacetoacetic ester or acetoacetic ester itself is treated with acetyl chloride in pyridine as solvent, the *O-acetyl* derivative of acetoacetic ester, acetoxycrotonic ester, is obtained, and not the carbon-linked compound (as above):



$$[CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ + CH_3\cdot COCl \xrightarrow{\text{pyridine}} CH_3\cdot \overset{O\cdot CO\cdot CH_3}{\overset{|}{C}}{:}CH\cdot CO_2C_2H_5 + NaCl$$

The reason for this unusual reaction is obscure.

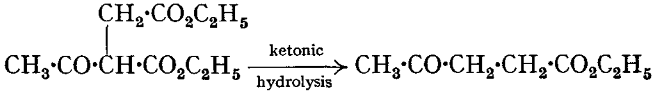
(ii) *Dicarboxylic acids.* Dicarboxylic acids may be prepared by interaction of sodioacetoacetic ester and a halogen derivative of an ester, *e.g.*, succinic acid from ethyl chloroacetate:



$$[CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ + ClCH_2\cdot CO_2C_2H_5 \longrightarrow$$

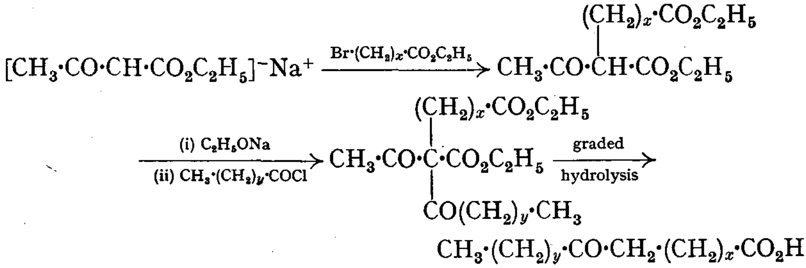
$$CH_3\cdot CO\cdot \overset{CH_2\cdot CO_2C_2H_5}{\overset{|}{C}H}\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{acid}} \begin{matrix}CH_2\cdot CO_2H\\ |\\ CH_2\cdot CO_2H\end{matrix}$$

Ketonic hydrolysis of this acetoacetic ester derivative gives the γ-keto-acid ester (ethyl ester of lævulic acid):



$$CH_3\cdot CO\cdot \overset{CH_2\cdot CO_2C_2H_5}{\overset{|}{C}H}\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot CO_2C_2H_5$$

(iii) *Long-chain fatty acids.* An ingenious method of synthesising long-chain fatty acids via acetoacetic ester involves a combination of methods (i) and (ii) described above (Mrs. Robinson, 1930):



$$[CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{Br\cdot(CH_2)_x\cdot CO_2C_2H_5} CH_3\cdot CO\cdot \overset{(CH_2)_x\cdot CO_2C_2H_5}{\overset{|}{C}H}\cdot CO_2C_2H_5$$

$$\xrightarrow[\text{(ii) } CH_3\cdot(CH_2)_y\cdot COCl]{\text{(i) } C_2H_5ONa} CH_3\cdot CO\cdot \underset{CO(CH_2)_y\cdot CH_3}{\underset{|}{\overset{(CH_2)_x\cdot CO_2C_2H_5}{\overset{|}{C}}}}\cdot CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{graded}}$$

$$CH_3\cdot(CH_2)_y\cdot CO\cdot CH_2\cdot(CH_2)_x\cdot CO_2H$$

These keto-acids are readily reduced to the corresponding fatty acid by means of the Clemmensen reduction (p. 150). Improved modifications of this method have now been developed (see p. 363).

(iv) *Ring compounds.* (*a*) When sodioacetoacetic ester is treated with certain dihalogen derivatives of the paraffins, carbocyclic compounds are obtained (see p. 470).

(*b*) Acetoacetic ester may be used to prepare a number of heterocyclic compounds (see Ch. XXX).

MALONIC ESTER SYNTHESES

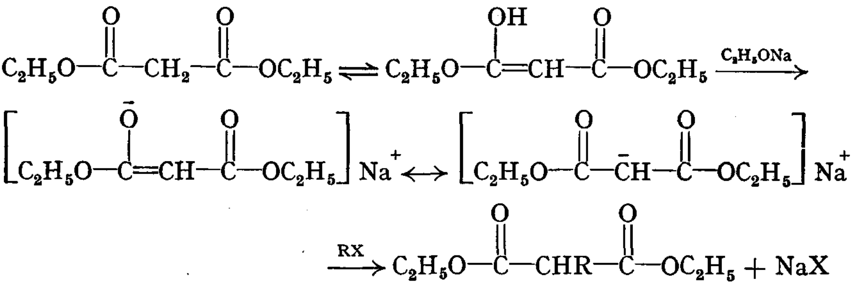
Malonic ester, $CH_2(CO_2C_2H_5)_2$, which is the diethyl ester of malonic acid $CH_2(CO_2H)_2$, is prepared by dissolving potassium cyanoacetate in ethanol, adding concentrated hydrochloric acid, and warming the mixture on the water-bath:

$$NC{\cdot}CH_2{-}CO_2K + 2C_2H_5OH + 2HCl \longrightarrow CH_2(CO_2C_2H_5)_2 + KCl + NH_4Cl \quad (v.g.)$$

Malonic ester may be prepared (yield 82–84 per cent.) by refluxing cyanoacetic acid in ethanol in the presence of chlorosulphonic acid (Dvornik *et al.*, 1953).

It is a pleasant-smelling liquid, b.p. 199°. Its use as a synthetic reagent depends on two chemical properties.

1. With sodium ethoxide it forms a sodium derivative, sodiomalonic ester, which reacts with compounds containing a reactive halogen atom, *e.g.*, alkyl halides, acid chlorides, halogen-substituted esters, etc. (*cf.* acetoacetic ester). In all cases the yields are *g.–v.g.* The anion of the sodium salt is probably a resonance hybrid, and when it reacts with a halogen reagent, the entering radical becomes attached to the carbon atom:



$$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \rightleftharpoons C_2H_5O-\overset{OH}{\overset{|}{C}}{=}CH-\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow{C_2H_5ONa}$$

$$\left[C_2H_5O-\overset{\bar{O}}{\overset{|}{C}}{=}CH-\overset{O}{\overset{\|}{C}}-OC_2H_5\right]Na^+ \longleftrightarrow \left[C_2H_5O-\overset{O}{\overset{\|}{C}}-\bar{C}H-\overset{O}{\overset{\|}{C}}-OC_2H_5\right]Na^+$$

$$\xrightarrow{RX} C_2H_5O-\overset{O}{\overset{\|}{C}}-CHR-\overset{O}{\overset{\|}{C}}-OC_2H_5 + NaX$$

The process may then be repeated to produce the disubstituted derivative of malonic ester:

$$R{\cdot}CH(CO_2C_2H_5)_2 \xrightarrow{C_2H_5ONa} [R{\cdot}C(CO_2C_2H_5)_2]^-Na^+ \xrightarrow{R'X} RR'C(CO_2C_2H_5)_2$$

These disubstituted derivatives of malonic ester can readily be prepared in *one* step by treating the ester with *two* equivalents of sodium ethoxide and then with *two* equivalents of alkyl halide. This procedure is only used if it is required to introduce two identical alkyl groups. The mechanism of this reaction is obscure; it will be represented as follows:

$$CH_2(CO_2C_2H_5)_2 \xrightarrow{2C_2H_5ONa} [C(CO_2C_2H_5)_2]^{2-}2Na^+ \xrightarrow{2RX} R_2C(CO_2C_2H_5)_2 + 2NaX$$

2. Malonic acid and its derivatives eliminate a molecule of carbon dioxide when heated just above the melting point of the acid (usually between 150° and 200°) to form acetic acid or its derivatives (the yields are *v.g.–ex.*):

$$CO_2H{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_3{\cdot}CO_2H + CO_2$$
$$CO_2H{\cdot}CHR{\cdot}CO_2H \longrightarrow R{\cdot}CH_2{\cdot}CO_2H + CO_2$$

Decarboxylation may also be effected by refluxing malonic acid or its derivatives in sulphuric acid solution.

In a number of cases ethyl cyanoacetate (b.p. 207°) may be used instead of malonic ester in many syntheses. The cyano-group is readily converted into the carboxyl group on hydrolysis.

Synthesis of fatty acids. Malonic ester is preferable to acetoacetic ester in synthesising acids, and should be used wherever possible. The structural formula of the acid required is written down, the acetic acid nucleus picked out, and the required alkyl groups introduced into sodiomalonic ester. The substituted ester is then refluxed with potassium hydroxide solution, acidified with hydrochloric acid, and the precipitated acid dried and then heated just above its melting point. Alternatively, the potassium salt may be refluxed with sulphuric acid:

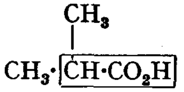
(i) n-*Valeric acid.* $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}\boxed{CH_2{\cdot}CO_2H}$

$$CH_2(CO_2C_2H_5)_2 \xrightarrow{C_2H_5ONa} [CH(CO_2C_2H_5)_2]^-Na^+ \xrightarrow{C_3H_7Br}$$

$$C_3H_7{\cdot}CH(CO_2C_2H_5)_2 \xrightarrow{KOH} C_3H_7{\cdot}CH(CO_2K)_2 \xrightarrow{HCl}$$

$$C_3H_7{\cdot}CH(CO_2H)_2 \xrightarrow{150-200^\circ} CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

(ii) *Dimethylacetic acid.*



$CH_3{\cdot}\boxed{\overset{\overset{CH_3}{|}}{C}H{\cdot}CO_2H}$

$$CH_2(CO_2C_2H_5)_2 \xrightarrow{C_2H_5ONa} [CH(CO_2C_2H_5)_2]^-Na^+ \xrightarrow{CH_3I} CH_3{\cdot}CH(CO_2C_2H_5)_2$$

$$\xrightarrow{C_2H_5ONa} [CH_3{\cdot}C(CO_2C_2H_5)_2]^-Na^+ \xrightarrow{CH_3I} (CH_3)_2C(CO_2C_2H_5)_2 \xrightarrow{KOH}$$

$$(CH_3)_2C(CO_2K)_2 \xrightarrow{HCl} (CH_3)_2C(CO_2H)_2 \xrightarrow{150-200^\circ} (CH_3)_2CH{\cdot}CO_2H$$

Since two methyl groups are required for this synthesis, their introduction can be carried out in one step (see above):

$$CH_2(CO_2C_2H_5)_2 \xrightarrow{2C_2H_5ONa} [C(CO_2C_2H_5)_2]^{2-}2Na^+ \xrightarrow{2CH_3I}$$

$$(CH_3)_2C(CO_2C_2H_5)_2 \xrightarrow{KOH,\ etc.} (CH_3)_2CH{\cdot}CO_2H$$

Synthesis of dicarboxylic acids. Dicarboxylic acids of the type $RR'C(CO_2H)_2$ are readily prepared from malonic ester as shown above. They are important only in so far as they are intermediates in the preparation of fatty acids.

Dicarboxylic acids of the type $CO_2H{\cdot}(CH_2)_n{\cdot}CO_2H$ are very important, and the malonic ester synthesis is particularly useful for their preparation. The actual procedure depends mainly on the value of n, and the following examples illustrate this point:

(i) *Adipic acid.* $\boxed{CO_2H{\cdot}CH_2{\cdot}}CH_2{\cdot}CH_2\boxed{{\cdot}CH_2{\cdot}CO_2H}$

The acetic acid is blocked off at *one* end, and the remaining fragment is considered from the point of view of accessibility. In this example the fragment required is γ-bromobutyric ester. This is not readily accessible, and so the procedure now is to block off the acetic acid nucleus at the *other* end of the adipic acid molecule, and then to use *two* molecules of malonic ester and the $\alpha\omega$-*dihalide* of the polymethylene fragment that joins together the two acetic acid nuclei. In this case it is ethylene bromide, and since this is readily accessible, the synthesis of adipic acid may be carried out as follows:

$$[(C_2H_5O_2C)_2CH]^-Na^+ + BrCH_2{\cdot}CH_2Br + Na^+[CH(CO_2C_2H_5)_2]^- \longrightarrow$$

$$(C_2H_5O_2C)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2C_2H_5)_2 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}}$$

$$(HO_2C)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2H)_2 \xrightarrow{150-200^\circ} CO_2H{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

Should the fragments required by either route be inaccessible, then a method not involving the use of malonic ester may be more satisfactory (see p. 379).

(ii) *Succinic acid.* $\boxed{CO_2H\cdot CH_2\cdot}CH_2\cdot CO_2H$

If *one* acetic acid nucleus is blocked off, the fragment required is ethyl chloroacetate. This is readily accessible and hence succinic acid may be synthesised from *one* molecule of malonic ester as follows:

$$[CH(CO_2C_2H_5)_2]^-Na^+ + ClCH_2\cdot CO_2C_2H_5 \longrightarrow (C_2H_5O_2C)_2CH\cdot CH_2\cdot CO_2C_2H_5$$
$$\xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} (HO_2C)_2CH\cdot CH_2\cdot CO_2H \xrightarrow{150\text{–}200^\circ} CO_2H\cdot CH_2\cdot CH_2\cdot CO_2H$$

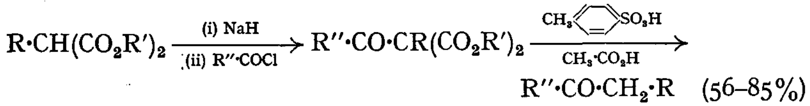
If the *other* acetic acid nucleus in succinic acid is blocked off, there is no intervening fragment left. Hence if two moelcules of malonic ester could be united *directly*, this would offer an alternative route for the synthesis of succinic acid. Actually, the union of two malonic ester molecules may be effected by means of iodine. Thus:

$$[(C_2H_5O_2C)_2CH]^-Na^+ + I_2 + Na^+[CH(CO_2C_2H_5)_2]^- \longrightarrow$$
$$(C_2H_5O_2C)_2CH\cdot CH(CO_2C_2H_5)_2 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} (HO_2C)_2CH\cdot CH(CO_2H)_2$$
$$\xrightarrow{150\text{–}200^\circ} CO_2H\cdot CH_2\cdot CH_2\cdot CO_2H$$

Synthesis of ketones. Bowman *et al.* (1952) have introduced the following general synthesis of ketones and β-keto-esters (R′ = tetrahydropyran-2-ol):

$$R\cdot CH(CO_2R')_2 \xrightarrow[\text{(ii) R}''\text{·COCl}]{\text{(i) Na}} R''\cdot CO\cdot CR(CO_2R')_2 \xrightarrow[\text{reflux}]{CH_3\cdot CO_2H}$$
$$R''\cdot CO\cdot CH_2\cdot R \quad (50\text{–}92\%)$$

Johnson *et al.* (1952) have used *tert.*-butyl esters of malonic acid (R′ = *tert.*-butyl):



$$R\cdot CH(CO_2R')_2 \xrightarrow[\text{(ii) R}''\text{·COCl}]{\text{(i) NaH}} R''\cdot CO\cdot CR(CO_2R')_2 \xrightarrow[CH_3\cdot CO_2H]{CH_3C_6H_4SO_3H}$$
$$R''\cdot CO\cdot CH_2\cdot R \quad (56\text{–}85\%)$$

Synthesis of higher ketonic acids. Sodiomalonic ester is treated with the acid chloride-ester derivative of a dibasic acid, *e.g.*, ε-ketoheptoic acid:

$$[(C_2H_5O_2C)_2CH]^-Na^+ + COCl\cdot(CH_2)_4\cdot CO_2C_2H_5 \longrightarrow$$
$$(C_2H_5O_2C)_2CH\cdot CO(CH_2)_4\cdot CO_2C_2H_5 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} (HO_2C)_2CH\cdot CO(CH_2)_4\cdot CO_2H$$
$$\xrightarrow{150\text{–}200^\circ} [CO_2H\cdot CH_2\cdot CO\cdot(CH_2)_4\cdot CO_2H] \longrightarrow CH_3\cdot CO\cdot(CH_2)_4\cdot CO_2H$$

The intermediate β-keto-dicarboxylic acid is unstable and is readily decarboxylated. This might have been anticipated, since it may be regarded as a derivative of acetoacetic acid, which is readily decarboxylated on warming.

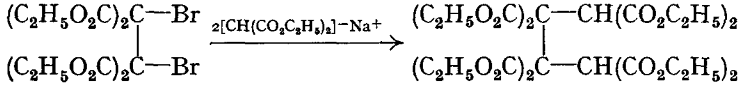
Synthesis of polybasic acids. It has been pointed out previously (p. 211) that the monoalkyl derivatives of malonic acid are readily brominated, and that these bromo-derivatives give α-bromo-fatty acids on decarboxylation.

Malonic ester is also readily brominated, and this monobromo-derivative may be used to synthesise polybasic acids, *e.g.*,

$$CH_2(CO_2C_2H_5)_2 \xrightarrow{Br_2} CHBr(CO_2C_2H_5)_2$$

$$CHBr(CO_2C_2H_5)_2 + [CH(CO_2C_2H_5)_2]^-Na^+ \longrightarrow$$

$$NaBr + (C_2H_5O_2C)_2CH{\cdot}CH(CO_2C_2H_5)_2 \xrightarrow{Br_2}$$



$$\begin{array}{l}(C_2H_5O_2C)_2C{-}Br\\ \quad\;\;|\\(C_2H_5O_2C)_2C{-}Br\end{array} \xrightarrow{2[CH(CO_2C_2H_5)_2]^-Na^+} \begin{array}{l}(C_2H_5O_2C)_2C{-}CH(CO_2C_2H_5)_2\\ \quad\;\;|\\(C_2H_5O_2C)_2C{-}CH(CO_2C_2H_5)_2\end{array}$$

Malonic ester may also be used for the preparation of unsaturated acids (Knoevenagel reaction, p. 280), alicyclic compounds (p. 469), and heterocyclic compounds (p. 386).

HYDROXYALDEHYDES AND HYDROXYKETONES

When naming a compound which contains more than one functional group, it is necessary to choose one as the principal function. The compound is then named by using the suffix of the principal function and the prefixes of the other functions. The carboxylic and the sulphuric acid group are *always* chosen as principal functions, and the usual order for choosing the principal function is:

Carboxylic, sulphonic, acid halide, amide, imide, aldehyde, cyanide, *iso*cyanide, ketone, alcohol, phenol, thioalcohol, amine, imine.

Examples. Acetoacetic acid contains a ketonic group and a carboxyl group, and since the latter is the principal function, acetoacetic acid is named as a ketone acid, *viz.*, β-ketobutyric acid. Acetoacetic acid may also be named propan-2-one-1-carboxylic acid—each functional group is indicated by its appropriate suffix.

TABLE V

Function	Prefix	Suffix
Acid	carboxy	carboxylic or -oic
Alcohol	hydroxy	ol
Aldehyde	oxo, aldo (for aldehydic O) or formyl (for CHO)	al
Amine	amino	amine
Azo-derivative	azo	—
Azoxy-derivative	azoxy	—
Carbonitrile (nitrile)	cyano	carbonitrile
Double bond	—	ene
Ether	alkoxy	—
Ethylene oxide, etc.	epoxy	—
Halogenide (halide)	halogeno (halo)	—
Hydrazine	hydrazino	hydrazine
Ketone	oxo or keto	one
Mercaptan	mercapto	thiol
Nitro-derivative	nitro	—
Nitroso-derivative	nitroso	—
" Quinquevalent " nitrogen	—	onium, inium
Sulphide	alkylthio	—
Sulphinic derivative	sulphino	sulphinic
Sulphone	sulphonyl	—
Sulphonic derivative	sulpho	sulphonic
Sulphoxide	sulphinyl	—
Triple bond	—	yne
Urea	ureido	urea

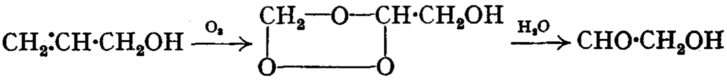
$CH_2OH{\cdot}CH_2{\cdot}CHO$. This is both an alcohol and an aldehyde, so that, bearing in mind the order of preference, the name of the compound will be β-hydroxypropionaldehyde.

Table V indicates the prefixes and suffixes used for designating the functions (in alphabetical order).

The simplest hydroxyaldehyde is **glycolaldehyde** (*hydroxyethanal*), $CH_2OH{\cdot}CHO$. It may be prepared by the oxidation of glycol with *Fenton's reagent* (hydrogen peroxide and ferrous sulphate):

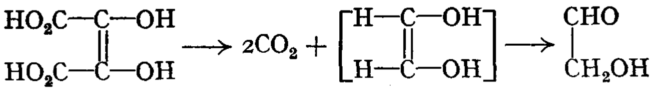
$$CH_2OH{\cdot}CH_2OH + H_2O_2 \xrightarrow{FeSO_4} CH_2OH{\cdot}CHO + 2H_2O$$

It may also be prepared by ozonolysis of allyl alcohol:



$$CH_2{:}CH{\cdot}CH_2OH \xrightarrow{O_3} \begin{array}{l} CH_2{-}O{-}CH{\cdot}CH_2OH \\ |\qquad\qquad | \\ O{-}{-}{-}{-}{-}O \end{array} \xrightarrow{H_2O} CHO{\cdot}CH_2OH$$

The most convenient means of preparing glycolaldehyde, however, is by heating dihydroxymaleic acid, which is obtained from the oxidation of tartaric acid (*q.v.*):

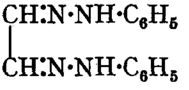


$$\begin{array}{l} HO_2C{-}C{-}OH \\ \qquad\;\; \| \\ HO_2C{-}C{-}OH \end{array} \longrightarrow 2CO_2 + \left[\begin{array}{l} H{-}C{-}OH \\ \quad\;\, \| \\ H{-}C{-}OH \end{array}\right] \longrightarrow \begin{array}{l} CHO \\ | \\ CH_2OH \end{array}$$

Glycolaldehyde exists in the solid form as the dimer, m.p. 96°; but in aqueous solution it exists as the monomer which forms the stable hydrate, $CH(OH)_2{\cdot}CH_2OH$ (*cf.* chloral, p. 168). Careful oxidation of glycolaldehyde with bromine water produces glycollic acid:

$$CH_2OH{\cdot}CHO + [O] \longrightarrow CH_2OH{\cdot}CO_2H$$

Glycolaldehyde is a powerful reducing agent, reducing ammoniacal silver nitrate and Fehling's solution at room temperature. With phenylhydrazine it forms the *osazone*. This osazone is identical with that formed from glyoxal, and the mechanism of its formation is still an open question (see carbohydrates, p. 443).



$$\begin{array}{l} CH{:}N{\cdot}NH{\cdot}C_6H_5 \\ | \\ CH{:}N{\cdot}NH{\cdot}C_6H_5 \end{array}$$

Glycolaldehyde undergoes the aldol condensation in the presence of alkali; with sodium hydroxide solution a tetrose sugar is formed, and with sodium carbonate solution, a hexose sugar:

$$2CH_2OH{\cdot}CHO \xrightarrow{NaOH} CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$$

$$3CH_2OH{\cdot}CHO \xrightarrow{Na_2CO_3} CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$$

Glycolaldehyde is formed in small amounts when formaldehyde is allowed to stand in the presence of calcium carbonate:

$$2H{\cdot}CHO \xrightarrow{CaCO_3} CH_2OH{\cdot}CHO$$

Glycolaldehyde is a useful starting material in a number of organic syntheses, but since it readily polymerises, the ethyl ether is used in synthetic work. The ethyl ether may be prepared by catalytically dehydrogenating ethyl cellosolve:

$$C_2H_5O{\cdot}CH_2{\cdot}CH_2OH \xrightarrow[250^\circ]{Cu} C_2H_5O{\cdot}CH_2{\cdot}CHO + H_2 \quad (43\%)$$

The ethyl group is easily eliminated when necessary by means of concentrated hydriodic acid or hydrobromic acid (p. 142).

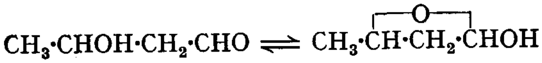
Aldol (*acetaldol, β-hydroxybutyraldehyde, 3-hydroxybutanal*), $CH_3\cdot CHOH\cdot CH_2\cdot CHO$, may be prepared by the aldol condensation of acetaldehyde (p. 157):

$$2CH_3\cdot CHO \xrightarrow{NaOH} CH_3\cdot CHOH\cdot CH_2\cdot CHO$$

It is a colourless syrupy liquid, b.p. 83°/20 mm., miscible with water and ethanol. When heated, it is dehydrated to crotonaldehyde:

$$CH_3\cdot CHOH\cdot CH_2\cdot CHO \longrightarrow CH_3\cdot CH{:}CH\cdot CHO + H_2O$$

There is some doubt about the structure of aldol. Recent work suggests it is an equilibrium mixture of β-hydroxybutyraldehyde and the cyclic hemiacetal:



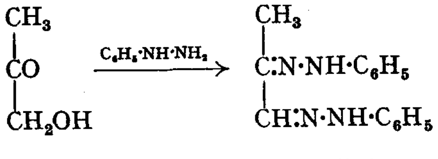
This is an example of ring-chain tautomerism.

The simplest hydroxyketone is **hydroxyacetone** (*acetol, pyruvic alcohol*), $CH_3\cdot CO\cdot CH_2OH$. The best method of preparation is by heating bromoacetone with potassium hydroxide in methanolic solution, and adding ethyl formate:

$$H\cdot CO_2C_2H_5 + KOH \longrightarrow H\cdot CO_2K + C_2H_5OH$$
$$CH_3\cdot CO\cdot CH_2Br + H\cdot CO_2K \longrightarrow CH_3\cdot CO\cdot CH_2\cdot OOC\cdot H + KBr$$
$$CH_3\cdot CO\cdot CH_2\cdot OOC\cdot H + CH_3OH \longrightarrow CH_3\cdot CO\cdot CH_2OH + H\cdot CO_2CH_3 \ (54\text{–}58\%)$$

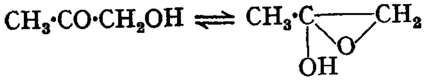
This is an example of alcoholysis, hydroxyacetone being replaced by methanol.

Hydroxyacetone is a colourless liquid, b.p. 145°, soluble in water, ethanol and ether. It reduces ammoniacal silver nitrate, thereby being oxidised to DL-lactic acid, and reduces Fehling's solution, thereby being oxidised to a mixture of formic and acetic acids. Although ketones do not normally reduce ammoniacal silver nitrate and Fehling's solution, α-hydroxyketones are exceptions. Similarly, ketones form phenylhydrazones with phenylhydrazine, but α-hydroxyketones form osazones; thus hydroxyacetone gives the same osazone as methylglyoxal (*cf.* glycolaldehyde):



$$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ CH_2OH \end{array} \xrightarrow{C_6H_5\cdot NH\cdot NH_2} \begin{array}{l} CH_3 \\ | \\ C{:}N\cdot NH\cdot C_6H_5 \\ | \\ CH{:}N\cdot NH\cdot C_6H_5 \end{array}$$

Hydroxyacetone appears to exist as an equilibrium mixture of hydroxyketone and cyclic hemiacetal forms:



The structure of this cyclic hemiacetal is related to that of ethylene oxide (p. 250), which has the property of reducing ammoniacal silver nitrate. It is therefore possible that the reducing properties of α-hydroxyketones are due to the presence of the oxide-ring form. This is an example of ring-chain tautomerism.

Diacetone alcohol (*4-hydroxy-4-methylpentan-2-one*),

$(CH_3)_2C(OH)\cdot CH_2\cdot CO\cdot CH_3$, may be prepared by the condensation of acetone in the presence of barium hydroxide:

$$2CH_3\cdot CO\cdot CH_3 \xrightarrow{Ba(OH)_2} (CH_3)_2C(OH)\cdot CH_2\cdot CO\cdot CH_3$$

Diacetone alcohol is a colourless liquid, b.p. 164°. When heated with a trace of acid or iodine, it eliminates a molecule of water to form mesityl oxide:

$$(CH_3)_2C(OH)\cdot CH_2\cdot CO\cdot CH_3 \xrightarrow{I_2} (CH_3)_2C{=}CH\cdot CO\cdot CH_3 + H_2O$$

Diacetone alcohol is oxidised by sodium hypobromite to β-hydroxy*iso*valeric acid (*cf.* haloform reaction):

$$(CH_3)_2C(OH)\cdot CH_2\cdot CO\cdot CH_3 \xrightarrow{[O]} (CH_3)_2C(OH)\cdot CH_2\cdot CO_2H$$

Diacetone alcohol is a very good solvent for cellulose esters.

DIALDEHYDES AND DIKETONES

Dialdehydes. The simplest dialdehyde is **glyoxal** (*oxaldehyde, ethanedial*), CHO•CHO. It may be obtained by the oxidation of ethanol, acetaldehyde or glycol with nitric acid, but the yields of glyoxal are poor. It is most conveniently prepared, as the bisulphite compound, by refluxing a mixture of paraldehyde, 50 per cent. aqueous acetic acid, dioxan, and selenious acid (yield 72–74 per cent. on the selenious acid):

$$(CH_3\cdot CHO)_3 + 3H_2SeO_3 \longrightarrow 3CHO\cdot CHO + 3Se + 6H_2O \xrightarrow{NaHSO_3} CHO\cdot CHO\cdot 2NaHSO_3\cdot H_2O$$

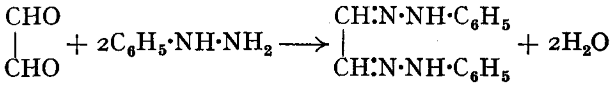
Glyoxal is manufactured by the vapour-phase oxidation of glycol with air at 250–300° in the presence of copper as catalyst.

Glyoxal exists as a colourless polymer giving, on distillation, the monomer. This is a green vapour, which condenses to yellow crystals (m.p. 15°) which polymerise on standing to a colourless solid of unknown molecular weight. Glyoxal exists in aqueous solution as the dihydrate, $CH(OH)_2\cdot CH(OH)_2$, which has been isolated (*cf.* chloral hydrate, p. 168).

Glyoxal undergoes many of the reactions of a dialdehyde; *e.g.*, it reduces ammoniacal silver nitrate, and forms addition compounds with two molecules of hydrogen cyanide and sodium hydrogen sulphite. It does *not* reduce Fehling's solution. Since it has no α-hydrogen atom, glyoxal undergoes the Cannizzaro reaction in the presence of alkali to form glycollic acid, one half of the molecule undergoing disproportionation at the expense of the other half:

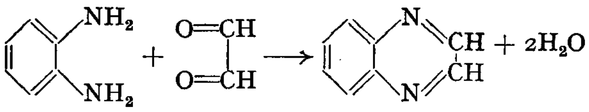
$$CHO\cdot CHO + NaOH \longrightarrow CH_2OH\cdot CO_2Na$$

With phenylhydrazine, glyoxal forms the osazone (this is identical with that from glycolaldehyde, see p. 236):

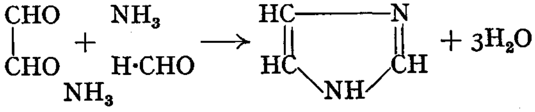


$$\begin{matrix} CHO \\ | \\ CHO \end{matrix} + 2C_6H_5\cdot NH\cdot NH_2 \longrightarrow \begin{matrix} CH{:}N\cdot NH\cdot C_6H_5 \\ | \\ CH{:}N\cdot NH\cdot C_6H_5 \end{matrix} + 2H_2O$$

It also combines with *o*-phenylenediamines to form *quinoxalines* (heterocyclic compounds); *e.g.*, with *o*-phenylenediamine it forms quinoxaline itself:



It combines with ammonia to form the heterocyclic compound *glyoxaline* (*iminazole*). The mechanism of this reaction is uncertain; one suggestion is that one molecule of glyoxal breaks down into formic acid and formaldehyde, and the latter reacts as follows:



Glyoxal is one of the simplest coloured organic compounds, and when reduced it forms the colourless compound glycol (see Ch. XXXI).

Methylglyoxal (pyruvaldehyde), $CH_3{\cdot}CO{\cdot}CHO$, may be prepared by the oxidation of hydroxyacetone or by the hydrolysis of oximinoacetone:

$$CH_3{\cdot}CO{\cdot}CH_2OH \xrightarrow{[O]} CH_3{\cdot}CO{\cdot}CHO$$

$$CH_3{\cdot}CO{\cdot}CH{:}NOH \xrightarrow{acid} CH_3{\cdot}CO{\cdot}CHO$$

It is manufactured by the vapour-phase oxidation of propylene glycol with air at 250–300° in the presence of copper as catalyst:

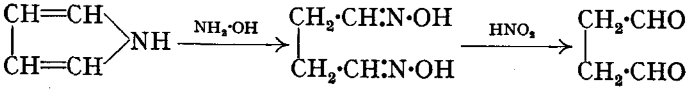
$$CH_3{\cdot}CHOH{\cdot}CH_2OH \xrightarrow[Cu]{O_2} CH_3{\cdot}CO{\cdot}CHO + 2H_2O$$

It is a yellow oil with a pungent odour, and begins to boil at 72° to give a light green vapour. The liquid form of methylglyoxal is the dimer, and this slowly polymerises at room temperature to form a glassy mass of unknown molecular weight (*cf.* glyoxal).

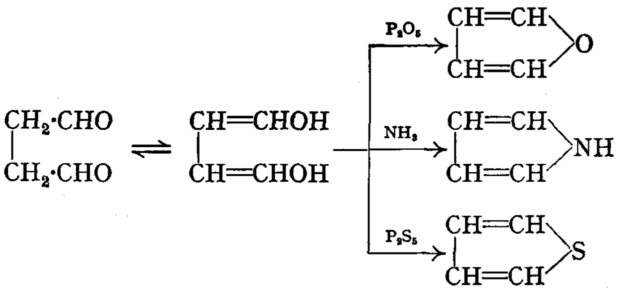
Succinaldehyde (succindialdehyde, butanedial), $CHO{\cdot}CH_2{\cdot}CH_2{\cdot}CHO$, may be prepared by the ozonolysis of hexa-1 : 5-diene:

$$CH_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH_2 \xrightarrow{ozonolysis} CHO{\cdot}CH_2{\cdot}CH_2{\cdot}CHO$$

Another method of preparation is to allow pyrrole and hydroxylamine to interact, and to treat the succinaldoxime so formed with aqueous nitrous acid:



Succinaldehyde is a colourless oil, b.p. 170°, which readily polymerises. It undergoes the usual reactions of a (di)aldehyde; *e.g.*, it reduces ammoniacal silver nitrate and Fehling's solution, forms addition compounds with two equivalents of hydrogen cyanide and sodium hydrogen sulphite; etc. When treated with phosphorus pentoxide, ammonia and phosphorus pentasulphide, it gives respectively furan, pyrrole and thiophen:



Diketones. These are classified as α, β, γ . . . diketones according as the two carbonyl groups are in the 1 : 2, 1 : 3, 1 : 4, . . . positions respectively.

Butane-2 : 3-dione, dimethylglyoxal (*diacetyl*), $CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3$, is the simplest α-diketone. It may be prepared:

(i) By the hydrolysis of oximinobutan-2-one formed by the action of nitrous acid on the ketone:

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3 \xrightarrow{HNO_2} CH_3{\cdot}CO{\cdot}C(:NOH){\cdot}CH_3 \xrightarrow{HCl} CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3$$

(ii) By the oxidation of butan-2-one with selenium dioxide:

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3 + SeO_2 \longrightarrow CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3 + Se + H_2O$$

(iii) By the catalytic dehydrogenation of acetoin:

$$CH_3{\cdot}CO{\cdot}CH(OH){\cdot}CH_3 \xrightarrow[300^\circ]{Cu} CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3 + H_2$$

Acetoin may be readily oxidised by bismuth oxide in acetic acid; the yield of dimethylglyoxal is almost quantitative (Rigby, 1951). Air may be used as the oxidising agent, with a small amount of bismuth oxide as catalyst (Rigby *et al.*, 1951).

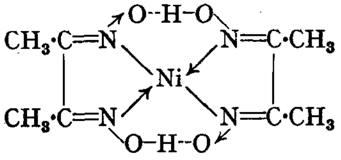
Butane-2 : 3-dione is a yellow oil, b.p. 88°. It gives the usual reactions of a diketone; *e.g.*, it forms the monoxime and di-oxime with hydroxylamine, the bisulphite compound with sodium hydrogen sulphite, etc. It is oxidised by hydrogen peroxide to acetic acid:

$$CH_3{\cdot}CO{\cdot}CO{\cdot}CH_3 \xrightarrow{H_2O_2} 2CH_3{\cdot}CO_2H$$

This reaction is unexpected since hydrogen peroxide does not usually break a carbon–carbon bond. Reduction with lithium aluminium hydride produces the corresponding diol.

Butane-2 : 3-dione forms a glyoxaline derivative with ammonia, and a quinoxaline derivative with *o*-phenylenediamine (*cf.* glyoxal, p. 238).

The dioxime of butane-2 : 3-dione, *i.e.*, *dimethylglyoxime*, $CH_3{\cdot}C(:NOH){\cdot}C(:NOH){\cdot}CH_3$, forms chelate compounds with many metals, and is used to estimate nickel, whose salts produce a red precipitate when treated with dimethylglyoxime. According to Brady *et al.* (1930), the structure of bisdimethylglyoxime nickel is I. The planar configuration round the nickel ion has been demonstrated (Sugden *et al.*, 1935), and confirmed by X-ray analysis (Rundle *et al.*, 1953).



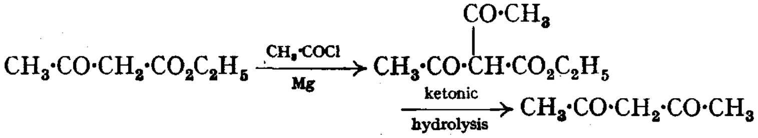
(I)

Pentane-2 : 4-dione, acetylacetone, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$, is the simplest β-diketone. It may be prepared:

(i) By means of the Claisen condensation between ethyl acetate and acetone (yield 38–45 per cent. on the acetone):

$$CH_3{\cdot}CO_2C_2H_5 + CH_3{\cdot}CO{\cdot}CH_3 \xrightarrow{C_2H_5ONa} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$$

(ii) By the ketonic hydrolysis of the acetyl derivative of acetoacetic ester:



$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 \xrightarrow[Mg]{CH_3{\cdot}COCl} CH_3{\cdot}CO{\cdot}\overset{\displaystyle CO{\cdot}CH_3}{\overset{|}{C}}H{\cdot}CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$$

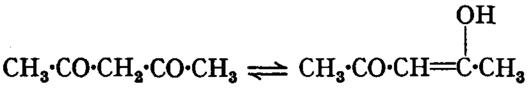
(iii) By the condensation of acetic anhydride with acetone in the presence of boron trifluoride as catalyst (yield 80–85 per cent. on the acetone):

$$CH_3{\cdot}CO{\cdot}CH_3 + (CH_3{\cdot}CO)_2O \xrightarrow{BF_3} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}CO_2H$$

Hauser *et al.* (1956) have prepared β-diketones as follows:

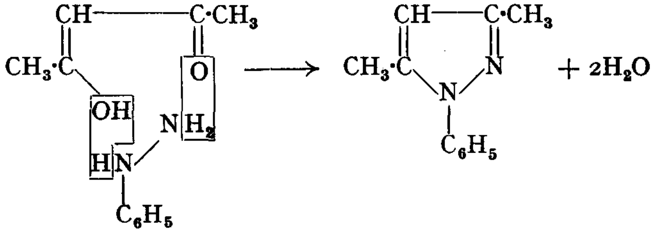
$$R{\cdot}CO{\cdot}CH_3 + NaNH_2 \longrightarrow NH_3 + R{\cdot}CO{\cdot}CH_2Na \xrightarrow{R'{\cdot}COCl} R{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}R'$$

Pentane-2 : 4-dione is a colourless liquid, b.p. 139°/746 mm. It exhibits tautomerism, *e.g.*, gives a red coloration with ferric chloride (*cf.* acetoacetic ester):

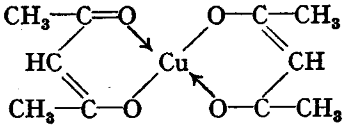


$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3 \rightleftharpoons CH_3{\cdot}CO{\cdot}CH{=}\overset{\displaystyle OH}{\overset{|}{C}}{\cdot}CH_3$$

It is readily oxidised to acetic acid, and is converted into a mixture of acetone and acetic acid when heated with potassium hydroxide solution (*cf.* acid hydrolysis of acetoacetic ester, p. 228). It forms pyrazoles when treated with hydrazine or its derivatives; *e.g.*, with phenylhydrazine it forms 3 : 5-dimethyl-1-phenylpyrazole:

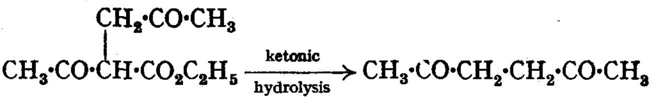


Pentane-2: 4-dione forms chelated compounds with various metals, *e.g.*, iron, aluminium, copper, etc.:



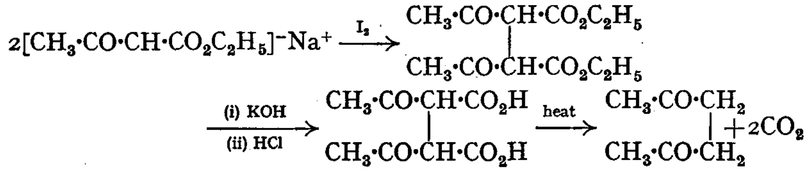
Hexane-2 : 5-dione, acetonylacetone, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3$, is the simplest γ-diketone. It may be prepared by means of the acetoacetic ester synthesis:

$$[CH_3{\cdot}CO{\cdot}CH{\cdot}CO_2C_2H_5]^-Na^+ + BrCH_2{\cdot}CO{\cdot}CH_3 \longrightarrow$$



$$CH_3{\cdot}CO{\cdot}\overset{\displaystyle CH_2{\cdot}CO{\cdot}CH_3}{\overset{|}{C}}H{\cdot}CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3$$

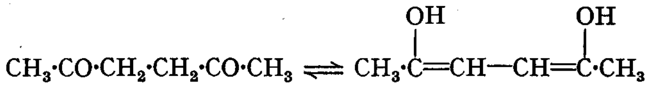
An alternative and more convenient acetoacetic ester synthesis is as follows:



$$2[CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5]^-Na^+ \xrightarrow{I_2} \begin{array}{l} CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5 \\ \qquad\quad | \\ CH_3\cdot CO\cdot CH\cdot CO_2C_2H_5 \end{array}$$

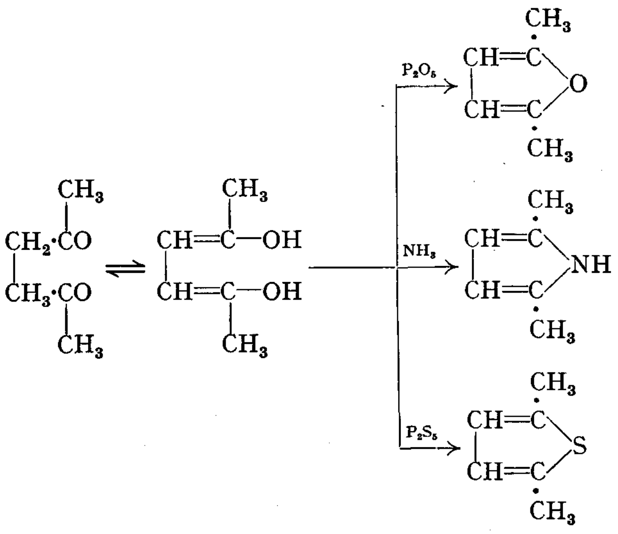
$$\xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} \begin{array}{l} CH_3\cdot CO\cdot CH\cdot CO_2H \\ \qquad\quad | \\ CH_3\cdot CO\cdot CH\cdot CO_2H \end{array} \xrightarrow{\text{heat}} \begin{array}{l} CH_3\cdot CO\cdot CH_2 \\ \qquad\quad | \\ CH_3\cdot CO\cdot CH_2 \end{array} + 2CO_2$$

Hexane-2 : 5-dione is a colourless liquid, b.p. 192–194°. It exhibits tautomerism:



$$CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot CO\cdot CH_3 \rightleftharpoons CH_3\cdot \overset{\overset{\displaystyle OH}{|}}{C}{=}CH{-}CH{=}\overset{\overset{\displaystyle OH}{|}}{C}\cdot CH_3$$

It readily forms five-membered rings: with phosphorus pentoxide, 2 : 5-dimethylfuran; with ammonia, 2 : 5-dimethylpyrrole; and with phosphorus pentasulphide, 2 : 5-dimethylthiophen (*cf.* succinaldehyde, p. 239):



ALDEHYDIC AND KETONIC ACIDS

Gloxylic acid (*glyoxalic acid, oxoethanoic acid*), $CHO\cdot CO_2H$, is the simplest aldehydic acid. It occurs in unripe fruits, *e.g.*, gooseberries, and disappears during ripening; it also occurs in animal tissues and fluids. It may be prepared by the oxidation of ethanol, glycol or glycollic acid with nitric acid (yields are poor). It may also be prepared by the reduction of oxalic acid either electrolytically or by means of magnesium and sulphuric acid, but it is most conveniently prepared by the hydrolysis of dichloroacetic acid with water:

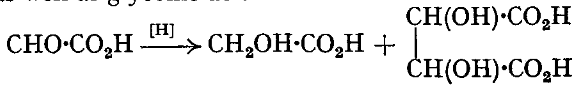
$$CHCl_2\cdot CO_2H + H_2O \longrightarrow CHO\cdot CO_2H + 2HCl$$

Glyoxylic acid crystallises from water with one molecule of water which is combined as water of constitution, $CH(OH)_2\cdot CO_2H$, *i.e.*, dihydroxy-acetic acid (*cf.* chloral hydrate). The anhydrous acid may be obtained as a thick syrup by evaporating the aqueous solution over phosphorus pentoxide *in vacuo.*

Glyoxylic acid gives all the reactions of an aldehyde and an acid; *e.g.*, it reduces ammoniacal silver nitrate, forms a bisulphite compound, etc. Since it has no α-hydrogen atoms, glyoxylic acid undergoes the Cannizzaro reaction to form glycollic and oxalic acids:

$$2CHO{\cdot}CO_2H \xrightarrow{NaOH} CH_2OH{\cdot}CO_2Na + (CO_2Na)_2$$

When glyoxylic acid is reduced by means of metal and acid, tartaric acid is obtained as well as glycollic acid:



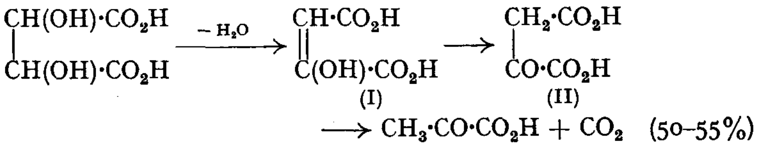
$$CHO{\cdot}CO_2H \xrightarrow{[H]} CH_2OH{\cdot}CO_2H + \begin{array}{l} CH(OH){\cdot}CO_2H \\ | \\ CH(OH){\cdot}CO_2H \end{array}$$

In this respect glyoxylic acid resembles acetone which also gives a bimolecular reduction product, pinacol (see p. 163).

Higher homologues of glyoxylic acid are known, but they are not important.

Pyruvic acid (*acetylformic acid, pyroracemic acid, α-ketopropionic acid, 2-oxopropanoic acid*), $CH_3{\cdot}CO{\cdot}CO_2H$, is the simplest keto-acid. It may be prepared:

(i) By heating tartaric acid alone, or better, with potassium hydrogen sulphate at 210–220°. The reaction is believed to take place via the formation of hydroxymaleic acid, I, which rearranges to oxalacetic acid, II:



$$\begin{array}{l} CH(OH){\cdot}CO_2H \\ | \\ CH(OH){\cdot}CO_2H \end{array} \xrightarrow{-H_2O} \underset{(I)}{\begin{array}{l} CH{\cdot}CO_2H \\ \| \\ C(OH){\cdot}CO_2H \end{array}} \longrightarrow \underset{(II)}{\begin{array}{l} CH_2{\cdot}CO_2H \\ | \\ CO{\cdot}CO_2H \end{array}} \longrightarrow CH_3{\cdot}CO{\cdot}CO_2H + CO_2 \quad (50\text{–}55\%)$$

This is the best method for preparing pyruvic acid, and it was this method which gave rise to the name pyroracemic acid.

(ii) By the oxidation of lactic acid with silver oxide suspended in water, or with Fenton's reagent:

$$CH_3{\cdot}CH(OH){\cdot}CO_2H + [O] \longrightarrow CH_3{\cdot}CO{\cdot}CO_2H + H_2O$$

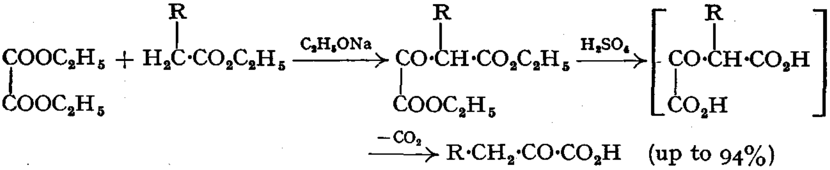
(iii) By the hydrolysis of α : α-dibromopropionic acid with water:

$$CH_3{\cdot}CBr_2{\cdot}CO_2H + H_2O \longrightarrow CH_3{\cdot}CO{\cdot}CO_2H + 2HBr$$

(iv) By the hydrolysis of acetyl cyanide formed by the action of potassium cyanide on acetyl chloride:

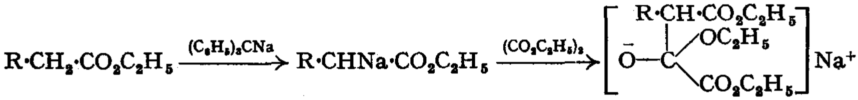
$$CH_3{\cdot}COCl \xrightarrow{KCN} CH_3{\cdot}CO{\cdot}CN \xrightarrow[H_2O]{HCl} CH_3{\cdot}CO{\cdot}CO_2H$$

A general method for preparing α-keto-acids is to reflux a mixture of oxalic ester, fatty acid ester and sodium ethoxide in ether for 16 hours, and then boil the oxalo-ester with 10 per cent. sulphuric acid for 6 hours (Adickes and Andresen, 1943):



$$\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array} + H_2\overset{\overset{R}{|}}{C}{\cdot}CO_2C_2H_5 \xrightarrow{C_2H_5ONa} \begin{array}{l} CO{\cdot}\overset{\overset{R}{|}}{C}H{\cdot}CO_2C_2H_5 \\ | \\ COOC_2H_5 \end{array} \xrightarrow{H_2SO_4} \left[\begin{array}{l} CO{\cdot}\overset{\overset{R}{|}}{C}H{\cdot}CO_2H \\ | \\ CO_2H \end{array}\right] \xrightarrow{-CO_2} R{\cdot}CH_2{\cdot}CO{\cdot}CO_2H \quad (\text{up to } 94\%)$$

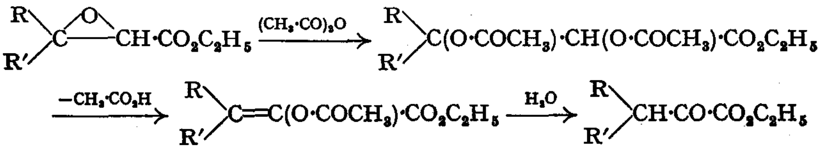
Shreiber (1954) has prepared α-keto-acids as follows:



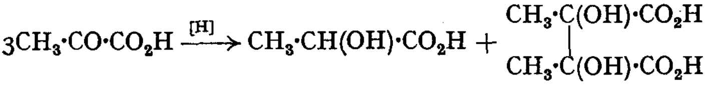
$$\longrightarrow C_2H_5ONa + CO_2C_2H_5{\cdot}CHR{\cdot}CO{\cdot}CO_2C_2H_5$$

$$\xrightarrow{\text{hydrolysis}} 2C_2H_5OH + R{\cdot}CH_2{\cdot}CO{\cdot}CO_2H$$

Another general method for preparing α-keto-esters is by the action of acetic anhydride on a glycidic ester (p. 159), followed by hydrolysis (Vogel *et al.*, 1950):



Pyruvic acid is a colourless liquid, b.p. 165° (with slight decomposition), and smells like acetic acid. It is miscible in all proportions with water, ethanol and ether. It behaves as a ketone and as an acid; it forms an oxime, hydrazone, etc. It is reduced by sodium amalgam to lactic acid and dimethyltartaric acid (*cf.* glyoxylic acid, above):



$$3CH_3{\cdot}CO{\cdot}CO_2H \xrightarrow{[H]} CH_3{\cdot}CH(OH){\cdot}CO_2H + \begin{array}{l} CH_3{\cdot}C(OH){\cdot}CO_2H \\ \quad | \\ CH_3{\cdot}C(OH){\cdot}CO_2H \end{array}$$

Pyruvic acid reduces ammoniacal silver nitrate, itself being oxidised to acetic acid:

$$CH_3{\cdot}CO{\cdot}CO_2H + [O] \longrightarrow CH_3{\cdot}CO_2H + CO_2$$

It is oxidised by warm nitric acid to oxalic acid:

$$CH_3{\cdot}CO{\cdot}CO_2H + 4[O] \longrightarrow (CO_2H)_2 + CO_2 + H_2O$$

Pyruvic acid is easily decarboxylated with warm dilute sulphuric acid to give acetaldehyde:

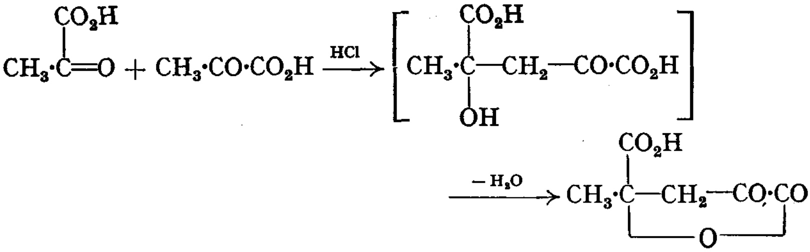
$$CH_3{\cdot}CO{\cdot}CO_2H \longrightarrow CH_3{\cdot}CHO + CO_2$$

On the other hand, when warmed with *concentrated* sulphuric acid, pyruvic acid eliminates a molecule of carbon monoxide to form acetic acid:

$$CH_3{\cdot}CO{\cdot}CO_2H \longrightarrow CH_3{\cdot}CO_2H + CO$$

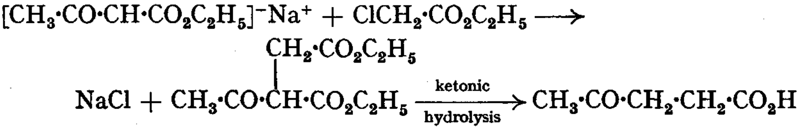
Both of these reactions with sulphuric acid are characteristic of α-ketoacids.

The methyl group is made reactive by the adjacent carbonyl group, and so pyruvic acid undergoes many condensation reactions characteristic of a compound containing an active methylene group; *e.g.*, in the presence of dry hydrogen chloride, pyruvic acid forms α-keto-γ-valerolactone-γ-carboxylic acid:



Pyruvic acid is a very important substance biologically, since it is an intermediate product in the metabolism of carbohydrates and proteins.

Lævulic acid (*β-acetylpropionic acid, γ-ketovaleric acid, butan-3-one-1-carboxylic acid*), $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, is the simplest γ-keto-acid. It may be prepared via acetoacetic ester as follows:



$$[CH_3{\cdot}CO{\cdot}CH{\cdot}CO_2C_2H_5]^-Na^+ + ClCH_2{\cdot}CO_2C_2H_5 \longrightarrow$$
$$NaCl + CH_3{\cdot}CO{\cdot}\overset{\displaystyle CH_2{\cdot}CO_2C_2H_5}{\overset{|}{C}}H{\cdot}CO_2C_2H_5 \xrightarrow[\text{hydrolysis}]{\text{ketonic}} CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

It may also be prepared by heating a hexose sugar, particularly lævulose, with concentrated hydrochloric acid:

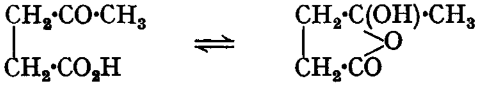
$$C_6H_{12}O_6 \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + H{\cdot}CO_2H + H_2O$$

In practice it is customary to use cane-sugar as the starting material:

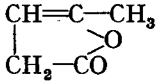
$$C_{12}H_{22}O_{11} \longrightarrow 2CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + 2H{\cdot}CO_2H + H_2O \quad (21\text{–}22\%)$$

By heating dilute solutions of sucrose under pressure with hydrochloric acid, the yield is increased to 50 per cent.

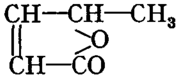
Lævulic acid is a crystalline solid; m.p. 34°, very soluble in water, ethanol and ether. It behaves as a ketone (forms oxime, etc.) and as an acid (forms esters, etc.). On the other hand, many of the reactions of lævulic acid indicate that it exists in the *lactol* form, *i.e.*, hydroxy-lactone (this is an example of ring-chain tautomerism):



When heated for some time, lævulic acid is converted into α- and β-*angelica* lactones:



α-



β-

It should be noted that α- and γ-keto-acids differ from β-keto-acids in that their esters do not form sodio-derivatives, and the acids are not readily decomposed by moderate heating (*cf.* acetoacetic acid).

A general method for preparing γ-keto-acids is to treat a ketone with lithium amide and lithium bromoacetate; the ketone undergoes α-carboxymethylation (Puterbaugh *et al.*, 1959):

$$R{\cdot}CO{\cdot}CH_2R' \xrightarrow[CH_2Br{\cdot}CO_2Li]{LiNH_2} R{\cdot}CO{\cdot}CHR'{\cdot}CH_2{\cdot}CO_2H$$

QUESTIONS

1. Show by means of equations how you would synthesise:—(*a*) hexane-2 : 5-dione, (*b*) methyl *n*-amyl ketone, (*c*) methyl *iso*propyl ketone, (*d*) α-methylsuccinic acid, (*e*) α : β-dimethylbutyric acid, (*f*) $Et_2CH{\cdot}CO_2H$, (*g*) $Me{\cdot}CO{\cdot}Pr$, (*h*) $CH_3{\cdot}CH(CO_2H){\cdot}CH(Me){\cdot}CO_2H$, (*i*) $CH_3{\cdot}CO{\cdot}CH(Me){\cdot}CH_2{\cdot}CO_2H$, (*j*) $CH_3{\cdot}CH_2{\cdot}CH(Me){\cdot}CO{\cdot}NH_2$, (*k*) $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, (*l*) $CH_2OH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, (*m*) $CH_3{\cdot}CH(CO_2H){\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CO_2H$, (*n*) $CH_3{\cdot}CH_2{\cdot}CH(Me){\cdot}CH(Et){\cdot}CO_2H$, (*o*) $Me_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(Me){\cdot}CH_2{\cdot}CO_2H$, (*p*) $Me_2CH{\cdot}CO{\cdot}CHMe_2$, (*q*) $Me_2EtC{\cdot}CO_2H$.

2. Starting with compounds containing three or less carbon atoms, how would you synthesise:—(*a*) $CH_3\cdot CO\cdot CH_2\cdot CHO$, (*b*) $CH_3\cdot CO\cdot CH_2\cdot CO\cdot CO_2Et$, (*c*) $CHO\cdot CH_2\cdot CO_2Et$, (*d*) $CH_3\cdot CHOH\cdot CH_2\cdot CH_2OH$, (*e*) $CH_3\cdot CHBr\cdot CH_2\cdot CO_2H$, (*f*) $Me_2CH\cdot CH_2\cdot CH_2\cdot CH_3$, (*g*) $CH_3\cdot CH_2\cdot CHCl\cdot CH_2\cdot CO_2H$, (*h*) $Me_2CBr\cdot CH_2\cdot CO_2H$?

3. Define and give examples of:—(*a*) tautomerism, (*b*) isomerism, (*c*) desmotropism, (*d*) resonance, (*e*) enolisation, (*f*) cationotropy, (*g*) anionotropy, (*h*) prototropy, (*i*) the Claisen condensation, (*j*) chelate compounds, (*k*) water of constitution.

4. Discuss the methods for determining the composition of keto-enol mixtures, and discuss the relation between structure and enol content.

5. Name the compounds and state the conditions under which they are formed when E.A.A. is treated with:—(*a*) NaOH, (*b*) H_3PO_4, (*c*) HNO_2, (*d*) $CuSO_4$, (*e*) NH_3, (*f*) $MeNH_2$, (*g*) MeMgI, (*h*) $CH_3\cdot CHO$, (*i*) AcCl, (*j*) ArN_2Cl, (*k*) O_3, (*l*) heated under reflux.

6. Give *one convenient* method for preparing:—(*a*) glycolaldehyde, (*b*) aldol, (*c*) acetol, (*d*) glyoxal, (*e*) methylglyoxal, (*f*) dimethylglyoxal, (*g*) succinaldehyde, (*h*) acetylacetone, (*i*) acetonylacetone, (*j*) glyoxylic acid, (*k*) pyruvic acid, (*l*) lævulic acid.

7. Which of the compounds in question 6 react with:—(*a*) $NaHSO_3$, (*b*) $C_6H_5\cdot NH\cdot NH_2$, (*c*) P_2O_5, (*d*) NH_3, (*e*) P_2S_5? Name the compounds and state under what conditions they are formed.

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