CHAPTER XVI

SATURATED DICARBOXYLIC ACIDS

THE general formula of the saturated dicarboxylic acids is $C_nH_{2n}(CO_2H)_2$ ($n = 0$ for oxalic acid), and the best-known examples are those which have the two carboxyl groups at the opposite ends of the carbon chain.

Nomenclature. The dicarboxylic acids are commonly known by names which indicate their source, *e.g.*, $CO_2H{\cdot}CO_2H$ oxalic acid; this occurs in plants of the *oxalis* group (for further examples, see the individual acids).

In this trivial system of nomenclature, the positions of side-chains or substituents are indicated by Greek letters, *e.g.*,
$CO_2H{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CH_2{\cdot}CHCl{\cdot}CO_2H$ α-chloro-α′-methyladipic acid.

According to the I.U.P.A.C. system of nomenclature, the class suffix is *-dioic*, *e.g.*,

$CO_2H{\cdot}CO_2H$ ethanedioic acid
$CO_2H{\cdot}CH_2{\cdot}CO_2H$ propanedioic acid
$CO_2H{\cdot}CH(CH_3){\cdot}CH(CH_3){\cdot}CH_2{\cdot}CO_2H$ 2 : 3-dimethylpentanedioic acid

When this method leads to cumbrous names, the alternative scheme is to regard the carboxyl group as a substituent, and the name of the acid is then obtained by adding the suffix *carboxylic acid*, *e.g.*,

$CO_2H{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ 1 : 2-ethanedicarboxylic acid or ethane-1 : 2-dicarboxylic acid

General methods of preparation. 1. By the oxidation of diprimary glycols, *e.g.*, ethylene glycol gives oxalic acid:

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

This method is not important, since the higher polymethylene glycols are inaccessible; in fact they are usually prepared from dicarboxylic acids (see p. 254).

2. By treating halogen derivatives of monocarboxylic acid esters with silver or zinc, *e.g.*, ethyl bromoacetate gives ethyl succinate:

$$2CH_2Br{\cdot}CO_2C_2H_5 + 2Ag \longrightarrow C_2H_5O_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2C_2H_5 + 2AgBr \quad (p.)$$

3. The *cyanide synthesis* of dicarboxylic acids is a very useful method; the starting material may be either a halogeno-acid or a polymethylene dibromide:

(i) $CH_2Cl{\cdot}CO_2H \xrightarrow{KCN} CH_2CN{\cdot}CO_2H \xrightarrow{H_2O} CH_2(CO_2H)_2$

(ii) $\begin{matrix}CH_2Br\\|\\CH_2Br\end{matrix} \xrightarrow{KCN} \begin{matrix}CH_2{\cdot}CN\\|\\CH_2{\cdot}CN\end{matrix} \xrightarrow{H_2O} \begin{matrix}CH_2{\cdot}CO_2H\\|\\CH_2{\cdot}CO_2H\end{matrix}$

4. The **Crum-Brown and Walker electrolytic method** (1891, 1893). This is the electrolysis of an aqueous solution of the potassium alkyl esters of the dicarboxylic acids (*cf.* Kolbe's method):

$$\begin{matrix}K{-}O_2C{-}(CH_2)_n{-}CO_2C_2H_5\\K{-}O_2C{-}(CH_2)_n{-}CO_2C_2H_5\end{matrix} + 2H_2O \longrightarrow \begin{matrix}(CH_2)_n{\cdot}CO_2C_2H_5\\|\\(CH_2)_n{\cdot}CO_2C_2H_5\end{matrix} + 2CO_2 + 2KOH + H_2 \quad (f.g.\text{-}g.)$$

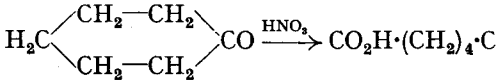
It is obvious that this method can be used to prepare only *even* homologues.

5. Dicarboxylic acids may be prepared by the acetoacetic ester synthesis (p. 231) and better, by the malonic ester synthesis (p. 233).

6. Several dicarboxylic acids may be prepared by the oxidation of unsaturated acids which occur in natural oils and fats, *e.g.*, oleic acid gives nonoic and azelaic acids:

$$CH_3{\cdot}(CH_2)_7{\cdot}CH{:}CH{\cdot}(CH_2)_7{\cdot}CO_2H \xrightarrow{HNO_3} CH_3{\cdot}(CH_2)_7{\cdot}CO_2H + CO_2H{\cdot}(CH_2)_7{\cdot}CO_2H$$

7. Cyclic ketones may be oxidised to dicarboxylic acids, *e.g.*, *cyclo*hexanone gives adipic acid:



$$\xrightarrow{HNO_3} CO_2H{\cdot}(CH_2)_4{\cdot}CO_2H$$

8. The preparation of higher homologues from lower homologues may be carried out in several ways; which method is used depends on the homologue desired. Many *even* higher homologues can be prepared by the Crum-Brown and Walker method (method 4). Any dicarboxylic acid can be " stepped up " by two carbon atoms as follows:

$$(CH_2)_n(CO_2C_2H_5)_2 \xrightarrow{Na/C_2H_5OH} (CH_2)_n(CH_2OH)_2 \xrightarrow{HBr}$$
$$(CH_2)_n(CH_2Br)_2 \xrightarrow{KCN} (CH_2)_n(CH_2{\cdot}CN)_2 \xrightarrow{H_2O} (CH_2)_n(CH_2{\cdot}CO_2H)_2$$

By using malonic ester instead of potassium cyanide, the acid may be " stepped up " by four carbon atoms:

$$(CH_2)_n(CH_2Br)_2 + 2[CH(CO_2C_2H_5)_2]^-Na^+ \longrightarrow$$
$$2NaBr + (CH_2)_n[CH_2{\cdot}CH(CO_2C_2H_5)_2]_2 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}}$$
$$(CH_2)_n[CH_2{\cdot}CH(CO_2H)_2]_2 \xrightarrow{150\text{–}200^\circ} (CH_2)_n(CH_2{\cdot}CH_2{\cdot}CO_2H)_2 + 2CO_2$$

Alkylation of t-butyl esters of acetic acid with various organic mono- and dihalides has been effected with lithium or sodium amide in liquid ammonia. Hydrolysis gives the mono- or dicarboxylic acid (Sisido *et al.*, 1959), *e.g.*,

$$CH_2Br{\cdot}CH_2Br + 2CH_3{\cdot}CO_2C_4H_9 \xrightarrow{LiNH_2}$$
$$(CH_2)_4(CO_2C_4H_9)_2 \xrightarrow{\text{hydrolysis}} CO_2H{\cdot}(CH_2)_4{\cdot}CO_2H \quad (33\%)$$

These higher homologues are used to prepare large carbon-ring compounds (p. 493).

General properties. All the dicarboxylic acids are crystalline solids, the lower members being soluble in water, the solubility decreasing with increase in molecular weight; the odd acids are more soluble than the even. None is steam volatile, and the solubility in ether increases with increase in molecular weight. Except for oxalic acid, the dicarboxylic acids are stable towards oxidising agents. Their melting points follow the oscillation rule (p. 176), the even acids having higher melting points than the odd. They dissociate in two steps, the dissociation constant of the first being much greater than that of the second. Furthermore, the acid strength of the dicarboxylic acids decreases as the series is ascended.

The reactions of the dicarboxylic acids depend, to a large extent, on the length of the carbon chain. The dicarboxylic acids, therefore, will be described individually.

Oxalic acid (*ethanedioic acid*), $CO_2H{\cdot}CO_2H$, is one of the most important dicarboxylic acids. It occurs in rhubarb, in sorrel and other plants of the *oxalis* group (hence its name). Oxalic acid is one of the final products of oxidation of many organic compounds, *e.g.*, sugars, starch, etc., give oxalic acid when oxidised with concentrated nitric acid.

Preparation. (i) An industrial method which is now almost obsolete is to heat saw-dust with a mixture of sodium and potassium hydroxides in iron pans at 200–220° in air. On cooling, the mass is extracted with water and the aqueous solution treated with a calcium hydroxide solution. The calcium oxalate, which is precipitated, is collected by filtration and then decomposed by the calculated quantity of dilute sulphuric acid. The precipitated calcium sulphate is filtered off, and the filtrate evaporated to crystallisation; oxalic acid dihydrate crystallises out.

(ii) Oxalic acid is now prepared industrially by heating sodium formate rapidly to 360.°

$$2H{\cdot}CO_2Na \longrightarrow (CO_2Na)_2 + H_2$$

The free acid is obtained from its sodium salt by the procedure described in method (i).

(iii) The usual laboratory method for preparing oxalic acid is to oxidise sucrose with concentrated nitric acid in the presence of vanadium pentoxide as catalyst:

$$C_{12}H_{22}O_{11} + 18[O] \xrightarrow[V_2O_5]{HNO_3} 6(CO_2H)_2 + 5H_2O \quad (25\%)$$

(iv) Oxalic acid may be prepared by the hydrolysis of cyanogen, the hydrolysis being best carried out with concentrated hydrochloric acid:

$$C_2N_2 + 4H_2O + 2HCl \longrightarrow (CO_2H)_2 + 2NH_4Cl$$

(v) An interesting synthesis of oxalic acid is to heat sodium in a stream of carbon dioxide at 360°:

$$2CO_2 + 2Na \longrightarrow (CO_2Na)_2$$

Properties and reactions. Oxalic acid crystallises from water as colourless crystals with two molecules of water of crystallisation; the melting point of the hydrate is 101·5°; that of the anhydrous acid is 189·5°. Oxalic acid is poisonous, soluble in water and ethanol but almost insoluble in ether. The dihydrate loses water when heated at 100–105°, and when heated at about 200°, oxalic acid decomposes into carbon dioxide, carbon monoxide, formic acid and water:

$$(CO_2H)_2 \longrightarrow CO_2 + H{\cdot}CO_2H$$
$$(CO_2H)_2 \longrightarrow CO_2 + CO + H_2O$$

The anhydrous acid is conveniently obtained by heating the hydrate with carbon tetrachloride.

When heated with concentrated sulphuric acid at 90°, oxalic acid is decomposed:

$$(CO_2H)_2 \xrightarrow{H_2SO_4} CO + CO_2 + H_2O$$

It is oxidised by permanganate to carbon dioxide:

$$(CO_2H)_2 + [O] \longrightarrow 2CO_2 + H_2O$$

It is only very slowly oxidised by concentrated nitric acid. When fused with potassium hydroxide, it evolves hydrogen:

$$(CO_2K)_2 + 2KOH \longrightarrow 2K_2CO_3 + H_2$$

The anhydride of oxalic acid is unknown. When *anhydrous* oxalic acid is refluxed with ethanol, ethyl oxalate is formed:

$$(CO_2H)_2 + 2C_2H_5OH \longrightarrow (CO_2C_2H_5)_2 + 2H_2O \quad (80—90\%)$$

A more general method for preparing diesters is to heat a mixture of the dicarboxylic acid, alcohol, toluene and concentrated sulphuric acid. Sulphuric acid is the catalyst, and the toluene removes the water by forming a ternary azeotrope of alcohol, water and toluene; the yield of diester is 94–98 per cent. from oxalic to sebacic acid. The esterification may be carried out in the absence of toluene; a larger amount of sulphuric acid is required and the yields are lower (70–90 per cent.).

The ethyl and propyl esters of oxalic acid are liquid; the methyl ester is solid, and hence has been used to prepare pure methanol by hydrolysis with sodium hydroxide solution. Ethyl oxalate undergoes the Claisen condensation with esters containing two α-hydrogen atoms to form keto-esters, *e.g.*, with ethyl acetate, *oxalacetic ester* is formed:

$$C_2H_5O_2C{\cdot}CO_2C_2H_5 + CH_3{\cdot}CO_2C_2H_5 \xrightarrow[\text{ethanol}]{C_2H_5ONa\ in}$$

$$\begin{matrix} CH{\cdot}CO_2C_2H_5 \\ \| \\ C(ONa){\cdot}CO_2C_2H_5 \end{matrix} \xrightarrow{CH_3{\cdot}CO_2H} \begin{matrix} CH_2{\cdot}CO_2C_2H_5 \\ | \\ CO{\cdot}CO_2C_2H_5 \end{matrix} \quad (60–70\%)$$

When oxalic acid is heated with ethylene glycol, the *cyclic* compound, *ethylene oxalate*, is obtained:

$$HOCH_2{\cdot}CH_2OH + HO_2C{\cdot}CO_2H \longrightarrow O\begin{matrix} CH_2—CH_2 \\ CO——CO \end{matrix}O + 2H_2O$$

This reaction is characteristic of oxalic acid; the other dicarboxylic acids usually react with glycol to form polyesters (see p. 374). When oxalic acid is heated with glycerol, formic acid (p. 180) or allyl alcohol (p. 267) is obtained according to the conditions.

Oxalic acid forms the diamide, *oxamide*. This may be prepared by shaking ethyl oxalate with concentrated ammonium hydroxide solution:

$$C_2H_5O_2C{\cdot}CO_2C_2H_5 + 2NH_3 \longrightarrow NH_2{\cdot}CO{\cdot}CO{\cdot}NH_2 + 2C_2H_5OH$$

It may also be prepared by passing cyanogen into *cold* concentrated hydrochloric acid:

$$C_2N_2 + 2H_2O \xrightarrow{HCl} (CO{\cdot}NH_2)_2 \quad (50\%)$$

Oxamide exists as white needles, almost insoluble in water. In aqueous solution it slowly changes into ammonium oxalate, a change which is brought about rapidly by hydrochloric acid (on warming):

$$\begin{matrix} CO{\cdot}NH_2 \\ | \\ CO{\cdot}NH_2 \end{matrix} + 2H_2O \longrightarrow \begin{matrix} CO_2NH_4 \\ | \\ CO_2NH_4 \end{matrix}$$

When heated with phosphorus pentoxide, oxamide is dehydrated to cyanogen:

$$(CO{\cdot}NH_2)_2 \xrightarrow{P_2O_5} C_2N_2 + 2H_2O$$

The monoamide of oxalic acid is also known. It is called *oxamic acid*; the suffix of the names of all the monoamides of the dicarboxylic acids is

-amic. Oxamic acid, m.p. 210°, may be prepared by the action of concentrated ammonium hydroxide solution on ethyl hydrogen oxalate, or by heating ammonium hydrogen oxalate.

When reduced with zinc and sulphuric acid, oxalic acid forms *glycollic acid*, $CH_2OH{\cdot}CO_2H$. Electrolytic reduction with a lead cathode gives glycollic and glyoxylic acids, the latter being obtained in better yield by reducing oxalic acid with magnesium and sulphuric acid.

When oxalic acid is treated with *excess* phosphorus pentachloride, *oxalyl chloride*, b.p. 64°, is formed:

$$(CO_2H)_2 \xrightarrow{PCl_5} (COCl)_2 \quad (f.\text{-}g.)$$

If an excess of phosphorus pentachloride is not used, oxalic acid is decomposed, possibly via the intermediate formation of the half acid chloride:

$$(CO_2H)_2 \xrightarrow{PCl_5} [CO_2H{\cdot}COCl] \longrightarrow CO_2 + CO + HCl$$

Paraffins can be carboxylated by oxalyl chloride under the influence of light (Kharasch and Brown, 1942):

$$RH + (COCl)_2 \longrightarrow R{\cdot}COCl + CO + HCl$$

Oxalic acid forms two series of salts, the normal, $(CO_2M)_2$, and the acid, $CO_2H{\cdot}CO_2M$ (M = univalent metal). Some acid salts crystallise with a molecule of free oxalic acid, *e.g.*, $CO_2K{\cdot}CO_2H{\cdot}(CO_2H)_2{\cdot}2H_2O$; these are known as *tetroxalates*, and the potassium compound is used as a standard for bases and oxidising agents, since it can be prepared pure and does not deteriorate on standing. The heavy metal oxalates are insoluble in water but soluble in solutions of alkali oxalates due to the formation of complex compounds, *e.g.*, potassium oxalo-chromate, $[Cr(C_2O_4)_3]^{3-}H_3^{3+}$. These complexes are chelate compounds, and are optically active.

Oxalic acid is used for the manufacture of ink and for bleaching straw. Its antimony salts are used as mordants in printing and dyeing.

Malonic acid (*propanedioic acid*) $CO_2H{\cdot}CH_2{\cdot}CO_2H$, was first obtained by the oxidation of malic acid (hence its name):

$$CO_2H{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H + [O] \xrightarrow{K_2Cr_2O_7/H_2SO_4}$$

$$CO_2H{\cdot}CO{\cdot}CH_2{\cdot}CO_2H \xrightarrow{[O]} CO_2H{\cdot}CH_2{\cdot}CO_2H + CO_2$$

oxalacetic acid

Malonic acid may be prepared by heating potassium chloroacetate with aqueous potassium cyanide and hydrolysing the product, potassium cyanoacetate, with hydrochloric acid:

$$CH_2Cl{\cdot}CO_2K \xrightarrow{KCN} CH_2CN{\cdot}CO_2K \xrightarrow{H_2O} CH_2(CO_2H)_2 \quad (84\%)$$

Malonic acid is a crystalline solid, m.p. 135·6°, soluble in water and ethanol but only slightly soluble in ether. When heated to 140–150°, or when refluxed in sulphuric acid solution, it eliminates carbon dioxide:

$$CO_2H{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_3{\cdot}CO_2H + CO_2$$

All dicarboxylic acids which have both carboxyl groups attached to the same carbon atom are decomposed in a similar manner. When malonic acid is heated with phosphorus pentoxide, a small amount of *carbon suboxide* is obtained:

$$CO_2H{\cdot}CH_2{\cdot}CO_2H \xrightarrow{P_2O_5} O{:}C{:}C{:}C{:}O + 2H_2O$$

Carbon suboxide, b.p. 7°, may be regarded as a diketen; it combines with water to form malonic acid. Malonic acid does not form a cyclic anhydride, but dimethylmalonic acid does (*cf.* p. 487).

When malonic acid is treated with nitrous acid and the product hydrolysed, **mesoxalic acid** (*ketomalonic acid*) is obtained:

$$(HO_2C)_2CH_2 \xrightarrow{HNO_2} (HO_2C)_2C{:}N{\cdot}OH \xrightarrow{H_2O} CO_2H{\cdot}CO{\cdot}CO_2H$$

Mesoxalic acid crystallises from water with one molecule of water which is held firmly, and hence is believed to be water of constitution: $\begin{matrix} HO \\ HO \end{matrix}\!\!>\!C(CO_2H)_2$ (*cf.* glyoxylic acid). Ethyl malonate may be oxidised directly to ethyl mesoxalate by selenium dioxide (yield: 23 per cent.).

Ethyl malonate is far more important than the acid because of its synthetic uses; the acid contains an active methylene group, the reactivity of which is more pronounced in the ester. Both the acid and ester may be readily brominated, *e.g.*, monobromomalonic acid, $CHBr(CO_2H)_2$, is formed when a suspension of malonic acid in ether is treated with bromine; owing to the high reactivity of the methylene group, no red phosphorus is required as catalyst (*cf.* p. 211).

Ethyl malonate, curiously enough, does not form the diamide, *malonamide*, when shaken with concentrated ammonium hydroxide solution; the dimethyl ester, however, gives a good yield of malonamide. Ethyl malonate forms *barbituric acid* when heated with urea in the presence of sodium ethoxide (see p. 386).

Succinic acid (*butanedioic acid*), $CO_2H{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, was originally obtained by the distillation of amber (Latin: *succinum*, amber). It is also formed during the fermentation of sugar and other substances. Succinic acid may be synthesised by the following methods:

(i) From ethylene bromide:

$$\begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix} \xrightarrow{KCN} \begin{matrix} CH_2{\cdot}CN \\ | \\ CH_2{\cdot}CN \end{matrix} \xrightarrow{H_2O} \begin{matrix} CH_2{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix} \quad (80\%)$$

(ii) By the reaction between malonic ester (1 molecule) and ethyl chloroacetate, or between malonic ester (2 molecules) and iodine (see p. 234).

Alkyl-substituted succinic acids may be prepared by using monoalkyl-malonic ester and α-halogeno-acid esters or iodine. Alternatively, they may be prepared by the addition of hydrogen cyanide to αβ-unsaturated esters and hydrolysing the β-cyano-complex produced (see p. 279).

(iii) By heating malic acid, in a sealed tube, with constant boiling hydriodic acid and red phosphorus:

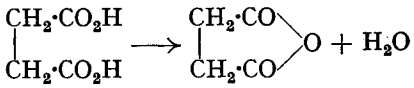
$$\begin{matrix} CHOH{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix} + 2HI \longrightarrow \begin{matrix} CH_2{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix} + I_2 + H_2O \quad (60\%)$$

Succinic acid is prepared industrially by the catalytic (or by the electrolytic) reduction of maleic acid:

$$\begin{matrix} CH{\cdot}CO_2H \\ \| \\ CH{\cdot}CO_2H \end{matrix} + H_2 \xrightarrow{Ni} \begin{matrix} CH_2{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix}$$

Succinic acid is a crystalline solid, m.p. 185°, moderately soluble in water and ethanol, but sparingly soluble in ether. When heated, a large amount

sublimes, the rest being converted into the *inner* anhydride, succinic anhydride:

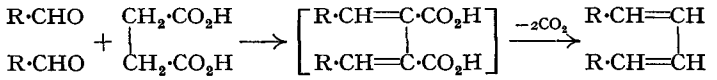


When heated with excess of glycol, succinic acid forms high-polymer esters (*polyesters*, which belong to the group known as the *alkyd resins*—see p. 257). These esters are acidic, the end groups being succinic acid residues:

$$CO_2H\cdot(CH_2)_2\cdot CO_2H + HOCH_2\cdot CH_2OH + HO_2C\cdot(CH_2)_2CO_2H + HOCH_2\cdot CH_2OH + \ldots \longrightarrow CO_2H\cdot(CH_2)_2\cdot CO{-}[{-}O\cdot(CH_2)_2\cdot O\cdot CO\cdot(CH_2)_2\cdot CO{-}]{-}OH$$

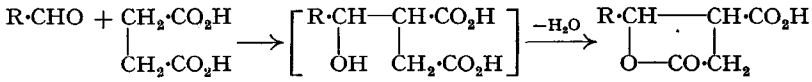
The apparent molecular weight of this ester is about 3000 (Carothers, 1930). It has been found that the dicarboxylic acids from malonic to adipic acid form these polyesters with ethylene glycol. These esters are linear polymers, but if glycerol is used instead of glycol, three dimensional polymeric esters are obtained.

Succinic acid condenses with aldehydes; if both methylene groups are involved, *polyenes* are obtained by elimination of carbon dioxide:



Polyenes have the general formula $R\cdot(CH{:}CH)_n\cdot R$, and by using conjugated aldehydes the value of n can be made fairly large.

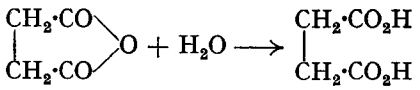
If only one methylene group in succinic acid reacts with the aldehyde, a *paraconic acid* is obtained:



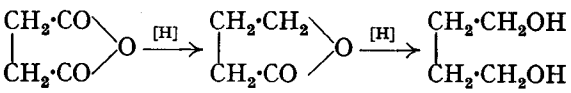
When these paraconic acids are heated, $\beta\gamma$-unsaturated acids are obtained (see p. 281).

Succinic anhydride (*butanedioic anhydride*) is obtained in excellent yield by distilling succinic acid with acetic anhydride, acetyl chloride, or phosphoryl chloride. The anhydride, and not the acid chloride, is obtained when succinic acid is heated with thionyl chloride (see later).

Succinic anhydride is a white crystalline solid, m.p. 119°, and when boiled with water or alkalis, is converted into succinic acid:

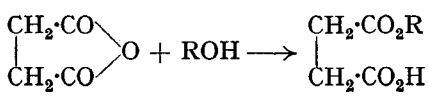


When reduced with sodium and ethanol, succinic anhydride is converted first into *γ-butyrolactone*, and finally into tetramethylene glycol:

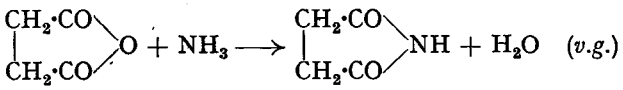


If the reduction is carried out with sodium amalgam in *acid* solution, the lactone is obtained in good yield; some butyric acid is also formed.

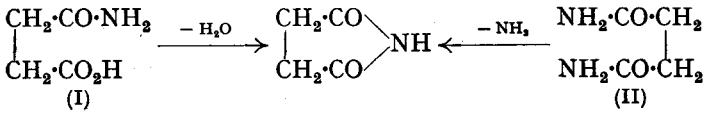
Succinic anhydride is very useful for preparing the "half-derivatives" of succinic acid, *e.g.*, with alcohols it forms the acid-ester:



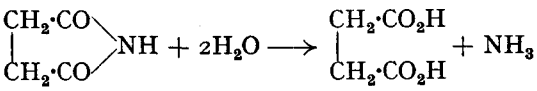
Succinimide (*butanimide*) is formed when succinic anhydride is heated in a current of dry ammonia:



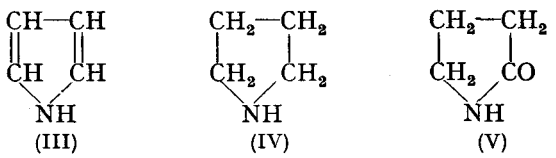
Succinamic acid (m.p. 157°), I, and *succinamide* (m.p. 243°), II, are both readily converted into succinimide when heated:



Succinimide is a white crystalline solid, m.p. 125°, readily soluble in water, and when boiled with water or alkalis is converted into succinic acid:



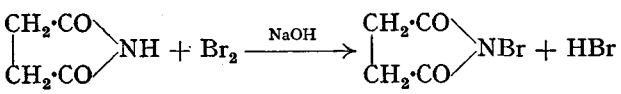
When succinimide is distilled with zinc dust, *pyrrole*, (III), is obtained. When reduced with sodium and ethanol, succinimide forms *pyrrolidine*, (IV), and when reduced electrolytically, it forms *pyrrolidone*, (V):



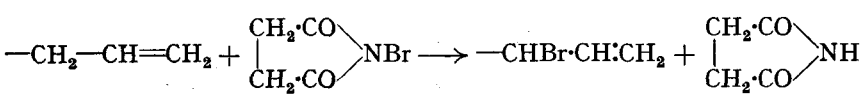
Succinimide is acidic, *e.g.*, it reacts with potassium hydroxide to form potassiosuccinimide, the formula of which may be (VI) or (VII):

Succinimide, however, is only very weakly acidic; the potassium salt is decomposed by carbon dioxide, the imide being regenerated.

A very important derivative of succinimide is N-*bromosuccinimide*, which may be prepared by the action of bromine on succinimide at 0° in the presence of sodium hydroxide:



N-bromosuccinimide is a valuable reagent for brominating olefinic compounds in the *allyl* position (Ziegler, 1942).



This reaction offers a means of splitting off *three* carbon atoms from a compound by oxidative degradation, provided the compound contains one double bond or can have one produced, *e.g.*,

$$R{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH \xrightarrow[350^\circ]{Al_2O_3} R{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH_2 \xrightarrow{N\text{-bromosuccinimide}}$$

$$R{\cdot}CH_2{\cdot}CHBr{\cdot}CH{:}CH_2 \xrightarrow[ethanol]{KOH} R{\cdot}CH{:}CH{\cdot}CH{:}CH_2 \xrightarrow{ozonolysis} R{\cdot}CHO$$

This method has found great use in steroid chemistry.

Normally, *N*-bromosuccinimide *substitutes* olefins in the allyl position, and this reaction is believed to take place by a free-radical mechanism; it is catalysed by peroxides and is promoted by light (both are free-radical producing agents).

The details of the mechanism are uncertain. According to Goldfinger *et al.* (1953, 1956), the function of the *N*-bromosuccinimide is to supply a *low concentration of molecular bromine*:

$$>NBr + HBr \longrightarrow >NH + Br_2$$

$$Br_2 \rightleftharpoons 2Br\cdot$$

$$Br\cdot + >CH{\cdot}CH{=}CH_2 \longrightarrow >\dot{C}{\cdot}CH{=}CH_2 + HBr$$

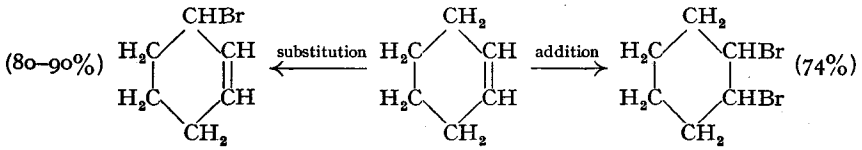
$$Br_2 + >\dot{C}{\cdot}CH{=}CH_2 \longrightarrow >CBr{\cdot}CH{=}CH_2 + Br\cdot$$

Tedder *et al.* (1960, 1961) have obtained evidence to support this mechanism.

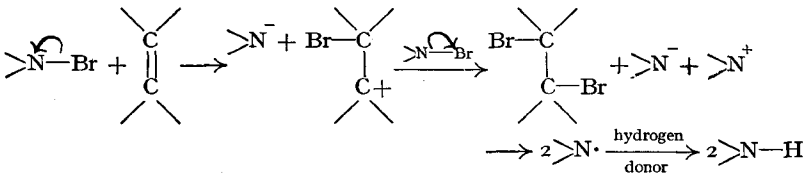
N-Bromosuccinimide also brominates unsaturated esters, *e.g.*,

$$CH_3{\cdot}CH{=}CH{\cdot}CO_2CH_3 \xrightarrow{>N-Br} CH_2Br{\cdot}CH{=}CH{\cdot}CO_2CH_3$$

In addition to substitution, *N*-bromosuccinimide may also produce *addition* compounds, but these are usually formed only in small amount. Braude *et al.* (1952), however, have shown that the *addition* reaction is catalysed by tetra-alkylammonium salts, *e.g.*, *N*-bromosuccinimide and *cyclo*hexene give 3-bromo*cyclo*hexene (Ziegler *et al.*, 1942), but in the presence of, *e.g.*, tetraethylammonium bromide, 1 : 2-dibromo*cyclo*hexane is the main product.



The addition reaction probably involves heterolytic fission:

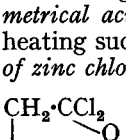


N-Bromosuccinimide can also behave as an oxidising agent; it will oxidise primary alcohols (and primary amines) to aldehydes, and secondary alcohols to ketones (Barakat *et al.*, 1952), *e.g.*,

$$C_2H_5OH + >NBr \longrightarrow CH_3{\cdot}CHO + >NH + HBr$$

$$(CH_3)_2CHOH + >NBr \longrightarrow (CH_3)_2CO + >NH + HBr$$

Succinyl chloride (butanedioyl chloride). When succinic acid is treated with a *large excess* of phosphorus pentachloride, a good yield of the *symmetrical acid chloride*, $(CH_2{\cdot}COCl)_2$, is obtained. This is also obtained by heating succinic acid with thionyl chloride *in the presence of a small amount of zinc chloride* (*cf.* succinic anhydride). On the other hand, when succinic acid is heated with phosphorus pentachloride *not in excess*, a small amount of the *s*-acid chloride is obtained; the main product is the *as*-acid chloride. The evidence for the structures of these acid chlorides is shown by the products formed by their reaction with benzene in the presence of anhydrous aluminium chloride. One (the *s*-) gives $C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$ and the other (the *as*-), $(C_6H_5)_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO$. This acid chloride is an example of ring-chain tautomerism (p. 221).



Isomeric with succinic acid is methylmalonic acid or iso*succinic acid*, $CO_2H{\cdot}CH(CH_3){\cdot}CO_2H$, m.p. 130°. It may be readily prepared from sodiomalonic ester and methyl iodide, or as follows:

$$CH_3{\cdot}CH_2{\cdot}CO_2H \xrightarrow{Br_2/P} CH_3{\cdot}CHBr{\cdot}CO_2H \xrightarrow{KCN} CH_3{\cdot}CH(CN){\cdot}CO_2H \xrightarrow{H_2O} CH_3{\cdot}CH(CO_2H)_2$$

Oxalacetic ester, $C_2H_5O_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5$, is the diethyl ester of ketosuccinic acid, and may be prepared by the Claisen condensation between ethyl oxalate and ethyl acetate (see p. 371). It is a colourless liquid which can be distilled under reduced pressure (b.p. 132°/24 mm.), but at atmospheric pressure it eliminates a molecule of carbon monoxide to form malonic ester:

$$C_2H_5O_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 \longrightarrow CH_2(CO_2C_2H_5)_2 + CO$$

Hydrogen of the methylene group adjacent to the carbonyl group may be replaced by alkyl groups by reactions similar to those used for acetoacetic ester, *e.g.*,

$$C_2H_5O_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [C_2H_5O_2C{\cdot}CO{\cdot}CH{\cdot}CO_2C_2H_5]^-Na^+ \xrightarrow{CH_3I}$$
$$C_2H_5O_2C{\cdot}CO{\cdot}CH(CH_3){\cdot}CO_2C_2H_5 \xrightarrow[(ii)\ C_2H_5I]{(i)\ C_2H_5ONa} C_2H_5O_2C{\cdot}CO{\cdot}C(CH_3)(C_2H_5){\cdot}CO_2C_2H_5$$

Oxalacetic ester and its alkyl derivatives undergo " acid hydrolysis " when boiled with alkalis, and " ketonic hydrolysis " when boiled with dilute sulphuric acid.

Acid hydrolysis

$$C_2H_5O_2C{\cdot}CO{\cdot}CHR{\cdot}CO_2C_2H_5 \xrightarrow{NaOH} (CO_2H)_2 + R{\cdot}CH_2{\cdot}CO_2H + 2C_2H_5OH$$

Ketonic hydrolysis

$$C_2H_5O_2C{\cdot}CO{\cdot}CHR{\cdot}CO_2C_2H_5 \xrightarrow{H_2SO_4} [CO_2H{\cdot}CO{\cdot}CHR{\cdot}CO_2H] \longrightarrow CO_2 + R{\cdot}CH_2{\cdot}CO{\cdot}CO_2H$$

Oxalacetic ester may be used to prepare citric acid by means of the Reformatsky reaction (see p. 422).

Hydrolysis of oxalacetic ester with concentrated hydrochloric acid in the cold gives *oxalacetic acid* (*ketosuccinic acid*):

$$C_2H_5O_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 + 2H_2O \xrightarrow{HCl} CO_2H{\cdot}CO{\cdot}CH_2{\cdot}CO_2H + 2C_2H_5OH$$

A simpler preparation of oxalacetic acid is to oxidise maleic acid with Fenton's reagent.

Oxalacetic acid is a fairly stable substance, soluble in water, the aqueous solution giving a red coloration with ferric chloride, thus indicating the existence of an enolic form. Oxalacetic acid exists in two forms, one with m.p. 155° and

the other 184°. These two forms are actually *hydroxymaleic acid*, I, and *hydroxyfumaric acid*, II, respectively:

(I) (II)

I is convertible into II by 30 per cent. sulphuric acid, and the salts of II give I on treatment with dilute acid. It is doubtful whether oxalacetic acid exists in the keto form.

Glutaric acid (*pentanedioic acid*), $CO_2H{\cdot}(CH_2)_3{\cdot}CO_2H$ (relationship to *glu*tamic acid and tar*taric* acid gave rise to its name), may be prepared by a number of methods, *e.g.*,

(i) By refluxing trimethylene cyanide with concentrated hydrochloric acid:

$$NC{\cdot}(CH_2)_3{\cdot}CN + 4H_2O \xrightarrow{HCl} CO_2H{\cdot}(CH_2)_3{\cdot}CO_2H + 2NH_3 \quad (83\text{–}85\%)$$

(ii) By the action of methylene iodide on sodiomalonic ester:

$$2[CH(CO_2C_2H_5)_2]^-Na^+ + CH_2I_2 \longrightarrow 2NaI + CH_2[CH(CO_2C_2H_5)_2]_2$$

$$\xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} CH_2[CH(CO_2H)_2]_2 \xrightarrow{150\text{–}200^\circ} CO_2H{\cdot}(CH_2)_3{\cdot}CO_2H + 2CO_2$$

(iii) By condensing formaldehyde with malonic ester in the presence of diethylamine:

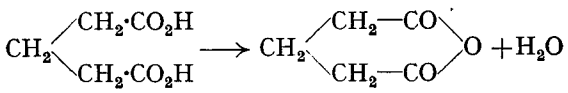
$$(C_2H_5O_2C)_2CH_2 + \overset{\overset{CH_2}{\|}}{O} + CH_2(CO_2C_2H_5)_2 \xrightarrow[\text{reflux}]{(C_2H_5)_2NH}$$

$$(C_2H_5O_2C)_2CH{\cdot}CH_2{\cdot}CH(CO_2C_2H_5)_2 \quad (61\%)$$

This tetracarboxylic ester may now be treated as in (ii), or may be converted into glutaric acid directly by refluxing with concentrated hydrochloric acid:

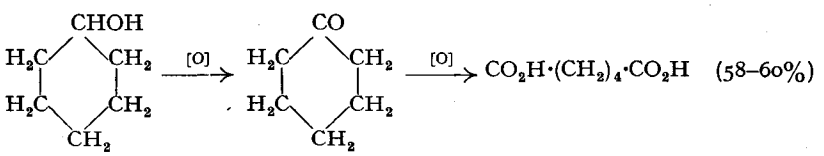
$$(C_2H_5O_2C)_2CH{\cdot}CH_2{\cdot}CH(CO_2C_2H_5)_2 \xrightarrow{HCl} CO_2H{\cdot}(CH_2)_3{\cdot}CO_2H \quad (76\text{–}80\%)$$

Glutaric acid is a crystalline solid, m.p. 97°. When heated with acetic anhydride or thionyl chloride, it is converted into glutaric anhydride:



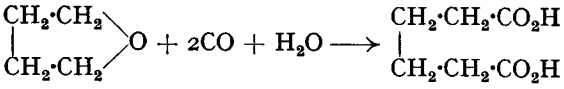
Succinic and glutaric acids differ from their higher homologues in that they readily form the cyclic anhydride when heated with acetic anhydride.

Adipic acid (*hexanedioic acid*), $CO_2H{\cdot}(CH_2)_4{\cdot}CO_2H$, received its name from the fact that it was first obtained by the oxidation of fats (Latin: *adeps*, fat). It may be synthesised from sodiomalonic ester and ethylene bromide (see p. 233), but is prepared industrially by the oxidation of *cyclo*hexanol with concentrated nitric acid, preferably in the presence of ammonium vanadate as catalyst:

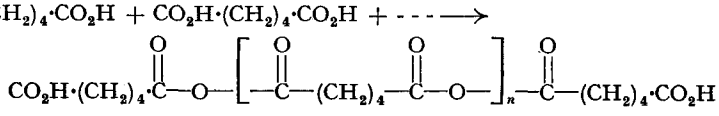


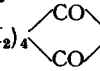
If selenium dioxide is used as catalyst instead of ammonium vanadate, the yield of adipic acid is 74 per cent. (Putnik, 1947). Succinic acid is also manufactured from benzene. This is reduced catalytically to *cyclo*hexane, which is then oxidised in two stages (the first stage is a mixture of *cyclo*hexanol and *cyclo*hexanone).

A potential commercial source of adipic acid is the reaction between tetrahydrofuran, carbon monoxide and water:



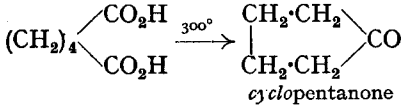
Adipic acid is a crystalline solid, m.p. 150°. When heated with acetic anhydride, it forms a *linear polymeric anhydride*:



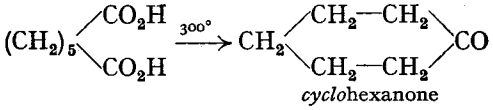
When this polymer is distilled *under reduced pressure*, the monomeric adipic anhydride,  , is obtained; this monomer very readily polymerises on heating. If the polymeric anhydride is heated in a *molecular still*, a " superpolymer ", *i.e.*, a polymer of very high molecular weight, is obtained as the residue, the distillate being the cyclic monomer or dimer.

All the dicarboxylic acids, $CO_2H{\cdot}(CH_2)_n{\cdot}CO_2H$, where n has a value 4 to 12, behave as adipic acid (Hill and Carothers, 1933).

On the other hand, when adipic and pimelic acids are heated with acetic anhydride and the product distilled at 300°, a cyclic *ketone* is obtained in each case:

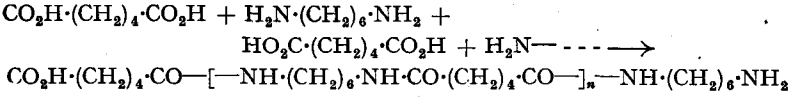


*cyclo*pentanone



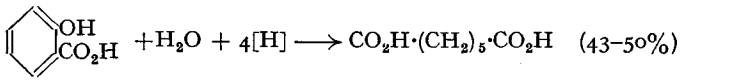
*cyclo*hexanone

Adipic acid is used for the preparation of resins (polyesters), and is an intermediate in the manufacture of *nylon*. Nylon is used as the generic name for all synthetic fibre-forming polymeric amides having a protein-like structure. Nylon yarns and fabrics are practically non-inflammable. The most important example of a polyamide is that formed from adipic acid and hexamethylenediamine:



Pimelic acid (*heptanedioic acid*), $CO_2H{\cdot}(CH_2)_5{\cdot}CO_2H$, m.p. 104°, received its name from the fact that it was obtained originally from the oxidation of fats (Greek: *pimele*, fat). It may be prepared by the hydrolysis of pentamethylene cyanide (formed by the action of potassium cyanide on pentamethylene bromide), or by the malonic ester synthesis, using trimethylene bromide (*cf.* adipic acid). A most remarkable method of preparing pimelic acid is the reduction of salicylic

acid with sodium and *iso*pentanol, followed by the addition of water and then hydrochloric acid; the mechanism of this reaction is obscure (see p. 683):



Suberic acid (*octanedioic acid*), $CO_2H{\cdot}(CH_2)_6{\cdot}CO_2H$, m.p. 144°, may be synthesised by the electrolysis of potassium ethyl glutarate (*cf.* p. 368). It is prepared industrially by the oxidation of cork (Latin: *suber*, cork) with concentrated nitric acid. A potential commercial source is the oxidation of *cyclo*-octane obtained by the catalytic reduction of *cyclo*-octatetraene (see p. 485).

Azelaic acid (*nonanedioic acid*), $CO_2H{\cdot}(CH_2)_7{\cdot}CO_2H$, m.p. 107°, may be synthesised from malonic ester and pentamethylene bromide. It may be obtained in the laboratory by refluxing castor oil with ethanolic potassium hydroxide, acidifying with sulphuric acid, and oxidising the crude ricinoleic acid so obtained with alkaline permanganate:

$$CH_3{\cdot}(CH_2)_5{\cdot}CHOH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}(CH_2)_7{\cdot}CO_2H \xrightarrow{[O]} CO_2H{\cdot}(CH_2)_7{\cdot}CO_2H \quad (32\text{–}36\%)$$

Azelaic acid is prepared industrially by the oxidation of oleic acid with concentrated nitric acid (p. 286).

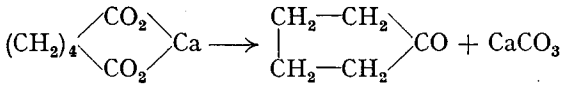
Sebacic acid (*decanedioic acid*), $CO_2H{\cdot}(CH_2)_8{\cdot}CO_2H$, m.p. 133°, is prepared industrially by heating castor oil with sodium hydroxide.

$$CH_3{\cdot}(CH_2)_5{\cdot}CHOH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}(CH_2)_7{\cdot}CO_2Na \xrightarrow{NaOH} CO_2Na{\cdot}(CH_2)_8{\cdot}CO_2Na + C_6H_{13}{\cdot}CHOH{\cdot}CH_3$$

Many higher dicarboxylic acids are known.

The acid esters of the dicarboxylic acids may be prepared by refluxing a mixture of the acid with half its equivalent of the di-ester in the presence of concentrated hydrochloric acid. This is an example of acidolysis (p. 193). Alternatively, the acid ester may be obtained by the half saponification of the di-ester. In either case the di-ester is separated from the acid ester by fractional distillation.

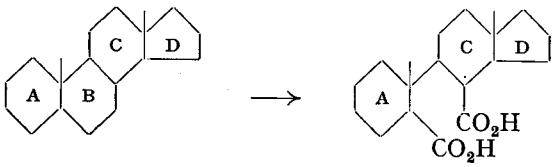
When the calcium, barium, or better still, the thorium salts of the carboxylic acids from adipic to nonadecanedioic are distilled, varying yields of cyclic ketones are obtained; *e.g.*, adipic acid gives *cyclo*pentanone:



The best yields of cyclic ketones are obtained for the five- and six-membered rings, *i.e.*, from adipic and pimelic acids respectively. This has some bearing on the problem of *Baeyer's Strain Theory* (p. 486).

Based on the experimental results of the ease of formation of cyclic anhydrides and cyclic ketones, is **Blanc's rule** (1905). Blanc found that dicarboxylic acids, on heating with acetic anhydride, and then distilling at 300° (or distilling directly at 300°), gave cyclic anhydrides or cyclic ketones according to the relative positions of the two carboxyl groups. 1 : 4- and 1 : 5-dicarboxylic acids gave cyclic anhydrides; 1 : 6- and 1 : 7- gave cyclic ketones: this is Blanc's rule. By using Blanc's rule it is possible to determine the size of rings. A double bond is introduced into the ring, and the ring opened by oxidation to the corresponding dicarboxylic acid. This is then heated with acetic anhydride and distilled. If a cyclic anhydride is obtained, the acid is either 1 : 4- or 1 : 5-; if a cyclic ketone, either 1 : 6- or 1 : 7-; if there is no change, the acid is 1 : 8- or more. In naturally occurring compounds the rings are usually five- or six-membered. Hence the formation of the anhydride is taken to mean a five-membered ring, and of the ketone a six-membered ring.

In certain cases, however, Blanc's rule is misleading, *e.g.*, in the investigation of sterols, wrong information on the structure was obtained because of the abnormal Blanc reaction in these compounds. It has been found that substituents in the chain bring about ring closure much more easily; *e.g.*, substituted adipic acids may give rise to the anhydride and not to the cyclic ketone. Hence in polynuclear compounds such as sterols (which have the skeleton shown), if ring B is opened, the resulting dicarboxylic acid is, in effect, a substituted adipic acid:



This, when distilled, gives the anhydride and not the expected ketone. Thus, in sterols, one of the rings (B) was thought to be five-membered when Blanc's rule was used. Further work showed it was six-membered. Blanc's rule is only satisfactory for simple cyclic compounds.

CARBONIC ACID AND ITS DERIVATIVES

Orthocarbonic acid, $C(OH)_4$, is unknown in the free state, but its esters have been prepared. They may be obtained by the reaction between sodium alkoxide and nitrochloroform:

$$4RONa + CCl_3{\cdot}NO_2 \longrightarrow C(OR)_4 + 3NaCl + NaNO_2$$

The alkyl orthocarbonates are ethereal smelling liquids.

Carbonic acid (*metacarbonic acid*), $O{:}C(OH)_2$, is unknown in the free state, but its salts and esters have been prepared. Alkyl carbonates may be readily formed by heating alcohols with carbonyl chloride:

$$COCl_2 + 2ROH \longrightarrow CO(OR)_2 + 2HCl$$

They may also be prepared by heating silver carbonate with alkyl iodide:

$$Ag_2CO_3 + 2RI \longrightarrow CO(OR)_2 + 2AgI$$

The alkyl carbonates are ethereal smelling liquids, readily soluble in water. In recent years they have found various uses in organic synthesis, *e.g.*,

(i) They may be used to introduce the carbalkoxy group, CO_2R, into ketones to produce β-ketoesters. The reaction is carried out by heating a ketone with sodium or sodium alkoxide in the presence of a large excess of alkyl carbonate:

$$R'{\cdot}CO{\cdot}CH_3 + (RO)_2CO + NaOR \longrightarrow$$
$$[R'{\cdot}CO{\cdot}CH{\cdot}CO_2R]^-Na^+ + 2ROH \xrightarrow{H_2O} R'{\cdot}CO{\cdot}CH_2{\cdot}CO_2R$$

(ii) Alkyl carbonates react with primary alkyl cyanides in the presence of sodium alkoxide to form α-cyanoesters:

$$R'{\cdot}CH_2{\cdot}CN + (RO)_2CO + NaOR \longrightarrow$$
$$[R'{\cdot}C(CN){\cdot}CO_2R]^-Na^+ + 2ROH \xrightarrow{H_2O} R'{\cdot}CH(CN){\cdot}CO_2R$$

(iii) Alkyl carbonates may be used to alkylate sodiomalonic esters:

$$[R'C(CO_2C_2H_5)_2]^-Na^+ + (RO)_2CO \longrightarrow RR'C(CO_2C_2H_5)_2 + RO{\cdot}CO{\cdot}ONa$$

The acid chloride of carbonic acid is *carbonyl chloride* (*phosgene*), $COCl_2$. It may be obtained by the action of chlorine on carbon monoxide under

the influence of sunlight, or in the presence of heated charcoal (200°) as catalyst; the latter is the commercial method. Carbonyl chloride may also be obtained by the action of oleum containing 45 per cent. free sulphur trioxide on carbon tetrachloride at 78°:

$$2SO_3 + CCl_4 \longrightarrow COCl_2 + \underset{\text{pyrosulphuryl chloride}}{S_2O_5Cl_2}$$

Carbonyl chloride is a colourless liquid, b.p. 8°, and has been used as a toxic gas in warfare. It is used in various organic syntheses, behaving as an acid chloride. It is very slowly decomposed by water:

$$COCl_2 + H_2O \longrightarrow CO_2 + 2HCl$$

When treated with slight excess of one equivalent of alcohol in the cold, carbonyl chloride forms chloroformic esters:

$$COCl_2 + ROH \longrightarrow Cl{\cdot}CO_2R + + HCl$$

When treated with an excess of alcohol in the presence of pyridine, alkyl carbonates are formed:

$$COCl_2 + 2ROH \longrightarrow CO(OR)_2 + 2HCl$$

Carbonyl chloride reacts with ammonia to form urea:

$$COCl_2 + 2NH_3 \longrightarrow CO(NH_2)_2 + 2HCl$$

With primary or secondary amines, substituted ureas are formed, *e.g.*,

$$COCl_2 + 2R{\cdot}NH_2 \longrightarrow CO(NH{\cdot}R)_2 + 2HCl$$

Chloroformic acid (*chlorocarbonic acid*), $Cl{\cdot}CO_2H$, is not known in the free state, but its esters have been prepared. These may be readily obtained by treating carbonyl chloride with slight excess of one equivalent of alcohol in the cold (see above). Chloroformic esters are acid-chloride esters, and the chlorine atom reacts with compounds containing active hydrogen; thus ethyl chloroformate, b.p. 94°, reacts with water, alcohols, ammonia, primary and secondary amines; *e.g.*, urethan is formed with ammonia:

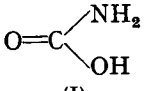
$$Cl{\cdot}CO_2C_2H_5 + NH_3 \longrightarrow NH_2{\cdot}CO_2C_2H_5 + HCl$$

Ethyl chloroformate is useful for introducing the carbethoxy group on a nitrogen atom; *e.g.*, ethyl-*N*-tricarboxylate is formed when ethyl chloroformate is added to a mixture of urethan, ether and sodium, this mixture having been previously heated:

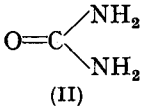
$$NH_2{\cdot}CO_2C_2H_5 + 2Cl{\cdot}CO_2C_2H_5 + 2Na \longrightarrow N(CO_2C_2H_5)_3 + 2NaCl + H_2 \quad (51\text{–}57\%)$$

Ethyl chloroformate may also be used to prepare ethyl esters by reaction with Grignard reagents (p. 356).

Amides of carbonic acid. Since carbonic acid is dibasic, two amides are possible: the mono- and diamide. These are known, respectively, as *carbamic acid*, (I), and *urea*, (II):



(I)



(II)

Carbamic acid, $NH_2{\cdot}CO_2H$, is not known in the free state, but its salts and esters have been prepared. Ammonium carbamate is formed when dry ammonia reacts with dry carbon dioxide:

$$2NH_3 + CO_2 \longrightarrow NH_2{\cdot}CO{\cdot}ONH_4$$

It is a white crystalline solid, very soluble in water. When its aqueous solution is warmed to 60°, ammonium carbamate is hydrolysed to ammonium carbonate:

$$NH_2{\cdot}CO{\cdot}ONH_4 + H_2O \longrightarrow CO(ONH_4)_2$$

Esters of carbamic acid are known as **urethans.** These may be prepared:

(i) By treating a chloroformic ester with ammonia, *e.g.*, ethyl chloroformate produces ethyl carbamate:

$$Cl{\cdot}CO_2C_2H_5 + NH_3 \longrightarrow NH_2{\cdot}CO_2C_2H_5 + HCl$$

(ii) By refluxing urea in an alcohol, *e.g.*, *n*-butanol gives *n*-butyl carbamate when refluxed for 30 hours:

$$CO(NH_2)_2 \longrightarrow NH_3 + HNCO$$

$$HNCO + CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH \longrightarrow NH_2{\cdot}CO_2CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \quad (75\text{–}76\%)$$

(iii) *N*-substituted urethans may be prepared by the Curtius reaction (p. 209). The acid azide is refluxed in benzene solution and then an alcohol is added:

$$R{\cdot}CO{\cdot}N_3 \longrightarrow N_2 + R{\cdot}NCO \xrightarrow{R'OH} R{\cdot}NH{\cdot}CO_2R'$$

N-phenyl urethans may be prepared by reaction between phenyl *iso*cyanate and alcohol:

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

These are crystalline solids and may be used to characterise the alcohols.

Ethyl carbamate, usually known as *urethan*, is a crystalline solid, m.p. 50°. It reacts with ammonia to form urea:

$$NH_2{\cdot}CO_2C_2H_5 + NH_3 \longrightarrow CO(NH_2)_2 + C_2H_5OH$$

It is decomposed by aqueous sodium hydroxide on warming:

$$NH_2{\cdot}CO_2C_2H_5 + 2NaOH \longrightarrow Na_2CO_3 + NH_3 + C_2H_5OH$$

Ethyl carbamate has hypnotic properties; many urethans are valuable hypnotics, *e.g.*, *aponal* (*tert.*-amyl carbamate, *tert.*-amyl urethan), $NH_2{\cdot}COOC(CH_3)_2(C_2H_5)$

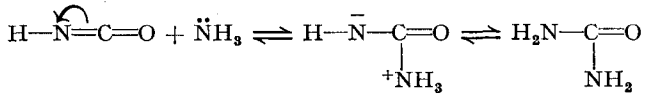
Urea (*carbamide*), $NH_2{\cdot}CO{\cdot}NH_2$, is very important physiologically. It is the chief nitrogenous product of protein metabolism; adults excrete about 30 g. per day in the urine, from which it can be extracted by evaporating the urine to small bulk and adding nitric acid, whereupon the slightly soluble urea nitrate, $CO(NH_2)_2{\cdot}HNO_3$, is precipitated. Urea is historically very important because Wöhler (1828) synthesised it by evaporating a solution containing potassium *iso*cyanate and ammonium sulphate; ammonium *iso*cyanate, which is formed first, undergoes molecular rearrangement:

$$NH_4{\cdot}NCO \rightleftharpoons CO(NH_2)_2$$

The reaction is reversible; the solution contains about 5 per cent. ammonium *iso*cyanate.

The mechanism of this rearrangement is uncertain. One possibility is as follows (via dissociation):

$$NH_4NCO \rightleftharpoons NH_3 + HNCO$$



Urea may be prepared in the laboratory by the action of ammonia on carbonyl chloride, alkyl carbonates, chloroformates or urethans, *e.g.*,

$$COCl_2 + 2NH_3 \longrightarrow CO(NH_2)_2 + 2HCl \quad (f.)$$
$$(C_2H_5O)_2CO + 2NH_3 \longrightarrow CO(NH_2)_2 + 2C_2H_5OH \quad (f.)$$

Industrially, urea is prepared:

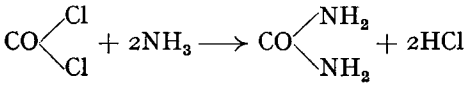
(i) By the partial hydrolysis of cyanamide in feebly acid solution:

$$H_2N{\cdot}CN + H_2O \longrightarrow CO(NH_2)_2$$

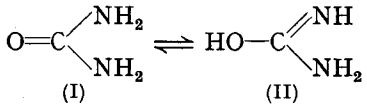
(ii) By allowing liquid carbon dioxide and liquid ammonia to interact, and heating the ammonium carbamate so formed to 130–150° under about 35 atm. pressure:

$$2NH_3 + CO_2 \longrightarrow NH_2{\cdot}CO{\cdot}ONH_4 \longrightarrow CO(NH_2)_2 + H_2O$$

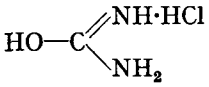
Structure of urea. Although urea appears to be a simple molecule, it is only recently that its structure has been ascertained with any degree of certainty. The diamide structure, $CO(NH_2)_2$, seems to be indicated by its synthesis from carbonyl chloride and ammonia:



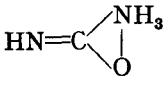
In some respects urea appears to behave as a diamide, but not in others, *e.g.*, it forms *stable* salts with strong inorganic acids—*amides* do not form stable salts. Furthermore, a peculiar feature of urea salts is that only *one* molecule of monobasic acid is present, *e.g.*, $CO(NH_2)_2{\cdot}HCl$. This was explained by assuming that urea was tautomeric, (I) being the neutral amide (urea) and (II) the basic amidine (*iso*urea):



The amidine structure is not possible with other amides; also amidines are much stronger bases than amides, and it was believed that it was the amidine form that produced the salts, *e.g.*, (III). Still another structure was suggested by Werner (1913), *viz.*, (IV).

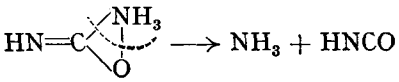


(III)

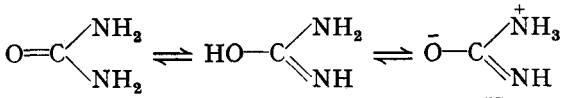


(IV)

(IV) was proposed to explain the ease with which urea loses ammonia to form cyanic acid:



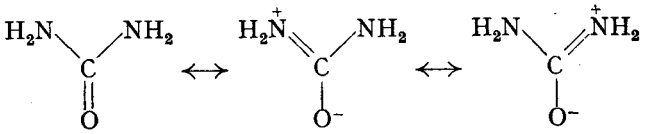
At the same time this formula explained the addition of one molecule of hydrochloric acid, since it has the strongly basic imido group, =NH. Werner's formula contains quinquevalent nitrogen, but rewritten according to modern electronic theory, it will be (V). Thus there is now the possibility of the following equilibria:



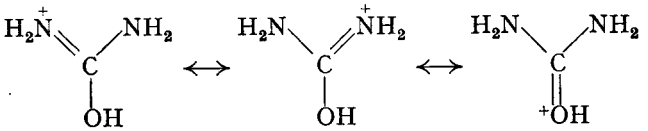
(I) (II) (V)

On the other hand, experience shows that compounds containing the group $>C(OH)\cdot NH_2$ readily eliminate ammonia to form the carbonyl group (*cf.* the group $>C(OH)_2$, p. 168). Thus structure (V) is unnecessary (although it is possible that the elimination of ammonia from (II) takes place through the intermediate formation of (V)). Hence structure (II) has been favoured by many, since it explained the " monoacidic " properties of urea and the elimination of ammonia.

Crystal structure studies have shown that in solid urea both nitrogen atoms are identical. This indicates structure (I), and not (II) or (V). Bond-length measurements in urea give the C—N distance as 1·37 A. In aliphatic amines the C—N bond length is 1·47 A. This indicates that the C—N bond in urea has some double bond character (about 28 per cent.); this can be explained by resonance:



Both the nitrogen atoms are identical in the hybrid molecule. Furthermore, the negatively charged oxygen atom is capable of co-ordinating with *one* proton (therefore urea will be a " monoacidic " base), and thus the salt may be formulated as a resonance hybrid:



Dipole moment work on urea also indicates that it is a resonance hybrid with charged forms contributing 20–30 per cent. Worsham *et al.* (1957) have also shown that the atoms in urea are coplanar; this is in keeping with all the bonds having double-bond character.

Properties and reactions of urea. Urea is a white crystalline solid, m.p. 132°, soluble in water and ethanol, but insoluble in ether. It is used for preparing formaldehyde-urea plastics, barbiturates, as a fertiliser, etc. A most recent use is for the manufacture of hydrazine; urea is treated with alkaline sodium hypochlorite (in effect, the Hofmann degradation is applied to urea):

$$NH_2\cdot CO\cdot NH_2 + NaOCl + 2NaOH \longrightarrow N_2H_4 + NaCl + Na_2CO_3 + H_2O$$

(i) Urea behaves as a " monoacidic " base; the nitrate and oxalate are the most important, since neither is very soluble in water.

When urea nitrate is added to cold concentrated sulphuric acid, *nitrourea* is formed:

$$NH_2\cdot CO\cdot NH_2\cdot HNO_3 \xrightarrow{H_2SO_4} NH_2\cdot CO\cdot NH\cdot NO_2 + H_2O \quad (70\text{–}87\%)$$

(ii) Urea is hydrolysed by boiling with acids or alkalis:

$$CO(NH_2)_2 + H_2O \longrightarrow CO_2 + 2NH_3$$

The enzyme urease (which occurs in soyabeans) produces the same change.

(iii) When gently heated, urea loses ammonia to form *biuret*:

$$2NH_2{\cdot}CO{\cdot}NH_2 \longrightarrow NH_2{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH_3$$

When an aqueous biuret solution is treated with sodium hydroxide solution and a drop of copper sulphate solution, a violet coloration is produced. This is known as the *biuret reaction*, which is characteristic of all compounds containing the grouping —CO·NH—, *e.g.*, proteins.

When urea is heated with thionyl chloride, biuret and triuret, $CO(NH{\cdot}CO{\cdot}NH_2)_2$, are obtained (Haworth and Mann, 1943). Thionyl chloride has no action on thiourea (q.v.). When heated rapidly, urea evolves ammonia and forms cyanic acid which rapidly polymerises to cyanuric acid (p. 298). When refluxed with alcohols, urea forms urethans (see above).

(iv) Nitrous acid reacts with urea with the liberation of nitrogen which, however, is not evolved quantitatively:

$$CO(NH_2)_2 + 2HNO_2 \longrightarrow CO_2 + 3H_2O + 2N_2$$

Nitrogen is also evolved, again not quantitatively, when urea is treated with *excess* alkaline hypobromite:

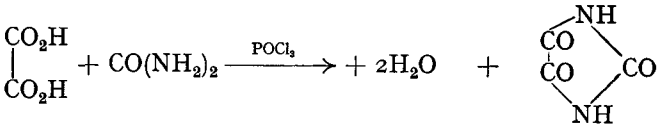
$$CO(NH_2)_2 + 3NaOBr + 2NaOH \longrightarrow N_2 + Na_2CO_3 + 3NaBr + 3H_2O$$

(v) Acid chlorides and acid anhydrides react with urea to form *ureides*, *e.g.*, acetyl chloride forms acetylurea:

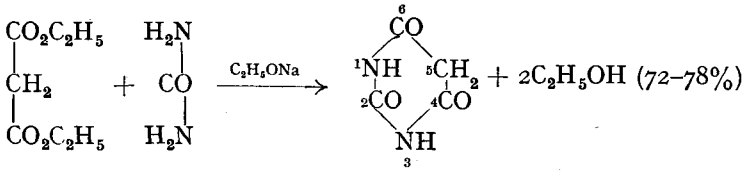
$$CH_3{\cdot}COCl + NH_2{\cdot}CO{\cdot}NH_2 \longrightarrow CH_3{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2 + HCl$$

Many of these ureides are useful drugs, particularly when the acid radical has a branched chain, *e.g.*, bromural (α-bromo*iso*valerylurea), $(CH_3)_2CH{\cdot}CHBr{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2$.

Dicarboxylic acids react with urea in the presence of phosphoryl chloride to form *cyclic* ureides; *e.g.*, oxalic acid forms *parabanic acid* (oxalylurea):

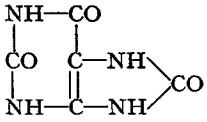


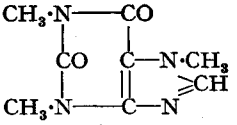
Cyclic ureides may also be prepared by refluxing a diester with urea in ethanolic solution containing sodium ethoxide; *e.g.*, malonic ester forms *barbituric acid* (*malonylurea*):



Barbituric acid and its 5- or 5 : 5-derivatives are used in medicine as hypnotics and sedatives, *e.g.*, *barbitone* (5 : 5-diethylbarbituric acid), and *phenobarbitone* (5-phenyl-5-ethylbarbituric acid).

A very important group of cyclic diureides is the *purine* group, *e.g.*, uric acid, caffeine, etc.:


uric acid


caffeine

Inclusion complexes. Several types of inclusion complexes are known, and in all of them molecules of one component are physically imprisoned in the cavities of the crystalline structure of the second component. Two important types of inclusion complexes are the *channel* (*canal*) *complexes* and the *clathrate* (*cage*) *complexes* (see p. 634 for a discussion of the latter).

Channel complexes are those cases where one component crystallises in a form with parallel, approximately cylindrical channels in which molecules of a second component are enclosed lengthwise. Urea normally forms a crystal structure which is closely packed, but in the presence of various *straight-chain* molecules, *e.g.*, *n*-paraffins, *n*-alcohols, *n*-acids, *n*-esters, etc., the urea crystallises in a more open structure which contains long channels enclosing molecules of the second component. These channels contain a number of molecules of the second component and, in general, the number is inversely proportional to the length of the enclosed molecule. Branched-chain and cyclic structures cannot "fit" into these channels, and so this property affords a means of separating straight-chain from branched-chain compounds. The complexes are decomposed by melting or by dissolving away the urea with water. The formula of the channel complexes is usually $A_n B$ (A is urea) where n, usually not a whole number, has values of 4 or more and increases as the length of B increases. Furthermore, since channel complexes are characterised by the fact that molecules of the second component bear some structural resemblance to each other, it is not possible to separate homologues by channel complexes. For each homologous series there is a certain minimum chain-length for channel complex formation, *e.g.*, six carbons for paraffins, seven for alcohols, five for acids, etc.

Channel complex formation has been used to resolve racemic modifications (p. 412).

Substituted ureas may be prepared by a reaction similar to Wöhler's synthesis of urea; the hydrochloride or sulphate of a primary or secondary amine is heated with potassium *iso*cyanate, *e.g.*, methylamine hydrochloride (1 molecule) forms methylurea:

$$CH_3{\cdot}NH_2{\cdot}HCl + KNCO \longrightarrow KCl + CH_3{\cdot}NH_2{\cdot}HNCO \longrightarrow CH_3{\cdot}NH{\cdot}CO{\cdot}NH_2$$

If *excess* amine salt is used, *s*-disubstituted ureas are obtained, *e.g.*, excess aniline hydrochloride forms *s*-diphenylurea:

$$C_6H_5{\cdot}NH_2{\cdot}HCl + KNCO \longrightarrow KCl + C_6H_5{\cdot}NH_2{\cdot}HNCO \longrightarrow$$
$$C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH_2 \xrightarrow{C_6H_5{\cdot}NH_2{\cdot}HCl} C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}C_6H_5 + NH_4Cl$$

Alternatively, *s*-diphenylurea may be obtained by refluxing an aqueous solution of aniline hydrochloride with urea:

$$C_6H_5{\cdot}NH_2{\cdot}HCl + NH_2{\cdot}CO{\cdot}NH_2 \longrightarrow C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH_4Cl$$
$$C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH_2 + C_6H_5{\cdot}NH_2{\cdot}HCl \longrightarrow C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}C_6H_5 + NH_4Cl$$

Both phenylurea (38–40 per cent.) and *s*-diphenylurea (52–55 per cent.) may be isolated.

s-Substituted ureas may be obtained by the action of carbonyl chloride on a primary or secondary amine:

$$COCl_2 + 2R{\cdot}NH_2 \longrightarrow CO(NH{\cdot}R)_2 + 2HCl$$

The reaction between phenyl *iso*cyanate and a primary or secondary amine also produces an *s*-disubstituted urea, *e.g.*, with ethylamine, *s*-ethylphenylurea is formed:

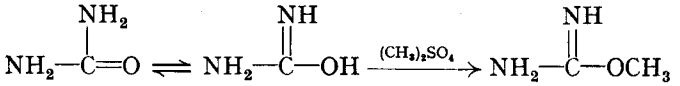
$$C_6H_5{\cdot}NCO + C_2H_5{\cdot}NH_2 \longrightarrow C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}C_2H_5$$

This reaction is used to characterise amines.

A very convenient method of preparing alkyl-ureas is to evaporate an aqueous or ethanolic solution of an amine and nitrourea (see above); the latter decomposes into cyanic acid and nitroamide, $NH_2{\cdot}NO_2$, which readily decomposes into nitrous oxide:

$$NH_2{\cdot}CO{\cdot}NH{\cdot}NO_2 \longrightarrow HNCO + NH_2{\cdot}NO_2$$
$$HNCO + R_2NH \longrightarrow R_2N{\cdot}CO{\cdot}NH_2$$
$$NH_2{\cdot}NO_2 \longrightarrow N_2O + H_2O$$

When urea is treated with methyl sulphate in faintly alkaline solution, *methyl*isou*rea* is obtained:



COMPOUNDS RELATED TO UREA

Semicarbazide (*aminourea*), $NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$, may be prepared by treating hydrazine sulphate with potassium cyanate:

$$H_2N{\cdot}NH_2{\cdot}HNCO \longrightarrow NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$$

It may also be prepared by heating urea with hydrazine hydrate.

$$NH_2{\cdot}CO{\cdot}NH_2 + N_2H_4{,}H_2O \longrightarrow NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2 + NH_3 + H_2O$$

A more recent method is the electrolytic reduction of nitrourea in sulphuric acid solution using a lead anode:

$$NH_2{\cdot}CO{\cdot}NH{\cdot}NO_2 + 6[H] \longrightarrow NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2 + 2H_2O \quad (61\text{–}69\%)$$

Semicarbazide is a white crystalline solid, m.p. 96°. It is an important reagent for the identification of carbonyl compounds, with which it forms *semicarbazones*; it is also used in the Wolff–Kishner reduction (p. 153).

Guanidine (*aminomethanamidine*), $NH{:}C(NH_2)_2$, is found in beet juice, and is one of the degradation products of the purines. It may be prepared:

(i) By heating cyanamide with ammonium chloride:

$$NH_2{\cdot}CN + NH_4Cl \longrightarrow (NH_2)_2C{:}NH{\cdot}HCl$$

(ii) By *prolonged* heating of ammonium thiocyanate at 180° (see also thiourea, below):

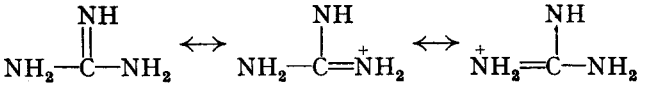
$$NH_4SCN \longrightarrow S{:}C(NH_2)_2 \xrightarrow{-H_2S} NH_2{\cdot}CN \xrightarrow{NH_4SCN} (NH_2)_2C{:}NH{\cdot}HSCN$$

(iii) By heating ethyl orthocarbonate with ammonia at 160°:

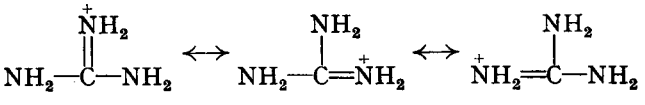
$$C(OC_2H_5)_4 + 3NH_3 \longrightarrow (NH_2)_2C{:}NH + 4C_2H_5OH$$

Guanidine is a white hygroscopic crystalline solid, and is a ***strong*** " mono-acid " base, even forming a carbonate. Its strength as a base may be explained by resonance.

Neutral molecule



Ion

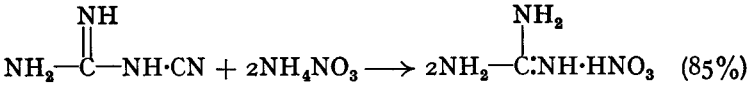


In the ion, the resonating structures are equivalent. Hence the ion is more stable than the neutral molecule. Thus the neutral molecule tends to form the ion, *i.e.*, it is strongly basic (more so than urea, the ions of which are not all equivalent). X-Ray analysis of guanidinium iodide shows that the three nitrogen atoms are symmetrically placed round the carbon atom. Furthermore, the C—N distance has been found to be 1·18 A (Theilacker, 1935; *cf.* urea). These facts are in keeping with the assumption that the guanidinium ion is a resonance hybrid.

Careful hydrolysis with barium hydroxide solution converts guanidine into urea:

$$(NH_2)_2C{:}NH + H_2O \longrightarrow (NH_2)_2C{:}O + NH_3$$

Guanidine nitrate may be prepared by heating dicyanodiamide with ammonium nitrate:

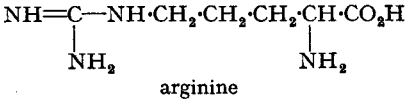


When treated with concentrated sulphuric acid, guanidine nitrate is converted into nitroguanidine, $NH_2{\cdot}C(:NH){\cdot}NH{\cdot}NO_2$ (*cf.* urea nitrate, p. 385). Nitroguanidine is used for making flashless powders.

A number of derivatives of guanidine are important, *e.g.*, **creatine** (N-*methylguanidinoacetic acid*), which is found in muscle fluids; **creatinine,** which is found in beef extract and human urine, and is the anhydride (lactam) of creatine; and **arginine** (α-amino-δ-guanidinovaleric acid), which is present in many proteins:

creatine

creatinine



arginine

Thiourea (*thiocarbamide*), $S{:}C(NH_2)_2$, may be prepared by heating ammonium thiocyanate at 170° for some time:

$$NH_4SCN \longrightarrow S{:}C(NH_2)_2 \quad (14\text{–}16\%)$$

It is a white crystalline solid, m.p. 180°, and behaves as a " monoacidic " base. Dipole moment studies show that thiourea is a resonance hybrid, and this is supported by the work of Truter *et al.* (1958), who have examined

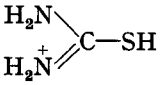
the crystal structure of thiourea by X-ray analysis. Thiourea, like urea, forms channel complexes. When heated with alkalis, thiourea is hydrolysed:

$$S{:}C(NH_2)_2 + 2H_2O \xrightarrow{NaOH} CO_2 + H_2S + 2NH_3$$

Oxidation with *alkaline* permanganate converts thiourea into urea:

$$S{:}C(NH_2)_2 + [O] \longrightarrow O{:}C(NH_2)_2 + S$$

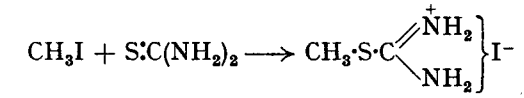
On the other hand, oxidation with *acid* permanganate converts it into *formamidine disulphide*, $NH_2{\cdot}C(:NH){\cdot}S{\cdot}S{\cdot}C(:NH){\cdot}NH_2$. This reaction is characteristic of all compounds containing the mercapto-group, and therefore suggests that in acid solution thiourea exists as



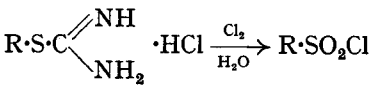
Oxides of lead, silver or mercury remove a molecule of hydrogen sulphide from thiourea at room temperature to form cyanamide:

$$(NH_2)_2CS + HgO \longrightarrow NH_2{\cdot}CN + HgS + H_2O$$

When treated with alkyl halide, thiourea forms S-*alkyl-ψ-thiouronium salts* (S-*alkyl*-iso*thiouronium salts*):



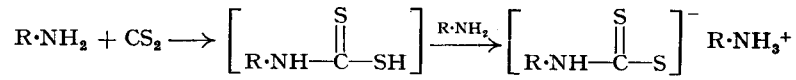
These compounds are used to characterise sulphuric acids, with which they form insoluble salts. They may also be used to prepare thioalcohols (p. 332), and also to prepare sulphonyl chlorides by oxidation with chlorine-water.



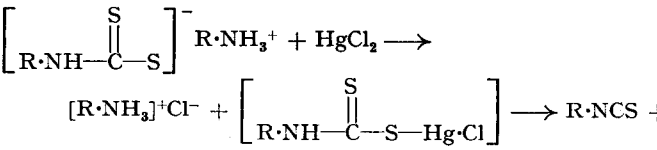
Thiourea is used to protect furs and clothing against insects.

s-*Diphenylthiourea* or *diphenylthiocarbanilide*, $(C_6H_5{\cdot}NH)_2CS$, which is used as a rubber accelerator, may be prepared by heating aniline with carbon disulphide in an ethanolic solution containing potassium hydroxide.

Dithiocarbamic acid, $S{:}C(NH_2){\cdot}SH$, although unstable in the free state, gives rise to stable salts. These may be prepared by heating a primary or secondary amine with carbon disulphide. This reaction is complicated and the mechanism is uncertain. A possibility is via the formation of the unstable *N*-alkyldithiocarbamic acid which forms the stable dithiocarbamic acid salt with another molecule of amine:



The *Hofmann mustard oil reaction* (p. 337) is believed to take place via the formation of a dithiocarbamic acid salt, which is then decomposed by the mercuric chloride, possibly as follows:



On the other hand, when heated alone, dithiocarbamic acid salts form thioureas:

$$\left[\begin{array}{l} \quad\quad S \\ \quad\quad \| \\ R{\cdot}NH{\cdot}C{\cdot}S \end{array}\right]^{-} R{\cdot}NH_3^+ \longrightarrow R{\cdot}NCS + R{\cdot}NH_2 + H_2S$$

$$R{\cdot}NCS + R{\cdot}NH_2 \longrightarrow R{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}R$$

QUESTIONS

1. How may oxalic acid be prepared? Name the compounds and state the conditions under which they are formed when oxalic acid is treated with:—(*a*) H_2SO_4, (*b*) KOH, (*c*) $KMnO_4$, (*d*) EtOH, (*e*) EtOAc, (*f*) $(CH_2OH)_2$, (*g*) H_2, (*h*) PCl_5, (*i*) $CH_2OH{\cdot}CHOH{\cdot}CH_2OH$, (*j*) when it is heated.

2. Describe the more important methods of preparing each of the following acids:—(*a*) malonic, (*b*) succinic, (*c*) glutaric, (*d*) adipic, (*e*) pimelic, (*f*) suberic, (*g*) azelaic, (*h*) sebacic.

Name the compounds and state the conditions under which they are formed when the calcium salt of each of the above acids is heated, and when each is treated with:—(*a*) H_2SO_4, (*b*) EtOH, (*c*) P_2O_5, (*d*) $(CH_2OH)_2$, (*e*) Ac_2O.

3. Describe the preparation and properties of the following compounds:—(*a*) mesoxalic acid, (*b*) oxamide, (*c*) oxamic acid, (*d*) malonamide, (*e*) Et_2 bromomalonate, (*f*) succinic anhydride, (*g*) succinamic acid, (*h*) succinimide, (*i*) succinamide, (*j*) succinyl chloride, (*k*) urethan, (*l*) carbonyl chloride, (*m*) acid ester of pimelic acid, (*n*) ethyl chloroformate, (*o*) nitrourea, (*p*) barbituric acid, (*q*) semicarbazide, (*r*) guanidine, (*s*) thiourea.

4. Suggest a *complete* synthesis for:—(*a*) succinic acid, (*b*) glutaric acid.

5. By means of equations show how you would synthesise:—

(*a*) $Me{\cdot}CH(CO_2Et){\cdot}CH(CO_2Et)_2$ (*b*) $Et{\cdot}CH(CN){\cdot}CO_2Et$

(*c*) $Et{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CO_2H$ (*d*) $CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$ (*e*) $Et{\cdot}N(CO_2Et)_2$

6. Show, by means of equations, how you would convert succinic acid into:—(*a*) glutaric acid, (*b*) adipic acid, (*c*) suberic acid, (*d*) malonic acid.

7. How could you prepare:—(*a*) *N* : *N*-dimethylurethan, (*b*) *s*-dimethylurea, (*c*) methylthiourea, (*d*) methyl*iso*thiourea, (*e*) barbitone?

8. Define and give examples of:—(*a*) The Crum-Brown and Walker electrolytic method, (*b*) oxidative degradation, (*c*) the Baeyer Strain Theory, (*d*) Blanc's rule, (*e*) the biuret reaction.

9. Discuss the preparation and uses of:—(*a*) *N*-bromosuccinimide, (*b*) oxalacetic ester, (*c*) ethyl carbonate.

10. Write an account of the preparation of urea and discuss its structure. Also give an account of the methods for preparing substituted ureas.

Name the compounds and state the conditions under which they are formed when urea is treated with:—(*a*) H·CHO, (*b*) NaOCl, (*c*) HCl, (*d*) NaOH, (*e*) HNO_2, (*f*) HNO_3 (*g*) gentle heating, (*h*) rapid heating, (*i*) $SOCl_2$, (*j*) ROH, (*k*) AcCl, (*l*) $(CO_2H)_2$, (*m*), $CH_2(CO_2Et)_2$, (*n*) Me_2SO_4, (*o*) $C_6H_5{\cdot}NH_2{\cdot}HCl$.

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CHAPTER XVII

HYDROXYACIDS. STEREOCHEMISTRY. UNSATURATED DICARBOXYLIC ACIDS

MONOBASIC HYDROXYACIDS

MONOBASIC hydroxyacids are fatty acids which contain one or more hydroxyl groups in the carbon chain.

Nomenclature. The usual method is to name the hydroxyacid as a derivative of the parent fatty acid (named according to the trivial system), the position of the hydroxyl group being indicated by a Greek letter, *e.g.*,

$CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H$ β-hydroxybutyric acid

According to the I.U.P.A.C. system of nomenclature, the position of the hydroxyl group is indicated by a number, *e.g.*,

$CH_3{\cdot}CH_2{\cdot}CHOH{\cdot}CO_2H$ 2-hydroxybutanoic acid or 1-hydroxypropane-1-carboxylic acid

Many hydroxyacids which occur in nature are given special names indicating the source, *e.g.*, $CH_3{\cdot}CHOH{\cdot}CO_2H$, lactic acid, occurs in sour milk (Latin : *lac*, milk).

General methods of preparation. 1. By the controlled oxidation of glycols using dilute nitric acid (the yields are usually poor); *e.g.*, propylene glycol gives lactic acid:

$$CH_3{\cdot}CHOH{\cdot}CH_2OH + 2[O] \xrightarrow{HNO_3} CH_3{\cdot}CHOH{\cdot}CO_2H + H_2O$$

2. By the hydrolysis of halogeno-acids with moist silver oxide, sodium hydroxide, or sodium carbonate solution, *e.g.*,

$$CH_2Cl{\cdot}CO_2H + H_2O \longrightarrow CH_2OH{\cdot}CO_2H + HCl \quad (v.g.\text{–}ex.)$$

This is a very good method for α-hydroxyacids, since the starting materials, α-halogeno-acids, are readily prepared.

3. By the reduction of aldehydic, ketonic or dicarboxylic acids under suitable conditions, *e.g.*,

$$CH_3{\cdot}CO{\cdot}CO_2H + 2[H] \xrightarrow[H_2O]{Na/Hg} CH_3{\cdot}CHOH{\cdot}CO_2H$$

In practice only the reduction of dicarboxylic acids is important, since aldehydic and ketonic acids are usually inaccessible:

$$CO_2H{\cdot}(CH_2)_n{\cdot}CO_2H \xrightarrow{C_2H_5OH} C_2H_5O_2C{\cdot}(CH_2)_n{\cdot}CO_2H \xrightarrow{Na/C_2H_5OH} CH_2OH{\cdot}(CH_2)_n{\cdot}CO_2H$$

4. By the action of nitrous acid on aminoacids, *e.g.*,

$$NH_2{\cdot}CH_2{\cdot}CO_2H + HNO_2 \longrightarrow CH_2OH{\cdot}CO_2H + N_2 + H_2O \quad (g.)$$

This method is mainly confined to preparing α-hydroxyacids, since naturally occurring aminoacids are α-derivatives.

5. By hydrolysing the cyanohydrins formed from aldehydes or ketones and hydrogen cyanide, *e.g.*,

$$CH_3{\cdot}CHO + HCN \longrightarrow CH_3{\cdot}CHOH{\cdot}CN \xrightarrow{H_2O} CH_3{\cdot}CHOH{\cdot}CO_2H \quad (g.\text{–}v.g.)$$

6. β-Hydroxyacids may be prepared by the hydrolysis of cyanohydrins prepared from chlorohydrins, *e.g.*,

$$CH_2OH{\cdot}CH_2Cl \xrightarrow{KCN} CH_2OH{\cdot}CH_2{\cdot}CN \xrightarrow{H_2O} CH_2OH{\cdot}CH_2{\cdot}CO_2H \quad (g.)$$

7. β-Hydroxyacids may be prepared by the Reformatsky reaction (p. 363).

8. Weygand *et al.* (1955) have introduced the following method for synthesising α-hydroxyacids. A diazoketone is treated with a sulphenyl chloride and the product hydrolysed with sodium hydroxide or better, first treated with sodium acetate and the resulting compound then treated with sodium hydroxide.

$$R{\cdot}CO_2H \xrightarrow{SOCl_2} R{\cdot}COCl \xrightarrow{CH_2N_2} R{\cdot}CO{\cdot}CHN_2$$

$$\xrightarrow{R'{\cdot}SCl} R{\cdot}CO{\cdot}CHCl{\cdot}SR' \xrightarrow{NaOH} R{\cdot}CHOH{\cdot}CO_2H$$

$$\downarrow CH_3{\cdot}CO_2Na \qquad \uparrow NaOH$$

$$R{\cdot}CO{\cdot}CH(O{\cdot}CO{\cdot}CH_3){\cdot}SR'$$

General properties and reactions. *Glycollic acid*, the first member of the series, is a solid; the higher members are liquids. All are soluble in water, generally more so than are either the corresponding fatty acid or alcohol. This is to be expected, since hydroxyacids have *two* functional groups which can form hydrogen bonds with water.

1. Hydroxyacids behave both as acids and alcohols; in many reactions the hydroxyl and carboxyl groups do not interfere with each other, particularly when they are far apart. Furthermore, by esterifying the carboxyl group, the ester then behaves predominantly as a hydroxy-compound, *i.e.*, esterification masks, to a large extent, the presence of the carboxyl group. The carboxyl group may be converted into the ester, amide, nitrile, acyl chloride, etc. The hydroxyl group (when the carboxyl group has been esterified) may be converted into the ester, ether, etc.; *e.g.*, glycollic acid reacts with acetyl chloride to form acetylglycollic acid (behaving as a hydroxy-compound):

$$CH_2OH{\cdot}CO_2H + CH_3{\cdot}COCl \longrightarrow CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CO_2H + HCl$$

Glycollic acid reacts with phosphorus pentachloride to form chloroacetyl chloride (behaving both as an alcohol and an acid); the chloroacetyl chloride is readily hydrolysed by water to chloroacetic acid:

$$CH_2OH{\cdot}CO_2H \xrightarrow{PCl_5} CH_2Cl{\cdot}COCl \xrightarrow{H_2O} CH_2Cl{\cdot}CO_2H$$

2. When hydroxyacids are oxidised under suitable conditions, a primary alcoholic group is converted into an aldehyde group, and a secondary into ketonic. The presence of a tertiary alcoholic group leads to the breakdown of the carbon chain (*cf.* alcohols, p. 132):

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

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

$$(CH_3)_2C(OH){\cdot}CO_2H \xrightarrow{[O]} (CH_3)_2CO + CO_2 + H_2O$$

Various oxidising agents may be used, *e.g.*, dilute nitric acid, Fenton's reagent, permanganate; which is used generally depends on the hydroxyacid involved.

3. When heated with dilute sulphuric acid or dilute permanganate, α-hydroxyacids are converted into aldehydes or ketones:

$$R{\cdot}CHOH{\cdot}CO_2H \xrightarrow{H_2SO_4} R{\cdot}CHO + H{\cdot}CO_2H \quad (v.g.)$$

$$R_2C(OH){\cdot}CO_2H + [O] \xrightarrow{KMnO_4} R_2CO + CO_2 + H_2O \quad (v.g.)$$

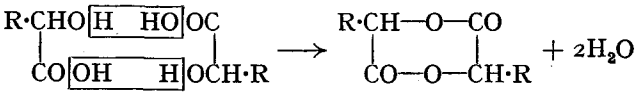
These reactions offer a very good means of stepping down the fatty acid series (via the H.V.Z. reaction), one carbon atom at a time.

4. When heated with concentrated hydriodic acid, hydroxyacids are reduced to the corresponding fatty acid:

$$CH_3{\cdot}CHOH{\cdot}CO_2H + 2HI \longrightarrow CH_3{\cdot}CH_2{\cdot}CO_2H + H_2O + I_2$$

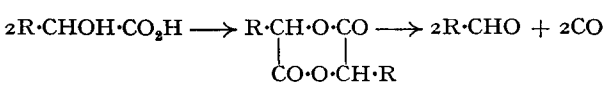
5. When hydroxyacids are heated, the product formed depends on the relative positions of the hydroxyl and carboxyl groups.

(i) α-Hydroxyacids form **lactides**; these are six-membered ring compounds formed by reaction between *two* molecules of the hydroxy-acid, and are named systematically as 3 : 6 dialkyl-1 : 4-dioxan-2 : 5-dione:



The tendency to form lactides is very pronounced, in many cases the lactide being formed by allowing the α-hydroxyacid to stand in a desiccator over concentrated sulphuric acid. Lactides are readily hydrolysed to the acid by alkali.

The distillation of α-hydroxyacids produces aldehydes via the lactide:

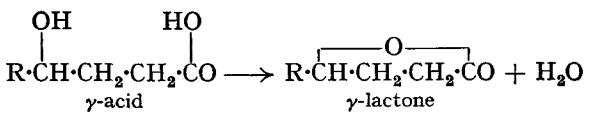


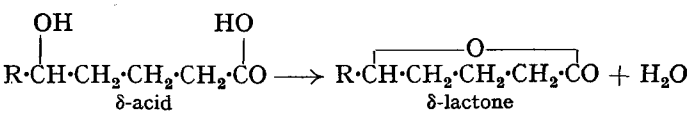
When heated with a trace of zinc chloride, lactides are converted into linear polyesters, HO—(—CHR·COO—)$_n$—H, which regenerate the lactide on distillation under reduced pressure.

(ii) When β-hydroxyacids are heated, they eliminate a molecule of water to form mainly the αβ-unsaturated acid and a very small amount of the βγ-unsaturated acid. The reaction is best carried out by refluxing the β-hydroxyacid with 10 per cent. sodium hydroxide solution:

$$R{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H \longrightarrow R{\cdot}CH{:}CH{\cdot}CO_2H + H_2O$$

(iii) On heating, γ- and δ-hydroxyacids readily form *internal* esters known as **lactones**:





β-Lactones from β-hydroxyacids can only be obtained under special conditions; in practice β-lactones may be prepared by shaking an aqueous solution of the sodium salt of the β-chloroacid with chloroform:

$$R{\cdot}CHCl{\cdot}CH_2{\cdot}CO_2Na \longrightarrow R{\cdot}\overset{\displaystyle O}{\overset{\frown}{CH}}{\cdot}CH_2{\cdot}CO + NaCl$$

They may, however, be prepared more readily by reaction between keten and a carbonyl compound; *e.g.*, β-propiolactone, which promises to be an important intermediate, is prepared from keten and formaldehyde:

$$CH_2{:}C{:}O + H{\cdot}CHO \longrightarrow \overset{\displaystyle O}{\overset{\frown}{CH_2{\cdot}CH_2}}{\cdot}CO$$

According to the I.U.P.A.C. system of nomenclature, lactones are known as *-olides*, *e.g.*, $\overset{\displaystyle O}{\overset{\frown}{CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO$, δ-valerolactone or 1 : 5-pentanolide. The systematic name of this lactone is *4-hydroxybutane-1-carboxylic acid lactone.*

Lactone formation takes place very readily, particularly with γ-hydroxy-acids, which often form the lactone on standing at room temperature, or even in aqueous solution when the sodium salt is acidified.

γ-Lactones may be prepared by the rearrangement of unsaturated acids by heating with concentrated sulphuric acid, *e.g.*, oleic acid forms γ-stearo-lactone:

$$CH_3{\cdot}(CH_2)_7{\cdot}CH{:}CH{\cdot}(CH_2)_7{\cdot}CO_2H \xrightarrow{H_2SO_4} CH_3{\cdot}(CH_2)_{13}{\cdot}\overset{\displaystyle O}{\overset{\frown}{CH{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO$$

γ-Butyrolactone is manufactured by the oxidation of tetramethylene glycol over a copper catalyst:

$$CH_2OH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2OH \xrightarrow[Cu]{O_2} \overset{\displaystyle O}{\overset{\frown}{CH_2{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO$$

It is an important intermediate in the preparation of polyamides.

Lactones are converted into alkali salts when refluxed with excess alkali:

$$R{\cdot}\overset{\displaystyle O}{\overset{\frown}{CH{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO + NaOH \longrightarrow R{\cdot}CHOH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Na$$

Lactones are reduced by sodium amalgam in acid solution to the corresponding fatty acid:

$$R{\cdot}\overset{\displaystyle O}{\overset{\frown}{CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO + 2[H] \longrightarrow R{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

On the other hand, lactones of polyhydroxyacids are reduced, under these conditions, to polyhydroxyaldehydes (see p. 447). Lithium aluminium hydride reduces lactones to diols, *e.g.*, γ-valerolactone forms pentane-1 : 4-diol.

When treated with concentrated halogen acid, lactones form the corresponding halogen-acid:

$$R{\cdot}\overset{\displaystyle O}{\overset{\frown}{CH{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO + HX \rightleftharpoons R{\cdot}CHX{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

With concentrated ammonium hydroxide solution, the hydroxyamide is formed:

$$R{\cdot}\overset{\displaystyle O}{\overset{\frown}{CH{\cdot}CH_2{\cdot}CH_2}}{\cdot}CO + NH_3 \rightleftharpoons R{\cdot}CHOH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH_2$$

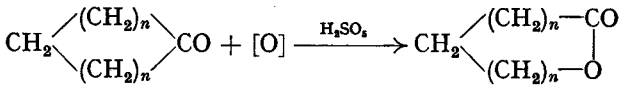
δ-Lactones can change spontaneously into linear polyesters:

$$HO{-}(CHR{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COO{-})_n{-}H$$

(iv) ε-Hydroxyacids, in certain cases, may form the lactone on heating. Usually they either eliminate a molecule of water to form two unsaturated acids, δε- and εζ- or form linear polyesters.

(v) Hydroxyacids with the hydroxyl group further removed than the ε-position, on heating, either eliminate a molecule of water to form unsaturated acids (of two types; *cf.* ε-hydroxyacids), or form linear esters.

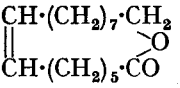
Large ring lactones (fourteen- to eighteen-membered rings) have been prepared by the oxidation of cyclic ketones with Caro's acid (Ruzicka and Stoll, 1928):



By using the high dilution principle of Ruggli (1912), large ring lactones have also been prepared from hydroxyacids in which the hydroxyl group is far removed from the carboxyl group. According to this principle, by using sufficiently dilute solutions of a hydroxyacid, the distance between *different* molecules can be made greater than the distance between the hydroxyl and carboxyl groups of the *same* molecule. Thus the cyclic compound (lactone) is formed instead of linear condensation taking place; *e.g.*, Stoll and his co-workers (1934) found that ω-hydroxypentadecoic acid gave a high yield of lactone in very dilute solution.

Hunsdiecker and Erlbach (1947) have also prepared large ring lactones by the dilution principle. These workers cyclised ω-bromo-aliphatic acids by boiling dilute solutions in butanone with excess potassium carbonate; they obtained lactones in yields varying from 56·3 to 96·8 per cent., the yield increasing with the size of the ring.

Some large ring lactones occur naturally, *e.g.*, *ambrettolide* (in musk):



Glycollic acid (*hydroxyacetic acid, hydroxyethanoic acid*), $CH_2OH{\cdot}CO_2H$, is the simplest hydroxyacid, and occurs in the juice of beet and sugar-cane, and in unripe grapes. It may be prepared by refluxing an aqueous solution of potassium chloroacetate with sodium carbonate and then acidifying with hydrochloric acid:

$$CH_2Cl{\cdot}CO_2K + H_2O \longrightarrow CH_2OH{\cdot}CO_2H + KCl \quad (80\%)$$

Glycollic acid may also be prepared by warming a solution of formalin with potassium cyanide, and then acidifying with hydrochloric acid:

$$H{\cdot}CHO + 2KCN + 2H_2O \longrightarrow CH_2OH{\cdot}CO_2K + NH_3 \xrightarrow{HCl} CH_2OH{\cdot}CO_2H \quad (70\%)$$

Glycollic acid is prepared industrially by the electrolytic reduction of oxalic acid. A more recent method of manufacture is to heat, at 160–170° and under pressure, a mixture of formaldehyde, carbon monoxide and water in acetic acid with sulphuric acid as catalyst:

$$H{\cdot}CHO + CO + H_2O \longrightarrow CH_2OH{\cdot}CO_2H$$

If methanol is used instead of water, methyl glycollate is obtained.

Glycollic acid is a crystalline solid, m.p. 80°, readily soluble in water, ethanol and ether. It is oxidised to oxalic acid by nitric acid. Its lactide is known as *glycollide*.

Lactic acid (*α-hydroxypropionic acid, 2-hydroxypropanoic acid*), $CH_3{\cdot}CHOH{\cdot}CO_2H$, may be prepared:

(i) By oxidising propylene glycol with dilute nitric acid:

$$CH_3{\cdot}CHOH{\cdot}CH_2OH + 2[O] \longrightarrow CH_3{\cdot}CHOH{\cdot}CO_2H + H_2O \quad (p.\text{-}f.)$$

(ii) By heating α-chloro- or α-bromopropionic acid with silver oxide in water, or with sodium hydroxide solution:

$$CH_3{\cdot}CHBr{\cdot}CO_2H + H_2O \longrightarrow CH_3{\cdot}CHOH{\cdot}CO_2H + HBr \quad (g.\text{-}v.g.)$$

(iii) By the hydrolysis of acetaldehyde cyanohydrin:

$$CH_3{\cdot}CHO + HCN \longrightarrow CH_3{\cdot}CHOH{\cdot}CN \xrightarrow{H_2O} CH_3{\cdot}CHOH{\cdot}CO_2H$$

(iv) By the action of nitrous acid on alanine:

$$CH_3{\cdot}CH(NH_2){\cdot}CO_2H + HNO_2 \longrightarrow CH_3{\cdot}CHOH{\cdot}CO_2H + N_2 + H_2O$$

(v) Milk contains the sugar lactose, which is fermented by the *Bacillus acidi lactiti*:

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 4CH_3{\cdot}CHOH{\cdot}CO_2H$$

This is the basis of the industrial preparation of lactic acid. A little sour milk is added to a solution of cane-sugar or glucose in the presence of excess chalk, and the temperature is maintained at 35°. As the lactic acid is produced, it is neutralised by the chalk, being precipitated as the insoluble calcium salt. The solution must be kept neutral, since the micro-organism ceases to function if the concentration of the lactic acid exceeds 1 per cent. The calcium lactate is filtered off and decomposed with the calculated quantity of dilute sulphuric acid. Lactic acid is also prepared by the fermentation of sucrose by *Rhizopus oryzae*.

Lactic acid is a colourless syrup, m.p. 18°, b.p. 122°/15 mm. It has a sour taste and smell, is hygroscopic, and is very soluble in water. It undergoes all the general reactions of α-hydroxyacids; oxidation with Fenton's reagent converts it into pyruvic acid:

$$CH_3{\cdot}CHOH{\cdot}CO_2H \xrightarrow{H_2O_2/Fe^{2+}} CH_3{\cdot}CO{\cdot}CO_2H$$

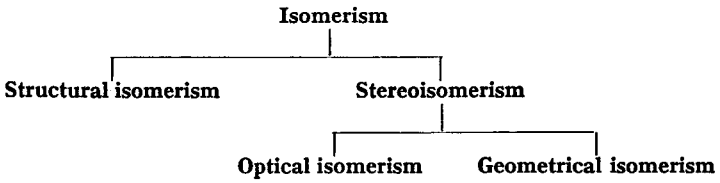
It is oxidised to acetic acid by permanganate. Lactic acid is used in the tanning industry to remove lime from the hides; it is used in the dyeing industry, and ethyl lactate is used as a solvent for cellulose nitrate.

Lactic acid exists in three distinct forms, all of which have been shown to possess the *same* chemical structure. The three kinds of lactic acids are: (i) dextrorotatory lactic acid; (ii) lævorotatory lactic acid; (iii) DL-lactic acid. The lactic acid prepared by the above methods is the DL-. Dextrorotatory lactic acid may be obtained from meat extract; this acid is also known as *sarcolactic acid* (Greek: *sarkos*, flesh). Lævorotatory lactic acid may be obtained by the fermentation of sucrose by *Bacillus acidi lævolactiti*.

The chemical properties of these isomeric lactic acids are identical in all respects, except in their behaviour towards other optically active compounds (see later). The differences appear only in certain physical properties. The dextrorotatory and lævorotatory lactic acids both melt at 26°; the DL- melts at 18°. The main difference between dextrorotatory and lævorotatory lactic acid is their respective action on polarised light. This is due to *stereochemical* differences in structure.

STEREOCHEMISTRY

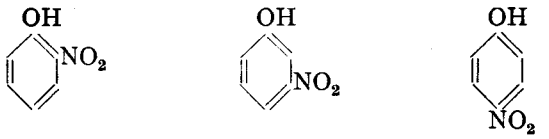
Isomerism consists of three types:



Structural isomerism is due to the difference in structure, and is exhibited in three different ways.

(i) *Chain* or *nuclear isomerism* is exhibited by compounds which differ in the arrangement of the *carbon atoms*, *e.g.*, *n*- and *iso*butane.

(ii) *Position isomerism* is exhibited by compounds having the *same* carbon skeleton but differing in the position occupied by a substituent group, *e.g.*, *n*- and *iso*propyl alcohols; α-, β- and γ-hydroxybutyric acids; *ortho-*, *meta-* and *para*-nitrophenols.



ortho- *meta-* *para-*

(iii) *Functional group isomerism* is exhibited by compounds having different functional groups, *i.e.*, compounds with the same molecular formula but belonging to different homologous series, *e.g.*, ethanol and dimethyl ether; acetone and propionaldehyde.

This type of isomerism was originally called *metamerism* by Berzelius, but he also included under this heading compounds in the same homologous series, *e.g.*, diethyl ether, methyl *n*-propyl ether and methyl *iso*propyl ether. The name metamerism is now reserved only for the latter type of isomerism (p. 144).

Tautomerism may be regarded as a special case of functional group isomerism.

Stereoisomerism is exhibited by isomers having the *same* structure but differing in their *spatial* arrangement, *i.e.*, having different *configurations*. Different configurations are possible because carbon forms mainly covalent bonds and these have direction in space.

Optical isomerism is characterised by compounds having the *same* structure but different configurations, and because of their *molecular asymmetry* these compounds rotate the plane of polarisation of plane-polarised light. Optical isomers have similar physical and chemical properties; the most marked difference between them is their action on polarised light (see below).

Geometrical isomerism or *cis-trans isomerism* is characterised by compounds having the *same structure but different configurations*, and because of their *molecular symmetry* these compounds do *not* rotate the plane of polarisation of plane-polarised light. Geometrical isomers differ in all their physical and in many of their chemical properties. They can also exhibit optical isomerism if the structure of the molecule, apart from giving rise to geometrical isomerism, also satisfies the requirements for optical isomerism.

Optical activity is the name given to the phenomenon exhibited by compounds which, when placed in the path of a beam of polarised light, are

capable of rotating the plane of polarisation to the left or right; such compounds are said to be optically active. The instrument used for measuring the rotatory power of a substance is the *polarimeter*.* Essentially it consists of two Nicol prisms, one the polariser (P) and the other, the analyser (A), and between them a tube (T) which contains the substance (a liquid or a solution) to be examined (Fig. 1). S is a source of monochromatic light.

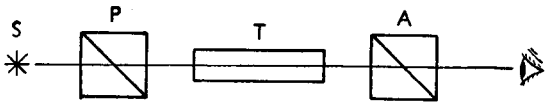


FIG. 17.1.

If the substance rotates the plane of polarisation to the right, *i.e.*, if the analyser has to be turned to the right (clockwise) to restore the original field, the substance is said to be *dextrorotatory*; if to the left (anticlockwise), *lævorotatory*.

It has been found that the amount of the rotation depends, for a given substance, on a number of factors, *e.g.*, (i) the thickness of the layer traversed, (ii) the nature of the solvent (if in solution), (iii) the temperature, and (iv) the wavelength of the light used. If $[\alpha]$ represents the *specific rotation*, l the thickness of the layer in decimetres, d the density of the liquid (if a solution is being examined, d is equal to the number of grams of substance per millilitre of solution), and the determination is carried out at temperature $t°$ using sodium light (the D line), then if α is the *observed* rotation (+ or −),

$$[\alpha]^t_D = \frac{\alpha^t_D}{l \times d}$$

Since the value of the rotation depends on the solvent, this should also be stated.

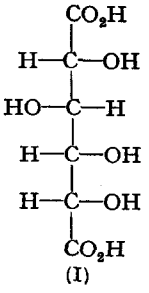
The original method of indicating optical isomers was to prefix each isomer by *d* or *l* according as it was dextrorotatory or lævorotatory. Van't Hoff (1874) introduced a + and − notation for designating the configuration of an asymmetric carbon atom. He used mechanical models (built of tetrahedra), and the + and − signs were given by observing the tetrahedra of the mechanical model from the centre of the model. Thus a molecule of the type *Cabd–Cabd* may be designated ++, −−, and +− (see also p. 409). E. Fischer (1891) pointed out that this + and − notation can lead to wrong interpretations when applied to molecules containing more than two asymmetric carbon atoms (the signs given depend on the point of observation in the molecule). Fischer therefore proposed the use of plane projection diagrams of the mechanical models instead of the + and − system.

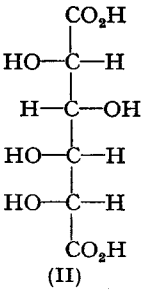
Fischer, working on the configurations of the sugars, obtained the plane formulæ (I) and (II) for the enantiomorphs of saccharic acid, and *arbitrarily* chose (I) for dextrorotatory saccharic acid, and called it *d*-saccharic acid. He then, *from this*, deduced formula (III) for *d*-glucose. Furthermore, Fischer thought it was more important to indicate stereochemical relationships than merely to indicate the actual direction of rotation. He therefore proposed that **the prefixes *d* and *l* should refer to stereochemical relationships and not to the direction of rotation of the compound.** The question now is: Is it possible to choose a standard to which all sugars may be referred? Fischer apparently intended to use the scheme whereby the

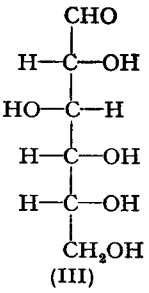
* All standard text-books of Practical Physical Chemistry describe the construction and operation of polarimeters.

compounds derived from a *given aldehyde sugar* should be designated according to the *direction of rotation of the parent aldose.*

Natural mannose is dextrorotatory. Hence natural mannose will be *d*-mannose, and all derivatives of *d*-mannose, *e.g.*, mannonic acid, mannose phenylhydrazone, etc., will thus belong to the *d*-series. Natural glucose is dextrorotary. Hence natural glucose will be *d*-glucose, and all its derivatives


(I)


(II)


(III)

will belong to the *d*-series. Furthermore, Fischer (1890) was able to convert natural mannose into natural glucose, and since the latter is *d*-glucose (according to Fischer's scheme), the prefix *d* for natural glucose *happens* to agree with its dextrorotation (with *d*-mannose as standard). Now natural fructose can also be prepared from natural mannose (or natural glucose), and so will be *d*-fructose. Natural fructose, however, is lævorotatory, and so is written as *d*(—)-fructose, the symbol *d* indicating its *stereochemical* relationship to the parent aldose glucose, and the symbol — placed in parentheses before the name indicating the *actual direction of rotation.*

More recently, the symbols *d* and *l* have been replaced by D and L for configurational relationships, *e.g.*, L(+)-lactic acid. Also, when dealing with compounds that cannot be referred to sugars, (+)- and (—)- are used to indicate the sign of rotation. The prefixes *dextro* and *lævo* (without hyphens) are also used.

Fischer's proposal to use *each aldose* as the arbitrary standard for its derivatives leads to some difficulties, *e.g.*, natural arabinose is dextrorotatory, and so is to be designated D-arabinose. Now this D-arabinose can be converted into mannonic acid, which, if D-arabinose is the parent aldose, will therefore be D-mannonic acid. This same acid, however, can also be obtained from L-mannose, and so should be L-mannonic acid. Thus in cases such as this the use of the symbol D or L will depend on the *historical order* in which the stereochemical relationships were established!

Rosanoff (1906) showed that if the enantiomorphs of glyceraldehyde (a molecule which contains only *one* asymmetric carbon atom) are chosen as the (arbitrary) standard, then a satisfactory system for correlating stereochemical relationships can be developed. He also proposed that the formula of dextrorotatory glyceraldehyde should be written as in Fig. 2 (*c*), in order that the arrangement of its asymmetric carbon atom should agree with the arrangement of C_5 (C_1 is the carbon of the CHO group) in Fischer's projection formula for natural glucose (see formula (III) above).

It is of great interest to note in this connection that in 1906 the active forms of glyceraldehyde had not been isolated, but in 1914 Wohl and Momber separated DL-glyceraldehyde into its enantiomorphs, and in 1917 they showed that dextrorotary glyceraldehyde was stereochemically related to natural glucose (*i.e.*, with D(+)-glyceraldehyde as arbitrary standard, natural glucose is D(+)-glucose).

The accepted convention for drawing D(+)-glyceraldehyde—the agreed

(*arbitrary*) standard—is shown in Fig. 2 (*a*). The tetrahedron is drawn so that three corners are imagined to be *above* the plane of the paper, and the fourth *below* this plane. Furthermore, the spatial arrangement of the four groups joined to the central carbon atom *must be placed as shown in* (*a*), *i.e.*, the accepted convention for drawing D(+)-glyceraldehyde places the *hydrogen atom at the left and the hydroxyl group at the right, with the aldehyde group at the top corner.* Now imagine the tetrahedron to rotate about the

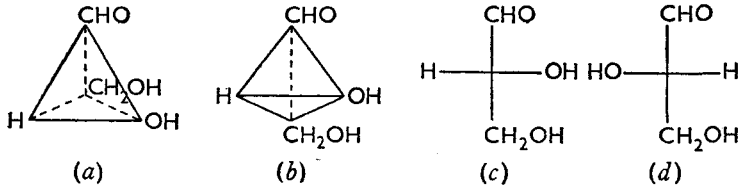
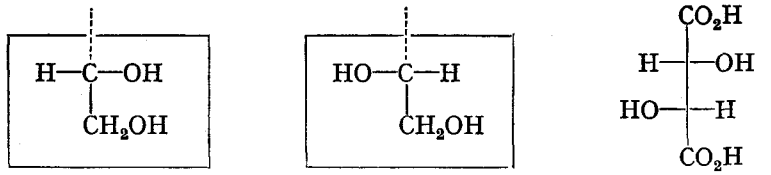


FIG. 17.2.

horizontal line joining H and OH until it takes up position (*b*). This is the conventional position for a tetrahedron, groups joined to *full horizontal* lines being *above* the plane of the paper, and those joined to *broken vertical* lines being *below* the plane of the paper. The *conventional plane-diagram* is obtained by drawing the full horizontal and broken vertical lines of (*b*) as full lines, placing the groups as they appear in (*b*), and taking the asymmetric carbon atom to be at the point where the lines cross. Although (*c*) is a plane-diagram, it is most important to remember that horizonal lines represent groups above the plane, and vertical lines groups below the plane of the paper. Fig. (*d*) represents the plane-diagram formula of L(−)-glyceraldehyde; here *the hydrogen atom is to the right and the hydroxyl group to the left.* Another way of drawing (*c*) and (*d*) is to use *broken vertical* lines (instead of the full lines shown). Thus any compound that can be prepared from, or converted into, D (+)-glyceraldehyde will belong to the D-series. Similarly, any compound that can be prepared from, or converted into, L(−)-glyceraldehyde will belong to the L-series. When representing relative configurational relationships of molecules containing more than one asymmetric carbon atom, *the asymmetric carbon atom of glyceraldehyde is always drawn at the bottom*, the rest of the molecule being built up from this unit.



Thus we have a scheme of classification of *relative* configurations based on D(+)-glyceraldehyde as *arbitrary* standard. Until recently there was no way of determining, with certainty, the *absolute* configuration of molecules. *Arbitrary choice* makes the configuration of D(+)-glyceraldehyde have the hydrogen to the left and the hydroxyl to the right. Bijvoet *et al.* (1951), however, have shown by X-ray analysis that dextrorotatory tartaric acid has the configuration assigned to it by E. Fischer. Hence tartaric acid can be used as an *absolute* standard (see p. 419).

In 1848, Pasteur separated sodium ammonium racemate (p. 421) into two kinds of crystals by hand, and found that the specific rotation of each kind of crystal was the same, but one was dextrorotatory and the other,

lævorotatory. Pasteur was able to separate the crystals by hand because he observed that they had hemihedral facets, one set of crystals being the mirror images of the other set. Such crystals, one being the mirror image of the other, are said to be *enantiomorphous*.

It has been found that only those structures, crystalline or molecular, which are *not* superimposable on their mirror images, are optically active. Such structures may be *asymmetric*, or *dissymmetric*. Asymmetric means completely devoid of the elements of symmetry. Dissymmetric means not completely devoid of symmetry, but possessing so few elements of symmetry as still to be capable of existing in two forms (one the mirror image of the other) which are not superimposable. To avoid unnecessary complications, we shall use the term asymmetric to cover both cases (of asymmetry and dissymmetry). If a compound is asymmetric, then it is to be expected that the original molecule and its mirror image might differ in some properties although their structures are identical. Experience shows that the most marked difference is their action on polarised light.

Optical activity may be due entirely to the *crystal structure being asymmetric*, *e.g.*, quartz. In such cases the substance is optically active only so long as it remains solid, the optical activity being lost when the solid is fused or dissolved in a solvent. Quartz crystals exist in hemihedral forms. Hemihedral faces are those faces not symmetrically placed with respect to other faces; they occur only in *half* the positions where they might be expected to occur, and thus give the crystal an asymmetric structure (actually dissymmetric). The (+)- and (−)-forms of quartz are mirror images; but it should be noticed that many optically active crystals do not possess hemihedral faces.

On the other hand, optical activity may be due entirely to *molecular* structure. In this case the *molecular structure is asymmetric*, *i.e.*, the compounds have molecules in which the *atoms* are arranged spatially so that the original molecule is not superimposable on its mirror image. Such compounds are optically active in the solid, fused, dissolved or gaseous state, *e.g.*, sucrose, lactic acid, limonene, etc.

A molecule and its mirror image, when they are not superimposable, are known as *enantiomorphs* (this name taken from crystallography) or *optical antipodes*. It appears that enantiomorphs are identical physically except in their manner of rotating polarised light; the rotations are equal but opposite. The crystal forms of enantiomorphs may be mirror images of each other, *i.e.*, the crystals themselves may be enantiomorphous, but this is unusual. Enantiomorphs are similar chemically, but their rates of reaction with other optically active substances are usually different. They may also be different physiologically, *e.g.*, (+)-histidine is sweet, (−)-tasteless; (−)-nicotine is more poisonous than (+)-; D(−) ascorbic acid (vitamin C) is more efficient than L(+)-.

In 1874, van't Hoff and Le Bel, independently, gave the solution to the problem of optical isomerism. Van't Hoff proposed the theory that if the four valencies of the carbon atom are arranged tetrahedrally with the carbon atom at the centre, then all the cases of isomerism known are accounted for. Le Bel's theory is substantially the same as van't Hoff's, but differs in that whereas van't Hoff believed that the valency distribution was definitely tetrahedral and fixed as such, Le Bel believed that the valency directions were not rigidly fixed, and did not specify the tetrahedral arrangement, but thought that *whatever* the spatial arrangement, the molecule C*abde* would be *asymmetric*. Van't Hoff's theory is more in keeping with later work, *e.g.*, in recent years physico-chemical evidence—X-ray and dipole moment studies—has shown that saturated carbon compounds exhibit a tetrahedral structure and that the carbon atom is situated inside

the tetrahedron at the centre. Before the tetrahedral theory was suggested, it was believed that the four valencies of carbon were planar.

Two postulates underlie the tetrahedral theory.

(i) *The principle of constancy of the valency angle.* Mathematical calculation of the angle subtended by each side of a regular tetrahedron at the central carbon atom (Fig. 3) gives a value of 109° 28′. Originally it was postulated (van't Hoff) that the valency angle was fixed at this value. It is now known, however, that the valency angle may deviate from this value, *e.g.*, in various ring structures; even so, great deviations lead to instability (see p. 487).

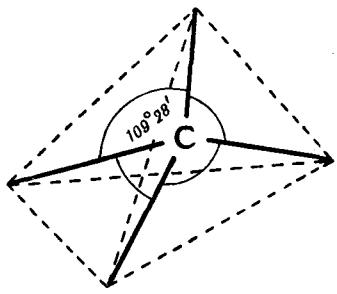


FIG. 17.3.

Quantum mechanical calculations show that the four valencies of carbon (in saturated compounds) are equivalent and directed towards the four corners of a regular tetrahedron; these four valencies are formed by the hybridisation of *2s* and $2p^3$ electrons (p. 25). Furthermore, quantum mechanical calculation require the carbon bond angles to be close to the tetrahedral value, since change from this value is associated with loss in bond strength and consequently decrease in stability (see also p. 487).

(ii) *The principle of free rotation about a single bond.* Consider the ethane molecule, CH_3—CH_3, and let us imagine that one methyl group is rotated about the C—C bond as axis with the other group at rest. The energy content, E, of the molecule will undergo the regular changes shown in Fig. 4 (*a*). Had there been complete free rotation, the graph would have been a horizontal straight line. Fig. (*b*) [the *projection formula*, obtained by viewing

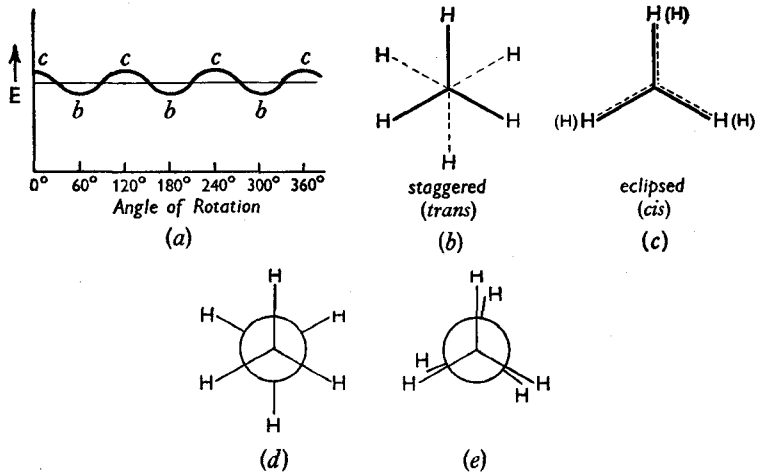


FIG. 17.4.

the molecule along the bonding line of the two carbon atoms] represents the *trans* or *staggered* form in which the hydrogen atoms (on the two carbon atoms) are as far apart as possible. To change from this form to the *cis* or *eclipsed* form in which the hydrogen atoms are as close together as possible (Fig. *c*), energy must be supplied to overcome, among other things, the repulsion between hydrogen atoms. Thus the energy content of the mole-

cule in the eclipsed conformation is greater than that in the staggered conformation. The actual energy difference is 2·75 kg. cal./mole. This is much too small for either form to remain stable, *i.e.*, the eclipsed and staggered forms are readily interconvertible, and so only one form of ethane can be isolated. Even so, the staggered conformation is the preferred form (see below). Newman (1952) has proposed projection formulæ 4(*d*) and 4(*e*) for 4(*b*) and 4(*c*) respectively. The carbon atom nearer the eye is designated by equally spaced radii, and the carbon atom further from the eye by a circle with three equally spaced radial extensions.

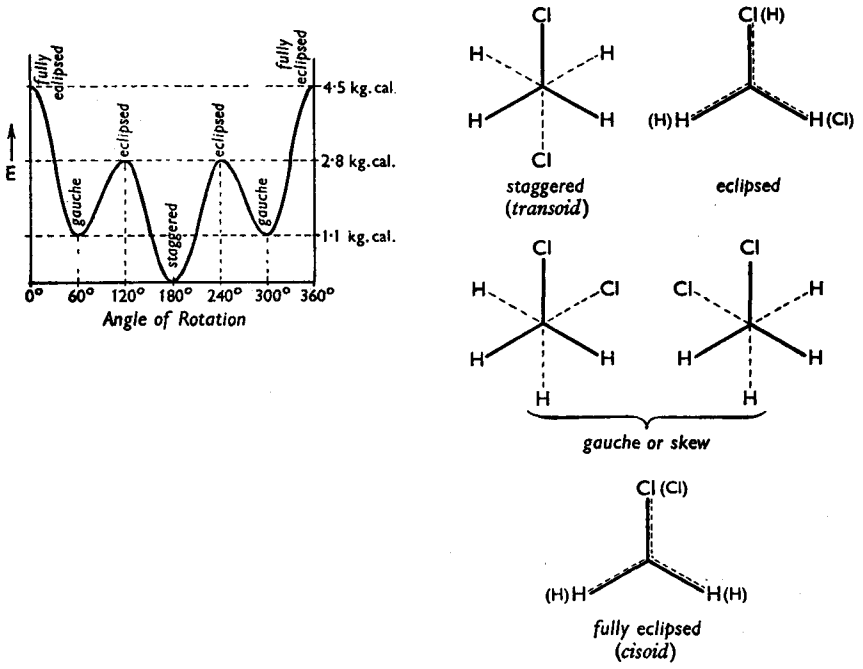


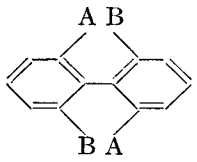
FIG. 17.5.

Now let us consider ethylene chloride. Here the energy changes are larger because (among other things) of the strong electrostatic repulsion between the chlorine atoms. According to Bernstein (1949), the potential energy of ethylene chloride undergoes the changes shown in Fig. 5. There are two positions of minimum energy, but the staggered conformation is the more preferred one, *i.e.*, the one in which the molecule largely remains. Dipole moment studies show that this is so in practice, and according to Mizushima *et al.* (1938), only the staggered form is present at low temperatures. (The student should draw the Newman projection formulæ of the above forms.)

Thus, in theory, there is no free rotation about a single bond, but in practice it may occur if the various forms do not differ very much in energy content (usually between 1 and 10 kg. cal./mole). Molecules which can form isomers by rotation about single bonds are called **flexible molecules,** and the different forms taken up are different **conformations** (see also p. 488) or **rotational isomers.** Usually, the staggered conformation is the most stable one, and the eclipsed form is always avoided where possible.

Free rotation about a single bond is generally accepted in *simple* molecules.

Restricted rotation about a single bond, however, may take place when the molecule contains groups large enough to impede free rotation, *e.g.*, in *ortho*-substituted diphenyls (p. 700), if groups A and B are sufficiently large, the two benzene rings cannot rotate through 360° about the single bond joining the two rings. In some cases, resonance may give rise to restricted rotation about a single bond (see, *e.g.*, p. 688).



It has been pointed out in the foregoing account that the basis of optical activity is that the molecule should be asymmetric. The simplest type of asymmetric structure is that which contains one carbon atom joined to four different atoms or groups, *i.e.*, a molecule of the type C*abde*, in which the groups, *a*, *b*, *d* or *e* may or may not contain carbon. The carbon atom in C*abde* is said to be asymmetric (actually, of course, it is the *group* which is asymmetric; a *carbon atom* cannot be asymmetric). Up to the present time, compounds of the type Ca_4 (*e.g.*, CCl_4), Ca_3b (*e.g.*, $CHCl_3$), Ca_2b_2 (*e.g.*, CH_2Cl_2), Ca_2bd (*e.g.*, $CH_2OH{\cdot}CO_2H$) have never been observed to exist as optical isomers. Only one form of each is known. This agrees with the tetrahedral configuration, *e.g.*, Ca_2bd (Fig. 6). (II), the mirror image of (I), is superimposable on (I); however the four groups are arranged in the tetrahedron, (II) is always superimposable on (I) (see footnote, p. 41). Thus there is only one form of Ca_2bd. Similarly, there is only one form of Ca_4, Ca_3b or Ca_2b_2. On the other hand, the tetrahedral structure of C*abde* gives two forms (no more), one related to the other as object and mirror image, which are *not* superimposable (Fig. 7). Thus a molecule of the type C*abde*

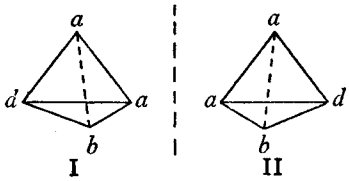


FIG. 17.6.

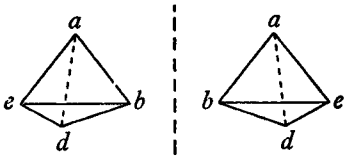


FIG. 17.7.

should exist in two forms; and these should be detectable if the difference between them (physical or chemical) is sufficiently great. This would account for the structural identity and optical activity of molecules of the type C*abde*, *e.g.*, the lactic acids, $CH_3{\cdot}CHOH{\cdot}CO_2H$ (Fig. 8). (III) and (IV)

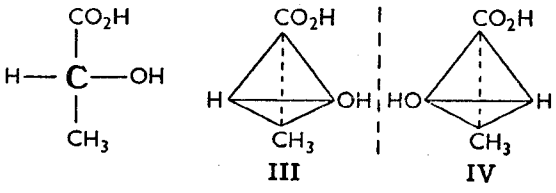


FIG. 17.8.

are mirror images and cannot be superimposed. Further evidence that optical activity is due to this arrangement is shown by the fact that if lactic acid is reduced to propionic acid, optical activity disappears; propionic acid, $CH_3{\cdot}CH_2{\cdot}CO_2H$, is a molecule of the type Ca_2bd, which is superimposable on its mirror image.

Groups *a*, *b*, *d*, *e* are all different, but two or more may be *structural* isomers, *e.g.*, propyl*iso*propylmethanol is optically active. The substitution of hydrogen by

deuterium has also been investigated in recent years to ascertain whether these two atoms are sufficiently different to give rise to optical isomerism. The earlier work gave conflicting results, but later work appears to be conclusive in favour of optical activity, *e.g.*, Eliel (1949) prepared optically active methylphenyldeuteromethane, $CH_3{\cdot}CHD{\cdot}C_6H_5$, by reducing optically active methylphenylmethyl chloride with lithium aluminium deuteride.

Lactic acid obtained from sour milk (and by any of the other methods described on p. 398) is *not* optically active. If we examine an equimolecular mixture of the dextrorotatory and lævorotatory lactic acids, we shall find that the mixture is optically inactive. This is to be expected, since optical isomers have equal but opposite rotatory power. Such a mixture (of equimolecular amounts) is said to be **optically inactive by external compensation,** and is known as a **racemic modification.** A racemic modification may be a purely mechanical mixture, a compound, or a solid solution; for this reason it is better to use the term *racemic modification* than *racemic mixture.* Lactic acid, which is optically inactive by external compensation, is known as racemic (*r*-) or DL-lactic acid.

We can now therefore account for the existence of three lactic acids:

(i) L(+)-lactic acid, m.p. 26°; prepared from meat extract (sarcolactic acid).

(ii) D(−)-lactic acid, m.p. 26°; prepared by the fermentation of sucrose by *Bacillus acidi lævolactiti.*

(iii) DL-lactic acid, m.p. 18°; prepared from *e.g.*, sour milk.

Thus a compound with *one* asymmetric carbon atom exists in three forms: D, L, and DL (or *r*-).

Isomeric with lactic acid is **hydracrylic acid** or **β-hydroxypropionic acid,** $CH_2OH{\cdot}CH_2{\cdot}CO_2H$. β-Hydroxypropionic acid may be prepared in a number of ways, *e.g.*, by the hydrolysis of ethylene cyanohydrin:

$$CH_2OH{\cdot}CH_2Cl \xrightarrow{KCN} CH_2OH{\cdot}CH_2{\cdot}CN \xrightarrow{NaOH} CH_2OH{\cdot}CH_2{\cdot}CO_2H \quad (28\text{–}31\%)$$

It may also be prepared by the action of silver oxide in boiling water on β-halogeno-propionic acid:

$$CH_2Br{\cdot}CH_2{\cdot}CO_2H + \text{“ AgOH ”} \longrightarrow CH_2OH{\cdot}CH_2{\cdot}CO_2H + AgBr$$

β-Hydroxypropionic acid is a sour, syrupy liquid. It is *not* optically active (it does not contain an asymmetric carbon atom). When heated, it loses a molecule of water to form acrylic acid.

$$CH_2OH{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_2{:}CH{\cdot}CO_2H + H_2O$$

When oxidised, β-hydroxypropionic acid forms malonic acid:

$$CH_2OH{\cdot}CH_2{\cdot}CO_2H \xrightarrow{[O]} CO_2H{\cdot}CH_2{\cdot}CO_2H$$

β-Hydroxybutyric acid (3-*hydroxybutanoic acid*), $CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H$, may be prepared by oxidising aldol with ammoniacal silver nitrate:

$$CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CHO + Ag_2O \longrightarrow CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H + 2Ag$$

It may also be prepared by reducing acetoacetic ester, and hydrolysing the product:

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5 \xrightarrow{[H]} CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2C_2H_5 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H$$

β-Hydroxybutyric acid can exist in D- and L-forms (it contains one asymmetric carbon atom). It occurs, together with acetoacetic acid, in diabetic urine; the acid found in urine is lævorotatory. When heated with sodium hydroxide solution, β-hydroxybutyric acid forms crotonic acid:

$$CH_3{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_3{\cdot}CH{:}CH{\cdot}CO_2H + H_2O$$

HYDROXY-DIBASIC AND POLYBASIC ACIDS

Before describing the individual acids, let us consider the stereochemistry of a molecule containing two asymmetric carbon atoms. First let us consider the case of a compound containing two structurally dissimilar carbon atoms, *i.e.*, compounds of the type *Cabd·Cabe, e.g.*, $CH_3{\cdot}CHBr{\cdot}CHBr{\cdot}CO_2H$. Investigation shows that there are four possible spatial arrangements for this type of structure (Fig. 9). (I) and (II) are enantiomorphs, and an equimolecular mixture of them forms a racemic modification; similarly for (III) and (IV). Thus there are four optically active forms. In general, a compound containing n different asymmetric carbon atoms exists in 2^n-optically active forms.

(I) and (III) are not identical in configuration and are not mirror images;

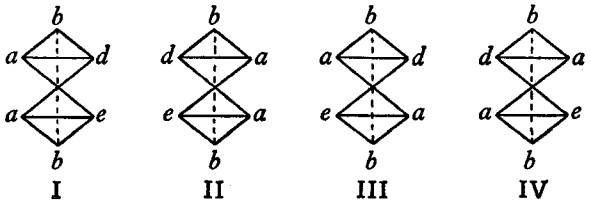
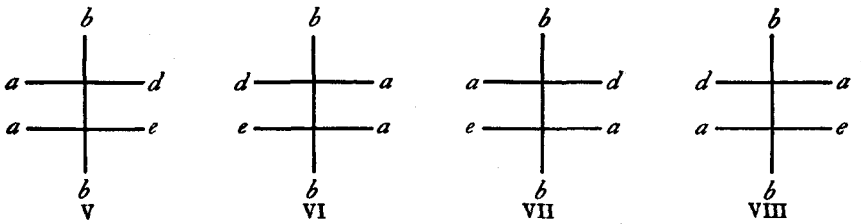


FIG. 17.9.

they are known as **diastereoisomers**, *i.e.*, they are optical isomers but not mirror images (not enantiomorphs). Thus a compound of the type *Cabd·Cabe* exists in six forms: two pairs of enantiomorphs, and two racemic modifications. Diastereoisomers differ in physical properties, such as melting point, solubility, specific rotation, etc. Chemically they are similar, but their rates of reaction with other optically active compounds are different.

The plane-diagrams of the molecules (I–IV) in Fig. 9 will be (V–VIII), respectively, as shown below:



When the formulæ are written as plane-diagrams, it is not always easy to see whether the mirror image in superimposable on the original molecule. A test for non-superimposability of plane-diagrams is to rotate the formula of the mirror image through 180° in the plane of the paper; if the result is the *same* formula as the original molecule, then the two molecules (orginal and image) are superimposable, and consequently not optically active (see also plane of symmetry, below).

Instead of writing down all the possible configurations, the number of optical isomers for a compound of the type *Cabd·Cabe* may be obtained by

indicating the *configuration* of each asymmetric carbon atom by the symbol + or —, or by D or L; thus:

Cabd	+ —	+ —	D_1 L_1	D_1 L_1
Cabe	+ —	— +	D_2 L_2	L_2 D_2
	(±)	(±)	DL	DL

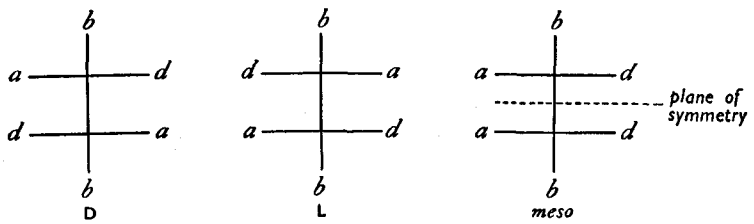
Now let us consider the case of a compound containing two asymmetric carbon atoms which are structurally the same, *i.e.*, compounds of the type *Cabd·Cabd*, *e.g.*, tartaric acid, $CO_2H{\cdot}CHOH{\cdot}CHOH{\cdot}CO_2H$. In compounds of this type, it is obvious that $D_1 = D_2$.

Cabd	D	L	D	L
Cabd	D	L	L	D
	(IX)	(X)	(XI)	(XII)

In molecules (IX) and (X), the upper and lower halves reinforce each other; hence (IX), as a whole, has the dextro-, and (X), the lævo-configuration, *i.e.*, (IX) and (X) are optically active, and enantiomorphous. On the other hand, in (XI) the two equal halves are in opposition, and hence the molecule, ***as a whole***, will not show optical activity. It is also obvious that (XI) and (XII) are identical, *i.e.*, there is only *one* optically inactive form of *Cabd·Cabd*. Molecule (XI) is said to be **optically inactive by internal compensation**; it is known as the ***meso*-form,** and is a diastereoisomer of (IX) and (X). Thus there are four possible forms: D-, L-, DL- and *meso*-. The *meso*-form is also known as the *inactive* form and is represented as the *i*-form. **The *meso*-form cannot be resolved.**

Molecule (XI) is an example of a *compound having two asymmetric carbon atoms, but is optically inactive* (by internal compensation). It is therefore obvious that inspection of the usual structural formula, which contains two (or more) asymmetric carbon atoms, is not sufficient to decide whether the molecule is optically active or not. *The molecule as a whole must be asymmetric.* The test of superimposing the original formula (tetrahedral) on its mirror image definitely indicates whether the molecule is symmetrical or not. The only satisfactory way in which superimposability may be ascertained is to build up models of the molecule and its mirror image. Usually, this is not convenient. Alternatively, superimposability may be determined by rotation of the plane-formula in the plane of the paper (see above). A much simpler device to decide whether a molecule is symmetrical or not is to ascertain whether it contains a *plane of symmetry*, a *centre of symmetry*, or an *alternating axis of symmetry*. If any one of these is present the molecule is symmetrical, *i.e.*, superimposable on its mirror image.

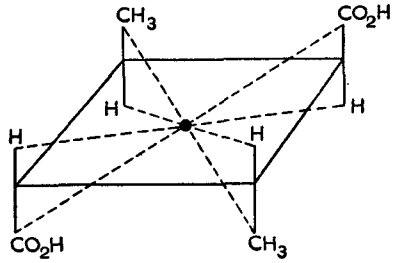
A **plane of symmetry** divides a molecule in such a way that points (atoms or groups of atoms) on the one side of the plane form mirror images of those on the other side. This test may be applied to both solid and plane-formulæ, *e.g.*, the plane-formula of the *meso* form of *Cabd·Cabd* possesses a plane of symmetry; the other two, D- and L-, do not:



It should also be observed that rotation of the formula of the mirror image of the *meso* form through 180° in the plane of the paper produces the formula of the original molecule. Similar treatment of the L-formula does not produce the D-formula.

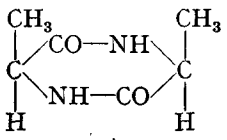
A **centre of symmetry** is a point from which lines, when drawn on one side and produced an equal distance on the other side, will meet exactly similar points in the molecule. This test can be satisfactorily applied only to three-dimensional formulæ, particularly those of ring systems, *e.g.*,

(i)

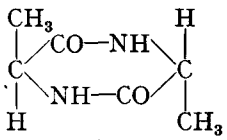


2 : 4-dimethyl*cyclo*butane-1 : 3-dicarboxylic acid. The form shown possesses a centre of symmetry which is the centre of the ring. This form is therefore optically inactive.

(ii) Dimethyldiketopiperazine exists in two geometrical isomeric forms, *cis* and *trans*:



cis

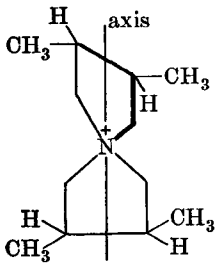


trans

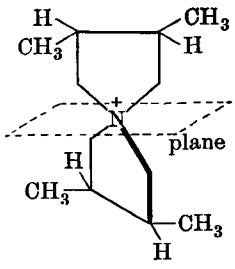
The *cis* isomer has neither a plane nor a centre of symmetry. It can therefore exist in two enantiomorphous forms; both are known. The *trans* isomer has a centre of symmetry and is therefore optically inactive.

It is important to note that only *even-numbered* rings can possibly possess a centre of symmetry.

Up to the present, all optically active *natural* compounds have been found to consist of molecules which owe their asymmetry to the absence of both a plane and centre of symmetry. It is possible, however, for these elements of symmetry to be *absent* and the molecule to be superimposable on its mirror image and hence not be optically active. Such a molecule will possess an **alternating axis of symmetry.** This may be defined as follows: a molecule possesses an *n*-fold alternating axis of symmetry if, when rotated



(XIII)



(XIV)

through an angle of $360°/n$ about this axis and then followed by reflection in a plane perpendicular to the axis, the molecule is the same as it was in the starting position.

McCasland and Proskow (1956) have now synthesised, for the first time, a compound which owes its symmetry to the presence of an alternating axis of symmetry only (this compound possesses neither a plane nor a centre of symmetry). It is the *N*-spiro-compound (XIII) (as the *p*-toluenesulphonate). If (XIII) is rotated through 90° about the co-axis of the two rings, (XIV) is obtained. Reflection of (XIV) through a central plane perpendicular to this axis gives a molecule identical and coincident with (XIII).

Resolution of Racemic Modifications

When optically active compounds are prepared by synthetic methods, the usual result is a racemic modification; *e.g.*, bromination of propionic acid results in the formation of DL-α-bromopropionic acid:

$$CH_3{\cdot}CH_2{\cdot}CO_2H \xrightarrow{Br_2/P} CH_3{\cdot}CHBr{\cdot}CO_2H$$

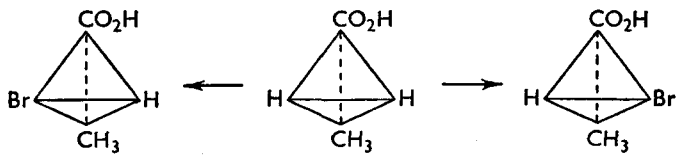


FIG. 17.10.

(II) and (III) (Fig. 10) are enantiomorphs, and since molecule (I) is symmetrical about its vertical axis, it can be anticipated from the theory of probability that either hydrogen atom should be replaced equally well to give DL-α-bromopropionic acid. This actually does occur in practice.

The process of separating a racemic modification into its enantiomorphs is known as *resolution*. Various methods have been introduced.

1. **Mechanical separation** (Pasteur, 1848). In this method the crystals are, if sufficiently well defined, actually separated by hand; the crystals must be enantiomorphous. This method is applicable only to racemic *mixtures*, and is mainly of historical interest. This method of resolution is also known as **spontaneous resolution.**

2. **Biochemical separation** (Pasteur, 1858). Certain bacteria and moulds, when they grow in a dilute solution of a racemic modification, destroy one optical isomer more rapidly than the other; *e.g.*, *Penicillium glaucum* (a mould), when grown in a solution of ammonium racemate, attacks the D-form leaving the L-.

3. **By means of salt-formation** (Pasteur, 1858). This method, which is the best of all the methods of resolution, consists in converting the optical isomers in a racemic modification into *diastereoisomers*; *e.g.*, if an optically active base is combined with a racemic acid, two diastereoisomers are obtained:

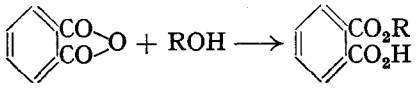
$$(D_{acid} + L_{acid}) + 2D_{base} \longrightarrow (D_{acid}D_{base}) + (L_{acid}D_{base})$$

Because of their different solubilities, these diastereoisomers may be separated by fractional crystallisation. After separation, the acids may be regenerated by hydrolysis with inorganic acids or with alkalis.

Bases which are used for the resolution of racemic acids are mainly alkaloids, *e.g.*, quinine, strychnine, brucine, cinchonine, morphine, etc.

Acids which are used for the resolution of racemic bases are, *e.g.*, tartaric acid, camphorsulphonic acid, bromocamphorsulphonic acid.

The method of salt-formation has been extended to compounds other than acids and bases, *e.g.*, (i) Racemic alcohols are converted into the acid ester derivative with phthalic anhydride:



The acid ester, consisting of equimolecular amounts of the D- and L-forms, may now be resolved by the method used for acids.

(ii) Racemic aldehydes and racemic ketones may be resolved by means of optically active derivatives of hydrazine, *e.g.*, (−)-menthylhydrazine.

Resolution of racemic modifications by means of salt formation may be complicated by the phenomenon of *asymmetric transformation*. This phenomenon is exhibited by compounds that are optically unstable, *i.e.*, the enantiomorphs are readily interconvertible:

$$(+)\text{-C} \rightleftharpoons (-)\text{-C}$$

It is possible to get *complete* conversion of C into the form (as salt) that crystallises from solution. The form may be (+) or (−), depending on the nature of the base (used for resolving acids) and the solvent.

4. **Selective adsorption.** Optically active substances may be selectively adsorbed by some optically active adsorbent, *e.g.*, Henderson and Rule (1939) resolved a racemic modification of a camphor derivative on D-lactose as adsorbent; Prelog and Wieland (1944) resolved Tröger's base on D-lactose (p. 433).

5. **Channel complex formation.** This method is possible because the complexes of each enantiomorph have different solubilities; *e.g.*, Schlenk (1952) has resolved (±)-2-chloro-octane by means of channel complex formation with urea (see p. 387).

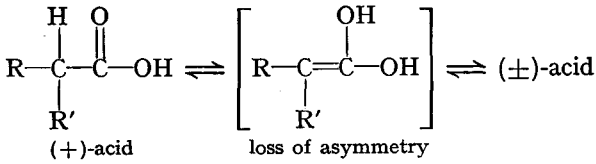
Racemisation

By using suitable conditions, it is possible to cause most optically active compounds to lose their optical activity without changing their structure. This means that the (+)- and (−)-forms of most optically active compounds are convertible one into the other, the final result being a racemic modification. Such a transformation is known as *racemisation*. The method of effecting racemisation depends on the nature of the compound in question; generally, heat, light or chemical reagents may be used. Thus, if the starting material is the (+)-form, then after treatment half will have been converted into the (−)-form; similarly, when starting with the (−)-form, half will be converted into the (+)-form, *e.g.*, when (+)- or (−)-lactic acid is warmed with sodium hydroxide solution, the result is (+)-lactic acid.

In some cases racemisation occurs spontaneously at room temperature; it is then known as *autoracemisation*, *e.g.*, dimethyl bromosuccinate autoracemises.

Many different types of compounds can racemise, and a number of mechanisms have been developed, each mechanism applying to a particular type of compound. One important type of compound that readily racemises is that in which the asymmetric carbon atom is joined to a hydrogen atom and a negative group. Since this type of compound can undergo tautomeric

change, the mechanism proposed for this racemisation is one via enolisation, *e.g.*,



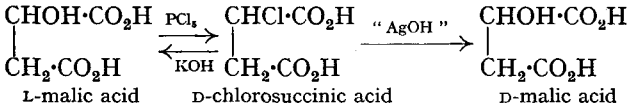
Clearly, when the intermediate enol form, which is no longer asymmetrical, reverts to the stable form, it can do so equally well to produce the (+)- or (−)-forms, *i.e.*, it will racemise.

Some compounds which cannot undergo tautomeric change can, nevertheless, be racemised, *e.g.*, (−)-limonene, some diphenyl compounds. The mechanism of these racemisations is uncertain.

The Walden Inversion (Optical Inversion)

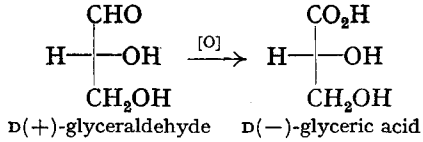
By a series of reactions, Walden (1893) was able to transform an optically active compound into its optical isomer. In some cases the product is 100 per cent. pure, *i.e.*, the *inversion* is quantitative; in other cases the product is a mixture of the (+)- and (−)-forms, but in unequal quantities, *i.e.*, a partial inversion has taken place.

The phenomenon was first discovered by Walden with the following reactions:



The change: L-malic acid to D-chlorosuccinic acid to D-malic acid, constitutes a Walden inversion. The Walden inversion may be defined as the conversion of the L-form into the D-, or vice versa, *without recourse to resolution.* In one of the two reactions there must be an interchange of position between two groups; *e.g.*, if the configuration of (I) corresponds with that of (II), the inversion must have taken place between (II) and (III). This "definition" of the Walden inversion was used by Fischer (1906). However, now that the mechanism of substitution at a saturated carbon atom has been well worked out, the term Walden inversion is now applied to *any single reaction in which inversion of configuration occurs.*

As the above experiment stands, there is no way of telling at which stage inversion has occurred. Change in the sign of rotation does not necessarily indicate an inversion of configuration; *e.g.*, when D(+)-glyceraldehyde is oxidised to glyceric acid, the acid obtained is D(−)-glyceric acid.



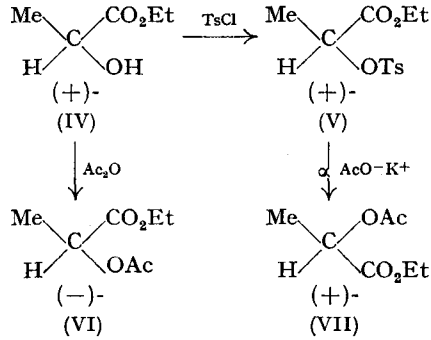
Both compounds are *stereochemically* related, but the signs of rotation are opposite. Thus it is necessary to have methods to determine relative configurations. The above example with glyceraldehyde is easy to solve; both have the same relative configurations, since the asymmetric carbon atom

is not affected in the reaction, and so inversion is not possible. When, however, the asymmetric carbon atom is involved in various reactions, the problem is far more difficult.

Kenyon *et al.* (1925) established a basis for the determination of relative configurations as follows. These authors carried out a series of reactions on optically active hydroxy compounds. Now it has been established that in the esterification of a monocarboxylic acid by an alcohol under ordinary conditions, acyl–oxygen fission occurs (see p. 187); *i.e.*,

$$R{\cdot}CO{-}\overset{\curvearrowright}{O}H + R'\overset{\curvearrowleft}{O}{-}H \longrightarrow R{\cdot}COOR' + H_2O$$

Kenyon *et al.* assumed that in all reactions of this type the R′—O bond remained intact, and consequently no inversion of the alcohol is possible. The following chart shows a series of reactions carried out on ethyl (+)-lactate; Ts = *p*-tosyl group, *i.e.*, *p*-toluenesulphonyl group, $CH_3{\cdot}C_6H_4{\cdot}SO_2$—, Ac = $CH_3{\cdot}CO$, and the symbol $\xrightarrow{\delta\rightarrow}$ is used to represent inversion in that step.



(IV) and (VI) have the same relative configurations although the sign of rotation has changed. Similarly, (IV) and (V) have the same relative configurations. Reaction of (V) with AcO^-K^+, however, produces (VII), the enantiomorph of (VI). It should be noted that if inversion is going to occur, the *complete group* attached to the asymmetric carbon atom must be removed. The converse, however, is not necessarily true, *i.e.*, removal of a complete group does not invariably result in inversion (see below).

In this way, Kenyon has been able to relate configurations of various compounds (see also p. 417).

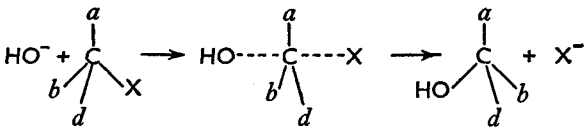
The outcome of much investigation has shown that many factors play a part in the Walden inversion, *e.g.*, the nature of the reagent, solvent and compound. According to the theory of Hughes and Ingold, nucleophilic substitution reactions may take place by either the S_N2 or S_N1 mechanism (p. 106).

(i) *The* S_N2 *mechanism.*

$$HO^{-}\overset{\curvearrowright}{}R{-}X \longrightarrow \overset{\delta-}{HO}\cdots R\cdots\overset{\delta-}{X} \longrightarrow HO{-}R + X^-$$

In the transition state, the groups OH and X are collinear and on opposite sides of the attacked carbon atom. Furthermore, the line joining OH and X is perpendicular to the plane containing the other three groups *a*, *b* and *d*. In the original molecule *Cabd*X, the four groups are arranged tetrahedrally. Hence to achieve a planar configuration of *Cabd* in the transition state, the carbon atom changes from tetrahedral to trigonal hybridisation, the remaining p_z orbital being used (by means of its two lobes) to hold the groups OH and X by " half-bonds ". When X is ejected, the carbon atom returns to its state of tetrahedral hybridisation (see diagram below).

The above reaction is a three-centre reaction, proceeding by an end-on approach.



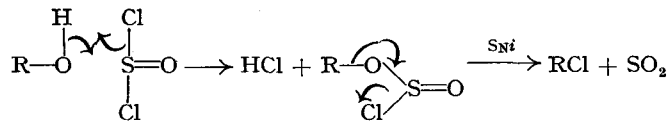
Hughes *et al.* (1935) studied: (*a*) the interchange reaction of (+)-2-iodo-octane with radioactive iodine (as NaI*) in acetone solution, and (*b*) the racemisation of (+)-2-iodo-octane by ordinary NaI under the same conditions. These reactions were shown to occur by the S_N2 mechanism, and the results showed that every halide–halide* displacement was always accompanied by inversion. Thus, this experiment leads to the *assumption that an* S_N2 *reaction always gives inversion*; this is fully supported by other experimental work.

(ii) *The* S_N1 *mechanism.*

$$R{-}X \overset{\text{slow}}{\rightleftharpoons} X^- + R^+ \xrightarrow[\text{fast}]{OH^-} ROH$$

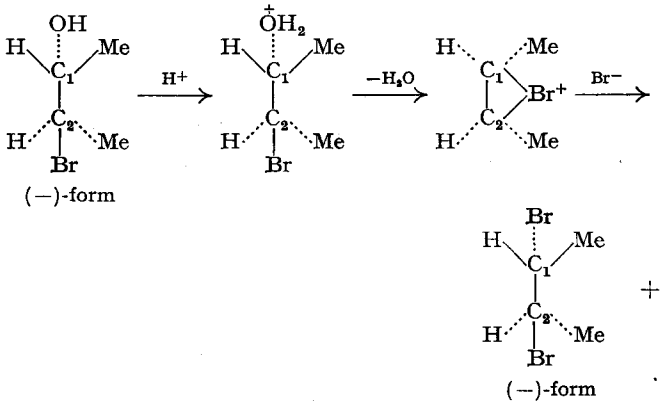
When the reaction proceeds by this mechanism, then inversion and retention (racemisation) will occur, the amount of each depending on various factors. The carbonium ion is flat (trigonal hybridisation), and hence attack by nucleophilic reagents can take place equally well on either side, *i.e.*, equal amounts of (+)- and (−)-forms are produced; this is racemisation. Complete racemisation, however, can be expected only if the carbonium ion is sufficiently long-lived; this is favoured by low reactivity of the carbonium ion and low concentration of the nucleophilic reagent. On the other hand, during the actual ionisation, the retiring negative group will shield attack on that side; this encourages end-on attack *on the other side*, thereby leading to inversion. In general, the S_N1 mechanism is accompanied by inversion and racemisation, but in some cases there may be complete inversion.

Arylmethanols react with thionyl chloride by the S_Ni mechanism (substitution, nucleophilic, internal), *e.g.*, Hughes, Ingold *et al.* (1937) have shown that optically active α-phenylethanol ($C_6H_5{\cdot}CHMe{-}$ = R) reacts with thionyl chloride to give a chloride with complete retention. The mechanism proposed is S_Ni via a chlorosulphinate.



Participation of neighbouring groups in nucleophilic substitution. So far, we have discussed polar and steric effects on rates and mechanisms of reactions (for solvent effects, see p. 109). We have already seen that the phenomenon of *neighbouring group participation* may operate in various rearrangements (p. 101). In the same way, this effect may also operate in nucleophilic substitution reactions. Here we have a group attached to the carbon atom *adjacent* to the carbon atom where nucleophilic substitution occurs and, during the course of the reaction, becomes bonded or partially bonded to the reaction centre. When the reaction is accelerated by neighbouring group participation, that reaction is said to be *anchimerically assisted*. As we have seen, various atoms exhibit this phenomenon of neighbouring group participation, *e.g.*, halogen. Brominium (bromonium) ions were first proposed by Roberts *et al.* (1937) as intermediates in the addition of bromine to olefins

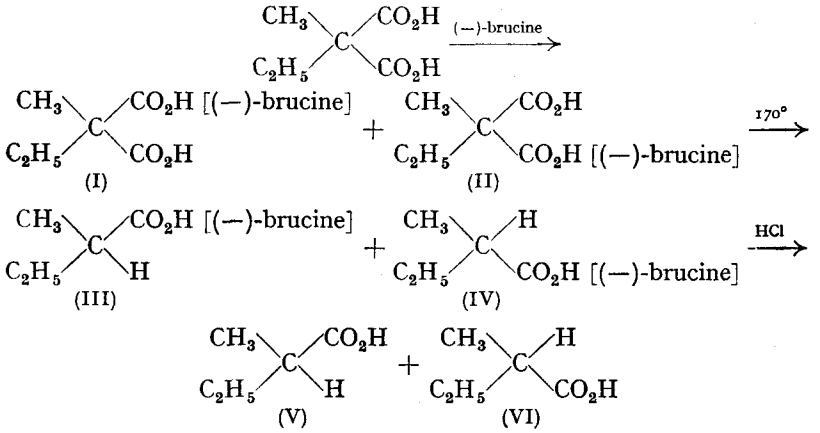
(see p. 429). The existence of this cyclic brominium ion (bridged ion) has been demonstrated by Winstein *et al.* (1939), who found that the action of fuming hydrobromic acid on (−)-*threo*-3-bromobutan-2-ol gave (±)-2 : 3-dibromobutane.



Had no neighbouring group participation occurred, then if the reaction were S_N2, complete inversion would have occurred only at C_1. If the reaction were S_N1, C_1 would have formed a classical carbonium ion, and so racemisation would have occurred at C_1 only. Since retention or inversion of *both* C_1 and C_2 occurs, the results are explained as shown above. If the Br^- ion attacks C_1 from the back, the (−)-form is produced; if it attacks C_2 from the back, the (+)-form is produced.

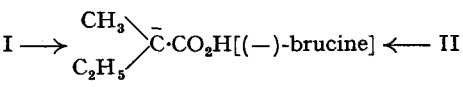
Asymmetric Synthesis

In ordinary laboratory preparations of optically active compounds, the racemic modification is always obtained. By special means, however, it is possible to prepare optically active compounds from symmetrical compounds (*i.e.*, not optically active) without the necessity of resolution. The method involves the use of optically active compounds, and is known as *asymmetric synthesis*. The first asymmetric synthesis was carried out by Marckwald (1904), who prepared an active (−)-valeric acid (lævorotatory to the extent of about 10 per cent. of the pure compound) by heating the half brucine salt of ethylmethylmalonic acid at 170°:



(I) and (II) are diastereoisomers; so are (III) and (IV). (V) and (VI) are enantiomorphs, and since the mixture is optically active, they must be present in unequal amounts. This was believed to be due to the different rates of decomposition of diastereoisomers (I) and (II).

This reaction was reinvestigated by Eisenlohr and Meier (1938), and they believed that the half-brucine salts were not present in *equal* amounts in the solid form (as thought by Marckwald). These authors suggested that as the *less* soluble salt crystallised out (during evaporation of the solution), some of the *more* soluble salt spontaneously changed into the *less* soluble salt to restore the equilibrium between the two; thus the final result was a mixture of the half-brucine salt containing a larger proportion of the *less soluble* diastereoisomer. If this be the case, then we are dealing with an example of asymmetric transformation (p. 412). Kenyon and Ross (1952) have also reinvestigated this reaction, and their work appears to show that the above reaction is a true asymmetric synthesis. According to these authors, when the half-brucine salt is heated, decarboxylation occurs with the intermediate formation of a *carbanion*. (I) and (II) both produce the *same* carbanion:



Combination of this carbanion with a proton would produce diastereoisomers (III) and (IV) in different amounts, since, in general, diastereoisomers are formed at different rates.

McKenzie (1905) reduced with aluminium amalgam pyruvic esters in which the alcohol was optically active, *e.g.*, (—)-amyl alcohol, (—)-menthol, etc. When the product, lactic acid ester, was hydrolysed, the resulting lactic acid was found to be slightly lævorotatory:

$$CH_3{\cdot}CO{\cdot}CO_2R + 2[H] \xrightarrow{Al/Hg} CH_3{\cdot}CHOH{\cdot}CO_2R \xrightarrow{H_2O} CH_3{\cdot}CHOH{\cdot}CO_2H$$

Prelog *et al.* (1953) have studied, by conformational analysis, the steric course of the addition of Grignard reagents to benzoylformic esters of asymmetric alcohols, and have found that the configuration of the

$$C_6H_5{\cdot}CO{\cdot}CO_2R \xrightarrow[\text{(ii) hydrolysis}]{\text{(i) } R'MgX} C_6H_5{\cdot}CHOH{\cdot}CO_2H$$

asymmetric carbon atom in the stereoisomer that predominated in this reaction could be correlated with the asymmetric carbon atom in R, *e.g.*, (—)-menthol and (—)-borneol are both configurationally related to (—)-glyceraldehyde, and both lead to a predominance of the (—)-hydroxyacid.

A special case of asymmetric synthesis is *absolute asymmetric synthesis*. This is the preparation of an optically active compound *without* the intermediate use of optically active reagents. The first conclusive evidence for an absolute asymmetric synthesis was obtained by Kuhn and Knopf (1930), who irradiated (±)-α-azidopropionic dimethylamide, $CH_3{\cdot}CH(N_3){\cdot}CO{\cdot}N(CH_3)_2$, with *dextro* circularly polarised light and obtained a product that was slightly dextrorotatory. When the amide was irradiated with *lævo* circularly polarised light, the product was slightly lævorotatory.

Tartronic acid (hydroxymalonic acid), $CO_2H{\cdot}CHOH{\cdot}CO_2H$, may be prepared by heating bromomalonic acid with silver oxide suspended in water:

$$CHBr(CO_2H)_2 + \text{“ AgOH ”} \longrightarrow CHOH(CO_2H)_2 + AgBr$$

It is a crystalline solid which, heated to 160°, melts with the evolution of carbon dioxide and the formation of polyglycollide, $(C_2H_2O_2)_n$.

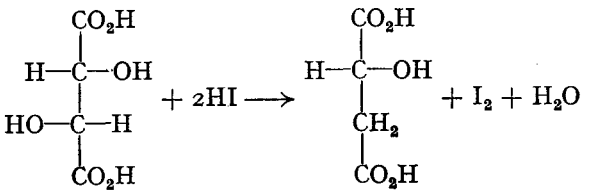
Malic acid (*hydroxysuccinic acid, hydroxybutanedioic acid*), $CO_2H{\cdot}CHOH{\cdot}CH_2{\cdot}CO_2H$, occurs in sour apples (Latin: *malum*, apple), fruits, berries, etc. It may be obtained from mountain-ash berries; the juice is expressed and boiled with calcium hydroxide solution. The precipitated calcium malate is collected by filtration and decomposed with the calculated quantity of dilute sulphuric acid. Malic acid is now being made synthetically by heating maleic acid with dilute sulphuric acid under pressure:

$$\begin{matrix} CH{\cdot}CO_2H \\ \| \\ CH{\cdot}CO_2H \end{matrix} + H_2O \xrightarrow{H_2SO_4} \begin{matrix} CHOH{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix} \qquad (100\%)$$

Malic acid may be conveniently prepared in the laboratory by heating bromosuccinic acid with silver oxide suspended in water:

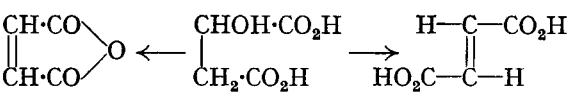
$$\begin{matrix} CHBr{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix} + \text{“ AgOH ”} \longrightarrow \begin{matrix} CHOH{\cdot}CO_2H \\ | \\ CH_2{\cdot}CO_2H \end{matrix} + AgBr$$

Malic acid contains one asymmetric carbon atom, and can therefore exist in the D-, L- and DL-forms. Malic acid from natural sources is L(−); synthetic malic acid is DL; D(+)-malic acid may be obtained by the careful reduction of D(+)-tartaric acid with concentrated hydriodic acid:



D(+)-Malic acid may also be obtained from the L(−)-isomer by means of the Walden inversion.

L(−)-Malic acid is a crystalline deliquescent solid, m.p. 100°, readily soluble in water and ethanol. It behaves both as an alcohol and acid. Inspection of the formula of malic acid shows it to be an α-hydroxyacid with respect to one carboxyl group, and a β-hydroxyacid with respect to the other. Such acids, when heated, undergo the reaction characteristic of the β-acid, *i.e.*, they eliminate a molecule of water to form an unsaturated acid (not the lactide). Thus, on heating, malic acid forms maleic anhydride and fumaric acid (*q.v.*):



Malic acid may be reduced to succinic acid by heating with hydriodic acid.

Malic acid is gradually replacing citric and tartaric acids in beverages, jellies, etc.

Tartaric acid (α : α′*dihydroxysuccinic acid*, 2 : 3-*dihydroxybutanedioic acid*), $CO_2H{\cdot}CHOH{\cdot}CHOH{\cdot}CO_2H$, contains two structurally identical carbon atoms, and can therefore exist in the D-, L-, DL- and *meso*-forms; all of these are known (Fig. 11).

The configurations of the tartaric acids are a troublesome problem.

Fischer wrote the configuration of the natural dextrorotatory acid (*i.e.*, the (+)-acid) as shown above. It is possible to synthesise (−)-tartaric acid from D(+)-glyceraldehyde, and on this basis the (+)-acid would be L(+)-tartaric acid. This is in agreement with Rosanoff's scheme of building *up* from D(+)-glyceraldehyde. It is also possible, however, to degrade (+)-tartaric acid into D(−)-glyceric acid, and hence (+)-tartaric acid will be D(+)-tartaric acid. Freudenberg assigned the D-configuration to the

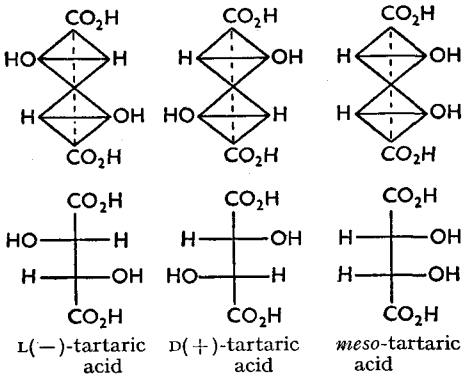


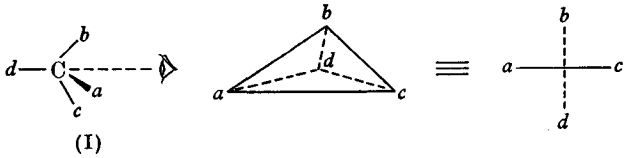
FIG. 17.11.

(+)-acid since this is the acid that is obtained by the direct oxidation of D-glucose. Since the relative configurations of (+)-tartaric acid and (+)-glyceraldehyde have been established, it is now possible to assign absolute configurations to many compounds whose relative configurations to (+)-glyceraldehyde are known (see p. 402). A notation for specifying *absolute* configurations has been suggested by Cahn *et al.* (1956).

The following account gives some idea for the procedure for a molecule containing one asymmetric carbon atom.

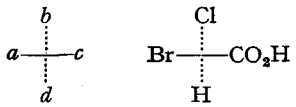
(1) The four groups are first ordered according to the *sequence rule*. According to this rule, the groups are arranged in *decreasing atomic number* of the atoms by which they are bound to the asymmetric carbon atom. If two or more of these atoms have the same atomic number, then the relative priority of the groups is determined by a similar comparison of the atomic numbers of the *next* atoms in the groups. If this fails, then the next atoms in the groups are considered. Thus one works *outwards* from the asymmetric carbon atom until a selection can be made for the sequence of the groups.

(2) It is next determined whether the sequence describes a right- or left-handed pattern on the molecular model as viewed according to the *conversion rule*. When the four groups in the molecule C*abcd* have been ordered in the priority *a*, *b*, *c*, *d*, the conversion rule states that their spatial pattern shall be described as right- or left-handed according as the sequence $a \rightarrow b \rightarrow c$ is clockwise or anticlockwise when viewed from an external point on the side *remote* from *d* (the atom with the lowest priority), *e.g.*, (I) shows a right-handed (*i.e.*, clockwise) arrangement.



(I)

(3) Absolute-configuration labels are then assigned. The asymmetry leading under the sequence and conversion rules to a right- and left-handed pattern, is indicated by *R* and *S* respectively (*R*; *rectus*, right; *S*, *sinister*, left).



(II)

Consider bromochloroacetic acid (II). Priority of the groups according to the sequence rule is Br (*a*), Cl (*b*), C [of CO_2H] (*c*), and H (*d*). Hence by the conversion rule, (II) is the *R*-form.

When fumaric acid is treated with dilute alkaline permanganate, DL-tartaric acid is formed; maleic acid, under the same conditions, forms *meso*-tartaric acid (see also p. 424):

$$CO_2H{\cdot}CH{:}CH{\cdot}CO_2H + [O] \xrightarrow{KMnO_4} CO_2H{\cdot}CHOH{\cdot}CHOH{\cdot}CO_2H$$

Both DL- and *meso*-tartaric acid are formed when α : α′-dibromosuccinic acid is boiled with silver oxide suspended in water:

$$\begin{matrix} CHBr{\cdot}CO_2H \\ | \\ CHBr{\cdot}CO_2H \end{matrix} + 2\text{ “ AgOH ” } \longrightarrow \begin{matrix} CHOH{\cdot}CO_2H \\ | \\ CHOH{\cdot}CO_2H \end{matrix} + 2AgBr$$

DL- and *meso*-Tartaric acids are also formed by the hydrolysis of glyoxal cyanohydrin:

$$\begin{matrix} CHO \\ | \\ CHO \end{matrix} + 2HCN \longrightarrow \begin{matrix} CHOH{\cdot}CN \\ | \\ CHOH{\cdot}CN \end{matrix} \xrightarrow{H_2O} \begin{matrix} CHOH{\cdot}CO_2H \\ | \\ CHOH{\cdot}CO_2H \end{matrix}$$

All the foregoing synthetic preparations clearly show the structure of tartaric acid.

***dextro* Tartaric acid, D(+)-tartaric acid,** occurs in the free state and as potassium hydrogen tartrate in the juice of grapes. During the fermentation of grapes, the acid potassium salt separates as a reddish-brown crystalline mass which is known as *argol*. When recrystallised, argol is converted into the purer substance (white), which is known as *cream of tartar*, from which D(+)-tartaric acid is obtained by dissolving it in water, and adding calcium hydroxide until the solution is nearly neutralised:

$$2KHC_4H_4O_6 + Ca(OH)_2 \longrightarrow K_2C_4H_4O_6 + CaC_4H_4O_6 + 2H_2O$$

The precipitated calcium tartrate is collected by filtration, and calcium chloride is added to the filtrate:

$$K_2C_4H_4O_6 + CaCl_2 \longrightarrow CaC_4H_4O_6 + 2KCl$$

The precipitate is collected by filtration, both lots of calcium tartrate are mixed and decomposed with the calculated quantity of dilute sulphuric acid:

$$CaC_4H_4O_6 + H_2SO_4 \longrightarrow H_2C_4H_4O_6 + CaSO_4$$

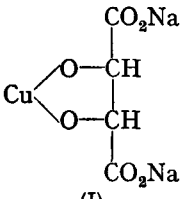
The precipitated calcium sulphate is removed by filtration and the filtrate evaporated to crystallisation; anhydrous crystals are obtained, m.p. 170°.

D(+)-Tartaric acid is soluble in water and ethanol but insoluble in ether. The calcium salt is insoluble in water but soluble in potassium hydroxide solution. When heated, tartaric acid is converted into pyruvic acid:

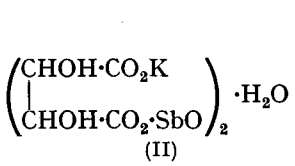
$$\begin{matrix} CHOH{\cdot}CO_2H \\ | \\ CHOH{\cdot}CO_2H \end{matrix} \longrightarrow CH_3{\cdot}CO{\cdot}CO_2H + CO_2 + H_2O$$

Tartaric acid is reduced by hydriodic acid, first to malic acid and then to succinic acid.

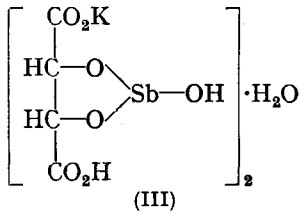
Sodium potassium D(+)-tartrate, $NaKC_4H_4O_6 \cdot 4H_2O$, is known as *Rochelle salt*, and is used in the preparation of Fehling's solution. Fehling's solution, which contains a complex copper tartrate, is prepared by adding copper sulphate solution to an aqueous solution of Rochelle salt containing sodium hydroxide. The structure of the complex is uncertain; it may be (I).



(I)



(II)



(III)

Potassium antimonyl D(+)-tartrate, known as *tartar emetic*, is usually given the formula (II). Its structure is uncertain; it may be (III).

Tartar emetic may be prepared by boiling antimonous oxide with an aqueous solution of potassium hydrogen tartrate.

When heated with sodium hydroxide solution (or even with water), D(+)-tartaric acid is converted into DL-tartaric acid (29–33 per cent.) and *meso*-tartaric acid (13–17 per cent.).

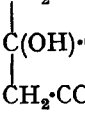
D(+)-Tartaric acid is used in the preparation of effervescent drinks. The acid and tartar emetic are both used as mordants in dyeing and printing.

***lævo*Tartaric acid, L(−)-tartaric acid,** does not occur naturally. It may be obtained by the resolution of DL-tartaric acid. Physically and chemically, it is similar to D(+)-tartaric acid.

***DL*-Tartaric acid, racemic tartaric acid,** crystallises as the hemihydrate, $(C_4H_6O_6)_2 \cdot H_2O$, m.p. 206°. In the solid state DL-tartaric acid exists as the *racemic compound*, but dissociates into the D- and L-forms in solution. DL-Tartaric acid is optically inactive by *external* compensation. It is obtained from the mother-liquors in the preparation of D(+)-tartaric acid, or by racemisation of the latter (together with *meso*-tartaric acid).

***meso*-Tartaric acid** (*i-tartaric acid*) crystallises as the monohydrate; the melting point of the anhydrous acid is 140°. *meso*-Tartaric acid is optically inactive by *internal* compensation, and may be obtained (together with DL-) by heating D(+)-tartaric acid with alkali. It may also be prepared by the oxidation of maleic acid with dilute alkaline permanganate. The prolonged oxidation of benzene with hydrogen peroxide in *tert.*-butanol containing a little osmium tetroxide produces *meso*-tartaric acid (and some allomucic and oxalic acids; Cook *et al.*, 1950).

Citric acid (β-*hydroxytricarballylic acid*, *2-hydroxypropane*-1 : 2 : 3-*tricarboxylic acid*) occurs in many fruits, especially unripe fruits of the *citrus* group, *e.g.*, lemon juice contains about 6–10 per cent. citric acid.

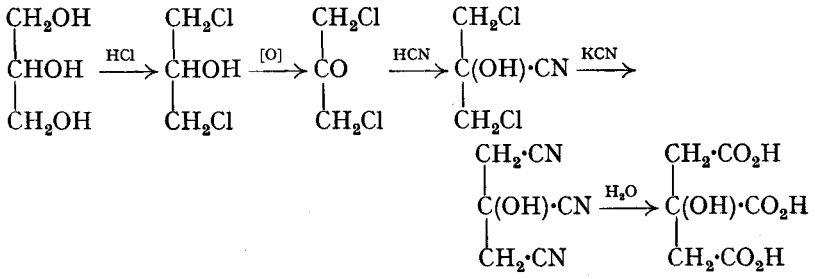


Citric acid is prepared from lemons by extracting the juice, boiling to coagulate the protein substances, and neutralising with calcium carbonate. The precipitated calcium citrate is collected by filtration and decomposed with the calculated quantity of dilute sulphuric acid. The precipitated calcium sulphate is removed by filtration and the filtrate evaporated to crystallisation; crystals of the monohydrate of citric acid are obtained.

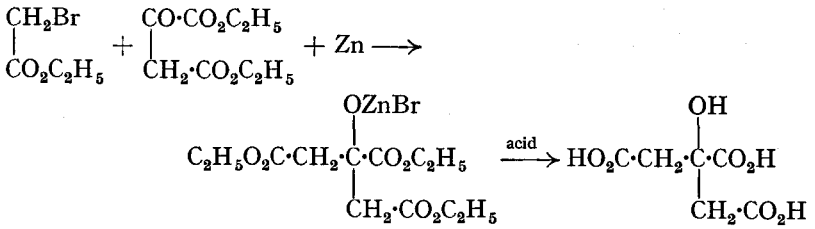
Citric acid is now also manufactured by the fermentation of solutions of glucose, sucrose, or purified cane-molasses in the presence of certain

inorganic salts, by various moulds or fungi, *e.g.*, *Citromyces pfefferianus*, *Aspergillus wentii*.

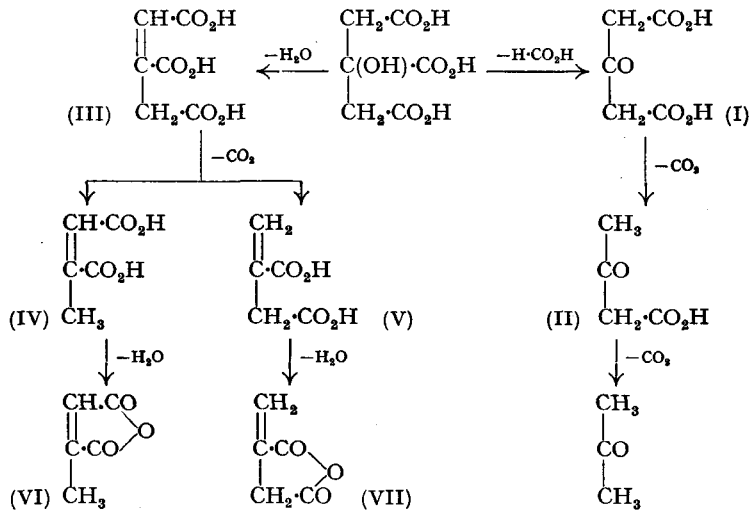
Citric acid may be synthesised from glycerol by the following reactions; this synthesis shows its structure:



Lawrence (1897) synthesised citric acid by means of the Reformatsky reaction (p. 363), starting with ethyl bromoacetate and oxalacetic ester:



The monohydrate of citric acid loses its water of crystallisation when heated at 130°, and melts at 153°. Citric acid is not optically active (it contains no asymmetric carbon atom). It behaves as an alcohol and a tribasic acid, *e.g.*, it forms the acetyl derivative and three series of salts. Calcium citrate is more soluble in cold water than in hot. Citric acid can



(I) is acetonedicarboxylic acid; (II) acetoacetic acid; (III) aconitic acid; (IV) citraconic and mesaconic acid (*cis-trans* isomers); (V) itaconic acid; (VI) citraconic (mesaconic) anhydride; (VII) itaconic anhydride.

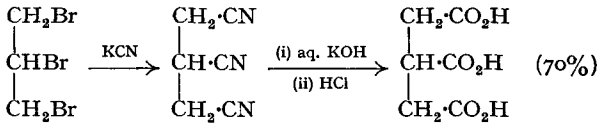
therefore be readily distinguished from tartaric acid, since, if aqueous calcium chloride is added to a neutral solution of a citrate, no precipitate is formed, whereas a neutral tartrate precipitates calcium tartrate. If the cold citrate solution is warmed after the addition of calcium chloride, calcium citrate, $(C_6H_5O_7)_2Ca_3 \cdot 4H_2O$, is precipitated. Furthermore, the calcium citrate precipitate is insoluble in aqueous potassium hydroxide, whereas calcium tartrate is soluble.

Citric acid is used for making beverages and as a mordant in dyeing.

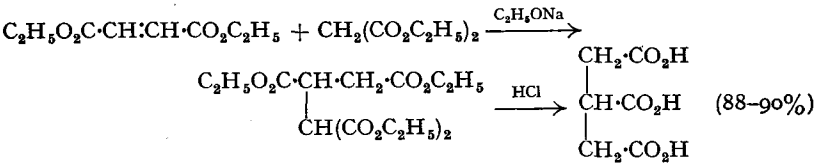
Citric acid is both an α- and β-hydroxy-acid; when heated to 150°, it eliminates a molecule of water to form *aconitic acid*. On pyrolysis, citric acid gives a number of products among which have been isolated *aconitic acid*, *citraconic* (*mesaconic*) and *itaconic anhydrides*, and acetone (I–VII).

When citric acid is heated with concentrated sulphuric acid, aconitic acid is obtained (41–44 per cent.). When treated with *fuming* sulphuric acid, citric acid forms acetonedicarboxylic acid (85–90 per cent.), a reaction which is characteristic of α-hydroxyacids.

Tricarballylic acid (*propane*-1 : 2 : 3-*tricarboxylic acid*), m.p. 166°, occurs in unripe beet-roots. It may be prepared by the reduction of aconitic acid, or from 1 : 2 : 3-tribromopropane as follows:



Tricarballylic acids may also be synthesised by the Michael condensation (p. 279) between diethyl fumarate and malonic ester, and heating the product, ethyl propane-1 : 1 : 2 : 3-tetracarboxylate, with concentrated hydrochloric acid:



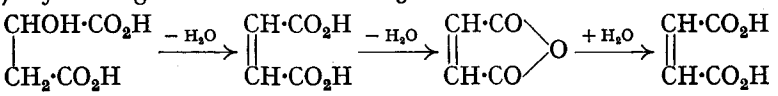
Tricarballylic esters have been used as plasticisers.

UNSATURATED DICARBOXYLIC ACIDS

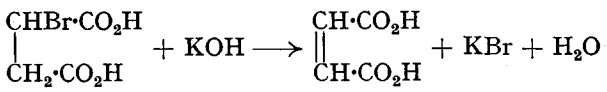
The formula of the simplest unsaturated dicarboxylic acid is $CO_2H \cdot CH{:}CH \cdot CO_2H$. This formula actually represents two isomers: maleic acid and fumaric acid.

Maleic acid may be prepared:

(i) By heating malic acid at about 250°:

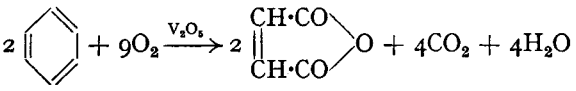


(ii) By heating bromosuccinic acid with aqueous alkali; some fumaric acid is also obtained:



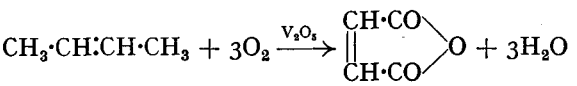
(iii) Maleic anhydride is prepared industrially:

(*a*) By the oxidation of benzene with air in the presence of vanadium pentoxide as catalyst at 410–430°:

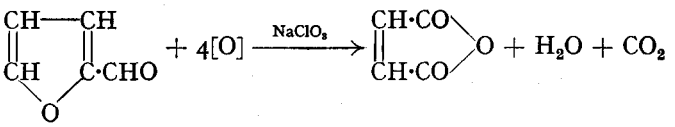


(*b*) As a by-product in the manufacture of phthalic anhydride from naphthalene (p. 693):

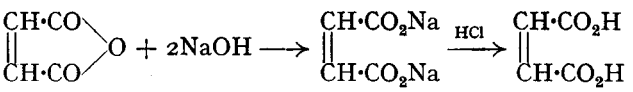
(*c*) By the oxidation of but-2-ene (from cracked petroleum) or crotonaldehyde with air in the presence of vanadium pentoxide as catalyst at 450°, *e.g.*,



(*d*) By the oxidation of furfural with sodium chlorate:



The anhydride is converted into the acid by boiling with alkali, and then acidifying:



Maleic acid is a synthetic compound. It is a crystalline solid, m.p. 130°, soluble in water (79 g. per 100 ml. at 25°). When heated, some distils unchanged; the rest is converted into maleic anhydride. A much better yield of maleic anhydride is obtained by heating the acid with acetic anhydride. Maleic acid may be reduced catalytically or electrolytically to succinic acid. This reduction may also be effected by *cyclo*hexene and palladium (Braude *et al.*, 1954; see p. 483). It is oxidised by dilute alkaline permanganate to *meso*tartaric acid; this may be obtained in excellent yield by replacing the permanganate by potassium chlorate and osmium tetroxide. Prolonged heating of maleic acid at 150° converts it into fumaric acid. Maleic acid and its anhydride are used in the Diels–Alder synthesis (p. 472).

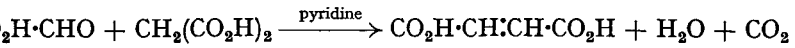
Maleic acid inhibits rancidity in milk powders, oils and fats. Maleic anhydride is used for making varnishes and lacquers.

Fumaric acid may be prepared:

(i) By heating maleic acid for some time at 150°.

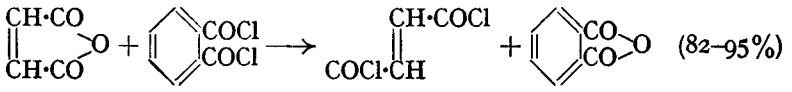
(ii) By heating bromosuccinic acid with alkali; maleic acid is also formed.

(iii) By the Knoevenagel reaction (p. 280); malonic acid is condensed with glyoxylic acid in the presence of pyridine:



(iv) Fumaric acid is prepared industrially by boiling maleic acid with hydrochloric acid or sodium hydroxide. Another industrial preparation is the fermentation of glucose (and other carbohydrates) by *e.g.*, *Rhizopus nigricans*.

Fumaric acid occurs in nature in many plants. It is a crystalline solid, m.p. 287°, slightly soluble in water (0·7 g. per 100 ml. at 25°). It does not form an anhydride of its own, but gives maleic anhydride when heated at 230°. It may be reduced to succinic acid, and is oxidised by alkaline permanganate to DL-tartaric acid; the latter is obtained in excellent yield if potassium chlorate and osmium tetroxide are used as the oxidising agent (*cf.* maleic acid). Fumaroyl chloride is formed when maleic anhydride is heated with phthaloyl chloride in the presence of zinc chloride.

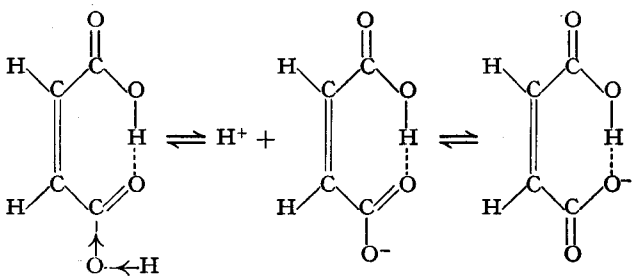


Many acid chlorides can be obtained in 95 per cent. yield by this method.

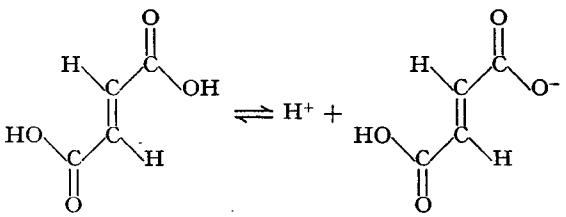
Maleic acid is a much stronger acid than fumaric acid (K_1 is the first dissociation constant, and K_2 the second):

	K_1	K_2	K_1/K_2
Maleic acid	$1{\cdot}2 \times 10^{-2}$	$6{\cdot}0 \times 10^{-7}$	20,000
Fumaric acid	$9{\cdot}55 \times 10^{-4}$	$4{\cdot}2 \times 10^{-5}$	22·6

At first sight, since the structures are identical, it might have been expected that the dissociation constants would be the same. The reason why they are so different is not certain. A possible explanation is that hydrogen bonding can occur in maleic but not in fumaric acid, thereby facilitating proton release in the former:



maleic acid



fumaric acid

Furthermore, since the maleic acid anion is stabilised by hydrogen bonding, and the corresponding fumaric anion is not, this offers an explanation why the second dissociation constant of maleic acid is less than that of fumaric acid.

GEOMETRICAL ISOMERISM

Maleic and fumaric acids both have the same molecular formula $C_4H_4O_4$, but differ in most of their physical and in many of their chemical properties, and neither is optically active. It was originally thought that they were structural isomers, and because of this, different names were assigned to

each form (this applies to many other geometrical isomers—see text). It was subsequently shown, however, that maleic and fumaric acids were not structural isomers, *e.g.*, both (i) are catalytically reduced to succinic acid; (ii) add on hydrogen bromide to form bromosuccinic acid; (iii) add on water to form malic acid; (iv) are oxidised by alkaline permanganate to tartaric acid (the stereochemical relationships in reactions (ii), (iii) and (iv) have been ignored). Thus both acids have the same structure, *viz.*, $CO_2H{\cdot}CH{:}CH{\cdot}CO_2H$. Van't Hoff suggested that if we assume there is *no free rotation about a double bond*, two spatial arrangements are possible for the formula $CO_2H{\cdot}CH{:}CH{\cdot}CO_2H$, and these would account for the isomerism exhibited by maleic and fumaric acids. Using tetrahedral diagrams, van't Hoff represented a double bond by placing the tetrahedra edge to edge (Fig. 12). From a *mechanical* point of view, such an arrangement would be rigid,

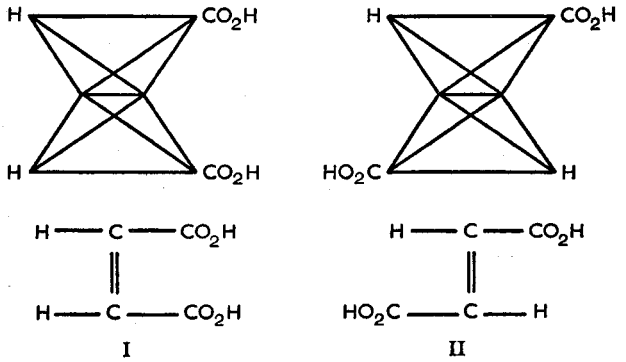


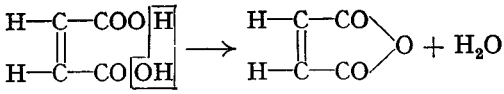
FIG. 17.12.

i.e., free rotation about the double bond is not to be expected. It is important to note that according to the above arrangement, *the two hydrogen atoms and the two carboxyl groups are all in one plane* (see also Fig. 13).

The problem now is to decide which formula represents maleic acid, and which fumaric acid. There is no general method for determining the configuration of geometrical isomers; the method used depends on the nature of the compound in question. The methods of cyclisation and dipole-moment measurements may be used to determine the configurations of maleic and fumaric acids.

Method of cyclisation. Wislicenus was the first to suggest the principle that *intramolecular* reactions are more likely to occur the closer together the reacting groups are in the molecule. This principle is generally true, but has led to incorrect results (as shown by other work) in certain cases, *e.g.*, the aromatic oximes (p. 666).

Of the two acids, only maleic acid forms the anhydride when heated. Fumaric acid does not form an anhydride of its own, but when strongly heated, gives maleic anhydride. If we accept the principle of cyclisation, then (I) is maleic acid, and (II) fumaric acid.



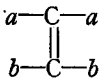
In fumaric acid, the two carboxyl groups are too far apart to react with each other.

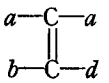
Cyclisation reactions must be carried out carefully, since one isomer may

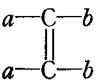
be converted into the other in the cyclising process, and so lead to unreliable results. In the above reaction, somewhat vigorous conditions have been used; hence there is the possibility that interconversion has occurred. The correctness of the conclusion for the configurations of the two acids may be tested by hydrolysing maleic anhydride in the cold; only maleic acid is obtained. Under these mild conditions it is most unlikely that interconversion occurs, and so we may accept (I) as the configuration of maleic acid.

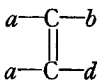
Method of dipole-moment measurements. The use of dipole moments to assign configurations to geometrical isomers must be used with caution. Since dipole moments are vector quantities, the sum of two equal and opposite group moments will be zero only if the two vectors are collinear or parallel. When the group moment is directed along the axis of the bond formed by the " key " atom of the group and the carbon atom to which it is joined, then that group is said to have a *linear* moment. Such groups are H, halogen, Me, CN, NO_2, etc. On the other hand, groups which have *non-linear* moments are OH, OR, CO_2H, NH_2, etc. Thus for *cis-* and *trans-*olefinic compounds, the dipole moments of the latter will be zero only if the groups attached have linear moments, *e.g.*, $CH_2{=}CH_2$, CHCl=CHCl, CHMe=CHMe. When the groups have non-linear moments, their vector sum is *not* zero, and the difference between the dipole moments of the *cis-* and *trans-*forms may be too small to assign configuration with any confidence, *e.g.*, the dipole moment of diethyl maleate is 2·54D and that of diethyl fumarate is 2·38D (see also p. 513).

The type of isomerism exhibited by maleic and fumaric acids is known as **geometrical isomerism.** For a compound to exhibit geometrical isomerism, the molecule must have a double bond about which there is no free rotation. Let us consider the compounds $Ca_2{:}Cb_2$, $Ca_2{:}Cbd$, $Cab{:}Cab$ and $Cab{:}Cad$:


(III)


(IV)


(V)


(VI)

Inspection of these formulæ shows that geometrical isomerism is possible in (V) and (VI), and impossible in (III) and (IV). Thus a double bond is not the only condition for geometrical isomerism; the groups attached to the two carbon atoms joined by the double bond must also be taken into consideration.

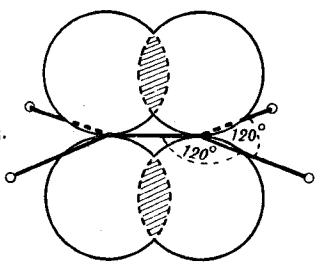


FIG. 17.13.

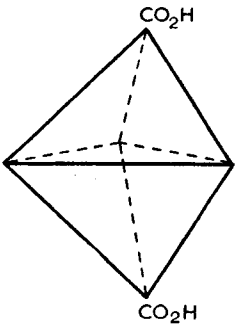


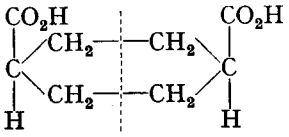
FIG. 17.14.

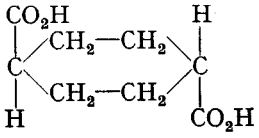
In the foregoing account of geometrical isomerism, the distribution of the carbon valencies was assumed to be tetrahedral (as postulated by van't Hoff). According to modern theory, in olefinic compounds the two unsaturated carbon atoms exhibit the *trigonal* mode of hydridisation, not the *tetrahedral*. Thus there are three coplanar valencies (σ-bonds), and the

fourth (π-bond) at right angles to the trigonal hybrids. It is the overlap of the π-electrons which causes the resistance to rotation about the carbon–carbon double bond (Fig. 13; see also p. 27).

When addition occurs at the double bond, the trigonal arrangement in the olefin changes to the tetrahedral arrangement in the saturated compound. As we have seen (p. 24), the electron distribution round the axis of a single bond is symmetrical; consequently there is no force in the bond itself restraining free rotation, and hence the saturated molecule takes up the position of least internal energy. This readily explains, *e.g.*, why maleic and fumaric acids both give the same succinic acid in reduction.

Geometrical isomerism is also possible in *cyclic* compounds, the ring structure being comparable to the double bond in olefinic compounds (in giving rise to a more or less rigid structure), *e.g.*, hexahydroterephthalic acids:

(VII) 

 (VIII)

Geometrical isomerism is also known as ***cis-trans* isomerism.** one isomer being the *cis* and the other *trans*. The *cis*-isomer is the one which (usually) has identical, or similar atoms or groups, on the *same* side. Thus maleic acid is *cis*-butenedioic acid, and fumaric acid is *trans*-butenedioic acid. Similarly, (VII) is *cis*-hexahydroterephthalic acid, and (VIII) *trans*-hexahydroterephthalic acid. It is interesting to note that both the hexahydroterephthalic acids are optically inactive; (VII) has a plane, and (VIII) a centre of symmetry.

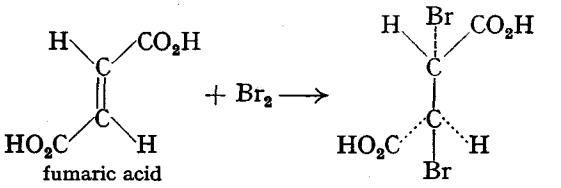
Compounds with a triple bond cannot exhibit geometrical isomerism, *e.g.*, acetylenedicarboxylic acid, $CO_2H{\cdot}C{:}C{\cdot}CO_2H$. According to van't Hoff's tetrahedral theory, a triple bond is represented as two tetrahedra placed face to face (Fig. 14). According to modern theory, in acetylenic compounds the two unsaturated carbon atoms exhibit the *digonal* mode of hybridisation. Examination of both the van't Hoff representation and the digonal structure shows that only one form of acetylenedicarboxylic acid is possible.

Properties of *cis-trans* isomers. Comparison of the properties of *cis*- and *trans*-isomers of known configurations shows certain regularities, *e.g.*, the melting point and stability of the *cis*- are *lower* than those of the *trans*-isomer; the density, refractive index, solubility, dipole moment, heat of combustion and the dissociation constant (if an acid) of the *cis*- are *greater* than those of the *trans*-isomer. It can be seen from these properties that the *cis*-isomer is usually the labile form. It is possible, by suitable means, to convert the labile *cis*-isomer into the stable *trans*-isomer; *e.g.*, maleic acid may be converted into fumaric acid by heating the solid, or a solution of the solid in water or benzene, to a temperature above its melting point (130°). The transformation may also be effected by treating it with a small amount of halogen in the presence of light. It is far more difficult to convert the *trans*-isomer into the *cis*-. Usually the best method is to irradiate the *trans*-isomer with ultra-violet light; the product is generally an equilibrium mixture of both isomers.

The mechanism of the conversion of *cis*- into *trans*-, and vice versa, is not fully understood.

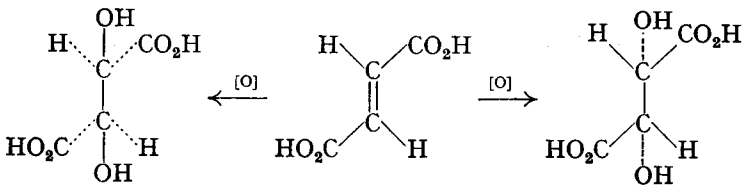
The addition of various substances to the double bond of, *e.g.*, maleic and fumaric acids is difficult to interpret. Experiment has shown that maleic acid adds on bromine to form DL-dibromosuccinic acid, and fumaric acid adds on bromine to form *meso*-dibromosuccinic acid. These additions

correspond to a *trans addition* of the two bromine atoms (full lines represent groups in front, and broken lines behind):



fumaric acid — *meso*-dibromosuccinic acid

Similar results, *i.e.*, *trans*-addition, are also obtained when the addenda are chlorine, halogen acid or hypohalous acid. On the other hand, oxidation with dilute alkaline permanganate leads to *cis-addition*, maleic acid forming *meso*-tartaric acid, and fumaric acid DL-tartaric acid:

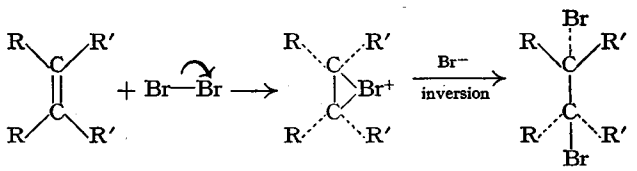


D- — fumaric acid — L-

The problem is further complicated by the fact that oxidation with Caro's acid causes the addition of the two hydroxyl groups to take place in the *trans*-position.

The results of many experiments indicate that *trans*-addition to a double bond is usually, but not invariably, the case.

The mechanisms of the stereochemical additions to a double and a triple bond are still not certain. The addition of halogen is *trans*. If the two halogen atoms approach on the same side of the attacked molecule and add *simultaneously* to the two carbon atoms, *i.e.*, we have a four-centre side-approach reaction, the resulting addition must be *cis*. If the two halogen atoms add on *singly*, then *cis* or *trans* addition could result. Since *trans*-addition occurs in practice, the addition must occur by a *two-step* mechanism (*i.e.*, the halogen atoms must add on one at a time; *cf.* ethylene, p. 66). Roberts and Kimball (1937) suggested the addition to a double bond occurs via the formation of a *cyclic* planar compound, *e.g.*,

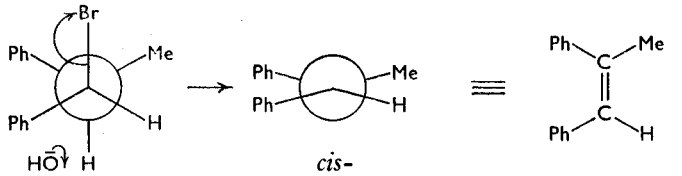


If the bromine ion attacks the planar compound from *behind*, then a Walden inversion occurs at this attacked carbon atom. Winstein and Lucas (1939) have demonstrated the existence of the above planar intermediate (p. 416).

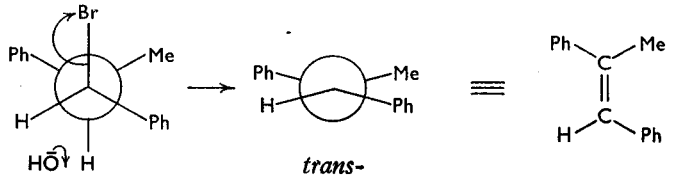
cis-Hydroxylation with permanganate is believed to proceed via a cyclic intermediate (see p. 72). *trans*-Hydroxylation probably proceeds through the epoxide which is then converted into the *trans* glycol (see p. 251).

The stereochemistry of elimination reactions also follows a definite pattern. According to Hughes and Ingold, *bimolecular elimination reactions* take place when the two groups (to be eliminated) are *trans*; in this way the planar transition state will be readily formed (see also p. 491). Let us consider the base-catalysed

dehydrobromination of the diastereoisomeric 1-bromo-1 : 2-diphenylpropanes (I and II). The results obtained by Cram *et al.* (1952) show that the olefins produced can arise only by *trans* elimination (Ph = C_6H_5):



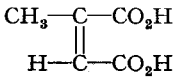
(I)



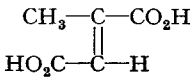
(II)

Geometrical isomerism accounts for the existence of many pairs of compounds, *e.g.*, the following acids: oleic (*cis*) and elaidic (*trans*); *iso*crotonic (*cis*) and crotonic (*trans*); angelic (*cis*) and tiglic (*trans*); etc.

Citraconic acid (*methylmaleic acid*) and **mesaconic acid** (*methylfumaric acid*) are geometrical isomers:



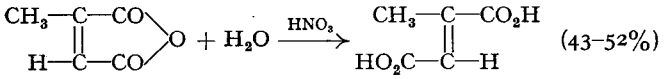
citraconic acid



mesaconic acid

Citraconic acid is a crystalline solid, m.p. 91°; it forms the anhydride. Citraconic acid may be prepared by heating itaconic anhydride and refluxing the product, citraconic anhydride, with water.

Mesaconic acid is a crystalline solid, m.p. 240°; it does not form an anhydride of its own. It may be prepared by evaporating a mixture of citraconic anhydride and dilute nitric acid:



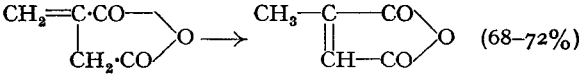
(43–52%)

Citraconic acid forms the anhydride more easily than maleic acid does, and mesaconic acid, when heated with acetic anhydride, readily gives citraconic anhydride.

Itaconic acid (*methylenesuccinic acid*), $CH_2{:}C(CO_2H)\cdot CH_2\cdot CO_2H$, m.p. 162°, may be prepared by heating citric acid until it melts, and refluxing the product, itaconic anhydride (which distils over), with water.

Itaconic acid may also be prepared by the fermentation of glucose by *Aspergillus terreus*.

When itaconic anhydride is distilled rapidly, a large portion of it rearranges to citraconic anhydride:



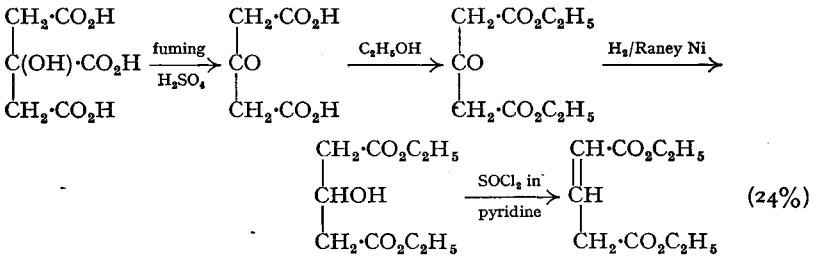
(68–72%)

Esters of itaconic acid can be polymerised to form plastics.

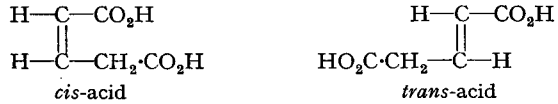
Glutaconic acid, $CO_2H{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$ (isomeric with the above acids), may be prepared by heating a mixture of sodiomalonic ester and chloroform with sodium ethoxide:

$$2[CH(CO_2C_2H_5)_2]^-Na^+ + CHCl_3 \xrightarrow{C_2H_5ONa} (C_2H_5O_2C)_2CH{\cdot}CH{:}C(CO_2C_2H_5)_2$$
$$\xrightarrow[\text{(ii) HCl}]{\text{(i) KOH}} (HO_2C)_2CH{\cdot}CH{:}C(CO_2H)_2 \xrightarrow{\text{heat}} CO_2H{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$$

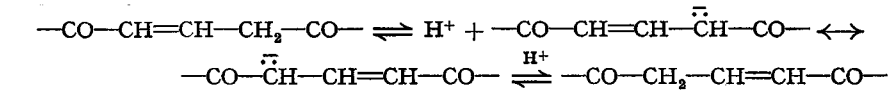
Glutaconic acid may also be prepared as follows (Lochte and Pickard, 1946):



Glutaconic acid is a crystalline solid, m.p. 138°. Although only one form has been prepared, in theory two geometrical isomers are possible:



Owing to the presence of two strongly negative (terminal) groups, the α-hydrogen atoms are readily eliminated as protons and can thereby give rise to a prototropic system:



This may be regarded as a three-carbon prototropic system. If, as is generally believed, this tautomeric system involves the enol form, it is, strictly speaking, a *pentad-enol* form (*cf.* p. 220). This prototropic change makes the *cis*- and *trans*-forms unstable; it has been shown that the known form is the *trans* isomer.

An interesting point in this connection is that the material, m.p. 115–116°, commonly accepted in the literature as *trans*-β-methylglutaconic acid is, in fact, a mixture of the *cis*- and *trans*-isomer, which have now been separated by Jackman *et al.* (1958), who showed the material was a mixture by means of nuclear magnetic resonance spectral studies, and found *cis*-acid, m.p. 150°, and *trans*-acid, m.p. 140°.

Glutaconic esters form sodio-derivatives with sodium ethoxide, and these react with alkyl halides:

$$C_2H_5O_2C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2C_2H_5 \xrightarrow{C_2H_5ONa} [C_2H_5O_2C{\cdot}CH{:}CH{\cdot}CH{\cdot}CO_2C_2H_5]^-Na^+$$
$$\xrightarrow{CH_3I} C_2H_5O_2C{\cdot}CH{:}CH{\cdot}CH(CH_3){\cdot}CO_2C_2H_5$$

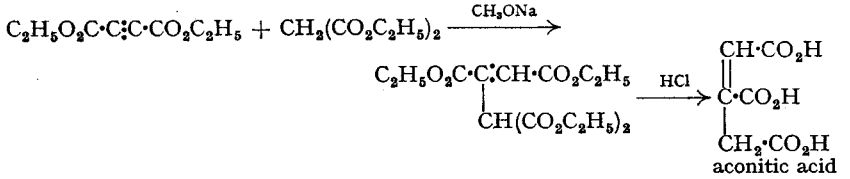
This is an example of vinylogy (p. 287).

Muconic acid, $CO_2H{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$, m.p. 306°, may be prepared by heating α : α′-dibromoadipic acid with ethanolic potassium hydroxide:

$$CO_2H{\cdot}CHBr{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2H \xrightarrow[\text{ethanol}]{KOH} CO_2H{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$$

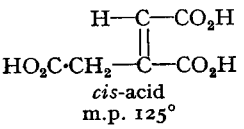
Muconic acid is formed by the oxidation of benzene in the animal body.

Aconitic acid (*propene*-1 : 2 : 3-*tricarboxylic acid*) occurs in the sugar-cane and beet-root, and in sorghum. It may be prepared by means of the Michael condensation between acetylenedicarboxylic ester and malonic ester:

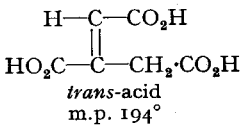


Aconitic acid is prepared industrially from calcium aconitate, which is recovered from sugar-cane syrup residues. Another industrial method is to dehydrate citric acid with concentrated sulphuric acid at 120–150°.

Aconitic acid is used in pain-preventive and fever-reducing medicines. Its esters have been used as plasticisers, and in the manufacture of wetting agents. On heating, aconitic acid is readily decarboxylated to itaconic acid. Aconitic acid exists in two forms (*cis*- and *trans*-), *both* of which form anhydrides:



cis-acid
m.p. 125°



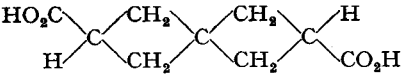
trans-acid
m.p. 194°

The Stereochemistry of Carbon Compounds not Containing an Asymmetric Carbon Atom

As pointed out previously (p. 403), the presence of an asymmetric carbon atom is not essential for optical activity; the essential requirement is *the asymmetry of the molecule as a whole*. Allenes are compounds whose *structures* are asymmetric, and so should be resolvable. Several compounds of this type have been obtained

in optically active forms, *e.g.*, where R = C_6H_5 (phenyl) and R′ = 1-$C_{10}H_7$ (1-naphthyl) [Mills and Maitland, 1936].

If both double bonds of allene are replaced by rings, *spirans* are obtained in which the rings are at right angles to each other. Hence by suitable substitution, it should be possible to obtain optically active *spiro*-compounds, *e.g.*, Backer (1928) resolved the following *spiro*heptane derivative.



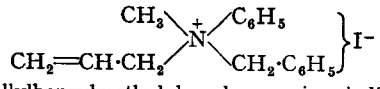
Suitably *ortho*-substituted diphenyls are also compounds whose structures are asymmetric, the asymmetry arising from restricted rotation about the single bond joining the two benzene rings (p. 700).

The Optical Isomerism of Elements other than Carbon

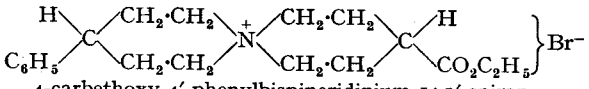
Many quadricovalent elements whose valencies are distributed tetrahedrally have also been obtained in optically active forms, *e.g.*, silicon and tin.

Nitrogen can be tercovalent or quadricovalent unielectrovalent. In the latter compounds, if the charge on the nitrogen atom is ignored, the molecule then

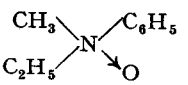
closely resembles carbon compounds. Thus, for example, the following compounds have been obtained in optically active forms.



allylbenzylmethylphenylammonium iodide
(Pope and Peachey, 1899)



4-carbethoxy-4′-phenylbispiperidinium-1:1′-spiran bromide (Mills and Warren, 1925)



ethylmethylphenylamine oxide (Meisenheimer, 1908)

Racemisation of compounds of the type $\overset{+}{N}abde\}X^-$ is effected far more readily than with the carbon compounds, *Cabde*. The mechanism is believed to be due to the ready dissociation:

$$\overset{+}{N}abde\}X^- \rightleftharpoons Nabd + eX$$

The amine, *Nabd* readily racemises (see below), and so the quaternary compound will racemise.

Tercovalent nitrogen offers a very interesting problem from the point of view of stereoisomerism. No tertiary amine, *Nabd*, has yet been resolved. It was therefore suggested that such molecules were planar, but physico-chemical evidence, *e.g.*, dipole moment measurements, absorption spectra, etc., shows that the configuration of ammonia and amines is tetrahedral, the nitrogen atom being at one corner of the tetrahedron with a valency angle of about 109°. Meisenheimer

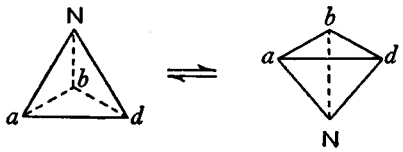
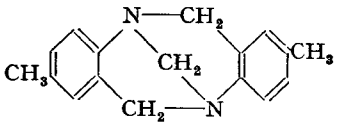
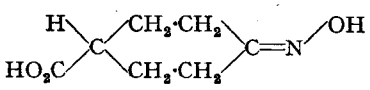


FIG. 17.15.

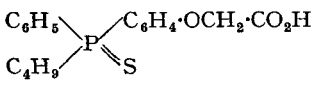
(1924) explained the failure to resolve tertiary amines as being due to the rapid oscillation of the nitrogen atom at right angles above and below the plane containing the three groups *a*, *b* and *d* (Fig. 15), *i.e.*, rapid optical inversion is occurring all the time. This explanation assumes that the nitrogen valency angles and bond lengths change. This inversion of amines, however, is better represented as an "umbrella" switch of bonds, *i.e.*, the bond lengths remain unaltered and only the nitrogen valency angles change. Theoretical considerations have shown that if the nitrogen atom were "anchored" by forming part of a ring, then the inversion (due to oscillation) would be inhibited. This has been confirmed by the resolution of Tröger's base.



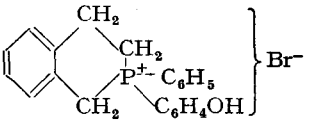
Oximes are also compounds of tercovalent nitrogen. They exhibit geometrical isomerism, and some have also been obtained in optically active forms, *e.g.*, the oxime of *cyclo*hexanone-4-carboxylic acid (Mills and Bain, 1910).



No tertiary phosphines have yet been resolved, but a number of quadricovalent phosphorus compounds have been obtained in optically active forms, *e.g.*,

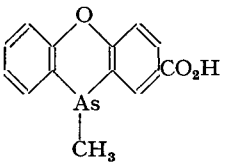


(Davies and Mann, 1944)

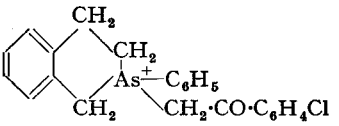


(Holliman and Mann, 1947)

Tercovalent and quadricovalent arsenic compounds have been resolved, *e.g.*,

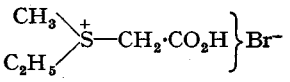


(Lesslie and Turner, 1934)

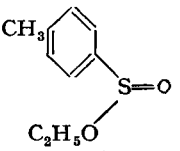


(Holliman and Mann, 1943)

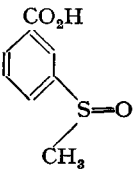
Various sulphur compounds have also been resolved, *e.g.*,



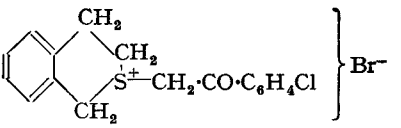
(Pope and Peachey, 1900)



(Phillips, 1925)



(Phillips, 1926)



(Mann and Holliman, 1946)

The shapes of molecules containing sulphur as the central atom have been discussed on p. 335.

QUESTIONS

1. Write out the structures and names of the isomeric hydroxyacids with the molecular formula $C_4H_8O_3$. How would you prepare each isomer, and how would you distinguish them from one another?

2. Name the products and state the conditions under which they are formed, when an α-, β-, γ- or δ-hydroxyacid is treated with:—(*a*) EtOH, (*b*) AcCl, (*c*) PCl_5, (*d*) $KMnO_4$, (*e*) H_2SO_4, (*f*) HI, (*g*) heat.

3. Write an account of the preparation and properties of lactones, and include in your answer the preparation of large-ring lactones.

4. Describe the preparation and properties of:—(*a*) glycollic acid, (*b*) lactic acid, (*c*) hydracrylic acid, (*d*) malic acid, (*e*) D(+), L(−), DL- and *meso*-tartaric acids, (*f*) citric acid, (*g*) tricarballylic acid, (*h*) maleic acid, (*i*) fumaric acid, (*j*) aconitic acid.

Give an account of the ***analytical*** evidence for the structure of each acid mentioned.

5. Write an account of the theoretical basis of optical and geometrical isomerism. Discuss the case of:—(*a*) lactic acid, (*b*) tartaric acid, (*c*) the isomers with the formula $C_4H_4O_4$.

6. How many possible stereoisomers are there for each of the following:—(*a*) $CH_3{\cdot}CHCl{\cdot}CO_2H$, (*b*) $CH_2Br{\cdot}CH_2{\cdot}CO_2H$, (*c*) $Me_2C(OH){\cdot}CO_2H$, (*d*) $Me{\cdot}CHOH{\cdot}CHOH{\cdot}CO_2H$, (*e*) $Me{\cdot}CHBr{\cdot}CHCl{\cdot}Me$, (*f*) $Et{\cdot}CHOH{\cdot}CHOH{\cdot}Et$, (*g*) $HO_2C{\cdot}CHBr{\cdot}CH_2{\cdot}CO_2Et$, (*h*) $CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$, (*i*) $CH_2{:}CH{\cdot}Me$, (*j*) $Me{\cdot}CH{:}CH{\cdot}Me$, (*k*) $MeCHBr{\cdot}CH{:}CH_2$, (*l*) $Me{\cdot}CHOH{\cdot}CH{:}CHMe$, (*m*) $HO_2C{\cdot}CMe{:}C(CO_2H){\cdot}CHMe{\cdot}CO_2H$?

7. Write an account of:—(*a*) the resolution of racemic modifications, (*b*) racemisation, (*c*) the Walden inversion, (*d*) asymmetric synthesis, (*e*) asymmetric transformation.

8. Write an account of the properties of *cis-trans* isomers, paying special attention to:—(*a*) their addition reactions, (*b*) their interconversion, (*c*) the methods of determining their configurations.

9. Define and give examples of:—(*a*) the Dilution Principle, (*b*) isomerism, (*c*) structural isomerism, (*d*) chain isomerism, (*e*) position isomerism, (*f*) functional group isomerism, (*g*) metamerism, (*h*) tautomerism, (*i*) stereoisomerism, (*j*) optical isomerism, (*k*) geometrical isomerism, (*l*) diastereoisomerism, (*m*) restricted rotation, (*n*) plane of symmetry, (*o*) centre of symmetry, (*p*) flexible molecules.

10. Starting with AcOH, indicate by means of equations how you would prepare:—(*a*) tartronic acid, (*b*) malic acid, (*c*) tartaric acid, (*d*) maleic acid, (*e*) aconitic acid.

11. Write an account of the preparation and properties of glutaconic acid.

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CHAPTER XVIII

CARBOHYDRATES

CARBOHYDRATES are substances with the general formula $C_x(H_2O)_y$, and were called carbohydrates (hydrates of carbon) because they contained hydrogen and oxygen in the same proportion as in water. Recently, a number of compounds have been discovered which are carbohydrates by chemical behaviour, but do not conform to the formula $C_x(H_2O)_y$, *e.g.*, rhamnose, $C_6H_{12}O_5$; rhamnohexose, $C_7H_{14}O_6$. It is also important to note that all compounds conforming to the formula $C_x(H_2O)_y$ are not necessarily carbohydrates, *e.g.*, formaldehyde, CH_2O; acetic acid, $C_2H_4O_2$; etc.

All carbohydrates are polyhydroxy aldehydes or ketones, or substances that yield these on hydrolysis.

Nomenclature. The names of the simpler carbohydrates end in *-ose*; carbohydrates with an aldehydic structure are known as *aldoses*, and those with ketonic, *ketoses*. The number of carbon atoms in the molecule is indicated by a Greek prefix, *e.g.*, a *tetrose* contains four carbon atoms, a *pentose* five, a *hexose* six, etc.

Carbohydrates are divided into two main classes, **sugars** and **polysaccharides** (*polysaccharoses*). Sugars are crystalline substances with a sweet taste and soluble in water. Polysaccharides are more complex than the sugars, their molecular weights being far greater. Most of them are non-crystalline substances which are not sweet, and are insoluble or less soluble in water, than the sugars.

Both classes of compounds have similar structures and both are produced by plants.

Sugars are subdivided into a number of groups as follows:

1. **Monosaccharides** (*monosaccharoses*). These are sugars which cannot be hydrolysed into smaller molecules. Their general formula is $C_nH_{2n}O_n$ (there are exceptions), where n is 2–10 (but see later). The most important monosaccharides are the pentoses and hexoses, and these are practically the only monosaccharides which occur naturally.
2. **Oligosaccharides.** These consist of:

   (i) **Disaccharides,** $C_{12}H_{22}O_{11}$, which yield *two* monosaccharide molecules on hydrolysis, *e.g.*, sucrose, maltose.

   (ii) **Trisaccharides,** $C_{18}H_{32}O_{16}$, which yield *three* monosaccharide molecules on hydrolysis, *e.g.*, raffinose.

   (iii) **Tetrasaccharides,** $C_{24}H_{42}O_{21}$, which yield *four* monosaccharide molecules on hydrolysis, *e.g.*, stachyose.

Polysaccharides (*polysaccharoses*) are carbohydrates which yield a large number of monosaccharide molecules on hydrolysis. The most widely spread polysaccharides have the general formula $(C_6H_{10}O_5)_n$, *e.g.*, starch, cellulose, etc.; a group of polysaccharides which are not so widely spread in nature is the *pentosans*, $(C_5H_8O_4)_n$.

Monosaccharides

The simplest monosaccharide is glycolaldehyde, $CH_2OH{\cdot}CHO$. This does not contain an asymmetric carbon atom and is therefore not optically active. Since all naturally occurring sugars are optically active, it is more

satisfactory to exclude glycolaldehyde from the group of sugars, and to define sugars as optically active polyhydroxy-aldehydes or ketones.

Triose, $C_3H_6O_3$. *Glyceraldehyde,* $CH_2OH{\cdot}CHOH{\cdot}CHO$, is an *aldotriose.* It contains one asymmetric carbon atom, and can therefore exist in two optically active forms, D- and L-; both are known. Glyceraldehyde has now been chosen as the standard configuration in sugar chemistry (p. 401).

Dihydroxyacetone, $CH_2OH{\cdot}CO{\cdot}CH_2OH$, is not optically active, and hence, by the definition given above, is not a sugar. If the definition be rejected, *i.e.*, the proviso that a sugar is always optically active is rejected, then dihydroxyacetone will be a *ketotriose.*

Tetroses, $C_4H_8O_4$. The structure of an aldotetrose is $CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$ (see p. 456).

There is only one structure possible for a *ketotetrose, viz.,* $CH_2OH{\cdot}CO{\cdot}CHOH{\cdot}CH_2OH$. This contains one asymmetric carbon atom, and corresponds to D- and L-*erythrulose,* which are synthetic compounds.

Pentoses, $C_5H_{10}O_5$. The *aldopentoses* are an important group of sugars (monosaccharides), and their structure has been elucidated as follows:

(i) Analysis and molecular-weight determinations show that the molecular formula of the aldopentoses is $C_5H_{10}O_5$.

(ii) When treated with acetic anhydride, aldopentoses form the tetra-acetate. This indicates the presence of four hydroxyl groups. Furthermore, since aldopentoses are not easily dehydrated, it can be assumed that no carbon atom is attached to two hydroxyl groups (*cf.* p. 168). As we shall see, this assumption is borne out by other reactions of the aldopentoses.

(iii) Aldopentoses form an oxime when treated with hydroxylamine, and therefore contain a carbonyl group.

(iv) When an aldopentose is oxidised with bromine-water, a tetrahydroxy-acid of formula $C_5H_{10}O_6$ is obtained. This indicates that the carbonyl group is present in an *aldehydic* group, since the acid obtained on oxidation contains the *same* number of carbon atoms as the original compound.

(v) When an aldopentose is oxidised with nitric acid, trihydroxyglutaric acid, $CO_2H{\cdot}(CHOH)_3{\cdot}CO_2H$, is obtained. This indicates that the five carbon atoms in the aldopentose are in a straight chain. This conclusion is supported by ascending the series by the *Kiliani reaction* (p. 447) and reducing the product, a polyhydroxyacid, with hydriodic acid; *n*-hexoic acid, $CH_3{\cdot}(CH_2)_4{\cdot}CO_2H$, is produced.

The foregoing reactions show that the structure of the aldopentoses is:

$$CHO{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CH_2OH$$

This contains three structurally different asymmetric carbon atoms, and can therefore exist in eight optically active forms. All are known, and correspond to the D- and L-forms of *arabinose, xylose, ribose* and *lyxose* (see p. 456).

L(+)-*Arabinose,* m.p. 158°, occurs naturally as pentosans (arabans) in various gums, *e.g.*, gum arabic. It is usually obtained by the hydrolysis of cherry-gum with dilute sulphuric acid.

D(−)-*Arabinose* occurs in certain glucosides.

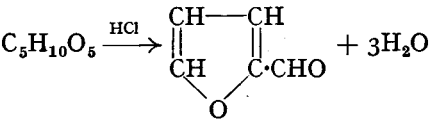
D(+)-*Xylose* (wood-sugar), m.p. 145°, occurs as pentosans (xylans) in wood gums, bran and straw, from which it may be obtained by hydrolysis with dilute sulphuric acid.

D(+)-*Ribose,* m.p. 95°, occurs in plant nucleic acids, and in liver and pancreas nucleic acids.

All the other aldopentoses are synthetic compounds.

The chemical properties of the aldopentoses are similar to those of the aldohexoses (see glucose, below); pentoses do *not* undergo fermentation. All

the aldopentoses are converted quantitatively into *furfural* when warmed with dilute acid:



Rhamnose is a hexose with the formula $CH_3{\cdot}(CHOH)_4{\cdot}CHO$; it is also known as *methylpentose* or 6-*deoxyhexose*. It occurs in several glycosides.

Ketopentoses with the structure $CH_2OH{\cdot}CO{\cdot}CHOH{\cdot}CHOH{\cdot}CH_2OH$ have been prepared. The molecule contains two structurally different asymmetric carbon atoms, and can therefore exist in four optically active forms. All are known, and correspond to D- and L-forms of *ribulose* and *xylulose*. All are synthetic compounds except L-xylulose which occurs in pentosuric urine.

Hexoses, $C_6H_{12}O_6$. The *aldohexoses* are another important group of monosaccharides, and their structure has been elucidated as follows (*cf.* aldopentoses):

(i) Analysis and molecular-weight determinations show that the molecular formula of the aldohexoses is $C_6H_{12}O_6$.

(ii) When treated with acetic anhydride, aldohexoses form the penta-acetate. This indicates the presence of five hydroxyl groups, and since aldohexoses are not easily dehydrated, it can be assumed that each hydroxyl group is attached to a different carbon atom.

(iii) Aldohexoses form an oxime when treated with hydroxylamine, and therefore contain a carbonyl group.

(iv) When an aldohexose is oxidised with bromine-water, a pentahydroxy-acid of formula $C_6H_{12}O_7$ is obtained. This indicates that the carbonyl group is present in an *aldehydic* group.

(v) When reduced with concentrated hydriodic acid and red phosphorus at 100°, aldohexoses give a mixture of 2-iodohexane and *n*-hexane. This indicates that the six carbon atoms in an aldohexose are in a straight chain. This conclusion is supported by ascending the series by the *Kiliani reaction* and reducing the product, a polyhydroxyacid, with hydriodic acid; *n*-heptoic acid, $CH_3{\cdot}(CH_2)_5{\cdot}CO_2H$, is produced.

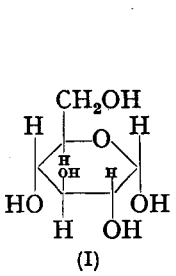
The foregoing reactions show that the structure of the aldohexoses is:

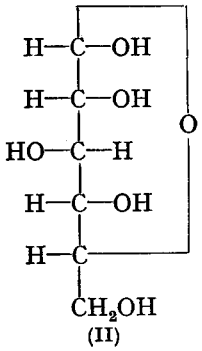
$$CHO{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CH_2OH$$

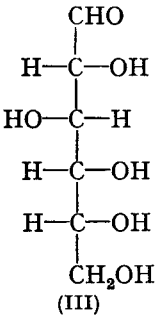
This contains four structurally different asymmetric carbon atoms, and can therefore exist in sixteen optically active forms. All are known, and correspond to the D- and L-forms of *glucose, mannose, galactose, allose, altrose, gulose, idose* and *talose* (see p. 457). The following aldoses occur naturally: D(+)-glucose, D(+)-mannose, D(+)-galactose, and D(+)-talose. D(−)-idose and D(+)-altrose have been isolated from the polysaccharide produced by the mould, *Penicillium varians*. L-Galactose-6-sulphate has been isolated from a seaweed polysaccharide (Turvey *et al.*, 1961).

Although the foregoing evidence indicates an open-chain structure, there is further evidence which shows that the sugars actually exist as *six-membered rings*. In many cases, however, it is more convenient to use the open-chain structure, and although this is incorrect, nevertheless it gives a simple picture of the properties of the sugars, since many reactions apparently involve first the opening of the ring (which is easily broken) and then reaction with the other reagent. The ring structure is hexagonal (I), but it is usually more convenient to use the planar formula (II), *e.g.*, α-D-glucose.

(II) corresponds to the open-chain formula (III) (see also p. 452), and it should be noted that the usual way of drawing the conventional planar formula of an aldose is with the carbon chain vertical and the aldehyde group at the top. In the D-series the hydroxyl group is always to the right on the bottom asymmetric carbon atom. The L-series is then the enantiomorphs of the D-series.


(I)


(II)


(III)

D(+)-**Glucose, dextrose** (*grape-sugar*), is found in ripe grapes, honey, and most sweet fruits; it is also a normal constituent of blood, and occurs in the urine of diabetics. Commercially, pure D(+)-glucose is manufactured by heating starch with dilute hydrochloric acid under pressure:

$$(C_6H_{10}O_5)_n + nH_2O \xrightarrow{HCl} nC_6H_{12}O_6$$

D(+)-Glucose is a white crystalline solid, m.p. 146°, readily soluble in water, but sparingly soluble in ethanol, and insoluble in ether. It has a sweet taste, but is not as sweet as cane-sugar. The relation between constitution and taste has not yet been worked out, but observations show that the groups —CHOH·CH_2OH and —CO·CHOH— confer a sweet taste on compounds containing either (or both) of them.

Naturally occurring glucose is dextrorotatory (hence name *dextrose*).

1. Glucose is a strong reducing agent, reducing both Fehling's solution and ammoniacal silver nitrate. It reduces more Fehling's solution than corresponds to one aldehyde group this indicates that other groups in the chain (besides the aldehyde group) must be involved in the reduction.

2. When heated with sodium hydroxide, an aqueous solution of glucose turns brown (see also p. 450).

3. Glucose forms a cyanohydrin with hydrogen cyanide (see also the Kiliani reaction, p. 447):

$$CH_2OH\cdot(CHOH)_4\cdot CHO + HCN \longrightarrow CH_2OH\cdot(CHOH)_5\cdot CN$$

4. When glucose is treated with hydroxylamine, the oxime is formed:

$$CH_2OH\cdot(CHOH)_4\cdot CHO + NH_2\cdot OH \longrightarrow CH_2OH\cdot(CHOH)_4\cdot CH{=}N\cdot OH + H_2O$$

5. The reaction between glucose and phenylhydrazine is complicated. Stempel (1934) found that glucose reacts with glucose in dilute inorganic acids in an atmosphere of nitrogen to form *glucose phenylhydrazone*. Addition of acetic acid caused the formation of *glucosazone* (see p. 443). On the other hand, Bloink *et al.* (1951) have shown that if the containing vessel is

filled with oxygen, then the osazone is obtained in the presence of inorganic acid. Diphenylhydrazine is a very good reagent for preparing sugar hydrazones.

6. When treated with a *mild* oxidising reagent, *e.g.*, bromine-water, glucose is oxidised to *gluconic acid*, m.p. 131°.

$$CH_2OH{\cdot}(CHOH)_4{\cdot}CHO + [O] \xrightarrow{Br_2/H_2O} CH_2OH{\cdot}(CHOH)_4{\cdot}CO_2H \quad (50\%)$$

The oxidation of only the aldehyde group in any sugar produces the corresponding *aldonic acid*, and is best carried out by electrolysing a solution of the aldose in the presence of calcium bromide and calcium carbonate (Isbell and Frush, 1931; Kiliani, 1933). Oxidation of a glucose solution with mercuric oxide in the presence of calcium carbonate gives a 70 per cent. yield of calcium gluconate (Candin, 1948). Gluconic acid is also formed by the fermentation of glucose by *Aspergillus niger* or *Penicillium chrysogenum*.

When treated with a *strong* oxidising agent, *e.g.*, nitric acid, glucose is oxidised to *saccharic acid* (some oxalic acid is also obtained):

$$CH_2OH{\cdot}(CHOH)_4{\cdot}CHO \xrightarrow[HNO_3]{[O]} CO_2H{\cdot}(CHOH)_4{\cdot}CO_2H \quad (40\text{–}46\%)$$

Oxidation of only the terminal —CH_2OH group in an aldose produces the corresponding *-uronic* acid, *e.g.*, glucose forms *glucuronic acid*:

$$CH_2OH{\cdot}(CHOH)_4{\cdot}CHO \xrightarrow{[O]} CO_2H{\cdot}(CHOH)_4{\cdot}CHO$$

This oxidation is extremely difficult to carry out in the laboratory. One of the best methods of preparing glucuronic acid is to feed borneol (a terpene alcohol) to dogs; bornyl glucuronate is excreted in the urine. Glucuronic acid may be prepared in the laboratory by reducing the lactone of saccharic acid (*cf.* Kiliani reaction). Uronic acids may also be prepared by the oxidation of glycosides (p. 454) with nitrogen peroxide (Maurer *et al.*, 1947), or with oxygen in the presence of platinum as catalyst (Marsh, 1951). Heyns *et al.* (1953) have obtained the lactone of D-glucuronic acid by oxidising corn starch with fuming nitric acid (26 per cent. yield).

7. When reduced with sodium amalgam in aqueous solution, glucose is converted into the hexahydric alcohol, *sorbitol*:

$$CH_2OH{\cdot}(CHOH)_4{\cdot}CHO + 2[H] \longrightarrow CH_2OH{\cdot}(CHOH)_4{\cdot}CH_2OH \quad (50\%)$$

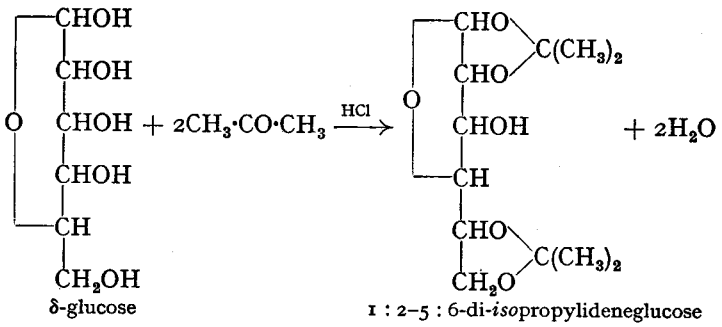
High-pressure catalytic reduction, or electrolytic reduction in acid solution of aldoses, is better than reduction with sodium amalgam, since aldoses tend to undergo rearrangement in alkaline solution (see p. 450). Sugars may also be reduced to the corresponding alcohols with sodium borohydride in aqueous solution (Abdel-Akher *et al.*, 1951).

Reduction of glucose with concentrated hydriodic acid and red phosphorus at 100° produces 2-iodohexane; prolonged heating finally gives *n*-hexane.

The electrolytic reduction of D-glucose in *alkaline* solution gives D-mannitol and the by-product *dodecitol*, m.p. 233–235°, formed by bimolecular reduction (Wolfrom *et al.*, 1951).

$$2CH_2OH{\cdot}(CHOH)_4{\cdot}CHO \xrightarrow{[H]} CH_2OH{\cdot}(CHOH)_{10}{\cdot}CH_2OH$$

8. Acetone condenses with glucose in the presence of hydrochloric acid to form 1 : 2-*iso*propylideneglucose and 1 : 2–5 : 6-di-*iso*propylideneglucose, *e.g.*, (see also mutarotation, p. 451):

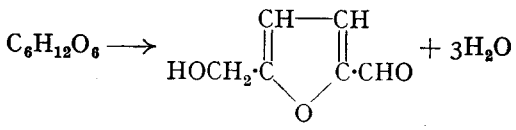


The two hydroxyl groups involved in the condensation are usually on adjacent carbon atoms. These *iso*propylidene derivatives are stable to alkali, but are readily hydrolysed by acid.

9. When heated with concentrated hydrochloric acid, glucose (and any other aldohexose) is converted into lævulic acid:

$$C_6H_{12}O_6 \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + H{\cdot}CO_2H + H_2O$$

Glucose can also form hydroxymethylfurfural on treatment with hydrochloric acid:



This compound yields lævulic acid on acid treatment. Hence it is possible that lævulic acid is produced from glucose via the intermediate formation of hydroxymethylfurfural.

10. Glucose is readily fermented by yeast to ethanol:

$$C_6H_{12}O_6 \longrightarrow 2C_2H_5OH + 2CO_2$$

11. Glucose forms *glucosates* with various metallic hydroxides, *e.g.*, with calcium hydroxide it forms calcium glucosate, $C_6H_{12}O_6{\cdot}CaO$; the structure of these glucosates is uncertain.

12. Glucose combines with monohydric alcohols, *e.g.*, methyl and ethyl alcohols, in the presence of hydrochloric acid, to form *glucosides* (pentoses behave in a similar manner).

D(+)-**Mannose,** m.p. 132°, may be obtained by carefully oxidising mannitol with nitric acid:

$$CH_2OH{\cdot}(CHOH)_4{\cdot}CH_2OH + [O] \xrightarrow{HNO_3} CH_2OH{\cdot}(CHOH)_4{\cdot}CHO + H_2O$$

Commercially, mannose is prepared by hydrolysing the polysaccharide *seminine* with boiling dilute sulphuric acid. Seminine (a *mannan*) occurs in many plants, particularly in the shell of the ivory nut, which is used as the starting material for D(+)-mannose.

Chemically, mannose behaves like glucose.

D(+)-**Galactose** (m.p. of monohydrate, 118°) is found in several polysaccharides (*galactans*), and is combined with glucose in the disaccharide *lactose*. Galactose may be prepared by hydrolysing lactose, and separating it from glucose by fractional crystallisation from water, in which glucose is more soluble than galactose.

Chemically, galactose behaves like glucose.

Ketohexoses. The only important ketohexose is **D(—)-fructose,** the structure of which has been elucidated as follows:

(i) Analysis and molecular-weight determinations show that the molecular formula of fructose is $C_6H_{12}O_6$.

(ii) When treated with acetic anhydride, fructose forms the penta-acetate. This indicates the presence of five hydroxyl groups, each being attached to a different carbon atom (*cf.* aldohexoses).

(iii) Fructose forms an oxime when treated with hydroxylamine, and therefore contains a carbonyl group.

(iv) When oxidised with nitric acid, fructose is converted into a mixture of trihydroxyglutaric, tartaric and glycollic acids. Since a mixture of acids each containing fewer carbon atoms than fructose is obtained, the carbonyl group in fructose must be present in a *ketonic* group.

(v) Fructose may be reduced to a hexahydric alcohol, *sorbitol*, which, on reduction with hydriodic acid and red phosphorus at 100°, gives a mixture of 2-iodohexane and *n*-hexane. The formation of the latter two compounds indicates that the six carbon atoms in fructose are in a straight chain.

(vi) On ascending the series by the *Kiliani reaction*, and reducing the product with hydriodic acid, *n*-butylmethylacetic acid, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CO_2H$, is obtained. This shows that the ketonic group in fructose is adjacent to one of the terminal carbon atoms (all the known ketohexoses have the ketonic group in this position).

The foregoing reactions show that the structure of fructose is:

$$CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CO{\cdot}CH_2OH$$

This contains three structurally different asymmetric carbon atoms, and can therefore exist in eight optically active forms. Of these the following six are known: D(—)- and L(+)-*fructose*, D(+)- and L(—)-*sorbose*, D(+)-*tagatose* and L(—)-*psicose*; only D(—)-fructose, L(—)-sorbose and D(+)-tagatose occur naturally (see also p. 458).

Naturally occurring fructose (*fruit-sugar*) is lævorotatory, and is therefore also known as *lævulose* (*cf.* dextrose). D(—)-Fructose is found in fruits and honey, and occurs combined with glucose in the disaccharide *cane-sugar*, from which it may be obtained by hydrolysis and fractional crystallisation. Fructose is prepared commercially by hydrolysis of *inulin*, a polysaccharide which occurs in dahlia tubers and Jerusalem artichokes:

$$(C_6H_{10}O_5)_n + nH_2O \xrightarrow{HCl} nC_6H_{12}O_6$$

Fructose is a white crystalline solid, m.p. 102° (with decomposition); it has a sweet taste, and is readily soluble in water but sparingly soluble in ethanol, and insoluble in ether.

1. Fructose is a strong reducing agent, reducing Fehling's solution and ammoniacal silver nitrate (*cf.* α-hydroxyketones, p. 237).

2. Fructose forms a cyanohydrin with hydrogen cyanide:

$$CH_2OH{\cdot}(CHOH)_3{\cdot}CO{\cdot}CH_2OH + HCN \longrightarrow CH_2OH{\cdot}(CHOH)_3{\cdot}C\begin{matrix}CH_2OH\\OH\\CN\end{matrix}$$

3. Fructose reacts with hydroxylamine to form the oxime:

$$CH_2OH{\cdot}(CHOH)_3{\cdot}CO{\cdot}CH_2OH + NH_2{\cdot}OH \longrightarrow CH_2OH{\cdot}(CHOH)_3{\cdot}C(=N{\cdot}OH){\cdot}CH_2OH + H_2O$$

4. When treated with phenylhydrazine, fructose forms the phenylhydrazone or osazone, according to the conditions (*cf.* glucose, above).

5. Nitric acid oxidises fructose to a mixture of trihydroxyglutaric, tartaric and glycollic acids. Fructose is *not* oxidised by bromine-water.

6. Fructose may be reduced to sorbitol (a hexahydric alcohol) by sodium amalgam and water, or catalytically, or electrolytically.

7. When heated with concentrated hydrochloric acid, fructose forms lævulic acid (in better yield than from any aldohexose; see glucose, above).

8. Fructose is fermented by yeast to ethanol:

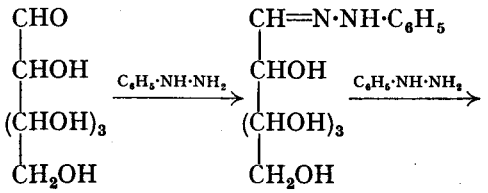
$$C_6H_{12}O_6 \longrightarrow 2C_2H_5OH + 2CO_2$$

9. When treated with monohydric alcohols in the presence of hydrochloric acid, fructose forms *fructosides* (p. 454).

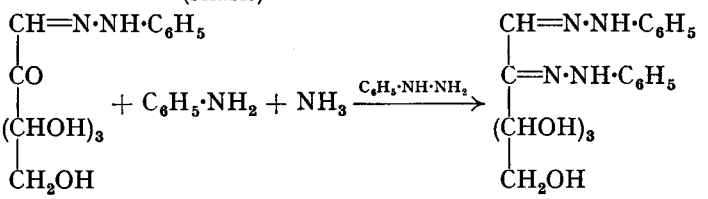
10. Fructose condenses with acetone to form an *iso*propylidene and a di-*iso*propylidene derivative (*cf.* glucose).

Reaction of glucose and fructose with phenylhydrazine. Fischer (1884, 1887) proposed the following series of reactions to account for the formation

Glucose

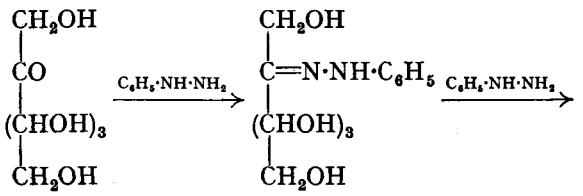


glucose phenylhydrazone (soluble)

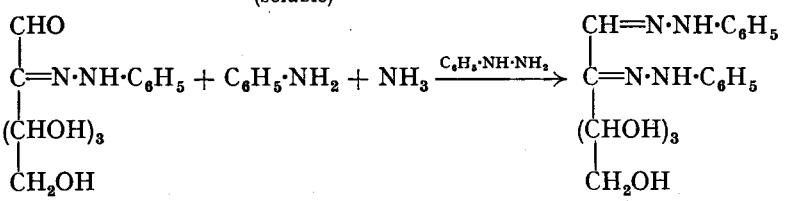


phenylhydrazone of glucosone — glucosazone (insoluble)

Fructose



fructose phenylhydrazone (soluble)

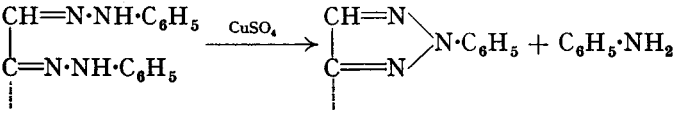


phenylhydrazone of fructosone — fructosazone (insoluble)

of an **osazone** when glucose or fructose is treated with excess of phenylhydrazine. According to this mechanism, a phenylhydrazone is first produced, and one of its hydroxyl groups, adjacent to the original aldehyde or ketonic group, is oxidised to a carbonyl group by a second molecule of phenylhydrazine which is reduced to aniline and ammonia; the carbonyl group now reacts with a third molecule of phenylhydrazine to form the osazone.

Although glucose and fructose are different sugars, both form the *same* osazone. This indicates that the two sugars differ only in the two carbon groups which take part in the formation of the osazone (see also below).

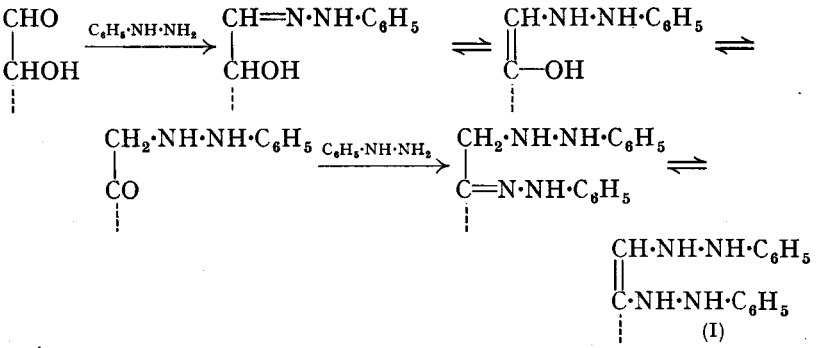
Osazones are yellow crystalline solids, and are used to characterise the sugars. All compounds containing the —CO·CHOH— group form osazones (p. 237). A better means of identifying sugars is to convert the osazone into an *osotriazole* by heating with copper sulphate solution (Hudson, 1944). These triazoles are readily purified, and have sharp melting points.



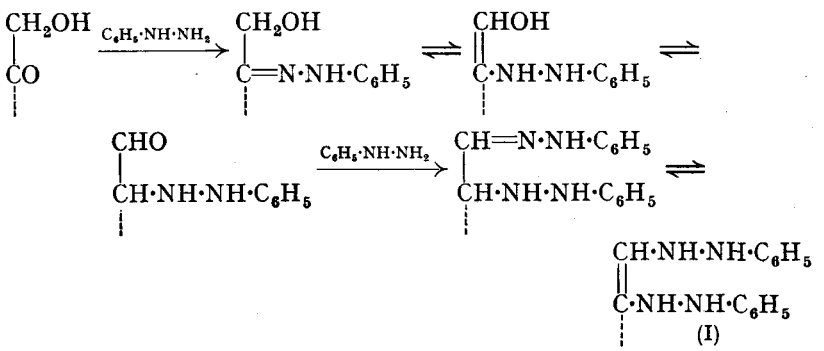
Fischer's mechanism of osazone formation is difficult to accept because phenylhydrazine is a powerful reducing agent; this is the only reaction in which it behaves as an oxidising agent. Furthermore, Fischer's mechanism does not explain why only two carbon atoms should be involved; it might have been expected that other hydroxyl groups would be attacked as well as the second one.

Weygand (1940) suggested that osazone formation occurred via the *Amadori rearrangement.*

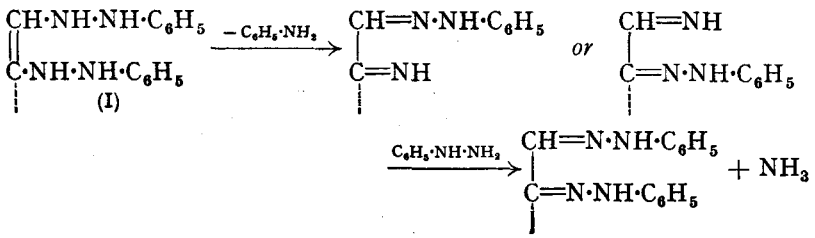
Glucose



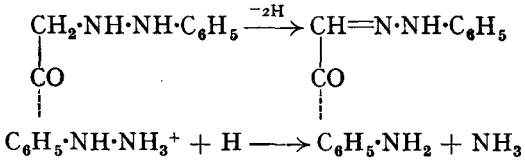
Fructose



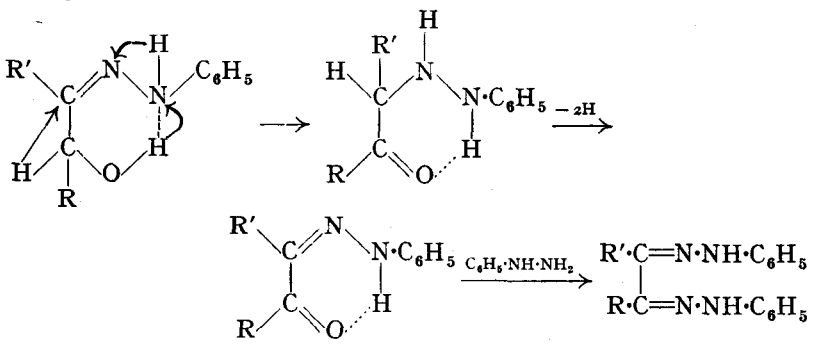
Both glucose and fructose give (I), and this then forms the osazone as follows:



Barry and Mitchell (1955) have given evidence to support the above mechanism in that it occurs via the Amadori rearrangement, but suggest that the two hydrogen atoms are removed by the hydrogen acceptor, the phenylhydrazinium cation:

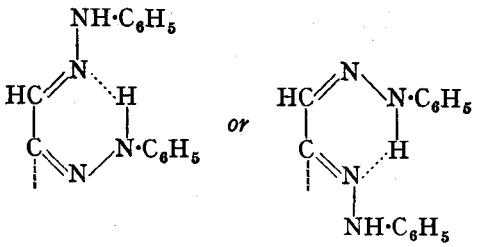


These authors also propose the following mechanism to explain the Amadori rearrangement:



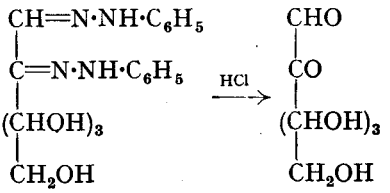
Aldose: R = sugar residue; R′ = H.
Ketose: R′ = sugar residue; R = H.

It should be noted that Weygand's mechanism also does not explain why only the first two carbon atoms should be involved (*cf.* Fischer's mechanism). Fieser and Fieser (1944), however, have suggested that the osazone is stabilised by chelation:



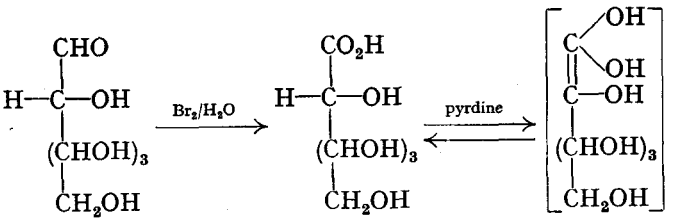
This is supported by work of Mester *et al.* (1955) who have obtained evidence to show that osazones are acyclic and that a chelate ring is present.

Osazones may be hydrolysed with hydrochloric acid, both phenylhydrazine radicals being eliminated; the dicarbonyl compound formed is known as an **osone,** *e.g.*, *glucosazone* forms *glucosone*:

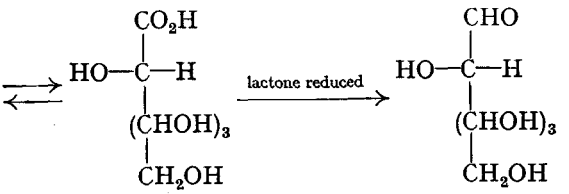


A more convenient method of obtaining the osone is to add benzaldehyde to a solution of the osazone; benzaldehyde phenylhydrazone is precipitated, leaving the osone in solution. The precipitate is removed by filtration and the filtrate evaporated; a white substance is obtained which is difficult to crystallise. Osones react with phenylhydrazine in the cold to form osazones.

Epimerisation. Aldoses which produce the same osazones must have identical configurations on all their asymmetric carbon atoms except the *alpha* (since only the aldehyde group and α-carbon atom are involved in osazone formation). Such sugars are known as **epimers.** Fischer (1890) changed an aldose into its epimer via the aldonic acid. The aldonic acid was heated with pyridine (or quinoline), whereupon it was converted into an equilibrium mixture of the original acid and its epimer. These were separated, and the epimeric acid lactone reduced to an aldose (see the Kiliani reaction below). The mechanism of epimerisation is not certain, but it is possibly similar to racemisation, *i.e.*, it takes place via the enol form; *e.g.*, epimerisation of glucose into mannose:



D(+)-glucose gluconic acid

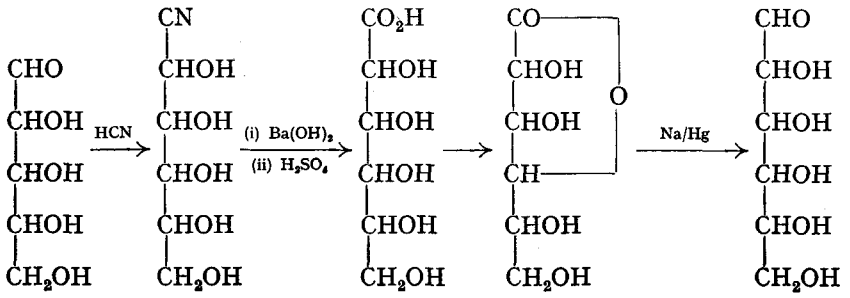


mannonic acid D(+)-mannose

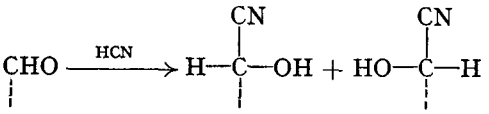
The function of the pyridine (or quinoline) is to prevent the formation of the lactone of the aldonic acid.

This change of configuration of one of the asymmetric carbon atoms in a compound containing two or more asymmetric carbon atoms is known as *epimerisation.*

Method of ascending the sugar series. An aldose may be converted into its next higher aldose, *e.g.*, an aldopentose into an aldohexose, by means of the **Kiliani reaction** (1886). The aldopentose is dissolved in dilute hydrocyanic acid, and the cyanohydrin formed is hydrolysed with aqueous barium hydroxide. After acidification with the calculated quantity of dilute sulphuric acid and subsequent filtration, there is obtained an aqueous solution of a polyhydroxyacid with one more carbon atom than the aldopentose (yield: 70 per cent.). When this solution is evaporated to dryness, the γ-lactone is obtained (*cf.* p. 395) and this, on reduction with sodium amalgam in faintly acid solution, is converted into the aldohexose (yield: 30–40 per cent. on the acid):



Theoretically, two lactones are possible, since two cyanohydrins may be formed when hydrogen cyanide adds on to the aldopentose (a new asymmetric carbon is produced), *viz.*,

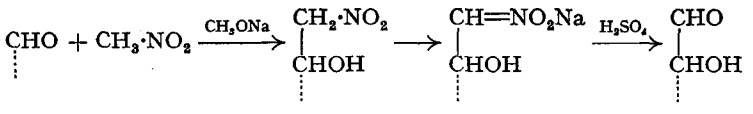


Thus two epimeric aldohexoses should be obtained. In practice, one cyanohydrin predominates because the asymmetry present in the molecule exerts a spatial directive influence on the addition of hydrogen cyanide (*cf.* asymmetric synthesis, p. 416). Hence the final product will be mainly one aldohexose, and very little of its epimer.

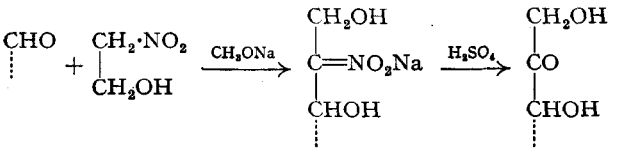
By means of the Kiliani reaction, it has been possible to prepare aldoses up to an aldodecose.

Hudson (1951) has modified the Kiliani reaction, using sodium cyanide instead of hydrocyanic acid. The proportions of the epimers were the reverse of those when hydrocyanic acid was used.

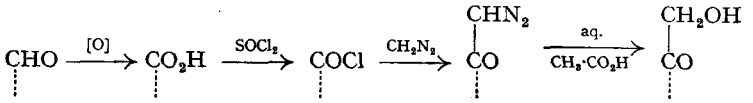
Sowden and Fischer (1947) have stepped up the aldose series by condensing the aldose with nitromethane in the presence of methanolic sodium methoxide, separating the 1-nitro-1-deoxy-compounds produced, converting each of these into its sodium salt and then hydrolysing with cold 60 per cent. sulphuric acid (*cf.* p. 305). The proportions of the epimers formed by this method are different from those produced by the Kiliani reaction.



Sowden (1950) has stepped up an aldose into a *ketose* containing *two* additional carbon atoms using the above method except that 2-nitroethanol is used instead of nitromethane.

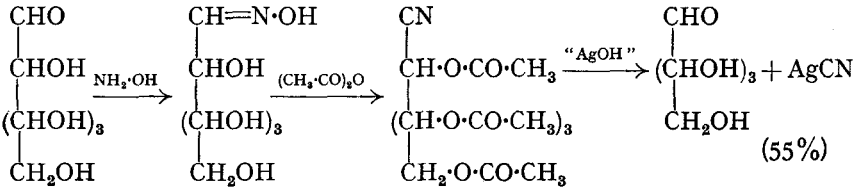


On the other hand, Wolfrom *et al.* (1946) have stepped up an aldose to a ketose with *one* more carbon atom by a modified Arndt–Eistert reaction (p. 327).



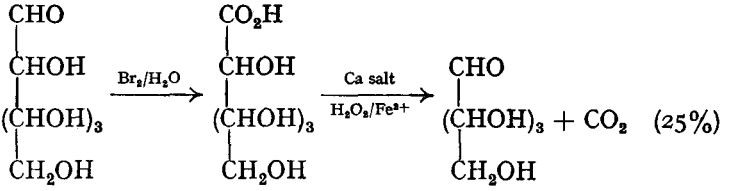
Method of descending the sugar series. There are various methods of converting a sugar into its next lower sugar, *e.g.*, a hexose into a pentose. All of these methods start with the aldohexose, and hence, in order to convert a ketohexose into a pentose, it is first necessary to transform it into an aldohexose (see later).

Wohl's method (1893). The aldohexose is converted into its oxime, which is then heated with acetic anhydride, whereupon the oxime is dehydrated to the cyano-compound with simultaneous acetylation of the hydroxyl groups. When this acetyl derivative is warmed with ammoniacal silver nitrate, the acetyl groups are removed by hydrolysis, and a molecule of hydrogen cyanide is eliminated with the formation of the aldopentose:



Zemplen (1917) modified Wohl's method by using a solution of sodium methoxide in chloroform instead of an aqueous solution of ammoniacal silver nitrate, to remove hydrogen cyanide and the acetyl groups, and thereby increased the yield of pentose to 60–70 per cent. Weygand *et al.* (1950) have treated the *oxime* with 1-fluoro-2 : 4-dinitrobenzene in aqueous sodium hydrogen carbonate; the products are the lower aldose (50–60 per cent. yield), hydrogen cyanide and 2 : 4-dinitrophenol.

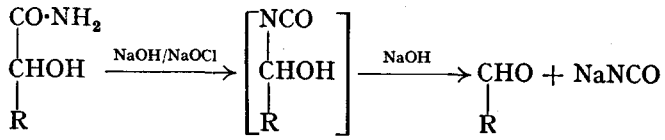
Ruff's method (1898). The aldohexose is oxidised (by bromine-water) to the corresponding aldonic acid; when the calcium salt of this acid is treated with Fenton's reagent it is converted into the aldopentose (*cf.* oxidation of α-hydroxyacids, p. 394):



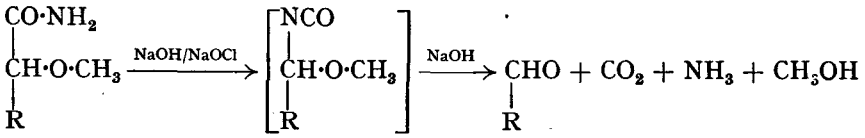
Berezovski *et al.* (1949) have shown that calcium gluconate can be oxidised with hydrogen peroxide in the presence of ferric sulphate and barium acetate to give D-arabinose (44%).

Weerman's reaction (1913). This is the reaction whereby an α-hydroxy- or α-methoxy-amide is degraded by means of a cold solution of sodium hypochlorite (*cf.* Hofmann degradation, p. 206). The mechanism of the Weerman reaction is not certain, but according to Ault, Haworth and Hirst (1934), the reaction takes place as follows:

α-Hydroxyamides

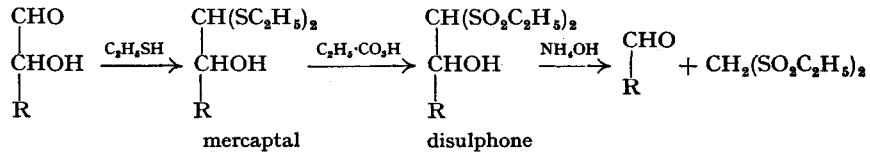


α-Methoxyamides

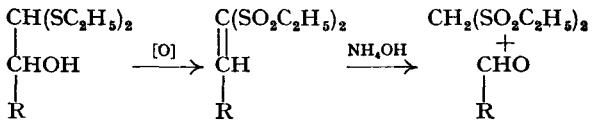


Haworth, Peat and Whetstone (1938) carried out the descent of the sugars by the Weerman reaction, and obtained a 55 per cent. yield from the methylated amides.

Macdonald *et al.* (1953) have stepped down an aldose as follows:

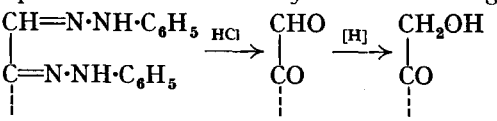


Hough *et al.* (1954) have found that this degradation is general, but that the structure of the disulphone may vary from one aldose to another.



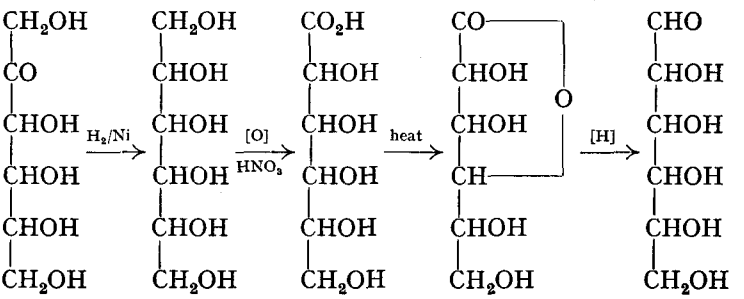
Perlin (1954) has shown that aldoses may be stepped down by direct oxidation with lead tetra-acetate or sodium bismuthate, *e.g.*, D-mannose gives D-arabinose (35%).

Conversion of an aldose into a ketose. The aldose is converted into its osazone, which is then hydrolysed with hydrochloric acid to the osone. On reduction with zinc and acetic acid, the osone is converted into the ketose (an aldehyde group is reduced more readily than a ketonic group):

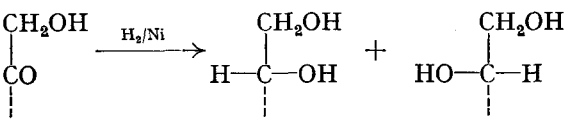


Conversion of a ketose into an aldose. The ketose is reduced (preferably by catalytic reduction, p. 450) to the corresponding polyhydric alcohol

which is then oxidised to a monocarboxylic acid (only one of the terminal CH_2OH groups being oxidised). On warming, the acid is converted into the γ-lactone which, on reduction with sodium amalgam in faintly acid solution, is converted into the aldose:

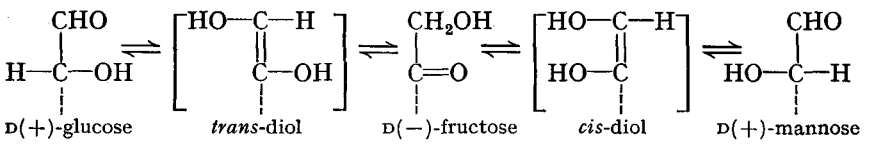


Theoretically, two polyhydric alcohols may be formed on reduction of the ketose, due to the formation of a new asymmetric carbon atom:



In practice, however, one predominates (*cf.* the Kiliani reaction). Furthermore, when these two alcohols are oxidised, oxidation may take place at *either* end of the chain, and hence the final product will be a mixture of *four* aldoses, but these will not be present to the same extent.

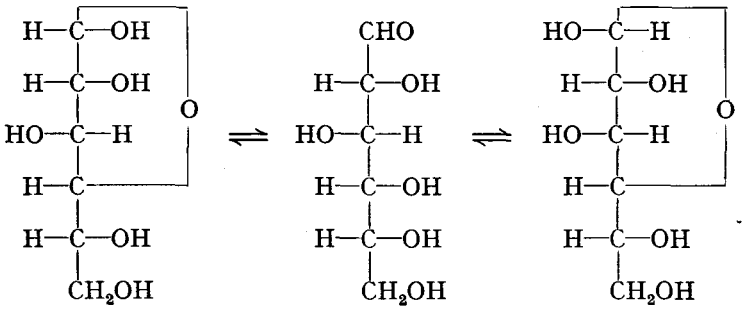
Lobry de Bruyn–van Ekenstein rearrangement (1890). When warmed with *concentrated* alkali, sugars first turn yellow, then brown and finally resinify (*cf.* aldehydes, p. 160). In the presence of *dilute* alkali or amines, sugars undergo rearrangement; *e.g.*, a dilute solution of glucose, in the presence of sodium hydroxide, is converted into an almost optically inactive solution from which have been isolated D(+)-glucose, D(+)-mannose, D(−)-fructose. The same mixture is obtained if the starting material is D(−)-fructose or D(+)-mannose. It has been suggested that the re-arrangement occurs through 1 : 2-enolisation. Topper *et al.* (1951), using deuterium oxide, support this enolisation mechanism, but conclude that mannose and fructose cannot arise from the same enediol, and suggest there are *two* geometrical isomeric enediol intermediates, both being capable of changing into fructose.



Since the Lobry de Bruyn–van Ekenstein rearrangement takes place in alkaline media, it is best to carry out reactions with the sugars in neutral or acid media.

Lobry de Bruyn's "glutose," obtained by heating fructose with lead hydroxide, has been shown by Schneider *et al.* (1952) to be D-psicose (p. 458). D-Psicose has also been isolated from the products formed by warming D-glucose with aqueous ammonia at 37° (Hough *et al.*, 1953).

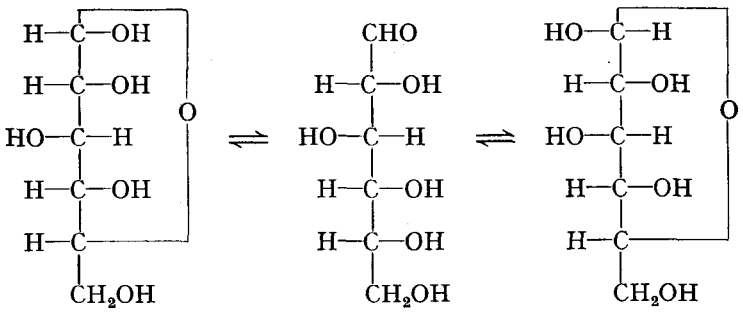
Mutarotation. When a monosaccharide is dissolved in water, the optical rotatory power of the solution gradually changes until it reaches a constant value. *E.g.*, a freshly prepared solution of glucose has a specific rotation of +110°; when this solution is allowed to stand, the specific rotation falls to +52·5°, and remains constant at this value. The final stage can be reached more rapidly either by heating the solution or by adding some catalyst which may be an acid or a base. This change in value of the specific rotation is known as **mutarotation.** All *reducing* sugars (except some ketoses) undergo mutarotation. To account for mutarotation, Tollens (1883) suggested an oxide ring structure for D(+)-glucose, whereby *two* forms would be produced, since, in the formation of the ring, another asymmetric carbon atom (which can exist in *two* configurations) is produced (*cf.* the Kiliani reaction). Tollens assumed that a five-membered ring (the γ-form) was produced (I) and (II). The difficulty of this suggestion was that there was no experimental evidence for the existence of these two forms. Tanret (1895), however, isolated two isomeric forms of D(+)-glucose, thus apparently verifying Tollens' supposition (see later). The two forms are called α- and β-D(+)-γ-glucose; (I) is the α-form, and (II) the β-.



(I) (II)

Ring formation of a sugar is really hemiacetal formation, one alcohol group of the sugar forming a hemiacetal with the aldehyde group of the *same* molecule, thus producing a ring structure which is known as the *lactol* form of the sugar. This equilibrium between the open and ring forms is an example of ring-chain tautomerism.

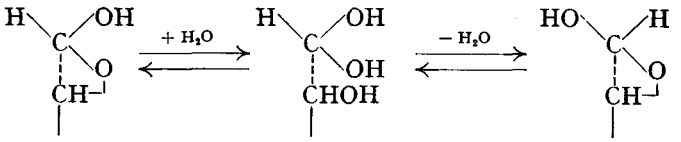
Later work by Haworth, Hirst and their co-workers (1926 onwards) has shown that glucose (and other sugars) exists, not as a five-membered ring, but as a six-membered ring, the two forms being α- and β-D(+)-δ-glucose:



α-D(+)-δ-glucose β-D(+)-δ-glucose

Mechanism of mutarotation. According to Lowry (1925), mutarotation is not possible without the presence of an amphiprotic solvent, *i.e.*, a solvent

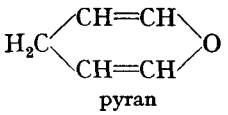
which can function both as an acid and a base, *e.g.*, water. It appears that when mutarotation takes place, the ring must open and then reclose in the inverted position or in the original position. Lowry suggested that in water the *aldehydrol* was formed as an intermediate product by a concerted mechanism (p. 222):



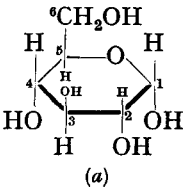
Lowry and Faulkner (1925) showed that mutarotation is arrested in pyridine solution (basic solvent) and in cresol solution (acidic solvent), but that it takes place in a mixture of pyridine and cresol.

The ordinary form of D(+)-glucose is the α-isomer, m.p. 146°, specific rotation +110°, and may be prepared by crystallisation of glucose from cold ethanol. The β-isomer, m.p. 148–150°, specific rotation +19·7°, may be obtained by crystallising glucose from hot pyridine. Both forms show mutarotation, the final value of the specific rotation being 52·56°. This corresponds to about 38 per cent. of the α-form and 62 per cent. of the β-. It is therefore assumed that whenever a sugar is formed in solution, it immediately changes into a mixture of the two isomeric forms, the open chain isomer being present in extremely small amount, if at all. The cyclic structure of the sugars accounts for the following facts: (i) the existence of two isomers, *e.g.*, α- and β-glucose; (ii) mutarotation; (iii) glucose and other aldoses do not give certain characteristic reactions of aldehydes, *e.g.*, Schiff's reaction, do not form a bisulphite or an aldehyde-ammonia compound. Recently, however, it has been shown that by preparing Schiff's reagent in a special way, it becomes very sensitive, simple aldoses restoring the pink colour to this solution; the monosaccharide aldoses react strongly, but the disaccharide aldoses react weakly (Tobie, 1942). This reaction with a sensitive Schiff's reagent appears to indicate that some, although a very small amount, of the open-chain form of a sugar is present in solution in equilibrium with the two ring forms.

Haworth (1926) proposed a six-membered ring formula (hexagonal formula) based on the *pyran* ring which is almost planar. The **pyranose** structure is applicable to nearly all the sugars, and is supported by X-ray



pyran

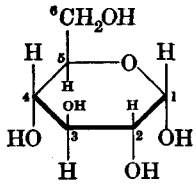


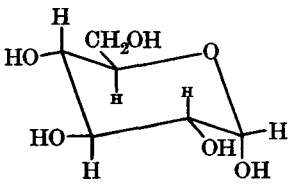
(*a*)

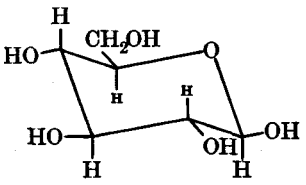
crystal analysis (of the sugars). Thus α-D(+)-δ-glucose is called α-D(+)-*glucopyranose*, and its perspective (*i.e.*, hexagonal) formula is (*a*).

Reeves (1950) has shown that the conformation of α-D(+)-glucopyranose is (*b*) and that of the β-form is (*c*). Both have the chair form, but in the former the glycosidic hydroxyl is axial and in the latter equatorial (see also p. 489).

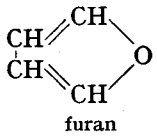
Furthermore, it has been shown (Irvine, Haworth *et al.*) that glucose, fructose, etc., can also exist as five-membered rings, which may be regarded as derivatives of *furan*. So far, the γ- or **furanose** sugars (corresponding to

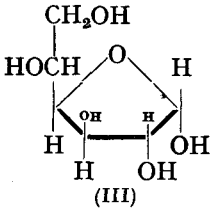

(a)

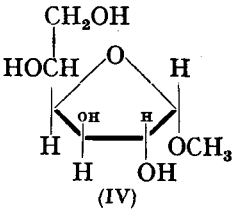

α-form (b)


β-form (c)

Tollens' suggestion) have not been isolated in the free state, but some of their derivatives have been prepared, *e.g.*, methyl α-D(+)-γ-glucoside (see below). Thus α-D(+)-γ-glucose or α-D(+)-glucofuranose would (if it existed) have perspective (*i.e.*, pentagonal) formula (III); methyl α-D(+)-γ-glucoside or methyl α-D(+)-glucofuranoside (a known compound) has formula (IV):

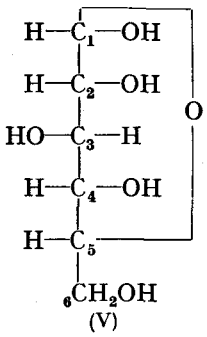

furan

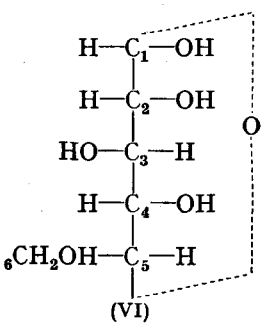

(III)

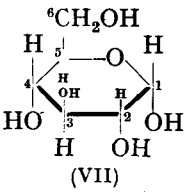

(IV)

Pentoses also normally exist in the pyranose form, and derivatives of the furanose form have been prepared.

Conversion of the plane-diagrams into the perspective formulæ may be done as follows. (V) is α-D-glucopyranose, and if the H on C_5 is interchanged with the group CH_2OH, then a Walden inversion has been effected;

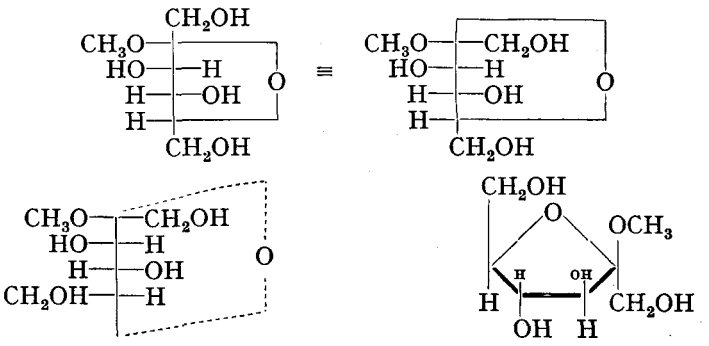

(V)


(VI)

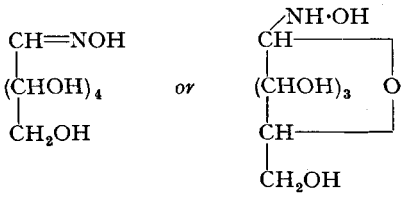

(VII)

and if the H is now interchanged with the point of attachment of the oxygen ring, another Walden inversion is effected, and so the original configuration of (V) is retained; thus we now have (VI) (with no change in configuration). Since all horizontal bonds indicate groups lying above the plane of the paper, and vertical bonds groups lying behind this plane (see p. 402), then by twisting (VI) so that the oxide ring is perpendicular to the plane of the paper, and placing the oxygen atom as shown, (VII) is obtained. Thus, to change from (VI) to (VII), first draw the hexagon (as shown in (VII)), and then place all the groups on the left-hand side in (VI) above the plane of the ring in (VII), and all those on the right-hand side in (VI) below the plane of the ring in (VII).

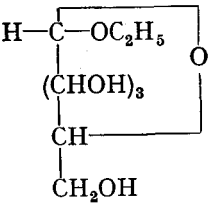
In a similar way, perspective formulæ may be obtained for the furanose sugars, *e.g.*, methyl β-D(+)-fructofuranoside.



There is a certain amount of evidence to show that oximes, phenylhydrazones and osazones exist in both the open-chain and cyclic forms; *e.g.*, the oxime of glucose may have either of the following structures (p. 442):



Just as simple hemiacetals react with another molecule of an alcohol to form acetals (p. 161), so can the hemiacetal form (lactol) of a sugar react with a molecule of an alcohol to form the acetal derivative, which is known under the generic name of **glycoside**; those of glucose are known as *glucosides*; of fructose, *fructosides*, etc. *E.g.*, ethyl α-D(+)-glucopyranoside, prepared by refluxing glucose in excess ethanol in the presence of a small amount of hydrochloric acid, is:

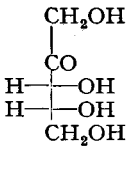


These glycosides are stable compounds, and do not undergo many of the reactions of the sugars, *e.g.*, they show no reducing properties, they do not mutarotate, etc. The non-sugar part of a glycoside is known as the *aglycon*, and in most of the glycosides which occur naturally the aglycon is a phenolic compound; *e.g.*, the aglycon in *salicin* is *salicyl alcohol*; in *indican*, *indoxyl*.

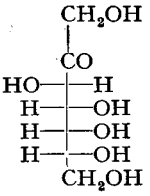
Synthesis of the monosaccharides. Plant cells convert carbon dioxide (of the atmosphere) into carbohydrates. Experimental work has shown that the oxygen evolved in this synthesis is provided by water, and so the overall equation may be written:

$$6CO_2 + 6H_2O \longrightarrow C_6H_{12}O_6 + 6O_2$$

This takes place in the presence of chlorophyll and sunlight, and the process is known as *photosynthesis*. Calvin *et al.* (1954) have shown that photosynthesis occurs via a complex series of reactions, and that two monosaccharides, ribulose and sedoheptulose, play an essential part in the photosynthesis of carbohydrates.



ribulose



sedoheptulose

In the laboratory, the sugars have been synthesised in various ways:

(i) By the aldol condensation (p. 157) of formaldehyde in the presence of calcium hydroxide; the product is a mixture of compounds among which is a number of hexoses. This hexose mixture, known as *formose*, has been shown to contain DL-fructose (Butlerow, 1861; Loew, 1886).

(ii) By the aldol condensation of glycolaldehyde in the presence of sodium hydroxide; the product is formose (E. Fischer, 1887):

$$3CH_2OH{\cdot}CHO \xrightarrow{NaOH} C_6H_{12}O_6$$

(iii) When oxidised with nitric acid or bromine-water, glycerol yields a product known as *glycerose*, which contains, among other things, glyceraldehyde and dihydroxyacetone. These, in the presence of barium hydroxide, are converted into a mixture of α- and β-*acrose* (E. Fischer, 1887); α-acrose is DL-fructose and β-acrose is DL-sorbose:

$$CH_2OH{\cdot}CHOH{\cdot}CHO + CH_2OH{\cdot}CO{\cdot}CH_2OH \longrightarrow CH_2OH{\cdot}CO{\cdot}(CHOH)_3{\cdot}CH_2OH$$

Starting with α-acrose, Fischer isolated DL-fructosazone (DL-glucosazone), and making use of reduction, oxidation and epimerisation, he converted DL-fructosazone into D(−)-fructose, D(+)-glucose, D(+)-mannose and other aldohexoses.

(iv) When hydrolysed with barium hydroxide solution, dibromoacraldehyde forms a mixture of α- and β-acrose (E. Fischer, 1887):

$$CH_2Br{\cdot}CHBr{\cdot}CHO \xrightarrow{Ba(OH)_2} CH_2OH{\cdot}CHOH{\cdot}CHO \xrightarrow{\text{dimerises}} CH_2OH{\cdot}CO{\cdot}(CHOH)_3{\cdot}CH_2OH$$

(v) When allowed to stand in a barium hydroxide solution containing a small amount of iodine, D(+)-glyceraldehyde is converted into a mixture of D(−)-fructose and D(+)-sorbose (H. Fischer and Baer, 1936). These authors believed that part of the glyceraldehyde rearranged to dihydroxyacetone (p. 257), which then condensed with unchanged glyceraldehyde to form the ketohexoses. They supported their belief by showing that the same products were obtained in a much shorter time when D(+)-glyceraldehyde and dihydroxyacetone were used as the starting materials.

(vi) By means of the Kiliani reaction, sugars up to a decose have been prepared.

Two ketoheptoses have been isolated from natural sources, *viz.*, *mannoheptulose* from the *Avocado pear*, and *altroheptulose* (*sedoheptulose*) from the leaves of *Sedum spectabile*.

(vii) A number of aldoses have been prepared by the oxidation of polyhydric alcohols, *e.g.*, mannitol, on oxidation with nitric acid, yields mannose.

Only three natural sugars are known which are not straight-chain compounds:

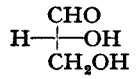
apiose $CH_2OH(CH_2OH)C{\cdot}CHOH{\cdot}CHO$

hamamelose $CH_2OH{\cdot}(CHOH)_2{\cdot}C(OH)(CH_2OH)(CHO)$

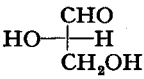
The third sugar, (−)-cordycepose (isolated from a glycoside in 1951), has been shown to be 3-deoxyapiose, $(CH_2OH)_2{\cdot}CH{\cdot}CHOH{\cdot}CHO$. This and D(+)-apiose have been synthesised by Raphael *et al.* (1955).

Configuration of the Monosaccharides

Aldotrioses. Glyceraldehyde is the only aldotriose, and has been chosen as arbitrary standard (p. 401).

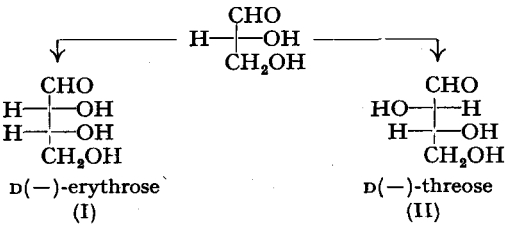


D(+)-glyceraldehyde



L(−)-glyceraldehyde

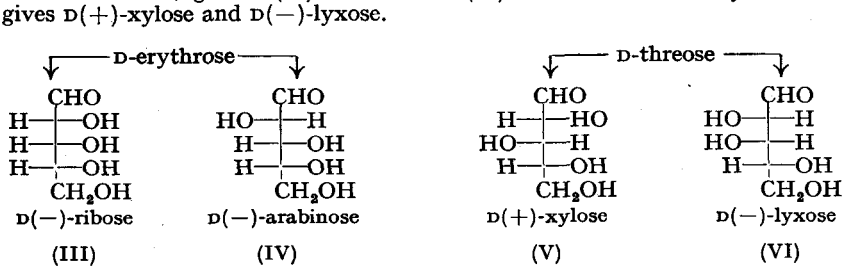
Aldotetroses, $CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$. This structure contains two asymmetric carbon atoms, and so there are four optical isomers (two pairs of enantiomorphs). All are known, and correspond to D- and L-threose and D- and L-erythrose. D(+)-Glyceraldehyde may be stepped up by the Kiliani reaction to give D(−)-threose and D(−)-erythrose. The question now is: which is which?



On oxidation, D-erythrose forms *meso*tartaric acid. Therefore D-erythrose must be (I), and consequently (II) must be D-threose.

The tetroses are synthetic compounds.

Aldopentoses, $CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$. This structure contains three asymmetric carbon atoms, and so there are eight optical isomers (four pairs of enantiomorphs). All are known. D-Erythrose, when stepped up by the Kiliani reaction, gives D(−)-ribose and D(−)-arabinose. Similarly, D-threose gives D(+)-xylose and D(−)-lyxose.

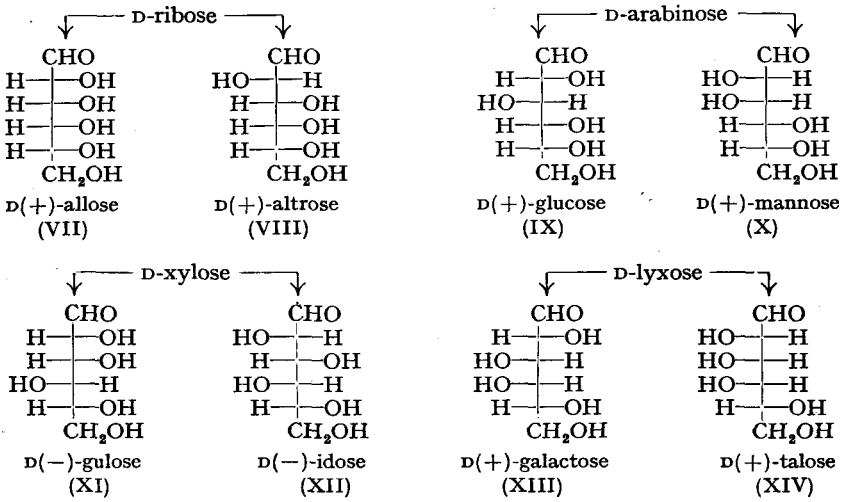


(III) and (IV) must be ribose and arabinose, but which is which? On oxidation with nitric acid, arabinose gives an optically active dicarboxylic acid (a trihydroxyglutaric acid), whereas ribose gives an optically inactive dicarboxylic acid. When the terminal groups (*i.e.*, CHO and CH_2OH) of (III) are oxidised to carboxyl

groups, the molecule produced possesses a plane of symmetry, and so this acid is inactive. The dicarboxylic acid produced from (IV), however, has no plane (or any other element) of symmetry, and so is optically active. Thus (III) is D-ribose and (IV) is D-arabinose.

(V) and (VI) must be xylose and lyxose, but which is which? The former, on oxidation, gives an optically inactive dicarboxylic acid, whereas the latter gives an optically active dicarboxylic acid. Therefore (V) is D-xylose and (VI) is D-lyxose.

Aldohexoses, $CH_2OH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHO$. This structure contains four asymmetric carbon atoms, and so there are sixteen optical isomers (eight pairs of enantiomorphs). All are known, and may be prepared by stepping up the aldopentoses: D-ribose gives D(+)-allose and D(+)-altrose; D-arabinose gives D(+)-glucose and D(+)-mannose; D-xylose gives D(−)-gulose and D(−)-idose, and D-lyxose gives D(+)-galactose and D(+)-talose.

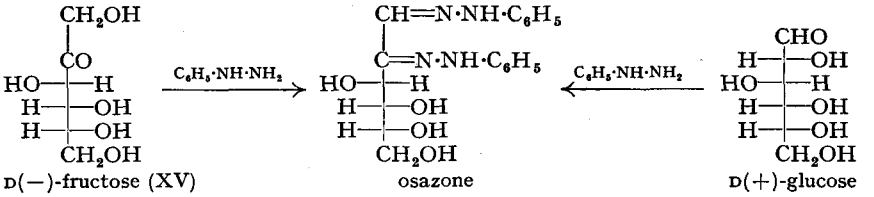


(VII) and (VIII) must be allose and altrose, but which is which? On oxidation with nitric acid, the former gives an optically inactive (allomucic) and the latter an optically active (talomucic) dicarboxylic acid. Therefore (VII) is allose and (VIII) is altrose.

(XIII) and (XIV) must be galactose and talose, but which is which? On oxidation with nitric acid, the former gives an optically inactive (mucic) and the latter an optically active (talomucic) dicarboxylic acid. Therefore (XIII) is galactose and (XIV) is talose.

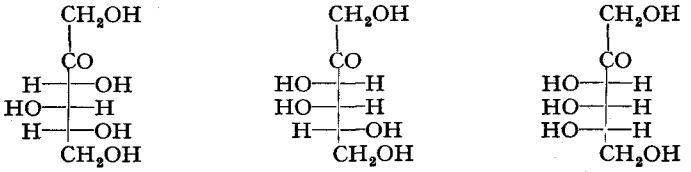
The elucidation of the configurations of the remaining four aldohexoses is not quite so simple, since, on oxidation with nitric acid, glucose and mannose *both* give optically active dicarboxylic acids, as also do gulose and idose; in all four configurations (IX, X, XI, XII), replacement of the two terminal groups (CHO and CH_2OH) by carboxyl groups leads to dicarboxylic acid whose structures have no plane (or any other element) of symmetry. It has been found, however, that the dicarboxylic acid from glucose (saccharic acid) is the same as that produced from gulose. Actually the two saccharic acids obtained are enantiomorphs, D-glucose giving D-saccharic acid and D-gulose L-saccharic acid. Since saccharic acid, $CO_2H{\cdot}(CHOH)_4{\cdot}CO_2H$, is produced by the oxidation of the terminal groups with the rest of the molecule unaffected, it therefore follows that the "rest of the molecule" must be the same for both glucose and gulose. Inspection of formulæ (IX, X, XI and XII) shows that only (IX) and (XI) have the "rest of the molecule" the same; by interchanging the CHO and CH_2OH groups of (IX), (XI) is obtained. Therefore (IX) must be glucose (since we know that glucose is obtained from arabinose), and (XI) must be gulose. Consequently (X) is mannose and (XII) is idose.

Ketohexoses. Fructose is a ketohexose, and natural fructose is lævorotatory. Since D-glucose gives the *same* osazone as natural fructose, the latter must be D(−)-fructose. Furthermore, since osazone formation involves only the first two carbon atoms in a sugar, it therefore follows that the configuration of the rest of the molecule in glucose and fructose must be the same. Hence the configuration of D(−)-fructose is (XV).



D(−)-fructose (XV) osazone D(+)-glucose

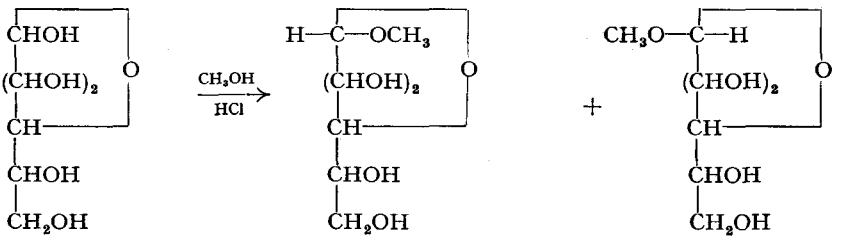
The configurations of the other ketohexoses are:



D(+)-sorbose D(+)-tagatose L(−)-psicose

Determination of the Size of Sugar-rings

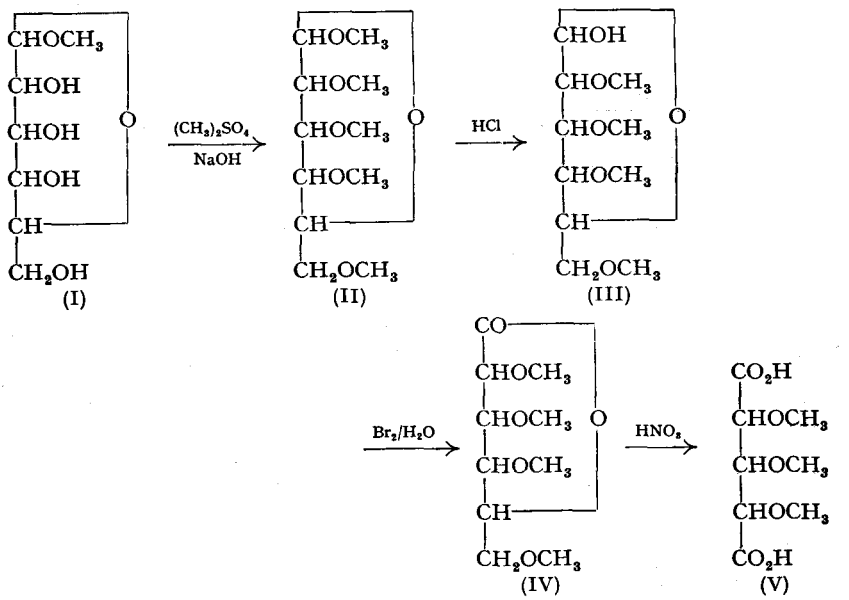
E. Fischer (1893) refluxed glucose with excess methanol in the presence of a small amount of hydrochloric acid and obtained a white crystalline solid containing *one* methyl group. This compound was no longer reducing, and also did not form an osazone. Thus Fischer had prepared methyl glucoside. Ekenstein (1894) isolated a second isomer from the same reaction, and Fischer explained the existence of these two isomers by suggesting a *ring* structure for them, and followed Tollens in believing that they were five-membered rings.



D-glucose methyl α-D-glucofuranoside + methyl β-D-glucofuranoside

There was no experimental evidence for the existence of a five-membered ring, and it was shown to be incorrect by Haworth, Hirst and their co-workers (1926 onwards). They proved that the above glucosides were *six-membered* rings, *i.e.*, glucopyranosides. Their method was to fully methylate the glucoside (I), hydrolyse the product, methyl tetramethyl-α-D-glucoside (II) to tetramethyl-α-D-glucose (III), oxidise this with bromine-water at 90° to the lactone (IV), and then to oxidise this with nitric acid. The product obtained was shown to be xylotrimethoxyglutaric acid (V; this can be obtained directly by the oxidation of methylated xylose). The most reasonable interpretation of these results is in

accordance with the assumption that methyl glucoside is a six- and *not* a five-membered ring. Thus:



Fischer (1914) also prepared methyl glucoside by dissolving glucose in methanol and letting it stand at *room temperature* in the presence of hydrochloric acid. He now obtained compounds which Haworth *et al.*, using the above method, showed to be *five*-membered rings, *i.e.*, methyl D-glucofuranosides.

Hudson (1937, 1939) has also determined the size of sugar-rings, but his method was to oxidise methyl glycosides with periodic acid. As we have seen (p. 73), periodic acid splits 1 : 2-glycols, and *one molecule of acid* is used for *each pair of adjacent alcoholic groups, e.g.*,

$$R{\cdot}CHOH{\cdot}CHOH{\cdot}R' \xrightarrow{1HIO_4} R{\cdot}CHO + R'{\cdot}CHO$$

$$R{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}R' \xrightarrow{2HIO_4} R{\cdot}CHO + H{\cdot}CO_2H + R'{\cdot}CHO$$

Compounds containing an aldehyde or ketonic group adjacent to an alcoholic group are also attacked by periodic acid in a similar manner to glycols:

$$R{\cdot}CHOH{\cdot}CHO \xrightarrow{1HIO_4} R{\cdot}CHO + H{\cdot}CO_2H$$

$$R{\cdot}CO{\cdot}CHOH{\cdot}R' \xrightarrow{1HIO_4} R{\cdot}CO_2H + R'{\cdot}CHO$$

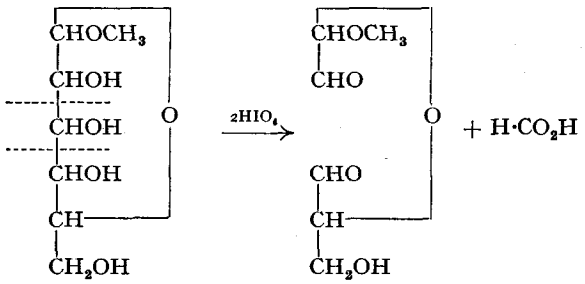
Thus an aldopentose, if it had an *open-chain* structure, would require *four* molecules of periodic acid, and the products would be four molecules of formic acid and one molecule of formaldehyde (from the terminal CH_2OH group).

$$CHO{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CH_2OH \xrightarrow{4HIO_4} 4H{\cdot}CO_2H + CH_2O$$

Thus estimating the periodic acid used and the formic acid and/or formaldehyde produced will indicate the number, in pairs, of *free* oxidisable groups (CHOH, CHO or CO).

Oxidation of methyl glucoside (produced under reflux conditions; see above)

uses *two* molecules of periodic acid and produces *one* molecule of formic acid. Only one structure fits these facts, namely, a *six-membered* ring.



The other product of the oxidation has also been isolated and characterised by Hudson. It should be noted that the successful application of this method depends on the fact that the oxide ring in glycosides is stable during the oxidation.

Since methylation of sugars under different conditions produces different sized rings, the question is: what is the size of the ring in the original sugar? Various sources of evidence, *e.g.*, X-ray analysis, show that the normal sugars are *pyranoses*.

One other point will be mentioned here, and that is the configuration of the *first* carbon atom. When the open-chain structure is closed to form the ring, two configurations of the new asymmetric carbon atom are possible, the one with the hydrogen to the left (the α-form), and the one with the hydrogen to the right (the β-). This is an *arbitrary* arrangement, but in recent years it has been shown quite conclusively that the α- and β-forms actually have the configurations originally arbitrarily assigned to them, *e.g.*, X-ray analysis of α-D-glucose has shown that the 1 : 2-hydroxyl groups are in the *cis*-position (McDonald *et al.*, 1950).

Disaccharides

All the disaccharides are crystalline solids, soluble in water, and fall into two classes, the *reducing* sugars and the *non-reducing* sugars.

Just as methanol forms methylglycosides with the monosaccharides, so can other hydroxy-compounds form similar unions with the monosaccharides. Since the latter are themselves hydroxy-compounds, it is possible that they can link up with themselves to form acetals, *i.e.*, glycosides in which the aglycon is another sugar molecule. Actually, three such compounds occur in nature: *sucrose*, *maltose* and *lactose*.

Sucrose, cane-sugar, $C_{11}H_{22}O_{11}$, is one of the most important compounds commercially, and is obtained from the sugar-cane and sugar-beet. Sugar-cane is cut into small pieces, crushed, and the juice pressed out. The juice is warmed and run into settling tanks; it is then decanted from the sediment and made alkaline with calcium hydroxide, whereupon some impurities are precipitated. The liquid is now steamed to coagulate protein matter, allowed to settle, and the clear juice concentrated to a syrup by evaporation under reduced pressure. The syrup is allowed to cool; some crystallises (about 65 per cent.), and the rest remains as a thick solution. The crystalline material is collected by centrifuging, and the thick liquid, which is known as *molasses*, will not crystallise.

The sugar so obtained is brown, and has an unpleasant odour. It is dissolved in water, the solution decolorised with animal charcoal or with norit (coconut charcoal), filtered, concentrated under reduced pressure, and allowed to crystallise.

If it is desired to recover the sugar from molasses, the latter may be mixed with a fresh lot of syrup or treated chemically. Chemical treatment consists in diluting the molasses with water and adding calcium hydroxide with vigorous agitation, whereupon calcium saccharate, $C_{12}H_{22}O_{11}\cdot 3CaO$, is precipitated. This is collected by filtration, suspended in water, and decomposed by passing in carbon dioxide. The precipitated calcium carbonate is removed by filtration and the filtrate is evaporated, etc. (see above).

The sugar-beet is sliced, extracted with hot water, the solution agitated with calcium hydroxide and carbon dioxide blown in. The calcium carbonate, which is precipitated, carries down with it nearly all the impurities. The liquid is filtered and the filtrate evaporated, etc.

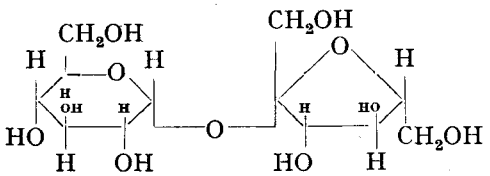
Sucrose is a white crystalline solid, m.p. 180°, soluble in water. When heated above its melting point, it forms a brown substance known as caramel. Concentrated sulphuric acid chars sucrose, the product being almost pure carbon. Sucrose is dextrorotatory, its specific rotation being +66·5°. On hydrolysis with dilute acids sucrose yields an equimolecular mixture of D(+)-glucose and D(−)-fructose:

$$C_{12}H_{22}O_{11} + H_2O \xrightarrow{HCl} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

Since D(−)-fructose has a greater specific rotation than D(+)-glucose, the resulting mixture is lævorotatory. Because of this, the hydrolysis of cane-sugar is known as *the inversion of cane-sugar* (this is not to be confused with the *Walden inversion*), and the mixture is known as *invert sugar*. The inversion (*i.e.*, hydrolysis) of cane-sugar may also be effected by the enzyme *invertase* which is found in yeast.

Controlled oxidation of sucrose in alkaline solution with air gives D-arabonic acid. Oxidation of sucrose with nitric acid under different conditions gives either oxalic acid (80 per cent.), tartaric acid (40 per cent.), or saccharic acid (30 per cent.). Hydrogenation of sucrose under controlled conditions gives a mixture of mannitol and sorbitol (these may be separated by fractional crystallisation).

Sucrose is *not* a reducing sugar, *e.g.*, it will not reduce Fehling's solution; it does not form an oxime or an osazone, and does not undergo mutarotation. This indicates that neither the aldehyde group of glucose nor the ketonic group of fructose is free in sucrose. Thus a tentative structure of sucrose is one in which the two molecules, glucose and fructose, are linked by the aldehyde group of the former and ketonic group of the latter. This has been amply confirmed by further work, and the structure of sucrose has been shown to be:

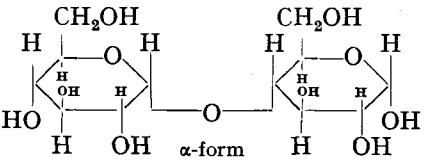


It should be noted that the fructose molecule in sucrose exists as the γ-form, and that when sucrose is hydrolysed, it is the δ-form of fructose which is isolated.

Maltose (*malt-sugar*), $C_{12}H_{22}O_{11}$, is produced by the action of malt (which contains the enzyme *diastase*) on starch:

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

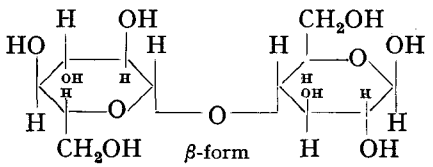
Maltose is a white crystalline solid, m.p. 160–165°, soluble in water, and is dextrorotatory. When it is hydrolysed with dilute acids or by the enzyme *maltase*, maltose yields two molecules of D(+)-glucose. Maltose is a reducing sugar, *e.g.*, it reduces Fehling's solution; it forms an oxime and an osazone, and undergoes mutarotation. This indicates that at least one aldehyde group (of the two glucose molecules) is free in maltose. Further work has shown that the structure of maltose is:



The hemiacetal link of one glucose molecule (the reducing half) is unchanged, but that of the other (the non-reducing half) has been converted into the acetal link.

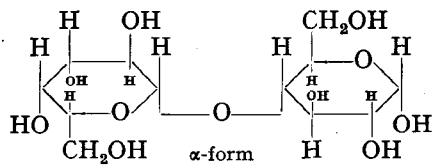
Cellobiose, $C_{12}H_{22}O_{11}$, may be obtained from cellulose by acetylating good filter paper (which is almost pure cellulose) with acetic anhydride in the presence of concentrated sulphuric acid. The octa-acetate of cellobiose so obtained is saponified with potassium hydroxide or with sodium ethoxide, whereupon cellobiose is produced.

Cellobiose is a white crystalline solid, m.p. 225°, soluble in water, and dextrorotatory. When hydrolysed with dilute acids or by the enzyme *emulsin*, it yields two molecules of D(+)-glucose. It is a reducing sugar, forms an oxime and osazone, and undergoes mutarotation. Its structure has been shown to be:



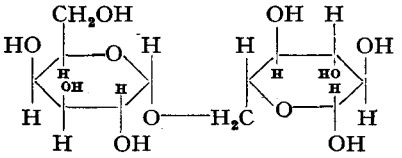
Lactose (*milk-sugar*), $C_{12}H_{22}O_{11}$, occurs in the milk of all animals, and is prepared commercially from whey by evaporation to crystallisation; whey is obtained as a by-product in the manufacture of cheese.

Lactose is a white crystalline solid, m.p. 203° (with decomposition), soluble in water, and is dextrorotatory. It is hydrolysed by dilute acids or by the enzyme *lactase*, to an equimolecular mixture of D(+)-glucose and D(+)-galactose. Lactose is a reducing sugar, forms an oxime and osazone, and undergoes mutarotation. Its structure has been shown to be:

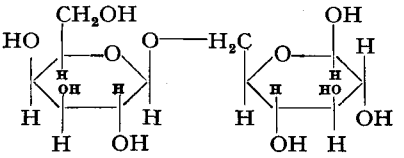


Sucrose, maltose and lactose are three disaccharides which occur naturally. Cellobiose may be prepared from cellulose. Two other disaccharides which have been prepared are **melibiose** (from the trisaccharide *raffinose*), and **gentiobiose** (from the trisaccharide *gentianose*). These differ from the other disaccharides in

that the two monosaccharide molecules are linked by the *sixth* carbon atom (the aldehyde carbon atom being number one) of the reducing monosaccharide:



melibiose (β-form)



gentiobiose (β-form)

Polysaccharides

The polysaccharides are high polymers of the monomeric sugars and are analogous to the synthetic long-chain polymers.

Inulin occurs in many plants, *e.g.*, in the roots of the dandelion, in the tubers of the dahlia and in certain lichens. It is a white powder, insoluble in cold water, and in hot water forms a colloidal solution which does not form a gel on cooling. Inulin solutions do not give any colour with iodine. Inulin is hydrolysed by dilute acids to D(−)-fructose, and therefore the structure of inulin is based on the fructose unit. The empirical formula of inulin is usually given as $(C_6H_{10}O_5)_n$, but more accurately, it is $(C_6H_{10}O_5)_n \cdot H_2O$, since in the formation of inulin n-1 molecules of water are eliminated from n-molecules of fructose. Molecular-weight determinations (by chemical methods) appear to indicate the value of 5000 (about 30 units).

Starch, $(C_6H_{10}O_5)_n$, occurs in all green plants; the commercial sources of starch are maize, wheat, barley, rice, potatoes, and sorghum. The plant cells are broken down by grinding and washing with water; the extract is passed over fine sieves, the starch granules passing through and the other materials being retained. The starch granules are collected and dried with hot air, the product now containing about 20 per cent. water.

Starch consists of two fractions, one being known as α-**amylose** (the " A " fraction), and the other as β-**amylose** or **amylopectin** (the " B " fraction); the former comprises 10–20 per cent. of starch, and the latter 80–90 per cent. α-Amylose is soluble in water, and the solution gives a blue colour with iodine. An aqueous solution of α-amylose slowly forms a precipitate, since α-amylose has a strong tendency to " revert " to the insoluble state in solution. Amylopectin is insoluble in water, is stable in contact with water, and gives a violet colour with iodine. α-Amylose and amylopectin are both hydrolysed to maltose by the enzyme diastase, and to D(+)-glucose by dilute acids (amylopectin gives about 50 per cent. of maltose).

The determination of the molecular weight of α-amylose by means of osmotic pressure measurements gives a value of 10,000–50,000; the molecular weight of amylopectin (by osmotic pressure measurements) is 50,000–100,000 (see also cellulose, below). The structures of α-amylose and amylopectin are not known with certainty, but the work done so far appears to indicate that α-amylose consists mainly of linear chains, and that amylopectin contains branched chains. Furthermore, the glucose units exist mainly in the α-form in starch.

The **dextrins,** $(C_6H_{10}O_5)_n$, are produced by the partial hydrolysis of starch by boiling with water under pressure at about 250°. They are white powders, and are used for making adhesives and confectionery, for sizing paper, etc.

Glycogen, $(C_6H_{10}O_5)_n$, is found in nearly all animal cells, occurring mainly in the liver; it is the reserve carbohydrate of animals, and so is often known as " *animal starch* ". It has also been isolated from plant sources (Hassid and McCready, 1941).

Glycogen is a white powder, soluble in water, the solution giving a purplish-red colour with iodine. On hydrolysis with dilute acid, glycogen gives D(+)-glucose. The molecular weight of glycogen has been given as 500,000–800,000, and it appears that glycogen contains highly branched chains.

Pectins are found in plant and fruit juices. Their characteristic property is the ability of their solutions to gelate, *i.e.*, form jellies. They have a high molecular weight, and appear to be polygalacturonic acids with the carboxyl groups partially esterified with methanol.

Cellulose, $(C_6H_{10}O_5)_n$, is the main constituent of the cell-wall of plants; it is the most widely distributed organic compound. Recently it has been found to occur in certain animal tissues.

The main source of cellulose is cotton and wood. Cotton is almost pure cellulose, but wood also contains *lignin*, which is not a polysaccharide. Lignin is separated from cellulose by digesting wood chips at 130–150° with an aqueous solution containing calcium and magnesium hydrogen sulphites; the lignin is soluble. This method of preparing cellulose is known as the *sulphite process*. Another method, the "*sulphate process*", consists in digesting wood with a solution of sodium hydroxide, sodium sulphide and sulphur; again only the lignin is soluble.

The **hemicelluloses** comprise a group of polysaccharides which also occur as the constituent of the cell-wall of plants. Many hemicelluloses give glucose, mannose and galactose on hydrolysis.

Cellulose is a white solid, insoluble in water but soluble in ammoniacal copper hydroxide solution (*Schweitzer's reagent*). Careful hydrolysis of cellulose gives cellobiose; it is also possible to isolate *cellotriose* (trisaccharide) and *cellotetrose* (tetrasaccharide). All of these saccharides, on further hydrolysis, yield only D(+)-glucose which exists in the β-form in cellulose (*cf.* starch).

Molecular-weight determinations of cellulose give different values according to the method used, *e.g.*, chemical methods give a value of 20,000–40,000; viscosity method, 150,000–200,000; and by means of the ultracentrifuge, 300,000–500,000. Of all the methods for measuring the molecular weight of large molecules (including the method of osmotic pressure), probably that by the ultracentrifuge is the most reliable. In any case, the value of n in $(C_6H_{10}O_5)_n$ is uncertain for all the polysaccharides.

Artificial silk. The term **rayon** is used collectively to cover all synthetic or manufactured fibres from cellulose, but it is usually most often applied to viscose yarns. There are four processes for obtaining synthetic fibres from cellulose; cellulose nitrate, cellulose acetate, cuprammonium and viscose processes. The cellulose for these purposes is best obtained from wood-pulp and cotton-linters; other sources give rise to inferior yarns.

Cellulose nitrates (*nitrocellulose*). When treated with a mixture of concentrated nitric and sulphuric acids, cellulose is converted into its highest nitrate ester, the trinitrate (each glucose unit in cellulose has three free hydroxyl groups). Cellulose trinitrate is known as *gun-cotton*; it is insoluble in a mixture of ethanol and ether, is explosive, and is used in the manufacture of smokeless powders.

By using a diluted mixture of nitric and sulphuric acid, the lower nitrates of cellulose, the mono- and di-nitrates, are obtained. These lower nitrates, in the *solid* state, are known as **pyroxylin.** Pyroxylin is soluble in a mixture of ethanol and ether, the solution being known as **colloidon.** When heated with ethanol and camphor or camphor substitutes, pyroxylin is converted into **celluloid.**

The oldest method—the *Chardonnet process*—of preparing artificial silk involves the use of cellulose nitrate (pyroxylin) in one of its stages. The pyroxylin is dissolved in a mixture of ethanol and ether to give collodion, which is then forced through glass capillary tubes into the air, whereupon the solvent evaporates, leaving filaments of cellulose nitrate. These filaments are digested

with sodium hydroxide or sodium hydrogen sulphate solutions to " denitrate " the cellulose nitrate to cellulose. This process of preparing artificial silk is expensive due to the high cost of the chemicals.

Cellulose acetate (*celanese silk*). When acetylated with acetic anhydride in the presence of sulphuric acid, cellulose is converted into cellulose triacetate. When the reaction is complete, water is added to decompose the triacetate into the diacetate (approximately). The diacetate is washed, dried, and dissolved in a mixture of organic solvents (of which acetone is generally the main constituent). The solution is then forced through a spinneret into a warm chamber, whereupon the solvent evaporates leaving behind fine threads of cellulose acetate.

Cellulose acetate silk burns with difficulty, but is expensive. Cellulose acetate is also used for making non-inflammable photographic and motion-picture films, non-shatterable glass, lacquers and varnishes.

Esters other than the acetate are also used for the above purposes, *e.g.*, cellulose formate, propionate and butyrate.

Cuprammonium process (*cupra silk*). In the cuprammonium process, cellulose is dissolved in ammoniacal copper hydroxide solution, which is then forced through a spinneret into a sulphuric acid bath, whereupon cellulose is precipitated as fine threads. Cupra silk has the very big advantage of being cheap.

Viscose rayon. In the viscose process, cellulose is digested with sodium hydroxide solution, and then carbon disulphide is passed into the solution. A mixture of sodium cellulose xanthates, soluble in sodium hydroxide, is formed (*cf.* p. 341): R = cellulose:

$$R{-}OH + CS_2 + NaOH \longrightarrow S{=}C\begin{matrix}OR\\SNa\end{matrix} + H_2O$$

This alkaline solution has a high viscosity, and hence the silk obtained by this process was named *viscose* rayon. The viscose solution is forced through a spinneret into a sulphuric acid bath, whereupon cellulose is precipitated as fine threads. Of all artificial silks, viscose rayon is produced in the largest quantity.

Cellophane is made by extruding a viscose solution through a long narrow slit into an acid bath, whereupon cellulose is precipitated as very thin sheets. These sheets are made moisture-proof by coating with a transparent nitrocellulose lacquer.

Some cellulose ethers, particularly the ethyl ether, are used in the manufacture of plastics.

When agitated with about 20 per cent. aqueous sodium hydroxide, cellulose swells; apparently cellulose combines with the sodium hydroxide to form a sodiocellulose. This is unstable, and is readily decomposed into cellulose by the addition of water, but the cellulose has a number of its physical properties changed, *e.g.*, it absorbs dyes more readily than untreated cellulose. This " reactive " form of cellulose is known as *mercerised cellulose*.

Cellulose may be oxidised by nitrogen dioxide to give a product which retains its original form and much of the original tensile strength. It appears that about half of the CH_2OH groups (alternately) are oxidised to carboxyl, thereby giving a compound readily soluble in sodium hydroxide. This oxidised cellulose is useful in medicine, *e.g.*, it possesses hæmostatic properties, and is useful as sterile gauze.

QUESTIONS

1. What are the carbohydrates and how are they classified?
2. Outline the evidence for the structural formulæ of:—(*a*) the aldopentoses, (*b*) the ketohexoses, (*d*) sucrose, (*e*) maltose, (*f*) lactose.
3. Name the compounds and state the conditions under which they are formed when glucose, fructose, sucrose and maltose, respectively, are treated with:—(*a*) Tollens' reagent, (*b*) Fehling's solution, (*c*) NaOH, (*d*) HCN, (*e*) $NH_2{\cdot}OH$, (*f*) $C_6H_5{\cdot}NH{\cdot}NH_2$, (*g*) oxidising agents, (*h*) reducing agents, (*i*) HCl, (*j*) $Ca(OH)_2$, (*k*) EtOH, (*l*) Me_2CO, (*m*) Ac_2O, (*n*) MeI, (*o*) Me_2SO_4, (*p*) micro-organisms, (*q*) enzymes.
4. How are the following compounds prepared commercially:—(*a*) D(+)-glucose, (*b*) D(+)-mannose, (*c*) D(+)-galactose, (*d*) D(−)-fructose, (*e*) D(−)-arabinose, (*f*) sucrose, (*g*) maltose, (*h*) lactose, (*i*) inulin, (*j*) starch, (*k*) cellulose?

5. Write an account of:—(*a*) the methods of descending and ascending the sugar series, (*b*) the conversion of an aldose into a ketose and vice versa, (*c*) the synthesis of the sugars.

6. Show, by means of equations, how you would convert D(+)-glucose into:—(*a*) D(+)-mannose, (*b*) D(−)-arabinose, (*c*) mannitol, (*d*) methylglucoside, (*e*) ethylfructoside.

7. Write an account of:—(*a*) mutarotation, (*b*) the pyranose structure of the sugars, (*c*) the furanose structure of the sugars, (*d*) the configuration of the sugars.

8. Define and give examples of:—(*a*) the Amadori rearrangement, (*b*) epimerisation, (*c*) the Kiliani reaction, (*d*) Wohl's method, (*e*) Zemplen's method, (*f*) Ruff's method, (*g*) Weerman's reaction, (*h*) the Lobry de Bruyn–van Ekenstein rearrangement, (*i*) glycoside, (*j*) the inversion of cane-sugar, (*k*) an enzyme.

9. Discuss the methods of determining the molecular weight of macromolecules.

10. Write an account of the chemistry involved in the utilisation of cellulose in industry.

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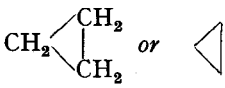
CHAPTER XIX

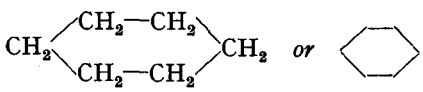
ALICYCLIC COMPOUNDS

THERE is a large number of compounds which contain closed rings comprised of carbon atoms only. These compounds are known collectively as **carbocyclic** or **homocyclic** compounds. In this group falls a class of compounds which resemble the aliphatic compounds in many ways, and hence they are often called **alicyclic** compounds (*ali*phatic *cyclic* compounds). The saturated alicyclic hydrocarbons have the general formula C_nH_{2n} (the same as that of the olefins); they do not contain a double bond but possess a ring structure.

Nomenclature. Since the saturated alicyclic hydrocarbons contain a number of methylene groups joined together to form a ring, they are known as the **polymethylenes,** the number of carbon atoms in the ring being indicated by a Greek or Latin prefix, *e.g.*,

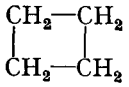


trimethylene

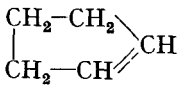


hexamethylene

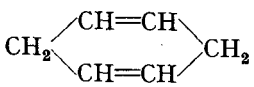
According to the I.U.P.A.C. system, the saturated monocyclic hydrocarbons take the names of the corresponding open-chain saturated hydrocarbons, preceded by the prefix *cyclo-*, and they are known collectively as the *cyclo*paraffins or *cyclo*alkanes, and if the alicyclic hydrocarbon is unsaturated, the rules applied to the olefins are used, *e.g.*,



*cyclo*butane

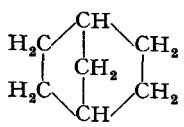


*cyclo*pentene

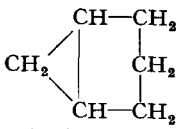


*cyclo*hexa-1 : 4-diene

In addition to the simple monocyclic compounds, there are more complicated compounds with bridges linked across the ring, *e.g.*,

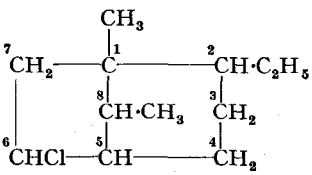


bicyclo-[2.2.1]-heptane



bicyclo-[3.1.0]-hexane

According to the I.U.P.A.C. system, saturated alicyclic hydrocarbons consisting of two rings only and having two or more atoms in common, take the prefix *bicyclo* followed by the name of the open-chain hydrocarbon *containing the same total number of carbon atoms.* The number of carbon atoms in each of the three bridges connecting the two tertiary carbon atoms is indicated in brackets in descending order. Numbering begins with one of the bridgeheads and proceeds by the longest possible path to the second bridgehead; numbering is then continued from this atom by the longer unnumbered path back to the first bridgehead and is completed by the shortest path, *e.g.*,



6-chloro-2-ethyl-1 : 8-dimethyl-
bicyclo-[3.2.1]-octane

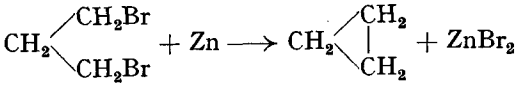
N.B. A bridged system is considered to have a number of rings equal to the number of scissions required to convert the system into an acyclic compound.

*CYCLO*ALKANES AND *CYCLO*ALKENES

Five- and six-membered *cyclo*paraffins occur in petroleum (the *naphthenes*; see p. 56); three-, four- and five-membered rings occur in terpenes, the most important class of alicyclic compounds. Many cyclic acids also occur in petroleum; these are known as the *naphthenic acids* and are mainly *cyclo*pentane derivatives. Some *cyclo*pentene derivatives of the fatty acids occur naturally, and are important in medicine.

General methods of preparation of alicyclic compounds. It is interesting to note that up to about 1880, organic chemists thought that there were only two classes of compounds, aliphatic and aromatic; *e.g.*, V. Meyer (1876) believed that rings smaller than six carbon atoms were never likely to be obtained. Since 1882, however, many methods have been introduced to prepare various sized rings. The following methods are typical.

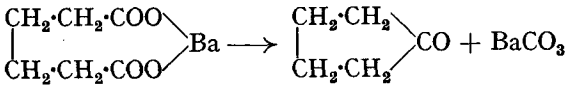
1. When αω-dihalogen derivatives of the paraffins are treated with sodium or zinc, the corresponding *cyclo*paraffin is formed (Freund, 1882), *e.g.*, 1 : 3-dibromopropane forms *cyclo*propane:



This method is really an extension of the Wurtz reaction and may be regarded as an *internal* Wurtz reaction.

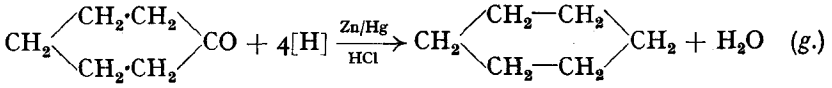
αω-Dihalogen derivatives of the paraffins in which the two halogen atoms are further apart than the 1 : 6 positions, do not form ring compounds but undergo the Wurtz reaction (at each end) to form long-chain paraffins; *e.g.*, decamethylene bromide, $Br{\cdot}(CH_2)_{10}{\cdot}Br$, in ether, reacts with sodium to form *normal* paraffins C_{20}, C_{30}, C_{40}, C_{50}, C_{60}, C_{70}, and higher members (Carothers, 1930).

2. When the calcium or barium salt of a dicarboxylic acid is distilled, a cyclic ketone is formed (Wislicenus, 1893), *e.g.*, barium adipate gives *cyclo*pentanone:



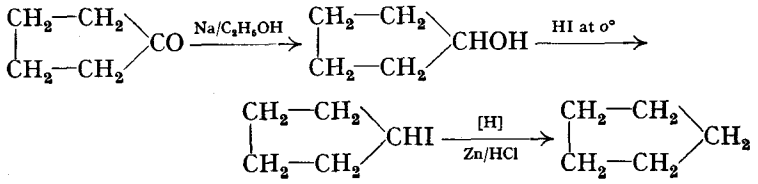
Actually, the slow distillation of adipic acid gives *cyclo*pentanone.

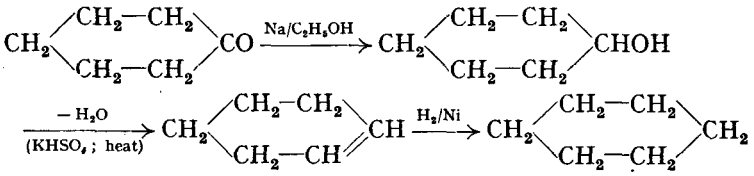
Cyclic ketones may readily be converted into the corresponding *cyclo*paraffins by means of the Clemmensen reduction, *e.g.*,



Alternatively, the conversion may be effected by either of the following two methods:

(i)



(ii) 

3. Six-membered alicyclic compounds may very conveniently be prepared by the reduction of benzene and its derivatives. Catalytic reduction under pressure using nickel is the most satisfactory, *e.g.*, phenol is almost quantitatively converted into *cyclo*hexanol:

$$C_6H_5OH + 3H_2 \xrightarrow[200^\circ]{NI} C_6H_{11}OH$$

Reduction may also be carried out at room temperature and at atmospheric pressure by using Adams' platinum catalyst (see p. 65).

4. Various alicyclic compounds may be prepared by the condensation between certain dihalogen derivatives of the paraffins and sodiomalonic ester or sodioacetoacetic ester (Perkin junior, 1883), *e.g.*,

(i) Ethylene bromide condenses with *one* molecule of malonic ester in the presence of *two* molecules of sodium ethoxide to form *cyclo*propane-1 : 1-dicarboxylic ester. This reaction may be formulated (see p. 232):

$$CH_2(CO_2C_2H_5)_2 + 2NaOC_2H_5 \longrightarrow CNa_2(CO_2C_2H_5)_2 + 2C_2H_5OH$$

$$\begin{matrix}CH_2Br\\|\\CH_2Br\end{matrix} + CNa_2(CO_2C_2H_5)_2 \longrightarrow \begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!C(CO_2C_2H_5)_2 + 2NaBr$$

This ester may be converted into *cyclo*propanecarboxylic acid by the usual procedure used in malonic ester syntheses:

$$\begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!C(CO_2C_2H_5)_2 \xrightarrow[(ii)\ HCl]{(i)\ KOH} \begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!C(CO_2H)_2 \xrightarrow{heat} \begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!CH\cdot CO_2H + CO_2$$

(ii) Ethylene bromide condenses with *two* molecules of sodiomalonic ester to form butane-1 : 1 : 4 : 4-tetracarboxylic ester:

$$\begin{matrix}CH_2Br\\|\\CH_2Br\end{matrix} + 2CHNa(CO_2C_2H_5)_2 \longrightarrow \begin{matrix}CH_2\cdot CH(CO_2C_2H_5)_2\\|\\CH_2\cdot CH(CO_2C_2H_5)_2\end{matrix} + 2NaBr$$

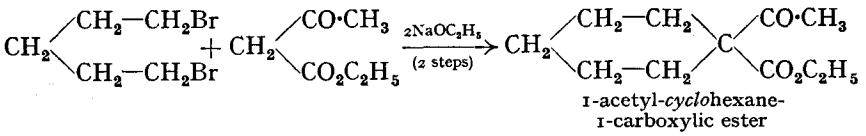
On treatment with excess sodium ethoxide, this tetracarboxylic ester forms the disodio-derivative, which, when treated with iodine, is converted into a *cyclo*butane derivative. If methylene iodide is used instead of iodine, the *cyclo*pentane derivative is obtained:

$$\begin{matrix}CH_2\cdot CH(CO_2C_2H_5)_2\\|\\CH_2\cdot CH(CO_2C_2H_5)_2\end{matrix} \xrightarrow{2NaOC_2H_5} \begin{matrix}CH_2\cdot CNa(CO_2C_2H_5)_2\\|\\CH_2\cdot CNa(CO_2C_2H_5)_2\end{matrix} \xrightarrow{I_2}$$

$$\begin{matrix}CH_2\cdot C(CO_2C_2H_5)_2\\|\\CH_2\cdot C(CO_2C_2H_5)_2\end{matrix} \xrightarrow[(ii)\ HCl]{(i)\ KOH} \begin{matrix}CH_2\cdot C(CO_2H)_2\\|\\CH_2\cdot C(CO_2H)_2\end{matrix} \xrightarrow{heat} \begin{matrix}CH_2\cdot CH\cdot CO_2H\\|\\CH_2\cdot CH\cdot CO_2H\end{matrix} + 2CO_2$$

Thus, by using the appropriate dihalogen derivatives of the paraffins under suitable conditions, it is possible to prepare rings containing 3–7 carbon atoms (the yield being highest for the 5- and lowest for the 7-membered ring; see later).

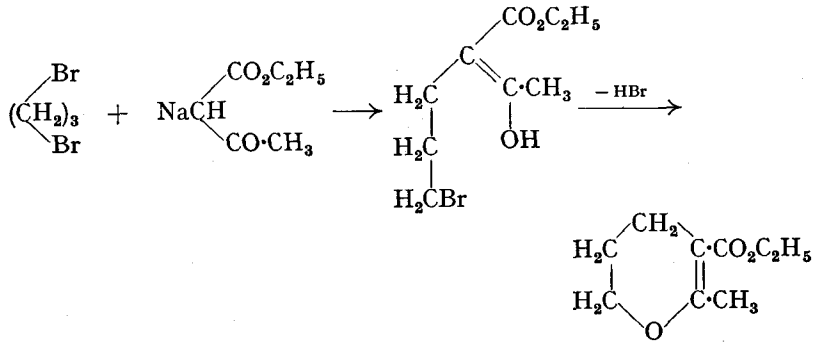
Acetoacetic ester may also be used to prepare ring compounds, *e.g.*,



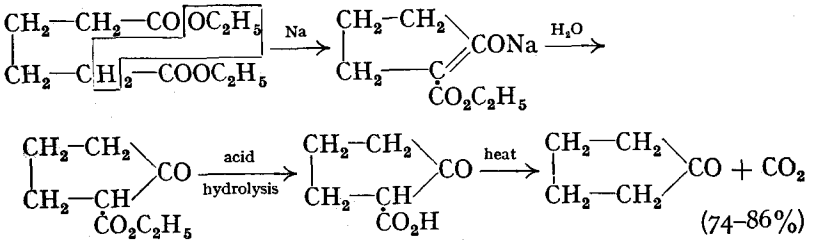
1-acetyl-*cyclo*hexane-1-carboxylic ester

Hydrolysis and decarboxylation of this compound produce *cyclo*hexyl methyl ketone.

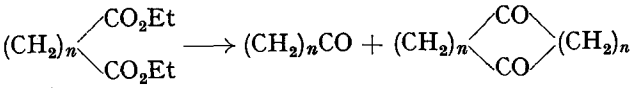
By using acetoacetic ester, it is possible to prepare rings containing 3, 5, 6 and 7 carbon atoms, but not 4; all attempts to prepare a 4-membered ring result in the formation of a dihydropyran derivative (p. 767):



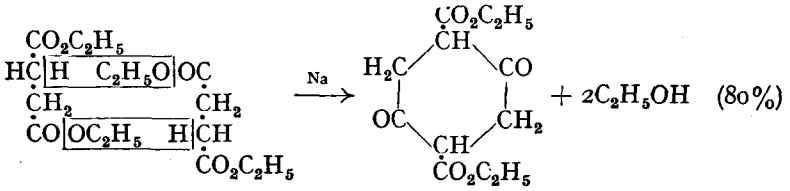
5. Certain cyclic ketones can be obtained by the **Dieckmann reaction** (1901). This reaction is an *intramolecular* acetoacetic ester condensation (Claisen condensation); the reaction is carried out by treating the esters of adipic, pimelic or suberic acids with sodium, whereupon 5-, 6- or 7-membered rings, respectively, are obtained; *e.g.*, adipic ester forms *cyclo*pentanone:



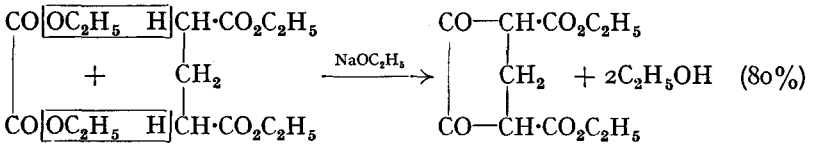
Leonard *et al.* (1958), however, have now cyclised α, ω-diesters with potassium t-butoxide in xylene under high dilution conditions (p. 397), and have obtained mono- and diketones for $n = 6$–14 (yields: variable):



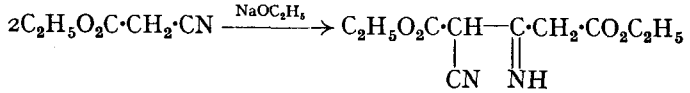
Esters lower than adipic ester may form products by *intermolecular* condensation and cyclisation, *e.g.*, in the presence of sodium or sodium ethoxide, ethyl succinate forms *succinosuccinic ester* (*cyclo*hexane-2 : 5-dione-1 : 4-dicarboxylic ester):



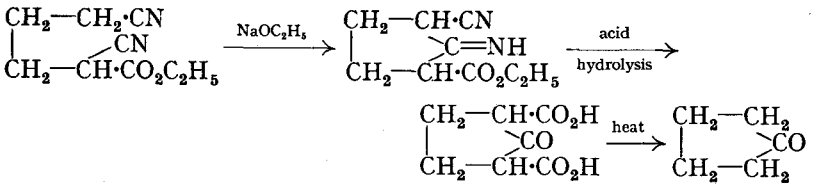
On the other hand, five-membered ring compounds may be prepared by the intermolecular condensation between oxalic and glutaric esters:



6. Cyclic ketones may be obtained by a modified Thorpe's reaction (1909). Thorpe's reaction is the condensation of cyano-compounds in the presence of sodium ethoxide to form the dimers; the cyano-compound must have at least one active hydrogen atom, *e.g.*,

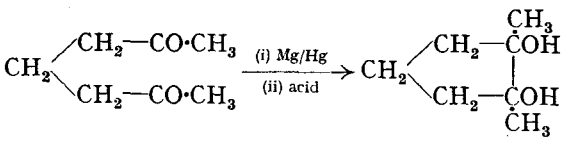


By using the dicyano-derivative of an ester, it is possible to obtain a cyclic ketonic acid; *e.g.*, α : δ-dicyanovaleric ester undergoes cyclisation in the presence of sodium ethoxide:



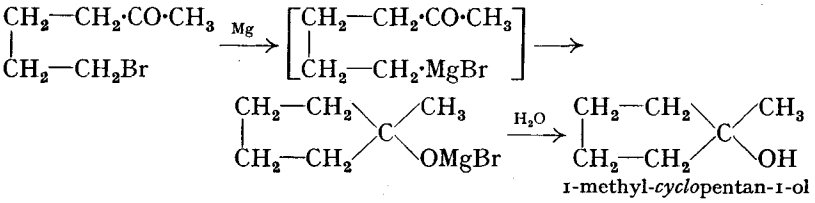
Dicyano-compounds have also been used to prepare large ring compounds (p. 493).

7. (i) Hydroxy-cyclic compounds may be prepared by reducing certain diketones with magnesium amalgam; the reaction is a pinacol reduction (*cf.* p. 163). *E.g.*, heptane-2 : 6-dione forms 1 : 2-dimethyl*cyclo*pentane-1 : 2-diol:



(ii) Hydroxycyclic compounds may also be prepared by an *intramolecular* Grignard reaction on certain bromo-ketones; *e.g.*, when treated with magnesium in ethereal solution, 6-bromohexan-2-one forms the corresponding

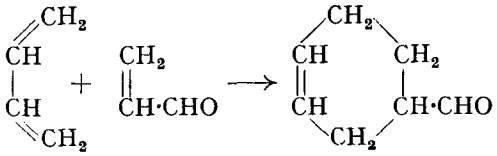
Grignard reagent which, due to the proximity of the carbonyl group, undergoes intramolecular reaction to form a cyclic compound:



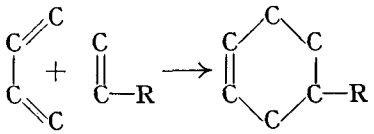
1-methyl-*cyclo*pentan-1-ol

Methods (i) and (ii) work very well for the preparation of *five-* and *six-*membered rings. The reason for this will be discussed later (p. 486), where it will also be seen why the Dieckmann reaction is limited to the formation of 5-, 6- and 7-membered rings.

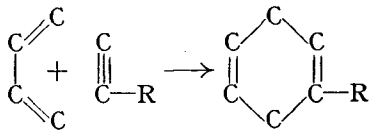
8. **Diels-Alder Reaction** or **Diene-Synthesis** (1928). A simple example of the Diels–Alder reaction is the addition to a conjugated diene of an ethylenic compound in which the double bond is adjacent to a carbonyl group; *e.g.*, butadiene combines with acraldehyde at 100° to form tetrahydrobenzaldehyde:



In general, the diene synthesis is the following type of condensation:



and

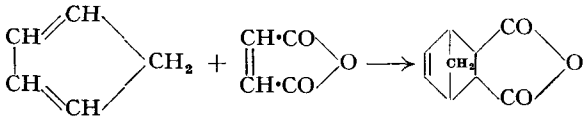


A B

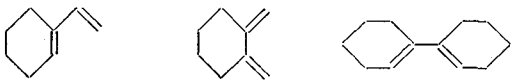
Compound A is usually referred to as the **diene** (whether it be a conjugated diene, polyene, enyne or diyne), and compound B is usually referred to as the **dienophile.** R is usually a group which contains a carbonyl group attached to one of the ethylenic or acetylenic carbon atoms, *i.e.*, the dienophile is usually an αβ-unsaturated carbonyl compound, *e.g.*, αβ-unsaturated acids, acid anhydrides, esters, aldehydes or ketones; the dienophile may also be a quinone (see p. 728). The presence of a carbonyl group (a negative group) in the dienophile is not essential: compounds which contain other negative groups such as nitro- or cyano-, can also behave as dienophiles. In certain cases, the dienophile may even be an unsaturated hydrocarbon (see p. 501). Nevertheless, the diene synthesis takes place most readily when the dienophile contains a carbonyl group, and the most useful dienophile is *maleic anhydride.* Tetracyanoethylene, $C(CN)_2{=}C(CN)_2$ [m.p. 200°], however, appears to be the most reactive dienophile discovered so far.

The compound formed by the condensation of A with B is known as the **adduct.** The adduct is always a six-membered ring, the addition taking place in the 1 : 4-positions (see also below).

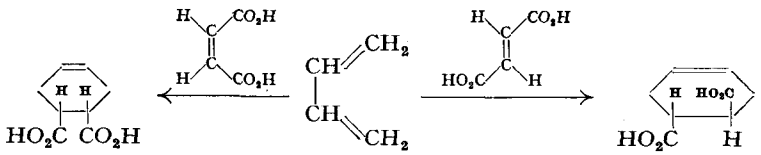
The diene may be of various types: acyclic, alicyclic, semi-cyclic compounds containing two double bonds in conjugation, bicyclic compounds, aromatic hydrocarbons containing at least three *linear* benzene rings (*e.g.*, anthracene; see p. 729), and certain heterocyclic compounds (*e.g.*, furan; see p. 742). No catalyst is required (but see later); the two compounds are heated together or heated in some solvent, *e.g.*, benzene. Cyclic dienes produce bridge-compounds, *e.g.*,



Some examples of various dienes are:

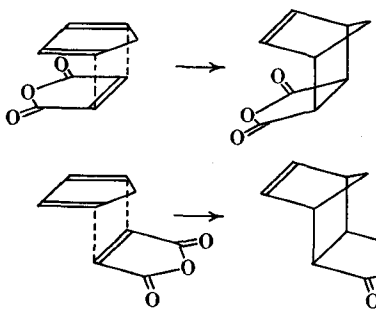


The addition reaction is always stereospecific in that it is a *cis*-addition, *e.g.*, butadiene reacts with maleic acid to give *cis*-1 : 2 : 5 : 6-tetrahydrophthalic acid, whereas fumaric acid gives the *trans* derivative:



cis- *trans-*

When the diene is cyclic, *two cis*-additions are possible, one giving the *endo*-compound and the other the *exo*-compound, *e.g.*,



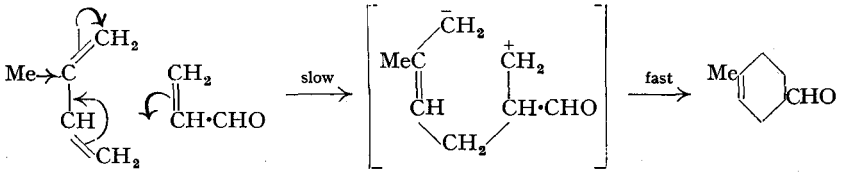
(I); ***endo*-compound**

(II); ***exo*-compound**

It has been found experimentally that the *endo*-product is usually obtained exclusively. It has been shown, however, that the diene synthesis is reversible and exothermic, and therefore raising the temperature shifts the equilibrium to the reactants (Wassermann, 1938). It has also been shown that the *endo*-compound is the kinetically controlled product and the *exo*-compound the thermodynamically controlled product. Thus raising the temperature of the reaction favours the formation of the *exo*-compound.

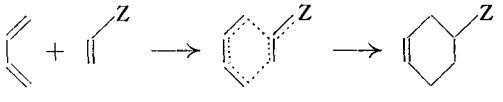
The mechanism of the Diels–Alder reaction is uncertain. A heterolytic mechanism has been suggested, and evidence in its favour is that when the diene contains an electron-repelling group, the rate of reaction is increased, *e.g.*, the

reaction between isoprene and acraldehyde is faster than when butadiene is the diene, and also the heterolytic mechanism explains the orientation of the product:



If the reaction proceeds in two stages, then it must be assumed that the second stage is extremely rapid to prevent time for rotation about the single bond in the intermediate. (With maleic acid as dienophile, when the first step has occurred, one would expect rotation to fumaric acid unless the second stage is so rapid that ring closure occurs before rotation can take place.) Wassermann (1950) has overcome this difficulty by proposing that ring formation occurs by *both* new bonds (of the addition) being formed *simultaneously*. This is imagined to proceed through a *non-planar* transition state, and is produced by bonds being formed simultaneously between diene and dienophile, which are in parallel planes, by overlap of the *p*-orbitals in an *endwise* fashion instead of the usual sideways overlap (see I and II; the broken lines represent the overlapping orbitals). It is difficult to explain polar effects with this mechanism. If, however, some complex is produced between the reactants *before* the transition state is formed, then one would expect that the less symmetrical the diene and dienophile, charge distribution in each is less symmetrical, and consequently complex formation would be facilitated. Keefer *et al.* (1955) and Berson *et al.* (1956) have obtained evidence for the preliminary formation of such a complex.

Dewar (1959) also favours a one-step mechanism passing through a *pseudo*-aromatic transition state:



On the other hand, Woodward *et al.* (1959) favour a two-stage mechanism, the two bonds being formed in *separate* processes, both reactants approaching each other initially in parallel planes. The formation of the first bond is the rate-determining step.

There is also some recent evidence for the heterolytic two-stage mechanism. Yates *et al.* (1960) have shown that the Diels–Alder reaction is accelerated by aluminium chloride. Robinson *et al.* (1961) have shown that Friedel–Crafts catalysts, *e.g.*, $AlCl_3$, $SnCl_4$, BF_3, etc., effect the Diels–Alder reaction under much milder conditions than when the compounds are absent.

General properties of the *cyclo*paraffins. *cyclo*Paraffins usually boil at higher temperatures than the corresponding paraffins. In many chemical respects they are similar to the paraffins, but in others they are different in that the lower members form addition products with ring *fission*. Hydrogen bromide attacks *cyclo*propane to form *n*-propyl bromide, but has no effect on other *cyclo*paraffins. Hydrogen iodide attacks both *cyclo*propane and *cyclo*butane to form *n*-propyl iodide and *n*-butyl iodide, respectively; *cyclo*butane is attacked only when heated, no action taking place at room temperature. The higher *cyclo*paraffins are not affected by hydrogen iodide in the cold or on moderate heating. Bromine attacks *cyclo*propane to form 1 : 3-dibromopropane; the higher members form *cyclo-substituted* products with bromine. When heated with hydrogen in the presence of nickel at 80°, *cyclo*propane is converted into propane; *cyclo*butane yields *n*-butane at 120°, and *cyclo*pentane yields *n*-pentane at 300°. The higher *cyclo*paraffins are not attacked by hydrogen in the presence of

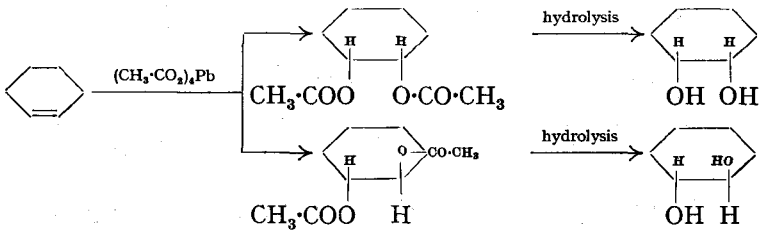
nickel. All the foregoing reactions indicate that the stability of the ring increases as the ring becomes larger.

Generally, derivatives of the *cyclo*paraffins very closely resemble the paraffins in those properties which do not involve ring fission, *e.g.*, cyclic acids may be converted into esters, acid chlorides, acid amides, etc.; cyclic ketones may be reduced to cyclic alcohols, etc. Owing to the presence of the ring, however, various derivatives of the *cyclo*paraffins are capable of exhibiting geometrical isomerism (see, *e.g.*, *cyclo*propane).

Opening of rings. Three- and four-membered rings may readily be opened by means of hydrogen iodide or by catalytic reduction. The rings of higher members may be opened by oxidation of the cyclic alcohol, or ketone, or *cyclo*olefin, and in some cases, by the oxidation of the *cyclo*alkane itself.

Changing the size of rings. On treatment with particular reagents, certain derivatives of the *cyclo*paraffins undergo rearrangement, the ring becoming either smaller or larger (see, *e.g.*, *cyclo*butylamine and *cyclo*pentanone, below).

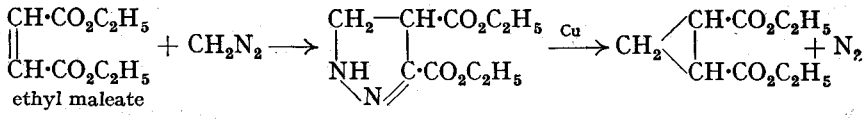
Acetoxylation of the double bond in *cyclo*olefins. Lead tetra-acetate attacks double bonds in *cyclo*-olefins to form 1 : 2-diacetates, the addition products usually being a mixture of the *cis* and *trans* compounds, *e.g.*, *cyclo*hexene forms a mixture of *cis*- and *trans-cyclo*hexanediol.



***cyclo*Propane.** b.p. −34°, may be prepared by the action of zinc on trimethylene bromide (p. 468). A recent method of preparation is to chlorinate propane, separate the 1 : 3-dichloro-isomer, and close the ring by means of zinc dust and sodium iodide.

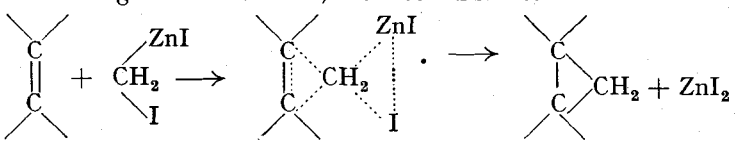
*cyclo*Propane is one of the best anæsthetics known. When heated to a high temperature, preferably in the presence of a catalyst, *e.g.*, platinum, *cyclo*propane is converted into propylene.

*cyclo*Propane derivatives may be prepared by the action of diazomethane on ethylenic compounds; the pyrazoline compounds formed eliminate nitrogen when heated with copper powder to form *cyclo*propane derivatives, *e.g.*,

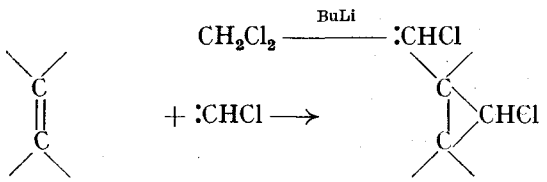


Improved yields of *cyclo*propanes are obtained by photochemical, rather than thermal, decomposition of the pyrazolines (Rinehart *et al.*, 1960).

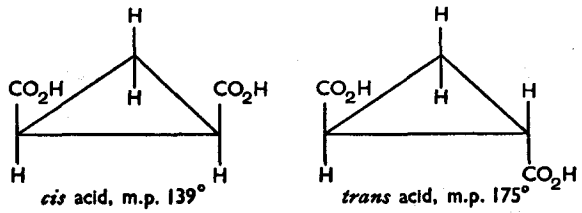
Dihalogenomethylenes add to double bonds to form *cyclo*propane derivatives (see, *e.g.*, pp. 83, 477). Methylene also does this, and the reaction may be carried out in ether solution by reaction between the olefin and methylene iodide in the presence of a zinc–copper couple (Simmons *et al.*, 1959). According to these authors, the mechanism is:



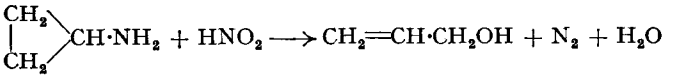
Chloro*cyclo*propanes are formed, via chloromethylene, from olefins by the action of methylene chloride and butyl-lithium (Closs *et al.*, 1959):



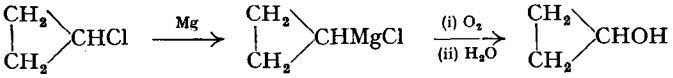
Many *cyclo*propanecarboxylic acids are known; some exhibit geometrical and optical isomerism, *e.g.*, *cyclo*propane-1 : 2-dicarboxylic acid exists in the *cis*-form (optically inactive; it has a plane of symmetry) and the *trans*-form which is optically active (it has neither a plane nor a centre of symmetry).



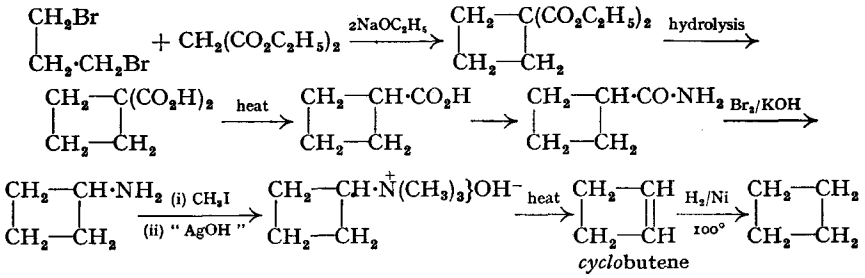
***cyclo*Propylamine,** b.p. 50°, on treatment with nitrous acid forms allyl alcohol instead of the expected *cyclo*propanol (see *cyclo*butylamine, below):



*cyclo*Propanol has not yet been prepared in a pure form; it readily rearranges to propionaldehyde. It has been prepared in a crude form by several methods (Roberts *et al.*, 1951), *e.g.*,

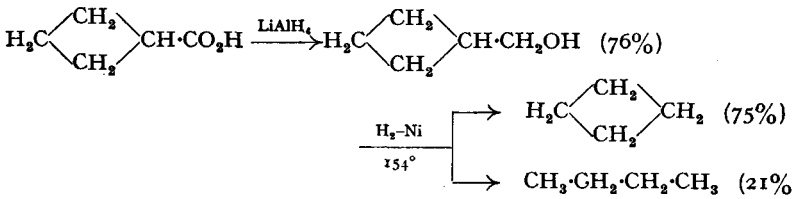


***cyclo*Butane,** b.p. −15°. *cyclo*Butane derivatives may be prepared by means of the malonic ester synthesis, and by polymerising certain ketens (p. 289). Curiously enough, it appears that *cyclo*butane cannot be prepared by ring closure of 1 : 4-dihalogen derivatives of *n*-butane (this is contrary to expectation by Baeyer's Strain Theory, p. 486). Many derivatives of *cyclo*butane were known long before the parent hydrocarbon was obtained. This was first prepared by Willstätter (1907) by the following laborious process, using the *Hofmann exhaustive methylation reaction* (p. 762):

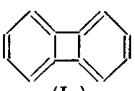


***cyclo*Propene** has been prepared in a similar manner from *cyclo*propylamine.

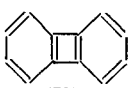
Pines *et al.* (1953) have prepared *cyclo*butane from *cyclo*butanecarboxylic acid as follows:



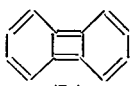
***cyclo*Butene,** b.p. 2°, shows the ordinary olefinic reactions. Willstätter was unable to convert *cyclo*butene into *cyclo*butadiene,  . The existence of this compound is doubtful; if it does exist, it is very unstable. Avram *et al.* (1959) appear to have prepared *cyclo*butadiene, and found its half-life to be about one minute. On the other hand, the following *aromatic* derivatives of *cyclo*butadiene are known: diphenylene (I; Lothrop, 1941), di-2:3-naphthylene (II; Curtis *et al.*, 1954), and di-1:2-naphthylene (III; Cava *et al.*, 1955).



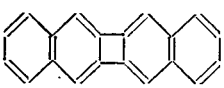
(I*a*)



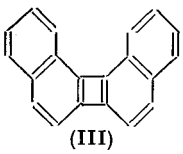
(I*b*)



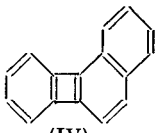
(I*c*)



(II)



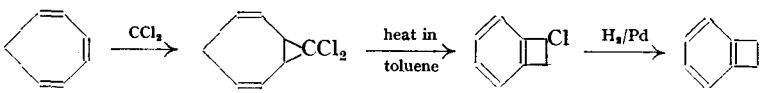
(III)



(IV)

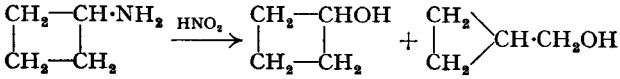
(V)

(I) and (II) are pale yellow in colour and stable thermally, but (III) is red and resinifies on heating. It might be noted that three resonating structures are possible for diphenylene, but only two can be regarded as *cyclo*butadiene derivatives, *viz.*, (I*b*) and (I*c*); (I*a*) is a *cyclo*butane derivative. Measurements of bond distances in diphenylene have been carried out by Mak *et al.* (1961), and the results indicate that (I*a*) makes the greatest contribution to the resonance hybrid of resonating structures (I*a*, I*b*, and I*c*). Cava *et al.* (1956) have prepared (IV) and (V) (the latter is a *cyclo*butene derivative). Borg *et al.* (1958) have prepared benzo*cyclo*butene (V) by the action of chloroform on a methanolic solution of sodium methoxide and *cyclo*heptatriene (the reaction proceeds via the formation of dichloromethylene, p. 117; *cf. cyclo*pentadiene, p. 479):



(V)

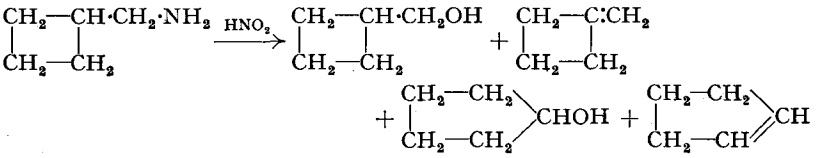
***cyclo*Butylamine,** b.p. 82°, when treated with nitrous acid, gives a mixture of *cyclo*butanol and *cyclo*propylcarbinol, the latter being produced by ring contraction:



This rearrangement of cyclic amines is known as the **Demjanov rearrangement** (1903).

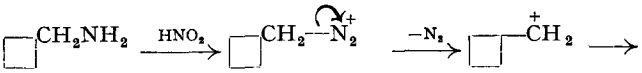
If *cyclo*butylmethylamine is treated with nitrous acid, ring expansion by the

Demjanov rearrangement takes place; four products are obtained: *cyclo*butylcarbinol, methylene*cyclo*butane, *cyclo*pentanol and *cyclo*pentene:

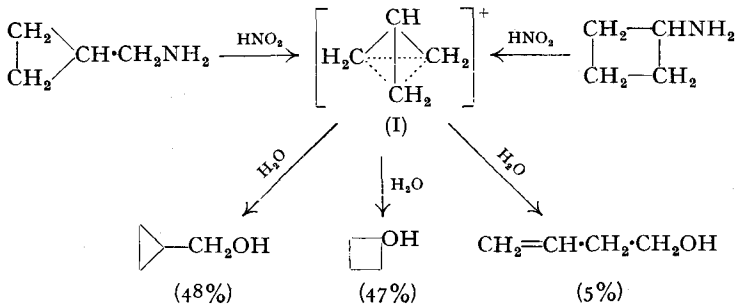


*cyclo*Propylmethylamine and some larger ring amines behave in a similar manner, and so by means of the Demjanov rearrangement it is possible to prepare seven- and eight-membered rings.

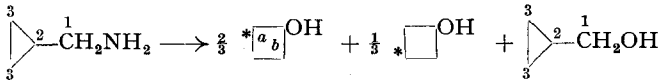
The Demjanov rearrangement is analogous to the pinacolic deamination (p. 171), and is an example of the 1,2-shift. It was at first suggested that the rearrangement occurred via a classical carbonium ion, *e.g.*,



Roberts *et al.* (1951), however, have obtained evidence that the structure of the intermediate carbonium ion is not the classical one, *e.g.*, these authors found that both *cyclo*propylmethylamine and *cyclo*butylamine, on treatment with nitrous acid, give about the same mixture of *cyclo*propylmethanol, *cyclo*butanol, and but-3-en-1-ol. This implies that the deamination proceeds through the same intermediate carbonium ion in both cases. The structure proposed for this ion is the bridged ion (I), and the deamination may therefore be written:

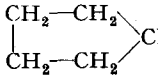


Examination of (I) shows that the three CH_2 groups are equivalent, and this equivalence was demonstrated by Roberts, who used *cyclo*propylmethylamine labelled with ^{14}C at position 1. The cyclic products obtained were:

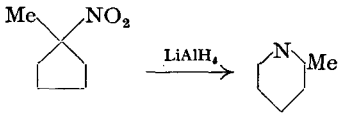


Thus the tracer atom is distributed equally among the three CH_2 carbon atoms in the *cyclo*butanol (positions *a* and *b* are equivalent). The *cyclo*propylmethanol contained 45 per cent. of ^{14}C at C_1 and 54 per cent. in the ring (at positions 3 and 3). Since the three CH_2 groups are equivalent in (I), the *cyclo*propylmethanol should have contained 33·3 per cent. of ^{14}C at C_1 and at each of the C_3 carbon atoms. Thus, although the major part of the reaction is proceeding through (I), there must be some other carbonium ion also produced. The structure of this ion is uncertain.

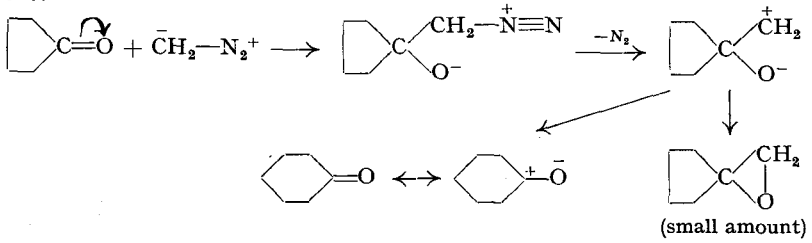
***cyclo*Pentane,** b.p. 50°, may be prepared by cyclising 1 : 5-dibromopentane with zinc or, better, by reducing *cyclo*pentanone by the Clemmensen method.

Methyl*cyclo*pentane,  , b.p. 72°, is an interesting com-

pound in that when heated above 450° in the presence of chromic oxide, it rearranges to *cyclo*hexane. On the other hand, when 1-methyl-1-nitro*cyclo*pentane is reduced with lithium aluminium hydride, 2-methylpiperidine (40 per cent.) is obtained (Lee *et al.*, 1958):



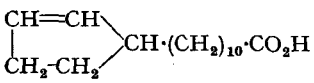
*cyclo*Pentanone, b.p. 130°, when treated with diazomethane, undergoes ring expansion to form *cyclo*hexanone. This reaction has been used to prepare seven- to ten-membered cyclic ketones (Kohler *et al.*, 1939). The mechanism is uncertain, but a strong possibility is the 1,2-shift (*cf.* the Arndt–Eistert synthesis, p. 327):



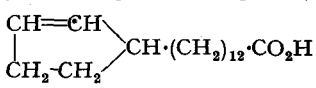
(small amount)

***cyclo*Pentene,** b.p. 45°, may be prepared by dehydrating *cyclo*pentanol or by heating *cyclo*pentyl bromide with ethanolic potassium hydroxide.

Some *cyclo*pentene derivatives of the fatty acids are very important, since they are useful in the treatment of leprosy and tuberculosis. Two acids, which occur in chaulmoogra oil, have been used from early times in the treatment of leprosy, both acids are optically active, the naturally occurring form being the (+);

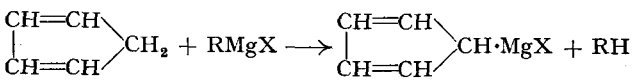


hydnocarpic acid, m.p. 60°

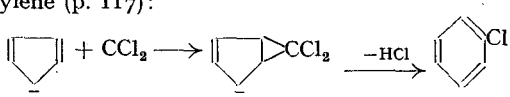


chaulmoogric acid, m.p. 68°

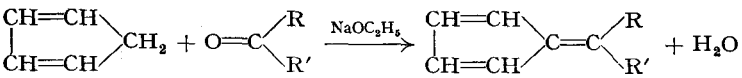
***cyclo*Pentadiene,** b.p. 41°, is found in the crude benzene that is obtained from coal tar. It readily polymerises at room temperature into the dimer, di*cyclo*pentadiene; at high temperature it forms high polymers. The hydrogen atoms of the methylene group are very reactive, *e.g.*, *cyclo*pentadiene reacts with Grignard reagents to form a hydrocarbon and *cyclo*pentadienylmagnesium halide:



Borg *et al.* (1958) have treated *cyclo*pentadienylsodium with chloroform and obtained chlorobenzene. The reaction is believed to proceed via the formation of dichloromethylene (p. 117):



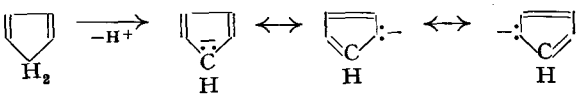
Owing to the presence of the reactive methylene group, *cyclo*pentadiene also condenses with aldehydes or ketones in the presence of sodium ethoxide to form *fulvenes*:



Fulvenes are derivatives of the unstable compound fulvene (R = R′ = H). The fulvenes are coloured substances, the colour deepening with increase in size of

the alkyl groups, R and R′. When irradiated with ultraviolet light, benzene is partially isomerised to fulvene (Blair *et al.*, 1957).

The reactivity of the methylene group may be due to the fact that when *cyclo*pentadiene loses a proton from the methylene group, the *cyclo*pentadiene carbanion produced can behave as a resonance hybrid. The ion contains less



energy than *cyclo*pentadiene itself (the former has acquired stabilisation due to resonance), and it is this possibility of becoming more stable that acts as the " driving force " to achieve this more stable state. It should also be noted that in the *cyclo*pentadienyl carbanion there is a sextet of electrons; this gives rise to aromatic properties (p. 509).

***cyclo*Pentadiene complexes.** Pauson *et al.* (1951) treated *cyclo*pentadienylmagnesium bromide with ferric chloride, their object being the preparation of di*cyclo*pentadienyl (*cf.* p. 359).

$$6C_5H_5MgBr + 2FeCl_3 \longrightarrow 3C_5H_5 - C_5H_5 + 2Fe + 3MgBr_2 + 3MgCl_2$$

The reaction, however, did not proceed in this manner; instead, these authors isolated di*cyclo*pentadienyliron, which is formed by the reduction of the ferric chloride to ferrous chloride, and the latter then reacting with the Grignard reagent:

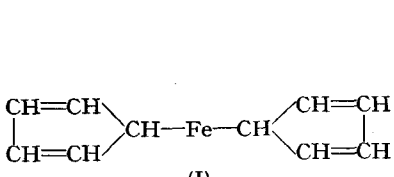
$$2C_5H_5MgBr + FeCl_2 \longrightarrow (C_5H_5)_2Fe + MgBr_2 + MgCl_2$$

This iron complex was named **ferrocene** by Woodward *et al.* (1952).

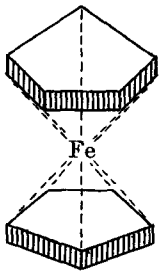
Many di*cyclo*pentadienyls have now been prepared, the methods of preparation being by the use of the Grignard reaction (as shown above), by direct reaction between *cyclo*pentadiene vapour and a heated metal or metal carbonyl, or by reaction between the sodium salt of *cyclo*pentadiene and a metal halide (in tetrahydrofuran or liquid ammonia solution); *e.g.*, $(C_5H_5)_2Cr$, $(C_5H_5)_2Mn$, $(C_5H_5)_2Co$, etc. A convenient preparation of ferrocene itself is the mercuration of *cyclo*pentadiene followed by treatment of the product with iron (Isslieb *et al.*, 1956). One of the best methods of preparing ferrocene is by reaction between ferrous chloride and *cyclo*pentadiene in diethylamine (Wilkinson, 1956):

$$2C_5H_6 + FeCl_2 + 2Et_2NH \longrightarrow (C_5H_5)_2Fe + 2Et_2NH{\cdot}HCl$$

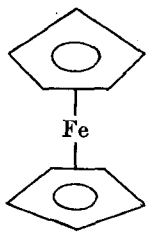
Originally, structure (I) was assigned to ferrocene, but the high stability of



(I)



(II)



(III)

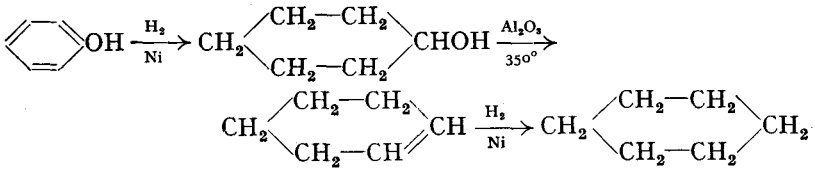
the molecule showed that this was unlikely. Ferrocene has a zero dipole moment, and the molecule is therefore symmetrical. Furthermore, the infrared spectrum showed that all of the C—H bonds are equivalent, and so, on this evidence, structure (II) was proposed and has been confirmed by X-ray analysis, *i.e.*, that the two five-membered rings lie in parallel planes with the iron atom placed symmetrically between the two. In ferrocene and other *cyclo*pentadienyls of the transition metals (Cr, Mn, Co, etc.), the entire ring is bonded uniformly to the metal atom; the bonding occurs by overlap of the sextet of π-electrons of the ring with the *d*-orbitals of the metal, thereby giving a *delocalised* covalent bond between the metal atom and the *cyclo*pentadienyl ring as a whole. This,

in ferrocene, is represented by (III). Structurally related compounds are bisbenzenechromium, etc. (see p. 541).

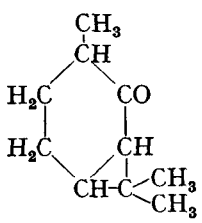
Derivatives of sodium, potassium, etc., are examples of ionic bonding; there is essentially an electron transfer from metal to ring, and compounds of this type are known as cyclo*pentadienides*. On the other hand, there are cases where the key atom, *e.g.*, silicon, and *one* carbon atom of the ring each contribute one electron to form essentially a σ-bond.

Ferrocene is an orange solid, and its reactions are aromatic, *e.g.*, it gives a mono- and diacetyl derivative by means of the Friedel–Crafts reaction under suitable conditions. Ferrocene forms an aldehyde by the *N*-methylformanilide method, and this undergoes the Cannizzaro reaction, the azlactone synthesis, etc. Ferrocene can also be sulphonated to the monosulphonic acid with chlorosulphonic acid in acetic anhydride (Pauson *et al.*, 1958). Ferrocene also undergoes mercuration and metalation, but because of its ease of oxidation, it cannot be directly halogenated or nitrated. It does *not* condense with maleic anhydride, and hence the conjugated system is absent in the rings.

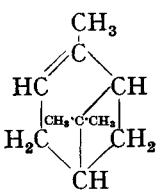
***cyclo*Hexane**, b.p. 81°, occurs in petroleum. When reduced with hydrogen iodide at 250°, benzene is converted into a mixture of *cyclo*hexane and methyl*cyclo*pentane. Pure *cyclo*hexane may be conveniently prepared by the reduction of *cyclo*hexanone, and is prepared industrially by the hydrogenation of benzene in the presence of nickel at 200°. Another industrial method is the hydrogenation of phenol, dehydrating the product *cyclo*hexanol to *cyclo*hexene, which is then catalytically hydrogenated to *cyclo*hexane; the process is carried out without isolating the intermediate compounds:



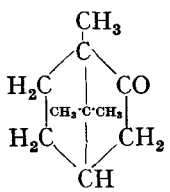
Many benzene derivatives may be reduced to the corresponding *cyclo*hexane compounds, and because of this, *cyclo*hexane and its derivatives are known as the **hydroaromatic compounds.** The cyclic terpenes are hydroaromatic compounds, *e.g.*,



carone

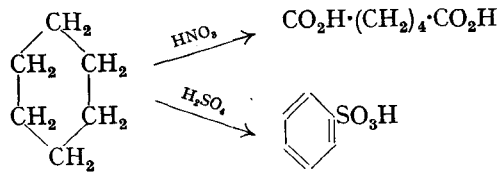


α-pinene



camphor

Hot concentrated nitric acid oxidises *cyclo*hexane to adipic acid, and fuming sulphuric acid converts it into benzenesulphonic acid:



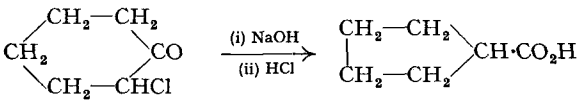
For a consideration of the spatial arrangement of the carbon atoms in *cyclo*hexane, see p. 488.

R

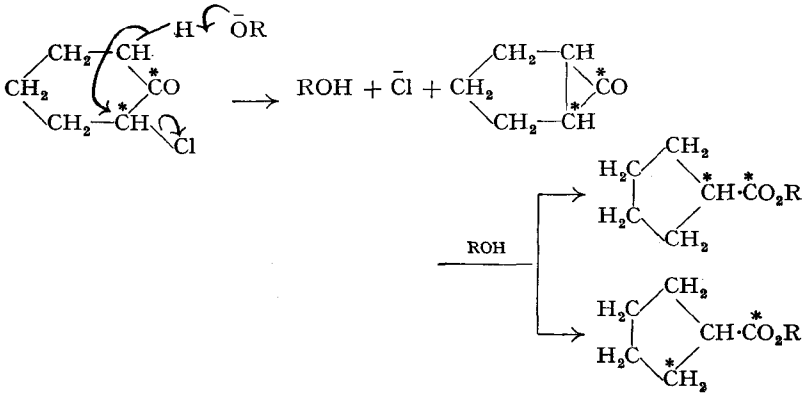
*cyclo*Hexane can be catalytically (Pt or Pd) dehydrogenated to benzene. Provided the ring contains at least one double bond, then dehydrogenation can be readily effected with sulphur of selenium. In general, this dehydrogenation is confined to six-membered rings.

***cyclo*Hexanol,** m.p. 24°, is prepared industrially by the catalytic hydrogenation of phenol. It undergoes the general reactions of an aliphatic secondary alcohol. It is converted by gentle oxidation (dilute nitric acid) into *cyclo*hexanone; vigorous oxidation (concentrated nitric acid) produces adipic acid.

***cyclo*Hexanone,** b.p. 157°, may be prepared by the oxidation of *cyclo*hexanol. α-Halogeno-*cyclo*hexanones undergo the *Favorsky reaction* (1894) when treated with alkali, *i.e.*, the six-membered ring changes to a five-membered ring carboxylic acid, *e.g.*,



Loftfield (1951), using the isotope ^{14}C as tracer, was led to suggest the following mechanism:

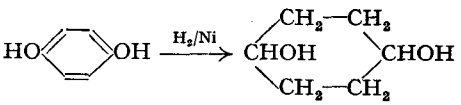


Acyclic α-halogeno-ketones also undergo the Favorsky rearrangement, *e.g.*,

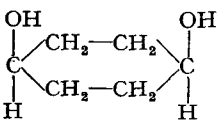
$$Me_2CBr{\cdot}COMe + OMe^- \longrightarrow Me_3C{\cdot}CO_2Me + Br^-$$

The rings of cyclic ketones may be opened by oxidation with Caro's acid to give lactones. This reaction has been used to prepare large ring lactones (p. 397).

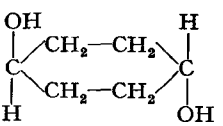
***cyclo*Hexane-1 : 4-diol,** *quinitol*, may be prepared by the catalytic reduction of quinol:



Quinitol exists in both the *cis*- and *trans*-forms:

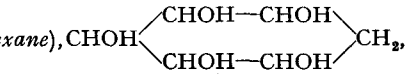


cis-quinitol, m.p. 102°

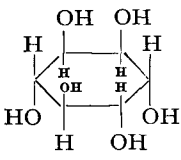


trans-quinitol, m.p. 139°

Both forms are optically inactive; the *cis* has a plane of symmetry, and the *trans* a centre of symmetry.

***cyclo*Hexanepentol** (*pentahydroxycyclohexane*),  , exists in a number of stereoisomeric forms. A (+)-form, m.p. 234°, occurs in acorns: this form is known as **(+)-quercitol.**

***cyclo*Hexanehexol, inositol,** *hexahydroxycyclohexane*, can exist in eight geometrical isomeric forms, of which only one is optically active (see formula). The (+)- and (−)-forms of this isomer (m.p. 248°) occur in plants as the hexaphosphoric ester, which is known as *phytin*. Some of the optically inactive forms also occur as their hexaphosphoric esters. One of the optically inactive forms is present in the vitamin B complex; it appears to have growth-promoting properties in chicks, and is an anti-alopecia factor (anti-baldness) in mice.

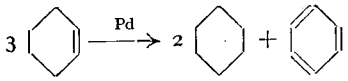


Hexachloro*cyclo*hexane, $C_6H_6Cl_6$, exists in a number of geometrical isomeric forms, one of which is a powerful insecticide (see p. 544).

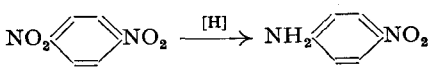
***cyclo*Hexene** (*tetrahydrobenzene*), b.p. 83°, may conveniently be prepared by dehydrating *cyclo*hexanol with sulphuric acid. It has the usual properties of an olefin.

A number of *cyclo*hexene derivatives may be prepared by means of the Diels–Alder reaction.

Braude, Linstead *et al.* (1952–) have shown that hydrogen transfer takes place in the presence of palladium as catalyst (and below 100°) between *cyclo*hexene and a wide variety of acceptors containing a multiple bond, *e.g.*, ethylenic and acetylenic compounds, nitro-, azo- and azoxy-compounds. It is also possible to reduce only one nitro-group in compounds containing two or more, *e.g.*, *p*-dinitrobenzene to *p*-nitroaniline:

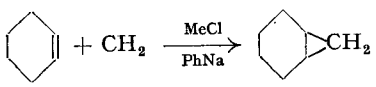


*cyclo*Hexene itself, under the above conditions, undergoes disproportionation to give benzene and *cyclo*hexane.



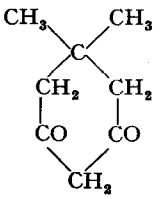
Thus an excess of *cyclo*hexene is required in reductions to off-set this competing disproportionation, and it has been shown that there is a direct hydrogen transfer between *cyclo*hexene and the hydrogen acceptor.

Friedman *et al.* (1960) have reported the formation of carbene by reaction between methyl chloride and, *e.g.*, phenylsodium in the presence of carbene acceptors, *e.g.*, *cyclo*hexene, to give norcarane:

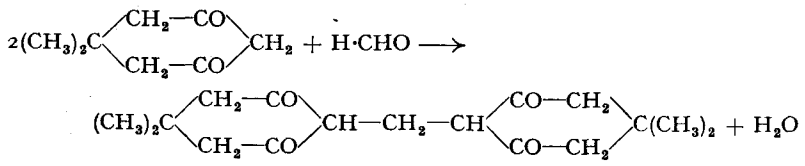


***cyclo*Hexadienes** (*dihydrobenzenes*). There are two isomeric *cyclo*hexadienes, the 1 : 3- (b.p. 81°) and the 1 : 4- (b.p. 86°). They readily polymerise and undergo the usual reactions of a diolefin. Since *cyclo*hexa-1 : 3-diene contains a conjugated system of double bonds, it can undergo both the 1 : 2- and 1 : 4-addition reactions (see p. 86).

***cyclo*Hexatriene** is **benzene,** and differs enormously in its chemical properties from the *cyclo*alkenes and *cyclo*alkadienes. Benzene has " *aromatic properties* " see benzene, p. 483).

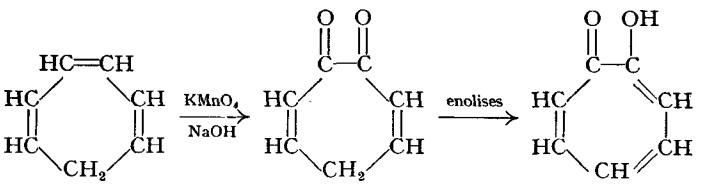


5 : 5-Dimethyl*cyclo*hexane-1 : 3-dione, dimedone, is a solid, m.p. 148°. It is a very sensitive reagent for formaldehyde, which may be estimated gravimetrically with this reagent:

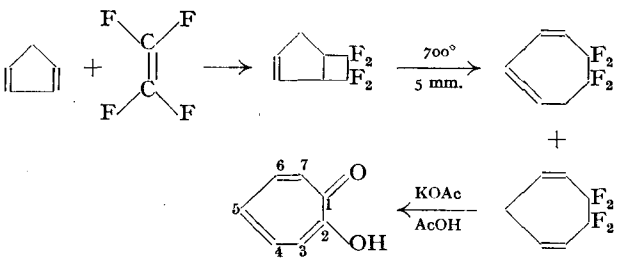


***cyclo*Heptane,** b.p. 118°, occurs in petroleum; it may be prepared by the reduction of *cyclo*heptanone.

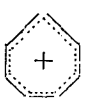
Tropolone (*cyclo*heptatrienolone) is a cyclic α-hydroxyketone; it has a seven-membered ring containing three double bonds. Dewar (1945), who proposed its structure, also predicted that it would have *aromatic* properties, and this has now been confirmed. The tropolone system occurs in certain natural products. It may be prepared from tropilidene (*cyclo*heptatriene) as follows:



A good method of synthesising tropolone is as follows (Drysdale *et al.*, 1958):

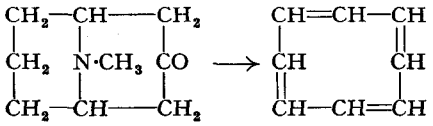


Tropolone is very weakly acidic; it is also basic, *e.g.*, it forms a hydrochloride. It is attacked by electrophilic reagents to give *substitution* products, *e.g.*, it is readily brominated and nitrated at the 3-, 5-, and 7-positions. On heating with alkali, it is isomerised to benzoic acid. Ultraviolet absorption studies have shown that tropolone is planar (see also p. 509). The fundamental structure of the seven-membered aromatic compounds is the tropylium ion. This is tropilidene with a hydride ion removed from the CH_2 group. Tropylium bromide may be prepared from tropilidene by the action of bromine followed by heating; the dibromide eliminates a molecule of hydrogen bromide (Doering *et al.*, 1954).



***cyclo*Octane,** m.p. 11·8°, may be obtained by the catalytic reduction of *cyclo*-octene, *cyclo*-octadiene or *cyclo*-octatetraene (Willstätter (1911).

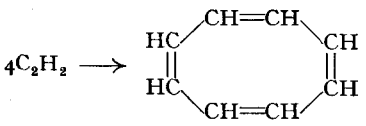
(1:3:5:7)-*cyclo*Octatetraene was first obtained by Willstätter (1911, 1913), who prepared it from the alkaloid *pseudo*-pelletierine (ψ-pelletierine) by means of the Hofmann exhaustive methylation method (p. 762):



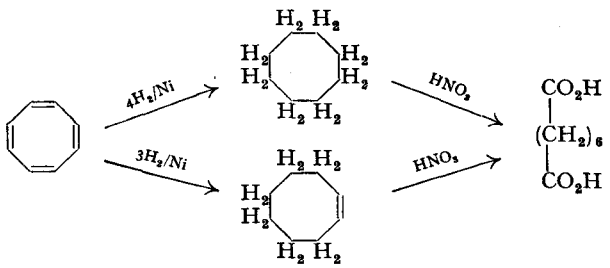
ψ-pelletierine *cyclo*-octatetraene

In 1939, Willstätter's results were questioned by a number of workers who believed that Willstätter had prepared, not *cyclo*-octatetraene, but *styrene*, $C_6H_5{\cdot}CH{:}CH_2$, which has somewhat similar properties to those recorded for *cyclo*-octatetraene. Cope and Overberger (1947), however, prepared *cyclo*-octatetraene from synthetic ψ-pelletierine, and found it to have the physical properties reported originally; these authors (1948) also duplicated Willstätter's work from natural ψ-pelletierine.

Reppe (1940) prepared *cyclo*-octatetraene in large quantities by the polymerisation of acetylene under pressure in the presence of a nickel compound, *e.g.*, nickel cyanide, as catalyst, in tetrahydrofuran solution:



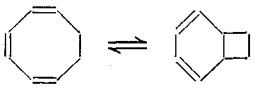
cyclo-Octatetraene is a yellow liquid, b.p. 142–143°. It behaves as a typical unsaturated compound, *e.g.*, it adds on bromine, halogen acids, etc. It can be reduced catalytically to *cyclo*-octane, and this, on oxidation with concentrated nitric acid, yields suberic acid. A better yield of suberic acid is obtained by reducing *cyclo*-octatetraene to *cyclo*-octene and oxidising this with nitric acid. *cyclo*-Octatetraene is therefore a potential commercial source of suberic acid:



The *olefinic* properties of *cyclo*-octatetraene are somewhat surprising at first sight. Since the molecule contains a *closed* conjugated system, one might have expected delocalisation of bonds, thereby giving rise to aromatic character (*cf.*, p. 509). If, however, delocalisation occurred, the molecule would be planar and therefore in a state of strain (the angle of a regular octagon is 135°, and that of carbon trigonally hybridised is 120°). X-Ray analysis has indicated that the *cyclo*-octatetraene molecule contains *alternate single and double bonds* and that the ring is non-planar (Kaufman *et al.*, 1948). The presence of this conjugated system has been supported by infrared and Raman absorption spectra studies. These results account for *aliphatic* properties. Treibs (1950) has shown from models of *cyclo*-octatetraene that one form—a basket shape (" tub ")—has no internal stresses. This conformation is supported by electron-diffraction studies (Karle, 1952).

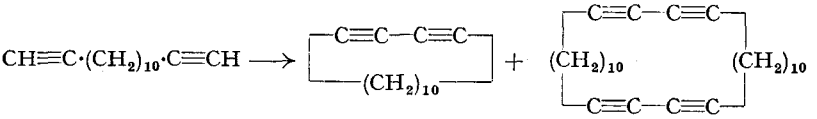
cyclo-Octa-1:3:5-triene. This exhibits *valence-tautomerism*; it behaves as (I) in that it can be reduced to *cyclo*-octane, and it behaves as (II) in that it can

be oxidised to *cis-cyclo*butane-1:2-dicarboxylic acid. The isomers have been separated, and heating of either tautomer at about 80° gives an equilibrium mixture of both (Cope *et al.*, 1950, 1952).



(I) (II)

***cyclo*Alkynes.** Ring compounds containing one triple bond have now been prepared (Eglinton *et al.*, 1956). The preparation of these compounds offers a new means of synthesising macrocyclic compounds (p. 493). The following example illustrates the method used. Tetradeca-1:13-di-yne, on treatment with excess of cupric acetate in methanolic pyridine, in high dilution (see p. 397), forms *cyclo*tetradeca-1:3-di-yne and also some of the cyclic dimer *cyclo*-octacosa-1:3:15:17-tetra-yne.



These, on catalytic hydrogenation (platinum), gave respectively *cyclo*tetradecane ($C_{14}H_{28}$) and *cyclo*octacosane ($C_{28}H_{56}$). Sondheimer *et al.* (1959) have carried out oxidative coupling with octa-1:7-di-yne and obtained 16-, 24-, 32-, and 40-membered polyacetylenes which, on hydrogenation, give *cyclo*alkanes. These authors have now prepared up to a 54-membered ring system; the largest ring hitherto contained 34 carbon atoms.

Baeyer's Strain Theory. Baeyer (1885) was the first to point out that the angle subtended by the corners and centre of a regular tetrahedron—190° 28′—lies between the values of the angles in a regular pentagon (108°) and a regular hexagon (120°). On this observation was based the **Baeyer Strain Theory.** According to the Strain Theory, the valency angle can be altered from this normal value (109° 28′), but when altered, a strain is set up in the molecule, and the greater the deviation from the normal angle, the greater is the strain. Thus, according to Baeyer, five- and six-membered rings form most readily, and are the most stable because they involve the least strain (or distortion) from the normal valency angle.

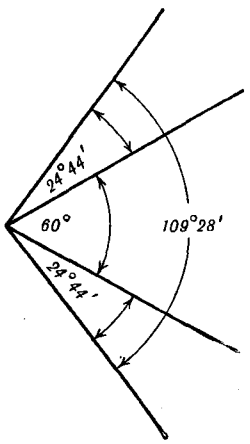


FIG. 19.1.

The following arguments are based on the assumption that the rings are planar. In *cyclo*propane the three carbon atoms each occupy a corner of an equilateral triangle. Since the angles of an equilateral triangle are 60°, the distortion in *cyclo*propane will be $\frac{1}{2}(109° 28' - 60°) = + 24° 44'$ (Fig. 1). When the carbon valencies are forced *together*, the strain is said to be *positive*; when forced *apart*, *negative*. Thus the *cyclo*propane molecule will be under a very large strain, and hence should be difficult to prepare, and should not be very stable.

In *cyclo*butane the distortion is $\frac{1}{2}$ (109° 28′ − 90°) = + 9° 44′, a value which is considerably less than that for *cyclo*propane. Experimental work shows that *cyclo*butane derivatives are more easily formed and are more stable than *cyclo*propane compounds; this supports the Strain Theory.

In *cyclo*pentane the distortion is $\frac{1}{2}$ (109° 28′ — 108°) = + 0° 44′; in *cyclo*hexane, $\frac{1}{2}$ (109° 28′ — 120°) = — 5° 16′; in *cyclo*heptane, $\frac{1}{2}$ (109° 28′ — 128° 34′) = —9° 33′; etc.

Thus five- and six-membered rings involve the least distortion and hence the ease of formation and stability should be a maximum in these compounds. The Strain Theory agrees reasonably well with the properties of ring compounds containing *six or less* carbon atoms; *e.g.*, we can now see why only the 1 : 4- and 1 : 5-dicarboxylic acids form cyclic anhydrides, and the 1 : 6- and 1 : 7-cycle ketones (p. 380); why only γ- and δ-hydroxyacids readily form lactones (p. 395); etc. Measurements of the dipole moments of simple compounds of oxygen, nitrogen and sulphur show that the valency angles of these elements lie between 100° and 110°. Hence the presence of these elements in ring compounds will not greatly affect the stability of five- and six-membered rings in which they are present (see also the heterocyclic compounds, Ch. XXX).

The Strain Theory has been used to account for the great reactivity of the double bond. The double bond was considered to be a *two-membered ring*; the distortion is therefore $\frac{1}{2}$ (109° 28′ —0°) = +54° 44′. This involves the greatest distortion (strain) and consequently the least stability, *i.e.*, the greatest tendency to open or react. This reasoning for the double bond may have been helpful, but further consideration shows it to be inadequate, *e.g.*, the double bond is formed so easily that it would appear to be under very small strain, if any (see also later).

A point of interest that may be mentioned here is that alkyl substituents in a chain often facilitate ring closure, *e.g.*, (i) β : β-dimethylglutaric acid forms an anhydride far more easily than does glutaric acid. (ii) Adipic acid is converted into *cyclo*pentanone when heated with acetic anhydride and then distilled at 300° (p. 380); α : α′-dimethyladipic acid forms the corresponding dimethyl*cyclo*pentanone derivative very easily when warmed with acetic anhydride. The reason for this is probably as follows. The carbon chain in unsubstituted dicarboxylic acids is believed to be zig-zag (Fig. 2). On the other hand, in β : β-

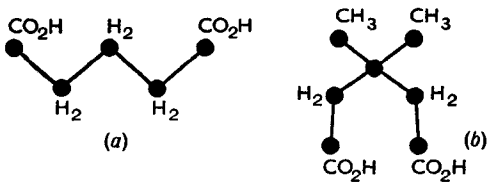


FIG. 19.2.

dimethylglutaric acid, it is possible that the presence of the two methyl groups gives rise to a different spatial arrangement. The methyl group, due to its large volume (relative to hydrogen), forces the carboxyl to take up the position shown in Fig. 2 (*b*). Thus, owing to steric effects, the zig-zag nature of the chain is forced to become coiled. This brings the reacting groups closer together, thereby facilitating anhydride formation.

Baeyer's Strain Theory is based on a mechanical concept of valency, and served its purpose in stimulating research in the field of cyclic compounds. Now we have the electronic theory of valency, and the reactivity of double bonds has been explained by the π-electrons. Furthermore, as pointed out on p. 26, when four identical groups are attached to a carbon atom, the four carbon valencies are equivalent, and the valency angle is 109° 28′. When the groups are different, the four valencies are no longer equivalent but now point towards the four corners of an *irregular* tetrahedron. Since there are no double bonds in *cyclo*propane, the carbon atoms cannot be in a state

of trigonal hybridisation. If the configuration of *cyclo*propane were an equilateral triangle, then the ring valency angle of each carbon atom would be 60°. This value is impossible, since the carbon valency angle can never be less than 90°(when they are pure *p*-orbitals). Furthermore, mixture of *p* with *s*-orbitals *opens* the valency angle. According to Coulson *et al.* (1949), calculation has shown that the smallest carbon valency angle that one can reasonably expect to have is 104°. Coulson has therefore suggested that in *cyclo*propane, the carbon hybridised orbitals are not pointing towards one another in the same straight line, and consequently there is a loss of overlap (Fig. 3*a*). It is this loss of overlap that gives rise to instability, the *cyclo*propane molecule being in a state of "strain" due to "bent" bonds. Applying this argument to *cyclo*butane (Fig. 3*b*), we see that this molecule also has "bent" bonds, but loss of overlap is less in this case than for *cyclo*propane, and so the former will be more stable than the latter (see also p. 28).

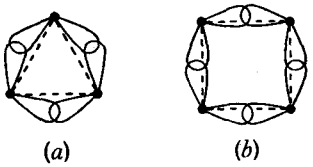


FIG. 19.3.

Theory of Strainless Rings. According to Baeyer's Strain Theory (which postulates planar rings), a parallel will exist between the ease of formation of a ring and the stability of that ring. This implied that very large rings were difficult, if at all possible, to prepare, due to the great strain involved

TABLE VII

Number of carbon atoms in the ring	Heat of combustion in kg. cal./CH_2
2	170
3	166·5
4	163·8
5	158·7
6	157·2
7	158·2
8, ---	158–159
n-paraffins	157·5

in the ring. Chemical stability may be measured in various ways, *e.g.*, by the heat of formation, heat of combustion, dipole moment, absorption spectra, etc. One of the most convenient to work with in respect to hydrocarbons is the heat of combustion. If the strain in a ring changes with the size of the ring, then this should be observed by changes in the heat of combustion.

According to the results shown in Table VII, stability increases up to the five- and six-membered rings and then remains effectively constant. This can be explained by rejecting the postulate that all rings are planar, and by assuming that rings with six or more carbon atoms are *puckered*, the *normal* valency angle being retained and thereby producing *strainless* rings. Such a suggestion was first made by Sachse (1890), and according to him, *cyclo*hexane exists in two forms, both of which are strainless (Fig. 4).

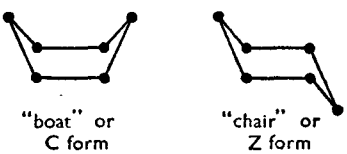


FIG. 19.4.

The two forms of *cyclo*hexane are also known as the chair and boat **conformations,** the term conformation being used to denote different spatial arrangements of the atoms of a given molecular structure, the arrangements being produced by twisting or rotation of bonds. The terms *rotational isomer* and *constellation* have also been used in the same sense as conformation.

Although the two conformations are free from *angle strain*, forces due to steric repulsion (p. 108) are present, and these are different in the two conformations. Turner (1952) has introduced a simple method of calculating this energy difference. In the chair form (Fig. 5*a*) all the C—H bonds on

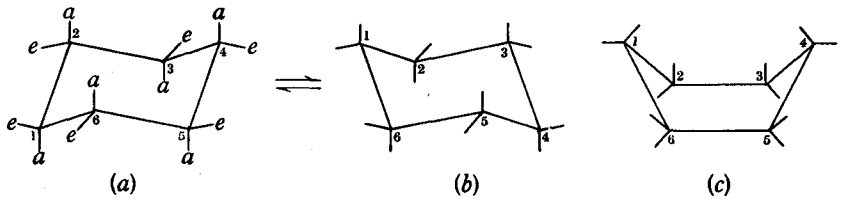


FIG. 19.5.

adjacent carbon atoms are in the skew position (projection of the hydrogen atoms on two adjacent carbon atoms on a plane perpendicular to the bonding line shows the hydrogen atoms are in the skew form; *cf.* ethylene chloride, p. 405). In the boat form (Fig. 5*c*), however, four of the C—H bonds are skew (1 : 2, 3 : 4, 4 : 5, and 6 : 1), and two are eclipsed (2 : 3 and 5 : 6). According to Pitzer (1940), a skew interaction of hydrogens in *n*-butane has a value of 0·8 kg. cal. and an eclipsed 3·6 kg. cal. (the conformations of *n*-butane are similar to those of ethylene chloride; replace Cl by CH_3) Thus the **steric strain** in the chair form is $6 \times 0{\cdot}8 = 4{\cdot}8$ kg. cal., and in the boat form $4 \times 0{\cdot}8 + 2 \times 3{\cdot}6 = 10{\cdot}4$ kg. cal. Hence the difference is 5·6 kg. cal. This is a minimum difference, since the steric repulsion between the hydrogens pointing towards each other at 1 and 4 (Fig. 5*c*) has been ignored (the actual value of this repulsion is uncertain). Thus the chair form will be more stable than the boat, but the energy difference of 5·6 kg. cal. between the two is too small for stability, and so neither retains its identity, each being readily converted into the other. Hassel (1943), however, has shown by electron diffraction studies that at room temperature most of the molecules exist mainly in the chair form, *i.e.*, the chair conformation is the preferred one.

Since the boat conformation occurs in relatively few cases, we shall confine our attention to the chair form. Consideration of the C—H bonds in this form shows that there are two sets of six In one set the six C—H bonds are parallel to the axis of the ring (Fig. 5*a*); these are the **axial** (*a*) **bonds** (or ε- or *polar* bonds). In the other set the six C—H bonds make an angle of 109° 28′ with the axis (or ±19° 28′ with the horizontal plane of the ring; Fig. 5*a*); these are the **equatorial** (*e*) **bonds** (or κ-bonds). Each carbon atom has one axial and one equatorial bond, and because of the flexibility of the chair conformation, one form (Fig. 5*a*) can readily change into the other (Fig. 5*b*), and when this occurs all hydrogens originally axial now become equatorial, and vice versa. The two forms are identical.

Calculations have shown that in the chair conformation the distances between pairs of hydrogen atoms are (Angyal and Mills, 1952):

1*e* : 2*e*, 2·49A; 1*e* : 2*a*, 2·49A;

1*a* : 2*a*, 3·06A; 1*a* : 3*a*, 2·51A.

The nearest four hydrogens to the equatorial hydrogen at 1 are those on 2 (*a* and *e*) and 6 (*a* and *e*) whereas for the axial hydrogen at 1 these four hydrogens are the axial hydrogens on 3 and 5 and the equatorial on 2 and 6 (see Fig. 5*a*). Thus a 1 : 2-interaction for two adjacent equatorial hydrogens or for an equatorial and an adjacent hydrogen is about the same as for a 1 : 3-interaction for two *meta* axial hydrogens.

Now let us consider the problem when one hydrogen atom in *cyclo*hexane is replaced by some substituent which, of necessity, must be larger than

a hydrogen atom. A study of accurate scale models has shown that in monosubstituted *cyclo*hexanes, an axial substituent at 1 is closer to the two axial hydrogens at 3 and 5 than an equatorial substituent at 1 is to the four hydrogens at 2 and 6. Thus 1 : 3-interactions will be greater than 1 : 2-interactions, and so, in general, a monosubstituted *cyclo*hexane will assume the conformation in which the substituent occupies an equatorial position. This has been confirmed experimentally, *e.g.*, Hassel (1950) has shown from electron-diffraction studies that the chlorine in chloro*cyclo*hexane is equatorial (predominantly).

From what has been said above, we can now say that **conformational analysis** is the study of the existence of one or more preferred conformations in a given molecular structure, and the relating of the physical and chemical properties to this preferred conformation.

Let us now consider the application of conformational analysis to 1 : 2-disubstituted *cyclo*hexanes in which the two substituents are identical. According to the classical ideas of stereochemistry, there are two forms possible, *cis* and *trans*. The conformation of the *cis* configuration *must*

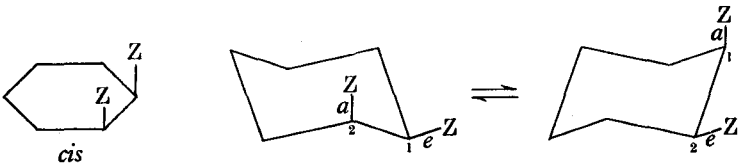


FIG. 19.6.

have one axial and one equatorial substituent (Fig. 6). The two conformations are mirror images and are *not* superimposable. Hence, if each were sufficiently stable, they would form a pair of enantiomorphs. Such compounds have never yet been resolved (their interconversion is very easy).

The *trans* configuration can exist in two different conformations, 1*a* : 2*a* and 1*e* : 2*e* (Fig. 7), but from what has been said above, the *trans*-1*e* : 2*e* form will be more stable than the *trans*-1*a* : 2*a*, and this *trans* form will be more stable than the *cis*.

The above arguments can be applied to the 1 : 3- and 1 : 4-disubstituted *cyclo*hexanes, and to the polysubstituted derivatives, and it will be found that the chair conformation with the maximum number of equatorial substituents will be the preferred form. This generalisation, however, is only true when other forces due to, *e.g.*, dipole interactions, hydrogen bonding, are absent. When these " disturbing " factors are present, they

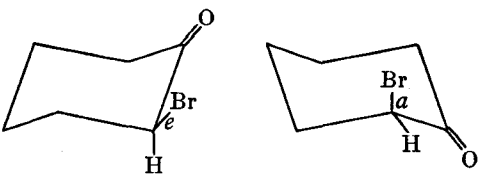


FIG. 19.7.

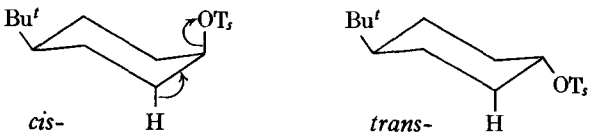
may be large enough to outweigh the 1 : 3-interactions, *e.g.*, infrared spectra studies have shown that the bromine in 2-bromo*cyclo*hexanone is predominantly *axial* (Fig. 7). The C—Br and C=O bonds are both strongly polar, and when the bromine is equatorial the dipolar repulsion is a maxi-

mum, and a minimum when the bromine is axial. Since the axial form predominates, the equatorial dipolar repulsion must be much larger than the 1 : 3-interactions.

It is also instructive to consider one example of a 1 : 2-disubstituted *cyclo*hexane in which the two substituents are different, *e.g.*, *cis*-2-methyl-*cyclo*hexanol. Since 1 : 3-interactions will be most powerful when the larger group is axial, the preferred form will therefore be the one in which the larger group is equatorial. Thus, since the methyl group is greater than hydroxyl, the preferred form of *cis*-2-methyl*cyclo*hexanol is 1*a*-OH: 2*e*-CH_3.

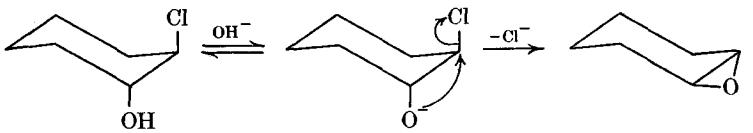
As an example of the effect of conformation on the rate of reactions let us consider hydroxy-derivatives. If the hydroxyl group is axial, then because of its proximity to the other two axial hydrogens (*i.e.*, because of the steric hindrance from 3 and 5), it would be expected that this hydroxyl would be esterified with greater difficulty than the corresponding equatorial compound. This has been shown to be so in many cases, *e.g.*, steroid alcohols.

Let us now consider the case of 4-*t*-butyl*cyclo*hexyl-*p*-toluenesulphonate (Eliel *et al.*, 1956). Two forms, *cis* and *trans*, are possible, but because of the large bulk of the *t*-butyl group, this group is *always* equatorial, *i.e.*, the conformations



of the two stereoisomers are made rigid. Under the same conditions (sodium ethoxide in ethanol at 70°), the *cis* form readily undergoes bimolecular elimination, but the *trans* does not. In the former the groups to be eliminated are in the *trans*-position (see p. 429).

The following example is of particular interest in that it illustrates the phenomenon of anchimeric assistance in neighbouring group participation (p. 415). Bartlett (1935) has shown that alkali converts *trans*-2-chloro*cyclo*hexanol into *cyclo*hexene oxide, and proposed the following mechanism:



Bergkvist (1947) showed that this reaction proceeds more than 100 times as fast as that when the *cis*-compound is used. This may be explained as follows. The *cis*-compound probably forms the alkoxide ion just as readily as does the *trans*-compound, but the *cis*-ion cannot attack at the rear of the adjacent carbon atom (where the chlorine is being ejected) without great distortion of the molecule.

Fused systems. Since the boat and chair forms of *cyclo*hexane are readily interconvertible, neither form can be isolated. Mohr (1918), however, elaborated Sachse's theory and predicted that the fusion of two *cyclo*hexane rings, *e.g.*, in decalin, should produce *cis* and *trans* forms which should be stable enough to retain their identities. Both forms have now been prepared. Several conventions have been introduced to represent these isomers. One uses *full* lines to represent groups *above* the plane of the molecule, and *broken* lines to represent those *below*. Another convention

uses a black dot to represent a hydrogen atom above the plane, and the ordinary lines of the formula to indicate a hydrogen atom below the plane. Thus the decalins may be drawn:

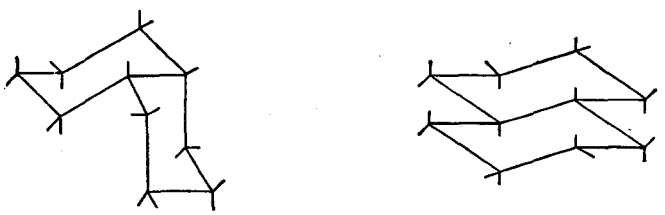
cis *trans*

Fig. 8 shows the original diagrammatical method of representing *cis*-decalin by the fusion of two boat forms, and *trans*-decalin by the fusion of two chair

***cis*-decalin** ***trans*-decalin**

FIG. 19.8.

forms. The configurations of decalin, however, are now known to be more complicated than this, the complication arising from the fact that a number of



***cis*-decalin** ***trans*-decalin**

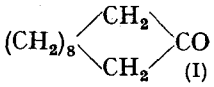
FIG. 19.9.

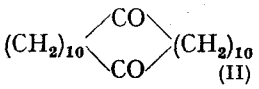
strainless modifications are possible which differ in the type of " locking ", *i.e.*, whether axial or equatorial bonds are used to fuse the rings. According to Hassel *et al.* (1946), *cis*- and *trans*-decalin are as shown in Fig. 9. In both cases the *cyclo*hexane rings are *all chair forms*; the *cis* form is produced by joining one axial and one equatorial bond of each ring, whereas the *trans* form is produced by joining the two rings by equatorial bonds only. Calculation has shown that the *cis* isomer has 2·4 kg. cal. energy content more than the *trans*. It is also of interest to note that if the decalins are regarded as 1 : 2-disubstituted *cyclo*hexanes, then the *trans* form (1*e* : 2*e*) would be expected to be more stable than the *cis* (1*e* : 2*a*).

From the foregoing account it can be seen that the Sachse–Mohr theory does not deny the existence of large rings. On the contrary, it implies that if it is possible to prepare large rings, these rings would be stable. This has been amply confirmed in recent years. Electron diffraction studies of *cyclo*hexane show it to be a puckered ring, the carbon atoms having the normal valency angle (109° 28′). Also, Ruzicka, from 1926 onwards, has prepared large rings which are stable (strainless).

Preparations of large ring compounds. Up to 1926, the largest ring compound known contained eight carbon atoms. Ruzicka and his co-workers (1926, onwards) prepared large rings containing up to thirty-four carbon

atoms. Their first method was to distil the calcium salts of dibasic acids, this method being limited to the preparation of *cyclo*pentanone, *cyclo*hexanone and *cyclo*heptanone; the yields were poor. Ruzicka and his co-workers increased the yields, and also were able to obtain larger rings, by


(I)

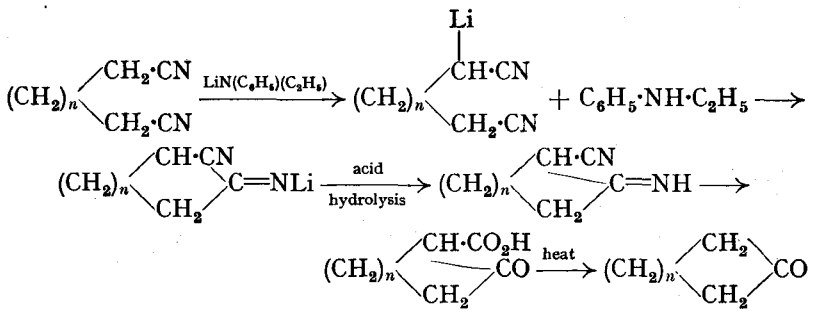

(II)

distilling *in vacuo* at about 300° the thorium, cerium or yttrium salt mixed with copper powder (which aids heat conduction). Usually a number of products was obtained by the distillation of a particular acid, *viz.*, a cyclic hydrocarbon, a cyclic monoketone and a cyclic diketone; *e.g.*, the yttrium salt of the dibasic acid $(CH_2)_{10}(CO_2H)_2$ gave a cyclic hydrocarbon, the cyclic monoketone I, and the cyclic diketone II.

The mechanism of these cyclisations is obscure. Ruzicka suggested that ring closure depends on: (*a*) the distance between the two carboxyl groups, and (*b*) the stability of the ring formed. He obtained the highest yield for five- and six-membered rings.

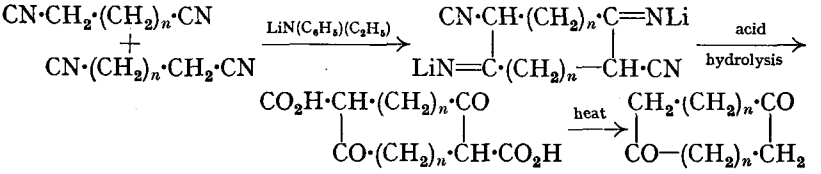
Reduction of the cyclic ketones and diketones by Clemmensen's method converted them into cyclic hydrocarbons. Conversion into the cyclic hydrocarbon was also carried out by reducing the cyclic ketone to the cyclic alcohol (with sodium and ethanol), dehydrating this (with potassium hydrogen sulphate), and then catalytically reducing the *cyclo*-olefin thus produced. By these methods, Ruzicka prepared cyclic compounds containing up to thirty-four carbon atoms in the ring. The structure of the ring compound (the cyclic ketone) was established by oxidation to the αω-dicarboxylic acid.

Ziegler and his co-workers (1933) used an entirely different method for preparing large ring compounds. They made use of the *high-dilution principle* (p. 397), obtaining large rings by the intramolecular condensation of αω-normal aliphatic dicyanides in the presence of alkali derivatives of secondary amines. In order to apply the high-dilution principle, it is necessary to have all the reactants in solution. Thus lithium derivatives (of secondary amines) are the most satisfactory, since they are soluble in ether (they are covalent compounds). The mechanism of the reaction is not certain; it may be as follows:



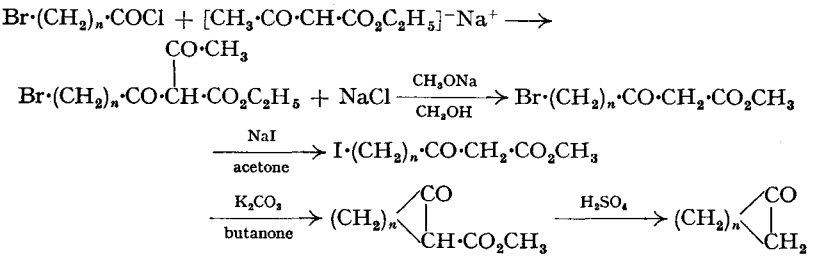
The high dilution was effected by very slowly adding a dilute solution of the dicyanide in ether to a solution of the lithium compound in ether. This method may be regarded as an extension of the Thorpe reaction (p. 471).

In addition to cyclic monoketones, cyclic diketones are obtained, and are believed to be formed as follows:

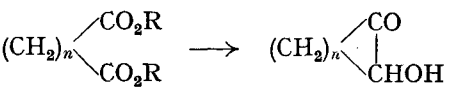


This method of preparing large ring compounds is superior to Ruzicka's, since the yields are better (up to 85 per cent.).

Hunsdiecker (1942) has prepared large rings by condensing an ω-bromoacyl chloride with sodioacetoacetic ester, subjecting the product to " acid hydrolysis " with methanolic sodium methoxide, then replacing the bromine atom by iodine, and finally cyclising the product by boiling in butanone in the presence of potassium carbonate. The cyclic keto-ester is then treated with sulphuric acid, whereupon the β-keto-acid produced spontaneously decarboxylates:

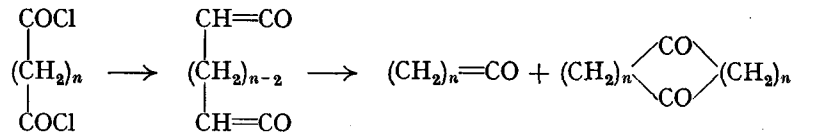


Prelog (1947) and Stoll (1947) have prepared large ring compounds from dicarboxylic esters containing nine or more carbon atoms. The ester is made to undergo the acyloin synthesis (p. 193) by heating in xylene solution with sodium, and finally acidifying.



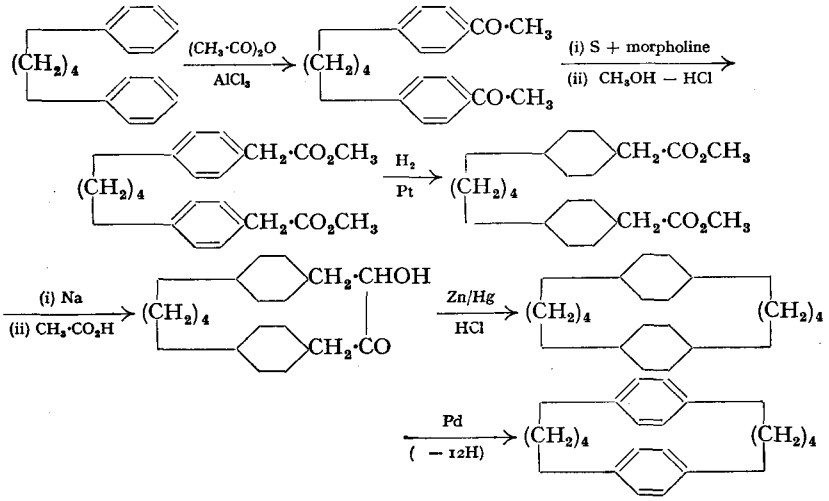
The yields by this method exceed those by any other given above, and an added advantage is that the reaction does not have to be carried out at high dilution (see also the Dieckmann reaction, p. 470).

Recently large rings have been prepared by treating the ethereal solution of acid chlorides of the dibasic acids with triethylamine; an aldoketen is formed first, and this then cyclises (Blomquist and Spencer, 1947, 1948):

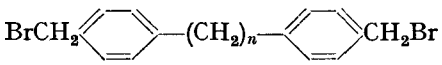


Large rings have also been prepared via *cyclo*-ynes and -di-ynes (p. 486).

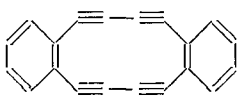
The **paracyclophanes** form another type of large ring system in that they contain two benzene rings joined in the *para*-positions. Cram *et al.* (1954) have prepared them as follows (using the Friedel–Crafts reaction (p. 529), the Willgerodt reaction (p. 663), and the acyloin synthesis), *e.g.*,



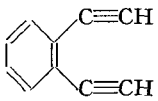
Cram *et al.* (1951) have also prepared paracyclophanes by the action of sodium on the following compound ($n \geq 2$):



Eglinton *et al.* (1959, 1960) have prepared the cyclic dimer (I) by oxidative coupling of *o*-diethynylbenzene (II; *cf. cyclo*alkynes, p. 486).



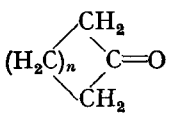
(I)



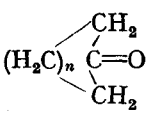
(II)

These large ring compounds are very stable, *e.g.*, they are not affected by hydrogen chloride at 200° or by hydrogen iodide at 250°. They cannot therefore be planar (the negative strain would be very large); X-ray analysis has shown that the rings are puckered—the carbon retaining its normal tetrahedral valency angle—and that they consist of two parallel portions (this applies to rings containing more than twenty carbon atoms).

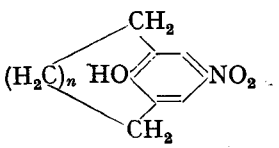
Although these large rings are free from angle strain, they are, however, subject to steric strain produced by steric repulsion (*cf. cyclo*hexane, p. 489). Since all puckered rings are subject to this strain, it was thought that the physical and chemical properties of large rings would be similar to those of *cyclo*hexane. It has now been shown, however, that the properties of large rings depend on the size of the ring. The reason for this is not certain, but one suggestion is that shielding of a reactive centre will vary with the size of the ring, *e.g.*, a cyclic ketone could be (III) (" O-outside ") or (IV)



(III)



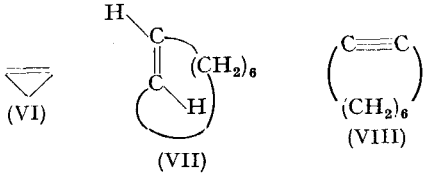
(IV)



(V)

(" O-inside "). Now medium-sized ketones combine with nitromalonaldehyde, $NO_2{\cdot}CH(CHO)_2$, to form *p*-nitrophenols, (V) (Prelog *et al.*, 1948). It therefore follows that the carbonyl group is shielded as in (IV).

Although large saturated rings are relatively strainless, rings containing multiple bonds present a different picture. Experiments, so far, have shown that the smallest ring that can contain a *cis*-double bond is three-membered (VI), and a *trans*-double bond is eight-membered (VII). The smallest ring yet made



(VI) (VII) (VIII)

containing a triple bond is eight-membered (VIII). All of these compounds show abnormal reactivity.

Two large carbon-ring compounds occurring in nature are *civetone* and *muscone*.

Civetone, $C_{17}H_{30}$, m.p. 31°, occurs in the civet and is the cause of the civet odour. Its constitution was elucidated by Ruzicka (1926, 1927). It was shown to be a ketone (carbonyl group present and compound non-reducing), and to contain a double bond (adds on bromine). When catalytically reduced, civetone absorbs one molecule of hydrogen (therefore one double bond present) to form *dihydrocivetone* (m.p. 63°). Oxidation of this compound with chromic acid gives a dicarboxylic acid, $C_{17}H_{32}O_4$, which was shown to be pentadecane-1:15-dicarboxylic acid; this acid was also synthesised. Since this acid contains the same number of carbon atoms as the original ketone, Ruzicka inferred that the ketone was a seventeen-membered ring compound; this was supported by evidence obtained from the study of the molecular refraction of the ketone. Thus the structure of dihydrocivetone is $\begin{matrix}CH_2{\cdot}(CH_2)_7\\ |\\ CH_2{\cdot}(CH_2)_7\end{matrix}\!\!>\!CO$.

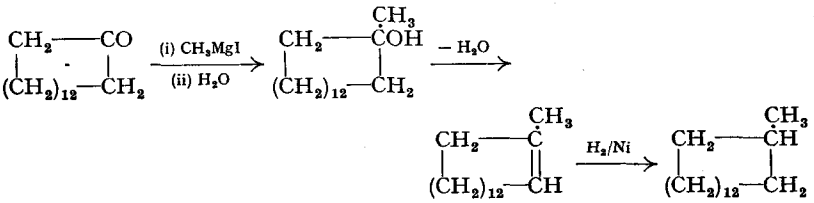
Reduction of civetone by Clemmensen's method produces *civetane* (which contains a double bond), and this, on ozonolysis, gives the same dicarboxylic acid as before (from dihydrocivetone). This again indicates a seventeen-membered ring containing one double bond. To find the position of the double bond in civetone, Ruzicka oxidised civetone with sodium hypobromite, and obtained a mixture of succinic, pimelic, suberic and azelaic acids. Since the structure of azelaic acid is $CO_2H{\cdot}(CH_2)_7{\cdot}CO_2H$, the double bond in civetone must be at least on C_9 (the carbon atom of the CO group being C_1), since to obtain azelaic acid there must be seven methylene groups between the carbonyl group and the double bond. The formula which fits this is $\begin{matrix}CH{\cdot}(CH_2)_7\\ \|\\ CH{\cdot}(CH_2)_7\end{matrix}\!\!>\!CO$. This structure was confirmed by controlled oxidation of civetone with potassium permanganate; a ketodibasic acid was obtained, and its structure was determined by synthesis by heating the methyl acid ester of azelaic acid with iron powder:

$$\begin{matrix}CH{\cdot}(CH_2)_7\\ \|\\ CH{\cdot}(CH_2)_7\end{matrix}\!\!>\!CO \xrightarrow{[O]} \begin{matrix}HO_2C{\cdot}(CH_2)_7\\ \\ HO_2C{\cdot}(CH_2)_7\end{matrix}\!\!>\!CO \xleftarrow[\text{(ii) hydrolysis}]{\text{(i) Fe}} 2\ \begin{matrix}CH_3O_2C\\ \\ HO_2C\end{matrix}\!\!>\!(CH_2)_7$$

The structure of civetone has been confirmed by a number of syntheses.

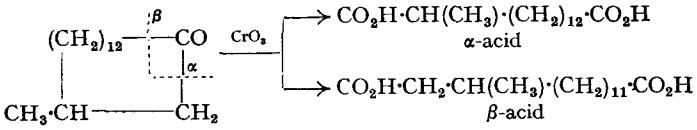
Muscone (*muskone*), $C_{16}H_{30}O$, occurs in natural musk (from the musk deer). It is a thick colourless oil and is optically active. Its structure was elucidated by Ruzicka. Its molecular formula is $C_{16}H_{30}O$, and it was shown to be a ketone. Since it was also shown to be saturated, it must therefore be cyclic, since if it were an open-chain compound, its formula would be $C_{16}H_{32}O$; if it had contained more than one ring, the number of hydrogen atoms would have been less than thirty. Since muscone is optically active, it must contain at least one asymmetric carbon atom: further work has shown it contains only one (see below).

The investigation of the odours of cyclic compounds was then used to elucidate the structure of muscone. Ruzicka was led to adopt this procedure because he had found that civetone and dihydrocivetone had about the same odour, *i.e.*, he assumed that similar structures gave rise to similar odours (this might be termed a *physiologico-chemical* method). Ruzicka found that the odour of muscone was identical with that of synthetic *cyclo*pentadecanone and its methyl derivatives (see also below). He believed that muscone was therefore a methyl derivative of the fifteen-membered cyclic ketone. This was proved by preparing *cyclo*pentadecanone (by distillation of the thorium salt of tetradecane-1: 14-dicarboxylic acid), treating it with methylmagnesium iodide, and dehydrating the tertiary alcohol so produced to the olefin which was then catalytically reduced to methyl*cyclo*pentadecane:



Methyl*cyclo*pentadecane is also obtained when muscone is reduced by the Clemmensen method.

The problem now was to determine the position of the methyl group with respect to the carbonyl group. When oxidised with chromic acid, muscone yields two acids with the formula $C_{14}H_{28}(CO_2H)_2$ and a mixture of lower dicarboxylic acids. The properties of the acids with the formula $C_{14}H_{28}(CO_2H)_2$ agreed with the properties of synthetic α- and β-methyltridecane-1: 11-dicarboxylic acids, both of which may be expected from the oxidation of a fifteen-membered ring ketone with a methyl group in the β-position with respect to the carbonyl group:



This evidence, however, is not conclusive for the structure of muscone. Muscone was finally shown to contain the methyl group in the β-position by synthesis.

Civetone and muscone are both used in perfumery. Investigation of the relationship between ring size and odours of cyclic ketones is as follows: C_5, bitter almonds; C_6, mint; C_7–C_9, transition to camphor; C_{10}–C_{13}, transition to cedar: C_{14}–C_{16}, transition to musk with maximum musk odour at C_{15}; C_{17}, civetone; C_{18}, very weak civetone; from C_{19} onwards, the odour decreases very rapidly.

*cyclo*Pentadecanone is used in perfumery under the name of *exaltone*.

QUESTIONS

1. Discuss the general methods for preparing alicyclic compounds.

2. Starting with any *readily accessible open-chain* compounds you like, suggest a synthesis for each of the following:—(*a*) *cyclo*pentane, (*b*) *cyclo*heptanone, (*c*) *cyclo*hexane-1: 3-dione, (*d*) *cyclo*pentane-1: 2-dione, (*e*) *cyclo*hexene, (*f*) 1: 5-diMe-*cyclo*penta-1: 4-diene, (*g*) hexahydrobenzoic acid, (*h*) endoethylene-hexahydrobenzoic acid, (*i*) endomethylene-hexahydrophthalic acid, (*j*) *cyclo*pentylacetic acid.

3. Describe *two* methods of preparation of each of the *cyclo*alkanes containing 3—6 carbon atoms.

Name the compounds and state the conditions under which they are formed when each of the above hydrocarbons is treated with:—(*a*) Br_2, (*b*) HBr, (*c*) HI, (*d*) HCl, (*e*) heat, (*f*) H_2, (*g*) HNO_3, (*h*) H_2SO_4.

4. Write an account of:—(*a*) the Baeyer Strain Theory, (*b*) the Theory of Strainless Rings, (*c*) the preparation of large-ring compounds.

5. What is meant by the term *chemical stability*? Discuss the various methods which may be used to measure chemical stability.

6. Discuss the structure of civetone and muscone.

7. Define and give examples of:—(*a*) the Freund reaction, (*b*) the Wislicenus reaction, (*c*) the Perkin junior reaction, (*d*) the Dieckmann reaction, (*e*) the Thorpe reaction, (*f*) the Diels–Alder reaction, (*g*) the Clemmensen reduction, (*h*) the Favorsky rearrangement, (*i*) the Demjanov rearrangement.

8. Discuss the preparation and properties of (*a*) tropolone, (*b*) ferrocene, (*c*) *cyclo*hexene, (*d*) the paracyclophanes.

9. Write an essay on conformational analysis.

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CHAPTER XX

AROMATIC COMPOUNDS

SIMPLE AROMATIC HYDROCARBONS

EARLY in the development of Organic Chemistry, organic compounds were arbitrarily classified as either aliphatic or aromatic. The aliphatic compounds were so named because the first members of this class to be studied were the fatty acids (see p. 38). The term *aliphatic* is now reserved for any compound that has an *open-chain* structure.

In addition to the aliphatic compounds, there was a large number of compounds which were obtained from natural sources, *e.g.*, resins, balsams, "aromatic" oils, etc., which comprised a group of compounds whose structures were unknown but had one thing in common: a pleasant odour. Thus these compounds were arbitrarily classified as *aromatic* (Greek: *aroma*, fragrant smell). Careful examination of these compounds showed that they contained a higher percentage carbon content than the corresponding aliphatic hydrocarbons, and that most of the simple aromatic compounds contained at least *six* carbon atoms. Furthermore, it was shown that when aromatic compounds were subjected to various methods of treatment, they often produced benzene or a derivative of benzene. If attempts were made to convert aromatic compounds into compounds with fewer carbon atoms than six (as in benzene), the whole molecule generally disrupted. It became increasingly evident that aromatic compounds were related to benzene, and this led to reserving the term aromatic for benzene and its derivatives. Thus aromatic compounds are *benzenoid* compounds; these are cyclic, but their properties are totally different from those of the alicyclic compounds.

Benzene (*phene*), C_6H_6, was first isolated by Faraday (1825) from cylinders of compressed illuminating gas obtained from natural sources. In 1845, benzene was found in coal-tar by Hofmann, and this is still the main source of benzene and its derivatives.

When coal is destructively distilled, four fractions are obtained: coal-gas, coal-tar, ammoniacal liquors and coke.

Coal-tar. The composition of coal-tar depends on the method of carbonisation, *viz.*, the type of retort used, the temperature and the time taken for

TABLE VIII

Number of fraction	Temperature range	Name of fraction	Specific gravity	Percentage by volume
1	Up to 170°	Crude light oil	0·970	2·25
2	170–230°	Middle oil or Carbolic oil	1·005	7·5
3	230–270°	Heavy oil or Creosote oil	1·033	16·5
4	270–360°	Green oil or Anthracene oil	1·088	12
5		Pitch (left in retort)		about 56

carbonisation. Water is removed from tar by slow heating and the tar is then fractionated. The number of fractions taken varies; a typical sample is shown in Table VIII.

The crude light-oil fraction is washed successively with concentrated sulphuric acid, water, sodium hydroxide and water. The sulphuric acid

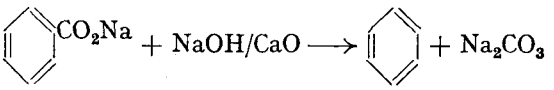
removes basic substances such as pyridine, and also removes some of the thiophen; the sodium hydroxide removes phenols. The washed light oil is now distilled. Various fractions may be taken, *e.g.*, the fraction collected up to 110° is known as " 90 per cent. *benzol* " (70 per cent. benzene, 24 per cent. toluene and some xylene). Pure xylene is obtained from the fraction between 110–140°. The distillate between 140–170° is known as " *solvent naphtha* " or *benzine* (consists mainly of xylenes, cumenes, etc.); it is used as a solvent for resins, rubber, paints, etc. The fraction " 90 per cent. benzol " gives pure benzene, toluene and xylene on careful fractionation; about 9·5 per cent. benzene and 8·7 per cent. toluene are obtained from the crude light-oil fraction. Enslin *et al.* (1956) have separated mixtures of benzene homologues by means of reversed-phase partition chromatography.

Benzene was first synthesised by Berthelot (1870) by passing acetylene through a red-hot tube:

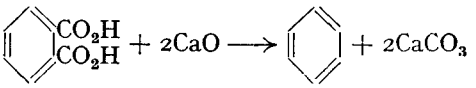
$$3C_2H_2 \longrightarrow C_6H_6$$

The polymerisation is more involved than this, since many other cyclic products are also obtained, *e.g.*, styrene and naphthalene (Goubeau *et al.*, 1953). Reppe *et al.* (1948) have shown that acetylene is converted into benzene (80 per cent. yield) in the presence of dicarbonyldi(triphenylphosphino)-nickel $[(CO)_2Ni(PPh_3)_2]$.

Benzene may be prepared in the laboratory by many methods, most of which depend on the decarboxylation of aromatic acids, *e.g.*, by heating benzoic acid with soda-lime:



or by heating phthalic acid with calcium oxide:



Preparation of benzene and its homologues from petroleum. Aromatic compounds can be extracted from petroleum in which they occur naturally. They are also prepared from the non-aromatic constituents of petroleum by two methods:

(i) **Hydroforming** or **catalytic reforming.** This method is based on dehydrogenation, cyclisation and isomerisation reactions, and the aromatic compounds obtained contain the same number of carbon atoms as the aliphatic starting materials. Very good catalysts which effect dehydrogenation and cyclisation are the oxides of chromium, vanadium and molybdenum carried on an alumina support. Hydroforming is carried out under a pressure of 150–300 lb./sq. in. at 480–550° in the presence of the catalyst. Cyclisation may be brought about on any paraffin or olefin having at least six carbon atoms in a straight chain. The mechanism of the reaction is not known with certainty, but it appears probable that the paraffin is first dehydrogenated to the olefin, which then cyclises to the aromatic hydrocarbon. The following are the most important examples of hydroforming:

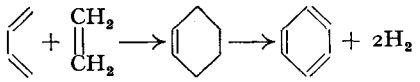
$$\underset{n\text{-hexane}}{CH_3{\cdot}(CH_2)_4{\cdot}CH_3} \longrightarrow \underset{\text{benzene}}{C_6H_6} + 4H_2$$

$$\underset{n\text{-heptane}}{CH_3{\cdot}(CH_2)_5{\cdot}CH_3} \longrightarrow \underset{\text{toluene}}{C_6H_5{\cdot}CH_3} + 4H_2$$

$$\underset{n\text{-octane}}{CH_3{\cdot}(CH_2)_6{\cdot}CH_3} \longrightarrow \underset{\text{xylene (three isomers)}}{C_6H_4(CH_3)_2} + \underset{\text{ethyl-benzene}}{C_6H_5{\cdot}C_2H_5}$$

It is interesting to note that catalytic reforming was originally intended to raise the octane number of petrol (see p. 57).

(ii) **High-temperature cracking in the presence of a catalyst.** This method was also originally used to raise the octane number of petrol. The charging stock may be cracked at about 650–680° in tubes packed with metallic dehydrogenation catalysts (which are the same as those used in hydroforming). By this means the following aromatic hydrocarbons have been isolated from the cracked paraffins: benzene, toluene, xylenes, naphthalene, anthracene and many other polynuclear hydrocarbons. There appears to be a large amount of evidence to show that the mechanism of the formation of the aromatic compounds is via the Diels–Alder reaction, *i.e.*, low-molecular-weight olefins and diolefins are produced in the cracking process, and these condense to form aromatic hydrocarbons as follows, *e.g.*,



If this is the mechanism of the reaction, then it is an example of the Diels–Alder reaction in which the dienophile does not contain a negative group (see p. 472). It should be noted, however, that the conditions used are not the same as those in the usual Diels–Alder reaction: this is carried out up to about 100°; cracking is carried out at a far higher temperature.

Properties of benzene. Benzene is a colourless liquid, m.p. 5·5°, b.p. 80°, with a peculiar smell. It is inflammable, burning with a smoky flame, a property which is characteristic of most aromatic but not of most aliphatic compounds, and is due to the high carbon content of the former. Benzene is insoluble in water, but is miscible with ethanol and ether in all proportions. It is a very good solvent for fats, resins, sulphur, iodine, etc., and is used in dry cleaning. It is also used as a motor fuel (" benzol ") and for the manufacture of nitrobenzene, dyes, drugs, etc.

Benzene is a very stable compound; it is very slowly attacked by a solution of chromic acid or acid permanganate (both powerful oxidising agents) to form carbon dioxide and water. It can be reduced catalytically to *cyclo*hexane, but the partially hydrogenated products, dihydro- and tetrahydrobenzene, have not been isolated in this reaction. Lithium in anhydrous ethylamine, however, reduces benzene to *cyclo*hexene and *cyclo*hexane (Benkeser *et al.*, 1955). It might also be noted here that nickel is an extremely good catalyst for the catalytic reduction of the benzene nucleus, whereas copper chromite is useful when it is desired to retain this nucleus, *i.e.*, to reduce a side-chain only. The heats of hydrogenation of benzene in stages have been calculated and the values found are

$$C_6H_6 \xrightarrow[-5{\cdot}6]{} C_6H_8 \xrightarrow[+26{\cdot}7]{} C_6H_{10} \xrightarrow[+28{\cdot}6]{} C_6H_{12} \quad \text{kg.cal./mole.}$$

These values indicate that the reduction of the first double bond is different from that of the second and third.

When heated with hydrogen iodide at 250°, benzene is converted into a mixture of *cyclo*hexane and methyl*cyclo*pentane. The action of chlorine and bromine on benzene depends on the conditions. In bright sunlight, halogen forms *addition* products with benzene, *e.g.*, chlorine adds on to form benzenehexachloride, $C_6H_6Cl_6$. In the absence of direct sunlight, benzene undergoes *substitution* with halogen; the reaction is slow, but in the presence of a halogen carrier, *e.g.*, iron or iodine, substitution is rapid. Thus, with chlorine, benzene forms chlorobenzene, C_6H_5Cl, dichlorobenzenes, $C_6H_4Cl_2$,

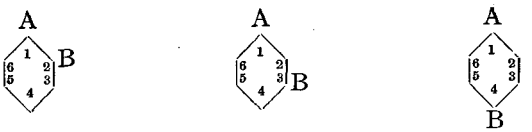
etc. When benzene is heated with concentrated nitric acid or concentrated sulphuric acid, substitution products of benzene are obtained:

$$C_6H_6 + HNO_3 \longrightarrow \underset{\text{nitrobenzene}}{C_6H_5{\cdot}NO_2} + H_2O$$

$$C_6H_6 + H_2SO_4 \longrightarrow \underset{\text{benzenesulphonic acid}}{C_6H_5{\cdot}SO_3H} + H_2O$$

Isomerism of benzene derivatives. Since all the six hydrogen atoms in benzene are equivalent (p. 508) only one monobromobenzene, mononitrobenzene, etc., is possible. In many compounds the univalent radical $C_6H_5^-$ is known as **phenyl,** and is represented by the abbreviation Ph or ϕ, *e.g.*, chlorobenzene may be written PhCl or ϕCl. When dealing with *any* univalent aromatic radical, the symbol Ar is used.

When two hydrogen atoms in benzene are replaced by two univalent radicals (which may be the same or different), three isomers are possible (position isomerism):

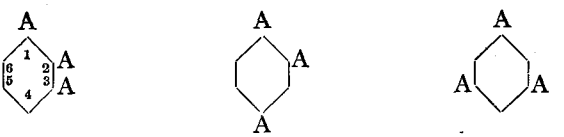


o- *m-* *p-*

Since the six hydrogen atoms in benzene are equivalent, the positions 1 : 2- and 1 : 6- are equivalent. The 1 : 2-(1 : 6-)disubstituted benzene derivative is known as the *ortho-* (*o-*) compound. The 1 : 3- and 1 : 5-positions are equivalent and a 1 : 3-(1 : 5)-disubstituted derivative is known as the *meta-* (*m*)-compound. The 1 : 4-disubstituted derivative is known as the *para-* (*p*)-compound. The bivalent radical $C_6H_4<$ is known as the **phenylene** radical, *e.g.*, *m*-phenylenediamine.

In the case of trisubstitution derivatives of benzene, the number of isomers depends on the nature of the substituent groups.

(i) If the three substituent groups are identical, then three isomers are possible:



vic- *as-* *s-*

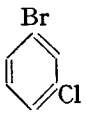
The 1 : 2 : 3-isomer is known as the *vicinal-* (*vic-*) compound; the 1 : 2 : 4- as the *unsymmetrical* or *asymmetrical* (*unsym-* or *as-*) compound; and the 1 : 3 : 5- as the *symmetrical* (*sym-* or *s-*) compound.

(ii) If two substituent groups are identical and the third different, then six isomers are possible.

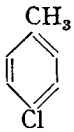
(iii) If all three substituent groups are different, then ten isomers are possible.

There are no characteristic names for the individual isomers in groups (ii) and (iii), and so the positions of side-chains and substituent groups are indicated by numbers (this may also be applied to (i) and to disubstituted derivatives). Prior to April, 1950, *British Chemical Abstracts* gave the number 1 to one of the following groups: CH_3, SO_3H, CO_2H, CN, CHO, OH, or NH_2. When two or more of these groups are present, the number 1 was

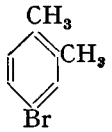
always assigned to the group *earlier* in the list. The *Chemical Society* has now adopted the alphabetical order for prefixes (see p. 46), but when two or more *functional groups* are present, number 1 is to be given to the *principal* function. The usual order for choosing the principal function is given on p. 235. For convenience of fixing the orientation (position of groups), the ring should be oriented with position 1 at the top and with the numbers proceeding in a *clockwise* direction. If a letter (*o*, *m*, *p*) is used, the principal function is still given position 1. The general rule is: **if the functional group is named as a suffix, this group is given number 1.** In many cases, however, it may be better to name aromatic compounds by using the *trivial* names of the *simple* (or *parent*) hydrocarbon. When this scheme is used, *the root name decides where numbering starts.* The following examples show the application of the above rules:



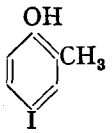
1-bromo-3-chlorobenzene; *m*-bromochlorobenzene



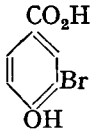
p-chlorotoluene



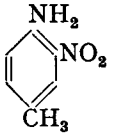
4-bromo-1 : 2-dimethylbenzene; 4-bromo-*o*-xylene



4-iodo-2-methylphenol; *p*-iodo-*o*-cresol (in both names, the suffix is -ol; therefore this group is given number 1)



3-bromo-4-hydroxybenzoic acid; 3-bromo-*p*-hydroxybenzoic acid



2-nitro-*p*-toluidine (the amino-group is in the suffix; therefore this group is given position 1); 4-amino-3-nitrotoluene (toluene is the parent, and so numbering starts at the *methyl* group).

Structure of benzene. Analysis and molecular-weight determinations show that the molecular formula of benzene is C_6H_6. The corresponding paraffin is hexane, C_6H_{14}, and since the number of hydrogen atoms in benzene is much less, it is to be expected that benzene would exhibit marked " unsaturated reactions ". This is found to be so in practice, *e.g.*,

(i) Benzene adds on halogen, the maximum number of halogen atoms being six.

(ii) Benzene may be catalytically hydrogenated to *cyclo*hexane, the maximum number of hydrogen atoms added is six.

(iii) Benzene forms a *triozonide*, $C_6H_6(O_3)_3$.

All these reactions indicate that benzene contains *three* double bonds. Further examination, however, shows that these double bonds behave in a most remarkable manner in comparison with double bonds in aliphatic compounds, *e.g.*,

(iv) Alkaline permanganate has no action on benzene in the cold, but on prolonged boiling, benzene is broken down into carbon dioxide and water.

(v) In the absence of sunlight (and preferably in the presence of a halogen carrier), benzene undergoes substitution when treated with halogen (*cf.* however, *iso*butene, p. 82).

(vi) Halogen acids do *not* add on to benzene.

Reactions (i)–(vi) lead to the conclusion that benzene contains three double bonds, but that these double bonds are different from aliphatic double

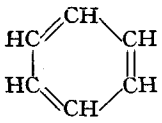
bonds. This difference gives rise to " aromatic properties " (unusual degree of saturation, stability, etc.; see also later). The problem was now to decide what is the structure of benzene, and this is one of the most interesting problems in organic chemistry; the final word still remains to be written.

Kekulé (1865) was the first to suggest a ring structure for benzene. He proposed formula I, and believed (*but did not prove*) that this formula satisfied the following points:

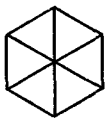
(i) That benzene contains three double bonds.

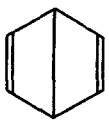
(ii) That all the six hydrogen atoms in benzene are equivalent; consequently there is only one possible mono-substituted derivative, and there are three possible disubstitution products of benzene.

Kekulé's theory stimulated a large amount of research into the structure of aromatic compounds, a notable result being achieved by Ladenburg in 1874, when he *proved experimentally* that all the six hydrogen atoms in benzene were equivalent.



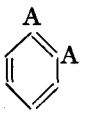
(I)


II

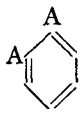

III

Kekulé's formula, however, did not explain the peculiar behaviour of the three double bonds in benzene. Claus (1867) therefore introduced his diagonal formula, (II), to overcome this difficulty. This formula also appeared to suggest a reason for the simultaneous formation of *o*- and *p*-compounds (see later). In 1882, Claus modified his formula, now postulating that the *para*-bonds were not like ordinary bonds, but could be easily ruptured.

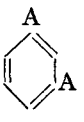
Dewar (1867) suggested a number of formulæ for benzene, one being (III). This is not perfectly symmetrical and therefore was unacceptable (but see later). Ladenburg (1869) attacked Kekulé's formula on the grounds that it should give *four* disubstituted derivatives:



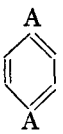
o-



o-



m-



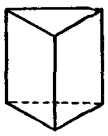
p-

Thus there should be *two ortho*-derivatives, 1 : 2- and 1 : 6-; these have never been observed in practice. Ladenburg therefore proposed his prism formula, (IV). The six carbon atoms are at the corners of a regular prism, the edges of which denote linkages. This formula does not contain any double bonds, and therefore does not account for the addition products of benzene.

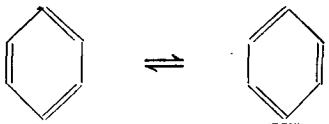
V. Meyer (1870) opposed Ladenburg; he pointed out that the 1 : 2- and 1 : 6-derivatives differed only in the position of double bonds and believed that this difference would be too slight to be noticeable. V. Meyer thus supported Kekulé's formula.

Kekulé (1872) felt that too much importance was being attached to the possible difference between the 1 : 2- and 1 : 6-positions, and pointed out that the difficulty arose from the inadequate representation of molecules by structural formulæ. According to Kekulé, the carbon atoms in benzene were continually in a state of vibration, and due to this vibration, each C—C pair had a single bond half of the time and a double bond the other half. This amounts to an oscillation between the two forms (V) and (VI),

each molecule spending half its time in (V) and the other half in (VI). Thus neither (V) nor (VI) represents the benzene molecule satisfactorily; benzene is a " combination " of the two, and so all bonds will be identical (neither single nor double), and hence there is no real difference between 1 : 2- and 1 : 6-disubstituted benzenes.

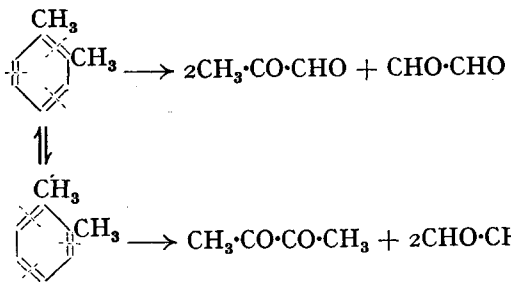


(IV)

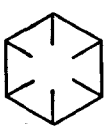


(V) (VI)

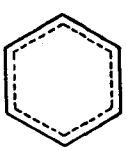
In 1932, Levine and Cole subjected *o*-xylene to ozonolysis and obtained glyoxal, methylglyoxal and dimethylglyoxal. These authors supported Kekulé's oscillation (tautomeric) hypothesis, arguing that the three carbonyl compounds could not be obtained unless *two* forms of *o*-xylene were present (see, however, p. 508):



Baeyer (from about 1884–1892) carried out a detailed investigation of benzene and some of its derivatives in order to decide between the formulæ of Kekulé and Ladenburg. One of the first things Baeyer proved was that hexamethylene (*cyclo*hexane) and hexahydrobenzene were identical, thus establishing the ring structure of benzene (which Kekulé had assumed). Baeyer observed that as soon as one double bond was removed from benzene, the " saturation " properties were lost, and that dihydrobenzene (*cyclo*-hexadiene) behaved as would be expected of a diolefin. Baeyer showed that no *para* linkage was apparently present and hence rejected Claus' diagonal formula; he also rejected Dewar's formula for similar reasons. Baeyer also showed, by investigation of various benzene derivatives, that Ladenburg's prism formula was untenable. Baeyer concluded that benzene contained six carbon atoms in a ring, but did not accept Kekulé's formula. He adopted a suggestion of Armstrong (1887) and proposed what is known as the Armstrong–Baeyer centric formula (VII). According to this, the



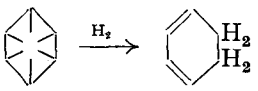
(VII)



(VIII)

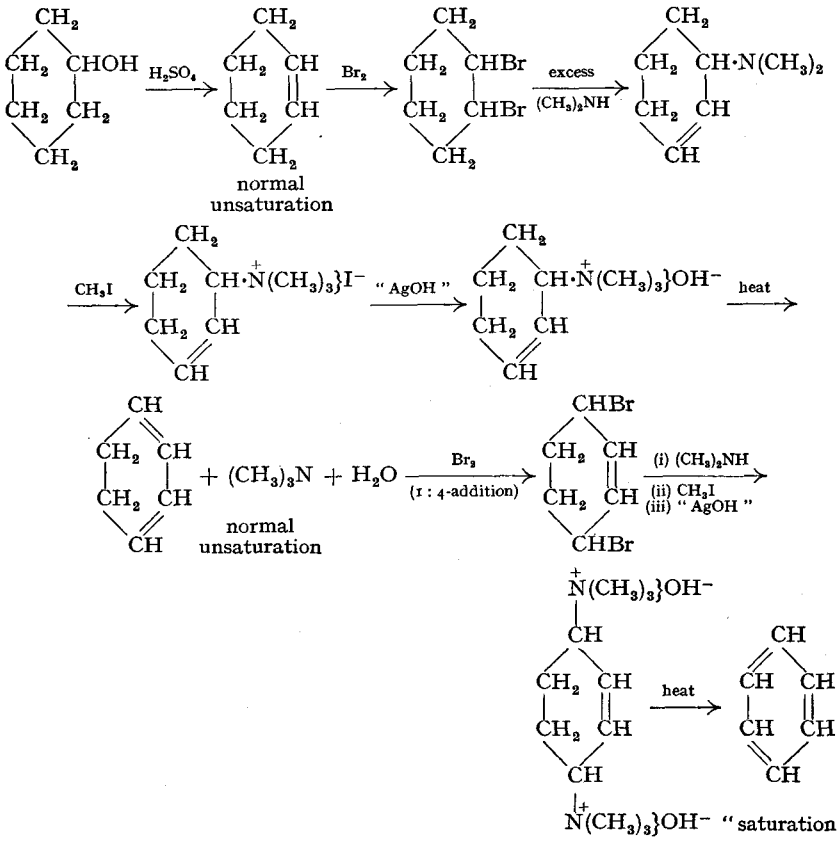
fourth valency of each carbon atom is represented as directed towards the centre of the ring but not actually linked to its opposite neighbour as in the Claus formula. This centric bond is not real but potential; by mutual

action the power of each is rendered latent and there is a condition of equilibrium. Such a centric formula is unknown in aliphatic chemistry, and thus this formula could account for " aromatic properties ". When benzene is converted into dihydrobenzene,* the condition of equilibrium is destroyed, resulting in the production of normal double bonds:



Thus this accounts for the difference in behaviour between benzene and its reduction products.

The centric formula, however, is unsatisfactory for several reasons, *e.g.*, it did not explain the stability of the ring or the behaviour of the polynuclear hydrocarbons. The outcome of Baeyer's work was that " aromatic properties " depend on the peculiar symmetrical arrangement of the fourth valency of each carbon atom in the ring.



Physico-chemical methods were also applied to the benzene problem, *e.g.*, Thomsen (1880) and Stohmann (1893) came to the conclusion that the heat of combustion of benzene was incompatible with the existence of three

* Dihydrobenzene cannot be obtained by the direct hydrogenation of benzene (p. 501), but since dihydrobenzene (*cyclo*hexadiene) exhibits the normal properties of a diolefin, the reduction of benzene to dihydrobenzene may be visualised as shown in the equation.

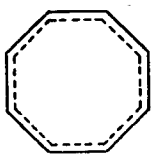
double bonds. On the other hand, Bruhl (1880) believed that the value of the refractive index of benzene proved their existence. These methods are particularly interesting in that they are some of the first examples of the application of physico-chemical methods to the elucidation of the structure of organic compounds.

In 1899, Thiele applied his theory of partial valency (p. 85) to the benzene problem, and suggested formula (VIII). This formula dispenses with Kekulé's oscillation hypothesis, and in this formula there is no real difference between " single " and " double " bonds, and so accounts for there being no difference between the 1 : 2- and 1 : 6-positions. At the same time it also accounts for the " saturation " of benzene.

The introduction of one double bond into *cyclo*hexane leads to normal unsaturated properties. Introduction of a second double bond enhances the addition reactivity, but the introduction of a third double bond causes " saturation ". Willstätter introduced successively one, two and three double bonds into *cyclo*hexanol as shown on p. 506 (using the method of exhaustive methylation; see p. 762).

The conclusion that may be drawn from this experiment is that the ring is intact, contains three double bonds, and that the introduction of the third double bond causes a complete change in properties of the resulting compound.

If Thiele's formula is correct, *i.e.*, " aromatic character " is due to the symmetrical conjugation of the benzene ring, then *cyclo*octatetraene should also exhibit " aromatic character ". Willstätter prepared this compound with a view to testing Thiele's formula for benzene, and found that it had typical unsaturated properties (see p. 485), whereas, owing to its symmetrical conjugation (structure IX), it would have been expected to resemble benzene (see also p. 509). This led to a revival of Kekulé's oscillation formulæ and some of the modifications mentioned (other than Thiele's formula). The difficulty with the Kekulé formula is that it represents benzene with three double bonds, and the oscillation does not account for the difference in behaviour between these and olefinic bonds.



(IX)

Present-day position regarding the formula of benzene. The approach at the present time is still an attempt to account for the fourth valency of each carbon atom in the benzene ring. Related to this is the question of defining " aromatic character ", about which there is still no agreement.

Originally, the term *aromaticity* was used to describe all compounds that had the properties of benzene, and was confined, in consequence, only to compounds which contained benzene rings or a condensed system of benzene rings. The reason for this description was that compounds which had " aromatic character " exhibited properties which were very much different from those of the analogous aliphatic and alicyclic compounds, *e.g.*, the ease of substitution (although the benzene ring was " unsaturated "), the stability of the benzene ring, the weaker basic properties of aromatic amines, the acidic properties of phenols (as compared with alcohols), etc. These differences in chemical properties led chemists to seek an explanation, and in consequence, to define *aromaticity*.

A very highly favoured theory for the aromatic properties of benzene uses the idea of resonance. According to this, benzene is believed to be a resonance hybrid of the resonating structures (X–XIV):

(X) (XI) (XII) (XIII) (XIV)

(X) and (XI) are Kekulé structures, which are far more stable that (XII), (XIII) and (XIV), which are Dewar structures. The instability of the latter is due to the formation of weak formal bonds (*cf.* butadiene, p. 87; it is interesting to note that a combination of the three Dewar structures gives, in effect, the Claus diagonal formula). Thus the Kekulé structures contribute far more to resonance (about 80 per cent.) than do the Dewar structures (about 20 per cent.). Furthermore, since the two Kekulé structures are equivalent the stability of the resulting resonance hybrid is very high; the resonance energy of benzene has been shown to be about 39 kg. cal./mole. Resonance therefore makes benzene relatively stable in comparison with aliphatic unsaturated compounds; hence its " aromatic properties".

Thermochemical calculations show that the heat change associated with the dehydrogenation of *cyclo*hexane to benzene, *i.e.*, the introduction of three double bonds, is about 85–95 kg. cal./mole. The experimental value is 48 kg. cal./mole. The difference, 37 kg. cal./mole, is attributed to resonance energy (this value agrees with that obtained by other methods). Thus benzene contains less energy than is expected and consequently is more stable than is expected.

Resonance gives each C—C bond in benzene some double bond character, and this has been shown to be so by measurements of the distance between two adjacent carbon atoms in various compounds. The C—C bond length (in ethane, propane, etc.) is 1·54A; the C=C bond (in ethylene) is 1·33A; and the C≡C bond (in acetylene) is 1·20A. The C—C bond length in benzene has been shown to be 1·30A, a value which lies between that of a single and that of a double bond. Furthermore, it has also been found that all the C—C bonds in benzene are the same, thus indicating the symmetrical nature of the benzene ring.

According to Haayman and Wibaut (1939), ozonolysis of *o*-xylene agrees with a resonating structure for the benzene ring. These authors found the composition of the mixture to be roughly 0·88 molecule dimethylglyoxal, 2 molecules methylglyoxal, and 3·2 molecules glyoxal. The calculated ratio should be 1 : 2 : 3 if the two Kekulé structures contribute equally; the experimental results agree fairly well with the theoretical value. The ozonolysis of *o*-xylene is an interesting example of the same experimental results being explained differently; one explanation is that *o*-xylene is a resonance hybrid (Haayman and Wibaut), and the other, a tautomeric mixture (Levine and Cole; p. 505).

In compounds of the type $Ca_2{=}Ca_2$, all the atoms are in the same plane (see p. 426). Since all the C—C bonds in benzene have double bond character due to resonance, it would therefore appear that the benzene ring should be planar, and that substituted groups should also be in the same plane (as the benzene ring). Evidence that the benzene ring is planar has been obtained from studies of X-ray analysis, dipole moments, Raman spectra, infrared spectra and electron diffraction photographs of benzene vapour.

The foregoing description of aromatic character has been in terms of valence-bond theory. An earlier modern theory is the *aromatic sextet theory*, which was proposed by Robinson (1925). The essence of this theory is that there are six electrons more than necessary to link together the six carbon atoms (of the benzene ring). These six electrons, one being contributed by each carbon atom, form a " closed group ", and it is this closed group which gives rise to " aromatic properties ". This closed group is not possible in aliphatic and alicyclic compounds, but is possible in heterocyclics, and so these also exhibit aromatic properties:

benzene

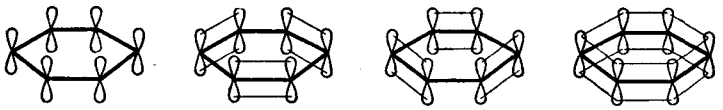
pyridine

pyrrole

furan

It should be noted that the hetero-atom in five-membered rings contributes *two* electrons to the aromatic sextet.

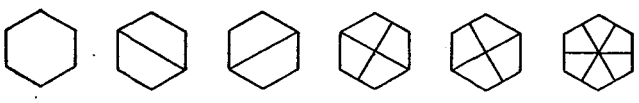
Let us first consider the benzene molecule from the point of view of M.O. theory. Spectroscopic studies and X-ray analysis have shown that benzene is a regular flat hexagon (angle 120°), with all six hydrogen atoms lying in the same plane (of the ring) and each C—C—H valency angle also being 120°. *Thus each carbon atom is in a state of trigonal hybridisation.* Hence, in benzene, there are six σ C—H bonds, six σ C—C bonds and six $2p_z$ electrons (one on each carbon atom) which are all parallel and perpendicular to the plane of the ring (Fig. 1*a*).



(*a*) (*b*) (*c*) (*d*)

FIG. 20.1.

These electrons can be paired in two ways, both being equally good (*b* and *c*). Each $2p_z$ electron, however, overlaps its neighbours equally, and therefore all six can be treated as forming *an M.O. embracing all six carbon atoms*, and so are completely delocalised (Fig. *d*; *cf.* p. 88). Since six $2p_z$ electrons are involved, six M.O.s are possible, three bonding and three antibonding (p. 30). These are as shown; ((I), (II), (III) are bonding, and (IV), (V), (VI) are anti-bonding); all have a node in the plane of the ring; but (II) and (III) have one node, (IV) and



I II III IV V VI

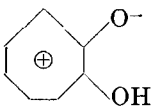
(V) two, and (VI) three nodes perpendicular to the plane of the ring. Now, as we have seen, no more than two electrons can occupy any particular M.O. Furthermore, in the ground state, the six $2p_z$ electrons of benzene will occupy, in pairs, the M.O.s of lowest energy. These three are (I), (II) and (III) (these are the M.O.s in which the number of nodes are fewer than in (IV), (V) and (VI). When benzene is in an excited state, one or more of the π-electrons will occupy the higher energy level M.O.s.

In the ground state, the total energy of the three pairs of *delocalised* π-electrons (Fig. *d*) is less than that of three pairs of *localised* π-electrons (Fig. *b* or *c*), and hence the benzene molecule is stabilised by delocalisation (resonance). It should also be noted that delocalisation of the π-electrons gives them the freedom to move round the ring, thereby producing ring currents. The flow is normally equal in both directions, but under the influence of a magnetic field perpendicular to the plane of the ring, the flow takes place preferentially in one direction to give an induced ring current (see also p. 511). Also, because of these induced currents, benzene shows a large diamagnetic susceptibility.

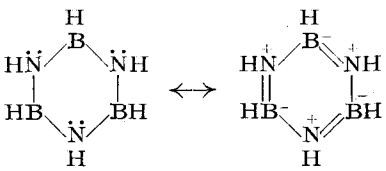
Hückel (1937) carried out an M.O. treatment of conjugated cyclic systems, and as a result connected aromatic stability (high-resonance energy) with the presence of $(4n + 2)$ π-electrons in a closed system. Thus the molecule must have 6, 10, . . π-electrons. It will be noticed in this description that no mention is made of the number of atoms in the ring; the essential requirement is $(4n + 2)$ π-electrons. However, another requirement of aromatic character is *planarity of the ring*. Thus, if a molecule has a " circular " planar system and contains $(4n + 2)$ π-electrons, that molecule will exhibit aromatic character. For benzene, $n = 1$, and the molecule has its closed shell of 6 π-electrons; benzene is regarded as the " ideal " aromatic compound. *cyclo*-Octatetraene has four double bonds (and hence

8 π-electrons), and is also not planar. Hence this molecule is *not* aromatic; it has typical olefinic properties (p. 485). *cyclo*-Octatetraene, however, forms a doubly charged anion on reaction with alkali metals.

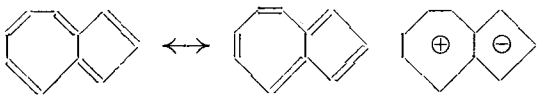
Katz (1960), from his nuclear magnetic resonance spectra studies, has shown that this dianion is *planar*, and suggests that its stability may be partly attributed to the fact that it obeys Hückel's $(4n + 2)$ rule with $n = 2$. *cyclo*-Pentadiene, by loss of a proton, forms the *cyclo*pentadienyl anion, which is a planar ring system and now has a closed shell of 6 π-electrons. This anion is very stable, and compounds containing it exhibit aromatic properties, *e.g.*, ferrocene (p. 480). The tropylium cation (p. 484) is a 7-membered ring system and contains a closed shell of 6 π-electrons. This cation is " aromatic ", and its symmetrical structure has been shown, *e.g.*, from spectral measurements (Fately *et al.*, 1955). Tropolone (p. 484), which has 7 π-electrons, " loses " one to the oxygen atom, and so is now a 7-ring system containing a closed shell of 6 π-electrons; tropolone exhibits aromatic properties. Infrared studies have shown the high polarity of the C=O bond.



Another ring system which fulfils " aromatic " requirements (for $n = 1$) borazole:



So ar, we have discussed aromatic compounds in which $n = 1$, *i.e.*, there are 6 π-electrons associated with the ring. All of these compounds which do not contain a benzene ring are referred to as *non-benzenoid aromatic compounds*. There are also non-benzenoid aromatics in which $n = 2$, *e.g.*, azulene (*cf.* the *cyclo*-octatetraene dianion, above).



dipolar structure

In the two Kekulé structures of azulene there are 10 π-electrons; the 5-membered ring has 5 and the 7-membered ring has 7 π-electrons. Because of the tendency for each ring to acquire a closed shell of 6 π-electrons, one electron passes from the 7-ring to the 5-ring, and now the molecule has a dipolar structure, each ring having an aromatic sextet.

Azulene undergoes many typical aromatic substitution reactions, *e.g.*, it can be nitrated and brominated, and undergoes the Friedel–Crafts reaction.

From the foregoing, it can be seen that " aromatic character " has been defined in different ways: " unexpected " chemical properties; possession by the molecule of a large resonance energy; presence of a planar cyclic system containing $(4n + 2)$ π-electrons.

Still other descriptions have been proposed. Diamagnetic susceptibility has been suggested as a test for aromaticity. It has been found that the value obtained in " aromatics " is much greater than the value calculated from atomic constants.

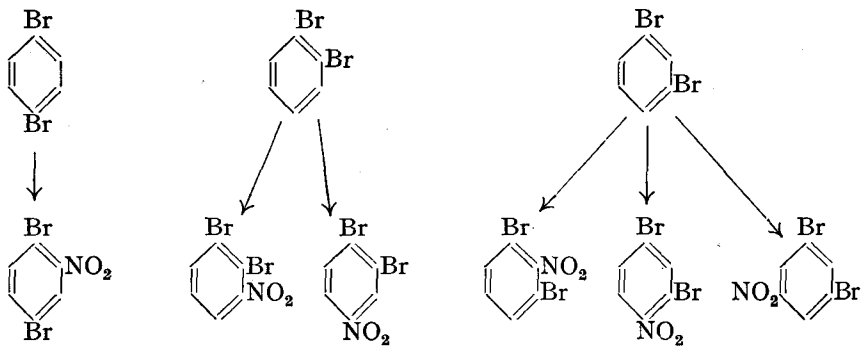
The most recent definition of aromaticity has been given by Elvidge and Jackman (1961). As we have seen, the essential feature of an aromatic

compound is a ring of atoms so linked that π-electrons are delocalised right round the ring. In these compounds there are induced circulations (or ring currents), and Elvidge and Jackman therefore define an aromatic compound as *a compound which will sustain an induced ring current.* The magnitude of the ring current will be a function of the delocalisation of the π-electrons around the ring and therefore is a measure of aromaticity (using the aromaticity of benzene as standard equal to 1). Thus Elvidge and Jackman have calculated that the 2-pyridone ring sustains only 36 per cent. of the induced ring current of benzene and so has a fractional aromaticity of 0·36.

The structural representation of aromatic compounds. According to the *Chemical Society*, the Kekulé type of structure should, in general, be used. On the other hand, large circles representing 6 delocalised π-electrons in cyclic systems (with or without positive or negative signs as appropriate) should be permitted for certain types of compounds, and in certain circumstances. Cyclic systems having more or fewer than 6 delocalised electrons may be represented by formulæ containing dotted lines.

Orientation. The problem of assigning positions of substituents in disubstituted and higher substituted derivatives of benzene is known as *orientation.* When the substitutent is a carbon radical joined to the *benzene ring* or *nucleus* it is known as a *side-chain.* The generic name of monocyclic (and polycyclic) aromatic hydrocarbons is *arene.*

(i) **Körner's absolute method** (1874). This method is based on the principle that the introduction of a third substituent into the *p*-isomer gives *one* trisubstituted product, the *o*-isomer *two*, and the *m*-isomer *three* trisubstituted products. Körner applied this principle to establish the orientation of the isomeric dibromobenzenes. He nitrated each isomer and examined the number of nitrated products. One isomer gave *one* dibromo-nitrobenzene; this isomer is therefore the *p*-compound. Another gave *two* dibromo-nitrobenzenes; this is therefore the *o*-compound; and the third gave *three* and is therefore the *m*-compound:

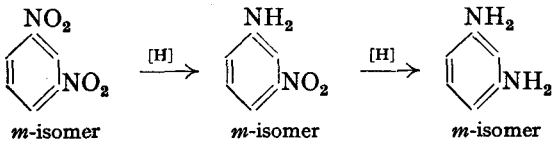


Körner also introduced a third bromine atom instead of a nitro-group (the number of isomers produced is independent of the nature of the third substituent).

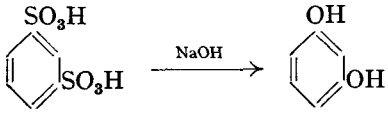
In practice, this method is often difficult, if not impossible, since all the trisubstituted products cannot always be isolated due to the formation of some in very small amount.

The reverse procedure to Körner's method is often useful, *i.e.*, one group of the isomeric trisubstituted derivatives is removed, *e.g.*, Griess (1874) distilled the six diaminobenzoic acids (all known) with soda-lime. He obtained three phenylenediamines; three acids gave the same diamine, which is therefore the *m*-isomer; two acids gave the same diamine, which is therefore the *o*-isomer; and one acid gave one diamine, which is therefore the *p*-isomer.

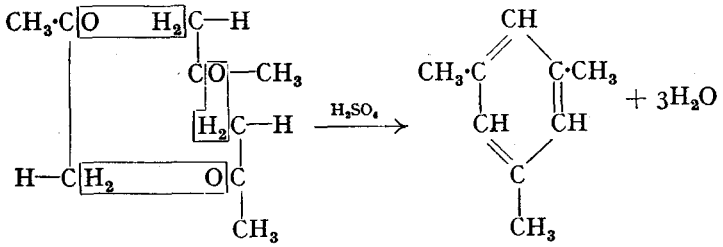
(ii) **The relative method.** In this method the compound in question is converted into or synthesised from a substance of *previously determined orientation*; *e.g.*, reduction of one or both nitro-groups in *m*-dinitrobenzene gives rise to *m*-nitroaniline and *m*-phenylenediamine respectively:



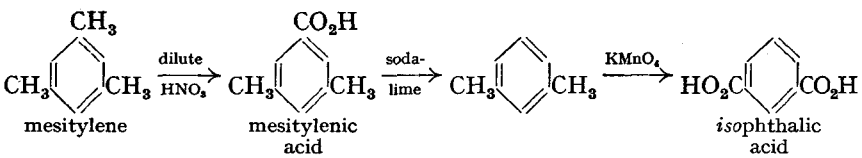
Another example is the *replacement* of one group by another, *e.g.*, *m*-benzenedisulphonic acid on fusion with sodium hydroxide gives *m*-dihydroxybenzene:



A classical example of the relative method of orientation is the case of the three benzenedicarboxylic acids. This starts with mesitylene. Mesitylene may be prepared by distilling acetone with sulphuric acid, and Baeyer *assumed* it to be *s*-trimethylbenzene, arguing that the reaction can be

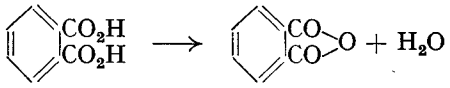


formulated only if the symmetrical structure of mesitylene is assumed. This assumption was later proved correct by Ladenburg (1874). Mesitylene may be converted into dimethylbenzene, which, in turn, may be converted into a benzenedicarboxylic acid:

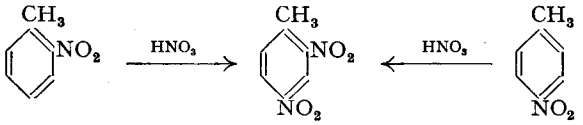


The dimethylbenzene must be the *m*-isomer whichever methyl group in mesitylene is oxidised. Hence the benzenedicarboxylic acid must be the *m*-isomer, which is known as *iso*phthalic acid. Of the three isomeric

benzenedicarboxylic acids only one, phthalic acid, forms the anhydride; the other two, *iso*phthalic acid and the one known as terephthalic acid, do not form anhydrides at all. Thus phthalic acid is the *o*-isomer (by analogy with succinic acid; *cf.* p. 374); and terephthalic acid is consequently the *p*-isomer:

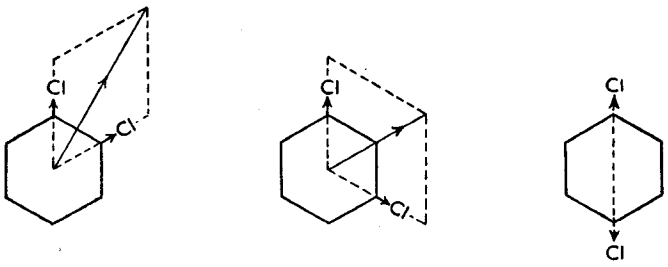


Another example of the relative method is the nitration of *o*- and *p*-nitrotoluenes; both give the *same* dinitrotoluene derivative, which, therefore, must be the *m*-dinitro-compound:



The relative method of orientation is based on the assumption that atoms or groups remain in the same positions or exchange positions with the incoming groups. It is also based on the assumption as to the structure of the *starting* material. Sometimes one or both of these assumptions are right, and sometimes they are wrong. Baeyer's assumption for the mesitylene formula was correct. On the other hand, *o*-, *m*- and *p*-bromobenzenesulphonic acids all give *m*-dihydroxybenzene (resorcinol) when fused with sodium hydroxide. These fusions are carried out at about 300°, and since the conditions are vigorous, the interpretation of the results always contains an element of doubt. Thus Körner's absolute method is more satisfactory theoretically, but unfortunately it is often difficult to carry out in practice (see below).

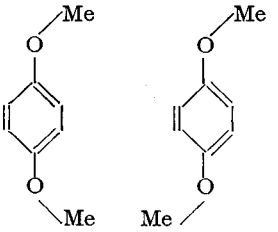
(iii) **Method of dipole measurements.** In those cases where the two substituents are either atoms or simple groups, the determination of the dipole moment of the compound may often be used to ascertain the orientation, *e.g.*, the dichlorobenzenes. The observed dipole moment of the C—Cl bond (in chlorobenzene) is 1·55D. By using this value, it is possible to calculate the dipole moments of the *o*-, *m*- and *p*-dichlorobenzenes, and by comparing these calculated values with those observed, the orientation of the isomers may be decided:



calc. 2·67D	1·55 D	0
obs. 2·3D	1·48D	0

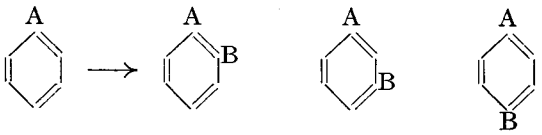
As pointed out on p. 427, the dipole moment of *p*-disubstituted benzenes will be zero only for groups which have *linear* moments, *e.g.*, *p*-dichloro-, dibromo-, dimethyl, and dinitro-benzene. When the groups have *non-linear*

moments, then the dipole moment of the *p*-disubstituted benzene will *not* be zero, *e.g.*, in *p*-dimethoxybenzene, the two extreme conformations (planar on the basis of resonance) are as shown. Thus



of these two, it is the latter molecule population which has zero dipole moment whereas the former will have some definite value. The overall result is that this compound will not have a zero dipole moment; the actual value has been shown to be 1·7D. However, this method of orientation may still be used, since the values (observed and calculated) for *o*-, *m*-, and *p*-disubstituted benzenes are very often sufficiently different to distinguish the isomers containing groups with non-linear moments.

Substitution in the benzene ring. When one group is introduced into the benzene ring, only one compound is produced. When, however, a second group is introduced, three isomers are possible:



Holleman (1895, onwards) studied aromatic substitution in great detail, and found that *when the second group enters the benzene nucleus, the main product is either a mixture of the* o- *and* p-*isomers or the* m-*isomer.* Pure *o-p*- or *m*-substitution is rare, all three isomers being obtained simultaneously; but since the velocities of their formation are very different, the slowest one results in the formation of very little of that derivative (hence the difficulty of Körner's absolute method of orientation). Holleman (1910) found that the rate of *o-p*-substitution is very much greater than *m*-; *e.g.*, if phenol is treated with bromine-water, *s*-tribromophenol is obtained extremely rapidly (and quantitatively); thus the *o*- and *p*-positions are very active. On the other hand, when nitrobenzene is brominated, *m*-bromonitrobenzene (60–70 per cent. yield) is obtained. This reaction, however, is slow; thus the *m*-position is not very active.

Experiments of this kind have led to the conclusion that usually *o-p*-substitution is associated with *activation* of the benzene nucleus, *i.e.*, reaction is faster than in benzene itself, whereas *m*-substitution is associated with *deactivation* of the nucleus, *i.e.*, reaction is slower than in benzene.

Rules of orientation. Experience shows that the nature of group A already present in the nucleus determines the position taken by the incoming group.

Class I directs the incoming group to the *o*- and *p*-positions. In this class, A may be any one of the following:—R, OH, OR, NH_2, NH·R, NR_2, NH·CO·CH_3, Cl, Br, I, F, CH_2Cl, SH, Ph, etc.

Class II directs the incoming group to the *m*-position. In this class, A may be any one of the following:—NO_2, CHO, CO_2H, CO_2R, SO_3H, SO_2Cl, CO·CH_3, CN, CCl_3, NH_3^+, NR_3^+, etc.

Very few groups direct *exclusively* to the *o*- and *p*- or to the *m*-positions. In most cases orientation is mainly *o*, *p* or *m*. Furthermore, the orienting effect of a given group may be affected by reaction conditions, *e.g.*, solvent or nature of the incoming group.

Many *empirical* rules have been formulated to predict the course of substitution in the benzene ring. These rules connected the orienting power of group A with

its acidic or basic nature (Körner, 1874; Hübner, 1875; Noelting, 1876); whether HA could be directly oxidised to HAO (Crum-Brown and Gibson, 1892); whether A was saturated or unsaturated (Vorländer, 1902). Flurscheim (1902) proposed a rule based on whether A was positive or negative, and subsequently Vorländer (1919), Lapworth (1920) and Fry (1921) all put forward a somewhat similar theory, *the theory of alternating polarities*.

The most satisfactory empirical rule is that of Hammick and Illingworth (1930). (i) If in the benzene derivative $C_6H_5{\cdot}XY$, Y is in a higher group in the periodic table than X, or if, being in the same group, Y is of lower atomic weight than X (*i.e.*, *higher* in the same group), then a second atom or group entering the nucleus goes to the *m*-position.

(ii) In all other cases, including that in which XY is a single atom, *o-p*-substitution takes place.

(iii) The effect of ionic charges on XY is given by the statement that a positive charge directs *m*- and a negative charge *o-p*-.

It is important to note that when the atoms joining the groups X and Y are the same, *e.g.*, —N=N—, —C=C—, the group XY is *o-p*-orienting (this follows from statement ii). For mixed groupings, *e.g.*, $CHCl_2$, CH_2Cl, etc., the strict rule may be applied and thereby the correct orientation will be obtained. Thus in $CHCl_2$ the part CH is *o-p*-orienting and the part CCl, *m*-; in practice, both orientations are obtained.

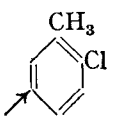
There are apparently only two exceptions, the nitroso- and iodoxy-groups (see p. 522).

Introduction of a third group into the benzene ring. The position taken up by a third group entering the ring depends on the nature of the two groups already present. Experiments by Holleman have shown that:—

(i) When both groups belong to class I, the directive power of each group is in the following order:

$$OH > NH_2 > NR_2 > NH{\cdot}CO{\cdot}CH_3 > Cl > Br > I > CH_3$$

If the *p*-position is unoccupied, then generally this position is entered preferably to the *o*-, *i.e.*, more of the *p*-isomer is formed than the *o*-, *e.g.*,



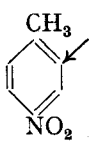
(ii) When both groups belong to class II, then it is difficult to introduce a third group, and the directive power of each group is:

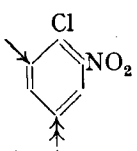
$$CO_2H > SO_3H > NO_2$$

The directive powers given above are due to Holleman, but study of more recent literature appears to show lack of agreement on this problem. However, it appears the order of *m*-directing groups is probably the reverse of that given above, *i.e.*, it appears to be

$$NO_2 > SO_3H > CO_2H$$

(iii) When the two groups direct differently, *i.e.*, belong to classes I and II, then class I takes precedence. Furthermore, if the orientations reinforce each other, the third group enters almost entirely one position, *e.g.*,





two isomers

Separation of isomers. This usually means the separation of the *o*- and *p*-isomers. There are three common methods:

(i) Steam distillation may be used, since the *o*-isomer is often steam-volatile whereas the *p*- is not. This method of separation is particularly applicable to *o*-hydroxy-compounds.

(ii) The boiling points of *o*- and *p*-isomers are often very close together and so it is difficult to separate them by fractional distillation. Their melting points, however, are usually very different, that of the *p*-isomer being much higher than that of the *o*-. Thus these isomers may be separated by filtration; it may be necessary to cool the mixture in order to get the *p*-isomer in the solid form.

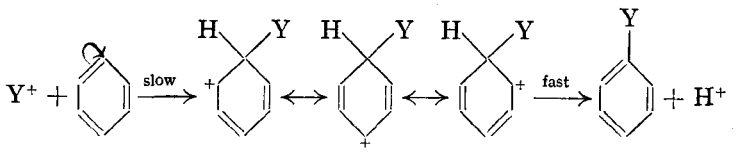
(iii) Chemical methods of separation may be used in certain cases (see, *e.g.*, p. 609).

MECHANISM OF AROMATIC SUBSTITUTION

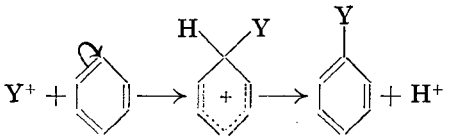
There are three possible mechanisms for aromatic substitution: electrophilic, nucleophilic and free-radical. Of these the common substitution reactions are those which involve electrophilic reagents.

Electrophilic substitution. A widely held theory of electrophilic aromatic substitution is that it proceeds by a bimolecular mechanism. This theory postulates the formation of an intermediate, and that the formation of this intermediate is the rate-determining step. Melander (1950) has shown that in nitration and bromination there is no kinetic isotope effect; he showed that tritium and protium are displaced at essentially identical rates. This indicates that the breaking to the C—H bond has made little or no progress in the rate-determining stages of these reactions. Recent kinetic studies, together with isotope effect measurements, have also established a two-step mechanism for certain coupling reactions, etc. (Zollinger, 1955; Schubert *et al.*, 1956).

Let us illustrate this mechanism for benzene itself. Theoretical considerations of Hughes and Ingold (1937) have shown that the entering group should approach the ring in a *lateral* direction with respect to the plane of the ring, *i.e.*, approach (and ejection) of groups can only occur in a direction at right angles to the ring. The problem now is: What is the structure of the intermediate? A theoretically possible intermediate is one in which the attacked carbon atom changes its state of hybridisation from trigonal to tetrahedral (Wheland, 1942). Thus this carbon atom is removed from conjugation with the rest of the system, but the latter, although no longer benzenoid, still has a conjugated system which exhibits resonance. This resulting positive ion is known as the *pentadienyl* (*pentadienate*) *cation* (*cf.* p. 480).



The three resonating structures contributing to the intermediate are often combined, and the intermediate is then represented as follows:



The resonance energy of this cation will not be as great as that of benzene, but by the expulsion of a proton the molecule can revert to the benzenoid state. The proton is not set free as such, but is removed by some base present.

Consideration of the mechanism of aromatic substitution from the M.O. point of view gives much the same picture as described above. An intermediate is formed as before, but now two of the original six π-electrons forming the " closed circuit " are localised to form a σ-bond with the attacking electrophilic reagent. Formation of this bond in the intermediate involves change from trigonal to tetrahedral hybridisation at the carbon atom where reaction actually occurs. The remaining four π-electrons occupy M.O.s embracing the other five carbon atoms, *i.e.*, a delocalised pentadienyl cation exists in the intermediate. Because of the partial localisation to form a σ-bond, this intermediate is also called a σ-complex.

The mechanism given above has been supported by the detection or isolation of intermediates, but according to Gold *et al.* (1955–58) and Brown (1959), this mechanism does not account for all the observed facts. Brown has proposed a mechanism involving unsymmetrical charge-transfer complexes as intermediates, and accounts for all the features of electrophilic substitution reactions.

$$\mathrm{Ar{-}H + Y^+ \rightleftharpoons {}^{+}Ar(Y){-}H \rightleftharpoons \left[Ar(Y)\cdots H\right]^+ \rightleftharpoons {}^{+}Ar(Y)\cdots H \overset{B}{\rightleftharpoons} Ar{-}Y + BH^+}$$

(I) (II) (III)

The first step is the formation of a charge-transfer complex (I), which, in the second step, isomerises to the charge-transfer complex (III) by way of a transition state (II). The final step is the base-catalysed loss of a proton from (III).

Effect of substituents in electrophilic substitution. It has been previously pointed out (p. 516) that the rules of orientation are empirical. It is possible, however, to obtain a definite physical basis for orientation from the electronic theories of organic chemistry. As a result of a very large amount of work, it has been found that at least three factors must be considered, the most widely studied of which is the polar effect of the substituent group on the nucleus. The other two factors are discussed later (see *ortho-para* ratio, p. 523). The effects of substituents described below hold for kinetically controlled products; they do not always apply to the thermodynamically controlled products (see, *e.g.*, pp. 530, 611).

Polar effects. In *o-p*-substitutions group A causes these positions to become points of high electron density; hence substitution will take place in the *o-p*-positions with electrophilic reagents. Furthermore, owing to the *increased electron density* in the *o-p*-positions, group A is associated with *activation* of the benzene ring, *i.e.*, further substitution is facilitated by the presence of an *o-p*-orienting group.

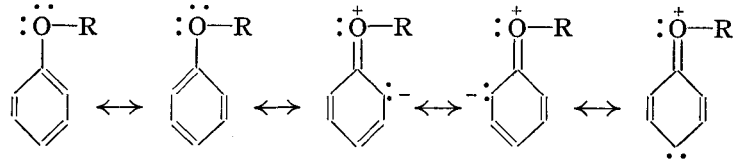
In *m*-substitution, group A causes a withdrawal of electrons from the *o*- and *p*-positions, leaving the *m*-position practically unaffected. Thus the *m*-position becomes a point of *relatively* high electron density, and so substitution takes place in the *m*-position with electrophilic reagents. Since the *m*-position is *almost unaffected*, and the *o*- and *p*-positions *decrease in electron density*, group A is associated with *deactivation* of the benzene ring, *i.e.*, further substitution is made more difficult by the presence of a *m*-orienting group.

A point of interest here is the methods used to determine the relative reactivity of the benzene ring due to the presence of substituent A. Various methods have been used; one of the best is by *competitive reactions*. An equimolecular mixture of two substrates is treated with insufficient reagent to lead to *complete* reaction with both compounds. Thus the two substrates

compete with each other, and analysis of the products will show which substrate has reacted with more of the reagent.

The problem that now confronts us is: How are changes in electron densities brought about by group A? The following detailed account shows that these are caused by the inductive, electromeric and resonance (mesomeric) effects.

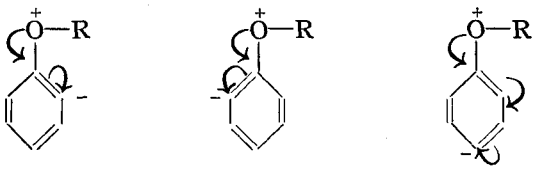
When the group present in the ring is OH, OR, NH_2, etc., the product of further substitution is mainly *o-p*. A property common to all these groups is that the atom adjacent to the nucleus—the " key atom "—has at least one lone pair of electrons. The resonance effect gives rise to *increased* electron densities in the *o-p*-positions, *e.g.*,



(I) (II) (III) (IV) (V)

(I) and (II) are the normal structures; (III) and (IV) are *o*-quinonoid and (V) is *p*-quinonoid. (I–V) are the resonating structures, $C_6H_5{\cdot}O{\cdot}R$ being a resonance hybrid of them. Hence the actual state of $C_6H_5{\cdot}O{\cdot}R$ is a molecule having small negative charges at the two *o*-positions and at the *p*-position. Thus substitution with electrophilic reagents takes place in these positions, and is facilitated owing to the excess electron densities, since it is reasonable to suppose that an electrophilic reagent will attack at the point where the electron density is highest.

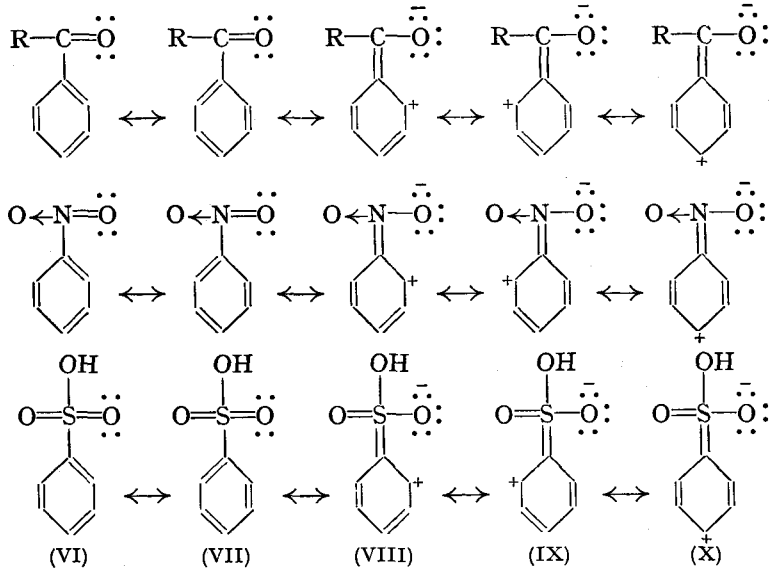
According to Ingold's terminology of mesomerism, etc. (p. 20), these electronic displacements are +M, and in addition to this +M effect, there will also be brought into play the +E effect; thus:



It therefore follows that *o-/p*-substitution takes place by the +T effect.

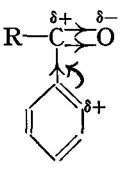
When the group present in the ring is NO_2, CO_2H, COR, SO_3H, etc., the product of further substitution is mainly *m*-. All these groups, by virtue of having at least one strongly electron-attracting atom and a double or triple bond conjugated to the benzene ring, cause an electron displacement *away* from the nucleus and towards the group (*i.e.*, a —M effect), *e.g.*, $C_6H_5{\cdot}CO{\cdot}R$, $C_6H_5{\cdot}NO_2$ and $C_6H_5{\cdot}SO_3H$. (VI–X) are resonating structures, and the actual states of $C_6H_5{\cdot}CO{\cdot}R$, $C_6H_5{\cdot}NO_2$ and $C_6H_5{\cdot}SO_3H$ are molecules which have small positive charges in the *o*- and *p*-positions, *i.e.*, the *m*-positions have a *relatively* high electron density with respect to the *o-p*-positions. The above groups are therefore *m*-orienting to electrophilic reagents.

The relative high electron density of the *m*-positions with respect to the *o-p*-positions is due to the *withdrawal* of electrons from the *o-p*-positions (*i.e.*, —M effect), and not due to a gain of electrons in the *m*-positions. Hence *m*-substitution is due to deactivation of the whole nucleus, particularly in the *o-p*-positions.



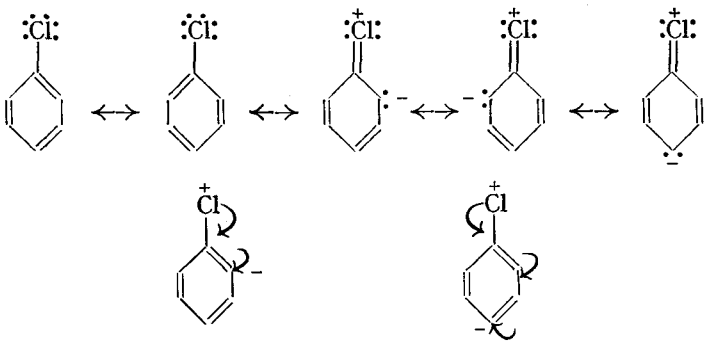
(VI) (VII) (VIII) (IX) (X)

The electromeric effect will assist the resonance effect in deactivating the ring, and so for *m*-substitution we have —M —E, *i.e.*, —T. Furthermore,



since all *m*-orienting groups contain at least one strongly electron-attracting atom, the inductive effect of this atom will also help to withdraw electrons from the *o-p*-positions. In this case the M, E and I effects all assist one another, the net result being —T —I.

The electron-attracting power (I effect) of an atom alone cannot decide whether the substituent atom or group will be *o-p*- or *m*-orienting; *e.g.*, Cl, OH, NH_2, etc. have a strong —I effect and therefore tend to withdraw electrons from the ring, *i.e.*, the —I effect tends to promote *m*-substitution, and not *o-p*- as is the case in practice. The " key-atom " in all of these groups, however, has at least one lone pair of electrons, and consequently both the resonance and electromeric effects are possible. Since these effects together are stronger than the I effect, the above atoms or groups become *o-p*-orienting, *e.g.*,



Thus for C_6H_5Cl, we have +T —I, and since T is greater than I, the result is *o-p*-substitution.

Although chlorine is *o-p*-orienting, it is more difficult to nitrate

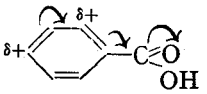
chlorobenzene than benzene, *i.e.*, chlorine *deactivates* the ring (*cf.* above). According to Ingold (1933), the —I effect of chlorine deactivates the ring, and the +M effect is too small to be significant. When, however, the +E effect is brought into play by the attacking reagent, the *o*- and *p*-positions are raised in electron density above the *m*-, but the increase is not as great as that which occurs in benzene itself. Consequently, although chlorine is *o*-*p*-orienting it deactivates the ring.

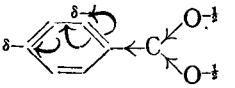
As we have seen in the foregoing, the amino-group in aniline is *o*-*p*-orienting; *e.g.*, bromination of aniline produces 2 : 4 : 6-tribromoaniline; nitration with nitric acid produces a mixture of *o*- and *p*-nitroanilines. On the other hand, if the nitration is carried out in the presence of concentrated sulphuric acid, a large amount of *m*-nitroaniline is obtained. This is believed to be due to the formation of the $-\overset{+}{N}H_3$ group, the positive charge of which exerts a strong —I effect, thereby withdrawing electrons from the ring; also, there is now no lone pair (on the nitrogen atom) available for the +M and +E effects. Thus the *o*- and *p*-positions become points of low electron densities and so *m*-substitution takes place. This effect of the positive charge is well brought out by the nitration of the following compounds (Ingold, 1926, 1927):

Side-chain . .	$\cdot\overset{+}{N}Me_3$	$\cdot CH_2\cdot\overset{+}{N}Me_3$	$\cdot(CH_2)_2\cdot\overset{+}{N}Me_3$	$\cdot(CH_2)_3\cdot\overset{+}{N}Me_3$
m- (per cent.) . .	100	88	19	5

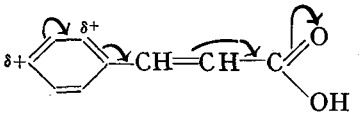
The amount of *m*-substitution decreases with increasing length of the carbon chain (the inductive effect decreases rapidly from the source). Other positive centres also behave in a similar manner, and it should be noted that positively charged substituents are the strongest types of *m*-orienting groups. Furthermore, the *m*-orienting power for key atoms in the same periodic group decreases as the atomic weight increases, *i.e.*, $\overset{+}{N}>\overset{+}{P}>\overset{+}{As}>\overset{+}{Sb}$. Although each of these atoms has a unit positive charge, the nucleus becomes progressively larger (from left to right) and consequently nuclear screening increases.

The *carboxyl group* is *m*-orienting, but the *carboxylate ion* is *o*-*p*-orienting. This is attributed to the negative charge on each oxygen atom giving the carboxylate ion electron-repelling properties (+I) in contrast to the carboxyl group which is electron-attracting (—I).

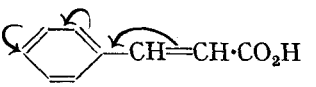




Similarly, on the —I effect of a carboxyl group, it would be expected that *m*-substitution would result in cinnamic acid. In practice, however, the main product is a mixture of the *o*- and *p*-compounds. The reason for this is uncertain, but a possible explanation is one similar to that given for nitrosobenzene (see below). The permanent electronic displacement is as shown in (I), but in the presence of electrophilic reagents a +E effect comes into operation (II).



(I)



(II)

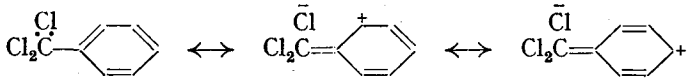
The polar effect of an alkyl group in the alkylbenzenes is particularly interesting. Since alkyl groups are electron-repelling (+I), the *o*-*p*-positions become points of high electron density, and consequently alkyl groups are

o-*p*-orienting. Since the order of the inductive effect of alkyl groups is (p. 16):

methyl<ethyl<propyl<*iso*propyl<*t*.-butyl

then the activating effect of an R group, if entirely due to the +I effect, would be in the same order. Actually, in a number of cases the order is the reverse. One explanation offered for this reversal is hyperconjugation (p. 260), this being greatest in the methyl group and least in the *t*-butyl group; thus:

Hyperconjugation may also be used to explain, for example, the *m*-orienting power of the CCl_3 group (as well as by the —I effect):



The general effect of a substituent on the introduction of a second group may be summarised as follows:

(i)	+I substituent	:	increases *o*-reactivity more than *p*-.
(ii)	—I ,,	:	decreases *o*- ,, ,, ,, *p*-.
(iii)	—M ,,	:	decreases *p*- ,, ,, ,, *o*-.
(iv)	+T ,,	:	increases *p*- ,, ,, ,, *o*-.
(v)	Steric factor	:	decreases *o*-reactivity.

From the M.O. point of view, the methyl group of toluene can behave as a " compound atom " with a π-orbital, and this conjugates with the benzene ring (Fig. 2; *cf.* p. 270). This produces an increase in charge densities at the *o*- and *p*-positions.

The *m*-orienting effect of the CCl_3 group may be explained by assuming that one chlorine atom ionises. This leaves the carbon atom with a positive charge. The " closed circuit " of the benzene ring can now extend itself to cover this carbon atom, thereby stabilising the molecule (Fig. 3). This extended conjuga-

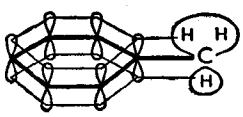


FIG. 20.2.

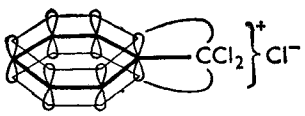


FIG. 20.3.

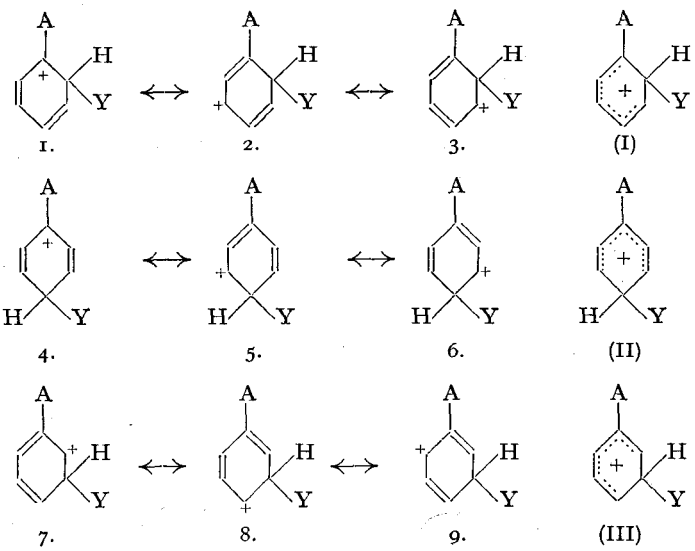
tion can probably be extended further by contributions of the p_z lone pairs on each of the two chlorine atoms remaining attached to the carbon atom. The final result is a decrease in charge densities at the *o*- and *p*-positions.

It has been pointed out (p. 515) that the nitroso- and iodoxy-groups are apparently exceptions to the Hammick–Illingworth rule. Thus, if the nitroso-group had the same effect as a nitro-group, then it should give rise to *m*-substitution

with electrophilic reagents. Unfortunately, electrophilic reagents, when used in the usual way, destroy the nitroso-group. Ingold (1925) and Le Fèvre (1931), however, nitrated and brominated nitrosobenzene under special conditions and obtained the *p*-derivatives. If we assume that no unusual factors (*e.g.*, dimerisation; see p. 307) were operating under these special conditions, the results may be explained by the operation of a + E effect (I) in nitrosobenzene. On the other hand, it appears that — E effect (II) can operate in the presence of a nucleophilic reagent, *e.g.*, in *o*- and *p*-bromonitrosobenzene the bromine is readily removed by hydrolysis. Thus nitrosobenzene can undergo two electromeric directions, and the direction will be determined by the nature of the attacking reagent.

According to the Hammick–Illingworth rule, the iodoxy-group, IO_2, would be expected to be *o*-*p*-orienting. It has been shown, however, that this group is *m*-orienting, *e.g.*, nitration of iodoxybenzene produces almost 100 per cent. of the *m*-derivative (Masson *et al.*, 1935).

An alternative way of predicting the effect of substituents in electrophilic substitution is to examine the stabilities of the carbonium ions produced as intermediates. Thus if A is the substituent and Y the entering group, then the various carbonium ions for *o*-, *p*- and *m*-substitution are as follows:



If A has a +I effect (*e.g.*, Me) or is an electron-donating group (*e.g.*, OH), then the positive charge in 1. and 4. will tend to be neutralised, and consequently these ions are stabilised. Therefore the pentadienyl cations (I) and (II) each have a stabilised resonating structure contributing to the resonance hybrid. There is no such stabilised resonating structure contributing to the pentadienyl cation (III). Thus cations (I) and (II) will be more stable than (III); consequently, A will be *o*,*p*-orienting. If A has a —I effect (*e.g.*, NR_3^+) or is an electron-withdrawing group (*e.g.*, NO_2), then these effects are opposed in 1. and 4., but not in 7., 8. or 9. (or to a far less extent). Thus, in this case cation (III) will be more stable than (I) or (II), and consequently A will be *m*-orienting.

***Ortho-para* ratio.** Since there are two *o*-positions and only one *p*-position, it might be expected that there would be twice as much *o*- as *p*-substitution if the group present affected the electron density of each position to the same extent, *i.e.*, the *o*/*p* ratio should be 2/1. This is rarely observed in practice; for some substituents *o*-substitution is favoured, and for others *p*-substitution.

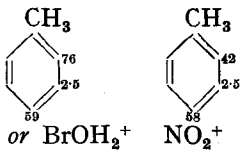
Since the approach of the incoming group is perpendicular to the ring, it is reasonable to infer that, in addition to its polar effects, the actual size of the *o*-substituent and the entering group, *i.e.*, steric (spatial) effects, will also operate in determining the amount of *o*- and *p*-substitution. This purely steric effect will affect only the *o*-positions. Polar effects, as we have seen, are transmitted mainly to the *o*- and *p*-positions, with very little change in the *m*-positions. Thus the *m*/*p* ratio will indicate only the polar influences at these two positions, whereas the *o*/*m* and *o*/*p* ratios will indicate effects due to both polar and steric influences. The following results have been obtained for mononitration (1, Jones *et al.*, 1947; 2 and 3, Brown *et al.*, 1954; 4, Nelson *et al.*, 1951):

No.	Compound	*o*	*m*	*p*	*o*/*p*	*o*/*m*	*p*/*m*
1	Ph·Me	58·5	4·4	37·2	1·57	13·3	8·5
2	Ph·Et	45	6·5	48·5	0·93	6·9	7·5
3	Ph·$CHMe_2$	30	7·7	62·3	0·48	3·9	8·1
4	Ph·CMe_3	15·8	11·5	72·7	0·22	1·4	6·3

It can be seen that as the size of the alkyl group increases, the proportion of the *o*-product decreases. The question then is: Is this purely a steric effect, or are there in addition some other factors operating? One possible influence is that due to hyperconjugation, since this decreases from methyl to *t*.-butyl (p. 521). The ratio *p*/*m*, however, does not vary much in this series, and so it may be concluded that the *polar* effects of the four alkyl groups are nearly the same (Nelson, 1951). This conclusion is supported by other work, and thus the decreased *o*-substitution can be attributed to the steric requirements of the alkyl substituents.

In addition to the steric effect of the substituent group, there is also the steric effect of the *entering* group. Thus it has been shown that in the alkylation of toluene, as the size of the entering group increases, so the *o*/*p* ratio decreases.

de la Mare *et al.* (1956) found that the ratio of isomers produced in the acid-catalysed bromination of toluene by hypobromous acid is: *o*-, 70·3%; *m*-, 2·3%; *p*-, 27·4%. The reagent was a positively charged brominating species, either the brominium cation Br^+ or the hypobromous acidium ion $BrOH_2^+$. The reaction is thus electrophilic, and there is a great similarity in partial rate factors between this bromination (I) and nitration (II). The results, however, show more resistance to the *o*-entry of the nitro-group than to the bromo-group. de la Mare has explained this by suggesting that in the transition state the initially *linear* nitronium ion now becomes distorted (*triangular*), and therefore the effective radius of the nitro-group in the direction of the flanking *o*-methyl group is likely to be greater than that of the spherical bromine substituent.



Br^+ *or* $BrOH_2^+$ (I) NO_2^+ (II)

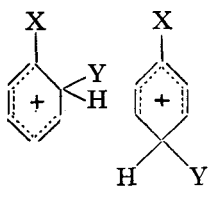
The existence of the steric factor is also supported by spectroscopic work. When, owing to steric hindrance, the two substituent groups are forced out of the same plane, one spectral effect is a decrease in absorption intensity.

The absorption intensity of the *p*-halogenonitrobenzenes is in the order I>Br>Cl>F, and the order of the *o*-compounds is the reverse. This difference is attributed to the steric inhibition of uniplanarity of the phenyl and nitro-groups by the *o*-halogen substituent. At the same time, the energy of activation (in the transition state) is also affected (Brown *et al.*, 1955).

Not only must the polar and steric factors be considered, but also one arising from the electrostatic forces set up between the substituent and the entering group, *e.g.*, Sandin *et al.* (1947) nitrated aryl halides and obtained the following results:

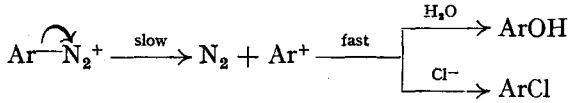
Compound	*o*	*p*	*o*/*p*
C_6H_5F . . .	12·6	87·4	0·14
C_6H_5Cl . . .	30·1	73·1	0·41
C_6H_5Br . . .	37·2	62·5	0·59

All the halogens are *o*-*p*-orienting, and since the halogen *increases* in size from fluorine to bromine, then, on the basis of the steric effect also operating, the ratio *o*/*p* would be expected to fall. This ratio, however, actually rises, and so some other factor must be operating. One explanation that has been offered is that there is interaction between the C—X bond moment and the entering group Y, and that these forces will be different for the *o*- and *p*-positions in the transition state (the C—X dipole *decreases* from F to Br).



Nucleophilic substitution. This term covers the replacement of *hydrogen* or a *substituent* by a nucleophilic reagent. Furthermore, this latter type includes *activated nucleophilic aromatic substitution* in which the replacement is facilitated by the presence of an electron-withdrawing group in the *o*- and/or the *p*-position. In general, there are three types of mechanism in nucleophilic aromatic substitution: unimolecular, bimolecular and the benzyne type (the last is discussed on p. 547).

Unimolecular substitution. This mechanism is most unusual in aromatic substitution. It appears that the only well-established example is the case of the uncatalysed decomposition of aryl diazonium cations to phenols in aqueous solution. Aryl halides may also be formed if halide ions (nucleophilic reagents) are present in solution, *e.g.*,

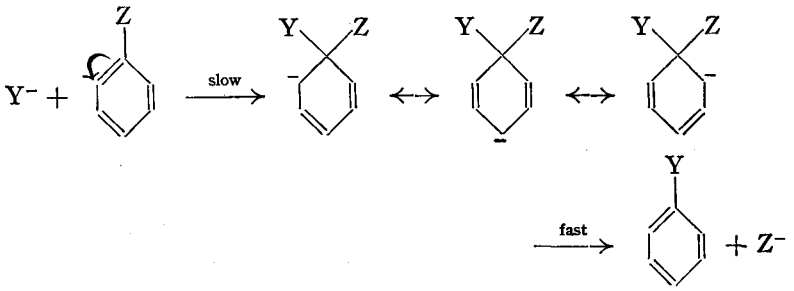


There is a great deal of evidence to support this unimolecular mechanism, *e.g.*:

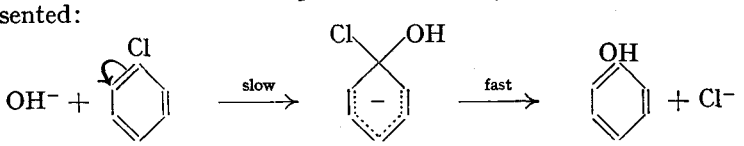
(i) Moelwyn-Hughes *et al.* (1940) showed that the decomposition of benzenediazonium chloride in water is a first-order reaction.

(ii) The decomposition of benzenediazonium borofluoride, $C_6H_5N_2^+BF_4^-$, in, *e.g.*, nitrobenzene solution, phenylates the latter compound in the *m*-position; the borofluoride also converts diphenyl ether, Ph_2O, into the oxonium ion Ph_3O^+ (Nesmeyanov *et al.*, 1957). These results are readily explained on the assumption that the active species is the phenyl cation.

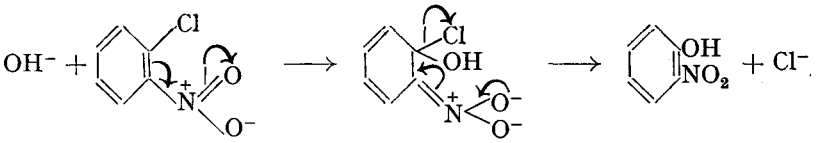
Bimolecular substitution. This is the common type of mechanism in nucleophilic aromatic substitution. Where kinetic studies have been made, the reaction has been shown to be of the second-order. The general belief is that the reaction proceeds through a negative ion intermediate, the ***pentadienyl anion.*** In general terms, this may be represented as follows:



As in the case of the pentadienyl cation, the resonating structures of the pentadienyl anion may be represented by a single formula, *e.g.*, the reaction between chlorobenzene and aqueous sodium hydroxide at 300° may be represented:

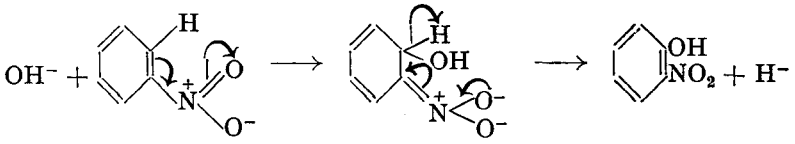


An example of activated nucleophilic substitution is the conversion of *o*-chloronitrobenzene into *o*-nitrophenol when heated with aqueous sodium hydroxide at 200° (see also p. 547):

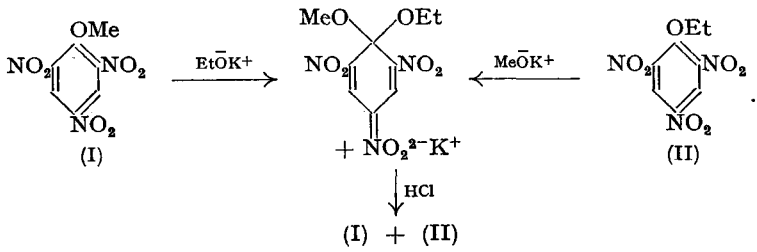


Here, because of the electron-withdrawing effect of the nitro group, the carbon of the C—Cl group acquires a positive charge, and so attack at this carbon atom is facilitated.

Although benzene itself does not undergo nucleophilic substitution, substitution of *hydrogen* by a nucleophilic reagent can occur when the ring contains a nitro group, *e.g.*,



Support for the above mechanism via intermediates is given by the isolation (at least in some cases) of these intermediates. Meisenheimer (1902) showed that the adduct formed from 2:4:6-trinitroanisole (I) and potassium ethoxide (in ethanolic solution) was identical with that obtained from 2:4:6-trinitrophenetole (II) and potassium methoxide (in methanol solution); he obtained the *same* mixture of (I) and (II) from each adduct on acidification:

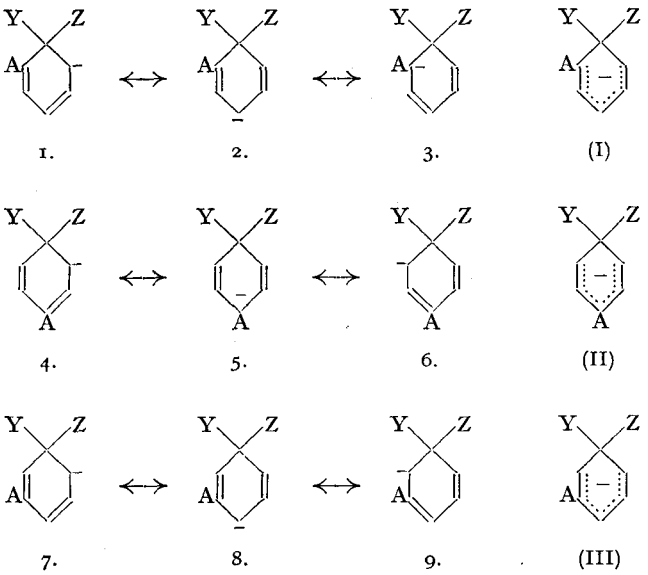


Foster *et al.* (1954, 1955) have also shown that (I) and OEt^- and (II) and OMe^- form compounds having identical infrared and visible spectra.

According to Reinheimer *et al.* (1958), ion-pairs (p. 109) play a part in the bimolecular reaction between 1-chloro-2:4-dinitrobenzene and methoxide ions. The nucleophilic reagent has been assumed to exist as an ion pair M^+OMe^-, and the reactivity sequence $M = Li < Na < K$ is as expected.

The bimolecular mechanism has been shown to be subject to polar and steric effects (*cf.* the section on the *ortho–para* ratio).

In the same way as it was possible to discuss electrophilic substitution from the point of view of the stabilities of the intermediate carbonium ions, so can one discuss nucleophilic substitution from the point of view of the stabilities of the carbanions.

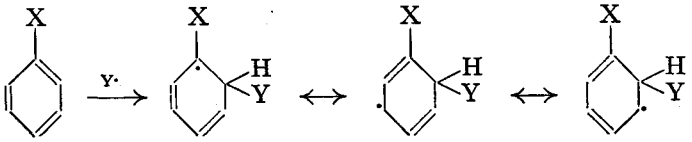


If A has a $-I$ effect or is an electron-withdrawing group, then the negative charge in 3. and 5. will tend to be neutralised, and consequently these ions are stabilised. Since there is no such stabilisation in 7., 8. and 9., the pentadienyl anions (I) and (II) will be more stable than (III). Consequently, A will favour nucleophilic substitution of a group in the *o*- or the *p*-position. If A has a $+I$ effect or is an electron-donating group, then these effects are opposed by the negative charge in 3. and 5., and consequently the pentadienyl anion (III) is more stable than (I) or (II), *i.e.*, an electron-donating group will favour nucleophilic substitution when the replaced group is in the *m*-position, and consequently *deactivates* the ring with respect to nucleophilic substitution when the replaced groups are in the *o*- or *p*-position.

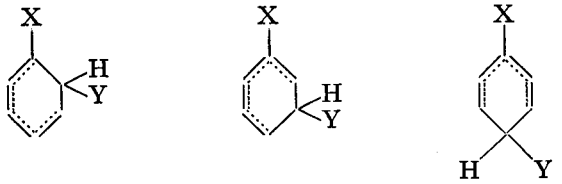
If A is an electron-attracting group in which the " key " atom can form a double bond with the ring, this will produce increased stability in 3. and 5. Such a group is the nitro group, and so when A is a nitro group, the nucleophilic substitution rate is increased (see above).

Free-radical substitution. In homolytic substitution, since the attacking agent is uncharged, it might be expected that the (polar) orienting influence of the substituent would be without effect, *i.e.*, the ratios of $o : m : p$ would be 2 : 2 : 1. In practice, however, substitution is mainly *o*- and *p*-, irrespective of the nature of the group already present in the ring. Three transition states are possible (*pentadienyl radicals*) for free-radical attack.

Let us first consider the *o*-pentadienyl radical; this will be a resonance hybrid of three resonating structures:



Thus the *o*-, *m*-, and *p*-transition state may be written as follows:

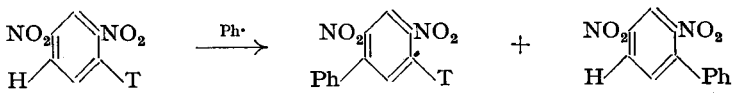


Since *o*- and *p*-substitution predominate, the energies of these transition states must be lower than that of the *m*-. The reason for this is uncertain.

The hydrogen atom is expelled, but is probably never free; it is rapidly removed by another free radical present in solution. Examples of free-radical substitution are chlorination of benzene at high temperature in the vapour phase or in the presence of sunlight (p. 544), the decomposition of diazonium salts under certain conditions (p. 585), mercuration with mercuric acetate (p. 539) and the Wurtz–Fittig reaction (p. 534).

Arylation of aromatic compounds may be effected by decomposing benzoyl peroxide in aromatic solvents. This type of reaction is of some interest in connection with some work of Price *et al.* (1957, 1958). These authors phenylated 2:4-dinitrotritiobenzene with benzoyl peroxide and obtained *equal* amounts of labelled (I) and unlabelled (II) products.

$$(Ph{\cdot}CO_2)_2 \longrightarrow 2Ph{\cdot} + 2CO_2$$



(I) (II)

Since there is no kinetic isotope effect, homolysis of the C—H bond *cannot* be the rate-determining step. The observed results are support for the rate-determining step being the *addition* of the phenyl radical to form the pentadienyl radical.

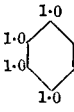
One method of studying organic reactions has been to calculate the *charge densities* (π-electron densities) of the various positions in the molecule. The assumption has then been made that these quantities are related to the chemical reactivities to charged reagents.

In conjugated systems, only the π-electrons are considered, since the σ-electrons are localised and consequently very little affected by external influences. The π-electrons cover the whole benzene nucleus, and since they are easily polarised, *i.e.*, readily affected by external electrical influences, any change at one point in the molecule will be propagated to another. Hence the presence of a substituent group in the benzene nucleus will affect the π-electron distribution throughout the whole molecule, *i.e.*, the charge densities, and consequently the chemical reactivities of distant positions will be affected by the substituent group. These changes will, as one might expect, depend largely on the nature of the substituent group.

Substitution reactions of benzene involve three types of reagents, electrophilic, nucleophilic and free-radical. Since electrophilic reagents are electron-seeking

reagents, they will attack the carbon atom which has the *highest* charge density. Since nucleophilic reagents supply a pair of electrons, these reagents will attack the carbon atom which has the *lowest* charge density. (Reactions involving free radicals are more difficult to deal with, and will not be discussed here.)

It can be seen from the foregoing discussion that if we know the charge densities of all the atoms in the molecule, we are in a position to say where attack will occur with electrophilic or nucleophilic reagents. π-Electron densities have been calculated for many molecules (particularly by Coulson and his co-workers). Let us first consider benzene itself. This is a symmetrical molecule, and so all the charge densities are equal, the value being unity (as shown by calculation). Thus all the carbon atoms in benzene are attacked equally well by electrophilic reagents.



Now let us consider aniline. The nitrogen atom has a lone pair of electrons which can conjugate with the π-electrons of the benzene ring (Fig. 4*a*). This

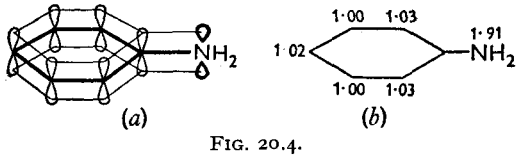


FIG. 20.4.

results in the nitrogen losing " full control " of this lone pair, but owing to the strong electron-attracting power of nitrogen, the loss of control is fairly small. The new π-electron densities are shown in (*b*). Since the nitrogen " started off " with full control of its lone pair, its π-electron density was originally 2. In the conjugated molecule, the value is 1·91. Thus the nitrogen atom acquires a small positive charge (*cf.* resonance theory), and the net result is increased charge densities on *o*- and *p*-carbon atoms, the *m*-carbon atoms remaining unaffected. Thus electrophilic attack on aniline will occur at the *o*- and *p*-positions, and according to the above figures, preferentially at the *o*-position. Similarly, a lone pair of electrons of the chlorine atom in chlorobenzene will conjugate with the benzene ring, the chlorine thereby acquiring a small positive charge and the *o*- and *p*-positions increasing their charges above unity, whereas the charge density of the *m*-position remains sensibly the same (unity).

Now let us consider nitrobenzene. The nitro-group itself is conjugated, with the nitrogen atom positively charged (Fig. 5*a*). When the nitro-group conjugates with the ring (Fig. *b*), the nitrogen atom *attracts* towards itself the ring

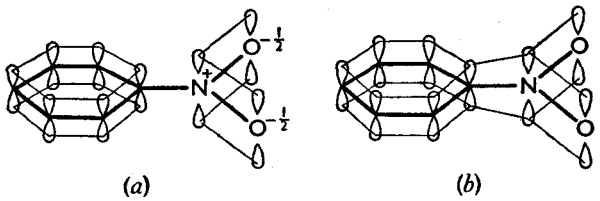
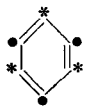


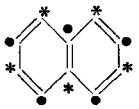
FIG. 20.5.

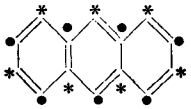
π-electron cloud, and thereby *decreases* the charge densities on the carbon atoms in the ring, more so at the *o*- and *p*-positions than at the *m*-position (as shown by calculation). Thus *electrophilic* attack will occur at the *m*-position, and *nucleophilic* attack at the *o*- and *p*-positions.

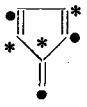
Calculation of the charge distribution in conjugated compounds is usually a laborious process. Coulson *et al.* (1940) have shown that the calculation is simple for *alternant hydrocarbons* (A.H.). In these it is possible to divide the atoms of the resonating part of the molecule into two groups (sometimes called *starred* and *unstarred*) such that no atom of one group is adjacent to another atom of the *same* group, but is always adjacent to one or more atoms of the *other* group. Thus benzene, naphthalene and anthracene are A.H.'s, but fulvene is not.

Furthermore, no odd-membered ring can be alternant, and with A.H.'s Coulson has shown that all the carbon atoms have a charge density of unity (which is not generally true for non-A.H.'s).


benzene


naphthalene


anthracene


fulvene

Another method of studying organic reactions has been to assume that the reactivity of a double bond is related to its double-bond character (or bond order; see p. 89). This assumption agrees quite well with the experimental results. The greater the double-bond character, the greater will be the reactivity at this point in the molecule. In benzene all the bonds have the same double-bond character, and so no particular carbon atom will be attacked preferentially. In the case of more complex aromatic hydrocarbons, *e.g.*, naphthalene, the double-bond character differs in various parts of the molecule, and so attack at some carbon atoms is easier than at others. Badger (1948–50) has found that osmium tetroxide is the most satisfactory reagent for the determination of the relative reactivity of aromatic double bonds. This reagent does not attack benzene, but attacks polycyclic compounds containing pronounced double-bond character (see, *e.g.*, naphthalene, p. 715).

General Methods of Preparation of the Benzene Homologues

Friedel–Crafts reaction (1877). This reaction involves the introduction of an alkyl or acyl group into the benzene ring in the presence of a catalyst. Recently, the Friedel–Crafts reaction has been applied to certain aliphatic and alicyclic compounds.

The aromatic compounds may be hydrocarbons, aryl chlorides and bromides, mono- and polyhydric phenols or their ethers, amines, aldehydes, acids, quinones, and certain derivatives of heterocyclic compounds. The alkylating agents may be alkyl halides, aliphatic alcohols, olefins, ethers and alkyl esters of organic and inorganic acids. From the point of view of convenience, the alkylating agent is usually confined to alkyl halides, alcohols and olefins. The acylating agents may be acid chlorides or anhydrides, acids, or esters.

Many catalysts may be used, *e.g.*, the chlorides of aluminium, iron (ferric), zinc, tin (stannic); boron trifluoride, hydrogen fluoride, sulphuric acid, phosphoric acid, and a mixture of silica and alumina. Acylations may also be effected in the presence of perchloric acid as catalyst (Burton *et al.*, 1950). Recently it has been found that benzene will react with an alkyl halide or acyl chloride in the *absence* of a catalyst, but in this case the reaction must be carried out under pressure (Sachanen and Cæsar, 1946).

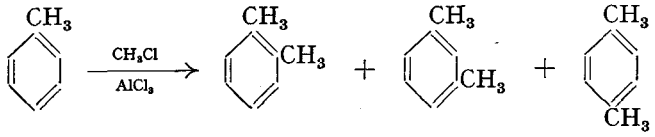
Of all the catalysts mentioned, aluminium chloride (the one originally used by Friedel and Crafts) is the best, and gives satisfactory yields when the alkylating agent is an alkyl halide, alcohol or an olefin. The amount of catalyst required depends on the nature of the alkylating agent used, *e.g.*, with alkyl halides or olefins, about 0·2–0·4 molecule of aluminium chloride (using the formula $AlCl_3$) is necessary. With alcohols (ethers, etc.), however, a larger amount of catalyst (one or more molecules) is necessary:

$$C_6H_6 + CH_3Cl \xrightarrow[(0\cdot2\ \text{mol.})]{AlCl_3} C_6H_5{\cdot}CH_3 + HCl$$

$$C_6H_6 + C_2H_4 \xrightarrow[(0\cdot2\ \text{mol.})]{AlCl_3} C_6H_5{\cdot}C_2H_5$$

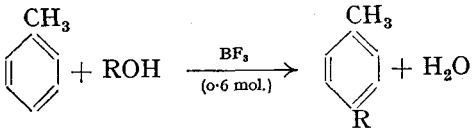
$$C_6H_6 + C_2H_5OH \xrightarrow[(1\ \text{mol.})]{AlCl_3} C_6H_5{\cdot}C_2H_5 + H_2O$$

The orientation of the products in the alkylation of an alkylbenzene with aluminium chloride as catalyst depends on the temperature of the reaction. Thus Norris *et al.* (1939) obtained the following yields (per cent.):



0°	53·5	27·3	19·2
55°	12·2	87·1	0·7
106°	1·8	98·2	0·0

The reason for this is not certain. One possibility is that the *o*- and *p*-compounds are the kinetically controlled products, whereas the *m*-compound is the thermodynamically controlled product. The Friedel–Crafts reaction is *reversible*, and consequently at high temperature the product formed will be the thermodynamically controlled one. On the other hand, with boron trifluoride, which is very useful with alcohols and olefins (as is hydrogen fluoride), the main product of disubstitution is the *p*-derivative; sulphuric acid also produces mainly the *p*-derivative.



Boron trifluoride does not catalyse alkylations with alkyl chlorides or bromides, but the reaction can be carried out in the presence of water or alcohol (Hennion *et al.*, 1943). On the other hand, alkylation with alkyl fluorides is readily carried out with boron trifluoride as catalyst (Burwell *et al.*, 1942; Oláh *et al.*, 1957).

The Friedel–Crafts reaction is often the most useful method of introducing an alkyl group into the benzene ring. The ease of alkylation with an alkyl halide depends on the nature of the alkyl radical and the halogen atom. The ease of alkylation for a given halogen atom is tertiary halide>secondary >primary; and for a given alkyl radical, alkyl fluoride>chloride>bromide >iodide (this is the reverse order of the usual reactivity of alkyl halides).

The Friedel–Crafts reaction is usually carried out in the presence of a solvent, but if one of the reactants is a liquid hydrocarbon, *e.g.*, benzene, this may be used as solvent as well. The solvents generally used are nitrobenzene, light petrol, or carbon disulphide, and the solvent sometimes affects the orientation (see p. 715). At the end of the reaction the complex (see later) is usually decomposed by ice-cold concentrated hydrochloric acid.

The Friedel–Crafts reaction has certain drawbacks:

(i) The structure of the alkyl group plays a part in the alkylation, *e.g.*, it is easy to introduce a methyl, ethyl or *iso*propyl group, but usually difficult to introduce a *n*-propyl or *n*-butyl group, since these tend to rearrange to the *iso*-radicals. *iso*Butyl halides very readily give a *tert.*-butyl substitution product. If the reaction is carried out in the cold with benzene and *n*-propyl chloride, the *n*-propyl radical is introduced:

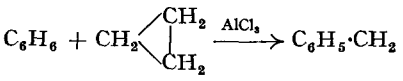
$$C_6H_6 + CH_3{\cdot}CH_2{\cdot}CH_2Cl \xrightarrow[\text{cold}]{AlCl_3} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 + HCl$$

If, however, the reaction is carried out at higher temperatures, the *iso*propyl radical is mainly introduced:

$$C_6H_6 + CH_3{\cdot}CH_2{\cdot}CH_2Cl \xrightarrow[\text{heat}]{AlCl_3} C_6H_5{\cdot}CH(CH_3)_2 + HCl$$

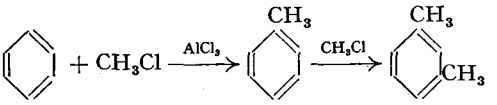
The catalyst itself also affects isomerisation, *e.g.*, *n*-alcohols usually alkylate at low temperatures without rearrangement taking place when aluminium chloride is used, but rearrangement occurs when boron trifluoride or sulphuric acid is used, a primary alcohol giving rise to a secondary alkyl radical, and a secondary alcohol to a tertiary alkyl radical.

A very good means of introducing the *n*-propyl radical is to use *cyclo*propane as the alkylating agent:



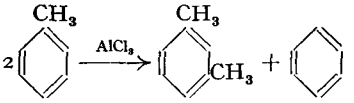
Acid chlorides may be used to introduce long straight-chain groups (see below).

(ii) It is not always possible to stop the reaction at the required stage, *i.e.*, there is always a tendency to over-alkylate, *e.g.*,



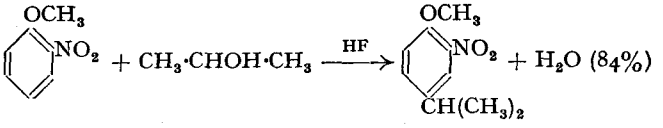
Over-alkylation, due to the presence of the first alkyl group in the ring increasing the ease of further alkylation, may be partly prevented by using a large excess of the hydrocarbon.

(iii) The Friedel–Crafts reaction is reversible, *i.e.*, an alkyl group may be removed, especially at high temperatures. This renders the structure of the

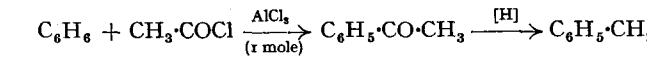


product uncertain in a number of cases.

(iv) The presence of a negative group (*m*-orienting group) in the ring hinders or inhibits the Friedel–Crafts reaction, *e.g.*, nitrobenzene, $C_6H_5{\cdot}NO_2$, and acetophenone, $C_6H_5{\cdot}CO{\cdot}CH_3$, do not undergo the Friedel–Crafts reaction. On the other hand, if a strongly activating group (*o*-*p*-orienting group) is present in either of the above two compounds, reaction can take place, *e.g.*, *o*-nitroanisole reacts with *iso*propanol in the presence of hydrogen fluoride to form 2-nitro-4-*iso*-propylanisole:

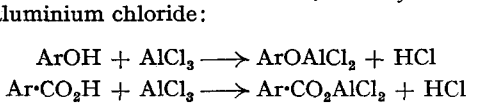


This hindering effect can be used to advantage for preparing a monoalkylated benzene (free from dialkylated-product):



The acetophenone (which is not further attacked) may be readily reduced to ethylbenzene by the Clemmensen method.

(v) For phenols and acids it is better to use boron trifluoride than aluminium chloride, since the latter forms aluminium salts, thereby necessitating the use of a large excess of aluminium chloride:



MECHANISM OF THE FRIEDEL–CRAFTS REACTION

Alkyl halides. Until recently it was generally believed that all Friedel–Crafts reactions proceeded by a free carbonium ion mechanism involving the intermediate formation of a complex (and a pentadienyl cation):

$$RCl + AlCl_3 \rightleftharpoons [R{-}Cl{-}AlCl_3] \rightleftharpoons R^+ + AlCl_4^-$$

$$ArH + R^+ \rightleftharpoons \left[Ar\begin{smallmatrix}H\\R\end{smallmatrix}\right]^+ \longrightarrow Ar{\cdot}R + H^+$$

$$H^+ + AlCl_4^- \longrightarrow HCl + AlCl_3$$

Brown *et al.* (1953), however, have shown that this mechanism is not general, and have presented strong evidence that for at least primary halides the reaction proceeds by a bimolecular nucleophilic substitution mechanism which involves the complex.

$$RCl + AlCl_3 \rightleftharpoons R{-}Cl{-}AlCl_3$$

$$ArH + R{-}Cl{-}AlCl_3 \rightleftharpoons Ar\begin{smallmatrix}\overset{\delta+}{H}\\ \cdots R\cdots Cl\cdots\end{smallmatrix}\overset{\delta-}{AlCl_3}$$

$$\rightleftharpoons \left[Ar\begin{smallmatrix}H\\R\end{smallmatrix}\right]^+ AlCl_4^- \rightleftharpoons Ar{\cdot}R + HCl + AlCl_3$$

Further work by Brown *et al.* (1956) on the alkylation of benzene and toluene with alkyl bromides in the presence of aluminium bromide supports the above mechanism. These authors also suggest that the transition state is best described in terms of a nucleophilic attack by the aromatic compound on a strongly polarised $RBr{-}AlBr_3$ addition compound, and that as branching in the alkyl bromide increases, the C—Br bond in the transition state becomes more and more ionic and finally, at some point in the series, the reaction proceeds through a free carbonium ion mechanism. It was also shown that the isomer distribution in *methylation* is not independent of the halogen atom in the methyl halide. This therefore precludes the free carbonium ion mechanism in methylation and suggests the bimolecular mechanism. It is also believed that the solvent S (which can also be a hydrocarbon) co-ordinates with the aluminium bromide

$$Al_2Br_6 + 2S \rightleftharpoons 2S{-}AlBr_3$$

$$RBr + S{-}AlBr_3 \rightleftharpoons R{-}Br{-}AlBr_3 + S$$

$$ArH + R{-}Br{-}AlBr_3 \rightleftharpoons \left[Ar\begin{smallmatrix}H\\R\end{smallmatrix}\right]^+ AlBr_4^-$$

$$\xrightarrow{S} Ar{\cdot}R + HBr + S{-}AlBr_3$$

It has previously been pointed out (p. 111) that *n*-propyl halides tend to rearrange, resulting in the introduction of an *iso*propyl radical. The mechanism of this reaction is uncertain. It has been observed that *n*-propyl halides isomerise in the presence of aluminium chloride:

$$CH_3{\cdot}CH_2{\cdot}CH_2Cl \xrightarrow{AlCl_3} CH_3{\cdot}CHCl{\cdot}CH_3$$

According to Mckenna and Sowa (1937), this rearrangement might take place first and then the *iso*propyl halide alkylates.

Alcohols. Here again the generally accepted mechanism is believed to be ionic, *e.g.*,

$$ROH + BF_3 \rightleftharpoons \left[\begin{array}{c} H \\ | \\ R{-}O{-}BF_3 \end{array}\right] \rightleftharpoons R^+ + HOBF_3^-$$

$$ArH + R^+ \rightleftharpoons \left[Ar\begin{array}{c}H\\ \diagup \\ \diagdown \\ R\end{array}\right]^+ \longrightarrow Ar{\cdot}R + H^+$$

$$H^+ + HOBF_3^- \longrightarrow [H_2O{\cdot}BF_3] \longrightarrow H_2O + BF_3$$

However, in view of the work done with alkyl halides, it is possible that alkylation with alcohols may also proceed by the bimolecular mechanism.

Olefins. It appears that a trace of water is necessary to catalyse this reaction, and based on this it has been suggested that the actual alkylating agent is the alkyl chloride which is produced as follows:

$$AlCl_3 + 3H_2O \longrightarrow Al(OH)_3 + 3HCl$$

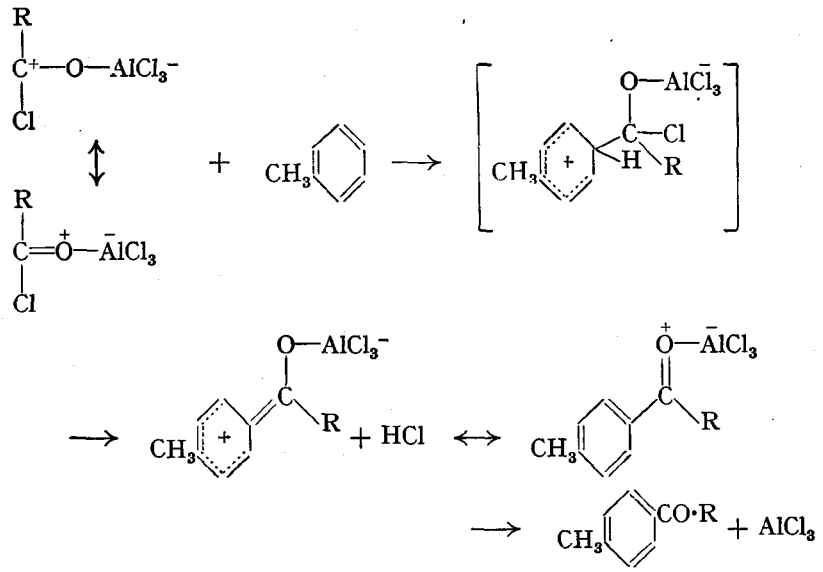
$$C_2H_4 + HCl \xrightarrow{AlCl_3} C_2H_5Cl$$

Acyl chlorides. The generally accepted mechanism of acylation, until recently, was an ionic one involving the intermediate formation of an acyl cation:

$$R{\cdot}COCl + AlCl_3 \rightleftharpoons [R{\cdot}CO{-}Cl{-}AlCl_3] \rightleftharpoons R{\cdot}CO^+ + AlCl_4^-$$

$$ArH + R{\cdot}CO^+ \rightleftharpoons \left[Ar\begin{array}{c}H\\ \diagup \\ \diagdown \\ CO{\cdot}R\end{array}\right]^+ \longrightarrow Ar{\cdot}CO{\cdot}R + H^+$$

According to Brown *et al.* (1954), this ionic mechanism cannot operate in the case of toluene, which acylates in the *p*-position. These authors suggest a substitution mechanism involving a " larger " attacking reagent to account for the steric requirements. This reagent may be the complex $R{\cdot}COX{\cdot}AlX_3$ itself or a solvated complex. Thus the following mechanism has been proposed:



It has been suggested that the bimolecular mechanism is general and that the ionic mechanism operates in such cases where either the aromatic compound or the acyl halide is sterically hindered, *e.g.*, Baddeley *et al.* (1954) have provided evidence that with substituted benzoyl halides the acyl cation is

the acylating agent. On the other hand, Tedder (1954) has suggested that acylations with acyl chloride and aluminium chloride take place by both ionic and substitution mechanisms. Reactive aromatic hydrocarbons are acylated by both processes simultaneously, but less activated hydrocarbons proceed through more of the bimolecular mechanism, and benzene itself almost exclusively through the bimolecular mechanism.

Wurtz–Fittig reaction (1863). Homologues of benzene may be prepared by warming an ethereal solution of an alkyl and aryl halide with sodium (*cf.* Wurtz reaction):

$$C_6H_5Br + C_2H_5Br + 2Na \longrightarrow C_6H_5{\cdot}C_2H_5 + 2NaBr \quad (60\%)$$

Diphenyl and *n*-butane (and some other compounds) are obtained as by-products.

The advantages of the Wurtz–Fittig method over the Friedel–Crafts are that the structure of the product is known and that long *n*-side-chains can be easily introduced:

$$C_6H_5Br + CH_3{\cdot}(CH_2)_2{\cdot}CH_2Br \xrightarrow{Na} C_6H_5{\cdot}(CH_2)_3{\cdot}CH_3 \quad (62\text{–}72\%)$$

The mechanism of the Wurtz–Fittig reaction is uncertain. Two have been suggested, and there is evidence for both (*cf.* Wurtz reaction):

I. The reaction proceeds via the formation of organo-metallic compounds:

(i) $C_6H_5Br + 2Na \longrightarrow C_6H_5^-Na^+ + NaBr$
(ii) $C_6H_5^-Na^+ + C_2H_5Br \longrightarrow C_6H_5 - C_2H_5 + NaBr$
(iii) $C_2H_5Br + 2Na \longrightarrow C_2H_5^-Na^+ + NaBr$
(iv) $C_2H_5^-Na^+ + C_2H_5Br \longrightarrow C_2H_5 - C_2H_5 + NaBr$
(v) $C_2H_5^-Na^+ + C_6H_5Br \longrightarrow C_6H_5{\cdot}C_2H_5 + NaBr$

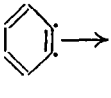
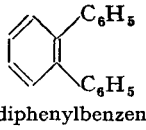
Since reaction (i) proceeds very much faster than (iii), (ii) will be the main reaction.

II. The reaction proceeds via the formation of free radicals:

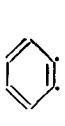
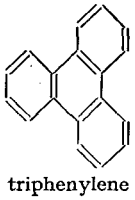
$C_6H_5Br + Na{\cdot} \longrightarrow C_6H_5{\cdot} + NaBr$
$2C_6H_5{\cdot} \longrightarrow C_6H_5 - C_6H_5$
$C_2H_5Br + Na{\cdot} \longrightarrow C_2H_5{\cdot} + NaBr$
$2C_2H_5{\cdot} \longrightarrow C_2H_5 - C_2H_5$
$C_6H_5{\cdot} + C_2H_5{\cdot} \longrightarrow C_6H_5{\cdot}C_2H_5$

In addition to diphenyl, other by-products are also obtained in the Wurtz–Fittig reaction, *viz.*, benzene, *o*-diphenylbenzene and triphenylene. The formation of these is readily explained by the free-radical mechanism, disproportionation of the free radicals taking place as follows:

$2C_6H_5{\cdot} \longrightarrow C_6H_6 +$ 

$2C_6H_5{\cdot} +$  $\longrightarrow$ 

o-diphenylbenzene

3  $\longrightarrow$ 

triphenylene

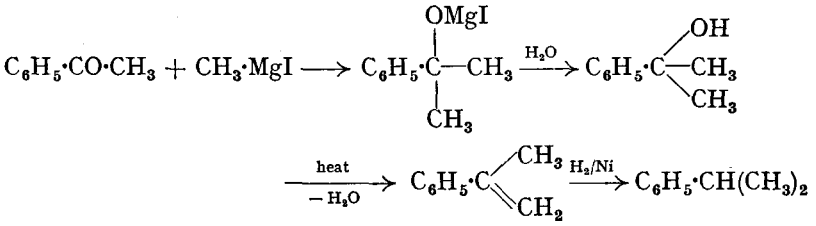
The formation of these polyphenyl compounds has, however, also been explained by non-radical mechanisms (*cf.* Wurtz reaction, p. 51). It should be noted that the free diradical, as written above, is one of the structures suggested for benzyne (p. 547); this has been reported to trimerise to triphenylene (Lüttringhaus *et a.*, 1955).

Method using a Grignard reagent. Homologues of benzene may be prepared by the action of an alkyl halide on phenylmagnesium bromide:

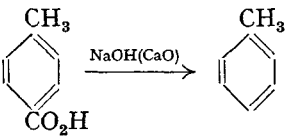
$$C_6H_5Br \xrightarrow{Mg} C_6H_5{\cdot}MgBr \xrightarrow{CH_3I} C_6H_5{\cdot}CH_3 \quad (v.g.)$$

For the introduction of a methyl or ethyl group, the corresponding alkyl sulphate may be used instead of the alkyl halide (*cf.* p. 352).

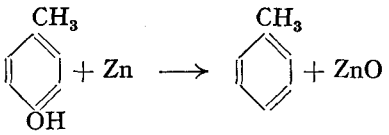
Benzene homologues with branched side-chains may be prepared by the action of alkyl-magnesium halide on an aromatic ketone, *e.g.*, *iso*propylbenzene from acetophenone:



Decarboxylation of aromatic acids. Many aromatic acids are readily decarboxylated when heated with soda-lime, *e.g.*, toluene from *p*-toluic acid:



Removal of oxygen from phenols. When distilled with zinc dust, phenols are converted (in poor yield) into the corresponding hydrocarbons, *e.g.*, *p*-cresol gives toluene:



Method of chloromethylation. This is the process whereby a hydrogen atom (generally of an aromatic compound) is replaced by a *chloromethyl group*, CH_2Cl. The reaction may be carried out by heating the aromatic hydrocarbon with formalin or paraformaldehyde and hydrochloric acid in the presence of zinc chloride as catalyst, *e.g.*, benzyl chloride from benzene:

$$C_6H_6 + CH_2O + HCl \xrightarrow{ZnCl_2} C_6H_5{\cdot}CH_2Cl + H_2O \quad (79\%)$$

Chloromethyl ether and dichloromethyl ether may be used instead of formalin or paraformaldehyde, but unlike the latter, do not require the presence of a catalyst. Many catalysts may be used with formalin (or paraformaldehyde), the most useful being zinc chloride, aluminium chloride, stannic chloride, acetic acid and sulphuric acid.

The introduction of a chloromethyl group is very useful, since this group is readily converted into other groups such as CH_3, CH_2OH, CHO, $CH_2{\cdot}CN$.

Chloromethylation is generally applicable to aromatic hydrocarbons such as benzene, naphthalene, anthracene, phenanthrene, diphenyl, and to many of their derivatives. Monoalkylbenzenes are converted mainly into the *p*-chloromethyl derivatives, together with a small amount of the *o*-compound. In certain cases it is possible to introduce a second chloromethyl group (see, *e.g.*, p. 716). The yields of the chloromethylated compounds are variable, usually lying between 50–80 per cent. The presence of a halogen atom in the ring reduces the yield of the chloromethylated derivative. A nitro-group behaves in a similar manner, and the presence of two nitro-groups inhibits the reaction altogether, *e.g.*, nitrobenzene gives only a small yield of the chloromethylated compound; *m*-dinitrobenzene gives none. Ketones of the type Ar·CO·R give very poor yields, and those of the type Ar·CO·Ar do not react at all. Phenols, however, are very reactive, so much so that polymers are often obtained.

According to Ogata *et al.* (1956), the mechanism of chloromethylation is:

$$CH_2O + H^+ \rightleftharpoons \overset{+}{C}H_2OH \xrightarrow{ArH} ArCH_2OH + H^+ \overset{HCl}{\rightleftharpoons} ArCH_2Cl + H_2O$$

Supporting evidence is that electron-releasing groups facilitate the reaction, whereas electron-withdrawing groups retard the reaction.

General properties of the benzene homologues. The benzene homologues are usually colourless liquids, insoluble in water, but miscible in all proportions with organic solvents. All burn with smoky flames.

Toluene (*methylbenzene*), $C_6H_5{\cdot}CH_3$, is obtained commercially from coal-tar, or by catalytically dehydrogenating *n*-heptane or methyl*cyclo*hexane (both obtained from petroleum; see p. 500):

$$CH_3{\cdot}(CH_2)_5{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CH_3 + 4H_2$$

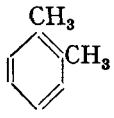
Toluene is also prepared by reaction between benzene and methane at high temperature.

Toluene is a colourless liquid, b.p. 111°, resembling benzene in many of its chemical properties. Since, however, it contains a side-chain, it undergoes some further reactions, *e.g.*, the side-chain may be oxidised in stages, first to give benzaldehyde and then to give benzoic acid:

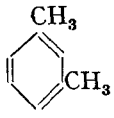
$$C_6H_5{\cdot}CH_3 \xrightarrow{[O]} C_6H_5{\cdot}CHO \xrightarrow{[O]} C_6H_5{\cdot}CO_2H$$

When toluene is nitrated or sulphonated, a mixture of the three possible isomers is obtained, mainly consisting of the *o*- and *p*- and very little of the *m*-isomer. Chlorine and bromine react with toluene in one of two ways, according to the conditions; the halogen may enter the nucleus or the side-chain (see p. 544).

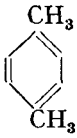
Xylenes, C_8H_{10}. Four isomers of the formula C_8H_{10} are known:



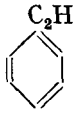
o-xylene
b.p. 144°



m-xylene
b.p. 139°



p-xylene
b.p. 138°



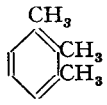
ethylbenzene
b.p. 136°

All of these isomers are present in the light oil fraction of coal-tar, and are difficult to separate because their boiling points are close together (see p. 609). The methyl groups in the xylenes may be oxidised by dilute nitric acid, one at a time, to give carboxylic acids; the *m*-isomer is not so easily oxidised as the *o*- and *p*-isomers:

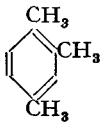
$$CH_3{\cdot}C_6H_4{\cdot}CH_3 \xrightarrow{[O]} \underset{\text{a toluic acid}}{CH_3{\cdot}C_6H_4{\cdot}CO_2H} \xrightarrow{[O]} \underset{\text{a phthalic acid}}{HO_2C{\cdot}C_6H_4{\cdot}CO_2H}$$

Potassium permanganate acts in a similar manner to nitric acid, but chromic acid oxidises the *o*-isomer to carbon dioxide and water.

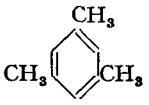
Hydrocarbons of formula C_9H_{12}. There are eight isomeric hydrocarbons of formula C_9H_{12}, *viz.*, three trimethylbenzenes, three methylethylbenzenes, one *n*-propylbenzene, and one *iso*propylbenzene. The three trimethylbenzenes occur in coal-tar:



hemimellitene
b.p. 175°

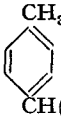


ψ-cumene
b.p. 169°



mesitylene
b.p. 164°

Mesitylene is the most important of these, and is usually prepared by distilling acetone with sulphuric acid (p. 170).



***iso*Propylbenzene** (*cumene*), $C_6H_5{\cdot}CH(CH_3)_2$, b.p. 153°, also occurs in coal-tar.

***p*-Cymene** (*cymene*, *p*-methyl*iso*propylbenzene), b.p. 177°, occurs in oil of thyme and eucalyptus oil, and is related to camphor and other terpenes.

Aromatic hydrocarbons with unsaturated side-chains. The only important unsaturated aromatic hydrocarbon is **styrene** (*phenylethylene*, *vinylbenzene*), $C_6H_5{\cdot}CH{=}CH_2$. This occurs in storax (a balsam) and in coal-tar (distilling with the xylenes). Styrene may be prepared as follows:

(i) By heating phenylmethylmethanol with sulphuric acid:

$$C_6H_5{\cdot}MgBr + CH_3{\cdot}CHO \longrightarrow C_6H_5{\cdot}\underset{CH_3}{C}HOMgBr \xrightarrow{H_2O}$$

$$C_6H_5{\cdot}CHOH{\cdot}CH_3 \xrightarrow[-H_2O]{\text{heat}} C_6H_5{\cdot}CH{=}CH_2$$

(ii) By heating 2-phenylethanol with alkali:

$$C_6H_5{\cdot}CH_2{\cdot}CH_2OH \longrightarrow C_6H_5{\cdot}CH{=}CH_2 + H_2O$$

(iii) The most convenient laboratory preparation is to heat cinnamic acid with a small amount of quinol:

$$C_6H_5{\cdot}CH{=}CH{\cdot}CO_2H \longrightarrow C_6H_5{\cdot}CH{=}CH_2 + CO_2$$

A small amount of quinol is also placed in the receiving vessel to prevent the polymerisation of the styrene.

Styrene is manufactured by dehydrogenating ethylbenzene catalytically:

$$C_6H_5{\cdot}C_2H_5 \xrightarrow[600°]{ZnO} C_6H_5{\cdot}CH{=}CH_2 + H_2$$

Ethylbenzene is prepared industrially by the action between benzene and ethylene in the presence of aluminium chloride.

Styrene is a colourless liquid, b.p. 145°. It adds on bromine to form the dibromide, and is readily reduced to ethylbenzene. It polymerises slowly to a solid on standing, and rapidly when exposed to sunlight or in the presence of sodium. This polymer, which is known as *metastyrene*, $(C_8H_8)_n$, may be depolymerised by heating. Styrene is used for making plastics and synthetic rubbers.

Substitution in the side-chain of styrene gives rise to two possibilities:

$C_6H_5{\cdot}CCl{=}CH_2$ — α-chlorostyrene

$C_6H_5{\cdot}CH{=}CHCl$ — β- or ω-chlorostyrene

Phenylacetylene, $C_6H_5{\cdot}C{:}CH$, may be prepared by decarboxylating phenylpropiolic acid, $C_6H_5{\cdot}C{:}C{\cdot}CO_2H$, or by heating ω-bromostyrene with ethanolic potassium hydroxide.

Phenylacetylene is a liquid, b.p. 142°, with acidic properties, *e.g.*, it forms metallic derivatives. It is reduced to styrene by zinc dust and acetic acid, and in the presence of sulphuric acid, phenylacetylene adds on a molecule of water to form acetophenone:

$$C_6H_5{\cdot}C{\equiv}CH + H_2O \longrightarrow C_6H_5{\cdot}CO{\cdot}CH_3$$

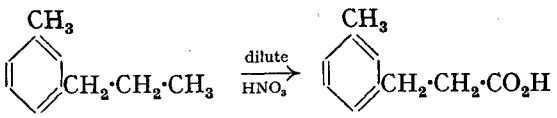
Oxidation of aromatic hydrocarbons. The benzene ring is usually very resistant to oxidation, and so when benzene homologues are oxidised, it is the side-chain which is attacked. Whatever the length of the side-chain, the ultimate oxidation product is benzoic acid; sometimes the intermediate products can be isolated, but it is usually difficult to control the oxidation. Cullis *et al.* (1955) have shown that when *n*- and *iso*propyl-benzene are oxidised with potassium permanganate, the initial attack is at the α-carbon, *e.g.*,

$$C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3 \xrightarrow{[O]} C_6H_5{\cdot}CO_2H + CH_3{\cdot}CO_2H + H_2O$$

Furthermore, these authors found that as the size of the alkyl group increased in a monoalkylbenzene, the extent of ring rupture decreases. The oxidations of toluene and ethylbenzene proceed as follows:

$$C_6H_5{\cdot}CH_3 \longrightarrow [C_6H_5{\cdot}CH_2OH] \longrightarrow C_6H_5{\cdot}CHO \longrightarrow C_6H_5{\cdot}CO_2H$$
$$C_6H_5{\cdot}CH_2{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CO{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CO_2H$$

When two side-chains are present, it is possible to oxidise them one at a time, *e.g.*, the xylenes may be oxidised first to a toluic acid and then to a phthalic acid. When the two side-chains are of unequal length, it is the longer one which is usually attacked first:



The usual oxidising agents for side-chains are dilute nitric acid, acid or alkaline permanganate, dichromate-sulphuric acid mixture, and chromic acid which may be chromium trioxide in either glacial acetic acid or concentrated sulphuric acid. All except permanganate usually attack the longer side-chain first. Recently, it has been found that selenium dioxide at 250–340° will oxidise a methyl side-chain to a mixture of aldehyde and carboxylic acid (Sultanov *et al.*, 1946):

$$Ar{\cdot}CH_3 \xrightarrow{SeO_2} Ar{\cdot}CHO + Ar{\cdot}CO_2H$$

Oxidation with chromic acid is selective, the *p*-isomer being more easily oxidised than the *m*-; the *o*-isomer is often completely oxidised to carbon dioxide, or the ring may be opened to give an aliphatic compound. Oxidation of *o*-compounds, however, is usually successful with permanganate (*i.e.*, no breakdown of the ring). When negative groups such as a halogen, nitro-, carboxyl or sulphonic acid group are attached to the ring, they are unaffected by oxidising agents, the result of oxidation being a substituted

benzoic acid; this therefore offers a means of preparing such compounds. The presence of a negative group, however, in the *o*-position to the side-chain generally makes oxidation difficult with *acidic* oxidising agents. The best oxidising agent for such *o*-compounds is probably alkaline permanganate. If there are two side-chains present as well as a negative group, then alkaline permanganate usually attacks the one *ortho* to the negative group.

An interesting oxidising agent is potassium ferricyanide. This will oxidise a methyl group to a carboxyl group only if there is a nitro-group *ortho* to the methyl group.

If a hydroxyl or amino-group is attached to the ring, the ring becomes very sensitive to oxidising agents, the ring usually breaking down completely, whatever the oxidising agent used. If, however, these groups are "protected" by acetylation, oxidation of side-chains may be effected without breakdown of the ring, but it is then best to use a *neutral* oxidising agent, *e.g.*, permanganate in the presence of magnesium sulphate, to prevent hydrolysis of the acetyl derivative. On the other hand, if the arylsulphonyl derivative, $Ar{\cdot}SO_2{-}$, is prepared instead of the acetyl derivative, oxidation of side-chains may be carried out in acid media, since the sulphonyl derivative is much more difficult to hydrolyse than the acetyl derivative.

Metalation of aromatic compounds. Metallic derivatives of aromatic compounds may be prepared by various methods; *e.g.*, benzene heated with an alkyl-sodium forms phenylsodium:

$$C_6H_6 + R^-Na^+ \longrightarrow C_6H_5^-Na^+ + RH$$

Phenylsodium may also be prepared by heating diphenylmercury with sodium:

$$(C_6H_5)_2Hg + 2Na \longrightarrow 2C_6H_5^-Na^+ + Hg$$

Diphenylmercury may be prepared by refluxing a mixture of bromobenzene, sodium amalgam, xylene and a small amount of ethyl acetate:

$$2C_6H_5Br + Na_2/Hg \longrightarrow (C_6H_5)_2Hg + 2NaBr \quad (32\text{–}37\%)$$

Phenyl-lithium may conveniently be prepared by the action of lithium on bromo- or iodobenzene in ethereal solution:

$$C_6H_5Br + 2Li \longrightarrow C_6H_5Li + LiBr$$

All these metalated aromatic compounds (*i.e.*, organo-metallic compounds) undergo the general reactions of the Grignard reagents. In practice, the lithium compound is generally used, since it is so readily prepared (see also p. 361).

A very important case of metalation is **mercuration.** Aromatic compounds containing almost all the common functional groups have been mercurated, and in general mercuration proceeds easily with the formation of mono-, di- and even polymercurated compounds. Mercuration is becoming an increasingly important substitution reaction, and aromatic mercurated compounds are increasing in importance in medicine and as intermediates in the preparation of other compounds (see text).

Aromatic mercuration is carried out in two ways:

(i) **Direct mercuration.** This is the reaction in which a hydrogen atom of benzene, a polynuclear hydrocarbon, or a heterocyclic compound, is replaced by the *mercuri-acid group*, the most common one being the *acetoxy-mercuri-group*, $-Hg{\cdot}O{\cdot}CO{\cdot}CH_3$. This group is usually introduced by

heating the hydrocarbon with mercuric acetate, or with the equivalent of mercuric oxide in glacial acetic acid, at 90–160°, for one or more hours, *e.g.*, *acetoxymercuribenzene* (*phenylmercury acetate*):

$$C_6H_6 + Hg(O{\cdot}CO{\cdot}CH_3)_2 \longrightarrow C_6H_5{-}Hg{\cdot}O{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}CO_2H$$

The monomercurated derivative is the main product, and is accompanied by a varying amount of polymercurated derivatives.

Mercuration may be effected by heating the aromatic compound with the mercury salt only, or together with acetic anhydride or with solvents such as methanol or ethanol.

The most important aromatic compounds that can be mercurated are the aromatic hydrocarbons, aryl chlorides, nitro-compounds, amino-compounds, phenols, acids and acid anhydrides. The aryl halides and nitro-compounds are mercurated with difficulty, whereas compounds containing a hydroxyl or an amino-group (activating groups) are mercurated more readily than the parent hydrocarbon.

The orienting influence of substituent groups may be unusual. With an *o-p*-orienting group the reaction is usually normal, *e.g.*, aniline and phenol give the expected *o*- and *p*-derivatives, but toluene gives about 20 per cent. of the *m*-compound. On the other hand, a *m*-orienting group may behave abnormally, *e.g.*, Klapproth *et al.* (1950) have shown that mercuration of nitrobenzene with mercuric perchlorate in aqueous perchloric acid at 23° gives 11 per cent. of *o*- and *p*-, and 89 per cent. of *m*-compound, whereas mercuration with mercuric acetate at 150° gives 57 per cent. of *o*- and *p*-, and 43 per cent. of *m*-. The reason offered for this is that in the former case the mercuric salt is ionised and so the reaction is heterolytic, *i.e.*, electrophilic, and consequently the usual orientation is observed. In the latter case the salt is unionised, and so this reaction proceeds largely through a homolytic process, *i.e.*, by a free-radical mechanism.

The position of the acetoxymercuri-group can be found by treating the mercurated compound with halogen, whereupon the group is replaced by a halogen atom:

$$Ar{-}Hg{\cdot}O{\cdot}CO{\cdot}CH_3 + Br_2 \longrightarrow ArBr + HgBr(O{\cdot}CO{\cdot}CH_3)$$

This reaction is the most characteristic reaction of mercurated compounds. On the other hand, if a mercurated compound is treated with sodium halide, the *acetyl group* is replaced by a halogen atom to form a *halogenomercuri*-compound (*phenylmercury halide*):

$$Ar{-}Hg{\cdot}O{\cdot}CO{\cdot}CH_3 + NaCl \longrightarrow Ar{-}HgCl + CH_3{\cdot}CO_2Na$$

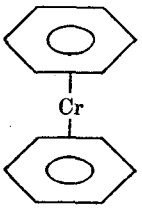
Mercuric nitrate readily reacts with excess benzene to form phenylmercury nitrate $C_6H_5{\cdot}HgNO_3$. The nitric acid liberated (from the mercuric nitrate) during the reaction decomposes the mercurated compound, but this can be avoided by using a mixture of mercuric nitrate and mercuric oxide (the latter neutralising the liberated nitric acid). If instead of mercuric nitrate, a solution of mercuric nitrate in nitric acid is used, the benzene is oxidised and nitrated to dinitrophenol and picric acid. In this case the reaction is known as *oxynitration* (see p. 628).

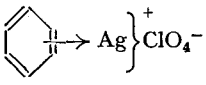
(ii) **Indirect mercuration.** This is the reaction in which a functional group is replaced by a mercuri-acid group, usually the *chloromercuri-group*, —HgCl. Mostly used for this purpose are the diazonium salts, sulphinic acids and aryl halides (see text).

The advantage of indirect over direct mercuration is that the former may

be used to prepare a particular isomer, whereas the latter usually produces a mixture of isomers.

It has now been found that benzene (and various other aromatics) forms metallic complexes similar to the ferrocenes (p. 480), *e.g.*, when benzene, chromic chloride, aluminium chloride and powdered aluminium are heated at 180°, a product containing the $(C_6H_6)_2Cr^+$ cation is obtained. This, on reduction with, *e.g.*, hypophosphorous acid, gives dibenzenechromium (0), $(C_6H_6)_2Cr$, a dark brown solid (Zeiss *et al.*, 1956).





(I)

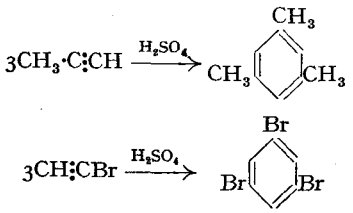
A point of interest in this connection is that benzene forms π-complexes with the silver ion; *e.g.*, crystallisation of silver perchlorate from benzene gives the π-complex (I) (*cf.* ethylene, p. 66).

Synthesis of aromatic compounds from aliphatic compounds. Many methods are available for the conversion of aliphatic compounds into aromatic, *e.g.*,

(i) From acetylenic compounds, *e.g.*, acetylene passed through a red hot tube forms benzene:

$$3C_2H_2 \longrightarrow C_6H_6$$

When methylacetylene or bromoacetylene is treated with a small amount of concentrated sulphuric acid, the *s*-trisubstituted benzene derivative is formed:

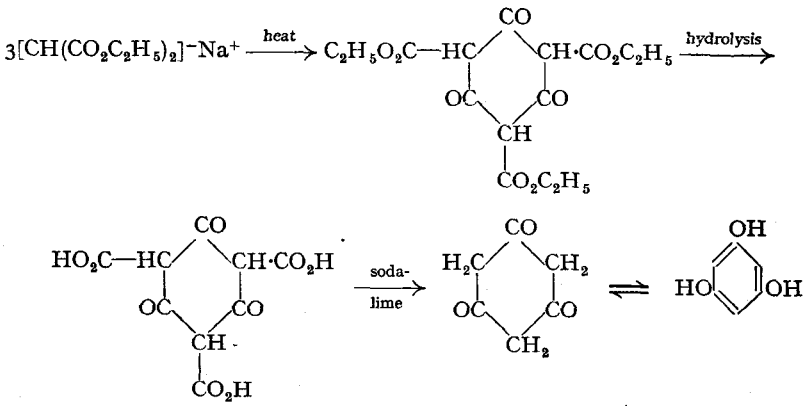


(ii) When acetone is distilled with sulphuric acid, mesitylene is formed (p. 170). Similarly, butanone forms *s*-triethylbenzene (and other products).

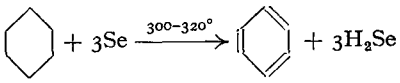
(iii) When carbon monoxide is passed over heated potassium, the potassium salt of hexahydroxybenzene is formed:

$$6CO + 6K \longrightarrow C_6(OK)_6$$

(iv) Phloroglucinol (*s*-trihydroxybenzene) may be prepared from sodiomalonic ester as follows:



(v) *cyclo*Hexane derivatives (prepared by the Diels–Alder reaction, p. 472) can be dehydrogenated to give aromatic compounds. Dehydrogenation may be carried out by heating the compound with sulphur, selenium, or a palladium–charcoal catalyst:



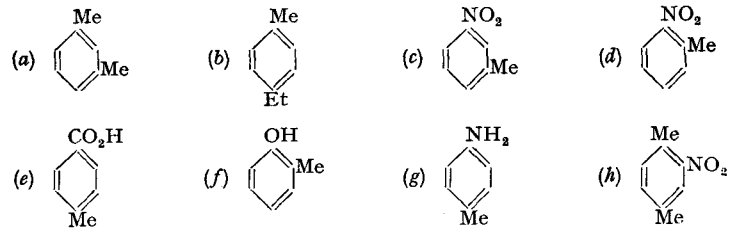
(vi) By means of hydroforming, and high-temperature cracking (p. 500).

Conversion of aromatic compounds into aliphatic compounds. Many methods are available for the conversion of aromatic compounds into aliphatic, but care must be exercised, since opening of the ring often results in its complete breakdown.

(i) By ozonolysis, *e.g.*, *o*-xylene (see p. 505).
(ii) When phenol is carefully oxidised, *meso*tartaric is formed (p. 421).
(iii) When benzene is oxidised by air in the presence of vanadium pentoxide as catalyst, maleic anhydride is formed. On the other hand, oxidation of benzene with hydrogen peroxide in *t*.-butanol in the presence of a little osmium tetroxide gives allomucic, *meso*tartaric and oxalic acids (p. 421).
(iv) When phenol is oxidised with peracetic acid, muconic acid is formed (p. 431).
(v) Phenol may be reduced to *cyclo*hexanol, which, on oxidation with concentrated nitric acid, gives adipic acid (p. 378).
(vi) A curious example of the opening of the benzene ring is the reduction of salicylic acid to give pimelic acid (see p. 683).

QUESTIONS

1. How are the following compounds prepared commercially:—(*a*) C_6H_6, (*b*) PhMe, (*c*) PhEt, (*d*) $PhCH{=}CH_2$?
2. Write out the structures and names of the isomers of each of the following formulæ: (*a*) $C_6H_4Cl_2$, (*b*) C_6H_4ClBr, (*c*) $C_6H_3(NO_2)_3$, (*d*) $C_6H_3Cl_2(NO_2)$, (*e*) $C_7H_6Cl(NH_2)$.
3. Write an account of the methods of orientation.
4. Discuss the structure of benzene.
5. Write an essay on aromatic substitution.
6. Starting with benzene and any other chemical you like, show how you would synthesise:—(*a*) PhMe, (*b*) PhEt, (*c*) *p*-$C_6H_4Me_2$, (*d*) *m*-$C_6H_4Et_2$, (*e*) $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$, (*f*) $Ph{\cdot}CH_2{\cdot}CN$, (*g*) $Ph{\cdot}CH_2OH$, (*h*) $Ph{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, (*i*) $Ph{\cdot}CHBr{\cdot}CH_3$, (*j*) $Ph{\cdot}CMe_3$, (*k*) *p*-$MeC_6H_4{\cdot}CH_2OH$, (*l*) $Ph{\cdot}CH{=}CH_2$, (*m*) $Ph{\cdot}C{\vdots}CH$, (*n*) PhLi, (*o*) PhHgOAc, (*p*) PhHgBr.
7. Name the compounds and state the conditions under which they may be obtained when each of the following compounds is oxidised:



8. Define and give examples of:—(*a*) the Friedel–Crafts reaction, (*b*) the Wurtz–Fittig reaction, (*c*) Chloromethylation, (*d*) Mercuration, (*e*) Metalation.
9. Describe a number of methods whereby aliphatics may be converted into aromatics, and vice versa.
10. Discuss methods that have been used for studying organic reactions.
11. Write an essay on the problem of the *ortho-para* ratio.
12. Give an account of hyperconjugation.
13. Discuss the problem of " aromatic character."

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