CHAPTER VI

MISCELLANEOUS REACTIONS

VI,1. ACETYLACETONE

A ketone having an α-hydrogen atom may be acylated with an ester or an acid anhydride to form a β-diketone :

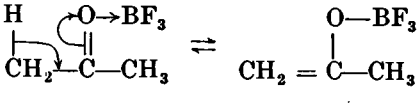
$$RCOX + HCH_2COR \longrightarrow RCOCH_2COR + HX \qquad (X = OR', OCOR)$$

The acylation of ketones with acid anhydrides may be effected by means of the acid reagent boron trifluoride, for example :

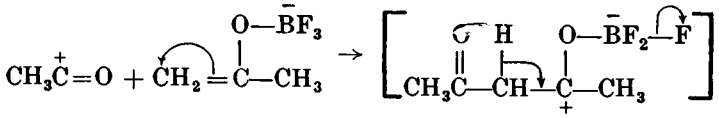
$$CH_3COCH_3 + (CH_3CO)_2O \xrightarrow[CH_3COONa]{BF_3\uparrow} \underset{\text{(acetylacetone)}}{CH_3COCH_2COCH_3} + CH_3COOH$$

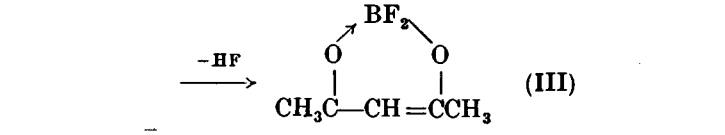
A mixture of an acid anhydride and a ketone is saturated with boron trifluoride ; this is followed by treatment with aqueous sodium acetate. The quantity of boron trifluoride absorbed usually amounts to 100 mol per cent. (based on total mols of ketone and anhydride). Catalytic amounts of the reagent do not give satisfactory results. This is in line with the observation that the β-diketone is produced in the reaction mixture as the boron difluoride complex, some of which have been isolated. A reasonable *mechanism* of the reaction postulates the conversion of the anhydride into a carbonium ion, such as (I) ; the ketone into an enol type of complex, such as (II) ; followed by condensation of (I) and (II) to yield the boron difluoride complex of the β-diketone (III) :

$$(CH_3CO)_2O{\rightarrow}BF_3 \rightleftharpoons CH_3\overset{+}{C}{=}O \ \text{(I)} + CH_3COO\bar{B}F_3$$



(II) + H^+





$$CH_3COO\bar{B}F_3 + H^+ + HF \longrightarrow [CH_3COOH_2]^+\,[BF_4]^-$$

The boron difluoride coordination complex is decomposed by heating under reflux with an aqueous solution of 2 mols of sodium acetate per mol of anhydride, whereupon the β-diketone (acetylacetone) is liberated.

The acylation of ketones with esters an example of the **Claisen condensation** is generally effected with a basic reagent, such as sodium ethoxide, sodium, sodamide or sodium hydride. Thus acetone and ethyl acetate condense in the presence of sodium ethoxide to yield **acetylacetone** :

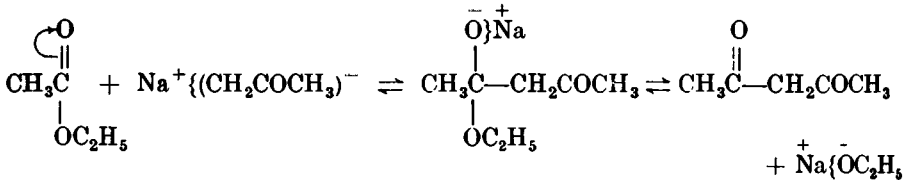
$$CH_3COCH_3 + CH_3COOC_2H_5 \xrightarrow[\text{dil. } H_2SO_4]{NaOC_2H_5;} CH_3COCH_2COCH_3 + HOC_2H_5$$

The *mechanism* of the base-catalysed acylation of ketones by esters probably involves several steps (compare acetoacetic ester condensation ; see discussion prior to Section III,151) :—

(1) Removal of an α-hydrogen atom of the ketone as a proton to form a carbanion (acetone anion) :

$$CH_3COCH_3 + \overset{+}{N}a\{\overset{-}{O}C_2H_5 \rightleftharpoons Na^+\{(CH_2COCH_3)^- + C_2H_5OH$$

(2) Reaction of the carbanion (acetone anion) with the carbonyl carbon of ethyl acetate, accompanied by the release of an ethoxide ion, to form acetylacetone :



(3) Removal of a methylene hydrogen of the acetylacetone to form acetylacetone anion :

$$CH_3COCH_2COCH_3 + \overset{+}{N}a\{\overset{-}{O}C_2H_5 \rightleftharpoons Na^+\{(CH_3COCHCOCH_3)^- + HOC_2H_5$$

The acetylacetone anion is a resonance hybrid :

$$CH_3\overset{-}{C}OCHCOCH_3 \longleftrightarrow CH_3COCH{=}C(\overset{-}{O})CH_3$$

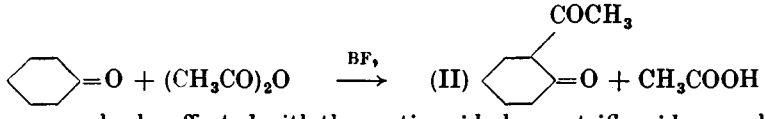
The equilibrium of the overall reaction is shifted in the direction of the condensation product by the precipitation of the β-diketone as its sodium salt.

It may be mentioned that the condensation in the presence of metallic sodium appears to be partly effected by the metal which displaces atomic hydrogen from the ketone :

$$CH_3COCH_3 + Na \longrightarrow Na^+\{(CH_2COCH_3)^- + \tfrac{1}{2}H_2$$

and partly by the ethoxide ion produced in the reaction mixture (compare Ethyl Acetoacetate).

Methylene ketones, such as *cyclo*pentanone and *cyclo*hexanone, are also readily acylated by boron trifluoride ; thus *cyclo*hexanone (I) affords **2-acetylcyclohexanone** (II) :



Acylation may also be effected with the acetic acid - boron trifluoride complexes $BF_3.CH_3COOH$ and $BF_3.2CH_3COOH$.

Boron trifluoride method. Fit a 1 litre three-necked flask with a gas inlet tube, a gas outlet leading to an alkali trap (compare Fig. *II,8*, 1*a* or *b*; for the unabsorbed boron trifluoride), and stopper the third neck. Place 58 g. (73 ml.) of pure, anhydrous acetone (1) and 255 g. (236 ml.) of A.R. acetic anhydride in the flask and cool in a freezing mixture of ice and salt. Connect the gas inlet tube through an empty wash bottle to a cylinder of commercial boron trifluoride (2), and bubble the gas through the reaction mixture at such a rate that 250 g. is absorbed in about 5 hours (2 bubbles per second). Pour the reaction mixture into a solution

of 400 g. of crystallised sodium acetate in 800 ml. of water contained in a 2·5 litre round-bottomed flask. Steam distil the mixture (Fig. *II*, *40*, 1), and collect the distillate in the following portions : 500 ml., 250 ml., 250 ml., and 250 ml. In the meantime prepare a solution of 120 g. of A.R. crystallised cupric acetate in 1500 ml. of water at about 85° ; if the solution is not clear, filter from any basic acetate. Precipitate the copper salt of acetylacetone by adding 700 ml. of the hot copper acetate solution to the first portion of the steam distillate, 350 ml. to the second, 250 ml. to the third, and 200 ml. to the fourth portion. Allow to stand for 3 hours, or better overnight, in the ice chest. Filter off the salt at the pump, wash once with water, and suck as dry as possible. Transfer the copper salt to a separatory funnel, add 400 ml. of 20 per cent. sulphuric acid and 400 ml. of ether, and shake. Remove the ether layer. Extract the aqueous layer with two 150 ml. portions of ether. Dry the combined extracts with 125 g. of anhydrous sodium sulphate (or the equivalent quantity of anhydrous magnesium sulphate), and distil off the ether. Distil the residue from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 4–5) and collect the acetylacetone at 134–136°. The yield is 80 g.

Sodium ethoxide method. Prepare " molecular " sodium from 46 g. of clean sodium and 250 ml. of sodium-dried xylene contained in a 1 litre round-bottomed flask (Section **II,50,***6*). Transfer the contents of the flask to a 2 litre three-necked flask and decant the xylene. Wash the sodium by decantation with two 75 ml. portions of sodium-dried ether. Cover the granulated sodium with 700 ml. of anhydrous ether, place the flask on a water bath, and fit the flask with a dropping funnel, a Hershberg stirrer (Fig. *II*, *7*, 8) and a reflux condenser ; insert guard tubes, containing absorbent cotton wool or anhydrous calcium chloride, into the funnel and the condenser. Place 117 ml. (92 g.) of absolute ethyl alcohol in the dropping funnel, start the stirrer, and introduce the alcohol over a period of 2 hours with gentle refluxing. Reflux the mixture with stirring for a further 6 hours ; by this time most, if not all, of the sodium should have reacted (a *little* residual sodium does no harm). Stop the stirrer, turn the condenser downward (compare Fig. *II*, *41*, 1), and distil off the ether as completely as possible on a water bath. The residual **sodium ethoxide** should be white and finely-divided. All moisture must be excluded during the preparation in order to avoid the formation of sodium hydroxide, which markedly lowers the yield. Return the condenser to the reflux position and add 800 ml. of pure, dry ethyl acetate (3) through the dropping funnel to the warm solid sodium ethoxide as rapidly as possible. Start the stirrer immediately and add *at once* 116 g. (147 ml.) of pure dry acetone during about 15 minutes ; if the mixture does not reflux, warm gently on a water bath. After about half of the acetone has been introduced, the mixture generally sets to a solid mass and mechanical stirring is impossible ; turn the stirrer by hand and continue the addition of the acetone. In a few minutes the mass can again be stirred mechanically. During the addition of the acetone, the solution acquires a red colour and eventually the mixture turns brown. Reflux the mixture for 1 hour : stop the stirrer and allow to stand for 12 hours, during which time crystals of the sodium salt separate.

Decant the liquid layer into a 2·5 litre flask, and dissolve the sodium derivative of acetylacetone in 1600 ml. of ice water ; transfer the solution to the flask. Separate the impure ethyl acetate layer as rapidly as possible ; extract the aqueous layer with two 200 ml. portions of ether and discard the ethereal extracts. Treat the aqueous layer with ice-cold dilute sulphuric acid (100 g. of concentrated sulphuric acid and 270 g. of crushed ice) until it is just acid to litmus. Extract the diketone from the solution with four 200 ml. portions of ether. Leave the combined ether extracts standing over 40 g. of anhydrous sodium sulphate (or the equivalent quantity of anhydrous magnesium sulphate) for 24 hours in the ice chest. Decant the ether solution into a 1500 ml. round-bottomed flask, shake the desiccant with 100 ml. of sodium-dried ether and add the extract to the ether solution. Distil off the ether on a water bath. Transfer the residue from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 4–5) : collect the fraction boiling between 130° and 139°. Dry this over 5 g. of anhydrous potassium carbonate, remove the desiccant, and redistil from the same flask. Collect the pure acetylacetone at 134–136°. The yield is 85 g.

Notes.

(1) A.R. acetone may be dried over anhydrous potassium carbonate or anhydrous calcium sulphate.

(2) Boron trifluoride is available commercially in cylinders, *e.g.*, from the Imperial Smelting Corporation Ltd., 37 Dover Street, London, W. 1, and from Matheson Company Inc., East Rutherford, N.J., U.S.A. It is advantageous to bubble the gas through 95 per cent. sulphuric acid. Boron trifluoride - acetic acid complex, largely $BF_3.2CH_3COOH$, containing about 40 per cent. BF_3 is obtainable from Imperial Smelting Corporation Ltd.

(3) Pure commercial ethyl acetate is allowed to stand for 2 days over anhydrous calcium chloride, the desiccant removed by filtration, and the ester is then finally dried over anhydrous calcium sulphate for several hours.

Cognate Preparation

2-Acetyl*cyclo*hexanone. *Method A.* Place a mixture of 24·5 g. of *cyclo*hexanone (regenerated from the bisulphite compound) and 51 g. (47·5 ml.) of A.R. acetic anhydride in a 500 ml. three-necked flask, fitted with an efficient sealed stirrer, a gas inlet tube reaching to within 1–2 cm. of the surface of the liquid combined with a thermometer immersed in the liquid (compare Fig. *II*, *7*, 12, *b*), and (in the third neck) a gas outlet tube leading to an alkali or water trap (Fig. *II*, *8*, 1). Immerse the flask in a bath of Dry Ice - acetone, stir the mixture vigorously and pass commercial boron trifluoride (via an empty wash bottle and then through 95 per cent. sulphuric acid) as fast as possible (10–20 minutes) until the mixture, kept at 0–10°, is saturated (copious evolution of white fumes when the outlet tube is disconnected from the trap). Replace the Dry Ice-acetone bath by an ice bath and pass the gas in at a slower rate to ensure maximum absorption. Stir for 3·5 hours whilst allowing the ice bath to attain room temperature slowly. Pour the reaction mixture into a solution of 136 g. of hydrated sodium acetate in 250 ml. of water, reflux for 60 minutes (or until the boron fluoride complexes are hydrolysed), cool in ice and extract with three 50 ml. portions of petroleum ether, b.p. 40–60° (1), wash the combined extracts free of acid with sodium bicarbonate solution, dry over anhydrous calcium sulphate, remove the solvent by

flash distillation, and distil the residue under reduced pressure. Collect the 2-acetyl*cyclo*hexanone at 95–97°/10 mm. The yield is 27 g.

Method B. Place 60 g. of glacial acetic acid in a 500 ml. three-necked flask equipped with a gas inlet tube, an efficient sealed stirrer, and an outlet tube leading to an alkali or water trap. Immerse the flask in an ice bath, stir vigorously and pass boron trifluoride in as rapidly as possible. Continue the passage of the gas (at a reduced rate as saturation is approached) until the contents of the flask become a powdery solid (2). Substitute a dropping funnel for the gas inlet tube, cool in an ice bath, and add a mixture of 24·5 g. of pure *cyclo*hexanone and 51 g. (47·5 ml.) of A.R. acetic anhydride during 3–5 minutes whilst stirring vigorously. Remove the ice bath after stirring for 30 minutes, allow to stand for 4 hours, and then work up as in *Method A*. The yield of 2-acetyl*cyclo*hexanone, b.p. 95–97°/10 mm., is 30 g.

Notes.

(1) Petroleum ether is preferable to diethyl ether because it removes very little acetic acid from the aqueous phase.

(2) To prevent the solid complex from caking (which occurs if the stirring is not sufficiently rapid) about 75 ml. of dry ethylene dichloride may be added.

The solid appears to be a mixture of the complexes $CH_3COOH.BF_3$ and $2CH_3COOH.BF_3$. The latter appears to be a liquid and is alone soluble in ethylene dichloride; the former is a solid. The solid monoacetic acid complex is obtained by saturating an ethylene dichloride solution of acetic acid with boron trifluoride, filtering and washing the precipitate with the solvent; it is hygroscopic and should be protected from moisture. It may be used as required; 0·75 mol is employed with 0·25 mol of ketone and 0·5 mol of anhydride.

VI,2. BENZOYLACETONE

The preparation of benzoylacetone is another example of the acylation of a ketone (acetophenone) by ethyl acetate to a β-diketone (**Claisen condensation**; compare preceding Section):

$$C_6H_5COCH_3 + CH_3COOC_2H_5 \xrightarrow[CH_3COOH]{NaOC_2H_5} C_6H_5COCH_2COCH_3 + C_2H_5OH$$

Prepare 34 g. of anhydrous sodium ethoxide in a 1 litre three-necked flask (Section **VI,1**, but use one-quarter of the quantities). Fit the flask with a dropping funnel, a mechanical stirrer and a reflux condenser: protect the dropping funnel and the condenser with absorbent cotton wool guard tubes. Surround the flask with ice and introduce 200 ml. of pure, dry ethyl acetate. Start the stirrer and add 60 g. (58 ml.) of acetophenone (Section **IV,136**) from the dropping funnel; the reaction commences (evolution of heat) after 10–20 g. of the ketone has been introduced, and the remainder is added at such a rate that gentle refluxing takes place. Continue the stirring for 2 hours, and then allow to stand in an ice box overnight. Pour the reaction mixture, with stirring, into ice water. The sodium salt of benzoylacetone separates. Filter this at the pump, wash with benzene or ether, and dry in the air. Dissolve the solid in cold water, and acidify the solution with acetic acid. Filter off the crude benzoylacetone, and dry in the air. Purify by distillation under reduced pressure; collect the benzoylacetone at 128–130°/10 mm. It solidifies on cooling to a colourless crystalline solid, m.p. 61°. The yield is 50 g.

VI,3. PHENYLGLYOXAL

Oxidation of acetophenone with selenium dioxide in the presence of dioxan or ethyl alcohol as solvent affords phenylglyoxal:

$$C_6H_5COCH_3 + SeO_2 \longrightarrow C_6H_5COCHO + Se + H_2O$$

This is one example of the oxidation by selenium dioxide of compounds containing a methylene group adjacent to a carbonyl group to the corresponding α-ketoaldehyde or α-diketone (see also Section **VII,23**).

Fit a 500 ml. three-necked flask with a liquid-sealed stirrer, a reflux condenser and a thermometer. Place 300 ml. of dioxan (1), 55·5 g. of selenium dioxide and 10 ml. of water in the flask, heat the mixture to 50–55° and stir until the solid has dissolved. Remove the thermometer momentarily and add 60 g. of acetophenone (Section **IV,136**) in one lot; replace the thermometer. Reflux the mixture, with stirring, for 4 hours; after about 2 hours the solution becomes clear and little further precipitation of selenium is observable. Decant the hot solution from the precipitated selenium through a fluted filter paper, and remove the dioxan and water by distillation through a short column. Distil the residual phenylglyoxal under reduced pressure from a 150 ml. Claisen flask and collect the fraction boiling at 95–97°/25 mm. The yield of pure phenylglyoxal (a yellow liquid) is 48 g.; this sets to a stiff gel on standing, probably as a result of polymerisation, but may be recovered without appreciable loss by distillation. The aldehyde is best preserved in the form of the hydrate, which is prepared by dissolving the yellow liquid in 3·5–4 volumes of hot water and allowing to crystallise. Phenylglyoxal hydrate also crystallises from chloroform, alcohol or ether-light petroleum (b.p. 60–80°); upon distillation under diminished pressure, the free aldehyde is obtained.

Note.

(1) Rectified spirit can also be used as solvent. The dioxan can, however, be recovered and used in a subsequent run (*cf.* Section **II,47,27**).

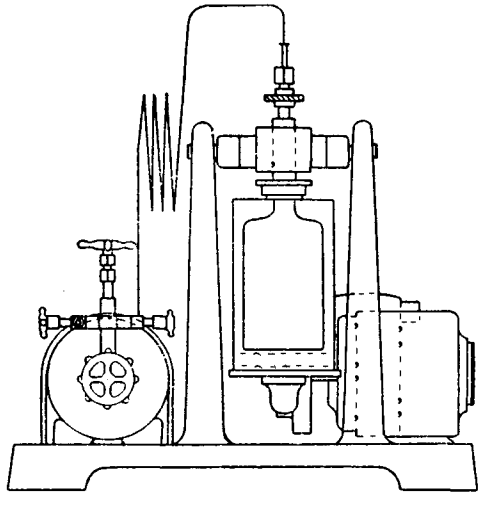
VI,4. APPARATUS FOR REACTIONS UNDER PRESSURE

The following account refers primarily to commercial apparatus suitable for conducting hydrogenations under pressure; the apparatus can, of course, be employed for other reactions under high pressures, but slight modifications of experimental procedure will probably be necessary.

The apparatus shown in Fig. *VI, 4*, 1, *a* and *b* * is suitable for use at working pressures up to 80–100 lb. per square inch (glass reaction bottle, capacity 470 ml.) or up to 500 lb. per square inch (steel reaction bottle, capacity 650 ml.). The glass or steel reaction bottle fits into a special bronze rocking frame of great strength and rigidly fixed to a solid cast iron base. Connexion between the reaction vessel and the storage tank is made by means of seamless, corrosion-resisting metal tubing coiled in such a manner as to prevent fatigue of the tubing. The frame carrying the reaction vessel may be rocked with a variable amplitude by means of a variable speed motor with a rheostat. The storage tank (40 cubic feet,

* Supplied by W. Edwards and Co. (London) Ltd. A similar apparatus is manufactured by C. W. Cook and Sons Ltd., 97, Walsall Road, Birmingham, 22B.

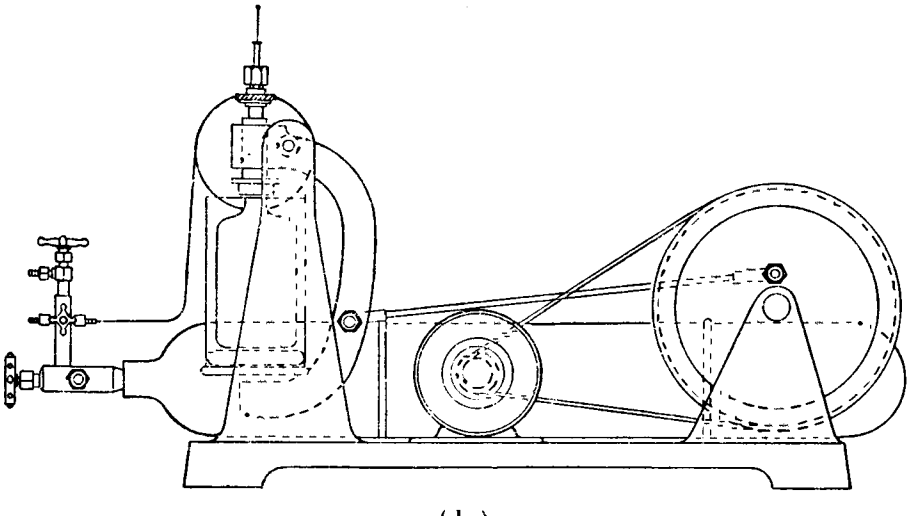
nominal) for hydrogen is a weldless forging capable of withstanding any pressure up to 2,000 lb. per square inch and is provided with a suitable pressure gauge. The steel reaction cylinder is fitted with a three-range heating coil giving a maximum temperature of about 450°. Four high pressure valves control the gas flow and provide for : (*a*) charging the



(a)

Fig. *VI*, *4*, 1.

storage tank to the required pressure ; (*b*) admission of gas to the reaction chamber ; (*c*) release of pressure in the reaction vessel to permit the removal of containers without loss of gas from the storage tank ; and (*d*) cutting off the high pressure cylinder. The weight of hydrogen



(b)

Fig. *VI. 4* 1.

absorbed may be computed from the change of pressure observed on the gauge. It should be mentioned that a perforated guard screen surrounds the glass bottle as a guard for flying glass in case of accidental explosion.

An excellent high pressure autoclave is illustrated in Fig. *VI*, *4*, 2.* The special feature of this apparatus, constructed almost entirely of

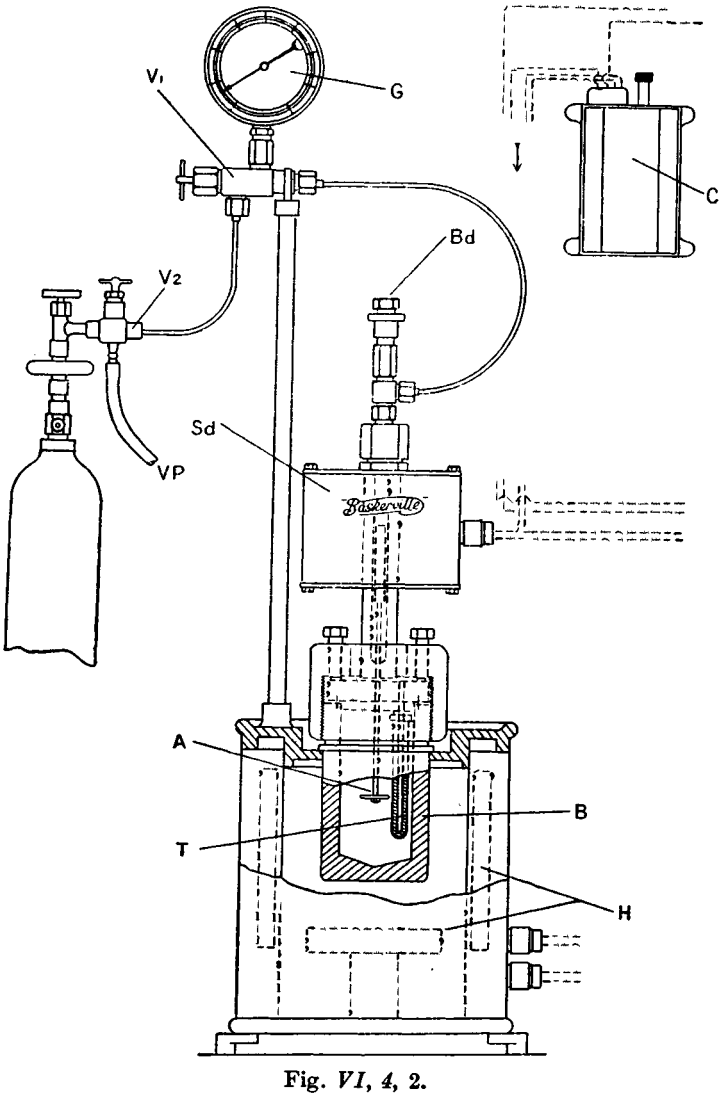


Fig. *VI*, *4*, 2.

stainless steel, is the incorporation of a totally-enclosed agitator in the form of a plunger which is operated electro-magnetically; agitation efficiency is at least as high as is achieved with "shaking" autoclaves and is very effective for hydrogenation purposes. The apparatus is

* Manufactured by Baskerville and Lindsay, 322c Barlow Moor Road, Chorlton-cum-Hardy, Manchester 21, England.

stationary, has no external moving parts, and can be made compact and convenient to use. The reaction vessel *B* is made of F.M.B. stainless steel machined out of the solid and is provided with a cover fitted respectively with a thermometer or thermo-couple pocket *T*, a central vertical tube, and an outer vessel nut with compression screws for making the pressure joint between the cover and the vessel. *Sd* is a solenoid operated through the contactor *C*, *Bd* is a bursting disc, *G* is a pressure gauge, V_1 is a control valve, V_2 is an evacuation valve (the last-named is connected through *VP* to a vacuum pump for complete evacuation of the apparatus). The agitator *A* consists of a stainless steel rod at the lower end of which is secured a circular stainless steel plate ; at the upper

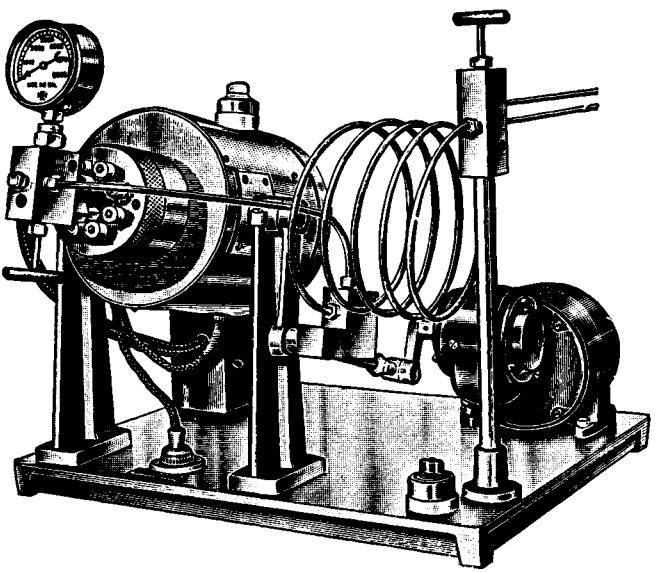


Fig. *VI*, *4*, 3.

end of the rod passing through the centre of the vertical tube is a stainless steel sheathed armature which, in its lowest position, just enters the lower end of the solenoid coil surrounding the central tube. The solenoid *Sd* through the contactor *C* operates at a rate between 20 and 90 cycles per minute controlled by an adjustable screw on the contactor, resulting in a vertical reciprocating movement of the agitator rod. The whole autoclave is placed in an electrically-heated air bath *H*. Autoclaves are available in capacities ranging from 200 ml. to 2 litres for use with pressures up to 350 atmospheres and to temperatures as high as 300°: special liners of Pyrex glass are supplied for use with substances which attack stainless steel or are affected by it.

A somewhat different type of high pressure reaction vessel * is illustrated in Figs. *VI*, *4*, 3–5. This is designed for hydrogenation reactions at working pressures from 1 to 300 atmospheres (4,500 lb. per square inch) and at temperatures from atmospheric up to 400°. Fig. *VI*, *4*, 3

* Obtainable from Parr Instrument Co., Moline, Illinois, U.S.A. An equivalent apparatus is manufactured by American Instrument Co., Silver Springs, Maryland, U.S.A., and by C. W. Cook and Sons Ltd., 97, Walsall Road, Birmingham, 22B, England.

depicts the complete apparatus. The stainless steel bomb (approximately 480 ml. capacity) is shown in Fig. *VI*, *4*, 4, and the bomb with heating shell in Fig. *VI*, *4*, 5. The heater is mounted on trunnions connected to a gear-head electric motor, which oscillates the bomb through an arc of 45° to " up-end the contents at the rate of 36 cycles per minute." Hydrogen may be admitted to the bomb while it is being shaken through a supply tube made of $\frac{1}{4}$ inch diameter by $\frac{1}{16}$ inch bore high pressure steel tubing, wound in a 9 inch helix. A safety plug is fitted into the

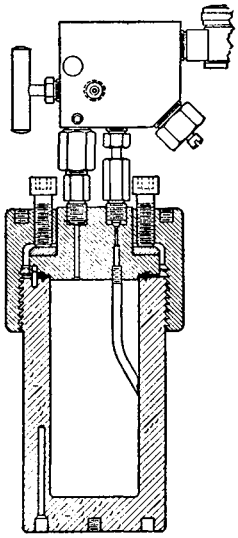


Fig. *VI*, *4*, 4.

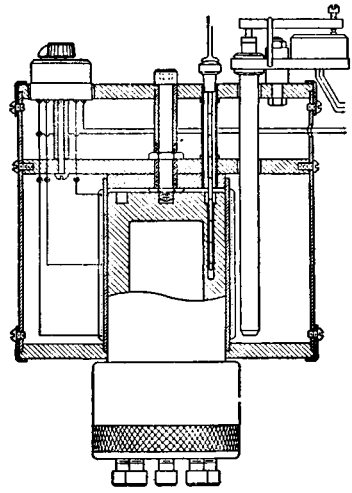


Fig. *VI*, *4*, 5.

bomb head containing a rupturable disc which will burst at approximately 6,000 lb. per square inch. The temperature of the bomb and its contents is observed by means of a copper - constantan thermo-couple inserted in a copper cup in the bottom of the bomb. The electric heater is controlled by a variable - voltage transformer mounted on the base of the apparatus.

VI,5. RANEY NICKEL (CATALYST)

One great advantage of hydrogenation with a platinum catalyst (compare Section III,150) is that the reaction can be controlled by the uptake of hydrogen. The introduction by Raney (1927) of a new form of nickel catalyst with enhanced activity at low pressures and temperatures in comparison with the usual form of nickel catalyst as employed by Sabatier and Senderens opened up a new field of controlled catalytic hydrogenation. A special alloy, prepared essentially by the fusion of approximately equal parts of aluminium and nickel at 1200–1500°, is treated with alkali, which dissolves the aluminium and leaves the nickel as a finely-divided black suspension. The catalyst is thoroughly washed to free it from alkali, is stored under absolute ethyl alcohol in an air-free container and is measured in the form of the suspension ; it must be handled under a solvent at all times as it is highly pyrophoric. The outstanding characteristic of Raney nickel is its activity at low temperatures and low to moderate pressures : thus both acetone and styrene can be hydrogenated at 23° and 2–5 atmospheres pressures. Raney nickel is conveniently

employed for the following hydrogenations (low temperatures, and pressures usually not greater than 100 lb. per square inch) :—

(*a*) olefines ;
(*b*) $>C=O \longrightarrow >CHOH$;
(*c*) $-CN \longrightarrow -CH_2NH_2$;
(*d*) aromatic and heterocyclic rings ;
(*e*) $CR_2=NOH$ (oximes) $\longrightarrow CHR_2NH_2 + H_2O$;
(*f*) nitroso compounds to amines ; and
(*g*) $RNO_2 \longrightarrow RNH_2$.

The advantages of this catalyst are that it is cheaper and less delicate than platinum, fairly large quantities can be hydrogenated, and the process is reasonably rapid.

It has been stated that the activity of the catalyst in low pressure hydrogenations is enhanced by the addition of small quantities of platinic chloride.

Place a solution of 190 g. of sodium hydroxide in 750 ml. of water in a 2 litre beaker equipped with an efficient stirrer (1), cool in an ice bath to 10°, and add 150 g. of nickel - aluminium alloy in small portions, with stirring, at such a rate that the temperature does not rise above 25°. If excessive foaming is encountered, add 1 ml. of *n*-octyl alcohol. When all the alloy has been introduced (about 2 hours), stop the stirrer, remove the beaker from the ice bath, and allow the contents to attain room temperature. When the evolution of hydrogen becomes slow, heat the reaction mixture gradually (2) on a water bath until the evolution again becomes slow (about 8–12 hours) ; add distilled water to restore the original volume, stir the mixture, allow to settle, and decant the supernatant liquid. Transfer the nickel to a stoppered graduated cylinder with the aid of distilled water, and decant the water again. Add a solution of 25 g. of sodium hydroxide in 250 ml. of water, shake to disperse the catalyst thoroughly, allow to settle, and decant the alkali solution. Wash the nickel by suspension in distilled water and decantation until the washings are neutral to litmus, then 10 times more to remove the alkali completely (25–40 washings are required) (3). Repeat the washing process three times with 100 ml. of rectified spirit (95 per cent. C_2H_5OH) and three times with absolute alcohol. Store the catalyst in bottles which are completely filled with absolute alcohol and tightly stoppered ; the product is highly pyrophoric and must be kept under liquid at all times. The Raney nickel contained in this suspension weighs about 75 g.

In the practical applications of Raney nickel it is more convenient to measure the catalyst than to weigh it. The product, prepared as above, contains about 0·6 g. of the catalyst per millilitre of settled material : a level teaspoonful is about 3 g. of nickel.

Notes.

(1) The stirrer should be provided with a motor which will not ignite the hydrogen—an induction motor or an air stirrer is suitable. The stirrer itself may be of glass, Monel metal or stainless steel (*cf.* Fig. *II*, 7, 6).

(2) The heating should not be too rapid initially or the solution may froth over.

(3) The number of washings may be reduced to about twenty, if time is allowed for diffusion of the alkali from the surface of the catalyst into the surrounding wash water. Use 750 ml. of water in each washing, allow diffusion to proceed for 3–10 minutes, stir again, and decant the supernatant liquid as soon as the catalyst settles to the bottom.

An example of the application of the Raney nickel catalyst is given in Section IV,35 (β-phenylethylamine from benzyl cyanide).

VI,6. COPPER-CHROMIUM OXIDE CATALYST

This catalyst is prepared by the decomposition of basic copper ammonium chromate ; the main reactions may be written as :

$$2Cu(NO_3)_2 + Na_2Cr_2O_7 + 4NH_3 + 3H_2O$$
$$\xrightarrow{55^\circ} 2CuNH_4(OH)CrO_4 + 2NaNO_3 + 2NH_4NO_3$$
$$\xrightarrow{300^\circ} CuO.CuCr_2O_4 + N_2 + 5H_2O$$

The most active varieties contain barium chromite, which is incorporated by adding barium nitrate in the preparation of the basic copper ammonium chromate : this is sometimes referred to as barium-promoted copper-chromium oxide. The barium in the catalyst gives protection against sulphate poisoning and is said to confer stabilisation against reduction. Copper-chromium oxide is an approximately equimolecular combination of cupric chromite and cupric oxide $CuCr_2O_4.CuO$; the barium-promoted catalyst contains some barium chromite. It is not a mechanical mixture of cupric chromite and cupric oxide nor is it a simple copper chromite ; the catalytic activity is not due to copper chromite alone since removal of the cupric oxide with an acid leaves cupric chromite which is inactive as a catalyst for the hydrogenation of esters. Reduction of the black cupric oxide to red copper results in deactivation, as does also excessive heating which leads to cuprous chromite $Cu_2Cr_2O_4$ and oxygen. For these reasons the name " copper chromite catalyst ", which is sometimes used, is misleading.

Hydrogenations with copper-chromium oxide catalyst are usually carried out in the liquid phase in stainless steel autoclaves at pressures up to 5000–6000 lb. per square inch. A solvent is not usually necessary for hydrogenation of an ester at 250° since the original ester and the alcohol or glycol produced serve as the reaction medium. However, when dealing with small quantities and also at temperatures below 200° a solvent is desirable : this may be methyl alcohol, ethyl alcohol, dioxan or methyl*cyclo*hexane.

The catalyst, which may be regarded as complementary to Raney nickel (Section VI,5) is largely used for the hydrogenation of esters (esters of monobasic and of dibasic acids to alcohols and glycols respectively) :

$$RCOOR' + 2H_2 \rightleftharpoons RCH_2OH + R'OH$$

Two *mechanisms* have been given :—(i) hydrogenation—

$$RCOR' + H_2 \rightleftharpoons RCH(OH)—OR' \rightleftharpoons RCHO + R'OH ; RCHO + H_2 \rightleftharpoons RCH_2OH$$

(ii) hydrogenolysis—

$$RCOR' + H_2 \rightleftharpoons RCHO + R'OH ; RCHO + H_2 \rightleftharpoons RCH_2OH$$

Other applications include :

(*a*) reduction of aldehydes and ketones to alcohols ;

(*b*) reduction of amides to amines ($RCONH_2 + 2H_2 \longrightarrow RCH_2NH_2 + H_2O$; some side reactions occur : dioxan is the best medium) ;

(*c*) reduction of lactones to glycols.

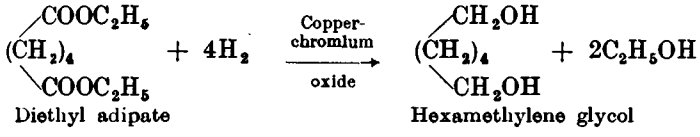
The catalyst is inactive for the hydrogenation of the (isolated) benzene nucleus and so may be used for the hydrogenation of aromatic compounds containing aldehyde, keto, carbalkoxy or amide groups to the corresponding alcohols, amines, etc., *e.g.*, ethyl benzoate to benzyl alcohol; methyl *p*-toluate to *p*-methylbenzyl alcohol; ethyl cinnamate to 3-phenyl-1-propanol.

Dissolve 15·5 g. of A.R. barium nitrate and 130 g. of A.R. cupric nitrate trihydrate in 450 ml. of water at 80°. Prepare a solution of sodium chromate by dissolving 89 g. of recrystallised sodium dichromate dihydrate in 200 ml. of water and adding 112·5 ml. of conc. ammonia solution (sp. gr. 0·90). Add the warm solution (80°) of nitrates in a thin stream, with stirring, to the sodium chromate solution (at 25°). Collect the orange precipitate by suction filtration, wash it with two 50 ml. portions of water, drain well, and dry at 75–80° for 12 hours; powder finely.

Equip a 500 ml. three-necked flask with a funnel for introducing a solid, a wide air condenser and a stainless steel stirrer with crescent blade, 1 cm. long and 8 cm. wide, so shaped that it conforms to the bottom of the flask. Immerse the flask in a metal bath at 350°. Add the powder through the funnel, with rapid stirring, during a period of 15 minutes. Heat with stirring at a bath temperature of 350° for 20 minutes after all the solid has been added. Leach the product by stirring for 30 minutes with 300 ml. of 10 per cent. acetic acid at room temperature. Allow to settle, decant the solution, and wash the residue with six 50–60 ml. portions of water. Filter with suction on a Buchner funnel, dry at 125° for 12 hours, and grind finely in a mortar. The yield of catalyst (a brownish-black powder) is 85 g. No special precautions are necessary in handling or storing the catalyst since it is unaffected by exposure to air or moisture.

VI,7. HEXAMETHYLENE GLYCOL (1 : 6-HEXANEDIOL)

This preparation illustrates the use of the copper-chromium oxide catalyst in the reduction of esters of dibasic acids to glycols:



Diethyl adipate — Hexamethylene glycol

In a stainless steel autoclave (or high pressure reaction vessel *with an adequate safety factor*) (see Section **VI,4**; Figs. *VI, 4*, 2 and *VI, 4*, 3) and possessing a capacity of at least 250 ml., place 126 g. of diethyl adipate (Sections **III,99** and **III,100**) and 10 g. of copper-chromium oxide catalyst. Close the reaction vessel, make it gas tight, remove the air, and introduce hydrogen until the pressure is about 2,000 lb. per square inch (1). Start the agitation, and heat as rapidly as possible to 255° and maintain this temperature. Continue the hydrogenation until hydrogen absorption is complete. As the hydrogenation proceeds, the pressure drops as indicated on the gauge: the progress of the reaction may be followed by the change in pressure readings, and the reaction is complete (after 6–12 hours) when

the pressure is constant (2). Stop the agitation, allow to cool, and release the pressure. Transfer the reaction mixture to a 400 ml. beaker with the aid of four 12 ml. portions of rectified spirit. Add 25 ml. of 40 per cent. sodium hydroxide solution to the combined alcoholic solutions, and reflux the mixture for 2 hours in order to hydrolyse any unchanged ester. Transfer the reaction mixture to a 500 ml. distilling flask and distil until the temperature of the vapour reaches 95° : this will remove the alcohol. Transfer the hot residue with the aid of 25 ml. of water to a continuous extraction apparatus (Fig. *II*, *44*, 2) and exhaustively extract the solution with ether (36–48 hours). Remove the ether and alcohol, and distil the residue under reduced pressure. Collect the hexamethyleneglycol at 146–149°/17 mm. ; it solidifies on cooling (m.p. 41–42°). The yield is 65 g. (compare Section **III,15**).

Notes.

(1) The original pressure should not be more than 2,000 lb. per sq. in. if the maximum working pressure for the autoclave is 5,000 lb. The full operating pressure is not applied at the beginning because the pressure will rise as the bomb is heated : thus at 255°, the pressure will be 1·8 times that at 20°.

(2) Unless a high pressure of hydrogen is used initially or the reaction vessel is large (about 1 litre), it will be necessary to introduce more hydrogen into the reaction vessel ; the pressure should not be allowed to fall below 1400–1500 lb. per sq. in. if the reaction is to run smoothly to completion.

VI,8. ETHYL β-PHENYL-β-HYDROXYPROPIONATE

(Reformatsky Reaction)

This preparation illustrates the **Reformatsky reaction**, which consists in the interaction of a carbonyl compound, an α-halogen ester (*e.g.*, ethyl bromoacetate) and zinc in the presence of ether or benzene, followed by hydrolysis.

Thus :

$$\underset{\text{Benzaldehyde}}{C_6H_5CHO} + \underset{\text{Ethyl bromoacetate}}{BrCH_2COOC_2H_5} + Zn \longrightarrow C_6H_5\overset{\displaystyle OZnBr}{\overset{|}{C}}HCH_2COOC_2H_5$$

$$C_6H_5\overset{\displaystyle OZnBr}{\overset{|}{C}}HCH_2COOC_2H_5 + H_2SO_4 \longrightarrow \underset{\text{Ethyl β-phenyl-β-hydroxypropionate}}{C_6H_5CH(OH)CH_2COOC_2H_5} + ZnSO_4 + HBr$$

It may be pointed out that dehydration of β-hydroxy esters with fused potassium hydrogen sulphate, acetic anhydride, phosphoric oxide or with thionyl chloride in benzene solution leads to αβ-unsaturated esters containing some βγ-unsaturated ester ; the proportion of the latter depends not only upon the structure of the ester but also upon the dehydrating agent used. Dehydration occasionally occurs during the reaction itself or upon attempted distillation.

It is probable that the reaction proceeds through an organic zinc derivative, analogous to a Grignard reagent, formed by interaction of the α-halogen ester

with the zinc ; this organic zinc compound then adds to the aldehyde or ketone exactly as does a Grignard reagent.

$$Br—CH_2COOC_2H_5 + Zn \longrightarrow Br—Zn—CH_2COOC_2H_5$$

$$RR'C{=}O + Br—Zn—CH_2COOC_2H_5 \longrightarrow RR'C(OZnBr)—CH_2COOC_2H_5 \xrightarrow{\text{Hydrolysis}} RR'C(OH)—CH_2COOC_2H_5 + ZnBrOH$$

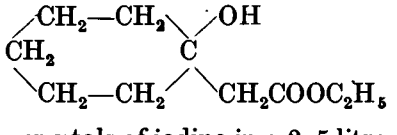
It is essential that all the apparatus and the reagents be scrupulously dry for successful results (compare Grignard reaction). Equip a 500 ml. three-necked flask with a 250 ml. separatory funnel, a mechanical stirrer, and a double surface condenser ; insert calcium chloride (or absorbent cotton wool) guard tubes in the funnel and condenser respectively. Place 40 g. of zinc wool (previously dried at 100°) in the flask, and a solution of 83·5 g. (55·5 ml.) of ethyl bromoacetate (Section **III,126** ; *CAUTION*—lachrymatory) (1) and 65 g. (62 ml.) of purified benzaldehyde (Section **IV,115**) in 80 ml. of sodium-dried benzene and 20 ml. of sodium-dried ether in the separatory funnel. Add about 10 ml. of the solution to the zinc and warm the flask gently until the reaction starts. When the reaction has commenced, but not before, stir the mixture and add the remainder of the solution at such a rate that moderate refluxing occurs (about 1 hour). Reflux the reaction mixture on a water bath for a further 30 minutes. Cool the flask in an ice bath, and add 200 ml. of cold 10 per cent. sulphuric acid with vigorous stirring. Transfer to a separatory funnel, remove the aqueous layer, wash the benzene layer twice with 50 ml. portions of 5 per cent. sulphuric acid, once with 25 ml. of 10 per cent. sodium carbonate solution, and finally with two 25 ml. portions of water. Extract the combined acid solutions with 100 ml. of ether, and dry the combined benzene and ether solution with 5 g. of anhydrous magnesium or calcium sulphate. Filter from the desiccant, remove the solvent by distillation under atmospheric pressure from a water bath (Fig. *II, 13,* 4 but with Claisen flask) and distil the residue under reduced pressure. Collect the ethyl β-phenyl-β-hydroxypropionate at 152–154°/12 mm. The yield is 60 g.

Note.

(1) Great care must be exercised in handling ethyl bromoacetate. Keep a 10 per cent. aqueous ammonia solution available to react with any bromoester which may be spilled.

Cognate Preparation

Ethyl 1-hydroxy*cyclo*hexylacetate,



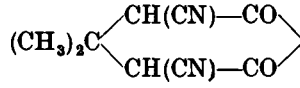
Place 65 g. of clean dry zinc wool and a few crystals of iodine in a 2·5 litre three-necked flask, equipped with an efficient reflux condenser with drying tube, a mechanical stirrer, and a dropping funnel. Prepare a mixture

of 400 ml. of sodium-dried benzene and 350 ml. of sodium-dried toluene with 167 g. (111 ml.) of ethyl bromoacetate and 98 g. (103·5 ml.) of pure *cyclo*hexanone (compare Section III,74,A). Transfer 150 ml. of this mixture to the flask, start the stirrer and heat the flask in a boiling water bath. A vigorous reaction soon sets in. Add the remainder of the mixture through the dropping funnel at such a rate that gentle refluxing is maintained. Continue the stirring for an additional 2 hours : practically all the zinc dissolves. Cool the mixture, add sufficient 10 per cent. sulphuric acid with stirring to dissolve all the zinc hydroxide. Separate the benzene-toluene layer, dry it with anhydrous sodium or magnesium sulphate, and distil under low pressure. Collect the ethyl 1-hydroxy-*cyclo*hexylacetate at 86–89°/2 mm. The yield is 125 g.

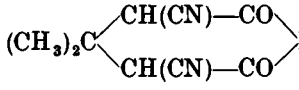
VI,9. ββ-DIMETHYLGLUTARIC ACID (*Guareschi Reaction*)

When acetone is condensed with ethyl cyanoacetate in the presence of a solution of anhydrous ammonia in absolute alcohol at — 5°, the ammonium salt of the dicyano-imide (I) is precipitated. Upon dissolving this salt in water and adding excess of concentrated hydrochloric acid, the crystalline dicyano-imide (II) is obtained. Hydrolysis of the last-named with strong sulphuric acid affords ββ-dimethylglutaric acid (III).

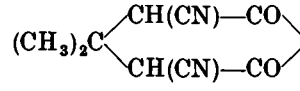
$$(CH_3)_2CO + 2CH_2(CN)COOC_2H_5 + 2NH_3 \longrightarrow$$



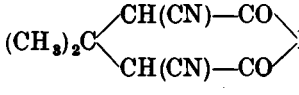
$$+ 2C_2H_5OH + H_2O$$



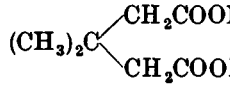
$$+ HCl \longrightarrow$$



$$+ NH_4Cl$$



$$+ 3H_2SO_4 + 6H_2O \longrightarrow$$



$$+ 2CO_2 + 3NH_4HSO_4$$

The above is an example of the **Guareschi reaction.** It is applicable to most dialkyl ketones and to alicyclic ketones (*e.g.*, *cyclo*hexanone, *cyclo*pentanone, etc.). The condensation product (I) is probably formed by a simple Knoevenagel reaction of the ketone and ethyl cyanoacetate to yield ethyl α-cyano-ββ-dimethylacrylate $(CH_3)_2C{=}C(CN)COOC_2H_5$, followed by a Michael addition of a second molecule of ethyl cyanoacetate ; finally, the carbethoxyl groups are converted to the cyclic imide structure by the action of ammonia.

Place 200 ml. of absolute ethyl alcohol in a 500 ml. all-glass wash bottle, and cool to — 5° by immersion in a bath of ice and salt. Pass a slow stream of ammonia, derived from a cylinder and dried by passage through a tower filled with small pieces of quicklime, into the alcohol until the

latter is saturated (about 4–5 hours); when necessary, siphon off the water formed in the freezing mixture and add more crushed ice. The volume of the alcohol will increase to about 250 ml. and about 17 g. of ammonia is absorbed. Meanwhile weigh out 113 g. of ethyl cyanoacetate (Section **III,131**) and 29 g. of pure dry acetone into a 500 or 750 ml. wide-mouthed, ground-stoppered bottle and cool it by immersion in a bath of ice and salt for about 2 hours. Add the alcoholic ammonia solution to the cold contents of the bottle, replace the stopper and transfer the bottle and bath to a ice chest; place a brick or some other heavy weight on the stopper of the bottle to hold it firmly in position. After three days, when a considerable amount of white solid (the ammonium salt of the " Guareschi imide ") has separated, filter at the pump and rinse the bottle with the filtrate until all the solid has been transferred to the filter. Drain well by pressing the solid with a large glass stopper, and then stir it with several small volumes of dry ether (sucking dry after each addition) in order to remove the excess of ketone and ethyl cyanoacetate. Dry the solid in the air for several hours in order to remove the ether completely, then dissolve it in the minimum volume of boiling water (350–400 ml.), and add concentrated hydrochloric acid (*FUME CUPBOARD!*) until the mixture is acid to Congo red paper and then add a further 50 ml. Allow to cool, filter off the dicyano-imide, wash with a little water, and dry upon clock glasses in the steam oven or at 100°. The yield of the dicyano-imide is 65 g.

Dissolve 64 g. ($\frac{1}{2}$ g. mol) of the *finely-powdered* dicyano-imide in 160 ml. of concentrated sulphuric acid in a 1-litre round-bottomed flask; *gentle* warming may be necessary and a clear reddish-brown solution is obtained. Keep the solution overnight and then add 150 ml. of water slowly and with frequent shaking. Attach a reflux condenser to the flask and heat very gently at first owing to the attendant frothing, which subsides after 2–3 hours. Heat the mixture under reflux for a total period of 18–24 hours and shake well at intervals of 3 hours. The acid separates upon cooling: collect it on a sintered glass funnel. It may be dried at about 90°; the yield of crude acid is nearly quantitative. To remove small quantities of imides which may be present, treat the crude acid with excess of saturated sodium bicarbonate solution, filter from any imide, strongly acidify with concentrated hydrochloric acid, saturate the solution with ammonium sulphate, and extract the acid with three or four 200 ml. portions of ether. Dry the ethereal extract with anhydrous sodium or magnesium sulphate and distil off the ether. Recrystallise the residual acid from concentrated hydrochloric acid, and dry at 70°. Pure ββ-dimethylglutaric acid, m.p. 101°, is obtained.

VI,10. REDUCTIONS WITH LITHIUM ALUMINIUM HYDRIDE

Lithium aluminium hydride $LiAlH_4$ is a useful and convenient reagent for the selective reduction of the carbonyl group and of various other polar functional groups. It is obtained by treatment of finely powdered lithium hydride with an ethereal solution of anhydrous aluminium chloride:

$$4LiH + AlCl_3 \longrightarrow LiAlH_4 + 3LiCl$$

The compound is generally employed in solution in dry ether; this solution is conducting and the reduction may be due to the transfer of a hydride ion:

$$[AlH_4]^- \rightleftharpoons H^- + AlH_3$$

The purpose of the ether may be to coordinate with the aluminium hydride and to facilitate the forward reaction in the first instance: subsequently coordination may occur with other anions available in the solution.

Some of the functional groups which are reduced by lithium aluminium hydride, the reduction product together with the theoretical mols of reducing agent required (in parenthesis) are listed below:—

aldehyde ⟶ primary alcohol (0·25); ketone ⟶ secondary alcohol (0·25); epoxide ⟶ alcohol (0·25); ester ⟶ primary alcohol (0·5); lactone ⟶ diol (0·5); carboxylic acid ⟶ primary alcohol (0·75); anhydride ⟶ primary alcohol (1·0); amide ($CONH_2$) ⟶ primary amine (1·0); nitrile ⟶ primary amine (1·0); acid chloride ⟶ primary alcohol (0·5); and alkyl chloride ⟶ hydrocarbon (0·25). Its most frequent use is for the reduction of esters, acids, aldehydes and ketones to the corresponding alcohols. It is of value for the reduction of unsaturated carbonyl compounds to unsaturated alcohols (*e.g.*, crotonaldehyde to crotyl alcohol—compare Section VI,12); also for the reduction of sensitive ketones (*e.g.*, acetyl*cyclo*propane) and hindered ketones (*e.g.*, acetomesitylene).

The following intermediate compounds in some reductions with lithium aluminium hydride have been formulated:

$$4RCHO + LiAlH_4 \longrightarrow RCH_2OLi + (RCH_2O)_3Al \quad \{or\ LiAl(OCH_2R)_4\}$$
$$4R_2CO + LiAlH_4 \longrightarrow (R_2CHO)_4LiAl$$
$$2RCOOR' + LiAlH_4 \longrightarrow LiAl(OR')_2(OCH_2R)_2$$
$$4RCOOH + 3LiAlH_4 \longrightarrow LiAl(OCH_2R)_4 + 2LiAlO_2 + 4H_2$$
$$2RCOCl + LiAlH_4 \longrightarrow LiAlCl_2(OCH_2R)_2$$
$$(RCO)_2O + LiAlH_4 \longrightarrow LiAlO(OCH_2R)_2$$

Experimental details for the following reductions are given below:

Diethyl adipate $EtOOC(CH_2)_4COOEt$ ⟶ 1:6-hexanediol $HOCH_2(CH_2)_4CH_2OH$
Diethyl nitrosamine $Et_2N—NO$ ⟶ *NN*-diethylhydrazine $Et_2N—NH_2$
Anthranilic acid o-NH_2–C_6H_4–COOH ⟶
o-aminobenzyl alcohol o-NH_2–C_6H_4–CH_2OH

The experimental conditions for the reduction are similar to those for the Grignard reaction. For compounds which are readily soluble in ether, a solution of the compound in dry ether is added to an ethereal solution of lithium aluminium hydride (excess) at such a rate that the reaction mixture boils gently. When the reduction is complete, the excess of the reagent is decomposed by the cautious addition of moist ether, an ethanol-ether mixture or by the dropwise addition of cold water with vigorous stirring: when water is used, it is desirable to employ a large flask because of the foaming which takes place. On the whole it is best to employ ethyl acetate, as its reduction product (ethanol) does not interfere in the subsequent isolation and no hydrogen is evolved. The reaction mixture is then poured gradually into excess of ice-cold dilute sulphuric acid to decompose the complex aluminium compounds and to dissolve the precipitated aluminium hydroxide; the product is usually in the ethereal layer but, if it is water-soluble, must be isolated from the aqueous solution. For bases, after extraction of any neutral or acidic products, the solution is rendered alkaline with 10*N* sodium hydroxide and the whole (including the precipitated aluminium hydroxide) is extracted with ether. For compounds which are slightly or sparingly soluble in ether, a Soxhlet apparatus is inserted between the flask and the reflux condenser and the compound is placed in the Soxhlet

thimble. In addition to ether, tetrahydrofuran has been used as a solvent for lithium aluminium hydride. The approximate solubilities in diethyl ether, tetrahydrofuran and di-*n*-butyl ether are 25–30 g., 13 g. and 2 g. respectively per 100 g. of solvent at 25°.

Lithium aluminium hydride reacts violently with water and *must be treated as a dangerous chemical* :

$$LiAlH_4 \text{ (excess)} + 2H_2O \longrightarrow LiAlO_2 + 4H_2$$
$$LiAlH_4 + 4H_2O \text{ (excess)} \longrightarrow LiOH + Al(OH)_3 + 4H_2$$

Operations with it must be conducted in a dry apparatus and with dry solvents. Owing to the toxic properties of the finely powdered solid, it must be weighed out in the fume cupboard. Adequate provision should be made to discharge hydrogen gas from the reaction mixture to the atmosphere or fume cupboard exhaust without risk from nearby flames, hot plates, etc. The solid reacts superficially with atmospheric moisture and carbon dioxide ; in ether solution, it reacts slowly with atmospheric oxygen, liberating hydrogen. The finely powdered reagent is available commercially and is kept under nitrogen ; it should all be used once the tin is opened. Only dry sand may be used to extinguish solid lithium aluminium hydride which has caught fire.

Hexamethylene glycol (1 : 6-hexanediol). All the apparatus and reagents must be thoroughly dry. Set up in a dry vessel (to serve later as a water bath) in the fume cupboard a 1500 ml. three-necked flask with a mercury-sealed stirrer, a 250 ml. dropping funnel and a double surface condenser (compare Fig. *II*, 7, 11, *a*) : attach guard tubes (containing anhydrous calcium chloride or cotton wool) to the open ends of the condenser and dropping funnel. The mechanical stirrer should be a powerful one. It must be emphasised that all operations, including weighing, with solid lithium aluminium hydride must be conducted in the fume cupboard ; during weighing, etc., the front of the fume chamber is pulled down so that there is a narrow opening to allow the student's hands to enter.

Weigh out 10·5 g. of lithium aluminium hydride into a clean, dry mortar and powder it finely, if necessary, with a glass pestle. Remove the dropping funnel and replace it by a funnel with a very short wide stem ; introduce the solid into the flask through this funnel and use about 300 ml. of sodium-dried ether to transfer the last traces of lithium aluminium hydride ; replace the dropping funnel and guard tube. Destroy any residual solid on the pestle or in the mortar (1). Set the stirrer in motion and place a solution of 50 g. of freshly distilled diethyl adipate, b.p. 133–135°/14 mm. (Sections **III, 99–100**) in 150 ml. of anhydrous ether in the dropping funnel. After stirring for 10 minutes (some lithium aluminium hydride may remain undissolved), add the diethyl adipate solution at such a rate that the ether refluxes gently ; the reaction mixture rapidly becomes viscous and four 50 ml. portions of anhydrous ether must be added during the reduction to facilitate stirring. Continue the stirring for 10 minutes after the diethyl adipate has been added. Decompose the excess of lithium aluminium hydride by the dropwise addition, with stirring, either of 75 ml. of water (2) or, preferably, by the more rapid addition of 22 g. (24·5 ml.) of ethyl acetate. Filter the reaction product from the sludge through a sintered glass funnel ; dry the ethereal solution with anhydrous magnesium sulphate and distil off the ether on a water bath ; the colourless viscous residue (18·5 g.) solidifies completely on cooling and has m.p.

41–42°, *i.e.*, is pure hexamethylene glycol. Dissolve the sludge remaining in the filter funnel in 20 per cent. sulphuric acid ; extract the resulting solution with six 100 ml. portions of ether or use a continuous ether extractor (Fig. *II*, *44*, 2). Distil off the ether on a water bath ; the residue (6 g.) crystallises completely upon cooling, m.p. 41–42°. The total yield of hexamethylene glycol is therefore 24·5 g. ; it boils sharply at 136–137°/ 10 mm.

Notes.

(1) The residual reagent must be carefully destroyed. That remaining in the mortar is slowly dropped into about 2 litres of water in a large beaker. The solid adhering to the pestle should be scraped off and added gradually to excess of water.

(2) Before adding water, remove the calcium chloride guard tubes and fit the reflux condenser with a long tube extending to the duct at the top of the fume cupboard (hood) ; this will carry the escaping hydrogen above the motor of the stirrer. A spark-proof stirring motor is recommended and should be used, if available. The dropwise addition of water must be conducted whilst the mixture is stirred vigorously ; foaming may occur and the reaction may be moderated by filling the bath surrounding the reaction vessel with cold water.

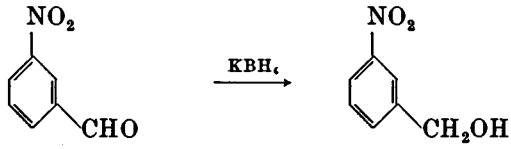
***NN*-Diethylhydrazine.** Fit a 1-litre three-necked flask with a double surface reflux condenser, a mercury-sealed stirrer and a dropping funnel, and insert calcium chloride guard tubes into the openings of the reflux condenser and dropping funnel. The apparatus must be dry. Place 10·0 g. of finely powdered lithium aluminium hydride and 500 ml. of sodium-dried ether in the flask, stir for 10 minutes, and add a solution of 23·5 g. of diethyl nitrosamine (Section **III,124**) in 135 ml. of anhydrous ether at the rate of 2–3 drops per second. After about 20 minutes, the ether refluxes gently and a white solid separates : henceforth adjust the rate of addition to maintain the reaction under control. After the addition of the nitrosamine is complete (about 1 hour), continue the vigorous stirring for 10 minutes, and then add an excess of ethyl acetate to decompose the residual lithium aluminium hydride. Now introduce 50 ml. of 10*N* sodium hydroxide solution, stir for 10 minutes, filter with suction, and wash the residue with two 50 ml. portions of ether. Dry the combined filtrate and washings first over potassium hydroxide pellets and then over anhydrous calcium sulphate, distil through an efficient fractionating column (*e.g.*, a 10″ vacuum-jacketed Widmer column) and collect the *as*-diethylhydrazine at 98–99·5°. The yield is 10 g.

***o*-Aminobenzyl alcohol.** This preparation illustrates the reduction of a compound of low solubility in ether. Equip a 2-litre three-necked flask with a mercury-sealed stirrer and a Soxhlet extractor surmounted by an efficient reflux condenser ; stopper the third neck. Attach a wide-bore drying tube to the opening of the reflux condenser. The apparatus must be dry. Place 9·1 g. of finely powdered lithium aluminium hydride and 600 ml. of anhydrous ether in the flask and 13·7 g. of pure anthranilic acid in the extraction thimble. Maintain the ether at a moderate rate of boiling by means of an electric heating mantle until the acid in the thimble dissolves completely. Allow the flask to cool, remove the Soxhlet extractor and insert the reflux condenser directly into the flask ; place a dropping funnel in the opening previously stoppered. Add sufficient ethyl acetate cautiously, with vigorous stirring, to decompose the excess of lithium aluminium hydride. Then introduce 250 ml. of 2·5*N* sodium hydroxide

solution. Separate the ether layer, extract the aqueous layer with two 200 ml. portions of ether, and dry the combined ethereal solutions with anhydrous magnesium sulphate. Distil off the ether and dry the residue in a vacuum desiccator. The resulting *o*-aminobenzyl alcohol has m.p. 82° and weighs 12·0 g.

VI,11. REDUCTIONS WITH POTASSIUM (OR SODIUM) BOROHYDRIDE

Potassium and sodium borohydride show greater selectivity in action than lithium aluminium hydride: thus ketones or aldehydes may be reduced to alcohols whilst the cyano, nitro, amido and carbalkoxy groups remain unaffected. Furthermore, the reagent may be used in aqueous or aqueous-alcoholic solution. One simple application of its use will be described, *viz.*, the reduction of *m*-nitrobenzaldehyde to *m*-nitrobenzyl alcohol:



m*-Nitrobenzyl alcohol. Clamp a 500 ml. three-necked flask, equipped with a mechanical stirrer, a thermometer and a burette, above the bench so that an ice bath can be placed beneath it. Place a solution of 15·1 g. of *m*-nitrobenzaldehyde (1) in 100 ml. of methanol in the flask and, whilst stirring, add a solution of potassium borohydride (2·0 g. of KBH_4 in 2 ml. of 2*N* sodium hydroxide diluted with 18 ml. of water) at the rate of 0·5 ml. per minute, with occasional cooling to keep the reaction at 18–25°. When about three-quarters of the solution has been added, there is no further tendency for the temperature to rise, and the addition is stopped. Treat a small portion of the reaction mixture with dilute sulphuric acid: hydrogen should be evolved.

Remove most of the methanol by distillation on a steam bath, and dilute the residue with 100 ml. of water. Extract the mixture with ether, wash the upper layer with water, and dry it rapidly with a little anhydrous magnesium sulphate. Remove the ether by "flash distillation", and distil the residual pale yellow oil under diminished pressure. Collect the *m*-nitrobenzyl alcohol at 183–185°/17 mm.; it solidifies to a pale yellow solid, m.p. 30°, when cooled in ice. The yield is 13 g.

Note.

(1) ***m*-Nitrobenzaldehyde** may be prepared as follows. Place 250 ml. of concentrated sulphuric acid and 21·5 ml. of fuming nitric acid, sp. gr. 1·5, in a 500 ml. three-necked flask fitted with a mechanical stirrer (unsealed) and a dropping funnel. Stir and cool to 0° in a bath of ice and salt. Add 62·5 g. (60 ml.) of purified benzaldehyde dropwise from the dropping funnel; do not allow the temperature to rise above 5°. Then warm the mixture gradually to 40°, cool to room temperature, and pour in a thin stream with vigorous stirring on to finely crushed ice. Filter through a sintered glass funnel, wash with a little water, press out the oil with a wide glass stopper, and dry in the air upon absorbent paper. The resulting crude *m*-nitrobenzaldehyde weighs 55 g. and melts at 48–50°. Melt the crude solid under excess of 10 per cent. sodium carbonate solution, stir, cool, filter and dry in the air: the

* The experimental details were kindly provided by the Chemical Research Laboratories of May and Baker Ltd., Dagenham.

product has m.p. 51–52°. Dissolve the solid in 120 ml. of hot benzene under reflux, decant from any solid present, and add light petroleum, b.p. 40–60°, until a slight turbidity results and cool. Collect the pure *m*-nitrobenzaldehyde and dry in the air ; the yield is 45 g., m.p. 58°. A further quantity may be obtained by concentrating the mother liquor.

VI,12. REDUCTIONS WITH ALUMINIUM ALKOXIDES

Aldehydes and ketones can be reduced smoothly to the corresponding alcohols by aluminium alkoxides. The most satisfactory alkoxide for general use is aluminium *iso*propoxide :

$$RR'CO + (CH_3)_2CHOal \rightleftharpoons RR'CHOal + (CH_3)_2CO \qquad (al = Al/3)$$

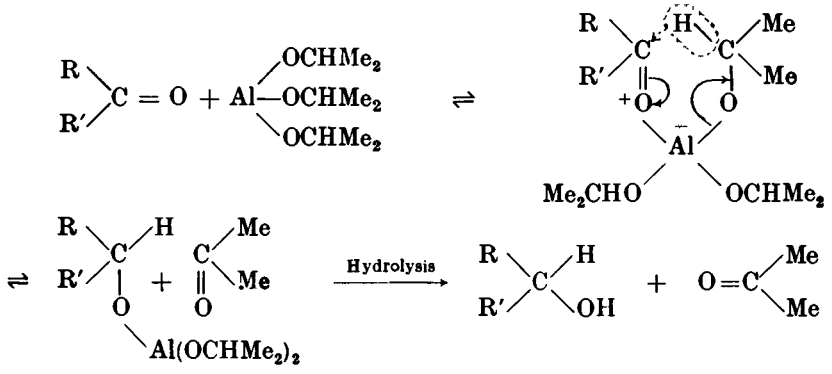
The carbonyl compound to be reduced is heated with aluminium *iso*propoxide in excess of *iso*propyl alcohol under a simple fractionating column with provision for slow distillation until no more acetone is detected in the distillate ; the alcoholic reduction product is recovered from the reaction mixture after acidification. The process is usually termed the **Meerwein - Ponndorf - Verley reduction.** This mild and speedy method of reducing carbonyl compounds in good yield is particularly valuable since other groups, *e.g.*, an αβ-double bond, a nitro group or a halogen atom, are unaffected. Experimental details for the following preparations are given :

$CH_3CH{=}CHCHO$	⟶	$CH_3CH{=}CHCH_2OH$
Crotonaldehyde		Crotyl alcohol
C_6H_5CHO	⟶	$C_6H_5CH_2OH$
Benzaldehyde		Benzyl alcohol
$(C_6H_5)_2CO$	⟶	$(C_6H_5)_2CHOH$
Benzophenone		Benzhydrol

The undermentioned reductions may be carried out by simple adaptations to the procedures : chloral to trichloroethyl alcohol ; *m*-nitroacetophenone of α-methyl-3-nitrobenzyl alcohol ; and o-nitrobenzaldehyde to o-nitrobenzyl alcohol.

The above reversible equation indicates that one mol of aluminium *iso*propoxide will reduce directly three mols of the carbonyl compound. It is generally desirable to use excess of the reductant except for aromatic aldehydes ; for the latter side reactions (*e.g.*, $2RCHO \longrightarrow RCOOCH_2R$; Tischenko reaction) tend to occur with excess of the reagent.

The following *mechanism* of the reaction has been suggested ; it includes the coordination of the carbonyl compound with the aluminium atom in aluminium *iso*propoxide and the transfer of a hydride ion :



Preparation of aluminium *iso*propoxide. Place 27·5 g. of clean aluminium foil in a 1 litre round-bottomed flask containing 300 ml. of anhydrous *iso*propyl alcohol (*e.g.*, refluxed with and distilled from lime) and 0·5 g. of mercuric chloride. Attach an efficient (for example, double surface) reflux condenser carrying a calcium chloride (or cotton wool) guard tube. Heat the mixture on a water bath or upon a hot plate. When the liquid is boiling, add 2 ml. of carbon tetrachloride (a catalyst for the reaction between aluminium and dry alcohols) through the condenser, and continue the heating. The mixture turns grey and, within a few minutes, a vigorous evolution of hydrogen commences. Discontinue the heating: it may be necessary to moderate the reaction by cooling the flask in ice water or in running tap water. After the reaction has slowed down, reflux the mixture until all the metal has reacted (6–12 hours). The mixture becomes dark because of the presence of suspended particles.* Pour the hot solution into a 500 ml. Claisen flask attached to a water condenser with a 250 ml. filter flask or distilling flask as receiver. Add a few fragments of porous porcelain and heat the flask in an oil bath at 90° under slightly diminished pressure (water pump). When nearly all the *iso*propyl alcohol has distilled over, raise the temperature of the bath to 170° and lower the pressure gradually to the full vacuum of the water pump. Immediately the temperature of the distillate rises above 90°, stop the distillation and remove the condenser. Attach a 500 ml. distilling flask directly to the Claisen flask, add a few fresh boiling chips and distil: use either an oil bath at 180–190° or an air bath (Fig. *II*, *5*, 3). The aluminium *iso*propoxide passes over as a colourless viscid liquid at 140–150°/12 mm.; the yield is 190 g. Pour the molten aluminium *iso*propoxide into a wide-mouthed, glass-stoppered bottle and seal the bottle with paraffin wax (or with cellophane tape) to exclude moisture. Generally the alkoxide (m.p. 118°) crystallises out, but the substance exhibits a great tendency to supercool and it may be necessary to cool to 0° for 1–2 days before solidification occurs.

The reagent is conveniently stored as a solution in *iso*propyl alcohol. The molten (or solid) alkoxide is weighed out after distillation into a glass-stoppered bottle or flask and is dissolved in sufficient dry *iso*propyl alcohol to give a one molar solution. This solution may be kept without appreciable deterioration provided the glass stopper is sealed with paraffin wax or cellophane tape. Crystals of aluminium *iso*propoxide separate on standing, but these may be redissolved by warming the mixture to 65–70°.

For many reductions it is not necessary to distil the reagent. Dilute the dark solution, prepared as above to the point marked with an asterisk, to 1 litre with dry *iso*propyl alcohol; this gives an approximately one molar solution. Alternatively, prepare the quantity necessary for the reduction, using the appropriate proportions of the reagents.

CROTYL ALCOHOL

This preparation illustrates the method to be adopted for aldehydes of boiling point below about 150°.

Prepare a solution of aluminium *iso*propoxide from 23·5 g. of aluminium, 0·5 g. of mercuric chloride and 250 ml. of dry *iso*propyl alcohol;

* These, in general, have no influence on the subsequent preparation.

add 105 g. of redistilled crotonaldehyde, b.p. 102–103° (Section **III,141**) and 500 ml. of dry *iso*propyl alcohol. Attach an efficient fractionating column (*e.g.*, Fig. *II*, *15*, 2 ; *II*, *15*, 3 ; *II*, *15*, 5 ; or *II*, *17*, 1) to the flask and arrange for distillation from an oil bath (*cf.* Fig. *II*, *16*, 1) so that the acetone distils as it is formed. Maintain the temperature of the bath at about 110° and the temperature at the top of the column at 60–70°. When the distillate no longer gives a test for acetone (8–9 hours) (1), distil off most of the remaining *iso*propyl alcohol, preferably under reduced pressure. Cool the residue to 40° and add 450 ml. of cold 6*N* sulphuric acid (from 72·5 ml. of concentrated sulphuric acid and 395 ml. of water) ; cooling is necessary. Separate the upper oily layer, wash it once with water, and distil at 60–70° whilst lowering the pressure slowly from about 275 mm. to 60 mm. ; then continue the distillation to 100° and 20 mm. In this way the crotyl alcohol (*A*) is separated from the higher boiling polymerisation products. Combine the aqueous layers and distil until the distillate no longer gives a test for unsaturation with a dilute solution of bromine in carbon tetrachloride. Saturate the aqueous distillate with potassium carbonate, separate the oily layer and add it to (*A*). Dry with 5 g. of anhydrous potassium carbonate, decant the oil and distil through an efficient fractionating column. Collect the crotyl alcohol at 119–121°. The yield is 65 g.

Note.

(1) The acetone test reagent consists of a 0·1 per cent. solution of 2 : 4-dinitrophenylhydrazine and is prepared as follows : Dissolve 0·25 g. of 2 : 4-dinitrophenylhydrazine in 50 ml. of water and 42 ml. of concentrated hydrochloric acid by warming on a water bath ; cool the clear yellow solution and dilute to 250 ml. with water. The acetone test is considered negative when 5 ml. of the reagent and 4–5 drops of the distillate give no cloudiness or precipitate of acetone 2 : 4-dinitrophenylhydrazone within 30 seconds. After a negative test is obtained, it is strongly recommended that the mixture in the flask be refluxed for 5–10 minutes with complete condensation and then to collect a few drops of distillate for another test. If no acetone is now detected, the reduction is complete.

The above test will detect 1 part of acetone in 500–1000 parts of *iso*propyl alcohol. The reagent should not be kept for more than 1–2 months since it deteriorates upon keeping.

BENZYL ALCOHOL

This preparation illustrates the reduction of an aromatic aldehyde.

Place 35 ml. of a 1*M* solution of aluminium *iso*propoxide or 7 g. of solid aluminium *iso*propoxide, 450 ml. of dry *iso*propyl alcohol and 21 g. of purified benzaldehyde (Section **IV,115**) in a 1 litre round-bottomed flask. Fit a short reflux condenser (no water in the cooling jacket) or better a Hahn condenser (2) (containing a 1 cm. layer of ethyl alcohol in the inner tube) to the flask and arrange for slow distillation from a water bath at the rate of 3–6 drops per minute. Continue the heating until a negative test for acetone is obtained after 5 minutes of total reflux (6–9 hours) ; if the volume of the mixture falls below 200 ml. during the reduction, add more *iso*propyl alcohol. Remove the reflux or Hahn condenser and distil off (Fig. *II*, *13*, 3) most of the *iso*propyl alcohol under atmospheric pressure from a suitable oil bath. Hydrolyse the

cooled residue with cold dilute hydrochloric acid (20 ml. of concentrated acid and 150 ml. of water), extract the mixture with three 50 ml. portions of benzene, wash the combined extracts with 50 ml. of water, and dry with 20 g. of anhydrous sodium or magnesium sulphate. Remove the benzene under atmospheric pressure (Fig. *II*, *13*, 4, but with a 50 ml. Claisen flask) and distil the residue under reduced pressure. Collect the benzyl alcohol (19 g.) at 89–91°/7 mm. A little benzyl benzoate remains in the flask.

Note.

(2) A modified Hahn condenser, a form of partial condenser, is illustrated in Fig. *VI*, *12*, 1; it is best constructed of Pyrex glass. The dimensions given are only approximate and may be varied slightly. The inside clearance should be approximately 0·3 cm.; a water jacket should be fitted over the central portion of the side arm by means of rubber stoppers. Alternatively, the side arm may have a length of about 10 cm. and a condenser fitted to this in the usual manner. An approximately 1 cm. layer of absolute alcohol is placed in the inner condensing tube and the top of the tube is connected to a reflux condenser. The outside of the condenser below the side arm should be insulated with asbestos cloth or paper. The refluxing mixture boils the ethyl alcohol in the inner tube, most of the *iso*propyl alcohol is returned to the flask and the acetone distils over.

BENZHYDROL

The following experimental procedure is suitable for ketones boiling above 175–200°.

Place 100 ml. of 1*M* solution of aluminium *iso*propoxide in *iso*propyl alcohol (the unpurified reagent is satisfactory) or a solution of 20 g. of the solid alkoxide in 100 ml. of dry *iso*propyl alcohol in a 250 ml. round-bottomed flask, and add 18 g. of benzophenone (Section IV,139). Attach a short (25 cm.) reflux condenser (no water through the cooling jacket) or a Hahn condenser (Fig. *VI*, *12*, 1) to the flask, and arrange for slow distillation (5–10 drops per minute) from a water bath. When the acetone test is negative (after 1–2 hours) (*Crotyl Alcohol, Note 1* above), stop the distillation: if more than 50 ml. of *iso*propyl alcohol distils over, add 25 ml. of dry *iso*propyl alcohol to maintain the volume. Remove most of the excess of *iso*propyl alcohol by distillation under slightly diminished pressure. To the cold residue

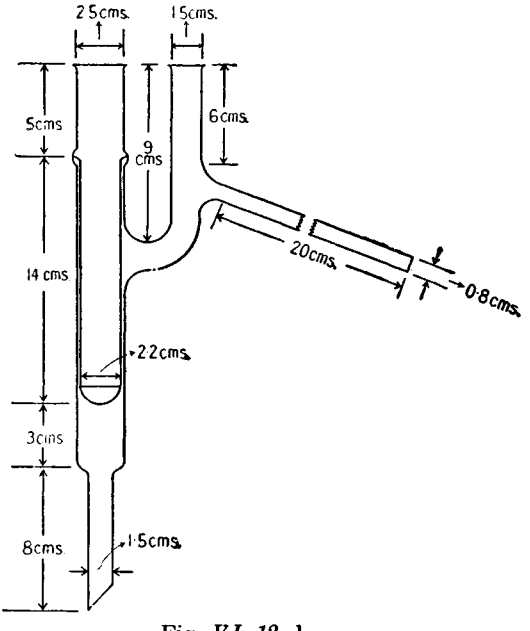


Fig. *VI*, *12*, 1.

add cold dilute hydrochloric acid (from 35 ml. of the concentrated acid and 175 ml. of water) slowly and with frequent shaking. Extract the benzhydrol which separates with ether or with benzene, wash the extract with cold dilute hydrochloric acid, then with water, and dry. Remove the solvent; the residual benzhydrol weighs 18 g. Recrystallise it from 20 ml. of hot alcohol or from 50 ml. of light petroleum (b.p. 60–80°) containing a little benzene, and cool in ice: 17·5 g. of pure benzhydrol, m.p. 68°, are obtained.

Recovery of the *iso*propyl alcohol. It is not usually economical to recover the *iso*propyl alcohol because of its low cost. However, if the alcohol is to be recovered, great care must be exercised particularly if it has been allowed to stand for several days: peroxides are readily formed in the impure acetone - *iso*propyl alcohol mixtures. Test first for peroxides by adding 0·5 ml. of the *iso*propyl alcohol to 1 ml. of 10 per cent. potassium iodide solution acidified with 0·5 ml. of dilute (1 : 5) hydrochloric acid and mixed with a few drops of starch solution: if a blue (or blue-black) coloration appears in one minute, the test is positive. One convenient method of removing the peroxides is to reflux each one litre of recovered *iso*propyl alcohol with 10–15 g. of solid stannous chloride for half an hour. Test for peroxides with a portion of the cooled solution: if iodine is liberated, add further 5 g. portions of stannous chloride followed by refluxing for half-hour periods until the test is negative. Then add about 200 g. of quicklime, reflux for 4 hours, and distil (Fig. *II*, *47*, 2); discard the first portion of the distillate until the test for acetone is negative (*Crotyl Alcohol, Note 1*). Peroxides generally redevelop in this purified *iso*propyl alcohol in several days.

VI.13 THE OPPENAUER OXIDATION

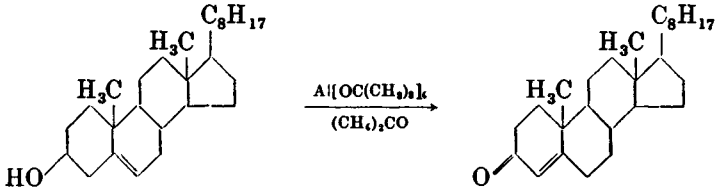
Secondary alcohols may be oxidised to the corresponding ketones with aluminium *tert.*-butoxide (or *iso*propoxide) in the presence of a large excess of acetone. This reaction is known as the **Oppenauer oxidation** and is the reverse of the Meerwein - Ponndorf - Verley reduction (previous Section); it may be expressed:

$$RR'CHOH + (CH_3)_2CO \underset{\text{butoxide}}{\overset{\text{Al } tert.\text{-}}{\rightleftharpoons}} RR'CO + (CH_3)_2CHOH$$

Acetone in conjunction with benzene as a solvent is widely employed. With *cyclo*hexanone as the hydrogen acceptor, coupled with toluene or xylene as solvent, the use of higher reaction temperatures is possible and consequently the reaction time is considerably reduced; furthermore, the excess of *cyclo*hexanone can be easily separated from the reaction product by steam distillation. At least 0·25 mol of alkoxide per mol of alcohol is used: however, since an excess of alkoxide has no detrimental effect 1 to 3 mols of aluminium alkoxide is recommended, particularly as water, either present in the reagents or formed during secondary reactions, will remove an equivalent quantity of the reagent. In the oxidation of steroids 50–200 mols of acetone or 10–20 mols of *cyclo*hexanone are generally employed.

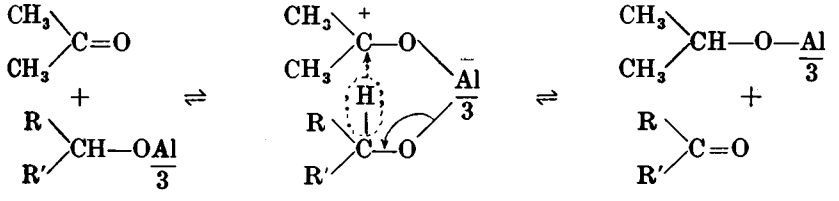
The Oppenauer oxidation has found wide application in investigations on steroids and related natural products. Its great advantage is that very mild conditions are utilised which are applicable to a variety of sensitive compounds: thus when other oxidisable groups, *e.g.*, olefinic bonds, are present in the molecule, they are usually unaffected. Among non-steroidal alcohols, both *cis* and *trans* decalols are converted in excellent yield to the corresponding decalones. The reaction has been extended to the conversion of unsaturated primary alcohols to the corresponding aldehydes by using quinone as the acceptor.

The reaction is illustrated by the preparation of **cholestenone** from cholesterol: the double bond migrates from the βγ to the αβ position during the oxidation;



Cholesterol Cholestenone

The following *mechanism* appears reasonable (compare Section **VI,12**), It assumes that the function of the aluminium *tert.*-butoxide, or other alkoxide. is to provide a source of aluminium ions and that the aluminium salt of the secondary alcohol is the actual reactant. Aluminium with its sextet of electrons has a pronounced tendency to accept a pair of electrons, thus facilitating the initial coordination and the subsequent transfer of a hydride ion :



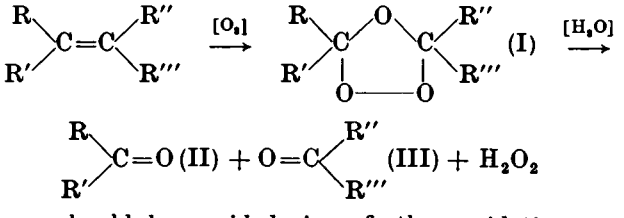
Aluminium *tert.*-butoxide. In a 500 ml. round-bottomed flask fitted with a reflux condenser protected by a calcium chloride or cotton wool tube, place 16 g. of aluminium turnings, 50 g. (63·5 ml.) of anhydrous *tert.*-butyl alcohol and 2 g. of aluminium *iso*propoxide (Section **VI,12**; to remove traces of water). Heat the mixture to boiling on a steam bath, add about 0·1 g. of mercuric chloride and shake vigorously : the object of the shaking is to distribute the mercuric chloride and thus assist an even amalgamation of the aluminium. Continue the heating on the steam bath; the colour of the reaction mixture gradually changes from clear to milky to black and hydrogen is evolved. Remove the flask from the steam bath when the mixture is black, allow the reaction to proceed for an hour, and then add 61 g. (77 ml.) of anhydrous *tert.*-butyl alcohol and 50 ml. of anhydrous benzene. Heat gently to restart the reaction; it will continue vigorously without further heating for about 2 hours : when the reaction subsides, reflux the mixture for 12 hours. Remove the benzene and unreacted *tert.*-butyl alcohol by distillation from a steam bath and the final traces under reduced pressure (water pump). Add 250 ml. of anhydrous ether ; dissolve the solid aluminium *tert.*-butoxide by refluxing for a short time. After cooling, add 9 ml. of *undried* ether and immediately shake vigorously ; the small amount of water thus introduced forms aluminium hydroxide, which assists the precipitation of the black suspended material. Allow to stand for 2 hours, centrifuge the mixture for 30 minutes to remove aluminium hydroxide, unused aluminium and mercury. After centrifuging, the solution should be colourless or almost so ; if it is still dark in colour, add a further 6 ml. of undried ether and centrifuge again. Now remove the solvent by distillation from a steam bath and the final

traces under reduced pressure (water pump). Allow the flask to cool with drying tube attached, crush the product with a spatula, and transfer it to a small bottle : seal the latter against moisture. The yield of white or pale gray aluminium *tert.*-butoxide is 105 g.

Cholestenone. Place a mixture of 20 g. of purified cholesterol (m.p. 149°–150° ; dried to constant weight at 80–100°), 150 ml. of A.R. acetone and 200 ml. of sodium-dried benzene in a dry 1-litre round-bottomed flask fitted with a reflux condenser and calcium chloride guard tube. Introduce a " boiling tube " (Fig. *I*, *3*, 1) to prevent bumping. Heat the mixture to boiling in an oil bath at 75–85°, add a solution of 16 g. of aluminium *tert.*-butoxide in 100 ml. of anhydrous benzene in one portion to the boiling solution. The mixture becomes cloudy and develops a yellow colour in 10 to 15 minutes. Continue gentle boiling at a bath temperature of 75–85° for 8 hours. Treat the cold mixture with 40 ml. of water, then with 100 ml. of 10 per cent. sulphuric acid, shake vigorously and transfer to a 1-litre separatory funnel. Dilute the mixture with 300 ml. of water, shake for 5 minutes (filter, if necessary), then run off the yellow aqueous layer into a second separatory funnel and extract the latter with 25 ml. of benzene. Wash the combined benzene extracts thoroughly with water, dry with anhydrous magnesium sulphate and remove the solvent (steam bath ; final traces at 60° under vacuum of water pump). The yellow oily residue solidifies when it is cooled in an ice-salt bath and scratched with a glass rod ; keep a small portion for " seeding " in the subsequent crystallisation. Dissolve the solid in a warm mixture of 14 ml. of acetone and 20 ml. of methanol, allow the solution to cool very slowly and seed, if necessary. When the bulk of the solid has crystallised, keep the mixture at 0° for 24 hours, filter with suction, wash with 20 ml. of ice-cold methanol, and dry in a vacuum desiccator. The yield of almost colourless cholestenone, m.p. 79–80°, is 17 g.

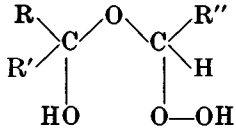
VI,14. OXIDATION OF UNSATURATED COMPOUNDS WITH OZONISED OXYGEN (OZONOLYSIS)

For the determination of the structure of unsaturated compounds, oxidation with ozone (as ozonised oxygen) possesses many advantages. Ozonolysis, unlike oxidation with excess of permanganate or chromic acid which, for example, will also oxidise primary and secondary alcohols, is a highly specific process. By passing ozonised oxygen through a solution of an ethylenic compound in an inert solvent, preferably at a low temperature, ozone adds on readily and quantitatively to the double bond to give an ozonide (I) :



(Excess of ozone should be avoided since further oxidation may occur to " oxozonides " or " perozonides.") The ozonides are usually not isolated since they are generally viscid oils or glasses, sometimes with violently explosive properties particularly on warming. They can, however, be completely

characterised by identifying the products of decomposition (II and III) by water or, preferably, by catalytic reduction. The decomposition with water produces some hydrogen peroxide, so that if an aldehyde is expected, this will be partially oxidised to the corresponding acid. The equation given for the hydrolytic decomposition of ozonides is certainly an over-simplification: other products, such as aldehyde and ketone peroxides are sometimes obtained as well as carboxylic acids, and these may arise by the rearrangement of the ozonide itself or of the hemiacetal compound

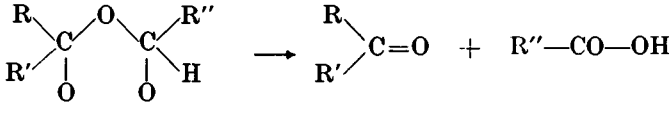


produced by the addition of water to (I) (R''' = H). The formation of the more highly oxidised products is prevented and the yields of aldehydes and ketones increased by subjecting the ozonide to catalytic reduction, *e.g.*, with palladium-calcium carbonate or with Adams' platinum oxide catalyst (Section III,150); hydrogenation is easily arrested with the formation of aldehyde and/or ketonic products.

The general method of ozonisation consists in passing dry ozonised oxygen through a dilute solution of the ethylenic compound in a solvent such as ethyl acetate, glacial acetic acid, chloroform, carbon tetrachloride, hexane or ethyl chloride, cooled in a freezing mixture (preferably at −20° to −30°). A wash bottle charged with potassium iodide solution and boric acid is attached to the outlet tube of the bottle containing the solution of the substance; the completion of the ozonisation is indicated by a sudden extensive separation of iodine. The following procedures may be used for decomposing the resulting ozonides:—

(i) The solvent is *cautiously* evaporated under reduced pressure (precautions against explosion should be taken). The crude ozonide is treated with cold water; if it is not decomposed, the mixture is heated under reflux until all the ozonide has disappeared. It is advisable to pass any volatile products into 2 : 4-dinitrophenylhydrazine reagent (Section VI,12, *Note 1*): this is most simply done by attaching a tube to the top of the condenser leading to a test-tube containing the reagent. When the decomposition is complete, the product is examined for volatile aldehydes, ketones or acids. The non-volatile products are first tested for their behaviour with Schiff's reagent and 2 : 4-dinitrophenylhydrazine. The main product is then extracted with ether, the acidic portion is removed from the ether by washing with aqueous sodium bicarbonate, and the neutral and acidic portions worked up separately.

(ii) It is preferable to conduct the ozonisation in dry ethyl acetate solution if the ozonide is to be reduced catalytically, since sparingly soluble polymeric ozonides are not formed in this medium and the reduction may be carried out in this solvent. If another solvent is employed, this must be removed first under reduced pressure and the ozonide dissolved in methanol, etc. Either palladinised calcium carbonate or Adams' platinum catalyst may be used. It is advisable to avoid a rise of the temperature during the hydrogenation, which is exothermic: the hydrogenation vessel is either cooled in ice, or a hydrogenation vessel containing an internal sealed-in glass cooling coil is used. If the temperature is allowed to rise during the reduction, acids are formed at the expense of the aldehyde, probably by the following reaction:



A commercial form of **ozoniser** is illustrated in Fig. *VI, 14,* 1 *; this produces about 170 ml. of ozonised oxygen, containing 6–7 per cent. of ozone, per minute. The apparatus consists of ten ozone tubes, each with its own effective annular space, bridged in parallel across an inlet and outlet manifold. The units are suspended in a lead-lined, hardwood tank fitted with a terminal : a ten-rod multiple high tension electrode, also fitted with a terminal, dips into the ozone tubes. The two terminals are connected by ozone-proof high tension leads to a transformer at 7,500 volts. The ozone tubes and tank are partially filled with 0·2 per cent. copper sulphate solution. Upon passing the silent high tension discharge across the annular space in the ozone tubes through which oxygen is flowing at a suitable rate†, ozone is formed in 6–7 per cent. yield.

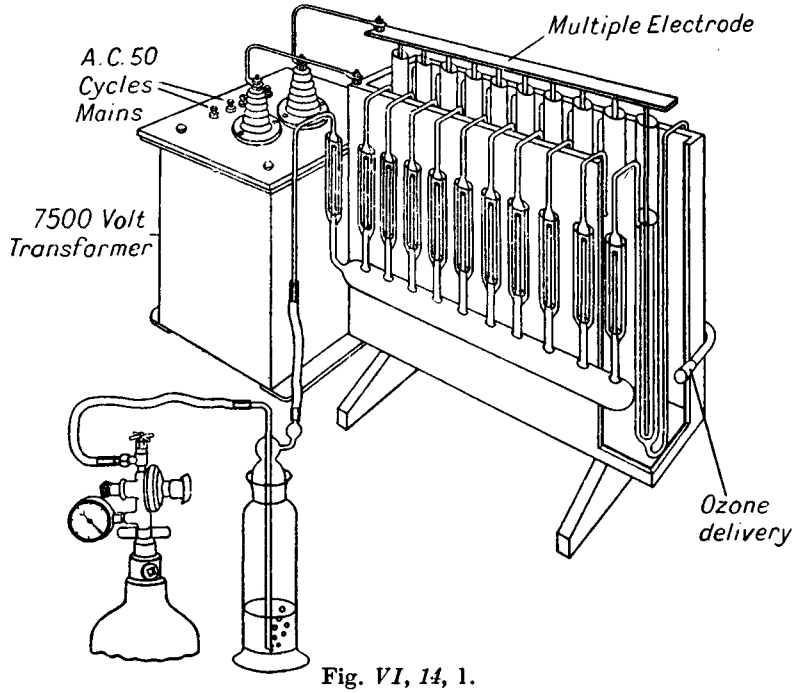


Fig. *VI, 14,* 1.

It must be emphasised that on the outlet side of the ozoniser, the use of grease and/or rubber at any joint must be avoided. Unlubricated ground glass joints should be used : PVC tubing may be employed for connexions. The ozonolysis is conducted in a wash-bottle of suitable size provided with a ground glass head ; it should be surrounded by a freezing mixture, preferably solid carbon dioxide and ether, contained in a Dewar vessel. This bottle should be connected to a similar, but smaller, wash bottle charged with acidified potassium iodide solution to indicate when the reaction is complete.

A simple semimicro laboratory ozoniser is illustrated in Fig. *VI, 14,* 2 : this gives reasonably satisfactory results for small quantities of organic

* Supplied by J. W. Towers and Co. Ltd.

† It is recommended that a flowmeter, charged with dibutyl phthalate, to be inserted between the ozoniser and wash bottle.

compounds. It consists of a wash bottle or small bubbler *A* to indicate the rate of flow of the oxygen, a Berthelot tube *B* for the generation of ozone, a vessel *C* to hold the solution of the compound to be ozonised, and a flask *D* containing 5 per cent. potassium iodide solution. The Berthelot tube is charged with dilute copper sulphate solution and is connected by a copper or stainless steel wire (2–4 mm. in diameter) to the high voltage terminal of a transformer (7,500–10,000 volts). The second electrode is the earthed aluminium foil covering most of the exterior of the Berthelot tube and is bound with insulating tape. As a precaution all high-voltage connexions are heavily insulated with rubber tape and the lead to the top of the electrode is covered with PVC, Tygon or equivalent tubing. The main dimensions are shown in the Figure. The ozoniser should be con-

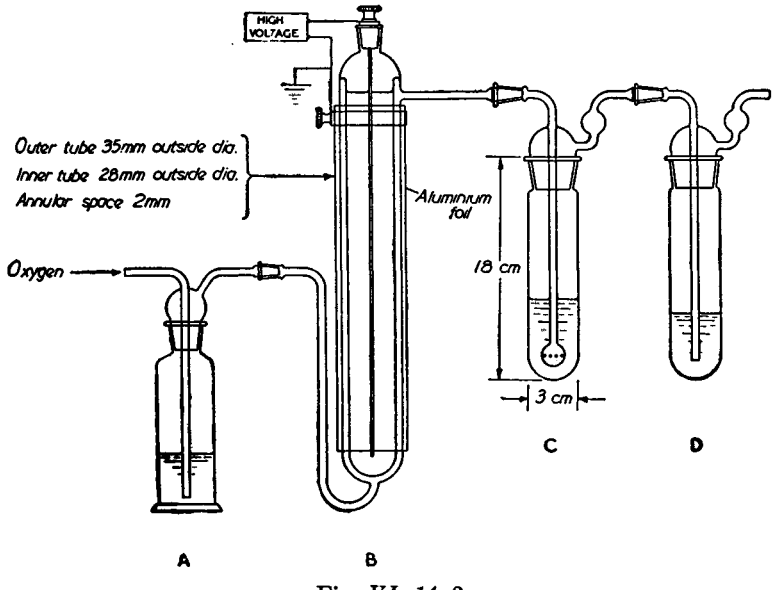


Fig. *VI*, *14*, 2.

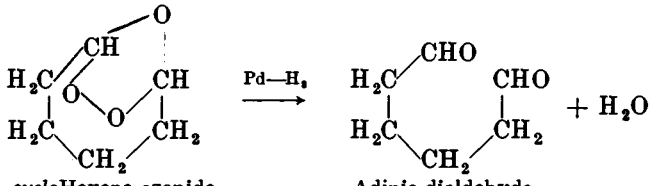
structed of soft soda-glass tubing (Pyrex glass is unsatisfactory): the glass should be thoroughly cleaned and the annular space through which the oxygen passes should be as uniform as possible. The complete apparatus should be placed in a fume cupboard (hood) behind a shatter-proof screen of laminated safety glass.

Organic peroxides are *highly explosive*, hence it is best to carry out the ozonisation in a solvent which dissolves both the original compound and the ozonide.

Preparation of palladium - calcium carbonate catalyst. Prepare 50 g. of precipitated calcium carbonate by mixing hot solutions of the appropriate quantities of A.R. calcium chloride and A.R. sodium carbonate. Suspend the calcium carbonate in water and add a solution containing 1 g. of palladium chloride. Warm the suspension until all the palladium is precipitated as the hydroxide upon the calcium carbonate, *i.e.*, until the supernatant liquid is colourless. Wash several times with

distilled water by decantation, filter with suction and wash sparingly until the washings are chloride-free, and dry. Keep the dry palladium - calcium carbonate in a tightly-stoppered bottle.

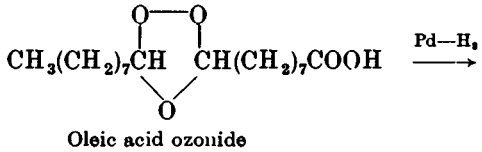
ADIPIC DIALDEHYDE FROM *CYCLO*HEXENE



*cyclo*Hexene ozonide Adipic dialdehyde

Dissolve 8·2 g. of *cyclo*hexene (Section **III,12**) in 200 ml. of pure dry ethyl acetate (Section **II,47,***19*) contained in a 500 ml. glass-stoppered wash bottle, cool the solution to −20° to −30° or below (*e.g.*, with solid carbon dioxide - acetone) and attach the wash bottle through a calcium chloride or cotton wool drying tube to another containing acidified potassium iodide solution. Pass ozonised oxygen until the reaction is complete, *i.e.*, until iodine is abundantly liberated. Then add 0·5 g. of palladium - calcium carbonate catalyst, and hydrogenate the cold solution of the ozonide in the usual manner (compare Fig. *III*, *150*, 1); cool the hydrogenation vessel in ice. Filter off the catalyst, remove the solvent (Fig. *II*, *13*, 4 but with a Claisen flask provided with a fractionating side arm) at normal pressure. Distil the residue under reduced pressure and collect the adipic dialdehyde at 92–94°/12 mm. The yield is 7 g. This aldehyde oxidises readily and should be kept in a sealed tube in an atmosphere of nitrogen or carbon dioxide. It may be converted into the dioxime by warming with aqueous hydroxylamine acetate solution: after recrystallisation from water, the dioxime has m.p. 172°.

n-NONYLALDEHYDE AND AZELAIC HEMIALDEHYDE FROM OLEIC ACID



Oleic acid ozonide

$CH_3(CH_2)_7CHO$ (I) + $OCH(CH_2)_7COOH$ (II) + H_2O

n-Nonylaldehyde Azelaic hemialdehyde

Dissolve 7 g. of pure oleic acid in 30 ml. of dry ethyl chloride (chloroform may be used but is less satisfactory), and ozonise at about −30°. Remove the solvent under reduced pressure, dissolve the residue in 50 ml. of dry methyl alcohol and hydrogenate as for adipic dialdehyde in the presence of 0·5 g. of palladium - calcium carbonate. Warm the resulting solution for 30 minutes with a slight excess of semicarbazide acetate and pour into water. Collect the precipitated semicarbazones and dry: the

yield is 8·5 g. Separate the mixture of semicarbazones by either of the following methods :—(*a*) Treat with dilute sodium bicarbonate solution to extract the semicarbazone of (II) ; upon acidifying the extract with dilute sulphuric acid, the semicarbazone of azelaic hemialdehyde is obtained (4·4 g., m.p. 162° after recrystallisation from methyl alcohol). The residue from the sodium bicarbonate extraction consists of the semicarbazone of *n*-nonylaldehyde, and melts at 101° after recrystallisation from methanol : yield, 3·8 g.

(*b*) Extract the dry mixture of semicarbazones with ether : only the semicarbazone of (I) dissolves easily.

Note.

The Adams platinum oxide catalyst gives satisfactory results in the reduction of ozonides.

VI,15. EPOXIDATION AND HYDROXYLATION OF ETHYLENIC COMPOUNDS

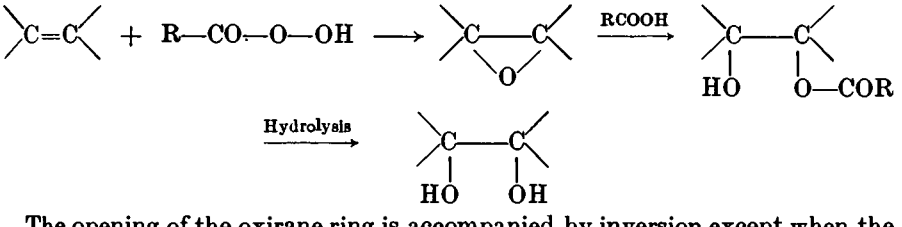
Ethylenic compounds when oxidised with perbenzoic acid or perphthalic acid in chloroform solution yield epoxides (or oxiranes). This is sometimes known as the **Prileschajew epoxidation reaction.** Thus styrene affords **styrene oxide** (or 2-phenyloxirane) :

$$C_6H_5CH{=}CH_2 + C_6H_5CO{-}O{-}OH \xrightarrow[\text{solution}]{CHCl_3} C_6H_5CH\!-\!CH_2 \quad (O) + C_6H_5COOH$$

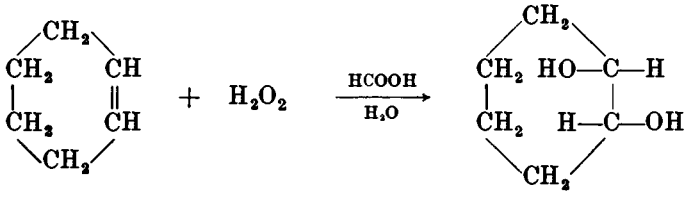
Styrene — Perbenzoic acid — Styrene oxide

It is usually assumed that the epoxidation reaction proceeds initially by *cis* addition to the double bond.

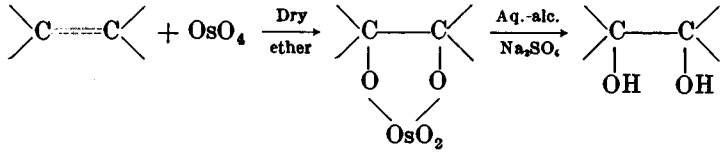
The epoxides may be converted into 1 : 2-glycols by hydrolysis. In some cases the 1 : 2-glycol may be produced directly by carrying out the epoxidation in the presence of water. If the 1 : 2-glycol is desired, it is usually better to employ performic acid or peracetic acid, the latter best in the presence of a trace of sulphuric acid. An epoxide is first formed, followed by the hydroxy-formate or hydroxy-acetate, and ultimately the 1 : 2-glycol :



The opening of the oxirane ring is accompanied by inversion except when the oxirane ring is in the terminal position of an aliphatic chain : the *ultimate* result is equivalent to *trans* addition to the double bond. Thus *cyclo*hexene yields ***trans*-1 : 2-*cyclo*hexanediol** :



Another method for the hydroxylation of the ethylenic linkage consists in treatment of the alkene with osmium tetroxide in an inert solvent (ether or dioxan) at room temperature for several days : an osmic ester is formed which either precipitates from the reaction mixture or may be isolated by evaporation of the solvent. Hydrolysis of the osmic ester in a reducing medium (in the presence of alkaline formaldehyde or of aqueous-alcoholic sodium sulphite) gives the 1 : 2-glycol and osmium. The glycol has the *cis* structure ; it is probably derived from the cyclic osmic ester :



The reagent is expensive and poisonous, consequently the hydroxylation procedure is employed only for the conversion of rare or expensive alkenes (*e.g.*, in the steroid field) into the glycols. Another method for hydroxylation utilises catalytic amounts of osmium tetroxide rather than the stoichiometric quantity : the reagent is hydrogen peroxide in *tert.*-butyl alcohol This reagent converts, for example, *cyclo*hexene into ***cis* 1 : 2-*cyclo*hexanediol.**

Styrene oxide (1 : 2-epoxyethylbenzene). Add 30 g. of styrene, b.p. 42–43°/18 mm. (cf. Section **X,6**), to a solution of 42 g. of perbenzoic acid (Section **IV,198**) in 450 ml. of chloroform (see *CAUTION* below). Keep the solution at 0° for 24 hours and shake frequently during the first hour. At the end of 24 hours only a slight excess of perbenzoic acid remains ; confirm this by mixing an aliquot portion with excess of acidified potassium iodide solution and titrating with standard sodium thiosulphate solution (Section **IV,198**). Separate the benzoic acid from the chloroform solution by shaking with an excess of 10 per cent. sodium hydroxide solution, remove the residual alkali by washing with water, and dry the chloroform solution with anhydrous magnesium sulphate. Distil with the aid of an efficient fractionating column. After the chloroform has been removed, the styrene oxide passes over at 189–192° (or at 101°/40 mm.) as a colourless liquid. The yield is 25 g.

***trans*-1 : 2-*cyclo*Hexanediol.** *CAUTION. All preparations and reactions with organic per-acids must be conducted behind a safety screen, because a reaction sometimes proceeds with uncontrollable violence.*

In a 500 ml. three-necked flask, equipped with a mechanical stirrer, thermometer and dropping funnel, place 300 ml. of 88–90 per cent. formic acid and add 70 ml. of 30 per cent. hydrogen peroxide.* Then introduce slowly 41 g. (51 ml.) of freshly distilled *cyclo*hexene (Section **III,12**) over a period of 20–30 minutes ; maintain the temperature of the reaction mixture between 40° and 45° by cooling with an ice bath and controlling the rate of addition. Keep the reaction mixture at 40° for 1 hour after all the *cyclo*hexene has been added and then allow to stand overnight at room temperature. Remove most of the formic acid and water by distillation from a water bath under reduced pressure. Add an ice-cold solution of 40 g. of sodium hydroxide in 75 ml. of water in small portions to the residual mixture of the diol and its formate : take care that the tempera-

* A number of per-acids and organic derivatives of hydrogen peroxides are manufactured by Laporte Chemicals Ltd., Luton, England.

ture does not rise above 45°. Warm the alkaline solution to 45° and add an equal volume (*ca.* 200 ml.) of ethyl acetate. Extract thoroughly, separate the lower layer and extract at 45° six times with equal volumes of ethyl acetate. Combine the seven ethyl acetate solutions (total volume about 1 litre), distil off the solvent from a water bath until the residual volume is about 150 ml. and solid commences to crystallise. Cool to 0° and separate the crude product (*ca.* 45 g.) by suction filtration. Concentrate the mother liquor on a steam bath to 30–40 ml., when more solid crystallises (*ca.* 8 g.). Cool and filter the mixture as before. Distil the combined crude products using an oil bath and a flask such as is shown in Fig. *II*, *19*, 3. The pure *trans*-1 : 2-*cyclo*hexanediol passes over at 128–132°/15 mm. (or at 120–124°/4 mm.), and solidifies immediately; m.p. 102–103°. The yield is 40 g. It may be crystallised from acetone or from ethyl acetate.

***cis*-1 : 2-*cyclo*Hexanediol.** Prepare the *reagent* as follows. To a mixture of 100 ml. of pure *tert.*-butyl alcohol and 25 ml. of 30 per cent. (100 vol.) hydrogen peroxide add anhydrous sodium sulphate (or, better, anhydrous magnesium sulphate) in small portions; two layers separate out. Remove the alcohol layer, which contains most of the hydrogen peroxide, and dry it with anhydrous magnesium sulphate, followed by anhydrous calcium sulphate. The resulting liquid is a solution of 6·3 per cent. hydrogen peroxide in *tert.*-butyl alcohol.

Free *cyclo*hexene from peroxides by treating it with a saturated solution of sodium bisulphite, separate, dry and distil: collect the fraction, b.p. 81–83°. Mix 8·2 g. of *cyclo*hexene with 55 ml. of the reagent, add a solution of 15 mg. of osmium tetroxide in anhydrous *tert.*-butyl alcohol and cool the mixture to 0°. Allow to stand overnight, by which time the initial orange colouration will have disappeared. Remove the solvent and unused *cyclo*hexene by distillation at atmospheric pressure and fractionate the residue under reduced pressure. Collect the fraction of b.p. 120–140°/15 mm.; this solidifies almost immediately. Recrystallise from ethyl acetate The yield of pure *cis*-1 : 2-*cyclo*hexanediol, m.p. 96°, is 5·0 g.

VI,16. REACTIONS IN LIQUID AMMONIA. SOME ACETYLENIC COMPOUNDS *

CONDENSATIONS WITH SODAMIDE IN LIQUID AMMONIA

Acetylenic compounds are conveniently prepared with the aid of liquid ammonia as a solvent. The preparation of a simple acetylenic hydrocarbon (*n*-butylacetylene or 1-hexyne) and also of phenylacetylene is described. Experimental details are also given for two acetylenic carbinols, *viz.*, 1-ethynyl-*cyclo*hexanol and 4-pentyn-1-ol. It will be noted that the scale is somewhat large; smaller quantities can readily be prepared by obvious modifications of the directions.

Sodamide is first prepared *in situ* by the reaction of sodium with liquid ammonia in the presence of a catalyst:

$$2Na + 2NH_3 \xrightarrow{\text{Catalyst}} 2NaNH_2 + H_2$$

* The experimental details for 1-hexyne, phenylacetylene and 1-ethynyl*cyclo*hexanol were kindly supplied by Professor E. R. H. Jones, F.R.S., Dr. H. B. Henbest and Dr. M. C. Whiting.

The catalyst is finely-divided iron and is produced by adding a little crystallised ferric nitrate and a slight excess of sodium to liquid ammonia ; the reaction is probably :

$$2Fe(NO_3)_3,9H_2O + 42Na + 6NH_3 \longrightarrow 2Fe + 6Na_2NO_2 + 24NaOH + 6NaNH_2 + 9H_2$$

A solution of mono-sodium acetylide in liquid ammonia is formed by passing excess of acetylene gas into the suspension of sodamide :

$$2NaNH_2 + HC{\equiv}CH \xrightarrow{\text{Liquid } NH_3} NaC{\equiv}CNa + 2NH_3$$

$$NaC{\equiv}CNa + HC{\equiv}CH \xrightarrow{\text{Liquid } NH_3} 2NaC{\equiv}CH^*$$

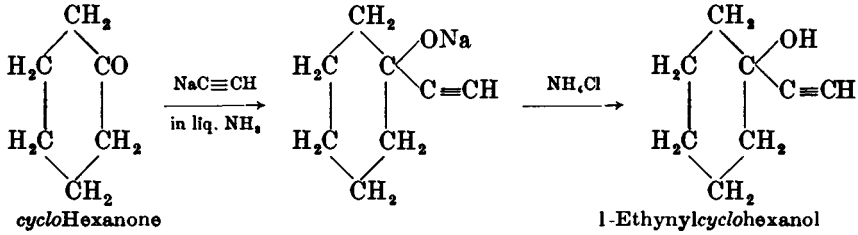
Addition of *n*-butyl bromide then gives ***n*-butylacetylene (1-hexyne)** :

$$NaC{\equiv}CH + n\text{-}C_4H_9Br \xrightarrow[NH_3]{\text{Liquid}} n\text{-}C_4H_9C{\equiv}CH + NaBr$$

Phenylacetylene is readily prepared by the dehydrohalogenation of styrene dibromide with a solution of sodamide in liquid ammonia :

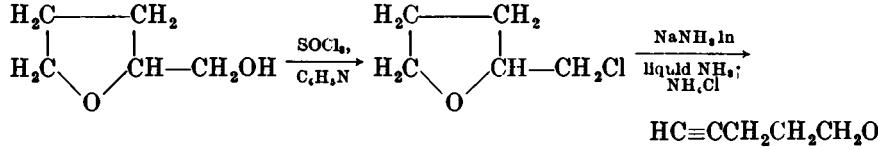
$$\underset{\text{Styrene dibromide}}{C_6H_5CHBr.CH_2Br} + 3NaNH_2 \xrightarrow[NH_3]{\text{Liquid}} C_6H_5C{\equiv}CNa \xrightarrow{NH_4Cl} \underset{\text{Phenylacetylene}}{C_6H_5C{\equiv}CH}$$

The reaction between sodium acetylide in liquid ammonia solution and carbonyl compounds gives α-acetylenyl carbinols (compare Section **III,148**), for example :



*cyclo*Hexanone — 1-Ethynyl*cyclo*hexanol

The acetylenic alcohol **4-pentyn-1-ol** is conveniently prepared by treatment of tetrahydrofurfuryl chloride with sodamide in liquid ammonia :



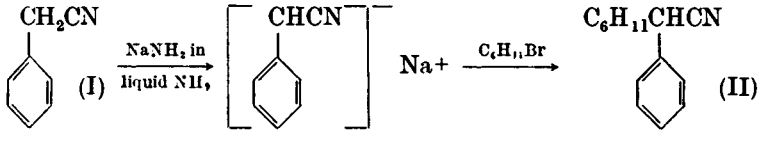
Tetrahydrofurfuryl alcohol — $HC{\equiv}CCH_2CH_2CH_2OH$ 4-Pentyn-1-ol

* Monosodium acetylide may also be prepared by the reaction of acetylene with sodium in liquid ammonia :

$$2Na + 3HC{\equiv}CH \xrightarrow[NH_3]{\text{Liquid}} 2NaC{\equiv}CH + H_2C{=}CH_2$$

Some unreacted sodium may be left on the walls of the flask in this method and this may partly reduce some product, such as an alkylacetylene, derived from the sodium acetylide. The preparation of sodamide is not attended by much splashing and little (if any) unreacted sodium remains on the walls of the flask. Although more manipulation and a somewhat longer time is required for the sodamide method, the latter is generally preferred as it is more adaptable and somewhat less troublesome.

A solution of sodamide in liquid ammonia (essentially the amide NH_2^- ion) is a very powerful alkylation catalyst, enabling condensations to be carried out with ease and in good yield which are otherwise either impossible or proceed with difficulty and are accompanied by considerable by-products. Thus 3-alkylpyridines, otherwise inaccessible, are easily prepared from 3-picoline (see 3-*n*-amylpyridine in Section V,20). Also benzyl cyanide (I) and *cyclo*hexyl bromide give **α-*cyclo*hexylphenylacetonitrile (II)** :



It is of interest to note that by substituting alkyl bromides for *cyclo*hexyl bromide the corresponding α-phenyl-α-alkyl-acetonitriles are obtained, which may be hydrolysed to the α-phenylaliphatic acids : thus with ethyl iodide α-phenylbutyronitrile is produced, hydrolysed by ethanolic potassium hydroxide to α-phenylbutyric acid.

n-BUTYLACETYLENE (1-HEXYNE)

Apparatus. It is advisable to have all the apparatus required in the various operations ready before commencing the actual preparation. Apart from the cylinder of acetylene, all the apparatus must be assembled in a spacious fume cupboard provided with an efficient exhaust system. Support a 5-litre, three-necked, bolt-headed flask on a cork (" suberite ") ring inside a large crock or bath, subsequently to be used as a cooling bath. Fit the central neck with a powerful stirrer, preferably driven by a flexible driving shaft between the motor and the stirrer (1) ; support the stirrer head in a metal framework attached to two heavy retort stands. Attach the stirrer by means of two short lengths of rubber " pressure " tubing in order to reduce the danger of breakage in the subsequent stirring (Fig. *VI*, *16*, 1, *a* ; this is a schematic diagram, *not* drawn to scale) : the blade of the stirrer may be a glass loop or a Hershberg wire stirrer (Fig. *II*, *7*, 7) of stout, corrosion resistant wire such as tantalum (or "Nichrome "). The glass sleeve bearing may be lubricated with a little silicone grease or with vaseline. The liquid ammonia is introduced by the device shown in Fig. *VI*, *16*, 1, *b*. Attach a rubber stopper carrying a length of glass tubing bent at right angles securely to the outlet of the cylinder by means of a stout wire.* Mount the ammonia cylinder above the level of the flask at an angle of about 60° from the vertical ; upon opening the screw valve any desired volume of liquid ammonia may be run into the reaction flask. It is helpful to mark a ring on the outside of the flask at volumes of 3 and 4 litres.

Acetylene is obtained from a cylinder (at ground level outside the fume chamber) and is freed from acetone by passing through two 500 ml. wash bottles, half-filled with concentrated sulphuric acid, at the rate of 2–3 litres per minute : when the acid in the second wash bottle becomes discoloured, the wash bottles should be recharged with fresh acid. The

* Alternatively a special gas reducing valve attached to the wide screw thread of the ammonia cylinder may be used.

gas passes via a mercury-filled safety trap (Fig. *VI*, *16*, 1, *c*) into the reaction vessel, which it enters through a wide tube (at least 0·5″ in diameter) reaching almost to the bottom of the flask ; the device depicted in Fig. *II*, *7*, 12, *b* is recommended since any solid formed inside the tube may be readily removed.

Sodamide. Assemble the apparatus shown in Fig. *VI*, *16*, 1, *a*. Fill the bath to a point about half-way up the side of the flask with methyl alcohol (or methylated spirit) and add solid carbon dioxide (Dry Ice or Drikold) in lump form until a white frost commences to form on the outside of the bath (2) : the bath temperature should be about — 35°.

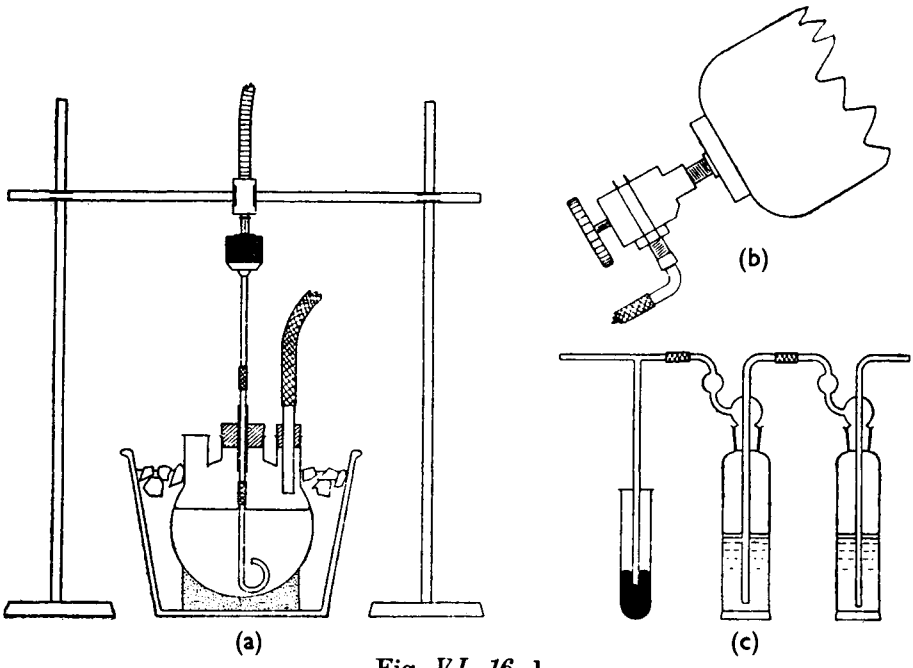


Fig. *VI*, *16*, 1.

Run liquid ammonia into the cooled flask from an inclined cylinder (Fig. *VI*, *16*, 1, *b*) until the flask is about two-thirds full (*ca.* 3·5 litres) (3). Stir vigorously and add 0·5 g. of finely-powdered crystallised ferric nitrate ; continue the stirring for 5 to 10 minutes to disperse the ammonolysis products of the ferric nitrate as finely as possible. Then add 1·5 g. of clean sodium (cut into small pieces) and continue the stirring until the blue colour has disappeared (about 10 minutes) (4). During the subsequent addition of sodium maintain the temperature of the cooling bath between — 30° and — 35° by the addition of dry ice when necessary. Introduce 138 g. of clean sodium (5) in 3 g. lumps during 1 hour ; stir slowly during the reaction. The solution at first acquires a deep blue colour : at the end of the reaction the fine suspension of sodamide is colourless or pale grey (6). Continue the stirring after all the sodium has been added until the blue colour just disappears. It is essential to ensure

that the blue colour should have disappeared before proceeding to the next stage: this is most easily detected with the aid of a "dip stick" (4). If the volume of liquid has appreciably decreased during the reaction, add liquid ammonia to restore the original volume (*ca.* 3·5 litres).

Sodium acetylide. Replace the ammonia-addition tube by a wide tube reaching almost to the bottom of the flask (or use the device depicted in Fig. *II*, 7, 12, *b*) and pass acetylene (Fig. *VI*, *16*, 1, *c*) into the suspension of sodamide in liquid ammonia: maintain the bath temperature at about — 35° so that little ammonia is lost. Continue the passage of acetylene until a uniformly black liquid is formed (usually 4–5 hours) (7). Carefully watch the wide gas entry tube; if much solid collects inside this tube, remove it before the tube is completely blocked. Add liquid ammonia, if necessary, to restore the original volume (*ca.* 3·5 litres).

***n*-Butylacetylene (1-hexyne).** Add Dry Ice to the cooling bath until the methanol becomes viscous (*ca.* — 50°). Introduce, with stirring, 685 g. (538 ml.) of redistilled *n*-butyl bromide, contained in a dropping funnel, during 1·5–2 hours whilst a slow stream of acetylene (*ca.* 500 ml. per minute) is passed through the reaction mixture. The reaction is an exothermic one: maintain the temperature of the cooling bath at about —50°. When all the alkyl bromide has been added, discontinue the supply of acetylene, close one neck of the flask with a cork and leave the other open to allow the ammonia to escape. Continue the stirring. Add more solid carbon dioxide to the bath until it is well above the level of the liquid in the flask. Allow the reaction mixture to stand overnight (about 15 hours), and then add with continued stirring 60 g. of ammonium chloride to decompose the excess of sodium acetylide (or sodamide, if present). Allow the residual ammonia to evaporate and then introduce 500 g. of crushed ice cautiously, followed by about 1·5 litres of distilled water. Subject the contents of the flask to steam distillation. The 1-hexyne passes over rapidly. Separate the hydrocarbon layer, dry it with anhydrous magnesium sulphate and fractionate (preferably through a Widmer or Fenske column). Collect the *n*-butylacetylene at 71–72°. The yield is 280 g.

Notes.

(1) The stirrer shown in Fig. *II*,7,3 is suitable. Corrosion of the motor by the ammonia fumes is thus reduced to a minimum. A powerful stirrer is essential since much solid is formed in the subsequent reaction.

(2) For precautions to be observed in handling Dry Ice, see Section III,84.

(3) The liquid ammonia may be slightly cloudy, due to the presence of a little water: this has no appreciable effect upon the yield.

(4) The absence of a colour can be readily ascertained by dipping a glass rod into the solution and withdrawing it rapidly: when the solution is colourless, all the sodium has been converted into sodamide by the catalyst present.

(5) It is advisable to use dry, clean sodium; it may be kept in dry ether or naphtha prior to the addition.

(6) This procedure may be used for the preparation of finely-divided sodamide. If the sodamide is to be used in any other solvent than liquid ammonia, the ammonia is allowed to evaporate whilst the new solvent is slowly added from a dropping funnel; alternatively, the new solvent may be added before the ammonia evaporates. If dry sodamide is required, the product may be freed from the last traces of ammonia by evacuation at 100°. The sodamide prepared by this method must be used immediately: if allowed to stand, it rapidly changes into explosive substances.

(7) Occasionally the reaction mixture does not become completely black nor free from suspended solid; here the acetylide is in an insoluble (or sparingly soluble) form, but it gives satisfactory results in the preparation of hex-1-yne. The saturated solution of the soluble form of mono-sodium acetylide in liquid ammonia at — 34° is about 4·1*M*.

PHENYLACETYLENE

Styrene dibromide (αβ-dibromoethylbenzene). Place a solution of 204 g. (224 ml.) of freshly distilled styrene (Section X,6) in 200 ml. of dry chloroform in a litre beaker, cooled in an ice bath, and provided with a mechanical stirrer. Support a dropping funnel over the beaker and charge the former with a solution of 340 g. (107 ml.) of dry bromine in 200 ml. of chloroform. Add the bromine solution with stirring at a rate to conform with the discharge of colour from red to pale yellow. This preparation is advantageously carried out in bright sunlight. When all the bromine has been added, continue the stirring until the reaction is complete. Evaporate the chloroform on a water bath; the residual crude styrene dibromide weighs 510 g. This may be used directly for the preparation of phenylacetylene. It may be purified by recrystallisation from dilute alcohol; m.p. 73–74°.

CAUTION. Styrene dibromide is a skin irritant and all contact with it should be avoided. Rubber gloves should be used in its preparation.

Phenylacetylene. Support a 5-litre glass Dewar flask in a wooden case. Equip the flask with a lid of clear Perspex, provided with suitable apertures for a mechanical stirrer, introducing solids (*e.g.*, sodium) or liquids, a calibrated dip stick for measuring the volume of liquid in the Dewar vessel, a gas inlet tube and an ammonia inlet: arrange for an electric light to shine downwards into the flask.

Charge the Dewar flask with 3 litres of liquid ammonia, set the stirrer into operation, and introduce 1·5 g. of powdered ferric nitrate followed by 5 g. of clean sodium. After 2 minutes, introduce 160 g. of clean sodium in 3 g. lumps during 30 minutes. Allow to stand until the initially deep blue reaction mixture assumes a light grey colour (about 20 minutes). Add a solution of 510 g. of styrene dibromide in 1500 ml. of dry ether slowly during 2 hours: a vigorous reaction ensues, accompanied by the loss of some ammonia by evaporation. Allow to stand for 4 hours, add 180 g. of finely-powdered ammonium chloride to the pasty mass (to decompose the sodio derivative), followed by 500 ml. of ether and continue the stirring for several minutes. Pour the contents of the Dewar flask with the aid of a purpose-made plastic spout into a cold beaker. Allow the ammonia to evaporate overnight. Add ether, filter off the inorganic salts and wash well with ether; keep the filtrate (*A*). Dissolve the inorganic salts in water, extract the solution with ether, and combine the ethereal extracts with the filtrate (*A*). Wash with dilute sulphuric acid until acid to Congo red paper, then with water, dry with anhydrous magnesium sulphate, distil off the ether on a water bath with the aid of a short but efficient column, and fractionate the residue through a well-lagged Widmer (or other efficient fractionating) column. Collect the phenylacetylene at

142–143°; the yield is 156 g. Alternatively, distil the residue under reduced pressure and collect the phenylacetylene at 82°/80 mm. (1).

Note.

(1) This pressure is readily attained by placing an air leak between the water pump and the apparatus or, better, with the aid of a manostat, Figs. *II*, *23*, 4–7.

1-ETHYNYL*CYCLO*HEXANOL

Use the same technique as detailed for 1-hexyne, but with a 3-litre three-necked flask. Charge the flask with 1·5 litres of liquid ammonia. Prepare the sodamide using 0·7 g. of ferric nitrate and 2 g. of sodium, followed by 46 g. of sodium, and convert it into a solution of sodium acetylide as before. Add, with stirring, a solution of 196 g. (206 ml.) of dry, redistilled *cyclo*hexanone (1) in 256 ml. of dry ether during 1 hour and continue the stirring for a further 2 hours. Decompose the sodium derivative of the product by the gradual addition of a slight excess (118 g.) of powdered ammonium chloride. Allow to stand overnight, preferably with stirring, by which time all the ammonia will have evaporated. Extract the residue repeatedly with ether, *i.e.*, until all the carbinol has been separated from the inorganic material (2). Wash the ethereal extract successively with water, dilute sulphuric acid and potassium bicarbonate solution, dry with anhydrous magnesium sulphate and distil. Collect the 1-ethynyl*cyclo*hexanol at 83°/20 mm. (3); the yield is 210 g.

Notes.

(1) Dry the *cyclo*hexanone over excess of anhydrous calcium chloride before distillation.

(2) A continuous ether extractor (Fig. *II*, *44*, 2) is recommended.

(3) The product has m.p. *ca.* 25°, but the m.p. depends upon the purity of the *cyclo*hexanone and the efficiency of the distillation. Pure 1-ethynyl*cyclo*hexanol has m.p. 32°.

4-PENTYN-1-OL

Tetrahydrofurfuryl chloride. Place 204 g. (194 ml.) of freshly distilled tetrahydrofurfuryl alcohol (b.p. 177°) and 174 g. (178 ml.) of dry pyridine in a 1-litre three-necked flask, fitted with a dropping funnel, mechanical stirrer and thermometer. Cool in an ice bath, stir vigorously and add 250 g. (153 ml.) of freshly distilled thionyl chloride at the rate of 3–5 drops per second. A pasty crystalline mass begins to separate and the temperature commences to rise rapidly when one-third to one-half of the thionyl chloride has been added; subsequently the mass largely redissolves and a dark brown liquid forms. Remove the ice bath when the addition is complete and stir the mixture for 3–4 hours. Pour the reaction product into a large separatory funnel and extract with seven 250 ml. portions of ether: break up any lumps that may form with a glass rod. Remove the ether from the combined extracts by distillation, wash the residue with three 50 ml. portions of water, dry with anhydrous magnesium sulphate and distil under reduced pressure. The yield of tetrahydrofurfuryl chloride, b.p. 47–48°/15 mm., is 180 g.

4-Pentyn-1-ol. Prepare a solution of sodamide in liquid ammonia as detailed for n-*Butylacetylene*. Use a 3-litre three-necked flask, equipped with a Dewar type of reflux condenser (Fig. *II*, *1*, 4, *h*) cooled with Dry Ice

and attached through a soda-lime guard tube to a gas-absorption trap (Fig. *II, 8,* 1,*c* or *d* or Fig. *II, 8,* 2), a mercury-sealed stirrer, and an inlet tube. Introduce 1-litre of anhydrous ammonia through the inlet tube, add 1 g. of hydrated ferric nitrate, followed by 80·5 g. of clean, freshly cut sodium ; add more liquid ammonia through the inlet tube if vaporisation reduces the volume below 750 ml. Replace the inlet tube by a 250 ml. dropping funnel, stir the mixture until all the sodium is converted into sodamide, and then add 120·5 g. (108·5 ml.) of tetrahydrofurfuryl chloride over a period of 25–30 minutes. Stir the mixture for a further hour, after which introduce 177 g. of solid ammonium chloride in portions at a rate that permits control of the exothermic reaction. Allow the flask to stand in the fume cupboard (hood), preferably overnight, while the ammonia evaporates. Extract the residue thoroughly with ten 250 ml. portions of ether and decant them through a Buchner funnel. Distil off the ether, and fractionate the residue through a column packed with glass helices (compare Fig. *II, 17,* 2) at a reflux ratio of about 5 to 1. Collect the 4-pentyn-1-ol at 70–71°/29 mm. The yield is 70 g.

The b.p. at atmospheric pressure has been given as 154–155°.

α-*CYCLO*HEXYLPHENYLACETONITRILE

In a 1-litre three-necked flask prepare a solution of sodamide in liquid ammonia, using 200 ml. of anhydrous ammonia, 0·2 g. of crystallised ferric nitrate and 8·1 g. of sodium : follow the experimental details given under n-*Butylacetylene*. Whilst cooling in a Dry Ice - trichloroethylene bath, add 41 g. (40 ml.) of benzyl cyanide (Section **IV,160**) during 10 minutes by means of a dropping funnel inserted into a neck of the flask. Remove the Dry Ice bath, stir the clear solution for 15 minutes, add 200 ml. of sodium-dried, sulphur-free toluene and 25 ml. of anhydrous ether dropwise through the funnel while the ammonia evaporates. Allow the solution to stand, or warm in a water bath, until all the ammonia has evaporated. At this stage, fit a reflux condenser to the flask already equipped with a mechanical stirrer and dropping funnel. Add 65·2 g. (49·1 ml.) of *cyclo*hexyl bromide (Section **III,34**) to the warm solution over a period of about 20 minutes; the reaction is vigorous and may require cooling. Reflux the mixture (oil bath) for 2 hours. Cool the reaction mixture and wash it with 250 ml. of water ; keep the toluene solution. Extract the aqueous layer with two 50 ml. portions of benzene ; wash the combined toluene and benzene solutions with two 50 ml. portions of water, and dry with anhydrous magnesium sulphate. Distil from a 500 ml. Claisen flask with fractionating side arm (Figs. *II, 24,* 3–5) and collect the α-*cyclo*hexylphenylacetonitrile at 174–176°/13 mm. ; it crystallises on cooling, m.p. 51–53° and the yield is 50 g. It may be recrystallised from commercial pentane ; m.p. 57–58°.

VI,17. THE ARNDT-EISTERT REACTION

The Arndt-Eistert reaction is a comparatively simple method for converting an acid into its next higher homologue or to a derivative of the homologous acid, such as an amide or an ester. The overall yield is generally good. The reaction

is applicable to aliphatic, aromatic, alicyclic and heterocyclic carboxylic acids. It involves three operations :

1. Formation of the acid chloride, *e.g.*, with thionyl chloride or with phosphorus pentachloride :

$$RCOOH \longrightarrow RCOCl$$

2. Reaction of the acid chloride with a cold solution of excess of diazomethane to yield a diazo ketone :

$$RCOCl + CH_2N_2 \longrightarrow RCO{-}CHN_2 + HCl\,;\ HCl + CH_2N_2 \longrightarrow CH_3Cl + N_2$$

(If excess of acid chloride is employed, *e.g.*, by adding the diazomethane solution slowly to the acid chloride, some halomethyl ketone is produced :

$$RCO{-}CHN_2 + HCl \longrightarrow RCO{-}CH_2Cl + N_2).$$

3. Rearrangement of the diazo ketone, with loss of nitrogen, in the presence of suitable reagents and a catalyst (colloidal silver, silver oxide, or silver nitrate in the presence of ammonia solution). An acid is formed in the presence of water, an amide results when ammonia or an amine is used, and an ester is produced in the presence of an alcohol :

$$RCO{-}CHN_2 \xrightarrow{HOH} R{-}CH_2COOH + N_2$$
$$RCO{-}CHN_2 \xrightarrow{R'OH} R{-}CH_2COOR' + N_2$$
$$RCO{-}CHN_2 \xrightarrow{NH_3} R{-}CH_2CONH_2 + N_2$$

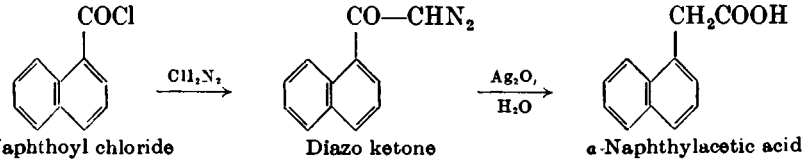
The third operation, involving the conversion of the diazo ketone into an acid or a simple derivative thereof, is known as the **Wolff rearrangement.**

In order to prepare an acid, a dioxan solution of the diazo ketone is added slowly to a suspension of silver oxide in a dilute solution of sodium thiosulphate. If the conversion to the acid yields unsatisfactory results, it is usually advisable to prepare the ester or amide, which are generally obtained in good yields ; hydrolysis of the derivative gives the free acid.

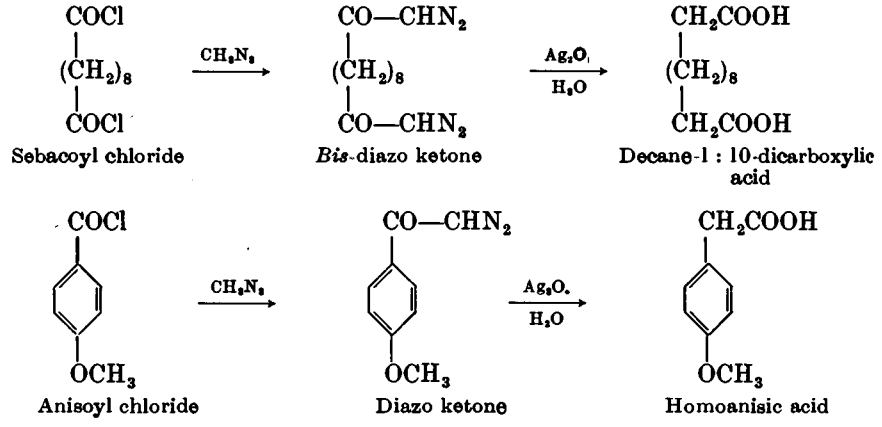
Esters of the homologous acids are prepared by adding silver oxide in portions rather than in one lot to a hot solution or suspension of the diazo ketone in an anhydrous alcohol (methyl, ethyl or *n*-propyl alcohol) : methanol is generally used and the silver oxide is reduced to metallic silver, which usually deposits as a mirror on the sides of the flask. The production of the ester may frequently be carried out in a homogeneous medium by treating a solution of the diazo ketone in the alcohol with a solution of silver benzoate in triethylamine.

The conversion of a diazo ketone to an acid amide may be accomplished by treating a warm solution in dioxan with 10–28 per cent. aqueous ammonia solution containing a small amount of silver nitrate solution, after which the mixture is heated at 60°–70° for some time. Precautions should be taken (by use of a safety glass shield) when heating mixtures containing ammoniacal silver nitrate.

The reaction is illustrated by the following examples :



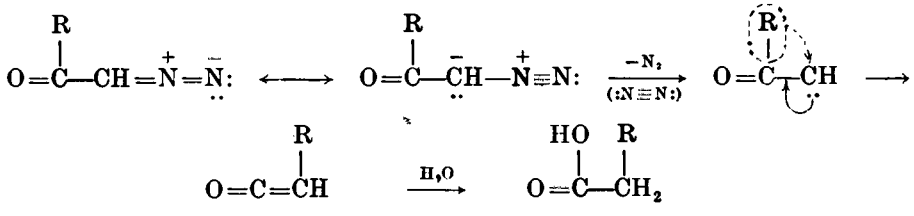
α-Naphthoyl chloride — Diazo ketone — α-Naphthylacetic acid



Sebacoyl chloride — *Bis*-diazo ketone — Decane-1 : 10-dicarboxylic acid

Anisoyl chloride — Diazo ketone — Homoanisic acid

The *mechanism* of the reaction probably involves the production of bivalent carbon during the initial loss of nitrogen : the group R shifts from an adjacent position to this carbon leading to the production of a keten ; the latter then reacts with the solvent to give an acid, an amide or an ester.



α-Naphthylacetic acid from α-naphthoic acid. Prepare α-naphthoyl chloride, b.p. 168°/10 mm., from α-naphthoic acid and phosphorus pentachloride following the procedure described for β-naphthoyl chloride (Section **IV,120**, *Note* 2). Add a solution of 19 g. of α-naphthoyl chloride in anhydrous ether at 5–10° to a solution of diazomethane prepared from 35 g. of nitrosomethylurea (Section **VII,20**) and 500 ml. of anhydrous ether. Keep the reaction mixture at 20–25° for 3–4 hours, then remove the ether under reduced pressure and finally at 30°. The yellow crystalline residue of α-naphthoyldiazomethane weighs 18 g.; it melts at 56° after recrystallisation from benzene - petroleum ether (b.p. 40–60°).

Introduce a solution of 15 g. of the diazo ketone in 100 ml. of dioxan dropwise and with stirring into a mixture of 2 g. of silver oxide (1), 3 g. of sodium thiosulphate and 5 g. of anhydrous sodium carbonate in 200 ml. of water at 50–60°. When the addition is complete, continue the stirring for 1 hour and raise the temperature of the mixture gradually to 90–100°. Cool the reaction mixture, dilute with water and acidify with dilute nitric acid. Filter off the α-naphthylacetic acid which separates and recrystallise it from water. The yield is 12 g., m.p. 130°.

Note.

(1) Prepare the silver oxide by adding a dilute solution of sodium hydroxide to 10 per cent. silver nitrate solution until precipitation is just complete, avoiding an excess of alkali. Wash the precipitate several times by decantation ; finally, filter at the pump and wash well with water.

Ethyl α-naphthylacetate is prepared as follows. To a solution of 10 g. of the diazo ketone in 150 ml. of ethanol at 55–60°, add a small amount of a slurry of silver oxide, prepared from 10 ml. of 10 per cent. aqueous silver nitrate and stirred with 25 ml. of ethanol. As soon as the evolution of nitrogen subsides, introduce more of the silver oxide and continue the process until all the slurry has been added. Reflux the mixture for 15 minutes, add 2–3 g. of decolourising carbon, filter and evaporate the alcohol on a water bath. Distil the residue and collect the ethyl α-naphthylacetate at 176–178°/11 mm.; the yield is 9 g.

Decane-1 : 10-dicarboxylic acid from sebacic acid. Convert sebacic acid into the acid chloride by treatment with phosphorus pentachloride (2 mols) and purify by distillation; b.p. 140–143°/2 mm.: the yield is almost quantitative. Dissolve the resulting sebacoyl chloride in anhydrous ether and add the solution slowly to an ethereal solution of excess of diazomethane (prepared from 50 g. of nitrosomethylurea): allow the mixture to stand overnight. Remove the ether and excess of diazomethane under reduced pressure: the residual crystalline 1 : 8-*bis*-diazoacetyloctane weighs 19·3 g. and melts at 91° after crystallisation from benzene.

Add, with stirring, a solution of 6·8 g. of the *bis*-diazo ketone in 100 ml. of warm dioxan to a suspension of 7·0 g. of freshly precipitated silver oxide in 250 ml. of water containing 11 g. of sodium thiosulphate at 75°. A brisk evolution of nitrogen occurs; after 1·5 hours at 75°, filter the liquid from the black silver residue. Acidify the almost colourless filtrate with nitric acid and extract the gelatinous precipitate with ether. Evaporate the dried ethereal extract: the residue of crude decane-1 : 10-dicarboxylic acid weighs 4·5 g. and melts at 116–117°. Recrystallisation from 20 per cent. aqueous acetic acid raises the m.p. to 127–128°.

Alternatively, treat a solution of 3·9 g. of the *bis*-diazo ketone in 50 ml. of warm dioxan with 15 ml. of 20 per cent. aqueous ammonia and 3 ml. of 10 per cent. aqueous silver nitrate under reflux in a 250 or 500 ml. flask on a water bath. Nitrogen is gently evolved for a few minutes, followed by a violent reaction and the production of a dark brown and opaque mixture. Continue the heating for 30 minutes on the water bath and filter hot: the diamide of decane-1 : 10-dicarboxylic acid is deposited on cooling. Filter this off and dry: the yield is 3·1 g., m.p. 182–184°, raised to 184–185° after recrystallisation from 25 per cent. aqueous acetic acid. Hydrolyse the diamide (1 mol) by refluxing for 2–5 hours with 3*N* potassium hydroxide (4 mols): acidify and recrystallise the acid from 20 per cent. acetic acid. The yield of decane-1 : 10-dicarboxylic acid, m.p. 127–128°, is almost quantitative.

***p*-Methoxyphenylacetic acid (homoanisic acid) from anisic acid.** Prepare anisoyl chloride, m.p. 24°, b.p. 262–263° (decomp.), by treating anisic acid (1 mol) with thionyl chloride (1·5 mols). Add 30 g. of anisoyl chloride to an etheral solution of diazomethane prepared from 38 g. of nitrosomethylurea: allow the solution to stand overnight. Distil off the ether (fume cupboard!) and recrystallise the solid residue from benzene - petroleum ether: the yield of diazo ketone (*p*-methoxy-α-diazoacetophenone), m.p. 90–91°, is 22 g.

Dissolve 20 g. of the diazo ketone in 100 ml. of warm dioxan and treat

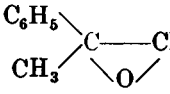
it with 150 ml. of concentrated ammonia solution and 30 ml. of 10 per cent. aqueous silver nitrate solution at 60–70°. Boil the mixture under reflux for 2 hours, cool and precipitate the ***p*-homoanisamide** by the addition of water. Collect the solid and recrystallise it from ethanol. The yield of the pure amide, m.p. 188–189°, is 15 g.

Reflux a mixture of 15 g. of homoanisamide, 30 g. of potassium hydroxide and 300 ml. of ethanol on a water bath for 5 hours. Dilute with 750 ml. of water, evaporate to 75 ml. and acidify to Congo red. Collect the acid and recrystallise it from ethyl alcohol. The yield of *p*-methoxyphenylacetic acid, m.p. 86–87°, is 13 g.

VI,18. THE DARZENS GLYCIDIC ESTER CONDENSATION

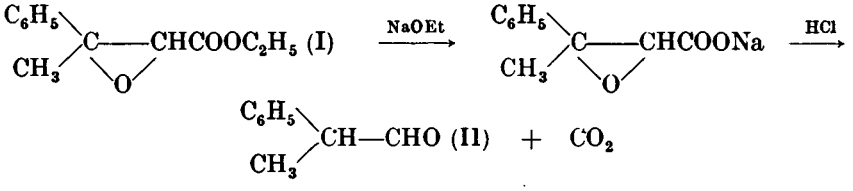
This reaction involves the condensation of an aldehyde or ketone with an α-halo ester in the presence of a basic condensing agent (sodium ethoxide, sodamide, finely divided sodium or potassium *tert.*-butoxide) to give a glycidic (or αβ-epoxy) ester. Thus acetophenone and ethyl chloroacetate yield **phenylmethylglycidic ester** (I) :

$$C_6H_5COCH_3 + ClCH_2COOC_2H_5 + NaNH_2 \longrightarrow$$



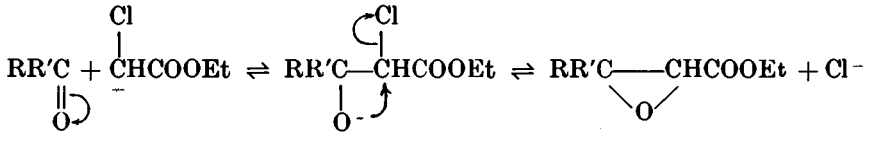
$$+ NH_3 + NaCl$$

The glycidic esters are of interest primarily because upon hydrolysis and decarboxylation they afford aldehydes (if $ClCH_2COOEt$ is used) or ketones (if substituted chloroacetic esters $ClCHRCOOEt$ are employed) having a higher carbon content than the original aldehyde or ketone. Thus (I) gives **α-phenylpropionaldehyde or hydratropaldehyde** (II) :

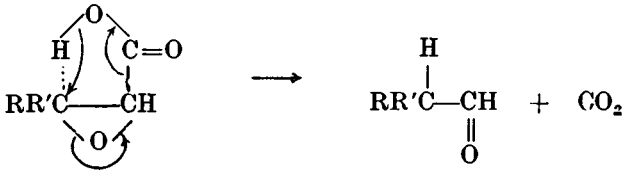


A possible *mechanism* of the Darzens condensation may be written as :

$$ClCH_2COOEt + \bar{N}H_2 \rightleftharpoons Cl\bar{C}HCOOEt + NH_3$$



The decomposition of a glycidic ester to an aldehyde and carbon dioxide may involve the formation of a *quasi* six-membered ring, followed by the shift of three electron pairs :



Phenylmethylglycidic ester. In a 500 ml. three-necked flask, fitted with a mechanical stirrer and a low temperature thermometer, place a mixture of 60 g. (59·5 ml.) of acetophenone, 61·5 g. (54·5 ml.) of ethyl chloroacetate (b.p. 142–143°) and 100 ml. of anhydrous benzene. Add, with stirring, 23·6 g. of finely powdered sodamide (recently prepared) over a period of 2 hours ; maintain the temperature at 15–20° with the aid of external cooling. Ammonia is evolved. Stir for 2 hours at room temperature and pour the reddish mixture upon 350 g. of crushed ice with hand stirring. Separate the organic layer and extract the aqueous layer with 100 ml. of benzene. Wash the combined benzene solutions with three 150 ml. portions of water, the last one containing 5 ml. of acetic acid, and then dry with anhydrous magnesium sulphate. After removal of the benzene by " flash distillation ", distil the residue under reduced pressure from a Claisen flask with fractionating side arm (Figs. *II*, *24*, 3–5). Collect the fraction of b.p. 111–114°/3 mm. as pure phenylmethylglycidic ester ; the yield is 67 g.

α-Phenylpropionaldehyde (hydratropaldehyde). Prepare a solution of sodium ethoxide in a 500 ml. round-bottomed flask from 7·75 g. of clean sodium and 150 ml. of absolute ethanol (Section **III,152**). Add 66·5 g. of phenylmethylglycidic ester slowly and with shaking. Cool the flask externally to 15° and add 8 ml. of water slowly ; much heat is evolved and the sodium salt soon separates. Keep the reaction mixture overnight. Collect the salt by suction filtration, wash it with 25 ml. of ethanol followed by 25 ml. of ether.

Add the salt to dilute hydrochloric acid (prepared from 28 ml. of the concentrated acid and 150 ml. of water) contained in a 500 ml. flask fitted with a reflux condenser. Warm the mixture gently ; carbon dioxide is evolved and an oil separates. Heat on a steam bath for 90 minutes, cool, and extract the oil with 75 ml. of benzene. Wash the extract with 100 ml. of water, and distil the benzene solution under reduced pressure from a Claisen flask. Collect the α-phenylpropionaldehyde at 90–93°/10 mm. ; the yield is 30 g.

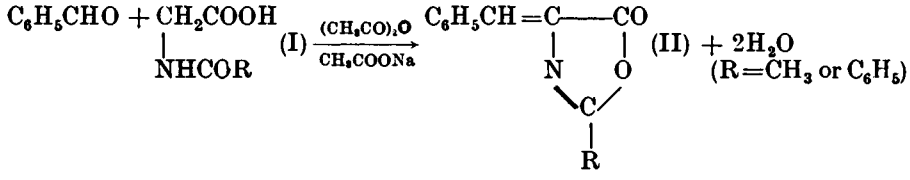
Cognate Preparation

Ethyl α-1-epoxy*cyclo*hexylacetate. Add a mixture of 55 g. (48 ml.) of ethyl chloroacetate and 43 g. of cyclohexanone dropwise to a suspension of finely divided sodium (11 g.) in anhydrous xylene (165 ml.) with stirring and cooling in an ice-salt bath. Regulate the rate of addition so that the temperature of the reaction mixture does not exceed 8°. Pour the resulting dark-red clear solution into water, wash the organic layer repeatedly with water, dry with anhydrous magnesium sulphate, and distil. Collect the glycidic ester at 81–83°/0·04 mm. or at 115–117°/10 mm. The yield is 37 g.

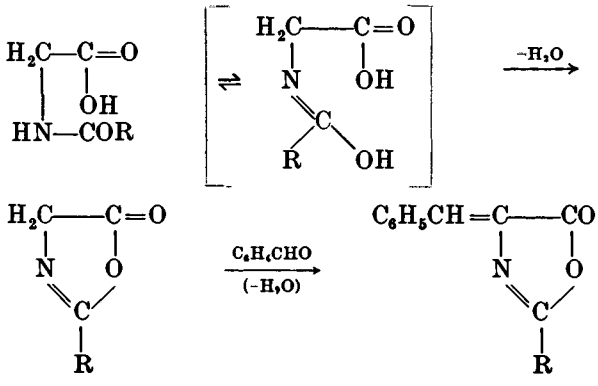
VI,19. THE ERLENMEYER AZLACTONE REACTION

Azlactones (anhydrides of α-acylamino acids) are formed by the condensation of aromatic aldehydes with acyl derivatives of glycine in the presence of acetic anhydride and anhydrous sodium acetate. Thus benzaldehyde and acetyl-

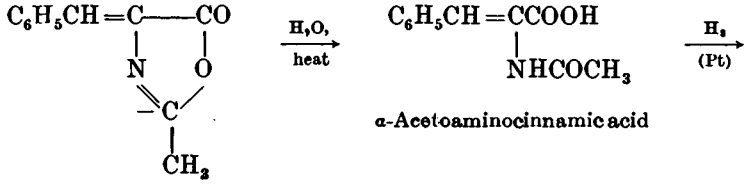
(or benzoyl-)glycine (I) yields the azlactone of α-acetamino- (or α-benzylamino-) cinnamic acid (II)



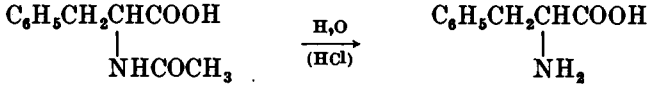
The reaction probably proceeds by an initial cyclisation of the acylaminoacetic acid, followed by a Perkin type of condensation of the aldehyde with the active methylene unit :



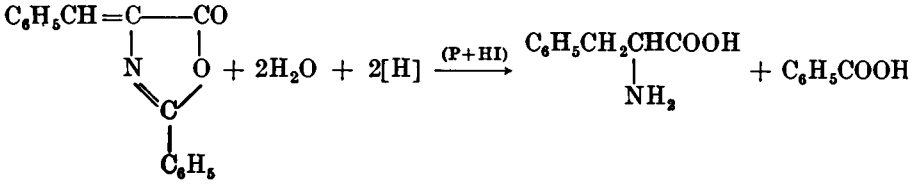
Hydrolysis of the azlactone leads to the acylaminocinnamic acid ; the latter may be be reduced catalytically (Adams PtO_2 catalyst : 40 lb. p.s.i.) and then hydrolysed by hydrochloric acid to the amino acid. Alternatively, the azlactone (say, of α-benzylaminocinnamic acid) may undergo reduction and cleavage with phosphorus, hydriodic acid and acetic anhydride directly to the α-amino acid (***dl*-β-phenylalanine**).



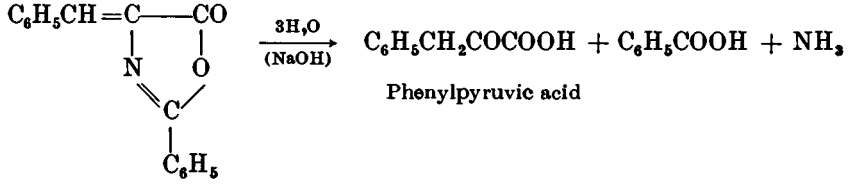
α-Acetoaminocinnamic acid



N-Acetylphenylalanine — *dl*-Phenylalanine



The azlactones may be hydrolysed by strong alkali to α-keto acids, for example:



The benzoic acid may be separated by steam distillation or by saturating the aqueous mixture of sodium salts with sulphur dioxide whilst maintaining the temperature below 40°; the benzoic acid precipitates and can be separated by filtration or extraction with ether. Acidification of the filtrate with hydrochloric acid liberates the pyruvic acid. The pyruvic acid may be oxidised with hydrogen peroxide to the arylacetic acid, for example:

$$C_6H_5CH_2COCOOH + H_2O_2 \longrightarrow C_6H_5CH_2COOH + H_2O + CO_2$$

Acetylglycine. Place 37·5 g. of glycine (Section **III,129**) and 150 ml. of water in a 500 ml. conical flask. Introduce a mechanical stirrer and stir vigorously until the solid has almost completely dissolved. Add 108 g. (100 ml.) of acetic anhydride (95 per cent.) in one portion and stir vigorously for 15–20 minutes; the solution becomes hot and some acetylglycine may crystallise. Cool in an ice box, preferably overnight; collect the precipitate on a Buchner funnel, wash with ice-cold water and dry at 100°. The product weighs 40 g. and melts at 207–208°. Evaporate the combined filtrate and washings to dryness under reduced pressure on a water bath at 50–60°, and recrystallise the residue from 40 ml. of boiling water: collect the solid which separates, wash and dry it as before. The second fraction of acetylglycine weighs 15 g. and melts at 207–208°.

Azlactone of α-acetylaminocinnamic acid. Warm a mixture of 29 g. of acetylglycine, 39·5 g. (37·5 ml.) of redistilled benzaldehyde (Section **IV,115**), 15 g. of anhydrous sodium acetate and 67 g. (62 ml.) of acetic anhydride (95 per cent.) in a 500 ml. conical flask (equipped with a reflux condenser) on a water bath with occasional stirring until solution is complete (10–20 minutes). Boil the resulting solution for 1 hour, cool and leave in a refrigerator overnight. Stir the solid mass of yellow crystals with 60 ml. of cold water, transfer to a Buchner funnel and wash well with cold water. (If the odour of benzaldehyde is still apparent, wash with a little ether.) Recrystallise from carbon tetrachloride or from ethyl acetate - light petroleum. The yield of azlactone, m.p. 150°, is 35 g.

α-Acetoaminocinnamic acid. Boil a mixture of 23·5 g. of the azlactone of α-acetylaminocinnamic acid (the crude product is satisfactory), 90 ml. of water and 225 ml. of acetone in a 500 ml. bolt-head flask under reflux for 4 hours. Remove most of the acetone by distillation on a water bath, dilute the residual solution with 200 ml. of water, heat to boiling for 5–10 minutes and filter through a hot water funnel. Dissolve any crystals which separate from the filtrate by heating, add 5 g. of decolourising carbon, boil for 5 minutes and filter with gentle suction through a warm Buchner funnel, and wash with four 25 ml. portions of boiling water. Place the combined filtrate and washings in a refrigerator overnight. Collect the colourless crystals by suction filtration, wash with about

100 ml. of cold water and dry at 100°. The yield of α-acetoaminocinnamic acid, m.p. 191–192°, is 22 g.

Azlactone of α-benzoylaminocinnamic acid. Place a mixture of 27 g. (26 ml.) of redistilled benzaldehyde, 45 g. of hippuric acid (Section IV,54), 77 g. (71·5) ml. of acetic anhydride and 20·5 g. of anhydrous sodium acetate in a 500 ml. conical flask and heat on an electric hot plate with constant shaking. As soon as the mixture has liquefied completely, transfer the flask to a water bath and heat for 2 hours. Then add 100 ml. of alcohol slowly to the contents of the flask, allow the mixture to stand overnight, filter the crystalline product with suction, wash with two 25 ml. portions of ice-cold alcohol and then wash with two 25 ml. portions of boiling water: dry at 100°. The yield of almost pure azlactone, m.p. 165–166°, is 40 g. Recrystallisation from benzene raises the m.p. to 167–168°.

***dl*-β-Phenylalanine.** In a 1-litre three-necked flask, fitted with a reflux condenser, mechanical stirrer and dropping funnel by means of new corks covered with tin foil, place 25 g. of the azlactone of α-benzoylaminocinnamic acid, 20 g. of purified red phosphorus (Section II,50,*5*) and 135 g. (125 ml.) of acetic anhydride. Add with stirring over a period of 1 hour 125 ml. of hydriodic acid (sp. gr. 1·56; 50 per cent.). Reflux the mixture for 3 hours, cool and filter with suction: wash the unreacted phosphorus on the filter with two 5 ml. portions of glacial acetic acid. Place the filtrate and washings in a 500 ml. Claisen flask supported on a water bath and evaporate to dryness under reduced pressure: collect the distillate (which may be used for another reduction) in a 250 ml. distilling flask cooled in ice. Add 100 ml. of water to the dry residue in the Claisen flask and repeat the evaporation to dryness. Shake the residue in the flask with 150 ml. of water and 150 ml. of ether until solution is complete; separate the aqueous layer and extract it with three 75 ml. portions of ether. Discard the ether extracts. Introduce 2–3 g. of decolourising carbon and a trace of sodium sulphite into the water solution, heat on a water bath until the dissolved ether has been removed, filter, heat the filtrate to boiling and neutralise to Congo red with conc. ammonia solution (sp. gr. 0·88; about 25 ml. are required). When cold, filter the colourless phenylalanine at the pump and wash with two 30 ml. portions of cold water and finally with alcohol; dry at 100°. The yield is 11 g., m.p. 284–288° (decomp.).

VI,20. THE MANNICH REACTION

The Mannich reaction consists in the condensation of formaldehyde with ammonia or a primary or a secondary amine and a compound containing at least one hydrogen atom of pronounced reactivity; the active hydrogen atom may be derived from a methylene group activated by a neighbouring keto group, or from a nitroparaffin, or it may be the o- or *p*-hydrogen atoms in phenols. Thus when acetophenone is boiled in alcoholic solution with formaldehyde and dimethylamine hydrochloride, the Mannich base **β-dimethylaminopropiophenone hydrochloride** (I) is readily formed:

$$C_6H_5COCH_3 + CH_2O + (CH_3)_2NH,HCl \rightarrow C_6H_5COCH_2CH_2N(CH_3)_2,HCl\,(I) + H_2O$$

The exact *mechanism* of the reaction is not known with certainty. It has

been suggested that the reaction may involve the intermediate formation of a methylolamine, which under the influence of acids is converted into a reactive methylene-ammonium salt. The latter condenses either with the ketone itself, or with the enol form of the ketone formed catalytically by the acid present.

$$(CH_3)_2NH + CH_2O \longrightarrow (CH_3)_2N{-}CH_2OH \xrightarrow{H^+} (CH_3)_2\overset{+}{N}{=}CH_2$$

$$(CH_3)_2\overset{+}{N}{=}CH_2 \quad H{-}CH_2 \quad \longrightarrow \quad (CH_3)_2N{-}CH_2{-}CH_2 \quad + H^+$$
$$\qquad\qquad\quad | \qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad COC_6H_5 \qquad\qquad\qquad COC_6H_5$$

$$(CH_3)_2\overset{+}{N}{=}CH_2 \quad CH_2 \quad \longrightarrow \quad (CH_3)_2N{-}CH_2{-}CH_2 \quad + H^+$$
$$\qquad\qquad\quad \| \qquad\qquad\qquad\qquad\quad |$$
$$\qquad\quad C_6H_5C{-}O{-}H \qquad\qquad\quad C_6H_5C{=}O$$

The Mannich bases have many synthetical applications. These include :—

1. Heating or steam distillation affords ethylenic compounds ; thus (I) yields phenyl vinyl ketone (II) :

$$C_6H_5COCH_2CH_2N(CH_3)_2HCl \longrightarrow C_6H_5COCH{=}CH_2\ (II) + (CH_3)_2NH,HCl$$

Reduction of the ethylenic compound gives a ketone, propiophenone (III), with one more methylene group than the ketone used in the original preparation :

$$C_6H_5COCH{=}CH_2 + 2H \longrightarrow C_6H_5COCH_2CH_3\ (III)$$

2. The β-substituted amino ketones can be reduced readily to the more stable β-dialkylamino alcohols, many of which are useful local anaesthetics. Thus the local anaesthetic Tutocaine is made from the Mannich base derived from formaldehyde, methyl ethyl ketone and dimethylamine, followed by reduction and conversion into the *p*-aminobenzoate :

$$CH_3COCH_2CH_3 + CH_2O + (CH_3)_2NH,HCl \longrightarrow CH_3COCHCH_2N(CH_3)_2,HCl \longrightarrow$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_3$$

$$p\text{-}H_2N{-}C_6H_4{-}CO{-}O{-}CH{-}CHCH_2N(CH_3)_2,HCl$$
$$\qquad\qquad\qquad\qquad\qquad\quad |\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad H_3C \quad CH_3$$

3. Tertiary amines capable of eliminating a secondary amine to form a conjugated system can react with hydrogen cyanide to form γ-keto nitriles by amine replacement. Thus (I) yields β-benzoylpropionitrile (IV) :

$$C_6H_5COCH_2CH_2N(CH_3)_2,HCl\ (I) + KCN \longrightarrow C_6H_5C(OH)CH_2CH_2N(CH_3)_2 + KCl$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CN$$

$$\longrightarrow C_6H_5COCH_2CH_2CN\ (IV) + HN(CH_3)_2$$

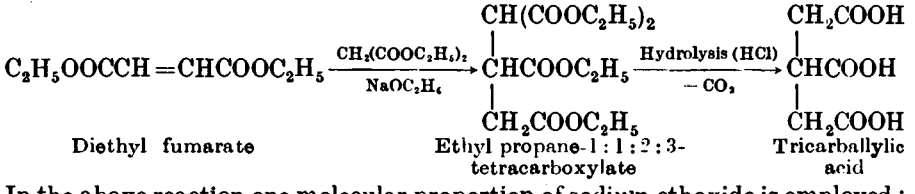
β-Dimethylaminopropiophenone hydrochloride. Place 26·5 g. of dry dimethylamine hydrochloride, 10 g. of powdered paraformaldehyde and 30 g. (29·3 ml.) of acetophenone (Section **IV,136**) in a 250 ml. round-bottomed flask attached to a reflux condenser. Introduce 40 ml. of 95 per cent. ethanol to which 0·5 ml. of concentrated hydrochloric acid has been added, and reflux the mixture on a water bath for 2 hours ; the reaction mixture should ultimately be almost clear and homogeneous. Filter the yellowish solution (if necessary) through a hot water funnel :

transfer the filtrate to a 500 ml. wide-mouthed conical flask and, while still warm, add 200 ml. of acetone. Allow to cool to room temperature and leave in a refrigerator overnight. Filter the crystals at the pump, wash with 10 ml. of acetone, and dry for 6 hours at 40–50° : the yield of crude product, m.p. 152–155°, is 38 g. Recrystallise the crude product by dissolving in 45 ml. of hot rectified spirit and slowly adding 225 ml. of acetone to the solution ; collect the solid which separates by suction filtration and dry at 70°. The purified material melts at 155–156° and the recovery is about 90 per cent.

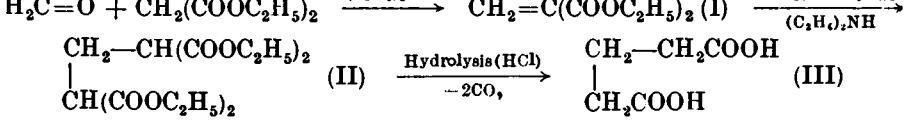
β-Benzoylpropionitrile. To a mixture of 21·4 g. of β-dimethylaminopropiophenone hydrochloride, 13·0 g. of potassium cyanide in a 500 ml. flask, add 260 ml. of boiling water ; heat the heterogeneous mixture under reflux for 30 minutes. Part of the dimethylamine, which is eliminated in the reaction, distils : collect this in dilute hydrochloric acid. Cool the reaction mixture in ice ; the oil solidifies and crystals form from the aqueous layer. Collect the solid (crude β-benzoylpropionitrile, 10·5 g.) by suction filtration and recrystallise it from benzene - light petroleum (b.p. 40–60°) ; it separates as almost colourless blades, m.p. 76°.

VI,21. THE MICHAEL REACTION

The addition of active methylene compounds (ethyl malonate, ethyl acetoacetate, ethyl phenylacetate, nitromethane, acrylonitrile, etc.) to the αβ-double bond of a conjugated unsaturated ketone, ester or nitrile in the presence of a basic catalyst (sodium ethoxide, piperidine, diethylamine, etc.) is known as the **Michael reaction** or **Michael addition.** The reaction may be illustrated by the addition of ethyl malonate to ethyl fumarate in the presence of sodium ethoxide ; hydrolysis and decarboxylation of the addendum (**ethyl propane-1 : 1 : 2 : 3-tetracarboxylate**) yields **tricarballylic acid :**



In the above reaction one molecular proportion of sodium ethoxide is employed ; this is Michael's original method for conducting the reaction, which is reversible and particularly so under these conditions, and in certain circumstances may lead to apparently abnormal results. With smaller amounts of sodium alkoxide (1/5 mol or so : the so-called catalytic method) or in the presence of secondary amines, the equilibrium is usually more on the side of the adduct, and good yields of adducts are frequently obtained. An example of the Michael addition of the latter type is to be found in the formation of **ethyl propane-1 : 1 : 3 : 3-tetracarboxylate** (II) from formaldehyde and ethyl malonate in the presence of diethylamine. Ethyl methylene-malonate (I) is formed intermediately by the simple Knoevenagel reaction and this is followed by the Michael addition. Acid hydrolysis of (II) gives **glutaric acid** (III).



It is of interest to note that the preparation of dimethyldihydroresorcinol (also named dimedone and methone ; Section VII,15) involves an initial Michael addition to mesityl oxide, followed by an internal Claisen condensation.

The *mechanism* of the Michael reaction probably follows the following course. Writing $RCH{=}CHCOOC_2H_5$ for $C_2H_5OOCCH{=}CHCOOC_2H_5$ and B for $\bar{O}C_2H_5$ or $(C_2H_5)_2NH$ for the sake of simplicity, we have :

(i) $$CH_2(COOC_2H_5)_2 + B \rightleftharpoons \bar{C}H(COOC_2H_5)_2 + BH^+$$

(ii) $$RCH{=}\overset{\delta+}{C}H{-}\overset{\delta-}{C}H{-}\overset{\overset{O^{\delta-}}{\|}}{C}{-}OC_2H_5 + \bar{C}H(COOC_2H_5)_2 \rightleftharpoons RCH{-}CH{=}\overset{\overset{O^-}{|}}{C}{-}OC_2H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH(COOC_2H_5)_2$$

(iii) $$RCH{-}\overset{\delta-}{C}H{=}\overset{\overset{O^-}{|}}{C}{-}OC_2H_5 + BH^+ \rightleftharpoons RCH{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 + B$$
$$\qquad\quad CH(COOC_2H_5)_2 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH(COOC_2H_5)_2$$

Ethyl propane-1 : 1 : 2 : 3-tetracarboxylate. In a 1-litre three-necked flask, fitted with an efficient reflux condenser, mechanical stirrer and a dropping funnel, prepare a solution of sodium ethoxide from 18·4 g. of clean sodium and 200 g. (253 ml.) of super-dry ethyl alcohol (see Section II,47,5). Cool the flask and add, with stirring, 160 g. (151 ml.) of redistilled diethyl malonate through the condenser. Warm the mixture gently on a water bath and introduce 140 g. (131·5 ml.) of redistilled diethyl fumarate (1) from the dropping funnel at such a rate that the mixture boils gently. When the addition is complete, boil for 1 hour, cool and add 50 g. (47·5 ml.) of glacial acetic acid. Distil off most of the alcohol on the water bath under slightly reduced pressure and pour the residue into sufficient distilled water to dissolve all the solid. Separate the ester layer : extract the aqueous layer with four 25 ml. portions of carbon tetrachloride. Wash the combined ester and carbon tetrachloride extracts twice with 25 ml. of water. Distil off the carbon tetrachloride under atmospheric pressure through a short column (the moisture is carried over with the solvent) and distil the residue under reduced pressure. Collect the ethyl propane-1 : 1 : 2 : 3-tetracarboxylate at 182–184°/8 mm. The yield is 250 g.

Note.

(1) The diethyl fumarate is readily prepared as follows. Reflux a mixture of 145 g. of fumaric acid (Section III,143), 185 g. (236 ml.) of absolute ethanol, 450 ml. of benzene and 20 g. of concentrated sulphuric acid for 12 hours. Pour into a large volume of water, separate the benzene layer, wash successively with water, saturated sodium bicarbonate solution and water, dry with anhydrous magnesium sulphate, and remove the solvent on a steam bath. Distil the residue and collect the diethyl fumarate at 213–215° : the yield is 150 g.

Tricarballylic acid. Place 228 g. (204 ml.) of ethyl propane-1 : 1 : 2 : 3-tetracarboxylate and 240 ml. of 1 : 1-hydrochloric acid in a 1-litre three-necked flask, fitted with a mechanical stirrer and a fractionating column with condenser set for downward distillation ; attach a receiver with side tube to the condenser and connect the side tube to a wash bottle containing water. Boil the mixture, with continual stirring, at such a rate that the

alcohol is removed as fast as it is formed, but without undue removal of water from the flask. The progress of the reaction may be followed from the rate at which carbon dioxide passes through the wash bottle. When the temperature at the head of the column approaches 100°, adjust the heating of the flask so that very little liquid distils over: continue the heating until the evolution of carbon dioxide ceases (*ca.* 12 hours). Disconnect the flask from the stirrer and column, and distil the contents as completely as possible on the steam bath under reduced pressure (water pump): remove the residual moisture and hydrochloric acid by drawing a slow stream of air (use a tube leading to the bottom of the flask) through whilst still heating on a steam bath and maintaining a partial vacuum. Dissolve the residue in distilled water, filter the solution through a short column of decolourising carbon and again evaporate to dryness under reduced pressure. Grind the dry residue to a fine powder, mix it to a paste with dry ether, filter by suction, wash with a little anhydrous ether, and dry in a steam oven. The resulting tricarballylic acid, m.p. 160–161°, is practically pure and weighs 118 g.

Ethyl propane-1 : 1 : 3 : 3-tetracarboxylate. Cool a mixture of 320 g. (302 ml.) of redistilled diethyl malonate and 80 g. of 40 per cent. formaldehyde solution ("formalin") contained in a 1-litre round-bottomed flask to 5° by immersion in ice, and add 5 g. (7 ml.) of diethylamine. Keep the mixture at room temperature for 15 hours and then heat under a reflux condenser on a boiling water bath for 6 hours. Separate the aqueous layer, dry the organic layer with anhydrous magnesium sulphate, and distil under reduced pressure. Collect the ethyl 1 : 1 : 3 : 3-tetracarboxylate at 200–215°/20 mm. The yield is 250 g.

Glutaric acid. Heat a mixture of 125 g. of the preceding ester and 250 ml. of 1 : 1-hydrochloric acid under reflux with stirring in a 1-litre three-necked flask equipped with a mechanical stirrer and reflux condenser (the third neck is stoppered). Continue the heating until the mixture becomes homogeneous (6–8 hours). Evaporate the contents of the flask to dryness on a steam bath, transfer the residual glutaric acid to a Claisen flask and distil under reduced pressure (compare Fig. *II*, *19*, 4). Collect the fraction boiling at 185–195°/10 mm.: it crystallises on cooling. Moisten with a little water (to convert any glutaric anhydride present into the acid), heat gently and dry at 30°. Recrystallise from benzene; the resulting practically pure glutaric acid, m.p. 96–97° (compare Section **III,158**) weighs 40 g.

VI,22. CYANOETHYLATION

Many inorganic and organic compounds possessing labile hydrogen atoms add acrylonitrile readily with the formation of compounds containing a cyancethyl grouping (—$CH_2.CH_2.CN$). This reaction is usually known as *cyanoethylation*:

$$R.H + CH_2{=}CH.CN \xrightarrow[\text{catalyst}]{\text{Basic}} R.CH_2.CH_2.CN$$

Typical compounds which undergo cyanoethylation include the following:

1. Compounds containing one or more —OH or —SH groups, such as water, alcohols, phenols, oximes, hydrogen sulphide and thiols.

2. Compounds containing one or more —NH— groups, *e.g.*, ammonia, primary and secondary amines, hydrazines, hydroxylamines and amides.

3. Ketones or aldehydes possessing a —CH—, $—CH_2—$, or $—CH_3$ group adjacent to the carbonyl group.

4. Compounds such as malonic esters, malonamide and cyanoacetamide, in which a —CH— or $—CH_2—$ group is situated between $—CO_2R$, —CN, or —CONH— groups.

The cyanoethylation reaction, except with certain amines, usually requires the presence of an alkaline catalyst (0·5 to 5 percent. of the weight of acrylonitrile) such as the hydroxides, alkoxides and amides of sodium and potassium and the strongly basic quaternary ammonium hydroxides, particularly benzyltrimethylammonium hydroxide (Triton B); the last-named are very effective because of their solubility in organic solvents. Many of the reactions are vigorously exothermic and require cooling to prevent excessive polymerisation of the acrylonitrile; the addition of inert solvents, such as benzene, dioxan and pyridine, may moderate the reaction. It is frequently advisable to dissolve or disperse the catalyst in the hydrogen donor, with or without the use of an inert solvent, and to add the acrylonitrile gradually while controlling the temperature of the reaction.

Anion exchange resins of the quaternary ammonium hydroxide type (*e.g.*, De-Acidite FF, IRA-400 or Dowex I) are strong bases and are useful catalysts for the cyanoethylation of alcohols and possibly of other active hydrogen compounds.

Experimental details are given for the cyanoethylation of primary alcohols and of secondary aliphatic amines:

$$R.OH + CH_2{=}CH.CN \longrightarrow RO.CH_2.CH_2.CN \text{ (β-alkoxypropionitrile)}$$

$$R_2NH + CH_2{=}CH.CN \longrightarrow R_2N.CH_2.CH_2.CN \text{ (β-dialkylaminopropionitrile)}$$

and also of substituted malonic esters:

$$R.CH(CO_2Et)_2 + CH_2{=}CH.CN \longrightarrow$$

$$\underset{\substack{\vert\\ CH_2.CH_2.CN}}{R.C(CO_2Et)_2} \xrightarrow[HBr]{48 \text{ per cent.}} \underset{\substack{\vert\\ CH_2.CH_2.CO_2H}}{R.CH.CO_2H}$$

Et alkyl (aryl)-2-cyanoethylmalonate

α-Alkyl (aryl) glutaric acid

The last-named reaction provides an excellent method for the preparation of α-substituted glutaric acids: the intermediate alkyl (aryl) -2-cyanoethylmalonate is both hydrolysed and decarboxylated readily by boiling with an excess of 48 per cent. hydrobromic acid solution.

The *mechanism* of cyanoethylation is similar to that given in Section VI,21 for the Michael reaction. Acrylonitrile is the simplest αβ-unsaturated organic nitrile.

$$H_2\overset{\delta+}{C}{=}CH{-}C{\equiv}\overset{\delta-}{N}$$

and the various condensations with active hydrogen compounds are merely Michael additions: the active hydrogen is replaced by the cyanoethyl group. Compounds containing hydrogen insufficiently active to undergo Michael condensations with the usual acceptors react readily with acrylonitrile, *e.g.*, alcohols, ammonia, amines, etc., as detailed above. Cyanoethylation reactions usually proceed until all active hydrogen atoms are used up.

Pure acrylonitrile boils at 78°. *Acrylonitrile vapour is highly toxic;* it should therefore be handled with due caution and all operations with it should be conducted in a fume cupboard provided with an efficient draught. Acrylonitrile forms an azeotropic mixture with water, b.p. 70·5° (12·5 per cent. water). The commercial product may contain the polymer; it should be redistilled before use and the fraction b.p. 76·5–78° collected separately as a colourless liquid.

β-Ethoxypropionitrile, $C_2H_5O.CH_2.CH_2.CN$. Place 25 ml. of 2 per cent. aqueous sodium hydroxide and 26 g. (33 ml.) of ethyl alcohol in a 250 ml. reagent bottle, add 26·5 g. (33 ml.) of acrylonitrile and close the mouth of the bottle with a tightly-fitting cork. Shake the resulting clear homogeneous liquid in a shaking machine for 2 hours. During the first 15 minutes the temperature of the mixture rises 15° to 20° and thereafter falls gradually to room temperature; two liquid layers separate after about 10 minutes. Remove the *upper* layer and add small quantities of 5 per cent. acetic acid to it until neutral to litmus; discard the lower aqueous layer. Dry with anhydrous magnesium sulphate, distil and collect the β-ethoxypropionitrile at 172–174°. The yield is 32 g.

The technique for using an *anion exchange resin as catalyst* is as follows. Regenerate the resin (De-Acidite FF or IRA-400) by washing it on a Buchner funnel with 5 per cent. sodium hydroxide solution (5–6 times the volume of the resin); rinse the resin with distilled water until the washings are neutral and dry in the air. In a 500 ml. three-necked flask equipped with a reflux condenser, stirrer and a dropping funnel, place 25 g. of the regenerated resin and 46 g. (58·5 ml.) of ethyl alcohol. Immerse the flask in an ice bath to control the subsequent initial exothermic reaction and to hold the temperature below 15–20° throughout the experiment. Add 67 g. (85 ml.) of redistilled acrylonitrile slowly to the well-stirred mixture in the flask over a period of 1–2 hours; continue the stirring for a further 1·5 hours. Separate the resin by filtration. Distil the filtrate at atmospheric pressure to 100° in order to remove unreacted acrylonitrile and ethanol, and the residue under reduced pressure. Collect the β-ethoxypropionitrile at 77–78°/25 mm. The yield is about 100 g.

β-*n*-Propoxypropionitrile, $C_3H_7{}^{\alpha}O.CH_2.CH_2.CN$. Introduce 0·15 g. of potassium hydroxide and 33 g. (41 ml.) of dry *n*-propyl alcohol into a 150 ml. bolt-head flask, warm gently until the solid dissolves, and then cool to room temperature. Clamp the neck of the flask and equip it with a dropping funnel, a mechanical stirrer and a thermometer (suitably supported in clamps). Introduce from the dropping funnel, with stirring, 26·5 g. (33 ml.) of pure acrylonitrile over a period of 25–30 minutes (1 drop every *ca.* 2 seconds). Do not allow the temperature of the mixture to rise above 35–45°; immerse the reaction flask in a cold water bath, when necessary. When all the acrylonitrile has been added, heat under reflux in a boiling water bath for 1 hour; the mixture darkens. Cool, filter and distil. Collect the β-*n*-propoxypropionitrile at 187–189°. The yield is 38 g.

β-Diethylaminopropionitrile, $(C_2H_5)_2N.CH_2.CH_2.CN$. Mix 42·5 g. (60 ml.) of freshly-distilled diethylamine and 26·5 g. (33 ml.) of pure acrylonitrile in a 250 ml. round-bottomed flask fitted with a reflux

condenser. Heat at 50° in a water bath for 10 hours and then allow to stand at room temperature for 2 days. Distil off the excess of diethylamine on a water bath, and distil the residue from a Claisen flask under reduced pressure. Collect the β-diethylaminopropionitrile at 75–77°/11 mm.; the yield is 54 g.

β-Di-*n*-butylaminopropionitrile, $(C_4H_9^{\alpha})_2N.CH_2.CH_2.CN$. Proceed as for the diethyl compound using 64·5 g. (85 ml.) of redistilled di-*n*-butylamine and 26·5 g. (33 ml.) of pure acrylonitrile. After heating at 50° and standing for 2 days, distil the entire product under diminished pressure (air bath); discard the low boiling point fraction containing unchanged di-*n*-butylamine and collect the β-di-*n*-butylaminopropionitrile at 120-122°/10 mm. The yield is 55 g.

***n*-Propylglutaric acid.** Add 8·0 g. (10·0 ml.) of redistilled acrylonitrile to a stirred solution of ethyl *n*-propyl malonate (30·2 g.) (Section **III,154**) and of 30 per cent. methanolic potassium hydroxide (4·0 g.) in *tert.*-butyl alcohol (100 g.). Keep the reaction mixture at 30°–35° C. during the addition and stir for a further 3 hours. Neutralise the solution with dilute hydrochloric acid (1 : 4), dilute with water and extract with ether. Dry the ethereal extract with anhydrous magnesium sulphate and distil off the ether: the residue (ethyl *n*-propyl-2-cyanoethylmalonate; 11 g.) solidifies on cooling in ice, and melts at 31°–32° after recrystallisation from ice-cold ethyl alcohol. Boil the cyanoethyl ester (10 g.) under reflux with 40 ml. of 48 per cent. hydrobromic acid solution for 8 hours, and evaporate the solution almost to dryness under reduced pressure. Add sufficient water to dissolve the ammonium bromide, extract several times with ether, dry the ethereal extract, and distil off the solvent. The residual oil (7·5 g.) soon solidifies: upon recrystallisation from water, pure *n*-propylglutaric acid, m.p. 70°, is obtained.

VI,23. THE SCHMIDT REACTION OR REARRANGEMENT

The conversion of a carboxylic acid into an amine by treatment with hydrazoic acid in concentrated sulphuric acid is known as the **Schmidt reaction or rearrangement**;

$$RCOOH + HN_3 \xrightarrow{H_2SO_4} RNH_2 + CO_2 + N_2$$

Other carbonyl compounds are within the scope of the reaction; ketones give amides, and aldehydes yield nitriles and formyl derivatives of amines:

$$RCOR' + HN_3 \xrightarrow{H_2SO_4} RCONHR' + N_2$$

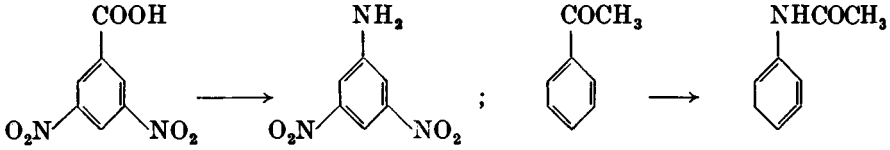
$$RCHO + HN_3 \xrightarrow{H_2SO_4} RCN + RNH.CHO + N_2$$

In the alkyl aryl ketones, the aryl groups migrate preferentially, yielding *N*-aryl amides.

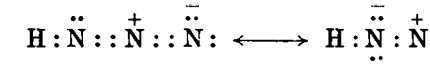
The Schmidt reaction (as applied to a carboxylic acid) is therefore a method for the degradation of an acid to an amine with one less carbon atom and in this respect resembles the Hofmann rearrangement (see discussion prior to Section **III,16**) of acid amides. The yields are often higher and the carboxylic acid may be employed directly. The disadvantages are the toxicity of the reagent (usually a 4–10 per cent. solution of hydrazoic acid in chloroform or benzene) thus necessitating rigorous precautions, and also the possibility of explosion during the

reaction ; the latter hazard is considerably reduced under controlled laboratory conditions. The use of the toxic hydrazoic acid may be avoided by generating the acid *in situ* by adding sodium azide in small portions to a stirred solution of the carbonyl compound in chloroform and concentrated sulphuric acid. The reaction cannot, of course, be used for carboxylic acids which are unstable to concentrated sulphuric acid.

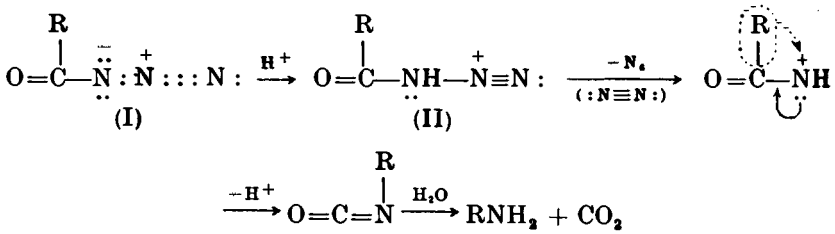
The reaction is illustrated by the conversion of 3 : 5-dinitrobenzoic acid into **3 : 5-dinitroaniline**, and of acetophenone into acetanilide :



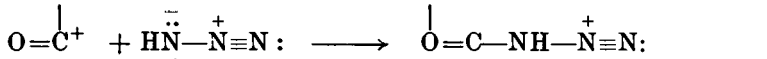
When considering the *mechanism* of the reaction, it must be realised that hydrazoic acid is best formulated as a resonance hybrid



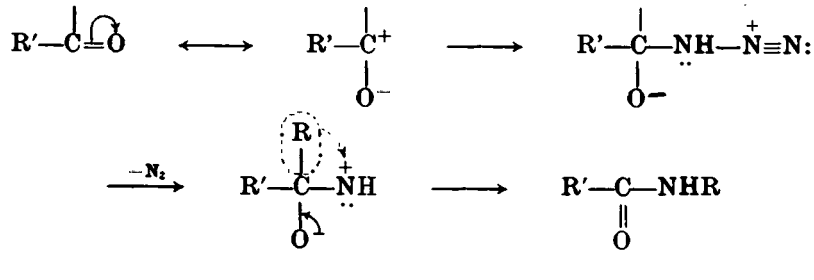
in which the second form is the more important. The carboxylic acid and hydrazoic acid may condense in the presence of sulphuric acid to give an acyl azide (I). Since sulphuric acid considerably accelerates the decomposition of the acyl azide, it is probable that the loss of nitrogen occurs more easily in the conjugate acid of (I), *i.e.*, in (II). The product is a nitrogenium ion with a sextet of electrons (electronically deficient nitrogen) ; rearrangement occurs to an *isocyanate*, which is decomposed by water to an amine and carbon dioxide :



The conjugate acid (II) may also be formed by the addition of hydrazoic acid to an acylium (carbonium) ion:

or 

For ketones, the mechanism may be written :



3 : 5-Dinitroaniline from 3 : 5-dinitrobenzoic acid. Place a solution of 50 g. of 3 : 5-dinitrobenzoic acid (Section **IV,168**) in 90 ml. of 10 per cent. oleum and 20 ml. of concentrated sulphuric acid in a 1-litre three-necked flask equipped with a reflux condenser, mechanical stirrer, a dropping funnel, and thermometer (*FUME CUPBOARD!*). Add 100 ml. of chloroform and raise the temperature to 45°. Stir rapidly and add 17·5 g. of sodium azide in small portions whilst maintaining the temperature at 35–45°. The reaction is accompanied by foaming, which usually commences after about 3 g. of sodium azide has been introduced. After all the sodium azide has been added raise the temperature so that the chloroform refluxes vigorously and maintain this temperature for 3 hours. Then cool the reaction mixture, pour it cautiously on to 500 g. of crushed ice, and dilute with 3 litres of water. After 1 hour, separate the yellow solid by filtration at the pump, wash well with water and dry at 100°. The yield of 3 : 5-dinitroaniline, m.p. 162–163°, is 39 g. The m.p. is unaffected by recrystallisation from dilute alcohol.

Acetanilide from acetophenone. Dissolve 12 g. of acetophenone in 100 ml. of glacial acetic acid containing 10 g. of concentrated sulphuric acid. To the stirred solution at 60–70°, add 9·8 g. of sodium azide in small portions at such a rate that the temperature does not rise above 70°. Stir the mixture with gentle heating until the evolution of nitrogen subsides (2–3 hours) and then allow to stand overnight at room temperature. Pour the reaction mixture on to 300 g. of crushed ice, filter the solid product, wash it with water and dry at 100°. The yield of crude acetanilide, m.p. 111–112°, is 13 g. Recrystallisation from water raises the m.p. to 114°.

VI,24. THE STOBBE CONDENSATION

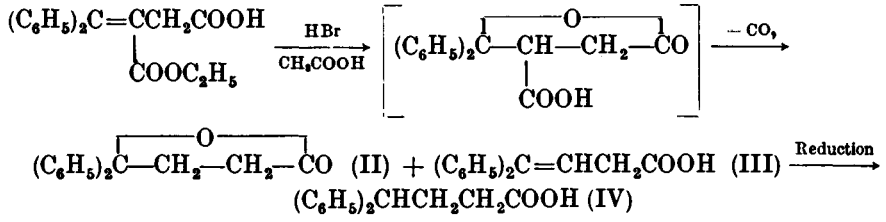
The condensation of aldehydes and ketones with succinic esters in the presence of sodium ethoxide is known as the **Stobbe condensation.** The reaction with sodium ethoxide is comparatively slow and a little reduction of the ketonic compound to the carbinol usually occurs ; a shorter reaction time and a better yield is generally obtained with the more powerful condensing agent potassium *tert.*-butoxide or with sodium hydride. Thus benzophenone condenses with diethyl succinate in the presence of potassium *tert.*-butoxide to give a 94 per cent. yield of **β-carbethoxy-γγ-diphenylvinylacetic acid** {(I) is the potassium salt} :

$$(C_6H_5)_2C{=}O + \begin{matrix} CH_2COOC_2H_5 \\ | \\ CH_2COOC_2H_5 \end{matrix} + KOC(CH_3)_3 \longrightarrow$$

$$\begin{matrix} (C_6H_5)_2C{=}CCOOC_2H_5 \\ | \\ CH_2COOK \end{matrix} \quad (I) + (CH_3)_3COH + C_2H_5OH$$

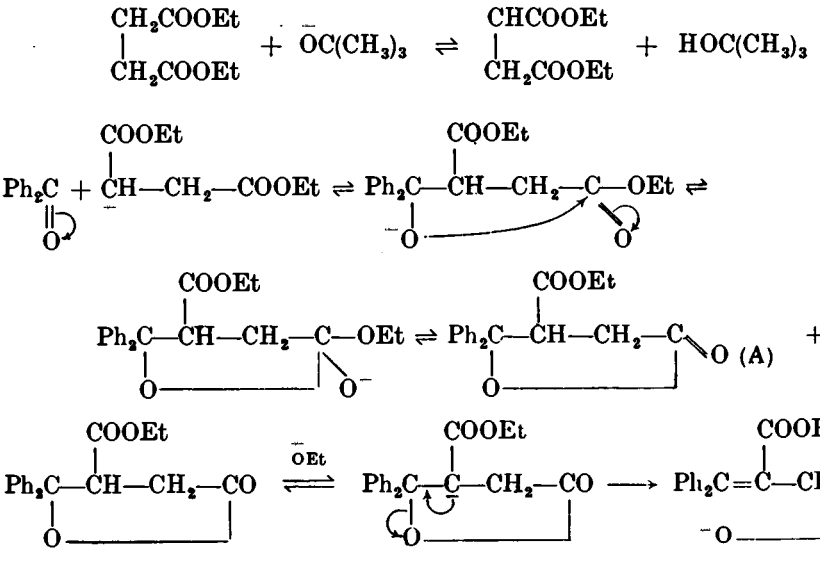
A simple application of the reaction may be mentioned. Refluxing of (I) with 48 per cent. hydrobromic acid and glacial acetic acid leads to hydrolysis and decarboxylation and the production of a mixture of the γ-lactone {γγ-diphenylbutyrolactone (II)} and the isomeric unsaturated acid {γγ-diphenylvinylacetic acid (III)} ; reduction by the Clemmensen method or catalytically

(copper-chromium oxide) affords the saturated acid {γγ-diphenylbutyric acid (IV)} :



The Stobbe condensation thus provides a method for introducing a propionic acid residue at the site of a carbonyl group.

The following *mechanism* for the reaction has been suggested. It postulates formation of an intermediate paraconic ester (A) ; the irreversible alkoxide cleavage of this cyclic ester drives the reaction to completion :



β-Carbethoxy-γγ-diphenylvinylacetic acid. *Potassium* tert.*-butoxide method.* Fit up the apparatus shown in Fig. *VI, 24,* 1 ; all parts of the apparatus must be thoroughly dry. Attach a 500 ml. round-bottomed flask by a ground glass joint (not shown) to the reflux condenser (coil type) and connect the top to a three-way stopcock leading through (A) to a cylinder of nitrogen with fine control valve and a mercury trap, and through (B) to a water filter pump. Thoroughly dry the flask and condenser by warming with a gentle flame whilst the system is under reduced pressure (stopcock turned to B to connect filter pump). Admit dry nitrogen (1) to the apparatus by turning the stopcock slowly to position A while nitrogen is bubbled through the mercury trap. Charge the cooled flask rapidly with 45 ml. of anhydrous *tert.*-butyl alcohol (2) and 2·15 g. of potassium (3) and reconnect it to the apparatus. Stop the stream of nitrogen, close the screw clip and boil the mixture under reflux until the

potassium dissolves completely (*ca.* 4 hours) ; the hydrogen evolved passes through the mercury trap. Allow the solution to cool to room temperature whilst admitting nitrogen to equalise the pressure. Disconnect the flask just long enough to introduce 9·11 g. of pure benzophenone and 13·05 g. (12·55 ml.) of redistilled diethyl succinate. Evacuate the system (until the alcohol commences to boil) and fill it with nitrogen. With the stop-cock in position A and the screw clip closed, reflux the mixture gently for 30 minutes; some of the potassium salt of the half ester may precipitate. Cool the flask in ice, acidify with 10 ml. of cold 1 : 1-hydrochloric acid and distil under reduced pressure (water pump) until most of the alcohol is removed. Add water to the residue, extract several times with ether, wash the combined ethereal extracts with *N* ammonia solution until a test portion gives no precipitate upon acidification. Extract the combined alkaline solutions once with a fresh portion of ether, and add the aqueous solution to an excess of dilute hydrochloric acid; the final mixture should still be acidic to Congo red. Collect the crystalline half-ester by filtration at the pump, wash it with water and dry at 100°. The yield is 14·5 g., m.p. 122–125°. Recrystallise by dissolving in about 40 ml. of warm benzene and adding an equal volume of petroleum ether (b.p. 40–60°) ; 13·5 g. of the colourless half-ester, m.p. 125–126°, are obtained.

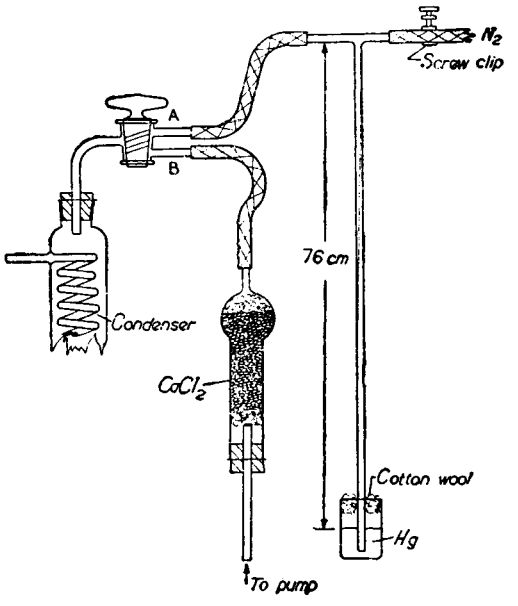


Fig. *VI*, *24*, 1.

Notes.

(1) Dry the cylinder nitrogen by passing through a train consisting of (*a*) a trap, (*b*) a wash bottle containing concentrated sulphuric acid, and (*c*) a drying tube containing fresh soda lime.

(2) Prepare anhydrous *tert.*-butyl alcohol by refluxing the commercial product with sodium (*ca.* 4 g. per 100 ml.) until the metal is about two-thirds dissolved and then distilling. Free metal should be present during the distillation.

(3) *Great care must be taken in the handling of potassium* and the following precautions must be rigidly observed. Cut the metal under xylene (which has been dried over sodium wire) contained in a mortar : do not use a beaker or a crystallising dish because it is too fragile. Cut off the outer oxide-coated surface and *immediately* transfer the scraps with tweezers to a second mortar containing dry xylene. Weigh the freshly-cut potassium by removing it with tweezers to a filter paper, blot it rapidly, and introduce it into a tared beaker containing dry xylene. Introduce the weighed potassium into the reaction mixture : take adequate precautions with regard to the exclusion of air and moisture, rate of addition, etc., depending upon the reaction involved.

The scraps of potassium should not be stored : they must be decomposed immediately by transferring the mortar to the rear of an empty fume cupboard (hood) and adding *tert.*-butyl alcohol (*not* methyl or ethyl alcohol) in small portions from a dropper pipette at such a rate that the reaction does not become vigorous. Keep a square sheet of asbestos, large enough to cover the mortar, at hand ; if the liquid should catch fire, it may be extinguished easily by covering the mortar with the asbestos sheet. Add sufficient *tert.*-butyl alcohol to react completely with all the potassium. Any specks of potassium remaining in the first mortar used for the cutting operation or small scraps that adhere to the knife must be disposed of in the fume cupboard by cautious treatment with *tert.*-butyl alcohol as described above.

Sodium hydride method. All apparatus must be thoroughly dry. Equip a 125 ml. round-bottomed flask (ground glass joints) with a coil condenser, a Hershberg tantalum wire stirrer passing through a glass bearing capped with a silicone-lubricated rubber sleeve (compare Fig. *II, 56,* 35) ; the third neck carries a ground glass stopper which is removed for the addition of reagents. Attach the top of the condenser to a source of dry nitrogen and to a filter pump as in Fig. *VI, 24,* 1. Evacuate the apparatus, dry it by heating gently with a flame and fill it with nitrogen as described above. Whilst nitrogen is flowing, remove the stopper, wash in 2·4 g. of sodium hydride (1) with the aid of about 25 ml. of sodium-dried benzene, followed by 9·11 g. of pure benzophenone and 26·13 g. of freshly distilled diethyl succinate, washed into the flask with an additional 25 ml. of dry benzene. Add a little absolute ethyl alcohol (0·75 ml.) (2), replace the stopper, arrest the flow of nitrogen and close the screw clip. Start the stirrer : hydrogen is evolved through the mercury trap, slowly at first and then more rapidly as the reaction progresses. Cool the flask with a cold water bath, as required, to maintain the temperature below 40°. After about 8 hours the evolution of gas has usually subsided and the reaction is essentially complete. Cool the mixture with an ice bath, and add 10·5 ml. of glacial acetic acid dropwise (to avoid excessive foaming), followed by water and ether : separate the aqueous layer and extract it with ether. Extract the combined ethereal solutions repeatedly with 5 per cent. sodium carbonate solution until a test portion shows no cloudiness upon acidification. Acidify the combined alkaline solutions with dilute hydrochloric acid, filter off the crystalline half-ester, wash and dry at 100°. The yield of almost pure product, m.p. 124–125°, is 15·0 g.

Notes.

(1) *Great care must be taken in handling sodium hydride* and experimental details for its manipulation with comparative safety are given below. Sodium hydride* is a white, crystalline, free-flowing powder ; it must be kept in air-tight containers for protection against moisture and oxygen. The hermetically sealed tin in which it is supplied may be opened without hazard in ordinary dry air and the solid *rapidly* transferred from the container to a reaction vessel. If exposed to the air unduly, traces of sodium hydroxide formed on the surface render the material hygroscopic ; rapid absorption of atmospheric moisture may then take place, and the heat generated by the reaction with water may suffice to ignite the solid. The fire is not violent and may be extinguished readily by excluding air either by the application of an asbestos blanket or by the use of anhydrous sodium carbonate ; carbon dioxide and carbon

* Available from New Metals and Chemicals Ltd., 16 Northumberland Avenue, London, W.C. 2., or from Electrochemicals Dept., E.I. du Pont de Nemours and Co., Wilmington, U.S.A.

tetrachloride must not be used since some metallic sodium may be liberated. Sodium hydride may be weighed on an ordinary balance provided a stream of nitrogen is passed through the balance case and directed over the balance pans, and the operation is conducted rapidly. It is better, however, to conduct all operations involving weighing of sodium hydride in a "*dry box*" constructed from an old balance case: the latter contains an inlet and outlet for dry nitrogen and also two openings, one on each side, to which are attached sleeves made of plastic material. The operator's hands pass through these sleeves and reasonable seals between the hands and the sleeves are made with rubber bands. Manipulation, including weighing, can be carried out inside the box in an atmosphere of dry nitrogen.

(2) A little ethyl alcohol (0·25 mol alcohol per mol of ketone) is usually required to initate the reaction. The alcohol reacts rapidly with the sodium hydride to produce sodium ethoxide, which may be the true condensing agent: as the reaction proceeds alcohol is formed as a by-product, which reacts with the sodium hydride, etc., and the rate of condensation gradually increases as shown by the increased evolution of hydrogen. The essential difference between this and the classical sodium ethoxide method is that there is no accumulation of alcohol: some self-condensation of the ester to give diethyl 1 : 4-diketo*cyclo*hexane-2 : 5-dicarboxylate occurs. The latter may be isolated by extracting the ethereal solution of the reaction product first with 5 per cent. sodium bicarbonate solution to remove the half-ester: a further extraction of the ethereal solution with 5 per cent. potassium hydroxide solution enables the self-condensation product to be isolated.

VI,25 THE WILLGERODT REACTION

When an alkyl aryl ketone is heated with yellow ammonium polysulphide solution at an elevated temperature, an aryl substituted aliphatic acid amide is formed; the product actually isolated is the amide of the ω-aryl carboxylic acid together with a smaller amount of the corresponding ammonium salt of the carboxylic acid. Thus acetophenone affords phenylacetamide (50 per cent.) and ammonium phenylacetate (13 per cent.):

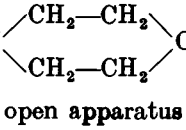
$$C_6H_5COCH_3 \xrightarrow[H_2O,\ 200\text{-}220^\circ]{(NH_4)_2S_x} C_6H_5CH_2CONH_2 + C_6H_5CH_2COONH_4$$

The conversion of a carbonyl compound by ammonium polysulphide solution into an amide with the same number of carbon atoms is known as the **Willgerodt reaction.** The procedure has been improved by the addition of about 40 per cent. of dioxan or of pyridine to increase the mutual solubility of the ketone and aqueous ammonium polysulphide; the requisite temperature is lowered to about 160° and the yield is generally better.

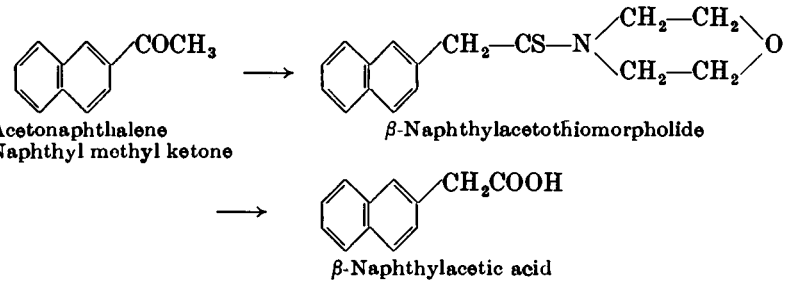
A further improvement is embodied in the **Kindler variation** of the Willgerodt reaction: this consists in heating the ketone with approximately equal amounts of sulphur and a dry amine instead of aqueous ammonium polysulphide. The principal product is a thioamide, and hydrolysis with acid or alkali affords the carboxylic acid, usually in good yield.

$$ArCOCH_3 + S + R_2NH \longrightarrow ArCH_2CSNR_2 + H_2O$$

$$ArCH_2CSNR_2 \longrightarrow ArCH_2COOH + H_2S + HNR_2$$

If the inexpensive morpholine  , b.p. 128°, is employed, the reaction may be conducted in an open apparatus in place of a bomb tube or

autoclave. The simplified procedure for carrying out the Willgerodt reaction is described for a number of ketones :



β-Acetonaphthalene
β Naphthyl methyl ketone

β-Naphthylacetothiomorpholide

β-Naphthylacetic acid

Propiophenone ⟶ hydrocinnamic acid

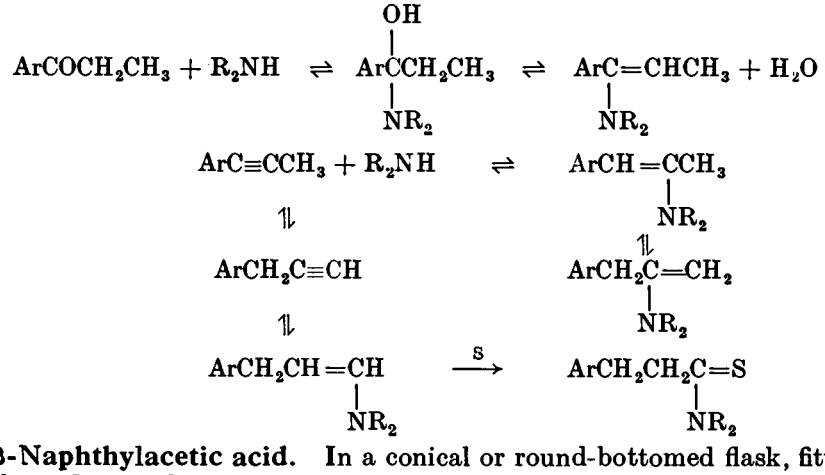
p Methoxyacetophenone ⟶ *p*-methoxyphenylacetic acid

p-Bromoacetophenone ⟶ *p*-bromophenylacetic acid

The *mechanism* of the reaction is not known with certainty. It is known from studies utilising ^{14}C as tracer that no change in the carbon skeleton occurs during the reaction, and also that unsaturated hydrocarbons can undergo reactions very similar to those of ketones; thus both styrene and phenylacetylene can react with sulphur and morpholine to produce phenylacetothiomorpholide, hydrolysis of which yields phenylacetic acid :

$$C_6H_5CH{=}CH_2 \text{ or } C_6H_5C{\equiv}CH \xrightarrow{S + HN(CH_2CH_2)_2O} C_6H_5CH_2CSN(CH_2CH_2)_2O$$

It has been tentatively suggested that one mechanism underlies the Willgerodt reaction and the Kindler modification of it. A labile intermediate is first formed which has a carbon—carbon bond in the side chain. The scheme is indicated below; it postulates a series of steps involving the addition of ammonia or amine (R = H or alkyl), elimination of water, re-addition and elimination of ammonia or amine until the unsaturation appears at the end of the chain : then an irreversible oxidation between sulphur and the nitrogen compound may occur to produce a thioamide.



β-Naphthylacetic acid. In a conical or round-bottomed flask, fitted with a reflux condenser by means of a ground glass joint, place a mixture of 128 g. of β-naphthyl methyl ketone (Section IV,136), 35 g. of sulphur and

97 g. (97 ml.) of morpholine (b.p. 126–128°). Reflux in the fume cupboard (hood) gently at first until the evolution of hydrogen sulphide subsides and then more vigorously for a total period of 14 hours. Pour the hot reaction mixture, which has separated into two layers, into 400 ml. of warm ethanol and leave to crystallise. The β-naphthylacetothiomorpholide separates as pale buff crystals. Filter at the pump and wash with a little cold ethanol; the yield of crude thiomorpholide, m.p. 103–108°, is 178 g.

Mix 130 g. of the crude thiomorpholide with 270 ml. of glacial acetic acid, 40 ml. of concentrated sulphuric acid and 60 ml. of water; raise the temperature of the mixture carefully to the boiling point and reflux for 5 hours. Decant the solution from a little tarry matter into 2 litres of water and keep overnight. Collect the solid by suction filtration and wash it well with cold water. Digest the solid with a solution of 50 g. of sodium hydroxide in 1 litre of water, filter and acidify the filtrate with hydrochloric acid; filter off the crude β-naphthylacetic acid, wash with water and dry. The yield of the crude acid, m.p. 137–140°, is 75 g. Recrystallisation from benzene raises the m.p. to 142–143°; the loss is about 10 per cent.

Hydrocinnamic acid. Reflux a mixture of 53·5 g. of propiophenone (Section **IV,137**), 20·5 g. of sulphur and 46 g. (46 ml.) of morpholine for 6 hours. Pour the reaction product into 400 ml. of 10 per cent. alcoholic sodium hydroxide solution and reflux for 7 hours. Distil off the alcohol, dilute with water, acidify with hydrochloric acid (to Congo red paper), and extract three times with ether. Wash the ether extracts with water, dry, remove the ether and distil. Collect the hydrocinnamic acid at 125–129°/6 mm.; it solidifies completely on cooling, m.p. 46–47°. The yield is 39 g.

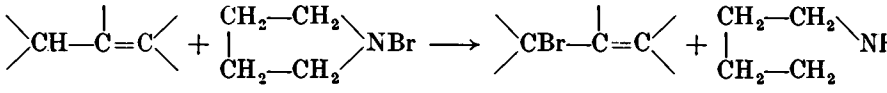
***p*-Methoxyphenylacetic acid.** Reflux a mixture of 42 g. of *p*-methoxyacetophenone (Section **IV,138**), 13·5 g. of sulphur and 30 g. (30 ml.) of morpholine for 5 hours. Pour the reaction mixture slowly into water, allowing the first addition to crystallise before the bulk of the mixture is added. Filter off the crude yellow solid, grind it up thoroughly with water, filter again and dry in the air. The yield of crude acetothiomorpholide, m.p. 65–67°, is 68 g. Recrystallisation from dilute methanol raises the m.p. to 71–72°.

Add 50 g. of the crude acetothiomorpholide to 400 ml. of 10 per cent. alcoholic sodium hydroxide solution and reflux the mixture for 10 hours. Distil off most of the alcohol, add 100 ml. of water to the residue, and strongly acidify the alkaline solution with hydrochloric acid. Cool, extract thrice with ether, dry the combined ether extracts, evaporate the solvent, and recrystallise the residue from water or dilute alcohol. The yield of *p*-methoxyphenylacetic acid, m.p. 85–86°, is 26 g. A further quantity of acid may be obtained by extracting the mother liquors with ether.

***p*-Bromophenylacetic acid.** Reflux a mixture of 50 g. of *p*-bromoacetophenone (Section **IV,138**), 12·8 g. of sulphur and 30 ml. of morpholine for 8 hours. Saponify the crude reaction product with 250 ml. of 10 per cent. alcoholic sodium hydroxide solution and work up as described for the *p*-methoxy acid. The yield of crude *p*-bromophenylacetic acid, m.p. 107–109°, is 25 g. Recrystallisation from water gives the pure acid, m.p. 113–114°.

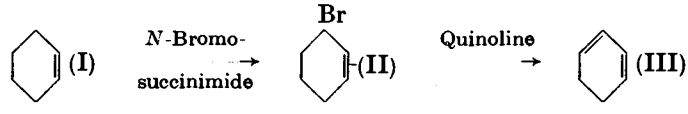
VI,26. THE WOHL-ZIEGLER REACTION. APPLICATIONS OF *N*-BROMOSUCCINIMIDE

The direct introduction of a halogen atom (usually bromine) by means of *N*-haloamine (generally *N*-bromosuccinimide) in the " allyl " position is known as the **Wohl-Ziegler reaction :**

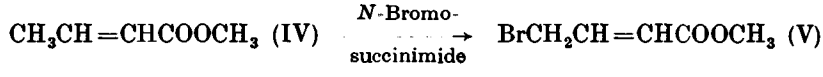


Bromination is carried out with anhydrous reagents (to avoid hydrolysis of the *N*-bromoimide), usually in boiling carbon tetrachloride or chloroform solution. The progress of the reaction can be followed by the fact that at first the heavy *N*-bromosuccinimide is at the bottom of the flask and is gradually replaced by succinimide, which rises to the surface : the reaction is complete when all the crystals are floating at the surface (detected by stopping the boiling momentarily). This can be confirmed (when equimolecular amounts are used) by transferring a drop of the solution to acidified potassium iodide - starch solution : iodine should not be liberated. After cooling, the insoluble succinimide is filtered off, washed with the solvent, and the product isolated, after removal of the solvent, by distillation or crystallisation.

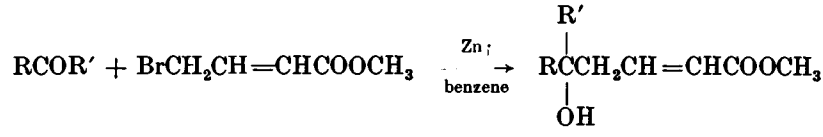
Two simple applications may be mentioned. With *cyclo*hexene (I) 3-bromo-*cyclo*hexene (II) is obtained in good yield ; the latter upon dehydrobromination with quinoline affords an 80–90 per cent. yield of 1 : 3-*cyclo*hexadiene (III) :



Methyl crotonate (IV) yields the valuable synthetic reagent methyl γ-bromocrotonate (V) :



This compound permits the introduction (in moderate yield) of a four carbon atom chain at the site of the carbonyl group by the use of the Reformatsky reaction (compare Section VI,8) :



METHYL γ-BROMOCROTONATE

***N*-Bromosuccinimide.** Dissolve, with the aid of rapid mechanical stirring, 80 g. of pure succinimide (Section V,14) in a mixture of 150 g. of finely crushed ice and a solution of 32 g. of sodium hydroxide in 200 ml. of water contained in a litre beaker and cooled externally by ice. Immediately the imide has dissolved, continue the vigorous stirring and introduce 42·5 ml. of bromine in one lot from a separatory funnel supported over the beaker : it is essential that the bromine be instantly suspended in the solution. After stirring vigorously for 2 minutes, filter at the pump and

wash with ice-cold water until the washings are colourless. Recrystallise *as quickly as possible* from the minimum volume of hot water; dry first on a porous plate or upon pads of filter paper and then in a vacuum desiccator. The yield of pure dry bromosuccinimide is 110 g. The melting point is 180° (capillary tube; rapid heating) or 182° (hot plate; compare Fig. *II*, *11*, 1). Recrystallisation from dry benzene does not affect the m.p.

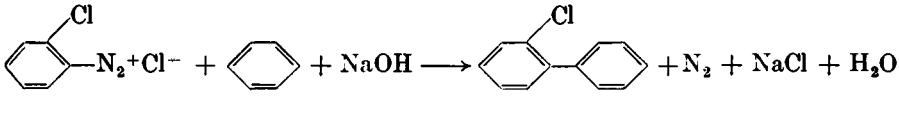
A more active product is obtained by the following slight modification of the above procedure. Dissolve the succinimide in a slight molar excess of sodium hydroxide solution and add the bromine dissolved in an equal volume of carbon tetrachloride rapidly and with vigorous stirring. A finely crystalline white product is obtained. Filter with suction and dry thoroughly; the crude product can be used directly. It may be recrystallised from acetic acid.

Methyl crotonate. Purify commercial crotonic acid by distilling 100 g. from a 100 ml. Claisen flask attached to an air condenser; use an air bath (Fig. *II*, *5*, 3). The pure acid passes over at 180–182° and crystallises out on cooling, m.p. 72–73°; the recovery is about 90 per cent. Place 75 g. of absolute methyl alcohol, 5 g. (2·7 ml.) of concentrated sulphuric acid and 50 g. of pure crotonic acid in a 500 ml. round-bottomed flask and heat under reflux for 12 hours. Add water, separate the precipitated ester and dissolve it in ether; wash with dilute sodium carbonate solution until effervescence ceases, dry with anhydrous magnesium sulphate, and remove the ether on a water bath. Distil and collect the methyl crotonate at 118–120°; the yield is 40 g.

Methyl γ-bromocrotonate. Mix 36 g. of *N*-bromosuccinimide, 40 g. of methyl crotonate and 60 ml. of dry, redistilled carbon tetrachloride in a 500 ml. round-bottomed flask. Reflux on a water bath for 12 hours; by this time all the solid should have risen to the surface of the liquid. Filter off the succinimide at the pump and wash it with a little dry carbon tetrachloride. Remove the solvent on a water bath and distil the residue under reduced pressure, preferably from a Widmer flask (compare Figs. *II*, *24*, 4–5). Collect the methyl γ-bromocrotonate at 77–78°/8 mm.: the yield is 31 g.

VI,27. SYNTHESIS OF UNSYMMETRICAL DIARYLS

Unsymmetrical diaryls may be prepared by treating an aryl diazonium salt solution with sodium hydroxide or sodium acetate in the presence of a liquid aromatic compound, Thus **2-chlorodiphenyl** is readily formed from o-chlorophenyl diazonium chloride and sodium hydroxide solution (or sodium acetate solution) in the presence of benzene:



This is sometimes called the **Gomberg** or the **Gomberg - Hey reaction.**

The *mechanism* of the reaction probably involves the intermediate formation of the covalent diazo-hydroxide from the diazonium salt; the former decomposes

into free aryl radicals which displace hydrogen from the aromatic hydrocarbon present :

$$ArN_2^+Cl^- + Na^+OH^- \rightleftharpoons Na^+Cl^- + ArN_2^+OH^- \rightleftharpoons ArN{=}N{-}OH$$
$$ArN{=}N{-}OH \longrightarrow Ar\cdot + N_2 + \cdot OH$$
$$Ar\cdot + C_6H_5{-}H \longrightarrow Ar{-}C_6H_5 + H\cdot$$
$$H\cdot + \cdot OH \longrightarrow H_2O$$

The usual directive influences are not operative in this and similar reactions for *ortho* - *para* substitution occurs (this may be modified by steric hindrance) irrespective of the nature of R in the aromatic liquid C_6H_5R, *e.g.* phenyldiazo hydroxide and nitrobenzene yield 4-nitrodiphenyl; this supports the assumption that neutral free radicals are formed.

2-Chlorodiphenyl. Diazotise 32 g. of *o*-chloroaniline (Section **IV,34**) in the presence of 40 ml. of concentrated hydrochloric acid and 22·5 ml. of water in the usual manner (compare Section **IV,61**) with concentrated sodium nitrite solution. Transfer the cold, filtered diazonium solution to a 1·5 litre bolt-head flask surrounded by ice water, introduce 500 ml. of cold benzene, stir vigorously, and add a solution of 80 g. of sodium acetate trihydrate in 200 ml. of water dropwise, maintaining the temperature at 5–10°. Continue the stirring for 48 hours : after the first 3 hours, allow the reaction to proceed at room temperature. Separate the benzene layer, wash it with water, and remove the benzene by distillation at atmospheric pressure ; distil the residue under reduced pressure and collect the 2-chlorodiphenyl at 150–155°/10 mm. The yield is 18 g. Recrystallise from aqueous ethanol ; m.p. 34°.

4-Bromodiphenyl. Diazotise 43 g. of *p*-bromoaniline (Section **IV,49**) in the presence of 40 ml. of concentrated hydrochloric acid and 22·5 ml. of water (see Section **IV,61**) with a concentrated solution of sodium nitrite. Mix the filtered diazonium solution with 500 ml. of cold benzene, stir vigorously and add a solution of 30 g. of sodium hydroxide in 150 ml. of water dropwise (during 30–45 minutes) whilst maintaining the temperature at 5–10°. Complete the reaction as for 2-chlorodiphenyl. The yield of 4-bromodiphenyl, b.p. 170–175°/8 mm., m.p. 90° (from ethanol) is 25 g.

VI,28. SYNTHESES WITH ORGANOLITHIUM COMPOUNDS

Many organolithium compounds may be prepared by the interaction of lithium with an alkyl chloride or bromide or with an aryl bromide in dry ethereal solution in a nitrogen atmosphere :

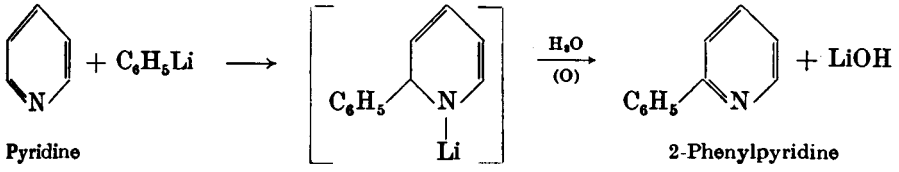
$$C_4H_9{}^{\alpha}Cl + 2Li \longrightarrow LiCl + C_4H_9{}^{\alpha}Li$$
n-Butyl-lithium

$$C_6H_5Br + 2Li \longrightarrow LiBr + C_6H_5Li$$
Phenyl-lithium

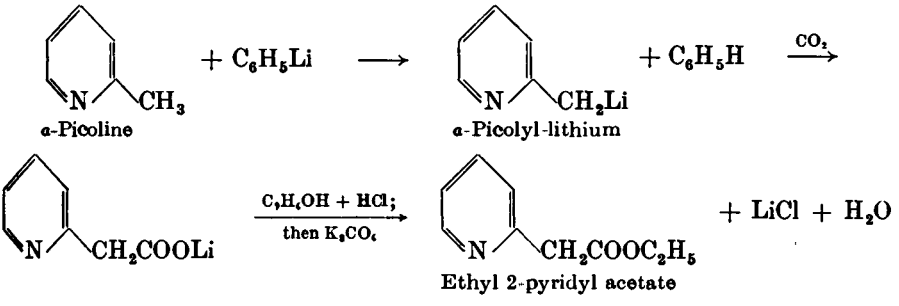
These compounds are soluble in ether, are comparatively stable, and exhibit many of the reactions of Grignard reagents but are more reactive. Because of their greater reactivity, organolithium compounds can often be used where Grignard reagents fail ; thus they add to the azomethine linkage in pyridines or

quinolines leading to 2-substituted compounds. This reaction is illustrated by the preparation of **2-phenylpyridine** from pyridine and **phenyl-lithium :**

$$C_6H_5Br + 2Li \longrightarrow C_6H_5Li + LiBr$$



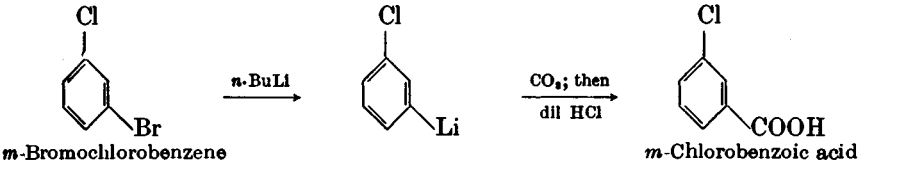
Another example illustrating the greater reactivity of organolithium compounds is the preparation of the otherwise difficultly accessible **esters of 2-pyridylacetic acid** by the following series of reactions from α-picoline :



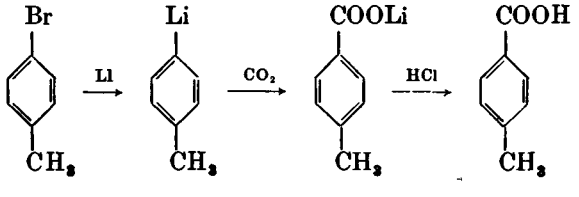
Many organic halides do not react satisfactorily with lithium to form RLi compounds or with metallic magnesium to form Grignard reagents. The desired organolithium compound can often be prepared by a halogen-metal interconversion reaction :

$$R'Li + RX \rightleftharpoons RLi + R'X$$

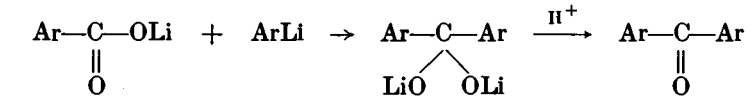
Thus o-hydroxyphenyl-lithium cannot be obtained from o-bromophenol and lithium but, under proper conditions, o-bromophenol reacts with *n*-butyl-lithium to give a good yield of the lithium salt of o-hydroxyphenyl-lithium. An interesting application is to the preparation from *m*-bromochlorobenzene and ***n*-butyl-lithium** of ***m*-chlorobenzoic acid**—an expensive chemical :



For initial experience in the use of lithium, the preparation of either ***p*-toluic acid** or of **α-naphthoic acid** may be undertaken. For the former, *p*-bromotoluene is converted into the lithium derivative and the latter carbonated with solid carbon dioxide :

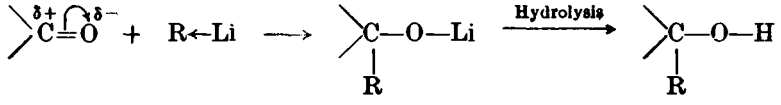


Some di-*p*-tolyl ketone is produced as a by-product, presumably by interaction of the lithium salt of the carboxylic acid with the aryl lithium :



α-Naphthoic acid is similarly prepared from α-bromonaphthalene.

The reactions of organolithium compounds with carbonyl compounds, including carbon dioxide, may be interpreted as follows:



***p*-Toluic acid.** Fit a 250 ml. three-necked flask with a reflux condenser, mechanical stirrer, and a dropping funnel combined with a gas inlet tube (see Fig. *II*, 7, 12,*a*) (1). Place 35 ml. of anhydrous ether in the flask, displace the air by nitrogen and continue passing the nitrogen in a slow stream throughout the duration of the experiment. Introduce 1·90 g. of lithium in the form of fine shavings (2) into the ether and start the stirrer. Place a solution of 21·5 g. of *p*-bromotoluene (Section **IV**,62) in 35 ml. of ether in the dropping funnel. Run in about 1 ml. of the solution into the stirred mixture. The ether in the flask soon becomes turbid ; if the ether does not reflux within 10 minutes, immerse the flask in a beaker of warm water and remove it immediately refluxing commences. Add the remainder of the *p*-bromotoluene solution dropwise or at such a rate that the solvent refluxes continuously (60–90 minutes). Stir the mixture whilst refluxing gently (warm water bath) for a further 45–60 minutes; at the end of this period most of the lithium will have disappeared. Cool the reaction mixture in ice water, dilute it with 50–60 ml. of anhydrous ether, and cool (with stirring) to about — 50° with the aid of an acetone-Dry Ice bath. Pour the contents of the flask slowly and with stirring (use a long glass rod) on to about 400 ml. of powdered Dry Ice-ether "slush" contained in a 5-litre beaker. Rinse the flask with a little of the solid carbon dioxide-ether slush and add the rinsings to the contents of the beaker. Allow the Dry Ice to evaporate (3–4 hours or preferably overnight). Add about 200 ml. of water to the contents of the beaker ; rinse the reaction flask with 10 ml. of 10 per cent. sodium hydroxide solution and pour the rinsings into the beaker. A white solid appears which dissolves upon stirring. (If most of the ether has evaporated on standing, add a further 50 ml.) Separate the two layers, extract the aqueous solution with 50 ml. of ether (to remove traces of neutral products) and combine the extract with the ether layer. Shake the combined ethereal solutions with 10 per cent. sodium hydroxide solution and add the alkaline extract to the aqueous layer. Warm the combined aqueous layers to 60–70° (hot plate) to drive off the dissolved ether, then cool to about 5° and strongly acidify with hydrochloric acid. Collect the precipitated *p*-toluic acid by suction filtration and wash it with a little cold water. The yield of the crude acid, m.p. 174–176°, is 11·9 g. ; recrystallisation from dilute alcohol gives pure *p*-toluic acid, m.p. 176–177°.

Evaporate the dried ethereal extract; the residue, m.p. 85–90°, weighs 3·3 g. Recrystallise it from alcohol: pure di-*p*-tolyl ketone, m.p. 95°, is obtained.

Notes.

(1) Alternatively, use a wide tube with sealed-on side arm; insert the dropping funnel into the wide tube and connect the side arm to the nitrogen supply.

(2) A convenient method of preparing the lithium shavings is as follows. Place a piece of lithium weighing about 3 grams and slightly moist with paraffin oil on a dry surface (slate or tiles) and pound it with a clean hammer or 500 g. weight into a thin sheet about 0·5 mm. thick. Cut the sheet into thin strips about 2–3 mm. wide and transfer it to a beaker containing anhydrous ether. Weigh out the quantity of lithium required under dry ether or paraffin oil. Dry each strip with filter paper, cut it by means of a pair of scissors into small pieces about 1 mm. wide and allow the small pieces to fall directly into the anhydrous ether in the reaction flask. The lithium thus retains its bright lustre.

The lithium may also be pressed into wire of about 0·5 mm. diameter; a rather sturdy press is necessary. The wire may be collected directly in sodium-dried ether.

α-Naphthoic acid. Proceed as detailed for p-*Toluic acid*, using 1·50 g. of lithium and 20·7 g. of α-bromonaphthalene (Section **IV,20**). After carbonation, etc., acidify the alkaline aqueous extract with hydrochloric or 50 per cent. sulphuric acid, collect the precipitated α-naphthoic acid by suction filtration, wash with a little cold water, dry at 90° for 1 hour, and finally in a vacuum desiccator. The yield of crude acid, m.p. 140–150°, is 9·3 g. Recrystallise from hot toluene; the pale yellow α-naphthoic acid has m.p. 159–160°.

2-Phenylpyridine. The first stage is the *preparation of a solution of phenyl-lithium in dry ether.* Equip a 1-litre three-necked flask with a dropping funnel, a mercury-sealed mechanical stirrer, and an efficient reflux condenser; provide the last-named with a drying tube filled with calcium chloride or cotton wool (1). Flush the apparatus with dry, oxygen-free nitrogen gas. Place 7·35 g. of lithium shavings or wire (2) in the flask, and introduce a solution of 78·5 g. (52·5 ml.) of dry, redistilled bromobenzene in 250 ml. of anhydrous ether into the dropping funnel. Start the stirrer. Run in about 2 ml. of the solution; when the reaction starts, as indicated by an initial cloudiness (3), add the remainder at such a rate that the solvent refluxes gently (about 45 minutes). Finally, add 50 ml. of anhydrous ether through the dropping funnel. Continue the stirring until all or most of the lithium disappears (1–1·5 hours) (4).

Now introduce slowly, and with stirring, 79 g. of pure anhydrous pyridine (Section **II,47,22**) dissolved in 200 ml. of anhydrous, sulphur-free toluene: remove the ether by distillation, replace the dropping funnel by a thermometer and stir the residual suspension at 110° (internal temperature) for 8 hours. Then cool to about 40°, and add cautiously 75 ml. of water through the condenser; filter the liquids, if necessary. Separate the upper toluene layer, dry it by shaking for an hour with 20 g. of potassium hydroxide pellets, and distil slowly using a Claisen flask with fractionating side arm (Figs. *II, 24*, 2–5). When the temperature reaches 150° at ordinary pressure (thus indicating the removal of most of the toluene, etc.), distil the residue under reduced pressure and collect the liquid passing over at 138–142°/12 mm. Upon redistillation 38 g. of pure 2-phenylpyridine, b.p. 140°/12 mm., is obtained.

Notes.

(1) If preferred, the apparatus depicted in Fig. *II*, 7, 13 may be used. This enables an oxygen-free nitrogen atmosphere to be maintained in the apparatus and leads to the best yield of phenyl-lithium.

(2) See *Note* 2 under p-*Toluic acid*.

(3) As pointed out in *Note* 1 a nitrogen atmosphere is preferred for the preparation of organolithium compounds. In the present example exclusion of oxygen is attained fairly satisfactorily by keeping the solution at the reflux point throughout; an atmosphere of ether vapour is thus maintained.

(4) The yield of phenyl-lithium generally exceeds 95 per cent. One interesting and instructive method of determination is to allow the phenyl-lithium to react with an excess of benzophenone and to weigh the triphenylcarbinol formed. It is assumed that the carbinol is formed quantitatively. A better method is to hydrolyse a 2 ml. aliquot portion of the filtered solution with distilled water and to titrate the hydrolysate with standard acid, using phenolphthalein as indicator. To obtain the filtered solution, the dropping funnel is replaced by a short L-shaped tube loosely plugged with glass wool, and the solution is decanted through this tube into a graduated funnel that has been swept out with nitrogen.

Ethyl 2-pyridylacetate. Prepare a solution of phenyl-lithium in anhydrous ether as detailed above for 2-*Phenylpyridine*, using 7·35 g. of lithium. Introduce 46·6 g. (48·5 ml.) of dry, redistilled α-picoline (Section **II**,47,28), with continued stirring dropwise during about 10 minutes. Stir the dark red-brown solution of picolyl-lithium for a further 30 minutes, and then pour it slowly (1) and with shaking upon about 400 g. of solid carbon dioxide (Dry Ice) contained in a 1·5 litre round-bottomed flask. Break up the lumpy residue of lithium salts before adding 375 ml. of absolute ethyl alcohol. Cool the solution in ice, and saturate it with dry hydrogen chloride. Allow the mixture to stand overnight, remove the alcohol under diminished pressure on a boiling water (or steam) bath, and dissolve the syrupy residue in 375 ml. of chloroform. Prepare a paste from 112·5 g. of potassium carbonate and 70 ml. of water, and add it slowly and with constant mechanical stirring to the chloroform solution; stir the almost boiling solution vigorously for 1 hour. Decant the chloroform solution from the inorganic salts, remove the solvent by distillation from a water bath, and distil the residue under diminished pressure from a Claisen flask with a fractionating side arm (Figs. *II*, *24*, 2–5). α-Picoline (*ca.* 20 g.) passes over first, followed by ethyl 2-pyridylacetate as a pale yellow liquid at 135–137°/28 mm. or 110–112°/6 mm. The yield is 30 g.

Note.

(1) It is advisable to filter the α-picolyl-lithium solution rapidly through a thin layer of glass wool (to remove any unreacted lithium) on to the solid carbon dioxide.

***m*-Chlorobenzoic acid.** *Prepare a solution of* n-*butyl-lithium in anhydrous ether* as follows. In a 500 ml. three-necked flask, equipped with a reflux condenser, a mercury-sealed stirrer, and a thermometer combined with a gas inlet tube (see Fig. *II*, 7, 12, *b*), place 100 ml. of sodium-dried ether. Displace the air by oxygen-free nitrogen and maintain a slow stream of nitrogen throughout the experiment. Introduce 4·3 g. of fine lithium shavings into the reaction flask. Place a solution of 34·5 g. (26·5 ml.) of *n*-butyl bromide in 50 ml. of anhydrous ether in a dropping funnel supported by means of a grooved cork at the top of the reflux con-

denser, start the stirrer, and run in 1–2 ml. of the solution into the reaction flask cooled to about —10° (Dry Ice-acetone bath). The reaction has commenced when bright spots appear on the lithium and the reaction mixture becomes slightly cloudy. Add the remainder of the *n*-butyl bromide solution during about 30 minutes whilst the internal temperature is maintained at about — 10°. Then allow the reaction mixture to warm up to 0–10° during 1 hour (with stirring) in order to complete the formation of *n*-butyl-lithium (1).

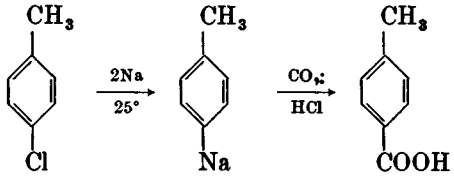
Cool the solution of *n*-butyl-lithium to — 35° in a Dry Ice - acetone bath and add, whilst stirring vigorously, a solution of 48 g. of *m*-chlorobromobenzene (Section **IV,62**) in 75 ml. of anhydrous ether. Stir for 8–10 minutes and pour the mixture with stirring on to a large excess of solid carbon dioxide in the form of a Dry Ice - ether slush contained in a 4-litre beaker. Isolate the acid as detailed above for *p-Toluic acid* and recrystallise it from hot water. The yield of *m*-chlorobenzoic acid, m.p. 150–151°, is 27 g.

Note.

(1) If a clear solution of *n*-butyl-lithium is required for any purpose, it may be decanted through a glass wool plug as detailed under *2-Phenylpyridine, Note* 4.

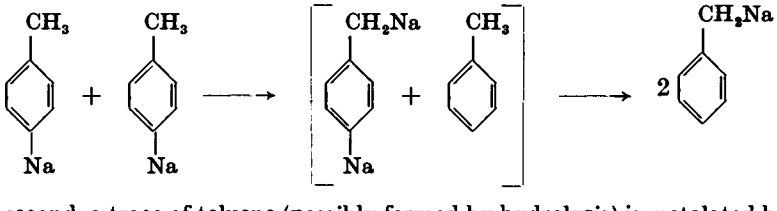
VI,29. SYNTHESES WITH ORGANOSODIUM COMPOUNDS

The formation of an organosodium compound (*p*-tolyl-sodium) is well illustrated by the interaction of sodium sand or wire with *p*-chlorotoluene in light petroleum (b.p. 40–60°) at about 25°, for when the reaction mixture is added to excess of solid carbon dioxide pure ***p*-toluic acid** is obtained directly in a yield exceeding 70 per cent. :



Upon prolonged standing or, more rapidly, upon refluxing for 4–18 hours, the sodium atom migrates and benzyl-sodium is formed, as is proved by the production of phenylacetic acid in good yield upon carbonation.

Two *mechanisms* for the formation of benzyl-sodium have been suggested. One is represented by the scheme :



In the second, a trace of toluene (possibly formed by hydrolysis) is metalated by the *p*-tolyl-sodium to give benzyl-sodium and toluene. Since the toluene is regenerated in the reaction, a small quantity would be adequate as a sort of catalyst.

The formation of alkylbenzenes, largely free from unsaturated compounds, provides another interesting application of organosodium compounds. Thus pure ***n*-butylbenzene** is readily obtained in good yield from benzyl-sodium and *n*-propyl bromide. Benzyl-sodium is conveniently prepared by first forming phenyl-sodium by reaction between sodium and chlorobenzene in a toluene medium, followed by heating the toluene suspension of the phenyl-sodium at 105° for about 35 minutes:

$$C_6H_5Cl + 2Na \longrightarrow C_6H_5Na + NaCl$$
$$C_6H_5Na + C_6H_5{-}CH_3 \longrightarrow C_6H_6 + C_6H_5{-}CH_2Na$$
$$C_6H_5{-}CH_2Na + n\text{-}C_3H_7Br \longrightarrow C_6H_5{-}C_4H_9^n + NaBr$$

Other alkylbenzenes may be prepared similarly by using the appropriate primary or secondary alkyl bromide.

Alkylbenzenes are also obtained (but in somewhat lower yield) from phenyl-sodium and alkyl bromides. Thus **ethylbenzene** is produced from phenyl-sodium and ethyl bromide:

$$C_6H_5Na + C_2H_5Br \longrightarrow C_6H_5{-}C_2H_5 + NaBr$$

About 2–3 per cent. of diphenyl is formed in the initial preparation of phenyl-sodium and, in consequence, careful fractionation is required in the case of alkylbenzenes with a b.p. near that of diphenyl.

Pure ***p*-xylene** may be prepared from *p*-tolyl-sodium and methyl iodide or methyl sulphate.

***p*-Toluic acid.** Equip a dry 250 ml. three-necked flask with a reflux condenser, a mercury-sealed stirrer (1) and a thermometer and gas inlet tube (compare Fig. *II*, 7, 12,*b*). Introduce 50 ml. of dry light petroleum (b.p. 40–60°) and 4·6 g. of sodium wire, and pass a slow stream of nitrogen through the apparatus. Add 12·6 g. of redistilled *p*-chlorotoluene (Section **IV**,61) by means of a dropping funnel supported at the top of the reflux condenser, whilst stirring vigorously, during 90 minutes: maintain the temperature at 25°. After the addition is complete, insert a calcium chloride tube into the open end of the reflux condenser, and continue the stirring for a further 2 hours at 25°. Prepare a " slush " of Dry Ice and ether (using 100–150 ml. of ether) in a 4-litre beaker and pour the reaction mixture rapidly on to the large excess of Dry Ice-ether. After 30–45 minutes, whilst some solid carbon dioxide still remains, add water cautiously to destroy the excess of sodium and to dissolve the sodium salt of the acid. Separate the aqueous layer, extract it once with 50 ml. of ether, and warm the aqueous solution on a hot plate to remove the dissolved solvent. Filter, if necessary, and acidify the aqueous solution with dilute hydrochloric acid. Collect the precipitated acid by suction filtration, wash it with a little water and dry at 100°. The yield of *p*-toluic acid, m.p. 175–176°, is 9·8 g.

Note.

(1) The mercury-sealed stirrer may be replaced by a Kyrides stirrer (Fig. *II*, 7, 12) formed from a P.V.C. gland and lubricated with a mixture of vaseline and light paraffin. The continuous passage of nitrogen may be dispensed with if a fairly wide tube dipping into a little mercury is connected to the top of the condenser; the latter serves to retain the nitrogen atmosphere.

***n*-Butylbenzene.** Equip a 500 ml. three-necked flask as detailed for p-*Toluic acid* and pass a slow stream of nitrogen through the apparatus. Charge the flask with 150 ml. of sodium-dried, sulphur-free toluene and

13·8 g. of sodium wire. Place 34 g. (31 ml.) of chlorobenzene (Sections IV,17 and IV,61) in a dropping funnel supported at the top of the condenser and add it dropwise through the condenser during 1 hour, with vigorous stirring, whilst maintaining the temperature inside the flask at 30–35°. The start of the reaction is indicated by the appearance of black specks on the sodium surface. (If the reaction is slow to start, it may be instantly initiated by a few drops of *n*-butyl alcohol.) Complete the formation of phenyl-sodium by stirring for 2–3 hours at 30°. Attach a calcium chloride tube to the top of the reflux condenser and reflux the mixture for 40 minutes. The reflux temperature, initially 107°, gradually falls to 103° as benzene is formed by the exchange reaction. Remove the heating bath and add 27·6 g. (20·5 ml.) of redistilled *n*-propyl bromide during 20–25 minutes at 103–105°; the reaction is strongly exothermic. Allow the reaction mixture to cool to room temperature: maintain the stirring and the slow stream of nitrogen. Add water slowly to destroy the excess of sodium. Separate the toluene layer, dry it (anhydrous magnesium sulphate), and distil it through a short, jacketed column filled with glass helices (19 cm. packed length, 14 mm. diameter; compare Fig. *II, 24*, 5). After removal of the toluene (up to 111°) and a small intermediate fraction (111–179°), pure *n*-butylbenzene passes over at 179·5–181°/752 mm. (23 g.). A brown residue (4 g.) remains in the flask.

Ethylbenzene. Prepare a suspension of phenyl-sodium from 23 g. of sodium wire, 200 ml. of light petroleum (b.p. 40–60°) and 56·3 g. (50·9 ml.) of chlorobenzene as described above for p-*Toluic acid*. Add 43·5 g. (30 ml.) of ethyl bromide during 30–45 minutes at 30° and stir the mixture for a further hour. Add water slowly to decompose the excess of sodium and work up the product as detailed for n-*Butylbenzene*. The yield of ethylbenzene, b.p. 135–136°, is 23 g.

***p*-Xylene.** Prepare *p*-tolyl-sodium, as described above for p-*Toluic acid*, using 76 g. of *p*-chlorotoluene and 27·5 g. of sodium wire in 250 ml. of light petroleum, b.p. 40–60°. Introduce, with vigorous stirring, a mixture of 78·5 g. (59 ml.) of dimethyl sulphate (*CAUTION*: toxic) with 30 ml. of dry benzene during 1 hour whilst maintaining the temperature at 30°. Add water to the colourless reaction mixture, separate the organic layer, and fractionate it until the vapour temperature reaches 90°. Then separate the crude xylene by steam distillation in the presence of potassium hydroxide; dry the upper layer from the steam distillate (anhydrous magnesium sulphate) and fractionate. Collect the *p*-xylene at 137–138°. The yield is 37 g.

VI,30. SYNTHESES WITH ORGANOCADMIUM COMPOUNDS

Organocadmium compounds may be prepared by the action of anhydrous cadmium chloride upon the corresponding Grignard reagents, for example:

$$2\ n\text{-}C_4H_9MgBr + CdCl_2 \longrightarrow (n\text{-}C_4H_9)_2Cd + MgBr_2 + MgCl_2$$

The cadmium chloride is added to a boiling ethereal solution of the Grignard reagent and the resulting mixture is stirred and heated under reflux until a negative Gilman test (compare Section III,10) is obtained, thus indicating the complete conversion of the Grignard reagent.

The main use of organocadmium compounds is for the preparation of ketones and keto-esters, and their special merit lies in the fact that they react vigorously with acid chlorides of all types but add sluggishly or not at all to multiple bonds (compare addition of Grignard reagents to carbonyl groups). Some typical syntheses are :

$$(n\text{-}C_4H_9)_2Cd + 2ClCOCH_2Cl \longrightarrow 2n\text{-}C_4H_9COCH_2Cl + CdCl_2$$

Di-*n*-butyl-cadmium Chloroacetyl chloride 1-Chloro-2-hexanone

$$(C_6H_5)_2Cd + 2ClCOCH_2CH_3 \longrightarrow 2C_6H_5COCH_2CH_3 + CdCl_2$$

Diphenyl-cadmium Propionyl chloride Propiophenone

$$(n\text{-}C_4H_9)_2Cd + 2ClCOCH_2CH_2COOCH_3 \longrightarrow 2n\text{-}C_4H_9COCH_2CH_2COOCH_3 + CdCl_2$$

Di-*n*-butyl-cadmium; β-Carbomethoxy-propionyl chloride; Methyl 4-keto-octanoate

The success of the last reaction depends upon the inertness of the ester carbonyl groups towards the organocadmium compound : with its aid and the use of various ester acid chlorides, a carbon chain can be built up to any reasonable length whilst retaining a reactive functional group (the ester group) at one end of the chain.* Experimental details are given for **1-chloro-2-hexanone** and **propiophenone.** The complete reaction (formation of ketones or keto-esters) can be carried out in one flask without isolation of intermediates, so that the preparation is really equivalent to one step.

For most purposes the use of 1·0 mol of an alkyl or aryl bromide (for the preparation of the organocadmium compound through the Grignard reagent) to 0·8 mol of the acid halide is recommended. This results in nearly equivalent molar ratios of the organocadmium compound and acid halide, since the overall yield of the former is usually about 80 per cent. It is generally advantageous to replace ether by benzene before the addition of the acid chloride: a higher reflux temperature is possible, thus reducing the time required for the reaction ; also the precipitate formed in the course of the reaction is more easily stirred in benzene than in ether.

1-Chloro-2-hexanone. Equip a 1-litre three-necked flask with a mercury-sealed Hershberg stirrer (preferably of tantalum wire) (see Fig. *II*, 7, 7), a reflux condenser and a 250 ml. dropping funnel (1). All apparatus must be thoroughly dry. Place 8·1 g. of dry magnesium turnings in the flask, add 60 ml. of anhydrous ether through the dropping funnel, and charge the latter with a solution of 46 g. (35·5 ml.) of *n*-butyl bromide in 110 ml. of dry ether. Start the stirrer and prepare the Grignard reagent in the usual manner (compare Sections **III,18** and **III,23**). When the formation of the Grignard reagent is complete, cool the flask in an ice bath with stirring, remove the dropping funnel and, when cold, add 32·7 g. of anhydrous cadmium chloride (2) in portions from a small conical flask during 5–10 minutes. Replace the dropping funnel, remove the ice bath, stir for 5 minutes, and then heat the mixture under reflux with stirring for 45 minutes ; at this point a test for the presence of Grignard reagent is made (3) : continue stirring and refluxing until the test is negative. Replace the reflux condenser by a " knee tube " connected to a condenser set for distillation, distil off the ether as stirring is continued ; continue the distillation, with stirring, on a water bath until it becomes very slow and a dark viscous residue remains. At this point add 120 ml. of

* For experimental details, see *Organic Syntheses*, 28, 75 (1948); Cason, *J. Amer. Chem. Soc.*, 68, 2080 (1946).

anhydrous, thiophene-free benzene from the dropping funnel, and continue the distillation until a further 35 ml. of liquid has passed over. Then add 120 ml. of dry benzene and replace the reflux condenser: reflux the mixture with vigorous stirring in order to break up the cake inside the flask. Remove the heating bath, cool the mixture to about 5° in an ice bath, and add a solution of 38 g. (25·5 ml.) of chloroacetyl chloride (b.p. 105°) in 70 ml. of anhydrous pure benzene from the dropping funnel during 2–3 minutes. After completion of the addition, stir the reaction mixture and hold the temperature at 15–20° for 3 hours and then at 20–25° for a further 1·5 hours. Add excess of crushed ice (*ca.* 200 g.) and dilute sulphuric acid. Separate the benzene and aqueous layers; extract the aqueous phase with two 30 ml. portions of benzene. Wash the combined benzene layers successively with 70 ml. of water, 70 ml. of saturated sōdium bicarbonate solution, 70 ml. of water and 35 ml. of saturated sodium chloride solution. Filter the benzene solution through a little anhydrous sodium sulphate (this separates most of the suspended water), remove the benzene by flash distillation at atmospheric pressure, and distil the residue under reduced pressure using a Claisen flask with fractionating side arm (Fig. *II*, *24*, 5). Collect the 1-chloro-2-hexanone at 71–72°/15 mm.; the yield is 24 g.

Notes.

(1) It is best to conduct the preparation in a nitrogen atmosphere; the apparatus shown in Fig. *II*, 7, 13 may be used.

(2) Dry A.R. hydrated cadmium chloride to constant weight at 110°; grind finely, dry again for 2–3 hours at 110° and then place in a screw-capped bottle and keep in a desiccator over calcium chloride.

(3) Remove 0·5 ml. of the reaction mixture with a dropper pipette and add it to an equal volume of a 1 per cent. solution of Michler's ketone in dry benzene contained in a small test-tube. Shake the mixture for about 1 minute, add 1 ml. of water, followed by a few drops of a 0·2 per cent. solution of iodine in glacial acetic acid. Finally, add 1 ml. of glacial acetic acid, mix well and allow to settle. A positive test is a greenish-blue colour; a negative test is a shade of yellow. The cadmium reagent does not give the Gilman test.

Propiophenone. Prepare a solution of diphenyl-cadmium in 110 ml. of dry benzene using 4·9 g. of magnesium, 32·4 g. of bromobenzene and 19·5 g. of anhydrous cadmium chloride. Cool the solution to 10°, and add during 3 minutes a solution of 14·8 g. of propionyl chloride (b.p. 78–79°) in 30 ml. of dry benzene; use external cooling with an ice bath to prevent the temperature from rising above 40°. Stir the mixture for 2 hours at 25–35°. Work up the product as detailed above except that 5 per cent. sodium carbonate solution should replace the saturated sodium bicarbonate solution. The yield of propiophenone, b.p. 100–102°/16 mm., is 17·5 g.

VI,31. SOME ELECTROLYTIC SYNTHESES

Hydrocarbons and di-esters, otherwise rather inaccessible in a pure state, are conveniently prepared by electrolytic (anodic) synthesis.* Thus simple coupling

* The preparations described below are based upon the work of Dr. R. P. Linstead, C.B.E., F.R.S., and co-workers; the author is indebted to Dr. Linstead for the experimental details concerning *n*-hexacosane.

at the anode is attained by electrolysis in anhydrous methanolic solution (containing a little sodium methoxide) of:—

(i) methyl hydrogen adipate to give **dimethyl sebacate**:

$$2CH_3OOC(CH_2)_4COO^- \longrightarrow CH_3OOC(CH_2)_8COOCH_3 + 2CO_2 + 2e$$

(ii) methyl hydrogen sebacate to give **dimethyl hexadecane-1 : 16-dicarboxylate**:

$$2CH_3OOC(CH_2)_8COO^- \longrightarrow CH_3OOC(CH_2)_{16}COOCH_3 + 2CO_2 + 2e$$

(iii) myristic acid (tetradecoic or tetradecanoic acid) to give ***n*-hexacosane**:

$$2CH_3(CH_2)_{12}COO^- \longrightarrow CH_3(CH_2)_{24}CH_3 + 2CO_2 + 2e$$

Electrolysis, under similar conditions, of a mixture of two carboxylic acids RCOOH and R'COOH leads, in addition to normal coupling products R—R and R'—R', to " cross " coupling R—R'. If a mixture of a saturated carboxylic acid and a half-ester of an αω-dicarboxylic acid is electrolysed, there are three main products, *viz.*, a hydrocarbon (I), a mono-ester (II), and a di-ester (III) and these are readily separable by distillation. Some unsaturated ester (IV) is often present in small quantity.

$$RCOOH + HOOC(CH_2)_nCOOCH_3 \longrightarrow R—R(I) + R(CH_2)_nCOOCH_3 \quad (II)$$
$$+ CH_3OOC(CH_2)_{2n}COOCH_3\ (III) + CH_2{=}CH(CH_2)_{n-2}COOCH_3\ (IV)$$

By increasing the molar proportion of the monocarboxylic acid, the yield of (II) is improved. Thus electrolysis of a mixture of decanoic acid (*n*-decoic acid; capric acid) (V) (2 mols) and methyl hydrogen adipate (VI) (1 mol) in anhydrous methanol in the presence of a little sodium methoxide gives, after hydrolysis of the esters formed, *n*-octadecane (VII), tetradecanoic or myristic acid (VIII) and sebacic acid (IX):

$$CH_3(CH_2)_8COOH\ (V) + HOOC(CH_2)_4COOCH_3\ (VI) \longrightarrow$$
$$CH_3(CH_2)_8(CH_2)_8CH_3\ (VII) + CH_3(CH_2)_8(CH_2)_4COOH\ (VIII) +$$
$$HOOC(CH_2)_4(CH_2)_4COOH\ (IX)$$

An excellent synthesis of **myristic acid** is thus achieved from readily accessible starting materials. An alternative synthesis of myristic acid utilises hexanoic acid (*n*-caproic acid ; *n*-hexoic acid) (X) (2 mols) and methyl hydrogen sebacate (XI) (1 mol); the products, after hydrolysis, are *n*-decane (XII), myristic acid (XIII) and hexadecane-1 : 16-dicarboxylic acid (XIV):

$$CH_3(CH_2)_4COOH\ (X) + HOOC(CH_2)_8COOCH_3\ (XI) \longrightarrow$$
$$CH_3(CH_2)_4(CH_2)_4CH_3\ (XII) + CH_3(CH_2)_4(CH_2)_8COOH\ (XIII) +$$
$$HOOC(CH_2)_8(CH_2)_8COOH\ (XIV)$$

Methyl hydrogen adipate. Place 175 g. of adipic acid, 50 ml. of absolute methanol, 15 ml. of concentrated hydrochloric acid and a few fragments of " porous pot " (" boiling chips ") in a 500 ml. round-bottomed flask provided with a reflux condenser. Heat cautiously at first until the mixture becomes homogeneous and then reflux for 8 hours. Transfer the mixture to a Claisen flask with fractionating side arm (Fig. *II*, *24*, 5) fill the side arm with glass helices and arrange for heating it electrically with a heating tape, the heat input to which is controlled by a Variac transformer. Careful fractionation under reduced pressure yields dimethyl adipate, b.p. 113–114°/6 mm. (21 g.) and methyl hydrogen

adipate, b.p. 154–156°/6 mm. (66 g.). Unchanged adipic acid remains in the flask.

Methyl hydrogen sebacate. Place 115 g. of sebacic acid, 20 ml. of absolute methanol, 6 ml. of concentrated hydrochloric acid and a few fragments of " porous pot " in a 500 ml. round-bottomed flask fitted with a reflux condenser. Warm the mixture on a water bath until it becomes homogeneous and then reflux gently in an air bath (Fig. *II*, 5, 3) for 8 hours. Transfer the mixture to a Claisen flask with fractionating side arm (Fig. *II*, *24*, 5) as for *Methyl hydrogen adipate* and fractionate under reduced pressure; due precautions must be taken so that the distillate does not solidify in the condenser or receiver. Collect the dimethyl sebacate at 153–154°/6 mm. (20 g., m.p. 26°) and the methyl hydrogen sebacate at 185–186°/6 mm. (46 g., m.p. 37°). The residue in the flask consists of unchanged sebacic acid.

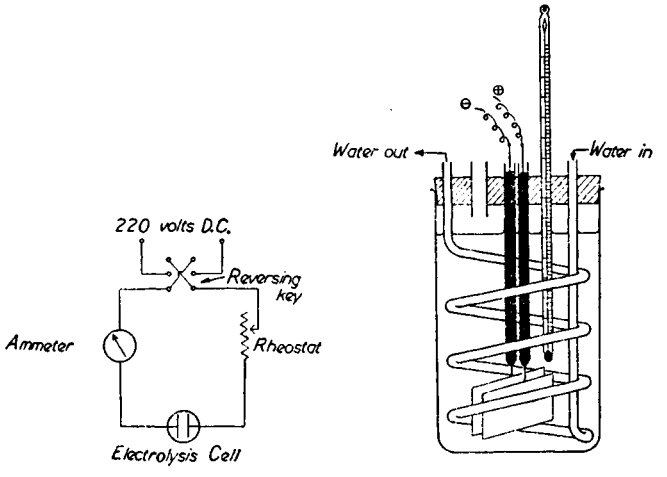


Fig. *VI*, *31*, 1.

Electrolysis cell. This is shown in Fig. *VI*, *31*, 1 and is almost self-explanatory. The cylindrical cell of Pyrex glass (6″ long by $2\frac{3}{4}$″ diameter) is cooled by immersion in a cooling bath. The electrodes consist of two platinum plates (4 cm. × 2·5 cm. × 0·3 mm.), which are placed about 2 mm. apart. The temperature of the electrolyte is maintained at 30–35° by means of the internal cooling coil and also by immersion of the cell in ice-water. A current of 1·5–2·0 amperes is passed until the electrolyte becomes slightly alkaline, which normally takes about 20–50 per cent. longer than the calculated time on the basis of the current and the amounts of acid employed. It is advantageous to reverse the direction of the current occasionally.

Sebacic acid. Dissolve 40 g. of methyl hydrogen adipate in 100 ml. of absolute methanol to which 0·1 g. of sodium has been added. Pass a current of about 2·0 amps. until the *p*H of the solution is about 8 (*ca.* 5 hours); test with B.D.H. narrow-range indicator paper. Transfer the contents of the electrolysis cell to a 500 ml. round-bottomed flask, render neutral with a little acetic acid, and distil off the methanol on a water

bath. Dissolve the residue in 150 ml. of ether, wash with three 50 ml. portions of saturated sodium bicarbonate solution, then with water, dry over anhydrous magnesium sulphate, and distil under reduced pressure. Collect the dimethyl sebacate at 155°/8 mm.; it melts at 26° and the yield is 14·6–16·0 g.

Reflux 14·6 g. of the ester with a solution of 10 g. of sodium hydroxide in 125 ml. of 80 per cent. methanol for 2 hours on a water bath. Add 200 ml. of water to dissolve the solid which separates, extract with two 30 ml. portions of ether, and warm the aqueous solution on a water bath to remove dissolved ether. Acidify the ice-cold aqueous solution to litmus by the addition of concentrated hydrochloric acid. Collect the precipitated acid by suction filtration, wash it with a little cold water, and dry at 100°. The yield of sebacic acid, m.p. 133°, is 11·5 g

Hexadecane-1 : 16-dicarboxylic acid. Dissolve 31·5 g. of methyl hydrogen sebacate in 140 ml. of absolute methanol to which 0·4 g. of sodium has been added. Electrolyse at 2·0 amps. until the *p*H of the electrolyte is 7·8–8·0 (3·5–4 hours). Work up as described for *Sebacic acid*. Upon distillation, an unsaturated ester passes over at 111–113°/20 mm. (4·6 g.), followed by dimethyl hexadecane-1 : 16-dicarboxylate at 212–219°/4 mm. (mainly at 214–215°/4 mm.), m.p. 56° (16·5 g.).

Reflux 6·8 g. of the dimethyl ester with a solution of 3·2 g. of sodium hydroxide in 150 ml. of 80 per cent. methanol for 2 hours on a water bath. When cold, filter off the solid and wash it with a little cold methanol. Dissolve the solid in 350 ml. of warm water, add concentrated hydrochloric acid to the solution at 60° until acidic to litmus, filter off the precipitated acid, wash with a little water and dry at 100°. The resulting hexadecane-1 : 16-dicarboxylic acid, m.p. 122°, weighs 5·3 g. Recrystallisation from absolute methanol raises the m.p. to 124·5°.

Myristic acid (*from hexanoic acid and methyl hydrogen sebacate*). Dissolve 23·2 g. of redistilled hexanoic acid (*n*-caproic acid), b.p. 204·5–205·5°/760 mm., and 21·6 g. of methyl hydrogen sebacate in 200 ml. of absolute methanol to which 0·13 g. of sodium has been added. Electrolyse at 2·0 amps., whilst maintaining the temperature between 30° and 40°, until the *p*H is about 8·0 (*ca.* 6 hours). Neutralise the contents of the electrolysis cell with a little acetic acid and distil off the methyl alcohol on a water bath. Dissolve the residue in 200 ml. of ether, wash with three 50 ml. portions of saturated sodium bicarbonate solution, once with water, dry with anhydrous magnesium sulphate, and distil with the aid of a fractionating column (see under *Methyl hydrogen adipate*). Collect the *n*-decane at 60°/10 mm. (3·0 g.), the methyl myristate at 158–160°/10 mm. (12·5 g.) and dimethyl hexadecane-1 : 16-dicarboxylate at 215–230°/7 mm. (1·5 g.)

Reflux a mixture of 7·3 g. of methyl myristate with a solution of 4·8 g. of sodium hydroxide in 200 ml. of 90 per cent. methanol for 2 hours, distil off the methanol on a water bath, dissolve the residue in 400 ml. of hot water, add 15 ml. of concentrated hydrochloric acid to the solution at 50° in order to precipitate the organic acid, and cool. Collect the acid by suction filtration, wash it with a little water and dry in a vacuum desiccator. The yield of myristic acid (tetradecanoic acid; tetradecoic acid), m.p. 57–58°, is 5·9 g.

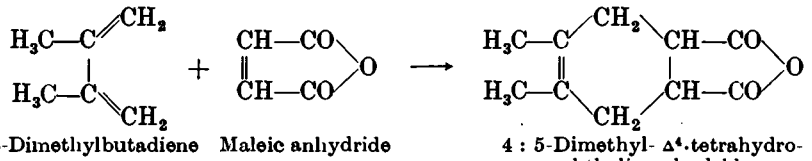
Myristic acid (*from decanoic acid and methyl hydrogen adipate*). Dissolve 55·2 g. of pure decanoic acid (capric acid; decoic acid), m.p. 31–32°, and 25·6 g. of methyl hydrogen adipate in 200 ml. of absolute methanol to which 0·25 g. of sodium has been added. Electrolyse at 2·0 amps. at 25–35° until the *p*H of the electrolyte is 8·2 (*ca.* 9 hours). Neutralise the contents of the electrolytic cell with acetic acid, distil off the methanol on a water bath, dissolve the residue in about 200 ml. of ether, wash with three 50 ml. portions of saturated sodium bicarbonate solution, and remove the ether on a water bath. Treat the residue with a solution of 8·0 g. of sodium hydroxide in 200 ml. of 80 per cent. methanol, reflux for 2 hours, and distil off the methanol on a water bath. Add about 600 ml. of water to the residue to dissolve the mixture of sodium salts: extract the hydrocarbon with four 50 ml. portions of ether, and dry the combined ethereal extracts with anhydrous magnesium sulphate. After removal of the ether, 23·1 g. of almost pure *n*-octadecane, m.p. 23–24°, remains. Acidify the aqueous solution with concentrated hydrochloric acid (*ca.* 25 ml.), cool to 0°, filter off the mixture of acids, wash well with cold water and dry in a vacuum desiccator. The yield of the mixture of sebacic and myristic acids, m.p. 52–67°, is 26 g. Separate the mixture by extraction with six 50 ml. portions of almost boiling light petroleum, b.p. 40–60°. The residue (5·2 g.), m.p. 132°, is sebacic acid. Evaporation of the solvent gives 20 g. of myristic acid, m.p. 52–53°; the m.p. is raised slightly upon recrystallisation from methanol.

***n*-Hexacosane.** Dissolve 5·0 g. of pure myristic acid in 25 ml. of absolute methanol to which 0·1 g. of sodium has been added. Place the solution in a cylindrical cell (25 cm. long, 3 cm. diameter) provided with two platinum plate electrodes (2·5 × 2·5 cm.) set 1–2 mm. apart. Electrolyse at about 1 amp. until the electrolyte is just alkaline (*p*H 7·5–8). Cool the cell in an ice bath during the electrolysis. Reverse the current from time to time; this will help to dislodge the coating of insoluble by-products on the electrodes. Neutralise the cell contents by adding a few drops of glacial acetic acid, and evaporate most of the solvent under reduced pressure. Pour the residue into water and extract the crude product with ether. Wash the ethereal solution with dilute sodium hydroxide solution, dry (anhydrous magnesium sulphate) and evaporate the solvent. Recrystallise the residue from light petroleum (b.p. 40–60°). The yield of *n*-hexacosane, m.p. 57–58°, is 2·4 g.

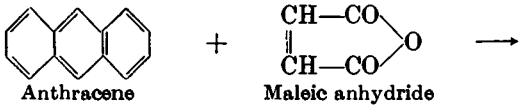
VI,32. THE DIENE SYNTHESIS (DIELS - ALDER REACTION)

Compounds containing a double or triple bond, usually activated by additional unsaturation (carbonyl, cyano, nitro, phenyl, etc.) in the αβ-position, add to the 1 : 4-positions of a conjugated (buta-1 : 3-diene) system with the formation of a six-membered ring. The ethylenic or acetylenic compound is known as the *dienophile* and the second reactant as the *diene*; the product is the *adduct*. The addition is generally termed the **Diels-Alder reaction** or the **diene synthesis.** The product in the case of an ethylenic dienophile is a *cyclo*hexene and in that of an acetylenic dienophile is a *cyclo*hexa-1 : 4-diene. The active unsaturated portion of the dienophile, or that of the diene, or those in both, may be involved in rings; the adduct is then polycyclic.

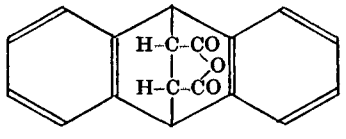
Simple examples include :—



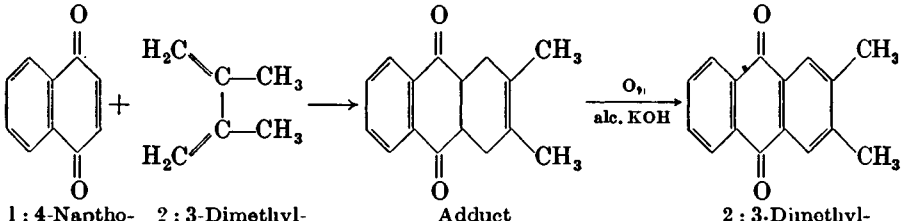
2 : 3-Dimethylbutadiene Maleic anhydride 4 : 5-Dimethyl- Δ^4-tetrahydrophthalic anhydride



Anthracene Maleic anhydride



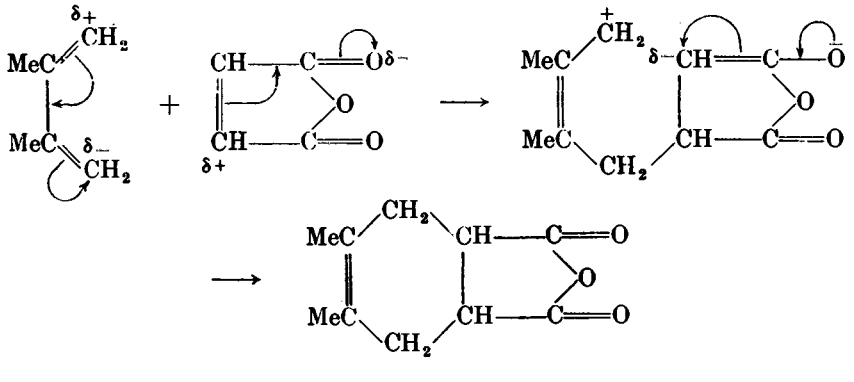
9 : 10-Dihydroanthracene-9 : 10-*endo*-$\alpha\beta$-succinic anhydride



1 : 4-Naptho-quinone 2 : 3-Dimethyl-butadiene Adduct 2 : 3-Dimethyl-anthraquinone

The last example is an interesting application of the diene synthesis, for the adduct upon dehydrogenation (most simply by the action of oxygen upon its solution in alcoholic potash) yields **2 : 3-dimethylanthraquinone.**

The *mechanism* of the diene synthesis appears to involve an electron transfer from the diene to the dienophile, *i.e.*, it is initiated by an ionic reaction. The following scheme may represent the addition of 2 : 3-dimethylbutadiene to maleic anhydride :



The Diels-Alder reaction is a purely *cis*-addition; the relative positions of the substituents are retained in the adduct (compare anthracene and maleic anhydride above).*

2 : 3-Dimethylbutadiene and maleic anhydride. Add 4 g. of freshly distilled 2 : 3-dimethyl-1 : 3-butadiene (Section **III,147**) to 5 g. of finely powdered maleic anhydride (Section **III,93**) contained in a small conical flask. Reaction occurs in a few minutes (indicated by evolution of heat). Allow to stand until the mixture attains room temperature. Remove the excess of maleic anhydride by extraction with cold water until the aqueous extract no longer gives an acid reaction to Congo red paper. Dry the residual white crystals upon filter paper in the air, and then recrystallise from light petroleum (b.p. 40–60°). The yield of 4 : 5-dimethyl-Δ^4-tetrahydrophthalic anhydride, m.p. 78–79°, is almost quantitative.

Anthracene and maleic anhydride. In a 50 ml. round-bottomed flask fitted with a reflux condenser, place 2·0 g. of pure anthracene, 1·1 g. of maleic anhydride (Section **III,93**) and 25 ml. of dry xylene. Boil the mixture under reflux for 20 minutes with frequent shaking during the first 10 minutes. Allow to cool somewhat, add 0·5 g. of decolourising carbon and boil for a further 5 minutes. Filter the hot solution through a small, preheated Buchner funnel. Collect the solid which separates upon cooling by suction filtration, and dry it in a vacuum desiccator containing paraffin wax shavings (to absorb traces of xylene). The yield of adduct (colourless crystals), m.p. 262–263° (decomp.), is 2·2 g. Place the product (9 : 10-dihydroanthracene-9 : 10-*endo*-$\alpha\beta$-succinic anhydride) in a well-stoppered tube, since exposure to air tends to cause hydration of the anhydride portion of the molecule.

2 : 3-Dimethylbutadiene and 1 : 4-naphthoquinone. 2 : 3-Dimethylanthraquinone. In a small round-bottomed flask, fitted with a reflux condenser, place a solution of 8 g. of freshly-distilled 2 : 3-dimethylbutadiene (Section **III,147**) and 8 g. of 1 : 4-naphthoquinone (Section **IV,149**) in 30 ml. of ethanol, and reflux for 5 hours. Keep the resulting solution in a refrigerator for 12 hours: break up the crystalline mass, filter, and wash with 5 ml. of alcohol. The yield of crude adduct, m.p. 147–149°, is 11·5 g.; recrystallisation from methanol raises the m.p. to 150°.

For the dehydrogenation, dissolve 10 g. of the adduct in 150 ml. of 5 per cent. potassium hydroxide solution (prepared by dissolving 7·5 g. of potassium hydroxide pellets in 142·5 g. of 95 per cent. ethanol) in a 250 ml. three-necked flask equipped with a reflux condenser and gas inlet tube. Bubble a current of air through the solution for 24 hours; the initial green colour changes to yellow and much heat is generated. Filter the yellow solid at the pump, wash successively with 50 ml. of water, 25 ml. of alcohol and 10 ml. of ether, and dry in the air. The yield of 2 : 3-dimethylanthraquinone, m.p. 209–210°, is 7·5 g.

* For a more detailed discussion, see *Organic Reactions*, 4, 10 (1948).

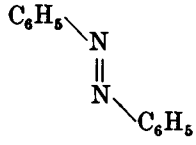
VI,33. SOME APPLICATIONS OF CHROMATOGRAPHIC ADSORPTION

An account of the general technique of chromatographic adsorption has been given in Section II,46. The simple applications to be described are :—

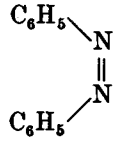
(i) Purification of anthracene (compare a similar purification of β-bromonaphthalene, Section IV,62).

(ii) Oxidation of cholesterol to **cholestenone** by cupric oxide (for formulae, see under *Oppenauer Oxidation* in Section VI,13) and isolation of the cholestenone chromatographically upon alumina.

(iii) Preparation of ***cis*-azobenzene.** Azobenzene, as normally encountered (see Section IV,86), is the *trans*-form. By exposure of a solution of *trans*-azobenzene in light petroleum, b.p. 50–60°, to ultraviolet light, some conversion into the yellow *cis*-form results; the latter can be separated by chromatographic adsorption upon alumina.



trans-Azobenzene



cis-Azobenzene

Purification of anthracene. Dissolve 0·3 g. of crude anthracene (usually yellowish in colour) in 150–200 ml. of hexane, and pass the solution through a column of activated alumina (1·5–2 × 8–10 cm.). Develop the chromatogram with 100 ml. of hexane. Examine the column in the light of an ultra-violet lamp. A narrow, deep blue fluorescent zone (due to carbazole, m.p. 238°) will be seen near the top of the column. Immediately below this there is a yellow, non-fluorescent zone, due to naphthacene (m.p. 337°). The anthracene forms a broad, blue-violet fluorescent zone in the lower part of the column. Continue the development with hexane until fluorescent material commences to pass into the filtrate. Reject the first runnings which contain soluble impurities and yield a paraffin-like substance upon evaporation. Now elute the column with hexane-benzene (1 : 1) until the yellow zone reaches the bottom region of the column. Upon concentration of the filtrate, pure anthracene, m.p. 215–216°, which is fluorescent in daylight, is obtained. The experiment may be repeated several times in order to obtain a moderate quantity of material.

Cholestenone.* Place a mixture of 1·0 g. of purified cholesterol and 0·2 g. of cupric oxide in a test-tube clamped securely at the top, add a fragment of Dry Ice in order to displace the air by carbon dioxide, and insert a plug of cotton wool in the mouth of the tube. Heat in a metal bath at 300–315° for 15 minutes and allow to cool ; rotate the test-tube occasionally in order to spread the melt on the sides. Warm with a few ml. of benzene and pour the black suspension directly into the top of a previously prepared chromatographic column (1) ; rinse the test-tube with a little more benzene and pour the rinsings into the column. With the aid of slight suction (≯ 3–4 cm. of mercury), draw the solution into the alumina column ; stir the top 0·5 cm. or so with a stout copper wire to

* The experimental details were kindly supplied by Professor D. H. R. Barton, F.R.S. and Dr. W. Rigby.

prevent blockage by the finely divided copper compounds. When all the black liquid has run in, there should be free flow without the necessity of further stirring. Continue the development with benzene until a distinctly yellowish diffuse zone approaches the bottom of the column ; some 150 ml. of liquid will have been collected. Now collect 5 ml. fractions until the yellow band is completely removed. Evaporate each of these fractions separately ; the earlier ones yield oils (giving a yellow 2 : 4-dinitrophenylhydrazone) and the later ones will crystallise upon rubbing (cholestenone). Continue the elution with a further 400 ml. of benzene ; the latter upon evaporation yields most of the cholestenone. Isolate the remaining cholestenone by continuing the elution with benzene containing 0·5 per cent. of absolute ethanol until a dark brown band approaches the bottom of the column. Collect all the crystalline residues with the aid of a little light petroleum, b.p. 40–60°, into a small flask and remove the solvent. Dissolve the residue in 40–50 ml. of hot methanol, add 0·2 g. of decolourising carbon, filter through a small bed of alumina (6 mm. × 6 mm.), concentrate to about 20 ml. and leave to crystallise overnight. The yield of cholestenone, m.p. 82°, is 0·5 g.

Note.

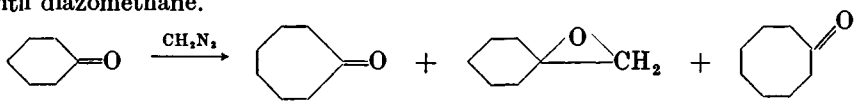
(1) Prepare the column for chromatography by mixing 100 g. of chromatographic alumina (Spence) with sufficient benzene to form a thin slurry when stirred. Pour this, stirring briskly, into a tube (40 cm. long and 20 mm. internal diameter) loosely plugged at its lower end with cotton wool, and rinse with a little more benzene. An evenly packed column, about 35 cm. long, should result. Allow to drain until the supernatant benzene is within 1 cm. of the alumina before adding the solution to be "chromatographed". Under no circumstances should air be permitted to enter the column.

***cis*-Azobenzene.** Dissolve 1·0 g. of azobenzene (Section IV,68 ; this is the *trans*-form) in 50 ml. of petroleum ether, b.p. 40–60°, in a 200 ml. beaker. Irradiate the solution for 30 minutes with ultraviolet light ; this is conveniently carried out by supporting a Hanovia fluorescent lamp, model 16, about 13 cm. above the surface of the liquid in the beaker. Meanwhile prepare a 20 cm. chromatographic column in a tube of 20 mm. bore (compare Fig. *II*, *46*, 4) as follows. Weigh out 50 g. of activated alumina ; mix small portions with sufficient petroleum ether, b.p. 40–60°, to form a paste and introduce it into the column in *ca.* 3 mm. layers and tamp down gently with a suitable wooden pestle or other form of ramrod (compare Fig. *II*, *46*, 6) after each addition. After the column has been formed in this way, place four well-fitting filter papers at the top of the column and pour the solution, immediately after it has been irradiated, slowly down a glass rod on to the filter papers until the column is filled with liquid ; take great care not to disturb the upper portion of the column. Develop the chromatogram with 100 ml. of petroleum ether, b.p. 40–60°. A sharp coloured band (*cis*-form), *ca.* 2 cm. in length, makes its appearance at the top of the column whilst a diffuse coloured region (containing the *trans*-form) moves down the column. The upper portion of the column should be screened from light by covering it with paper, held in position by a rubber band, during the development process ; this will largely prevent the reconversion of the *cis*- into the *trans*-form. Remove the coloured 2 cm. band from the top of the column with a glass spatula

and shake it with 150 ml. of petroleum ether, b.p. 40–60°, containing 1·5 ml. of absolute methanol; filter off the alumina, with suction, and wash the filtrate with two 15 ml. portions of water to remove the methyl alcohol present. Dry the petroleum ether extract by shaking it with *ca.* 1 g. of anhydrous sodium sulphate for 10 minutes, filter and evaporate the solvent at the laboratory temperature in a current of air. The residual coloured solid, m.p. 71·5°, is practically pure *cis*-azobenzene. Its individuality and its purity may be confirmed by ultraviolet absorption spectra measurements in chloroform solution as soon as possible after its isolation; the absorption spectrum is compared with that of the *trans*-compound (see Section A,7, Table XIII).

VI,34. RING ENLARGEMENT WITH DIAZOMETHANE *CYCLO*HEPTANONE FROM *CYCLO*HEXANONE

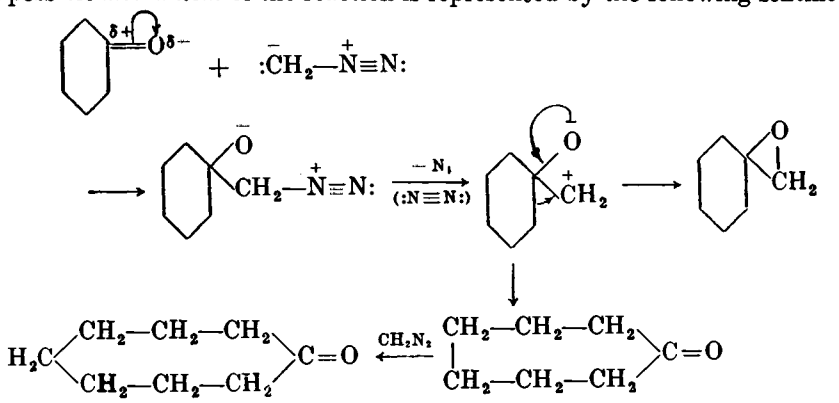
Reaction of cyclic ketones with diazomethane leads to ring enlargement. Thus *cyclo*hexanone (I) (1 mol) and diazomethane (1 mol) give ***cyclo*heptanone** (II) in about 60 per cent. yield together with a little epoxide (III) as by product and some *cyclo*octanone (IV) resulting from further reaction of *cyclo*heptanone with diazomethane.



(I) (II) (III) (IV)

The *cyclo*heptanone is readily separated by taking advantage of the experimental fact that it alone forms a solid bisulphite compound. Diazomethane is conveniently generated *in situ* from *p*-tolylsulphonylmethylnitrosamide (Section VII,20).

A possible *mechanism* of the reaction is represented by the following scheme:



CAUTION: *Carry out the preparation in an efficient fume cupboard (hood) since diazomethane is very toxic.*

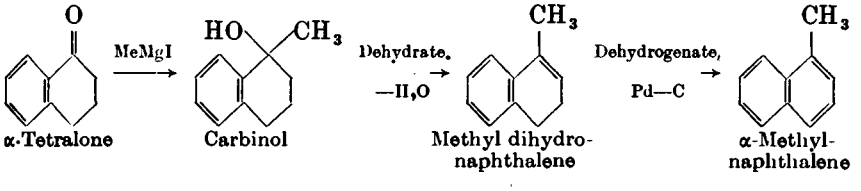
In a 1-litre three-necked flask equipped with a thermometer, a mechanical stirrer and a dropping funnel, place 49 g. of redistilled *cyclo*hexanone, 125 g. of *p*-tolylsulphonylmethylnitrosamide, 150 ml. of 95 per cent. ethanol and 10 ml. of water. The nitrosamide is largely undissolved. Adjust the height of the stirrer so that only the upper part of the solution is stirred and the precipitate moves slightly; place the thermometer so that the bulb is in the liquid. Cool the mixture to about 0° in an ice-salt

bath. Whilst stirring gently, add a solution of 15 g. of potassium hydroxide in 50 ml. of 50 per cent. aqueous ethanol dropwise very slowly from the dropping funnel: after 0·5–1 ml. of the solution has been added, a vigorous evolution of nitrogen commences and the temperature rises. Adjust the rate of addition so that the temperature is maintained at 10–20°; the duration of the addition of alkali is about 2 hours and the nitroso compound ultimately disappears. Stir the orange-yellow solution for a further 30 minutes, and then add 2*N*-hydrochloric acid until the solution is acidic to litmus paper (*ca.* 50 ml.).

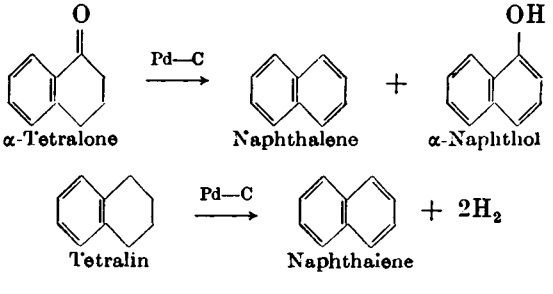
Introduce a solution of 100 g. of sodium bisulphite in 200 ml. of water and continue the stirring, preferably for 10 hours with exclusion of air. A thick precipitate separates after a few minutes. Collect the bisulphite compound by suction filtration, wash it with ether until colourless, and then decompose it in a flask with a lukewarm solution of 125 g. of sodium carbonate in 150 ml. of water. Separate the ketone layer, extract the aqueous layer with four 30 ml. portions of ether, dry the combined organic layers over anhydrous magnesium sulphate, remove the ether at atmospheric pressure, and distil the residual oil under reduced pressure from a Claisen flask with fractionating side arm (Fig. *II*, *24*, 5). Collect the *cyclo*heptanone at 64–65°/12 mm.; the yield is 23 g.

VI,35. DEHYDROGENATION OF HYDROAROMATIC COMPOUNDS

Dehydrogenation (the conversion of alicyclic or hydroaromatic compounds into their aromatic counterparts by removal of hydrogen and also, in some cases, of other atoms or groups) finds wide application in the determination of structure of natural products of complex hydroaromatic structure. Dehydrogenation is employed also for the synthesis of polycyclic hydrocarbons and their derivatives from the readily accessible synthetic hydroaromatic compounds. A very simple example is the formation of β-methylnaphthalene from α-tetralone (which is itself prepared from benzene—see Section IV,143):



α-Tetralone may also be directly dehydrogenated to a mixture of naphthalene and α-naphthol, whilst tetralin yields naphthalene under similar conditions.



The principal dehydrogenating agents are (i) sulphur, (ii) selenium, and (iii) catalytic metals.

Sulphur. The general method is to heat the compound at 200–260° with the theoretical amount of sulphur required to bring it to the aromatic state:

$$C_{10}H_{12}\text{ (tetralin)} + 2S \longrightarrow C_{10}H_8\text{ (naphthalene)} + 2H_2S$$
$$C_{15}H_{24}\text{ (a sesquiterpene)} + 3S \longrightarrow C_{15}H_{18}\text{ (cadalene)} + 3H_2S$$

Selenium. The substance is heated with a large excess of selenium at 280–350° for 36–48 hours. Better yields (and less side reactions) are usually obtained than with sulphur, but, owing to the higher temperature, rearrangements are more likely. Oxygen-containing groups are particularly prone to elimination.

Palladium and platinum catalysts. These catalysts are generally employed with a charcoal or asbestos carrier. The dehydrogenation can be conducted in the vapour phase by distilling the compound through a tube containing the catalyst heated to 300–350°, but the liquid phase method is generally more convenient. Charcoals or asbestos are employed containing 10–30 per cent. of the metal. It has been established that the best results are obtained by conducting the process in an actively boiling medium (*e.g.*, mesitylene, b.p. 165°; *p*-cymene, b.p. 177°; naphthalene, b.p. 218°; and α-methylnaphthalene, b.p. 242°) and to provide for the elimination of the hydrogen as it is formed (*e.g.*, by sweeping the system with a stream of carbon dioxide).

Preparation of 30 per cent. palladium or platinum catalysts (charcoal or asbestos carrier).

Purification of charcoal. Heat "Norit" charcoal on a water bath for 6 hours with 10 per cent. nitric acid, filter, wash free from acid, and dry at 100°. If the acid-washed form of "Norit" charcoal is available, it may be used directly without further purification.

Purification of asbestos. Boil Gooch asbestos (tremolite, not chrysolite variety) with concentrated nitric acid, filter, wash free from acid, and dry at 100°.

Method A. Cool a solution of the nitrate-free dichloride, prepared from or equivalent to 5·0 g. of palladium or platinum, in 50 ml. of water and 5 ml. of concentrated hydrochloric acid in a freezing mixture, and treat it with 50 ml. of formalin (40 per cent. formaldehyde) and 11 g. of the carrier (charcoal or asbestos). Stir the mixture mechanically and add a solution of 50 g. of potassium hydroxide in 50 ml. of water, keeping the temperature below 5°. When the addition is complete, raise the temperature to 60° for 15 minutes. Wash the catalyst thoroughly by decantation with water and finally with dilute acetic acid, collect on a suction filter, and wash with hot water until free from chloride or alkali. Dry at 100° and store in a desiccator.

Method B. For some purposes a slightly more active catalyst is obtained when it is prepared in more concentrated solutions. The procedure is the same as above, but the volumes of solution for 5 g. of metal are: dilute acid, 25 ml.; formaldehyde, 35 ml.; potassium hydroxide, 32 g. in 32 ml. of water.

The above catalysts contain about 30 per cent. of metal: catalyst with 10 per cent. of metal may be readily prepared by reducing the quantity of platinum or palladium chloride used.

Broadly speaking, the differences in effectiveness of palladium and platinum catalysts are very small; the choice will generally be made on the basis of availability and current price of the two metals. Charcoal is a somewhat more efficient carrier than asbestos.

DEHYDROGENATION OF TETRALIN

For small scale dehydrogenations, the apparatus shown in Fig. *VI, 35,* 1 may be used. Place 2·5 g. of purified tetralin (1) and 0·25 g. of palladised charcoal in the apparatus and heat to boiling for 4 hours in a slow current of dry carbon dioxide. Naphthalene, m.p. 81°, collects on the condenser in almost quantitative yield. If it is desired to follow the progress of the dehydrogenation, attach the side tube through a "sofnolite" (or soda lime) U-tube to a nitrometer filled with potassium hydroxide solution: almost the theoretical quantity of hydrogen will be collected.

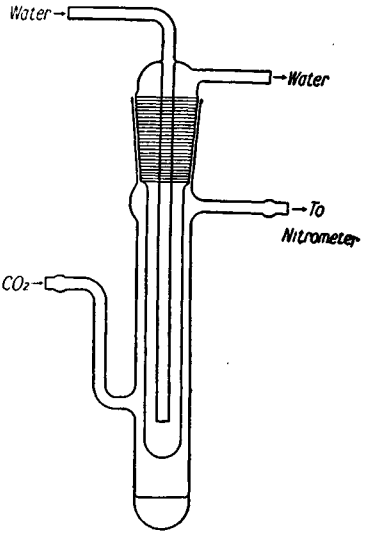


Fig. *VI, 35,* 1.

If the current of inert gas is omitted, the reaction is complete after about 22 hours.

Note.

(1) **Commercial tetralin may be purified as follows. Wash the technical product repeatedly with 10 per cent. of its volume of concentrated sulphuric acid, then with 10 per cent. sodium carbonate solution, followed by water, dry with anhydrous calcium sulphate, filter from the desiccant, reflux over sodium, and finally distil from sodium. Collect the pure tetralin at 206–207°.**

VI,36. PREPARATION OF PALLADIUM CATALYSTS FOR HYDROGENATION

Palladium catalysts are useful alternatives to Adams' platinum oxide catalyst described in Section III,150. The nearest equivalent to the latter is palladium chloride upon carbon and it can be stored indefinitely; the palladium salt is reduced to the metal as required:

$$PdCl_2 + H_2 \longrightarrow Pd + 2HCl$$

The catalyst is also employed in the form of the finely-divided metal deposited upon activated carbon (usually containing 5 or 10 per cent. Pd); two methods of preparation are described, in one reduction is effected with alkaline formaldehyde solution and in the other with hydrogen:

$$Na_2PdCl_4 + HCHO + 3NaOH \longrightarrow Pd + HCOONa + 4NaCl + 2H_2O$$

Catalysts reduced with formaldehyde contain no adsorbed hydrogen and are less pyrophoric.

Barium sulphate is frequently used as a support for the palladium (compare the Rosenmund reduction of acid chlorides, Section IV,120); barium carbonate

may also be employed when it is required to maintain the neutrality of the hydrogenation mixture. At times these are to be preferred to carbon which may, in some instances, so strongly adsorb the hydrogenation product that recovery is incomplete or difficult.

A. **Palladium chloride on carbon.** Prepare a solution of 4·2 g. of anhydrous palladium chloride (1) in 10 ml. of concentrated hydrochloric acid and 25 ml. of water by heating on a boiling water bath for 2 hours or until solution is complete. Add 70 ml. of water and pour all the resulting solution over 46 g. of nitric acid - washed activated carbon (2) contained in an evaporating dish or Pyrex crystallising dish. Mix the palladium chloride solution thoroughly with the carbon, and dry the mixture first on a water bath and then in an oven at 100° : stir occasionally. Powder the mass (49 g.) and store in a tightly-stoppered bottle.

This palladium chloride catalyst does not deteriorate during storage. When required for use, place the required quantity in a hydrogenation bottle (compare Fig. *III, 150,* 1) and reduce it with hydrogen in the solvent to be used for the hydrogenation ; a neutral solvent is to be preferred for the reduction of the palladium chloride. When no more hydrogen is absorbed by the catalyst, collect it on a sintered glass funnel, wash it with more of the solvent to remove the hydrogen chloride and then return it, with the aid of a little fresh solvent, to the reduction bottle : it is essential to keep the catalyst moist with the solvent during the washing process as it is pyrophoric. The presence of hydrogen chloride during the hydrogenation of many organic compounds is desirable (see introductory paragraph to Section **III,150**) or is without effect ; in such cases, the palladium chloride on carbon is added to the solvent and hydrogen acceptor before reduction.

B. **Palladium on carbon catalyst (10 per cent. Pd).** Add a solution of 2·1 g. of palladium chloride (1) in 1·5 ml. of concentrated hydrochloric acid and 10 ml. of water (prepared as in *A*) to a solution of 44 g. of A.R. crystallised sodium acetate in 125 ml. of water contained in a 250–500 ml. reduction bottle, introduce 11·5 g. of nitric acid - washed activated carbon (2) and hydrogenate the mixture at 1·1 atmospheres until absorption ceases (2–5 hours). Collect the catalyst on a Buchner funnel, wash it with five 100 ml. portions of water, and suck as dry as possible. Dry the catalyst at room temperature (3) and then over potassium hydroxide pellets or anhydrous calcium chloride in a vacuum desiccator. Powder the catalyst (12–12·5 g.) and store it in a tightly-stoppered bottle.

C. **Palladium on carbon catalyst (5 per cent. Pd).** Suspend 41·5 g. of nitric acid - washed activated carbon in 600 ml. of water in a 2-litre beaker and heat to 80°. Add a solution of 4·1 g. of anhydrous palladium chloride (1) in 10 ml. of concentrated hydrochloric acid and 25 ml. of water (prepared as in *A*), followed by 4 ml. of 37 per cent. formaldehyde solution. Stir the suspension mechanically, render it alkaline to litmus with 30 per cent. sodium hydroxide solution and continue the stirring for a further 5 minutes. Filter off the catalyst on a Buchner funnel, wash it ten times with 125 ml. portions of water, and dry and store as in *B*. The yield is 46 g.

D. **Palladium on barium sulphate catalyst (5 per cent. Pd).** (4) Prepare a solution of 4·1 g. of anhydrous palladium chloride (1) in 10 ml. of concentrated hydrochloric acid and 25 ml. of water (as in *A*). Add all at once 60 ml. of 6*N*-sulphuric acid to a rapidly stirred, hot (80°) solution of 63·1 g. of A.R. crystallised barium hydroxide in 600 ml. of water contained in a 2-litre beaker. Add more 6*N*-sulphuric acid to render the suspension just acid to litmus (5). Introduce the palladium chloride solution and 4 ml. of 37 per cent. formaldehyde solution into the hot mechanically-stirred suspension of barium sulphate. Render the suspension slightly alkaline with 30 per cent. sodium hydroxide solution, continue the stirring for 5 minutes longer, and allow the catalyst to settle. Decant the clear supernatant liquid, replace it by water and resuspend the catalyst. Wash the catalyst by decantation 8–10 times and then collect it on a medium - porosity sintered glass funnel, wash it with five 25 ml. portions of water and suck as dry as possible. Dry the funnel and contents at 80°, powder the catalyst (48 g.), and store it in a tightly-stoppered bottle.

Notes.

(1) Alternatively, the equivalent quantity of palladium chloride dihydrate may be used.

(2) Any of the commercial forms of activated carbon (Norit, Darco, etc.) may be employed ; the carbon should be heated on a steam bath with 10 per cent. nitric acid for 2–3 hours, washed free from acid with water, and dried at 100–110° before use.

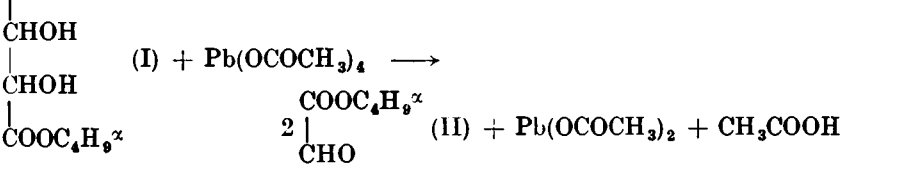
(3) Heating may cause ignition of the carbon.

(4) This is an improvement on the procedure described in Section IV,120,*Note* 3.

(5) Where it is advantageous to maintain the neutrality of the hydrogenation mixture, **palladium upon barium carbonate catalyst** is recommended : the barium hydroxide and sulphuric acid are then replaced by 46·5 g. of precipitated barium carbonate and the volume of hydrochloric acid is reduced to 4·1 ml.

VI,37. OXIDATION WITH LEAD TETRA-ACETATE *n*-BUTYL GLYOXYLATE

An interesting application of lead tetra-acetate is to the preparation of the otherwise difficulty-accessible *n*-butyl glyoxylate (II) by oxidation of di-*n*-butyl *d*-tartrate (I) :



Place a mixture of 125 ml. of A.R. benzene and 32·5 g. of di-*n*-butyl *d*-tartrate (1) in a 500 ml. three-necked flask, equipped with a Hershberg stirrer (Section **II,7**) and a thermometer. Stir the mixture rapidly and add 58 g. of lead tetra-acetate (Section **II,50**,*15*) in small portions over a period of 20 minutes whilst maintaining the temperature below 30° by occasional cooling with cold water. Continue the stirring for a further 60 minutes. Separate the salts by suction filtration and wash with two

25 ml. portions of benzene. Remove the benzene and acetic acid from the filtrate by flash distillation (compare Section **II,13**) and distil the residue under diminished pressure, preferably in a slow stream of nitrogen. Collect the *n*-butyl glyoxylate (2) at 66–69°/5 mm. The yield is 26 g.

Notes.

(1) The purified commercial di-*n*-butyl *d*-tartrate, m.p. 22°, may be used. It may be prepared by using the procedure described under *iso*-propyl lactate (Section **III,102**). Place a mixture of 75 g. of *d*-tartaric acid, 10 g. of Zeo-Karb 225/H, 110 g. (135 ml.) of redistilled *n*-butyl alcohol and 150 ml. of sodium-dried benzene in a 1-litre three-necked flask equipped with a mercury-sealed stirrer, a double surface condenser and an automatic water separator (see Fig. *III, 126*, 1). Reflux the mixture with stirring for 10 hours : about 21 ml. of water collect in the water separator. Filter off the ion-exchange resin at the pump and wash it with two 30–40 ml. portions of hot benzene. Wash the combined filtrate and washings with two 75 ml. portions of saturated sodium bicarbonate solution, followed by 100 ml. of water, and dry over anhydrous magnesium sulphate. Remove the benzene by distillation under reduced pressure (water pump) and finally distil the residue. Collect the di-*n*-butyl *d*-tartrate at 150°/1·5 mm. The yield is 90 g.

(2) Store the *n*-butyl glyoxylate under nitrogen ; it undergoes autoxidation in air. The product decomposes on boiling (159–161°) at atmospheric pressure.