CHAPTER V

SOME HETEROCYCLIC AND ALICYCLIC COMPOUNDS

V,1. QUINOLINE

Quinoline may be prepared by heating a mixture of aniline, anhydrous glycerol and concentrated sulphuric acid with an oxidising agent, such as nitrobenzene. The reaction with nitrobenzene alone may proceed with extreme violence, but by the addition of ferrous sulphate, which appears to function as an oxygen carrier, the reaction is extended over a longer period of time and is under complete control.

The formation of quinoline probably takes place through the following stages :—

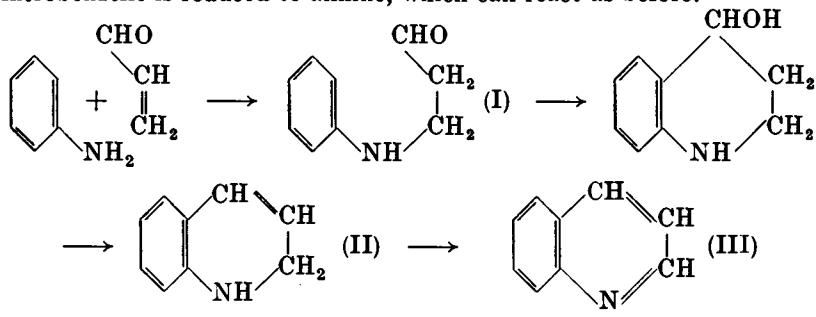
(i) The glycerol and sulphuric acid react together to give acrolein :

$$CH_2OHCHOHCH_2OH \xrightarrow{-2H_2O} CH_2{=}CHCHO$$

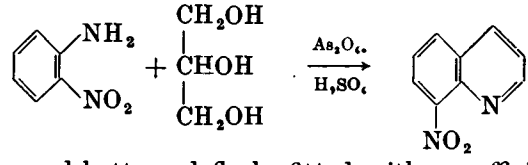
(ii) Addition of aniline to acrolein to form β-phenylaminopropionic aldehyde (I).

(iii) Ring closure of I, followed by dehydration, to produce 1 : 2-dihydroquinoline (II).

(iv) Oxidation of the dihydroquinoline by the nitrobenzene to quinoline (III); the nitrobenzene is reduced to aniline, which can react as before.



The synthesis can be carried out with most aromatic amines and is usually termed the **Skraup reaction.** The nitrobenzene is frequently replaced by arsenic acid, as in the preparation of **8-nitroquinoline** from o-nitroaniline :



In a 2 litre round-bottomed flask, fitted with an efficient reflux condenser, place, in the following order, 16 g. of powdered crystallised ferrous sulphate, 173 g. (137·5 ml.) of anhydrous glycerol (1), 43 g. (42 ml.) of aniline and 34 g. (28 ml.) of nitrobenzene. Mix thoroughly and add slowly, and with shaking, 80 ml. of concentrated sulphuric acid. With the reflux condenser in place, heat the mixture cautiously either with a free flame or over a wire gauze until the mixture just begins to boil, and then remove the flame at once. The heat evolved in the reaction will suffice to keep the mixture boiling for about 20 minutes. (If the reaction is too vigorous at the outset, the action of the reflux condenser

may be assisted by placing a wet towel or cloth upon the upper part of the flask.) When boiling ceases, replace the burner, and boil the mixture for 5 hours longer. Allow the mixture to cool, add 100 ml. of water and steam distil from the same flask (Fig. *II*, *40*, 1) in order to remove the excess of nitrobenzene. Change the receiver and allow the contents of the flask to cool : add a solution of 150 g. of sodium hydroxide in 300 ml. of water cautiously and with shaking to the flask and again steam distil until no further oil passes over with the water (collect 1500–2000 ml. of distillate). The distillate contains the quinoline and some aniline. Extract the oil with ether and distil off the ether.

To remove the aniline present in the residual crude quinoline, advantage is taken of the fact that quinoline chlorozincate $[(C_9H_7N)_2ZnCl_4]H_2$ is almost insoluble in water and crystallises out, whilst, under the same experimental conditions, aniline chlorozincate $[(C_6H_7N)_2ZnCl_4]H_2$ remains in solution (2). Dissolve the crude quinoline in 600 ml. of dilute hydrochloric acid (1 : 4 by volume), warm the solution to 60°, and add a solution of 70 g. of zinc chloride in 120 ml. of dilute hydrochloric acid. The quinoline chlorozincate soon commences to crystallise. Cool the well-stirred mixture thoroughly in ice water, and, when crystallisation is complete, filter with suction, wash well with dilute hydrochloric acid, and drain thoroughly. Transfer the solid to a beaker, add a little water, then 10 per cent. sodium hydroxide solution until the initial precipitate of zinc hydroxide completely redissolves. Extract the quinoline with two 100 ml. portions of ether, and dry the combined extracts with about 5 g. of anhydrous magnesium sulphate. Distil off the ether from a 100 ml. distilling (better, Claisen) flask (Fig. *II*, *13*, 4) ; replace the water condenser by an air condenser and distil the quinoline, using an air bath (Fig. *II*, *5*, 3). Collect the fraction b.p. 235–238° (mainly 235°). The yield of quinoline (a very pale yellow liquid) is 52 g. To obtain a colourless product, the quinoline should be distilled under reduced pressure : b.p. 118–120°/20 mm.

Notes.

(1) **Anhydrous glycerol may be prepared by heating commercial glycerol in a porcelain evaporating dish carefully over a wire gauze (preferably in a fume cupboard), stirring it steadily with a thermometer until the temperature rises to 180°, allowing it to cool to about 100°, pouring it into a Pyrex beaker and transferring the beaker to a large desiccator containing concentrated sulphuric acid. It must be remembered that glycerol is a very hygroscopic substance.**

If the approximate water content of commercial glycerol is known, the above dehydration may be avoided by adding sufficient SO_3 in the form of oleum to the concentrated sulphuric acid employed in the Skraup reaction to combine with all the water present.

(2) ***An alternative method of removing the aniline*** **is to add 30 ml. of concentrated sulphuric acid carefully to the steam distillate, cool the solution to 0–5°, and add a concentrated solution of sodium nitrite until a drop of the reaction mixture colours potassium iodide-starch paper a deep blue instantly. As the diazotisation approaches completion, the reaction becomes slow ; it will therefore be necessary to test for excess of nitrous acid after an interval of 5 minutes, stirring all the while. About 12 g. of sodium nitrite are usually required. The diazotised solution is then heated on a boiling water bath for an hour (or until active evolution of nitrogen ceases), treated with a solution of 60 g. of sodium hydroxide in 200 ml. of water, the mixture steam-distilled, and the quinoline isolated from the distillate by extraction with ether as above.**

COGNATE PREPARATIONS

8-Nitroquinoline. Place a mixture of 69 g. of *o*-nitroaniline, 86 g. of arsenic pentoxide and 184 g. of *anhydrous* glycerol in a 500 ml. three-necked flask, fitted with a glycerine-sealed stirrer, a thermometer, and a reflux condenser. Set the stirrer in motion, heat to 100° (oil bath), and add 220 g. (120 ml.) of concentrated sulphuric acid gradually through the condenser at such a rate that the temperature does not rise above 120° (about 20 minutes). Insert a cotton wool (or calcium chloride) guard tube into the top of the condenser, gradually raise the temperature to 130–135° and maintain this temperature for 7–8 hours. Watch the reaction during the first hour of heating: should the reaction become very vigorous, lower the oil bath momentarily. Allow the contents of the flask to cool and pour into 1500 ml. of water contained in a 2-litre beaker. Add 15 g. of decolourising carbon, stir mechanically, heat at 90° for 1 hour, and filter. Neutralise the cold filtrate slowly with dilute ammonium hydroxide solution (1 : 1), filter off the crude nitro compound at the pump, and wash with a little water. Recrystallise from hot water or from methyl alcohol. The yield of 8-nitroquinoline, m.p. 92°, is 45 g.

8-Hydroxyquinoline ("**oxine**"). The technique adopted in this preparation is based upon the fact that, in general, the reactants glycerol, amine, nitro compound and sulphuric acid can be mixed with temperature control, and then maintained at any convenient temperature below 120° without any appreciable chemical reaction taking place. A pre-mix of the amine, glycerol and sulphuric acid, maintained at a temperature which keeps it fluid (60–90°), is added in portions to a reaction vessel containing the nitro compound and warmed with stirring to 140–170° at which temperature the Skraup reaction takes place.

Place 170 ml. of concentrated sulphuric acid in a 1-litre three-necked flask provided with a stirrer, and add 112·5 g. of *o*-aminophenol, followed by 287 g. of glycerol: maintain the temperature below 80° by cooling, if necessary. Keep the mixture in a fluid state by placing the flask on a steam bath.

In a 3-litre three-necked flask, fitted with a thermometer, stirrer and reflux condenser, place 72·5 g. of *o*-nitrophenol and 10 g. of crystallised ferrous sulphate, and heat to 100–120°. Add the liquid amine - glycerol - sulphuric acid pre-mix in about 10 portions over 2 hours: allow the reaction to proceed at 135–150° before adding the subsequent portions. Reflux the mixture for a further 4 hours, during which time the temperature drops to about 130°. Neutralise the cooled reaction mixture with sodium hydroxide (250 g. in 50 per cent. solution) with rapid stirring and addition of ice so that the temperature does not rise above 40°. The *p*H of the resulting solution is about 7, and the 8-hydroxyquinoline together with tarry by-products precipitate. Filter the precipitate at the pump, dry at 50–60°, and then distil under reduced pressure from a Claisen flask with fractionating side arm. A little water passes over first and this is followed by 8-hydroxyquinoline at 100–110°/5 mm. It crystallises on cooling to a white solid, m.p. 74–75°. The yield of "oxine" is 140 g.

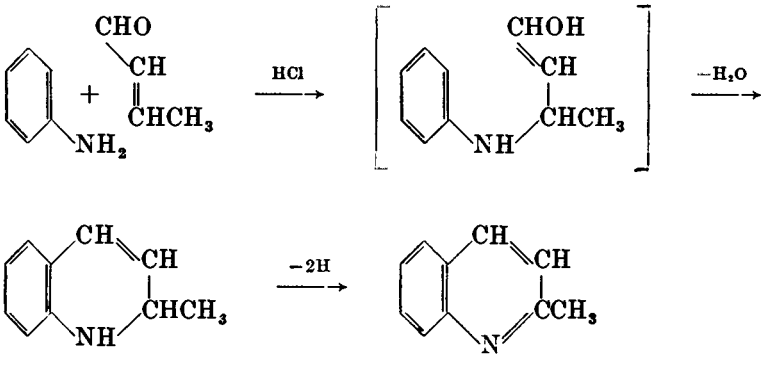
V,2. QUINALDINE

Quinoline derivatives may be synthesised by heating an aromatic amine with an aldehyde or a mixture of aldehydes in the presence of concentrated hydrochloric or sulphuric acid : this synthesis is known as the **Doebner - Miller reaction.** Thus aniline and paraldehyde afford 2-methylquinoline or quinaldine.

The reaction probably proceeds as follows. Crotonaldehyde is first formed by condensation of the depolymerised acetaldehyde in the presence of acid :

$$CH_3CHO + CH_3CHO \xrightarrow{H^+} [CH_3CH(OH)CH_2CHO] \longrightarrow CH_3CH{=}CHCHO + H_2O$$

The aniline then reacts with the $\alpha\beta$-unsaturated aldehyde by 1 : 4-addition; the addition product, under the influence of strong acid, cyclises to form 1 : 2-dihydroquinaldine.* The latter is dehydrogenated by the condensation products of aniline with acetaldehyde and with crotonaldehyde simultaneously produced (*i.e.*, ethylideneaniline and crotonylideneaniline) : these anils act as hydrogen acceptors and are thereby converted into ethylaniline and *n*-butylaniline respectively.



1 : 2-Dihydroquinaldine Quinaldine

$$C_6H_5NH_2 + CH_3CHO \xrightarrow{-H_2O} C_6H_5N{=}CHCH_3 \xrightarrow{2H} C_6H_5NHCH_2CH_3$$

$$C_6H_5NH_2 + OCHCH{=}CHCH_3 \xrightarrow{-H_2O} C_6H_5N{=}CHCH{=}CHCH_3 \xrightarrow{4H} C_6H_5NHCH_2CH_2CH_2CH_3$$

The quinaldine is separated from any unreacted aniline and from the alkylanilines by treatment with acetic anhydride, basified with sodium carbonate and steam distilled. Only the primary and secondary amines are acetylated ; the acetylated amines are now much less volatile so that separation from the steam-volatile quinaldine (a tertiary amine) is facile.

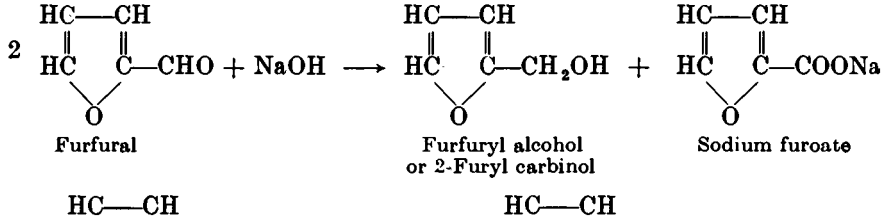
In a 1-litre round-bottomed flask, fitted with a condenser and trap (compare Fig. *II*, *13*, 8), place 62 g. (61 ml.) of aniline. Cool the flask in an ice bath, add 120 ml. of concentrated hydrochloric acid slowly, followed by 90 g. of paraldehyde : swirl the contents of the flask to ensure thorough mixing. Remove the flask from the ice bath and shake it frequently at

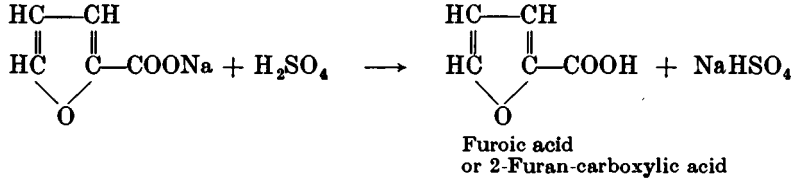
* The anil of the addition product may be the intermediate just prior to cyclisation which then takes place with the elimination of aniline.

room temperature during 1–2 hours. Heat cautiously to the boiling point: keep an ice-water bath at hand in case the reaction mixture should become unduly vigorous and require moderating. Reflux the mixture for 3 hours and allow to cool. Render alkaline with about 100 ml. of 12*N* sodium hydroxide solution and steam distil the mixture: collect about 2·4 litres of distillate. Separate the upper oily layer and extract the dissolved bases with a little chloroform (or with ether or benzene) and combine the extract with the crude oil. Dry the combined oil and extract with anhydrous magnesium sulphate, remove the solvent, and heat the residue under reflux for 20 minutes with 20 ml. of acetic anhydride. After cooling, render alkaline with sodium carbonate solution and steam distil; collect about 2·4 litres of distillate. Extract the latter with two 50 ml. portions of benzene. Distil off the benzene from the combined benzene extracts (Fig. *II*, *13*, 4) and distil the residue with the aid of an air bath (Fig. *II*, *5*, 3). Collect the pure quinaldine at 245–248°: the yield is 40 g. Alternatively, distil the quinaldine under reduced pressure; b.p. 116–118°/12 mm. Keep the colourless liquid in a well-stoppered bottle since it darkens on exposure to air.

V,3. FURFURYL ALCOHOL AND FUROIC ACID

Furfural undergoes the Cannizzaro reaction (compare *Benzaldehyde* Section IV,123) when treated with sodium hydroxide solution:





Place 200 g. (172·5 ml.) of redistilled furfural (1) in a 1 litre beaker, provided with a mechanical stirrer and surrounded by an ice bath. Start the stirrer and, when the temperature has fallen to 5–8°, add a solution of 50 g. of sodium hydroxide in 100 ml. of water from a separatory funnel at such a rate that the temperature of the reaction mixture does not rise above 20° (20–25 minutes); continue the stirring for a further 1 hour. Much sodium furoate separates during the reaction. Allow to cool to room temperature, and add just enough water to dissolve the precipitate (about 65 ml.). Extract the solution at least five times with 60 ml. portions of ether in order to remove the furfuryl alcohol: the best results are obtained by the use of the continuous extraction apparatus (charged with 350 ml. of ether) depicted in Fig. *II*, *44*, 2. Keep the aqueous layer. Dry the ethereal extract with a little anhydrous

magnesium sulphate, and distil the solution until the temperature of the *liquid* reaches 95°. Distil the residue under reduced pressure (Fig. *II,20,*1) and collect the furfuryl alcohol (a very pale yellow liquid) at 75–77°/15 mm.; the yield is 65 g. Because of the tendency to undergo polymerisation, add about 1 per cent. of its weight of urea as stabiliser if the furfuryl alcohol is to be stored.

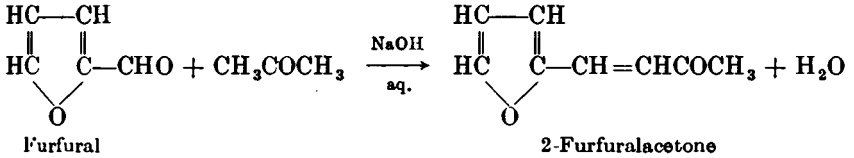
Treat the aqueous solution, containing the sodium furoate, with 40 per cent. sulphuric acid until it is acid to Congo red paper, and cool. Filter off the furoic acid, contaminated with a little sodium hydrogen sulphate, at the pump. Dissolve it in 240 ml. of boiling water, add 12 g. of decolourising carbon, boil the solution for about 45 minutes, filter hot, and cool the filtrate with stirring to 16–20°; below 16°, sodium hydrogen sulphate also separates. Filter off the furoic acid with suction, and dry. The yield is 65 g., m.p. 123–124°. It may be further purified either by recrystallisation from carbon tetrachloride to which a little decolourising carbon is added or by distillation under reduced pressure, b.p. 142–144°/20 mm.; the resulting pure acid softens at 125° and is completely melted at 132°.

Note.

(1) Furfural is best purified by distillation under reduced pressure: b.p. 54–55°/17 mm.

V,4. 2-FURFURALACETONE

Furfural condenses with acetone in the presence of sodium hydroxide solution to yield 2-furfuralacetone (compare *Benzalacetone*, Section IV,128):

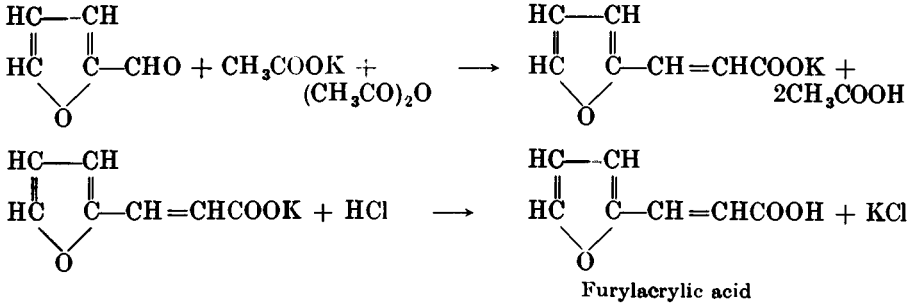


Furfural 2-Furfuralacetone

In a 1 litre bolt-head flask, equipped with a mechanical stirrer, mix 75 g. (65 ml.) of redistilled furfural (see *Note 1* to Section V,3) and 600 ml. of water. Add 100 g. (126 ml.) of A.R. acetone. Stir the mixture, cool to 10°, and add a solution of 5 g. of sodium hydroxide in 10 ml. of water; some heat is generated. Continue the stirring, without cooling, for 4 hours. Then add 10 per cent. sulphuric acid (about 70 ml.) until the mixture is acid to litmus, whereupon the milkiness disappears and the liquid separates out into layers. Separate the lower organic layer, dry it with a little anhydrous magnesium sulphate, and distil under reduced pressure from a Claisen flask with fractionating side arm (Figs. *II, 24,* 2–5). Collect the furfuralacetone at 114–118°/10 mm.; it solidifies on cooling (m.p. 38–39°) and weighs 65 g. The residue of high boiling point material in the flask contains much difurfuralacetone (compare *Dibenzalacetone*, Section IV,128).

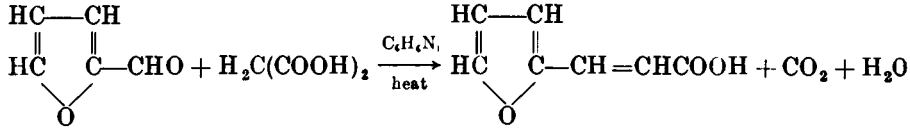
V,5. FURYLACRYLIC ACID

Furfural condenses with acetic anhydride and potassium acetate to give furylacrylic acid (compare Perkin reaction, *Cinnamic Acid*, Section IV,124):



Furylacrylic acid

The acid may also be prepared by the condensation of furfural with malonic acid in the presence of pyridine; furylmalonic acid is intermediately formed, which is decomposed upon heating in the presence of the base:



Method 1. Place 48 g. (41·5 ml.) of freshly distilled furfural (see *Note 1* to Section V,3), 77 g. (71 ml.) of pure acetic anhydride and 49 g. of dry, powdered, freshly fused potassium acetate in a 500 ml. two- or three-necked flask, provided with a mechanical stirrer and a long air condenser. Heat the flask, with stirring, in an oil bath at 150° (bath temperature) for 4 hours: when the temperature approaches 145–150°, a vigorous exothermic reaction sets in and must be controlled by the application of cold wet towels (or cloths) to the flask in order to avoid too vigorous boiling. Allow to cool slightly, transfer the reaction mixture to a 1 litre round-bottomed flask and add 600 ml. of water: use part of this to rinse out the reaction flask. Boil the mixture with 6 g. of decolourising charcoal for 10 minutes, and filter hot through a pre-heated Buchner funnel into a pre-heated filter flask. Transfer the hot filtrate to a beaker, add dilute hydrochloric acid (1 : 1) until it is acid to Congo red paper, and cool to about 10° with stirring. Allow to stand for at least one hour, filter at the pump, and wash with a little ice water. The yield of crude furylacrylic acid (a light tan solid), m.p. 138–139°, is 41 g. A perfectly pure acid (white solid), m.p. 140°, is obtained by recrystallisation from benzene or light petroleum, b.p. 80–100°, with the addition of a little decolourising carbon; the loss is about 20 per cent.

Method 2. Place 48 g. (41·5 ml.) of freshly-distilled furfural, 52 g. of dry malonic acid (1), and 24 ml. of dry pyridine (2) in a 500 ml. round-bottomed flask, fitted with a reflux condenser. Heat the flask on a boiling water bath for 2 hours, cool the reaction mixture and dilute with 50 ml. of water. Dissolve the acid by the addition of concentrated ammonia solution, filter the solution and wash the filter paper with a

little water. Add dilute hydrochloric acid (1 : 1), with stirring, to the combined filtrate and washings until acid to Congo red paper, and cool in an ice bath for at least one hour. Filter the furylacrylic acid and wash it with a little ice water ; it weighs 63 g. after drying and melts at 139–140°. A purer acid may be obtained by recrystallisation as in *Method 1.*

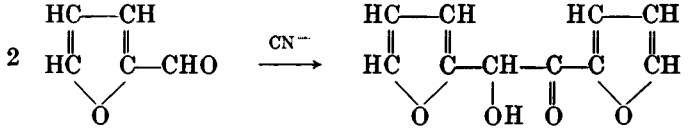
Notes.

(1) Commercial malonic acid is dried at 90–100° for 2 hours.

(2) The pyridine is dried by allowing it to stand, with frequent shaking, over potassium hydroxide pellets and then filtering.

V,6. FUROIN

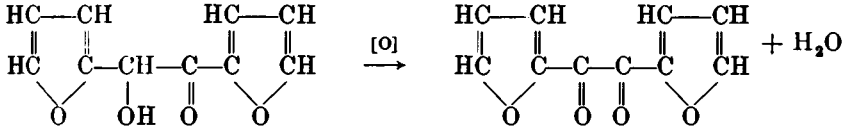
Furfural undergoes condensation to furoin under the catalytic influence of cyanide ions in aqueous alcohol solution (compare *Benzoin*, Section IV,125) :



In a 1 litre three-necked flask, equipped with a mechanical stirrer, a reflux condenser and a separatory funnel, place 400 ml. of water, 200 g. (172·5 ml.) of freshly distilled furfural (see Section V,3, *Note 1*) and 150 ml. of rectified spirit. Heat the reaction mixture to boiling, remove the flame and, when the liquid has just ceased to boil, add with stirring a solution of 10 g. of potassium cyanide in 30 ml. of water from the separatory funnel as rapidly as the vigour of the reaction permits. When the ebullition subsides (exothermic reaction), heat to boiling for a further 5 minutes. Acidify the reaction mixture with glacial acetic acid (use litmus paper) and allow to cool overnight, preferably in an ice chest or a refrigerator. Filter off the dark crystals at the pump, wash with cold water, and then with cold methyl alcohol to remove as much of the tar (colouring matter) as possible. Recrystallise from methyl alcohol with the addition of about 10 g. of decolourising carbon. The yield of furoin, m.p. 135–136°, is 75 g. If the m.p. is slightly low, another recrystallisation from toluene - ethyl alcohol will give satisfactory results.

V,7. FURIL

Furoin is conveniently oxidised by a copper sulphate - pyridine mixture to furil.



Furoin Furil

Mount a 1 litre bolt-head flask, fitted with a mechanical stirrer, on a water bath. Place 158 g. of powdered copper sulphate pentahydrate, 210 g. (214 ml.) of pyridine and 90 ml. of water in the flask, start the

stirrer, and heat the mixture on the water bath until it is homogeneous. Add 57·5 g. of powdered furoin (Section V,6). Stir and heat the mixture for 2 hours : the colour changes from a deep blue to a deep green with a brownish tinge after a short time. Pour the reaction mixture into 1 litre of water (1), filter the solid with suction, and wash it with water until the washings are colourless. Wash the black residue with 500 ml. of cold methyl alcohol, and recrystallise from methyl alcohol to which 25 g. of decolourising carbon has been added (2). The yield of furil (yellow needles), m.p. 165–166°, is 36 g.

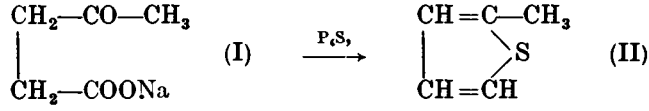
Notes.

(1) If preferred, the reaction mixture may be cooled, and the crude furil filtered through a sintered glass funnel. The filtrate (containing the copper sulphate-pyridine mixture) is re-oxidised by passing oxygen through it for about 15 hours. An excellent alternative method of preparation is provided by suitable adaptation of Section IV,126, *Method 2*.

(2) Benzene is an alternative solvent.

V,8. 2-METHYLTHIOPHENE

Dry distillation of sodium laevulinate (I) with phosphorus sulphide gives 2-methylthiophene (II) as the main product :



Mix intimately in a mortar 100 g. of sodium laevulinate, 250 g. of phosphorus sulphide (1) and 50 g. of clean dry sand. Place the mixture in a flask fitted with a condenser for distillation and a receiver (2). Heat the flask with a free flame until the reaction commences, and then remove the flame. When the reaction subsides, continue the heating until distillation ceases. Wash the distillate with 10 per cent. sodium hydroxide solution to remove acidic by-products and steam distil. Separate the crude 2-methylthiophene from the steam distillate, dry over anhydrous calcium sulphate, and distil from a little sodium. Collect the pure compound at 113° ; the yield is 30 g.

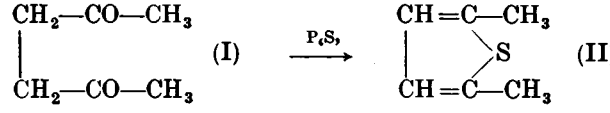
Notes.

(1) Commercial " phosphorus trisulphide " is largely P_4S_7. Phosphorus heptasulphide is available *inter alia* from the Oldbury Electrochemical Company.

(2) A slightly improved yield is obtained by conducting the dry distillation in a stream of carbon dioxide.

V,9. 2 : 5-DIMETHYLTHIOPHENE

2 : 5-Dimethylthiophene (II) is readily prepared by interaction of phosphorus sulphide and acetonylacetone (I) :



To 125 g. of finely powdered phosphorus sulphide (1) contained in a 500 ml. round-bottomed flask fitted with a reflux condenser, add 60 g. (62 ml.) of redistilled acetonylacetone (2). Heat cautiously at first until

a spontaneous reaction sets in : when the reaction is over, heat under reflux for 15 minutes. Arrange the condenser for distillation and distil until crystals commence to form in the condenser. Wash the distillate successively with 10 per cent. sodium hydroxide solution and water, dry over anhydrous calcium sulphate, and distil. Collect the 2 : 5-dimethylthiophene at 135–136°. The yield is 42 g.

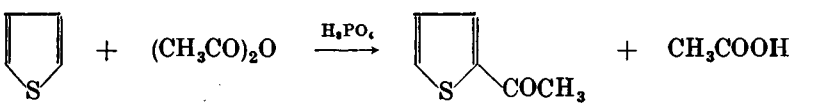
Notes.

(1) See *Note* 1 in Section V,8.

(2) Acetonylacetone is available commercially as a by-product of the manufacture of acetic acid from acetylene. It may be prepared by condensation of chloroacetone with ethyl sodioacetoacetate ; the resulting ethyl acetonylacetoacetate when heated with water under pressure at 160° undergoes ketonic scission to give acetonylacetone.

V,10. 2-ACETYLTHIOPHENE

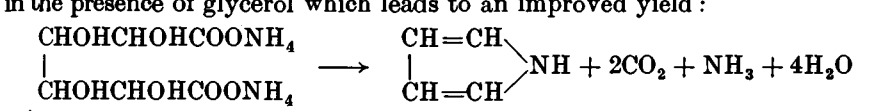
2-Acetylthiophene is prepared by the acetylation of thiophene with acetic anhydride in the presence of orthophosphoric acid :



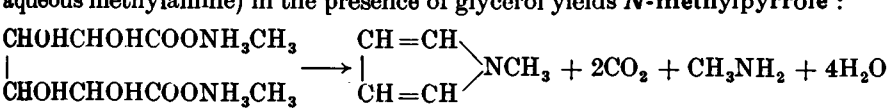
Place 84 g. (79 ml.) of thiophene and 58 g. (54 ml.) of acetic anhydride in a 500 ml. three-necked flask, fitted with a thermometer, mechanical stirrer and reflux condenser. Heat the stirred solution to 70–75°, remove the source of heat, and add 5 g. (6 ml.) of 85–89 per cent. orthophosphoric acid. An exothermic reaction occurs after 2–3 minutes and the temperature may rise to 90° ; immerse the flask in a bath of cold water to control the reaction. When the boiling subsides (*ca.* 5 minutes), reflux the mixture for 2 hours. Add 125 ml. of water, stir for 5 minutes, transfer the cold reaction mixture to a separatory funnel, remove the water layer, wash with two 50 ml. portions of 5 per cent. sodium carbonate solution, and dry over anhydrous magnesium sulphate. Distil the orange-red liquid through a short fractionating column (or from a Claisen flask with fractionating side arm, Figs. *II*, *24*, 3–5) at atmospheric pressure and thus recover 38 g. of unchanged thiophene at 83–84°. Distil the residue under reduced pressure and collect the 2-acetylthiophene at 89–90°/10 mm. ; this solidifies on cooling in ice, m.p. 10° The yield is 50 g.

V,11. PYRROLE

Pyrrole is obtained by distilling the ammonium salt of mucic acid, preferably in the presence of glycerol which leads to an improved yield :



Pyrolysis of the methylamine salt (produced by neutralising mucic acid with aqueous methylamine) in the presence of glycerol yields ***N*-methylpyrrole** :



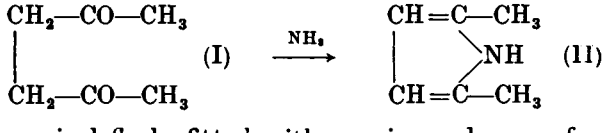
Place 210 g. of mucic acid (Section **III,138**) and 300 ml. of concentrated ammonia solution (sp. gr. 0·88) in a large evaporating dish and rapidly stir the mixture to a smooth paste (*FUME CUPBOARD!*). Evaporate the paste to dryness on a water bath, powder the resulting ammonium mucate and mix it with 120 ml. of glycerol in a 2-litre round-bottomed Pyrex flask. Allow to stand overnight. Arrange for distillation with a filter or distilling flask as receiver; connect the latter to a gas trap (Fig. *II*, *8*, 1, *c*). Distil the mixture carefully with a free flame. Apply the heat initially to one side of the flask so that only a portion of the mass is heated to the reaction temperature: considerable frothing ensues and this must be controlled by removing the flame from below the flask and heating the upper portion of the vessel above the surface of the boiling mixture. Extend the heating as rapidly as possible throughout the mass with due regard to the control of the foaming. Continue the distillation until a sample of the distillate no longer gives oily drops when treated with solid potassium hydroxide; the total volume of distillate is 300–350 ml. Redistil the distillate until no further oil separates in the liquid which passes over. Separate the oil, dry it *rapidly* with potassium hydroxide pellets, and distil. Collect the pyrrole (a colourless liquid) at 127–131°: the yield is 25 g. The pyrrole should be stored in a sealed vessel; it darkens upon exposure to light.

Cognate Preparation

***N*-Methylpyrrole.** Prepare the methylamine salt of mucic acid by adding slowly and with vigorous stirring 260 ml. of 10*N* aqueous methylamine to 210 g. of mucic acid; if difficulty is experienced in stirring the mixture, add up to 100 ml. of water. Complete the preparation following the experimental conditions given above for *Pyrrole*. The yield of *N*-methylpyrrole, b.p. 110–113°, is 32 g. The compound is very hygroscopic and darkens on standing; keep it in a tightly-stoppered, brown bottle.

V,12 2 : 5-DIMETHYLPYRROLE

2 : 5-Dimethylpyrrole (II) is obtained by heating acetonylacetone (I) with ammonium carbonate at 100°:

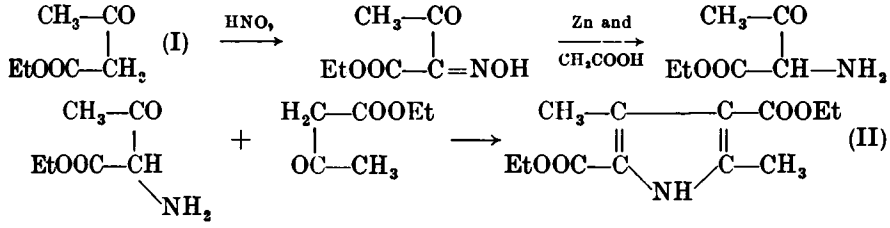


In a 250 ml. conical flask, fitted with an air condenser of wide bore, place 50 g. (51·5 ml.) of acetonylacetone (see Section **V,9**, *Note* 2) and 100 g. of ammonium carbonate (lump form). Heat the mixture in an oil bath at 100° until effervescence stops (60–90 minutes); some ammonium carbonate (or carbamate) sublimes into the condenser and this must be pushed back into the reaction mixture by means of a stout glass rod. Replace the air condenser by a Liebig's condenser with wide bore inner tube and reflux the mixture gently (bath temperature, 115°) for a further 30 minutes; dissolve the solid which has sublimed into the condenser in about 5 ml. of hot water and return the solution to the reaction mixture.

Cool: separate the upper yellow layer of crude dimethylpyrrole; extract the lower layer with 10 ml. of chloroform and combine it with the crude dimethylpyrrole. Carry out the foregoing operations with minimum exposure to air. Dry over anhydrous magnesium sulphate in a tightly stoppered flask filled with nitrogen. Transfer to a Claisen flask with fractionating side arm (Figs. *II,24*, 2–5); displace the air from the apparatus by nitrogen and distil under reduced pressure, preferably in a stream of nitrogen. Collect the 2 : 5-dimethylpyrrole at 78–80°/25 mm. The yield is 36 g. Store the product in an inert atmosphere in a sealed, dark glass container.

V,13. 2 : 4-DIMETHYL-3 : 5-DICARBETHOXYPYRROLE

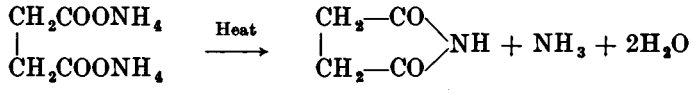
The preparation of 2 : 4-dimethyl-3 : 5-dicarbethoxypyrrole (II) is an example of the **Knorr synthesis of pyrrole derivatives**, involving the reaction of an α-aminoketone (or a derivative thereof) with a reactive methylene ketone (or a derivative thereof). The stages in the present synthesis from ethyl acetoacetate (I) may be represented as follows:



In a 1500 ml. three-necked flask, fitted with a dropping funnel and a liquid-sealed mechanical stirrer, place 195 g. (190 ml.) of ethyl acetoacetate (Section **III,151**) and 450 ml. of glacial acetic acid. Cool the solution in an ice-salt mixture to 5°; add a cold solution of 52 g. of A.R. sodium nitrite in 75 ml. of water dropwise and with vigorous stirring at such a rate that the temperature remains between 5° and 7° (about 30 minutes) stir for a further 30 minutes, and keep at room temperature for 4 hours. Replace the dropping funnel by a wide-bore condenser: close the third neck with a stopper. Stir the solution vigorously and add 100 g. of zinc powder (of purity $\not<$ 80 per cent.; the weight given is for 100 per cent. material) in portions of about 10 g.; introduce the first 3 or 4 portions quickly so that the liquid is kept boiling. Keep a bath of ice water and also wet towels at hand to control the reaction should it become violent or foam badly. When all the zinc has been added (about 45 minutes), reflux the mixture for 1 hour; if stirring becomes difficult, add some acetic acid. While still hot, decant the contents of the flask into 5 litres of water vigorously stirred in a crock. Wash the zinc residue with two 25 ml. portions of hot glacial acetic acid and decant these into the water also. Keep overnight, collect the crude product by suction filtration, wash with two 250 ml. portions of water, and dry in the air to constant weight. The yield of crude product is 114 g., m.p. 127–130°. Recrystallisation from hot 95 per cent. ethanol gives pure 2 : 4-dimethyl-3 : 5-dicarbethoxypyrrole as pale yellow crystals, m.p. 136–137°; the recovery is about 80 per cent.

V,14. SUCCINIMIDE

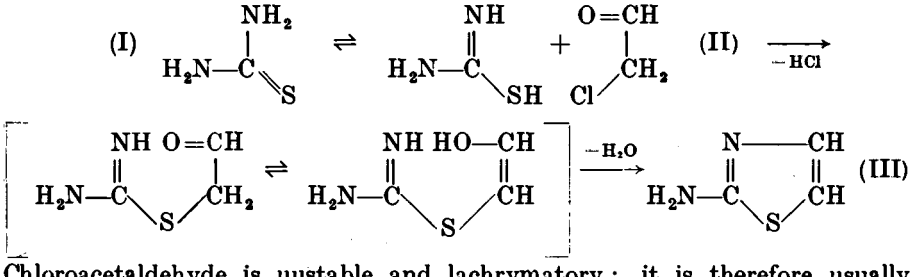
The thermal decomposition of ammonium succinate gives a good yield of succinimide :



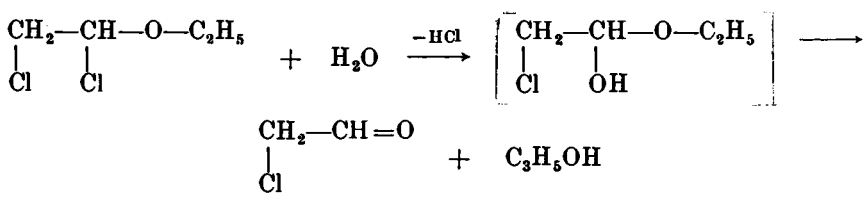
In a 250 ml. distilling flask, fitted with an air condenser 40 cm. long and 10 mm. in diameter, place 59 g. of succinic acid, and add slowly, with cooling and shaking, 70 ml. of concentrated ammonia solution, sp. gr. 0·88. Most of the acid dissolves forming a clear solution ; insert a thermometer into the mouth of the flask. Attach a 150 ml. distilling flask to the lower end of the air condenser and support it in a large funnel so that it may be water-cooled ; attach the side arm of the distilling flask receiver to a device for the absorption of ammonia (*e.g.*, Fig. *II*, *8*, 1, *c*). Heat the mixture gently with a free flame ; the temperature soon rises to 100° and remains at this point until about 50 ml. of water has passed over. Then heat more strongly : the ammonium succinate commences to decompose with evolution of ammonia and the temperature falls to about 97° during the distillation of the next 7 ml. When the temperature rises to 102°, change the receiver and collect an intermediate fraction from 102° to 275°. Change the receiver again and collect the succinimide at 275–290° (largely 285–289°) ; stop the distillation when the tarry residue begins to decompose with the evolution of yellow fumes. The crude succinimide solidifies completely and weighs 42 g. Recrystallise from rectified spirit (1 ml. per gram of solid), cool the solution to 0° for some hours, filter the crystals at the pump, and wash them with 6 ml. of ice-cold alcohol. The yield of pure succinimide, m.p. 124–125°, is 39 g.

V,15. 2-AMINOTHIAZOLE

2-Aminothiazole (III) is prepared by the condensation of chloroacetaldehyde (II) with thiourea (I). The reaction may be represented as follows :



Chloroacetaldehyde is unstable and lachrymatory : it is therefore usually generated *in situ* by the action of water upon αβ-dichloroethyl ethyl ether :



αβ-Dichloroethyl ethyl ether is obtained commercially by the chlorination of diethyl ether.

Monochloroacetone and thiourea yield **2-amino-5-methylthiazole.**

Place a solution of 76 g. of thiourea in 200 ml. of warm water in a 500 ml. three-necked flask equipped with a dropping funnel, sealed mechanical stirrer and reflux condenser. Add 143 g. (122 ml.) of αβ-dichloroethyl ethyl ether and heat the mixture under gentle reflux with stirring for 2 hours. As the reaction proceeds, the two layers gradually merge. To the cold solution add sufficient solid sodium hydroxide to liberate the 2-aminothiazole from its salt. Add ether to dissolve the product, dry the ethereal extract with anhydrous magnesium sulphate, and evaporate the ether. Recrystallise the crude 2-aminothiazole from ethanol; the resulting yellow crystalline solid has m.p. 90°. The yield is 80 g.

COGNATE PREPARATION

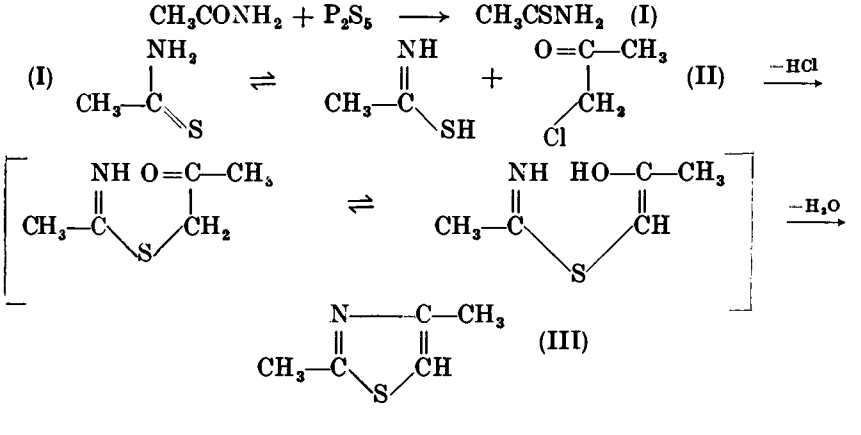
2-Amino-5-methylthiazole. Suspend 76 g. of thiourea in 200 ml. of water in a 500 ml. three-necked flask equipped as in the preceding preparation. Stir and add 92·5 g. (80 ml.) of monochloroacetone (1) over a period of 30 minutes. The thiourea dissolves as the reaction proceeds and the temperature rises. Reflux the yellow solution for 2 hours. To the cold solution immersed in an ice bath add, with stirring, 200 g. of solid sodium hydroxide. Transfer to a separatory funnel, add a little ice water, separate the upper oil layer and extract the aqueous layer with three 100 ml. portions of ether. Dry the combined oil and ether extracts with anhydrous magnesium sulphate, remove the ether by distillation from a steam bath, and distil the residual oil under diminished pressure. Collect the 2-amino-5-methylthiazole at 130–133°/18 mm.; it solidifies on cooling in ice to a solid, m.p. 44–45°. The yield is 84 g.

Note.

(1) Redistilled commercial chloroacetone, b.p. 118–120°, is used. The compound is lachrymatory. It is prepared *inter alia* by the chlorination of acetone in the cold.

V,16. 2 : 4-DIMETHYLTHIAZOLE

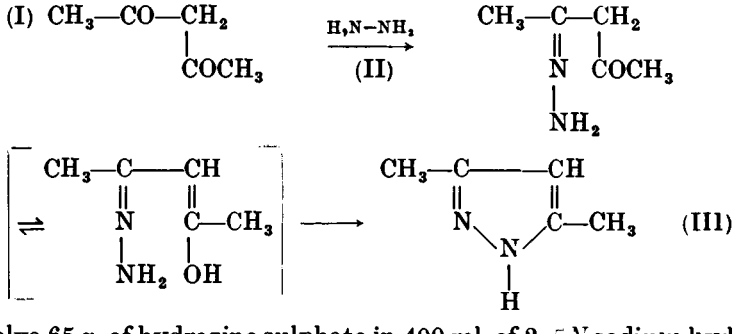
2 : 4-Dimethylthiazole (III) may be prepared from thioacetamide (I) and monochloroacetone (II). The thioacetamide is conveniently formed in the reaction mixture from acetamide and phosphorus pentasulphide.



Equip a 1-litre round-bottomed flask with a reflux condenser and a dropping funnel (compare Figs. *II, 13,* 9 and *III, 71,* 1). Prepare a mixture of 150 g. of finely powdered acetamide and 100 g. of powdered phosphorus pentasulphide quickly, transfer it rapidly into the flask and immediately add 100 ml. of dry benzene. Set up the apparatus in a fume cupboard. Prepare a mixture of chloroacetone (b.p. 118–120° : *CAUTION*—the compound is lachrymatory) and 75 ml. of dry benzene ; place it in the dropping funnel and insert a calcium chloride drying tube in the mouth. Add about 10 ml. of the chloroacetone-benzene mixture to the contents of the flask and warm gently on a water bath : remove the water bath immediately the exothermic reaction commences. Introduce the remainder of the chloroacetone in *ca.* 10 ml. portions at such intervals that the reaction is under control. When all the chloroacetone has been added, reflux the mixture on a water bath for 30 minutes. Then add 400 ml. of water to the reaction mixture with shaking ; after 20 minutes, transfer the contents of the flask to a separatory funnel, run off the lower layer into a beaker and discard the reddish upper layer containing the benzene. Make the lower layer alkaline by the addition of 20 per cent. sodium hydroxide solution : test the highly coloured aqueous solution (and not the dark dimethylthiazole floating on top of the liquid) with phenolphthalein paper. Separate the black upper layer of crude dimethylthiazole with 50 ml. of ether, and extract the aqueous layer with five 60 ml. portions of ether. Dry the combined ethereal extracts over anhydrous magnesium sulphate, and filter through glass wool. Remove the ether by distillation from a steam bath using a Claisen flask with fractionating side arm (compare Fig. *II, 13,* 4 ; insert a calcium chloride drying tube into the dropping funnel since the thiazole is hygroscopic) and fractionate the residue. Collect the fraction boiling at 140–150° and redistil it. The yield of 2 : 4-dimethylthiazole, b.p. 143–145°, is 115 g.

V,17 3 : 5-DIMETHYLPYRAZOLE

3 : 5-Dimethylpyrazole (III) may be prepared from acetylacetone (I) and hydrazine (II) (produced from hydrazine sulphate and aqueous alkali). The reaction may be represented as :

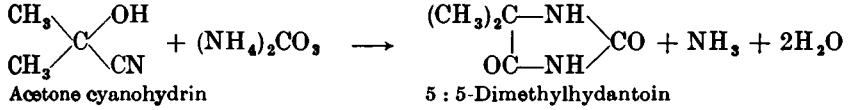


Dissolve 65 g. of hydrazine sulphate in 400 ml. of 2·5*N* sodium hydroxide solution contained in a 1-litre three-necked flask, equipped with a thermometer, mechanical stirrer and dropping funnel. Immerse the flask in an ice bath and when the temperature reaches 15° (some sodium sulphate

may separate at this point), add 50 g. (51·5 ml.) of acetylacetone (Section **VI,1**) dropwise, with stirring, whilst maintaining the temperature at 15°. When the addition is complete (after about 30 minutes), stir for 1 hour at 15° ; the dimethylpyrazole separates during this period. Add 200 ml. of water, stir to dissolve inorganic salts, transfer the contents of the flask to a separatory funnel and shake with 100 ml. of ether. Separate the layers and extract the aqueous layer with four 40 ml. portions of ether. Wash the combined ethereal extracts with saturated sodium chloride solution, dry over anhydrous potassium carbonate, remove the ether by distillation from a steam bath, and dry the residual pale yellow, crystalline 3 : 5-dimethylpyrazole under reduced pressure (*ca.* 20 mm.). The yield of solid, m.p. 107–108°, is 38 g. Recrystallise from about 250 ml. of light petroleum, b.p. 80–100°, and dry in a vacuum desiccator containing paraffin wax shavings : the yield of 3 : 5-dimethylpyrazole, of unchanged m.p., is 36 g.

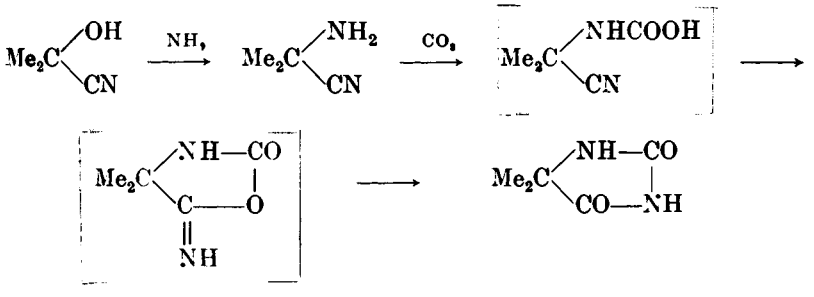
V,18. 5 : 5-DIMETHYLHYDANTOIN

Hydantoins with one or two substituents in the 5-position may be obtained by heating cyanohydrins with ammonium carbonate or with urea. Thus :



Acetone cyanohydrin 5 : 5-Dimethylhydantoin

The above reaction is an example of **Bucherer's hydantoin synthesis.** The following *mechanism* has been proposed :

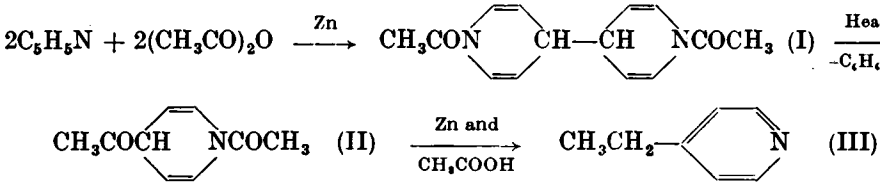


Mix 42·5 g. of acetone cyanohydrin (Section **III,75**) and 75 g. of freshly powdered ammonium carbonate in a small beaker, warm the mixture on a water bath (*FUME CUPBOARD*) and stir with a thermometer. Gentle action commences at 50° and continues during about 3 hours at 70–80°. To complete the reaction, raise the temperature to 90° and maintain it at this point until the mixture is quiescent (*ca.* 30 minutes). The colourless (or pale yellow) residue solidifies on cooling. Dissolve it in 50 ml. of hot water, digest with a little decolourising carbon, and filter rapidly through a pre-heated Buchner funnel. Evaporate the filtrate on a hot plate until crystals appear on the surface of the liquid, and then cool in ice. Filter off the white crystals with suction, drain well, and then wash twice with 4 ml. portions of ether ; this crop of crystals of dimethylhydantoin is almost pure and melts at 176°. Concentrate the mother liquor to the crystallisation point, cool in ice, and collect the

second crop of crystals (m.p. *ca.* 167°) as before. Dissolve the dimethylhydantoin (35 g.) in the minimum volume of boiling water (about 32 ml.), digest with a little decolourising carbon, and filter the hot solution through a pre-heated Buchner funnel. Cool the filtrate in ice, filter the separated crystals at the pump and wash sparingly with cold water. The yield of pure product, m.p. 178°, is 29 g.

V,19. 4-ETHYLPYRIDINE (*from Pyridine*)

When pyridine is treated with zinc dust and acetic anhydride, a type of reductive coupling occurs and the product is diacetyltetrahydrodipyridyl (I); this undergoes a curious change on heating yielding pyridine and a new diacetyl compound, 1 : 4-diacetyl-1 : 4-dihydropyridine (II). The latter is reduced by zinc and acetic acid to 4-ethylpyridine (III).



Other 4-alkylated pyridines may be prepared by the use of the appropriate anhydride.

Place a mixture of 500 ml. of acetic anhydride and 100 g. (102 ml.) of dry pyridine (Section **II,47**,*22*) in a 2-litre three-necked flask fitted with a reflux condenser, mercury-sealed stirrer and thermometer. Introduce, with stirring, 100 g. of activated zinc powder (1) in 5 g. portions over a period of 1·5–2 hours ; remove the thermometer or reflux condenser momentarily as required. The temperature rises almost immediately : maintain it at 25–30° by means of a bath of cold water. The reaction mixture acquires a green colour after 20 minutes and a yellow solid separates gradually. When the addition of the 100 g. of zinc powder is complete, stir for a further 15 minutes, and run in 100 ml. of glacial acetic acid through the condenser. Add a further 40 g. of zinc powder in 5–10 g. portions at intervals so timed that the vigorous reaction is under control and the mixture refluxes gently. Then reflux the reaction mixture, with stirring, for 30 minutes : add a further 60 g. of zinc powder all at once and continue the refluxing for 30 minutes more.

Neutralise the cold contents of the flask with 500–600 ml. of 40 per cent. aqueous sodium hydroxide solution, equip the flask for steam distillation and steam distil until about 1 litre of distillate is collected. The steam distillate separates into two layers. Add solid sodium hydroxide ($\lessdot$ 100 g.) to complete the separation of the two layers as far as possible. Remove the upper (organic) layer and extract the aqueous layer with three 50 ml. portions of chloroform. Dry the combined organic layer and chloroform extracts with anhydrous potassium carbonate and distil the mixture through a short fractionating column (*e.g.*, an 8″ Dufton column) : after a fore-run of chloroform, followed by pyridine, collect the crude 4-ethylpyridine at 150–166° (49 g.). Redistil through a Fenske-

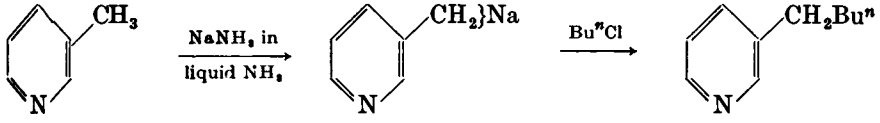
type column, 15 mm. in diameter and packed with glass helices for a length of 20 cm. (compare Fig. *II*, *24*, 5): collect the pure base at 163–165°/760 mm. (44 g.).

Note.

(1) Activate the zinc by stirring 400 g. of zinc powder with 150 ml. of 10 per cent. hydrochloric acid for 2 minutes, filter and wash with 300 ml. of water, followed by 100 ml. of acetone.

V,20. *n*-AMYLPYRIDINES (*from Picolines*)

The three picolines react with alkyl halides in liquid ammonia solution in the presence of sodamide to yield the corresponding monoalkylpyridines. α-Picoline also reacts with alkyl chlorides in the presence of sodamide either alone or in the presence of xylene to give a fair yield of monoalkylpyridine $C_5H_4N.CH_2R$. With γ-picoline under similar experimental conditions disubstitution of the alkyl group ($C_5H_4N.CHR_2$) occurs to an appreciable extent. The preparation of the three *n*-amylpyridines is described: the 3- and 4-compounds by the liquid ammonia - sodamide method and the 2-compound by the sodamide-xylene procedure.



2-*n*-Amylpyridine. Into a 500 ml. three-necked flask (fitted with a dropping funnel, mercury-sealed stirrer and reflux condenser protected by a drying tube) place a finely divided suspension (1) of 40 g. of recently prepared sodamide * in about 150 ml. of anhydrous xylene. Introduce 37·5 g. (40 ml.) of α-picoline (Section **II**,**47**,*28*) through the dropping funnel and rinse the latter with a few ml. of dry xylene. Set the stirrer in motion and add 44·5 g. (50·5 ml.) of *n*-butyl chloride over a period of 1 hour: reflux the mixture with stirring for 2–3 hours. When cold, destroy the excess of sodamide by the cautious addition of 100 ml. of water. Transfer the contents of the flask to a separatory funnel and discard the lower aqueous layer. Extract the xylene solution with four 50 ml. portions of 1 : 1-hydrochloric acid. Steam distil the acid extracts to remove traces of xylene, cool the aqueous solution and render strongly alkaline by the addition of solid sodium hydroxide: a brown oil appears. Steam distil again and collect about 700 ml. of distillate. Separate the upper layer in the steam distillate, extract the aqueous layer with ether, and dry the combined upper layer and ether extract with anhydrous potassium carbonate. After removing the ether, distil through a Fenske-type column (15 cm. diameter and packed with glass helices for a length of 12–15 cm.; compare Fig. *II*, *24*, 5) at a pressure of 50 mm. (see Fig. *II*, *23*, 7), and collect the 2-*n*-amylpyridine (42 g.) at 122·5–124·5°/50 mm. Upon redistillation, the product boils almost entirely at 105°/17 mm.

* See Section II.50,*8*. The commercial product, obtained soon after its preparation from the manufacturers, is satisfactory.

Note.

(1) The finely divided sodamide may be prepared with xylene as the medium in an improvised *ball mill*. The latter is constructed from a pair of rubber rollers, suitably mounted on a board and driven by a geared-down electric motor which is controlled by a Variac transformer. The 40 g. of recently prepared sodamide is placed with 60–100 ml. of dry xylene and 12–16 porcelain spheres of ½" diameter in a 500 ml. bottle : the bottle is closed by a cork covered with tin foil and carrying a soda-lime guard tube. Three rubber bands are placed round the bottle to prevent slipping between the bottle and the rubber rollers. The rollers are rotated at a rate of about 1 revolution per second for about 90 minutes by which time the sodamide is almost colloidal. The liquid is then poured through a slit sieve glass funnel directly into the 500 ml. three-necked flask ; the bottle is rinsed with two 25 ml. portions of dry xylene and the rinsings transferred to the flask.

4-*n*-Amylpyridine. Charge a 1-litre three-necked flask (equipped with a mercury-sealed stirrer, a dropping funnel and a short air condenser) with 600 ml. of liquid ammonia : support the flask inside a 5-litre beaker (*FUME CUPBOARD* with efficient draught !). Stir vigorously, add 0·5 g. of powdered ferric nitrate followed, after 1 minute, by 11·9 g. of clean sodium in small pieces through the short air condenser over a period of half an hour (1). Continue the stirring until the initial blue colour is replaced by a colourless or pale grey suspension of sodamide (2). Now introduce 42·0 g. (44·0 ml.) of pure γ-picoline (Section **II**,47,*30*) through the air condenser ; a green colour develops immediately. Stir for 15–20 minutes and add 46·3 g. (52·6 ml.) of *n*-butyl chloride (or an equivalent amount of *n*-butyl bromide) from the dropping funnel at such a rate that the reaction does not become unduly vigorous (*ca.* 10 minutes) : upon completion of the addition the green colour will have been discharged. Stir for a further 10–15 minutes, pour the reaction mixture into a 2-litre beaker : allow the liquid ammonia to evaporate overnight. Rinse the reaction flask with 100 ml. of water and add the rinsings to the residue in the beaker ; two layers form. Separate them and keep the upper layer of base : extract the lower layer with a little xylene and wash the xylene extract with 25 ml. of 1 : 1-hydrochloric acid. Dissolve the base in 1 : 1-hydrochloric acid, combine it with the acid washings of the xylene extract and steam distil to remove traces of xylene ; cool, add solid sodium hydroxide until strongly alkaline and steam distil again. Isolate the 4-*n*-amylpyridine as described above for the 2-*n*-amyl compound. The yield of the pure base, b.p. 95°/6 mm., is 46 g.

Notes.

(1) If the sodium is added too rapidly, the ammonia will boil vigorously and considerable loss of solvent may result.

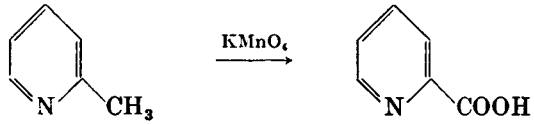
(2) It is recommended that the outside of the flask be sprayed occasionally with alcohol in order to prevent " misting " : if a small lamp is placed behind the apparatus, the colour of the liquid in the flask may be seen easily.

If much liquid ammonia is lost during the preparation of the sodamide, the volume should be made up to 500–600 ml. before adding the γ-picoline.

3-*n*-Amylpyridine. Proceed exactly as described for 4-n-*Amylpyridine* using 11·9 g. of sodium, 42 g. of β-picoline (Section **II**,47,*29*) and 46·3 g. of *n*-butyl chloride. The yield of pure 3-*n*-amylpyridine, b.p. 100·5°/9 mm., is 46 g.

V,21. PICOLINIC ACID

Picolinic acid is readily prepared by the oxidation of α-picoline with potassium permanganate :



Equip a 3-litre three-necked flask with a thermometer, mercury-sealed stirrer and a reflux condenser (Liebig pattern with a wide inner tube). Place a solution of 100 g. (106 ml.) of α-picoline (1) in 1 litre of water in the flask and heat to 70° on a water bath. Add 450 g. of potassium permanganate in 10 equal portions through the condenser over a period of 3–4 hours ; maintain the temperature at 70° for the first five additions and at 85–90° for the last five. Make each successive addition of potassium permanganate only after the preceding amount is decolourised and wash it down with 20–25 ml. of water. After the last charge of potassium permanganate is decolourised, raise the temperature to 95°, filter the hot reaction mixture with suction and wash the manganese dioxide cake on the filter with four 200 ml. portions of hot water : allow each portion to soak into the cake without application of vacuum and finally suck dry before adding fresh wash water. Evaporate down the combined filtrate and washings to a volume of about 400 ml. : allow to cool and adjust to a *p*H of 3·2 (the isoelectric point) using B.D.H. narrow-range indicator paper (about 125 ml. of concentrated hydrochloric acid are required). Picolinic acid is very soluble in water (90 g. in 100 ml. of water at 9°) and therefore does not separate at this stage. The water is best removed by azeotropic distillation with benzene, a solvent which simultaneously extracts the picolinic acid.

Fit the 3-litre three-necked flask used in the original oxidation with a thermometer, a glycerine-sealed stirrer (Fig. *II*, *7*, 10), and a large automatic water separator (*ca.* 200 ml. capacity ; see Fig. *III*, *126*, 1) surmounted by a double surface reflux condenser. Support a small funnel upon three indentations immediately above the side tube of the water-separator ; its stem should be well below the side tube so that liquid falling from the condenser cannot splash over into the flask. Transfer the solution to the flask and add 1500 ml. of benzene : heat on a water bath at 90° and stir vigorously. Continue the refluxing and stirring until no more water collects in the trap (about 12 hours). Filter the hot benzene solution through a hot water funnel and evaporate to dryness on a boiling water bath. Evaporation is best carried out under reduced pressure (water pump) since this leads to an almost colourless acid and most of the benzene is recovered ; the apparatus may consist of a 2-litre bolt-head flask, still head, double surface condenser and receiver. Return the recovered benzene to the extraction flask, stir and extract the residual solid at the temperature of a boiling water bath for a further 2 hours : evaporate the benzene extract under reduced pressure and thus obtain a second crop of picolinic acid. Carry out a third extraction with the benzene recovered

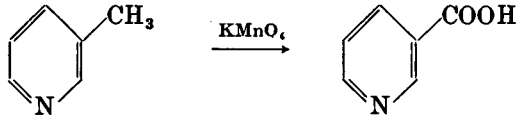
from the second extraction and thus isolate a further quantity of acid. The yields of picolinic acid, m.p. 138°, from the three extractions are 49 g., 32 g., and 3 g. respectively, *i.e.*, a total yield of 84 g. The m.p. is unaffected by recrystallisation from ethanol.

Note.

(1) Carefully fractionate the commercially "pure" α-picoline (purity > 95 per cent.) and collect the fraction of b.p. 129–130°. If time permits, this should be purified as described in Section II,47, *28*; a pure acid is thus assured.

V,22. NICOTINIC ACID

Nicotinic acid is prepared in good yield by the oxidation of β-picoline with potassium permanganate:



Dissolve 100 g. (104·5 ml.) of purified β-picoline (Section II,47,*29*) in 1 litre of water and oxidise it with 450 g. of potassium permanganate: follow the experimental details given under *Picolinic Acid* (preceding Section). Wash the manganese dioxide cake with four 500 ml. portions of water; evaporate the combined filtrate and washings to about 1250 ml. Adjust the *p*H to 3·4 (the isoelectric point) with the aid of B.D.H. narrow-range indicator paper; 120–130 ml. of concentrated hydrochloric acid are required. Allow to cool overnight, collect the voluminous precipitate of nicotinic acid by suction filtration, wash with three 50 ml. portions of cold water, and dry at 90–100°. Concentrate the filtrate to about 650 ml. and cool *slowly* to 5° and so obtain a second crop of nicotinic acid: the purpose of the slow cooling is to reduce the contamination by potassium chloride. The first crop of acid weighs 90 g. and has a purity of about 90 per cent. (1); the second crop weighs 10 g. and the purity is about 80 per cent. Recrystallise from hot water (2) and dry at 100°; the yield of pure nicotinic acid, m.p. 235°, from 90 g. of the crude acid is 67 g. A further quantity may be obtained by concentrating the mother liquor.

Notes.

(1) The impurity is potassium chloride. The approximate acid content is determined by heating a weighed sample of the acid in a crucible gently at first and finally at a red heat until no trace of black residue remains, and weighing the white residual potassium chloride.

(2) The solubility of pure nicotinic acid in 1000 ml. of water at 0°, 40°, 80° and 100° is 1·0, 2·6, 8·2 and 12·7 g. respectively.

Cognate Preparation

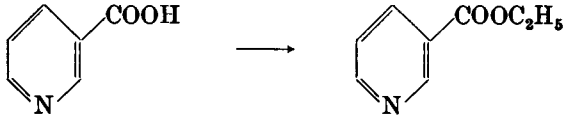
***iso*Nicotinic acid** (*pyridine-4-carboxylic acid*). This acid is prepared by oxidation of γ-picoline by potassium permanganate. Use 100 g. (104·5 ml.) of purified γ-picoline (Section II,47,*30*) and oxidise it with 450 g. of potassium permanganate: follow the experimental details given for *Nicotinic Acid*. Evaporate the combined filtrate and washings to about 1500 ml., and add concentrated hydrochloric acid until the *p*H is 3·6; *iso*nicotinic

acid precipitates. Heat to 90–95° (not all the acid dissolves) and allow the mixture to crystallise slowly. Collect the crude *iso*nicotinic acid by suction filtration, wash well with water and dry at 100°. Concentrate the mother liquor to about half the original volume and so obtain a second crop of acid. The first crop of acid weighs 85 g. (99 per cent. pure) and the second crop weighs 7 g. (80 per cent. pure). Recrystallise from hot water: the resulting *iso*nicotinic acid is pure and has a m.p. of 311° (sealed tube).

The solubility of *iso*nicotinic acid in 1000 ml. of water at 0°, 40°, 80° and 100° is 3, 9, 24 and 34 g. respectively. The solubility is appreciably less in the presence of potassium chloride.

V,23. ETHYL NICOTINATE

Ethyl nicotinate may be prepared *either* by direct esterification of the acid with ethanol and sulphuric acid, followed by pouring into water and rendering ammoniacal *or* by interaction of the acid with thionyl chloride, followed by reaction of nicotinyl chloride hydrochloride with ethanol and subsequent neutralisation.



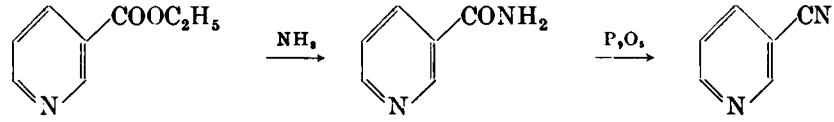
Method 1. Reflux a mixture of pure nicotinic acid (Section V,22), 84 g. (105 ml.) of absolute ethanol and 90 g. (50 ml.) of concentrated sulphuric acid in a flask for 4 hours on a steam bath. Cool the solution and pour it slowly and with stirring on to 200 g. of crushed ice. Add sufficient ammonia solution to render the resulting solution strongly alkaline: generally, some ester separates as an oil but most of it remains dissolved in the alkaline solution. Extract the solution with five 25 ml. portions of ether, dry the combined ethereal extracts with anhydrous magnesium sulphate, remove the ether and distil under reduced pressure. The ethyl nicotinate passes over at 117–118°/16 mm.: the yield is 34 g. The b.p. under normal pressure is 222–224°.

Method 2. In a 250 ml. three-necked flask, fitted with a reflux condenser, mercury-sealed stirrer and dropping funnel, place 20·5 g. of pure nicotinic acid. Cool the flask in a bath of cold water and add 90 g. (55 ml.) of redistilled thionyl chloride by means of the dropping funnel; the initial reaction is vigorous but soon subsides. Reflux the mixture on a water bath for 2 hours. Replace the reflux condenser by a condenser arranged for downward distillation and distil off the excess of thionyl chloride under reduced pressure (water pump; water bath). An almost white solid, nicotinyl chloride hydrochloride, remains. Now restore the reflux condenser to the third neck of the flask. Introduce 70 ml. of sodium-dried benzene, stir, and immerse the flask in a bath of ice water. Add 20 ml. of absolute ethanol from the dropping funnel, with stirring, during a period of 30 minutes; then reflux for 2 hours. After cooling, add 200 ml. of 20 per cent. sodium carbonate solution and continue the stirring for 10 minutes: transfer the contents of the flask to a separatory funnel, separate the benzene layer and extract the aqueous layer with two 25 ml. portions

of ether. Dry the combined benzene and ether extracts (anhydrous magnesium sulphate), distil off the solvents under atmospheric pressure from a water bath, and the residue under reduced pressure. Collect the ethyl nicotinate at 117–118°/16 mm.; the yield is 20 g.

V,24 β-CYANOPYRIDINE

Ethyl nicotinate upon treatment with concentrated ammonia solution yields nicotinamide, which gives β-cyanopyridine upon heating with phosphoric oxide:

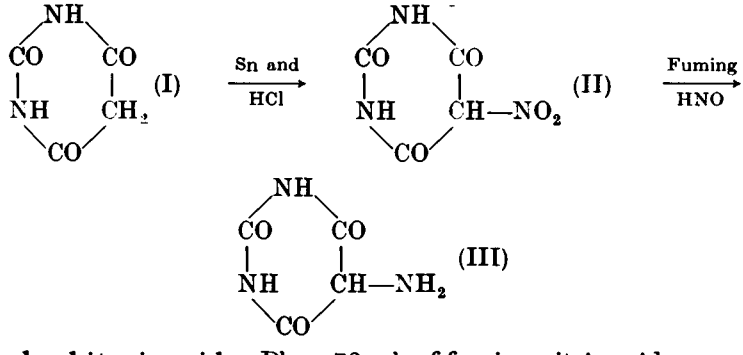


Nicotinamide. Place 50 g. of pure ethyl nicotinate (Section V,23) in a 350 ml. bolt-head flask and add 75 ml. of concentrated aqueous ammonia saturated at 0°. Keep the flask loosely stoppered for 18 hours, after which time the lower layer generally dissolves on shaking. Saturate the solution with ammonia and allow it to stand for a further 4 hours. Repeat the saturation with ammonia; crystals of the amide commence to appear in the solution. Evaporate to dryness in a dish on the steam bath and dry at 120°. The yield of nicotinamide, m.p. 130°, is usually quantitative.

β-Cyanopyridine. Mix 25 g. of powdered nicotinamide with 30 g. of phosphoric oxide in a 150 ml. distilling flask by shaking. Immerse the flask in an oil bath and arrange for distillation under a pressure of about 30 mm. Raise the temperature of the oil bath rapidly to 300°, then remove the oil bath and continue the heating with a free flame as long as a distillate is obtained. The nitrile crystallises on cooling to a snow-white solid. Redistil the solid at atmospheric pressure; practically all of it passes over at 201° and crystallises completely on cooling. The yield of β-cyanopyridine, m.p. 49°, is 20 g.

V,25. URAMIL

Uramil (aminobarbituric acid) (III) may be prepared by the oxidation of barbituric acid (I) to nitrobarbituric acid (II), followed by reduction of the latter:



Nitrobarbituric acid. Place 72 ml. of fuming nitric acid, sp. gr. 1·52, in a 1-litre flask equipped with a mechanical stirrer and surrounded by an

ice bath. Add 50 g. of barbituric acid (Section IX,6), with stirring, over a period of 2 hours ; keep the temperature below 40° during the addition. Stir for a further 1 hour, and continue the stirring while 215 ml. of water is added and the solution is cooled to 10°. Filter with suction through a sintered glass funnel, wash with cold water, and dry on a clock glass at 60–80°. Dissolve the crude nitrobarbituric acid in 450 ml. of boiling water, filter, and allow to stand overnight. Collect the crystals by suction filtration, wash well with cold water, and dry at 90–95° for 2–3 hours. The product is the trihydrate, m.p. 181–183° (decomp. ; rapid heating) and weighs 70 g. Drying at 110–115° for 2–3 hours gives 47 g. of anhydrous nitrobarbituric acid, m.p. 176° (decomp.).

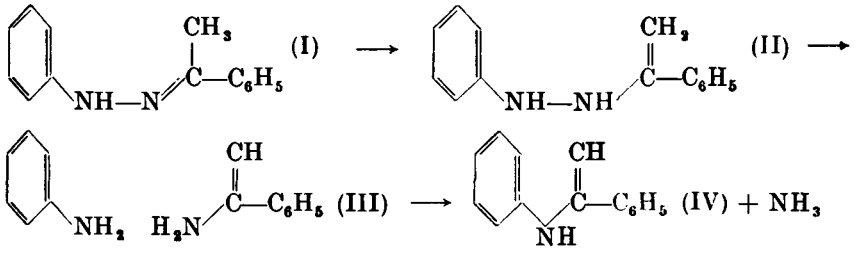
Uramil. In a 3-litre flask place 38 g. of anhydrous nitrobarbituric acid and 300 ml. of concentrated hydrochloric acid ; heat the mixture on a boiling water bath. Add 125 g. of granulated tin and 200 ml. of concentrated hydrochloric acid over a period of about 30 minutes : continue the heating until the yellow colour, due to the nitro compound, in the liquid is no longer visible. Introduce 1500 ml. more of concentrated hydrochloric acid and heat until all the white solid dissolves ; add a little decolourising charcoal, and filter the hot mixture through a sintered glass funnel. Keep the filtrate at 0° overnight, collect the uramil by filtration with suction, wash well with dilute hydrochloric acid and finally with water. Concentrate the filtrate under reduced pressure (water pump) to about 500 ml. and cool overnight. Collect the second crop of uramil, wash it as before, and combine it with the first product. Dry in a vacuum desiccator over concentrated sulphuric acid. The resulting uramil (23 g.) is a fine white powder ; it does not melt below 400°, and becomes pink to red on standing, particularly if ammonia is present in the air.

V,26. 2-PHENYLINDOLE

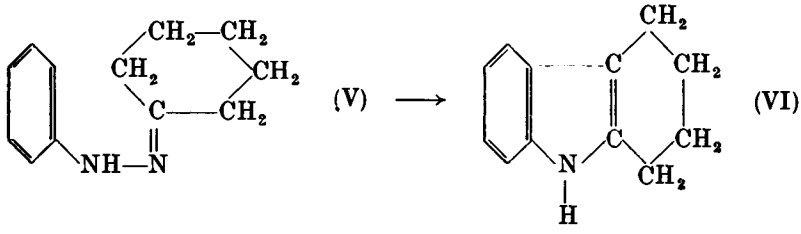
An important general method of preparing indoles, known as the **Fischer indole synthesis**, consists in heating the phenylhydrazone of an aldehyde, ketone or keto-acid in the presence of a catalyst such as zinc chloride, hydrochloric acid or glacial acetic acid. Thus acetophenone phenylhydrazone (I) gives 2-phenylindole (IV). The synthesis involves an intramolecular condensation with the elimination of ammonia. The following is a plausible *mechanism* of the reaction :

(i) The tautomer (II) of the hydrazone (I) rearranges to a substituted *o*-amino-phenylethylene-amine (III) by a type of ortho-benzidine rearrangement.

(ii) The resulting diamine (III) undergoes ring closure with elimination of ammonia (as ammonium salt) ; this is analogous to the formation of a cyclic imine from the dihydrochloride of a 1 : 4-diamine.



An interesting application is the preparation of **1 : 2 : 3 : 4-tetrahydrocarbazole** (VI), which is formed when phenylhydrazine is added to a boiling solution of *cyclo*hexanone in acetic acid ; the phenylhydrazone (V) intermediately produced undergoes ring closure directly :



Prepare **acetophenonephenylhydrazone** by warming a mixture of 20 g. of acetophenone (Section **IV,136**) and 18 g. of phenylhydrazine on a water bath for 1 hour. Dissolve the hot mixture in 40 ml. of rectified spirit, and shake or stir to induce crystallisation. Cool the mixture in ice, filter and wash with 12 ml. of rectified spirit. Dry in a vacuum desiccator over anhydrous calcium chloride for at least half an hour. The yield of phenylhydrazone, m.p. 105–106°, is 28 g.

Place an intimate mixture of 125 g. of powdered, anhydrous zinc chloride and 26·5 g. of acetophenonephenylhydrazone in a tall 500 ml. beaker in an oil bath at 170°. Stir the mixture vigorously by hand. After 3–4 minutes the mass becomes liquid and evolution of white fumes commences. Remove the beaker from the bath and stir the mixture for 5 minutes. Then stir in 100 g. of clean, white sand in order to prevent solidification to a hard mass. Digest the mixture for 12–16 hours on a water bath with 400 ml. of water and 12 ml. of concentrated hydrochloric acid in order to dissolve the zinc chloride. Filter off the sand and the crude 2-phenylindole, and boil the solids with 300 ml. of rectified spirit. Treat the hot mixture with a little decolourising carbon and filter through a pre-heated Buchner funnel ; wash the residue with 40 ml. of hot rectified spirit. Cool the combined filtrates to room temperature, filter off the 2-phenylindole and wash it three times with 10 ml. portions of cold alcohol. Dry in a vacuum desiccator over anhydrous calcium chloride. The yield of pure 2-phenylindole, m.p. 188–189°, is 16 g.

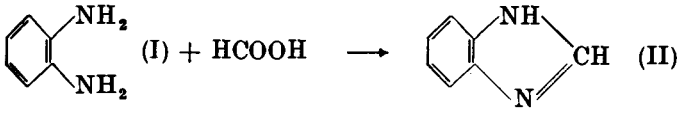
Cognate Preparation

1 : 2 : 3 : 4-Tetrahydrocarbazole. In a 500 ml. three-necked flask fitted with a dropping funnel, glycerine-sealed stirrer (Fig. *II*, 7, 10) and reflux condenser, place a mixture of 49 g. of pure *cyclo*hexanone (or 55 g. of the commercial ketone ; assumed purity 90 per cent.) and 180 g. of glacial acetic acid. Heat under reflux with stirring and add 54 g. (49 ml.) of redistilled phenylhydrazine during 1 hour ; continue the stirring for a further hour. Pour the reaction mixture into a 1-litre beaker and stir vigorously while it solidifies. Cool to 5° and filter at the pump through a Buchner funnel ; cool the filtrate in ice and refilter through the same Buchner funnel. Wash the solid on the filter with 50 ml. of water, suck almost dry, and then wash with 50 ml. of 75 per cent. ethanol. Spread the crude solid upon absorbent paper and dry in the air overnight. Recrystallise the slightly damp solid from 350 ml. of methanol : add a

little decolourising carbon and filter through a hot water funnel. The yield of 1 : 2 : 3 : 4-tetrahydrocarbazole, m.p. 116–117°, is 65 g. A further 5 g. of product may be obtained by concentrating the mother liquor to one quarter of the original volume.

V,27. BENZIMIDAZOLE

o-Phenylenediamine (I) condenses with formic acid to yield benzimidazole (II):



With acetic acid, 2-methylbenzimidazole, m.p. 173–174°, is formed: indeed the conversion of aliphatic acids into 2-alkylbenzimidazoles has been proposed as a method for preparing solid derivatives for the identification of monobasic aliphatic acids.

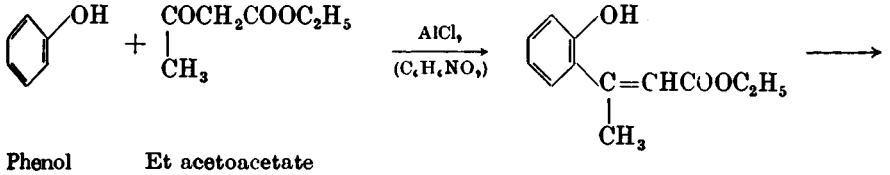
Place 27 g. of *o*-phenylenediamine (Section IV,92) in a 250 ml. round-bottomed flask and add 17·5 g. (16 ml.) of 90 per cent. formic acid (1). Heat the mixture on a water bath at 100° for 2 hours. Cool, add 10 per cent sodium hydroxide solution slowly, with constant rotation of the flask, until the mixture is just alkaline to litmus. Filter off the crude benzimidazole at the pump, wash with ice-cold water, drain well and wash again with 25 ml. of cold water. Dissolve the crude product in 400 ml. of boiling water, add 2 g. of decolourising carbon, and digest for 15 minutes. Filter rapidly at the pump through a pre-heated Buchner funnel and flask. Cool the filtrate to about 10°, filter off the benzimidazole, wash with 25 ml. of cold water, and dry at 100°. The yield of pure benzimidazole, m.p. 171–172°, is 25 g.

Note.

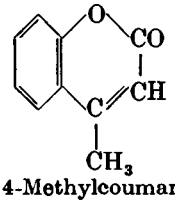
(1) Satisfactory results can also be obtained with more dilute acid, *e.g.*, of 40 per cent. concentration.

V,28. 4-METHYLCOUMARIN

The preparation of 4-methylcoumarin is an example of the **Pechmann reaction**, which consists in the interaction of a phenol with a β-ketonic ester in the presence of a condensing agent (sulphuric acid, aluminium chloride, phosphorus oxychloride or phosphoric oxide):



Phenol Et acetoacetate



4-Methylcoumarin

Resorcinol condenses similarly with ethyl acetoacetate in the presence of concentrated sulphuric acid to give **4-methyl-7-hydroxycoumarin.**

Place 94 g. of phenol and 134 g. (130·5 ml.) of ethyl acetoacetate in 150 ml. of redistilled nitrobenzene in a 3-litre three-necked flask, fitted with a dropping funnel, sealed stirrer and an air condenser, the open end of which is connected to a gas absorption trap (Figs. *II*, *8*, 1–2). Heat the mixture to 100° in an oil bath, stir, and add a solution of 266 g. of anhydrous aluminium chloride in 1 litre of nitrobenzene (1) from the dropping funnel over a period of 45 minutes. Replace the dropping funnel by a thermometer, raise the temperature of the solution to 130° and maintain this temperature, with stirring, for 3 hours, by which time evolution of hydrogen chloride will have almost ceased. Cool the reaction mixture to room temperature and add 250 ml. of 1 : 1-hydrochloric acid with stirring in order to decompose the excess of aluminium chloride. Equip the flask for steam distillation, warm it and pass steam into the reaction mixture: this will remove any unchanged keto-ester and some of the nitrobenzene: collect about 100 ml. of distillate. Transfer the residue in the flask whilst hot to a large separatory funnel; separate and discard the aqueous layer. Filter the organic layer (with the addition of a filter aid, if necessary) through a Buchner or slit-sieve funnel to remove tarry matter. Distil under reduced pressure from a 1-litre Claisen flask; the nitrobenzene passes over first, followed by crude 4-methylcoumarin at 180–195°/15 mm. (75 g.) as a red-yellow oil which solidifies on cooling. Dissolve the crude product in ether, shake the ether solution with small volumes of 5 per cent. sodium hydroxide solution until the aqueous layer is colourless, dry, evaporate the ether and recrystallise the residue from a 4 : 1 mixture of light petroleum (b.p. 60–80°) and benzene. The resulting 4-methylcoumarin (62 g.) is almost colourless and melts at 83–84°.

Note.

(1) Add the aluminium chloride in 25 g. portions to the 1-litre of dry nitrobenzene contained in a 2·5-litre round-bottomed flask; stir after each addition. The temperature may rise to about 80° during the addition: cool the flask occasionally under running water. When all the aluminium chloride has been added, cool the solution to room temperature: a little solid may settle to the bottom.

Cognate Preparation

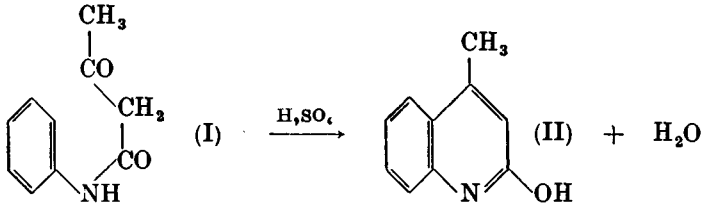
4-Methyl-7-hydroxycoumarin. Place 1 litre of concentrated sulphuric acid in a 3-litre three-necked flask fitted with a thermometer, mechanical stirrer and a dropping funnel. Immerse the flask in an ice bath. When the temperature falls below 10°, add a solution of 100 g. of resorcinol in 134 g. (130·5 ml.) of redistilled ethyl acetoacetate dropwise and with stirring. Maintain the temperature below 10° by means of an ice-salt bath during the addition (*ca.* 2 hours). Keep the reaction mixture at room temperature for about 18 hours, then pour it with vigorous stirring into a mixture of 2 kg. of crushed ice and 3 litres of water. Collect the precipitate by suction filtration and wash it with three 25 ml. portions of cold water. Dissolve the solid in 1500 ml. of 5 per cent. sodium hydroxide solution, filter, and add dilute (1 : 10) sulphuric acid (about 550 ml.) with vigorous stirring until the solution is acid to litmus. Collect the crude 4-methyl-7-hydroxycoumarin by filtration at the pump, wash it

with four 25 ml. portions of cold water, and dry at 100° : the yield is 155 g. Recrystallise from 95 per cent. ethanol : the pure compound separates in colourless needles, m.p. 185°.

A simplified procedure is possible by using **polyphosphoric acid** as the condensing agent. Add 160 g. of polyphosphoric acid * to a solution of 11 g. of resorcinol in 13 g. of ethyl acetoacetate. Stir the mixture and heat at 75–80° for 20 minutes, and then pour into ice-water. Collect the pale yellow solid by suction filtration, wash with a little cold water, and dry at 60°. The yield of crude 4-methyl-7-hydroxycoumarin, m.p. 178–181°, is 17 g. Recrystallisation from dilute ethanol yields the pure, colourless compound, m.p. 185°.

V,29 2-HYDROXYLEPIDINE (4-METHYLCARBOSTYRIL)

2-Hydroxylepidine (II) is readily prepared by cyclisation of acetoacetanilide (I) with concentrated sulphuric acid :



Place 95 ml. of concentrated sulphuric acid in a 500 ml. three-necked flask equipped with a mechanical stirrer and a thermometer ; the thermometer must dip in the liquid. Have a bath of cold water at hand so that the reaction flask can be cooled rapidly, if required. Heat the acid to 75°, remove the source of heat, stir and add 89 g. of acetoacetanilide (1) in portions by means of a spatula. Maintain the temperature of the reaction mixture at 70–75° by intermittent cooling until nearly all the acetoacetanilide has been introduced : add the last 7–10 g. without cooling. The duration of the addition is 25–30 minutes. During the last addition without external cooling, the temperature will rise to about 95° and the heat of the reaction will maintain this temperature for about 15 minutes. Keep the reaction mixture at 95° for a further 15 minutes by external heating. When the solution has cooled to 60–65°, pour it into 2·5 litres of water with vigorous stirring. Cool, collect the product by suction filtration, wash with four 250 ml. portions of water, two 125 ml. portions of methanol, and dry in the air. The crude 2-hydroxylepidine, m.p. 219–221°, weighs 70 g. Recrystallise from 95 per cent. ethanol (*ca.* 16 ml. per gram) : the pure product melts at 223–224° and the recovery is about 85 per cent.

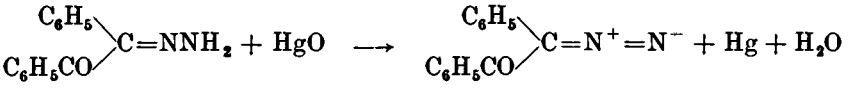
Note.

(1) Acetoacetanilide is an inexpensive commercial product. If necessary, it may be recrystallised from 50 per cent. ethanol ; m.p. 84–85°.

* Supplied, for example, by Albright & Wilson Limited, 49 Park Lane, London, W.1.

V,30. PHENYLBENZOYLDIAZOMETHANE

Phenylbenzoyldiazomethane may be prepared by the oxidation of benzil-monohydrazone with mercuric oxide in the presence of dry ether as a solvent. The addition of a little alcoholic potassium hydroxide serves to catalyse the reaction :



Benzil monohydrazone. *Method 1.* Boil a mixture of 26 g. of hydrazine sulphate, 55 g. of crystallised sodium acetate and 125 ml. of water for 5 minutes, cool to about 50°, and add 115 ml. of methyl alcohol. Filter off the precipitated sodium sulphate and wash with a little alcohol. Dissolve 25 g. of benzil (Section **IV,126**) in 40 ml. of hot methyl alcohol and add the above hydrazine solution, heated to 60°. Most of the benzil hydrazone separates immediately, but reflux for 30 minutes in order to increase the yield. Allow to cool, filter the hydrazone and wash it with a little ether to remove the yellow colour. The yield is 25 g., m.p. 149-151° (decomp.).

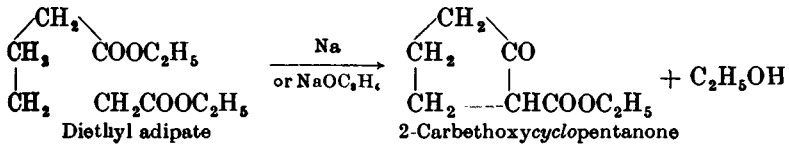
Method 2. Drop 10 g. of hydrazine hydrate (85 per cent. aqueous solution : see Section **II,49,***10*) into a hot solution of 35 g. of benzil (Section **IV,126**) in 70 ml. of alcohol with stirring. When about three-fourths of the hydrazine hydrate has been introduced, the product begins to separate. After all the reagent has been added, heat the solution under reflux for 5 minutes, cool to 0°, filter at the pump, and wash twice with 20 ml. portions of alcohol. The yield of benzil monohydrazone, m.p. 149–151° (decomp.), is almost quantitative.

Phenylbenzoyldiazomethane. Grind together in a mortar 15 g. of benzil monohydrazone, 30 g. of yellow mercuric oxide and 8 g. of anhydrous sodium sulphate (the last-named to absorb the water formed in the subsequent reaction). Introduce the mixture into a 250 ml. glass-stoppered bottle, add 100 ml. of sodium-dried ether and 2 ml. of a cold saturated solution of potassium hydroxide in alcohol : shake the mixture for 10–15 minutes. Filter the solution by gravity through a fine filter paper, and wash the residue several times with anhydrous ether until the filtrate is only slightly coloured. Evaporate the combined ethereal extracts under reduced pressure (water pump) by heating the flask on a water bath at 30–35° but no higher : if evaporation is carried out at atmospheric pressure on a water bath, the product may explode. Spread the yellow, crystalline material on a porous plate, and recrystallise it from anhydrous ether. The yield of " azibenzil," m.p. 79° (decomp.), is 13·5 g.

V,31. 2-CARBETHOXY*CYCLO*PENTANONE

Esters of dicarboxylic acids having hydrogen on the δ or ε carbon atoms undergo intramolecular cyclisation when heated with sodium or with sodium ethoxide. This cyclisation is known as the **Dieckmann reaction.** It is essentially an application of the Claisen (or acetoacetic ester) condensation to the formation of a ring system ; the condensation occurs internally to produce a

cyclic β-keto ester. The only useful practical application is to the formation of five and six membered rings. A typical example is :

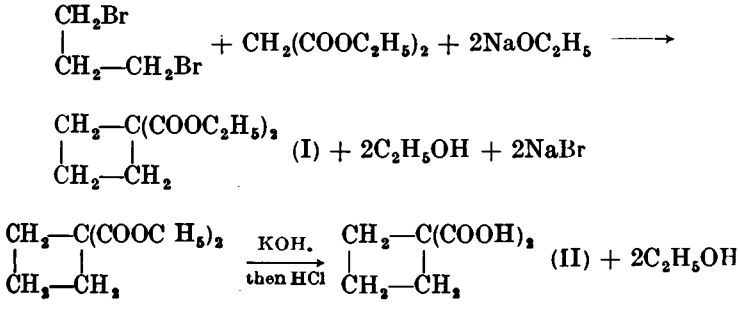


Diethyl adipate — 2-Carbethoxy*cyclo*pentanone

Prepare 25 g. of " molecular " sodium in a 1500 ml. round-bottomed flask (Section **II,50,6**, *Method 1*). Cover the sodium with 625 ml. of sodium-dried A.R. benzene ; fit the flask with an efficient reflux condenser protected from the air by means of a calcium chloride (or cotton wool) guard tube. Add 151·5 g. of diethyl adipate (Sections **III,99** and **III,100**) in one lot, followed by 1·5 ml. of absolute ethyl alcohol. Warm the flask on a water bath until, after a few minutes, a vigorous reaction sets in and a cake of the sodio compound commences to separate. Keep the flask well shaken by hand during the whole of the initial reaction. After the spontaneous reaction has subsided, reflux the mixture on a water bath overnight, and then cool in ice. Decompose the product with ice and dilute hydrochloric acid (1 : 1) ; add the acid until Congo red paper is turned blue. Separate the benzene layer, and extract the aqueous layer with 100 ml. of benzene. Wash the combined extracts with 100 ml. of 5 per cent. sodium carbonate solution and 150 ml. of water : dry over a little anhydrous magnesium sulphate. Remove the benzene under atmospheric pressure (Fig. *II*, *13*, 4, but with modified Claisen flask), and fractionate the residue under reduced pressure. Collect the 2-carbethoxy-*cyclo*pentanone at 108–111°/15 mm. (95 g.). Upon redistillation, the product boils at 102°/11 mm.

V,32. *CYCLO*BUTANE-1 : 1-DICARBOXYLIC ACID AND *CYCLO*BUTANECARBOXYLIC ACID

Trimethylene dibromide (1 mol) condenses with ethyl malonate (1 mol) in the presence of sodium ethoxide (2 mols) to form ethyl *cyclo*butane-1 : 1-dicarboxylate (I). Upon hydrolysis of the latter with alcoholic potassium hydroxide, followed by acidification *cyclo*butane-1 : 1-dicarboxylic acid (II) is obtained.



When *cyclo*butane-1 : 1-dicarboxylic acid is heated above its melting point until the evolution of carbon dioxide ceases, *cyclo*butanecarboxylic acid (III) is formed in good yield :

$$\begin{array}{l} CH_2—C(COOH)_2 \\ \quad\quad | \quad\quad | \\ CH_2—CH_2 \end{array} \xrightarrow{\text{Heat}} \begin{array}{l} CH_2—CHCOOH \\ \quad\quad | \quad\quad | \\ CH_2—CH_2 \end{array} \text{(III)} + CO_2$$

Equip a 3 litre three-necked flask with a thermometer, a mercury-sealed mechanical stirrer and a double-surface reflux condenser. It is important that all the apparatus be thoroughly dry. Place 212 g. of trimethylene dibromide (Section **III,35**) and 160 g. of ethyl malonate (Section **III,153**) (dried over anhydrous calcium sulphate) in the flask. By means of a separatory funnel, supported in a retort ring and fitted into the top of the condenser with a grooved cork, add with stirring a solution of 46 g. of sodium in 800 ml. of " super-dry " ethyl alcohol (Section **II,47,5**) (1) at such a rate that the temperature of the reaction mixture is maintained at 60–65° (50–60 minutes). When the addition is complete, allow the mixture to stand until the temperature falls to 50–55°, and then heat on a water bath until a few drops of the liquid when added to water are no longer alkaline to phenolphthalein (about 2 hours). Add sufficient water to dissolve the precipitate of sodium bromide, and remove the alcohol by distillation from a water bath. Arrange the flask for steam distillation (Fig. *II,41,1* : this merely involves replacing the stirrer from the previous distillation by a steam-delivery tube). Steam distil until all the ethyl *cyclo*butane-1 : 1-dicarboxylate and unchanged ethyl malonate are removed ; collect about 4 litres of distillate during 9–10 hours. Extract the entire steam distillate with three 350 ml. portions of ether ; remove the ether from the combined extracts on a water bath. Reflux the residual liquid with a solution of 112 g. of potassium hydroxide in 200 ml. of alcohol for 2 hours. Distil off most of the alcohol and then evaporate the residue to dryness on a water bath. Dissolve the solid residue in 100 ml. of hot water, and add concentrated hydrochloric acid (*ca.* 80 ml.) cautiously until the solution is just acid to litmus. Boil for a few minutes to remove carbon dioxide, render slightly alkaline with dilute ammonia solution, and add a slight excess of aqueous barium chloride to the boiling solution. Filter the hot solution to remove the barium malonate, cool the filtrate and render it strongly acid with concentrated hydrochloric acid (90–100 ml. of acid : use Congo red paper). Extract the solution with four 250 ml. portions of ether. Dry the combined extracts with anhydrous calcium chloride and remove the ether on a water bath ; complete the evaporation in a beaker or crystallisation dish. Place the beaker or dish in a vacuum desiccator for a few minutes to remove the last traces of ether, spread the solid on a porous tile and allow to stand overnight. The beautifully crystalline product (55 g.) consists of pure *cyclo*butane-1 : 1-dicarboxylic acid, m.p. 158°. It may be recrystallised from hot ethyl acetate, but the m.p. is unchanged.

Place 30 g. of *cyclo*butane-1 : 1-dicarboxylic acid in a 100 ml. distilling flask, fitted with a thermometer, and connect the side arm to a 50 ml. Claisen flask supported in a funnel so that it can be cooled externally by running water. Heat the distilling flask in a metal bath at 160–170°

until all effervescence ceases. Then raise the temperature of the bath to 210°; the *cyclo*butanecarboxylic acid passes over at 191–197°. Redistil the acid from the Claisen flask, using an air bath (Fig. *II*,*5*, 3): the pure acid distils at 195–196°. The yield of *cyclo*butanecarboxylic acid (a colourless liquid) is 18 g.

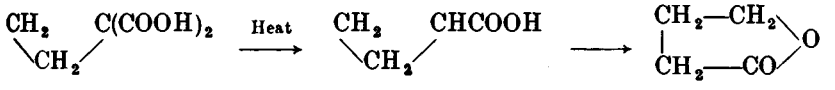
Note.

(1) The sodium ethoxide solution is conveniently prepared as follows. Place 46 g. of clean sodium (Section III,7, *Note 1*) in a 2 litre round-bottomed flask provided with a 25 cm. double surface condenser. The apparatus must be perfectly dry. Cool the flask in a bath of crushed ice. Add 800 ml. of "super-dry" ethyl alcohol in one operation. A vigorous reaction will ensue, but it will remain under control. When the initial reaction is over, remove the ice bath and allow the residual sodium to react. If small quantities of sodium remain, warm the flask on a water bath until solution is complete.

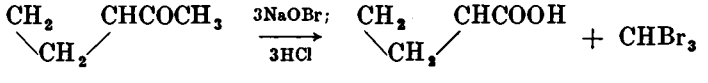
If commercial absolute ethyl alcohol is used, the yield of *cyclo*butane-1 : 1-dicarboxylic acid is reduced to 34 g.

V,33. *CYCLO*PROPANECARBOXYLIC ACID

The procedure (with ethylene dibromide replacing trimethylene dibromide) described for *cyclo*butanecarboxylic acid (previous Section) does not give satisfactory results when applied to the *cyclo*propane analogue; the yield of the *cyclo*propane-1 : 1-dicarboxylic acid is considerably lower and, furthermore, the decarboxylation of the latter gives a considerable proportion (about 30 per cent.) of butyrolactone:



Good results are obtained by the oxidation of the commercially available *cyclo*propyl methyl ketone with sodium hypobromite solution, and the preparation may be regarded as an excellent example of the oxidation of the $-COCH_3$ group to $-COOH$:



Equip a 3 litre three-necked flask with a dropping funnel, a mechanical stirrer and a thermometer. Place a solution of 165 g. of sodium hydroxide in 1400 ml. of water in the flask and cool in a freezing mixture to 0°. Add from the dropping funnel 240 g. (77 ml.) of bromine slowly so that the temperature of the stirred solution does not rise above 10°. Cool the resulting sodium hypobromite solution to 0°, add 42 g. (47 ml.) of *cyclo*propyl methyl ketone (1) slowly and at such a rate that the temperature is kept below 10°. When the addition is complete, the solution should be colourless indicating that all the sodium hypobromite has reacted: remove the freezing mixture and continue the stirring for 1·5 hours at the laboratory temperature. Transfer the mixture to a large separatory funnel, remove the lower layer of crude bromoform (114 g.), and then steam distil (Fig. *II*, *41*, 1) the aqueous solution for 30 minutes: a further 2 g. of bromoform is recovered (2). Cool and acidify cautiously to Congo red with 250 ml. of concentrated hydrochloric acid. The solution acquires

a very pale yellow colour ; add a little sodium bisulphite solution until it is colourless. Saturate the solution with salt and extract with four 300 ml. portions of ether : dry the combined extracts with anhydrous magnesium sulphate, and distil off the ether on a water bath through a short column. Distil the residue under reduced pressure and collect the pure *cyclo*propanecarboxylic acid (a colourless liquid) at 92°/22 mm. (3). The yield is 33 g.

Notes.

(1) Commercial *cyclo*propyl methyl ketone (Matlieson Company) is redistilled through a Widmer column : over 95 per cent. passes over at 110·8–111·8°/757 mm. It is quite pure since it yields a semicarbazone, m.p. 117° : the m.p. is unaffected by recrystallisation from aqueous alcohol. The ketone may be prepared from ethylene dibromide, ethyl acetoacetate and an excess of sodium ethoxide.

(2) It is better not to remove the lower bromoform layer in a separatory funnel, but to do so entirely by steam distillation ; complete oxidation of the ketone is thus ensured. The weight of recovered bromoform may be somewhat smaller (100–105 g.), but the yield of pure acid is increased to 36 g. The steam distillation must be carefully watched as a solid (carbon tetrabromide) may crystallise in the condenser ; this can easily be removed by turning off the water supply when the solid will soon melt and pass on into the distillate.

(3) Appreciable decomposition occurs upon distillation at atmospheric pressure.