CCLIV.—*Phthalazines. Part I.*

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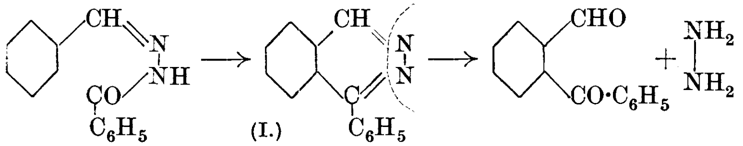
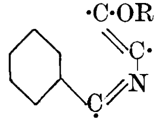
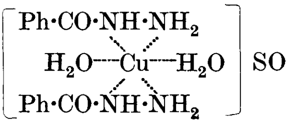
A possible method for the synthesis of a large class of alkaloids, particularly of the berberine group, depends on the accessibility of aldehydo-acids and ketones of the aromatic series (*e.g.*, opianic acid), but unfortunately these substances are difficult to prepare synthetically, the few known methods being only of theoretical interest and unsuitable as starting points in a long synthetical scheme. Attention was therefore directed to the following method which promised to be of use.

Benzoylhydrazine has been condensed with benzaldehyde by Curtius (*Ber.*, 1890, **23**, 3028) and with propaldehyde and acetone by Sturve (*J. pr. Chem.*, 1894, **50**, 304). It appeared that if an aromatic aldehyde were condensed with benzoylhydrazine, the product could be induced to undergo a further intramolecular condensation to give a phthalazine which, in turn, should be capable of hydrolysis to an *o*-aldehydo-benzophenone :


(I.)

In view of the success that has attended similar condensations in this laboratory in the preparation of quinazoline derivatives with urethane, it was expected that the ring closure could easily be effected. Moreover, Staub (*Helv. Chim. Acta*, 1922, **5**, 888), from a detailed study of the Bischler–Napieralsky *iso*quinoline synthesis (*Ber.*, 1893, **26**, 1903), found that the essential conditions for the intramolecular dehydration were (*a*) a conjugated double bond, actual or potential, and (*b*) a hydroxy- or alkyloxy-group attached to the carbon atom in the β-position to the nitrogen atom ; *i.e.*, dehydration would take place in compounds of the type (II).

(II.)




$$\left[\begin{array}{c} Ph{\cdot}CO{\cdot}NH{\cdot}NH_2 \\ H_2O\text{---}Cu\text{---}H_2O \\ Ph{\cdot}CO{\cdot}NH{\cdot}NH_2 \end{array}\right] SO_4$$

(III.)

Since the scheme under consideration is similar to that of the *iso*quinoline synthesis, it seemed extremely probable that the condensation would take place with readiness. This has been realised, but it is peculiar that phosphoric oxide (the agent employed in the Bischler–Napieralsky synthesis) is almost useless here, for, except in one isolated case (*viz.*, with *veratraldehydebenzoylhydrazone*), no product could be isolated with its aid. Phosphorus oxychloride in chloroform gave only indifferent yields, and after many trials we found that amyl alcohol saturated with hydrogen chloride is the best reagent for the transformation, giving yields as high as 50%. It is of interest that Curtius (*Ber.*, 1900, **33**, 2560) found that benzaldehydebenzoylhydrazone was decomposed to benzoic acid, benzaldehyde, and hydrazine by hydrochloric acid, so our success is obviously due to the avoidance of water.

Thus a variety of phthalazines has been synthesised from easily available sources in good yields, and the method is superior to the older methods. The hydrolysis of the phthalazines to the aldehydoketones has been accomplished and will be described in a future communication.

In order to test the validity in this series of one of Staub's generalisations for the *iso*quinoline ring closure (see above), we reduced certain substituted benzaldehydebenzoylhydrazones

$$(C_6H_5\cdot CO\cdot NH\cdot N\colon CHR)$$

and found that the resulting products ($C_6H_5\cdot CO\cdot NH\cdot NH\cdot CH_2R$) did not undergo intramolecular dehydration, thus confirming our anticipation that the lack of an incipiently conjugate system would prevent ring closure.

The well-known tendency of copper salts to liberate nitrogen from a molecule when two nitrogen atoms are in juxtaposition led us to try the action of copper sulphate solution on benzoylhydrazine in alcoholic solution. An almost quantitative precipitation of a complex *copper* salt occurred, however, and analysis indicates that it has the constitution (III). The possibility of utilising this salt for the rapid estimation of copper is being explored.

EXPERIMENTAL.

Condensation of Benzoylhydrazine with Veratraldehyde.—Benzoylhydrazine (16 g.) and veratraldehyde in absolute alcohol were mixed with concentrated sodium hydroxide solution (1 c.c.) and refluxed on the water-bath for 3 hours. The mixture was filtered hot, and the brownish crystals which separated on cooling were recrystallised from absolute alcohol and then formed colourless needles, m. p. 176°, yield 20 g., of *veratraldehydebenzoylhydrazone* (Found : C, 67·3; H, 5·4; N, 9·9. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·6; N, 9·9%).

6 : 7-*Dimethoxy*-1-*phenylphthalazine*.—(1) To the foregoing hydrazone (6 g.), dissolved in chloroform (30 c.c.), phosphorus oxychloride (20 c.c.) was added and the mixture was refluxed on the water-bath for 3 hours and then poured over crushed ice. The

chloroform solution was separated from the aqueous layer, dried by anhydrous sodium sulphate, and the solvent distilled off. The residue was kept in a vacuum, and the *phthalazine* crystallised in yellowish-brown needles after the addition of a few drops of alcohol and scratching; when ground with sodium hydroxide solution, filtered, washed with water to remove alkali, and recrystallised from absolute alcohol, it separated in yellowish needles, m. p. 193—194°; yield 0·5 g. (Found: C, 71·9; H, 5·5; N, 10·5. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3; N, 10·5%). The substance is sparingly soluble in alcohol, but more soluble in benzene. It dissolves in hydrochloric acid to a yellow solution from which the sparingly soluble hydrochloride is soon precipitated. This precipitate on treatment with acetic acid redissolves to a colourless solution.

(2) Veratraldehydebenzoylhydrazone (6 g.) was thoroughly mixed with phosphoric oxide (12 g.), xylene (25 c.c.) was added, and the mixture was heated in an oil-bath at 130—140°. After removal of the xylene, the solid residue was treated with cold water, care being taken to avoid frothing. Hydrochloric acid (1 c.c.) was then added and the whole heated on the water-bath. The cooled solution was filtered and neutralised with sodium hydroxide solution. The precipitate so obtained was crystallised from absolute alcohol, separating in yellow needles (yield, 0·2 g.), m. p. 193—194°, not depressed by addition of the product described under (1). On evaporation of the xylene solution, colourless crystals, m. p. 176°, were obtained which proved to be the unchanged initial substance.

(3) The hydrazone (6 g.) was heated with amyl alcohol (60 c.c.), saturated with hydrogen chloride, first for an hour on the water-bath and then for an hour over the flame. The mixture was cooled and filtered, the dark brown residue ground with sodium hydroxide solution, and the yellowish product recrystallised from alcohol, forming yellow needles (yield 50%), m. p. 193—194°, not depressed by admixture with either of the two foregoing products.

s-*Benzoyl*-3 : 4-*dimethoxybenzylhydrazine.*— Veratraldehyde-benzoylhydrazone (8 g.), dissolved in the minimum quantity of absolute alcohol, was thoroughly shaken with 3% sodium amalgam containing 5 g. of sodium. After the reaction, the solution was filtered and nearly neutralised with acetic acid. Excess of alcohol was removed by distillation under diminished pressure at 40—50°, and the solution diluted with water. The oily mass which was formed was treated with dilute hydrochloric acid, and the insoluble portion removed by shaking with ether. The hydrochloric acid solution was then neutralised with ammonium hydroxide and the substance so obtained was extracted with ether. An oily mass was obtained on the removal of ether, and solidified in a vacuum; when crystallised from benzene–light petroleum (charcoal), it had m. p. 79° (Found : C, 66·9; H, 6·42; N, 9·9. $C_{16}H_{18}O_3N_2$ requires C, 67·1; H, 6·3; N, 9·8%).

The above compound was not converted into the corresponding phthalazine on treatment with the usual reagents.

Condensation of Benzoylhydrazine with Anisaldehyde.—A mixture of benzoylhydrazine (13 g.) and anisaldehyde (13 g.) in alcohol, treated and worked up in the same way as for veratraldehyde, yielded 17 g. of the *hydrazone*, needles, m. p. 147° (Found : N, 11·1. $C_{15}H_{14}O_2N_2$ requires N, 11·0%).

7-*Methoxy*-1-*phenylphthalazine.*—When this hydrazone (5 g.) was treated in exactly the same way as the dimethoxy-compound, the resulting *phthalazine* crystallised from absolute alcohol in yellow needles, m. p. 167° (Found : N, 11·5. $C_{15}H_{12}ON_2$ requires N, 11·9%); it is sparingly soluble in alcohol but more soluble in benzene. The *picrate*, prepared in the usual way in alcoholic solution, crystallised from alcohol in yellow needles, m. p. 208° (Found : N, 14·9. $C_{21}H_{15}O_8N_5$ requires N, 15·1%).

s-*Benzoyl*-4-*methoxybenzylhydrazine.* — Anisaldehydebenzoylhydrazone (5 g.), dissolved in the minimum quantity of absolute alcohol, was reduced with 100 g. of 3% sodium amalgam. The reduction product was isolated in the same way as before, except that in this case no ether was used, the product being precipitated as well-defined crystals on dilution with water after removal of excess of alcohol by distillation under low pressure. The s-*benzoyl*-4-*methoxybenzylhydrazine*, after treatment with dilute hydrochloric acid and subsequent neutralisation with alkali, was recrystallised from absolute alcohol and separated in shining plates, m. p. 96° (Found : N, 11·1. $C_{15}H_{16}O_2N_2$ requires N, 10·9%). It was not changed into a phthalazine by the usual reagents.

Piperonaldehydebenzoylhydrazone, from benzoylhydrazine and piperonal, was isolated as in the previous cases; it crystallised from absolute alcohol in shining needles, m. p. 170° (Found: N, 10·2. $C_{15}H_{12}O_3N_2$ requires N, 10·4%).

6 : 7-*Methylenedioxy*-1-*phenylphthalazine.*—The hydrazone (6 g.), dissolved in chloroform (50 c.c.), was refluxed with phosphorus oxychloride (30 c.c.), and the product worked up as before. The *phthalazine* crystallised from benzene–light petroleum in yellow needles, m. p. 200° (Found : N, 11·1. $C_{15}H_{10}O_2N_2$ requires N, 11·2%); it is slightly soluble in alcohol, but more soluble in benzene.

s-*Benzoyl*-4 : 5-*methylenedioxybenzylhydrazine*, prepared by reduction as above, crystallised from alcohol in shining plates, m. p. 130° (Found : N, 10·7. $C_{15}H_{14}O_3N_2$ requires N, 10·4%).

Benzaldehydebenzoylhydrazone, prepared by refluxing an alcoholic solution of the reactants with a little alkali, had m. p. 203° after crystallisation from alcohol (Curtius, *Ber.*, 1890, **23**, 3028, also gives m. p. 203°) (Found : N, 12·5. Calc. : N, 12·5%).

1-*Phenylphthalazine* (I) was prepared and isolated in the usual way, except that in this case, after the removal of chloroform and addition of a few drops of alcohol, the reddish-brown oil which was precipitated crystallised spontaneously in yellow needles on the addition of more alcohol. The phthalazine so obtained was ground with alkali, washed, and recrystallised from dilute alcohol; m. p. 174—175° (Found : N, 13·5. $C_{14}H_{10}N_2$ requires N, 13·6%).

s-*Benzoylbenzylhydrazine* crystallised from alcohol in needles, m. p. 115° (Found : N, 12·7. $C_{14}H_{14}ON_2$ requires N, 12·4%). This substance was not converted into a phthalazine.

m-*Nitrobenzaldehydebenzoylhydrazone* crystallised from absolute alcohol (charcoal) in colourless needles, m. p. 190° (Found : N, 15·7. $C_{14}H_{11}O_3N_3$ requires N, 15·6%).

The corresponding 6(or 8)-*nitro*-1-*phenylphthalazine* crystallised from alcohol in yellow needles, m. p. 165° (Found : N, 16·8. $C_{14}H_9O_2N_3$ requires N, 16·7%).

o-*Methoxybenzaldehydebenzoylhydrazone* crystallises in colourless needles, m. p. 179° (Found : N, 11·2. $C_{15}H_{14}O_2N_2$ requires N, 11·0%).

5-*Methoxy*-1-*phenylphthalazine* crystallises in yellow needles, m. p. 135° (Found : N, 12·0. $C_{15}H_{12}ON_2$ requires N, 11·9%).

s-*Benzoyl*-o-*methoxybenzylhydrazine*, prepared by the usual reduction process and purified by fractional crystallisation from light petroleum, formed colourless needles, m. p. 80° (Found : N, 11·2. $C_{15}H_{16}O_2N_2$ requires N, 10·9%).

Action of Copper Sulphate on Benzoylhydrazine.—An alcoholic solution of benzoylhydrazine (2·72 g.) was added to a cold aqueous solution of copper sulphate (2·49 g.), and the resulting precipitate, consisting of bluish silky needles, was well washed, first with water, then with alcohol, and finally with ether (Found : N, 12·1; Cu, 13·7; S, 6·9. $C_{14}H_{20}O_8N_4SCu$ requires N, 12·0; Cu, 13·5; S, 6·9%).

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