LII.—*Syntheses in the Phenazine Series.*

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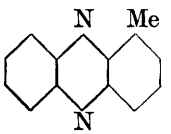
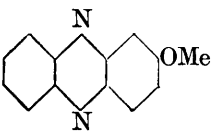
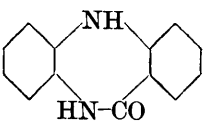
OF the simpler homologues and substitution derivatives of phenazine itself, very few substances other than amino- or oxy-derivatives have been recorded in the literature, and the properties of these substances are quite unknown.

2-Methylphenazine (Merz, *Ber.*, 1886, **19**, 725; Bernthsen and Schweitzer, *Annalen*, 1886, **236**, 337), 2 : 3-dimethylphenazine (Diepholder, *Ber.*, 1909, **42**, 2922), and 2 : 6-dimethylphenazine (Bamberger and Ham, *Annalen*, 1911, **382**, 82) have been prepared, but no other homologues of phenazine are known. Of the halogen derivatives, the only substances on record are the 2 : 6-disubstituted compounds prepared from nitroso-derivatives by Bamberger and Ham (*loc. cit.*). Only two nitro-derivatives of phenazine are known, both of which may be prepared from phenazine itself (Kehrmann and Havas, *Ber.*, 1913, **46**, 347). None of these substances, however, has been obtained except in very small quantities.

With a view to the eventual examination of the properties of substituted phenazine derivatives, the known general methods for the formation of the phenazine ring system have been applied to the synthesis of certain simple substituted compounds. As a result, completed syntheses of 1-*methylphenazine* (I), 2-*methoxyphenazine* (II), 2-*chlorophenazine*, and 2-*bromophenazine* are described in the experimental portion of this paper, together with an attempted synthesis of 1-methoxyphenazine.

(I.) 

(II.) 

(III.) 

Search of the literature has shown that only two *general* methods for the formation of the phenazine ring system exist : both of these have been utilised.

Of these methods, however, the condensation of an *o*-quinone with an *o*-phenylenediamine derivative (Kehrmann and Cherpillod, *Helv. Chim. Acta*, 1924, **7**, 975; Kehrmann and Mermod, *ibid.*, 1927, **10**, 62) can never be of practical value on the large scale unless the difficulties in the preparation of suitable quantities of *o*-benzoquinones can be overcome.

The alternative method of preparation of a derivative of *o*-nitrodiphenylamine, reduction to the *o*-amino-derivative, and subsequent

ring closure by eliminating 4 hydrogen atoms would appear far more suitable, but severe practical difficulties have been encountered. It has been found that the method of the final ring closure with the use of anhydrous sodium acetate, as described by Kehrmann and Havas (*loc. cit.*) for the preparation of phenazine itself, although suitable for the production of moderate quantities of this substance, is not successfully applicable for the preparation of substituted phenazines, as, in the cases studied, great charring took place and at most only traces of the desired product could be obtained. The earlier method of ring closure, by heating the *o*-aminodiphenylamine derivative with litharge (O. Fischer and Heiler, *Ber.*, 1893, **26**, 378), however, has been found of general application, except in the case of *2-amino-2'-methoxydiphenylamine*, which loses its methoxy-group, presumably by the elimination of methyl alcohol, yielding phenazine itself and not a substituted phenazine. The yields in this reaction, however, are always of the order of 5% of that demanded by the theory. As, in addition, considerable difficulty has been experienced, in the first stages of the syntheses, in obtaining satisfactory yields of certain of the *o*-nitrodiphenylamine derivatives, it cannot be said that any convenient method has yet been found for the preparation of phenazine derivatives in bulk.

The phenazine derivatives prepared are all slightly volatile in steam and sublime unchanged. They form bright yellow solutions in mineral acids, from which they may be precipitated by dilution or by neutralisation of the acid. They give no coloration with ferric chloride, in contrast to the *o*-phenylenediamines from which they have been prepared, and this difference in behaviour has been utilised as a test of the purity of the phenazine derivatives. The mono-substituted phenazines all have lower melting points than phenazine itself.

The syntheses of the methoxyphenazines are of considerable interest in connexion with the elucidation of the structure of the bacterial pigment " pyocyanine " that has been under investigation by two of the authors (J., 1923, **123**, 3278). Recent work by Wrede and Strack (*Z. physiol. Chem.*, 1924, **140**, 1; 1925, **142**, 103) has shown that pyocyanine on hydrolysis with weak alkali yields a yellow sublimable substance, " hemipyocyanine," m. p. 157°, of formula $C_{13}H_{12}ON_2$ (or possibly formula III), which yields phenazine on distillation with zinc dust. Hemipyocyanine in consequence might probably have the structure of a methoxyphenazine, or of a *C*- or *N*-methylhydroxyphenazine. Further, the yellow colour and the ease of sublimation of hemipyocyanine are both typical of the behaviour of phenazine derivatives. The synthesis

described in this paper of 2-methoxyphenazine, and the fact that it is not identical with hemipyocyanine, have eliminated one of the more probable of the formulæ for this substance.

The alternative structure of a 7-membered ring lactam (III) as suggested by Wrede and Strack (*loc. cit.*) has been considered. Attempts were made to synthesise this substance from *2-amino-diphenylamine-2'-carboxylic acid*, but it has not yet been found possible to bring about the desired ring closure. No products have been obtained having properties resembling those of "hemipyocyanine."

EXPERIMENTAL.

1-*Methylphenazine* was prepared by the following methods: (*a*) 4 G. of 3-nitro-*o*-toluidine, dissolved in 200 c.c. of moist ether, were reduced to 2 : 3-tolylenediamine by means of 3 g. of aluminium amalgam, and the resulting solution was dried over fused sodium sulphate. This was then mixed with a solution of 2 g. of *o*-benzoquinone (Willstätter and Müller, *Ber.*, 1908, **41**, 2580) in 200 c.c. of dry ether and kept for 2 days over 10 g. of finely powdered fused sodium sulphate. The dark-coloured solution was shaken successively with dilute hydrochloric acid and with dilute sodium hydroxide solution till no more colouring matters were removed. The residual pale yellow ethereal layer, on evaporation, yielded a small quantity of 1-methylphenazine which, after crystallisation from hot water, melted at 108° alone or mixed with the product prepared by the alternative method (*b*).

(*b*) *2-Nitro-2'-methyldiphenylamine* was obtained in 10% yield by heating at 220—240° for 20 hours a mixture of 50 g. of *o*-chloronitrobenzene, 70 g. of *o*-toluidine, and 50 g. of powdered anhydrous sodium acetate. The required product was separated by removing all volatile substances by steam distillation and then repeatedly crystallising the dark-coloured residue from alcohol, orange-yellow needles, m. p. 76°, being obtained (Found: C, 68·45; H, 5·3. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3%). On reduction with stannous chloride and hydrochloric acid in alcoholic solution this substance yielded the tin double salt of *2-amino-2'-methyldiphenylamine*. This double salt was dissolved in hot alcohol, the tin hydroxide precipitated by the addition of excess of concentrated ammonia, and the free base isolated from the filtrate by dilution with water, sodium hyposulphite ($Na_2S_2O_4$) being added to prevent atmospheric oxidation of the diamine to a purple azine dye. The *base* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 64° (Found: N, 14·1. $C_{13}H_{14}N_2$ requires N, 14·15%). The dry diamine, mixed with four times its weight of litharge, was heated to 200—240° under reduced pressure in a boat placed in a

long wide combustion tube. The vapours were passed through a heated column of litharge supported on pumice, to complete the reaction, and then condensed in the further cool portion of the tube. The sublimate of 1-*methylphenazine*, after further purification by distillation in steam, crystallised from hot water in pale yellow needles, m. p. 108° (Found : N, 14·45. $C_{13}H_{10}N_2$ requires N, 14·45%). The substance gave no coloration with ferric chloride. The *chloroplatinate* [Found : Pt, 23·2. $(C_{13}H_{10}N_2)_2,H_2PtCl_6,HCl$ requires Pt, 23·4%] formed fine orange needles that decomposed gradually on heating above 200°.

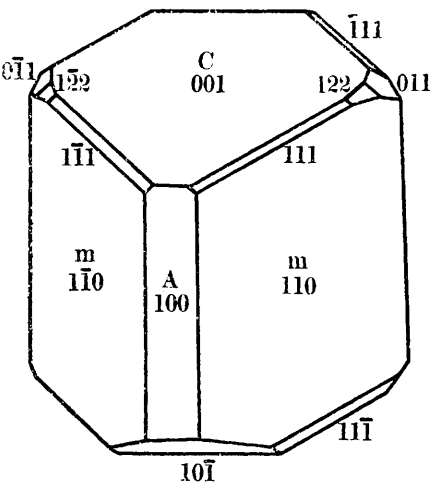
2-*Chlorophenazine* was prepared from 4′-chloro-2-nitrodiphenylamine, m. p. 146°, which was obtained from *o*-chloronitrobenzene and *p*-chloroaniline, and was then reduced to the corresponding diamine, m. p. 119° (Wilberg, *Ber.*, 1902, **35**, 957). By heating with litharge, by the method already described for the preparation of 1-methylphenazine, 2-*chlorophenazine* was obtained. After crystallisation from dilute ethyl alcohol, it formed yellow needles, m. p. 139° (Found : Cl, 16·7; C, 67·2; H, 3·4. $C_{12}H_7N_2Cl$ requires Cl, 16·5; C, 67·15; H, 3·3%). Only minute quantities of this substance could be obtained by the condensation with sodium acetate as described for phenazine by Kehrmann and Havas (*loc. cit.*).

2-*Bromophenazine* was prepared from 4′-*bromo*-2-*nitrodiphenylamine*, which was obtained in 10—20% yield by heating at 200° for 20 hours a mixture of 30 g. of *o*-chloronitrobenzene, 40 g. of *p*-bromoaniline, and 50 g. of powdered anhydrous sodium acetate, and isolated by removing all volatile matter by steam distillation, extracting the residual black solid with ether, and recrystallising the extract from a large volume of alcohol; it then formed red needles, m. p. 167° (Found : Br, 27·2. $C_{12}H_9O_2N_2Br$ requires Br, 27·3%). This substance was converted into 4′-*bromo*-2-*aminodiphenylamine* by reduction with the requisite amount of stannous chloride and hydrochloric acid in alcoholic solution. (With excess of stannous chloride, bromine was eliminated, 2-aminodiphenylamine being formed.) The pure base crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 128° (Found : Br, 30·7. $C_{12}H_{11}N_2Br$ requires Br, 30·4%). The diamine, on heating with excess of litharge, gave 2-*bromophenazine*, which crystallised from methyl alcohol in long, yellow needles, m. p. 150° (Found : Br, 30·65; C, 56·0; H, 2·7. $C_{12}H_7N_2Br$ requires Br, 30·9; C, 55·6; H, 2·7%).

2-*Methoxyphenazine* was prepared from 2-*nitro*-4′-*methoxydiphenylamine* by heating together 30 g. of each of *o*-chloronitrobenzene, *p*-anisidine, and powdered anhydrous sodium acetate at 200—220° for 16 hours (yield, 40 g.). The nitro-amine was separated by

removing all volatile matter by steam distillation, extracting the solid residue with ether, and crystallising the extract from alcohol; it formed orange-red prisms, m. p. 89° (Found: C, 63·6, 63·8; H, 5·1, 5·1. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 5·0%). Well-formed crystals could easily be obtained from solutions in ether, and a crystallographic examination of these has been carried out by Mr. E. C. Bullard, of Clare College, in the Mineralogical Museum, Cambridge, under the direction of Professor A. Hutchinson, F.R.S., to whom the authors are indebted for the following report.

Fig. 1.



The crystals were of a typical oblique habit showing *m* (110), *C* (001) large; *x* (101) medium; *A* (100), and *o* (111) small; together with small faces of *r* (011); *e* (111) and σ (122) on certain of the crystals.

The best faces were measured on six crystals, a one-circle goniometer being used:

Angle measured.	Mean angle.	Possible error.
$A : C = (100) : (001)$	55° 14′	12′
$x : A' = (\bar{1}01) : (\bar{1}00)$	74° 21′	10′
$A : m = (100) : (110)$	39° 22′	12′

From these results the calculated angular elements of the crystal are: $180° - \beta = 55° 14'$; $a : b : c = 1{\cdot}008 : 1 : 0{\cdot}799$. The optical properties of the crystal were found to be: Mean refractive index = 1·73—1·74 for red light; extinction angle on plane $B = 61°$ from edge $m : A$; optic axial angle, $2V = 74°$; dispersion $\rho < \nu$.

On reduction of 2-nitro-4′-methoxydiphenylamine with stannous chloride and hydrochloric acid in alcoholic solution 2-*amino*-4′-*methoxydiphenylamine* was produced, and this was isolated from the tin double salt by the method previously described for the preparation of 2-amino-2′-methyldiphenylamine. The pure base crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 78° (Found: C, 72·6; H, 6·55. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5%). This base, when heated with litharge according to the standard procedure already given, yielded 2-*methoxyphenazine*, which crystallised from hot water in fine, yellow needles, slightly

volatile in steam; m. p. 126° (Found: C, 73·9; H, 4·7; N, 13·3. $C_{13}H_{10}ON_2$ requires C, 74·25; H, 4·8; N, 13·3%). The *chloroplatinate* [Found: Pt, 21·95, 21·9. $(C_{13}H_{10}ON_2)_2,H_2PtCl_6,2HCl$ requires Pt, 21·6%] formed fine, orange plates which gradually decomposed on heating above 250°.

Attempted Synthesis of 1-Methoxyphenazine.—30 G. each of *o*-chloronitrobenzene, *o*-anisidine, and powdered anhydrous sodium acetate, on heating together for 20 hours at 200°, condensed to form *2-nitro-2′-methoxydiphenylamine* (20 g.), which was separated by the method used for the 4′-methoxy-isomeride. It crystallised from alcohol in red needles, m. p. 83° (Found: C, 63·8; H, 5·0; N, 11·55. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 5·0; N, 11·5%). On reduction with stannous chloride and hydrochloric acid *2-amino-2′-methoxydiphenylamine* was obtained, which crystallised from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 58° (Found: N, 13·3. $C_{13}H_{14}ON_2$ requires N, 13·1%). On heating with litharge a yellow sublimate was obtained from which only phenazine, m. p. 171°, alone or mixed with a specimen prepared by the method of Kehrmann and Havas (*loc. cit.*), could be isolated. Other methods of ring closure were attempted, none of which yielded any trace of a phenazine derivative.

Investigation of 2-Aminodiphenylamine-2′-carboxylic Acid.—2-Nitrodiphenylamine-2′-carboxylic acid (Ullmann and Maag, *Annalen*, 1907, **355**, 327; Goldberg, *Ber.*, 1906, **39**, 1691) was prepared conveniently from anthranilic acid and *o*-chloronitrobenzene. On reduction with stannous chloride and hydrochloric acid in alcoholic solution, the tin double salt of *2-aminodiphenylamine-2′-carboxylic acid* crystallised in needles. These on decomposition with ammonia yielded a soluble salt of the acid, and the free acid was obtained on acidification. It crystallised from alcohol in plates, m. p. 204° (decomp.), and was practically insoluble in boiling benzene or boiling toluene (Found: N, 12·2. $C_{13}H_{12}O_2N_2$ requires N, 12·3%). It readily oxidised in moist air to a purple azine dye.

On passing dry hydrogen chloride into a solution in absolute alcohol, the *hydrochloride* of the amino-acid was obtained as long, colourless needles that remained unchanged even after prolonged boiling of the solution (Found: N, 10·6. $C_{13}H_{12}O_2N_2,HCl$ requires N, 10·6%) and gave ionic chlorine on treatment with water. The hydrochloride decomposed at about 240°. The same substance was obtained as the main product on treatment of the amino-acid with thionyl chloride at room temperature. There was also a small quantity of a substance easily soluble in light petroleum, from which no pure product could be isolated.

The free amino-acid, on heating at 250° for 1 hour, charred with

evolution of some carbon dioxide. From the residue, a green solid, m. p. 255° (decomp.), has been obtained which may possibly correspond to 4-aminoacridone (Ullmann and Maag, *Ber.*, 1907, **40**, 2522). A similar substance appears to be produced by the action of concentrated sulphuric acid on the amino-acid.

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