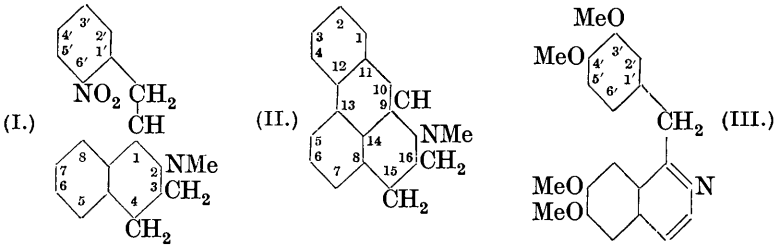
LXXVII.—*Synthetical Experiments on the Aporphine Alkaloids. Part I. A Synthesis of* 5 : 6-*Dimethoxyaporphine.*

By JOHN MASSON GULLAND and ROBERT DOWNS HAWORTH.

IN attempts to synthesise aporphine alkaloids of type (II), the most usual starting points have been the substituted nitro*iso*quinolines of type (I), because these bases on reduction yield the corre-

sponding 2′-amino-derivatives, which may be converted by Pschorr's method (*Ber.*, 1896, **29**, 496) into the aporphine bases.

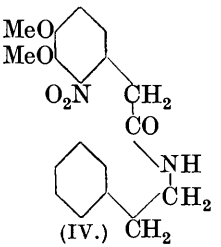


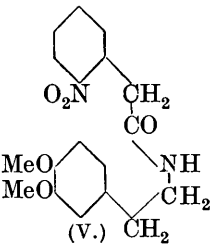
The difficulty of preparing bases of type (I) has, however, until now precluded the synthesis of the naturally occurring alkaloids of type (II), with the exception of glaucine (Gadamer, *Arch. Pharm.*, 1911, **249**, 680) and dicentrine (Haworth, Perkin, and Rankin, J., 1925, **127**, 2018; 1926, 29). Both these alkaloids are exceptional in containing ethereal oxygen atoms in the 2 : 3-positions, and the necessary nitro*iso*quinoline bases are readily prepared by direct nitration of the requisite 1-benzyl*iso*quinoline derivative in which the 3′ : 4′-positions are occupied by methoxy-groups. Thus papaverine (III) readily yields 6′-nitropapaverine, which is convertible into glaucine (Pschorr, *Ber.*, 1904, **37**, 1926; Gadamer, *loc. cit.*). Many alkaloids of the aporphine group contain phenolic or ethereal oxygen in the 3 : 4-positions and in order to prepare bases of this constitution by the method of direct nitration it would be necessary to introduce a nitro-group into the 2′-position of a base of the papaverine type (III)—an operation which has not yet been accomplished.

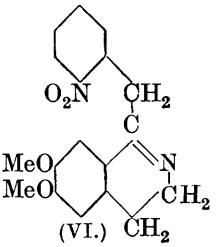
The discovery by Hope and Robinson (J., 1911, **99**, 2114), that cotarnine and the allied pseudo-bases condense with derivatives of *o*-nitrotoluene, provided a new method for the preparation of bases of type (I). Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) have employed this method for the synthesis of aporphine (II), but it has not yet been applied to the synthesis of the naturally occurring alkaloids of the series, partly owing to the inability of some pseudo-bases to condense with *o*-nitrotoluene derivatives and partly on account of the inactivity of the methyl group of 2-nitrohomoveratrole, as opposed to that of the 6-nitro-derivative. Derivatives of dinitrotoluene, however, readily condense with pseudo-bases (Hope and Robinson, *loc. cit.*; Graesser-Thomas, Gulland, and Robinson, J., 1926, 1971; Robinson and West, *ibid.*, p. 1985; Robinson and Shinoda, *ibid.*, p. 1987), but this modification introduces complications which greatly increase the practical difficulties in the preparation of bases of the 1-(2′-aminobenzyl)-2-

methyltetrahydro*iso*quinoline type (compare Robinson and Shinoda, *loc. cit.*).

A review of the literature convinced us that the well-known Bischler–Napieralski synthesis of *iso*quinoline bases had not been sufficiently investigated. From the observations made by Pictet and Kay (J., 1913, **103**, 950) during an attempt to synthesise *apo*morphine dimethyl ether by a modification of this synthesis, it might be concluded that bases of type (I) cannot be prepared by this method. For example, these authors failed to obtain any basic material by the action of phosphorus pentoxide on 2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-phenylethylamide (IV), and Gadamer, Oberlin, and Schoeler (*loc. cit.*) were unable to employ 2′-nitrophenylaceto-β-phenylethylamide in a synthesis of aporphine (II).



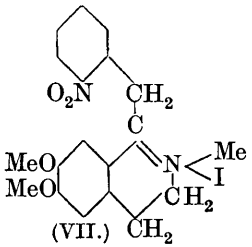




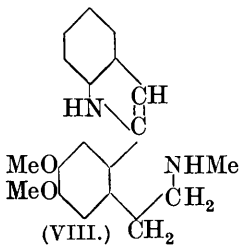
We have now achieved the stage of ring closure at which those attempted syntheses broke down, and as a preliminary case we have examined the action of a number of condensing agents on 2′-*nitrophenylaceto*-β-3 : 4-*dimethoxyphenylethylamide* (V). This amide was selected as being more favourable than the amide (IV), which Pictet and Kay investigated, because the activating influence of the methoxy-groups might be expected to facilitate *iso*quinoline formation. Treatment of the amide (V) with phosphorus pentoxide or phosphorus oxychloride under a variety of conditions did not produce any *iso*quinoline base. It was found, however, that 2′-*nitro*-6 : 7-*dimethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (VI) was obtained in a yield of 90% by the action of phosphorus pentachloride on a cold chloroform solution of the amide (V). This orange-coloured, crystalline base (VI) yielded a pale yellow, crystalline *hydrochloride*, and the stability of the base is remarkable when it is remembered that 1-benzyl-3 : 4-dihydro*iso*quinoline bases readily undergo atmospheric oxidation (Buck, Haworth, and Perkin, J., 1924, **125**, 2176). The base (VI) readily yielded a sparingly soluble, pale yellow, crystalline *methiodide* (VII), the constitution of which was proved by fission with dilute sodium hydroxide solution in the manner described by Pschorr (*Ber.*, 1904, **37**, 1932). The products of this alkaline fission were *o*-nitrotoluene and 6 : 7-dimethoxy-2-methyl-

3 : 4-dihydro*iso*quinolone (Pyman, J., 1909, **95**, 1272; 1910, **97**, 269), the latter being identified by comparison with an authentic specimen which was presented to us by Dr. H. A. D. Jowett, on behalf of Burroughs Wellcome and Co., to whom we are greatly indebted.

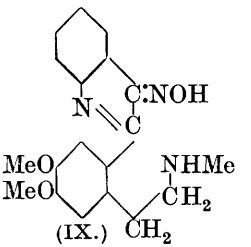
When the methiodide (VII) was reduced with zinc dust and dilute sulphuric acid in *faintly* acid solution, a colourless, crystalline base, $C_{19}H_{22}O_2N_2$, m. p. 132°, was obtained which showed unexpected properties. The base was monoacidic; it formed a crystalline *monohydrochloride* on treatment with an excess of hydrochloric acid, and it was converted into a crystalline, non-basic *monoacetyl* derivative by the action of acetic anhydride. As a result of these and other observations, we have concluded that the substance $C_{19}H_{22}O_2N_2$ is 2-(4′ : 5′-*dimethoxy*-2′-β-*methylaminoethyl*)*phenylindole* (VIII). The presence of the indole nucleus was confirmed



(VII.)



(VIII.)

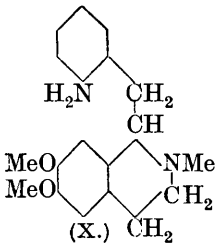


(IX.)

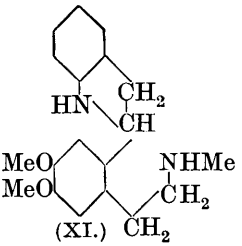
by the positive colour reactions observed on testing with a pine shaving and with *p*-dimethylaminobenzaldehyde. On treatment with nitrous acid, the base, which did not diazotise, yielded a deep red solution, from which a colourless, crystalline compound, $C_{19}H_{21}O_3N_3$, has been isolated. We consider this compound to be the 3-*oximino*-derivative (IX), as it is soluble in sodium hydroxide and dissolves in dilute mineral acids with the production of a red colour, and this view is confirmed by the fact that the compound $C_{19}H_{21}O_3N_3$ does not give the Liebermann nitrosoamine reaction. We are at present unable to explain why the nitrous acid attacks the indole nucleus in preference to the basic methylamino-group.

When the methiodide (VII) was reduced with zinc dust and hydrochloric acid in *strongly* acid solution, a different product was obtained. This new base was an oil which yielded a crystalline *dihydrochloride*, and its *monoacetyl* derivative still possessed strongly basic properties. The base could be diazotised and showed the characteristic reactions of a primary aromatic amine, and there can be no doubt that it is 2′-*amino*-6 : 7-*dimethoxy*-1-*benzyl*-2-*methyltetrahydro*isoquinoline (X). A small quantity of an oily base, isomeric with (X), has been isolated from the mother-liquor of the

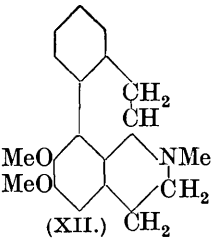
dihydrochloride of the base (X). This isomeric base, which gave a crystalline *dihydrochloride*, did not diazotise; it showed no indole colour reactions, but it yielded an oily *nitrosoamine* which gave the nitroso-reaction. We suggest that this base is 2-(4′ : 5′-*dimethoxy*-2′-β-*methylaminoethyl*)*phenyldihydroindole* (XI).



(X.)



(XI.)



(XII.)

The base (X) was converted into 5 : 6-*dimethoxyaporphine* (XII), either (*a*) by diazotising it in 2*N*-sulphuric acid and adding copper powder, or (*b*) by diazotising it in a mixture of methyl alcohol and 2*N*-sulphuric acid and heating the solution on the water-bath. The yield of 5 : 6-dimethoxyaporphine was poor (10—15% of the theoretical), the chief by-products being the dilaudanosine derivative and the phenolic base, the former predominating in method (*a*) and the latter in method (*b*). 5 : 6-Dimethoxyaporphine is a crystalline base, m. p. 137°, which yields a sparingly soluble crystalline *hydrochloride* and a characteristic *methiodide*. A number of colour reactions are described in the experimental section.

We have obtained several substituted benzyl*iso*quinoline derivatives by the action of phosphorus pentachloride on amides analogous to (V), and we are using this method in the synthesis of the naturally occurring aporphine bases. *dl*-Bulbocapnine methyl ether has already been synthesised, and we hope to publish accounts of this and other researches at an early date.

Experimental.

o-Nitrophenylacetic acid (10 g.; prepared by a slight modification of Reissert's method, *Ber.*, 1897, **30**, 1030, potassium ethoxide being used instead of sodium ethoxide) in chloroform (150 c.c.) was gently refluxed with thionyl chloride (40 c.c.) for 1½ hours. The solvent was then removed by careful distillation under 13 mm. pressure, the liquid being occasionally warmed for a few minutes on the water-bath, with shaking. This procedure is necessary to avoid explosive decomposition of the *o*-nitrophenylacetyl chloride. The residual oil was used without further purification.

2′-*Nitrophenylaceto*-β-3 : 4-*dimethoxyphenylethylamide* (V).—*o*-Nitrophenylacetyl chloride (from 45 g. of acid), dissolved in benzene

(150 c.c.), was gradually added, with cooling and shaking, to β-veratrylethylamine (45 g.) in benzene (100 c.c.), and the slimy, buff-coloured precipitate was decomposed by the gradual addition of 10% sodium hydroxide solution. The amide (V), which separated from the benzene, was collected, combined with a small second crop, obtained by evaporating the benzene layer of the filtrate, and recrystallised from methyl alcohol, giving very pale buff-coloured, slender needles (73 g.), m. p. 112° (Found : C, 62·3; H, 5·9. $C_{18}H_{20}O_5N_2$ requires C, 62·8; H, 5·8%). The *amide* dissolves with sulphonation in concentrated sulphuric acid, giving an orange-coloured solution which is completely miscible with water. No basic material was isolated after the amide had been heated with phosphorus pentoxide or oxychloride in benzene, toluene, or xylene for various times; the products invariably consisted of unchanged amide and a brown, amorphous, non-basic material which could not be obtained in the crystalline condition. After a chloroform solution of the amide had been boiled with phosphorus pentachloride for 2 hours, a large amount of non-basic tar was isolated together with a very small amount of impure basic material.

2′-*Nitro*-6 : 7-*dimethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (VI).—The amide (V) (4 g.) was mixed with a solution of phosphorus pentachloride (5 g.) in chloroform (30 c.c.) and kept for 24 hours at room temperature. The solvent was evaporated under reduced pressure from the crystalline material which had separated, the latter was extracted with boiling water and filtered from traces of tar, and the base (VI) was precipitated, by the addition of ammonia to the cooled filtrate, as an amorphous, pink solid which changed to a buff-coloured, crystalline solid after remaining in the liquor for several hours. The crude base crystallised from methyl alcohol in large, stout, orange, rhombic prisms (3·5 g.), m. p. 132°, which developed a deeper colour on heating to 100°, the colour reverting to orange on cooling (Found : C, 66·5; H, 5·7. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5%). The *hydrochloride*, pale yellow prisms, m. p. 228° (decomp.), was obtained by evaporating to dryness the pale yellow solution of the base in dilute hydrochloric acid and recrystallising the residue from absolute alcohol (Found : Cl, 9·7. $C_{18}H_{18}O_4N_2$,HCl requires Cl, 9·8%). The base dissolves in acetic anhydride, giving a pale yellow solution, and the absence of a deep green coloration indicates that spontaneous oxidation has not occurred (Buck, Haworth, and Perkin, *loc. cit.*).

2′-*Nitro*-6 : 7-*dimethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline *methiodide* (VII) may be prepared quantitatively (*a*) by heating a chloroform solution of the base (VI) and the calculated quantity of methyl iodide in a sealed tube at 100° for 4 hours, and (*b*) more con-

veniently by dissolving the base (VI) in an excess of warm methyl iodide, cooling the solution to room temperature, removing the excess of methyl iodide after 12 hours, and recrystallising the residue from rectified spirit. It forms pale sulphur-yellow needles, m. p. 208°, which are sparingly soluble in water and absolute alcohol (Found: C, 49·0; H, 4·7. $C_{19}H_{21}O_4N_2I$ requires C, 48·7; H, 4·5%). When ammonia was added to an aqueous solution of the methiodide, a deep red solution was obtained from which an ether-soluble, red, amorphous solid was precipitated; this redissolved on addition of water.

Alkaline fission. The methiodide (2 g.) was boiled with 3% sodium hydroxide solution (20 c.c.) for ½ hour, and the product was distilled in steam until the distillate was no longer turbid. From this, ether extracted *o*-nitrotoluene, which was reduced to *o*-toluidine (acetyl and *m*-nitrobenzoyl derivatives, m. p. 110° and 150°, respectively). The non-volatile residue from the steam distillation was evaporated to dryness; from the residual oil, chloroform extracted 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolone, which crystallised from benzene in colourless prisms, m. p. 124—125° (compare Pyman, *loc. cit.*), and was identified by comparison with an authentic specimen.

2-(4′ : 5′-*Dimethoxy*-2′-β-*methylaminoethyl*)*phenylindole* (VIII).—A solution of the methiodide (VII) (2 g.) in hot methyl alcohol (30 c.c.) was treated with zinc dust (6 g.) and heated on the water-bath while 10% sulphuric acid was added gradually. The methyl alcohol was allowed to evaporate, and the cooled, filtered solution was made alkaline with ammonia and extracted with ether. The extract was dried with sodium sulphate, the solvent removed, and the crystalline residue recrystallised from a little absolute ethyl alcohol. The *indole* derivative (VIII) separated with solvent of crystallisation in colourless, slender prisms (1 g.) which melted at 85°, resolidified, and remelted at 132° (Found: loss at 90°, 12·7. $C_{19}H_{22}O_2N_2,C_2H_5{\cdot}OH$ requires loss, 12·8%. Found in material dried at 90°: C, 73·5; H, 7·4. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·3%). This substance does not give the carbylamine reaction, but it shows characteristic indole reactions, *e.g.*, a violet coloration in the pine shaving test and a deep pink coloration in dilute hydrochloric acid on treatment with *p*-dimethylaminobenzaldehyde hydrochloride. The *hydrochloride* separated from a concentrated solution of the base (VIII) in ethyl-alcoholic hydrogen chloride in colourless, slender needles, which retained alcohol of crystallisation, melted at about 105°, resolidified, and remelted at a higher but somewhat indefinite temperature (Found in air-dried material: loss at 100°, 9·5; Cl, 9·0. $C_{19}H_{22}O_2N_2,HCl,C_2H_5{\cdot}OH$ requires loss, 11·7;

Cl, 9·0%. Found in material dried at 100° : C, 65·6; H, 6·7. $C_{19}H_{22}O_2N_2$,HCl requires C, 65·8; H, 6·6%). The *monoacetyl* derivative separated as a white solid when an excess of acetic anhydride was allowed to react with a benzene solution of the base (VIII) for 3 days at room temperature. The mixture was shaken with ammonia, the solid collected, and a further quantity obtained by concentration of the benzene layer of the filtrate. The acetyl derivative crystallised from methyl alcohol, in which it was moderately easily soluble, in small prisms, m. p. 138° (Found : C, 71·4; H, 6·8. $C_{21}H_{24}O_3N_2$ requires C, 71·6; H, 6·8%). It is quite devoid of basic properties and resists hydrolysis by dilute aqueous acids and alkalis.

2-(4′ : 5′-*Dimethoxy*-2′-β-*methylaminoethyl*)*phenyl*-3-*oximinoindole* (IX).—When the base (VIII) was dissolved in dilute hydrochloric acid and treated with sodium nitrite, a deep blood-red solution was obtained, the colour of which was not destroyed by boiling. The solution contained no diazonium salt, since no azo-dye was precipitated on adding it to an alkaline solution of β-naphthol. Before the nature of the base (VIII) was established, an attempt was made to bring about the Pschorr reaction, and the *oximino*-derivative (IX) was isolated from the experiment. The hydrochloride (0·2 g.) of the base (VIII), dissolved in 2*N*-sulphuric acid (5 c.c.) and methyl alcohol (5 c.c.), was diazotised below 0° by the gradual addition of the calculated quantity of *N*/20-sodium nitrite (freshly standardised); water (10 c.c.) was added, the solution warmed on the water-bath for 30—40 minutes, cooled, made alkaline with sodium hydroxide, and the slight precipitate extracted twice with ether. The extract was washed with water and dried with potassium carbonate, and the solvent removed; the residual yellow gum deposited colourless needles, m. p. 177—178°, after rubbing with warm ethyl alcohol. A much larger quantity of the oximino-derivative (IX) was obtained by adding solid ammonium chloride to the sodium hydroxide solution, and extracting the colourless solid precipitate with much ether. The extract, which showed a magnificent blue fluorescence, was dried with potassium carbonate, and concentrated until the solution was filled with a mass of colourless needles, m. p. 178° (Found : C, 67·0; H, 6·5. $C_{19}H_{21}O_3N_3$ requires C, 67·2; H, 6·2%). The oximino-compound (IX) is sparingly soluble in ether or ethyl alcohol. It dissolves in dilute hydrochloric acid to a strawberry-coloured solution, and slowly in sodium hydroxide, giving a pale yellow solution, from which it is precipitated by the addition of ammonium chloride. With phenol and concentrated sulphuric acid a yellow coloration was observed, but the characteristic nitroso-reaction was absent.

2'-Amino-6 : 7-dimethoxy-1-benzyl-2-methyltetrahydroisoquinoline (X).—The methiodide (VII) (8 g.), suspended in hot water (80 c.c.) and concentrated hydrochloric acid (160 c.c.), was gradually treated with zinc dust (25 g.) with vigorous shaking. The liquid was filtered, made alkaline with ammonia, cooled, and extracted with ether, the extract dried with sodium sulphate, and the solvent removed. The *base* (X) remained as an oil which could not be crystallised. The *dihydrochloride* was prepared by treating the base with alcoholic hydrogen chloride; it was readily soluble in water, but very sparingly soluble in absolute alcohol, from which it separated in small, colourless prisms, m. p. 243—244° (decomp.) (Found: C, 59·3; H, 6·7. $C_{19}H_{24}O_2N_2,2HCl$ requires C, 59·2; H, 6·7%). A solution of the dihydrochloride, when diazotised, formed a pale orange-coloured solution, which deposited a crimson azo-dye on being poured into an alkaline solution of β-naphthol; the dye dissolved in concentrated sulphuric acid, producing an intense magenta solution. The *monoacetyl* derivative was prepared by the action of the calculated amount of acetic anhydride on an ethereal solution of the base (X). After 2 hours, the acetate which separated was decomposed with ammonia, and the ether removed in a current of air; the acetyl derivative crystallised from methyl alcohol in splendid, colourless prisms, m. p. 153—154° (Found: C, 71·1; H, 7·5. $C_{21}H_{26}O_3N_2$ requires C, 71·1; H, 7·5%). This acetyl derivative is basic; it dissolves in cold dilute hydrochloric acid to a colourless solution, from which it is precipitated by the addition of alkali.

2-(4' : 5'-Dimethoxy-2'-β-methylaminoethyl)phenyldihydroindole (XI).—The *dihydrochloride* of this base gradually separated from the alcoholic hydrogen chloride mother-liquor from which the dihydrochloride of the base (X) had crystallised. It separated from ethyl alcohol, in which it was readily soluble, in colourless prisms which softened slightly at 180° and melted with evolution of gas but no darkening at 186° (Found in material dried at 100°: C, 59·2; H, 6·8. $C_{19}H_{24}O_2N_2,2HCl$ requires C, 59·2; H, 6·7%). The *base* was liberated as an oil by the addition of sodium hydroxide to an aqueous solution of the hydrochloride. It gave no coloration with a pine shaving or with *p*-dimethylaminobenzaldehyde. The addition of sodium nitrite to a solution of the dihydrochloride in dilute sulphuric acid produced a pale yellow solution which did not couple with alkaline β-naphthol. From the solution, basified with ammonia, ether extracted a *nitrosoamine*, a light brown oil which gave the Liebermann nitroso-reaction. The nitroso-group is probably connected to the methylamino-group, as we were unable to isolate a migration product by the action of alcoholic hydrogen chloride.

5 : 6-*Dimethoxyaporphine* (XII).—(*a*) A mechanically stirred solution of the base (X) (from 7·5 g. of dihydrochloride) in 2*N*-sulphuric acid (30 c.c.) was mixed with ice (60 g.) and diazotised by the calculated amount of 2*N*-sodium nitrite (freshly standardised). Copper powder (3 g.) was added to the orange-coloured solution, nitrogen was evolved, and after 6 hours the filtered mixture was reduced with zinc dust (3 g.) and concentrated hydrochloric acid (10 c.c.), and again filtered. The filtrate was made alkaline with ammonia, and thoroughly extracted with ether. Objectionable emulsions, which often made filtration necessary, were produced at this stage, since large quantities of the dilaudanosine derivative separated as a brown amorphous powder. The ethereal extract was washed with sodium hydroxide to remove a small amount of phenolic base, dried with sodium sulphate, and concentrated, and the brown, oily residue mixed with 50% hydrochloric acid (30 c.c.). After 12 hours, the *hydrochloride* of 5 : 6-dimethoxyaporphine (XII) was collected, washed with 50% hydrochloric acid, and recrystallised from hot water (yield 0·7 g.).

(*b*) The dihydrochloride (8 g.) of the base (X) in 2*N*-sulphuric acid (40 c.c.) and methyl alcohol (40 c.c.) was cooled below 0° and treated with the calculated amount of 2*N*-sodium nitrite. The orange-coloured solution was heated on the water-bath for ½ hour, reduced with zinc (4 g.) and concentrated hydrochloric acid (12 c.c.), and filtered, and the pale yellow solution was made alkaline with ammonia and extracted with ether. No dilaudanosine derivative was precipitated, but a large amount of phenolic base was removed by washing the ethereal extract with sodium hydroxide. The ether was dried with sodium sulphate and evaporated, 50% hydrochloric acid (30 c.c.) was added to the residual brown oil, and the hydrochloride (1·2 g.) was isolated as described above in method (*a*). 5 : 6-*Dimethoxyaporphine* (XII) was precipitated by the addition of sodium hydroxide to an aqueous solution of the hydrochloride. The oil, which rapidly hardened, was extracted with ether, the extract dried with sodium sulphate, and the solvent removed until 5 : 6-dimethoxyaporphine began to separate in colourless, large, stout, rhombic prisms, m. p. 136—137° (Found : C, 77·1; H, 7·1. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·2%). The base gives a colourless solution in concentrated sulphuric acid, a pinkish-purple coloration with Erdmann's reagent, a deep bluish-purple with Frohde's reagent, and a green coloration, which rapidly turns brown, with Mandelin's reagent. The *hydrochloride* is sparingly soluble in water, from which it separates in colourless, small prisms, m. p. 258° (decomp.) (Found : C, 68·8; H, 6·6; Cl, 10·7. $C_{19}H_{21}O_2N,HCl$ requires C, 68·8; H, 6·6; Cl, 10·7%). The *methiodide* was prepared by reflux-

ing the base (XII) for a few minutes with an excess of methyl iodide; the excess of methyl iodide was removed, and the solid residue recrystallised from absolute alcohol, from which the methiodide separated in magnificent, colourless, hexagonal plates, m. p. 223° (Found : C, 55·0; H, 5·5. $C_{20}H_{24}O_2NI$ requires C, 54·9; H, 5·5%).

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