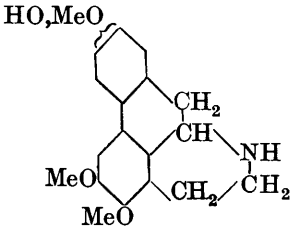
XCV.—*Synthetical Experiments on the Aporphine Alkaloids. Part V. Laurotetanine. Syntheses of* 2 : 3 : 6 : 7- *and* 3 : 4 : 6 : 7-*Tetramethoxyaporphines.*

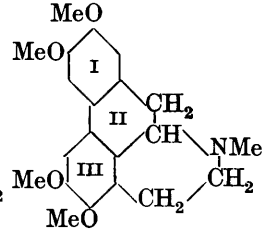
By Robert Kenneth Callow, John Masson Gulland, and Robert Downs Haworth.

Gorter (*Bull. Jard. bot. Buitenzorg*, 1921, [iii], **3**, 180) assigned the constitution (I) to laurotetanine, an aporphine alkaloid which causes tetanic convulsions when injected. It has been isolated from the bark of various *Lauraceæ*, particularly from *Litsea* species native to Java (Greshoff, "Verslag v.h. onderzoek v.d. Plantenstoffen Ned. Indie," 1890, 98; *Ber.*, 1890, **23**, 3537; Filippo, *Arch. Pharm.*, 1898, **236**, 601). Gorter prepared from laurotetanine a substance which he regarded as the dimethyl derivative, and named *iso*glaucine. The similarity in chemical and physiological

properties of *iso*glaucine and glaucine (III) (Gadamer, *Arch. Pharm.*, 1911, **249**, 680) suggested to Gorter that the two bases must contain the same carbon skeleton, and he assigned the constitution (II) to *iso*glaucine. The positions of the oxygen atoms in this structure were deduced from two considerations. In the first place, the oxidation of laurotetanine by alkaline permanganate yielded 1 : 2-dimethoxybenzene-3 : 4 : 5-tricarboxylic acid, thus establishing the relative positions of the methoxy-groups in ring III. This acid might be obtained with equal ease from the base (I), where the methoxyls are in the 6 : 7-positions, or from a substance of the nature of glaucine, in which the methoxyls are in the 5 : 6-positions, and Gorter based his choice of the 6 : 7-positions on the fact that *iso*glaucine appeared to differ both from glaucine and from corytuberine dimethyl ether (III, but with methoxyls in the 3 : 4-positions). Secondly, the close similarity of the colour reactions exhibited by *iso*glaucine with those shown by glaucine convinced Gorter that the arrangement of the methoxyl groups in ring I was that present in glaucine.



(I.)



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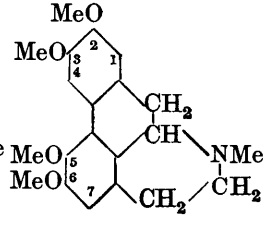
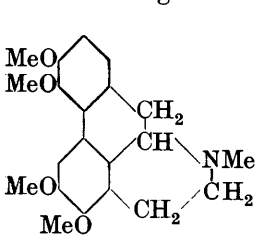


(III.)

The recent investigations of Barger and Silberschmidt (J., 1928, 2919) and of Späth and Strauhal (*Ber.*, 1928, **61**, 2395) have shown that *iso*glaucine was in reality impure glaucine, and therefore did not contain the vicinal homocatechol group in ring III. Some time before the appearance of these results, theoretical considerations had convinced us that this vicinal arrangement does not occur in the aporphine series, and it then became evident that syntheses of 2 : 3 : 6 : 7-tetramethoxyaporphine (II) and of 3 : 4 : 6 : 7-tetramethoxyaporphine (IV) would be of great value in elucidating the true nature of laurotetanine. The inclusion of the base (IV) as a possible structure of *iso*glaucine was the result of a comprehensive comparison of the colour reactions of the aporphines (p. 669), which made it evident that the colours developed by the base (II) need not necessarily be those exhibited by glaucine, and consequently that reliance could not be placed on Gorter's assumption as to the position of the oxygen atoms in ring I. 2 : 3 : 6 : 7-Tetra-

methoxyaporphine and 3 : 4 : 6 : 7-tetramethoxyaporphine have therefore been prepared synthetically. As is to be expected in the light of the work of Barger and of Späth, neither substance resembles *iso*glaucine.



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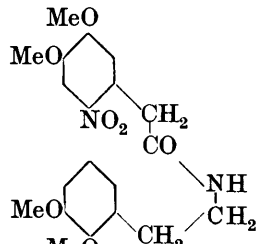

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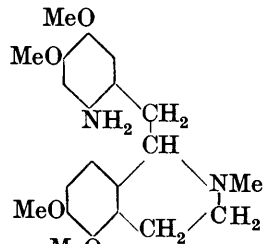


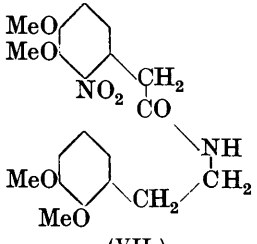
(VI.)

6-Nitro-3 : 4-dimethoxyphenylacetic acid was prepared both by the nitration of 3 : 4-dimethoxyphenylacetic acid, and also from 6-nitrohomoveratrole by a modification of the method of Oxford and Raper (J., 1927, 417). β-2 : 3-Dimethoxyphenylethylamine was obtained as described by Haworth (J., 1927, 2282) from β-2 : 3-dimethoxyphenylpropionic acid (Perkin and Robinson, J., 1914, **105**, 2387) and the corresponding amide. The last substance was also prepared from methyl β-2 : 3-dimethoxyphenylpropionate by the action of concentrated ammonia solution.

Some difficulty was experienced in preparing 6′-*nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-2 : 3-*dimethoxyphenylethylamide* (V), owing to the instability of 6-nitro-3 : 4-dimethoxyphenylacetyl chloride. Since this behaviour is unlike that of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (Part II, J., 1928, 1132), it would seem that this is an example of the greatly enhanced reactivity of the methyl group of 6-nitrohomoveratrole derivatives as compared with those of 2-nitrohomoveratrole (compare Part I, J., 1928, 581), and that the formation of 6-nitro-3 : 4-dimethoxyphenylacetyl chloride is followed by the interaction of the carboxyl chloride with the activated methylene group of another molecule. Yet a further example of this difference in activity was observed during an attempt to prepare the amide (V) by heating a mixture of 6-nitro-3 : 4-dimethoxyphenylacetic acid and β-2 : 3-dimethoxyphenylethylamine. At about 130°, carbon dioxide was smoothly evolved, and pure 6-nitrohomoveratrole remained in theoretical yield. In a parallel experiment, no reaction took place between 2-nitro-3 : 4-dimethoxyphenylacetic acid and β-2 : 3-dimethoxyphenylethylamine below 175°, and when the temperature was raised above this point no homogeneous material could be isolated. Ultimately, the amide (V) was obtained by adding a chloroform solution of the acid

chloride (prepared by means of phosphorus pentachloride, and containing phosphorus oxychloride) to a mixture of a chloroform solution of β-2 : 3-dimethoxyphenylethylamine and a dilute aqueous solution of sodium hydroxide.

The action of phosphorus pentachloride in cold chloroform solution converted the amide (V) into 6′-*nitro*-3′ : 4′ : 5 : 6-*tetramethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline. The *methiodide* of this base was reduced by means of zinc dust and hydrochloric acid to 6′-*amino*-3′ : 4′ : 5 : 6-*tetramethoxy*-1-*benzyl*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VI), which was isolated as the crystalline *dihydrochloride*, and yielded dl-2 : 3 : 6 : 7-*tetramethoxyaporphine* (II) when diazotised in methyl-alcoholic sulphuric acid. Attempts to resolve this base by means of *d*- and *l*-tartaric acids were unsuccessful. The colours developed with sulphuric acid, nitric acid, Mandelin's, Fröhde's, and Erdmann's reagents did not resemble those described by Gorter for *iso*glaucine.



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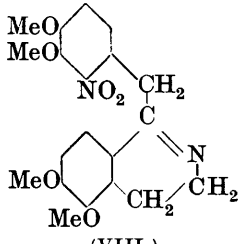

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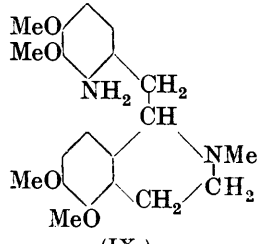

(IX.)

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-2 : 3-*dimethoxyphenylethylamide* (VII), prepared by the interaction of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (Part II, J., 1928, 1132) with β-2 : 3-dimethoxyphenylethylamine, yielded 2′-*nitro*-3′ : 4′ : 5 : 6-*tetramethoxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (VIII) when submitted to the action of phosphorus pentachloride in cold chloroform solution. The reduction of the *methiodide* of this base by means of zinc dust and hydrochloric acid produced crystalline 2′-*amino*-3′ : 4′ : 5 : 6-*tetramethoxy*-1-*benzyl*-2-*methyltetrahydro*isoquinoline (IX), which was converted into dl-3 : 4 : 6 : 7-*tetramethoxyaporphine* (IV) by diazotisation in methyl-alcoholic sulphuric acid. This *dl*-base was purified by conversion into the crystalline *hydriodide* and, after being regenerated from this salt, crystallised readily from ligroin. The resolution of the *dl*-base by means of *d*- and *l*-tartaric acids yielded d-3 : 4 : 6 : 7-*tetramethoxyaporphine hydrogen* d-*tartrate* and l-3 : 4 : 6 : 7-*tetramethoxyaporphine hydrogen* l-*tartrate* in crystalline condition, and from these salts were isolated d-3 : 4 : 6 : 7-*tetramethoxyaporphine*, m. p. 125—125·5°, $[\alpha]_D^{20°}$ 168°, and l-3 : 4 : 6 : 7-

tetramethoxyaporphine, m. p. 125·5—126°, $[\alpha]_D^{20°}$ — 167°. The crystalline *methiodide* was readily obtained by heating the *l*-base with methyl iodide.

EXPERIMENTAL.

β-2 : 3-Dimethoxyphenylpropionamide was obtained in 95% of the theoretical yield by the interaction of the acid chloride with ammonia (Haworth, *loc. cit.*), and also, in lower yield, by the interaction of the methyl ester with ammonia. β-2 : 3-Dimethoxyphenylpropionic acid (35 g.) was heated under reflux for 3 hours with an excess of methyl alcohol containing hydrogen chloride. The liquid was poured into brine, and the oily ester completely extracted with sodium carbonate, dried, and distilled, finally under reduced pressure. Methyl β-2 : 3-dimethoxyphenylpropionate passed over at 166—176°/15 mm. The ester (28 g.) and concentrated aqueous ammonia (250 c.c.) were shaken together for 40 hours; the clear solution obtained yielded crystals of the amide (15·1 g.) when evaporated in an open basin to remove excess of ammonia. The amide crystallised from light petroleum in colourless needles, m. p. 98—99°, b. p. 233—235°/16 mm. It was converted into β-2 : 3-dimethoxyphenylethylamine, b. p. 158—159°/25 mm., in the manner described by Haworth (*loc. cit.*). (In the description there given, p. 2283, line 1, 33 g. should read 3·3 g.)

In the preparation of 6-nitro-3 : 4-dimethoxyphenylacetic acid by the method of Oxford and Raper (*loc. cit.*), the yield of 6-nitro-3 : 4-dimethoxyphenylpyruvic acid was improved by increasing the proportions of potassium ethoxide and ethyl oxalate to 6-nitrohomoveratrole. The quantities used by Oxford and Raper for 50 g. of 6-nitrohomoveratrole were used for 41 g., and the yield (42 g.) rose from 60% to 77% of the theoretical.

The process for the conversion of the phenylpyruvic acid into the phenylacetic acid was also modified. "Perhydrol" was slowly added to an ice-cold solution of 6-nitro-3 : 4-dimethoxyphenylpyruvic acid (42 g.) in 2*N*-sodium hydroxide (300 c.c.) until the violet colour was discharged. A small quantity of white slimy material was removed, and acidification of the filtrate with dilute sulphuric acid yielded 6-nitro-3 : 4-dimethoxyphenylacetic acid, m. p. 203—204° (31 g.; 83% of the theoretical yield). When crystallised from alcohol, this acid formed brown needles, m. p. 206—207°.

The preparation of 6-nitro-3 : 4-dimethoxyphenylacetic acid by nitration was performed as follows: A mixture of 3 : 4-dimethoxyphenylacetic acid (36 g.) and glacial acetic acid (80 c.c.) was stirred mechanically and cooled in ice. Fuming nitric acid (24 c.c.) in

acetic acid (20 c.c.) was added slowly, and the mixture poured into water. The precipitated acid was dried; it crystallised from glacial acetic acid in faintly yellow needles, m. p. 206—207°, or from ethyl acetate in colourless needles having the same melting point (Found: C, 50·0; H, 4·8. Calc. for $C_{10}H_{11}O_6N$: C, 49·8; H, 4·6%). It was very sparingly soluble in benzene, chloroform, and cold water, and sparingly soluble in glacial acetic acid and ethyl acetate. Oxford and Raper record the melting point as 202—204°, and state that the acid is readily soluble in glacial acetic acid and in ethyl acetate. The specimen prepared by their method was identical in every respect with that just described.

6′-Nitro-3′ : 4′-dimethoxyphenylaceto-β-2 : 3-dimethoxyphenylethylamide (V).—Preliminary experiments showed that 6-nitro-3 : 4-dimethoxyphenylacetyl chloride could not be prepared in the same way as the 2-nitro-derivative. When the mixture of the acid with thionyl chloride in benzene was gently warmed, decomposition occurred, accompanied by blackening, and no crystalline amide could be prepared from the product obtained after removal of thionyl chloride. The chloride appeared to be formed when slightly more than one molecular proportion of phosphorus pentachloride was added to a suspension of the acid in chloroform. Heating or the addition of pyridine to this solution caused decomposition, since the liquid darkened considerably, and no amide could be separated from the tarry product obtained after the addition of β-2 : 3-dimethoxyphenylethylamine and treatment in the usual way. Some of the desired product was obtained, however, by the addition of an excess of the amine to the solution containing the acid chloride, and finally the following process was adopted. The acid (13·1 g.) was suspended in dry chloroform, and phosphorus pentachloride (25 g.) gradually added. After being shaken for 20 minutes, all the phosphorus pentachloride and acid had passed into solution, and the liquid was then added slowly to a vigorously stirred mixture of the amine (12 g.) in chloroform (50 c.c.) and dilute aqueous sodium hydroxide (250 c.c. of 2*N*-solution and 400 c.c. of water) which was cooled in ice. After about 20 minutes, the chloroform was separated, the aqueous layer extracted with chloroform, and the combined chloroform solutions were washed with dilute acid, dried, and evaporated. The residual gum was dissolved in hot methyl alcohol, and on cooling, the product separated in colourless needles (9·5 g.). When recrystallised from methyl alcohol and from benzene, *6′-nitro-3′ : 4′-dimethoxyphenylaceto-β-2 : 3-dimethoxyphenylethylamide* separated as needles, m. p. 144·5—145·5° (Found: C, 59·8; H, 6·2. $C_{20}H_{24}O_7N_2$ requires C, 59·4; H, 5·9%).

6′-Nitro-3′ : 4′ : 5 : 6-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline.

—A mixture of the amide (9·5 g.) and a solution of phosphorus pentachloride (11 g.) in chloroform (60 c.c.) was kept in a closed vessel. Separation of nodular crystals began after 3 days and appeared to be complete after 4 days. The mixture was poured into dilute hydrochloric acid, the chloroform evaporated by heating, and the residual tar removed by filtration. When the filtrate was made alkaline with ammonia, a tar was precipitated which soon solidified (6 g.). After crystallisation from methyl alcohol, in which it was sparingly soluble, and from benzene, in which it dissolved rather readily, *6′-nitro-3′ : 4′ : 5 : 6-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline* was obtained as colourless prisms, m. p. 187·5—189·5° (Found : C, 62·2; H, 5·9. $C_{20}H_{22}O_6N_2$ requires C, 62·2; H, 5·7%). This substance melted to a deep red liquid, and the colour faded on resolidification. The formation of the *iso*quinoline was incomplete, since the tar which was insoluble in hydrochloric acid yielded 1·0 g. of unchanged amide on treatment with methyl alcohol.

The *methiodide* was prepared by heating the base (3·1 g.) with purified methyl iodide under reflux for 12 hours, and separated as yellow crystals (4·95 g.), m. p. 111° (decomp. with effervescence). Good analytical figures could not be obtained for this substance. When recrystallised from absolute alcohol, it separated as an oil, which solidified only when rubbed. This solid, m. p. 146—147° (with decomposition to a red liquid, after softening at 140°), was dried in a vacuum (Found : C, 50·2; H, 5·3. $C_{21}H_{25}O_6N_2I$ requires C, 47·7; H, 4·7%). The solution in alcohol was red, and when crystallisation took place slowly in a not too concentrated solution, a mixture of yellow and red crystals separated, m. p. 115—124° (decomp.). An apparently homogeneous product was slowly precipitated as a yellow powder, m. p. 146—148° (decomp.; softening at 140°), when an excess of benzene was added to a solution of the methiodide in absolute alcohol (Found : C, 49·6; H, 5·4%). The analytical figures do not correspond to any simple addition of solvent. When heated at 100°, the substance darkened slowly and the m. p. fell to 108—120° (decomp. at 137°). The addition of ammonia to an aqueous solution of the methiodide precipitated reddish-purple flocks. These formed a bright red solution in benzene (compare the behaviour of the 2′-nitro-derivative, p. 667), and were probably 6′-nitro-3′ : 4′ : 5 : 6-tetramethoxy-1-benzylidene-2-methyltetrahydro*iso*quinoline, since the methiodide was regenerated by the action of hydriodic acid.

6′-Amino-3′ : 4′ : 5 : 6-tetramethoxy-1-benzyl-2-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline (VI).—The methiodide (3·5 g.) was suspended in a mixture of concentrated hydrochloric acid (80 c.c.) and water

(35 c.c.), heated on the water-bath, and zinc dust (25 g.) added slowly until the solution was decolorised. The filtered solution was basified with an excess of ammonia, and the mixture extracted thoroughly with ether. Evaporation of the ethereal solution yielded a gum, which could not be induced to crystallise and was therefore dissolved in chloroform and converted into the dihydrochloride by means of hydrogen chloride. The addition of ether precipitated a copious white solid (2·2 g.). When purified by two recrystallisations from absolute alcohol, 6′-*amino*-3′ : 4′ : 5 : 6-*tetramethoxy*-1-*benzyl*-2-*methyltetrahydroisoquinoline dihydrochloride* formed microscopic short needles, m. p. 233·5—235° (decomp.) (Found: C, 56·7; H, 6·8. $C_{21}H_{28}O_4N_2$,2HCl requires C, 56·6; H, 6·8%). The addition of sodium nitrite to the solution in dilute hydrochloric acid caused the development of a deep blue coloration, which faded in a few minutes through blue-green to yellow. A red precipitate of an azo-dye was obtained when this solution was added to an alkaline solution of β-naphthol.

dl-2 : 3 : 6 : 7-*Tetramethoxyaporphine* (II).—A solution of the preceding dihydrochloride (1·94 g.) in a mixture of methyl alcohol (10 c.c.) and 2*N*-sulphuric acid (10 c.c.) cooled in a freezing mixture was diazotised with the calculated quantity of sodium nitrite solution. After being kept at the ordinary temperature for 2 hours, the solution was boiled under reflux for 1 hour, concentrated hydrochloric acid (3 c.c.) added, and the mixture reduced by the gradual addition of zinc dust (1 g.). From the filtered solution, rendered alkaline with an excess of sodium hydroxide, ether extracted a gum. This was dissolved in dilute hydrochloric acid, an excess of sodium iodide added, the supernatant liquid poured off, and the precipitated gum stirred with alcohol; the crude hydriodide, thus obtained as a white powder (0·55 g.), melted at 227·5—230·5° (decomp.; after darkening above 200°). When the hydriodide was ground with sodium hydroxide solution, a brown viscous oil was formed; this was extracted with chloroform, and the extract dried and evaporated. dl-2 : 3 : 6 : 7-*Tetramethoxyaporphine*, m. p. 115·5—116·5°, was obtained in very pale yellow nodules from the gummy residue by repeated recrystallisation from light petroleum (b. p. 60—80°) (Found, by microanalysis: C, 71·0; H, 6·9. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%). The methiodide, obtained as a colourless solid when the base was warmed with a little alcohol and excess of methyl iodide, was freed from solvent by heating on the water-bath; it crystallised from much methyl alcohol in needles, m. p. 204—208°.

An attempt was made to resolve the *dl*-base by forming the hydrogen *d*-tartrate, but this could only be obtained as a gum.

By a fractional separation from absolute alcohol, and the conversion of the more soluble fraction into the hydrogen *l*-tartrate, a second gum was obtained which did not become crystalline by repeated separations from absolute alcohol. Both yielded the unchanged base, m. p. 115·5—116·5°, which showed no evidence of optical activity.

The following colour reactions were given by the *dl*-base :

Concentrated sulphuric acid :	Emerald-green, becoming intensely green on warming, and red on dilution.
Concentrated nitric acid :	Indigo, becoming deep purple and finally brown on warming.
Fröhde's reagent :	Colourless.
Erdmann's reagent :	Deep reddish-purple.
Mandelin's reagent :	Transient green, becoming reddish-purple and finally brown.

2'-Nitro-3' : 4'-dimethoxyphenylaceto-β-2 : 3-dimethoxyphenylethylamide (VII).—To a cooled solution of β-2 : 3-dimethoxyphenylethylamine (14 g.) in dry benzene (30 c.c.), a solution of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (from 19 g. of the acid) in dry benzene (70 c.c.) was slowly added, followed by a slight excess of 2*N*-sodium hydroxide. The benzene layer was separated, the aqueous layer again extracted with benzene, and the combined extracts washed with dilute acid and with water and evaporated. The tarry residue was with some difficulty induced to crystallise by rubbing with methyl alcohol (yield, 26 g. ; m. p. 81—89°). After recrystallisation from a small quantity of methyl alcohol and from 60% ethyl alcohol, *2'-nitro-3' : 4'-dimethoxyphenylaceto-β-2 : 3-dimethoxyphenylethylamide* was obtained as colourless needles, m. p. 95—96° (Found : N, 6·7. $C_{20}H_{24}O_7N_2$ requires N, 6·9%). It was very soluble in benzene, readily soluble in methyl or ethyl alcohol, fairly soluble in carbon tetrachloride, and insoluble in light petroleum.

2'-Nitro-3' : 4' : 5 : 6-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline (VIII).—The amide (4·5 g.) was mixed with phosphorus pentachloride (5 g.) in chloroform suspension (30 c.c.) and kept in a closed vessel. After 36 hours a mass of nodular crystals had separated. These appeared to consist of an additive compound of the product and phosphorus pentachloride or phosphoryl chloride, since a portion of the solid, when separated and washed with chloroform, was highly hygroscopic, and the solution in water gave strong positive reactions for both phosphate and chloride. The reaction mixture was poured into water, the chloroform evaporated on the water-bath, and the solution filtered from the residual tar. The addition of an excess of ammonia yielded a gummy precipitate which soon solidified (2·5 g.). When recrystallised twice from

methyl alcohol, *2'-nitro-3' : 4' : 5 : 6-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline* was obtained as peach-coloured prisms, melting at 152—156° to a red liquid (Found : C, 62·4; H, 5·7. $C_{20}H_{22}O_6N_2$ requires C, 62·2; H, 5·7%).

The *methiodide* separated in clusters of small needles containing methyl iodide of crystallisation, m. p. 110—116° (efferv.), when a solution of the base in excess of boiling methyl iodide was allowed to cool (Found : loss at 95°, 20·3. $C_{21}H_{25}O_6N_2I,CH_3I$ requires loss, 21·2%). After drying at 95°, the methiodide melted at 183—184° (decomp.) (Found : C, 47·8; H, 5·1. $C_{21}H_{25}O_6N_2I$ requires C, 47·7; H, 4·7%). It could not be recrystallised satisfactorily, and the specimen used for analysis was prepared from the pure base. The methiodide was very soluble in methyl or ethyl alcohol and in chloroform and very sparingly soluble in carbon tetrachloride. When ammonia was added to an aqueous solution, an orange-red amorphous precipitate separated, which formed an orange solution in benzene (compare p. 664).

2'-Amino-3' : 4' : 5 : 6-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline (IX).—The methiodide (6 g.) was suspended in a mixture of hydrochloric acid (120 c.c.) and water (80 c.c.), heated on the water-bath, and zinc dust (18 g.) added gradually until the solution was completely decolorised. The solution was filtered while hot, and basified with concentrated ammonia solution. The resulting purple solution was extracted with ether (500 c.c.), and the extract dried over sodium sulphate and evaporated to dryness. A mixture of crystals with a little gum remained (3·7 g.). An attempt to isolate the product by passing hydrogen chloride into the ethereal solution yielded a sticky product which could not be made to crystallise, and the method just described was more satisfactory. When purified by recrystallisation from ether, *2'-amino-3' : 4' : 5 : 6-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline* was obtained as colourless rhombic plates, m. p. 117·5—119·5° (Found : C, 67·7; H, 7·4. $C_{21}H_{28}O_4N_2$ requires C, 67·7; H, 7·5%). A diazotised solution of the amine in hydrochloric acid gave with an alkaline solution of β-naphthol a scarlet azo-dye.

dl-*3 : 4 : 6 : 7-Tetramethoxyaporphine* (IV).—The preceding amine (3·72 g.) was dissolved in a mixture of ice-cold 2*N*-sulphuric acid (20 c.c.) and methyl alcohol (20 c.c.) and diazotised with the calculated amount of sodium nitrite solution. After 20 minutes, the mixture was boiled on the water-bath for ½ hour, reduced with concentrated hydrochloric acid (6 c.c.) and zinc dust (2 g.), cooled, and made strongly alkaline by the addition of sodium hydroxide. The product was only slowly extracted by ether, and a large volume (900 c.c.) was found to be necessary. The ethereal solution, when

dried over sodium sulphate and evaporated, left a gummy residue, which was dissolved in the minimum quantity of dilute hydrochloric acid and treated with an excess of sodium iodide. A gum separated; the supernatant liquid was poured off, and the gum stirred with methyl alcohol (20 c.c.). dl-3 : 4 : 6 : 7-*Tetramethoxyaporphine hydriodide* was thus obtained as a white powder, which formed long prisms from methyl alcohol, m. p. 257—262° after darkening (Found: C, 52·6; H, 5·4. $C_{21}H_{25}O_4N$,HI requires C, 52·2; H, 5·4%). The free base was obtained by grinding the hydriodide with a slight excess of sodium hydroxide; the dried solid (0·87 g., m. p. 122—127°) was repeatedly crystallised from light petroleum, dl-3 : 4 : 6 : 7-*tetramethoxyaporphine* being obtained as clear yellow plates, m. p. 131—132° (Found, by microanalysis: C, 70·9; H, 7·2. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%). The substance was very soluble in methyl and ethyl alcohols, acetone, benzene, and ether, but insoluble in water.

Resolution of dl-3 : 4 : 6 : 7-*Tetramethoxyaporphine.*—The crude base (0·7404 g.) was treated with a saturated solution of *d*-tartaric acid (1 mol.; 0·3336 g.) in absolute alcohol. No separation took place, even after some time, but a caseous precipitate (0·5 g.) was obtained by the addition of benzene to a solution in slightly aqueous alcohol. The filtrate yielded a gum (0·7 g.) when evaporated to dryness. The precipitate, after being twice recrystallised from 96% alcohol, yielded d-3 : 4 : 6 : 7-*tetramethoxyaporphine hydrogen* d-*tartrate* in bunches of needles, m. p. 174—185° after softening (Found: loss at 80° in a vacuum over P_4O_{10}, 6·4, 7·0; loss at 110° in a vacuum over P_4O_{10}, 7·3. $C_{25}H_{31}O_{10}N,2H_2O$ requires loss, 6·7%). The anhydrous salt regained water rapidly in the air. When it was heated at 110°, slight decomposition occurred, for the salt then crystallised poorly from alcohol and low values were obtained for the rotations of the salt and of the base as compared with those of the optical isomerides. Concordant values were given, however, by a specimen obtained by repeating the process of resolution. In water, the hydrogen *d*-tartrate had $[\alpha]_D^{21°}$ + 84·9° (c = 0·930). The base was liberated from the bitartrate by sodium hydroxide, and extracted with chloroform. The residue left by evaporation of the chloroform was recrystallised from light petroleum, yielding d-3 : 4 : 6 : 7-*tetramethoxyaporphine* as long, pale yellow prisms, m. p. 125—125·5°. In chloroform (c = 0·459), $[\alpha]_D^{20°}$ = + 168°.

From the mother-liquors and residues of the isolation of the *d*-base *d*-bitartrate, the basic material was liberated, and extracted with ether, and the extracts were evaporated in a weighed dish. The gum (0·4955 g.) obtained was treated with *l*-tartaric acid

(0·2235 g.) in alcohol. Crystals readily separated from the solution, and after three recrystallisations from alcohol, l-3 : 4 : 6 : 7-*tetramethoxyaporphine hydrogen* l-*tartrate* was obtained as needles, m. p. 170—180° after softening (Found, by microanalysis : loss at 100° over P_4O_{10} in a vacuum, 7·5. Found in anhydrous material : C, 58·7; H, 6·1. $C_{25}H_{31}O_{10}N,2H_2O$ requires loss, 6·7%. $C_{25}H_{31}O_{10}N$ requires C, 58·1; H, 6·1%). In water (c = 2·044), $[\alpha]_D^{18·5°}$ = − 85·2°. l-3 : 4 : 6 : 7-*Tetramethoxyaporphine* was obtained from this salt, and formed long, pale yellow prisms from light petroleum, m. p. 125·5—126°. In chloroform (c = 0·978), $[\alpha]_D^{20°}$ = − 167° (Found, by microanalysis : C, 70·8; H, 6·8. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%).

l-3 : 4 : 6 : 7-Tetramethoxyaporphine methiodide was obtained as a white solid when the *l*-base was warmed with excess of methyl iodide. After being freed from methyl iodide by heating on the water-bath, it melted at 208—210°.

The following colour reactions were given by the *l*-base :

Concentrated sulphuric acid :	Very pale green, or blue-green in larger amount. Changed to orange-red by addition of nitric acid.
Concentrated nitric acid :	Immediate orange-red colour.
Fröhde's reagent :	Barely perceptible straw colour.
Erdmann's reagent :	Immediate deep greenish-blue, changing quickly to orange-red.
Mandelin's reagent :	Deep blue-green, changing to brown.

Colour Reactions of the Aporphines.

Aporphine.	Mandelin.	Erdmann.	Fröhde.	H_2SO_4.	HNO_3.
Glaucine	Green, blue-violet.	Blue, green-blue.	Green, blue, indigo, violet.	Nil, deep blue at 100°.	Green, deep red.
Laurotetanine	Indigo, brown, yellow.	Deep blue, brown, violet.	Indigo, brown.	Rose-red or green-blue, violet at 100°.	Red-brown.
Bulbocapnine	Blue, darker.	Blue, blue-violet.	Dark blue.	Orange, violet.	Red-brown.
Bulbocapnine methyl ether	Red, violet, blue.	Deep red.	Deep green-blue.	Nil, orange-red.	—
Corytuberine	Grey-blue, dark green.	Green, blue-violet.	Steel-blue, indigo, blue-green.	Nil, green, red, violet.	Blood-red.
Corytuberine dimethyl ether	Pale red, green, olive.	Nil, bright green.	Nil, moss-green.	Nil.	Instant blood-red.
Corydine	Transient violet, green.	Emerald.	Malachite-green.	Nil.	Blood-red.
*iso*Corydine	Violet.	Pale yellow, green.	Pale violet, green-brown.	Nil.	Red-brown.
Dicentrine	Deep blue.	Nil, soon blue.	Deep blue, green-blue, violet.	Nil, soon violet-red.	Nil, blue-green, yellow, brown.
*epi*Dicentrine	—	—	—	Red-violet.	Blue-green.
Domesticine and *iso*-D.	—	—	—	—	Blue.

Aporphine.	Mandelin.	Erdmann.	Fröhde.	H_2SO_4.	HNO_3.
5 :6-Di-methoxy-	Green, soon brown.	Pink-purple.	Deep blue-purple.	Nil.	
3 : 4 : 6 : 7-Tetra-methoxy-	Deep blue-green, soon brown.	Instant green-blue, orange-red.	Pale straw.	Pale green.	Orange-red.
2 : 3 : 6 : 7-Tetra-methoxy-	Instant green, red-purple, dull brown.	Deep red-purple.	Nil.	Emerald, intense green at 100°, red with H_2O.	Indigo, purple at 100°, brown.
Morpho-thebaine	Dirty violet, lighter.	Yellow, reddish.	Steel-blue, grey-blue, tinge violet, yellow-green.	Nil.	Blood-red, red-brown.
Morpho-thebaine dimethyl ether	Violet, brown.	Pale yellow.	Dull green.	Nil.	Bright brown, duller.
*iso*Thebaine	Olive, brown.	Yellow.	Blue, green, olive. bright green.	Nil.	Dark violet, red-brown, yellow.
*iso*Thebaine methyl ether	Olive-green, dull brown.	Yellow.	Nil, bright green.	Nil.	Dark violet, red-violet, brown.
Apomorphine	Instant green, indigo, dull green.	Dull green, blood-red.	Violet, brown, dull purple.	Pale straw, brown-violet at 100°.	Purple-red, orange-red at 100°.
Boldine	—	Green.	—	Blue (in acetic acid)	—

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