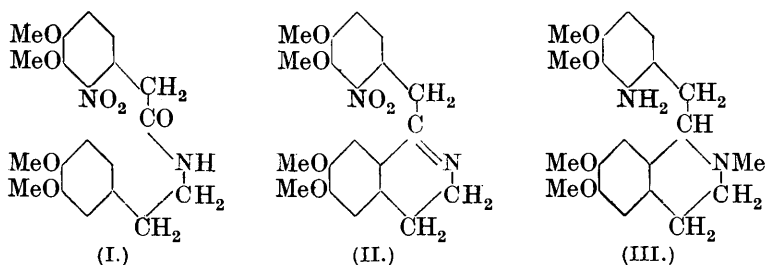


CCXXXVII.—*Synthetical Experiments on the Aporphine Alkaloids. Part III. A Synthesis of Corytuberine Dimethyl Ether.*

By JOHN MASSON GULLAND and ROBERT DOWNS HAWORTH.

THE method described in Parts I and II of this series (this vol., pp. 581, 1132) has now been applied to the synthesis of 3 : 4 : 5 : 6-tetramethoxyaporphine (IV), the *d*-form of which is identical with corytuberine dimethyl ether (corydine and *isocorydine* monomethyl ether).

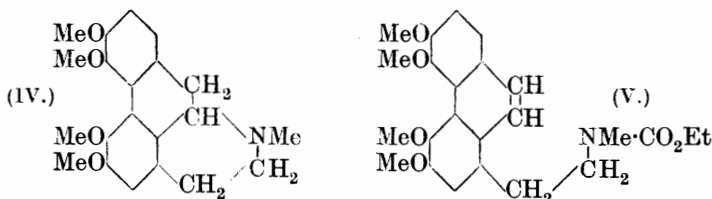
2'-Nitro-3' : 4'-dimethoxyphenylaceto- $\beta$ -3 : 4-dimethoxyphenylethylamide (I) was prepared from 2-nitro-3 : 4-dimethoxyphenylacetyl chloride and  $\beta$ -veratrylethylamine, and converted into 2'-nitro-6 : 7 : 3' : 4'-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline (II) by the action of phosphorus pentachloride. This pale yellow, crystalline base, which forms a crystalline *hydrochloride*, was converted into its *methiodide*, and the latter was reduced with zinc dust and hydrochloric acid to 2'-amino-6 : 7 : 3' : 4'-tetramethoxy-1-benzyl-2-methyl-tetrahydroisoquinoline (III). This oily base, which yields a crystalline *dihydrochloride*, diazotises readily and the diazonium salts couple with  $\beta$ -naphthol in alkaline solution.



The base (III) was diazotised in a mixture of methyl alcohol and sulphuric acid and converted into 3 : 4 : 5 : 6-tetramethoxyaporphine (IV) by warming. This *dl*-base is a pale yellow oil from which a crystalline *methiodide* has been prepared. The *dl*-base (IV) was resolved by means of *d*-tartaric acid, and 1-corytuberine dimethyl ether *d*-bitartrate was thus obtained in crystalline

condition. *d*-Corytuberine dimethyl ether *l*-bitartrate was then prepared by liberating the base from the mother-liquors and combining it with *l*-tartaric acid. The *d*- and *l*-bases were obtained from the bitartrates in the form of oils. These gave the colour reactions described by Gadamer (*Arch. Pharm.*, 1911, **249**, 547) for the oily corytuberine dimethyl ether, which he prepared by methylating naturally occurring *d*-corytuberine.

As we do not possess a sample of the natural product, direct comparison has not been possible, but the melting points, solubilities, and rotation values of the *l*-bitartrate and the methochloride of the synthetical *d*-base are in close agreement with those which Gadamer (*loc. cit.*) records for the corresponding derivatives of the *d*-base obtained from natural sources. Further, the optically inactive carbethoxycorytuberine dimethyl ether (V), prepared by the action of sodium hydroxide and ethyl chloroformate on the synthetical *d*- or *dl*-base, appears to be identical with the product obtained by Osada (*Arch. Pharm.*, 1924, **262**, 501) in a similar manner from the *d*-base of natural origin.



This synthesis confirms the structure which Gadamer (*loc. cit.*) suggested for corytuberine dimethyl ether (corydine and *isocorydine* monomethyl ether), and we hope to determine by analogous syntheses the positions of the phenolic hydroxyl groups in these alkaloids.

#### EXPERIMENTAL.

*2'*-Nitro-*3'*:*4'*-dimethoxyphenylaceto- $\beta$ -*3*:*4*-dimethoxyphenylethylamide (I).—A benzene solution of 2-nitro-3:4-dimethoxyphenylacetyl chloride (prepared from 5 g. of acid as described in this vol., p. 1134) and  $\beta$ -veratrylethylamine (3.7 g.) was cooled and shaken with a slight excess of 15% sodium hydroxide solution. The benzene layer was washed with dilute hydrochloric acid and dried with sodium sulphate, and the solvent removed. The residual oil was dissolved in a little methyl alcohol (in which it is very soluble) and mixed with ether, the alcohol was removed by washing with water, and the ether was dried and allowed to evaporate slowly; the *amide* separated in almost colourless nodules, m. p. 64–65°, containing solvent of crystallisation which is lost at 100° (Found in material dried at 110°: C, 60.2; H, 6.2. C<sub>20</sub>H<sub>24</sub>O<sub>7</sub>N<sub>2</sub> requires

C, 59.6; H, 5.7%). This amide is very soluble in the usual organic solvents with the exception of light petroleum.

*2'-Nitro-6 : 7 : 3' : 4'-tetramethoxy-1-benzyl-3 : 4-dihydroisoquinoline* (II).—A solution of the amide (I) (5 g.), chloroform (50 c.c.), and phosphorus pentachloride (6 g.) was allowed to remain at room temperature for 36 hours. The solvent was removed in a vacuum from the buff-coloured solid, the residue was dissolved in hot water, and the filtered solution made alkaline with ammonia. The solid base, collected after 3 hours, crystallised from ethyl alcohol in pale yellow prisms (3.9 g.), m. p. 159—160° (Found : C, 61.9; H, 5.9.  $C_{20}H_{22}O_6N_2$  requires C, 62.2; H, 5.7%). This base is almost insoluble in light petroleum, sparingly soluble in ether and cold alcohol, but readily soluble in benzene and chloroform. It dissolves in hot dilute hydrochloric acid, and on cooling, the *hydrochloride* separates in very pale yellow needles, m. p. 227° (decomp.). The *methiodide* was prepared by allowing the base to react with an excess of methyl iodide at room temperature for 12 hours. The excess of methyl iodide was then removed, and the residue crystallised from ethyl alcohol, in which it was readily soluble. It forms rosettes of yellow needles, which contain solvent of crystallisation and melt at 105—107°, resolidify, and decompose gradually between 180° and 190° (Found in material dried at 100° : C, 47.7; H, 5.0.  $C_{21}H_{25}O_6N_2I$  requires C, 47.7; H, 4.7%).

*2'-Amino-6 : 7 : 3' : 4'-tetramethoxy-1-benzyl-2-methyltetrahydroisoquinoline* (III).—A hot solution of the methiodide (2.3 g.) in water (25 c.c.) and concentrated hydrochloric acid (25 c.c.) was reduced by the gradual addition of zinc dust (7.5 g.). The liquid having been filtered and made alkaline with ammonia, the base was extracted with ether and dried, and the solvent removed. The residual oil was dissolved in chloroform and saturated with dry hydrogen chloride; the *dihydrochloride* of the base (III) separated in colourless needles (1.7 g.), m. p. 188—190° (Found in material dried at 100° : C, 56.8; H, 6.7.  $C_{21}H_{28}O_4N_2 \cdot 2HCl$  requires C, 56.6; H, 6.7%). The dihydrochloride was hygroscopic and dissolved readily in ethyl alcohol. The addition of sodium nitrite to an aqueous solution of the dihydrochloride produced a bright yellow solution which coupled with alkaline  $\beta$ -naphthol, yielding a vermilion azo-dye which became deep port-wine in colour when dissolved in concentrated sulphuric acid.

*dl-Corytuberine dimethyl ether* (IV).—The dihydrochloride of the base (III) (2 g.), dissolved in methyl alcohol (10 c.c.) and sulphuric acid (10 c.c. of 2*N*), was diazotised by the gradual addition of the calculated amount of 2*N*-sodium nitrite. The bright yellow liquid became deep red after boiling for  $\frac{1}{2}$  hour; zinc dust (1 g.) and con-

centrated hydrochloric acid (3 c.c.) were then added, and the boiling was continued for 15 minutes. The mixture was filtered, and the residue extracted with boiling water. The combined filtrate and washings were rendered alkaline with ammonia and extracted with ether, the extract was washed with sodium hydroxide solution and dried, and the ether was removed. *dl*-Corytuberine dimethyl ether (0.3 g.) remained as a pale yellow oil which did not crystallise. The *hydrochloride* was very soluble in water and alcohol, and the *hydriodide* separated as a gum when potassium iodide was added to an aqueous solution of the hydrochloride. The *methiodide*, which was obtained by heating the *dl*-base with an excess of methyl iodide, crystallised from ethyl alcohol in colourless prisms which darken slightly at about 220° and decompose at 248° (Found: C, 52.9; H, 5.5.  $C_{22}H_{28}O_4NI$  requires C, 53.1; H, 5.6%).

*Resolution of dl-Corytuberine Dimethyl Ether.*—When *dl*-corytuberine dimethyl ether (1 g.) in absolute ethyl alcohol (15 c.c.) was mixed with an absolute-ethyl-alcoholic solution of *d*-tartaric acid (3 c.c. of 2*N*), a gum separated. This dissolved on boiling, and the colourless crystals of *l*-corytuberine dimethyl ether *d*-bitartrate which rapidly separated were collected by filtering the boiling solution and recrystallised from rectified spirit, forming colourless needles, m. p. 219—221° (decomp.) (Found in material dried at 100°: C, 59.2; H, 6.3.  $C_{25}H_{31}O_{10}N$  requires C, 59.4; H, 6.1%). In aqueous solution:  $l = 1$ ,  $c = 1.005$ ,  $\alpha_D = -1.49^\circ$ , whence  $[\alpha]_D = -148.2^\circ$ . On cooling, the hot filtrate deposited a gum; the clear supernatant liquid was decanted and evaporated to dryness and the base was liberated by the action of sodium hydroxide solution and extracted with ether. The ethereal extract was dried, the solvent removed, and the residual oil was dissolved in absolute ethyl alcohol (15 c.c.) and mixed with an absolute-ethyl-alcoholic solution of *l*-tartaric acid (3 c.c. of 2*N*). *d*-Corytuberine dimethyl ether *l*-bitartrate separated; it crystallised from rectified spirit in colourless needles, m. p. 219—222° (decomp.). Gadamer (*loc. cit.*) gives 219—224° (decomp.) (Found: C, 59.3; H, 6.3. Calc. for  $C_{25}H_{31}O_{10}N$ : C, 59.4; H, 6.1%). In aqueous solution,  $l = 1$ ,  $c = 1.017$ ,  $\alpha_D = +1.53^\circ$ , whence  $[\alpha]_D = +149.7^\circ$ . Gadamer (*loc. cit.*) gives  $[\alpha]_D = +150^\circ$ .

The *d*- and the *l*-base were liberated as oils from the bitartrates by the action of sodium hydroxide solution. With concentrated sulphuric acid, concentrated nitric acid, Erdmann's reagent, Fröhde's reagent, Mandelin's reagent, and a solution of selenic acid in concentrated sulphuric acid, the *d*- or the *l*-base gave colour reactions which were in agreement with those described by Gadamer (*loc. cit.*) for *d*-corytuberine dimethyl ether.

*d*-Corytuberine dimethyl ether methochloride was prepared by refluxing the *d*-base with an excess of methyl iodide for 1 hour, removing the excess of methyl iodide, digesting the residual methiodide with an aqueous suspension of silver chloride for 2 hours, filtering the solution, and evaporating the filtrate to dryness. When ether was added gradually to a solution of the gummy residue in a little absolute ethyl alcohol, the methochloride separated in slender needles, m. p. 243° (decomp.). Gadamer gives m. p. 234—237° (decomp.). In aqueous solution:  $l = 1$ ,  $c = 1.112$ ,  $\alpha_D = +2.17^\circ$ , whence  $[\alpha]_D = +196^\circ$ . Gadamer gives 197.6°.

Carbethoxycorytuberine dimethyl ether (V), m. p. 93°, was prepared from the synthetical *d*- or *dl*-base by the process described by Osada (*loc. cit.*) and appeared to be identical with that obtained from natural sources.

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THE UNIVERSITY OF DURHAM,  
ARMSTRONG COLLEGE,  
NEWCASTLE-ON-TYNE.

THE DYSON PERRINS LABORATORY,  
OXFORD.

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