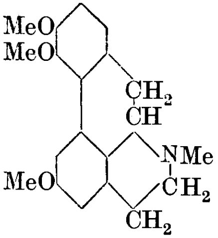
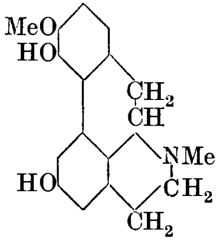
CCLXXIII.—*Synthetical Experiments on the Aporphine Alkaloids. Part IV. A Synthesis of Morphothebaine Dimethyl Ether.*

By John Masson Gulland and Robert Downs Haworth.

The method for the preparation of bases of the aporphine group which was described in Part I of this series (this vol., p. 581) has now been extended to the synthesis of 3 : 4 : 6-*trimethoxyaporphine* (I). The lævo-form of this base is identical with morphothebaine dimethyl ether (Klee, *Arch. Pharm.*, 1914, **252**, 242), and thus the structure for morphothebaine (II) advanced by Pschorr and Halle (*Ber.*, 1907, **40**, 2004) is substantiated. Morphothebaine is produced when hot concentrated hydrochloric acid acts on thebaine, and as a phenanthreno*iso*quinoline base, it forms one of the connecting links between the morphine and aporphine groups of alkaloids.

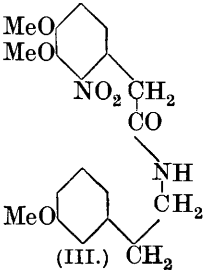
(I.)



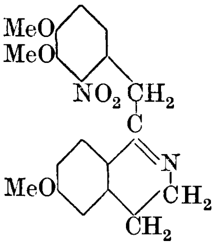


(II.)

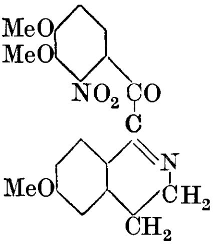
2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-*methoxyphenylethylamide* (III), prepared by the interaction of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride and 3-methoxy-β-phenylethylamine (Helfer, *Helv. Chim. Acta*, 1924, **7**, 945), was converted into 2′-*nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (IV) by the action of phosphorus pentachloride. This pale yellow crystalline base, which forms a sparingly soluble *hydrochloride*, *sulphate*, and *methiodide*, is remarkably stable to atmospheric oxidation, but a small quantity of feebly basic 2′-*nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzoyl*-3 : 4-*dihydro*-



(III.)



(IV.)



(V.)

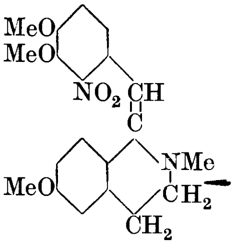
iso*quinoline* (V) was actually isolated from the mother-liquor of the preparation of the base (IV), and was converted into the amorphous, alkali-soluble *oxime*.

The methiodide of the base (IV), which was abnormal in that it did not appear to undergo alkaline scission but yielded only the crystalline anhydro-base, 2′-*nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzylidene*-2-*methyltetrahydro*iso*quinoline* (VI), was reduced with zinc dust and hydrochloric acid to 2′-*amino*-6 : 3′ : 4′-*trimethoxy*-1-*benzyl*-2-*methyltetrahydro*iso*quinoline* (VII), an oily base which yielded a crystalline *dihydrochloride* and diazotised readily. The base (VII) was diazotised in a mixture of methyl alcohol and sulphuric acid, and converted by heating into 3 : 4 : 6-*trimethoxyaporphine* (I), an oil from which a crystalline *hydriodide* has been prepared.

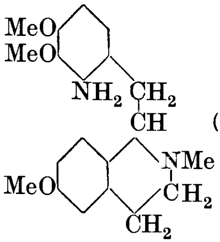
This *dl*-base (I) was resolved by means of *d*-tartaric acid, and *l*-morphothebaine dimethyl ether hydrogen *d*-tartrate obtained in crystalline condition. It appeared from its crystalline form, melting point, and rotation, and by a mixed melting-point determination, to be identical with the salt prepared from morphothebaine in the manner described by Klee (*loc. cit.*). The *l*-base was obtained from the hydrogen tartrate as an uncrystallisable oil, which showed the same colour reactions and rotation as a specimen of natural morphothebaine dimethyl ether. Further, the *methiodides* of the two preparations appeared from a comparison of their crystalline form, melting point, and rotations to be similar in every respect, and there can be no doubt that the synthetical and natural products are identical.

d-*Morphothebaine dimethyl ether hydrogen* l-*tartrate* was obtained from the mother-liquor of the resolution by liberating the crude *d*-base and allowing it to combine with *l*-tartaric acid. The *d*-base is an oil which has not crystallised.

(VI.)



(VII.)



EXPERIMENTAL.

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-*methoxyphenylethylamide* (III).—2-Nitro-3 : 4-dimethoxyphenylacetyl chloride (from 10 g. of acid) in benzene (50 c.c.) was added gradually to a solution of

3-methoxy-β-phenylethylamine (7 g.) in benzene (50 c.c.). After a short time, the dull yellow precipitate which had separated was mixed with 8% sodium hydroxide solution, and the benzene layer was washed with water and dried. When the solvent had been removed, the residual brown oil solidified; it was then crystallised from methyl alcohol, from which the *amide* separated in colourless needles, m. p. 107—108° (Found: C, 60·7; H, 5·9. $C_{19}H_{22}O_6N_2$ requires C, 61·0; H, 5·9%).

*2′-Nitro-6 : 3′ : 4′-trimethoxy-1-benzyl-3 : 4-dihydro*iso*quinoline* (IV).—A solution of the amide (III) (10 g.) and phosphorus pentachloride (12 g.) in chloroform (80 c.c.) was kept at room temperature for 36 hours. After the solvent and phosphorus oxychloride had been removed from the mass of felted needles by distillation under reduced pressure, the residue was dissolved in boiling water, and the solution was filtered and cooled. The sparingly soluble *hydrochloride* of the base (IV) which separated was collected (see below for examination of the mother-liquor), suspended in hot water, and decomposed by ammonia. The *base* (IV) thus liberated crystallised from methyl alcohol in faintly yellow, blunt-ended prisms, m. p. 121—123° (7·5 g.) (Found: C, 64·2; H, 5·5. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6%).

The *hydrochloride* separated in colourless needles, m. p. 217—218° (decomp.), when a solution of the base in hot dilute hydrochloric acid was cooled (Found: Cl, 9·0. $C_{19}H_{20}O_5N_2,HCl$ requires Cl, 9·0%). It is moderately easily soluble in water and ethyl alcohol, but very sparingly soluble in dilute hydrochloric acid. The *sulphate*, prepared by dissolving the base in dilute sulphuric acid, forms colourless needles, m. p. 237° (decomp.).

The *methiodide* was obtained in a yield exceeding 90% when a mixture of the base and an excess of methyl iodide was heated under reflux on the water-bath for 30 minutes, and the excess of methyl iodide removed. It crystallised from ethyl alcohol in yellow needles, m. p. 220° (decomp.), which were sparingly soluble in water (Found: C, 48·4; H, 4·9. $C_{20}H_{23}O_5N_2I$ requires C, 48·2; H, 4·6%). This substance appeared to be unusually stable to alkaline fission, and attempts to decompose it with sodium hydroxide of various concentrations led only to *2′-nitro-6 : 3′ : 4′-trimethoxy-1-benzylidene-2-methyltetrahydro*iso*quinoline* (VI), which separated as a red oil and was extracted with benzene. When the solution was dried and the solvent removed, the base (VI) solidified; after twice crystallising from benzene–ligroin, it was obtained in prisms, m. p. 108—109°, which appeared as red diamond-shaped tablets or as yellow prisms, according to the angle from which they were observed (Found in material dried at 100°: C, 64·9; H, 6·0. $C_{20}H_{22}O_5N_2$ requires

C, 64·9; H, 5·9%). By adding sodium iodide to a solution of the base (VI) in dilute hydrochloric acid, the methiodide of the base (IV) was regenerated as an oil which crystallised when rubbed with ethyl alcohol.

2′-*Nitro*-6 : 3′ : 4′-*trimethoxy*-1-*benzoyl*-3 : 4-*dihydro*iso*quinoline* (V).—The acid mother-liquor from which the hydrochloride of the base (IV) had separated (see above) was rendered alkaline with ammonia; the precipitate obtained, when crystallised twice from methyl alcohol, formed faintly yellow prisms, m. p. 164° (decomp.) (Found: C, 61·5; H, 4·9; N, 7·5. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9; N, 7·5%). This substance is insoluble in alkali, but dissolves in warm dilute hydrochloric acid and is reprecipitated by sodium acetate. A consideration of its properties leads us to assign to it the constitution (V), and in this connexion it is noteworthy that the colour of a solution of the compound in boiling acetic anhydride is yellow, whereas the non-nitrated 1-benzoyl-3 : 4-dihydro*iso*quinolines develop a characteristic green coloration under the same conditions (Buck, Haworth, and Perkin, J., 1924, **125**, 2176). The *oxime*, prepared by the action of hydroxylamine hydrochloride and pyridine at 100°, is amorphous and dissolves readily in dilute sodium hydroxide solution.

2′-*Amino*-6 : 3′ : 4′-*trimethoxy*-1-*benzyl*-2-*methyltetrahydro*iso*quinoline* (VII).—The methiodide (8 g.) of the base (IV), suspended in water (80 c.c.) and concentrated hydrochloric acid (150 c.c.), was heated on the water-bath and reduced by the gradual addition of zinc dust (31 g.). The clear, colourless solution was then cooled, and on several occasions a zinc chloride double salt separated in characteristic, colourless, fan-shaped aggregates of needles. After the addition of an excess of sodium hydroxide solution, the base was isolated by repeated extraction with ether; this extract, when washed with water, dried, and distilled, yielded a pale yellow, uncrystallisable oil. This was converted into its *dihydrochloride* by treating an absolute alcoholic solution with dry hydrogen chloride and evaporating the solution to dryness under reduced pressure. The residual oil crystallised from dry chloroform in colourless needles which softened and shrank at 135°, melted at 155°, and retained solvent when dried in a vacuum desiccator (Found in material dried in a vacuum desiccator: Cl, 32·0. $C_{20}H_{26}O_3N_2,2HCl,CHCl_3$ requires Cl, 33·2%). This substance diazotises readily, and the diazonium salts couple with β-naphthol in alkaline solution, yielding a scarlet dye which develops a reddish-purple colour with concentrated sulphuric acid.

dl-3 : 4 : 6-*Trimethoxyaporphine* (I).—A solution of the hydrochloride of the base (VII) (5 g.) in 2*N*-sulphuric acid (30 c.c.) was boiled in order to free it from chloroform, cooled in ice, and diazotised by the calculated amount of 2*N*-sodium nitrite. After the addition of methyl alcohol (30 c.c.), the orange solution was boiled under reflux for 30 minutes, mixed with concentrated hydrochloric acid (6 c.c.), reduced by zinc dust (2 g.), cooled, filtered, and made alkaline with 30% sodium hydroxide solution. The base (I) was isolated as a pale yellow oil by repeated extraction with ether, followed by the removal of the solvent, and was converted into the *hydriodide* by the addition of sodium iodide to a solution in dilute hydrochloric acid. This salt separated as a gum, but crystallised when rubbed with ethyl alcohol after the mother-liquor had been decanted, and when recrystallised from the same solvent formed almost colourless needles, m. p. 227° (decomp.) (Found in material dried at 100° : C, 53·2; H, 5·2. $C_{20}H_{23}O_3N,HI$ requires C, 53·0; H, 5·3%). It is sparingly soluble in water and separates as a granular, non-crystalline mass when a hot solution is cooled.

Resolution of dl-3 : 4 : 6-*Trimethoxyaporphine.* l-*Morphothebaine Dimethyl Ether.*—The oily *dl*-base (I) was liberated from the hydriodide by sodium carbonate and extracted with ether, and the solvent evaporated. The residue, dissolved in a little 95% ethyl alcohol, was mixed with an alcoholic solution of an equimolecular amount of *d*-tartaric acid; in a few moments, the colourless *l*-morphothebaine dimethyl ether hydrogen *d*-tartrate separated. It crystallised from ethyl alcohol in stellate aggregates of shining needles, m. p. 208—209° (decomp.) (Found in material dried at 100° : C, 60·3; H, 6·3. Calc. for $C_{24}H_{29}O_9N$: C, 60·6; H, 6·1%). In aqueous solution, $c = 1{\cdot}123$, $l = 1$, $\alpha_D = -0{\cdot}84°$, whence $[\alpha]_D = -74{\cdot}8°$. *l*-Morphothebaine was liberated as a colourless oil from the hydrogen tartrate (0·1684 g.) and carefully extracted by successive small quantities of chloroform, and the mixed extracts were dried with a little sodium sulphate and made up to 20 c.c.; $l = 1$, $\alpha_D = -1{\cdot}00°$, whence $[\alpha]_D = -173{\cdot}5°$. The colour reactions with Erdmann's and Fröhde's reagents were indistinguishable from those given by the natural *l*-base (see below). The *methiodide* separated in crystalline condition when a solution of the base and methyl iodide in ethyl acetate was warmed for a few minutes on the water-bath; it crystallised from ethyl alcohol in colourless needles which became pasty at 190° and melted at 195° (Found in material dried at 100° : C, 54·0; H, 5·6. $C_{21}H_{26}O_3NI$ requires C, 54·0; H, 5·6%). In aqueous solution, $c = 0{\cdot}448$, $l = 1$, $\alpha_D = -0{\cdot}39°$, whence $[\alpha]_D = -87{\cdot}1°$.

Natural l-*Morphothebaine Dimethyl Ether.*—For comparison, a specimen of natural morphothebaine dimethyl ether was prepared by methylating morphothebaine with diazomethane as described by Klee (*loc. cit.*). The oil obtained in this way was converted into the hydrogen *d*-tartrate, which crystallised from 95% ethyl alcohol in stellate clusters of shining needles, m. p. 208—209° (decomp.) (Klee gives 205°), and there was no depression of the melting point of a mixture of this material with the synthetical product. In aqueous solution, $c = 1{\cdot}040$, $l = 1$, $\alpha_D = -0{\cdot}78°$, whence $[\alpha]_D = -75{\cdot}0°$ (Klee gives $-74{\cdot}3°$). The oily base, which was liberated by sodium carbonate solution from the hydrogen *d*-tartrate (0·2150 g.), was extracted with chloroform (20 c.c.) as described in the case of the synthetical substance; $l = 1$, $\alpha_D = -1{\cdot}27°$, whence $[\alpha]_D = -172{\cdot}7°$ (Klee gives $-184{\cdot}8°$). With Erdmann's reagent an olive-green colour was immediately developed which changed to a dirty violet-blue and then became red on dilution, and with Fröhde's reagent a deep bluish-green colour was produced which finally became dull violet. The methiodide, prepared as described for the synthetical material, crystallised in needles which became pasty at 190° and melted at 195°, and this melting point was not altered on admixture with the synthetical preparation. In aqueous solution, $c = 0{\cdot}533$, $l = 1$, $\alpha_D = -0{\cdot}47°$, whence $[\alpha]_D = -88{\cdot}2°$.

d-*Morphothebaine Dimethyl Ether.*—The alcoholic mother-liquor from which the *l*-morphothebaine dimethyl ether hydrogen *d*-tartrate had separated (see above) was concentrated, mixed with ammonia, and extracted with ether. The extracts were washed with water, dried, and distilled, and the residue was converted into d-*morphothebaine dimethyl ether hydrogen* l-*tartrate* by mixing an alcoholic solution with an alcoholic solution of the requisite amount of *l*-tartaric acid. This salt separated when the vessel was rubbed, and crystallised from ethyl alcohol in stellate clusters of shining needles, m. p. 208—209° (decomp.) (Found in material dried at 100°: C, 60·6; H, 6·3. $C_{24}H_{29}O_9N$ requires C, 60·6; H, 6·1%). In aqueous solution, $c = 0{\cdot}821$, $l = 1$, $\alpha_D = +0{\cdot}62°$, whence $[\alpha]_D = +75{\cdot}5°$. The colourless oily d-*base*, liberated from the hydrogen *l*-tartrate (0·1231 g.), was dissolved in chloroform (20 c.c.); $l = 1$, $\alpha_D = +0{\cdot}76°$, whence $[\alpha]_D = +174{\cdot}2°$.

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