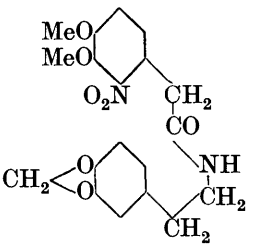
CXLIII.—*Synthetical Experiments on the Aporphine Group. Part II. A Synthesis of Bulbocapnine Methyl Ether.*

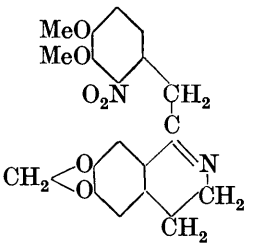
By JOHN MASSON GULLAND and ROBERT DOWNS HAWORTH.

THE synthesis of 5 : 6-dimethoxyaporphine described in Part I (this vol., p. 581) depended on the discovery of experimental conditions which allowed the Bischler–Napieralski synthesis to be utilised in the preparation of 1′-nitrobenzyl-3 : 4-dihydro*iso*quinoline bases. The present communication contains an account of an extension of the method to the synthesis of bulbocapnine methyl ether (V).

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3 : 4-*methylenedioxyphenylethylamide* (I) was prepared by condensing β-piperonylethylamine and 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (Kay and Pictet, J., 1913, **103**, 952). By treating a cold chloroform solution of the amide (I) with phosphorus pentachloride, a good yield of 2′-*nitro*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*isoquinoline (II) was obtained. This pale yellow crystalline base, which yielded a sparingly soluble, almost colourless, crystalline *hydrochloride*, did not undergo atmospheric oxidation. When heated in a sealed tube at 100° with methyl iodide, the base (II) was converted into the *methiodide* (III); this yielded oxyhydrastinine and 2-nitrohomoveratrole on heating with dilute alkali.



(I.)



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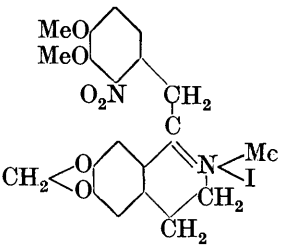
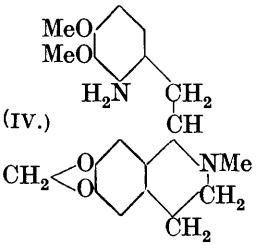


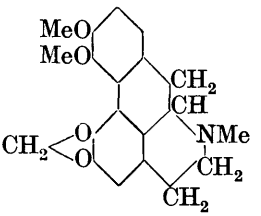
(III.)

The methiodide (III), in strongly acid solution, was reduced with zinc dust to 2′-*amino*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-2-*methyltetrahydro*isoquinoline (IV), which, although itself an oil, yielded a crystalline *dihydrochloride*. The addition of sodium nitrite to a solution of the base (IV) in dilute hydrochloric acid yielded a diazo-solution, which coupled with alkaline β-naphthol. These facts support the constitution assigned to the base (IV) and exclude the possibility of indole formation, which was observed in Part I of this series (pp. 584, 587).

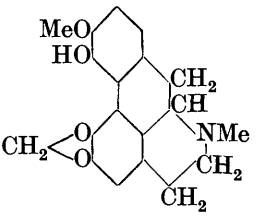
The phenanthrene ring-closure was effected by diazotising the base (IV) in a mixture of methyl alcohol and 2*N*-sulphuric acid, but considerable difficulty was experienced in the isolation of the *dl*-bulbocapnine methyl ether from the reaction mixture. Previously it had been possible to isolate the aporphine bases in the form of their sparingly soluble hydrochlorides, but the solubility of the hydrochloride of *dl*-bulbocapnine methyl ether precluded the use of this method. Eventually the alkaloid was isolated in the form of a crystalline *hydriodide*, from which *dl*-bulbocapnine methyl ether (V) was liberated by the action of sodium hydroxide.



(IV.)



(V.)



(VI.)

The synthetical base crystallised from ether in well-defined rhombs, m. p. 135°, which were identical with a specimen of *dl*-bulbocapnine methyl ether, prepared from natural *d*-bulbocapnine as described by Gadamer (*Arch. Pharm.*, 1911, **249**, 508). Its colour reactions and *methiodide* also were indistinguishable from those of *dl*-bulbocapnine methyl ether prepared from naturally occurring *d*-bulbocapnine.

As Gadamer (*loc. cit.*, p. 509) has resolved *dl*-bulbocapnine methyl ether into its optically active modifications, this synthesis of the *dl*-form completes the synthesis of *d*-bulbocapnine methyl ether. The structure of *d*-bulbocapnine is therefore now limited to one of the two formulæ which are obtained by replacing one of the methoxyl groups in structure (V) by the hydroxyl group. Gadamer (*loc. cit.*) has selected formula (VI) as the more probable constitution of bulbocapnine, and we are engaged in an attempt to synthesise this base.

EXPERIMENTAL.

2-Nitro-3 : 4-dimethoxyphenylacetyl Chloride.—2-Nitroveratraldehyde was prepared as described by Pisovschi (*Ber.*, 1910, **43**, 2137), and was converted into 2-nitro-3 : 4-dimethoxyphenylacetic acid by the method of Kay and Pictet (*loc. cit.*). No attempt was made to purify the intermediate products, and the following description indicates briefly the modifications which were adopted in the preparation of large quantities of the acid. 2-Nitroveratraldehyde was subjected to the action of alcoholic potassium hydroxide as

described by Kay and Pictet, and the mixture was poured into water and extracted thoroughly with benzene. After being washed with sodium bisulphite solution, the extract was dried with sodium sulphate, and the benzene removed. The residual 2-nitro-3 : 4-dimethoxybenzyl alcohol, which solidified on cooling, was converted into the corresponding chloride by the action of phosphorus pentachloride in benzene solution; the benzene and phosphorus oxychloride were removed under diminished pressure, and the crude chloride which remained was converted into the corresponding cyanide as described by Kay and Pictet. The excess of alcohol was removed by distillation, water was added, and the cyanide extracted with benzene; the extract was dried with sodium sulphate and the benzene removed. The residual oil was sufficiently pure for conversion into 2-nitro-3 : 4-dimethoxyphenylacetic acid, more especially as the separation of the imino-ether hydrochloride provided a convenient purification.

2-Nitro-3 : 4-dimethoxyphenylacetic acid (5 g.), chloroform (20 c.c.), and thionyl chloride (3 c.c.) were warmed for 1 hour on the water-bath. The solvent was removed in a vacuum, and the residual 2-nitro-3 : 4-dimethoxyphenylacetyl chloride, which solidified on cooling, was employed without further purification for the following experiments.

2'-Nitro-3' : 4'-dimethoxyphenylaceto-β-3 : 4-methylenedioxyphenylethylamide (I).—2-Nitro-3 : 4-dimethoxyphenylacetyl chloride (from 6 g. of acid) in benzene (30 c.c.) was gradually added to a cooled solution of β-piperonylethylamine (5 g.) in benzene (20 c.c.), which was constantly shaken, and the buff-coloured precipitate which separated was decomposed by the addition of 10% sodium hydroxide solution. The amide (I), which rapidly separated from the benzene, was collected, combined with a small second crop obtained by concentrating the benzene layer of the filtrate, and crystallised from ethyl alcohol; it formed colourless needles (8 g.), m. p. 158° (Found: C, 58·9; H, 5·4. $C_{19}H_{20}O_7N_2$ requires C, 58·8; H, 5·2%). This amide is sparingly soluble in light petroleum, ether, benzene, and cold methyl or ethyl alcohol, but readily soluble in chloroform.

2'-Nitro-3' : 4'-dimethoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydroisoquinoline (II).—Phosphorus pentachloride (6 g.) was added to a cooled solution of the amide (I) (5 g.) in chloroform (50 c.c.), and the mixture kept at room temperature for 36 hours, a pale yellow solid gradually separating. The chloroform and phosphorus oxychloride were removed under diminished pressure, the solid residue was extracted with much hot water and filtered off while hot from a small amount of tar, and the filtrate was made alkaline with ammonia. The dihydro*iso*quinoline (II) separated as a cream-coloured, amorph-

ous powder, which rapidly became crystalline. On recrystallisation from ethyl alcohol it formed pale yellow prisms (3·8 g.), m. p. 164° (Found : C, 61·6; H, 4·9. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9%). This base is sparingly soluble in light petroleum, ether, and cold methyl or ethyl alcohol and readily soluble in chloroform. The sparingly soluble *sulphate* and *nitrate* separate when the base is dissolved in dilute sulphuric and nitric acids respectively. When a solution of the base in hot dilute hydrochloric acid was cooled, the *hydrochloride* separated in very pale yellow plates, m. p. 230° (decomp.) (Found : C, 56·0; H, 4·8. $C_{19}H_{18}O_6N_2$,HCl requires C, 56·1; H, 4·7%).

2′-*Nitro*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*-iso*quinoline Methiodide* (III).—The base (II) (3·2 g.) and methyl iodide (10 c.c.) were heated at 100° in a sealed tube for 1 hour and the excess of methyl iodide was then removed by distillation. The residue crystallised from rectified spirit in bright yellow needles, m. p. 215° (decomp.) (Found : C, 47·1; H, 4·2. $C_{20}H_{21}O_6N_2I$ requires C, 46·9; H, 4·1%). The methiodide (III) is sparingly soluble in water, methyl and ethyl alcohol. The methiodide (2 g.) and 5% sodium hydroxide solution (20 c.c.) were heated on a water-bath for 2 hours, and the colourless solution was subjected to steam distillation. The distillate was extracted with ether, the extract dried with sodium sulphate, and the solvent removed, leaving 2-nitrohomoveratrole as an oil. This was oxidised by a hot dilute solution of potassium permanganate to 2-nitroveratric acid, m. p. 201°, which was identified by comparison with a specimen prepared by the method of Pschorr and Sumuleanu (*Ber.*, 1899, **32**, 3409). The non-volatile portion was evaporated to dryness, and the solid residue extracted with chloroform. The residue from the dried, evaporated extract crystallised from aqueous alcohol in colourless needles, m. p. 98°. These were identified as oxyhydrastinine by comparison with a specimen of the latter prepared by the action of potassium hydroxide on hydrastinine (Freund and Will, *Ber.*, 1887, **20**, 2400; Freund, *Ber.*, 1889, **22**, 457).

2′-*Amino*-3′ : 4′-*dimethoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-2-*methyl*-*tetrahydro*iso*quinoline* (IV).—A suspension of the methiodide (III) (3·5 g.) in water (35 c.c.) and concentrated hydrochloric acid (70 c.c.) was heated on the water-bath and shaken vigorously while zinc dust (11 g.) was gradually added. A colourless crystalline salt gradually separated as the reduction proceeded. The hot solution was filtered, the residue thoroughly extracted with hot water, and the combined filtrate and washings made alkaline with ammonia and extracted with ether. The ethereal extract was dried with sodium sulphate, the ether removed, and the residual oil, which did not

crystallise, was dissolved in alcohol containing hydrogen chloride. The dihydrochloride of the base (IV), which rapidly separated, was collected (2·3 g.) and washed with alcohol. The *dihydrochloride* crystallised from alcohol, in which it is sparingly soluble, in colourless, glistening prisms, m. p. 231° (decomp.) (Found in material dried at 110° : C, 56·2; H, 6·0. $C_{20}H_{24}O_4N_2,2HCl$ requires C, 55·9; H, 6·1%). The bright yellow solution obtained on addition of sodium nitrite to the dihydrochloride in water gave, on treatment with alkaline β-naphthol, a crimson azo-dye, which formed a deep magenta-coloured solution in concentrated sulphuric acid.

dl-*Bulbocapnine Methyl Ether* (V).—An ice-cold solution of the dihydrochloride (5·5 g.) of the base (IV) in sulphuric acid (27 c.c. of 2*N*) and methyl alcohol (27 c.c.) was diazotised by the gradual addition of the calculated amount of 2*N*-sodium nitrite (freshly standardised). The bright yellow solution was heated on the water-bath for 40 minutes, and the deep-red solution obtained was reduced with zinc dust (3 g.) and concentrated hydrochloric acid (9 c.c.). The hot liquid was filtered, the residue washed thoroughly with boiling water, and the combined filtrate and washings were decomposed with ammonia and extracted with much ether; at this stage a considerable quantity of the amorphous dilaudanosine derivative separated. The pale yellow ethereal extract was washed with sodium hydroxide solution and dried with sodium sulphate, and the ether removed. The residual oil was dissolved in dilute hydrochloric acid, and a concentrated solution of potassium iodide added; the hydriodide separated as a gum. The clear supernatant liquid was decanted, and the gum dissolved in hot alcohol; on cooling, dl-*bulbocapnine methyl ether hydriodide* (1·2 g.) separated in almost colourless prisms, which darken at 240° and melt with decomposition at 250° (Found : C, 51·5; H, 4·9. $C_{20}H_{21}O_4N,HI$ requires C, 51·4; H, 4·7%). *dl*-Bulbocapnine methyl ether was obtained as a gum by decomposing a hot aqueous solution of the hydriodide with sodium hydroxide. This was extracted with ether, the extract dried with sodium sulphate, and the ether allowed to evaporate slowly. dl-*Bulbocapnine methyl ether* separated in large, very pale yellow rhombs, m. p. 135°, and no alteration was observed in the melting point of a mixture of the synthetical base and a specimen of *dl*-bulbocapnine methyl ether prepared from *d*-bulbocapnine as described by Gadamer (*loc. cit.*). The synthetical base and the specimen obtained from natural sources gave identical colour reactions. They dissolved in concentrated sulphuric acid to form colourless solutions which rapidly became orange-red; they yielded deep red solutions with Erdmann's reagent, deep greenish-blue colorations with Frohde's reagent, and with Mandelin's reagent a

red coloration was first produced, which rapidly became violet, then purple and finally blue. dl-*Bulbocapnine methyl ether methiodide* was prepared by heating the base with an excess of methyl iodide for 1 hour. The excess of methyl iodide was removed by distillation; the residue crystallised from methyl alcohol in long, colourless needles, m. p. 243° (Found : C, 52·5; H, 5·2. $C_{21}H_{24}O_4NI$ requires C, 52·4; H, 5·0%). The methiodide obtained from *dl*-bulbocapnine methyl ether of natural origin was prepared in a similar manner, and no alteration was observed in the melting point of a mixture of the methiodides obtained from the two sources.

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