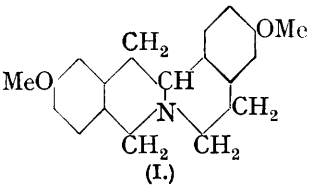
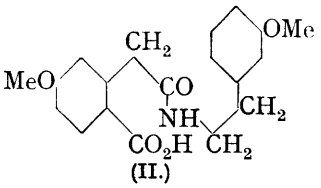
61. *A New Synthesis of* 3 : 11-*Dimethoxyoxyprotoberberine, and Syntheses of* 2 : 3-*Methylenedioxy*-11 : 12-*dimethoxyoxyprotoberberine and* 2 : 3 : 11 : 12-*Tetramethoxyoxyprotoberberine.*

By Satyendra N. Chakravarti and M. Swaminathan.

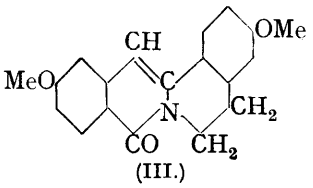
In order to obtain experimental evidence for the structure (I) assigned to 3 : 11-dimethoxytetrahydroprotoberberine by Chakravarti, Haworth, and Perkin (J., 1927, 2267), 3 : 11-dimethoxyoxyprotoberberine (III) has been synthesised in the following manner: 5-*methoxyhomophthalo*-β-m-*methoxyphenylethylimide*, prepared from 5-methoxyhomophthalic acid and β-*m*-methoxyphenylethylamine, was converted by hydrolysis into the corresponding *amic acid* (II), the *methyl* ester of which, on treatment with phosphoryl chloride, gave a 50% yield of 3 : 11-dimethoxyoxyprotoberberine, m. p. 143°, identical with that obtained by Chakravarti, Haworth, and Perkin from 3 : 11-dimethoxytetrahydroprotoberberine (*loc. cit.*).



(I.)



(II.)



(III.)

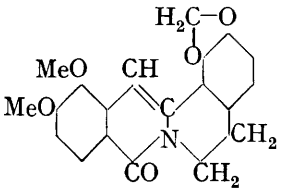
This synthesis proves that in the conversion of formyl-6-methoxy-1-(3′-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro*iso*quinoline into 3 : 11-dimethoxydihydroprotoberberine the ring closure takes place in the para-position to the 3′-methoxy-group, but still leaves

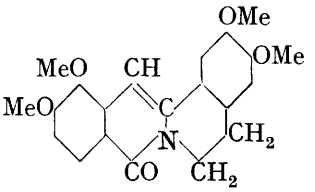
the constitution of the dimethoxytetrahydroprotoberberine undetermined, since in (II) ring closure can occur in the para-position (giving III) or in the ortho-position to the methoxy-group. To decide this point a new method of synthesis is being developed, an account of which is reserved for a future communication.

In order to throw further light on the constitutions of 2 : 3-methylenedioxy-11 : 12-dimethoxytetrahydroprotoberberine and 2 : 3 : 11 : 12-tetramethoxytetrahydroprotoberberine obtained by us (*J. Indian Chem. Soc.*, 1934, **11**, 107), the corresponding oxyberberine analogues have been synthesised.

Synthesis of 11 : 12-*Dimethoxy*-2 : 3-*methylenedioxyoxyprotoberberine*.—This follows the lines of the preceding synthesis : 5 : 6-dimethoxyhomophthalic acid ⟶ 5 : 6-*dimethoxyhomophthalo*-β-*piperonylethylimide* ⟶ *amic acid* (as II), the *methyl* ester of which, on treatment with phosphoryl chloride, gives a substance, m. p. 231°, having the properties of an oxyberberine. This substance is represented by a formula as (III), the alternative formula (IV) being very improbable. The substance is identical with 11 : 12-

(IV.)





(V.)

dimethoxy-2 : 3-methylenedioxyoxyprotoberberine obtained from the corresponding tetrahydroprotoberberine (Chakravarti and Swaminathan, *loc. cit.*).

The method of synthesising 2 : 3 : 11 : 12-*tetramethoxyoxyprotoberberine* (V) from 5 : 6-dimethoxyhomophthalic acid and β-veratrylethylamine is similar to those outlined above. The substance is identical with 2 : 3 : 11 : 12-tetramethoxyoxyprotoberberine obtained from 2 : 3 : 11 : 12-tetramethoxytetrahydroprotoberberine.

Experimental.

5-*Methoxyhomophthalo*-β-m-*methoxyphenylethylimide*.—A mixture of 5-methoxyhomophthalic acid (10 g.) and β-*m*-methoxyphenylethylamine (10·5 g.) was heated at 180° for 3 hours. The *imide* crystallised from glacial acetic acid in silky needles, m. p. 133° (Found : C, 70·0; H, 5·6. $C_{19}H_{19}O_4N$ requires C, 70·2; H, 5·8%).

5-*Methoxyhomophthalo*-β-m-*methoxyphenylethylamic acid* (II).—The imide (3·5 g.) was heated with *N*-sodium hydroxide (40 c.c.) for 12 hours on the steam-bath, and the solution was cooled, saturated with carbon dioxide, filtered, and acidified with hydrochloric acid; the *amic acid* crystallised from methyl alcohol in colourless needles, m. p. 167° (Found : C, 66·7; H, 6·2. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%).

The methyl ester. The amic acid (2·5 g.) was dissolved in a solution of sodium bicarbonate (0·6 g.) in water (50 c.c.), and the silver salt precipitated by silver nitrate (2 g.) was washed successively with water, alcohol, and ether, dried in a vacuum, suspended in dry ether, and refluxed with excess of methyl iodide for 8 hours. The *methyl* ester deposited by the concentrated solution crystallised from benzene–light petroleum in colourless needles, m. p. 85° (Found : C, 67·0; H, 6·7. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4%). A little more of the ester was obtained by extracting the silver residues with boiling methyl alcohol.

3 : 11-*Dimethoxyoxyprotoberberine*.—The methyl ester (1 g.) was boiled with phosphoryl chloride (5 c.c.) for 10 minutes, a bright red solution being obtained. The excess of chloride was distilled in a vacuum, the residue dissolved in hot water, and the filtered solution basified with sodium hydroxide. The grey precipitate obtained, after being washed with water and with methyl alcohol, crystallised from dilute acetic acid in colourless needles, which did not depress the m. p. of 3 : 11-dimethoxyoxyprotoberberine (Found : C, 74·1; H, 5·7. Calc. for $C_{19}H_{17}O_3N$: C, 74·3; H, 5·5%).

5 : 6-*Dimethoxyhomophthalo*-β-*piperonylethylimide*.—5 : 6-Dimethoxyhomophthalic acid (10 g.) and β-piperonylethylamine (9 g.) were heated at 180° for 3 hours. The solid product was triturated with alcohol and crystallised from glacial acetic acid, the *imide* separating in colourless needles, m. p. 223° (Found : C, 64·9; H, 5·2. $C_{20}H_{19}O_6N$ requires C, 65·0; H, 5·1%).

5 : 6-*Dimethoxyhomophthalo*-β-*piperonylethylamic Acid*.—This was prepared from the imide

(2·6 g.) and *N*-sodium hydroxide (20 c.c.) in the same way as the preceding amic acid. It dissolved readily in glacial acetic acid, and crystallised on dilution with an equal bulk of boiling water; m. p. 245° (Found : C, 61·7; H, 5·5. $C_{20}H_{21}O_7N$ requires C, 62·0; H, 5·4%).

The *methyl* ester, prepared from the silver salt and methyl iodide, separated from dry methyl alcohol in colourless needles, m. p. 169—170° (Found : C, 62·6; H, 6·0. $C_{21}H_{23}O_7N$ requires C, 62·8; H, 5·7%).

11 : 12-*Dimethoxy***-2 : 3-***methylenedioxyoxyprotoberberine*.—The methyl ester (1 g.) was treated with phosphoryl chloride (5 c.c.) in the manner described above. The product was crystallised from boiling glacial acetic acid containing a little water; 11 : 12-dimethoxy-2 : 3-methylenedioxyoxyprotoberberine separated in almost colourless needles, m. p. 230—231° alone or mixed with an authentic specimen.

5 : 6-*Dimethoxyhomophthalo*-β-*veratrylethylimide*, obtained by heating 5 : 6-dimethoxyhomophthalic acid (10 g.) and β-veratrylethylamine (10 g.) at 180° for 3 hours, crystallised from glacial acetic acid in colourless needles, m. p. 180° (Found : C, 65·0; H, 6·1. $C_{21}H_{23}O_6N$ requires C, 65·4; H, 6·0%). The *amic acid* crystallised from methyl alcohol in needles, m. p. 165° (Found : C, 62·8; H, 6·4. $C_{21}H_{25}O_7N$ requires C, 62·5; H, 6·2%), and its *methyl* ester from benzene–light petroleum in silky needles, m. p. 123° (Found : C, 63·2; H, 6·5. $C_{22}H_{27}O_7N$ requires C, 63·3; H, 6·4%). Treatment of the ester (1 g.) with phosphoryl chloride (5 c.c.) in the manner already described furnished 2 : 3 : 11 : 12-*tetramethoxyoxyprotoberberine*, which crystallised from dilute acetic acid in colourless needles, m. p. 190—191° (Found : C, 68·4; H, 5·8. $C_{21}H_{21}O_5N$ requires C, 68·6; H, 5·7%).

Conversion of **2 : 3 : 11 : 12-***Tetramethoxytetrahydroprotoberberine into* **2 : 3 : 11 : 12-***Tetramethoxyoxyprotoberberine*.—The tetramethoxytetrahydroprotoberberine (1·5 g.), dissolved in the minimum quantity of boiling alcohol, was mixed with anhydrous sodium acetate (4 g.), and an alcoholic solution of iodine (2%, 150 c.c.) slowly added until the coloration was permanent. The dark brown, granular periodide was collected, washed with water, suspended in hot water, and decomposed by sulphurous acid. The *iodide* separated from water, in which it was sparingly soluble, in yellow needles, m. p. 245° (Found : C, 52·4; H, 4·8. $C_{21}H_{22}O_4NI$ requires C, 52·6; H, 4·6%). The chloride was readily obtained by digesting an aqueous suspension of the iodide with excess of silver chloride for 3 hours on the steam-bath. When the filtrate was concentrated and treated with hydrochloric acid, the chloride separated as yellow needles, m. p. 225°. Hot aqueous solutions of the chloride (1·5 g.) and of potassium hydroxide (6 g. in water, 24 c.c.) were mixed and heated on the steam-bath for 3 hours. The yellow mass which separated was collected and thoroughly extracted with dilute hydrochloric acid. The residue was dissolved in hot glacial acetic acid and mixed with an equal volume of boiling water; 2 : 3 : 11 : 12-tetramethoxyoxyprotoberberine identical with the above (mixed m. p.) then separated in colourless needles, m. p. 190—191°

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