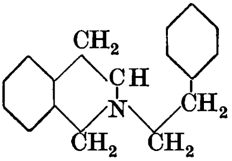
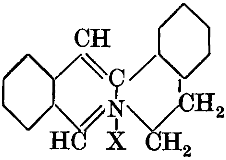
XXVII.—*Synthesis of* 3 : 10-*Dimethoxytetrahydroprotoberberine.*

By Satyendra Nath Chakravarti and William Henry Perkin, jun.

Attention has been directed (J., 1927, 2267, 2275) to the interest attaching to the synthesis of alkaloids which, although built up on the palmatine–berberine skeleton, do not contain the pyrocatechol nuclei so widely met with in the substances of this group which occur in nature. With the object of synthesising such substances and also of determining their ease of formation and of comparing their properties and the properties of their salts with those of the naturally occurring alkaloids, two series of experiments were undertaken. In the first place, the synthesis of the parent substance of this group, tetrahydroprotoberberine (I), was successfully carried out and it was shown (i) that this substance is much more difficult to synthesise than the derivatives, such as tetrahydroberberine, which contain two pyrocatechol nuclei, and (ii) that the protoberberinium salts (II) derived from it by oxidation differ in many ways from the corresponding berberinium salts; for example, instead of being bright orange or orange-yellow, they are only very slightly coloured.

(I.)



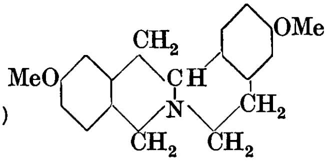


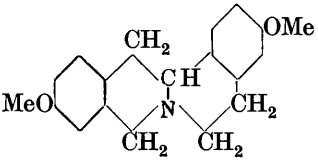
(II.)

The second series of experiments was concerned with the synthesis of alkaloids of an intermediate type containing, in the place of the two pyrocatechol nuclei, two benzene rings each containing one methoxy-group. The two substances selected for synthesis were

3 : 11-dimethoxytetrahydroprotoberberine (III) and 3 : 10-dimethoxytetrahydroprotoberberine (IV).*

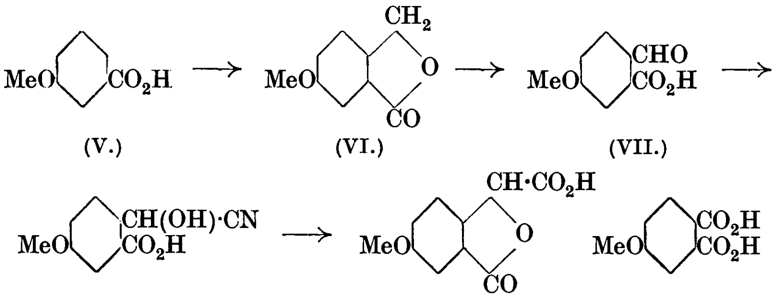
(III.)





(IV.)

The synthesis and properties of the substance (III) have already been described (*loc. cit.*, p. 2267) and the present communication deals with the synthesis and properties of the isomeride (IV). After several attempts to effect the synthesis on lines similar to those laid down in the case of the alkaloid (III) had proved unavailing, the desired result was achieved by making use of a scheme of synthesis based on the conversion of meconinecarboxylic acid into oxyberberine by Perkin, Rây, and Robinson (J., 1925, **127**, 740). In employing this method, it was necessary in the first place to prepare 4-methoxyphthalidecarboxylic acid (VIII), and this we thought might be obtained by making use of the following series of changes :



(V.) (VI.) (VII.)

(VIII.) (IX.)

m-Methoxybenzoic acid (V) readily condenses with formaldehyde in the presence of hydrochloric acid under the conditions described by Edwards, Perkin, and Stoyle (J., 1925, **127**, 197), giving a good yield of 4-methoxyphthalide (VI), and the attempt was made to oxidise this with manganese dioxide and sulphuric acid to 4-methoxyphthalaldehydic acid (VII) under the conditions which so readily convert meconine into opianic acid. Unfortunately the oxidation could not be arrested at this stage, the main product being always 4-methoxyphthalic acid (IX) and therefore the scheme had to be abandoned. This easy method of preparation of 4-methoxyphthalic acid is, however, of interest, because this acid has been obtained as a degradation product both of thebaol (Pschorr, Seyden, and Stöhrer, *Ber.*, 1902,

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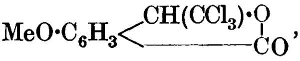
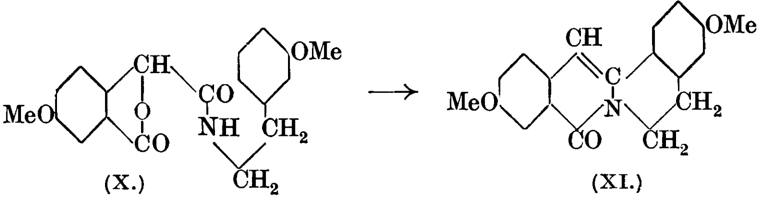
* The nomenclature and numbering are discussed in J., 1925, **127**, 1462.

35, 4401) and of colchicine (Windaus and Schiele, *Nachr. Ges. Wiss. Göttingen*, 1923, 17). We ultimately succeeded in preparing 4-methoxyphthalidecarboxylic acid (VIII) by acting on methyl 4-methoxybenzoate with chloral hydrate and sulphuric acid under the conditions recommended by Fritsch (*Annalen*, 1897, **296**, 351) for the preparation of substituted trichloromethylphthalides. The 4-methoxytrichloromethylphthalide,  $MeO\cdot C_6H_3\left<\begin{matrix}CH(CCl_3)\cdot O\\ \hphantom{CH(CCl_3)\cdot}|\\ \hphantom{CH(CCl_3)\cdot}CO\end{matrix}\right.$, obtained in this way yielded 4-methoxyphthalidecarboxylic acid on hydrolysis with sodium hydroxide.

The acid chloride, obtained on treatment with thionyl chloride, condensed readily in benzene solution with β-*m*-methoxyphenylethylamine (Helfer, *Helv. Chim. Acta*, 1924, **7**, 945), yielding 4-*methoxyphthalidecarboxy*-β-m-*methoxyphenylethylamide* (X). When this was heated with phosphorus oxychloride, and the product decomposed with ice, a basic substance separated which, on reduction with zinc dust and acetic acid, was converted into a colourless substance, m. p. 180°, having all the properties of a compound of the oxyberberine type and this is doubtless 3 : 10-*dimethoxyoxyprotoberberine* (XI) (compare Perkin, Rây, and Robinson, *loc. cit.*).



(X.) (XI.)

When this substance was reduced electrolytically, it yielded a colourless crystalline tetrahydro-alkaloid, m. p. 139°, which is doubtless 3 : 10-*dimethoxytetrahydroprotoberberine* (IV), and in all its properties this isomeride shows the closest resemblance to the 3 : 11-dimethoxytetrahydroprotoberberine (III), m. p. 111°, obtained in the manner described in the earlier communication (J., 1927, 2267).

The points of general interest emphasised in connexion with the synthesis and properties of the 3 : 11-isomeride (*loc. cit.*, p. 2269) are equally applicable to the present case and need not be repeated.

EXPERIMENTAL.

m-Methoxybenzoic acid may be obtained in a yield of 90% by the following method : *m*-Methoxybenzaldehyde (10 g.) (Chakravarti, Haworth, and Perkin, J., 1927, 2269) is oxidised, in hot acetone solution, with 10% aqueous permanganate (120 c.c.), sufficient acetone being added from time to time to keep the aldehyde in solution. After the manganese precipitate has been filtered off and washed, the alkaline solution is distilled to remove acetone, filtered, and acidified; a voluminous precipitate of almost pure *m*-methoxybenzoic acid then separates which may be obtained in colourless needles, m. p. 109—110°, by crystallisation from water.

Methyl *m*-methoxybenzoate is readily prepared by saturating a solution of the acid (10 g.) in methyl alcohol (50 c.c.) with hydrogen chloride and refluxing for 4 hours. Water is added, the oil extracted with ether, the ethereal solution well washed with dilute aqueous sodium carbonate and dried over sodium sulphate, and the ether removed; when the residue is distilled under 10 mm. the methyl ester passes over at 121—124°.

4-*Methoxyphthalide* (VI).—(i) *m*-Methoxybenzoic acid (2 g.), formaldehyde solution (6 c.c. of 40%), and concentrated hydrochloric acid (10 c.c.) were heated together on the steam-bath for 1 hour. The product was diluted with water and cooled; 4-methoxyphthalide containing some unchanged acid then separated. The solid was shaken with dilute sodium carbonate solution, and the undissolved part crystallised from methyl alcohol and then from water, from which the substance separated in long needles, m. p. 120°, identical with the 4-methoxyphthalide obtained by Fritsch (*loc. cit.*) (Found: C, 65·8; H, 4·9. Calc. for $C_9H_8O_3$: C, 65·8; H, 4·9%).

(ii) A slightly improved yield was obtained when *m*-methoxybenzoic acid (3 g.), dissolved in hot glacial acetic acid (10 c.c.), was mixed with concentrated hydrochloric acid (15 c.c.) and formaldehyde (6 c.c. of 40%) and boiled for an hour. Excess of sodium carbonate was added, the whole shaken with chloroform, the extract dried over potassium carbonate, the solvent removed, and the 4-methoxyphthalide recrystallised as before.

4-*Methoxyphthalic Acid* (IX).—The phthalide (2 g.), dissolved in warm sodium hydroxide solution (100 c.c. of 5%), was oxidised in the cold by the gradual addition of permanganate solution (3 g. in 100 c.c. of water). After 24 hours, the mixture was warmed for a few minutes on the steam-bath, sulphur dioxide passed in, hydrochloric acid added, and the whole concentrated to a small bulk and left in the ice-chest; 4-methoxyphthalic acid then separated in needles. The acid crystallised from water, in which it is readily soluble, in needles, melting at 168—170° with loss of water and formation of the anhydride, m. p. 95° (Found: C, 55·0; H, 4·1. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%).

4-*Methoxyphthalidecarboxylic Acid* (VIII).—This acid was prepared by the following modification of Fritsch's method (*loc. cit.*,

p. 355). A mixture of methyl *m*-methoxybenzoate (10 g.), chloral hydrate (10 g.), and sulphuric acid (100 g.) was left for 5 days, being shaken from time to time. The product was poured on ice, and the precipitate was collected, washed, and crystallised from alcohol, a nearly quantitative yield of 4-methoxytrichloromethylphthalide, m. p. 135°, being obtained. This substance was warmed with an equal weight of sodium hydroxide in water (6 parts) until solution was complete. After being extracted with ether, the alkaline solution was acidified with concentrated hydrochloric acid and left for several hours; almost pure 4-methoxyphthalidecarboxylic acid then separated : after recrystallisation from benzene, it had m. p. 170°.

4-*Methoxyphthalidecarboxy*-β-m-*methoxyphenylethylamide* (X).—4-Methoxyphthalidecarboxylic acid (5 g.) and thionyl chloride (20 c.c.) were gently boiled for 2 hours in a reflux apparatus fitted with a calcium chloride tube. The excess of thionyl chloride was completely removed by distillation below 100° in a vacuum, and the acid chloride was dissolved in benzene (50 c.c.) and gradually added to a benzene solution of β-*m*-methoxyphenylethylamine (prepared from 5·5 g. of the hydrochloride). After 12 hours, the mixture was boiled under reflux for 2 hours, concentrated, and left in the ice-chest; most of the *amide* then crystallised. It was ground with very dilute sodium carbonate solution, collected, and recrystallised from alcohol, separating in rosettes of needles (8 g.), m. p. 129° (Found : C, 66·6; N, 5·5. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·5%).

3 : 10-*Dimethoxyoxyprotoberberine* (XI).—The above amide (5 g.) and freshly distilled phosphorus oxychloride (50 c.c.) were heated together in a reflux apparatus, fitted with a calcium chloride tube, on the steam-bath for 6 hours. The product was decomposed by the careful addition of crushed ice, the liquid filtered, and the bright yellow filtrate rendered faintly alkaline with dilute sodium hydroxide solution. The ochre-coloured base which was precipitated was collected, washed with water, and dried in the air on porous porcelain. As the attempt to recrystallise the substance was unsuccessful, the whole was mixed with glacial acetic acid (125 c.c.), zinc dust (25 g.), and a few small crystals of copper sulphate and boiled for 5 minutes; a second similar portion of zinc dust was then added and the boiling continued for ½ hour. The cold product was diluted with a large volume of ethyl acetate, the solution washed several times with dilute hydrochloric acid, then with aqueous sodium hydroxide and with water, dried over potassium carbonate, and filtered, and the solvent removed by distillation. The pale yellow, crystalline residue was recrystallised several times from alcohol and obtained as a mass of almost colourless needles (3 g.),

m. p. 180° (Found : C, 74·5; H, 5·4; N, 4·7. $C_{19}H_{17}O_3N$ requires C, 74·3; H, 5·5; N, 4·6%).

3 : 10-*Dimethoxyoxyprotoberberine* dissolves to a faint violet solution in concentrated sulphuric acid, and the addition of a drop of concentrated nitric acid develops first a green and then a deep bluish-violet coloration which finally changes to a fine orange-red : on dilution with water the colour is discharged.

3 : 10-*Dimethoxytetrahydroprotoberberine* (IV).—3 : 10-Dimethoxyoxyprotoberberine (1 g.), dissolved in a mixture of alcohol (60 c.c.) and concentrated sulphuric acid (30 c.c.), was reduced in an electrolytic cell by a current of 6 amps. for 24 hours, the temperature being kept below 30°. The colourless solution was diluted with water and filtered, and the filtrate made strongly alkaline with sodium hydroxide and extracted with chloroform. The extract was dried over potassium carbonate, the solvent removed, and the solid residue converted into the sparingly soluble hydrochloride by the addition of dilute hydrochloric acid. This was recrystallised from water with the aid of norite, and the pure hydrochloride was dissolved in water and mixed with sodium hydroxide. The nearly pure 3 : 10-*dimethoxytetrahydroprotoberberine* separated from methyl alcohol in colourless prisms, m. p. 139° (Found : C, 77·5; H, 7·1. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·1%).

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