575. *Syntheses of Protoberberine Alkaloids.*

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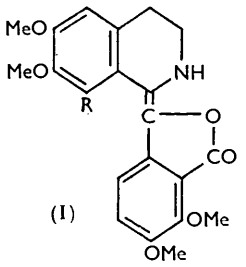
The synthesis of *O*-methylcapauridine, a new synthesis of (±)-tetrahydropalmatine, and a simplified synthesis of (±)-ophiocarpine are reported.

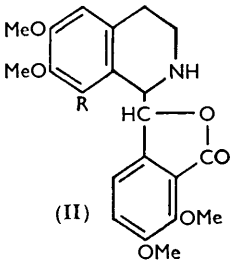
Synthesis of the hydroxyprotoberberine alkaloid, ophiocarpine, using a phthalide–*iso*quinoline intermediate, was recorded recently.[1] The present paper illustrates an extension of the method to syntheses of two protoberberine derivatives, *O*-methylcapauridine [2] and (±)-tetrahydropalmatine,[3] and a simpler synthesis of (±)-ophiocarpine.[1]

Meconine-α-carboxyl chloride was condensed with mescaline, and the amide cyclised to α-(1 : 2 : 3 : 4-tetrahydro-6 : 7 : 8-trimethoxy-1-*iso*quinolylidene)meconine (Ia). This was reduced catalytically to the impure tetrahydro*iso*quinolyl compound (IIa) and then



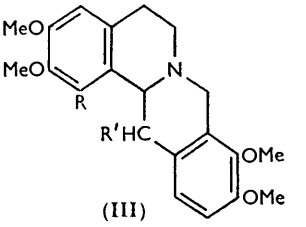
(I)

(Ia) R = OMe
(Ib) R = H



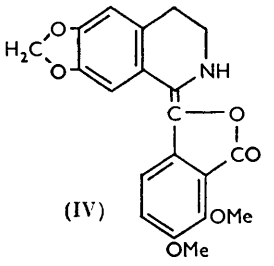
(II)

(IIa) R = OMe
(IIb) R = H

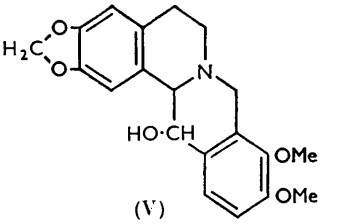


(III)

(IIIa) R = OMe, R' = OH
(IIIb) R = OMe, R' = H
(IIIc) R = H, R' = OH
(IIId) R = R' = H



(IV)



(V)

by lithium aluminium hydride to a mixture of the two diastereoisomeric 13-hydroxy-1 : 2 : 3 : 9 : 10-pentamethoxyprotoberberines (IIIa), one of which was properly characterised. Treatment of the hydroxy-compound (IIIa) with thionyl chloride and hydrogenation afforded *O*-methylcapauridine (IIIb), identical with an authentic specimen.

Repetition of the sequence with 3 : 4-dimethoxyphenethylamine yielded (±)-tetrahydropalmatine (IIId), through the intermediates (Ib), (IIb), and (IIIc), both pairs of diastereoisomers represented by (IIb) and (IIIc) being isolated and characterised.

Reduction of the product (IV) with lithium aluminium hydride yielded ophiocarpine (V) directly.

The syntheses described so far illustrate the general utility of the method for synthesis of the protoberberines, provided appropriately substituted phthalidecarboxylic acids are available.

[1] Govindachari and Rajadurai, *J.*, 1957, 557.
[2] Manske and Holmes, *J. Amer. Chem. Soc.*, 1945, **67**, 95.
[3] Späth, Mosettig, and Trothandl, *Ber.*, 1923, **56**, 877.

Experimental

O-*Methylcapauridine*.— (a) N-3 : 4 : 5-*Trimethoxyphenethylmeconine-α-carboxyamide*. Meconine-α-carboxyl chloride [4] (from 2·2 g. of acid) in dry benzene (25 ml.) was added dropwise to a stirred mixture of mescaline (2 g.) (prepared according to directions of Benington and Morin [5] and distilled, the fraction of b. p. 150—155°/5 mm. being used), benzene (25 ml.), and N-sodium hydroxide (11 ml.), cooled in ice. The mixture was shaken for 3 hr. at 30° and left overnight. The benzene layer was washed with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, then concentrated at <50° and dried *in vacuo*. The residue crystallised under methanol (10 ml.) overnight. Recrystallisation from methanol yielded the *amide* (1·6—1·8 g.), m. p. 173—174° (Found : C, 61·6; H, 5·7; N, 3·6. $C_{22}H_{25}O_8N$ requires C, 61·3; H, 5·8; N, 3·2%).

(b) α-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxy*-1-iso*quinolylidene*)*meconine* (Ia). The pure amide (2 g.) was heated with phosphorus oxychloride (20 ml.) on a vigorously boiling water bath for 5 hr., then cooled and poured on crushed ice (400 g.). The solution was filtered, cooled in ice, and neutralised with 20% sodium hydroxide solution to pH 7—7·5. The yellow precipitate (1·1 g.) was filtered off, washed with water, and dried *in vacuo*. (The yield was drastically reduced if impure samples of amide were used.) A part was recrystallised from cold methanol–ether, giving the *tetrahydroisoquinolylidene derivative*, m. p. 204° (preheated bath). It was dried below 50° above which it tended to decompose (Found : C, 61·1; H, 5·3. $C_{22}H_{23}O_7N,H_2O$ requires C, 61·3; H, 5·8%).

(c) 13-*Hydroxy*-1 : 2 : 3 : 9 : 10-*pentamethoxyprotoberberine* (IIIa). The preceding crude compound (2 g.) in glacial acetic acid (80 ml.) was shaken with Adams catalyst (0·1 g.) at a hydrogen pressure of 30 lb./sq. in. till absorption ceased (1—2 hr.). The solution was filtered and concentrated *in vacuo* below 60°. Water and 2N-ammonia were added and the precipitate was filtered off, washed, and dried, yielding the tetrahydro*iso*quinoline (2 g.). The substance was heat-sensitive and did not crystallise.

The tetrahydro*iso*quinoline (1·2 g.) (IIa), in tetrahydrofuran (20 ml.) and ether (20 ml.), was added with stirring to lithium aluminium hydride (1 g.) in ether (100 ml.), and the mixture was stirred for 1 hr. The product was worked up as usual, and the ether–tetrahydrofuran solution after evaporation left 0·7 g. of material. A part of it was chromatographed in benzene on alumina; the earlier eluates gave a substance which, recrystallised from methanol–ether, yielded the *hydroxyprotoberberine* (IIIa), m. p. 183° (Found : C, 65·3; H, 6·6. $C_{22}H_{27}O_6N$ requires C, 65·8; H, 6·7%).

(d) O-*Methylcapauridine* (IIIb). The crude base from the previous reaction (0·2 g.) in dry chloroform (3 ml.) was gently refluxed for 10 min. with thionyl chloride (0·2 ml.), and the solution was left overnight at 30°. The solvent and thionyl chloride were removed *in vacuo*. The residue was decomposed with sodium hydrogen carbonate solution and immediately extracted with chloroform. The extract was evaporated *in vacuo* at 30°, and the residue was shaken in ethanol (40 ml.) with Adams catalyst (0·1 g.) under a hydrogen pressure of 30 lb./sq. in. After 3 hr. the solution was filtered and concentrated *in vacuo*. Sodium hydrogen carbonate solution was added to the residue and the mixture was extracted with chloroform. The chloroform solution was concentrated *in vacuo*, and the residue was chromatographed in dry chloroform on alumina. The first 50 ml. of the eluate gave a substance which on recrystallisation from methanol–ether yielded O-*methylcapauridine* (IIIb) (7 mg.), m. p. and mixed m. p. 137—140° (Found : C, 68·4; H, 7·0. $C_{22}H_{27}O_5N$ requires C, 68·6; H, 7·0%).

Tetrahydropalmatine.—(a) N-3 : 4-*Dimethoxyphenethylmeconine-α-carboxyamide*. The amide was prepared from meconine-α-carboxyl chloride (from 2·2 g. of the acid) and 3 : 4-dimethoxyphenethylamine (2 g.) according to the procedure described above. The residue after removal of the benzene *in vacuo* crystallised from cold methanol, to give needles of the *amide* (1·1—1·5 g.), m. p. 144—145° (Found : C, 63·1; H, 5·9. $C_{21}H_{23}O_7N$ requires C, 62·9; H, 5·7%). The amide was sensitive to heat, being converted into an uncyclisable isomer.

(b) α-(1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolyl*)*meconine* (IIb). The amide (2 g.) was cyclised with phosphorus oxychloride (20 ml.) as above. The precipitated *iso*quinolylidene derivative (Ib) was filtered off quickly and washed with water. It rapidly darkened and was

[4] Perkin, Ray, and Robinson, *J.*, 1925, 740.
[5] Benington and Morin, *J. Amer. Chem. Soc.*, 1951, **73**, 1353.

immediately reduced with Adams catalyst (0·1 g.) as above. The solution was filtered and the acetic acid removed *in vacuo* below 60°. The residual gum was basified with concentrated aqueous ammonia. The yellow solid was filtered off, washed with water, and dried *in vacuo* at 30°, to give the tetrahydro-base (IIb) (0·5 g.). This was digested with dry ether. The ether solution was filtered and treated with dry hydrogen chloride; the precipitated *hydrochloride*, recrystallised from alcohol–ether in the cold, had m. p. 204° (Found: C, 59·8; H, 5·5. $C_{21}H_{24}O_6NCl$ requires C, 59·8; H, 5·7%). The ether-insoluble residue was crystallised from benzene–light petroleum (b. p. 40—60°), to give pale yellow crystals of the diastereoisomeric *base*, m. p. 142—144° (Found: C, 65·9; H, 5·8. $C_{21}H_{23}O_6N$ requires C, 65·5; H, 6·0%), yielding a hygroscopic hydrochloride.

(c) 13-*Hydroxy*-2 : 3 : 9 : 10-*tetramethoxyprotoberberine* (IIIc). The crude tetrahydro*iso*quinoline (0·5 g.) in tetrahydrofuran (5 ml.)–ether (20 ml.) was reduced as before with lithium aluminium hydride (1 g.) in ether (50 ml.), to give a red gum (0·4 g.). A portion of this solidified on addition of methanol (2 ml.) and was filtered off and crystallised from benzene, to give colourless needles of one of the *hydroxyprotoberberines*, m. p. 186° (Found: C, 64·4; H, 6·9. $C_{21}H_{25}O_5N,H_2O$ requires C, 64·8; H, 6·9%). The methanol solution on evaporation left a reddish gum which, after passage of its chloroform solution through alumina and crystallisation from ether–light petroleum (b. p. 40—60°), gave pale yellow crystals of the second *hydroxyprotoberberine*, m. p. 158° (Found: C, 68·3; H, 6·3. $C_{21}H_{25}O_5N$ requires C, 67·9; H, 6·7%).

(d) *Tetrahydropalmatine* (IIId). The crude hydroxyprotoberberine mixture (0·2 g.) in dry chloroform (10 ml.) was treated with thionyl chloride (0·2 ml.) as before. Reduction of the product with Adams catalyst (0·1 g.) and chromatography in chloroform on alumina yielded *tetrahydropalmatine* (IIId) (10 mg.), pale yellow crystals (from ether), m. p. 147—148°, alone or when mixed with a sample prepared by the demethylenation and methylation of (±)-tetrahydroberberine [6] (Found: C, 70·6; H, 6·6. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%).

Ophiocarpine (V).—α-(1 : 2 : 3 : 4-Tetrahydro-6 : 7-methylenedioxy-1-*iso*quinolylidene)-meconine [1,4] (IV) (0·6 g.) in tetrahydrofuran (5 ml.) and ether (10 ml.) was added dropwise with stirring to lithium aluminium hydride (0·6 g.) in ether (50 ml.). The mixture was stirred for an hour and left overnight. The lithium complex was decomposed with wet ether (200 ml.). The ether solution on evaporation left a red gum, part of which crystallised on the addition of a little methanol (2 ml.). The precipitate was filtered off and crystallised from chloroform–methanol, to give colourless needles of ophiocarpine-a [1] (20 mg.), m. p. and mixed m. p. 252°. Evaporation of the methanolic filtrate, chromatography of the residual gum in chloroform on alumina, and crystallisation from a small volume of methanol gave ophiocarpine-b [1] (30 mg.), m. p. and mixed m. p. 176°.

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[6] Späth and Mosettig, *Ber.*, 1926, **59**, 1496.