111. *Synthesis of* (±)*-Ophiocarpine.*

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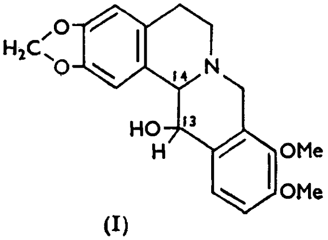
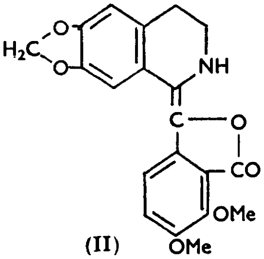
The synthesis of the two racemates corresponding to structure (I) is reported, and one of these is shown to have an infrared spectrum identical with that of (−)-ophiocarpine.

THE alkaloid ophiocarpine, isolated and assigned structure (I) by Manske,[1] is of interest because it is the sole representative of a type which is probably a link[2] between the protoberberine and the protopine alkaloids. The synthesis of the two racemates corresponding to structure (I) is reported here.

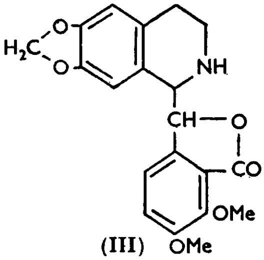
Cyclisation of *N*-(3 : 4-methylenedioxyphenethyl)meconine-α-carboxyamide yielded a base assumed to be dehydronorhydrastine (II) by Perkin, Rây, and Robinson[3] who did not report any analysis. In the present study, the base was characterised as a crystalline hydrochloride, and shown to correspond in composition to dehydronorhydrastine. Its reduction in presence of Adams catalyst yielded a mixture from which one pure component corresponding to norhydrastine (III) was isolated as a crystalline hydrochloride. Reduction of the crude norhydrastine mixture with lithium aluminium hydride yielded (±)-ophiocarpine-*a*, m. p. 252°, and -*b*, m. p. 176°, neither of which could be resolved.



(I)



(II)



(III)

The infrared spectra of (±)-ophiocarpine-*a* and (−)-ophiocarpine in chloroform were identical and differed from that of (±)-ophiocarpine-*b*. (±)-Ophiocarpine-*a* and and (−)-ophiocarpine were dehydrated in refluxing concentrated hydrochloric acid to dihydroberberine, while (±)-ophiocarpine-*b* was recovered unchanged under these conditions. Evidently, the 13-hydroxyl group and the 14-hydrogen atom are *trans*-related in (−)-ophiocarpine.

EXPERIMENTAL

N-(3 : 4-*Methylenedioxyphenethyl*)*meconine-α-carboxyamide*.—Meconine-α-carboxyl chloride (15 g.)[3] in benzene (30 ml.) was added dropwise, with cooling, to a mixture of 3 : 4-methylenedioxyphenethylamine (12·5 g.) in benzene (30 ml.) and aqueous N-sodium hydroxide solution (75 ml.). The mixture was shaken for 3 hr., and after 12 hr. the amide which gradually separated was collected, washed with water, and crystallised from methyl alcohol: it had m. p. 148° (10 g.); Perkin, Ray, and Robinson[3] report m. p. 148°.

Dehydronorhydrastine.—This was prepared as described by Perkin *et al.*[3] It gave a yellow *hydrochloride*, m. p. 172° (from alcohol-ether) (Found: C, 58·7; H, 5·6. $C_{20}H_{17}O_5N,HCl,H_2O$ requires C, 59·2; H, 5·1%).

Norhydrastine.—Crude dehydronorhydrastine (1·5 g.) in acetic acid (80 ml.) was shaken with Adams catalyst (0·1 g.) in hydrogen for 2 hr., whereafter uptake ceased. The solution was filtered, and the solvent removed *in vacuo*. The residual gum was treated with aqueous ammonia, giving a white solid with a wide melting-point range. Dissolving this in benzene, filtration and treatment with dry hydrogen chloride furnished a single *hydrochloride*, which on

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[1] Manske, *Canad. J. Res.*, 1939, **17**, *B*, 51.

[2] Manske and Holmes, "The Alkaloids, Chemistry and Physiology," Academic Press Inc., New York, 1954, Vol. IV, p. 5.

[3] Perkin, Rây, and Robinson, *J.*, 1925, **127**, 740.

crystallisation from alcohol–ether had m. p. 220° (Found : C, 61·0; H, 5·4. $C_{20}H_{19}O_5N,HCl$ requires C, 61·3; H, 5·6%).

Ophiocarpine-a *and* -b.—To a stirred suspension of lithium aluminium hydride (1·5 g.) in ether (50 ml.) was added dropwise a solution of crude norhydrastine (3 g.) in tetrahydrofuran (20 ml.). The mixture was stirred for 6 hr. Next morning, the complex was decomposed with moist ether (200 ml.). The ether layer was decanted and the residue extracted repeatedly with chloroform. The combined ether and chloroform extracts after drying (Na_2SO_4) and removal of solvent furnished a gum. This was rubbed with methanol to yield a white solid (0·2 g.), which when washed with hot methanol and crystallised from chloroform–methanol gave *ophiocarpine*-a, needles, m. p. 252° (Found : C, 67·6; H, 5·9; N, 3·6. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·9; N, 3·9%). The *acetate* (prepared by acetic anhydride in pyridine at 100°), colourless needles from light petroleum (b. p. 40—60°), had m. p. 172—174° (Found : C, 67·0; H, 6·2. $C_{22}H_{23}O_6N$ requires C, 66·5; H, 5·8%).

From the methanolic mother-liquor, removal of solvent, chromatography over alumina in chloroform, and crystallisation from the minimum amount of methanol gave *ophiocarpine*-b (0·8 g.), needles, m. p. 176° (Found : C, 67·3; H, 5·9; N, 3·8%). The *acetate*, colourless needles (from methanol), melted at 186° (Found : C, 66·4; H, 6·0%).

(−)-*Ophiocarpine Acetate*.—This *salt* was obtained as colourless needles [from light petroleum (b. p. 40—60°)], m. p. 165—167° (Found : C, 67·0; H, 6·3%).

Dehydration of Ophiocarpine-a.—Ophiocarpine-a (20 mg.) and 8N-hydrochloric acid (8 ml.) were refluxed for 3 hr. After removal of the acid *in vacuo*, the residue was dissolved in a small amount of water and rendered alkaline with aqueous ammonia. The mixture was extracted with ether. Removal of solvent and crystallisation from ether, furnished dihydroberberine, m. p. and mixed m. p. 164°.

Ophiocarpine-b, subjected to this procedure, gave only the starting material.

We thank Dr. R. H. F. Manske for the gift of a specimen of (−)-ophiocarpine, Dr. L. Dorfman for measurement of infrared spectra, and the Government of India for the award of a scholarship (to S. R.).

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[*Received, September* 10*th*, 1956.]