222. *The Alkaloids of the* Amaryllidaceae. *Part V.** *A New Alkaloid Epihœmanthidine from* Haemanthus natalensis.

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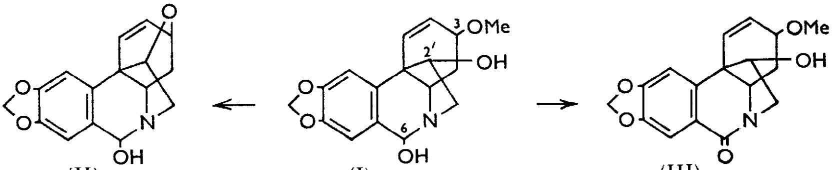
Epihæmanthidine has been isolated from *Haemanthus natalensis.* It yields apohæmanthidine on treatment with hydrochloric acid so that the basic structure and the configuration of the benzylic group in hæmanthidine and epihæmanthidine are the same, and the difference is attributed to difference in configuration of the methoxy-group. On oxidation with manganese dioxide the epi-compound gave oxoepihæmanthine.

The basic residue obtained after the separation of hæmanthamine (natalensine)[1] from the alkaloidal mixture from *Haemanthus natalensis* has now yielded a new alkaloid which is seemingly epihæmanthidine, $C_{17}H_{19}O_5N$ (I). It has two hydroxyl (strong absorption in Nujol at 3422 cm.$^{-1}$ and a diacetyl derivative showing an OAc band at 1745 cm.$^{-1}$) and one methoxyl group. The infrared absorption in Nujol further indicated a symmetrically disubstituted ethylene (1645 cm.$^{-1}$), an aromatic nucleus (1618 cm.$^{-1}$), and a methylenedioxy-group (1250 and 931 cm.$^{-1}$). The formula may accordingly be expanded to $C_{15}H_{12}N(O_2CH_2)(OMe)(OH)_2$. Further, the nitrogen atom is tertiary, in that the alkaloid gave a methiodide and methopicrate.



(II) (I) (III)

The alkaloid gave phenanthridine on distillation with zinc dust. On treatment with hydrochloric acid it gave " apohæmanthidine "[2] (anhydrodemethylhæmanthidine) (II) identical with that obtained from hæmanthidine, so that the basic structure and the configuration of the benzylic hydroxyl group in hæmanthidine and epihæmanthidine are identical. Oxidation of the benzylic hydroxyl group with manganese dióxide gave the expected 6-oxoepihæmanthine † (III).[3]

The difference between epihæmanthidine and hæmanthidine is attributed to the epimerisation of the methoxyl group. The configuration of the 2'-hydroxyl group in epihæmanthidine is envisaged as the same as in hæmanthidine, namely *cis* to the methoxyl group.[2] The formation of the same apo-compound (II) from both alkaloids is then readily understood in that the methoxy-group is removed to leave the same intermediate, resonance-stabilised carbonium ion in each case, and ring closure can occur readily with the vicinal *cis*-oxygen atom in the 2'-position.

Experimental

Extraction.—The sliced bulbs of *H. natalensis* were soaked in ethanol, dried, ground, and further extracted with ethanol. The extracts were concentrated, steam-distilled, filtered through kieselguhr (Celite 545), acidified to pH 2 with hydrochloric acid and extracted with

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* Part IV, *J.*, 1958, 4701.

† Hæmanthidine is the 6-hydroxy-derivative (cf. I) of hæmanthine. Since the prefix oxo denotes a change $CH_2 \longrightarrow CO$, the ketone (III) is 6-oxohæmanthine, and not oxohæmanthidine as in previous literature. The same nomenclature applies in the epi-series which differs stereochemically from the parent series only in the configuration of the methoxyl group. Ed.

[1] Warren and Wright, *J.*, 1958, 4701; Wildman and Kaufman, *J. Amer. Chem. Soc.*, 1955, **77**, 1245.

[2] Fales and Wildman, *Chem. and Ind.*, 1958, 561.

[3] Uyeo, Fales, Highet, and Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2591.

chloroform. The aqueous phase was basified with sodium carbonate and extracted with chloroform. The chloroform extract gave a gum (42 g.) which was chromatographed in benzene containing 12% of ethyl acetate (1200 ml.) over alumina (1 kg.). Elution with pure ethyl acetate (800 ml.) gave hæmanthamine (11·7 g.), and then with chloroform gave 3-*epihæmanthidine* (9·0 g.) which crystallised from acetone–light petroleum as prisms, m. p. 211°, $[\alpha]_D^{20}$ +44° (*c* 1 in $CHCl_3$) (Found: C, 64·0, 64·2; H, 5·8, 6·15. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0%). It crystallised from ethanol in a solvated *form* (Found: C, 62·6; H, 6·8; H, 4·2. $C_{17}H_{19}O_5N,C_2H_6O$ requires C, 62·8; H, 6·9; N, 3·9%). It showed bands in ethanol at 242 and 293 mμ (log ε 3·75 and 3·67 respectively) and in Nujol at 3422 (OH), 1645 (CH:CH), 1618 (Ar), 1250 and 931 cm.$^{-1}$ (CH_2O_2). Crystallisation from aqueous acetone gave a *hydrate*, m. p. 146° (Found after drying at 20°/0·01 mm.: C, 62·2; H, 6·2; N, 4·2; OMe, 9·5. $C_{17}H_{19}O_5N,\frac{1}{2}H_2O$ requires C, 62·5; H, 6·1; N, 4·3; OMe, 9·5%). It gave a *picrate* (Found: C, 49·3; H, 4·4; N, 9·6. $C_{23}H_{22}O_{12}N_4,H_2O$ requires C, 48·9; H, 4·3; N, 9·9%).

With acetic anhydride and pyridine it gave amorphous OO-*diacetylepihæmanthidine* (Found: C, 62·0; H, 5·7; Ac. 18·0. $C_{21}H_{23}O_7N$ requires C, 62·8; H, 5·8; Ac, 21·4%), $\nu_{max.}$ 1745 cm.$^{-1}$ (vs) (ester CO). On one occasion this crystallised from ether–ethanol in rhombohedra, m. p. 182—184°.

Epihæmanthidine (400 mg.), methyl iodide (1 ml.), and chloroform were warmed to 50° for 1 hr., during which an oil separated. This *methiodide* crystallised from water as prisms, m. p. 174°, $[\alpha]_D^{23}$ +57° (*c* 1 in EtOH) (Found: C, 44·0; H, 5·6. $C_{18}H_{22}O_5NI,2H_2O$ requires C, 43·6; H, 5·3%), and afforded a *methopicrate*, m. p. 146° (Found after drying at 100°/0·01 mm.: C, 51·1; H, 4·0. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3%).

Zinc-dust Distillation of Epihæmanthidine.—Epihæmanthidine (0·3 g.) and zinc (8 g.) were heated strongly in hydrogen. The product with picric acid crystallised from ethanol to give phenanthridine picrate which sublimed at 139° to small needles; these changed at 174° to large needles, m. p. 222—223°, thus behaving similarly to authentic phenanthridine picrate.

Apohæmanthidine.—Pure epihæmanthidine and 6N-hydrochloric acid were heated at 80—90° for 2 hr. The solution was cooled to 0°, basified with sodium carbonate, and extracted with chloroform. The gummy product in benzene was chromatographed over alumina; benzene–methanol eluted apohæmanthidine, m. p. 195—196° (from ethyl acetate), $[\alpha]_D^{23}$ +125° (*c* 0·73 in $CHCl_3$) (Found: C, 67·0; H, 5·8; OMe, 0. Calc. for $C_{16}H_{15}O_4N$: C, 67·35; C, 5·3%), $\nu_{max.}$ in Nujol 3090, 2745, and 1611 cm.$^{-1}$, $\lambda_{max.}$ in EtOH 293 mμ (log ε 3·75) and 240(sh) mμ (log ε 3·59). Uyeo *et al.*[3] give m. p. 195—196°, $[\alpha]_D^{23}$ +123°, λ 294 mμ (log ε 3·70) and 240(sh) mμ (log ε 3·57).

6-*Oxo*-3-*epihæmanthine.*—3-Epihæmanthidine (200 mg.) in dry chloroform (50 ml.) was shaken for 30 min. with manganese dioxide (2 g.) prepared according to Attenburrow *et al.*[4] The solution was refluxed for 2 min. and the manganese dioxide was filtered off and washed with ethanol. The filtrate gave a gum (130 mg.) which, twice crystallised from ethyl acetate, gave 6-*oxo*-3-*epihæmanthine* as prisms, m. p. 195—196°, $[\alpha]_D^{23}$ +29° (*c* 0·9 in $CHCl_3$) (Found: C, 64·2; H, 5·5. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4%), $\nu_{max.}$ in Nujol 1677 (vs broad), 1616 (vs; Ar·CO) and in CCl_4 3605 cm.$^{-1}$ (OH), $\lambda_{max.}$ in ethanol 234, 275, and 326 mμ (log ε 4·36, 3·79, and 3·71 respectively).

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[4] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1104.