493. *The Alkaloids of the Amaryllidaceae. Part II.* Hæmanthine and a New Alkaloid Distichine from* Boöphone disticha *Herb.*

By Angela N. Bates, J. K. Cooke, L. J. Dry, A. Goosen, H. Krüsi, and F. L. Warren.

The extract of *Boöphone disticha* Herb. contains lycorine, hæmanthine (now obtained crystalline), and a small quantity of another alkaloid isolated as its picrate, $C_{21}H_{22}O_{11}N_4$, whilst the principal constituent is a new alkaloid (distichine) $C_{19}H_{21}O_5N$. Derivatives and ultraviolet and infrared spectra of hæmanthine and distichine are recorded.

The extract of the bulbs of *Boöphone disticha* Herb. (*B. toxicaria, Buphane disticha*) has been used as an arrow poison by the bushmen and Hottentots whilst the Xosas employed it to combat " red water " in cattle.[1] Juritz [2] showed that the bulbs contained alkaloids, but the first thorough analysis of the different constituents was made by Tutin [3] in 1911, who isolated lycorine and an alkaloid buphaninine, and indicated the presence of three minor alkaloids. Lewin [4] reported another alkaloid, hæmanthine, $C_{18}H_{23}O_7N$, which he characterised as the hydrochloride, nitrate, and chloroplatinate, though Tutin [5] maintained that it was a mixture. Cooke and Warren [6] recently isolated Lewin's liquid hæmanthine again from *B. disticha* and corrected the formula to $C_{18}H_{21}O_5N$; finally Goosen and Warren [7] identified it with buphanitine.

The bulbs of *B. disticha* have been collected from different parts of Southern Africa and at different seasons during ten years. On no occasion have we isolated an alkaloid corresponding to $C_{17}H_{19}O_4N$, m. p. 189°, which Humbold and Taylor [8] recently reported from this plant. Following Tutin's procedure [3] we confirmed the isolation of the non-alkaloidal material, but copper was never detected in the extract. The alkaloid fraction has now been separated to give lycorine, hæmanthine, a new alkaloid distichine, and a water-soluble alkaloid, isolated as the picrate, $C_{21}H_{22}O_{11}N_4$. The extraction procedure recorded in this paper, devised for the ready extraction of distichine and hæmanthine, was based on the facts that hæmanthine is much less soluble in ether, more readily adsorbed on alumina, and more basic than distichine, and that distichine hydrochloride is soluble in chloroform.

Distichine is the main alkaloid in *B. disticha* collected in the environs of Pietermaritzburg, Pretoria, Bloemfontein, and Grahamstown. It crystallised from aqueous methanol as a hydrate, $C_{19}H_{21}O_5N,0{\cdot}75H_2O$, from which the anhydrous alkaloid was obtained by distillation under reduced pressure. It is extremely stable to heat and some unchanged alkaloid was recovered from zinc dust distillation of the alkaloid. It gave a crystalline platinichloride, perchlorate, picrate, and styphnate, whose analyses corresponded to the above formula when the salts were prepared directly from the pure alkaloid but only after numerous crystallisations if made from the non-crystalline base (the melting points were no criterion of purity). The molecular weight was measured by comparison

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* Part I, *J. S. African Chem. Inst.*, 1953, **6**, 2.

[1] Watt and Breyer-Brandwyk, " The Medicinal and Poisonous Plants of Southern Africa," Livingstone, Edinburgh, 1932, p. 25; Steyn, " The Toxicology of Plants in South Africa," Central News Agency, S. Af., 1934, p. 539.

[2] Juritz, *Rep. Senior Analyst for* 1903, *Cape of Good Hope*, 1904, **59**, 63; *Rep. S. African Assoc. Adv. Sci.*, 1911, **8**, 98.

[3] Tutin, *J.*, 1911, **99**, 1240.

[4] Lewin, *Arch. Exp. Path. Pharm.*, 1912, **68**, 333; 1912, **70**, 302.

[5] Tutin, *ibid.*, 1912, **69**, 314.

[6] Cooke and Warren, *J. S. African Chem. Inst.*, 1953, **6**, 2.

[7] Goosen and Warren, *Chem. and Ind.*, 1957, 267.

[8] Humbold and Taylor, *Canad. J. Chem.*, 1955, **33**, 1268.

of the ultraviolet extinction coefficient [9] of the picrates of distichine and lycorine. Formation of a methiodide and a methoreineckate established presence of a tertiary nitrogen atom. Zeisel determination showed two methoxy-groups, and Berzoa's test [10] indicated a methylenedioxy-group.

Hæmanthine, $C_{18}H_{21}O_5N$, has now been obtained as hemihydrated needles, m. p. 230°, and as rhombohedra, m. p. 240°, which lost solvent of crystallisation at 130° to give a sublimate, m. p. 228°. Its hydrochloride likewise was obtained as a sesquihydrate, monohydrate, and semihydrate. It gave a crystalline nitrate, perchlorate, and picrate, also a methiodide and methoreineckate so that the nitrogen atom is tertiary, and it contains a methoxyl and a methylenedioxy-group.[10] Zerewitinov's reaction disclosed two active hydrogen atoms and hæmanthine readily formed an amorphous diacetate, and once a crystalline monoacetate.

Infrared bands at 9·0, 9·67, and 10·57 μ for distichine and at 9·71 and 10·72 μ for hæmanthine indicate a methylenedioxyphenyl group in both alkaloids. Bands at 2·82 and 2·87 μ for hæmanthine are attributed to the hydroxyl groups. Strong absorption at 6·18 and 6·16 μ for distichine and hæmanthine respectively is in contrast with the weak absorption in this region for lycorine, and, by analogy with observations by Wildman and his co-workers,[11] may be attributed to the methoxy-group in the benzene nucleus. The ultraviolet spectrum of distichine [$\lambda_{\text{min.}}$ 260 mμ (log ε 2·49); $\lambda_{\text{max.}}$ 285 mμ (log ε 3·15)] is almost identical with that of hæmanthine ($\lambda_{\text{min.}}$ 260; $\lambda_{\text{max.}}$ 285 mμ; log ε 2·66 and 3·23 respectively). The similarity with hydrocotarnine ($\lambda_{\text{max.}}$ 287 mμ, log ε 3·23) supports the assignment of the methoxy-group to the benzene nucleus.

EXPERIMENTAL

Microanalyses are by Y. Merchant, ultraviolet and infrared measurements by Dr. E. C. Leisegang and M. E. von Klemperer.

Extraction.—Seventy bulbs of *Boöphone disticha* Herb., collected in late May on the outskirts of Pietermaritzburg, were sliced and dropped into boiling ethanol, then dried, crushed (7 kg.), and extracted with ethanol (Soxhlet). The extract together with the first ethanol solution was flash-evaporated under reduced pressure and the concentrate (4 l.) steam-distilled for 2 hr. The cooled solution was filtered, washed with ether (2 × 1 l.), basified with sodium carbonate, and extracted with chloroform (6 × 1 l.). The extract gave a dark brown gum (200 g.) which was ground to a powder with plaster of Paris and extracted with boiling ether (E) (5 × 1 l.) and then with chloroform (F_1) (4 × 1 l.).

The ether extract (E) gave a gum (120 g.) which was treated with N-hydrochloric acid (300 ml.), filtered, and extracted with ether (4 × 100 ml.), which removed acetovanillone, and with chloroform (F_2) (6 × 200 ml.). The acid solution was made alkaline with sodium carbonate, to give a voluminous precipitate, and extracted with ether (E_2) (4 × 250 ml.) and chloroform (F_3) (3 × 200 ml.). The hydrochloride from (F_2) gave a base soluble in ether (E_1).

The ether solutions E_1 and E_2 gave gums which were lixiviated with ether, and this ether solution was extracted stepwise with 2N-hydrochloric acid (4 × 2·5 ml.; 50 ml.; 4 × 2·5 ml.). Each fraction was basified and extracted with chloroform. Fractions 1—3 gave crystals (H) on the addition of ether; fractions 4—7 were ether-soluble gums which slowly crystallised (D).

The combined chloroform extracts (F_1 and F_3) gave a gum (60 g.) which in a little chloroform was percolated through alumina (360 g.; grade II). The column was washed with ether; the first runnings (200 ml.) gave coloured amorphous alkaloidal material, and the later fraction (1·2 l.) on concentration gave only a small quantity of crystals (H), m. p. *ca.* 226°. The column was fractionally eluted with (i) chloroform–ether (1 : 1; 3 × 400 ml.), (ii) chloroform (3 × 400 ml.), and (iii) methanol (2 l.). Fraction (i) gave gums which were dissolved in chloroform and fractionally precipitated with ether, to give first resin and later crystals (H), m. p. *ca.* 226°. Fraction (ii) behaved similarly. The resin and that from fraction (iii) were

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[9] Cunningham, Dawson, and Spring, *J.*, 1951, 2305.

[10] Berzoa, *Analyt. Chem.*, 1954, **26**, 1971.

[11] Wildman and Kaufman, *J. Amer. Chem. Soc.*, 1955, **77**, 4807; cf. Brigs, Highet, Highet, and Wildman, *ibid.*, 1956, **78**, 2899.

re-chromatographed, to give a further quantity of crystals (H) (3·7 g.), m. p. *ca.* 226°, and a little lycorine, m. p. 260°.

Distichine.—The crystals (D) recrystallised from methanol–water as needles of *distichine*, m. p. 144°, $[\alpha]_D^{20}$ −39° (*c* 1 in $CHCl_3$) (Found: C, 64·2, 63·7; H, 6·8, 6·8; OMe, 19·5. $C_{19}H_{21}O_5N,0·75H_2O$ requires C, 64·0; H, 6·35; 2OMe, 17·4%). Distichine distilled at 140°/0·3 mm. to an oil, which solidified (m. p. 90—92°) (Found: C, 66·7, 66·8; H, 6·2, 6·4. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2%). The *platinichloride* crystallised from water as orange-yellow rods, m. p. 223° (Found: C, 40·7, 40·8; H, 4·4, 4·2; Pt, 18·7, 18·7. $C_{38}H_{44}O_{10}N_2PtCl_6,H_2O$ requires C, 40·9; H, 4·2; Pt, 17·5%). The *perchlorate*, obtained by the addition of sodium perchlorate to distichine hydrochloride, crystallised from water in rhombohedra, m. p. 247° (Found: C, 51·8; H, 4·9. $C_{19}H_{22}O_9NCl$ requires C, 51·4; H, 5·0%). The *picrate* crystallised from alcohol in yellow needles, m. p. 235° (Found: C, 52·9, 52·7, 52·2, 52·6; H, 4·45, 3·95, 4·1, 4·6; N, 10·1; OMe, 10·4%; *M*, 563. $C_{25}H_{24}O_{12}N_4$ requires C, 52·5; H, 4·2; N, 9·8; 2OMe, 10·8%; *M*, 572). The *styphnate* crystallised from ethanol as yellow rectangular laminæ, m. p. 239—241° (Found: C, 50·5, 50·6; H, 4·1, 3·7. $C_{25}H_{24}O_{13}N_4$ requires C, 51·0; H, 4·1%).

Distichine methiodide crystallised from hot methanol as long colourless needles, m. p. 271°, $[\alpha]_D^{24}$ +7·7° (*c* 0·9 in EtOH) (Found: C, 49·7, 49·8, 49·6; H, 5·2, 5·4, 5·5; N, 2·5. $C_{20}H_{24}O_5NI$ requires C, 49·5; H, 5·0; N, 2·9%). The *methoreineckate* was obtained as an amorphous pink solid by the addition of water to an acetone solution (Found: C, 41·2; H, 5·0. $C_{24}H_{32}O_5N_7S_4Cr,2H_2O$ requires C, 41·3; H, 5·0%).

Hæmanthine.—The combined crystals (H) (13 g.) in chloroform were treated with ether until the solution was slightly turbid; hæmanthine separated as needles, m. p. 224°, raised only after several recrystallisations to 230°, $[\alpha]_D^{20}$ −101·6° (*c* 1 in EtOH) (Found: C, 63·8; H, 6·7; N, 4·5; OMe, 8·9. $C_{18}H_{21}O_5N,0·5H_2O$ requires C, 63·6; H, 6·5; N, 4·1; OMe, 9·1%). The crystals sublimed at 180°/0·1 mm. as needles, m. p. 197—199° (Found: C, 65·4; H, 6·8. $C_{18}H_{21}O_5N$ requires C, 65·2; H, 6·4%). Hæmanthine crystallised from ethanol in rhombohedra which lost solvent of crystallisation at 130° and then had m. p. 240° with sublimation (Found: C, 63·8; H, 6·7%). The sublimate had m. p. 228°.

Hæmanthine Hydrochloride.—Hæmanthine in dilute hydrochloric acid was evaporated at 100° and the product crystallised twice from water gave *hæmanthine hydrochloride* as colourless needles, m. p. 180° (Found: C, 54·4; H, 6·4; N, 3·8. $C_{18}H_{22}O_5NCl,1·5H_2O$ requires C, 54·7; H, 6·4; N, 3·5. Found, after drying at 100°/0·1 mm.: C, 56·1; H, 6·5; N, 3·2. $C_{18}H_{22}O_5NCl,H_2O$ requires C, 56·0; H, 6·3; N, 3·6%). Hæmanthine in ethanol was treated with 1 mol. of concentrated hydrochloric acid, and ether was added until the solution was turbid. The crystals were recrystallised in the same manner, to give *hæmanthine hydrochloride* as needles, m. p. 265°, $[\alpha]_D$ +13° (*c* 1 in H_2O) (Found: C, 57·4; H, 6·4; Cl, 10·0. $C_{18}H_{22}O_5NCl,0·5H_2O$ requires C, 57·4; H, 6·2; Cl, 9·7%). The *platinichloride* separated from hot water as light orange crystals, m. p. 204° (Found: C, 39·6; H, 4·5; Pt, 19·8. $C_{36}H_{48}O_{12}N_2Cl_6Pt$ requires C, 39·0; H, 4·4; Pt, 17·6%). The *nitrate* crystallised from alcohol and moist ether as needles, m. p. 129° (Found: C, 52·2; H, 6·2. $C_{18}H_{22}O_8N_2,H_2O$ requires C, 52·4; H, 5·9%). The *perchlorate* formed as above crystallised from water in flat needles, m. p. 99—100° (Found: C, 46·8; H, 5·8. $C_{18}H_{22}O_9NCl,1·5H_2O$ requires C, 47·1; H, 5·5%). The *picrate*, purified by the addition of water to its alcoholic solution, and finally by cooling a hot aqueous solution, was obtained as a yellow powder (Found: C, 51·2; H, 4·4. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3%). The *methiodide*, prepared in hot methanol, crystallised therefrom as needles, m. p. 248°, $[\alpha]_D^{18}$ −70·3° (*c* 1 in H_2O) (Found: C, 46·7; H, 5·8; N, 2·4. $C_{19}H_{24}O_5NI,H_2O$ requires C, 46·4; H, 5·3; N, 2·8%). The *methoreineckate* was precipitated as a pink amorphous powder (Found: C, 40·1; H, 5·1. $C_{23}H_{32}O_6N_7S_4Cr$ requires C, 40·5; H, 4·7%).

Mono- and Di-acetylhæmanthine.—Hæmanthine (0·5 g.), acetic anhydride (10 ml.), benzene (20 ml.), and acetyl chloride (4 ml.) were refluxed for 1 hr. The product in chloroform was chromatographed over alumina, and the concentrated benzene eluate treated with light petroleum until turbid. *Monoacetylhæmanthine* crystallised in needles, m. p. 199° (*c* 1 in $CHCl_3$) (Found: C, 64·6; H, 6·2; Ac, 10·6. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; Ac, 11·3%). On all other occasions *diacetylhæmanthine* separated as an amorphous white solid (Found: C, 62·2; H, 6·2; Ac, 21·3. $C_{22}H_{25}O_7N,0·5H_2O$ requires C, 62·3; H, 6·2; Ac, 19·8%).

Alkaloid Picrate, m. p. 129—131°.—The bulbs were extracted by Tutin's method.[3] The pentyl alcohol extract was poured into ether, filtered, and washed with water. The aqueous solution was filtered from a little lycorine, and treated with picric acid, and the product recrystallised from hot water to give a *picrate*, m. p. 129—131° (Found: C, 49·8; H, 4·4. $C_{21}H_{22}O_{11}N_4$ requires C, 49·8; H, 4·4%).

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THE DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY,
UNIVERSITY OF NATAL, PIETERMARITZBURG, SOUTH AFRICA. [*Received, January* 28*th*, 1956.]