224. *The Alkaloids of the* Amaryllidaceae. *Part VII.** *The Alkaloids from* Boöphone disticha *Herb., Buphanitine ("Crystalline" Hæmanthine), Buphanamine, and Buphanidrine (Distichine).*

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Distichine and its sublimate have been identified as hydrated forms of buphanidrine, and the formula for buphanitine ("crystalline" hæmanthine) is corrected to $C_{17}H_{21}O_5N$. Lewin's derivatives of his "oily" hæmanthine are shown to be derivatives of buphanamine.

SEVERAL workers have isolated different individuals from the complex mixture of alkaloids from *Boöphone disticha*. We have re-investigated this mixture and found the alkaloids to exist in several different forms. The preparation of appropriate derivatives has permitted a comparison of the reported alkaloids with known alkaloids in this family

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* Part VI, preceding paper.

and given further quantities for structural studies. The mixed alkaloids were freed from phenolic alkaloids and lycorine, and then separation was effected by shaking a chloroform solution with hydrochloric acid. Buphanidrine (distichine) hydrochloride was soluble in the chloroform whilst buphanamine and buphanitine hydrochlorides were preferentially soluble in water; and the last two bases were separated chromatographically.

Buphanidrine, $C_{18}H_{21}O_4N$, was first reported as a gum from *B. fischerii*[1] and later obtained as crystals, m. p. 88—89°.[2] Distichine, m. p. 144°, was isolated by us[3] from *B. disticha*. Warnhoff and Wildman,[4] however, suggested that " distichine is in all probability undulatine contaminated with traces of buphanidrine since the infrared spectrum of a specimen ' (supplied by us) ' was identical with a 3 : 1 mixture of undulatine, $C_{18}H_{21}O_5N$, m. p. 149°, and buphanidrine." Distichine crystallised from aqueous methanol in needles, whose m. p. (144°) was not changed by recrystallisation from ether; but when an ethereal solution was seeded with a sample of buphanidrine, kindly supplied by Dr. Wildman, it crystallised in prisms, m. p. 90—92°. Further, when Dr. Wildman's sample of anhydrous buphanidrine was crystallised from aqueous methanol the melting point was raised; but once the anhydrous form had been obtained three or four crystallisations were necessary to obtain m. p. 144° again. Our analytical figures for the derivatives of distichine fit equally well as derivatives of buphanidrine, and the infrared spectra of the perchlorate, picrate, and methiodide of buphanidrine (kindly supplied by Dr. Wildman) and of distichine were all appropriately identical. Distichine, $C_{18}H_{21}O_4N,1\frac{1}{2}H_2O$, and sublimed distichine, $C_{18}H_{21}O_4N,\frac{1}{2}H_2O$, are accordingly hydrated forms of buphanidrine.

Buphanitine, m. p. 240°, was isolated from *B. disticha* by Tutin[5] who reported a hydrochloride, m. p. 265°, and a methiodide, m. p. 278°. Lewin[6] held that buphanitine was a mixture, one component of which he reported as an oil, hæmanthine, which gave a hydrochloride, m. p. 175°, and nitrate, m. p. 125°. The re-isolation[7] of these salts confirmed the chemical individuality of Lewin's hæmanthine. Later[8] a crystalline alkaloid, m. p.s 230° and 240°, which was called hæmanthine, was identified with Tutin's buphanitine and the formula corrected to $C_{18}H_{21}O_5N,\frac{1}{2}H_2O$ since it sublimed to a compound thought to be the anhydrous form, m. p. 197—199°. This sublimate is best obtained by sublimation from alumina under reduced pressure, and does not give the " crystalline " hæmanthine derivatives. Buphanitine has been further studied: the needles, m. p. 230°, after numerous crystallisations from chloroform–ether gave needles, m. p. 234°, changing crystalline form at 210°, and prisms, m. p. 232°; at 180°/0·1 mm. the needles and prisms sublimed to needles and prisms respectively, without changing their characteristic melting habits. Both forms when recrystallised from acetone gave prisms, m. p. 232°. Buphanitine hydrochloride and nitrate have m. p.s 265° and 222—224° respectively. A new formula for buphanitine, $C_{17}H_{21}O_5N$, is accordingly now proposed which fits well the reported analyses as well as its degradation products. It is probable that Tutin's buphanitine methiodide,[5] m. p. 278°, is buphanidrine methiodide, m. p. 271°.

Buphanamine, m. p. 184—186° (perchlorate, $C_{17}H_{20}O_8NCl$, m. p. 232—234°), was isolated by Renz, Stauffacher, and Seebeck[1] from *B. fisherii*. The unnamed alkaloid, m. p. 189° (perchlorate $C_{17}H_{20}O_8NCl,1\frac{1}{2}H_2O$, m. p. 119°), previously isolated from *B. disticha* by Humbold and Taylor[9] was shown by Wildman to be identical with buphanamine.[10] We have also obtained this alkaloid and prepared its hydrochloride, m. p. 180°, and nitrate, m. p. 130°, which seemingly are identical with Lewin's salts from

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[1] Renz, Stauffacher, and Seebeck, *Helv. Chim. Acta*, 1955, **38**, 1209.
[2] Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.
[3] Bates, Cooke, Dry, Goosen, Krüsi, and Warren, *J.*, 1957, 2537.
[4] Warnhoff and Wildman, *Chem. and Ind.*, 1957, 1385.
[5] Tutin, *J.*, 1910, 1240.
[6] Lewin, *Arch. expt. Path. Phar.*, 1912, **68**, 333.
[7] Cooke and Warren, *J. S. African Chem. Inst.*, 1953, **6**, 2.
[8] Goosen and Warren, *Chem. and Ind.*, 1957, 267.
[9] Humbold and Taylor, *Canad. J. Chem.*, 1955, **33**, 1268.
[10] Wildman, personal communication.

his "oily" hæmanthine[6] and are not derivatives of buphanitine ("crystalline" hæmanthine) as previously reported.[8,3] In view of the confusion which has been associated with the name hæmanthine it is proposed that Lewin's "oily" hæmanthine be known as buphanamine.

EXPERIMENTAL

The alcoholic extract of *B. disticha* was processed as previously. The chloroform extract was concentrated, filtered from precipitated lycorine, washed with sodium hydroxide, and extracted with hydrochloric acid.

Buphanidrine (*Distichine*).—The chloroform solution was shaken with sodium carbonate solution, concentrated, and chromatographed over alumina to give a solid which, crystallised four times from aqueous methanol, gave the previously reported distichine (hydrated buphanidrine) as needles, m. p. 144°. A solution in ether seeded with a sample of buphanidrine, kindly supplied by Dr. Wildman, deposited prisms, m. p. 90—92° (Found: C, 68·1; H, 6·6. Calc. for $C_{18}H_{21}O_4N$: C, 68·5; H, 6·7%). Wildman's anhydrous buphanidrine, crystallised three times from aqueous methanol, gave needles, m. p. 110—125°. The *oxalate* (Found: C, 59·0; H, 5·7. $C_{20}H_{23}O_8N$ requires C, 59·25; H, 5·7%). The analyses for the previously reported distichine (hydrated buphanidrine) (Found: C, 64·2; H, 6·8. Calc. for $C_{18}H_{21}O_4N,1\frac{1}{2}H_2O$: C, 64·3; H, 7·1%), sublimate (Found: C, 66·8; H, 6·4%), chloroplatinate (Found: C, 40·7; H, 4·4; Pt, 18·7. Calc. for $C_{18}H_{21}O_4N,PtCl_6,H_2O$: C, 40·9; H, 4·2; Pt, 18·4%), and styphnate (Found: C, 50·5; H, 4·1. Calc. for $C_{24}H_{24}O_{12}N_4,\frac{1}{2}H_2O$: C, 50·6; H, 4·4%), as well as the perchlorate, picrate, and methiodide, m. p. 271°, which are unsolvated, fit the formulation as derivatives of buphanidrine.

Buphanitine.—The hydrochloric acid extract was basified and extracted with chloroform. The gum from the chloroform extract was dissolved in acetone and set aside; buphanitine ("crystalline" hæmanthine) separated. These crystals together with the later fraction after the chromatographic separation of buphanamine (see below) crystallised from chloroform–ether to give *buphanitine* first in needles, changing crystalline form at 210°, m. p. 234°, $[\alpha]_D^{20}$ $-102°$ (*c* 1 in $CHCl_3$) (Found: C, 63·4; H, 6·4. $C_{17}H_{21}O_5N$ requires C, 63·9; H, 6·6%), and later in prisms, m. p. 232°, $[\alpha]_D^{20}$ $-101°$ (*c* 1 in $CHCl_3$) (Found: C, 63·4; H, 6·4%). These needles and prisms, sublimed at 180°/0·1 mm., gave needles and prisms respectively without changing their characteristic melting habits or infrared spectra. Both forms when crystallised from acetone gave prisms, m. p. 232°, and from alcohol gave previously reported rhombohedra which lost solvent of crystallisation at 130°, m. p. 240° subliming to needles, m. p. 234°. The *nitrate* had m. p. 222—224° (Found: C, 53·1; H, 5·9. $C_{17}H_{22}O_8N_2$ requires C, 53·4; H, 5·8%). The previously reported analyses for the derivatives of crystalline hæmanthine, namely, the perchlorate (Found: C, 46·8; H, 5·8. Calc. for $C_{17}H_{22}O_9NCl,H_2O$: C, 46·6; H, 5·5%) the hydrochloride, methiodide, m. p. 248°, and diacetyl derivative which are unsolvated, fit their formulation as derivatives of buphanitine.

Buphanamine.—The acetone mother-liquors from the separation of buphanitine (see above) gave a gum which was chromatographed in chloroform over alumina. The earlier fractions gave buphanamine which crystallised from acetone in prisms, m. p. 192—194° (Found: C, 67·7; H, 6·3. Calc. for $C_{17}H_{19}O_4N$: C, 67·8; H, 6·4%). Humbold and Taylor[9] report an alkaloid, m. p. 189°, and Renz[1] *et al.* report buphanamine, m. p. 184—186°.

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[*Received, October 5th,* 1959.]