223. *The Alkaloids of the* Amaryllidaceae. *Part VI.*[1] *The Isomerisation of Epihæmanthidine to Epitazettine, and the Absolute Configuration of the Alkaloids from* 5,10*b*-*Ethanophenanthridine.**

By P. W. Jeffs, F. L. Warren, and Winifred G. Wright.

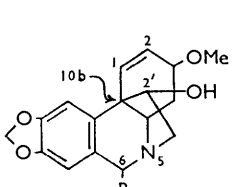
Epihæmanthidine (I; R = OH) and its methiodide are converted by treatment with alkali into de-*N*-methylepitazettine (II; R = R′ = H) and epitazettine (II; R = H, R′ = Me) respectively. The structure of epitazettine is established by oxidation to epitazettamide (III) and by the Hofmann degradation to *NN*-dimethylglycine 4,5-methylenedioxy-2-phenylbenzyl ester (IV; R = O·CO·CH_2·NMe_2), and 4,5-methylenedioxy-2-phenylbenzyl chloride (IV; R = Cl) and alcohol (IV; R = OH).

A study of the molecular rotations of epimeric forms of tazettinol, tazettine, hæmanthidine, and 6-oxohæmanthine,† leads to the extension of Mills's observations on allylic terpenoid and steroid alcohols to their methyl ethers. Absolute configurations are determined for the derivatives of (+)-crinane (hæmanthidine, epihæmanthidine, hæmanthamine, crinamine, vittatine, and hæmultine), and of (−)-crinane (crinine, epicrinine, buphanisine, powelline, epipowelline, and buphanidrine).

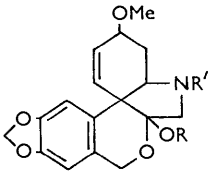
Epihæmanthidine was recently[1] isolated from a difficultly separable mixture of alkaloids from *H. natalensis*. In view of the ready conversion, reported previously, of hæmanthidine into tazettine,[2] we have investigated a parallel reaction of epihæmanthidine.

Hæmanthidine was originally thought to be de-*N*-methyltazettine in that with methyl iodide[3] or with formaldehyde and formic acid[4] it gave tazettine (II; R = H, R′ = Me). Uyeo, Fales, Highet, and Wildman,[2] however, established the formula (I; R = OH) for hæmanthidine.

When epihæmanthidine was treated with 10% potassium hydroxide at 100° the substance gradually dissolved to form an isomer, readily isolated as hydrochloride, which is formulated as de-*N*-methylepitazettine (II; R = R′ = H). This gave a diacetyl derivative (II; R = R′ = Ac) showing infrared bands corresponding to *O*- and *N*-acetyl groups. With methyl iodide it gave epitazettine (II; R = H, R′ = Me) hydriodide, m. p. 245—246°, yielding a picrate, m. p. 233°, which compounds differ from epihæmanthidine methiodide, m. p. 174°, and methopicrate, m. p. 146°.[1] When epihæmanthidine methiodide is treated with dilute alkali it isomerises rapidly to epitazettine (II; R = H, R′ = Me), obtained also from epitazettine hydriodide. The same route is probably followed in the conversion of hæmanthidine (I; R = OH) into tazettine, namely, by way of hæmanthidine methiodide and not directly into tazettine.[3]



(I)



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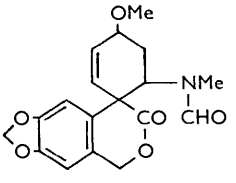

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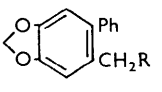

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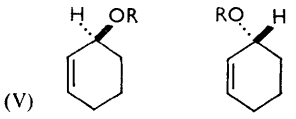
Identification of the isomeric compound as epitazettine was confirmed by its ready oxidation with manganese dioxide to epitazettamide, whose infrared bands at 1733 and

* Phenanthridine numbering as in I.U.P.A.C. Rules and the Ring Index.
† Cf. footnote to Part V, p. 1088.

[1] Part V, Goosen, Graham, Jeffs, Warren, and Wright, preceding paper.
[2] Uyeo, Fales, Highet, and Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2590.
[3] Boit, *Chem. Ber.*, 1954, **87**, 1339; Boit and Stander, *ibid.*, 1956, **89**, 161.
[4] Wildman, *Chem. and Ind.*, 1956, 123.

1673 cm.$^{-1}$ correspond to similar bands (1736 and 1666 cm.$^{-1}$) for tazettamide (III) [5] and attributed to a six-ring lactone and an amide group respectively. Further, epitazettine (II; R = H, R′ = Me) gave with methyl iodide a quaternary salt characterised as its picrate. Hofmann degradation of this quaternary salt gave *NN*-dimethylglycine 4,5-methylenedioxy-2-phenylbenzyl ester (IV; R = O·CO·CH_2·NMe_2) (isolated as its picrate) and 4,5-methylenedioxy-2-phenylbenzyl chloride (IV; R = Cl) (characterised by conversion into the alcohol). These products have previously been isolated [6] after Hofmann degradation of tazettine (II; R = H, R′ = Me).

Tazettine has been smoothly demethylated [7] with 10% hydrochloric acid to two isomeric alcohols, tazettinol and isotazettinol, whose molecular rotations, assessed on the basis of Mills's rule [8] for terpenoid and steroid allylic alcohols, assigned absolute configurations to the methoxy-groups of tazettine and the then unknown epitazettine. The present isolation of epitazettine from epihæmanthidine, paralleling the formation of tazettine from hæmanthidine,[3,4] permits a comparison of the molecular rotations of the epimeric allylic ethers of known configuration. It will be seen in Table 1 that tazettine, hæmanthidine, and 6-oxohæmanthine, are more lævorotatory than their epimers. It



(V) (VI)

seems, therefore, that, in this series at least, Mills's rule [8] for allylic alcohols and certain of their esters can be extended to allylic methyl ethers, namely, that compound (V; R = Me) is more lævorotatory than its stereoisomer (VI; R = Me). It follows that crinamine, known to be epimeric with hæmanthamine,[9] belongs to the epi-series (see Table 1).

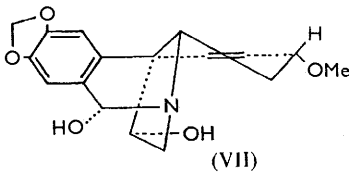
TABLE 1. *Molecular rotations of epimeric allylic alkaloid alcohols and ethers.*

	(V) OR axial (*S*)-configuration	(VI) OR equatorial; (*R*)-configuration	$\Delta[M]_D$ (VI) − (V)
Tazettinol	+377° [7]	+827° [7]	450°
Tazettine	+526	+953	427
Hæmanthidine	−129 [3]	+152	281
6-Oxohæmanthine	−130 [2]	+91 [1]	221
Hæmanthamine	+59 [3]	+496	437
Crinamine			
Crinine	−385 [10]	−51 [10]	334
Epicrinine			
Powelline	−310 [10]	0 [10]	310
Epipowelline			

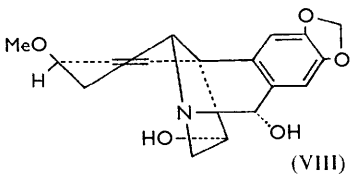
Wildman [9] pointed out that hæmanthamine (I; R = H) and hæmanthidine (I; R = OH) must possess the nucleus represented by (XI; $R^1 = R^2 = R^3 = R^4 = H$) or its mirror image (VIII), and that the hydroxyl group in these two alkaloids must be *cis* to the methoxyl group to permit the formation of apohæmanthamine (IX; R = H) and apohæmanthidine (IX; R = OH). The benzylic hydroxyl group in hæmanthidine (I; R = OH) may be assigned the pseudo-equatorial orientation since it can be oxidised to, and obtained by reduction from, 6-oxohæmanthine; [2] and since epihæmanthidine gives the same apohæmanthidine as is obtained from hæmanthidine,[1] it must have the same orientation at position 6. The absolute configuration of the methoxyl group in epihæmanthidine established above from molecular rotations limits the possible formulæ to (VII) and (VIII).

[5] Highet and Wildman, *Chem. and Ind.*, 1951, 1159.
[6] Ikeda, Taylor, and Uyeo, *Chem. and Ind.*, 1955, 1088; Taylor, Uyeo, and Yajima, *J.*, 1955, 2962.
[7] Ikeda, Taylor, Tsuda, Uyeo, and Yajima, *J.*, 1956, 4749.
[8] Mills, *J.*, 1952, 4977.
[9] Wildman and Fales, *Chem. and Ind.*, 1958, 561; *J. Amer. Chem. Soc.*, 1958, **80**, 6465.
[10] Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.

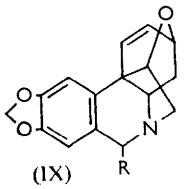
A decision between these two is forthcoming from two considerations. Although tazettine is readily demethylated, epitazettine is very stable to boiling acid. This can be explained if epitazettine has formula (X) since the proton of the conjugate acid would stabilise the methoxyl group by hydrogen bonding. A similar interaction has been advanced by Ikeda *et al.*[7] to explain the greater basicity of deoxyisotazettinol than of deoxytazettinol and fits in well with the configuration of tazettine advanced by these authors. It follows that epihæmanthidine has formula (VII), and not (VIII).



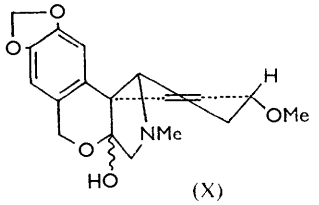
(VII)



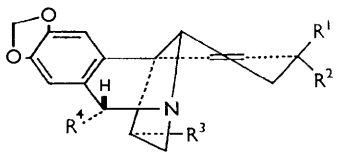
(VIII)



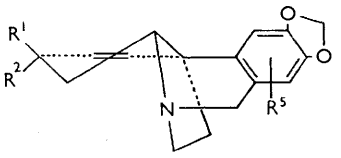
(IX)



(X)



(XI) (+)-Crinane skeleton.



(XII) (−)-Crinane skeleton.

Since hæmanthamine is deoxyhæmanthidine [2] and crinamine is epihæmanthamine,[9] these two alkaloids can be represented by the same general formula (XI). Vittatine, considered by Boit [11] as the optical antipode of crinidine, which is identical with

TABLE 2. *Absolute configuration of* Amaryllidaceae *alkaloids from 5,10b-ethanophenanthridines.*

Alkaloid	Formula	R [1]	R [2]	R [3]	R [4]	R [5]
(+)-Crinane	XI	H	H	H	H	—
Hæmanthidine	XI	OMe	H	OH	OH	—
Epihæmanthidine	XI	H	OMe	OH	OH	—
Hæmanthamine	XI	OMe	H	OH	H	—
Crinamine	XI	H	OMe	OH	H	—
Vittatine	XI	OH	H	H	H	—
Hæmultine	XIa	H	H	OH	H	—
(−)-Crinane	XII	H	H	—	—	H
Crinine	XII	OH	H	—	—	H
Epicrinine	XII	H	OH	—	—	H
Buphanisine	XII	OMe	H	—	—	H
Powellane	XII	H	H	—	—	OMe
Powelline	XII	OH	H	—	—	OMe
Epipowelline	XII	H	OH	—	—	OMe
Buphanidrine	XII	OMe	H	—	—	OMe

crinine [12] (see below), is therefore of this series (XI), as also is hæmultine [13] which is obtained from hæmanthamine and crinamine by reduction and demethoxylation (see Table 2).

[11] Boit, *Chem. Ber.*, 1954, **87**, 1704.
[12] Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.
[13] Boit and Dopke, *Chem. Ber.*, 1958, **91**, 1965.

In the enantiomorphic (—)-crinane series [basic skeleton (XII)] are included crinine, powelline, buphanidrine, buphanisine, undulatine, and buphanamine.[14] Comparison of the molecular rotations of crinine and powelline with their respective epimers (see Table 1) shows that the epimeric forms are the more lævorotatory. This result differs from that in the (+)-crinane series, and it therefore seems that the normal forms have the hydroxyl or methoxyl group axial in both the (+)- and the (—)-crinane series.

Crinine and powelline are then assigned absolute configurations as in Table 2. Buphanidrine is the methyl ether of powelline,[15,12] undulatine is 1,2-epoxydihydropowelline,[16] buphanisine is *Ar*-demethoxybuphanidrine,[12] and buphanamine [15] is known to have the powellane nucleus.

These relative configurations are confirmed by the observation that deoxydihydrohæmanthamine is the optical enantiomorph of dihydrobuphanisine.[9] The basic structure (+)-crinane is (4a*R*,10b*R*)-1,2,3,4,4a,5,6,10b-octahydro-8,9-methylenedioxy-5,10b-ethanophenanthridine.

Experimental

*Isomerisation of Epihæmanthidine to De-*N*-methylepitazettine.*—Epihæmanthidine gradually dissolved in 10% potassium hydroxide solution at 90—100°. After 30 min. the dark solution was cooled and extracted with chloroform. The chloroform extract gave a gum which with 5N-hydrochloric acid yielded a white precipitate. This precipitate was washed with 5N-hydrochloric acid, and dissolved in water; the solution was washed with ether, decolorised with charcoal, and concentrated, to give *de-*N*-methylepitazettine hydrochloride*, needles, m. p. 248—250°, $[\alpha]_D^{24}$ +198° (*c* 1·1 in H_2O) (Found, after drying at 20°/0·01 mm.: C, 54·9, 54·9; H, 5·7, 6·0; Cl, 9·3. Found, after crystallisation from ethanol: C, 54·5; H, 5·9; N, 3·2; Cl, 9·3; OMe, 8·1; *N*-Me, 0. $C_{17}H_{20}O_5NCl,H_2O$ requires C, 54·9; H, 6·0; N, 3·8; Cl, 9·6; OMe, 8·4. Found, after drying at 100°/0·01 mm.: C, 56·1; H, 5·4. $C_{17}H_{20}O_5NCl,\frac{1}{2}H_2O$ requires C, 56·3; H, 5·8%). The sample crystallised from water gave $\lambda_{max.}$ in EtOH at 241 and 290 mμ (log ε 3·66 and 3·64 respectively) and $\nu_{max.}$ in Nujol at 3400 (OH), 3180 (NH), 1624 (C=C), 1237 and 939 cm.$^{-1}$ (CH_2O_2).

*De-*N*-methylepitazettine*, generated from the hydrochloride by the addition of aqueous potassium hydroxide, was amorphous, with $[\alpha]_D^{25}$ +227° (*c* 1 in $CHCl_3$) (Found, after drying at 20°/0·01 mm.: C, 61·2; H, 5·7. $C_{17}H_{19}O_5N,H_2O$ requires C, 60·9; H, 6·3. Found, after drying at 112°/0·01 mm.: C, 62·7; H, 6·2; loss of wt., 3·1. $C_{17}H_{19}O_5N,\frac{1}{2}H_2O$ requires C, 62·5; H, 6·2; $\frac{1}{2}H_2O$, 2·7%), $\lambda_{max.}$ in EtOH 240 and 292 mμ (log ε 3·75 and 3·66 respectively). Trituration of the electrostatically charged substance with acetone gave needles, m. p. 195°, subliming above 162° to stellate clusters. The crystals gave, with methyl iodide, epitazettine hydriodide, m. p. 245° (see below). The *picrate* crystallised from ethanol in needles, m. p. 243—244° (Found: C, 50·1; H, 4·4; N, 10·7. $C_{23}H_{22}O_{12}N_4$ requires C, 50·1; H, 4·05; N, 10·2%). The *picrolonate* had m. p. 230—235° (Found, after drying at 100°/0·01 mm.: C, 55·7; H, 4·6; N, 10·1. $C_{27}H_{27}O_{10}N_5$ requires C, 55·9; H, 4·7; N, 12·0%).

*Acetylde-*N*-methylepitazettine.*—Demethylepitazettine (209 mg.), pyridine (1 ml.), and acetic anhydride (1 ml.) were allowed to react and the product crystallised from ethanol to give O-*acetylde-*N*-methylepitazettine* in prisms, m. p. 210—212° (Found: C, 62·7; H, 5·85; Ac, 12·1, 12·2. $C_{21}H_{23}O_7N$ requires C, 62·8; H, 5·8; Ac, 24·45), $\nu_{max.}$ in Nujol 930 and 1482 (CH_2O_2), 1641 vs (NAc), 1758 vs, and 1235 cm.$^{-1}$ (OAc), $\lambda_{max.}$ 239 and 292 mμ (log ε 3·76 and 3·62 respectively). Grove *et al.*[17] found two acetyl groups for amino-3,5-dimethoxyphenol triacetates on normal analysis.

Epitazettine.—Demethylepitazettine (230 mg.) chloroform and methyl iodide (3 ml.) were set aside for 2 hr. The product crystallised from ethyl acetate–ethanol and then from ethanol to give *epitazettine hydriodide* as prisms, m. p. 245—246° (Found: C, 47·2, 47·2; H, 4·8, 4·85; OMe, 6·4; *N*-Me, 3·1. $C_{18}H_{22}O_5NI$ requires C, 47·1; H, 4·8; OMe, 6·7; *N*-Me, 6·3%). The hydriodide was treated with aqueous picric acid and the product crystallised from ethanol, to

[14] Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 6466.
[15] Wildman, *Chem. and Ind.*, 1956, 1090.
[16] Warnhoff and Wildman, *ibid.*, 1958, 1293.
[17] Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3667; Groves, Jeffs, and Rustidge, *J.*, 1956, 1962.

give *epitazettine picrate*, m. p. 233° (Found: C, 51·2; H, 4·4. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3%). The hydriodide was basified with sodium carbonate and extracted with ether and chloroform, and the product crystallised from acetone to give *epitazettine*, m. p. 214° (forming at 192° a characteristic sublimate of perfectly square crystals), $[\alpha]_D^{23}$ +288° (*c* 1·0 in $CHCl_3$) (Found: C, 65·2; H, 6·6; OMe, 9·4; N, 4·2; *N*-Me, 7·1. $C_{18}H_{21}O_5N$ requires C, 65·2; H, 6·4; OMe, 9·3; N, 4·2; *N*-Me, 8·7%).

In boiling chloroform (45 min.) and methyl iodide it gave, after treatment with picric acid, the *methopicrate*, plates (from ethanol), m. p. 260° (Found: C, 52·3; H, 4·35. $C_{25}H_{26}O_{12}N_4$ requires C, 52·2; H, 4·6%).

Isomerisation of Epihæmanthidine Methiodide to Epitazettine.—Epihæmanthidine methiodide with cold potassium hydroxide gave epitazettine, m. p. and mixed m. p. 214° (Found, after drying at 100°/0·01 mm.: C, 65·1; H, 6·3%).

Oxidation of Epitazettine with Manganese Dioxide.—Epitazettine (350 mg.), dry chloroform (100 ml.), and manganese dioxide (3 g.), prepared according to Attenburrow *et al.*,[18] were shaken for 42 hr. The product (240 mg.) crystallised from acetone in plates and then from ethanol in needles, m. p. 276°, $[\alpha]_D^{24}$ +187° (*c* 0·75 in $CHCl_3$) (Found, after drying at 100°/0·01 mm.: C, 62·6; H, 5·6. $C_{18}H_{19}O_6N$ requires C, 62·6; H, 5·6%), $\lambda_{max.}$ 238 and 292 mμ, $\nu_{max.}$ in Nujol 1723 (6-ring lactone), 1673 (amide), and 1650 cm.$^{-1}$ (CH=CH), and in $CHCl_3$ the band at 1723 had moved to 1733 cm.$^{-1}$. Tazettamide, m. p. 174°, $[\alpha]_D^{23}$ +113°, showed bands at 1736 and 1666 cm.$^{-1}$.

Hofmann Degradation of Epitazettine.—Epitazettine was refluxed with methyl iodide as above and the product in water stirred with silver oxide, filtered, and evaporated to dryness. The clear gum was heated at 103°/0·01 mm. for 90 min., cooled, and treated with N-hydrochloric acid. The oily precipitate was removed with ether, and the hydrochloric acid solution divided into two portions. One portion was evaporated to dryness in a desiccator to give 4,5-methylenedioxy-2-phenylbenzyl chloride, m. p. 59° (Found: C, 67·7; H, 4·7. Calc. for $C_{14}H_{11}O_2Cl$: C, 68·1; H, 4·5%); Taylor, Uyeo, and Yajuma [6] give m. p. 58—59°. On alkaline hydrolysis this substance yielded the alcohol, m. p. 101°. The other portion with picric acid gave a precipitate which crystallised from ethanol to yield *NN*-dimethylglycine 4,5-methylenedioxy-2-phenylbenzyl ester picrate, m. p. 178° (Found: C, 53·0; H, 4·2. Calc. for $C_{24}H_{22}O_{11}N_4$: C, 53·1; H, 4·1%); Taylor *et al.*[6] give m. p. 178°.

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Department of Chemistry and Chemical Engineering, University of Natal,
Durban and Pietermaritzburg, South Africa. [*Received, September 15th*, 1959.]

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