758. *Stereochemistry of Lycorenine, Homolycorine, Pluviine, and their Hydrogenation Products.*

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The hydrogenation products of the alkaloids, lycorenine, homolycorine, and pluviine have been interrelated chemically and their steric structures elucidated. The absolute configurations of these alkaloids are also discussed.

The structures of hippeastrine and tazettine have been confirmed by conversion into lycorine β-methiodide and epihæmanthamine methiodide, respectively.

KONDO and IKEDA,[1,2] studying the hydrogenation of lycorenine, $C_{18}H_{23}O_4N$ (II; R = OH), an alkaloid isolated from bulbs of *Lycoris radiata* of the *Amaryllidaceae*, concluded that with Adams catalyst in acetic acid it gave two epimeric products, $C_{18}H_{25}O_3N$, which they called lævorotatory and dextrorotatory " desoxydihydro-R-lycorenine," where R denoted formation of a new ring; when palladium–charcoal was used they obtained in addition a third base which they named " desoxydihydrolycorenine; " this was assigned the formula, $C_{18}H_{25}O_3N,H_2O$, although the assumed water of crystallisation could not be removed even under drastic conditions.

Since both lævorotatory and dextrorotatory " desoxydihydro-R-lycorenines " were also obtained by hydrogenation of deoxylycorenine, which was originally obtained by electrolytic reduction [2] of lycorenine and later shown to be identical with anhydrotetrahydrohomolycorine [3] (II; R = H), they must be represented by the formulæ (I and III; R = H_2; or *vice versa*). Accordingly the lævorotatory and the dextrorotatory bases are now renamed α- and β-deoxydihydrolycorenine,* respectively.

On hydrogenation of *O*-acetyl-lycorenine, on the other hand, Kondo and Ikeda [2] isolated exclusively a product designated " acetyldesoxydihydrolycorenine," $C_{18}H_{21}O_3NAc,H_2O$, which gave on alkaline hydrolysis the above mentioned " desoxydihydrolycorenine."

* It will be shown that the compounds of the α-series have a *cis*-fused perhydroindole ring system as in α-dihydrocaranine, and those of the β-series a *trans*-fused one as in β-dihydrocaranine. In view of this, it is preferable to change the prefix α in dihydro-α-deoxylycorenine used provisionally [4] for the dextrorotatory base to β, as here.

[1] Kondo and Ikeda, *Ber.*, 1940, **73**, 867.
[2] Kondo and Ikeda, *Ann. Report ITSUU Lab.*, 1952, **3**, 55.
[3] Kitagawa, Taylor, Uyeo, and Yajima, *J.*, 1955, 1066.
[4] Uyeo and Yajima, *J.*, 1955, 3392.

" Acetyldesoxydihydrolycorenine " and " desoxydihydrolycorenine " can now be formulated, in accord with the structure of *O*-acetyl-lycorenine (V; R = CHO, R′ = Ac), as (IV or VII; R = CH_2·OH, R′ = OAc, R″ = H) and (IV or VII; R = CH_2·OH, R′ = OH, R″ = H), respectively. In confirmation, tetrahydrohomolycorine (V; R = CH_2·OH, R′ = H) gave as the only isolatable hydrogenation product the expected hexahydrohomolycorine which was identical with Kondo's " desoxydihydrolycorenine." Since the hexahydrohomolycorine was convertible by acid into α-deoxydihydrolycorenine (I; R = H_2), it seemed preferable to rename Kondo's " acetyldesoxydihydrolycorenine " and " desoxydihydrolycorenine " as α-*O*-acetylhexahydrohomolycorine (IV; R = CH_2·OH, R′ = OAc, R″ = H) and α-hexahydrohomolycorine (IV; R = CH_2·OH, R′ = OH, R″ = H) respectively.

Hydrogenation of di-*O*-acetyltetrahydrohomolycorine (V; R = CH_2·OAc, R′ = Ac) gave, as was the case with acetyl-lycorenine, exclusively α-di-*O*-acetylhexahydrohomolycorine (IV; R = CH_2·OAc, R′ = OAc, R″ = H), identical with the product of acetylation of α-hexahydrohomolycorine (IV; R = CH_2·OH, R′ = OH, R″ = H). The same diacetate was also obtained by acetolysis of α-deoxydihydrolycorenine (I; R = H_2), although Kondo and Ikeda reported the isolation of the monoacetyl derivative (IV; R = CH_2·OH, R′ = OAc, R″ = H), identical with the product of hydrogenation of *O*-acetyl-lycorenine, probably owing to partial hydrolysis during their working up of the diacetate originally formed.

Reinvestigation of the acetolysis of β-deoxydihydrolycorenine (III; R = H_2) yielded the product obtained by Kondo and Ikeda who assigned to it the molecular formula $C_{20}H_{27}O_4N,H_2O$ containing one acetyl group. Our analytical values were, however, in accord with the formula, $C_{22}H_{31}O_6N$, containing two acetyl groups. Alkaline hydrolysis of the acetate, β-di-*O*-acetylhexahydrohomolycorine (VII; R = CH_2·OAc, R′ = OAc, R″ = H) afforded β-hexahydrohomolycorine (VII; R = CH_2·OH, R′ = OH, R″ = H), which reverted to β-deoxydihydrolycorenine (III; R = H_2) on treatment with dilute sulphuric acid.

Boit, Paul, and Stender [5] reported previously that homolycorine, $C_{18}H_{21}O_4N$ (II; R = O), gave, on hydrogenation with Adams catalyst in ethanol, a dihydrohomolycorine, m. p. 188°, together with a tetrahydro-derivative, characterised only as its methiodide, m. p. 290—291°. We have shown, however, that hydrogenation of the alkaloid under the conditions similar to those used by Boit *et al.* yielded, as expected, a pair of diastereoisomeric products (I and III; R = O), $C_{18}H_{23}O_4N$, m. p. 188—189° and 158—159°, respectively, which were characterised also as their methiodides, m. ps. 245—246° and 292—293°. The former was probably identical with Boit's dihydrohomolycorine, and the latter with the tetrahydrohomolycorine of the German authors.

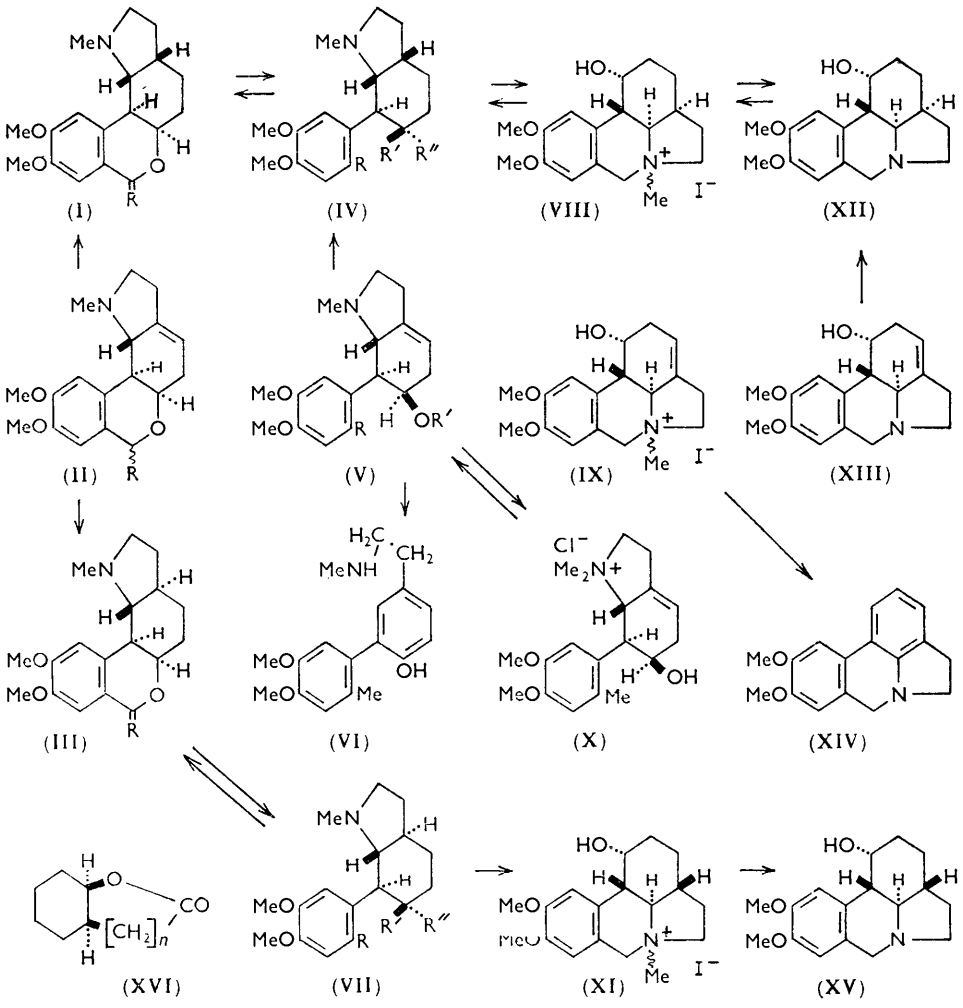
Treatment of the higher-melting dihydrohomolycorine with lithium aluminium hydride yielded α-hexahydrohomolycorine (IV; R = CH_2·OH, R′ = OH, R″ = H), whereas the lower-melting one gave β-hexahydrohomolycorine (VII; R = CH_2·OH, R′ = OH, R″ = H). Thus the stereochemical relation between two pairs of hydrogenation products of lycorenine and homolycorine has been established, and it would be appropriate to give the revised names, α- and β-dihydrohomolycorine, to Boit's dihydrohomolycorine and tetrahydrohomolycorine, respectively.

In order to relate the structure and configuration of lycorenine or homolycorine to those of pluviine [6] (XIII), we converted tetrahydrohomolycorine (V; R = CH_2·OH, R′ = H) into pluviine as follows. Tetrahydrohomolycorine with toluene-*p*-sulphonyl chloride in pyridine furnished a quaternary salt, isolated as its crystalline iodide, m. p. 232—233°, diastereoisomeric with the known pluviine methiodide (IX), m. p. 259—261°, since pyrolysis of the corresponding methochloride afforded pluviine and anhydromethylpseudolycorine [6-8]

[5] Boit, Paul, and Stender, *Chem. Ber.*, 1955, **88**, 133.
[6] Boit, Ehmke, Uyeo, and Yajima, *ibid.*, 1957, **90**, 363.
[7] Uyeo and Yanaihara, *J.*, 1959, 172.
[8] Fales, Giuffrida, and Wildman, *J. Amer. Chem. Soc.*, 1956, **78**, 4145.

(XIV). In this pyrolysis, the possibility of change in structure or configuration other than that at the nitrogen atom was highly improbable, since we have demonstrated that the model compound (V; R = Me, R′ = H), obtained previously by Wolff–Kishner reduction of lycorenine [4] and now named deoxolycorenine, was regenerated from its methochloride (X) by distillation in a high vacuum.

The methiodide, m. p. 259—261°, is now designated pluviine α-methiodide and its diastereoisomer, m. p. 232—233°, pluviine β-methiodide; isomeric pairs have been noted



previously in this series, *e.g.*, lycorine α- and β-methiodide [9] and caranine α- and β-methiodide.[10] This view was confirmed by conversion of α- and β-hexahydrohomolycorine (IV and VII; R = CH_2·OH, R′ = OH, R″ = H) into the corresponding dihydropluviines (XII and XV). Thus α-hexahydrohomolycorine with toluene-*p*-sulphonyl chloride in pyridine, as above, gave α-dihydropluviine β-methiodide, which was obtained with its α-isomer by quaternisation with methyl iodide of α-dihydropluviine which was in turn prepared by hydrogenation of pluviine with Adams catalyst in acetic acid.

Vacuum-pyrolysis of α-dihydropluviine β-methiodide afforded, in a low yield, α-dihydropluviine (XII). From β-hexahydrohomolycorine we obtained by a similar

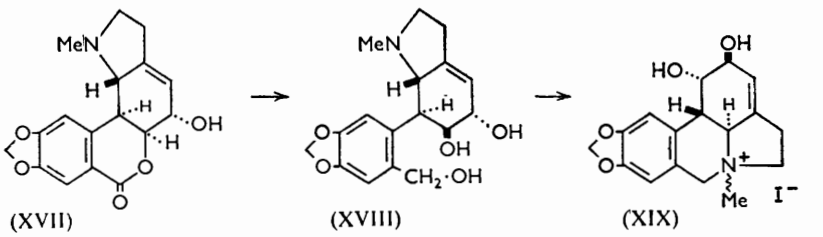
[9] Kondo, Katsura, and Uyeo, *Ber.*, 1938, **71**, 1529.
[10] Warnhoff and Wildman, *J. Amer. Chem. Soc.*, 1957, **79**, 2192.

sequence of reactions a base indistinguishable from the β-dihydropluviine (XV) which was formed by hydrogenation of pluviine in ethanol in the presence of palladium–charcoal.

Emde degradation of pluviine β-methiodide furnished deoxolycorenine (V; R = Me, R′ = H); likewise α-dihydropluviine β-methiodide afforded a base, named α-deoxodihydrolycorenine (IV; R = Me, R′ = OH, R″ = H), identical with the sole product obtained by the hydrogenation of deoxolycorenine with Adams catalyst in acetic acid. Since deoxolycorenine was obtained from lycorenine not only by Wolff–Kishner method but also under mild conditions by desulphurisation with Raney nickel of the thioacetal (V; R = $CH<^{S-CH_2}_{S-CH_2}$, R′ = H), it appears that all the bonds linked to the hydroaromatic ring of deoxolycorenine retained the configurations of those in lycorenine. Accordingly, the configurations of the substituents attached to the hydroaromatic ring of α-deoxodihydrolycorenine (IV; R = Me, R′ = OH, R″ = H) must be identical with those of α-deoxydihydrolycorenine (I; R = H_2), α-hexahydrohomolycorine (IV; R = CH_2·OH, R′ = OH, R″ = H), and α-dihydrohomolycorine (I; R = O).

In an attempt to determine the configuration of the hydroxyl group in deoxolycorenine, we have oxidised it by a modified Oppenauer method [11] and have isolated an optically inactive base, $C_{18}H_{23}O_3N$, whose infrared spectrum exhibited no carbonyl band but a strong absorption in the OH and/or NH stretching region, while the ultraviolet absorption spectrum suggested a somewhat hindered diphenyl grouping. Acetylation of this product yielded a neutral oil which showed *O*- and *N*-acetyl bands in the infrared spectrum. With methyl iodide in acetone it gave an *N*-methyl methiodide, and with dimethyl sulphate in alkali followed by potassium iodide it gave an *ON*-dimethyl methiodide which in contrast to the starting material gave no colour with an alkaline solution of diazotised sulphanilic acid. Thus the base, $C_{18}H_{23}O_3N$, must be 2′-hydroxy-4,5-dimethoxy-2-methyl-5′-(2-methylaminoethyl)biphenyl (VI) which could readily be formed from the originally expected cyclohexenone by elimination of nitrogen and isomerisation of the resulting cyclohexadienone to the energetically more stable phenol.

On the other hand, Oppenauer oxidation of α-deoxodihydrolycorenine yielded as expected, α-deoxodihydrolycorenone (IV; R = Me, R′, R″ = O). α-Deoxodihydrolycorenone reverted to α-deoxodihydrolycorenine on catalytic reduction with Adams catalyst in



acetic acid, while with lithium aluminium hydride or sodium borohydride it was reduced to an epimer, α-deoxodihydroepilycorenine (IV; R = Me, R′ = H, R″ = OH). Since catalytic hydrogenation of cyclohexanones in acid solution usually gives axial hydroxy-compounds and metal-hydride reduction equatorial ones, we assigned to the hydroxyl

[11] Woodward, Wendler, and Brutschy, *J. Amer. Chem. Soc.*, 1945, **67**, 1425.

group in α-deoxodihydrolycorenine the axial conformation and to that in its epimer the equatorial conformation. Accordingly, the benzene ring linked to the hydroaromatic ring in lycorenine or homolycorine must be equatorial, since the oxygen atom linked to the cyclohexene ring of the respective alkaloids must be axial, as is that of α-deoxodihydrolycorenine, and *trans*-fusion of two six-membered rings through two vicinal axial linkages is sterically impossible. The C–N bond on the cyclohexene ring in lycorenine or homolycorine must be equatorial, otherwise a pair of diastereoisomeric dihydro-derivatives of deoxylycorenine or homolycorine cannot be produced by saturation of the ethylenic bond in the respective molecules. Thus lycorenine and homolycorine must have the structures and configurations shown in (II; R = OH and O, respectively). Moreover, the steric structure of pluviine can be represented by the formula (XIII), if we exclude the most unlikely possibility of stereochemical change during conversion of tetrahydrohomolycorine into pluviine.

The structure and configuration of pluviine thus deduced are identical with those of caranine [10,12] except for the difference between two methoxyl groups and a methylenedioxy-group. Thus the stereochemical behaviour of the two alkaloids toward hydrogenation ought to be very similar. Since both α- and β-dihydropluviine were prepared from pluviine under the conditions used for the preparation of α- and β-dihydrocaranine [10] from caranine, it followed that the configurations of the former pair must be comparable with those of the latter which have been elucidated by Takeda and Kotera.[13] α- and β-Dihydropluviine can be represented, therefore, by (XII) and (XV), respectively.

As to the absolute configuration of lycorenine, homolycorine, and pluviine, strong evidence can be gained from molecular-rotation considerations. According to the Hudson's lactone rule extended by Klyne,[14] lactones of the general formula (XVI) are more positive in molecular rotation that the corresponding hydroxy-acids or their equivalents. If we can apply the rule to homolycorine and related compounds containing six-membered lactone rings, all the values given in the annexed Table are consistent with the assumption that homolycorine has the absolute configuration represented by the formula (II; R = O).

Consequently lycorenine and pluviine have absolute configurations (II; R = OH) and

Molecular rotations of homolycorine and related compounds.

Compound	$[M]_D$	$\Delta[M]_D$
Homolycorine	+268°	
Tetrahydrohomolycorine	−322	+590°
Deoxolycorenine	−445	+713
Lycorenine oxime	−542	+810
α-Dihydrohomolycorine	−164	
α-Hexahydrohomolycorine	−234	+70
α-Deoxodihydrolycorenine	−170	+6
β-Dihydrohomolycorine	−85	
β-Hexahydrohomolycorine	−143	+58

(XIII), respectively, which are comparable with those of lycorine and caranine, reported in the preceding paper.[15]

In connection with the studies mentioned above, we have converted hippeastrine [16] and tazettine,[17,18] two alkaloids of the *Amaryllidaceae*, into lycorine and epihæmanthamine methiodide, respectively.

For hippeastrine, $C_{17}H_{17}O_5N$, Boit [16] proposed structure (XVII), in analogy with homolycorine, since it contains a δ-lactone along with a methylenedioxy- and an acetylatable hydroxy-group. To prove this structure, we treated tetrahydrohippeastrine (XVIII),

[12] Takeda, Kotera, and Mizukami, *J. Amer. Chem. Soc.*, 1958, **80**, 2562.
[13] Takeda and Kotera, *Chem. and Ind.*, 1956, 347; *Pharm. Bull.* (*Japan*), 1957, **5**, 234.
[14] Klyne, *Chem. and Ind.*, 1954, 1198.
[15] Nakagawa and Uyeo, preceding paper.
[16] Boit, *Chem. Ber.*, 1956, **89**, 1129, 2093, 2462.
[17] Ikeda, Taylor, Tsuda, Uyeo, and Yajima, *J.*, 1956, 4749.
[18] Irie, Tsuda, and Uyeo, *J.*, 1959, 1446.

the product of reduction of hippeastrine with lithium aluminium hydride, with toluene-*p*-sulphonyl chloride in pyridine as in the conversion of homolycorine into pluviine β-methiodide: we obtained lycorine β-methiodide (XIX). Since the structure and absolute configuration of lycorine [15] have been firmly established, hippeastrine is represented by the formula (XVII).

As reported in a previous paper,[17] tazettine (XX) can be converted into tazettadiol (XXI) which appeared to serve as a useful precursor to the hæmanthamine ring system.[19] An attempt was therefore made, but without success, to convert tazettadiol into hæmanthamine methiodide or a stereoisomer by toluene-*p*-sulphonyl chloride and pyridine as above. On the other hand, thionyl chloride in pyridine was found suitable as a reagent to quaternise the nitrogen atom of tazettadiol with the benzyl group in the same molecule. The product thus obtained in a good yield was shown to be identical with epihæmanthamine methiodide (XXII) in which the secondary hydroxyl group is epimeric with that of hæmanthamine.

Experimental

Ultraviolet absorption spectra were determined for 95% EtOH solutions, rotations are for EtOH solutions, and infrared spectra refer to Nujol mulls unless otherwise stated. The light petroleum used had b. p. 45—65°.

Hydrogenation of Lycorenine.—Catalytic hydrogenation of lycorenine (1 g.) with Adams catalyst (0·3 g.) in acetic acid (10 ml.) was carried out as described by Kondo and Ikeda.[2] The products were separated by chromatography in benzene–light petroleum (1 : 2) over alumina, yielding from the first fractions α-deoxydihydrolycorenine (0·3 g.), needles (from methanol), m. p. 127—128°, $[\alpha]_D$ −15·3° (*c* 1·5), $\lambda_{max.}$ 285 mμ (log ε 3·55) (Found: C, 70·8; H, 8·2. Calc. for $C_{18}H_{25}O_3N$: C, 71·3; H, 8·3%), and from the second fractions β-deoxydihydrolycorenine (0·35 g.), needles (from acetone), m. p. 168—169°, $[\alpha]_D$ +19·9° (*c* 0·3), $\lambda_{max.}$ 285 mμ (log ε 3·55) (Found: C, 71·6; H, 8·2%).

α-Hexahydrohomolycorine (IV; R = CH_2·OH, R′ = OH, R″ = H).—Tetrahydrohomolycorine (0·5 g.) in acetic acid (15 ml.) was shaken with Adams catalyst (0·1 g.) in hydrogen for 5 hr. Evaporation of the filtered solution *in vacuo* and isolation of the product with ether after basification with aqueous ammonia yielded α-hexahydrohomolycorine (0·45 g.), plates (from acetone), m. p. 175—176°, $[\alpha]_D$ −73·0° (*c* 0·6), $\lambda_{max.}$ 281 mμ (log ε 3·45) (Found: C, 67·3; H, 8·2. Calc. for $C_{18}H_{27}O_4N$: C, 67·3; H, 8·5%), identical in m. p. and mixed m. p. with Kondo's desoxydihydrolycorenine.[2]

α-Di-O-acetylhexahydrohomolycorine (IV; R = CH_2·OAc, R′ = OAc, R″ = H).—(*a*) Di-*O*-acetyltetrahydrohomolycorine [3] (0·61 g.) in acetic acid (20 ml.) was hydrogenated over Adams catalyst (0·11 g.) for 5 hr. Working up in the usual manner and crystallisation from ether gave *α-di-O-acetylhexahydrohomolycorine* (0·6 g.), as needles, m. p. 101—102°, $[\alpha]_D$ −34·5° (*c* 0·55), $\lambda_{max.}$ 281 mμ (log ε 3·43), $\nu_{max.}$ 1733 cm.$^{-1}$ (Found: C, 65·4; H, 7·7; N, 3·8; Ac, 20·9. $C_{22}H_{31}O_6N$ requires C, 65·2; H, 7·7; N, 3·5; 2Ac, 21·2%).

(*b*) α-Deoxydihydrolycorenine (0·11 g.) was kept in acetic anhydride (6 ml.) and sulphuric acid (0·1 ml.) at room temperature overnight. After addition of water (10 ml.), the mixture was basified with aqueous ammonia and extracted with chloroform. Evaporation of the extract gave a residue (55 mg.) which was filtered through alumina (1 g.) in benzene to furnish α-di-*O*-acetylhexahydrohomolycorine, m. p. and mixed m. p. 101—102°.

(*c*) α-Hexahydrohomolycorine (50 mg.) in acetic anhydride (3 ml.) containing sulphuric acid (0·1 ml.) was set aside at room temperature for 24 hr. The acetic anhydride was decomposed with water, and the mixture basified with aqueous sodium carbonate and extracted with ether, to give α-di-*O*-acetylhexahydrohomolycorine (25 mg.), m. p. and mixed m. p. 101—102°.

(*d*) α-*O*-Acetylhexahydrohomolycorine [2] (50 mg.) obtained by hydrogenation of *O*-acetyllycorenine was treated with acetic anhydride (3 ml.) containing sulphuric acid (0·1 ml.) at room temperature for 24 hr. The resulting acetate (30 mg.) was identical with α-di-*O*-acetylhexahydrohomolycorine obtained as above.

β-Diacetylhexahydrohomolycorine (VII; R = CH_2·OAc, R′ = OAc, R″ = H).—β-Deoxydihydrolycorenine (0·12 g.) was heated in acetic anhydride (3 ml.) at 50—55° for 1·5 hr. After dilution with water, the mixture was basified with aqueous ammonia and extracted with ether.

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

The extract gave on concentration β-di-*O*-acetylhexahydrohomolycorine (90 mg.) as prisms (from ether–light petroleum), m. p. 122—123°, $[\alpha]_D$ −36·5° (*c* 0·5), $\lambda_{max.}$ 281 mμ (log ε 3·42), $\nu_{max.}$ 1737, 1724 cm.$^{-1}$ (OAc) (Found: C, 65·5; H, 7·7; Ac, 20·6%), identical with Kondo and Ikeda's sample obtained by the same procedure.[2]

β-Hexahydrohomolycorine (VII; R = CH_2·OH, R′ = OH, R″ = H).—β-Di-*O*-acetylhexahydrohomolycorine (40 mg.) and potassium hydroxide (1 g.) were refluxed in methanol (10 ml.) for 2 hr. Isolation of the product in the usual manner and crystallisation from acetone gave *β-hexahydrohomolycorine* (30 mg.) as prisms, m. p. 165°, $[\alpha]_D$ −44·5° (*c* 0·83), $\lambda_{max.}$ 281 mμ (log ε 3·45) (Found: C, 67·3; H, 8·4; N, 4·4. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5; N, 4·4%).

Heating this (50 mg.) in 5% aqueous sulphuric acid (5 ml.) on a water-bath for 2 hr. converted it into β-deoxydihydrolycorenine (35 mg.), m. p. and mixed m. p. 168—169°.

Hydrogenation of Homolycorine.—Homolycorine (1·1 g.) in ethanol (30 ml.) was shaken with Adams catalyst (0·3 g.) in hydrogen for 5 hr. Evaporation of the filtered solution and crystallisation from acetone afforded α-dihydrohomolycorine (0·33 g.) as plates, m. p. 188–189°, $[\alpha]_D$ −51·9° (*c* 0·65), $\lambda_{max.}$ 226, 267, and 302 mμ (log ε 4·32, 3·92, and 3·70), $\nu_{max.}$ 1698 cm.$^{-1}$ (lactone) (Found: C, 67·9; H, 7·3; N, 4·3. Calc. for $C_{18}H_{23}O_4N$: C, 68·1; H, 7·3; N, 4·4%). The methiodide formed plates (from ethanol), m. p. 245—246° (decomp.), $[\alpha]_D$ −10·8° (*c* 0·37 in 50% aqueous EtOH). The methopicrate had m. p. 218° (decomp.) (from methanol).

The mother-liquors from α-dihydrohomolycorine were combined and evaporated to dryness, and the residue was dissolved in ether. The material remaining undissolved gave, on crystallisation from acetone, an additional crop (50 mg.) of α-dihydrohomolycorine. Concentration of the ethereal solution and crystallisation from ether gave *β-dihydrohomolycorine* (0·35 g.) as plates, m. p. 158—159°, $[\alpha]_D$ −26·9° (*c* 0·85), $\lambda_{max.}$ 227, 268, and 303 mμ (log ε 4·32, 3·91, and 3·69), $\nu_{max.}$ 1715 cm.$^{-1}$ (lactone) (Found: C, 67·9; H, 7·2; N, 4·1%). The methiodide formed long prisms (from methanol), m. p. 292—293° (decomp.), $[\alpha]_D$ −25·3° (*c* 0·35 in 50% aqueous EtOH). The *methopicrate* had m. p. 241—242° (decomp.) (from methanol) (Found: C, 53·2; H, 5·1; N, 10·0. $C_{25}H_{28}O_{11}N_4$ requires C, 53·6; H, 5·1; N, 10·0%).

Reduction of α- and β-Dihydrohomolycorine by Lithium Aluminium Hydride.—α-Dihydrohomolycorine (70 mg.) and lithium aluminium hydride (100 mg.) were refluxed in dry ether (30 ml.) for 5 hr. After addition of moist ether and filtration of the precipitate, the filtrate and washings were combined and evaporated, to give α-hexahydrohomolycorine (50 mg.), m. p. and mixed m. p. 175—176°.

In a similar way, β-dihydrohomolycorine (80 mg.) was converted into β-hexahydrohomolycorine (30 mg.), m. p. and mixed m. p. 165°.

Conversion of Tetrahydrohomolycorine into Pluviine β-Methiodide.—Toluene-*p*-sulphonyl chloride (1·15 g.) was added to a solution of tetrahydrohomolycorine (1·6 g.) in dry pyridine (20 ml.), and the whole set aside at room temperature overnight. The mixture was evaporated to dryness under reduced pressure, and the residue passed in water through a column of Amberlite I.R.A.-400 resin (OH-form). The column was washed with water, and the combined eluate and washings were washed with ether several times to remove pyridine, then acidified with dilute hydriodic acid, filtered, and concentrated under reduced pressure, yielding *pluviine β-methiodide*, which on crystallisation from methanol formed prisms (0·98 g.), m. p. 231—232°, $[\alpha]_D$ +38·2° (*c* 0·9 in H_2O) (Found: C, 50·6; H, 5·5; N, 3·4. $C_{18}H_{24}O_3NI$ requires C, 50·4; H, 5·6; N, 3·3%). The *methopicrate* prepared in water formed yellow prisms (from ethanol), m. p. 234—235° (Found: C, 54·5; H, 5·0; N, 10·6. $C_{24}H_{26}O_{10}N_4$ requires C, 54·5; H, 4·9; N, 10·6%).

For comparison, *pluviine α-methopicrate* was prepared from pluviine α-methiodide and picric acid in hot water, forming scales, m. p. 169—171° (from ethanol) (Found: C, 54·5; H, 4·9; N, 10·7%).

The *β-methotoluene-*p*-sulphonate* was prepared by passage of an aqueous solution of the β-methiodide through a column of Amberlite I.R.A-400 resin (OH-form) followed by neutralisation of the eluate and washings with toluene-*p*-sulphonic acid and concentration to dryness. Recrystallisation from acetone–ethanol gave prisms, m. p. 198—200° (Found: C, 63·6; H, 6·5; N, 2·9. $C_{25}H_{31}O_6NS$ requires C, 63·4; H, 6·6; N, 3·0%).

Vacuum-pyrolysis of Pluviine β-Methochloride.—Pluviine β-methiodide (0·8 g.) was converted into its methochloride by shaking its aqueous solution with an excess of silver chloride. The filtered solution was evaporated to dryness under reduced pressure and the resulting chloride (0·6 g.) immediately distilled at 220—260° (bath)/0·01—0·005 mm. The distillate (0·25 g.) was taken up in dilute hydrochloric acid, washed with ether, basified with aqueous ammonia,

and extracted with chloroform. Evaporation of the chloroform left a residue which was chromatographed in benzene over alumina. Elution with benzene afforded anhydromethylpseudolycorine (60 mg.), needles (from methanol), m. p. and mixed m. p. 174—176° (Found: C, 76·1; H, 6·4; N, 5·3. Calc. for $C_{17}H_{17}O_2N$: C, 76·4; H, 6·4; N, 5·2%). Elution with chloroform yielded pluviine (80 mg.), m. p. and mixed m. p. 224—226° (from methanol), $[\alpha]_D$ −146·3° (*c* 0·8) (Found: C, 71·0; H, 7·2; N, 5·0. Calc. for $C_{17}H_{21}O_3N$: C, 71·1; H, 7·4; N, 4·9%). The infrared spectrum was identical with that of authentic pluviine.

α-Dihydropluviine.—Pluviine (0·26 g.) in acetic acid (20 ml.) was shaken in hydrogen in the presence of Adams catalyst (40 mg.) for 30 min. Evaporation of the filtered solution under reduced pressure yielded a residue which was taken up in 3% aqueous hydrochloric acid, washed with benzene, basified with aqueous ammonia, and extracted with benzene. Concentration of the benzene gave *α-dihydropluviine* which on crystallisation from acetone formed needles, m. p. 130—133°, or cubes, m. p. 136—139° (dimorphous, since they were interconvertible on seeding of a concentrated solution of one form in acetone with the other), $[\alpha]_D$ −87·2° (*c* 0·92), $\lambda_{max.}$ 232 and 282 mμ (log ε 3·88 and 3·55) (Found: C, 70·6; H, 8·0; N, 4·8. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 8·0; N, 4·8%).

α-Dihydropluviine α- and β-Methiodide.—α-Dihydropluviine (82 mg.) was heated in methanol (1 ml.) with methyl iodide (0·5 ml.) on the water-bath for 4 hr. The mixture was evaporated to dryness and the residue crystallised from ethanol, to give *α-dihydropluviine α-methiodide* (40 mg.) as needles, m. p. 219—221°, raised to 223—224° on repeated crystallisations, $[\alpha]_D$ −74·4° (*c* 1·0 in H_2O) (Found: C, 49·3; H, 6·2. $C_{18}H_{26}O_3NI,\frac{1}{2}H_2O$ requires C, 49·1, H, 6·1%).

The mother-liquors from the crystallisations of the α-methiodide were evaporated to dryness and passed in acetone through a column of alumina. Elution with acetone yielded *α-dihydropluviine β-methiodide* (60 mg.) which formed prisms (from ethanol), m. p. 136—139°, raised on drying *in vacuo* to 231—233°, $[\alpha]_D$ −43·2° (*c* 0·92 in H_2O) [Found, for a sample (m. p. 136—139°): C, 48·2; H, 6·2. $C_{18}H_{26}O_3NI,H_2O$ requires C, 48·1; H, 6·2%. Found, for a sample dried *in vacuo* (m. p. 231—233°): C, 48·8; H, 6·1. $C_{18}H_{26}O_3NI,\frac{1}{2}H_2O$ requires C, 49·1; H, 6·1%]. The m. p. was depressed on admixture with α-dihydropluviine α-methiodide and the infrared spectrum was not identical with that of the latter.

α-Dihydropluviine β-Methiodide from α-Hexahydrohomolycorine.—α-Hexahydrohomolycorine (0·3 g.) and toluene-*p*-sulphonyl chloride (0·23 g.) in dry pyridine (10 ml.) were kept at room temperature overnight. The mixture was evaporated to dryness under reduced pressure and the residue, dissolved in water, was passed through a column of Amberlite I.R.A.-400 resin (OH-form). The combined eluate and washings were washed repeatedly with ether to remove pyridine and then neutralised with hydriodic acid. The solution was filtered, evaporated to dryness, and crystallised from chloroform and ethanol, to give α-dihydropluviine β-methiodide as prisms, m. p. and mixed m. p. 231—233° (after drying *in vacuo*), $[\alpha]_D$ −45·5° (*c* 0·8 in H_2O) (Found: C, 49·7; H, 6·2. Calc. for $C_{18}H_{26}O_3NI,\frac{1}{2}H_2O$: C, 49·1; H, 6·1%). The infrared spectrum was identical with that of the same compound derived from α-dihydropluviine.

Vacuum-pyrolysis of α-Dihydropluviine β-Methochloride.—α-Dihydropluviine β-methiodide (0·1 g.) in methanol was shaken with freshly prepared silver chloride. After removal of the silver salts, the solution was evaporated to dryness and distilled at 200—260°/0·01—0·002 mm. The distillate, dissolved in chloroform, was extracted with 3% hydrochloric acid, and the aqueous layer was washed with ether, basified with aqueous ammonia, and extracted with chloroform. The chloroform was removed and the residue (10 mg.) passed in benzene through alumina. The column was washed with benzene and benzene–chloroform (9 : 1) and eluted with chloroform. The concentrated eluate was crystallised from acetone, giving α-dihydropluviine as prisms (3 mg.), m. p. and mixed m. p. 137—138°.

β-Dihydropluviine.—Pluviine (40 mg.) was hydrogenated in ethanol (10 ml.) with 2·5% palladium–charcoal (0·2 g.) for 1 hr. After isolation in the usual way, the product was chromatographed in benzene over alumina. Elutions with benzene and benzene–chloroform (9 : 1) gave no crystalline substance. Elution with chloroform yielded *β-dihydropluviine* (20 mg.) as prisms, m. p. 176—178° (from acetone), $[\alpha]_D$ −168° (*c* 0·8) (Found: C, 70·2; H, 8·1; N, 5·1. $C_{17}H_{23}O_3N$ requires C, 70·6; H, 8·0; N, 4·8%). This was not identical with α-dihydropluviine in mixed m. p. and infrared spectrum.

β-Dihydropluviine from β-Hexahydrohomolycorine.—β-Hexahydrohomolycorine (0·3 g.) and toluene-*p*-sulphonyl chloride (0·23 g.) were allowed to react in pyridine (10 ml.) as for tetrahydrohomolycorine. After working up, *β-dihydropluviine methiodide* (0·12 g.) crystallised

from methanol in prisms, m. p. 265—267°, $[\alpha]_D$ −30·7° (*c* 0·62 in H_2O) (Found: C, 50·0; H, 6·1; N, 3·2. $C_{18}H_{26}O_3NI$ requires C, 50·1; H, 6·1; N, 3·3%).

β-Pluviine methiodide (0·1 g.) thus obtained was converted into its chloride in the usual way and distilled at 200—240°/0·01—0·002 mm., to give a distillate which was dissolved in benzene and passed through alumina. A chloroform eluate afforded prisms (4 mg.), m. p. 169—173°, identified as β-dihydropluviine by m. p. and mixed m. p.

Deoxolycorenine (V; R = Me, R′ = H).—(*a*) A modified Wolff–Kishner reduction of lycorenine has been reported earlier,[4] but the following mild conditions gave a better yield of the product.

Lycorenine (1 g.), 100% hydrazine hydrate (10 ml.), and potassium hydroxide (7 g.) were heated in diethylene glycol (20 ml.) at 150—155° for 3 hr. Then water (40 ml.) was added and the mixture extracted with ether which was washed with water, dried, and evaporated to dryness, giving deoxolycorenine (850 mg.) (from ether–light petroleum), m. p. 128—129°.

(*b*) A mixture of lycorenine (1·1 g.), ethanedithiol (1·8 ml.), and boron trifluoride–ether complex (2 ml.) was heated on a water-bath for 10 min. After being kept at room temperature overnight, the mixture was concentrated under reduced pressure and the residue washed 3 times with ether and then crystallised from methanol, to give a lycorenine ethylene dithioacetal boron trifluoride complex (1·55 g.) as prisms, m. p. 230° (decomp.). A solution of the complex in methanol (5 ml.) and water (20 ml.) was basified with aqueous ammonia and extracted with chloroform which gave on evaporation *lycorenine ethylene dithioacetal* (1 g.), m. p. 168—169° (from ethanol), $[\alpha]_D$ +17·2° (*c* 1·1) (Found: C, 60·9; H, 6·8; N, 3·5. $C_{20}H_{27}O_3NS_2$ requires C, 61·1; H, 7·0; N, 3·6%).

The thioacetal (0·6 g.) and Raney nickel (2 g.) were refluxed in ethanol (30 ml.) for 5 hr. Evaporation of the filtered solution gave an oil (420 mg.) which was taken up in ether and converted into the picrate (310 mg.) with an excess of ethereal picric acid. Crystallisation of the precipitated picrate afforded α-deoxodihydrolycorenine picrate (see below), m. p. and mixed m. p. 231—232°.

An ethereal solution of the mother-liquor from the filtration of the picrate was washed with aqueous sodium hydroxide to remove the excess of reagent, dried, and evaporated to give an oil (0·17 g.), which was chromatographed in benzene over alumina (3 g.). A benzene eluate gave deoxolycorenine (80 mg.), m.p. 128—129° (from ether–light petroleum), identical in m. p. and mixed m. p. with a sample derived by the method (*a*) above.

Vacuum-pyrolysis of Deoxolycorenine Methochloride.—Deoxolycorenine (0·18 g.) and methyl iodide (1 g.) in methanol (3 ml.) were refluxed for 2 hr., to give the *methiodide* as plates (0·2 g.), m. p. 244° (decomp.) (from methanol) (Found: C, 51·2; H, 6·1; N, 3·3. $C_{19}H_{28}O_3NI$ requires C, 51·2; H, 6·3; N, 3·1%). The methiodide (0·2 g.) was shaken with silver chloride (2 g.) in 50% aqueous methanol (10 ml.) for 1 hr. Evaporation of the filtered solution to dryness and distillation of the residue in an oil-bath at 220—240°/0·01—0·005 mm. gave a sublimate (70 mg.) which crystallised on trituration with ether, to give deoxolycorenine, m. p. and mixed m. p. 128—129°.

Emde Degradation of Pluviine β-Methiodide.—Pluviine β-methochloride, prepared from pluviine β-methiodide (0·3 g.) and silver chloride, was dissolved in water (4 ml.) and heated with sodium amalgam (15 g.) on a water-bath for 10 hr. After cooling, the separated oil was taken up in ether which was washed with water, dried, and evaporated to an oil. Crystallisation from ether gave prisms (60 mg.), m. p. 126—127° alone or mixed with deoxolycorenine (Found: C, 71·4; H, 8·3; N, 4·7. Calc. for $C_{18}H_{25}O_3N$: C, 71·3; H, 8·3; N, 4·6%).

Emde Degradation of α-Dihydropluviine β-Methiodide.—α-Dihydropluviine β-methiodide (80 mg.) was subjected to the Emde degradation in a similar manner to that described for the degradation of pluviine β-methiodide. Crystallisation of the product from ether gave prisms (25 mg.), m. p. 98—99°, identical in m. p. and mixed m. p. with α-deoxodihydrolycorenine.

2′-Hydroxy-4,5-dimethoxy-2-methyl-5′-(2-methylaminoethyl)biphenyl (VI).—A solution of deoxolycorenine (0·3 g.), benzophenone (0·9 g.), and potassium t-butoxide (0·5 g.) in dry benzene (30 ml.) was refluxed for 6 hr. After cooling, the mixture was extracted with 5% hydrochloric acid, and the aqueous layer washed with ether, basified with aqueous ammonia, and extracted with ether. The ethereal extract gave on evaporation *2′-hydroxy-4,5-dimethoxy-2-methyl-5′-(2-methylaminoethyl)biphenyl* as prisms (0·2 g.) (from acetone), m. p. 133—134°, $[\alpha]_D$ 0 (*c* 1·3), $\lambda_{max.}$ 285 mμ (log ε 3·92), $\nu_{max.}$ 3300 cm.$^{-1}$ (OH and NH) (Found: C, 71·5; H, 7·7; N, 4·5. $C_{18}H_{23}O_3N$ requires C, 71·7; H, 7·7; N, 4·7%).

The biphenyl gave with acetic anhydride and sodium acetate an oily diacetate whose infrared spectrum showed carbonyl bands at 1757 (OAc) and 1639 cm.$^{-1}$ (NAc).

The N-*methyl methiodide* was prepared with methyl iodide in boiling acetone and formed prisms (from acetone), m. p. 228° (decomp.), $\lambda_{max.}$ 285 mμ (log ε 3·90) (Found: C, 52·6; H, 6·2. $C_{20}H_{28}O_3NI$ requires C, 52·5; H, 6·2%). The ON-*dimethyl methiodide* was obtained by the action of dimethyl sulphate in alkali followed by treatment with potassium iodide. It formed prisms (from acetone), m. p. 212—213° (decomp.), $\lambda_{max.}$ 285 mμ (log ε 3·90) (Found: C, 53·3; H, 6·3; N, 3·1; OMe, 19·4. $C_{21}H_{30}O_3NI$ requires C, 53·5: H, 6·4; N, 3·0; 3OMe, 19·7%).

α-*Deoxodihydrolycorenine* (IV; R = Me, R′ = OH, R″ = H).—Deoxolycorenine (1·7 g.) in acetic acid (20 ml.) was shaken in hydrogen in the presence of Adams catalyst (0·12 g.) for 3 hr. Working up in the usual manner gave α-*deoxodihydrolycorenine* (1·6 g.) as plates, m. p. 98° (from ether), $[\alpha]_D$ −55·3° (*c* 1·63) (Found: C, 70·4; H, 8·8; N, 4·3. $C_{18}H_{27}O_3N$ requires C, 70·8; H, 8·9; N, 4·6%). The *picrate* formed needles (from methanol), m. p. 232° (decomp.) (Found: C, 54·0; H, 5·8; N, 10·6. $C_{24}H_{30}O_{10}N_4$ requires C, 53·9; H, 5·7; N, 10·5%). The *methiodide* formed plates (from methanol), m. p. 216° (decomp.) (Found: C, 51·3; H, 7·0. $C_{19}H_{30}O_3NI$ requires C, 51·0; H, 6·8%).

α-*Deoxodihydrolycorenone* (IV; R = Me, R′, R″ = O).—A solution of deoxodihydrolycorenine (0·5 g.), benzophenone (1 g.), and potassium t-butoxide (0·7 g.) in dry benzene (50 ml.) was heated under reflux for 5 hr. After cooling, the mixture was extracted with 2% hydrochloric acid which was washed with ether, basified with aqueous ammonia, and extracted with ether. Evaporation of the ethereal extract yielded α-deoxodihydrolycorenone as an oil (0·4 g.) which was immediately converted into its *picrate* (0·55 g.), needles (from methanol), m. p. 148°, $\nu_{max.}$ 1727 cm.$^{-1}$ (CO) (Found: C, 54·0; H, 5·4; N, 10·6. $C_{24}H_{28}O_{10}N_4$ requires C, 54·1; H, 5·3; N, 10·5%). The base, regenerated by passing the picrate through alumina, is an oil, $[\alpha]_D$ +95·9° (*c* 0·83).

The *oxime hydrochloride* was prepared in the usual manner and crystallised from methanol in plates, m. p. 256—257° (decomp.), $[\alpha]_D$ +16·4° (*c* 0·24 in 50% aqueous EtOH) (Found: C, 60·6; H, 7·4; N, 7·5. $C_{18}H_{27}O_3N_2Cl$ requires C, 60·9; H, 7·8; N, 7·9%).

Hydrogenation of α-Deoxodihydrolycorenone with Adams Catalyst.—α-Deoxodihydrolycorenone (120 mg.) in acetic acid (10 ml.) was hydrogenated with Adams catalyst (100 mg.) for 5 hr. The product was isolated in the usual way and converted into the picrate (60 mg.), m. p. 231—232° (decomp.), identified as α-deoxodihydrolycorenine picrate by mixed m. p. and infrared spectrum.

Reduction of α-Deoxodihydrolycorenone by Lithium Aluminium Hydride.—α-Deoxodihydrolycorenone (0·3 g.) and lithium aluminium hydride (0·2 g.) in dry ether (100 ml.) were refluxed for 3 hr. After addition of moist ether and filtration of the precipitate, the ethereal solution was concentrated to 10 ml. and an excess of a saturated ethereal solution of picric acid was added. A yellow precipitate (0·3 g.) formed was collected and crystallised from methanol, to give α-*deoxodihydroepilycorenine picrate*, m. p. 215—216° (decomp.), depressed to 200—205° on admixture with α-deoxodihydrolycorenine picrate (Found: C, 53·9; H, 5·7; N, 10·3. $C_{24}H_{30}O_{10}N_4$ requires C, 53·9; H, 5·7; N, 10·5%). The infrared spectrum was not identical with that of α-deoxodihydrolycorenine picrate. The base regenerated from the picrate was an oil, $[\alpha]_D$ +16·0° (*c* 0·88).

The same compound was obtained by the reduction of α-deoxodihydrolycorenone with sodium borohydride in methanol.

Reduction of Hippeastrine by Lithium Aluminium Hydride.—Hippeastrine (0·9 g.) and lithium aluminium hydride (0·3 g.) were heated under reflux in tetrahydrofuran (20 ml.) for 5 hr. The mixture was worked up in the usual manner, and the isolated tetrahydrohippeastrine crystallised from ether as deliquescent prisms. The *tri*-p-*nitrobenzoate* was prepared with *p*-nitrobenzoyl chloride in pyridine and had m. p. 184° (decomp.) (Found: C, 58·2; H, 3·7; N, 7·2. $C_{36}H_{30}O_{14}N_4$ requires C, 58·2; H, 4·1; N, 7·6%).

Lycorine β-*Methiodide from Tetrahydrohippeastrine.*—Dry tetrahydrohippeastrine (0·4 g.) and toluene-*p*-sulphonyl chloride (0·275 g.) were kept in dry pyridine (10 ml.) at room temperature overnight, then heated at 80—90° for 1 hr. After evaporation under reduced pressure, the residue taken up in water (40 ml.), washed with ether and chloroform, and passed through a column of Amberlite I.R.A.-400 resin (OH-form). The column was washed with water, and the combined eluate and washings were washed 5 times with ether and then acidified with dilute hydriodic acid. After evaporation of the solution under reduced pressure, the residue was

passed in ethanol through alumina. Elution with ethanol yielded prisms (0·15 g.), m. p. 280° (decomp.) (from ethanol), $[\alpha]_D$ +136° (*c* 0·95 in H_2O), identical in mixed m. p. and infrared spectrum with authentic lycorine β-methiodide (Found: C, 46·1; H, 5·0. Calc. for $C_{17}H_{20}O_4NI,H_2O$: C, 45·7; H, 5·0%).

Epihæmanthamine Methiodide from Tazettadiol.—Dry tazettadiol (0·3 g.) was dissolved in dry pyridine (3 ml.) and freshly distilled thionyl chloride (0·15 ml.) added in portions under cooling. The mixture was kept overnight at 0°, then water was added to decompose the excess of reagent, and the whole evaporated under reduced pressure. The residue dissolved in water, was passed through a column of Amberlite I.R.A.-400 resin (OH-form). The eluate and washings were combined, washed several times with ether, neutralised with dilute hydriodic acid, and concentrated to dryness under reduced pressure. The residue was chromatographed in ethanol over alumina. Elution with ethanol yielded no crystalline substance. Elution with methanol gave prisms, m. p. 280° (decomp.), identical in m. p. and infrared spectrum with authentic epihæmanthamine methiodide (for which we thank Drs. Wildman and Fales) (Found: C, 48·4; H, 5·4; N, 3·2. Calc. for $C_{18}H_{22}O_4NI$: C, 48·8; H, 5·0; N, 3·2%).

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