757. *Stereochemistry of Reduction Products of* 1-*Acetyl-lycorin-2-one.*

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The isolated double bond in lycorine (I; R = R′ = H) has been unequivocally fixed by interconversion of the alkaloid and 1-*O*-acetyl-lycorin-2-one (II). The absolute stereochemistry of lycorine and 2-epilycorine (IV; R = R′ = H) and their hydrogenation products has been elucidated.

Recently, we showed [1] that the isolated double bond in lycorine (I; R = R′ = H) is allylic to the 2-hydroxyl group, since oxidation of 1-*O*-acetyl-lycorine (I; R = Ac, R′ = H) with manganese dioxide gave 1-*O*-acetyl-lycorin-2-one (II) (identified by the ultraviolet and infrared spectra).

Takeda and Kotera [2] previously assigned a diaxial conformation to the hydroxyl groups in dihydrolycorine, in agreement with our experimental results described below. In view of this, one might have assumed that 1-*O*-acetyl-lycorin-2-one was a product of epimerisation at position 1 during the oxidation of 1-*O*-acetyl-lycorine, *i.e.*, that the axial acetoxyl group was inverted, as a result of keto–enol tautomerism, to an equatorial configuration which is generally supposed to be the more stable. This possibility was, however, ruled out, since hydrogenation of 1-*O*-acetyl-lycorin-2-one (II) with Adams catalyst in acetic acid afforded 1-*O*-acetyldihydrolycorine (III; R = Ac), convertible by hydrolysis to the known dihydrolycorine (III; R = H).

Another possibility which merited more serious consideration was that the double bond in lycorine was actually at position 3a,4 and shifted to the adjacent position (3,3a) only when 1-*O*-acetyl-lycorine was oxidised to the ketone (II). However, reduction of the ketone (II) with sodium borohydride followed by hydrolysis yielded lycorine along with its epimer, 2-epilycorine (IV; R = R′ = H). Since migration of a double bond during this sort of reaction is highly improbable, it is certain that the double bond in lycorine is at the same place as that in 1-*O*-acetyl-lycorin-2-one (II) and accordingly was not affected in

[1] Nakagawa, Uyeo, and Yajima, *Chem. and Ind.*, 1956, 1238.
[2] Takeda and Kotera, *ibid.*, p. 347; *Pharm. Bull.* (*Japan*), 1957, **5**, 234.

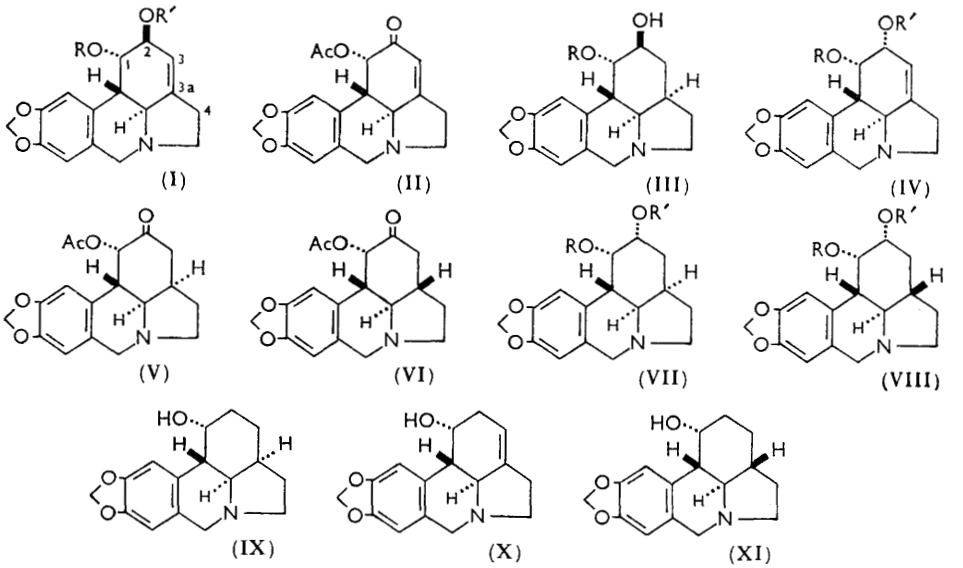
the course of transformation into the latter. Thus the position of double bond in lycorine has been fixed conclusively at position 3,3a rather than 3a,4.

2-Epilycorine (IV; R = R′ = H), which was also obtained from 1-*O*-acetyl-lycorin-2-one (II) by treatment with lithium aluminium hydride as the only isolable product, gave on condensation with acetone an isopropylidene derivative (IV; R, R′ = CMe_2), while all attempts to obtain an analogous derivative from lycorine were unsuccessful. Therefore the two hydroxyl groups in 2-epilycorine are *cis* to each other. Since the hydroxyl group allylic to the double bond in 2-epilycorine was inferred from the route of formation to have a quasi-equatorial conformation, the adjacent *cis*-1-hydroxyl group must be axial. Consequently the hydroxyl groups are *trans* and diaxial in lycorine whose configuration differs from that of 2-epilycorine only in respect of the allylic hydroxyl group. This conclusion is in accord with the stereochemistry of dihydrolycorine advanced by Takeda and Kotera [2] who formulated it as (III; R = H) or its mirror image. If Mills's rule [3] concerning absolute configurations of allylic alcohols is valid for this series, the absolute configuration of lycorine can be represented by the formula (I; R = R′ = H), since, as shown in the annexed Table, lycorine and its acetate have molecular rotations more positive than those of their 2-epimers.

Optical rotations $[M]_D$ *of lycorine and its derivatives.*

Lycorine	−261°	2-Epilycorine	−623°
Diacetyl-lycorine	+117°	Diacetyl-2-epilycorine	−588°

Hydrogenation of 2-epilycorine in ethanol over palladium–carbon gave two products, α- and β-dihydro-2-epilycorine (VII and VIII respectively; R = R′ = H), the latter somewhat predominating. On the other hand, α-dihydro-2-epilycorine was the main product when the hydrogenation was carried out in acetic acid over Adams catalyst. These results parallel the case of caranine [4] (X) which lacks a 2-hydroxyl group 8 but is



otherwise identical with lycorine. It was therefore considered probable that the stereochemistry of the ring systems of α- and β-dihydro-2-epilycorine was identical with that of α- and β-dihydrocaranine (IX and XI), respectively. This inference has been proved by converting the lycorine into the caranine compounds by treatment of the monotoluene-*p*-sulphonates (VII and VIII; R = H, R′ = *p*-$C_6H_4Me{\cdot}SO_2$) with lithium aluminium

[3] Mills, *J.*, 1952, 4976.
[4] Warnhoff and Wildman, *J. Amer. Chem. Soc.*, 1957, **79**, 2192.

hydride. It is concluded that the quasi-equatorial hydroxyl group allylic to the double bond in 2-epilycorine is less effective in directing the orientation of the entering hydrogen atoms to the double bond than the quasi-axial 2-hydroxyl group in lycorine which invariably gave on hydrogenation under varying conditions the known dihydrolycorine belonging to the α-dihydrocaranine series. Our attempt to obtain an epimer of dihydrolycorine having the ring system of β-dihydrocaranine and diaxial hydroxyl groups was unsuccessful. Hydrogenation of 1-*O*-acetyl-lycorine-2-one with palladium–carbon afforded predominantly 1-*O*-acetyl-β-dihydrolycorin-2-one (VI) which on reduction with lithium aluminium hydride or on hydrogenation in acetic acid over Adams catalyst followed by hydrolysis gave β-dihydro-2-epilycorine (VIII; R = R′ = H). The minor product of the hydrogenation of 1-*O*-acetyl-lycorin-2-one was 1-*O*-acetyl-α-dihydrolycorin-2-one (V), since it gave α-dihydro-2-epilycorine (VII; R = R′ = H) on treatment with lithium aluminium hydride.

Experimental

1-O-*Acetyl-lycorine* (I; R = Ac, R′ = H).—Di-*O*-acetyl-lycorine (I; R = R′ = Ac) (200 mg.) in methanol (25 ml.) and 35% hydrochloric acid (5 ml.) was heated on a water-bath for exactly 5 min. After cooling, the mixture was cautiously neutralised with aqueous sodium hydroxide, concentrated, diluted with aqueous ammonia, and extracted with ether. Lycorine (60 mg.) which remained undissolved was filtered off, and the ethereal extract dried and evaporated to give a residue which was chromatographed in benzene over alumina. The chloroform eluate gave 1-O-*acetyl-lycorine* (100 mg.), prisms (from ethanol), m. p. 215—216°, $[\alpha]_D$ −69·3° (*c* 0·95 in EtOH), $\nu_{max.}$ 3610 (OH) and 1733 cm.$^{-1}$ (OAc) in $CHCl_3$, $\lambda_{max.}$ 240 and 290 mμ (log ε 3·60 and 3·70) in EtOH (Found: C, 65·8; H, 5·7; N, 4·1; Ac, 12·9. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·3; Ac, 13·1%). The *hydrochloride* formed needles (from ethanol), m. p. 266° (decomp.) (Found: C, 55·2; H, 5·8; N, 3·4. $C_{18}H_{19}O_5N$,HCl,1·5H_2O requires C, 55·0; H, 5·9; N, 3·6%).

Lycorine from 1-O-*Acetyl-lycorine*.—1-*O*-Acetyl-lycorine (80 mg.) was saponified under reflux in 5% ethanolic potassium hydroxide (10 ml.) for 0·5 hr. After evaporation of the mixture, water was added, and the precipitate which formed was crystallised from ethanol to give lycorine, m. p. and mixed m. p. 277° (decomp.).

Di-O-acetyl-lycorine from 1-O-*Acetyl-lycorine*.—1-*O*-Acetyl-lycorine (50 mg.) in acetic anhydride (2 ml.) was heated on a water-bath for 1 hr. to furnish diacetyl-lycorine (50 mg.), m. p. and mixed m. p. 215—216° (from ethanol).

1-O-*Acetyl-lycorin-2-one* (II).—1-*O*-Acetyl-lycorine (300 mg.) was stirred with activated manganese dioxide (2 g.) in chloroform (30 ml.) for 16 hr. The manganese dioxide was removed by filtration, the filtrate was treated with charcoal and evaporated to dryness, and the residue in benzene was passed through a column of alumina. A benzene eluate gave 1-O-*acetyl-lycorin-2-one* (II) (100 mg.), which formed cubic crystals (from ethanol–chloroform), m. p. 191° (decomp.), $[\alpha]_D$ −323·8° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ 1739 (OAc) and 1675 cm.$^{-1}$ (αβ-unsaturated carbonyl) in Nujol, $\lambda_{max.}$ 235 and 290 mμ (log ε 4·20 and 3·70) in EtOH (Found: C, 65·8; H, 5·3; N, 4·5; Ac, 13·1. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2; N, 4·3; Ac, 13·2%).

Dihydrolycorine (III; R = H) *from* 1-O-*Acetyl-lycorin-2-one* (II).—1-*O*-Acetyl-lycorin-2-one (305 mg.) in acetic acid (20 ml.) was stirred with Adams catalyst (150 mg.) in hydrogen for 2·5 hr. (hydrogen uptake: 48 ml. Calc. for $2H_2$: 44 ml.). After removal of the catalyst, the mixture was evaporated *in vacuo* and the residue made alkaline and extracted with chloroform which afforded 1-O-*acetyldihydrolycorine* (III; R = Ac) (95 mg.), m. p. 199—200°, needles (from alcohol), $[\alpha]_D$ −126·1° (*c* 0·92 in $CHCl_3$), $\nu_{max.}$ 3030 (OH), 1730 cm.$^{-1}$ (OAc) in Nujol (Found: C, 65·4; H, 6·5. $C_{18}H_{21}O_5N$ requires C, 65·2; H, 6·4%).

Hydrolysis of 1-*O*-acetyldihydrolycorine (20 mg.) with 2% ethanolic sodium hydroxide (10 ml.) for 50 min. on the water-bath yielded dihydrolycorine (III; R = H), m. p. and mixed m. p. 255° (decomp.). The infrared spectrum was also identical with that of an authentic specimen.

Reduction of 1-O-*Acetyl-lycorin-2-one by Lithium Aluminium Hydride*.—1-*O*-Acetyl-lycorin-2-one (II) (100 mg.) and lithium aluminium hydride (50 mg.) in dry tetrahydrofuran (25 ml.) were kept at room temperature for 0·5 hr. and then heated on a water-bath for further 20 min. After cooling, the excess of the reagent was destroyed by dropwise addition of water and the

mixture was filtered. The filtrate was evaporated under reduced pressure, and the residue chromatographed in chloroform over alumina. Elution with chloroform furnished 2-epilycorine (IV; R = R′ = H) (75 mg.), m. p. 167—168°, needles (from isopropyl alcohol), $[\alpha]_D$ −217·0° (*c* 1·1 in $CHCl_3$), $\lambda_{max.}$ 290 mμ (log ε 3·67), $\nu_{max.}$ 3472 and 3413 cm.$^{-1}$ (OH) (Found: C, 66·7; H, 6·0; N, 5·1. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0; N, 4·9%).

Di-O-acetyl-2-epilycorine (IV; R = R′ = Ac).—2-Epilycorine (100 mg.) in pyridine (7 ml.) and acetic anhydride (200 mg.) was kept at room temperature for 42 hr. The mixture was added to water (20 ml.), basified with aqueous ammonia, and extracted with chloroform. The chloroform extract was washed with water, dried, and concentrated and the residue in benzene was passed through alumina to furnish *di-O-acetyl-2-epilycorine* (20 mg.), needles (from alcohol), m. p. 192—194·5°, $[\alpha]_D$ −158·2° (*c* 1·04 in $CHCl_3$), $\nu_{max.}$ 1733 cm.$^{-1}$ (OAc) in Nujol [Found: C, 65·0; H, 5·6; N, 3·9; Ac, 23·2. $C_{16}H_{15}O_4N(CH_3{\cdot}CO)_2$ requires C, 64·7; H, 5·7; N, 3·8; 2Ac, 23·2%].

Reduction of 1-*Acetyl-lycorin-2-one by Sodium Borohydride.*—1-*O*-Acetyl-lycorin-2-one (100 mg.) and sodium borohydride (50 mg.) in tetrahydrofuran (30 ml.) and water (2 ml.) were kept at room temperature for 48 hr. The excess of the reagent was destroyed by acetic acid, the mixture evaporated under reduced pressure, and the residue basified with aqueous ammonia and extracted with chloroform. The extract was washed with water, dried, and concentrated. Hydrolysis of the residue (80 mg.) on a water-bath in 10% ethanolic sodium hydroxide (20 ml.) for 15 min. afforded lycorine (20 mg.), m. p. 275° (from alcohol), identical with an authentic specimen in mixed m. p. and infrared spectrum. The mother-liquor gave a residue which, on crystallisation from isopropyl alcohol, afforded 2-epilycorine (40 mg.), m. p. 160—163°; acetylation of this with acetic anhydride (50 mg.) and pyridine (5 ml.) at room temperature for 5 days gave di-*O*-acetyl-2-epilycorine, m. p. and mixed m. p. 193—194° (superimposable infrared spectrum).

Isopropylidene-2-epilycorine (IV; R, R′ = CMe_2<) .—Anhydrous zinc chloride (2 g.) and phosphoric acid (0·5 ml.) in dry acetone (5 ml.) were added dropwise to a stirred solution of 2-epilycorine (70 mg.) in dry acetone (10 ml.). After 45 hours' stirring at room temperature, potassium carbonate (2 g.) and water (2 g.) were added in one portion with cooling in ice, and stirring was continued for an additional hour. After removal of the solid, the acetone was evaporated and the residue extracted with chloroform. The chloroform extract was passed through alumina; the eluate furnished the *isopropylidene derivative* (IV; R, R′ = CMe_2<) (70 mg.), needles (from alcohol), m. p. 184—186°, $[\alpha]_D$ −191·5° (*c* 0·66 in $CHCl_3$), $\lambda_{max.}$ 235 and 290 mμ (log ε 3·51 and 3·61), $\nu_{max.}$ 1364 cm.$^{-1}$ (=CMe_2) in Nujol (Found: C, 70·2; H, 6·6; N, 4·2. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·5; N, 4·3%).

Treatment of lycorine (100 mg.) with dry acetone (5 ml.), zinc chloride (2 g.), and phosphoric acid (0·5 ml.) for 48 hr. in a similar manner furnished the starting material in almost quantitative yield.

Hydrolysis of Isopropylidene-2-epilycorine.—Treatment of the isopropylidene derivative (IV; R, R′ = CMe_2<) (10 mg.) with 5% sulphuric acid (2 ml.) on a water-bath for 0·5 hr. regenerated 2-epilycorine (5 mg.), m. p. and mixed m. p. 167—168°.

Hydrogenation of 2-Epilycorine.—(*a*) 2-Epilycorine (300 mg.) in ethanol (20 ml.) was stirred in hydrogen in the presence of 10% palladium–carbon (300 mg.) for 2 hr. After removal of the catalyst, the solvent was evaporated under reduced pressure of nitrogen, and the residue was extracted with chloroform after addition of aqueous ammonia. The chloroform extract was dried and evaporated, and the residue (150 mg.) was chromatographed in benzene over alumina. The chloroform eluate (50 ml.) gave β-*dihydro-2-epilycorine* (VIII; R = R′ = H) (50 mg.) which formed needles (from ethyl methyl ketone), m. p. 146—147°, $[\alpha]_D$ −175·8° (*c* 0·8 in $CHCl_3$) (Found: C, 64·5; H, 6·5. $C_{16}H_{19}O_4N,\frac{1}{2}H_2O$ requires C, 64·4; H, 6·8%). The acetone eluate furnished α-*dihydro-2-epilycorine* (30 mg.), needles (from acetone), m. p. 196—197°, $[\alpha]_D$ −136·9° (*c* 0·9 in EtOH) (Found: C, 64·6; H, 6·5. $C_{16}H_{19}O_4N,\frac{1}{2}H_2O$ requires C, 64·4; H, 6·8%).

(*b*) 2-Epilycorine (250 mg.) in acetic acid (20 ml.) was hydrogenated with Adams catalyst (50 mg.) for 2 hr. After removal of the catalyst, the solvent was evaporated under reduced pressure under nitrogen, aqueous ammonia was added to the residue, and the mixture extracted with chloroform. A portion (50 mg.) of α-dihydro-2-epilycorine produced remained undissolved in the solvent and was collected by filtration. The chloroform extract was evaporated and the residue crystallised from acetone, to give a further crop of α-dihydro-2-epilycorine

(150 mg.), m. p. and mixed m. p. 196—197°. The mother-liquor gave material whence crystallisation from ethyl methyl ketone afforded β-dihydro-2-epilycorine (15 mg.), m. p. and mixed m. p. 146—147°.

α-Dihydrocaranine from α-Dihydro-2-epilycorine.—α-Dihydro-2-epilycorine (80 mg.) and toluene-*p*-sulphonyl chloride (120 mg.) in pyridine (1 ml.) were kept at 17—21° for 18 hr. After evaporation of the pyridine under reduced pressure under nitrogen, aqueous ammonia was added to the residue and the whole was extracted with chloroform. The dried extract was evaporated and chromatographed in benzene over alumina. A benzene eluate furnished the *monotoluene*-p-*sulphonate* (VII; R = H, R′ = *p*-$C_6H_4Me{\cdot}SO_2$) (60 mg.), needles (from ethyl methyl ketone), m. p. 174° (Found: C, 60·5; H, 5·5. $C_{23}H_{25}O_6NS,\frac{2}{3}H_2O$ requires C, 60·6; H, 5·8%).

This toluene-*p*-sulphonate (100 mg.) in dry tetrahydrofuran (10 ml.) was added dropwise to lithium aluminium hydride (70 mg.) in dry tetrahydrofuran (10 ml.), and the mixture was refluxed for 10 hr. The excess of the reagent was destroyed by a little water, and the clear filtrate was evaporated to dryness under nitrogen under reduced pressure. The residue was taken up in 10% hydrochloric acid, washed with ether, made alkaline with aqueous ammonia, and extracted with chloroform. Evaporation of the chloroform, and chromatography of the residue (50 mg.) in chloroform over alumina furnished from a chloroform eluate α-dihydrocaranine (IX), needles (from acetone), m. p. 166—169° (20 mg.), identical with an authentic specimen in m. p., mixed m. p., and infrared spectrum.

β-*Dihydrocaranine* (XI).—β-Dihydro-2-epilycorine (VIII; R = R′ = H) (200 mg.) and toluene-*p*-sulphonyl chloride (200 mg.) in dry pyridine (4 ml.) were kept at 21° for 19 hr. After evaporation of pyridine under reduced pressure under nitrogen, the residue was made alkaline with aqueous ammonia and extracted with chloroform. The toluene-*p*-sulphonate (130 mg.) was not obtained crystalline even after chromatography.

The crude toluene-*p*-sulphonate (130 mg.) in dry tetrahydrofuran (15 ml.) was treated with lithium aluminium hydride (70 mg.) in dry tetrahydrofuran (10 ml.) under reflux for 9 hr. Working up as described above, followed by repeated chromatography over alumina with benzene–ether (2 : 1) as eluant, gave β-dihydrocaranine in a low yield (7 mg.). It crystallised from ethyl acetate as prisms, m. p. 164—165°, identical in mixed m. p. and infrared spectrum with an authentic specimen.

Hydrogenation of 1-O-*Acetyl-lycorin*-2-*one with Palladium–Carbon.*—The ketone (1 g.) in dioxan (50 ml.) was stirred in hydrogen in the presence of palladium–carbon (1 g.) for 5 hr. Hydrogen uptake was 85 ml. (calc. for $1H_2$: 72 ml.).

After removal of the catalyst, the solvent was evaporated to dryness under reduced pressure under nitrogen, and the residue chromatographed in benzene over alumina. The first benzene eluate furnished 1-O-*acetyl-α-dihydrolycorinone* (V) (30 mg.) which after crystallisation from propan-2-ol had m. p. 196—197°, $[\alpha]_D$ −262·0° (*c* 0·68 in $CHCl_3$), $\lambda_{max.}$ 236 and 292 mμ (log ε 3·50 and 3·60) in EtOH, $\nu_{max.}$ 1724 (OAc), 1712 cm.$^{-1}$ (C=O) in KBr (Found: C, 65·1; H, 5·8. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8%). The second benzene eluate gave 1-O-*acetyl*-β-*dihydrolycorinone* (VI) (450 mg.), needles (from propan-2-ol), m. p. 200° (depressed the m. p. of the α-isomer to 185°), $[\alpha]_D$ −84·3° (*c* 0·59 in $CHCl_3$), $\lambda_{max.}$ 236 and 292 mμ (log ε 3·50 and 3·60), $\nu_{max.}$ 1739 (OAc) and 1715 cm.$^{-1}$ (C=O) in KBr (Found: C, 64·7; H, 5·9. $C_{18}H_{19}O_5N,\frac{1}{3}H_2O$ requires C, 64·5; H, 5·9%).

Reduction of 1-O-*Acetyl*-β-*dihydrolycorinone.*—(*a*) 1-*O*-Acetyl-β-dihydrolycorinone (VI) (20 mg.) and lithium aluminium hydride (30 mg.) in dry tetrahydrofuran (10 ml.) were kept at room temperature for 20 min., then heated under reflux for a further 20 min. After cooling, the excess of the reagent was destroyed with a little water, and the whole filtered; the filtrate afforded a residue which when crystallised from acetone gave β-dihydro-2-epilycorine (VIII; R = R′ = H), m. p. and mixed m. p. 145°.

(*b*) 1-*O*-Acetyl-β-dihydrolycorinone (150 mg.) was hydrogenated in acetic acid (30 mg.) with Adams catalyst (50 mg.) for 1 hr. The catalyst was removed and the mixture concentrated under reduced pressure, basified with aqueous ammonia, and extracted with chloroform. Evaporation of the chloroform afforded 1-O-*acetyl*-β-*dihydro*-2-*epilycorine* (VIII; R = Ac, R′ = H) (100 mg.), needles (from ethyl methyl ketone), m. p. 193—194°, $[\alpha]_D$ −142·6° (*c* 0·55 in $CHCl_3$), $\nu_{max.}$ 3367 (OH), 1718 cm.$^{-1}$ (OAc) (Found: C, 65·2; H, 6·6. $C_{18}H_{21}O_5N$ requires C, 65·2; H, 6·4%).

β-*Dihydro*-2-*epilycorine.*—1-*O*-Acetyl-β-dihydro-2-epilycorine (VIII; R = Ac, R′ = H) (70

mg.) was refluxed in 5% ethanolic potassium hydroxide (10 ml.) for 30 min. Evaporation of the ethanol and extraction of the residue with chloroform gave β-dihydro-2-epilycorine (VIII; R = R′ = H) (50 mg.), identical with an authentic specimen in m. p., mixed m. p., and infrared spectrum.

Reduction of the Ketone (V) *by Lithium Aluminium Hydride*.—The ketone (V) (9 mg.) and lithium aluminium hydride (30 mg.) in dry tetrahydrofuran (10 ml.) were set aside at room temperature for 20 min., then refluxed for further 20 min. Working up gave α-dihydro-2-epilycorine (VII; R = R′ = H) (3 mg.), m. p. and mixed m. p. 196—197°.

1-O-*Acetyldihydrolycorine from* 1-O-*Acetyl-lycorine*.—1-*O*-Acetyl-lycorine (300 mg.) and 10% palladium–carbon (400 mg.) in alcohol (30 ml.) were stirred in hydrogen for 3 hr. After working up in the usual manner, 1-*O*-acetyldihydrolycorine (III; R = Ac) (250 mg.), m. p. and mixed m. p. 199—200°, was obtained. Hydrolysis of this in boiling 10% alcoholic potassium hydroxide for 30 min. yielded dihydrolycorine, m. p. 255°, identical with the hydrogenation product of lycorine.

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