The Constitution of Homolycorine and Lycorenine.

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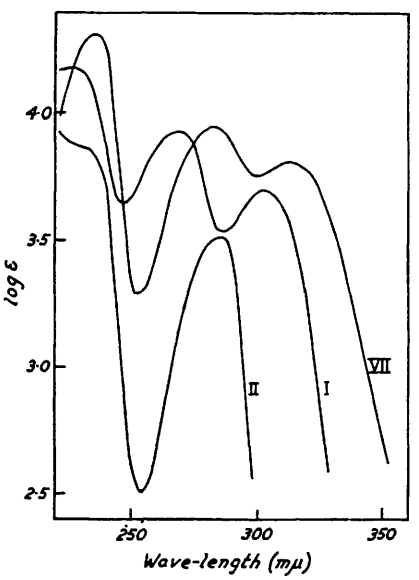
Homolycorine has been shown to be an *N*-methyl tertiary base containing a δ-lactone grouping and to give deoxylycorenine on lithium aluminium hydride reduction followed by treatment with acid. Lycorenine, which has a cyclic hemiacetal moeity, was converted into homolycorine either by oxidation or by disproportionation in alkali. From these and other results structures have been assigned to both alkaloids.

TWENTY-FIVE years ago Kondo and Tomimura (*J. Pharm. Soc. Japan*, 1929, **49**, 438) isolated from the alkaloids of *Lycoris radiata* Herb. a base, homolycorine, m. p. 175°, whose isolation was facilitated by the solubility of its hydrochloride in chloroform. Homolycorine, to which the formula $C_{19}H_{23}O_4N$ was ascribed, contained 2 methoxyl groups and also an *N*-methyl group. At that time the above authors placed little value on the latter determination because in their hands lycorine which has a bridgehead nitrogen atom also gave an apparent *N*-methyl content by the macro-method of Herzig and Meyer. Kolle and Gloppe later (*Pharm. Zentralhalle*, 1934, **75**, 237) extracted from the bulbs of *Narcissus poeticus* a base of m. p. 172°, very similar to homolycorine but named by them narcipoetine in case it was not identical with homolycorine. Very recently Boit (*Chem. Ber.*, 1954, **87**, 681) announced the separation from *Leucojum vernum* L. as well as from *Narcissus poeticus* var. *ornatus* of an alkaloid whose properties were almost identical with those recorded for homolycorine except in the empirical formula and specific rotation. Dr. H. G. Boit has now shown by direct comparison that his compounds are identical with the original sample of homolycorine (Dr. H. Kondo, personal communication).



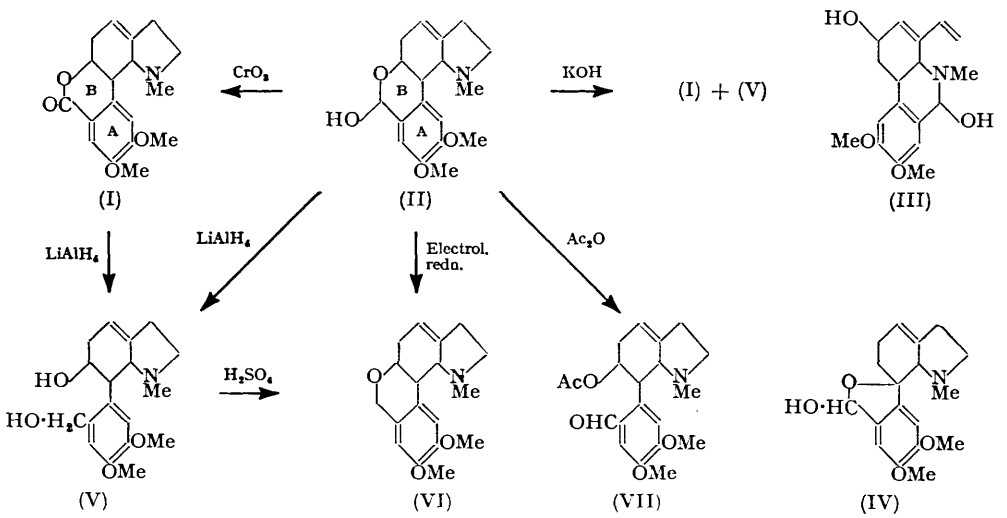
Ultra-violet absorption of (I) *homolycorine*, (II) *lycorenine, and* (VII) *acetyl-lycorenine, all in* 95% EtOH.

We have independently confirmed the formula $C_{18}H_{21}O_4N$ as assigned by Boit (*loc. cit.*) and also the fact that besides the two methoxyl groups there is one *N*-methyl group. While homolycorine was reported by Kondo and Tomimura (*loc. cit.*) to give a diacetyl derivative, m. p. 173°, we have been unable to confirm this, the base being always recovered unchanged after attempted acetylation, so that the nature of two oxygen atoms still remained to be elucidated. It was found that although the base was insoluble in cold sodium carbonate or sodium hydroxide solution it dissolved in hot sodium hydroxide to yield a salt which could not be extracted from aqueous solutions by organic solvents; after acidification of the alkaline solution homolycorine was isolated as its hydrochloride in quantitative yield. Thus the two oxygen atoms were present in a lactone. Both the infra-red (ν_{CO} 1712 cm.$^{-1}$) and the ultra-violet absorption spectrum (curve I) of the alkaloid were consistent with a partial structure indicated by rings A and B of formula (I), which contain a veratroyl residue and a δ-lactone grouping. δ-Lactones have carbonyl stretching frequencies in the same position as the corresponding open-chain esters, in this case at *ca.* 1720 cm.$^{-1}$ (Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1073); γ-lactones absorb at much higher frequencies, *e.g.*, the methoxyphthalides have ν_{CO} 1750 cm.$^{-1}$ (Duncanson, Grove, and Zealley, *J.*, 1953, 1331).

Reduction of homolycorine by lithium aluminium hydride gave tetrahydrohomolycorine,

$C_{18}H_{25}O_4N$, m. p. 154°, which with hot dilute sulphuric acid afforded anhydrotetrahydrohomolycorine, $C_{18}H_{23}O_3N$, m. p. 117—118°. The latter compound was identical with deoxylycorenine, m. p. 117—118°, obtained by Kondo and Ikeda (*Ann. Report ITSUU Lab.*, 1952, **3**, 55) on electrolytic reduction of lycorenine, a base also isolated from *Lycoris radiata* (Kondo, Tomimura, and Ishiwata, *J. Pharm. Soc. Japan*, 1932, **52**, 433; Kondo and Mitsuhashi, *ibid.*, 1934, **54**, 1001; Kondo and Ikeda, *Ber.*, 1940, **73**, 867). The close relation between the two alkaloids was further demonstrated by the following experiments. Reduction of lycorenine with lithium aluminium hydride yielded tetrahydrohomolycorine, and although lycorenine was stable to potassium ferricyanide it was readily oxidised by chromic acid to homolycorine. Finally, as expected, with hot alcoholic potassium hydroxide lycorenine underwent disproportionation to homolycorine and tetrahydrohomolycorine. Lycorenine must therefore have the cyclic hemiacetal structure shown in rings A and B of formula (II). The results of the last experiment suggest that homolycorine could actually be produced from lycorenine during the isolation procedure.

On the basis of their extensive investigations into the chemistry of lycorenine Kondo and Ikeda (*loc. cit.*, 1952) put forward as working hypothesis the structure (III) for the alkaloid. Wenkert and Hansen (*Chem. and Ind.*, 1954, 1262) after a re-analysis of Kondo's



data and biogenetic considerations have suggested formula (IV). While we are essentially in agreement with the general correctness of Wenkert and Hansen's formula it can be criticized on the grounds that in a number of degradation product of lycorenine the potential tertiary benzylic hydroxyl group should have been eliminated, *e.g.*, on acetylation of lycorenine. It is clear from our results that the cyclic hemiacetal ring in lycorenine must be six-membered, leading to (II) as the formula. Thus homolycorine, tetrahydrohomolycorine, and deoxylycorenine are (I), (V), and (VI) respectively.

Lycorenine (ultra-violet spectrum, curve II) on acetylation yields (VII) as indicated by the ultra-violet absorption spectrum (curve VII) (which is very similar to that of veratraldehyde) rather than the acetate of the hemiacetal form. Further aspects of the chemistry of lycorenine and a discussion of Wenkert's newer biogenetic scheme for *Amaryllidaceae* alkaloids will be presented later.

Experimental

Absorption spectra were taken in 95% ethanol.

Homolycorine.—Homolycorine was crystallized from water to constant m. p. 175°, $[\alpha]_D$ +85° (*c*, 0·43 in EtOH), ν_{CO} 1712 cm.$^{-1}$, $\lambda_{max.}$ 225, 267, and 305 mμ (log ε 4·18, 3·91, and 3·69) (Found: C, 68·5; H, 6·6; N, 4·4; OMe, 19·6; NMe, 4·0. Calc. for $C_{18}H_{21}O_4N$: C, 68·6; H, 6·7; N, 4·5; 2OMe, 19·7; NMe, 4·8%). The *hydrochloride* had m. p. 278° (decomp.), $[\alpha]_D$ +100°

(*c*, 0·5 in H_2O; dried sample), $[\alpha]_D$ +15° (*c*, 0·33 in $CHCl_3$; dried sample), $\lambda_{max.}$ 227, 270, 301 mμ (log ε 4·21, 3·94, 3·77) (Found, after being dried at 105° for 6 hr.: C, 61·7; H, 6·3. $C_{18}H_{21}O_4N$,HCl requires C, 61·5; H, 6·3%).

Treatment of Homolycorine with Alkali.—Homolycorine (0·1 g.) was dissolved in hot aqueous sodium hydroxide (8 ml.; 5%), then heated on a water-bath for 2 hr. After cooling, homolycorine could not be induced to crystallize nor could it be extracted from the aqueous alkaline solution by ether, benzene, or chloroform. After acidification (HCl), the chloroform extract was evaporated to dryness to yield homolycorine hydrochloride (90 mg.), m. p. and mixed m. p. 278° (decomp.).

Tetrahydrohomolycorine.—Homolycorine (0·2 g.) and lithium aluminium hydride (0·2 g.) were refluxed in dry ether for 7 hr. After addition of ice-water and filtration the ethereal solution was evaporated to dryness and chromatographed over aluminium oxide. After elution first with benzene, the ethanol eluate yielded *tetrahydrohomolycorine* (plates from acetone) (140 mg.), m. p. 154·5°, $[\alpha]_D$ −101° (*c*, 0·33 in EtOH), $\lambda_{max.}$ 281 mμ (log ε 3·45) (Found: C, 67·7; H, 7·9. $C_{18}H_{25}O_4N$ requires C, 67·6; H, 7·9%). The diacetate had m. p. 133—134° (from ether–light petroleum) (Found: C, 65·7; H, 7·1; N, 3·6; Ac, 21·3. Calc. for $C_{22}H_{29}O_6N$: C, 65·5; H, 7·3; N, 3·5; 2Ac, 21·3%) and was identical with the so-called acetyldeoxylycorenine described by Kondo and Ikeda (*loc. cit.*, 1952).

Reduction of lycorenine (0·5 g.) with lithium aluminium hydride in ether afforded tetrahydrohomolycorine (0·32 g.), m. p. and mixed m. p. with the above sample 153—155°, $[\alpha]_D$ −106° (*c*, 0·39 in EtOH).

Deoxylycorenine (*Anhydrotetrahydrohomolycorine*).—Tetrahydrohomolycorine (0·1 g.) in 1·5% sulphuric acid (15 ml.) was heated at 100° for 2 hr., then basified with ammonia and extracted five times with ether (10 ml.). The ethereal extract (80 mg.) was chromatographed over activated aluminium oxide, and the benzene and chloroform eluates furnished anhydrotetrahydrohomolycorine (40 mg.), m. p. 94—99° after crystallisation from ether, raised to 117—118° after drying *in vacuo*, $[\alpha]_D$ +95° (*c*, 0·65 in EtOH), $\lambda_{max.}$ 285 (log ε 3·52) (Found: C, 71·6; H, 7·5. Calc. for $C_{18}H_{23}O_3N$: C, 71·7; H, 7·7%). This product gave an undepressed mixed m. p. with deoxylycorenine (m. p. 118—119°, $[\alpha]_D$ +91°), kindly provided by Dr. H. Kondo.

Oxidation of Lycorenine.—Chromic oxide (80 mg.) in acetic acid (9 ml.) was added during 2 hr. to a stirred solution of lycorenine (0·2 g.) in acetic acid (5 ml.). The temperature was raised to 40° for 3 hr., and after a further 12 hr. at room temperature ethanol was added and the solution evaporated to dryness. The residue was taken up in 3% hydrochloric acid (8 ml.) and extracted with chloroform (3 × 8 ml.), which yielded on evaporation the crude hydrochloride (120 mg.), m. p. 262—268° (decomp.). After two crystallizations from ethanol the pure hydrochloride (78 mg.) was obtained with m. p. and mixed m. p. 278° (decomp.), $[\alpha]_D$ +23° (*c*, 2·3 in $CHCl_3$), identical with homolycorine hydrochloride. For analysis the sample was dried *in vacuo* at 105° for 6 hr. (Found: C, 61·1; H, 6·1. Calc. for $C_{18}H_{21}O_4N$,HCl: C, 61·4; H, 6·3%). The hydrochloride was also converted into homolycorine, m. p. 173—175°, identical with authentic material. Lycorenine (42 mg.) was recovered from the above aqueous solution after basification and extraction with chloroform.

Lycorenine was recovered in 75% yield after attempted oxidation in aqueous alkaline potassium ferricyanide solution.

Disproportionation of Lycorenine.—Lycorenine (0·3 g.) and potassium hydroxide (4 g.) in ethanol (20 ml.) were refluxed for 8 hr., then, after removal of the ethanol, water (35 ml.) was added and the solution extracted 4 times with chloroform (6 ml.). The chloroform extract afforded a residue (0·18 g.) which after chromatography over activated aluminium oxide gave from the benzene eluate a product (78 mg.), m. p. 197—199° alone or mixed with lycorenine, and from the chloroform eluate a compound (34 mg.), m. p. 153—154° alone or mixed with tetrahydrohomolycorine. The aqueous solution was acidified (HCl) and extracted with chloroform (4 × 6 ml.), to yield homolycorine hydrochloride (100 mg.), m. p. 276° (decomp.), which gave the free base, m. p. 173—175° alone or in admixture with homolycorine.

Acetyl-lycorenine.—The acetyl derivative prepared by acetylation of lycorenine (Kondo and Ikeda, *loc. cit.*, 1952) had $\lambda_{max.}$ 235, 281, and 313 (log ε 4·31, 3·95, 3·81).

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