Lycoris *Alkaloids. Part XXXI.* A Structural Inter-relationship of Lycorine and Lycorenine.*

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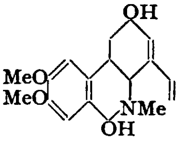
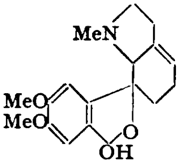
The Wolff–Kishner reduction of lycorenine (III) gave the dihydrodeoxy-compound (VI) which was converted by dehydrogenation into an indole (VII) identical with the compound derived from the Emde base (X) of lycorine by demethylenation followed by methylation and dehydrogenation.

The structure of lycorenine advanced previously has thus been confirmed.

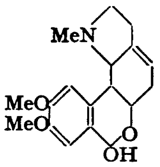
On the basis of theoretical discussions the formula (I) assigned by Kondo and Ikeda (*Ann. Rep. Itsuu Lab.*, 1952, **3**, 55) to lycorenine was recently changed by Wenkert and Hansen (*Chem. and Ind.*, 1954, 1262) to the semiacetal structure (II). However, as has been pointed out by us, lycorenine can be oxidized to homolycorine which is a δ-lactone, and this and other evidence leads to the revised formula (III) (Part XXIX *). Boit, Paul, and Stender (*Chem. Ber.*, 1955, **88**, 133) have independently shown that oxidation of lycorenine yields homolycorine, but in spite of the use of infrared spectra they considered that homolycorine was a γ-lactone, thereby favouring Wenkert's formula for lycorenine. We now report experiments which substantiate our earlier conclusion.



(I)

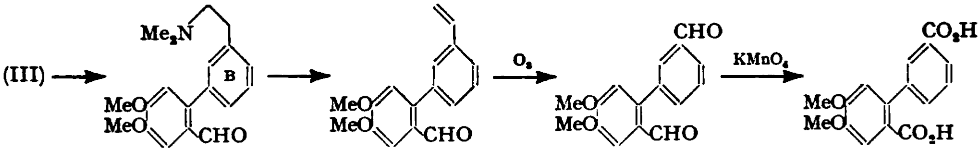


(II)

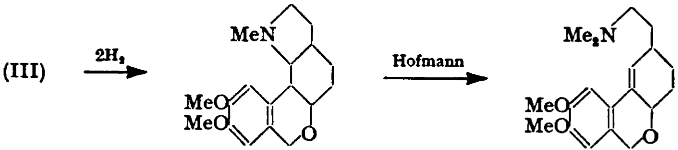


(III)

The Hofmann degradation of lycorenine on the basis of (III) and later steps can be readily interpreted as follows :



This degradation, however, does not fix the point of attachment of the nitrogen atom to ring B, but this could be inferred from the fact that the ultraviolet absorption spectrum of the methine (V) formed from dihydro-α-deoxylycorenine (IV), originally called "*d*-desoxydihydro-R-lycorenine," shows a double bond conjugated to the aromatic nucleus.



(IV) (V)

Conclusive proof that the nitrogen occupies the position shown in (III), and that the potential hydroxyl group must be secondary and not tertiary is provided by the following experiments. Wolff–Kishner reduction of lycorenine afforded the dihydrodeoxy-compound (VI) which on dehydrogenation by palladium–charcoal gave two compounds separable by

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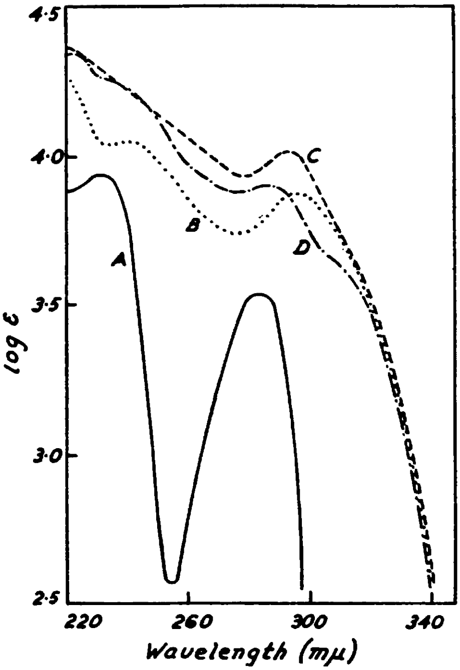
* Part XXIX. The constitution of homolycorine and lycorenine, *J.*, 1955, 1066. Part XXX. The structure of tazettine methine, *J.*, 1955, 2962.

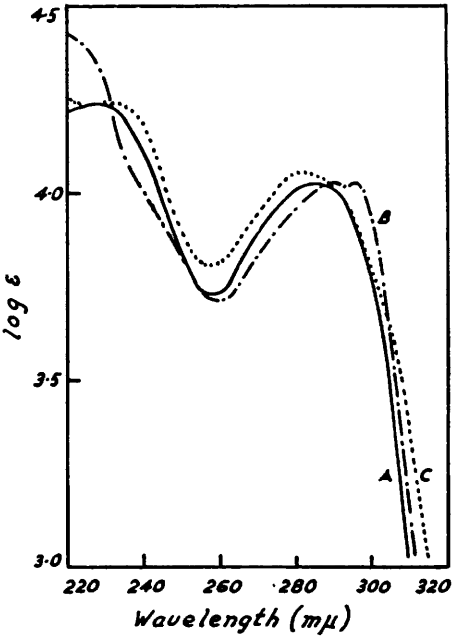
chromatography. The neutral product gave analyses correct for the expected 7-(3 : 4-dimethoxy-6-methylphenyl)-1-methylindole (VII) and exhibited the typical indole colour reactions. The second product was insoluble in acids but soluble in alkali, gave a green ferric chloride reaction, and was shown to be an indole by colour reactions : this information along with its ultimate analysis is consistent with the structure (VIII). It is interesting that it is not possible to obtain a phenol by this sequence of reactions from Wenkert's formula (II), if one excludes the unlikely possibility of a molecular rearrangement. The neutral product (VII) is closely related to the Emde base of lycorine, lycorine anhydrohydromethine (X), which we have synthesized (Humber, Kondo, Kotera, Takagi, Takeda, Taylor, Thomas, Tsuda, Tsukamoto, Uyeo, Yajima, and Yanaihara, *J.*, 1954, 4622), and in the experiments described below this has been smoothly converted into the neutral product (VII). The base (X), when treated with aluminium chloride (Prosskurnina, *Izvest. Akad. Nauk S.S.S.R.*, 1953, **90**, 565; *Chem. Zentr.*, 1954, **125**, 1025), gave the phenolic base (XI) which ethereal diazomethane converted into the ether (XII), m. p. 69—71°. This is possibly identical with the Emde base, m. p. 69—71°, formed from galanthine (Prosskurnina, *loc. cit.*), which is closely related to lycorine and for which partial formula (XIII) has been suggested. Dehydrogenation of the ether (XII) gave the product (VII) derived from lycorenine. This synthesis also confirms the structure assigned to the phenolic product (VIII) and unequivocally establishes lycorenine as (III).

Fig. 1.



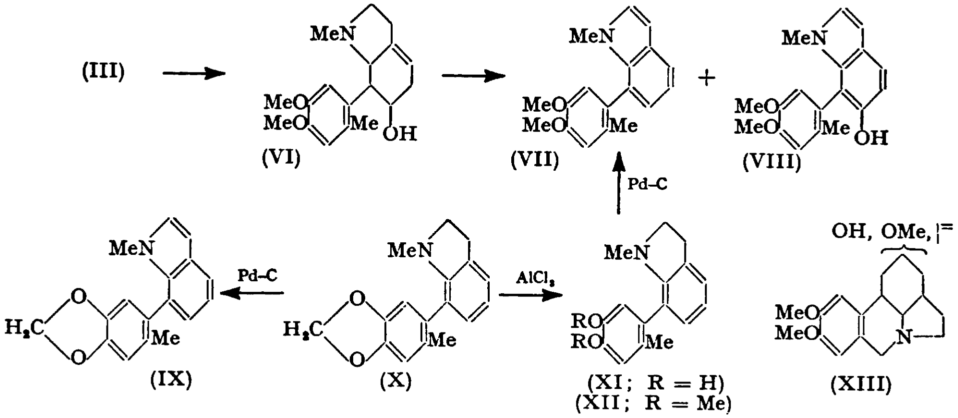
Curve	Substance
A, ———	(VI)
B, - - - - -	(X)
C, — — —	(XI)
D, — · — ·	(XII)

Fig. 2.



Curve	Substance
A, ———	(VII)
B, — · — ·	(IX)
C, - - - - -	(VIII)

In the course of this work we have prepared the indole (IX) by catalytic dehydrogenation of the Emde base of lycorine. The ultraviolet absorption spectra of the various dihydroindoles are given in Fig. 1 and those of the indoles in Fig. 2. It is worth noting that free rotation about the bond linking the two aromatic nuclei results in spectra due to addition of the separate chromophores and different from that obtained when the rings are forced into the same plane as in 9 : 10-methylenedioxy-7*H*-dibenzo(*f,hi*)pyrrocoline (Cook, Loudon, and McCloskey, *J.*, 1954, 4176), the catalytic dehydrogenation product of anhydrolycorine.



EXPERIMENTAL

The ultraviolet absorption spectra were measured in 95% EtOH.

Wolff–Kishner Reduction of Lycorenine.—Lycorenine (0·6 g.) was heated in diethylene glycol (14 c.c.) containing 92% hydrazine hydrate (1 c.c.) for 1·5 hr. at 130°. Sodium (0·3 g.) was added and the resultant solution heated to 190—195° for 3 hr., then diluted with water (30 c.c.) and extracted with ether (5 × 10 c.c.). The ethereal extracts were combined, dried (K_2CO_3), and evaporated, to give an oil (0·508 g.) which was chromatographed on alumina. Elution with benzene gave an oil which crystallized on trituration with ether. Two crystallizations from ether–light petroleum (b. p. 40—60°) gave the *dihydrodeoxy-compound* (VI) (0·27 g.) as prisms, m. p. 126—128°, $[\alpha]_D^{24·5}$ −146·8° (*c*, 0·374 in EtOH) (Found: C, 71·0; H, 8·2; N, 4·9. $C_{18}H_{25}O_3N$ requires C, 71·3; H, 8·3; N, 4·6%).

Dehydrogenation of the Base (VI).—The above product (0·13 g.) and 30% palladium–carbon (0·1 g.) were heated in nitrogen at 250—260° for 10 min. and the product was extracted in benzene (40 c.c.). The extract was filtered and evaporated, yielding a dark violet oil (0·118 g.) which was chromatographed in benzene on alumina. The first portion (7 c.c.) of the benzene eluate yielded on crystallization from ether–ethanol the neutral *product* (VII) (36 mg.), m. p. 94—96°. Recrystallization from the same solvent mixture gave colourless crystals (25 mg.), m. p. 98—99°, raised after further crystallization from ether to m. p. 116—118° (dimorphous). The product gave a pink colour with dimethylaminobenzaldehyde and sulphuric acid, and a positive pine splinter test (Found: C, 76·3; H, 6·7; N, 4·8. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·8; N, 5·0%).

A phenolic *product* (VIII) was obtained by further elution with benzene, and after crystallization from ether and then methanol had m. p. 168—169°. It gave a green colour with ferric chloride and a positive Ehrlich reaction (Found: C, 72·6; H, 6·4; N, 4·8. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%).

Action of Aluminium Chloride on the Emde Base of Lycorine.—To a solution of this base (X) (1 g.) in chlorobenzene (16 c.c.) was added aluminium chloride (3 g.), and the mixture was heated under reflux for 3 hr. A few pieces of ice were added to the chilled mixture, the solvent was removed by steam-distillation, and the water-insoluble reddish-brown oil was extracted with ether (4 × 10 c.c.). The ether layers were concentrated to 15 c.c. and extracted with 4% aqueous sodium hydroxide (4 × 8 c.c.). The alkaline extracts were combined and saturated with ammonium chloride, and the separated phenolic material was extracted with ether (4 × 10 c.c.). The ether solutions were dried (K_2CO_3) and evaporated, to a pale yellow oil (0·526 g.) which crystallized slowly. The phenol (XI), recrystallized twice from benzene, melted at 159—161° (lit., m. p. 159—161°) and gave a green colour with ferric chloride (Found: C, 75·5; H, 6·6; N, 5·4. Calc. for $C_{16}H_{17}O_2N$: C, 75·3; H, 6·7; N, 5·5%).

Methylation of the Phenol (XI).—The phenol (0·3 g.) was set aside with ethereal diazomethane (60 c.c.) at room temperature for 4 days. After removal of the excess of diazomethane the solution was extracted with 5% hydrochloric acid (4 × 8 c.c.), the acid solutions were made alkaline with aqueous sodium hydroxide, and the non-phenolic base was taken into ether. The ethereal solution was dried (K_2CO_3) and evaporated to dryness to an oil (0·296 g.) which solidified in ether. Recrystallization from a small amount of ether gave the *compound* (XII) (0·198 g.) as colourless cubes, m. p. 69—71° (Found: C, 76·1; H, 7·5; N, 4·9; OMe, 22·3. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9; 2OMe, 21·9%). The *picrate* formed yellow needles, m. p. 169° (decomp.), from ethanol (Found: C, 56·5; H, 4·7; N, 11·2. $C_{18}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 56·3; H, 4·7; N, 10·9%).

Dehydrogenation of the Dimethoxy-compound (XII).—This compound (0·15 g.) and 30% palladium–carbon (0·1 g.) were heated in nitrogen at 200—210° for 8 min. The product was taken up in ether (30 c.c.), and the solution filtered and washed with 5% hydrochloric acid (2 × 5 c.c.), then once with water, dried (K_2CO_3), and evaporated to a residue (0·145 g.) which crystallized slowly and melted at 102—108°. From ether, crystals (0·109 g.) were obtained having m. p. 116—118° alone or mixed with a sample of (VII) derived from lycorenine (Found: C, 77·1; H, 6·8; N, 4·8%).

Dehydrogenation of the Emde Base of Lycorine.—A mixture of the Emde base of lycorine (X) (0·2 g.) and 30% palladium-carbon (0·1 g.) was heated in nitrogen at 200° for 8 min. The product was dissolved in ether (30 c.c.), and the solution was filtered and washed twice with 5% hydrochloric acid. The ethereal layer was shaken with water, then dried (K_2CO_3), and the solvent was removed, yielding an oil (0·184 g.), which crystallized on addition of a few drops of ether. Recrystallization from ether–ethanol gave the *product* (IX) (0·139 g.), m. p. 65—67°, which gave a m. p. depression on admixture with the Emde base (Found: C, 77·0; H, 5·5; N, 5·2. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

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