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THE STRUCTURE AND STEREOCHEMISTRY OF LYCODOLINE

(LYCOPODIUM ALKALOID L.8)

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THE Lycopodium alkaloid, L.8, for which we now propose the name lycodoline, was first isolated from L. annotinum L. by Manske and Marion.[1] It has subsequently been found in several other Lycopodium species,[2] and has been shown[2d] to be identical to alkaloid L.30. We now wish to report evidence in favor of structure I for this alkaloid.

Earlier work[1,2,3] has shown that lycodoline has the molecular formula $C_{16}H_{25}O_2N$,[1,2] that the oxygens are present as a ketone and a hydroxyl group[3] and that the nitrogen is tertiary.[2c,3]

Our analytical and spectroscopic data confirmed these conclusions and revealed the presence of a secondary C-methyl group (0.68 mole of volatile acid on Kuhn-Roth oxidation, doublet at 9.14τ in the NMR spectrum). Lycodoline failed to take up hydrogen on attempted catalytic hydrogenation and the NMR spectrum (no absorption below 6.5τ) revealed that there were no olefinic protons. The lack of absorption in the region 5.4-6.4τ, coupled with the fact that lycodoline is recovered unchanged from attempted

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[1] R.H.F. Manske and L. Marion, Canad. J. Res. B21, 92 (1943).

[2a] R.H.F. Manske and L. Marion, J. Amer. Chem. Soc. 69, 212 (1947);

[b] O. Achmatowicz and W. Rodewald, Roczniki Chem. 30, 233 (1956);

[c] R.H. Burnell, J. Chem. Soc. 3091 (1959);

[d] B. Douglas, D.G. Lewis and L. Marion, Canad. J. Chem. 31, 272 (1953).

[3] G.S. Perry and D.B. MacLean, Canad. J. Chem. 34, 1189 (1956).

oxidation with chromium trioxide-pyridine and also is resistant to acetylation suggested that the hydroxyl group is tertiary. Infrared studies suggested that the hydroxyl group is intramolecularly hydrogen-bonded to the tertiary nitrogen. It is known[4] that intramolecular hydrogen-bonding causes a concentration independent shift of the -OH stretching band from the non-bonded 3615-3635 cm^{-1} region to lower frequency. Lycodoline shows a single concentration independent -OH stretching band at 3545 cm^{-1}.[5] Dihydrolycodoline (II), m.p. 187°-188° (C, 72.16; H, 10.14%), prepared by lithium aluminum hydride reduction of lycodoline, shows -OH bands at 3625 cm^{-1} (non-bonded) and 3550 cm^{-1} (bonded). The possibility that the -OH group in lycodoline is H-bonded to the carbonyl was ruled out when it was found that desoxolycodoline (III), m.p. 122.5°-123.5° (C, 76.84; H, 10.74%), prepared by Wolff-Kishner reduction of lycodoline, also shows an H-bonded hydroxyl (3545 cm^{-1}). The vicinal relationship of the amino and hydroxyl functions suggested by the hydrogen-bonding studies was confirmed by the finding that the quaternary salt IV, m.p. $> 330^\circ$, ν_{max}^{Nujol} 3240, 1753, 1717 cm^{-1} (C, 55.51; H, 7.46%) prepared from lycodoline and ethyl bromoacetate, was transformed into the lactone V, m.p. $> 330^\circ$, ν_{max}^{Nujol} 1756, 1709 cm^{-1} (C, 55.85; H, 6.64; Br, 21.50%) on hydrolysis with hot 4 N hydrobromic acid.

The environment about the carbonyl group was shown in the following way. The infrared spectrum of lycodoline displays a band at 1410 cm^{-1}, indicative of a methylene group α to the carbonyl.[6] Dehydration of dihydrolycodoline (II) with thionyl chloride in methylene chloride (lycodoline itself is stable under these conditions) gave anhydrodihydrolycodoline (VI),

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[4] A.R.H. Cole, Fortschritte der Chemie Organischer Naturstoffe Vol. XIII, p. 30. Springer-Verlag, Vienna (1956).

[5] Hydrogen-bonding studies were carried out in dilute CCl_4 using a Perkin-Elmer Model 221 spectrometer. The values quoted are considered accurate to ± 10 cm^{-1}.

[6] See reference 4, page 42.

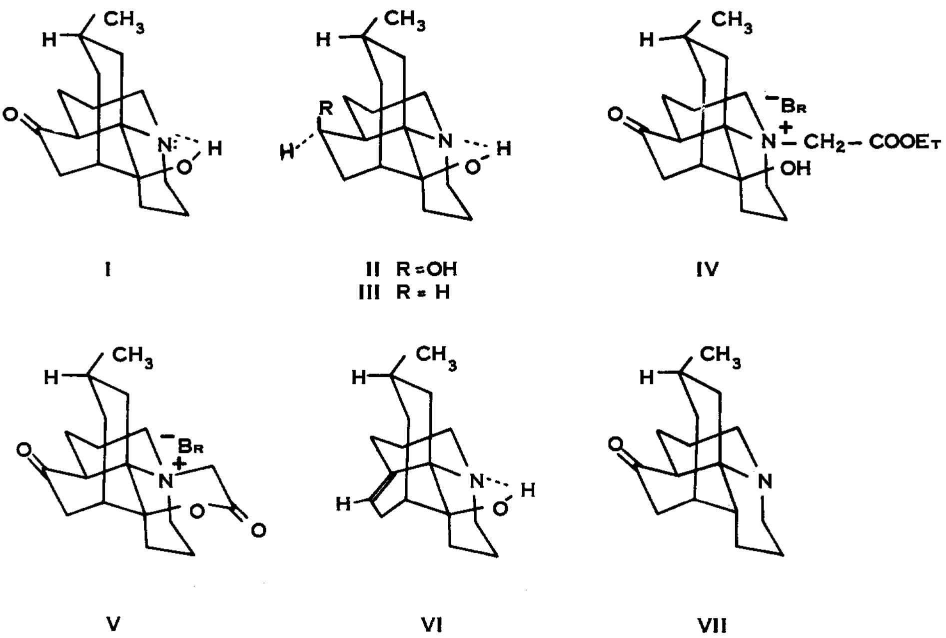

CHART I.

characterized as its hydrobromide, m.p. 293-295° (C, 58.62; H, 8.11%). The infrared spectrum of the free base showed the retention of the H-bonded hydroxyl (3565 cm^{-1}). The NMR spectrum of VI revealed the presence of a single olefinic proton (poorly resolved multiplet centered at 4.56τ), indicating the original carbonyl was flanked on one side by a methine group. The optical rotatory dispersion curve of lycodoline showed a positive Cotton effect ($[\alpha]_{308}^{MeOH}$ + 2660°, $[\alpha]_{265}^{MeOH}$ -6900°) which was very similar to that of lycopodine (VII) ($[\alpha]_{307}^{MeOH}$ + 2300°, $[\alpha]_{265}^{MeOH}$ -6300°). The similarity of the ORD curves (assuming both compounds have the same absolute configuration) together with the other evidence presented suggested structure I as a possibility for lycodoline.

Proof of this structure was obtained in the following manner. Desoxolycodoline (III) was dehydrated with P_2O_5 in refluxing toluene to yield anhydrodesoxolycodoline (VIII) as a mobile, hydroscopic oil, which was shown to be homogeneous by chromatography. VIII was characterized as its hydrochloride hemihydrate, m.p. 232-233.5° (C, 69.19; H, 9.77%). The NMR spectrum of VIII showed one olefinic proton (poorly resolved triplet at 4.64τ). The assignment of the conformation about the nitrogen (inverted with respect to lycodoline itself) is based upon the fact that VIII showed strong bands in the infrared (CCl_4 solution) at 2750 and 2810 cm^{-1} (no such bands are observed in lycodoline and the derivatives mentioned previously) characteristic of a quinolizidine ring system in which at least two α-hydrogen atoms are <u>trans</u> diaxial to the electron pair on the bridgehead nitrogen.[7] Hydrogenation of the hydrochloride of VIII over platinum yielded dihydroanhydrodesoxolycodoline (IX), characterized as its crystalline perchlorate, m.p. 240-241° (C, 57.18; H, 8.51%). The assignment of configuration at C-12[8] (and hence the nitrogen) is based on the expectation that hydrogenation would occur from the less hindered underside of the anhydrodesoxolycodoline (VIII), and on the appearance of the characteristic bands at 2755 and 2805 cm^{-1} in the infrared spectrum of IX.

Compounds VIII and IX have been synthesized from acrifoline, which has been shown to have structure (X).[9] Since acrifoline also exhibits the characteristic <u>trans</u>-quinolizidine bands (2750 and 2830 cm^{-1} in $CHCl_3$) in the infrared it appears that it exists mainly in conformation XI. The diketone XII, prepared previously by French and MacLean,[9] was stable to both acid and base and since the oxidation of the C-5 hydroxyl to carbonyl

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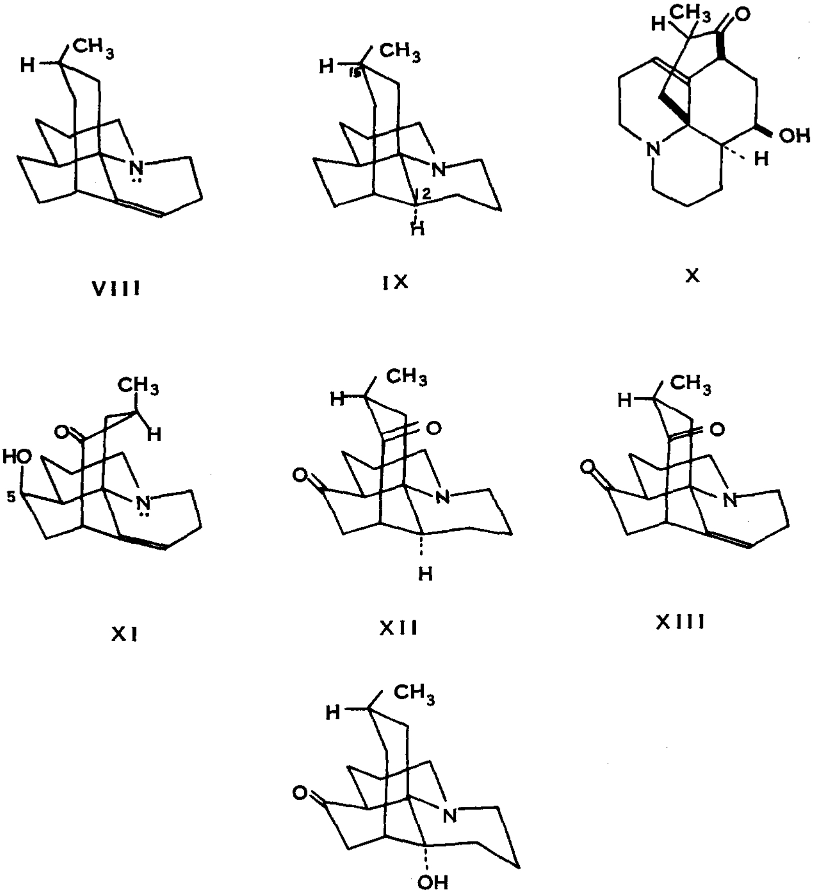
[7a] F. Bohlmann, <u>Chem. Ber.</u> <u>91</u>, 2157 (1958);

[b] F. Bohlmann and C. Arndt, <u>Chem. Ber.</u> <u>91</u>, 2167 (1958).

[8] The numbering system used is that suggested by K. Wiesner, <u>Fortschritte der Chemie Organischer Naturstoffe</u>. In press.

[9] W.N. French and D.B. MacLean, <u>Canad. J. Chem.</u> <u>39</u>, 2100 (1961).



VIII IX X

XI XII XIII

XIV

CHART 2.

should remove the non-bonded interaction which forces the ring carrying the methyl group into the boat conformation,[10] we assign the diketone the stereochemistry indicated in XII, with the methyl group in the equatorial conformation. Wolff-Kishner reduction (Barton conditions[11]) of XII yielded

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[10] F.A.L. Anet, Tetrahedron Letters No. 20, 13 (1960).

[11] D.H.R. Barton, D.A.J. Ives and B.R. Thomas, J. Chem. Soc. 2056 (1955).

dihydroanhydrodesoxolycodoline (IX) identical (I.R. of free base and perchlorate, m.p. and m.m.p. of perchlorates) with the material prepared from lycodoline. Since the Wolff-Kishner reduction could lead to epimerization at C-15,[12] this sequence does not rigorously define the stereochemistry at that position.

Oppenauer oxidation of acrifoline yielded dehydroacrifoline (XIII), characterized as its hydrobromide, m.p. 309-310° (sealed tube), $\nu_{\max}^{\text{Nujol}}$ 1728, 1714 cm^{-1} (C, 56.21; H, 6.67%), assigned the stereochemistry shown on the basis of the same arguments as used for the diketone XII. Wolff-Kishner reduction of XIII gave anhydrodesoxolycodoline (VIII), identical (I.R. spectrum, m.p. and m.m.p. of hydrochloride, rotation) to that obtained from lycodoline. This transformation rigorously establishes the position of the double bond in anhydrodesoxolycodoline and thus provides further evidence for the position of the hydroxyl group. Structure XIV, which would lead to the same anhydro compound and which also would account for the intramolecular hydrogen bonding, is considered less likely for lycodoline because of the absence of the *trans*-quinolizidine bands in the infrared spectra of lycodoline, dihydrolycodoline and desoxolycodoline.

The absolute configuration of lycopodine is known,[13] and since acrifoline has been related to lycopodine,[10] these transformations establish that the absolute configuration of lycodoline is as depicted in I. The results reported do not, however, establish unequivocally the stereochemistry at the carbon bearing the methyl group.

We wish to thank Drs. Z. Valenta (University of New Brunswick) and M.M. Marsh (Eli Lilly, Indianapolis) for the rotatory dispersion curves and the National Research Council for financial support.

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[12] C. Djerassi, T.T. Grossnickle and L.B. High, *J. Amer. Chem. Soc.* *78*, 3166 (1956).

[13] K. Wiesner, J.E. Francis, J.A. Findlay and Z. Valenta, *Tetrahedron Letters* No. 20, 13 (1960).