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THE STRUCTURE OF LYCONNOTINE: A NOVEL LYCOPODIUM ALKALOID

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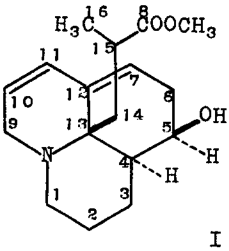
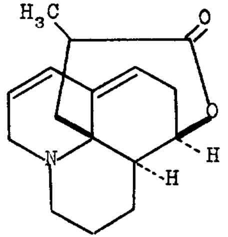
We wish to report the results of our study leading to structure I for a minor alkaloid from Lycopodium annotinum L., $C_{17}H_{25}O_3N$, m.p. 123°, picrolonate m.p. 230-231°, $[\alpha]^{20}_{D}$ + 125°, M.W. (mass-spec.) 291, pK_a 7.5 (80% methylcellosolve).

The alkaloid, for which we propose the name lyconnotine, was obtained from the mother-liquors of annotinine crystallization by chromatography on alumina. Its ultraviolet spectrum ($\lambda_{max.}$ 235 mμ, log ε 4.3 in EtOH) indicates a transoid diene and its infrared spectrum ($CHCl_3$) shows the presence of an ester (1730 cm^{-1}) and a non-bonded OH (3640 cm^{-1}). One methoxyl group and one $C-CH_3$ group were found analytically.



I



II

Acetylation of the alkaloid and its derivatives led to basic compounds, while treatment with CH_3I yielded the methiodide, $C_{18}H_{28}O_3NI$, m.p. 264°[*], showing the tertiary nature of the N atom.

Hydrolysis of lyconnotine with KOH/MeOH followed by acidification gave the lactone II, $C_{16}H_{21}NO_2$, m.p. 233°. The lactone was also obtained after the alkaloid had stood for one year in CH_3OH solution at room temperature.

TABLE 1

Position of Proton(s)	No. of H's	Lyconnotine	Lactone	Appearance of Band
		Chemical shifts in τ units		
C_{11}	1	4.07	3.90	br. d. (J ≈ 10 c.p.s.
C_{10}	1	4.45	4.27	d. (a) (J ≈ 10 c.p.s. of tr. (J ≈ 2 c.p.s.
C_7	1	4.54	4.40	tr. (J ≈ 3 c.p.s.)
C_5	1	5.98	5.39	(b)
OCH_3	3	6.46	-	s.
C_9	2	6.88	6.80	br. s.
	5-6	7.45	7.35	m.
	7-8	8.25	8.25	m.
C_{16}	3	8.95	8.81	d. (J ≈ 6.5 c.p.s.)

s. = singlet; d. = doublet; tr. = 1:2:1 triplet; m. = multiplet; br. = broad.

(a) The high-field component of the doublet overlaps the band of the proton on C_7.

(b) In lyconnotine this band is a broad doublet (splitting 6 c.p.s.), with each component about 6 c.p.s. wide. In the lactone the band is an equal-intensity octet with splittings of 8.3, 3.1 and 1.5 c.p.s.

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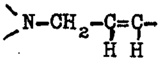
[*] All compounds reported in this communication gave the correct analysis.

N.M.R. Data.[*] The N.M.R. spectra of lyconnotine and the lactone are summarized in Table 1.

Decoupling experiments were performed on both lyconnotine and the lactone. The assignments given in Table 1 are used for simplicity in the following discussion.

(a) Irradiation of the band of the protons on C_9 results in the sharpening of the lines of H_{10} and H_{11} to a simple AB quartet, with very little effect on the band of H_7. Therefore, the grouping  $>N{-}CH_2{-}\underset{H}{C}{=}\underset{H}{C}{-}$ must be present in the molecule.

(b) Partial collapse of the band of H_7 occurs on irradiation over a range of frequencies centered on 7.3 τ. This implies that the two protons on C_6 have different chemical shifts and that their mean position is about 7.3 τ. This experiment was performed only on the lactone.

(c) The band of H_5 ($\underline{H}{-}C{-}O{-}$) collapses to a broad singlet on irradiation at 7.6 τ (lyconnotine) or at 7.0 τ (lactone) and is unaffected on irradiation of the vinylic H's. The proton at 7.6 τ (or 7.0 τ) is probably the quasi-equatorial proton on C_6, in keeping with the relatively large coupling constant (6 to 8 c.p.s.) observed. The homoallylic nature of H_5 is confirmed by the fact that the band of H_5 narrows to a broad singlet (half-width 7 c.p.s.) in several derivatives in

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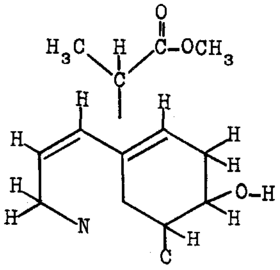
[*] All N.M.R. spectra were taken at 60 Mc in $CDCl_3$ with Me_4Si as an internal reference.

which the double bonds are reduced.[*] In the lactone, irradiation at 7.95 τ results in a change of the band of H_5 from an octet to a quartet because of the disappearance of the 3.1 c.p.s. splitting. The chemical shift of the proton at 7.95 τ is consistent with the environment of H_4. The two small splittings (3.1 and 1.3 c.p.s.) shown by H_5 are also in agreement with the dihedral angles of the C-H bonds around $C_4C_5C_6$.

(d) The $C-CH_3$ doublet collapses on irradiation at 7.20 τ (lyconnotine) or 7.37 τ (lactone). This is in agreement with the expected chemical shift of H_{15} as this proton is deshielded by the carbomethoxyl group.

Thus, N.M.R. data establish the presence of partial structure III in lyconnotine.



III

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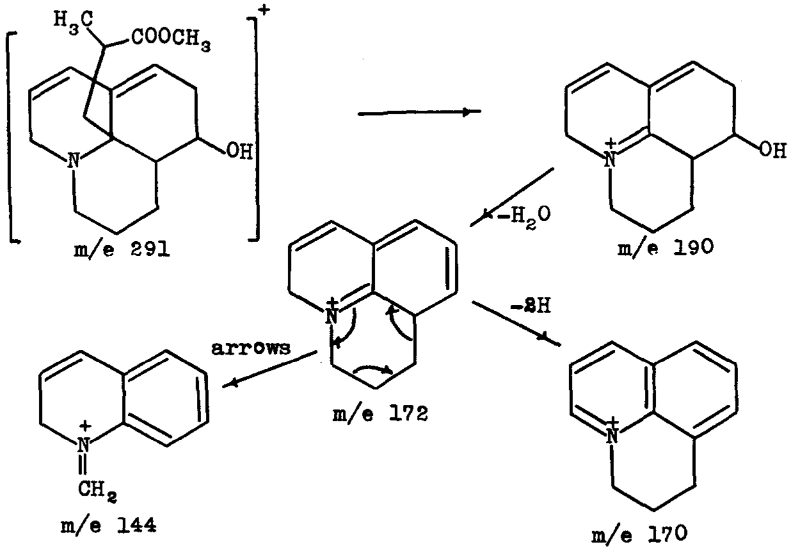
[*] A tentative chemical confirmation comes also from a CrO_3-pyridine oxidation. Lyconnotine yielded a mixture of non-conjugated (1705 cm^{-1}) and conjugated ketones, from which a crystalline conjugated dienone, m.p. 82.5-84°, M.W. (mass-spec.) 289, $\lambda_{max.}^{EtOH}$ 283 mμ (12,700), 285.5 mμ (12,800), $IR_{max.}$ (Nujol) 1722 (ester), 1660, 1637, 1570 cm^{-1} (dienone) was isolated. Due to high instability, reproducible analysis of this compound could thus far not be obtained.

Mass-spectrum. The mass-spectrum of lyconnotine shows, besides a parent peak at m/e 291, strong peaks at 190, 172, 170 and 144, consistent with the following fragmentation pattern:



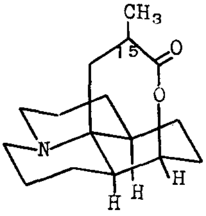
In addition, a peak at m/e 259 ($-CH_3OH$) indicates the formation of the lactone, which can thus also act as the starting material for some of the above fragments.

The fragmentation pattern conforms with that generally encountered in the Lycopodium alkaloid series (1) and gives good evidence for the presence of the ester side-chain and a hydrojulolidine skeleton.

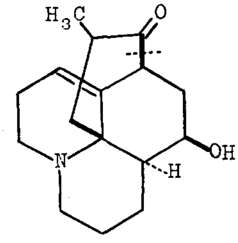
Chemical Degradation. The nature of the side-chain was also established chemically. Dehydrogenation of lyconnotine at 300° with Pd/C yielded, in addition to a small amount of as yet unidentified quinolines, a volatile acid which was identified as isobutyric acid by the comparison of its methyl ester with an authentic specimen by vapour-phase chromatography. The specific high-yield loss of the side-chain on electron impact and in the dehydrogenation strongly suggests its attachment at C_{13}.

Stereochemistry.[*] The relative configuration at C_4, C_5 and C_{13} follows from the lactone formation and from the study of the tetrahydrolactone IV, $C_{16}H_{25}NO_2$, obtained by the hydrogenation of II with PtO_2 in acetic acid. Its infrared spectrum shows the presence of the three Bohlmann bands in the 2900 cm^{-1} region characteristic of a trans-fused quinolizidine ring system (2). Only configuration IV satisfies this condition and, at the same time, allows the lactone formation.

The configuration at C_{15} in the alkaloid and its derivatives is at the present time not rigorously established. There is some evidence that an epimerization occurs at C_{15} in the process I ⟶ II.



IV



V

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[*] Absolute configuration is not implied. The one used in this communication is that found for other Lycopodium alkaloids (3).

Biogenesis. The alkaloid can in the simplest hypothesis be visualized to arise by an oxidative split of acrifoline V (4) or a close derivative.

ACKNOWLEDGMENTS

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