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# LYCOFLEXINE, A NEW TYPE OF LYCOPODIUM ALKALOID

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Examination of the alkaloids obtained by methanol extraction of Lycopodium clavatum var. inflexum, collected in the Eastern Transvaal, has resulted in the isolation of five alkaloids. Four of these are the known (1) $C_{16}$ compounds lycopodine, dihydrolycopodine, lycodoline, and fawcettimine. The fifth compound, for which we propose the name lycoflexine, is a $C_{17}$ compound possessing a carbon-nitrogen skeleton differing from those previously encountered in this group of alkaloids.

Lycoflexine, $C_{17}H_{25}NO_2$ (2), m.p. 130-131° (hydrochloride, m.p. 225-226° (dec.); hydroperchlorate, m.p. 200-201°; methiodide, m.p. 243-244°) was isolated by column chromatography (basic alumina) followed by p.t.l.c. (aluminum oxide G, eluent chloroform containing 0.75% ethanol, $R_f$ 0.45). The ir spectrum ($CHCl_3$) shows carbonyl absorption at 1740 and 1695 $cm^{-1}$, and active methylene at 1410 $cm^{-1}$. The n.m.r. spectra revealed the presence of a secondary C-methyl group ($\delta$1.01, J=6Hz, $CDCl_3$) and the absence of olefinic protons. A comparison of the spectrum of the free base with that of the methiodide ($-\overset{|}{\underset{|}{\overset{(+)}{N}}}-\underline{CH_3}$, $\delta$3.12, $D_2O$) suggested the presence of 5-6 hydrogens $\alpha$ to nitrogen. The mass spectrum shows, besides the parent peak at m/e 275 (65%), a base peak at m/e 84 ($C_5H_{10}N$ by h.r. m.s.). No such fragmentation has been previously encountered in this group of alkaloids (3,4). The evidence thus pointed to a tetracyclic alkaloid possessing

a structure different from any of the known alkaloids and an X-ray crystallographic study was initiated.

Lycoflexine hydrobromide, m.p. 266-267° (dec.), $\underline{d}^{25°}$=1.385 g/cm³, crystallizes from methanol-ether in the monoclinic form, space group $P2_1$ with two molecules per unit cell of dimensions $\underline{a}$=12.05, $\underline{b}$=7.79, $\underline{c}$=9.08 Å and β=95.2°. X-ray reflections were collected by automatic diffractometer using MoKα radiation. The structure was solved by the heavy atom method and refined by full-matrix least squares method to an R-factor of 9.7%. The structure so derived is shown in Figure 1. It is also represented by the conformational drawing 1 and by 2, which illustrates the relationship between lycoflexine and fawcettimine(3) (5).

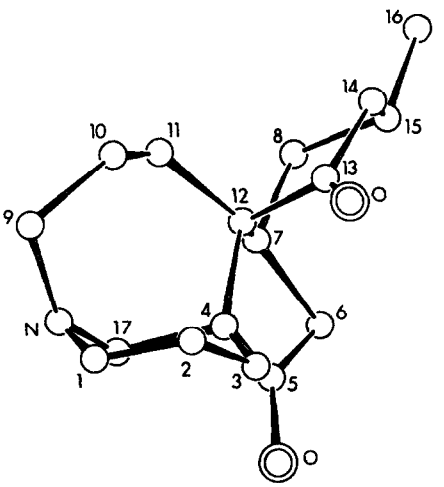
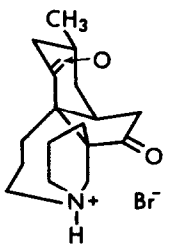



Fig. 1. The molecular structure of lycoflexine hydrobromide viewed along the $\underline{b}$ axis.

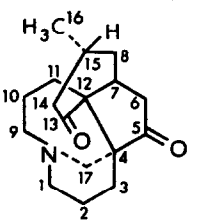
A chiroptical method(6) was used to establish the absolute stereochemistry depicted in 1 and 2. The five membered ketone and the nitrogen in lycoflexine form a β-aminoketone system in which the nitrogen lone pair is transcoplanar with the Cα-Cβ band. The circular dichroism (c.d.) spectrum of lycoflexine shows a strongly negative $\eta \rightarrow \pi^*$ band ($\Delta\varepsilon$-2.01) at 300 nm along with a strongly positive band ($\Delta\varepsilon$+5.95) at 240 nm. The hydrobromide shows a single, positive, c.d. band at 299 nm ($\Delta\varepsilon$+2.98). These data agree(6) with the absolute configuration shown. Reduction of lycoflexine with $NaBH_4$ in methanol gives an

amorphous dihydro compound (hydroperchlorate, m.p. 250-252°) (2), $\nu_{max}^{CHCl_3}$ 1730, 1410 $cm^{-1}$, in which only the six-membered ketone has been reduced(7). The c.d. spectra of the dihydro compound ($\Delta\varepsilon^{293}$-2.37, $\Delta\varepsilon^{232}$+4.48) and its hydrochloride ($\Delta\varepsilon^{292}$+0.78) show that it is the cyclopentanone carbonyl which interacts strongly with the nitrogen lone pair, and confirm the absolute configurational assignment.

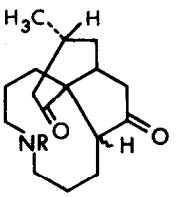
Lycoflexine(2) differs from fawcettimine(3) in that the nitrogen and C-4 are linked through a methylene bridge. A possible biogenetic intermediate is the immonium ion 5. In nature 5 could arise by oxidation of N-methylfawcettimine (6, not as yet isolated from natural sources) similar to the oxidation encountered in the formation of the "berberine bridge"(8), or by condensation of fawcettimine with formaldehyde or its equivalent. We have found that the latter sequence, an intramolecular Mannich reaction, may be utilized to effect the laboratory transformation 3 → 2. When fawcettimine(3) is treated with formaldehyde (2 eq.) in hot methanol containing a trace of HBr for 24 hours, lycoflexine(2) is formed in ca. 50% yield(9). Since fawcettimine also has been correlated with serratinine(4), the absolute stereochemistry of which is known(10), this confirms the absolute configuration of lycoflexine.



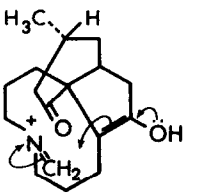

1




2




3 R=H
4 R=Ac
6 R=CH3




5

Since lycoflexine may be formed from fawcettimine, which is present in the plant, we were led to examine the possibility that lycoflexine is an artefact

produced during the isolation process. When fawcettimine was refluxed for 4 days with technical grade methanol of the type used in the extraction, lycoflexine was produced, albeit in low yield [ca. 10% (9)]. However, when the plant material was extracted directly with 5% aq. HCl, lycoflexine was isolated. Both the aqueous extract and the steam distillate therefrom showed negligible amounts ($<1x10^{-5}M$) of formaldehyde as determined by the chromotropic acid test (11). Lycoflexine was detected (tlc) in an ether extract of the ground plant. We conclude that lycoflexine(2) is a true alkaloid present in the plant (12).

## REFERENCES AND NOTES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(12) We wish to thank Prof. R. H. Burnell (Université Laval) for a generous sample of fawcettimine and Prof. M. N. G. James (University of Alberta) for use of the X-ray diffraction equipment.