

TOTAL SYNTHESIS OF
(+)-ANHYDROLYCODOLINE AND (+)-LYCOPODINE

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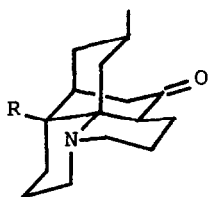
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In the course of the synthetic studies on the Lycopodium alkaloids, it was reported that the tricyclic intermediate (1) for lycodoline did not cyclize to give the tetracyclic lactam (2) for a stereoelectronic reason.¹⁾ At this stage anhydrolycodoline was chosen as a target compound, which was isolated from Lycopodium alopecuroides L. in 1968.²⁾ In this communication, we wish to describe the first total synthesis of this base. The present work also constitutes a formal total synthesis of lycopodine,³⁾ since anhydrolycodoline was already converted into it.⁴⁾

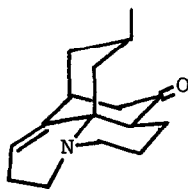
Although dehydration⁴⁾ of 1 with phenylphosphonic dichloride was unsuccessful, it proceeded smoothly with conc. sulfuric acid in methylene chloride to give the unsat. amide (3) in 85% yield [mp. 110-111°, ms M^+ =259; ir $\nu(\text{CHCl}_3)$ 1700, 1640, 1610; nmr(δ) 0.93(3H, d, J=5.5), 5.92(1H, t, J=5), 5.78(1H, d-d, J=3 and 10), 6.18(1H, d-d, J=3 and 18), 6.67(1H, d-d, J=10 and 18)]. To construct the tetracyclic framework of the alkaloid, the intramolecular Michael reaction was attempted without success under various conditions in the presence of catalysts such as p-toluenesulfonic acid, potassium tert-butoxide etc.¹⁾ Reaction of 3 with a catalytic amount of sodium ethoxide in boiling ethanol gave a mixture of the desired lactam [4, 45% yield, mp. 182-184°, ms M^+ =259; ir $\nu(\text{CHCl}_3)$ 1710, 1620; nmr(δ) 0.83(3H, fused d), 5.79(1H, t, J=5.5), 4.67(1H, d-t, J=10 and 3, C₉-equatorial H deshielded by the lactam carbonyl group)] and the ethanol adduct [5, 36% yield, an oil, ms M^+ =305; ir $\nu(\text{CHCl}_3)$ 1700, 1640; nmr(δ) 0.90(3H, d, J=5.5), 1.18(3H, t, J=6), 3.50(2H, q, J=6) 5.82(1H, t, J=4.5)]. The former was also obtained exclusively in 56% yield on treatment of 3 with a catalytic amount of sodium ethoxide and dicyclohexyl-18-crown-6 in boiling dimethylformamide. Reduction of 4 with lithium aluminum hydride, followed by oxidation with Jones' reagent, gave (+)-anhydrolycodoline in 63% yield, which solidified on standing, but

turned dark on exposure to air⁵⁾ [$m_s M^+ = 245$; $nmr(\delta)$ 0.79(3H, d, $J=5$), 5.59(1H, t, $J=4$); HCl salt mp. 204-205.5°(dec.)]. Its ir spectrum in carbon tetrachloride was superimposable with that of natural anhydrolycodoline, exhibiting characteristic absorption bands at 2700-2850 (Bohlmann bands) and 1703 cm^{-1} .

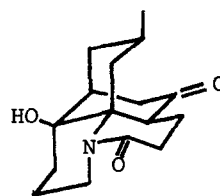
Acknowledgement: The authors are indebted to Professor W. A. Ayer, University of Alberta, for the ir spectrum of anhydrolycodoline.



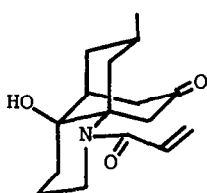
lycodoline (R=OH)
lycopodine (R=H)



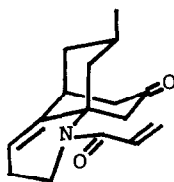
anhydrolycodoline



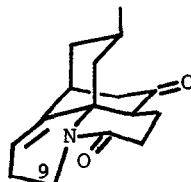
(2)



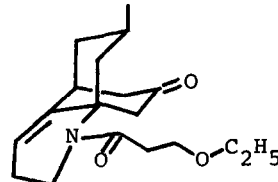
(1)



(3)



(4)



(5)

References and Footnotes

- * NMR spectra were taken at 60Mc in $CDCl_3$ using TMS as internal standard.
- 1) T. Momose, S. Uchida, T. Imanishi, S. Kim, N. Takahashi, and Z. Horii, Heterocycles, **6**, 1105 (1977).
 - 2) W. A. Ayer, B. Altenkirk, S. Valverde-Lopez, B. Douglas, R. F. Raffauf, and J. A. Weisbach, Can. J. Chem., **46**, 15 (1968).
 - 3) Total syntheses of lycopodine. a) G. Stork, R. A. Kretchmer, and R. H. Schlessinger, J. Am. Chem. Soc., **90**, 1647 (1968), b) W. A. Ayer, W. R. Bowman, T. C. Joseph, and P. Smith, ibid., **90**, 1648 (1968).
 - 4) W. A. Ayer, and G. G. Iverach, Can. J. Chem., **42**, 2514 (1964).
 - 5) The natural base is reported to be an unstable oil. See reference 2.