Tetrahedron Letters No. 20, pp. 13-17, 1960. Pergamon Press Ltd. Printed in Great Britain

STRUCTURE, STEREOCHEMISTRY AND INTERRELATION OF SOME LYCOPODIUM ALKALOIDS

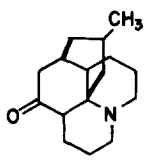
F.A.L. Anet

Department of Chemistry, University of Ottawa,

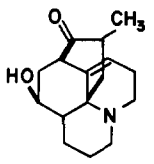
Ottawa, Canada

(Received 26 July 1960)

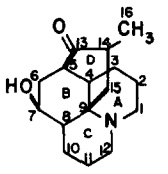
A considerable amount of degradative work has been carried out recently on lycopodine[1], acrifoline[2], and on annofoline[3], which has led to assignments of structures I, II and III respectively for these Lycopodium alkaloids.



I



II



III

However, these structures are not completely certain. We have now succeeded for the first time in interrelating these three alkaloids, a result which establishes their structures

---

1 W.A. Harrison and D.B. MacLean, Chem. and Ind. 261 (1960), and references therein.

2 W.N. French and D.B. MacLean, Chem. and Ind. 659 (1960), and references therein.

3 F.A.L. Anet and N.H. Khan, submitted for publication. F.A.L. Anet and N.H. Khan, Canad. J. Chem. 37, 1589 (1959).

rigorously. Moreover the relative stereochemistry of these alkaloids is also established by this work.

Catalytic hydrogenation of acrifoline hydrobromide (pure by paper chromatography) gave not only the known dihydroacrifoline[1], m.p. 168-172°, but also about 10% of annofoline, which was separated by preparative paper chromatography and identified by m.p., mixed m.p. and infrared spectrum. Thus the previously known dihydroacrifoline and annofoline are diastereoisomeric at C_4.

Previously[3], a compound, m.p. 88-92°, to which structure I was assigned, was obtained from annofoline, but this was not identical with lycopodine, m.p. 115°, and the compounds were thought to be diastereoisomers. It is now shown that they differ in the configuration of the carbon atom (C_{14}) bearing the methyl group.

The reduction of annofoline with $NaBH_4$ in boiling aqueous ethanol was reported[3] to give a mixture of α- and β-dihydroannofoline (the latter identical[3] to deacetylfawcettiine[4]), and these compounds are now shown not to be epimeric alcohols as might be thought. Indeed, reduction with $NaBH_4$ under neutral conditions, or with $LiAlH_4$ in ether, gave only the α-isomer. In the presence of sodium hydroxide, $NaBH_4$ gave as much as 50% of the β-isomer, which is therefore not a reduction product of annofoline, but of a ketone having the methyl group in the opposite configuration to that of annofoline. This was confirmed by the non-identity of O-acetyl-

---

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

annofoline hydrobromide[5] and of dehydrofawcettiine[3,6] hydrobromide, even though both compounds[5,6] were hydrolyzed to annofoline by base. Thus, annofoline is the stable isomer, but under alkaline conditions it must be isomerized to some extent to the less stable ketone, which is reduced faster than annofoline.

Since annofoline and acrifoline exist[2,3,5] as mixtures of hemiketal and internally hydrogen-bonded hydroxyketone forms, ring D must exist predominantly in the boat form. Indeed, in the chair form there is a very strong repulsion between C_{14} and the axial hydroxyl group on C_7. Also, since annofoline was shown above to be the stable isomer at C_{14}, it may be deduced that the methyl group is equatorial on ring D in the boat form as in IV.

If the hydroxyl group were not present at C_7, and even more so if a double bond were present at 6,7 or 7,8, then the chair form of ring D should be the preferred conformation. In this conformation the stable isomer at C_{14} (i.e. equatorial methyl group as in V) has the opposite configuration to that in IV.

Compound V was consequently prepared by the chromium trioxide-pyridine oxidation of anhydrodeacetylfawcettiine[4]

---

[5] F.A.L. Anet and N.H. Khan, unpublished.

[6] R.H. Burnell and D.R. Taylor, submitted for publication. We wish to thank Dr. Burnell for informing us that dehydrofawcettiine gave annofoline on hydrolysis.

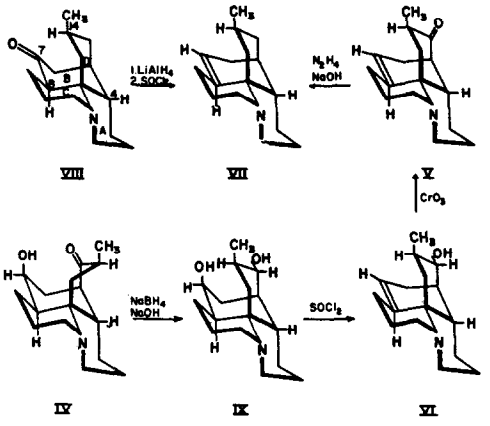
(VI), previously prepared by Burnell from deacetylfawcettiine, and hence available from annofoline by the reactions previously discussed. The oily ketone (V), $\nu_{max.}$ (CCl_4) 1705 cm^{-1}, gave a perchlorate, m.p. 190°. Calc. for $C_{16}H_{23}ON.HClO_4$: C, 55.67; H, 7.00%. Found: C, 55.08; H, 7.10%. Wolff-Kishner reduction of the ketone gave an oily base, identified as anhydrodihydrolycopodine (VII) by its infrared spectrum, and by the m.p., mixed m.p., infrared spectrum and rotation of its perchlorate. Compound VII has been obtained[7] from lycopodine by reduction with $LiAlH_4$ followed by dehydration. We have found that the dehydration step proceeds under very mild conditions, and the NMR spectrum shows that VII is the $\Delta^{7,8}$ isomer.

As anticipated, Wolff-Kishner reduction of dehydrofawcettiine gave largely the isomerized product, although traces of dihydrolycopodine may have been present.

The stability of lycopodine and dihydrodeoxyannofoline[3] to base shows that rings B and C are fused trans, a conclusion supported by the ready dehydration of dihydrolycopodine to the $\Delta^{7,8}$ isomer. Rings A and B must be fused cis to allow formation of a cyclic compound from α-cyanobromolycopodine[1] by internal alkylation at either C_6 or C_8. This is also consistent with the resulting assignment of trans-fused rings A and B in the major hydrogenation product of acrifoline, as hydrogenation would be expected to take place from the less hindered side of the double bond.

---

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



VIII VII V

IV IX VI

Thus lycopodine is VIII and annofoline is IV. The chair form of ring D for β-dihydroannofoline (IX) should be favoured as in the boat form the methyl group is in the unfavourable flag-pole position. Evidence for this comes from the fact[5] that neither fawcettiine nor lofoline, which are epimeric[3] at C_{17} and have the 7-hydroxyl group acetylated are hydrogen bonded in dilute CCl_4 solutions. Burnell and Taylor[6] have recently observed that VI is stable to further dehydration and have concluded that the hydroxyl group is trans to the methyl group, in agreement with the above conclusions. They have also suggested that these groups are diaxial, with ring D in the boat form, but from our results this does not appear to be the stable conformation.

The present work establishes the structures of a number of other alkaloids, previously related to compounds discussed above, and these will be enumerated in a full paper.

This work was supported by the National Research Council, Ottawa.