Tetrahedron Letters No.44, pp. 4597-4600, 1968. Pergamon Press. Printed in Great Britain.

THE STRUCTURE OF ANNOPODINE, A NEW TYPE OF LYCOPODIUM ALKALOID

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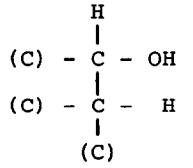
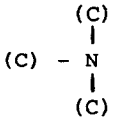
(Received in USA 21 June 1968; received in UK for publication 5 August 1968)

Lycopodium annotinum L. has proven to be a very rich source of alkaloids, over thirty bases having been isolated to date(1). We wish now to report the isolation, characterization, and structure determination of yet another alkaloid from this plant. Concentration of the acetone mother liquors remaining after the isolation of α-obscurine, lycodoline, and annotoxine(2) gave a small amount(0.2 g from 250 g crude alkaloid) of a crystalline alkaloid $C_{17}H_{25}O_3N$(3), m.p. 211-212°, characterized as its hydroperchlorate(m.p. 210-212°), methiodide(m.p. 240-242°), and hydrobromide(m.p. 230-232°). Since these properties do not correspond with those of any of the known alkaloids(1) we suggest the trivial name annopodine for this base.

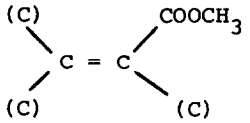
An examination of the infrared, ultraviolet, and n.m.r. spectra of annopodine, O-acetylannopodine(an oil, m.p. of hydroperchlorate, 250-252°(3)) and anhydroannopodine(an oil, prepared by dehydration of annopodine with $POCl_3$-pyridine at room temperature(3)) revealed that annopodine contains the part structures a, b, c, and d below:



a



b



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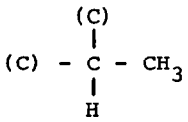


d

a. Infrared absorption at 3625 cm^{-1}(CCl_4 soln., concentration independent) and the formation of a mono O-acetyl derivative(lacking OH absorption in the i.r.) indicated the presence of a single hydroxyl group in annopodine.

Its secondary nature was revealed by the one-proton peak at τ5.99 in the n.m.r., shifted to τ4.84(complex multiplet, $W_{1/2}$ = 10 cps) in O-acetylannopodine. Anhydroannopodine shows a single olefinic proton(absent in the n.m.r. of annopodine itself) at τ4.52, showing that the hydroxyl-bearing carbon is flanked on one side by a methine carbon.

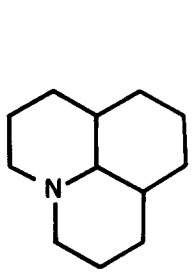
b. The tertiary nature of the nitrogen is revealed by the following observations: annopodine forms a C_{18} methiodide; it fails to undergo N-acetylation; the i.r. spectra of annopodine, O-acetylannopodine, and anhydroannopodine do not show NH absorption. Also, the n.m.r. spectra show that the nitrogen does not carry a simple alkyl group.

c. The i.r. spectrum of annopodine shows absorption at 1715 and 1640 cm^{-1}, and the U.V. spectrum shows a maximum at 225 mμ(log ε 3.8) attributed to the α,β-unsaturated ester(4). The n.m.r. spectrum shows a 3-proton singlet at τ6.28($COOCH_3$) and no olefinic protons. Annopodine is resistant to catalytic hydrogenation.

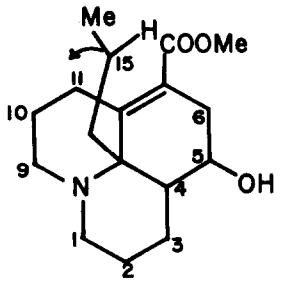
d. The n.m.r. spectra of annopodine, O-acetylannopodine, and anhydroannopodine show 3-proton doublets at τ8.96, 8.90, and 8.84, respectively.

The molecular formula and the nature of the functional groups require that the molecule be tetracyclic. Most of the known mononitrogeneous Lycopodium alkaloids possess a perhydrojulolidine(1) ring system and these afford quinolines on dehydrogenation(1). Dehydrogenation of annopodine gives basic products which from their U.V. and mass spectra appear to be C_{15} and C_{16} alkylquinolines. The base peak in the mass spectra of both annopodine and anhydroannopodine appears at M^+-43 and corresponds to the loss of C_3H_7 (high resolution mass spectrum). The partial structure 2 accounts for all of the data given and fits nicely into the biogenetic pattern of the Lycopodium alkaloids(5), the position of the hydroxyl group and the C-methyl group being dictated in part by biogenetic considerations. To account for the fact that both annopodine and anhydroannopodine readily loss C_3H_7 on electron impact it was felt that the final ring was not formed between C-15 and C-6(anhydroannopodine should then readily loss the elements of propene), but must be

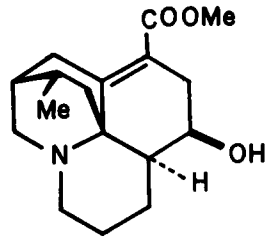
formed by attachment of C-15 to either C-1, C-2, C-3, C-9, C-10, or C-11.



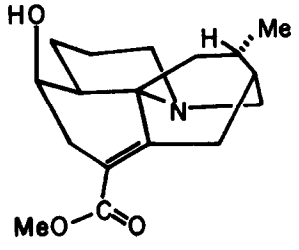
1



2



3



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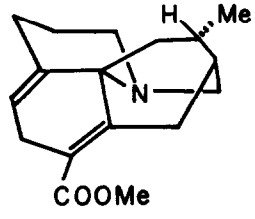
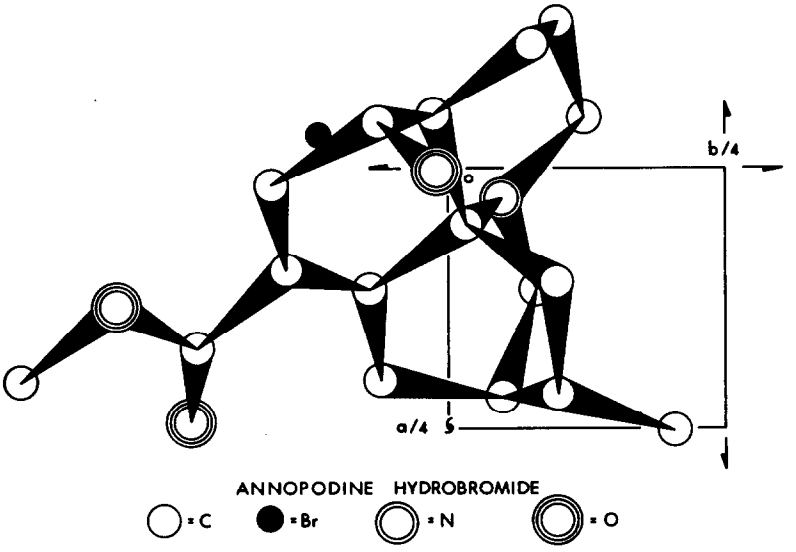


5

Since the quantity of annopodine available was extremely small, and since the partial structure 2 is based in part on biogenetic arguments, we have undertaken an X-ray analysis of annopodine hydrobromide. Annopodine hydrobromide crystallizes from ethyl acetate-dichloromethane in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell of dimensions a=13.4, b=14.0, c=9.0 Å. 1390 reflections from equiiclination Weissenberg photographs taken along the [a] and [c] axes with CuKα radiation were measured. The structure was solved by the heavy atom method and refined by full-matrix least squares methods to an R-factor of 11.3%(6). The molecular structure so derived is depicted below, where all the atoms in the asymmetric unit of the crystal, excluding hydrogen, are shown. Annopodine itself thus has structure 3(=4) and represents a new type of skeleton in this group of alkaloids. The absolute configuration shown was determined from anomalous

dispersion calculations using the observed differences in intensities of Bijvoet pairs of reflections in the Weissenberg photographs.



Dehydration of annopodine gives the unconjugated diene 5. Inspection of molecular models reveals that in the conjugated diene there is a severe distortion of the diene system from coplanarity imposed by the nature of the ring system, whereas the unconjugated system 5 is completely strain free. A complete discussion of the chemistry of annopodine and of the biogenetic implications inherent in its structure will be presented in our full paper.

References

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6. Full details of the X-ray analysis will be published separately.