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THE TRANSFORMATION OF LYCOPODINE INTO ANNOFOLINE

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It has been suggested that lycopodine (I) may be the central intermediate in the biosynthesis of the Lycopodium alkaloids (1), and that it may be oxygenated at C-8 to yield alkaloids of the annofoline (II) type. The C-8 oxygenated compounds may then serve as intermediates in the biosynthesis of alkaloids such as annotinine (III). We wish to report the laboratory realization of the first step in this scheme, i.e. the transformation of lycopodine (I) into annofoline (II, written in the hemiketal form to emphasize the similarity to annotinine).

Lycopodine (I) was first converted to the corresponding lactam (IV) in 45% yield by oxidation with potassium permanganate in acetone[1]. Sodium borohydride reduction of the lactam IV gave, in high yield, the dihydrolactam V (3), m.p. 189-190°, $\nu_{max.}^{nujol}$ 3400, 1600 cm^{-1}. Reduction of the dihydrolactam V with lithium aluminium hydride yielded dihydrolycopodine, confirming the axial orientation of the hydroxyl group in V (4).

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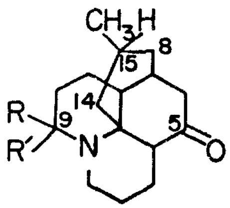
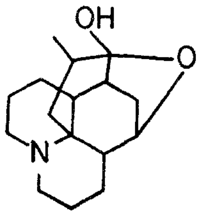
1. The lactam IV has been prepared previously by a different method (2). This transformation was necessary in order to protect the nitrogen atom in some of the subsequent steps.

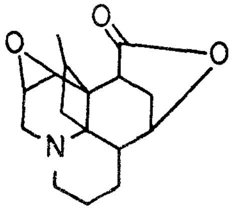


I R = R′ = H

IV R = R′ = O



II



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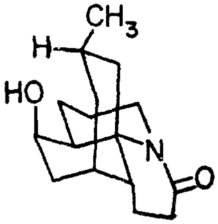
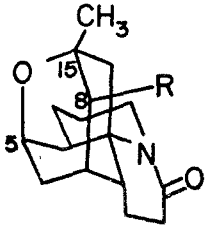


V

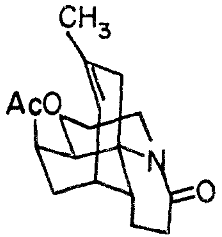


VI R = H

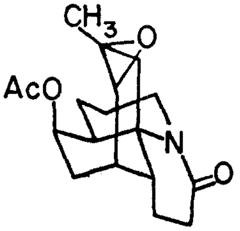
IX R = OAc

X R = OH

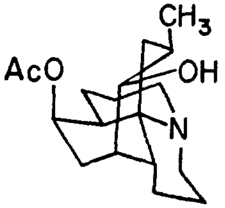
XI R = Carbonyl



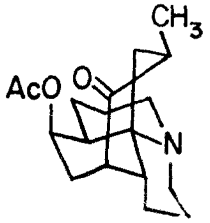
VII



VIII



XII



XIII

Oxidation of hydroxylactam V with lead tetraacetate in refluxing benzene (5) gave, in 90% yield, a compound $C_{16}H_{23}O_2N$(3), m.p. 178-180°, to which we assign the C-5, C-15 ether structure (VI). Compound VI showed lactam absorption (1622 cm^{-1}) but no hydroxyl absorption in the infrared. The n.m.r. spectrum showed singlet methyl absorption at $\tau = 8.78$ as well as a one proton signal at $\tau = 6.33$ due to the hydrogen at C-5.

Treatment of a dilute ethereal solution of VI with boron trifluoride and acetic anhydride yielded the acetoxy olefin VII (3), m.p. 151-152°; $\nu_{max.}^{nujol}$ 1730, 1230, (OAc), 1635 cm^{-1}(lactam). The fact that the doublebond was in the 8,15 position was apparent from the n.m.r. spectrum which showed, besides the $OCOC\underline{H}_3$ signal at $\tau = 8.07$ and the $C\underline{H}OAc$ signal at $\tau = 5.15$, an allylic methyl at $\tau = 8.32$ and a vinyl hydrogen as a doublet (splitting, 6 cps) at $\tau = 4.44$. The relatively large size of the coupling constant is in good agreement with a vicinal coupling but not with a 1,3-allylic coupling (6), and thus excludes the $\Delta^{14(15)}$-olefin. Refluxing the olefin VII with aq. hydrobromic acid regenerated VI.

Oxidation of the olefin VII with m-chloroperbenzoic acid in chloroform gave the epoxide VIII(3), m.p. 212-214°, $\nu_{max.}^{nujol}$ 1730, 1625 cm^{-1}. In agreement with the assigned structure the n.m.r. spectrum showed the methyl signal as a singlet at $\tau = 8.63$.

Attempted rearrangement of the epoxide to the C-8 ketone was unsuccessful, instead treatment of VIII with boron trifluoride-etherate in benzene yielded the acetoxy ether IX (3), m.p. 204-205°, $^{CCl_4}_{max.}$ 1738, 1630 cm^{-1}, n.m.r. signals at τ= 8.85 (3H, singlet, C-16 protons), 7.79 (3H, singlet, acetoxyl methyl), 6.42 (1H, broadened singlet, C-5 hydrogen), 5.3 (1H, multiplet C$\underline{H}$OAc). Hydrolysis of IX with aq. hydrobromic acid yielded the alcohol X(3), m.p. 211-212°, $\nu^{CHCl_3}_{max.}$ 3605, 1605 cm^{-1}. Reaction of VIII with aq. hydrobromic acid gave X directly. Oxidation of X with chromic acid in acetic acid furnished the ketone XI (3), m.p. 215-216°, $\nu^{nujol}_{max.}$ 1720, 1620 cm^{-1}. The ketone XI showed a negative Cotton effect as expected if the ketone is located at C-8. Preliminary attempts to reductively cleave the C-15, oxygen bond $\underline{\alpha}$ to the carbonyl met with failure, and this route was abandoned when it was found that reaction of the olefin VII with excess diborane in tetrahydrofuran followed by treatment of the reaction mixture with alkaline hydrogen peroxide (7) gave a basic product, $C_{18}H_{29}O_3N$ (3), m.p. 178-180°, which showed all the properties expected of the alcohol XII. Infrared spectrum: $\nu^{CHCl_3}_{max.}$ 3600(OH), 1730 and 1240 cm^{-1}(OAc), no lactam absorption. N.m.r. spectrum: τ = 8.90(3H, doublet, splitting 5.5 cps, CHC$\underline{H}_3$) 7.95 (3H, singlet, OCOC$\underline{H}_3$), 6.46 (1H, mult., C$\underline{H}$OH), 5.01(1H, C$\underline{H}$OAc). The assignment of stereochemistry at C-8 and C-15 is based on the assumption that addition of diborane will occur from the less hindered side of the doublebond(7). The reduction of the lactam carbonyl during the hydration was unexpected, and is being investigated in more detail.

Oxidation of the hydroxy compound XII with chromium trioxide-pyridine yielded O-acetylannofoline (XIII) (8), identical (infrared spectrum, thin-layer chromatographic behavior, m.p. and m.m.p. of methiodide) with an authentic sample. Hydrolysis of XIII gave annofoline (II), identical with an authentic sample.

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