THE ALKALOIDS OF *LYCOPODIUM* SPECIES

XII. RELATIONSHIP BETWEEN SOME OF THE MINOR ALKALOIDS AND LYCOPODINE[1]

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ABSTRACT

Reduction of the carbonyl group of lycopodine with lithium aluminum hydride gives rise to dihydrolycopodine which contains a secondary alcoholic group. The new base can be dehydrated to form anhydrodihydrolycopodine and this is identical with alkaloid L14($C_{16}H_{25}N$). Acetylation of dihydrolycopodine produces O-acetyldihydrolycopodine which is identical with alkaloid L2($C_{18}H_{29}O_2N$). On distillation at atmospheric pressure alkaloid L2 is pyrolyzed and gives rise to 7-methylquinoline. Alkaloids L8 and L30 which had been reported previously as different have now been found to be identical.

Lycopodine ($C_{16}H_{25}ON$), the most widely distributed alkaloid in the *Lycopodium* species, contains a carbonyl group as indicated in its infrared absorption spectrum, and confirmed by the formation of a hydrazone and by conversion to a tertiary carbinol via the action of phenyl-lithium (5). It has now been possible also to prepare an oxime of lycopodine. The Beckmann rearrangement of this oxime, however, failed to take place under the usual conditions. Attempted condensation of lycopodine with benzaldehyde failed to give a benzylidene derivative. As previously reported the reduction of lycopodine with the aid of lithium aluminum hydride converted the carbonyl group to a secondary alcoholic group giving rise to dihydrolycopodine (5), a base which could be oxidized with chromic acid back to lycopodine.

Through the action of phosphorus pentachloride it was possible to remove the elements of water from dihydrolycopodine. The product of the reaction, anhydrodihydrolycopodine ($C_{16}H_{25}N$), was an oily base forming a crystalline perchlorate. Whereas the infrared absorption spectrum of dihydrolycopodine showed an absorption band at 3625 $cm.^{-1}$ indicative of a hydroxyl group, that band was absent in the spectrum of anhydrodihydrolycopodine. Alkaloid L14 which occurs in *L. tristachyum* (9) is isomeric with this base and gives rise to a perchlorate having the same optical rotation and the same melting point as anhydrodihydrolycopodine perchlorate. Admixture failed to alter the melting point and the X-ray diffraction patterns of both salts were superimposable. It can therefore be concluded that alkaloid L14 is anhydrodihydrolycopodine.

Dihydrolycopodine could be acetylated readily to O-acetyldihydrolycopodine, $C_{18}H_{29}O_2N$, which was crystalline and formed a crystalline perchlorate. The acetylated base was isomeric with alkaloid L2 occurring in *L. flabelliforme* (6). The infrared absorption spectrum of alkaloid L2 showed no absorption in the OH region, but contained a sharp absorption peak in the carbonyl region at 1730 $cm.^{-1}$ Further, the spectrum showed absorption in the region

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near 1239 cm.$^{-1}$ normally displayed by acetates. This absorption consisted of a double peak at 1228 and 1241 cm.$^{-1}$ The occurrence of a single maximum near 1239 cm.$^{-1}$ or of multiple peaks in this region has been related to cis–trans configuration (1, 4) or to the equatorial or polar orientation of the acetoxy group (2, 3). When the structure of lycopodine becomes better known this observation may prove useful. Both O-acetyldihydrolycopodine and its perchlorate had the same respective melting points as alkaloid L2 and its perchlorate, and admixture of the two bases and the two salts failed to alter these melting points. X-ray powder diagrams of the two perchlorates were exactly identical. Hence, alkaloid L2 is naturally occurring O-acetyldihydrolycopodine. Distillation of the acetylated base at atmospheric pressure brought about partial decomposition, the distillate consisting mostly of the unchanged material and a small quantity of an oily base which proved to be 7-methylquinoline. This supplied further evidence of the readiness with which lycopodine gives rise to 7-methylquinoline.

Alkaloid L8, $C_{15}H_{25}O_2N$, m.p. 180° (perchlorate, m.p. 318°), has been reported as occurring in *L. annotinum* (7). Later, alkaloid L30, m.p. 178°, forming a perchlorate melting at 311°, was found in *L. annotinum* var. *acrifolium* (8). On closer examination it has now been established that alkaloids L8 and L30 are identical, admixture of the bases and of their perchlorates failing to depress the respective melting points.

EXPERIMENTAL[3]

Lycopodine

Lycopodine had $[\alpha]_D^{26} -24.5°$ (c, 1.10 in absolute ethanol). Its pK, 7.44 (pH at half titration), was obtained by titration of the perchlorate in 50% methanol. The equivalent of the salt thus found was 347 (calcd. 347.4).

Lycopodine Oxime

Lycopodine (620 mgm.) dissolved in aqueous ethanol (20 ml.) was treated with molar hydroxylamine solution (2.5 ml.) and molar sodium acetate solution (3 ml.). The mixture was heated on the steam bath for three hours, cooled, and a drop of 10 *N* sodium hydroxide added. A solid was precipitated which was filtered and dried (307 mgm.), m.p. 220–230°. Recrystallization from aqueous ethanol gave colorless prismatic needles, m.p. 262–264°. Calcd. for $C_{16}H_{26}ON_2$: C, 73.25; H, 9.99; N, 10.68. Found: C, 72.74, 72.82; H, 9.77, 9.85; N, 11.02, 10.94%. The mother liquors yielded unchanged lycopodine (80 mgm.).

Dihydrolycopodine

This was prepared by the action of lithium aluminum hydride on lycopodine as previously described (5). It crystallized from ether as colorless prisms, m.p. 168°. Calcd. for one active hydrogen, 0.40; found, 0.44% (Zerewitinow). Its pK was 9.2 (value of pH at half titration of the perchlorate in 50% aqueous methanol), and the equivalent weight of the salt was 349 (calcd. 349.5). The infrared absorption spectrum of dihydrolycopodine contained no absorp-

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[3] *All melting points are corrected.*

tion in the carbonyl region, but contained an absorption band at 3625 cm.$^{-1}$ indicative of a hydroxyl group.

Oxidation of Dihydrolycopodine

The base (94 mgm.) and chromic oxide (180 mgm.) were dissolved in purified glacial acetic acid (20 ml.) and the mixture maintained at 25° for six days. The brown solution was diluted with water (5 ml.), made slightly alkaline with sodium hydroxide, and extracted exhaustively with chloroform. The chloroform extract was washed repeatedly with 2*N* hydrochloric acid and the combined aqueous washings made alkaline with sodium hydroxide and extracted repeatedly with chloroform. This final combined chloroform solution was dried over anhydrous sodium sulphate and concentrated to yield an oil which solidified on seeding with a minute crystal of lycopodine (72 mgm.). After recrystallization the product melted at 116° either alone or after admixture with an authentic sample of lycopodine.

Anhydrodihydrolycopodine

Dihydrolycopodine (122 mgm.) and phosphorus pentachloride (200 mgm.) were dissolved in hot dry xylene (20 ml.) and heated under reflux in an atmosphere of nitrogen for six hours, during which time a considerable volume of hydrogen chloride was liberated. Water (20 ml.) was added to the cooled solution and the mixture shaken vigorously. The aqueous layer was separated and the xylene solution further extracted with three 20 ml. portions of 2 *N* hydrochloric acid. The combined acid extract was extracted once with a little chloroform, made slightly alkaline with sodium hydroxide, and extracted exhaustively with chloroform. This extract was dried and evaporated, leaving a brown syrup (103 mgm.) which was distilled *in vacuo*. A colorless oil was thus obtained, b.p. 125–130° at 1 mm., which slowly became yellow on standing. The infrared absorption spectrum of anhydrodihydrolycopodine in chloroform showed no hydroxyl absorption.

The bulk of the distilled oil was converted to the perchlorate in methanol by the usual procedure. The crystalline perchlorate separated from aqueous methanol as plates, m.p. 234–237°. Two recrystallizations from acetone yielded colorless prisms, m.p. 238–239°. Calcd. for $C_{16}H_{25}N.HClO_4$: C, 57.91; H, 7.90. Found: C, 57.94; H, 7.85%. $[\alpha]_D^{26}-107°$ (c, 1.10 in methanol). In admixture with the perchlorate of alkaloid L14 (m.p. 238°) the melting point of anhydrodihydrolycopodine perchlorate was unchanged. Alkaloid L14 perchlorate has $[\alpha]_D^{26}-105.5°$ (c, 1.86 in methanol). The X-ray diffraction patterns of both perchlorates were superimposable.

Acetyldihydrolycopodine

Dihydrolycopodine (200 mgm.), trifluoracetic anhydride (0.16 ml.), and acetic acid (0.1 ml.) were mixed and maintained at 25° overnight. The solution was poured into excess sodium bicarbonate solution, extracted exhaustively with ether, and the dried (anhydrous sodium sulphate) extract evaporated down to a pale yellow oil which solidified on scratching, m.p. 90–95°. This product was dissolved in methanol and converted to a perchlorate in the usual way (yield 140 mgm., m.p. 240–242°). Recrystallization three times from methanol yielded colorless prisms, m.p. 246–247° when immersed at 205°. The melting point, however, varies with the rate of heating and the temperature of immersion. When heated from room temperature the melting point can be as low as 230°. Calcd. for $C_{18}H_{29}O_2N.HClO_4$: C, 55.15; H, 7.71; N, 3.57. Found: C, 55.10, 55.27; H, 7.72, 7.71; N, 3.37, 3.53%. The pK of the base determined by titration of the perchlorate in 50% methanol with 0.063 *N* sodium hydroxide was 8.4 (value of pH at half titration) and the equivalent weight of the salt was 390 (calcd. 392). Alkaloid L2 perchlorate (m.p. 231°) was isomeric with the perchlorate of acetyldihydrolycopodine and in admixture with it melted at 246–247° when immersed at 205°. X-ray diffraction patterns of the two perchlorates were superimposable.

Acetyldihydrolycopodine perchlorate was dissolved in the minimum volume of water, the solution made alkaline with ammonia and the precipitated white needles collected, washed with water, and dried, m.p. 95–96°. In admixture with alkaloid L2 (m.p. 97°) the base melted at 95–96°. The acetylated base was also obtained by the action of acetic anhydride on dihydrolycopodine. The infrared absorption spectrum of acetyldihydrolycopodine shows absorption bands at 1730 $cm.^{-1}$ in the carbonyl region and at 1238 and 1241 $cm.^{-1}$ in the "acetyl region."

A 5 *N* solution of sodium hydroxide in 50% methanol (2 ml.) was added to acetyldihydrolycopodine (50 mgm.) dissolved in methanol (3 ml.) and the solution maintained at 40–50° overnight. The bulk of the solvent evaporated during this time. The aqueous solution was cooled and the separated oil which solidified was collected, washed, and dried (43 mgm.), m.p. 160–163°. In admixture with an authentic specimen of dihydrolycopodine (m.p. 168°) it melted at 164–165°.

Thermal Decomposition of Acetyldihydrolycopodine

Acetyldihydrolycopodine (700 mgm.) was heated in a stream of nitrogen under the vacuum of a water-pump in a small distilling flask. Almost all of the compound distilled unchanged. The distillate was redistilled at atmospheric pressure. A first fraction was obtained which was slightly yellow (480 mgm.) and a second high boiling fraction (155 mgm.) consisted of a colorless oil with a strong quinoline-like odor. The first fraction was converted to a perchlorate in acetone–ether, m.p. 216–220°. Recrystallization from methanol gave colorless rhombs, m.p. 246–247° (immersed at 205°) which showed no depression when mixed with acetyldihydrolycopodine perchlorate. The high boiling fraction was dissolved in dilute hydrochloric acid and extracted with ether. The ether extract yielded only a small trace of oil which was discarded. The acidic solution was made alkaline with sodium hydroxide and extracted exhaustively with chloroform. The extract was dried over anhydrous sodium sulphate and distilled on the steam bath to remove the solvent. There was left an oil (20 mgm.) which was converted to a picrate in methanol. After recrystallization from methanol the picrate consisted of lemon-yellow needles, m.p. 235–236° either alone or in admixture with an authentic specimen of 7-methylquinoline picrate.

Alkaloids L8 and L30

Alkaloid L8 ($C_{16}H_{25}O_2N$) was reported as having m.p. 180° and forming a perchlorate, m.p. 318° (4). Alkaloid L30 ($C_{16}H_{25}O_2N$), m.p. 178°, formed a perchlorate, m.p. 311°. In admixture, the two bases had the same melting point and so had the two perchlorates.

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REFERENCES

1. Dauben, W. G., Hoerger, E., and Freeman, N. K. J. Am. Chem. Soc. 74: 5206. 1952.
2. Fürst, A., Kuhn, H. H., Scotoni Jr., R., and Günthard, H. H. Helv. Chim. Acta, 35: 951. 1952.
3. Hirschmann, H. J. Am. Chem. Soc. 74: 5357. 1952.
4. Jones, R. N., Humphries, P., Herling, F., and Dobriner, K. J. Am. Chem. Soc. 73: 3215. 1951.
5. MacLean, D. B., Manske, R. H. F., and Marion, L. Can. J. Research, B, 28: 460. 1950.
6. Manske, R. H. F. and Marion L. Can. J. Research, B, 20: 87. 1942.
7. Manske, R. H. F. and Marion, L. Can. J. Research, B, 21: 92. 1943.
8. Manske, R. H. F. and Marion, L. J. Am. Chem. Soc. 69: 2126. 1947.
9. Marion, L. and Manske, R. H. F. Can. J. Research, B, 22: 1. 1944.