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THE ALKALOIDS OF LYCOPODIUM CERNUUM

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In 1948 Marion and Manske reported (1) an examination of the alkaloids of Lycopodium cernuum L. We were prompted to reexamine this species since it was reported to contain none of the commonly occuring Lycopodium alkaloids (2) but to contain an alkaloid, named cernuine, which was unique to this species. Besides cernuine the earlier workers (1) reported the isolation of nicotine and small amounts of a crystalline substance, m.p. 218°, which was designated alkaloid L.33 but which was not further characterized. By column chromatography (alumina) of the crude bases of L. cernuum we have succeeded in isolating in approximately equal amounts two crystalline bases. The less polar compound melted at 106° and was identical with a sample of cernuine supplied by R. H. Manske (1). The more polar compound, which melted at 230° and for which we suggest the name lycocernuine, was identical to alkaloid L.33(1).

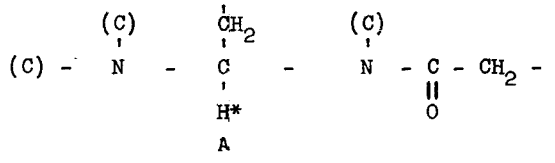
Our analytical and mass spectral data (3) confirmed the molecular formula $C_{16}H_{26}ON_2$ for cernuine and established

the formula $C_{16}H_{26}O_2N_2$ for lycocernuine. Both cernuine and lycocernuine titrate as monoacidic bases (pK (50% MeOH) 6.3 and 6.4, respectively) and form C_{17} methiodides suggesting that in both cases the basic nitrogen is tertiary. This is confirmed in the case of cernuine by the fact that the infrared spectrum (CCl_4) shows no absorption above 3000 cm^{-1}. The absence of NH absorption coupled with the presence of a strong band at 1640 cm^{-1} suggests that the second (non-basic) nitrogen and the oxygen are present as part of a tertiary amide or lactam grouping. The infrared spectrum (CCl_4) of lycocernuine shows, besides the lactam carbonyl at 1640 cm^{-1}, absorption at 3620 cm^{-1}, indicative of a non H-bonded hydroxyl. Besides the above mentioned bands, both compounds show moderately intense absorption at 1410 cm^{-1}, indicative of a methylene group adjacent to the carbonyl group (4). This latter band disappears when the carbonyl is reduced. Acetylation of lycocernuine with acetic anhydride - pyridine yields basic O-acetyllycocernuine, $C_{18}H_{28}O_3N_2$(3), $\gamma_{max.}^{CCl_4}$ 1737, 1645, 1410, 1225 cm^{-1}. The appearance of a peak at 5.06 τ(1H, quartet, shifted down from 6.2 τ in lycocernuine itself) in the NMR spectrum of O-acetyllycocernuine revealed the secondary nature of the hydroxyl group.

Reduction of cernuine with lithium aluminum hydride gave dihydrodeoxycernuine, $C_{16}H_{28}N_2$(3), m.p. 64-65°, pK_{mcs} 8.55, 6.90. Similarly, reduction of lycocernuine yielded dihydrodeoxylycocernuine. Both of the dihydrodeoxy compounds lacked carbonyl and olefinic absorption in the

infrared and olefinic protons in their NMR spectra, indicating the lack of further unsaturation and hence the tetracyclic nature of the bases.

The NMR spectra of cernuine and lycocernuine were very similar except for those peaks associated with the hydroxyl group in lycocernuine. Both compounds showed signals for a secondary C-methyl at 9.13τ(J=6.5 cps) and both showed a one proton quartet at 4.54τ. This latter signal is assigned to the starred hydrogen in partial structure A, which also incorporates the structural features outlined above. In cernuine methiodide this signal appears at 4.13τ while in dihydrodeoxycernuine it has moved upfield to 6.40τ. The large shift which occurs on reduction of the carbonyl group probably indicates that the starred hydrogen lies in the deshielding region (6a) of the carbonyl group. Careful integration of the cernuine spectrum reveals a total of six protons at lower field than 7.8τ, suggesting that the



A

bracketed carbons in part structure A carry a total of only three hydrogens.

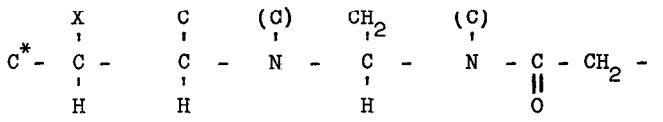
Oxidation of lycocernuine with chromic acid in acetone (7) yielded dehydrolycocernuine, $C_{16}H_{24}O_2N_2$(3), m.p. 162 - 164°, $\nu_{max.}^{nujol}$ 1700, 1635, 1410 cm^{-1}. Dehydrolycocernuine does not display basic properties, i.e. it is insoluble in dilute

mineral acid and its titration curve shows no inflection when it is titrated with 1 N H_2SO_4 in 80% methyl cellosolve. The likelihood that the newly introduced carbonyl group is an α-aminoketone rather than a γ-lactam is indicated by the fact that dehydrolycocernuine shows carbonyl n→π* absorption at 318 mμ (ε=64) and a single Cotton effect ($[\alpha]_{337}$ + 1280° (peak), $[\alpha]_{295}$ - 1560° (trough)) in its ORD spectrum. The newly introduced carbonyl group is readily reduced with sodium borohydride to give isolycocernuine, $C_{16}H_{26}O_2N_2$(3), m.p. 211-212°. In the NMR spectrum of dehydrolycocernuine the low field quartet is now shifted to 3.91τ and a new one proton signal appears at 6.28τ (-CO-C<u>H</u>-N<).

Treatment of lycocernuine with methanesulfonyl chloride in pyridine, followed by reaction of the crude mesylate with hot alcoholic sodium hydroxide furnished anhydrolycocernuine, $C_{16}H_{24}ON_2$(3), m.p. 139-142°, $\nu_{max.}^{nujol}$ 1655, 1635, 1420 cm^{-1}. The NMR spectrum showed the presence of a single olefinic proton as a complex multiplet centered at 5.22τ. The chemical shift indicated an enamine β-proton (8). Catalytic hydrogenation of anhydrolycocernuine gave two products as evidenced by thin layer chromatography (t.l.c.). The minor component was identical by t.l.c. (on both alumina and silica gel and with several solvent systems) with cernuine. Lack of material has so far prevented further characterization of the minor hydrogenation product.

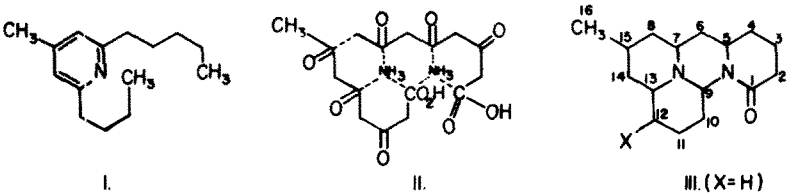
On the basis of this evidence we may now write partial structure B for cernuine (X=H) and lycocernuine (X=OH). The

bracketed carbons carry a total of two hydrogens and the starred carbon is not fully substituted.

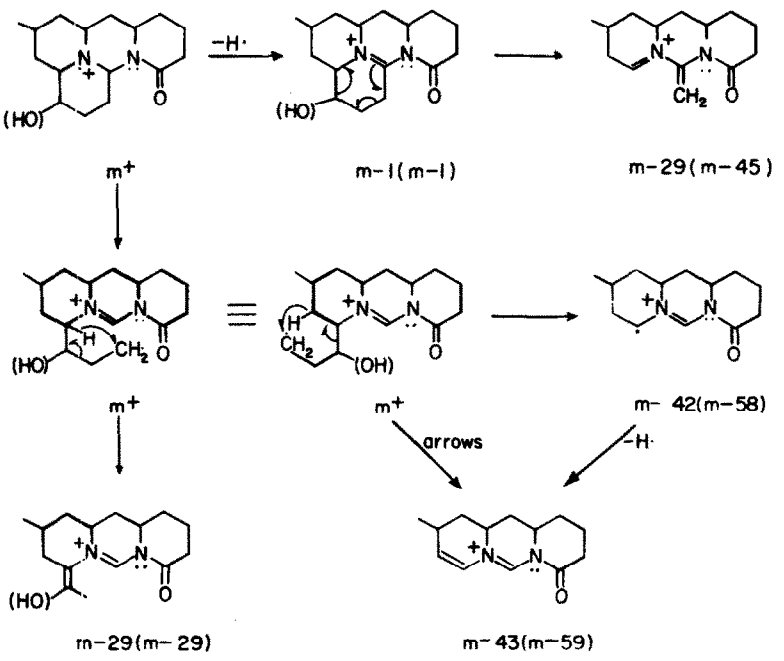


B

From partial structure B it is clear that these alkaloids must differ from the known types (2,9) of Lycopodium alkaloids. Dehydrogenation of cernuine with palladium-charcoal at 300° followed by preparative t.l.c. of the basic components provided, in about 10% yield, 2-n-butyl-4-methyl-6-n-pentylpyridine (I), the structure of which followed from an examination of its spectral properties. The UV spectrum ($\lambda_{max.}^{EtOH}$ 264, 268, 271.5 mμ) was almost identical with that of sym-collidine, the NMR spectrum confirmed the lack of β-substituents (signal at 3 19τ(6b) corresponding to two protons using the methyl absorption (three protons) at 7.69τ as an internal standard) and indicated the presence of a methyl group at the 4-position (7.69τ, triplet, J=0.5 cps, collapses to a singlet when the signal at 3.19 is simultaneously irradiated). A 4-proton triplet at 7.22τ suggested there were two benzylic methylenes and a complex 6-proton signal at 9.0-9.15τ indicated two methyl groups on saturated carbon. A broad signal at 8.1 - 8.7τ contained 10 - 12 protons. The mass spectrum showed the parent peak at m/e 219 ($C_{15}H_{25}N$), the base peak at 163 (loss of butene from pentyl side chain (10)), and the second most intense peak at 177 (loss of propene



I. II. III. (X=H) IV. (X=OH)



FRAGMENTATION SCHEME

from butyl side chain (10)). Both the mass spectrum and the NMR spectrum were identical to an authentic sample of 2-n-butyl-4-methyl-6-n-pentylpyridine (m.p. of chloroplatinate, 189 - 191° (3)) prepared by alkylation of 2-n-butyl-4-methylpyridine (11) with n-pentyllithium.

A plausible biogenetic scheme for the Lycopodium alkaloids has been suggested by Conroy (12). This scheme involves the condensation of ammonia and two 3,5,7-triketooctanoic acid equivalents (II). If we assume that the C-4 methyl of the pyridine I represents the C-methyl group of cernuine and that this group is derived from the terminal methyl of one of the polyketooctanoic acid chains, aldol condensation of the C-7 carbonyl of this chain with the methyl group of the other chain followed by condensation with two equivalents of ammonia (dashed lines in II) and adjustment of the oxidation level leads to a structure, III (13), for cernuine which incorporates part structure B and which readily accounts for the formation of the pyridine I (loss of lactam carbonyl and nitrogen).

The mass spectrum of cernuine shows intense peaks (percentage of base peak in brackets) at M^+=262 (48), M-29 (100), M-42(74) and M-43(48) while that of lycocernuine shows M^+=278(20), M-29(23), M-45(12), M-58(60), M-59(100). The fact that the M-42 and M-43 peaks of cernuine are shifted to M-58 and M-59 in lycocernuine while the M-29 peak is in part retained and in part shifted to M-45 is best explained if the hydroxyl group of lycocernuine is located at C-12 as shown in the Fragmentation Scheme (14).

Structure IV for lycocernuine also incorporates the features of partial structure B. Cernuine (III) and lycocernuine (IV) thus represent an interesting new type of Lycopodium alkaloid.

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(13) The numbering system used is an adaptation of the scheme suggested by Wiesner (ref. 9) for the Lycopodium alkaloids.

(14) For a discussion of the mass spectra of piperidines see H. Budzikiewicz, C. Djerassi, D. H. Williams, Interpretation of Mass Spectra of Organic Compounds, Holden-Day, San Francisco, 1964. p. 100.