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THE STRUCTURE OF SELAGINE

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THE results of our investigation of the alkaloid selagine, isolated from Lycopodium selago, can be rationalized by the complete structure I. Selagine, m.p. 224-226°, $[\alpha]_D^{25}$ = -99° (CH_3OH) (Found: C, 73.82; H, 7.58; O, 6.73; N, 11.81; C-CH_3, 10.23. $C_{15}H_{18}ON_2$ requires C, 74.35; H, 7.46; O, 6.63; N, 11.56; 1 C-CH_3, 6.2), contains an α-pyridone grouping (λ_{max} (C_2H_5OH) 231 mμ, ε 10700; 313 mμ, ε 8500; ν max ($CHCl_3$) 1653, 1620, 1553 cm^{-1}), a basic nitrogen atom (pK_a = 7.18) and two C-methyl groups. Reduction of the alkaloid with Adams catalyst in acetic acid gave tetrahydroselagine (II), m.p. 260° (Found: C, 72.87; H, 8.80; O, 6.40; N, 11.49. $C_{15}H_{22}ON_2$ requires C, 73.14; H, 9.00;

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[3] Holder of an N.R.C. postdoctoral fellowship on leave from Kyushu University, Japan.

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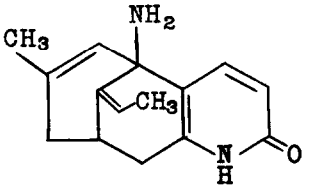

I

O, 6.49; N, 11.37), while a similar reduction in ethanol yielded dihydroselagine (III), m.p. 260-265° (Found: C, 73.82; H, 8.35; O, 6.97; N, 11.41. $C_{15}H_{20}ON_2$ requires C, 73.74; H, 8.29; O, 6.55; N, 11.46). The fact that I, II and III have identical ultraviolet spectra shows that selagine contains two isolated double-bonds in addition to the α-pyridone grouping, and is therefore tricyclic. This conclusion is supported by NMR spectra, which also give valuable information about the substitution of the α-pyridone ring. [5] The low-field region of the spectrum of II contains only two doublets at 946 and 999 cycles/sec. corresponding to two pyridone protons (J_{H-H} = 8.5 cycles/sec.). The spectrum of selagine contains, in addition to the pyridone peaks, a multiple peak at 1039 cycles/sec.

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[5] All NMR spectra, with the exception of pyridine (VII), were measured in $CDCl_3$ with a 56.4 Mc. Varian instrument and toluene as an external reference. The chemical shifts are recalculated to the 40 Mc. scale with the aromatic proton of toluene set arbitrarily at 1000 cycles/sec.

with an integrated surface corresponding to 2 protons and dihydroselagine shows a singlet at 1045 cycles/sec. (1 proton). Selagine therefore contains a disubstituted pyridone ring and the two remaining double-bonds are both trisubstituted. The singlet at 1045 cycles/sec. in the spectrum of dihydroselagine indicates that there is no hydrogen in the position α to the vinylic hydrogen in this compound.

The high-field portions of the NMR spectra of I, II and III revealed the relative position of the two unconjugated double-bonds and the two methyl groups in selagine. While the peak corresponding to protons with the greatest shielding is situated at 1192 cycles/sec. in selagine, dihydroselagine shows one peak with an area of 3H at 1215 cycles/sec., and tetrahydroselagine two peaks at 1216 and 1227 cycles/sec., each with an area of 3H. Both isolated double-bonds in selagine are therefore directly joined to a methyl group. Additional information about the environment of the double bonds was obtained by the oxidation of I, II and III under Kuhn-Roth conditions followed by steam distillation and chromatography of the volatile acids on silicic acid according to Marvel and Rands. [6] Selagine

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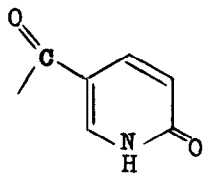
[6] C. S. Marvel and R. D. Rands, Jr., J. Amer. Chem. Soc. 72, 2642 (1950).

gave only acetic acid, while dihydro- and tetrahydroselagine yielded propionic acid and acetic acid under the same conditions. Compounds II and III therefore contain an ethyl group, while selagine itself must contain an ethylidene grouping and an endocyclic double-bond substituted in the way indicated in structure I.

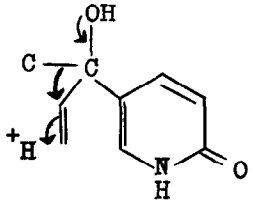
Treatment of selagine with nitrous acid gave selaginol (IV), m.p. 265-267°, $[\alpha]_D^{25} = -103°$ (CH_3OH) (Found: C, 73.40; H, 7.19; O, 13.63; N, 5.78. $C_{15}H_{17}O_2N$ requires C, 74.04; H, 7.04; O, 13.15; N, 5.76). The similarity of rotation and ultraviolet, infrared and NMR spectra of IV and I indicated that no rearrangement had occurred during the diazonium ion decomposition. Catalytic reduction of selaginol gave tetrahydroselaginol (V), m.p. 236-238° (Found: C, 72.86; H, 8.57; O, 12.99; N, 5.64. $C_{15}H_{21}O_2N$ requires C, 72.88; H, 8.50; O, 12.96; N, 5.67), which on treatment with phenylphosphonic dichloride yielded an oily dichlorocompound (VI) (ν max ($CHCl_3$) 1577, 1563 cm^{-1}; no OH or α-pyridone peaks in the IR spectrum). Catalytic reduction of VI removed both chlorine atoms and gave the oily pyridine (VII) which was purified through a crystalline picrate, m.p. 154-158°, and by distillation (Found: C, 83.61; H, 9.99; N, 6.64. $C_{15}H_{21}N$ requires C, 83.67; H, 9.83; N, 6.50). The NMR spectrum of compound VII (a

quartet at -144 cycles/sec. for α-hydrogen; an unsymmetrical doublet at -108 and -103 cycles/sec. for γ-hydrogen; an unsymmetrical quartet at -95 to -87 cycles/sec. for β-hydrogen; Jα-β = 4.5 cycles/sec.; Jα-γ = 1.5 cycles/sec.; Jβ-γ = 8 cycles/sec.) clearly showed the presence of a 2,3-disubstituted pyridine ring. [7] Selagine must therefore contain a 5,6-disubstituted α-pyridone ring.

While selagine was completely inert to 6N hydrochloric acid, treatment of selaginol with concentrated hydrochloric acid yielded the ketone (VIII), m.p. 268-270° (Found: C, 73.69; H, 7.04; O, 13.94; N, 5.77. $C_{15}H_{17}O_2N$ requires C, 74.04; H, 7.04; O, 13.15; N, 5.76). The ultraviolet spectrum of VIII (λ_{max} (C_2H_5OH) 284 mμ, ε 19300) indicated the presence of the chromophore (VIIIa).



VIIIa



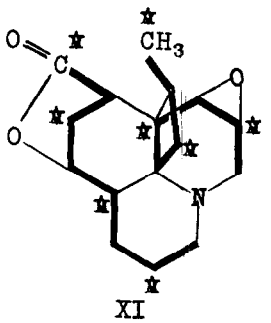
VIIIb

[7] The spectrum was taken with a 40 Mc. Varian instrument in $CDCl_3$. The chemical shifts are calculated (at 40 Mc./sec. frequency) relative to water. For comparison, see e.g., F.A.L. Anet and C.R. Eves, Canad. J. Chem. 36, 902 (1958).

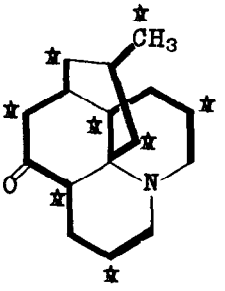
Catalytic reduction of VIII followed by a reduction with sodium borohydride yielded the alcohol (IX), m.p. 203-205° (ultraviolet spectrum identical with V) (Found: C, 71.91; H, 8.31; O, 13.65; N, 5.60. $C_{15}H_{21}O_2N$ requires C, 72.88; H, 8.50; O, 12.96; N, 5.67), which was not identical with tetrahydroselaginol (V). The possibility that the formation of the ketone (VIII) involved a skeletal rearrangement was supported by the finding that the hydroxyl group in tetrahydroselaginol (V) could not be oxidized with chromium trioxide in acetic acid or acetylated in boiling acetic anhydride/sodium acetate. The primary amino group of selagine is therefore attached to a tertiary carbon atom. The formation of the ketone (VIII) can be formulated as indicated in the structure VIIIb and it establishes the relative position of the primary amino group, the α-pyridone ring, and one of the two double-bonds in selagine.

Dehydrogenation of selagine with palladium on charcoal at 300° yielded 6-methyl-2-pyridone; dehydrogenation with selenium at 320° yielded an oily base (X) characterized as a crystalline picrate, m.p. 195-198° (Found: C, 58.29; H, 4.00. $C_{21}H_{16}O_7N_4$ requires C, 57.79; H, 3.69). Base (X) is an azaanthracene (ultraviolet spectrum) and on the basis of its analysis and the proposed structure I for selagine can be formulated as 5,7-dimethyl-1-azaanthracene.

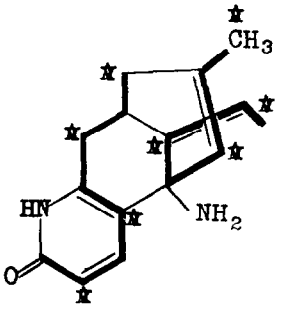
A close inspection of structure I and the structure of annotinine (XI) [8] and lycopodine (XII) [9] reveals an interesting biogenetic relationship. The biogenesis of annotinine (XI) is best visualized as the condensation of



XI



XII



XIII ≡ I

two eight-carbon chains (each formed from 4 acetate units). [10,11] Lycopodine is then built up on the same

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[8] K. Wiesner, Z. Valenta, W.A. Ayer and C. Bankiewicz, Chem. and Ind. 1019 (1956); K. Wiesner, W.A. Ayer, L.R. Fowler and Z. Valenta, Chem. and Ind. 564 (1957); K. Wiesner, Z. Valenta, W.A. Ayer, L.R. Fowler and J.E. Francis, Tetrahedron 4, 87 (1958); M. Przybylska and F.R. Ahmed, Acta Cryst. 11, 718 (1958).

[9] Formula (XII) was proposed for lycopodine by Dr. D.B. McLean, McMaster University, Canada. (Private communication)

[10] When structure XI was first proposed for annotinine at the U.N.B. summer seminar (Grand Manan, 1956), Professor H. Conroy proposed this ingenious biogenetic possibility. (H. Conroy, forthcoming communication)

[11] "Methyl" carbons are marked with an asterisk.

principle and differs from annotinine only by a different condensation of the two chains. Selagine (XIII ≡ I) differs from lycopodine only by the attachment of one of the chains to another nitrogen atom and by the absence of a terminal carboxyl group in the other chain. The clarification of the structure of α- and β-obscurine by W. A. Ayer et al. [12] establishes these two alkaloids as biogenetic links between lycopodine and selagine.

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[12] W. A. Ayer and G. G. Iverbach, Tetrahedron Letters No. 10, 19 (1960), preceding paper.