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BIOGENESIS OF *LYCOPODIUM* ALKALOIDS[1]

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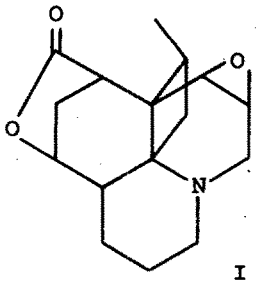
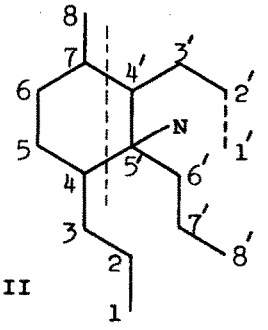
IN 1956, shortly after the brilliant elucidation of structure of the *Lycopodium* alkaloid annotinine (I) by Wiesner, Valenta and their coworkers[2], we considered that



I



II

the skeleton inherent in I might owe its biogenetic derivation to the condensation of two eight-carbon

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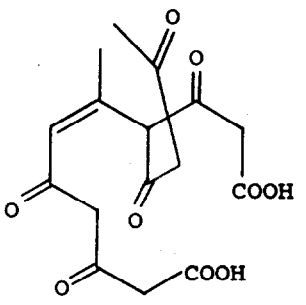
[1] Contribution number 1612 from the Sterling Chemistry Laboratory at Yale University.

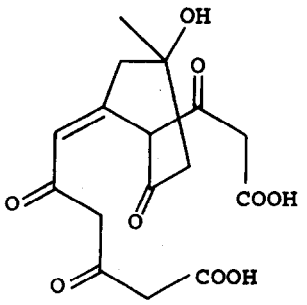
[2] K. Wiesner, Z. Valenta, W. A. Ayer and C. Bankiewicz, *Chem. and Ind.* 1019 (1956); K. Wiesner, W. A. Ayer, L. R. Fowler and Z. Valenta, *Chem. and Ind.* 564 (1957); K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis, *Tetrahedron* 4, 87 (1958); *Cf.* M. Przybylska and F. R. Ahmed,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

polyacetate straight chains of the type believed to play a part, for example, in fatty acid biosynthesis, or in the formation of macrolide antibiotics[3]. With the recent elaboration of structures of further alkaloids of this class, notably selagine[4], lycopodine[5], lycodine[6] and the obscurines[6], whose formulae are all based upon the framework (II), this hypothesis is seen to gain support. A speculative biosynthesis beginning with two molecules of a 3,5,7-triketo-octanoic acid equivalent accounts not only for the grosser aspects (II) but for many structural details as well. Of course, while the scheme is plausible enough, it will nontheless require experimental scrutiny.

The order of steps is somewhat uncertain; however the sequences shown will serve for illustration. The common intermediate (III) results from aldol condensation between the C-7 carbonyl and the C-4′ methylene, followed by dehydration. A second aldol condensation links C-8 and C-7′,



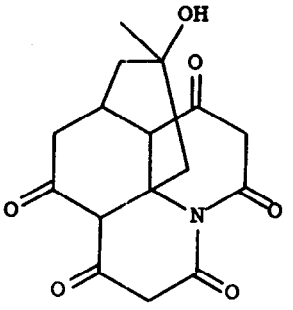
III



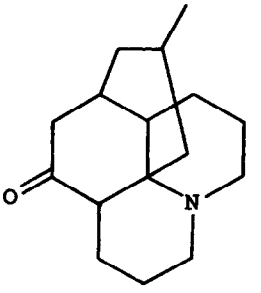
IV

[3] R.B. Woodward, Angew. Chem. 69, 50 (1957).
[4] Z. Valenta, H. Yoshimura, E.F. Rogers, M. Ternbah and K. Wiesner, Tetrahedron Letters No. 10, 26 (1960).
[5] D.B. MacLean and J.A. Harrison, In press. Cf. ref. 4.
[6] W.A. Ayer and G.G. Iverach, Tetrahedron Letters No. 10, 19 (1960).

as in (IV), and after reduction of the double bond, Mannich condensation with an ammonia molecule joins C-4 and C-5'. Completion of both δ-lactam rings gives (V), and further reduction at carbons 1, 1', 3, 3', and 7' results in lycopodine (VI)[5].

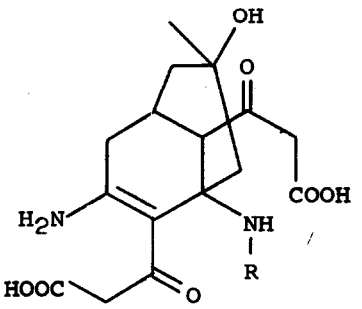


V

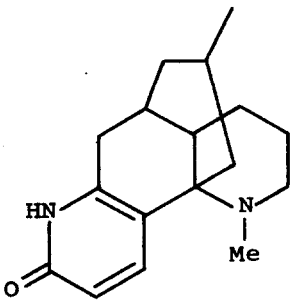


VI

Similarly, formation of the obscurines requires the intermediate (VII), where the first nitrogen has been methylated and the second nitrogen has been introduced at the site of the C-5 carbonyl. After lactam closure and removal of oxygen we have the pyridone (VIII) (β-obscurine)[6],



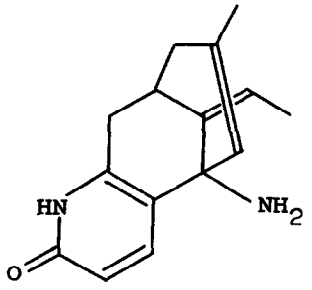
VII, R = Me
X, R = H



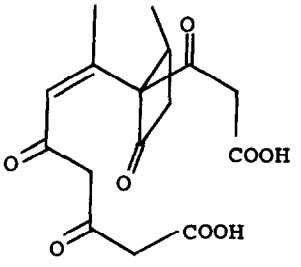
VIII

the corresponding dihydropyridone (α-obscurine), or the pyridine (lycodine)[6].

In the case of selagine (IX)[4], we proceed from X, but the carboxyl carbon (C-1′) is lost (decarboxylation of a β-ketoacid) signs of unsaturation at C-3′ and C-7′ are still present in the final alkaloid.



IX



XI

The scheme for annotinine (I) represents only a minor deviation from these pathways. We suggest that, in III or at least prior to the formation of IV, the methyl carbon C-8 becomes oxidized to the level of carboxyl. With aldolization at C-8 prohibited, an alternative involves closure at C-4′, with formation of the cyclobutane ring of XI. Again, Mannich condensation and lactamization (as in IV⟶V), adjustment of oxidation state and, in this case, lactonization, results in the naturally occurring alkaloid (I).

It is a fact that each and every oxygenated position of the postulated two 3,5,7-triketooctanoic acid precursor molecules either i) takes a direct part in the formation of the final skeleton or ii) can otherwise be accounted for as an oxygenated or unsaturated center in one or the other of the final alkaloids.

We wish to thank Professor Wiesner for many stimulating discussions and for the opportunity to read his manuscript in advance of publication.