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# ON THE STRUCTURE OF DENUDATINE

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Some time ago Singh, Singh and Malik (1) described a new Delphinium alkaloid, denudatine (m.p. 248-249°C., $C_{21}H_{33}NO_2$) and assigned the structure (I) to this compound. Selenium dehydrogenation of denudatine yielded the typical aromatic compounds (II) and (III) and thus the atisine skeleton (2) seemed indicated. On the other hand, the functionality portrayed in formula (I) had no experimental basis and seemed to be prima facie incorrect. In the course of a survey of plant materials for medicinal purposes, we had the opportunity to repeat the isolation of denudatine from Delphinium denudatum. While the properties of the alkaloid agreed with those reported earlier (1), elemental analysis and mass spectrometry established the molecular formula $C_{22}H_{33}NO_2$. On the basis of the few reactions described in the sequel we have arrived at the conclusion that denudatine must be formulated as (IV) or (V). In these structures one carbon-carbon bond is still missing and all biogenetic precedents (3) demand that this bond connects the carbon marked by the asterisk with one of the two carbons marked by the arrows. We have submitted a sample of denudatine to Dr. Maria Przybylska (N.R.C., Ottawa) and an X-ray structure determination performed by Dr. F. Brisse in her laboratory resulted in the formula (VI).

Thus denudatine turns out to be the first authenticated representative of the skeletal type postulated a long time ago (3) for possible intermediates in the biogenetic transformation of the atisine skeleton into the skeleton of the

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polyfunctional aconitine type alkaloids.

Treatment of denudatine with palladium on calcium carbonate in ethanol gave amorphous isodenudatine represented by the partial structure (VII). [I.R. ($CHCl_3$): 1710 $cm^{-1}$ (six-membered ketone); N.M.R.: singlet (3H) $\tau$ = 9.23 p.p.m. ( $\overset{C}{\underset{C}{\diagdown}}C-CH_3$), doublet (3H) $\tau$ = 8.82, 8.97 p.p.m. ( $\overset{C}{\diagdown}C(H)-CH_3$), triplet (3H), coinciding with previous doublet, $\tau$ = 8.70, 8.82, 8.97 p.p.m. ($N-CH_2-CH_3$).] Isodenudatine was characterized as the basic O-acetate $C_{24}H_{35}NO_3$.** [M.p. 192°C.; I.R. (KBr): 1723, 1710, 1245 $cm^{-1}$; m/e = 385.] This isomerization is characteristic of the exocyclic allylic alcohol present in many diterpene alkaloids (3).

Oxidation of denudatine by chromium trioxide in pyridine yielded the keto lactam oxodenudatine $C_{22}H_{29}NO_3$ portrayed by the partial formula (VIII). [M.p. 327°C.; I.R. (KBr): 3380 (OH), 1705 (six-membered ketone conjugated with exocyclic double bond), 1625 $cm^{-1}$ (lactam); U.V.: $\lambda_{max}$ = 230 m$\mu$ (log $\varepsilon$ = 3.54); N.M.R.: singlet (3H) $\tau$ = 8.95 p.p.m. ($O=\overset{N}{C}-\overset{C}{\underset{CH_3}{C}}-C$), triplet (3H) centered around $\tau$ = 8.86 p.p.m. ($N-CH_2-CH_3$), doublet (2H) $\tau$ = 3.96, 4.68 p.p.m. (vinylic hydrogen).]

The above oxidation experiment yielded as a by-product a secondary lactam $C_{20}H_{25}NO_3$, m.p. 282°C., represented by the same partial formula (VIII). The spectral and analytical data were in agreement with the loss of the N-ethyl group in this compound.

Oxodenudatine was oxidized by permanganate-periodate in aqueous dioxane. The dicarboxylic acid $C_{21}H_{29}NO_6.0.5H_2O$, m.p. 260°C., represented by the partial formula (IX) was isolated in a high yield from this reaction. For characterization the diacid was esterified with diazomethane to the dimethyl ester $C_{23}H_{33}NO_6$, m.p. 125°C. All spectral and analytical data of this compound were in agreement with the partial structure (X).

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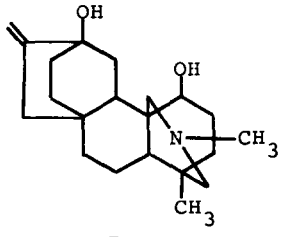
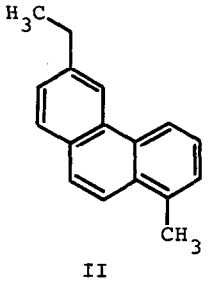
** All crystalline compounds gave correct elemental analyses.

Dehydration of the dimethyl ester with thionyl chloride in pyridine at 0°C. yielded the amorphous anhydro derivative represented by (XI). [I.R. ($CHCl_3$): no OH, 1725, 1711 (esters), 1630 $cm^{-1}$ (lactam); N.M.R.: unresolved multiplet (1H) $\tau$ = 3.03 p.p.m. (vinylic hydrogen), singlet (6H) $\tau$ = 6.31 p.p.m. (2 $-OCH_3$).]

Saponification of (XI) by 2N sodium hydroxide in refluxing ethanol yielded the crystalline half-ester $C_{22}H_{29}NO_5$, m.p. 302°C. represented by the partial formula (XII). [I.R. (KBr): 1730 (ester), 1710 (conjugated carboxyl), 1615 $cm^{-1}$ (lactam); U.V.: $\lambda_{max}$ = 216 mμ (log ε = 4.29).]




I

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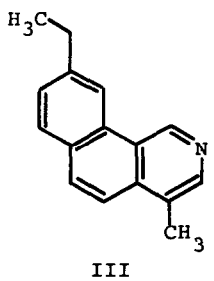


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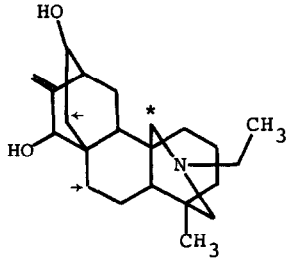


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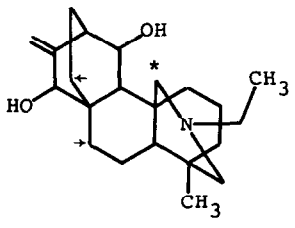
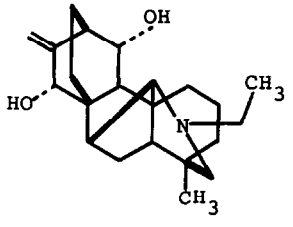
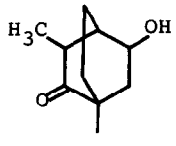


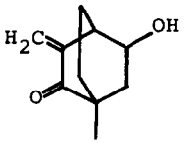

V



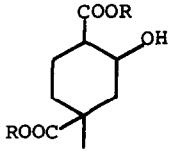

VI



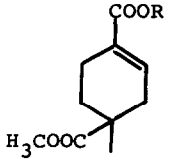

VII




VIII




IX (R = H)
X (R = $CH_3$)




XI (R = $CH_3$)
XII (R = H)

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2. K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, Chemistry and Industry 132 (1954).
3. Cf. K. Wiesner and Z. Valenta, Progress in the Chemistry of Natural Products XVI (1958), Wien, Springer-Verlag.

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