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THE STRUCTURES OF CONDELPHINE, ISOTALATIZIDINE AND TALATIZIDINE

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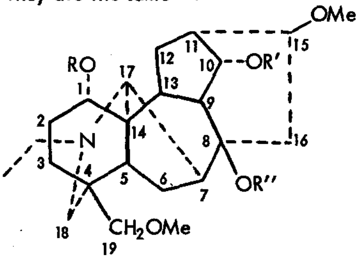
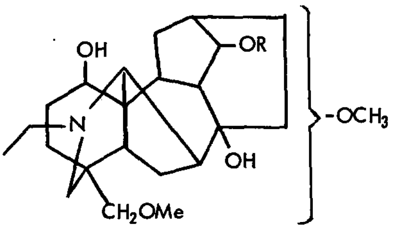
Recent reports[1-3] describe the isolation of the alkaloids denudatine and denudatidine from the roots of Delphinium denudatum. We found neither of these compounds in our extraction of these roots* but instead found two different alkaloids: 0.25% of an alkaloid (I) which melted 158-159° and a small amount of another (II) which melted 116-117° and is identical with the saponification product of I. A later comparison of I with an authentic sample of condelphine has shown conclusively that they are the same**.





I R = R" = H, R' = Ac
II R = R' = R" = H
III R = R' = R" = H (β-OR)
IV R = R' = Ac, R" = H
V R = R' = R" = Ac
XIII R = Bz, R' = Ac, R" = H

VI R = Ac } OH at C(1)α
VII R = H } OH at C(1)α
VIII R = H, OH at C(1)β

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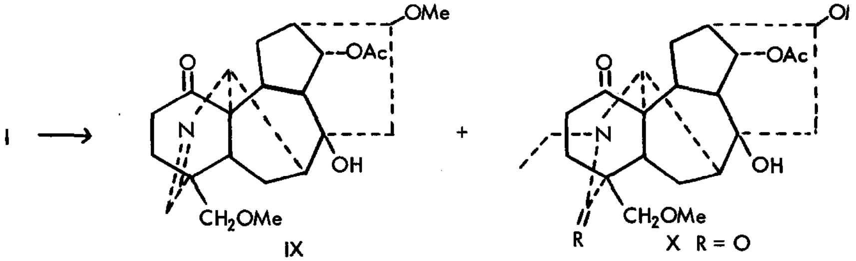
*The roots were identified by comparison with authentic specimens at 1) Botanical Survey of India and 2) Indian Botanic Garden, Shibpur/Calcutta.

**The authors wish to thank Dr. A. D. Kuzovkov for the sample of condelphine with which the comparison was made.

Partial structures for condelphinine (VI), isotalatizidine (VII), and talatizidine (VIII) have been postulated on the basis of limited chemical data and analogy to other Aconite alkaloids[4]. We wish to report evidence which demonstrates the location of the functional groups in VI, VII, and VIII and in addition elucidates the configuration of the C(10) groups, the assignment of position and configuration of the remaining methoxyl group and the conformation of ring A in several of the derivatives of condelphine and isotalatizidine.

Under varying conditions three products (IX, X, and XI) were obtained from the oxidation of I with Sarett reagent.

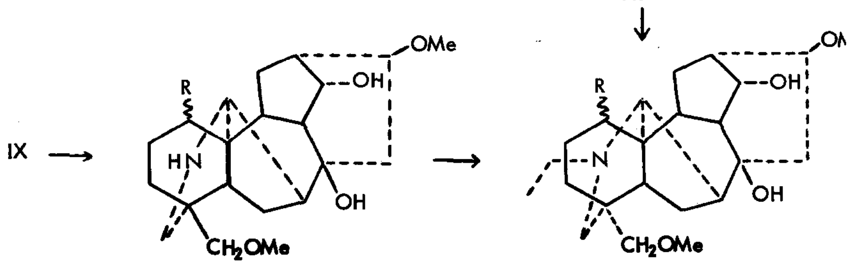


IX

X R = O

XI R = H_2

Reduction of IX with sodium borohydride followed by reaction with ethyl iodide gave a mixture of II and III thus confirming the presence of the N-ethyl group which was also indicated by the downfield shifts of the $C\underline{H}_3$-CH_2-triplet in the NMR spectra of various salts of I and its derivatives. Reduction of XI with sodium borohydride produced the same mixture of II and III.



XII R = α- + β-OH

II R = α-OH

III R = β-OH

Since an aldehyde is not produced in any of these oxidations it is clear there is no primary hydroxyl group and hence C(19) must be substituted with one of the methoxyl groups. This was further substantiated by the NMR spectrum of X in which the 2H signal of this methylene is shifted 0.43 p.p.m. downfield from its position in the NMR spectrum of I, an observation consistent with its position in the molecule in which it is within the deshielding cone of the lactam carbonyl. However, there was no shift in this signal in the NMR spectrum of XI, clearly showing that the keto group must be far removed from C(19). Dreiding models show that the C(3) and C(18) positions are equidistant from C(19) (Fig. 1) thus precluding C(3) as a possible site of the ring A hydroxyl.

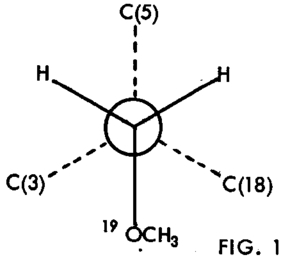


FIG. 1

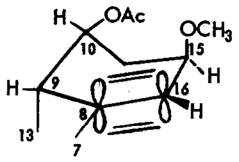
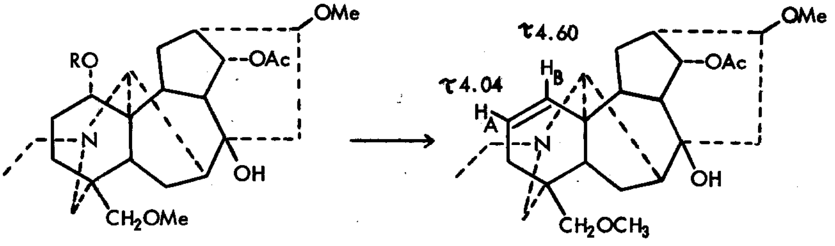


FIG. 2

The NMR spectrum of XIII contained a signal at τ 4.80, 1H quartet (J_{AX} = 10 c.p.s., J_{BX} = 7 c.p.s., X proton of an ABX type quartet, CH_2-C$\underline{H}$OBz-C). If the benzoate had been at C(2) a multiplet should have been observed. This same quartet pattern is also partially distinguishable in the 2H multiplet of V.

Elimination in XIV or XV gave only one olefin (XVI) whose NMR spectrum contained a signal at τ 4.60, 1H doublet (J=9.5 c.p.s., $-\overset{|}{\underset{|}{C}}$-C$\underline{H}$=CH) and one at τ 4.04, 1H octet (J_{AB}=9.8 c.p.s., J_{AX}=2.6 c.p.s., J_{AY}=4.2 c.p.s., CH_2-C$\underline{H}$=CH). Decoupling of H_A resulted in H_B appearing as a singlet at τ 4.60. If the sulfonate esters had been at C(2) two olefins should have been produced from the elimination reactions.

Having eliminated C(2) and C(3) as possible positions for the ring-A hydroxyl it must of necessity be at C(1). The large coupling constants of the C(1) proton in the benzoate and acetate derivatives of I require large dihedral angles between vicinal protons. This may occur when the ester is in the α-chair or β-boat conformation but

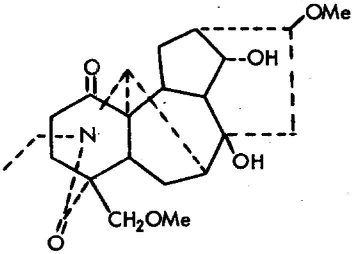


XIV $R = CH_3SO_2^-$

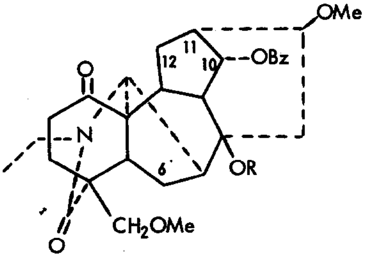
XV $R = \underline{p}\text{-}CH_3C_6H_5SO_2^-$

XVI

in the β-boat conformation the hydroxyl of I would be too far from the nitrogen to explain the observed intramolecular hydrogen bonding, the carbonyl of the acetate would be too distant to be influenced by a change in the electronic environment around the nitrogen, and the formation of an inner carbinolamine ether as noted by previous workers[4] would be impossible. Condelphine (I) must exist an appreciable amount of its time in the α-boat conformation as indicated by the intramolecular hydrogen bonding and most likely exists as an equilibrium between the α-chair and α-boat conformations as evidenced by the fact that the NMR spectra always show the C(1) proton as a multiplet when the C(1) hydroxyl is not esterified.



XVII

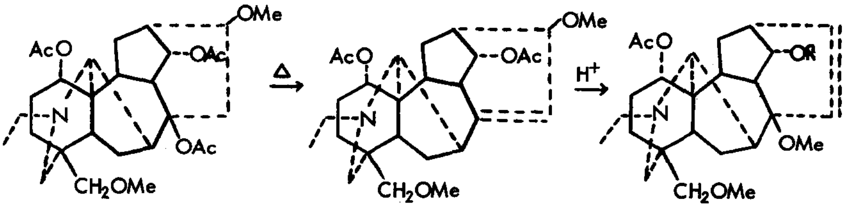


XVIII R = H

XIX R = Ac

Conversion of XVII to XVIII and then to XIX gave substantial evidence that the hydroxyl group in the 5-membered ring is at C(10) and that the tertiary hydroxyl is at C(8). In the NMR spectrum of XIX the acetate signal appeared at an unusually high field (τ 8.62) due to the shielding by the strongly anisotropic effect of the aromatic nucleus in close proximity. This has been observed to be a common feature of several delphinine-type alkaloids when they are substituted with a C(10) benzoate and a C(8) acetate[5]. If the benzoate had been at C(12) it would have been too far away to shield the C(8) acetate. If the benzoate had been at C(6) where the dihedral angles are about 20^0 and 95^0 a doublet with J = 9 c.p.s. should have been observed. The observed coupling constant of the 1 proton triplet of CH-C$\underline{\text{H}}$OR-CH is 4.5 c.p.s. Dreiding models indicate an H-H dihedral angle of 45^0 ($J_{calcd.}$ = 4-5 c.p.s.) if -OR is α and about 80^0 ($J_{calcd.} \doteq 1$ c.p.s.) if -OR is β; thus the configuration at C(10) must be α-OR.

Additional evidence for a tertiary hydroxyl at C(8) was obtained by pyrolysis of V to XX. The latter shows UV absorption at 240 mμ in neutral solution which disappears when a drop of acid is added. This is a characteristic which has been noted in the UV spectra of pyrodiacetylneoline and pyrodelphonine[6].



V XX XXI R = H

XXII R = Ac

Refluxing XX in perchloric acid converted it to XXI which was acetylated to give XXII. This characteristic rearrangement has been shown by Wiesner[7] to be an allylic rearrangement and this requires that the pi electrons of the double bond at C(8)=C(16) and the methoxyl (leaving group) be in the same plane. This condition is met when the C(15) methoxyl is in the β-configuration described when ring D of XX is in the frozen pseudo-chair conformation but not if it is in the α-configuration (Fig. 2). This configuration also agrees with the coupling constant of 6 c.p.s. (dihedral angle = 30^0) between the olefinic and the C(15) protons. If the C(15) proton had been β the coupling constant should have been 0. The NMR spectrum of XXII shows one methoxyl signal which is more highly shielded than usual and is consistent with its assignment to the tertiary C(8) position. These results lead to structures I, II, and III for condelphine, isotalitizidine, and talitizidine, respectively.

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