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THE STRUCTURE OF DELPHININE

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Some time ago we deduced the structure and substitution of the C-D ring system of delphinine.[1,2] At the same time we have also shown that the considerable body of evidence accumulated by Jacobs [3] can be fitted extremely well into the complete structures I and II. Besides these structures, we have also discussed two structures with a rearranged ring B to account for the positive outcome of the Hofmann degradation [4] reported by Jacobs and Schneider.

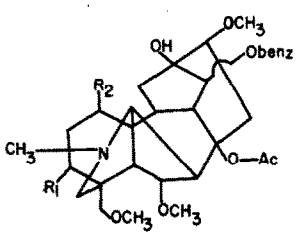
We now wish to present evidence that structure I is the correct representation of delphinine. Delphonine formed a crystalline methiodide which melted at 208-211°. Calc. for $C_{25}H_{42}O_7NI$: C, 50.42; H, 7.11; I, 21.33; 4 OCH_3, 20.77%. Found: C, 50.73: H, 7.02; I, 21.25; OCH_3, 20.44%. The methiodide was converted into the methohydroxide on a column of amberlite IRA-400 and the methohydroxide was heated with 10% aqueous sodium hydroxide until most of the water evaporated. A threefold countercurrent distribution of the resulting bases between buffer pH 5.8 and chloroform resulted in the isolation (in a 5% yield) of compound III which was further purified by sublimation and recrystallized to a melting point of 153°. Calc. for $C_{23}H_{37}O_5N$: C, 67.78; H, 9.15; 3 OCH_3, 22.85%. Found: C, 67.52, 67.52; H, 9.30, 9.02; OCH_3, 22.48%.

The infrared spectrum of III shows a strong ketonic peak at 1707 cm^{-1} and no peak in the hydroxyl region. The presence of two keto groups was corroborated by the preparation of a bis 2,4-dinitrophenylhydrazone which was microcrystalline and decomposed at 157°. Calc. for $C_{35}H_{45}O_{11}N_9$: C, 54.74; H, 5.90; N, 16.41; 3 OCH_3, 12.12%. Found: C, 53.70; H, 5.73; N, 16.45; OCH_3, 12.37, 10.22%.

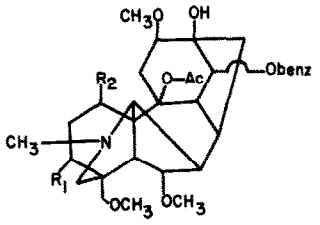
The N.M.R. spectrum of compound III which was recorded and interpreted by Mr. J. Atkinson (Chemistry Department, M.I.T., Cambridge, Mass.) is in agreement with the presence of a disubstituted double bond.

The formation of III is easily rationalized by a 1-3 cleavage, followed by the elimination of the ring D methoxyl, a reverse aldole reaction and cleavage of a vinylogous β-keto aldehyde. Thus, the supposed Hofmann degradation of delphinine is explained and it is conceivable that compound III is identical with the "methine" described by Schneider.[4] Treatment of a very small amount of compound III with bromine followed by alkali gave an impure mixture which, nevertheless, exhibited an ultraviolet spectrum both in acidic and basic solution strongly resembling a brominated γ-tropolone.[5]

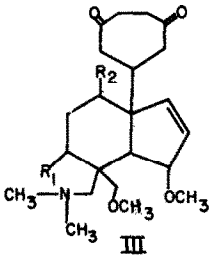
We have postulated in our previous work that the pyro-isopyro change of delphinine derivatives is an allylic rearrangement of a methoxyl [2]



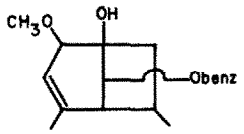
I $R_2 = OCH_3, R_1 = H$
$R_2 = H, R_1 = OCH_3$



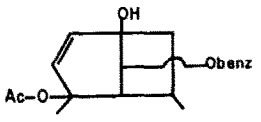
II



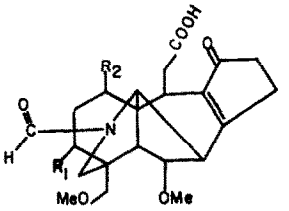
III



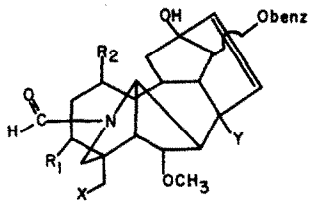
IV



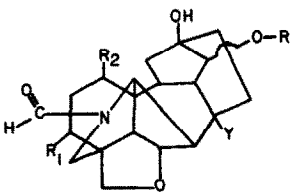
V



X



XI (X, Y = Cl)
XII (X, Y = OH)
XIII ($X = CO_2H$, Y = OH)
XV ($X, Y = OCD_3$)



XIV ($Y = OCH_3$, R = hexahydrobenzoyl)
XVI ($Y = OCD_3$, R = hexahydrobenzoyl)

The following evidence was assembled in support of this assumption:

(a) The identity of the skeletal structure of delphinine and isopyrodelphinine derivatives was proved.
(b) It was shown that delphinine and isopyrodelphinine derivatives differ in the site of attachment of one methoxyl.
(c) It was shown that one methoxyl is exchanged when the pyro-isopyro rearrangement is carried out in radioactive methanol.

However, no direct proof was provided that the same methoxyl which is exchanged in the rearrangement eliminates in the formation of the secoacid X.

We have now shown that this prediction is correct. Pyrooxodelphinine IV was rearranged in glacial acetic acid in the presence of a small amount of p-toluene sulphonic acid to the acetoxyisopyro compound V (m.p. 305°) in quantitative yield. Calc. for $C_{32}H_{39}O_9N$; C, 66.07; H, 6.76; 3 OCH_3, 16.00%. Found: C, 66.35; H, 6.75; OCH_3, 15.51%.

Compound V was converted into the octahydroderivative VI (m.p. 229°) by hydrogenation with platinum oxide in glacial acetic acid. Calc. for $C_{32}H_{47}O_9N$: C, 65.17; H, 8.03; 3 OCH_3, 15.82%. Found: C, 65.45; H, 7.97; OCH_3, 15.96%. Compound VI was then hydrolysed to the corresponding triol VII which melted at 239°. Calc. for $C_{23}H_{35}O_7N$; C, 63.14; H, 8.06; 3 OCH_3, 21.28%. Found; C, 63.29; H, 8.04; OCH_3, 20.87%. Compound VII was then converted into the crystalline acid X (m.p. 138°) by oxidation with chromium trioxide, esterification of the resulting seco keto acid with diazomethane, treatment of the keto ester with hot methanolic sodium methoxide and alkaline hydrolysis. The identical acid X has previously [2] been obtained by a completely analogous series starting from isopyrooxodelphinine. This shows conclusively that, as predicted by our scheme, the methoxyl which is exchanged in the pyro-isopyro reaction is also the one which eliminates in the formation of compound X.

We have further verified our explanation [2] of the demethylation experiments of Jacobs.[3] This author has shown that treatment of isopyrooxodelphinine with methanolic hydrochloric acid will result in the replacement of two methoxyls by chlorine and give a dichloride which we now formulate as XI. Treatment of XI with methanol gives back isopyrooxodelphinine. The chlorines of XI may also be replaced by hydroxyls to give the triol XII. This last compound may be oxidized to the hydroxy acid XIII.

It is clear that the tertiary hydroxyl displaced by chlorine must be the one engaged in the pyro-isopyro rearrangement. The fact that the same dichloride XI is obtained both from pyro- and isopyrooxodelphinine is sufficient proof of this assumption.

Jacobs has further shown that octahydro-isopyrooxodelphinine on treatment with aqueous zinc chloride gives a dimethoxy ether formulated

by us as XIV. Jacobs believed that the internal ether formation took place between the same two methoxyls which undergo easy displacement by chlorine. While he has undoubtedly shown that the primary methoxyl is involved in the internal ether, he provided no experimental evidence for the identity of the second methoxy group.

We have now shown conclusively that in agreement with our formulation of XIV one of the two methoxyls which gave rise to the internal ether is not identical with either of the two methoxyls displaced by chlorine in compound XI. The dichloride XI was converted by refluxing with CD_3-OH into labelled isopyrooxodelphinine XV. This compound showed the same melting point (285°) and practically the same infrared spectrum as isopyrooxodelphinine; the two materials gave no melting point depression. Calc. for $C_{31}H_{33}D_6O_8N$: 15.4 atom % xss D. Found: 13.0 atom % xss D.

The labelled isopyrooxodelphinine XV was then converted into the cyclic ether XVI which had the same melting point (266°) and practically the same infrared spectrum as compound XIV but retained one deuterated methoxyl. Calc. for $C_{29}H_{38}D_3O_7N$: 2 OCH_3, 11.97%; 7.3 atom % xss D. Found; OCH_3, 10.71%; 6.83 atom % xss D.

If we compare the recently deduced [6] structure of aconitine with the delphinine formula which we have conclusively established in this Communication, it appears exceedingly probable that aconitine is a dihydroxy delphinine. Attempts at direct correlation of these two important alkaloids are in progress.

We are indebted to the National Research Council, Ottawa for postdoctoral fellowships to F.B. and M.G. and to the Research Corporation, New York for a grant which enabled us to undertake the isolation of delphinine on a large scale.

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