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DIRECT CORRELATION OF ACONITINE AND DELPHININE

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Some time ago complete structures for aconitine I[1] and delphinine II[2] have been deduced. In these structures the only ambiguity was the fact that the methoxyl in ring A and the group R_2 could possibly be exchanged in position.

This ambiguity was now removed for aconitine by chemical studies[3] and also X-ray crystallography.[4] Consequently, the formula I for aconitine is fully established.

It was considered probable that delphinine had the same orientation of the ring A methoxyl corresponding to the formula II, and that this fact would be most conveniently established by direct correlation of aconitine and delphinine. Such a correlation would have the additional advantage of reinforcing the structural arguments for both compounds.

After several unsuccessful attempts, the desired correlation was accomplished by a conversion of aconitine into the aromatic compound VIII, which has previously been obtained from delphinine[1].

Pyrooxonitine[1] was reduced by means of sodium borohydride in methanol and the product was directly

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[1]K. Wiesner, M. Gotz, D. L. Simmons and L. R. Fowler; F. W. Bachelor, R. F. C. Brown and G. Buchi, Tetrahedron Letters No. 2, 15 (1959).

[2]K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Gotz, Tetrahedron Letters No. 3, 11 (1959).

[3]G. Buchi, Private Communication

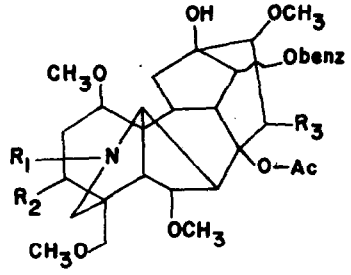
[4]M. Przybylska and L. Marion, Can. J. Chem. 37, 1116 (1959).

saponified by refluxing with aqueous ethanolic potassium hydroxide. The amorphous dihydropyrooxonine III was continuously extracted with chloroform and purified by chromatography on silicic acid. The infrared spectrum of III showed a single peak in the carbonyl region at 1655 cm^{-1} which belongs to the N-acetyl group.

Compound III took up one mole of periodic acid and the amorphous product IV was immediately aromatized by heating under extreme dilution in 0.01m ethanolic potassium hydroxide in a current of oxygen to 60-65°. After acidification and continuous extraction with chloroform, the products of the aromatization were separated by chromatography on silicic acid. The desired product V, which is distinguished by a characteristic p-hydroxyacetophenone spectrum, was obtained as a spectroscopically pure, but amorphous, white foam. Ultraviolet spectrum: (0.01m KOH in ethanol) λ_{max} = 337 mμ (log ε=4.13), shoulder 248 mμ (log ε=4.00); (0.01m H_2SO_4 in ethanol) λ_{max} = 286 mμ (log ε=3.9), λ_{max} = 231 mμ (log ε=4.0). Infrared spectrum: 1668 cm^{-1}, 1600 cm^{-1}, 1575 cm^{-1}.

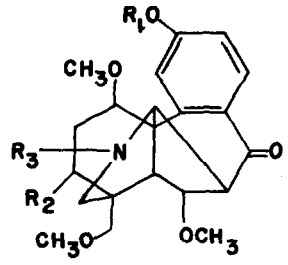
The phenol V was converted into the methyl ether VI by treatment with ethereal diazomethane.

Compound VI was purified by chromatography on alumina and remained oily. Ultraviolet spectrum in ethanol: λ_{max} = 280 mμ (log ε=3.8), 229 mμ (log ε=3.9). Compound VI was heated for 1 hour with an excess of dichlorophenylphosphine oxide to 115° and the chloroderivative VII was purified by chromatography on Florisil. It had an ultraviolet spectrum identical with compound VI and the infrared spectra of VI and VII were practically identical except for the absence of an OH peak in VII. Also, compound VII remained oily in spite of repeated chromatography and apparent spectroscopic purity. However, it was possible to convert VII readily into the crystalline compound VIII which has previously been obtained[1] from delphinine.



I (R_1 = $-CH_2-CH_3$, R_2 = OH, R_3 = OH)

II (R_1 = $-CH_3$, R_2 = H, R_3 = H)

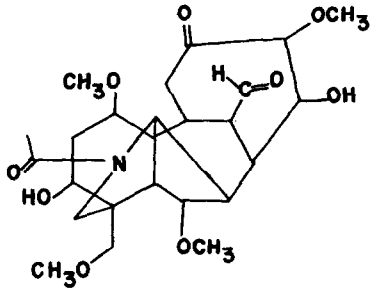


V (R_1 = H, R_2 = OH, R_3 = CH_3-CO-)

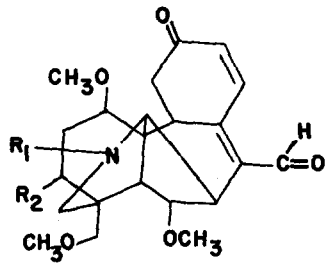
VI (R_1 = $-CH_3$, R_2 = OH, R_3 = CH_3-CO-)

VII (R_1 = $-CH_3$, R_2 = Cl, R_3 = CH_3-CO-)

VIII (R_1 = CH_3, R_2 = R_3 = H)

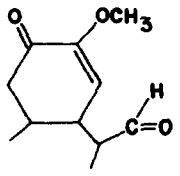


IV

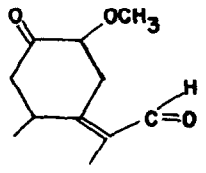


IX (R_1 = $C(=O)H$, R_2 = H)

X (R_1 = CH_3-CO-, R_2 = $-OH$)



XI



XII

To this end, compound VII was first refluxed with glacial acetic acid and zinc dust, and the crude product of this reaction was again refluxed with methanolic hydrochloric acid. The product of this last reaction VIII was basic and it was purified by chromatography on alumina followed by crystallization of the highly insoluble oxalate. The oxalate reached a constant melting point of 194°, and showed no melting point depression with the corresponding derivative VIII prepared from delphinine. Decomposition of the oxalate gave base VIII, m.p. 144°, which did not show melting point depression with VIII, m.p. 144°, obtained from delphinine. Also the infrared and ultraviolet spectra of both samples were identical.

It has been postulated previously[1] that the aromatization of the secoketoaldehyde from α-oxoisopyro-delphonine proceeds via the intermediate IX. The analogous intermediate X may be obtained from the secoketoaldehyde IV in a series of base catalyzed reactions proceeding via the intermediates XI and XII portrayed by partial structures. The precise mechanism of the aromatization reactions will be discussed in a full communication on aconitine chemistry.

Two points of special significance of the present correlation should be emphasized. This is the already-mentioned rigorous location of the ring A methoxyl in delphinine and the rigorous location of the ring B methoxyl in aconitine at C_6. This group was previously placed in aconitine[1] only by analogy, but rigorous evidence exists for its location in delphinine chemistry.[2]