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THE CONFIGURATION OF DELPHININE

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THE complete structure of delphinine (XIV)[1] and aconitine (I)[2] have been proposed with a remaining ambiguity in the location of the ring A substituents. This ambiguity was subsequently removed[3] and the two compounds directly correlated[4].

Independently, the structure, relative and absolute configuration of desmethanol aconinone was determined by X-ray crystallography[5,6].

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[1] K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Gőtz, Tetrahedron Letters 3, 12 (1959).

[2] K. Wiesner, M. Gőtz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters 2, 15 (1959).

[3] F. W. Bachelor, R.F.C. Brown and G. Büchi, Tetrahedron Letters 10, 1 (1960).

[4] K. Wiesner, D. L. Simmons and L. R. Fowler, Tetrahedron Letters 18, 1 (1959).

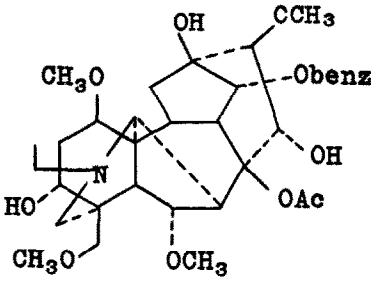
[5] M. Przybylska and L. Marion, Can. J. Chem. 37, 1116 (1959).

[6] M. Przybylska and L. Marion, Can. J. Chem. 37, 1843 (1959).

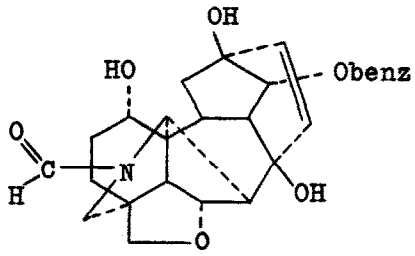
The X-ray work[5,6] settled the configuration of all asymmetric centres in aconitine except the configuration of the ring A substituents. The configuration of the C_3 hydroxyl was rigorously proved by Büchi[3] and the configuration of the C_1 methoxyl suggested by the same author on the basis of an ingenious conformational argument[3]. Thus, it is possible[3] to write the complete expression I for aconitine.

We have now proved rigorously that the configuration of the C_1 methoxyl in delphinine is trans to the nitrogen bridge. Since in the correlation[4] of aconitine and delphinine, the C_1 and C_6 substituents remain undisturbed, our result constitutes a corroboration of Büchi's conformational argument.

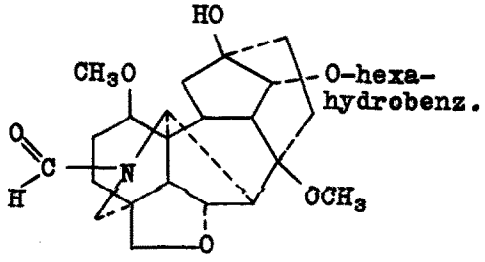
Our starting materials were the two demethylation products II and III[1]. We have proved that in II the C_1 hydroxyl is cis to the nitrogen bridge and that the demethylation of the C_1 methoxyl proceeds with inversion of configuration. Compound II was hydrogenated with platinum oxide in glacial acetic acid to the octahydroderivative IV (m.p. 241°). Found: C, 63.76; H, 7.62; OCH_3, 0.0. Calc. for $C_{27}H_{37}O_7N.H_2O$: C, 64.14; H, 7.78%. Compound IV was saponified for three hours with 3% aqueous ethanolic barium hydroxide. The product was a mixture of compounds V and VI.



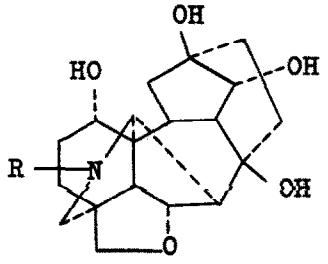
(I)



(II)

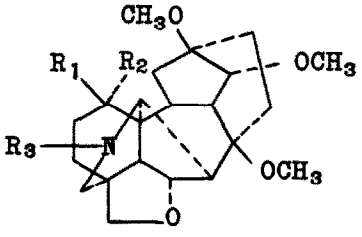


(III)



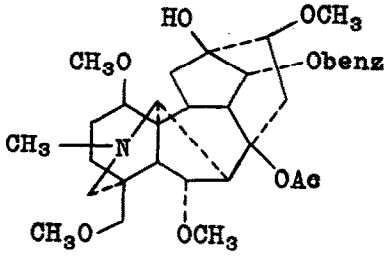
(V) R = H

(VI) R = -C(=O)H

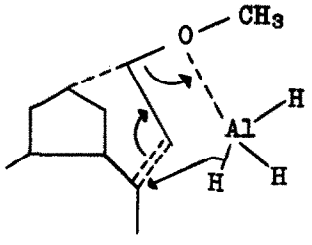


(IX) R_2=OCH_3, R_1=H

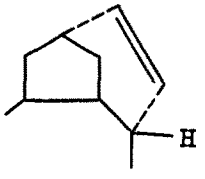
(X) R_2=H, R_1=OCH_3



(XIV)



(XII)



(XIII)

V (m.p. 265°C) Found: C, 63.19; H, 7.75. Calc. for $C_{19}H_{27}O_5N \cdot \frac{1}{2}H_2O$: C, 63.65; H, 7.87%. I.R.: no formamide band.

VI (m.p. 164°) Found: C, 61.15; H, 7.51. Calc. for $C_{20}H_{27}O_6N.H_2O$: C, 60.75; H, 7.39%. I.R. (KBr): 1645 cm^{-1} (formamide).

The easy hydrolysis of the formamide group may be explained by the participation of the C_1 hydroxyl in this process.

The oxidation of II with chromium trioxide gave the corresponding C_1 ketone VII[7]. Treatment of this compound with sodium borohydride resulted in the reduction of the C_1 keto group and saponification of the benzoyl group. The product VIII thus obtained (m.p. 310°, Found: C, 64.25; H, 6.79. Calc. for $C_{20}H_{25}O_6N$: C, 63.96; H, 6.72. I.R.: 1650 cm^{-1} (formamide)) was found to be identical with the product of a very mild direct saponification of II. This proves conclusively the configuration of the C_1 hydroxyl in II since the formation of a equatorial C_1 alcohol is favoured both by thermodynamic and by kinetic factors in the reduction of a C_1 ketone.

Compound VI was methylated first with methyliodide and

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[7] W. A. Jacobs and S. W. Pelletier, J. Am. Chem. Soc. 76, 161 (1954).

silver oxide in dimethyl formamide[8] and the amorphous product of this reaction was methylated again with diazomethane-borontrifluoride in methylene chloride[9]. The product of the second methylation, after purification by chromatography on alumina, was a glass which showed in the infrared spectrum no hydroxyl peak and a formamide peak at 1672 cm^{-1}. Clearly, this material had the structure IX ($R_3 = -C\leqslant^{O}_{H}$). It was reduced by lithium aluminum hydride, and the resulting basic product was purified by chromatography on alumina. Benzene-ether (9:1) eluted the crystalline base IX ($R_3 = -CH_3$). It melted after several crystallizations from petroleum ether at 156° and was sublimed in high vacuo for analysis. Found: C, 68.81; H, 8.94; OCH_3, 29.88. Calc. for $C_{24}H_{37}O_5N$: C, 68.79; H, 8.90; 4-OCH_3, 29.63%.

The hexahydrobenzoyl ester III was saponified to the corresponding alcohol XI (m.p. 256°). Found: C, 63.40; H, 7.57; OCH_3, 15.23. Calc. for $C_{22}H_{31}O_6N \cdot \frac{1}{2}H_2O$: C, 63.75; H, 7.78; OCH_3, 14.98%.

Compound XI was now subjected to the same methylation procedure which was applied previously to compound VI. The product X ($R_3 = -C\leqslant^{O}_{H}$) was crystalline and was recrystal-

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[8] J. Goerdeler and J. Galinke, Chem. Ber. 90, 203 (1957).

[9] E. Müller and W. Rundel, Angew. Chemie p. 105 (1958).

lized from methanol to a melting point of 203°. Found: C, 66.48, 66.76; H, 8.10, 8.27; OCH_3, 28.75. Calc. for $C_{24}H_{35}O_6N$: C, 66.57; H, 8.17; 4-OCH_3, 28.67. I.R. (CCl_4): no OH band, 1668 cm^{-1} (formamide).

The above compound was reduced by lithium aluminum hydride to the basic compound X (R_3 = $-CH_3$). This product crystallized after chromatography on alumina (eluent, benzene-ether 9:1) and was recrystallized from methanol to a melting point of 185°. Found: C, 68.53, 68.86; H, 8.62, 8.98; OCH_3, 29.56, 29.95. Calc. for $C_{24}H_{37}O_5N$: C, 68.79; H, 8.90; 4-OCH_3, 29.63%.

Both compounds IX and X (R_3 = $-CH_3$) are clearly epimeric at C_1. Since IX has been shown to have an equatorial C_1 methoxyl, compound X, which contains the undisturbed original C_1 methoxyl of delphinine, must have this substituent in the axial configuration portrayed in the formula X. The fact that IX and X (R_3 = $-CH_3$) differ in nothing but the configuration of one asymmetric centre is supported by the great similarity of their infrared spectra (which, however, clearly show nonidentity) and by the practical identity of their N.M.R. spectra.

It has been already proposed by Büchi[3] that all remaining substituents of delphinine have the same configuration as the corresponding substituents of aconitine. This is, of course, biogenetically very plausible, but it is rigorously

proved only for the C_1 and C_6 methoxyls which remained unaffected in the correlation[4]. Of the remaining substituents of delphinine, only the configuration of the C_{14} methoxyl and C_{19} benzoxy group could be different in delphinine and aconitine. There are some tentative chemical arguments which suggest that these substituents have, in fact, the identical configuration in delphinine and aconitine. The stability of compound II under conditions where all methoxyls have undergone an acid catalyzed cleavage suggests that the benzoxy group may have a configuration syn to the double bond. If the configuration were anti to the double bond, one might expect a great reactivity of the corresponding homoallylic system[10].

If the pyro-isopyro rearrangement (which is an extremely unusual bridgehead allylic rearrangement[11]) is a concerted process which does not involve the mesomeric allylic cation as intermediate, it would be favoured by a cis relationship of the C_{14} and C_8 substituents; especially the allylic rearrangement of pyro derivatives[12] on lithium aluminum hydride reduction may be conveniently formulated as XII $\longrightarrow$ XIII.

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[10] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, J. Am. Chem. Soc. 77, 4183 (1955).

[11] K. Wiesner, F. Bickelhaupt and D. R. Babin, Experientia 15, 93 (1959).

[12] K. Wiesner, H.W. Brewer, D.L. Simmons, D.R. Babin, F. Bickelhaupt, J. Kallos and T. Bogri, Tetrahedron Letters 3, 17 (1960).

Thus, it seems to be very probable that the formula XIV is a correct expression for both the absolute and relative configuration of delphinine.