ALKALOID STUDIES LXIV.⁽¹⁾ THE CRYSTAL STRUCTURE AND ABSOLUTE CONFIGURATION OF (-) 17-O-METHYL-ASPIDODISPERMINE N_b -HYDROBROMIDE

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In 1968 we reported the isolation of seven novel indole alkaloids from <u>Aspidosperma</u> <u>dispermum</u>⁽³⁾ (family, <u>Apocynaceae</u>). On the basis of spectral and chemical evidence, we tentatively concluded that two of them, (-) deoxyaspidodispermine (I) and (+) aspidodispermine (II), ³ possess the aspidospermine skeleton but with the $C-5^{(4)}$ ethyl side chain replaced by a hydroxyl group. Since this biogenetically unprecedented structure rested on circumstantial evidence and was not based on direct correlation with an indole alkaloid of established constitution, we undertook an X-ray diffraction analysis of (-) 17-Omethyl-aspidodispermine N_b-hydrobromide.





Treatment of (+) aspidodispermine (II) with dimethyl sulfate yielded (-) 17-Omethyl-aspidodispermine (III, m.p. 189-191°), which was converted to its hydrobromide by passing hydrogen bromide gas over an etheral solution of III. (-) 17-O-Methylaspidodispermine N_b-hydrobromide crystallized from acetone to give orthorhombic plates (m.p. 259-261°). The space group is P2₁2₁2₁ with unit cell dimensions of a = 12.177 \pm 0.005, b = 21.893 \pm 0.005, c = 7.369 \pm 0.005 A; V = 1964.4 A³. The density (measured by flotation) and microanalysis indicate four molecules of alkaloid per unit cell (calculated density: 1.431 \pm 0.001 g/cm³, found: 1.429 \pm 0.005 g/cm³. <u>Anal.</u> Calcd. for C₂₀H₂₇N₂O₃Br: C, 56.74; H, 6.43; N, 6.62. Found: C, 56.72; H, 6.52; N, 6.74).

A total of 2,083 diffraction intensities was collected by a Syntex P_1 Autodiffractometer using intensity-weighted average Cu Ka radiation. Averaging according to Friedel's law gave 1,217 unique reflections, of which 1,196 were not systematically extinct. The unique bromine position was determined from a sharpened three-dimensional Patterson function and it was further refined by one cycle of full-matrix least-squares calculation with all the data. A three-dimensional bromine-phased difference Fourier map was then calculated, which revealed the position of all of the alkaloid atoms (except hydrogen). After several cycles of full-matrix least-squares refinements with all the data, the discrepancy factor ($R = \sum (IIFol - 1FcII)/\sum IFoI$) was lowered to 8.7%. The complete structure determination (including collection of diffraction data) required less than two weeks.



Q_carbon Ø=nitrogen @=oxygen

Fig. 1.

A three-dimensional projection of (-) 17-O-methyl-aspidodispermine, showing its relative stereochemistry as determined by X-ray analysis, is illustrated in Fig. 1. The chair conformation of rings C and D as well as the envelope-shaped B and E rings are evident. Since the absolute configuration of (-) aspidospermine (IV) has been determined by the anomalous dispersion method, ⁽⁵⁾ we proceeded to correlate the absolute configuration of (-) 17-O-methyl-aspidodispermine with that of (-) aspidospermine by means of optical rotatory dispersion. The complete identity of the ORD curves (methanol solution) of III and IV demonstrates that the two alkaloids possess the same absolute configuration. Consequently Fig. 1 correctly depicts the structure as well as the absolute configuration of (-) 17-O-methyl-aspidodispermine. We are indebted to Syntex Analytical Instruments, Palo Alto, California, for assistance in collecting the diffraction data and to Professor P. G. Simpson for use of the computer programs. Financial support from the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged.

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