The Stereochemistry of Kobusine and Pseudokobusine

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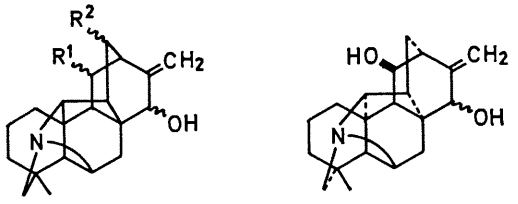
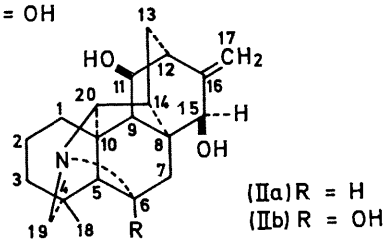
Summary The structures of kobusine and pseudokobusine have been determined by *X*-ray structural analysis of kobusine methiodide.

KOBUSINE, a diterpene alkaloid native to several Japanese *Aconitum* species, was initially assigned structure (Ia) or (Ib) on the basis of chemical studies.[1] A later communication[2] assigned (Ic) (with absolute configuration indicated)



(Ia) R^1 = OH, R^2 = H
(Ib) R^1 = H, R^2 = OH

(Ic)



(IIa) R = H
(IIb) R = OH

as the correct structure of kobusine without presentation of evidence to eliminate structure (Ib); a recent communication described an attempt to correlate hetisine and kobusine.[3] We now report the results of a structural determination of kobusine methiodide by *X*-ray diffraction analysis.

Kobusine methiodide was prepared by treating kobusine with methyl iodide in chloroform solution. Recrystallization of the methiodide from methanol–acetone gave thin plates, m.p. 294—297° corr. The crystal was monoclinic: $a = 7{\cdot}18$, $b = 10{\cdot}20$, $c = 13{\cdot}43$ Å and $\beta = 98{\cdot}83°$, measured from precession films recorded with Mo-K_α radiation. $D_m = 1{\cdot}547$ g/cm^3, $D_c = 1{\cdot}557$ g/cm^3, assuming $Z = 2$. Systematic absences along $0k0$ ($k = 2n + 1$), coupled with the knowledge that the molecules are asymmetric, indicated space groups $P2_1$. Diffraction maxima were collected on film by the multiple-film equi-inclination technique using Cu-K_α radiation. The diffraction data were estimated visually employing a standard intensity strip made from the same crystal. In all, 1644 unique non-zero reflections were recorded.

The structure was solved by the heavy-atom technique[4] and refined by full-matrix least-squares to $R = 16{\cdot}6\%$. The iodide ion was treated anisotropically; all other atoms were assumed to have isotropic thermal factors. The thin-plate crystal produced considerable distortion in spot shapes, particularly on upper level Weissenberg films. An empirical correction for the spot shapes as well as the usual spot-length variation on Weissenberg upper levels[5] was applied to the data. The length of each spot was measured and an average spot length per level calculated. The ratio of a spot length to the average spot length was multiplied by the measured intensity of the reflection, and the corrected intensities used in further least-squares refinement. The corrected data reduced R to 14·7%.

A projection of the molecule is shown in the Figure. The

numbering scheme of the carbon skeleton corresponds to that suggested for these alkaloids.[6] Bond lengths between carbon, nitrogen, and oxygen have standard deviations of approximately 0·06 Å and bond angles have standard deviations of approximately 3°. All bond lengths and bond angles are within twice the quoted standard deviations of accepted values. The *X*-ray analysis shows that (IIa) is the correct stereochemical structure of kobusine, with both hydroxy-groups having the β-configuration. The O(1)–O(2) contact distance was calculated to be 2·81 Å, indicating a strong hydrogen bond between the hydroxy-groups.

By virtue of the previous correlation[1] of kobusine with pseudokobusine, the structure of the latter is (IIb). The absolute configuration indicated for (IIa) and (IIb) is based on analogy with the other diterpene alkaloids.

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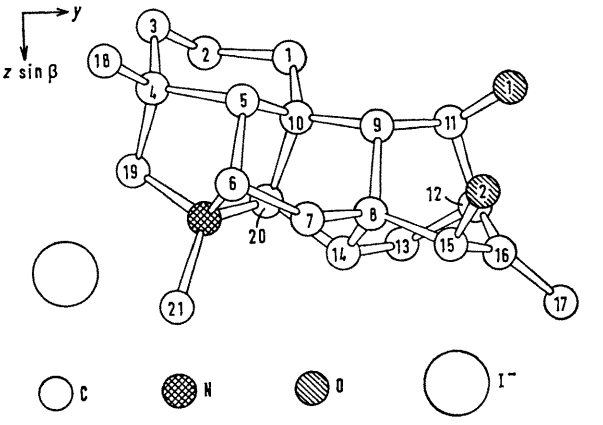

FIGURE. *A projection of one molecule of kobusine methiodide on to the* y — z sin β *plane.*

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