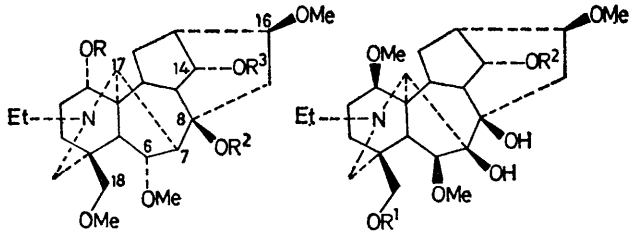
Proof of the Structure of the Diterpene Alkaloid Chasmanine: the Crystal and Molecular Structure of Chasmanine 14α-Benzoate Hydrochloride

By S. WILLIAM PELLETIER,* WILSON H. DE CAMP, and ZOLTAN DJARMATI

(*Natural Products Laboratory, Department of Chemistry, University of Georgia, Athens, Georgia* 30602)

Summary The diterpene alkaloid chasmanine, previously reported to have a 1β-methoxy-substituent, has been shown to have a 1α-methoxy-group by *X*-ray crystallography; it is shown that the reported chemical correlation between browniine and chasmanine is in error.

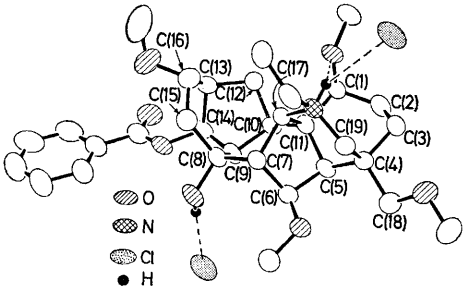
CHASMANINE (**1**) occurs in the roots of *Aconitum chasmanthum* Stapf, along with several other C_{19} diterpene alkaloids.[1] On the basis of degradative studies, its structure was established except for one methoxy-group, which was assumed to be at C(1) on ring A by analogy.[2] Further studies reported the correlation of chasmanine with browniine (**2**)[3] and neoline (**3**),[4] leading to the assignment of a β orientation for the C(1) oxygenated substituent in both



(1) R^1=Me, R^2=R^3=H
(2) R^1=Me, R^2=H
(3) R^1=R^2=R^3=H
(6) R^1=H, R^2=Me
(4) R^1=H, R^2=R^3=COMe
(5) R^1=R^2=Me, R^3=H

chasmanine and neoline. A subsequent correlation of neoline with delphisine (**4**)[5] (which bears a 1α-substituent) cast strong doubt on the correctness of this assignment. We present evidence here that (**1**) is actually the correct structure for chasmanine, reversing the orientation proposed for the C(1) methoxy-group.

The benzoyl derivative of chasmanine was prepared following the published procedure.[1] The hydrochloride crystallized readily from acetone (m.p. 250—252 °C, lit. 248—249 °C). Crystals of chasmanine 14α-benzoate hydrochloride are orthorhombic, space group $P2_12_12_1$, a = 11·259(2), b = 26·093(3), c = 10·383(1) Å. Integrated intensities were measured for all reflexions to a limit of 75° in θ, using Cu-K_α radiation (graphite monochromator, λ = 1·5418 Å). 2493 reflexions with $I \geqslant 2\sigma(I)$ out of 3542 measurements were used in the refinement. The structure was solved by the direct method using MULTAN[6] and refined using the programs of the X-RAY system.[7] All atoms were located, and all atomic positional and thermal (isotropic for H, anisotropic for C, N, O, and Cl) parameters were varied in the refinement. The final agreement residuals are R = 0·048 and R_w = 0·056 for the observed data only. Of 1049 unobserved data, all but 133 calculated below threshold. A final difference electron density map showed no maxima or minima greater than 0·22 e/Å^3.



FIGURE

The molecular structure is shown in the Figure (viewed from the α-face of the molecule), with the carbon atoms of

the skeleton numbered according to the standard numbering scheme for C_{19} diterpene alkaloids. Hydrogen atoms have been omitted for clarity, except for the two involved in hydrogen bonding. Ring A bears a 1-methoxy-substituent in the α orientation, and is stabilized in a boat form by intramolecular hydrogen bonding. Similar conformations of ring A have been found in delphisine hydrochloride[5] and lappaconine hydrobromide.[8] As in the latter case, the intramolecular hydrogen bond in chasmanine 14α-benzoate hydrochloride is bifurcated, with N acting as a donor atom and Cl and O both being acceptors; such hydrogen bonds appear to be quite unusual. The chloride ion also accepts a hydrogen bond from the C(8) hydroxy-group of another molecule.

Except for the orientation of the C(1) methoxy-group, the position and orientation of all substituents is as proposed on the basis of the chemical work, and structure (**1**) may be taken to be the correct representation of chasmanine. This provides further support for the assignment of an α orientation for the C(1) hydroxy-group of neoline (**3**), which has now been chemically correlated directly with two alkaloids for which the structure has been determined by *X*-ray crystallography. Homochasmanine has been correlated with chasmanine, and this work therefore confirms the structure of homochasmanine as (**5**).[9]

A comment is in order regarding the reported lycoctonine–browniine and browniine–chasmanine correlations. A ^{13}C n.m.r. investigation of 26 aconitine-type alkaloids and derivatives[10] provides a foundation for unambiguous assignment of all resonances for chasmanine, as well as most for browniine (**2**), lycoctonine (**6**), and certain of their derivatives. All but two resonances for browniine and lycoctonine are essentially identical, suggesting a very close structural relationship in confirmation of other published data.[11] The difference between (**2**) and (**6**) is that the substituents on C(14) and C(18) are interchanged. The spectra of the corresponding acetate derivatives allow the complete assignment of resonances for (**2**) and (**6**).

These observations are consistent only with identical stereochemistry for ring A [C(1)-C(5), C(11)] in lycoctonine and browniine, and provide spectral evidence that the procedure used in the reported correlation[3] of browniine and chasmanine did not work as expected. In retrospect, because in the attempted correlation fission of the C(7)–C(17) bond, followed by epimerization of the C(6) methoxy-group, does not affect C(1), where the two alkaloids are different, the procedure could not be expected to lead to a common derivative. The above results demonstrate that the reported chemical correlation between browniine and chasmanine is in error.

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