FUZILINE, A NEW ALKALOID FROM THE CHINESE DRUG "FUZI" (*Aconitum carmichaeli* Debx.)

S. W. Pelletier*, Naresh V. Mody*, and Kottayil I. Varughese
Institute for Natural Products Research and The Department of Chemistry
The University of Georgia, Athens, Georgia 30602, U.S.A.

Chen Szu-Ying
Laboratory of Phytochemistry, Kunming Institute of Botany
The Academy of Sciences of China, Kunming, Yunnan, CHINA

Abstract: Chemical investigation of the famous Chinese drug "Fuzi" (*Aconitum carmichaeli* Debx) resulted in the isolation of a new alkaloid, fuziline, along with the known alkaloids, aconitine, hypaconitine, mesaconitine, neoline and songorine. The structure of fuziline (1) has been established by the use of carbon-13 and proton NMR spectroscopy. Subsequently this structure was confirmed by a single-crystal X-ray analysis.

*Aconitum carmichaeli* Debx. is widely used as the famous drug "Fuzi" in Chinese folklore medicine. In this communication we report the isolation and structure determination of a new C19-diterpenoid alkaloid named fuziline (1) obtained from a fine variety of the crude drug "Fuzi" from Si-Chuan. Along with this new alkaloid, the known alkaloids aconitine, hypaconitine, mesaconitine, neoline (2), and songorine were also isolated and characterized.

Fuziline, C24H39NO7 (M+ 453.2694), crystallized from acetone, mp. 214-216°C (corr.), [α]D25 + 11.6° (c 1.0, CHCl3). Infrared absorption (Nujol) showed the presence of several hydroxy groups at 3560(sharp), 3480(sharp) and 3260(broad) and methoxy groups at 905.
1100 and 1115 cm\(^{-1}\). The \(^{1}H\) NMR spectrum of fuziline in CDCl\(_3\) exhibited the presence of an \(\text{N-CH}_2\text{-CH}_3\) (3H) centered at 6 1.11, three methoxy groups (each 3H, s) at 6 3.33, 3.35 and 6 3.45. The spectrum also indicated a broad peak at 6 3.63 for C(4)-CH\(_2\)-OCH\(_3\), an undefined one-proton triplet at 6 3.71 for the C(11)-\(\beta\)-H, an undefined triplet at 6 4.11 for the C(14)-\(\beta\)-H and a doublet at 4.38 for the C(15)-\(\beta\)-H.

The carbon-13 NMR spectrum of fuziline (1) in CDCl\(_3\) showed twenty-three signals for twenty-four carbon atoms in the molecule. The chemical shifts of twenty-four carbons in fuziline have been assigned on the basis of noise decoupled spectra, single-frequency off-resonance decoupling (SFORD), and by direct comparison with the \(^{13}C\) NMR spectra of neoline (2) and isodelphinine (3). The chemical shifts pattern in fuziline is very similar to that of neoline except for changes in the shifts of C(8), C(15) and C(16). The presence of a doublet at 78.7 ppm and the absence of a triplet at 42.7 ppm (compared with neoline) indicate that a secondary hydroxy group is present at C(15) in fuziline. The presence of the C(15)-hydroxy group also moved the chemical shifts of the C(8) and C(16) carbons of fuziline significantly downfield compared with neoline. The \(\alpha\)-configuration of the C(15)-hydroxyl group was assigned on the basis of the \(^{13}C\) NMR spectra of isodelphinine [C(15): 78.8 ppm], naquarine [C(15): 68.1 ppm], and other relatedaconitine-type alkaloids. The chemical shifts of the remaining carbons are in agreement with the assigned structure 1 for fuziline. Subsequently, this structure (1) was confirmed by X-ray analysis.

The crystals of fuziline belong to the orthorhombic space group \(P2_12_12_1\) with \(a=10.046(2)\AA, b=13.885(7)\AA, c=16.555(4)\AA\) and \(Z=4\). The X-ray intensity data were measured using a CAD-4 diffractometer using monochromated CuKa (\(\lambda=1.5418\AA\)) radiation to a \(2\theta\) limit of 150°. Of 2703 unique reflections measured, 261 of them had intensities less than 3\(\sigma\) (1) and were excluded from the least squares calculations. The crystal structure was solved by multisolution methods using the computer program MULTAN \(^5\) and refined by block diagonal least squares technique to an R of 0.039 and an Rw of 0.040 for 2442 observed reflections. Although the ring system of the \(\text{C}_{19}\)-diterpenoid alkaloids is rather rigid, C(2) may be located either cis- or trans- to C(5) with reference to the plane passing through C(1), C(3), C(4), and C(11), making the A ring either a boat or a chair, respectively. In the case of fuziline the A ring has a boat conformation. The endocyclic torsion angles about the C(3)-C(4) and C(1)-C(11) bonds are 5° and 4°, respectively, indicating that atoms C(2), C(3), C(4), and C(5) lie nearly in a plane and atoms C(1), C(2), C(5) and C(11) lie nearly in another plane (Figure 1).
Interestingly, fuziline is the second naturally-occurring example of an alkaloid bearing a C(15)-α-hydroxyl group, but lacking a C(13)-hydroxyl group. Recently we reported the isolation of nagarine, the C(15)-epimer of fuziline, from another Chinese drug, *Aconitum nectarum* var. *heterotrichum* f. *dielsianum* W. T. Wang.

REFERENCES AND NOTES

1. The stereochemistry indicated for the C(14)-OH group is with reference to the cyclopentane ring.

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