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

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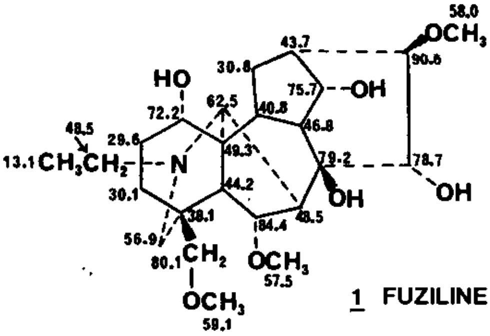
Abstract: Chemical investigation of the famous chinese drug "Fuzi" (Aconitum carmichaeli Debx) resulted in the isolation of a new alkaloid, fuziline, along with the known alkaloids, aconitine, hypaconitine, mesaconitine, neoline and songorine. The structure of fuziline (1) has been established by the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

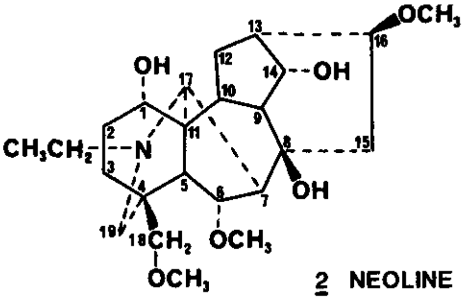
Aconitum carmichaeli Debx. is widely used as the famous drug "Fuzi" in Chinese folklore medicine. In this communication we report the isolation and structure determination of a new C_{19}-diterpenoid alkaloid named fuziline (1)[1] obtained from a fine variety of the crude drug "Fuzi" from Si-Chuan. Along with this new alkaloid, the known alkaloids[2] aconitine, hypaconitine, mesaconitine, neoline (2), and sorgorine were also isolated and characterized.



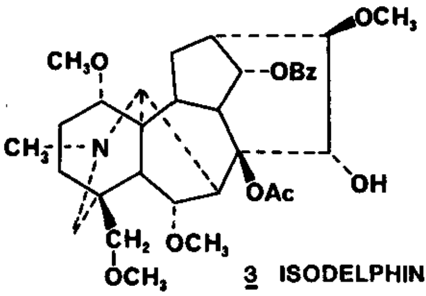
1 FUZILINE

Fuziline, $C_{24}H_{39}NO_7$ (M^+ 453.2694), crystallized from acetone, mp. 214-216°C (corr.), $[\alpha]_D^{26}$ + 11.6° (c 1.0, $CHCl_3$). Infrared absorption (Nujol) showed the presence of several hydroxy groups at 3560(sharp), 3480(sharp) and 3260(broad) and methoxy groups at

1100 and 1115 cm^{-1}. The ^{1}H NMR spectrum of fuziline in $CDCl_3$ exhibited the presence of an N-CH_2-$C\underline{H}_3$ (3H, t) centered at δ 1.11, three methoxy groups (each 3H, s) at δ 3.33, 3.35 and δ 3.45. The spectrum also indicated a broad peak at δ 3.63 for C(4)-$C\underline{H}_2$-OCH_3, an undefined one-proton triplet at δ 3.71 for the C(1)-β-H, an undefined triplet at δ 4.11 for the C(14)-β-H and a doublet at 4.38 for the C(15)-β-H.



2 NEOLINE



3 ISODELPHININE

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)[3] and isodelphinine (3).[4] 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 α- 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][4], nagarine [C(15): 68.1 ppm][7], and other related aconitine-type alkaloids.[3] 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) Å, b=13.885(7) Å, c=16.555(4) Å and Z=4. The X-ray intensity data were measured using a CAD-4 diffractometer using monochromated CuKα (λ=1.5418 Å) radiation to a 2θ limit of 150°. Of 2703 unique reflections measured, 261 of them had intensities less than 3σ (I) and were excluded from the least squares calculations. The crystal structure was solved by multi solution methods[5] using the computer program MULTAN[6] 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 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).

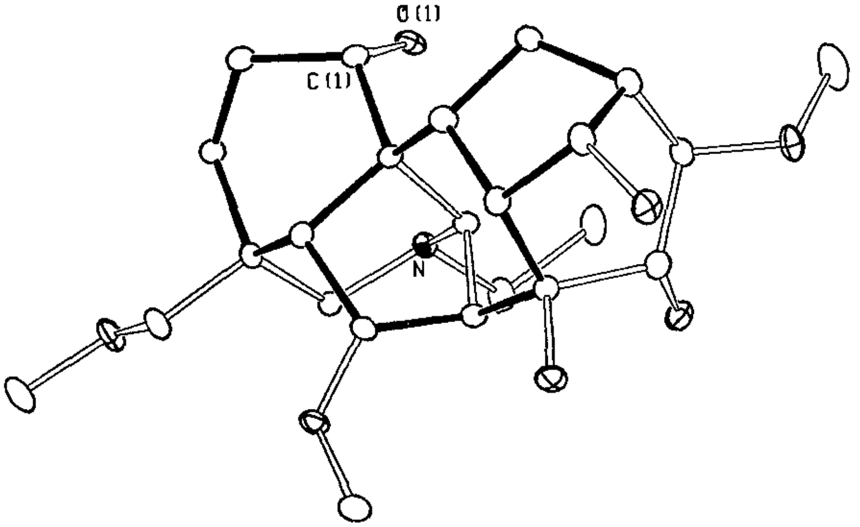


Figure 1. The thermal ellipsoid plot of fuziline. The bonds in the A, B, and C rings are shaded for clarity.

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 [7] the isolation of nagarine, the C(15)-epimer of fuziline, from another Chinese drug, Aconitum nagarum var. heterotrichum f. dielsianum W. T. Wang.

REFERENCES AND NOTES

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