

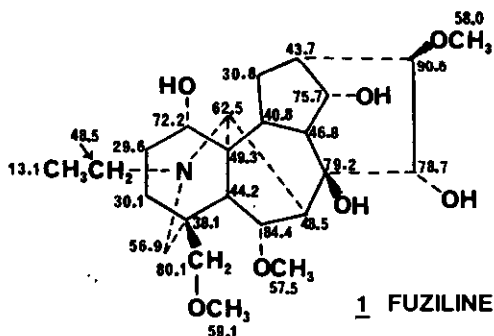
FUZILINE, A NEW ALKALOID FROM THE CHINESE DRUG "FUZI" (Aconitum carmichaeli Debx.)

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

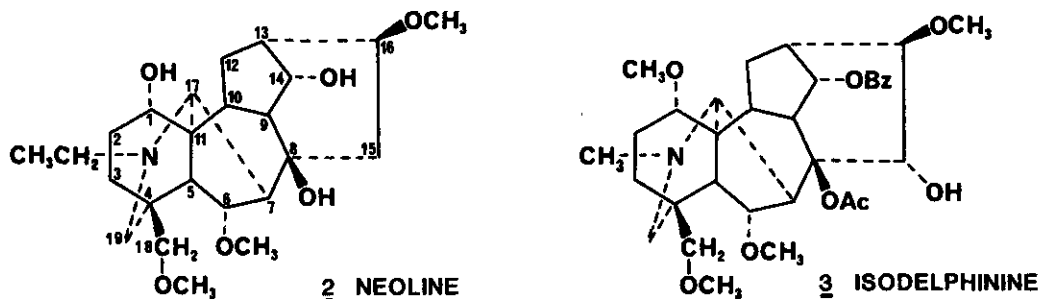
Abstract: Chemical investigation of the famous chinese drug "Fuzi" (Aconitum carmichaeli Debx) resulted in the isolation of a new alkaloid, fuziline, along with the known alkaloids, aconitine, hyaconitine, mesaconitine, neoline and songorine. The structure of fuziline (1) has been established by the 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<sub>19</sub>-diterpenoid alkaloid named fuziline (1)<sup>1</sup> obtained from a fine variety of the crude drug "Fuzi" from Si-Chuan. Along with this new alkaloid, the known alkaloids<sup>2</sup> aconitine, hyaconitine, mesaconitine, neoline (2), and songorine were also isolated and characterized.



Fuziline, C<sub>24</sub>H<sub>39</sub>NO<sub>7</sub> (M<sup>+</sup> 453.2694), crystallized from acetone, mp. 214-216°C (corr.), [α]<sub>D</sub><sup>26</sup> + 11.6° (c 1.0, CHCl<sub>3</sub>). Infrared absorption (Nujo1) showed the presence of several hydroxy groups at 3560(sharp), 3480(sharp) and 3260(broad) and methoxy groups at

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



The carbon-13 NMR spectrum of fuziline (1) in  $\text{CDCl}_3$  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  $^{13}\text{C}$  NMR spectra of neoline (2)<sup>3</sup> and isodelphinine (3).<sup>4</sup> The chemical shifts pattern in fuziline is very similar to that of neoline except for changes in the shifts of  $\text{C}(8)$ ,  $\text{C}(15)$  and  $\text{C}(16)$ . 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  $\text{C}(15)$  in fuziline. The presence of the  $\text{C}(15)$ -hydroxy group also moved the chemical shifts of the  $\text{C}(8)$  and  $\text{C}(16)$  carbons of fuziline significantly downfield compared with neoline. The  $\alpha$ - configuration of the  $\text{C}(15)$ -hydroxyl group was assigned on the basis of the  $^{13}\text{C}$  NMR spectra of isodelphinine [ $\text{C}(15)$ :78.8 ppm]<sup>4</sup>, naqarine [ $\text{C}(15)$ :68.1 ppm]<sup>7</sup>, and other related aconitine-type alkaloids.<sup>3</sup> 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  $a=10.046(2)\text{ \AA}$ ,  $b=13.885(7)\text{ \AA}$ ,  $c=16.555(4)\text{ \AA}$  and  $Z=4$ . The X-ray intensity data were measured using a CAD-4 diffractometer using monochromated  $\text{CuK}\alpha$  ( $\lambda=1.5418\text{ \AA}$ ) radiation to a  $2\theta$  limit of  $150^\circ$ . Of 2703 unique reflections measured, 261 of them had intensities less than  $3\sigma(I)$  and were excluded from the least squares calculations. The crystal structure was solved by multi solution methods<sup>5</sup> using the computer program MULTAN<sup>6</sup> and refined by block diagonal least squares technique to an  $R$  of 0.039 and an  $R_w$  of 0.040 for 2442 observed reflections. Although the ring system of the  $\text{C}_{19}$ -diterpenoid alkaloids is rather rigid,  $\text{C}(2)$  may be located either *cis*- or *trans*- to  $\text{C}(5)$  with reference to the plane passing through  $\text{C}(1)$ ,  $\text{C}(3)$ ,  $\text{C}(4)$ , and  $\text{C}(11)$ , 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  $\text{C}(3)\text{-C}(4)$  and  $\text{C}(1)\text{-C}(11)$  bonds are  $5^\circ$  and  $4^\circ$ , respectively, indicating that atoms  $\text{C}(2)$ ,  $\text{C}(3)$ ,  $\text{C}(4)$ , and  $\text{C}(5)$  lie nearly in a plane and atoms  $\text{C}(1)$ ,  $\text{C}(2)$ ,  $\text{C}(5)$  and  $\text{C}(11)$  lie nearly in another plane (Figure 1).

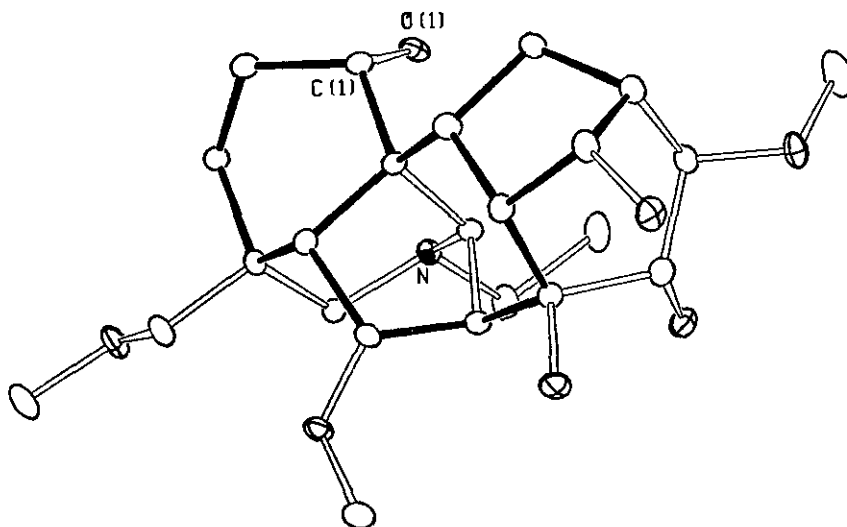


Figure 1. The thermal ellipsoid plot of fuziline. The bonds in the A, B, and C rings are shaded for clarity.

Interestingly, fuziline is the second naturally-occurring example of an alkaloid bearing a C(15)- $\alpha$ -hydroxyl group, but lacking a C(13)-hydroxyl group. Recently we reported <sup>7</sup> 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

1. The stereochemistry indicated for the C(14)-OH group is with reference to the cyclopentane ring.
2. S. W. Pelletier and N. V. Mody in *The Alkaloids*, vol. 17, Edited by R.H.F. Manske and R. Rodrigo, Academic Press, New York, 1979, Chapter 1.
3. S. W. Pelletier and Z. Djarmati, *J. Am. Chem. Soc.*, **98**, 2626 (1976).
4. S. W. Pelletier, N. V. Mody, and N. Katsui, *Tetrahedron Letters*, 4027 (1977).
5. G. Germain, P. Main and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
6. P. Main, University of York (1978). A computer program to solve crystal structures by multiresolution methods.
7. N. V. Mody, S. W. Pelletier, and Chen Szu-Ying, *Heterocycles*, in press.

Received, 13th August, 1981