

THE STRUCTURE AND PARTIAL SYNTHESIS OF NAGARINE. A NOVEL ALKALOID FROM THE CHINESE DRUG, *ACONITUM NAGARUM* VAR. *HETEROTRICHUM* F. *DIELSII* W. T. WANG

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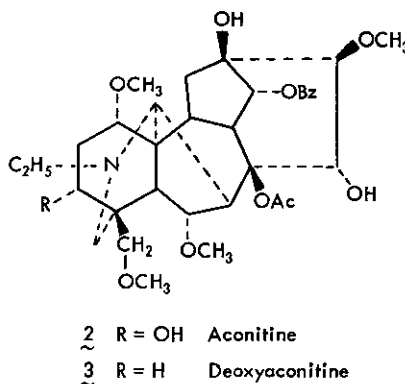
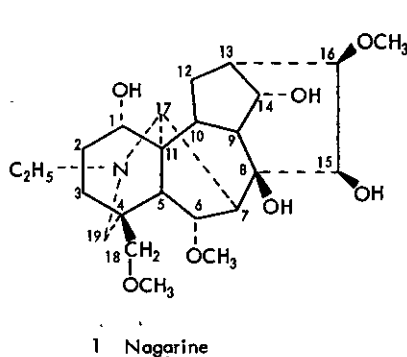
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Abstract: Chemical investigation of the roots of *Aconitum nigrum* var. *heterotrichum* f. *dielsianum* W. T. Wang resulted in the isolation of a novel alkaloid, nagine, along with two known alkaloids, aconitine and 3-deoxyaconitine. The structure of nagine (1) was based on the carbon-13 NMR analysis. Subsequently, this structure was confirmed by a partial synthesis from delphisine. The structure of nagine is unusual because it is the only C₁₉-diterpenoid alkaloid in which the C(15) hydroxyl group exists in the β-configuration.

As a part of a program to investigate the constituents of the well-known crude drugs of China, we have investigated the roots of *Aconitum nigrum* var. *heterotrichum* f. *dielsianum* W. T. Wang, which are used in the traditional Chinese medicine for treatment of rheumatism and neuralgia. In this communication, we report the isolation, structure elucidation, and partial synthesis of a novel C₁₉-diterpenoid alkaloid named nagine (1). Along with this new alkaloid, we have also isolated and fully characterized the major and minor known alkaloids, aconitine (2) and 3-deoxyaconitine (3),¹ respectively.



3600 gm of the roots (collected in Da-Li during the month of October, 1980) were extracted with benzene. The alkaloids were isolated from the benzene extract by a combination of acid-base extraction, alumina column chromatography and crystallization techniques. Nagine, C₂₄H₃₉NO₇ (M⁺ 453.272),² mp 190-191°C

(corrected), $[\alpha]_D^{20} + 20.4^\circ$ ($c = 0.88$, CHCl_3), was crystallized from acetone. Nagarine showed IR absorption in nujol at 3450 and 3170 (hydroxyl), 1105 (ether) cm^{-1} and other characteristic peaks of the C_{19} -diterpenoid alkaloid skeleton. The 90 MHz ^1H NMR spectrum of **1** in deuteriochloroform (exchange with D_2O) exhibited signals at δ 1.11 (3H, $\underline{\text{t}}$, $\text{NCH}_2\text{-C}\underline{\text{H}}_3$), 3.33, 3.38 and 3.49 (each 3H, $\underline{\text{s}}$, OCH_3) and 3.97 (1H, $\underline{\text{t}}$, C(14)- β -H).

The ^{13}C NMR spectrum of nagarine showed twenty-three signals for twenty-four carbon atoms in the molecule. The ^{13}C NMR spectrum of nagarine was compared with those of neoline (**4**)³ and 15-epihypaconine (**5**).⁴ The pattern of chemical shifts in nagarine is similar to that of the alkaloid, neoline, (Table 1). The appearance of a new doublet at 68.1 ppm, disappearance of a triplet at 42.7 ppm, and downfield and upfield shifts of C(16) and C(16)' carbon atoms in the ^{13}C NMR spectrum of nagarine in comparison with that of neoline and 15-epihypaconine, respectively, suggested that the secondary hydroxyl group must be present at the C(15) position in nagarine. The β -configuration of the C(15) hydroxyl group in nagarine was established by observing the chemical shifts of a hydroxyl at C(15) in 15-epihypaconine and hypaconine (**6**).⁵ Therefore, structure **1** was assigned to nagarine. Subsequently, this structure was confirmed by a partial synthesis of nagarine from delphisine,⁶ as outlined below.

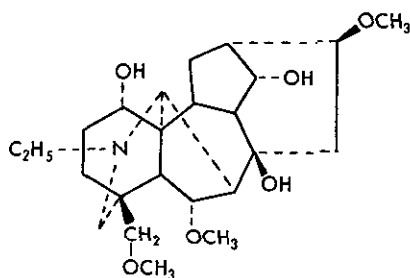
Table 1. Chemical Shifts and Assignments for Nagarine (**1**), Neoline (**4**), 15-Epihypaconine (**5**) and Hypaconine (**6**).[†]

	1	4	5	6		1	4	5	6
C(1)	72.2	72.3	85.7	85.2	C(13)	44.2	44.3	76.3	76.4
C(2)	29.5*	29.5*	25.5	26.5	C(14)	74.8	75.9	79.2	79.0
C(3)	29.8*	29.9*	34.9	34.9	C(15)	68.1	42.7	68.2	78.9
C(4)	38.1	38.2	39.6	39.3	C(16)	83.9	82.3	88.1	91.2
C(5)	44.2	44.9	49.0	49.2	C(17)	62.1	63.6	63.3	62.4
C(6)	83.4	83.3	82.5	83.6	C(18)	80.2	80.3	80.4	80.4
C(7)	52.9	52.3	50.1	50.0	C(19)	56.9	57.2	56.1	56.1
C(8)	74.5	74.3	73.2	75.7	N- CH_2	48.0	48.2	42.4	42.8
C(9)	48.4	48.3	48.3	48.1	CH_3	13.0	13.0	-	-
C(10)	42.1	40.7	42.4	42.0	C(1)'	-	-	56.3	56.5
C(11)	49.6	49.6	50.3	50.1	C(6)'	57.9	57.8	57.2	57.9
C(12)	30.6*	29.8*	36.6	35.3	C(16)'	58.1	56.3	62.5	61.5
					C(18)'	59.2	59.1	59.2	59.0

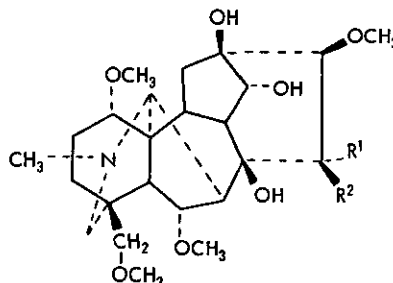
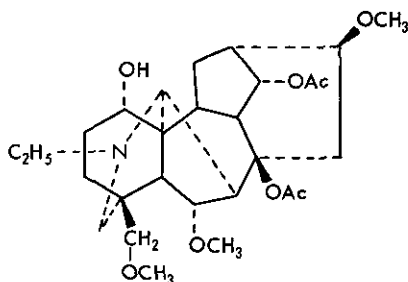
[†] In ppm downfield to TMS; solvent is deuteriochloroform.

* Values within any vertical column may be interchanged.

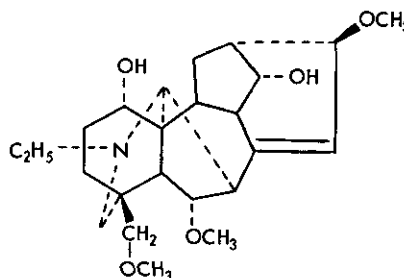
Pyrolysis of 80 mg of delphisine (**7**) was achieved at 205–215°C at 0.1 mm for 10 min. to afford pyrodelphisine. Without further purification, the latter was hydrolyzed (1% KOH in methanol, 2 hr reflux) to give the known compound, pyroneoline (**8**, 48 mg),⁷ mp 170–172°C, ^1H NMR (CDCl_3), δ 1.08 (3H, $\underline{\text{t}}$, $\text{NCH}_2\text{-CH}_3$), 3.30, 3.33, 3.39 (each 3H, $\underline{\text{s}}$, OCH_3), 3.93 (1H, broad signal, C(14)- β -H), 4.34 (1H, $\underline{\text{d}}$, $J = 6.0$ Hz, C(16)- α -H), and 5.50 (1H, $\underline{\text{d}}$, $J = 6.0$ Hz, C(15)-H). The ^{13}C NMR spectrum of pyroneoline in deuteriochloroform exhibited these signals: 13.2, 27.6, 30.3, 31.7, 36.5, 39.0, 46.5, 47.2, 48.1, 48.6, 49.3, 51.2, 55.9, 57.0, 58.5, 59.2, 73.4, 73.4, 79.5, 80.3, 80.6, 84.1, 116.3, and 148.9 ppm. To the solution of pyroneoline



4 Neoline

5 R¹ = H; R² = OH 15-Epihyaconine6 R¹ = OH; R² = H Hyaconine

7 Delphisine



8 Pyroneoline

(42 mg) in 2 ml of dry pyridine, 27 mg of osmium tetroxide in 2 ml of dry dioxane was added and the resulting mixture was stirred at room temperature for 1 hr. To this mixture was added a solution of sodium bisulfite (100 mg) in 2 ml of water and 3 ml of pyridine. When a clear orange solution was obtained after 15 min, it was extracted with chloroform (3 x 25 ml). The chloroform extract was dried over anhydrous Na₂SO₄ and evaporated *in vacuo* to give 15-β-hydroxyneoline (40 mg), which was crystallized from acetone, mp 190–191°C. The synthetic 15-β-OH neoline and nagarine were identical in all respects (TLC, mp, mmp, and ¹³C NMR spectra).

The occurrence of the C(15)-β-hydroxyl group in nagarine appears to be unique because this group exists in the α-configuration in all other known diterpenoid alkaloids.⁸

References and Notes

1. The roots of *Aconitum nagarum* var. *heterotrichum* f. *dielsianum* W.T. Wang which were collected in Da-Li in 1977 did not yield any deoxyaconitine (3).
2. C₂₄H₃₉NO₇ requires C 63.55; H 8.67 and N 3.09%; Found C 63.64; H 9.03 and N 3.39%.
3. S. W. Pelletier and Z. Djarmati, *J. Am. Chem. Soc.*, **98**, 2626 (1976).
4. N. V. Mody, Y. Ohtsuka and S. W. Pelletier, unpublished results. 15-Epihyaconine (5) was prepared from pyrodelphinine in four steps.
5. S. W. Pelletier, N. V. Mody, and R. S. Sawhney, *Can. J. Chem.*, **57**, 1652 (1979).

6. S. W. Pelletier, Z. Djarnati, S. Lajsic and W. H. DeCamp, J. Am. Chem. Soc., 98, 2617 (1976).
7. K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Bobin, F. Bickelhaupt, J. Kallos, and T. Bogri, Tetrahedron Lett., 17 (1960).
8. S. W. Pelletier and N. V. Mody in The Alkaloids, Edited by R. H. F. Manske and R. Rodrigo, Vol. 17, Chapter 1, pp. 1 - 103, Academic Press, New York, 1979.

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