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

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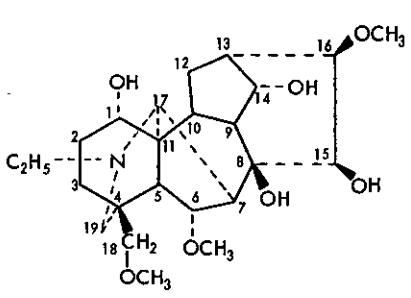
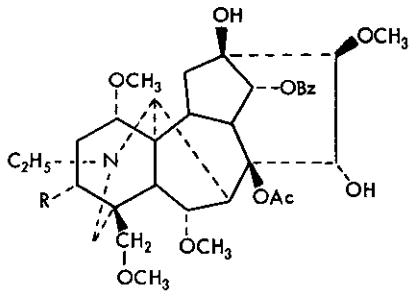
Abstract: Chemical investigation of the roots of *Aconitum nagarum* var.*heterotrichum* f. *dielsianum* W. T. Wang resulted in the isolation of a novel alkaloid, nagarine, along with two known alkaloids, aconitine and 3-deoxyaconitine. The structure of nagarine (1) was based on the carbon-13 NMR analysis. Subsequently, this structure was confirmed by a partial synthesis from delphisine. The structure of nagarine is unusual because it is the only C_{19}-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 nagarum* 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 C_{19}-diterpenoid alkaloid named nagarine (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.



1 Nagarine



2 R = OH Aconitine
3 R = H Deoxyaconitine

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. Nagarine, $C_{24}H_{39}NO_7$ (M^+ 453.272),[2] mp 190-191°C

(corrected), $[\alpha]_D^{20}$+ 20.4° (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, t, NCH_2-CH_3), 3.33, 3.38 and 3.49 (each 3H, s, OCH_3) and 3.97 (1H, 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.

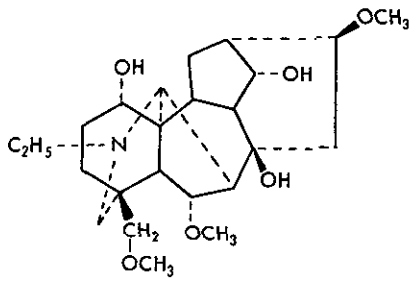
Table 1. Chemical Shifts and Assignments for Nagarine (1), Neoline (4), 15-Epihypaconine (5) and Hypaconine (6).†

	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

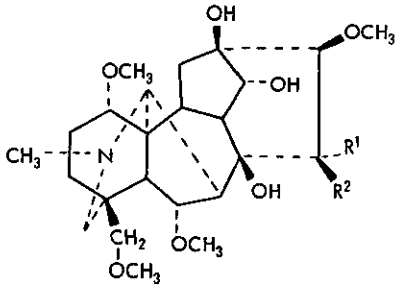
† In ppm downfield to TMS; solvent is deuteriochloroform.

* 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, t, NCH_2-CH_3), 3.30, 3.33, 3.39 (each 3H, s, OCH_3), 3.93 (1H, broad signal, C(14)-β-H), 4.34 (1H, d, J = 6.0 Hz, C(16)-α-H), and 5.50 (1H, 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

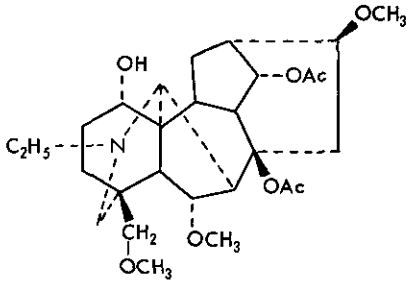


4 Neoline

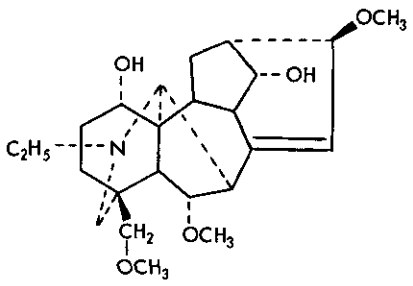


5 $R^1 = H$; $R^2 = OH$ 15-Epihypaconine

6 $R^1 = OH$; $R^2 = H$ Hypaconine



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 Na_2SO_4 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 ^{13}C 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. $C_{24}H_{39}NO_7$ requires C 63.55; H 8.67 and N 3.09%; Found C 63.64; H 9.03 and N 3.39%.
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4. N. V. Mody, Y. Ohtsuka and S. W. Pelletier, unpublished results. 15-Epihypaconine (5) was prepared from pyrodelphinine in four steps.
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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.

Received, 27th July, 1981