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SEPTENTRIONINE AND SEPTENTRIODINE: TWO NEW C_{19}-DITERPENOID ALKALOIDS FROM ACONITUM SEPTENTRIONALE KOELLE

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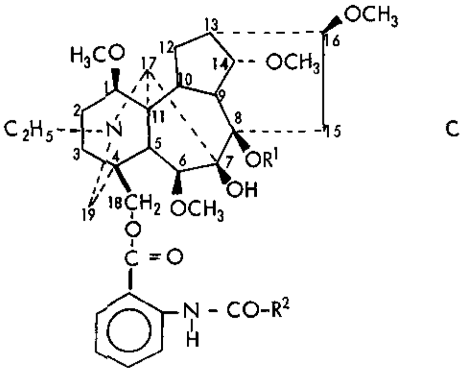
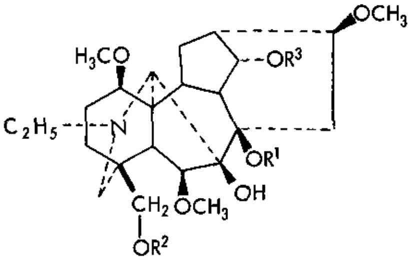
Investigation of the alkaloids of Aconitum septentrionale has led to the isolation and structure elucidation of two new diterpenoid alkaloids, septentrionine (1) and septentriodine (2). These are the first reported examples of C_{19}-diterpenoid alkaloids bearing a carboxy ester group on the amide side chain. ^{13}C nmr chemical shifts and assignments for these and related alkaloids are presented.

In 1967 Marion et al[1] reported the isolation and characterization of seven alkaloids from the roots of Aconitum septentrionale Koelle. Two alkaloids, lappaconitine and deacetyllappaconitine, were identified, but the structures of five other alkaloids were not elucidated. We have reinvestigated this plant (collected in Norway) and now report the complete structures of two new alkaloids, septentrionine (1) and septentriodine (2).

Septentrionine, $C_{38}H_{54}N_2O_{11}$, mp 123-125° (corr.), $[\alpha]^{26}_{D}$ + 21.2° (c 1.0, $CHCl_3$), was isolated from the 85% ethanol extract of the root by a combination of gradient pH separation, thick-layer, and column chromatographic techniques. The alkaloid showed ir absorption at 3540 (OH), 3275 (NH), 1750, 1708, 1688 (carbonyls) and 1608, 1590 (aromatic) cm^{-1}. The 100 MHz ^1H nmr spectrum of septentrionine exhibited absorption characteristic of $N\text{-}CH_2\text{-}C\underline{H}_3$ (3H, t, J=6.8Hz) centered at δ 1.08; $\text{-}CO\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}COOCH_3$ (4H, s) at δ 2.80; and six methoxyl groups at δ 3.25 (3H), 3.37 (6H), 3.47 (6H), 3.70 (3H). A group of signals appearing in the region δ 7.04-8.74 (two d, two t) ppm are indicative of the aromatic protons of the anthranoyl group.[2] In the downfield region, the spectrum also showed a signal at δ 11.15 attributable to a secondary amide proton.

The ^{13}C nmr spectrum showed 38 signals corresponding to 38 carbon atoms in the molecule. These signals have been assigned on the basis of noise-decoupled spectra, direct analysis of non-protonated carbons, and by comparison with ^{13}C nmr spectra of other related C_{19}-diterpenoid alkaloids.[3] The ^{13}C nmr spectrum of septentrionine indicates the presence of a lycoctonine-type skeleton. The pattern of chemical shifts of the aromatic carbons in septentrionine is similar to that of ajacine (3) and delsemine (4), indicating that the alkaloid has a straight chain rather than an imide moiety. [3] The singlets at 90.4 and 80.9 ppm (Table 1) clearly demonstrate the presence of C(7)-OH and C(8)-OCH_3 substitution in septentrionine. [4]



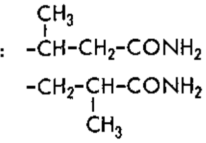


1 $R^1 = CH_3$; $R^2 = -(CH_2)_2 - COOCH_3$

2 $R^1 = H$; $R^2 = -(CH_2)_2 - COOCH_3$

3 $R^1 = H$; $R^2 = CH_3$

4 $R^1 = H$; R^2 = mixture of:



$-\overset{CH_3}{\overset{|}{C}}H-CH_2-CONH_2$

and $-CH_2-\underset{CH_3}{\underset{|}{C}}H-CONH_2$

5 $R^1 = R^3 = CH_3$; $R^2 = H$

6 $R^1 = R^2 = CH_3$; $R^3 = COCH_3$

7 $R^1 = R^3 = CH_3$; $R^2 = COCH_3$

8 $R^1 = H$; $R^2 = COCH_3$; $R^3 = CH_3$

9 $R^1 = R^2 = H$; $R^3 = CH_3$

Hydrolysis (5% methanolic KOH, 25°C) of septentrionine afforded a new alkamine (5) and an amino acid, $C_{11}H_{11}NO_5$, mp 183-184°. The ^1H nmr spectrum of the alkamine shows the presence of N-CH_2-$C\underline{H_3}$ (3H, t, J=7Hz) centered at δ 1.05 and five aliphatic methoxyl groups at δ 3.25 (3H), 3.37 (6H) and 3.47 (6H).

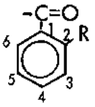
Obviously, the methoxyl group which is lost during hydrolysis of septentrionine must be present in the aminoacid moiety. The ^{13}C nmr spectrum of the alkamine shows 26 carbons which are interpretable on the basis of structure (5). This structure (5) was confirmed by comparison of its ^{13}C nmr spectrum with that of ambiguine (6), a new alkaloid recently isolated from Consolida ambigua. [4] The alkamine (5) was relatively unstable and decomposed when attempts were made to crystallize it. On acetylation with Ac_2O/Py, 5 gave a monoacetate (7) whose ^{13}C nmr spectrum was similar to that of 5 except for some differences in the chemical shifts of C(4) and C(18) (Table 1). The additional signals at 171.5 and 21.0 ppm in compound 7 must be assigned to the acetyl group.

The aminoacid, mp 183-184°, was identified as N-succinoylanthranilic acid by comparison of the ir and ^{13}C nmr spectra with those of an authentic sample prepared from anthranilic acid and succinic anhydride. [5]

On the basis of the above data, septentrionine is assigned structure 1, and is probably identical with alkaloid "A" (mp 123-129°) of Marion et al. [6]

Table 1. Carbon-13 Chemical Shifts and Assignments for
Septentrionine (1), Septentriodine (2) and Related Alkaloids[a]

Carbon[c]	1	5	7	6	2	8
1	83.1	83.2	82.9[b]	83.4	84.0	84.0
2	25.6	25.5	25.3	25.3	26.1	26.1
3	31.9	31.2	30.9	31.5	31.6	31.9
4	37.7	38.7	37.2	38.3	37.6	37.2
5	40.6	40.8	40.2	40.9	43.3	43.3
6	91.5	91.4	91.3	91.1	91.1	90.9
7	90.4	89.7	90.1	90.0	88.7	88.5
8	80.9	80.6	81.0	80.4	77.6	77.5
9	51.9	52.1	51.9	52.0	50 4	50.4
10	37.7	37.9	37.9	35.9	38.1	38.1
11	47.6	47.2	47.7	47.2	49.1	49.0
12	27.9	27.9	28.1	27.4	28.7	28.7
13	46.7	46.7	46.5	46.1	46.1	46.1
14	83.5	83.6	83.6[b]	75.0	84.0	84.0
15	27.9	27.9	28.1	28.5	33.7	33.7
16	82.8	82.9	82.9	81.9	82.7	82.6
17	66.2	66.9	66.7	66.7	64.6	64.6
18	70.6	68.8	69.7	79.3	69.9	69.1
19	53.2	53.5	53.5	53.6	52.4	52.4
N-CH_2	51.9	52.2	51.9	52.6	51.0	51.0
CH_3	14.8	15.0	14.5	14.9	14.1	14.1
1'	55.7	55.6	55.7	55.6	55.9	55.7
6'	60.0	59.8	60.0	59.4	57.9	57.8
8'	54.4	53.6	53.5	53.7	-	-
14'	57.7	57.7	57.7	-	58.1	58.0
16'	56.5	56.5	56.6	56.3	56.4	56.3

Carbon		1		7	6	2	8
		168.4	(172.6)[d]			168.3	
	1	115.1	(117.2)			114.7	
	2	141.8	(142.3)			141.9	
	3	120.6	(121.3)			120.8	
	4	134.9	(135.1)			135.2	
	5	122.7	(123.8)			122.8	
	6	130.8	(132.4)			130.5	
R = NH-CO		170.6	(171.3)			170.6	
CH_2		29.0	(29.8)			28.9	
CH_2		32.7	(33.5)			32.7	
CO		173.3	(176.1)			173.3	
OCH_3		51.9				51.9	
-CO				171.5	171.3		170.9
CH_3				21.0	21.4		20.8

[a] In ppm downfield to Me_4Si; solvent deuterochloroform.

[b] These assignments may be interchanged in any vertical column.

[c] Primed numbers correspond to CH_3O- groups attached to non-primed C-atoms.

[d] Values in parentheses are those of N-succinoylanthranilic acid.

The second alkaloid, septentriodine (2), $C_{37}H_{52}N_2O_{11}$, $[\alpha]_D^{25}$ + 36.2° (c, 1.0, $CHCl_3$) could not be induced to crystallize. The 100 MHz ^1H nmr spectrum of septentriodine is similar to that of septentrionine except for the absence of one methoxyl absorption. It reveals the presence of $N-CH_2-C\underline{H_3}$ (3H, t, J 7.1 Hz) centered at δ 1.07; $-COC\underline{H_2}-C\underline{H_2}-COOCH_3$ (4H, s) at δ 2.80; five aliphatic methoxyl groups at δ 3.26, 3.34, 3.38, 3.42 and 3.71. The presence of four aromatic protons is shown by a group of signals in the region δ 7.0–8.7. The secondary amide (N$\underline{H}$-CO) proton was located at δ 11.10. The alkaloid showed ir bands at 3470 (-OH), 3310 (NH), 1740, 1705, 1687 (carbonyls), 1605, 1590 (aromatic) and 1085 (C-O) cm^{-1}. The base peak at m/e 669 (M^+ -31) in the mass spectrum of septentriodine confirms the presence of a methoxyl group at C(1).[7]

The ^{13}C nmr spectrum of septentriodine resembles that of septentrionine. The singlets at 88.7 and 77.6 ppm (Table 1) show the presence of a hydroxy group at C(8) in septentriodine. The chemical shifts of the alkamine part of septentriodine are very close to those of the corresponding carbons of tricornine (8). The structure (2) for septentriodine was confirmed by its hydrolysis (5% methanolic KOH) to lycoctonine (9) and N-succinoylanthranilic acid.

Septentrionine and septentriodine represent the first examples of C_{19}-diterpenoid alkaloids bearing a carboxy ester group in the amide side chain.

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