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# SEPTENTRIOSINE—A NEW $C_{20}$-DITERPENOID ALKALOID FROM *ACONITUM SEPTENTRIONALE*

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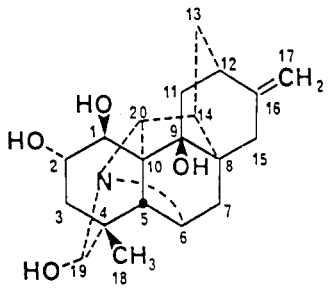
ABSTRACT.—From the roots of *Aconitum septentrionale*, a new alkaloid, septentriosine [**1a**] (hetisan-1β,2α,9β,19α-tetrol), was isolated, and its structure was determined by spectroscopic and X-ray data.

The presence of alkaloids in *Aconitum septentrionale* Koelle (Ranunculaceae) was recorded almost a century ago (1). In 1967, Marion *et al.* (2) reported the isolation and characterization of seven alkaloids of which two were the known $C_{19}$-diterpenoid alkaloids, lappaconitine and deacetyllappaconitine. The structures of the remaining have not been determined (2). In previous communications, we have reported the isolation of lapaconidine (3) and also the structures of two $C_{19}$-diterpenoid alkaloids, septentriodine and septentrionine (4). In the present paper, we wish to report the isolation and structure of a minor alkaloid, septentriosine, obtained in 0.015% yield from the roots of *A. septentrionale*.

## RESULTS AND DISCUSSION

Septentriosine, $C_{20}H_{27}NO_4$, formed colorless crystals, mp 260–262°. In the ir spectrum it showed the presence of four hydroxyl groups at 3540, 3460, 3360, 3280 $cm^{-1}$, an exocyclic methylene at 1660 $cm^{-1}$, and no absorption in the carbonyl region. The hydrochloride also crystallized as colorless cubes, mp 299–300°. These data together with the $^1$H- and $^{13}$C-nmr spectral analysis indicated that septentriosine is a $C_{20}$-diterpenoid alkaloid.

In the $^1$H-nmr spectrum (270 MHz), septentriosine exhibited signals at δ 1.02 (3H, s, *tert*-methyl), 3.30 (1H, H-6), 3.60 (1H, H-20), indicative of the hetisan skeleton (5). The $^{13}$C-nmr spectrum ($CDCl_3$ + MeOH) showed 20 signals for the twenty carbon atoms of the molecule. The SFORD spectrum indicated that septentriosine contains 5 singlets due to quaternary carbons, 8 doublets due to methine carbons, 6 triplets




**1a** septentriosine
**1b** septentriosine HCl

due to methylene carbons, and 1 quartet indicative of a methyl group. The spectral data indicated that septentriosine contains a tertiary methyl group and an exocyclic methylene. It does not contain any methoxyl groups, and in all probability the four oxygen functions are present as hydroxyl groups.

The only methyl group is attached at the C-4 position (28.4 ppm). As the nitrogen atom is linked to the C-19 methine bearing an oxygen atom (95.3 ppm) and C-20 (60.5 ppm), the remaining bond of the nitrogen atom should be attached to C-6.

One of the three hydroxyl groups that is tertiary (79.8 ppm) can be located either at C-6, C-9, or C-14. The remaining two secondary hydroxyl groups (69.0, 70.4 ppm) can be placed at C-1, C-2, C-3, C-7, C-11, C-13, or C-15.

Because of the uncertainty of positioning of the hydroxyl groups in the molecule and the paucity of compound available for extensive chemical studies, the structure was completed by X-ray diffraction studies on crystals of septentriosine and its hydrochloride (Tables 1 and 2); the structure of the alkaloid was shown to be **1** (hetisan-1β-2α,9β,19α-tetrol).

TABLE 1. Positional Parameters for Septentriosine [**1a**] ($C_{20}H_{27}NO_4 \cdot H_2O$).

| Atom | x [SIG(x)] | y [SIG(y)] | z [SIG(z)] |
|---|---|---|---|
| O-1 | −0.1105(5) | −0.0257(9) | 0.2778(3) |
| O-2 | 0.0322(4) | −0.0702(8) | 0.0138(3) |
| O-3 | −0.1279(4) | −0.2407(9) | 0.4035(2) |
| O-4 | −0.1371(5) | −0.2509(9) | −0.1174(2) |
| O-9 | 0.9790(6) | −0.2918(9) | 0.6650(3) |
| N-1 | −0.1142(5) | −0.3697(9) | 0.0603(3) |
| C-1 | −0.0175(6) | −0.0887(9) | 0.2084(3) |
| C-2 | −0.0980(6) | −0.0410(9) | 0.0755(4) |
| C-3 | −0.3036(6) | −0.0819(9) | 0.0017(4) |
| C-4 | −0.3442(5) | −0.2103(9) | 0.0109(3) |
| C-5 | −0.2681(5) | −0.2521(9) | 0.1496(3) |
| C-6 | −0.2405(5) | −0.3819(9) | 0.1346(3) |
| C-7 | −0.1397(6) | −0.4478(9) | 0.2567(4) |
| C-8 | 0.0554(5) | −0.3915(9) | 0.3367(3) |
| C-9 | 0.0248(5) | −0.2634(9) | 0.3573(3) |
| C-10 | −0.0504(5) | −0.2163(9) | 0.2181(3) |
| C-11 | 0.2202(6) | −0.2128(9) | 0.4502(4) |
| C-12 | 0.3890(6) | −0.2944(9) | 0.4650(4) |
| C-13 | 0.3781(6) | −0.3251(9) | 0.3324(4) |
| C-14 | 0.1784(5) | −0.3795(9) | 0.2555(3) |
| C-15 | 0.1627(7) | −0.4556(9) | 0.4586(4) |
| C-16 | 0.3606(6) | −0.4046(9) | 0.5275(4) |
| C-17 | 0.4943(7) | −0.4476(10) | 0.6316(5) |
| C-18 | −0.5677(6) | −0.2267(9) | −0.0521(4) |
| C-19 | −0.2404(6) | −0.2975(9) | −0.0480(3) |
| C-20 | 0.0480(5) | −0.2995(9) | 0.1505(3) |
| H-1 | 0.1313 | −0.0739 | 0.2570 |
| H-2 | −0.1108 | 0.0362 | 0.0814 |
| $H\text{-}3_1$ | −0.3753 | −0.0412 | 0.0352 |
| $H\text{-}3_2$ | −0.3527 | −0.0622 | −0.0996 |
| H-5 | −0.3553 | −0.2292 | 0.1956 |
| H-6 | −0.3618 | −0.4250 | 0.0820 |
| $H\text{-}7_1$ | −0.1249 | −0.5248 | 0.2457 |
| $H\text{-}7_2$ | −0.2408 | −0.4520 | 0.3070 |
| $H\text{-}9_1$ | −0.1223 | −0.0759 | 0.3380 |
| $H\text{-}9_2$ | 0.0551 | 0.0000 | 0.0000 |
| $H\text{-}9_3$ | −0.0646 | −0.2421 | 0.4956 |
| $H\text{-}9_4$ | −0.0587 | −0.1876 | −0.0755 |
| $H\text{-}9_5$ | 0.9952 | −0.3843 | 0.6708 |

TABLE 1. Continued.

| Atom | *x* [SIG(*x*)] | *y* [SIG(*y*)] | *z* [SIG(*z*)] |
|---|---|---|---|
| H-$9_5$ | 0.9952 | −0.3843 | 0.6708 |
| H-$9_6$ | 0.9210 | −0.2835 | 0.7190 |
| H-$11_1$ | 0.1898 | −0.2161 | 0.5335 |
| H-$11_2$ | 0.2162 | −0.1269 | 0.4393 |
| H-12 | 0.5192 | −0.2643 | 0.5111 |
| H-$13_1$ | 0.4170 | −0.2585 | 0.2952 |
| H-$13_2$ | 0.4554 | −0.3827 | 0.3236 |
| H-14 | 0.1873 | −0.4555 | 0.2233 |
| H-$15_1$ | 0.0809 | −0.4357 | 0.5073 |
| H-$15_2$ | 0.1674 | −0.5299 | 0.4547 |
| H-$17_1$ | 0.4818 | −0.5360 | 0.6446 |
| H-$17_2$ | 0.6221 | −0.4227 | 0.6601 |
| H-$18_1$ | −0.6304 | −0.2186 | −0.1443 |
| H-$18_2$ | −0.6126 | −0.1596 | 0.0000 |
| H-$18_3$ | −0.5835 | −0.3065 | −0.0419 |
| H-19 | −0.3441 | −0.3537 | −0.1016 |
| H-20 | 0.1083 | −0.2570 | 0.1021 |

TABLE 2. Positional Parameters for Septentriosine Hydrochloride [**1b**] ($C_{20}H_{27}NO_4 \cdot HCl$).

| Atom | *x* [SIG(*x*)] | *y* [SIG(*y*)] | *z* [SIG(*z*)] |
|---|---|---|---|
| Cl-1 | −0.3474(3) | 0.2919(2) | −0.5414(5) |
| O-1 | −0.0164(7) | 0.3301(6) | −0.3759(12) |
| O-2 | −0.2615(7) | 0.4067(5) | −0.2795(13) |
| O-3 | 0.0403(5) | 0.2049(5) | −0.0942(12) |
| O-4 | −0.2881(10) | 0.4241(8) | 0.0496(20) |
| N-1 | −0.1995(8) | 0.3187(7) | 0.1437(15) |
| C-1 | −0.1120(11) | 0.3238(8) | −0.3065(18) |
| C-2 | −0.1509(13) | 0.4045(8) | −0.3008(20) |
| C-3 | −0.1059(12) | 0.4507(8) | −0.1656(21) |
| C-4 | −0.0977(11) | 0.4162(9) | 0.0182(24) |
| C-5 | −0.0538(10) | 0.3344(9) | 0.0137(18) |
| C-6 | −0.0948(12) | 0.3016(10) | 0.1847(20) |
| C-7 | −0.0776(11) | 0.2166(9) | 0.2072(18) |
| C-8 | −0.1173(10) | 0.1701(9) | 0.0479(19) |
| C-9 | −0.0663(9) | 0.2040(8) | −0.1168(18) |
| C-10 | −0.1102(9) | 0.2865(7) | −0.1171(15) |
| C-11 | −0.0956(10) | 0.1536(8) | −0.2718(17) |
| C-12 | −0.1835(12) | 0.1007(7) | −0.2206(22) |
| C-13 | −0.2670(10) | 0.1469(8) | −0.1475(23) |
| C-14 | −0.2246(9) | 0.1908(7) | 0.0111(18) |
| C-15 | −0.0970(11) | 0.0860(9) | 0.0652(23) |
| C-16 | −0.1449(11) | 0.0438(8) | −0.0885(19) |
| C-17 | −0.1532(12) | −0.0331(9) | −0.0951(29) |
| C-18 | −0.0354(15) | 0.4631(10) | 0.1459(29) |
| C-19 | −0.1966(11) | 0.4064(10) | 0.1165(22) |
| C-20 | −0.2151(9) | 0.2770(8) | −0.0270(17) |
| H-1 | −0.1555 | 0.2886 | −0.3801 |
| H-2 | −0.1378 | 0.4290 | −0.4231 |
| H-$3_1$ | −0.1406 | 0.5032 | −0.1598 |
| H-$3_2$ | −0.0355 | 0.4669 | −0.2070 |
| H-5 | 0.0230 | 0.3360 | 0.0125 |
| H-6 | −0.0602 | 0.3268 | 0.2904 |
| H-$7_1$ | −0.1091 | 0.1966 | 0.3129 |

TABLE 2. Continued.

| Atom | x [SIG(x)] | y [SIG(y)] | z [SIG(z)] |
|---|---|---|---|
| H-7$_2$ | −0.0050 | 0.2053 | 0.2160 |
| H-8$_1$ | −0.2648 | 0.2999 | 0.2124 |
| H-11$_1$ | −0.0365 | 0.1237 | −0.3129 |
| H-11$_2$ | −0.1155 | 0.1853 | −0.3742 |
| H-12 | −0.2049 | 0.0699 | −0.3217 |
| H-13$_1$ | −0.3255 | 0.1162 | −0.1157 |
| H-13$_2$ | −0.2916 | 0.1841 | −0.2377 |
| H-14 | −0.2666 | 0.1803 | 0.1136 |
| H-15$_1$ | −0.1257 | 0.0672 | 0.1767 |
| H-15$_2$ | −0.0245 | 0.0775 | 0.0714 |
| H-9$_1$ | −0.4495 | 0.2053 | 0.3332 |
| H-9$_3$ | −0.4093 | 0.3026 | 0.1983 |
| H-9$_4$ | −0.3395 | 0.4613 | 0.1710 |
| H-18$_1$ | −0.0077 | 0.4700 | 0.2700 |
| H-18$_2$ | 0.0000 | 0.4831 | 0.0847 |
| H-18$_3$ | −0.0507 | 0.5000 | 0.1389 |
| H-19 | −0.1883 | 0.4361 | 0.2307 |
| H-20 | −0.2757 | 0.2951 | −0.0849 |

Projection views of the structure are shown in Figures 1 and 2. For comprehension of connectivity, the atoms O-3 and O-4 have been drawn with isotropic spheres of arbitrary (small) size.

Septentriosine [**1a**] and its hydrochloride [**1b**] are both $C_{20}$-diterpenoid alkaloids of the hetisine type (6). Four hydroxyl groups are attached at C-1, C-2, C-9, and C-19 showing the absolute configuration as: C-1 *S*, C-2 *S*, C-9 *S*, and C-19 *R*. The hydroxyl groups at C-1 and C-2 are *trans* (C-1-β, C-2-α) and appear diaxially disposed relative to the chair conformation of the C-1–C-5, C-10 ring. The hydroxyl at C-9 is β (axial), as is the hydrogen at C-9 in the hetisan skeleton. The α-hydroxyl group at C-19 is directed *endo* to the C-1–C-5, C-10 ring. One $H_2O$ molecule is included in the asymmetric unit of septentriosine [**1a**]. Protonation of the nitrogen in the hydrochloride does not cause extreme differences in bonding details at N-1.

The hydrogen atom of the quarternary nitrogen atom of **1b** is 2.18 Å from a chloride ion, indicating a hydrogen bond. The chloride atom is 2.26 Å from the hydrogen atom of O-1 and 2.16 Å from the hydrogen atom of O-3. Intramolecular hydrogen bonds in **1a** are indicated by the O-2–HO-4 and O-3–HO-1 distances. Hydrogen bonding to $H_2O$ is evident in the O-1–HOH and O-3-H–$OH_2$ distances. An intermolecular hydrogen bond links N-1 and HO-2.

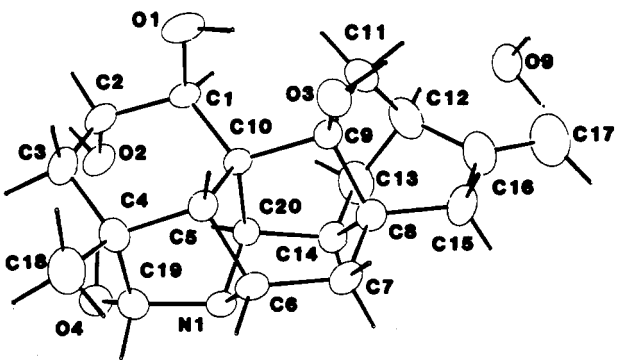



FIGURE 1. Projection view of septentriosine [**1a**].

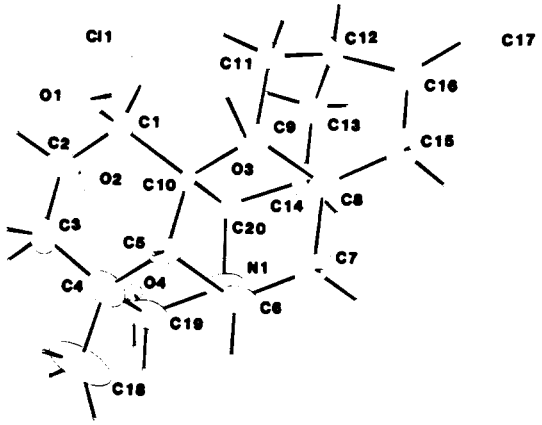



FIGURE 2. Projection view of septentriosine hydrochloride [**1b**].

Structure **1b** is less well determined than **1a** due to the poor crystalline quality of the solid, which is manifest in the errors in cell dimensions, in the scarcity of observed diffraction data, and in the nonappearance of three hydrogen atom positions in the final difference Fourier maps of **1b**. While the details of bonding within the carbon skeletons of **1a** and **1b** are similar within the limits of the experimental error, the C-1–C-10 distance of 1.59 (2) Å in **1b** seems excessively long; however, both **1a** and **1b** show longer bond distances to C-10.

## EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Thomas-Kofler hot stage equipped with a microscope and polarizer and are corrected. $^1$H-nmr spectra were determined in $CDCl_3$ with TMS as an internal standard on a JEOL-270 MHz instrument. $^{13}$C-nmr spectra were taken in $CDCl_3$ with TMS as internal standard at 22.49 MHz in the Fourier mode with a JEOL FX-90 Q spectrometer. Mass spectra were recorded on a Finnegan Quadrupole 4023 mass spectrometer at an ionizing voltage of 70 eV.

PLANT MATERIAL.—The plant material was collected by one of the authors (A.J.A.) in Norway in 1979; a voucher specimen is deposited in the Herbarium of the Department of Pharmacy, University of Oslo.

ISOLATION OF SEPTENTRIOSINE [**1a**] AND SEPTENTRIOSINE HYDROCHLORIDE [**1b**].—Powdered roots of *A. septentrionale* (7.8 kg) were first extracted with hexane (room temperature) and then with 75% EtOH (room temperature, ca. 30 days) to give a residue that on usual work-up afforded a crude basic fraction (324 g, 4.15%). The crude alkaloid (250 g) was adsorbed on $Al_2O_3$ (800 g) and chromatographed over $Al_2O_3$ (1.9 kg; E. Merck-1077; Act. III). The column was eluted with hexane-toluene (1:1), toluene, and $CH_2Cl_2$ with increasing percentages of MeOH. Finally, the column was washed with MeOH (3 liters). The MeOH eluates, on evaporation in vacuo, gave a dark brown residue (7.0 g) that was dissolved in $Me_2CO$ (150 ml), stoppered, and left for 4 days at room temperature.

The crystalline precipitate collected by filtration showed it to be a mixture of two types of crystals. The pinkish colored clusters of septentriosine [**1a**] (1.55 g) were separated from the whitish crystals (0.15 g) of septentriosine hydrochloride [**1b**]. Recrystallization of the major alkaloid from MeOH gave colorless cubes (0.93 g, 0.015%), mp 260–262°; $[\alpha]^{28}D$ +20.78° ($c$=0.55, MeOH). Recrystallization of the minor alkaloid **1b** from MeOH gave the hydrochloride (0.12 g, 0.002%), mp 299–300°, $[\alpha]D$ −7.5° ($c$=1.0, MeOH). Compound **1a**: Found C 69.45, H 7.92, N 4.03; $C_{20}H_{27}NO_4$ requires C 69.54, H 7.88, N 4.06%; ms *m/z* $[M]^+$ 345 (45%), 328 (100), 310 (18), 299 (12), 280 (15), 264 (18), 218 (50); ir (Nujol) $\nu$ max 3540, 3460, 3360, 3280, 1660, 1450, 1430, 1415, 1370, 1345, 1320, 1300, 1275, 1210, 1240, 1200, 1170, 1155, 1140, 1120, 1100, 1070, 1030, 980, 925, 905, 890, 870 cm$^{-1}$; $^1$H nmr ($CDCl_3$ + MeOH) δ 1.02 (3H, s, C-18-Me), 3.30 (1H, br s, H-6), 3.60 (1H, br s, H-20), 4.08 (1H, s, H-19), 4.48, 4.65 (each 1H, s, H-17); $^{13}$C nmr ($CDCl_3$) ppm 69.0 d C-1, 70.4 d C-2, 39.1 t C-3, 39.7 s C-4, 58.8 d C-5, 60.5 d C-6, 31.1 t C-7, 42.1 s C-8, 79.8 s C-9, 53.0 s C-10, 33.5 t C-11*, 36.2 d C-

12, 33.1 t C-13*, 43.3 d C-14, 30.7 t C-15, 150.3 s C-16, 104.8 t C-17, 28.4 q C-18, 95.2 d C-19, 60.5 d C-20 (the values marked • may be interchanged).

X-RAY STRUCTURE DETERMINATION.[1]—Crystals of septentriosine [**1a**] and its hydrochloride **1b** were mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (Table 3) were determined by least squares refinement of the best angular positions for 15 independent reflections ($2\theta > 15°$) during normal alignment procedures using Mo radiation ($\lambda = 0.71069$ Å). Data, 2231 points for septentriosine, 1397 points for the hydrochloride, were collected at room temperature using a variable scan rate, a $\theta$–$2\theta$ scan mode, and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum $2\theta$ value of 50.0°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections, and as the intensities of these reflections showed less than 6% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization, and background effects. After removal of space group forbidden data, observed data, and redundant data (**1a** only), [980 points (**1b**); 1815 points (**1a**)] [$I > 3.0\sigma$ (**1b**)] were used for solution and refinement. Crystal data are given in Table 3. The structures were solved for carbon, nitrogen, chloride, and oxygen positions using direct methods (7). Least squares refinement (8) converged with anisotropic thermal parameters. Hydrogen positions were located from a difference Fourier synthesis with the exception of those attached to C-17 and O-2 of **1b**. The hydrogen positions were included in the final refinement with isotropic thermal parameters but held invariant. A difference Fourier revealed no electron density of interpretable level. Scattering factors were taken from Cromer and Mann (9). The final cycle of refinement-function minimized $\Sigma(|F_o| - |F_c|)^2$ led to final agreement factor, $R = 7.9\%$ (**1b**), 4.9% (**1a**) $R = (\Sigma||F_o| - |F_c||/\Sigma|F_o|) \times 100$. Unit weights were used until the final cycles of refinement when weights equal to $1/\sigma F$ were introduced. $R_w = 10.1\%$ (**1b**), 6.4% (**1a**).

TABLE 3. Crystal Data for Septentriosine [**1a**] and Septentriosine Hydrochloride [**1b**].

| Parameters | Compound | |
|---|---|---|
| | **1a** | **1b** |
| Mol wt | 345.4 | 381.9 |
| *a* | 7.457 (8) Å | 13.363 (13) Å |
| *b* | 11.636 (6) | 17.622 (11) |
| *c* | 11.470 (8) | 7.646 (4) |
| α | 90.0° | 90.0° |
| β | 112.46° (6) | 90.0° |
| γ | 90.0° | 90.0° |
| V | 919.6 (12) Å$^3$ | 1800.4 (22) Å$^3$ |
| F (000) | 372 | 816 |
| μMoKα | 1.247 cm$^{-1}$ | 2.346 cm$^{-1}$ |
| λMoKα | 0.71069 Å | 0.71069 Å |
| $D_{calc}$ | 0.805 g cm$^{-3}$ | 1.409 g cm$^{-3}$ |
| Z | 2 | 4 |
| Obs. refl. | 1815 | 980 |
| R | 4.9% | 7.9% |
| Space group | $P2_1$ | $P2_12_12_1$ |

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[1]Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK.

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