*Chemistry of Natural Compounds, Vol. 31, No. 1, 1995*

# THE STRUCTURE OF SEPTEDINE

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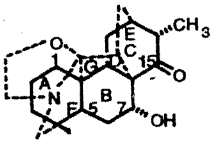
UDC 547.944/945

*The new diterpene alkaloid septedine has been isolated from the roots of* Aconitum septentrionale *Koelle. On the basis of spectral characteristics and x-ray structural analysis (diffractometer, $CuK_\alpha$ radiation, 1537 reflections, direct method, R = 0.055) it has been established that septedine has an atisine skeleton including an oxazolidine ring with a C14—C20 bridge.*

Continuing the separation of the total alkaloids from the roots of wolfbane monkshood *Aconitum septentrionale* Koelle *(A. lycoctonum)* [1], we have isolated from the lappaconitine mother liquors a minor crystalline base with the composition $C_{22}H_{31}NO_3$ (1), mp 160—161°C, readily soluble in chloroform, more sparigly in ethanol, methanol, and acetone.

The IR spectrum of (**1**) contained absorption bands at 3175 $cm^{-1}$ (OH) and 1710 $cm^{-1}$ (C=O). In its PMR spectrum the following signals were observed (ppm): 4.26 (1H, s, OH, exchangeable with deuterium), 4.07 (1H, t, J = 9 Hz, CH—O), 3.65 and 2.87 (m, 2H each, O—$CH_2$—$CH_2$—N), 2.60 and 2.32 (d, 1H each, J = 12 Hz, 2H-19), 1.04 (3H, d, J = 7.5 Hz, $CH_3$-17), 0.97 (3H, s, $CH_3$-18). These facts permitted (1) to be assigned to the alkaloids with a diterpene structure including, like coryphine, an oxazolidine ring with a C14—C20 bridge [2] and, probably, a hydroxy group at C7 and a carbonyl group at C15. The base is new and has been called septedine. The structure and stereochemistry of septedine were established unambiguously by x-ray structural analysis.



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The spatial structure of septedine is shown in Fig. 1, from which it is possible to see the presence of an oxazolidine ring and the fact that the molecule has a rigid atisine skeleton with a C14—C20 bridge. The methyl group at C16 and the hydroxyl at C7 are α-oriented, and the methyl group at C4 β-oriented.

The conformations of the rings are as follows. The six-membered ring *A* (the C1—C5 and C10 atoms) has a chair conformation with $C_2$ symmetry, and the asymmetry parameters according to [3] have $\Delta C_2$ (2-3) = 9.5°, where the C1 and C4 atoms deviate from the plane of the other four by −0.61 and 0.75 Å, respectively. Ring *B* is present in a distorted boat form with $C_S$ symmetry, as was shown by the degree of asymmetry $\Delta C_S$ (9) = 169°. Rings *C, D,* and *E,* forming a bicyclo[2.2.2]octane system are present in the boat form with $C_S$ symmetry. It must be mentioned that ring *E* has a slightly distorted boat form, the asymmetry parameters for *E* being $\Delta C_S$ (13—14) = 16.2°, and for ring *C* $\Delta C_S$ (8—12) = 4.24°, while, finally, for *D* $\Delta C_S$ (8—12) = 4.43°. Heterocycle *F* also has the boat form with $\Delta C_S$ symmetry, the asymmetry parameters being $\Delta C_S$ (N—5) = 9.8°, the C4, C10, C19, and C20 atoms lying in one plane (±0.04°) and N and C5 deviating from it by −0.52 and −0.70 Å, respectively. The five-membered ring *G* has an envelope conformation with $C_S$ symmetry, where $\Delta C_S$ (8) = 6.5°, with the C8 atom deviating in the α-direction by −0.80 Å from the plane of the other four atoms.

The linkage of rings *A/B* is *trans* (C20C10C5H5 torsional angle — 172.0°C), B/C — *cis* (C15C8C9H9 torsional angle −75°C).

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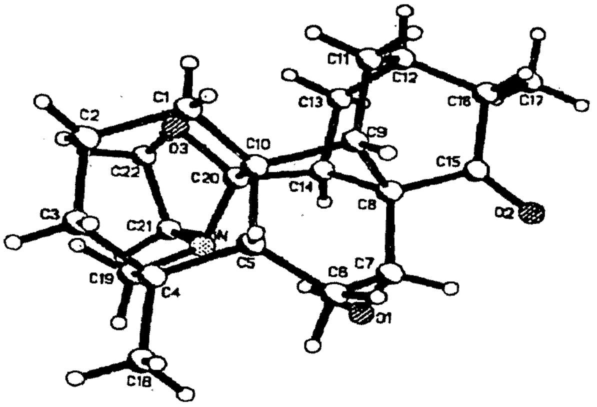

Fig. 1

The boat conformation of ring *B* in septedine is apparently stabilized by an O1—H···N hydrogen bond (O1···N distance 2.80 Å, N···H 1.78 Å, O1—H···N angle 175°), since in the related compound coryphine it has the chair form, and in spirasine VI [4], with a carbonyl group at C6, this ring assumes the sofa form with the deviation of the C9 atom in α-direction by 0.84 Å. It follows from what has been said above that ring *B* in the atisine alkaloids assumes all the canonical forms, depending on the nature and position of substituents.

The bond lengths and valence angles are given in Table 1. The lengths of the ordinary $C_{sp}3$-$C_{sp}3$ bonds vary within the range of 1.51-1.56 Å; however, within the 3σ limits of error they agree with the generally accepted value of 1.54 Å, while the scatter in the lengths of the bonds with the heteroatoms is small and their values are close to the standard ones [5]. The valence angles were determined with an error of 0.5°.

## EXPERIMENTAL

The individuality of the alkaloids was checked by TLC on plates with KSK 63 nm alumina or KSK 80 nm silica gel in the solvent systems ether, benzene—acetone (5:1) and (20:1), and chloroform—methanol (20:1), respectively [sic].

IR, mass, and PMR spectra were obtained on UR-20 (KBr), MKh-1321, MS 3301, and BS-567A, 100 MHz (δ scale, $CDCl_3$, 0 — TMS) instruments.

**Isolation of Septedine.** The ethanolic mother solution of the total alkaloids of *Aconitum sepentrionale* after the separation of lappaconitine (the basis of allapinin) was evaporated. The residue (366 g) was dissolved in 2% sulfuric acid (2 liters), and the solution was filtered and extracted with chloroform (2 × 1 liter) (fraction A). The acid solution was made alkaline fractionally with sodium carbonate to pH 7 and 10, and the alkaloids were extracted with chloroform. Distillation of the chloroform yielded mixtures of alkaloids (56, 64, and 8 g, respectively).

The alkaloids were extracted from chloroform extracts (A) with 5% acid, and the extract was made alkaline with sodium carbonate and was extracted with chloroform, the distillation of which gave 158 g of alkaloids. Part of this mixture (66 g) was chromatographed on alumina (KSK, 90-130 nm, elution with benzene). The first benzene eluates were combined (43 g) and rechromatographed on alumina (1300 g), with elution by hexane—ether (5:2). Fractions with a volume of 120 ml were collected. Fraction 2 gave a substance (0.09 g) which was crystallized from acetone, mp 160-161°C, yield 50 mg. Leuconine, mp 195-197°C [6], and anthranoyllycoctine, mp 153-155°C [1], were isolated from the later eluates.

**Septedine**, mp 160-161°C (from acetone). IR spectrum ($cm^{-1}$): 3175, 2960, 2925, 2892, 1710, 1460, 1450, 1370, 1340, 1315, 1290, 1280, 1260, 1230, 1210, 1165, 1120, 1100, 1080, 1060, 1030, 1010, 990, 960. Mass spectrum: 357 ($M^+$, 3.1%), 356 (2.8%), 340 (3.6%), 329 (100%), 328 (3.3%), 314 (6.9%), 312 (10.8%), 300 (42.0%), 286 (40.0%), 274 (10.9%). MCBP: estimated for $C_{22}H_{31}NO_3$ ($M^+$) 357.23038; found 357.22810.

**X-Ray Structural Analysis of Septedine.** The space group and the parameters of the unit cell were determined on a Syntex $P2_1$ automatic four-circle diffractometer ($CuK_\alpha$ radiation, graphite monochromator, θ/2θscanning I > 2σ (1)): *a* = 7.451(1), b = 10.520 (2), c = 22.545 (10) Å. Space group $P2_12_12_1$, Z = 4, d = 1.344 g/cm³. In the calculations we used 1537 reflections. The structure was interpreted by the direct method using the SHELXS-86 program [7] and was refined by

TABLE 1. Bond Lengths $r$ (Å) and Valence Angles (degrees) in Structure (1)

| Bond | $r$ | Angle | $\omega$ | Angle | $\omega$ |
|---|---|---|---|---|---|
| C1–C2 | 1.519(9) | C2C1C10 | 113.3(5) | C1C2C3 | 113.2(6) |
| C2–C3 | 1.530(10) | C2C3C4 | 113.2(6) | C3C4C5 | 106.8(5) |
| C4–C5 | 1.556(9) | C3C4C18 | 107.9(6) | C5C4C18 | 111.5(6) |
| C4–C19 | 1.544(9) | C3C4C19 | 109.0(6) | C5C4C19 | 110.4(5) |
| C5–C10 | 1.543(9) | C18C4C19 | 11.0(6) | C4C5C6 | 118.6(5) |
| C7–C8 | 1.550(9) | C4C5C10 | 109.0(5) | C6C5C10 | 113.8(5) |
| C8–C9 | 1.548(8) | C5C6C7 | 118.9(5) | C6C7C8 | 113.1(5) |
| C8–C15 | 1.524(8) | C6C7O1 | 110.9(5) | C8C7O1 | 112.2(5) |
| C9–C11 | 1.561(9) | C7C8C9 | 112.1(5) | C7C8C14 | 113.8(5) |
| C11–C12 | 1.522(9) | C9C8C14 | 97.8(5) | C7C8C15 | 110.2(5) |
| C12–C16 | 1.5515(9) | C9C8C15 | 114.2(5) | C14C8C15 | 108.2(5) |
| C14–C20 | 1.556(8) | C8C9C10 | 101.5(5) | C8C9C11 | 110.2(5) |
| C15–O2 | 1.214(8) | C10C9C11 | 115.0(5) | C1C10C5 | 107.7(5) |
| C19–N | 1.489(8) | C1C10C9 | 114.8(5) | C5C10C9 | 106.8(5) |
| C20–N | 1.470(8) | C1C10C20 | 114.6(5) | C5C10C20 | 109.9(5) |
| C21–N | 1.482(8) | C9C10C20 | 102.6(5) | C9C11C12 | 109.9(5) |
| C1–C10 | 1.531(8) | C11C12C13 | 108.8(5) | C11C12C16 | 108.0(5) |
| C3–C4 | 1.530(10) | C13C12C16 | 109.5(5) | C12C13C14 | 111.4(5) |
| C4–C18 | 1.520(10) | C8C14C13 | 109.1(5) | C8C14C20 | 101.4(5) |
| C5–C6 | 1.517(9) | C13C14C20 | 114.1(5) | C8C15C16 | 114.0(6) |
| C6–C7 | 1.530(9) | C8C15O2 | 123.2(6) | C16C15O2 | 122.7(6) |
| C7–O1 | 1.440(8) | C12C16C15 | 108.3(5) | C12C16C17 | 115.0(6) |
| C8–C14 | 1.556(9) | C15C16C17 | 11.4(6) | C4C19N | 115.1(5) |
| C9–C10 | 1.541(8) | C10C20C14 | 106.0(5) | C10C20O3 | 111.1(5) |
| C10–C20 | 1.566(8) | C14C20O3 | 112.3(5) | C10C20N | 114.5(5) |
| C12–C13 | 1.522(9) | C14C20N | 108.0(5) | O3C20N | 105.1(5) |
| C13–C14 | 1.531(9) | C22C21N | 106.0(5) | C21C22O3 | 105.3(5) |
| C15–C16 | 1.500(10) | C20O3C22 | 107.0(5) | C19NC20 | 114.2(5) |
| C16–C17 | 1.549(9) | C19NC21 | 110.7(5) | C20NC21 | 101.6(5) |
| C20–O3 | 1.440(7) | | | | |
| C21–C22 | 1.510(10) | | | | |
| C22–O3 | 1.432(8) | | | | |

TABLE 2. Coordinates (× $10^4$) of the Nonhydrogen Atoms and Temperature Factors $U_{eq}$ (Å$^2$ × $10^3$) in Structure (1)

| Atom | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| C1 | –434(9) | 5286(6) | 2139(3) | 34(2) |
| C2 | –528(10) | 6346(7) | 2596(3) | 47(3) |
| C3 | –2447(10) | 6708(7) | 2763(3) | 47(2) |
| C4 | –3656(9) | 6929(7) | 2223(3) | 38(2) |
| C5 | –3595(8) | 5690(6) | 1847(3) | 33(2) |
| C6 | –5049(9) | 5472(7) | 1387(3) | 41(2) |
| C7 | –4541(8) | 5487(6) | 730(3) | 31(2) |
| C8 | –2590(9) | 5040(6) | 614(3) | 29(2) |
| C9 | –1754(8) | 4388(6) | 1164(3) | 28(2) |
| C10 | –1674(8) | 5501(6) | 1607(3) | 26(2) |
| C11 | 102(10) | 3794(6) | 1001(3) | 41(2) |
| C12 | 625(9) | 4174(6) | 374(3) | 38(2) |
| C13 | 566(9) | 5616(6) | 325(3) | 41(2) |
| C14 | –1217(8) | 6146(6) | 554(3) | 30(2) |
| C15 | –2507(10) | 4244(5) | 49(3) | 33(2) |
| C16 | –732(9) | 3600(6) | –49(3) | 38(2) |
| C17 | –184(11) | 3631(8) | –712(3) | 62(3) |
| C18 | –5544(10) | 7203(8) | 2448(3) | 54(3) |
| C19 | –2918(9) | 8062(6) | 1862(3) | 39(2) |
| C20 | –1140(8) | 6650(6) | 1203(3) | 27(2) |
| C21 | –1204(9) | 8780(6) | 1001(3) | 37(2) |
| C22 | 715(9) | 8403(6) | 1135(3) | 43(2) |
| O1 | –4899(6) | 6714(4) | 471(2) | 44(2) |
| O2 | –3762(7) | 4131(4) | –290(2) | 47(2) |
| O3 | 609(6) | 7130(4) | 1357(2) | 33(1) |
| N | –2345(7) | 7752(4) | 1246(2) | 29(2) |

the SHELX-76 program [8] in the anisotropic approximation. The theoretically calculated positions of the hydrogen atoms were included in the calculation, the hydrogen atom of the hydroxy group being found experimentally. The final residuals were R = 0.055 and $R_w$ = 0.064. All the calculations were performed on a personal computer of the IBM PC/AT type. The coordinates of the nonhydrogen atoms of the molecule are given in Table 2.

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