

This work has received partial support from FAPESP (Proc. 94/1213-5), CNPq, CAPES and FINEP.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1311). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). **C53**, 1284–1286

(–)-Galanthaminium Bromide†

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(Received 1 April 1997; accepted 23 April 1997)

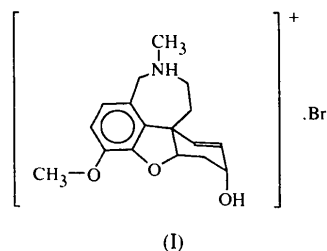
Abstract

The crystal structure and absolute configuration of the title compound, C₁₇H₂₂NO₃·Br[−], the hydrobromide salt of the alkaloid galanthamine, is reported. The tetrahydroazepine ring is in a chair conformation, the dihydrofuran ring in an envelope conformation and the cyclohexene ring between an envelope and a half-chair conformation. The axial hydroxy group forms an intramolecular hydrogen bond with the O atom of the dihydrofuran ring. The *N*-methyl group is in an axial position, while in galanthamine it is in an equatorial position.

† Internal code of the Janssen Research Foundation: R113675.

Comment

Galanthamine, a tertiary alkaloid extracted from several species of Amaryllidaceae, is an established competitive cholinesterase inhibitor. Although galanthamine has been used in the past as a treatment for a variety of neurological disorders, it nowadays attracts attention as a possible agent in the treatment of Alzheimer's disease (Thomson & Kelwitz, 1990). The three-dimensional structure and absolute configuration of the alkaloid galanthamine were first obtained from the crystal structure determination of the derivative galanthamine methiodide by Williams & Rogers (1964) and were later confirmed by Carroll, Furst, Han & Joullié (1990). The latter authors also reported the crystal structure of galanthamine itself. We report here the crystal structure of the title compound, (I).



Bond lengths and angles are not outstanding. The seven-membered tetrahydroazepine ring is in a chair conformation [puckering parameters $q_2 = 0.208(4)$, $q_3 = 0.611(4)$, $Q_T = 0.645(4)$ Å, $\varphi_2 = 162(1)$, $\varphi_3 = 2.6(3)$ and $\theta_2 = 18.8(3)^\circ$, for the sequence C10—N11—C12—C12a—C3b—C8a—C9] with a pseudosymmetry plane through C10 [asymmetry parameter $\Delta C_s(C10) = 0.039(1)$]. The cyclohexene ring is in a conformation halfway between an envelope and a half-chair, with major puckering at C5. The dihydrofuran ring is in an envelope conformation with the flap at C4a. Two intramolecular hydrogen bonds are present in the structure, one between the axial hydroxy group and the O atom of the dihydrofuran ring [$O6 \cdots O4 = 2.870(4)$, $H6a \cdots O4 = 2.25$ Å and $O6—H6a \cdots O4 = 134^\circ$] and the other between the protonated N atom and the Br[−] anion [$N11 \cdots Br = 3.185(3)$, $H11 \cdots Br = 2.29$ Å and $N11—H11 \cdots Br = 169^\circ$]. R.m.s. fits (Hypercube, 1993) of the four-ring system of (I) with galanthamine, norgalanthamine (Roques & Lapasset, 1976), norgalanthaminium chloride (Roques, Rossi, Declercq & Germain, 1980), galanthamine methiodide and (–)-*N*-(chloromethyl)galanthaminium chloride (Matusch, Kreh & Müller, 1994) give r.m.s. error values of 0.077, 0.064, 0.065, 0.035 and 0.092 Å, respectively. This indicates that the four-ring system has a rigid conformation in the crystal structures. The largest difference occurs between the C6 positions due to the presence of an intramolecular or intermolecular hydrogen bond of the hydroxy group. The most striking difference between

(I) and galanthamine is the configuration of the N atom. In the latter compound, the methyl group is in an equatorial position, while in (I) it is in an axial position. The axial *N*-methyl configuration is also found in (–)-*N*-(chloromethyl)galanthaminium chloride, formed from the reaction of dichloromethane with galanthamine base (Matusch, Kreh & Müller, 1994). The change in configuration by the formation of the tetravalent N atom is probably a result of stereoelectronic effects.

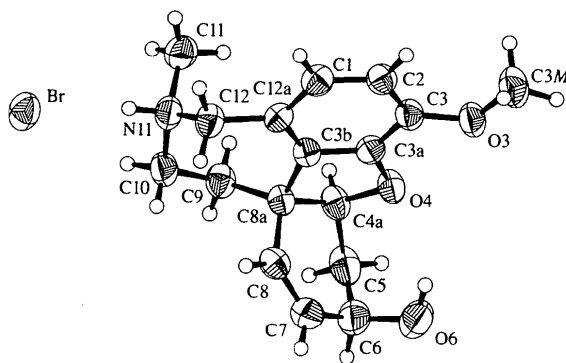


Fig. 1. A perspective view of the title compound with the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

Experimental

A sample of the title compound was obtained from the Janssen Research Foundation, Beerse, Belgium. Suitable crystals were prepared by slow evaporation of an aqueous solution.

Crystal data

$C_{17}H_{22}NO_3 \cdot Br^-$

$M_r = 368.27$

Orthorhombic

$P2_12_12_1$

$a = 7.3706$ (3) Å

$b = 14.3273$ (7) Å

$c = 15.9318$ (8) Å

$V = 1682.4$ (1) Å³

$Z = 4$

$D_x = 1.454$ Mg m⁻³

$D_m = 1.454$ Mg m⁻³

D_m measured by flotation in *n*-heptane/CCl₄

Cu $K\alpha$ radiation

$\lambda = 1.54184$ Å

Cell parameters from 39 reflections

$\theta = 11-28^\circ$

$\mu = 3.430$ mm⁻¹

$T = 293$ K

Prism

$0.54 \times 0.14 \times 0.10$ mm

Colourless

2241 reflections with $F^2 > 2\sigma(F^2)$

$R_{int} = 0.032$

$\theta_{max} = 57.01^\circ$

$h = -8 \rightarrow 8$

$k = -15 \rightarrow 15$

$l = -17 \rightarrow 17$

3 standard reflections every 100 reflections
intensity decay: none

Refinement

Refinement on F^2

$R[F^2 > 2\sigma(F^2)] = 0.030$

$wR(F^2) = 0.081$

$S = 1.044$

2275 reflections

203 parameters

H-atom parameters

constrained

$w = 1/[\sigma^2(F_o^2) + (0.0455P)^2$

$+ 0.651P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.001$

$\Delta\rho_{max} = 0.20$ e Å⁻³

$\Delta\rho_{min} = -0.21$ e Å⁻³

Extinction correction:

SHELXL93 (Sheldrick, 1993)

Extinction coefficient:

0.0011 (2)

Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Absolute configuration:

Flack (1983)

Flack parameter = 0.00 (2)

Table 1. Selected torsion angles ($^\circ$)

C3—C3a—O4—C4a	-166.9 (3)	C5—C6—C7—C8	-17.4 (6)
C3b—C3a—O4—C4a	14.5 (3)	C7—C8—C8a—C4a	-5.9 (5)
C3a—C3b—C8a—C4a	-19.7 (3)	C3b—C8a—C9—C10	-61.2 (4)
C8a—C3b—C12a—C12	-2.5 (5)	C8a—C9—C10—N11	67.1 (4)
C12a—C3b—C8a—C8	-79.3 (4)	C9—C10—N11—C11	57.3 (4)
C12a—C3b—C8a—C9	47.1 (5)	C9—C10—N11—C12	-75.3 (4)
C8a—C4a—C5—C6	-56.0 (4)	C10—N11—C12—C12a	76.0 (4)
C4a—C5—C6—O6	-79.4 (4)	N11—C12—C12a—C3b	-49.5 (4)

The structure was solved by direct methods and refined by full-matrix least-squares on F^2 for all reflections. H atoms were calculated at geometric positions and allowed to ride on their parent atom.

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *DIAMOND* (Bergerhoff, 1996). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

We thank Dr Wim Lauwers of the Janssen Research Foundation, Beerse, Belgium for kindly supplying the powdered sample of R113675.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1303). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). **C53**, 1286–1288

An Assessment of Ionic and Hydrogen Bonding in the Crystal Structure of (DL-Serine.H⁺)₂.SO₄²⁻.H₂O

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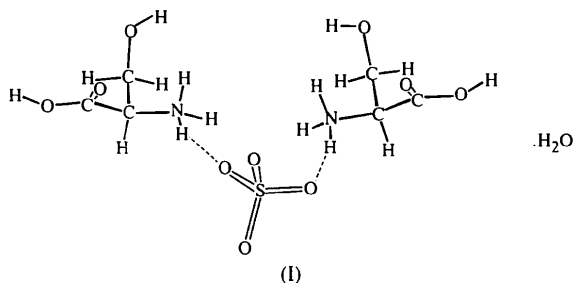
(Received 9 January 1997; accepted 8 May 1997)

Abstract

The crystal structure of DL-diserinium sulfate hydrate, 2C₃H₈NO₃⁺·SO₄²⁻·H₂O, consists of sulfate-containing 'ionic complexes' interconnected by extensive hydrogen bonds to form a complex network, creating channels which are filled by water molecules.

Comment

In its fully protonated form, the amino acid serine, 2-amino-3-hydroxypropionic acid, is a dibasic acid with p*K*_a values of 2.21 and 9.15 for the α-COOH and the α-NH₃⁺ moieties, respectively (Lehninger, 1975). Under normal conditions, the hydroxy side chain (β-OH) of serine is not active during titration since it is both weakly acidic and weakly basic (p*K*_a = 16). All three functional groups in serine in its fully protonated form, however, can function as proton donors in hydrogen bonding. Judging from the p*K*_a values, the proton-donating power of the three functional groups follows the trend α-COOH ≫ α-NH₃⁺ ≫ β-OH. In addition, the charged α-NH₃⁺ group is expected to be involved in electrostatic interactions (ionic bonding). In order to assess the relative effects of ionic and hydrogen bonding on the crystal packing (Aakeroy *et al.*, 1995; Kinbara, Hashimoto, Sukegawa, Nohira & Saigo, 1996), we have determined the molecular and crystal structure of (DL-serine.H⁺)₂.SO₄²⁻.H₂O, (I). The crystal structure is dictated by strong ionic and/or hydrogen-bonding interactions among the charged (α-NH₃⁺ and SO₄²⁻) and uncharged (α-COOH and β-OH) groups, forming channels which are filled by the solvated H₂O molecules.



The asymmetric unit of the crystal structure of the title compound, (I), consists of two serine.H⁺ monocations, one sulfate anion and one water molecule (Fig. 1). The two crystallographically independent serine.H⁺ ions exist as a DL racemic mixture. The O atom of the water molecule in the asymmetric unit is disordered in two positions, O1W and O2W, each with an occupancy factor of 0.5. The O1W...O2W distance is 0.7 Å. It is interesting to note that, despite the coexistence of a racemic mixture of D and L serine.H⁺ ions in the crystal, the compound crystallizes in a non-centrosymmetric space group. We believe this is caused by strong ionic and hydrogen-bonding interactions between the tetrahedral SO₄²⁻ anion and the serine.H⁺ cations.

All intramolecular bond lengths and angles are normal (Table 1). The two serine.H⁺ (one D and one L) cations are related by a pseudo-mirror containing S1, O3s and O4s of the sulfate ion. The crystal lattice is held together by strong ionic interactions between the

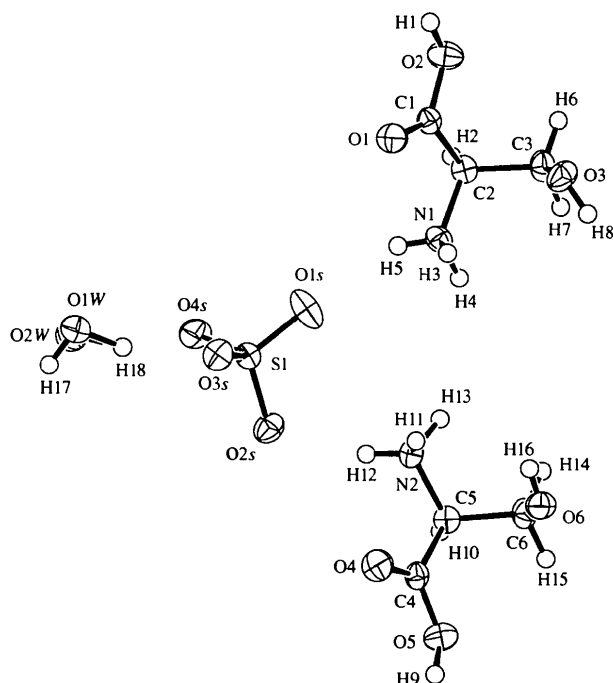


Fig. 1. Molecular structure of (I) showing 50% probability ellipsoids.