

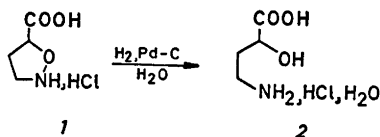
A New Synthesis and the Crystal Structure of (*RS*)-2-Hydroxy-4-aminobutyric Acid Hydrochloride Monohydrate, an Inhibitor of GABA Uptake

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(*RS*)-2-Hydroxy-4-aminobutyric acid hydrochloride monohydrate (**2**) was prepared by hydrogenolysis of (*RS*)-isoxazolidine-5-carboxylic acid hydrochloride (**1**).

Crystals of the title compound are monoclinic, with space group $P2_1/c$, and cell dimensions $a = 10.455(3)$, $b = 6.460(2)$, $c = 13.178(3)$ Å, and $\beta = 116.82(1)^\circ$. The structure was solved by direct methods and refined by full-matrix least-squares methods to a final R -value of 0.030. The crystal structure is stabilized by hydrogen bonds ($N-H \cdots O$, $OH \cdots O$, $N-H \cdots Cl$ and $O-H \cdots Cl$).



As part of our interest in the relationship between structure and biological activity of inhibitors of GABA (γ -aminobutyric acid) uptake processes^{1,2} the crystal structure of (*RS*)-2-hydroxy-4-aminobutyric acid hydrochloride monohydrate (**2**) has been determined. Compound **2** was prepared by an unequivocal synthesis based on hydrogenolysis of (*RS*)-isoxazolidine-5-carboxylic acid hydrochloride (**1**). Compound **2** has been shown to be a relatively potent inhibitor of GABA uptake in rat brain slices.³ 2-Hydroxy-4-aminobutyric acid prepared *via* selective diazotation of (*S*)-(+)-2,4-diaminobutyric acid but with unknown stereochemistry has previously been shown to be a very potent inhibitor of GABA uptake in rat brain slices.⁴

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected. Elemental analyses were made by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen. A Perkin-Elmer grating infrared spectrophotometer model 247 and a JEOL JMN-C-60HL (60 MHz) 1H NMR instrument were used. The pK_A values were determined as earlier described.⁵

The computations in connection with the X-ray structure determination were performed on an IBM 370/165 computer using *INDIFF*,⁶ a local version of the *NRC 2A Picker Data Reduction Program*,⁷ *MULTAN* (1974 version),⁸ *The X-Ray System* (1972 version)⁹ and *ORTEP II*.¹⁰

Synthesis

(*RS*)-2-Hydroxy-4-aminobutyric acid hydrochloride monohydrate (**2**). A solution of **1**¹¹ (5.1 g; 33 mmol) in water (120 ml) was hydrogenated (*ca.* 250 kPa) in a PARR hydrogenolyzed apparatus using a 10% Pd-C catalyst (0.5 g). The reaction mixture was filtered and evaporated, and the residue recrystallized (water-ethanol) to give **2** (4.2 g; 73%) as colourless crystals, m. p. 52–57°C. Anal. $C_4H_{10}ClNO_3 \cdot H_2O$: C, H, Cl, N. IR (KBr): 3600–2400 (several bands, s), 1725 (s), 1620 (s) cm^{-1} . 1H NMR [D_2O ; internal standard: sodium 3-(trimethylsilyl)propanesulfonate]: δ 4.5–4.3 (1 H, dd), 3.4–3.0 (2 H, m), 2.4–1.8 (2 H, m). pK_A values (H_2O , 21°C): 3.17 ± 0.03 ; 10.25 ± 0.03 .

X-Ray analysis

Crystal data. (*RS*)-2-Hydroxy-4-aminobutyric acid hydrochloride monohydrate, $C_4H_{10}NO_3 \cdot HCl \cdot H_2O$, $M = 173.61$. Monoclinic,

$a = 10.455(3)^*$, $b = 6.460(2)$, $c = 13.178(3)$ Å,
 $\beta = 116.82(1)^\circ$, $V = 794.3$ Å³, D_m (floatation) =
 1.46 g cm⁻³, $D_x = 1.452$ g cm⁻³, $\mu(\text{MoK}\alpha) =$
 4.48 cm⁻¹. Space group $P2_1/c$ (No. 14).

Cell-dimensions were obtained by least-squares refinement of the 2θ -values of 28 reflections measured on the diffractometer.

Data collection. Three-dimensional diffraction intensity data were measured on a Nonius three-circle automatic diffractometer using graphite monochromated $\text{MoK}\alpha$ ($\lambda = 0.71069$ Å) radiation. The ω -scan technique with a scan speed of $1.2^\circ \text{ min}^{-1}$ was employed. Background counts were taken for half the scanning time at each of the scan range limits. The crystal ($0.32 \times 0.42 \times 0.26$ mm) was sealed in a glass capillary and oriented with the b axis parallel to the ϕ axis of the goniostat. The one standard reflection sampled every 25 intensity measurements showed several intensity levels over the period of data collection. These fluctuations were mainly due to temperature changes ($22 \pm 5^\circ\text{C}$). The data set was therefore divided into different scale groups and rescaled using scale factors evaluated from the relative intensities of the standard.

Intensities within one complete half of the reciprocal sphere were measured in the range $2.5 \leq \theta \leq 30.0^\circ$. The data were corrected for Lorentz and polarization factors but not for absorption. The equivalent reflections were averaged and a set of 2316 independent reflections was obtained. Of these reflections 1838 had net intensities greater than $2.5\sigma(I)$, where $\sigma(I)$ is the standard deviation from counting statistics. These were regarded as observed reflections and used in the refinement procedure.

Structure solution and refinements. The phases for 100 individual $|E|$'s with $|E| > 2.0$ were derived with the program MULTAN⁸ leading to an E map which revealed the position of the chloride ion. The positions of the remaining non-hydrogen atoms were deduced from successive three-dimensional electron density maps. After initial least-squares refinement of this trial "heavy-atom" model the 12 hydrogen atoms were located in a subsequent difference Fourier map ($0.7 - 0.4$ e Å⁻³). In subsequent full-matrix least-squares calculations, an overall scale factor, atomic coordinates of all atoms and anisotropic thermal parameters of the non-hydrogen atoms were refined. The thermal parameters for the hydrogen atoms were fixed at isotropic values corresponding to those of the non-hydrogen atoms to which they are bonded. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/(4\sigma^2(F_o) + 0.5/\sin \theta + 5 \times 10^{-6} F_o^3)$. The final R -value is 0.030 ($R_w = 0.035$) for all observed independent reflections. A final difference Fourier map showed no peaks or depressions

* Numbers in parentheses here and throughout this paper are the estimated standard deviations of the last significant digits.

Table 1. Atomic coordinates and thermal parameters ($\text{Å}^2 \times 10^3$). The temperature factors are of the form: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}k lb^*c^*)]$ or $\exp[-2U_{\text{iso}}(2 \sin \theta/\lambda)^2]$.

| Atom | x | y | z | U_{11} | U_{22} | U_{33} | U_{12} | U_{13} | U_{23} | U_{iso} |
|-------|------------|-----------|------------|------------------|----------|----------|----------|----------|------------------|------------------|
| C(1) | .51270(14) | .3701(2) | .31128(11) | 3.16(6) | 2.96(6) | 2.73(5) | 0.09(5) | 1.28(5) | 0.23(5) | 0.23(5) |
| C(2) | .64250(14) | .3829(2) | .42730(10) | 3.24(6) | 3.88(7) | 2.39(5) | -0.43(5) | 1.36(5) | -0.24(5) | -0.24(5) |
| C(3) | .64675(14) | .2046(2) | .60530(10) | 3.00(6) | 3.93(7) | 2.42(5) | -0.36(6) | 1.06(4) | 0.01(5) | 0.01(5) |
| C(4) | .77769(15) | .2258(2) | .61969(11) | 3.33(6) | 3.57(7) | 2.47(5) | -0.35(5) | 0.95(4) | 0.00(5) | 0.00(5) |
| N | .78369(15) | .0578(2) | .69884(10) | 3.64(6) | 4.11(7) | 2.49(5) | -0.04(5) | 1.36(5) | 0.10(5) | 0.10(5) |
| O(1) | .39239(11) | .3612(2) | .32026(9) | 5.74(7) | 5.13(6) | 3.12(5) | 0.07(5) | 1.21(4) | 0.50(5) | 0.50(5) |
| O(2) | .51917(11) | .3719(2) | .22207(8) | 3.90(5) | 5.13(6) | 2.46(4) | 0.07(5) | 1.32(4) | 0.24(4) | 0.24(4) |
| O(3) | .76613(12) | .3855(2) | .41011(9) | 3.36(5) | 7.71(9) | 3.08(5) | -1.60(5) | 1.63(4) | 0.84(6) | 0.84(6) |
| O(W) | .14860(14) | .3898(3) | .14242(11) | 4.90(7) | 7.34(10) | 3.56(6) | 2.37(7) | 0.65(5) | -0.84(6) | -0.84(6) |
| Cl | .92268(4) | .72335(6) | .59956(3) | 3.57(2) | 4.75(2) | 3.12(2) | -0.02(2) | 1.24(1) | 0.05(1) | 0.05(1) |
| Atom | x | y | z | U_{iso} | Atom | x | y | z | U_{iso} | |
| H(71) | .791(2) | -.065(3) | .671(2) | 3.4 | H(32) | .650(2) | .070(3) | .471(1) | 3.1 | |
| H(72) | .860(2) | .073(3) | .763(2) | 3.4 | H(21) | .633(2) | .514(3) | .462(1) | 3.2 | |
| H(73) | .711(2) | .059(3) | .711(2) | 3.4 | H(83) | .827(2) | .455(4) | .460(2) | 3.9 | |
| H(41) | .777(2) | .355(3) | .654(1) | 3.1 | H(81) | .325(2) | .372(3) | .260(2) | 4.7 | |
| H(42) | .864(2) | .216(3) | .613(1) | 3.1 | H(W1) | .133(2) | .349(4) | .077(2) | 5.3 | |
| H(31) | .559(2) | .206(3) | .515(1) | 3.1 | H(W2) | .105(3) | .494(3) | .133(2) | 5.3 | |

greater than $0.25 e \text{ \AA}^{-3}$. Table 1 lists the final atomic coordinates and thermal parameters. The terminal set of structure factors listed with the observed data is available by request. The X-ray atomic scattering factors for O, N, and C were taken from Cromer and Mann,¹² those for H from Stewart, Davidson and Simpson,¹³ and those for Cl⁻ from *International Tables for X-Ray Crystallography*.¹⁴ The real part of the anomalous dispersion correction for Cl used in the last stages of refinement was taken from *International Tables for X-Ray Crystallography*.¹⁵

RESULTS

The molecular structure and the numbering system used are shown in Fig. 1. The cation of 2-hydroxy-4-aminobutyric acid can be characterized by two almost planar groups, the *trans* zig-zag chains of atoms C(1)–C(2)–C(3)–C(4)–N (plane I) and the four atoms O(1), O(2), C(1), and C(2) (plane II). The oxygen atom of the hydroxy group O(3) lies at a distance of 0.05 Å from plane II. The angle between the two planes is 54°. Selected torsion angles are given in Table 2, and bond lengths and angles are given in Tables 2–3. The latter are in good agreement with those found for, e.g., GABA,^{16–18} (*RS*)-3-hydroxy-4-aminobutyric acid,¹⁹ (*2RS,4RS*)-2-hydroxy-4-aminovaleric acid hydrochloride,²⁰ and with the weighted average values in the α -amino acid residues with an unionized carboxyl

Table 2. Molecular dimensions.
Bond lengths (Å)

| | |
|-----------|----------|
| C(1)–O(1) | 1.317(2) |
| C(1)–O(2) | 1.208(2) |
| C(2)–O(3) | 1.409(2) |
| C(1)–C(2) | 1.521(2) |
| C(2)–C(3) | 1.531(2) |
| C(3)–C(4) | 1.518(2) |
| C(4)–N | 1.487(2) |

Valency angles (°)

| | |
|----------------|----------|
| O(1)–C(1)–O(2) | 124.3(1) |
| O(1)–C(1)–C(2) | 111.5(1) |
| O(2)–C(1)–C(2) | 124.2(1) |
| C(1)–C(2)–O(3) | 107.8(1) |
| C(3)–C(2)–O(3) | 111.5(1) |
| C(1)–C(2)–C(3) | 112.1(1) |
| C(2)–C(3)–C(4) | 109.8(1) |
| C(3)–C(4)–N | 111.4(1) |

Torsion angles (°)

| | |
|---------------------|----------------|
| O(1)–C(1)–C(2)–O(3) | $\pm 178.3(1)$ |
| O(1)–C(1)–C(2)–C(3) | $\pm 55.2(2)$ |
| O(2)–C(1)–C(2)–O(3) | $\mp 3.1(2)$ |
| O(2)–C(1)–C(2)–C(3) | $\mp 126.2(2)$ |
| C(1)–C(2)–C(3)–C(4) | $\mp 179.7(1)$ |
| C(2)–C(3)–C(4)–N | $\pm 178.7(1)$ |

group.²¹ The five C–H bond distances are found to be within the range 0.95–0.99 Å.

The *intra*-molecular distances from N to O(1), O(2), and O(3) are 5.201(2), 5.963(2), and 4.285(2) Å, respectively.

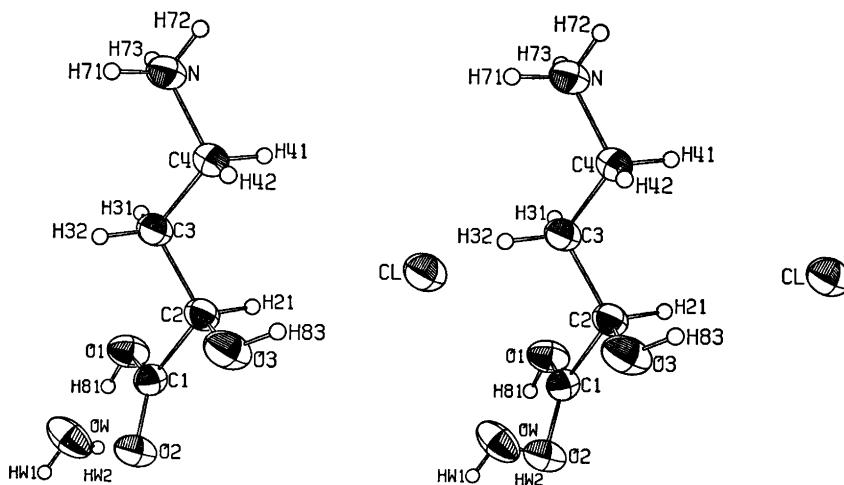


Fig. 1. A stereo view of (*R*)-2-hydroxy-4-aminobutyric acid hydrochloride monohydrate. The thermal ellipsoids are drawn at the 50% probability level.

Table 3. Selected *inter-atomic* distances (Å) and angles (°).

Symmetry code:

| | |
|---------------------------------------------------|-------------------------------------------------|
| (i) x, y, z | (iv) $x, y - 1, z$ |
| (ii) $1 - x, y - \frac{1}{2}, \frac{1}{2} - z$ | (v) $2 - x, y - \frac{1}{2}, 1 \frac{1}{2} - z$ |
| (iii) $x - 1, 1 \frac{1}{2} - y, z - \frac{1}{2}$ | (vi) $x, \frac{1}{2} - y, \frac{1}{2} + z$ |

| A—H···B | A—H | H···B | A···B | ∠AHB |
|--------------------------------|---------|---------|----------|--------|
| O(1)—H(81)···OW ⁱ | 0.80(2) | 1.79(2) | 2.575(2) | 166(3) |
| O(3)—H(83)···Cl ⁱ | 0.81(2) | 2.39(2) | 3.161(1) | 158(2) |
| OW···HW(1)···Cl ⁱⁱ | 0.84(3) | 2.28(3) | 3.120(2) | 175(2) |
| OW···HW(2)···Cl ⁱⁱⁱ | 0.79(3) | 2.53(3) | 3.308(2) | 168(3) |
| N···H(71)···Cl ^{iv} | 0.89(2) | 2.41(2) | 3.195(2) | 147(2) |
| N···H(72)···Cl ^v | 0.87(2) | 2.38(2) | 3.204(1) | 158(2) |
| N···H(73)···O(2) ^{vi} | 0.84(2) | 2.12(2) | 2.952(2) | 167(2) |
| N···H(72)···O(3) ^{vi} | 0.87(2) | 2.55(3) | 2.895(2) | 105(2) |
| N···H(73)···O(3) ^{vi} | 0.84(2) | 2.45(3) | 2.895(2) | 114(1) |

A stereo view of the crystal structure is shown in Fig. 2. The structure is stabilized by a system of hydrogen bonds. All hydrogen atoms which are covalently bonded to nitrogen and oxygen atoms are utilized in the formation of hydrogen bonds. The chloride ions and water molecules form infinite layers parallel to (100) at about $x=0$. The cations are situated between these chloride-water

layers. The *c*-glideplane-related cations are bound head to tail by the hydrogen bonds N—H(73)···O(2)^{vi} thereby forming infinite chains along the *c* axis. In addition further stabilization is attained in the contacts H(72)···O(3)^{vi} and H(73)···O(3)^{iv}. The chains are connected to the chloride-water layers by the hydrogen bonds N—H(71)···Cl^{iv}, N—H(72)···Cl^v, O(3)—H(83)···Clⁱ, and O(1)—H(81)···OWⁱ.

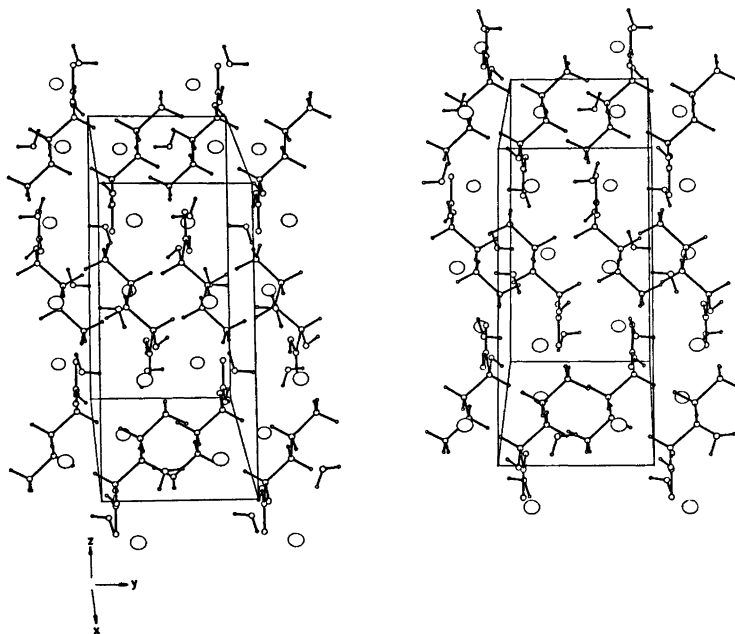


Fig. 2. Stereo view of the molecular packing of (*RS*)-2-hydroxy-4-aminobutyric acid hydrochloride monohydrate.

Furthermore OW donates two protons for hydrogen bonding with Clⁱⁱ and Clⁱⁱⁱ. Selected *inter-atomic* distances and angles are given in Table 3.

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