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4-Aminomethyl-5-methyl-3-isoxazolol Hemihydrate, a Compound Structurally Related to GABA

BY LOTTE BREHM

Royal Danish School of Pharmacy, Department of Chemistry BC, DK-2100 Copenhagen, Denmark

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Abstract. $C_5H_8N_2O_2.\frac{1}{2}H_2O$, $M_r = 137{\cdot}14$, monoclinic $C2/c$, $a = 22{\cdot}743\,(8)$, $b = 4{\cdot}939\,(2)$, $c = 11{\cdot}617\,(5)$ Å, $\beta = 100{\cdot}10\ (3)°$, $V = 1284{\cdot}7$ Å^3, $Z = 8$, D_m (flotation) $= 1{\cdot}42$, $D_x = 1{\cdot}418$ g cm^{-3}. The structure was solved by direct methods and refined by full-matrix least-squares calculations to $R = 0{\cdot}044$.

Introduction. Platelet-shaped crystals were grown at room temperature by evaporating an aqueous solution of 4-aminomethyl-5-methyl-3-isoxazolol (Bowden, Crank & Ross, 1968; Hjeds & Krogsgaard-Larsen, 1976). X-ray intensities were measured with a Nonius three-circle automatic diffractometer using graphite-monochromated Mo $K\alpha$ ($\lambda = 0{\cdot}71069$ Å) radiation. The ω-scan technique with a scan speed of $1{\cdot}2°$ min^{-1} was employed. Background counts were taken for half the scanning time at each of the scan-range limits. The crystal ($0{\cdot}10 \times 0{\cdot}34 \times 0{\cdot}30$ mm) was sealed in a glass capillary and oriented with the b axis parallel to the φ axis of the goniostat. Because of instrumental difficulties the one standard reflexion sampled every 50 intensity measurements showed three distinct intensity levels over the period of data collection. The data set was therefore divided into three parts each given a scale factor evaluated from the relative intensities of the standard. Of the 1866 independent reflexions measured in the range $2{\cdot}5 \le \theta \le 30{\cdot}0°$, 1016 had net intensities greater than $3{\cdot}0\sigma(I)$, where $\sigma(I)$ is the standard deviation from counting statistics. These were regarded as observed reflexions and used in the refinement procedure. Lorentz and polarization corrections were applied, but no absorption corrections were made [μ(Mo $K\alpha$) $= 1{\cdot}23$ cm^{-1}]. The unit-cell parameters were refined by least-squares techniques using the 2θ angles measured on the diffractometer from 30 reflexions.

The positions of the non-hydrogen atoms of the structure were determined by direct methods with *MULTAN* (Germain, Main & Woolfson, 1971). After initial least-squares refinement of the trial 'heavy-atom' model, the nine H atoms were located in a difference Fourier map phased on the structural parameters thus obtained. 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 H atoms were fixed at isotropic values corresponding to those of the non-hydrogen atoms to which they are bonded. The quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = (|F_o|/A)^2$ for $|F_o| \le A$ and $w = (A/|F_o|)^2$ for $|F_o| > A$, where $A = 14$. The final R value is 0·044 ($Rw = 0{\cdot}053$). A final difference Fourier map showed no peaks or depressions greater than 0·21 e Å^{-3}. Table 1 lists the final atomic coordinates and thermal parameters.*

The X-ray atomic scattering factors used were those of Cromer & Mann (1968) for O, N and C and of Stewart, Davidson & Simpson (1965) for H. The computations were performed on an IBM 370/165 computer. The programs used were a local version of the *NRC 2A Picker Data Reduction Program* (Ahmed, 1968), *MULTAN* (Germain, Main & Woolfson, 1971), the X-RAY system (1972) and the drawing program *ORTEP* (Johnson, 1965).

Discussion. γ-Aminobutyric acid (GABA) is an inhibitory transmitter in the central nervous system (Curtis & Johnston, 1974). The present study forms part of an investigation of the relationship between structure and biological activity of compounds related to GABA and muscimol (5-aminomethyl-3-isoxazolol) (Krogsgaard-Larsen & Johnston, 1975; Krogsgaard-Larsen, Johnston, Curtis, Game & McCulloch, 1975). The X-ray diffraction analysis of 4-aminomethyl-5-methyl-3-isoxazolol hemihydrate confirms the expected zwitterionic structure [pK_A values (H_2O, 20°C) $4{\cdot}74 \pm 0{\cdot}05$, $9{\cdot}95 \pm 0{\cdot}03$]. The previously proposed intramolecular hydrogen bond is not found in the crystal structure (Krogsgaard-Larsen, Johnston, Curtis, Game & McCulloch, 1975).

The molecular dimensions are shown in Fig. 1. The isoxazole ring is planar within the limits of experi-

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31986 (37 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Atomic coordinates and thermal parameters* ($\times 10^2$ Å^2)

The anisotropic temperature parameters are of the form:

$$T = \exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2hka^*b^*U_{12} + 2hla^*c^*U_{13} + 2klb^*c^*U_{23})].$$

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

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0·82976 (8)	0·4896 (4)	0·3320 (1)	4·81 (8)	4·38 (9)	3·61 (8)	−0·59 (8)	1·37 (6)	0·43 (7)
N(2)	0·87777 (9)	0·6352 (4)	0·4028 (1)	4·79 (11)	4·46 (11)	2·62 (8)	0·06 (10)	0·72 (7)	0·43 (8)
C(3)	0·90160 (9)	0·7909 (4)	0·3297 (2)	3·16 (10)	3·42 (11)	2·38 (8)	0·88 (9)	0·59 (7)	−0·02 (8)
C(4)	0·86937 (9)	0·7530 (5)	0·2118 (2)	3·01 (9)	3·38 (10)	2·32 (8)	0·39 (9)	0·51 (6)	0·01 (8)
C(5)	0·82687 (9)	0·5704 (5)	0·2195 (2)	3·55 (11)	3·84 (12)	3·02 (9)	0·23 (9)	0·89 (8)	−0·07 (9)
C(51)	0·77874 (12)	0·4480 (7)	0·1330 (3)	3·98 (13)	6·16 (18)	5·15 (14)	−1·02 (13)	0·73 (10)	−1·43 (13)
C(41)	0·88264 (10)	0·8969 (5)	0·1070 (2)	3·78 (11)	4·07 (13)	2·56 (9)	0·03 (10)	0·54 (8)	0·44 (9)
N(1)	0·93351 (9)	0·7776 (5)	0·0607 (2)	3·72 (10)	4·98 (12)	2·50 (8)	−0·53 (10)	0·77 (7)	−0·28 (9)
O(2)	0·94597 (7)	0·9488 (4)	0·3627 (1)	3·53 (8)	5·05 (10)	3·08 (7)	−0·41 (8)	0·49 (6)	−0·83 (7)
O(W)	1·00000	1·3670 (6)	0·2500	5·83 (17)	4·80 (15)	7·25 (19)	0·0	2·65 (15)	0·0

	x	y	z	U_{iso}		x	y	z	U_{iso}
H(411)	0·8491 (10)	0·896 (5)	0·043 (2)	3·5	H(11)	0·9404 (10)	0·886 (5)	−0·008 (2)	3·7
H(412)	0·8951 (11)	1·080 (6)	0·125 (2)	3·5	H(12)	0·9264 (12)	0·618 (6)	0·035 (2)	3·7
H(511)	0·7430 (14)	0·522 (6)	0·143 (2)	5·1	H(13)	0·9656 (11)	0·769 (5)	0·116 (2)	3·7
H(512)	0·7855 (13)	0·478 (6)	0·051 (3)	5·1	H(W)	0·9773 (12)	1·249 (8)	0·282 (3)	6·1
H(513)	0·7806 (13)	0·261 (7)	0·140 (2)	5·1					

Table 2. *Selected interatomic distances and angles*

Symmetry code

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

A–H···B	A–H	H···B	A···B	∠AHB
O(W)–H(W)···O(2)	0·90 (3) Å	1·95 (4) Å	2·838 (3) Å	166 (3)°
N(1)–H(11)···O(2^{i})	1·00 (3)	1·73 (3)	2·725 (3)	173 (2)
N(1)–H(12)···N(2^{iii})	0·85 (3)	2·13 (3)	2·883 (3)	147 (2)
N(1)–H(13)···O(2^{ii})	0·88 (2)	2·17 (3)	2·857 (3)	134 (2)
N(1)–H(13)···O(W^{iv})	0·88 (2)	2·56 (3)	3·173 (3)	127 (2)

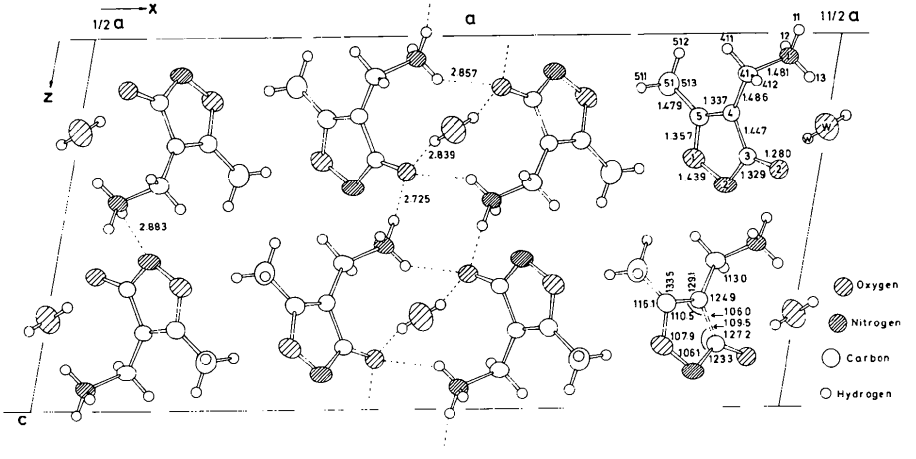

Fig. 1. Projection of the structure down the *b* axis. Thermal ellipsoids for non-hydrogen atoms are scaled to 50% probability; H atoms are represented as spheres of arbitrary radius. Hydrogen bonds are shown as broken lines. The numbering of the atoms and some interatomic distances (e.s.d.'s 0·003 Å) and angles (e.s.d.'s 0·2°) between non-hydrogen atoms are shown. Bond lengths and angles involving H atoms range from 0·85 to 1·00 Å (e.s.d.'s 0·02–0·03 Å) and from 100 to 113° (e.s.d.'s 2–3°) respectively. The intramolecular distances N(1)–O(2), N(1)–N(2) and N(1)–O(1) are 3·571 (3), 4·434 (3) and 4·487 (3) Å respectively.

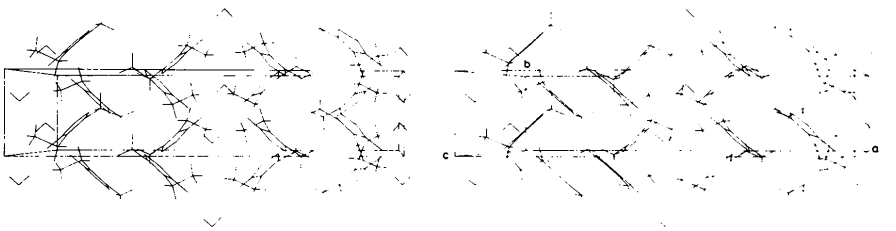

Fig. 2. Stereo diagram illustrating the molecular packing.

mental error. The exocyclic oxygen atom O(2) is situated in the least-squares plane through the isoxazole ring, while the exocyclic carbon and nitrogen atoms C(51), C(41), and N(1) are at distances ±0·03, ±0·02, and ∓1·32 Å, respectively, from this plane. The torsion angle C(3)–C(4)–C(41)–N(1) is ±80·3 (3)°. The bond lengths and angles agree well with their equivalents in other isoxazole compounds (Simon, Sasvári, Dvortsák, Horváth & Harsányi, 1974; Brehm, Krogsgaard-Larsen & Hjeds, 1974; Brehm & Krogsgaard-Larsen, 1974; Brehm & Larsen, 1976).

The packing of the molecules in the crystals is stabilized by a system of hydrogen bonds. All H atoms which are covalently bonded to N and O atoms are used in the formation of hydrogen bonds (Figs. 1 and 2). The O atoms of the water molecules are situated on twofold axes and form infinite sheets of water molecules parallel to (100) at $x = 0$ and $\frac{1}{2}$. The charged parts of the zwitterions are directed towards these sheets so that infinite zwitterion/water/zwitterion 'sandwiches' are formed. Hydrogen bonds [N(1)–H(13)···O(2^{ii}); O(2)···H(13^{ii})–N(1^{ii})] connect pairs of molecules related to a twofold axis. These molecules are further interlinked *via* the water molecule [O(2)···H(*W*)–O(*W*]–H(*W*^{ii})···O(2^{ii})]. Additional hydrogen bonds are formed between each molecule and two *c*-glide-plane-related molecules [N(1)–H(11)···O(2^{i}), N(1)–H(12)···N(2^{iii})]. Intermolecular contacts between the 'sandwiches' correspond to van der Waals interactions. Selected interatomic distances and angles are listed in Table 2.

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