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Structure of 1-[(3-Methyl-4-isothiazolyl)methyl]guanidinium Hemisulfate, CG-8345-GO, $C_6H_{10}N_4S.\frac{1}{2}H_2SO_4$

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Abstract. Noradrenaline depletor. $M_r = 219{\cdot}28$, monoclinic, $P2_1/c$, $a = 8{\cdot}653$ (1), $b = 7{\cdot}473$ (2), $c = 32{\cdot}042$ (5) Å, $\beta = 92{\cdot}36$ (1)°, $V = 2070{\cdot}1$ (4) Å^3, $Z = 8$ (two independent molecules), $D_x = 1{\cdot}41$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 34{\cdot}7$ cm^{-1}, $F(000) = 920$, room temperature, $R = 0{\cdot}059$ for 2136 reflections. The two independent molecules exhibit two different conformations in which the position of the guanidine group relative to the ring differs. The two conformations are compared with a model of the α-adrenoceptor ligand. The protonation occurs on double-bonded N(2), which makes the terminal N(1), N(3) equivalent. The molecules are held together by strong hydrogen bonds, which involve the solvate ions.

Introduction. The title compound attracted attention because of its potent depleting action on myocardial noradrenaline. It also blocks selectively the adrenergic transmission to the heart. Its mechanism of action, very similar to that of guanethidine, has been recently elucidated (Kaul & Grewal, 1981).

It seemed interesting to compare the solid-state conformation of CG-8345-GO with those of dihydroimidazole or guanidine α-adrenoceptor ligands (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982).

Experimental. Small white prisms (from methanol), 0·30 × 0·18 × 0·10 mm, Enraf–Nonius CAD-4 diffractometer with graphite monochromator, 20 reflections ($6 < \theta < 14°$) used to refine orientation matrix, systematic absences: $h0l$ for l odd, $0k0$ for k odd, 3074 ($\pm h,k,l$) independent with $\theta < 60°$, h −10 to +10, k 0 to +8, l 0 to +37, 2136 with $I \geq 3\sigma(I)$, Lp correction, absorption ignored; two check reflections (122, 014) every 5400 s showed no unusual variation (all within $\pm 3\sigma$); direct methods, *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), anisotropic diagonal matrix, refinement on F using observed reflections, $w = 1$ if $|F_o| < P$, $P = (F^2_{o\max}/10)^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$, H from ΔF synthesis – isotropic, $R = 0{\cdot}059$, $wR = 0{\cdot}076$, $S = 1{\cdot}19$ (2136 reflections, 332 parameters), max. $\Delta\rho$ excursion $\pm 0{\cdot}5$ e Å^{-3} in final ΔF map; in final cycle mean and max. $\Delta/\sigma = 0$ and 0·1; H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974), S corrected for anomalous dispersion; Mini 6, CII computer.

Discussion. Table 1 gives the atomic coordinates and Table 2 the bond distances and angles.* Diagrams of the two independent molecules with the atom numbering are shown in Fig. 1.

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and mean planes of atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39967 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic temperature factors*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}(Å^2)
Molecule (I)				
C(1)	9322 (6)	2658 (7)	9657 (2)	3·4 (2)
C(2)	7786 (7)	3055 (8)	9669 (2)	4·3 (3)
S(3)	7287 (2)	3244 (3)	10171 (1)	5·6 (1)
N(4)	9021 (7)	2805 (8)	10372 (1)	5·5 (3)
C(5)	9991 (8)	2516 (7)	10066 (2)	4·3 (3)
C(6)	10203 (7)	2351 (7)	9268 (2)	3·9 (2)
N(7)	9249 (5)	2477 (6)	8887 (1)	3·7 (2)
C(8)	8862 (6)	4032 (7)	8702 (2)	3·3 (2)
N(9)	7960 (6)	3982 (6)	8361 (1)	4·1 (2)
N(10)	9356 (6)	5594 (6)	8851 (1)	4·2 (2)
C(11)	11646 (8)	2029 (9)	10171 (2)	5·8 (3)
Molecule (II)				
C(51)	3099 (6)	2802 (8)	3485 (2)	3·7 (2)
C(52)	2985 (7)	1050 (9)	3371 (2)	5·1 (3)
S(53)	3982 (2)	−181 (2)	3740 (1)	6·4 (1)
N(54)	4543 (6)	1527 (7)	4030 (2)	5·2 (3)
C(55)	4002 (7)	3016 (8)	3860 (2)	4·0 (3)
C(56)	2316 (6)	4270 (10)	3235 (2)	5·4 (3)
N(57)	3472 (4)	5447 (6)	3057 (1)	3·7 (2)
C(58)	3107 (5)	6755 (7)	2792 (2)	3·1 (2)
N(59)	4220 (5)	7735 (7)	2639 (1)	4·1 (2)
N(60)	1644 (4)	7103 (6)	2676 (1)	3·8 (2)
C(61)	4388 (10)	4788 (10)	4067 (2)	6·9 (4)
Sulfate				
S(12)	2131 (1)	849 (2)	1879·9 (4)	2·91 (4)
O(13)	3390 (3)	−493 (4)	1855 (1)	3·2 (1)
O(14)	1117 (4)	282 (6)	2206 (1)	4·5 (2)
O(15)	2783 (4)	2622 (5)	1980 (1)	4·4 (2)
O(16)	1264 (4)	931 (5)	1480 (1)	3·9 (2)

Table 2. *Bond distances* (Å) *and angles* (°)

Molecule (I)		Molecule (II)	
C(1)–C(2)	1·364 (8)	C(51)–C(52)	1·362 (8)
C(1)–C(5)	1·415 (8)	C(51)–C(55)	1·416 (8)
C(1)–C(6)	1·504 (7)	C(51)–C(56)	1·503 (8)
C(2)–S(3)	1·689 (6)	C(52)–S(53)	1·704 (7)
S(3)–N(4)	1·641 (6)	S(53)–N(54)	1·640 (6)
N(4)–C(5)	1·334 (8)	N(54)–C(55)	1·316 (8)
C(5)–C(11)	1·504 (9)	C(55)–C(61)	1·512 (10)
C(6)–N(7)	1·449 (7)	C(56)–N(57)	1·466 (8)
N(7)–C(8)	1·341 (7)	N(57)–C(58)	1·325 (7)
C(8)–N(9)	1·318 (7)	C(58)–N(59)	1·319 (7)
C(8)–N(10)	1·326 (7)	C(58)–N(60)	1·330 (7)
C(2)–C(1)–C(5)	110·7 (5)	C(52)–C(51)–C(55)	111·6 (5)
C(2)–C(1)–C(6)	125·8 (5)	C(52)–C(51)–C(56)	122·2 (5)
C(5)–C(1)–C(6)	123·6 (5)	C(55)–C(51)–C(56)	126·2 (5)
C(1)–C(2)–S(3)	109·4 (4)	C(51)–C(52)–S(53)	107·7 (5)
C(2)–S(3)–N(4)	95·2 (3)	C(52)–S(53)–N(54)	95·8 (3)
S(3)–N(4)–C(5)	109·8 (4)	S(53)–N(54)–C(55)	109·4 (4)
C(1)–C(5)–N(4)	114·9 (5)	C(51)–C(55)–N(54)	115·4 (5)
C(1)–C(5)–C(11)	125·1 (5)	C(51)–C(55)–C(61)	125·1 (5)
N(4)–C(5)–C(11)	119·9 (5)	N(54)–C(55)–C(61)	119·4 (5)
C(1)–C(6)–N(7)	113·4 (4)	N(51)–C(56)–N(57)	110·2 (5)
C(6)–N(7)–C(8)	123·6 (4)	C(56)–N(57)–C(58)	122·9 (5)
N(7)–C(8)–N(9)	118·2 (5)	N(57)–C(58)–N(59)	119·2 (5)
N(7)–C(8)–N(10)	122·2 (5)	N(57)–C(58)–N(60)	121·5 (5)
N(9)–C(8)–N(10)	119·6 (5)	N(59)–C(58)–N(60)	119·3 (5)
		Sulfate	
S(12)–O(13)	1·485 (3)	O(13)–S(12)–O(14)	107·9 (2)
S(12)–O(14)	1·456 (4)	O(13)–S(12)–O(15)	110·2 (2)
S(12)–O(15)	1·470 (4)	O(13)–S(12)–O(16)	109·4 (2)
S(12)–O(16)	1·460 (4)	O(14)–S(12)–O(15)	110·1 (2)
		O(14)–S(12)–O(16)	109·9 (2)
		O(15)–S(12)–O(16)	109·4 (2)

The mean bond-length difference between the two independent molecules is 0·008 Å with the largest 0·018 (8) Å [affecting the N(4)–C(5) bond]. In Table 3, we compare the geometry of the isothiazolyl ring with that of thiadiazole (Brückner & Malpezzi, 1982) and benzisothiazole (Shimizu & Nishigaki, 1983) given in recent literature (there is a lack of data concerning the geometry of isothiazole).

Two different conformations appear for the methylguanidine group, which differ mainly in two torsion angles (±1°). C(2)–C(1)–C(6)–N(7) = −1°, C(52)–C(51)–C(56)–N(57) = −115°; C(1)–C(6)–N(7)–C(8) = 82°, C(51)–C(56)–N(57)–C(58) = 174°. Consequently, the angle φ between the plane of the guanidine and the plane of the ring is 97 (1)° in molecule (I) and 65 (1)° in molecule (II).

As the protonation occurs on the double-bonded nitrogen, the two terminal nitrogens of the guanidine are chemically equivalent [although one can see the slight difference in the C^+–NH_2 bond lengths already found in dihydroimidazoles (Carpy, 1981)]. We calculated the two corresponding distances required in α-adrenoceptor agonists, *i.e. D* (distance from a protonated nitrogen to the center of the aromatic ring) and *h* (height of this nitrogen from the plane of the ring) and found the values given in Table 4. Only two sets of

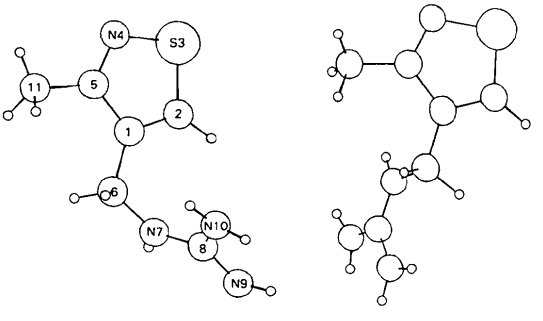

Fig. 1 Perspective views of the two independent molecules showing the numbering of atoms. The bare numbers are for C atoms. Add fifty for the atoms of molecule (II).

Table 3. *Comparison of some distances and angles in isothiazole, thiadiazole and benzisothiazole rings*

	S–C (Å)	S–N (Å)	N–S–C (°)
Isothiazolyl I	1·689 (6)	1·641 (6)	95·2 (3)
Isothiazolyl II	1·704 (7)	1·640 (6)	95·8 (3)
Thiadiazole	1·691 (2)	1·681 (2)	92·7 (1)
Benzisothiazole	1·743	1·615	96·7 (7)

Table 4. *Spatial positions of the two terminal nitrogens relative to the ring*

	N(9)–π_1	N(10)–π_1	N(59)–π_2	N(60)–π_2
D (Å)	5·29	4·24	5·70	5·49
h (Å)	0·80	2·21	−2·64	−0·65
φ (°)	97		65	

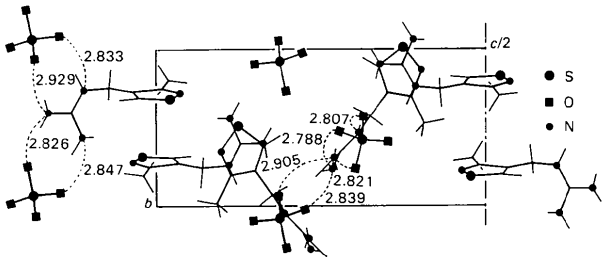

Fig. 2. Packing of the molecules projected along [100] showing the hydrogen bonds (e.s.d.'s 0·006 Å).

values, including N(9) and N(60), are close to but slightly different from those found in dihydroimidazoles and guanidines related to clonidine: $D \simeq 5$ Å, $h \simeq 1$ Å, $\varphi = 90$, 75 or 60° (Carpy *et al.*, 1982). These differences could explain the different pharmacological actions of the present compound compared with drugs related to clonidine.

The crystalline cohesion is ensured by strong hydrogen bonds involving the sulfate ions (Fig. 2).

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Structure of α-Isopropyl-α-[(*N*-methyl-*N*-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile Hydrochloride,* Verapamil, $C_{27}H_{38}N_2O_4.HCl$

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Abstract. Ca^{2+} channel antagonist; major therapeutic indications: angina, hypertension. $M_r = 491{\cdot}08$, triclinic, $P\bar{1}$, $a = 7{\cdot}086$ (3), $b = 10{\cdot}591$ (2), $c = 19{\cdot}196$ (4) Å, $\alpha = 100{\cdot}10$ (1), $\beta = 93{\cdot}73$ (3), $\gamma = 101{\cdot}55$ (3)°, $V = 1382{\cdot}1$ (3) Å^3, $Z = 2$, $D_x = 1{\cdot}18$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 14{\cdot}88$ cm^{-1}, $F(000) = 524$, room temperature, $R = 0{\cdot}048$ for 1182 reflections. The bond lengths and angles have the values expected, with the normal folding of the bridge chain around the N atom. Critical sites for antagonism of α_1- and α_2-adrenoceptors are investigated. The title compound is unusual in having a methyl substituent on the protonated N atom.

* IUPAC name: 5-[*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

Introduction. Verapamil has a number of therapeutic indications. Firstly, it is an antianginal agent but it is also used in supraventricular tachycardia, in ventricular tachyarrhythmia, in atrial flutter and fibrillation and in hypertension (Stone, Antman, Muller & Braunwald, 1980; Flaim & Zelis, 1982). The description of this drug as a Ca^{2+} channel antagonist is due to the investigations of Fleckenstein (1964) who first observed that it mimics the cardiac effect of Ca^{2+} withdrawal.

On the other hand, verapamil and D600 (a methoxy analogue of verapamil) block some Na^+ channels, K^+ channels and a variety of receptor types (adrenergic α_1 and α_2, muscarinic cholinergic and opiate) (Janis & Triggle, 1983). Of particular interest for our purpose are the results of Glossmann & Hornung (1980) showing that these two molecules interact with both α_1- and α_2-adrenoceptors with higher affinity for the α_1

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