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A β-Adrenergic Agonist: Protonated Terbutaline Hemisulfate

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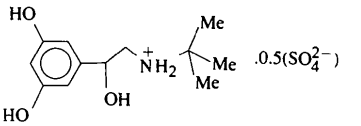
Abstract

The title molecule, *tert*-butyl[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl]ammonium hemisulfate, $C_{12}H_{20}NO_3^+.0.5(SO_4^{2-})$, consists of a phenethylamine skeleton in which the N atom is protonated. The ethylamine side chain is in an extended conformation for both molecules in the asymmetric unit. The distance of the N atom from the centre of the benzene ring is 5.1 Å. The molecules in the unit cell are stabilized by N—H···O and O—H···O hydrogen bonds.

Comment

Compounds having a phenethylamine backbone with an OH group substituted at the *meta* position are potent β-adrenergic agonists (O'Donnell & Wanstall, 1974). Terbutaline has a structure of this type. It is a well known β-adrenergic agonist and clinically used as a bronchodilator. The three-dimensional structure of this compound has been determined and compared with those of a few similar drug molecules.

The interatomic bond lengths and angles are similar in the two molecules (*A* and *B*) of the asymmetric unit of the title compound (I) and show no significant



(I)

deviation from the average model values (Herbert, 1979) obtained by averaging the bond lengths and angles in 34 similar adrenergic compounds, except in the case of the N1—C9 bond length. This N—C bond distance is 1.529 (4) Å in molecule *A* and 1.525 (4) Å in molecule *B*, compared with the average model value of 1.486 Å. All the bond lengths and angles, however, compare well with the values obtained for terbutaline hemisulfate hydrate (Hickel, Carpy, Laguerre & Leger, 1982). Similar deviation of the N—C bond length from the average model value has also been seen in some other β-adrenergic agonists like salbutamol sulfate (Leger, Goursolle, Gadret & Carpy, 1978), clenbuterol hydrochloride (Carpy, Leger & Colleter, 1980), Alupent and orciprenaline (Beale, 1972), and fenoterol hydrobromide (Dattagupta & Sengupta, 1995).

The conformation of the ethylamine side chain with respect to the benzene ring is usually described by the torsion angles C2—C1—C7—C8 (τ_1) and C1—C7—C8—N (τ_2). Molecule *A* has an extended conformation with $\tau_1 = -56.1\,(3)$ and $\tau_2 = 170.3\,(2)°$. The corresponding angles in molecule *B* are 127.3 (3) and $-157.0\,(2)°$, respectively. Although the bond lengths and angles are similar, the torsion angles in the present structure differ somewhat from those in terbutaline hemisulfate hydrate (Hickel, Carpy, Laguerre & Leger, 1982) in which τ_1 is 62 (1) in *A* and 59 (1)° in *B* and τ_2 has a value of 182 (1) in *A* and 180 (1)° in *B*. A study of these torsion angles in other β-adrenergic agonists like salbutamol sulfate (Leger, Goursolle, Gadret & Carpy, 1978), clenbuterol hydrochloride (Carpy, Leger & Colleter, 1980), Alupent and orciprenaline (Beale, 1972), fenoterol hydrobromide (Dattagupta & Sengupta, 1995) also show that τ_1 is distributed around $\pm$ 90 and τ_2 around $\pm$ 180°. This indicates that a maximally extended ethylamine side chain approximately perpendicular to the benzene ring, may be the receptor preferred conformation for this class of drugs.

The distance of the amino-N atom from the centre of the benzene ring is 5.1 Å in both of the molecules in the asymmetric unit. This distance seems to be fairly constant in similar biologically active amines like *p*-hydroxyephedrine hydrochloride (Dattagupta, Pattanayek & Saha, 1981), synephrine monohydrogenphosphate monohydrate (Dattagupta, Meyer & Mukhopadhyay, 1982), L-phenylephrine hydrochloride (Bhaduri, Saha, Dattagupta & Meyer, 1983), 2,2′-di-*N*-methylamino-1,1′-di-*p*-hydroxyphenyldiethylene ether dihydrobromide (Mukhopadhyay & Dattagupta, 1988) and also in β-adrenergic agonists like salbutamol sulfate (Leger, Goursolle, Gadret & Carpy, 1978), Alupent and

orciprenaline (Beale, 1972) and fenoterol hydrobromide (Dattagupta & Sengupta, 1995). This distance also appears to be of significance for sympathomimetic activity and may be important for drug-receptor interaction. The perpendicular distance of the N atom from the plane of the benzene ring is 0.8 and 1.4 Å for molecules *A* and *B*, respectively.

All of the hydroxyl groups and the protonated-N atom in *A* and *B* are involved in hydrogen bonding. All the O atoms of the SO_4^{2-} ion participate as acceptors in hydrogen bonding.

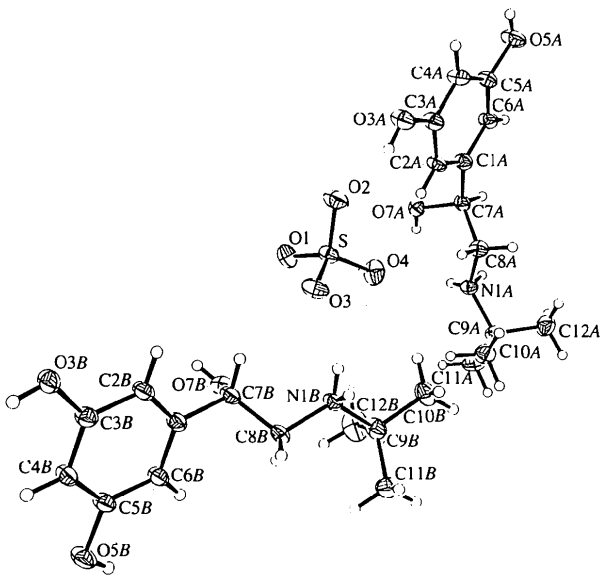


Fig. 1. *ORTEX* (McArdle, 1993) drawing of protonated terbutaline hemisulfate showing the atom-numbering scheme for molecules *A* and *B*. Thermal ellipsoids are drawn at the 40% probability level.

Experimental

The title compound was prepared by evaporation from an aqueous solution.

Crystal data

$C_{12}H_{20}NO_3^+.0.5(SO_4^{2-})$
M_r = 274.32
Triclinic
$P\bar{1}$
a = 9.968 (2) Å
b = 11.207 (4) Å
c = 13.394 (1) Å
α = 100.86 (1)°
β = 104.42 (2)°
γ = 101.63 (1)°
V = 1373.7 (6) Å^3
Z = 4
D_x = 1.326 Mg m^{-3}
D_m = 1.332 Mg m^{-3}
D_m measured by flotation method
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 12–48°
μ = 1.534 mm^{-1}
T = 293 (2) K
Needle
0.80 × 0.40 × 0.40 mm
White

Data collection

CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
5121 measured reflections
5121 independent reflections
4964 observed reflections [$I > 2\sigma(I)$]
θ_{max} = 70.1°
$h = -12 \rightarrow 11$
$k = -13 \rightarrow 13$
$l = 0 \rightarrow 16$
3 standard reflections monitored every 200 reflections
intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0623
$wR(F^2)$ = 0.2326
S = 0.863
5071 reflections
334 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.2164P)^2 + 1.5267P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.020
$\Delta\rho_{max}$ = 0.373 e Å^{-3}
$\Delta\rho_{min}$ = −0.761 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S	0.41329 (6)	0.58895 (5)	0.78396 (5)	0.0294 (3)
O1	0.2681 (2)	0.5617 (2)	0.7065 (2)	0.0388 (7)
O2	0.4743 (3)	0.7257 (2)	0.8203 (2)	0.0452 (8)
O3	0.3991 (2)	0.5395 (2)	0.8760 (2)	0.0414 (7)
O4	0.5042 (2)	0.5302 (2)	0.7313 (2)	0.0451 (8)
C1*A*	0.7732 (3)	0.7716 (2)	0.5959 (2)	0.0309 (9)
C2*A*	0.7182 (3)	0.7825 (2)	0.6824 (2)	0.0328 (9)
C3*A*	0.7486 (3)	0.8981 (3)	0.7526 (2)	0.0325 (9)
C4*A*	0.8374 (3)	1.0041 (2)	0.7406 (2)	0.0348 (10)
C5*A*	0.8989 (3)	0.9901 (2)	0.6584 (2)	0.0342 (10)
C6*A*	0.8651 (3)	0.8757 (3)	0.5841 (2)	0.0351 (10)
O3*A*	0.6920 (2)	0.9139 (2)	0.8359 (2)	0.0426 (8)
O5*A*	0.9919 (3)	1.0915 (2)	0.6464 (2)	0.0467 (8)
C7*A*	0.7282 (3)	0.6466 (2)	0.5153 (2)	0.0293 (8)
O7*A*	0.5767 (2)	0.6201 (2)	0.4639 (2)	0.0328 (7)
C8*A*	0.7604 (3)	0.5412 (2)	0.5672 (2)	0.0319 (9)
N1*A*	0.6931 (2)	0.4159 (2)	0.4897 (2)	0.0282 (8)
C9*A*	0.7456 (3)	0.3038 (3)	0.5177 (2)	0.0339 (10)
C10*A*	0.7321 (4)	0.2932 (3)	0.6254 (3)	0.0430 (11)
C11*A*	0.6477 (4)	0.1894 (3)	0.4312 (3)	0.0513 (13)
C12*A*	0.9009 (4)	0.3238 (3)	0.5153 (3)	0.0493 (12)
C1*B*	0.0722 (3)	0.3051 (2)	1.0137 (2)	0.0292 (9)
C2*B*	0.0580 (3)	0.4032 (2)	1.0865 (2)	0.0313 (9)
C3*B*	−0.0355 (3)	0.3792 (2)	1.1476 (2)	0.0289 (8)
C4*B*	−0.1139 (3)	0.2569 (2)	1.1350 (2)	0.0308 (9)
C5*B*	−0.0982 (3)	0.1609 (2)	1.0616 (2)	0.0315 (9)
C6*B*	−0.0047 (3)	0.1826 (2)	1.0015 (2)	0.0314 (9)
O3*B*	−0.0469 (2)	0.4792 (2)	1.2180 (2)	0.0342 (7)
O5*B*	−0.1791 (2)	0.0419 (2)	1.0504 (2)	0.0410 (8)
C7*B*	0.1714 (3)	0.3310 (2)	0.9456 (2)	0.0303 (9)
O7*B*	0.0938 (2)	0.3033 (2)	0.8341 (2)	0.0364 (7)
C8*B*	0.2771 (3)	0.2504 (2)	0.9533 (2)	0.0319 (9)
N1*B*	0.4081 (2)	0.3079 (2)	0.9254 (2)	0.0282 (8)
C9*B*	0.4762 (3)	0.2202 (3)	0.8648 (2)	0.0350 (9)
C10*B*	0.6215 (3)	0.3022 (3)	0.8706 (3)	0.0460 (12)
C11*B*	0.4968 (4)	0.1163 (3)	0.9218 (3)	0.0505 (14)
C12*B*	0.3797 (4)	0.1716 (4)	0.7512 (3)	0.0646 (16)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···A	H···A	D···A	D—H···A
O3*A*—H3O*A*···O2	1.86	2.639 (3)	159
N1*B*—H2N*B*···O3	2.00	2.810 (3)	149

O5A—H5OA···O7B^{i}	2.13	2.914 (3)	160
N1A—H1NA···O1^{ii}	1.90	2.800 (3)	179
O7A—H7OA···O4^{ii}	1.94	2.658 (3)	145
N1A—H2NA···O7A^{ii}	2.05	2.876 (3)	153
N1B—H1NB···O3^{iii}	1.95	2.848 (2)	172
O3B—H3OB···O1^{iv}	1.86	2.641 (3)	158
O7B—H7OB···O3B^{iv}	2.15	2.754 (3)	131
O5B—H5OB···O3A^{v}	2.26	2.798 (3)	123

Symmetry codes: (i) $1+x, 1+y, z$; (ii) $1-x, 1-y, 1-z$; (iii) $1-x, 1-y, 2-z$; (iv) $-x, 1-y, 2-z$; (v) $x-1, y-1, z$.

All of the H atoms were placed in geometrically calculated positions with average distances C—H 0.956, N—H 0.90 and O—H 0.82 Å. All hydrogen bond calculations were made using *PARST* (Nardelli, 1983).

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *SDP* (Enraf–Nonius, 1985). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEX* (McArdle, 1993). Software used to prepare material for publication: *SHELXL93*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: VJ1027). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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An α-Adrenergic Agonist: Protonated Oxymetazoline Hydrochloride Monohydrate

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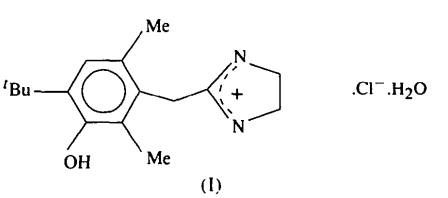
Abstract

The title compound, 2-[4-*tert*-butyl-2,6-dimethyl-3-hydroxyphenyl)methyl]-4,5-dihydro-1*H*,3*H*$^+$-imidazolium chloride monohydrate, $C_{16}H_{25}N_2O^+.Cl^-.H_2O$, is a sympathomimetic amine containing an imidazole ring. The ring is protonated with the positive charge dispersed over both of the N atoms, which are involved in hydrogen bonding, one with the Cl^- ion and the other with a water-O atom. The dihedral angle between the phenyl and imidazole rings is 86.3 (3)°.

Comment

The adrenergic imidazoli(di)nes are generally selective for α-adrenergic receptors. Oxymetazoline hydrochloride belongs to this class of compound and acts as an α-adrenergic agonist. It is clinically used as a nasal decongestant. The crystal structure analysis of the title compound (I) has been undertaken to compare its conformation with those of a few similar drug molecules and with a view to gain insight into the nature of the interaction of these drugs at α-adrenergic receptors.



(I)

The C16—N1 and C16—N2 bond lengths in the imidazole ring are 1.30 (1) and 1.29 (1) Å, respectively. These values, which are comparable within experimental error, are intermediate between those for a single and a double bond, indicating dispersion of positive charge over both N atoms in the imidazole ring. This has been seen in the case of other α-adrenergic agonists like xylometazoline hydrochloride (Ghose & Dattagupta, 1986), clonidine hydrochloride (Cody & DeTitta, 1979), naphazoline hydrochloride