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Tolterodinium (+)-(2*R*,3*R*)-hydrogen tartrate

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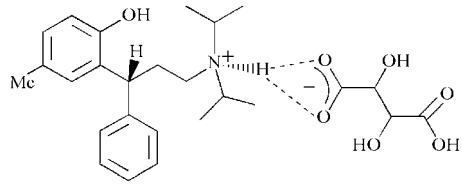
In the crystal structure of (*R*)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylaminium (2*R*,3*R*)-hydrogen tartrate, $C_{22}H_{32}NO^{+}\cdot C_4H_5O_6^{-}$, the hydrogen tartrate anions are linked by O—H···O hydrogen bonds to form helical chains built from $R_2^2(9)$ rings. These chains are linked by the tolterodine molecules *via* N—H···O and O—H···O hydrogen bonds to form separate sheets parallel to the (101) plane.

Comment

Tolterodine is the generic name for (*R*)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, which acts as a muscarinic receptor antagonist. Muscarinic receptors are the receptor sites for acethylcholine, a neurotransmitter of the parasympathetic autonomic nervous system. These receptors are located on the postsynaptic cell membranes of smooth muscle, cardiac muscle and glandular tissue at the end of parasympathetic nerve activity. Five different subtypes of muscarinic receptors, M1–M5, have been identified (Caulfield & Birdsall, 1998).

In the case of overactive bladder (OAB), antimuscarinics act by blocking the muscarinic receptors (mainly M2 and M3) on the detrusol muscle, causing relaxation and retention of more urine (Chapple, 2000; Beneton & De Parisot, 2003). As a competitive muscarinic receptor antagonist, tolterodine shows greater selectivity for the urinary bladder over other tissues containing muscarinic receptors (*e.g.* the salivary glands or the eyes). Unlike oxybutynin (which targets muscarinic receptors M1 and M3) and darifenacin (selective to the M3 subtype), tolterodine is non-selective with respect to the M1–M5 subtype (Nilvebrant, 2002). As a medication, tolterodine is used in the form of a hydrogen tartrate salt. After oral administration, tolterodine is metabolized in the liver by the CYP2D6 enzyme (cytochrome P_{450} 2D6) to its major active 5-hydroxymethyl metabolite, which has similar pharmacological activity to the parent compound (Brynne *et al.*, 1997).

Although tertiary and quaternary amines have been used in the treatment of OAB for many years, their structure–activity relationship with respect to their selectivity towards muscarinic receptor subtypes M1–M5 is still to be elucidated. To date, X-ray structural data are available only for terodiline hydrochloride (Carlström & Hacksell, 1983). In this paper, we present the crystal and molecular structures of tolterodinium (+)-(2*R*,3*R*)-hydrogen tartrate, (I), determined from single-crystal X-ray data at 100 K.



(I)

The structure of (I) is shown in Fig. 1. The compound crystallizes in the monoclinic space group $P2_1$, with a monoprotonated tolterodinium cation and a hydrogen tartrate anion in the asymmetric unit. The main feature of the tolterodinium cation is the two benzene rings (C2–C7 and C8–C13), which are almost planar; the maximum deviation from planarity of −0.0100 Å is for atom C7 in the C2–C7 ring. The dihedral angle between these two benzene rings is 65.91 (10)°. The C1—C14—C15—N16 aliphatic chain is maximally extended, with a torsion angle of 174.4 (2)°, as found in other diphenylpropylamines (Carlström & Hacksell, 1983; Carpy & Lemrabett, 1989). Both isopropyl groups and the H atom bonded to the ammonium N atom are in an eclipsed conformation with respect to the C15 H atoms and atom C14; the torsion angles C14—C15—N16—C17, C14—C15—N16—C20 and C14—C15—N16—H16 are 124.0 (3), −108.1 (3) and 13 (3)°, respectively.

The configuration of the hydrogen tartrate anion was known to be *R*,*R* and it thus follows that the configuration of the tolterodine chiral atom C1 is *R*.

The hydrogen tartrate anion in (I) adopts a normal conformation, with the two hydroxyl groups *gauche* and the

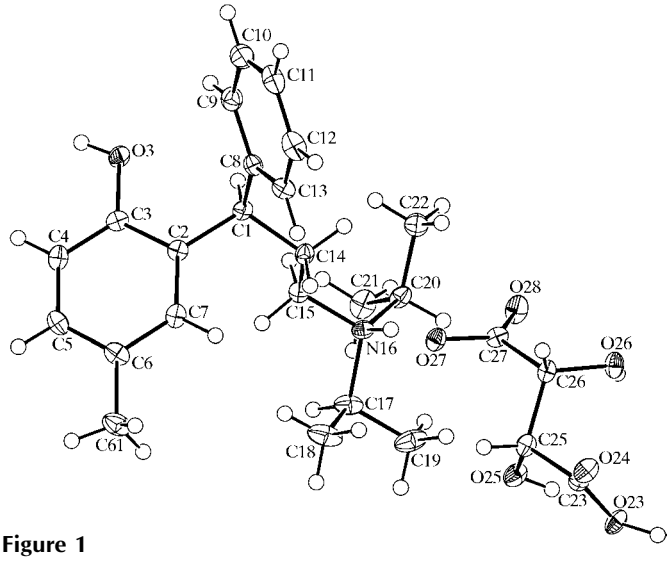


Figure 1
A view of the asymmetric unit of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of van der Waals radii. O and N atoms are shown as octant-shaded ellipsoids.

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carboxyl and carboxylate groups *trans* to each other, as has already been observed in numerous crystal structures involving the tartaric acid molecule or anions [Cambridge Structural Database (CSD), Version 5.25; Allen, 2002]. The values of the C23—C25—C26—C27 and O25—C25—C26—O26 torsion angles are 175.0 (2) and −76.2 (3)°, respectively.

The bond lengths and angles in the tartrate moiety clearly indicate the monoionized form, with C—O distances of 1.322 (4) and 1.212 (4) Å in the carboxyl group for C23—O23 and C23—O24, respectively, and 1.270 (4) and 1.254 (4) Å in the carboxylate group for C27—O27 and C27—O28, respectively. The O23—C23—C25—O25 torsion angle of 15.3 (3)° shows that the O25—H25 hydroxyl group is oriented on the same side of the molecule as the O23—H23 atoms of the carboxyl group with respect to the plane formed by the four C atoms. Moreover, hydroxyl atom H25 and carboxyl atom O23 form an intra-ionic O25—H25···O23 hydrogen bond (Table 1). A CSD search for tartaric acid and hydrogen tartrate anions with respect to the O23—C23—C25—O25 torsion angle revealed only about 20 structures in which a similar orientation to that observed in (I) of adjacent hydroxyl and carboxyl groups has been observed. Among these, the most similar conformation of hydrogen tartrate anions is that observed in the crystal structure of PUMSEV (Lacroix *et al.*, 1998).

The crystal packing in (I) is determined mainly by intermolecular hydrogen bonds. Hydroxyl atom O26 of the hydrogen tartrate anion at (x, y, z) acts as hydrogen-bond donor to carboxyl atom O24 at ($1-x$, $y+\frac{1}{2}$, $1-z$), producing a $C(6)$ chain generated by the 2_1 screw axis along ($\frac{1}{2}$, y, $\frac{1}{2}$). At the same time, carboxyl atom O23 at ($1-x$, $y+\frac{1}{2}$, $1-z$) acts as hydrogen-bond donor to carboxylate atom O28 at (x, y, z), producing a second $C(7)$ chain generated by the same screw axis as before, so that the resulting chain of rings of hydrogen tartrate molecules running parallel to [010] (Fig. 2) has the descriptor $C(6)C(7)[R_2^2(9)]$ (Bernstein *et al.* 1995). Only one chain of this type runs through each unit cell.

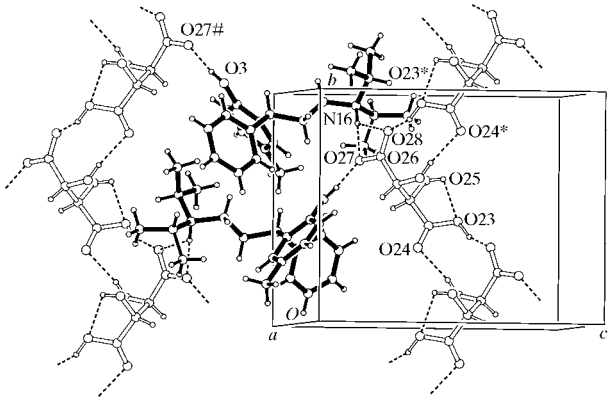

Figure 2
A packing diagram for (I). The helices of the hydrogen tartrate anions run parallel to the crystallographic b axis. For clarity, bonds in the tolterodinuim cation are shown as solid and those in the tartrate anion are shown as open. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions ($1-x$, $\frac{1}{2}+y$, $1-z$) and ($2-x$, $\frac{1}{2}+y$, $-z$), respectively.

The tolterodinium cation acts as both an O—H···O and an N—H···O hydrogen-bond donor, linking the hydrogen tartrate helices into separate sheets parallel to the (101) plane. The ammonium N—H group forms a bifurcated hydrogen bond with carboxylate atoms O27 and O28, while the O3—H3 hydroxyl group is hydrogen bonded to carboxylate atom O27($2-x$, $\frac{1}{2}+y$, $-z$) of a symmetry-related hydrogen tartrate anion belonging to other chain. In this way, the carboxylate O atoms act as double acceptors in N—H and O—H hydrogen bonds (Fig. 2). Between adjacent sheets there are only van der Waals interactions.

Experimental

Tolterodinium (+)-(2*R*,3*R*)-hydrogen tartrate was prepared by a known four-step method, starting from 4-hydroxytoluene and *trans*-cinnamic acid *via* racemic tolterodinium hydrochloride (Gage & Cabaj, 1998). To obtain single crystals of (I), a sample of tolterodinium (+)-(2*R*,3*R*)-hydrogen tartrate was dissolved in 1,2-propylene carbonate (8 ml) with heating. The resulting solution was cooled slowly to room temperature. After 24 h, plate-shaped crystals of (I) crystallized (m.p. 489 K).

Crystal data

$C_{22}H_{32}NO^+\cdot C_4H_5O_6^-$
M_r = 475.57
Monoclinic, $P2_1$
a = 9.204 (1) Å
b = 10.502 (1) Å
c = 13.009 (1) Å
β = 93.061 (4)°
V = 1255.7 (2) Å^3
Z = 2
D_x = 1.258 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 2348 reflections
θ = 4.8–65.1°
μ = 0.74 mm^{-1}
T = 100 (2) K
Plate, colourless
0.40 × 0.15 × 0.10 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.756, T_{max} = 0.929
3572 measured reflections
3565 independent reflections
3105 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 65.1°
$h = -10 \rightarrow 10$
$k = -12 \rightarrow 11$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.148
S = 1.11
3429 reflections
327 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1083P)^2 + 0.2134P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Absolute structure: Flack (1983), with 1298 Friedel pairs
Flack parameter: 0.1 (2)

Table 1
Hydrogen-bond and short-contact geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N16—H16N···O27	1.02 (5)	1.89 (5)	2.902 (3)	172 (4)
N16—H16N···O28	1.02 (4)	2.57 (4)	3.303 (3)	129 (3)
O3—H3···O27^{i}	0.88 (4)	1.78 (4)	2.665 (3)	174 (4)
O25—H25O···O23	0.83 (5)	2.20 (5)	2.614 (3)	110 (4)
O23—H23O···O28^{ii}	1.03 (7)	1.48 (6)	2.460 (3)	158 (6)
O26—H26O···O24^{iii}	0.88 (5)	1.98 (5)	2.821 (3)	157 (6)

Symmetry codes: (i) $-x+2, y+\frac{1}{2}, -z$; (ii) $-x+1, y-\frac{1}{2}, -z+1$; (iii) $-x+1, y+\frac{1}{2}, -z+1$.

The positions of H atoms on O and N atoms were determined from difference Fourier maps and their positional and U_{iso} parameters were refined. H atoms on C atoms were calculated in their ideal positions and refined using a riding model, with C—H distances in the range 0.93–0.98 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$ for CH and CH_2 groups, and $1.5U_{eq}(C)$ for CH_3 groups. The absolute configuration was determined from the known configuration of the starting material.

Data collection: *COLLECT* (Hooft, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON2000* (Spek, 2000); software used to prepare material for publication: *SHELXL97* and *PARST96* (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1190). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Beneton, C. & De Parisot, O. (2003). *Neurochirurgie*, **49**, 369–376.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Brynne, N., Stahl, M. M. S., Hallen, B., Edlund, P. O., Palmer, L., Hoglund, P. & Gabrielsson, J. (1997). *Int. J. Clin. Pharmacol. Ther.* **35**, 287–295.
Carlström, D. & Hacksell, I. (1983). *Acta Cryst.* C**39**, 1130–1132.
Carpy, A. & Lemrabett, A. (1989). *Acta Cryst.* C**45**, 273–275.
Caulfield, M. P. & Birdsall, N. J. (1998). *Pharmacol. Rev.* **50**, 279–290.
Chapple, C. R. (2000). *Urology*, **55** (Suppl. 5A), 33–46.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Gage, J. R. & Cabaj, J. E. (1998). Patent No. W098/29402.
Hooft, R. (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Lacroix, P. G., Daran, J. C. & Nakatani, K. (1998). *Chem. Mater.* **10**, 1109–1114.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Nilvebrant, L. (2002). *Pharmacol. Toxicol.* **90**, 260–267.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2000). *PLATON2000*. University of Utrecht, The Netherlands.