Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Bis[(4-acetamidophenoxy-2-hydroxypropyl)-isopropylammonium] succinate dihydrate

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Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.003 Å
R factor = 0.045
wR factor = 0.126
Data-to-parameter ratio = 16.8

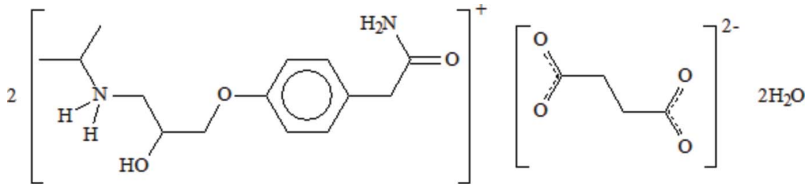
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 18 September 2006
Accepted 30 September 2006

Atenolol, 4-(3-isopropylaminomethyl-2-hydroxypropoxy)-phenylacetamide, crystallizes as a hydrated succinate salt, $2C_{14}H_{23}N_2O_3^+\cdot C_4H_4O_4^{2-}\cdot 2H_2O$. It is isostructural with its fumarate salt. The carboxylic acid transfers its acid H atoms to two molecules of atenolol; the cation, anion and water molecule are linked through hydrogen bonds into a three-dimensional network motif. The succinate anion is located on an inversion center.

Comment

Atenolol, 4-(3-isopropylaminomethyl-2-hydroxypropoxy)-phenylacetamide, a β-adrenergic receptor-blocking agent, is used for the treatment of hypertension and angina in its racemic form. Whereas some pharmacodynamic studies have suggested that the *S*-enantiomer rather than the *R*-enantiomer contributes to the blocking effect, *e.g.* see Stoschitzky *et al.* (1993), other studies did not find any significant difference between the two enantiomers, *e.g.* see McCoy *et al.* (1994). Nevertheless, enantiomeric purity is critical to an understanding of its cardiovascular activity, and although the compound can be prepared in a one-pot synthesis from 4-hydroxyphenylacetamide and epichlorohydrin (of either *R* or *S* configuration) to a purity of 95%, further purification is required to attain a purity of 99.8% (Kitaori *et al.*, 1998). A patent claimed benzoic acid as well as other 4-substituted analogs could be used to form salts with atenolol for the purpose of purification (Takehira *et al.*, 1991). The use of a carboxylic acid for the purpose of isolating pure atenolol has been claimed previously but the patent listed only diphenylacetic acid (Zölss & Pfarrhofer, 1987). Another patent mentions the oxalate, fumarate, succinate, maleate, tartrate and citrate salts as exhibiting such an effect (Puigdellivol *et al.*, 1983) but did not specify their chemical nature.



(I)

The succinate cited in this paper is, in fact, the hydrate $2C_{14}H_{23}N_2O_3^+\cdot C_2H_4O_4^{2-}\cdot 2H_2O$, (I) (Fig. 1), isostructural with its fumarate salt. The succinate anion is located on an inversion center. Bond distances and angles are normal; the cation, anion and water molecules are linked by hydrogen bonds (Table 1) into a three-dimensional network motif.

As atenolol is technically a secondary amine, it should be capable of forming salts with other organic as well as with inorganic acids; interestingly, the phosphomolybdate and phosphotungstate salts have been isolated (Dragan *et al.*, 2005).

Experimental

Atenolol (0.067 g, 0.25 mmol) was dissolved in a mixture of dioxane/water 9:1 (10 ml) along with succinic acid (0.015 g, 0.125 mmol). More water was added to dissolve the solid compound that precipitated; the clear solution was set aside for several days; yield 50%. Elemental analysis calculated for $C_{32}H_{54}N_4O_{12}$: C 55.96, H 8.62, N 8.16%; found C 55.90, H 8.62, N 8.34%. TGA: release of water: 353–388 K, 4.5% (calculated 5.2%).

Crystal data

$2C_{14}H_{23}N_2O_3^+\cdot C_4H_4O_4^{2-}\cdot 2H_2O$
M_r = 686.79
Monoclinic, $P2_1/c$
a = 11.677 (2) Å
b = 9.377 (1) Å
c = 17.225 (2) Å
β = 106.682 (3)°
V = 1806.6 (4) Å^3
Z = 2
D_x = 1.263 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 295 (2) K
Block, colorless
0.50 × 0.20 × 0.16 mm

Data collection

Bruker SMART 1K area-detector diffractometer
φ and ω scans
Absorption correction: None
11319 measured reflections
4126 independent reflections
2498 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 27.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.126
S = 1.04
4126 reflections
245 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0582P)^2 + 0.1974P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O6—H6A···O1	0.85 (1)	2.06 (1)	2.903 (2)	171 (3)
O6—H6B···O4	0.85 (1)	2.03 (1)	2.880 (2)	173 (3)
O3—H3O···O4^{i}	0.87 (1)	1.74 (1)	2.602 (2)	176 (2)
N1—H1C···O1^{ii}	0.85 (1)	2.17 (1)	2.981 (2)	159 (2)
N1—H1D···O5^{iii}	0.85 (1)	2.00 (1)	2.824 (2)	163 (2)
N2—H2C···O3^{iv}	0.87 (1)	1.99 (1)	2.821 (2)	162 (2)
N2—H2D···O5^{i}	0.88 (1)	1.86 (1)	2.743 (2)	179 (2)

Symmetry codes: (i) $-x+2, -y+2, -z+1$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$; (iii) $x, -y+\frac{5}{2}, z+\frac{1}{2}$; (iv) $-x+2, -y+1, -z+1$.

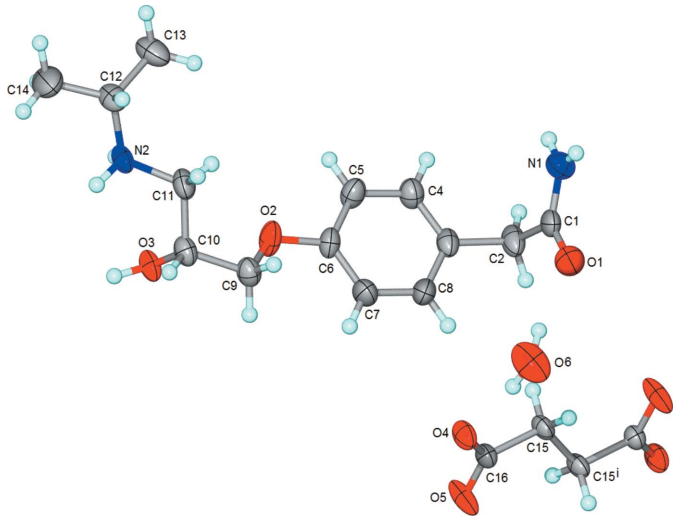


Figure 1
The molecular structure of (I), the hydrated succinate salt. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as spheres of arbitrary radii. [Symmetry code: (i) $1+x, \frac{5}{2}-y, \frac{1}{2}+z$.]

The C-bound H atoms were placed at calculated positions (C—H = 0.93–0.98 Å) and were included in the refinement in the riding-model approximation, with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C). The water and amino H atoms were located in a difference Fourier map and were refined with a distance restraint of O—H = N—H = 0.85 (1) Å; the displacement factors were freely refined.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT* (Bruker, 1998); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *X-SEED* (Barbour, 2001); software used to prepare material for publication: *SHELXL97*.

We thank the Natural Science Foundation of Guangdong (grant No. 04105493), Sun-Yat Sen University and the University of Malaya for generously supporting this study.

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