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(*S*)-(+)-2-[2-(Biphenyl-2-yl)-1-methylethyl]-4,5-dihydro-1*H*-imidazolium hydrogen oxalate

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.003 Å
R factor = 0.035
wR factor = 0.083
Data-to-parameter ratio = 9.1

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

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The (+)-enantiomer of 2-[2-(biphenyl-2-yl)-1-methylethyl]-4,5-dihydro-1*H*-imidazole is known to produce interesting hypotensive effects *via* inhibition of I_1-imidazoline receptors. The crystal structure of its hydrogen oxalate salt, $C_{18}H_{21}N_2^+\cdot C_2HO_4^-$, has now been determined at 170 K, allowing the assignment of the absolute configuration of the parent molecule. The solid-state structure is stabilized by a network of hydrogen bonds between the ions.

Comment

The widespread occurrence and dangerous increase in the incidence of cardiovascular diseases have stimulated extensive efforts to obtain new effective antihypertensive agents (Sierra & Ruilope, 2004). One relatively recent therapeutic target is represented by the I_1-imidazoline receptors (I_1-Rs), discovered by Bousquet *et al.* (1984) while studying the cardiovascular effects of clonidine. Specific drugs for this target offer the advantage of not displaying the side effects typical of α_2-adrenoreceptor (α_2-ARs) stimulation, such as sedation and salivary secretion inhibition (Head & Burke, 2000). Recently, it has been reported by some of us (Quaglia *et al.*, 1999; Gentili *et al.*, 2003) that I_1-Rs interact with their respective ligands in a stereospecific manner, similar to the majority of the other members of the vast family of seven-transmembrane (7TM) receptors, also referred to as seven-membrane-spanning receptors and G-protein-coupled receptors (GPCRs). For this

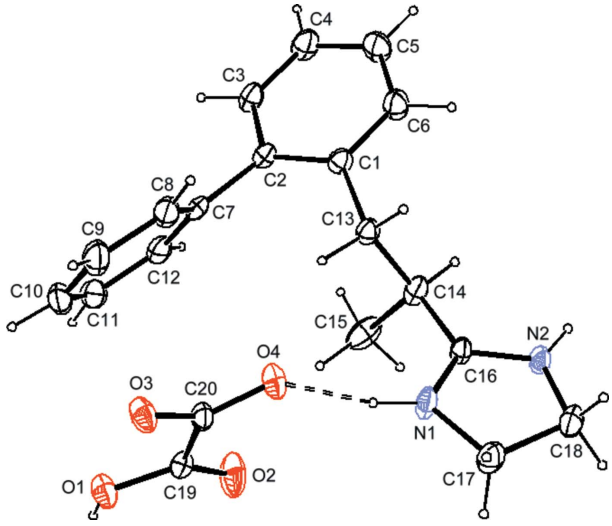
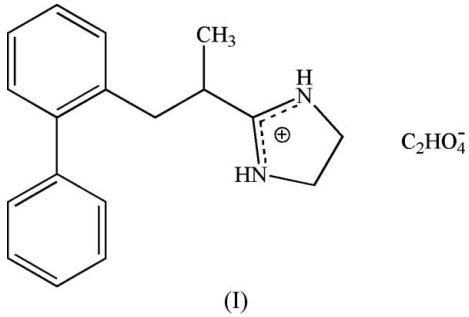


Figure 1
A view of the contents of the asymmetric unit of (I), consisting of the protonated (S)-(+)-enantiomeric molecule and hydrogen oxalate anion. Displacement ellipsoids are at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The hydrogen-bond interaction is indicated by a dashed line.

reason, the racemate (±)-2-[2-(biphenyl-2-yl)-1-methylethyl]-4,5-dihydro-1*H*-imidazole, which exhibits significant selectivity for I_1-Rs compared with α_2-ARs, was resolved into the two enantiomers, (+)-1 and (−)-1, characterized as the oxalate salts (Gentili *et al.*, 2005). Hypotensive tests showed that only the dextrorotatory enantiomer, (+)-1, produced relevant cardiovascular effects. An X-ray diffraction study was undertaken on this enantiomer, in the form of the title oxalate salt, (I), in order to attempt determination of the absolute configuration of the species. We are confident that, in spite of the absence of atoms heavier than oxygen, this could be unambiguously assigned (Fig. 1), with a value of −0.1 (2) for the Flack parameter (Flack & Bernardinelli, 1999), compared with the value of 1.1 (2) from the refinement of the enantiomeric structure.



(I)

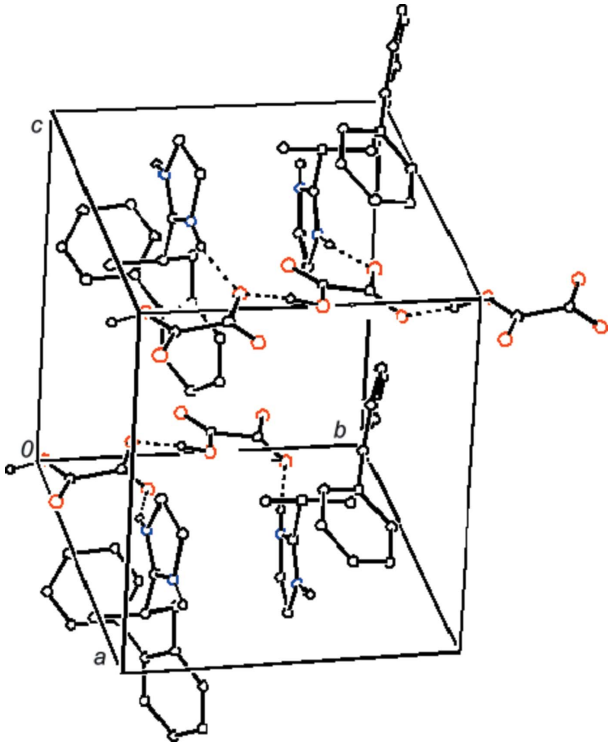


Figure 2
A view of the packing of (I), showing the hydrogen-bond interactions (dashed lines). H atoms not involved in hydrogen bonding have been omitted.

Selected values of the geometric parameters for (I) are given in Table 1. The asymmetric unit contains the ion pair resulting from transfer of one H atom from the oxalic acid molecule to the other component. Upon protonation, the dihydroimidazole ring attains a substantially symmetric geometry (Table 1), with the H atoms attached to N atoms deviating by at most 0.14 (2) Å from the plane of the ring (Nardelli, 1995). The planes of the aromatic rings form a dihedral angle of 59.6 (1)°.

In the crystal structure, the cations are arranged in layers normal to the crystallographic *b* axis, in which they are linked by hydrogen bonds to the anions (Fig. 2, Table 2). The anions, besides participating in the above layers, form tightly hydrogen-bonded sequences parallel to *b*.

Experimental

The synthesis of the racemate (±)-2-(2-biphenyl-2-yl-1-methylethyl)-4,5-dihydro-1*H*-imidazole, (±)-(1), and its resolution into the two enantiomers was performed according to Gentili *et al.* (2005). Crystals of the oxalate salt, (I), of the dextrorotatory enantiomer were obtained by slow evaporation of a 1:1 methanol–butanol solution.

Crystal data

$C_{18}H_{21}N_2^+\cdot C_2HO_4^-$
M_r = 354.40
Monoclinic, $P2_1$
a = 9.4761 (6) Å
b = 10.0886 (6) Å
c = 10.5018 (6) Å
β = 111.697 (6)°
V = 932.85 (10) Å^3
Z = 2
D_x = 1.262 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 4415 reflections
θ = 6.0–40.0°
μ = 0.72 mm^{-1}
T = 173 (2) K
Elongated plate, colourless
0.70 × 0.35 × 0.10 mm

Data collection

Oxford Excalibur PX Ultra CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1986)
T_{min} = 0.698, T_{max} = 0.930
10735 measured reflections
2761 independent reflections
2497 reflections with $I > 2\sigma(I)$
R_{int} = 0.051
θ_{max} = 60.5°
$h = -10 \rightarrow 10$
$k = -11 \rightarrow 11$
$l = -11 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.083
S = 0.99
2761 reflections
302 parameters
Only H-atom coordinates refined
$w = 1/[\sigma^2(F_o^2) + (0.0587P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0163 (18)
Absolute structure: Flack & Bernardinelli (1999), with 1282 Friedel pairs
Flack parameter: −0.1 (2)

Table 1
Selected geometric parameters (Å, °).

C2—C7	1.492 (3)	C18—N2	1.447 (3)
C14—C16	1.492 (3)	O1—C19	1.307 (2)
C16—N2	1.300 (2)	O2—C19	1.207 (2)
C16—N1	1.306 (2)	O3—C20	1.258 (2)
N1—C17	1.464 (3)	O4—C20	1.235 (2)
C17—C18	1.510 (3)	C19—C20	1.536 (3)
C6—C1—C13—C14	−75.8 (2)	C13—C14—C16—N2	−121.3 (2)
C2—C1—C13—C14	100.6 (2)	C13—C14—C16—N1	58.8 (3)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O3^{i}	1.01 (3)	1.55 (3)	2.558 (2)	171 (3)
N1—H1N···O4	0.89 (2)	1.90 (3)	2.744 (2)	158 (2)
N2—H2N···O3^{ii}	0.81 (3)	1.98 (3)	2.757 (2)	162 (2)

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

Data collection was limited to $\theta < 60.5°$, as it appeared that very few measurable intensities could be found at higher angles. The position of the unique oxalate H atom was assigned by consideration of the C—O distances and hydrogen-bond interactions. In the refinement, H-atom positions were initially positioned geometrically and were allowed to refine without geometrical restraints, with U_{iso}(H) = 1.2U_{eq}(C,N), or 1.5U_{eq}(C,O) for methyl and hydroxyl H atoms. The ranges of the bond distances involving H atoms are as follows: secondary CH_2 0.83 (3)–1.00 (2) Å, methyl CH_3 1.02 (3)–1.07 (3) Å, tertiary CH 0.95 (2) Å, aromatic CH 0.92 (3)–1.01 (3) Å, N—H 0.81 (3)–0.89 (2) Å and O—H 1.01 (3) Å.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2001); cell refinement: *CrysAlis CCD*; data reduction: *CrysAlis RED* (Oxford Diffraction, 2001); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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References

Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Bousquet, P., Feldman, J. & Schwartz, J. (1984). *J. Pharmacol. Exp. Ther.* **230**, 232–236.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. & Bernardinelli, G. (1999). *Acta Cryst.* A**55**, 908–915.
Gentili, F., Bousquet, P., Brasili, L., Dontenwill, M., Feldman, J., Ghelfi, F., Giannella, M., Piergentili, A., Quaglia, W. & Pigini, M. (2003). *J. Med. Chem.* **46**, 2169–2176.
Gentili, F., Bousquet, P., Feldman, J., Ghelfi, F., Giannella, M., Piergentili, A., Quaglia, W., Vesprini, C. & Pigini, M. (2005). *J. Med. Chem.* Submitted.
Head, G. A. & Burke, S. L. (2000). *Am. J. Hypertens.* **13**, 89S–98S.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Oxford Diffraction (2001). *CrysAlis CCD* (Version 1.171) and *CrysAlis RED* (Version 1.171). Oxford Diffraction Ltd, Abingdon, Oxfordshire, England.
Quaglia, W., Bousquet, P., Pigini, M., Carotti, A., Carrieri, A., Dontenwill, M., Gentili, F., Giannella, M., Maranca, F., Piergentili, A. & Brasili, L. (1999). *J. Med. Chem.* **42**, 2737–2740.
Sheldrick, G. M. (1986). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Sierra, C. & Ruilope, L. M. (2004). *Expert Opin. Investig. Drugs.* **13**, 987–998.