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Absolute configuration of (+)-(*S*)-2-(5-fluoro-2-methoxy-1,4-benzodioxan-2-yl)imidazolinium bromide

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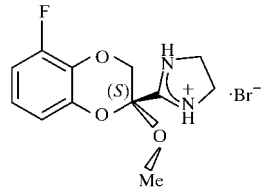
The title compound, $C_{12}H_{14}FN_2O_3^+\cdot Br^-$, crystallizes in the non-centrosymmetric $P2_12_12_1$ space group. The absolute configuration of the pharmacologically active molecule could be resolved in the hydrobromide salt, the structure of which is reported. The molecule of the title compound has the *S* configuration. The molecular packing in the crystal is stabilized by weak N—H···Br [N···Br = 3.240 (4) and 3.302 (4) Å] hydrogen bonding.

Comment

The title compound, (I), is a potent and highly selective α-2-adrenoreceptor antagonist. (+)-2-(5-Fluoro-2-methoxy-1,4-benzodioxan-2-yl)imidazoline was prepared following the method described in a patent (registration number 9908302). The 5-fluoro position was obtained during the first step of the synthesis by cyclization of 3-fluorocatechol with 2,3-dibromopropionamide, providing a mixture of 2-carboxamido-5-fluorobenzo[1,4]dioxane (70%) and 2-carboxamido-8-fluorobenzo[1,4]dioxane (30%). The separation of these regioisomers was carried out by successive crystallization from hot ethanol to give a material 100% (*w*/*w*) pure by high-pressure liquid chromatography (HPLC). This carboxamide was oxidized to the nitrile compound which was brominated in the 2-position with *N*-bromosuccinimide. Successive reaction with sodium methoxide and ethylenediamine gave the racemic mixture. Both enantiomers were separated by successive crystallizations from methanol of the (+)-*o*,*o*-dibenzoyl tartaric acid salt, providing the (+)-isomer. The X-ray structure of (I) confirmed the chemical structure deduced by NMR.

The fluorine position was deduced unambiguously by recording a ^{13}C, ^{1}H heteronuclear multiple bond correlation spectrum (HMBC) and a ^{13}C, ^{1}H heteronuclear multiple quantum correlation spectrum (HMQC). The C^{13} NMR spectrum was characterized by large coupling constants between ^{19}F and neighbouring ^{13}C nuclei. Atom C1 at δ 150 p.p.m. exhibited a large coupling constant ($^1J_{C1-F}$ = 243.8 Hz) with the F atom. This value is typical for fluoro-aromatic compounds (Pretsch *et al.*, 1983). Geminal couplings



(I)

were found to be $^2J_{F-C2}$ = 17.4 Hz and $^2J_{F-C6}$ = 14.5 Hz. The HMBC spectrum allowed us to confirm the assignment of C6 based on this correlation with the two H7 atoms. The ^{19}F NMR spectrum exhibited one signal under proton noise decoupling at δ −55.0 p.p.m. and showed a doublet of doublets with a coupling constant of 8.2 Hz ($^3J_{F-H}$) and of 6.5 Hz ($^4J_{F-H}$) without proton noise decoupling. These results were in good agreement with the molecular structure (Günther, 1980).

The *S* configuration of the molecule of the title compound is shown in Fig. 1. The methoxyfluorobenzodioxane is attached through the asymmetric C8 atom (*S* configuration) to an imidazoline cycle protonated at one N atom. The sums of the angles around the N atoms are very close to 360° (359.7 and 359.9°). The positions of H atoms HN1 and HN2, attached to N1 and N2 respectively, of the imidazole cycle have been refined. Each Br^- anion is involved in two weak hydrogen bonds with the HN1 and HN2 atoms. The N···Br distances of 3.240 and 3.302 Å are short compared with the sum of the van der Waals radii of the elements (3.40 Å). Such distances have already been observed in similar compounds, as for example in

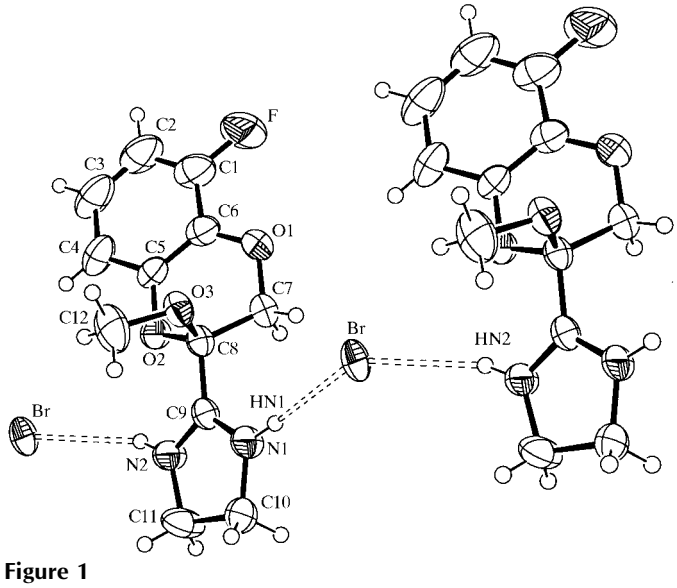


Figure 1
A view of the molecule of (I). Displacement ellipsoids are drawn at the 50% probability level for non-H atoms.

benzodiazoxane imidazolinium bromide (Brunel *et al.*, 1999), where hydrogen bonds are slightly stronger (N···Br = 3.217 and 3.226 Å). An analysis of bonding has been carried out by means of extended Hückel molecular orbital calculations (Hoffmann, 1963; Ammeter *et al.*, 1978; Whangbo *et al.*, 1978). At the N1—C9—N2 edges of the imidazole cycle, bonding results from σ overlapping of sp^2-hybridized orbitals. Furthermore, the remaining p_z orbitals (out of the imidazole plane) combine into a delocalized π bond which involves the N1, N2 and C9 atoms, and a non-bonding pair delocalized over the N1 and N2 atoms. Calculated overlap populations of 1.04, 1.01, 0.60 and 0.60 for N1—C9 (1.292 Å), N2—C9 (1.308 Å), N1—C10 (1.465 Å) and N2—C11 (1.458 Å), respectively, are consistent with bond orders of 1.5 and 1.0.

Experimental

The hydrobromide salt of the compound (+)-2-(5-fluoro-2-methoxy-1,4-benzodioxan-2-yl)imidazoline was obtained as follows: to a solution of the imidazoline (5 g, 0.0198 mol) in ethanol (30 ml) was added 60% aqueous hydrobromic acid up to pH < 4. The solvent was evaporated to dryness and the residue crystallized with isopropyl ether and then filtered and dried to give a white powder (5.84 g, 88%). Recrystallization from hot ethanol gave white needles (m.p. 536 K). Elemental analyses gave an atomic C/H/N ratio (%) of 43.19/4.45/8.29 (calculated ratio is 43.26/4.24/8.41). MS: ESI > 0 MH^+, m/z = 253. All the NMR spectra were recorded non-spinning on a Bruker Avance 400 spectrometer operating at the proton nominal frequency of 400 MHz equipped with a 5 mm inverse multinuclear gradient probe-head. The spectrometer frequency was 400.12 MHz for ^{1}H and 100.58 MHz for ^{13}C. The sample was dissolved in DMSO-d_6 (isotopic enrichment for 99.8%, Euristop, D310-B) and was maintained at 298 K throughout. ^{1}H NMR (DMSO-d_6): δ 10.8 (NH, *s*, 2H), 7 (H_{ar}, *m*, 3H), 4.5 (C7, *d*, J = 11.6 Hz, 1H), 4.3 (C7, *d*, J = 11.6 Hz, 1H), 4 (C10 and C12, *s*, 4H), 3.3 (C12, *s*, 3H). The optical rotation of the compound was $[\alpha]_D$ = +81.4° (0.5MeOH) at 298 K. The chemical and optical purity of batch JLM3006300 was determined using HPLC with the following conditions: chemical purity, chromatographic column: symmetry C8, 5 μm, 4.6 × 250 mm, Waters; eluent, CH_3CN/MeOH/KH_2PO_4: 150 ml/50 ml/800 ml/6.8 g at pH = 4 and at 1 ml min^{-1}; detection wavelength: 220 nm; optical purity, chromatographic column: Chiralcel OD, 10 μm, 4.6 × 250 mm, Daicel; eluent, hexane/EtOH: 90 ml/10 ml; detection wavelength: 220 nm. The chemical purity was found to be 99.79% (*w*/*w*, by internal normalization) and the optical purity was 99.9% (*w*/*w*, by internal normalization). Crystals were selected under a microscope and checked for singularity by X-ray investigations. Parameters and crystallographic space groups were initially determined by oscillation and Weissenberg techniques. The best diffracting crystal was used for accurate determination of the cell parameters and for data collection.

Crystal data

$C_{12}H_{14}FN_2O_3^+\cdot Br^-$
M_r = 333.16
Orthorhombic, $P2_12_12_1$
a = 8.220 (3) Å
b = 9.365 (3) Å
c = 17.890 (3) Å
V = 1377.2 (7) Å^3
Z = 4
D_x = 1.607 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 6.05–17.62°
μ = 3.00 mm^{-1}
T = 293 (2) K
Needle, colourless
0.7 × 0.15 × 0.15 mm

Table 1
Selected bond lengths (Å).

Br—N1^{i}	3.240 (4)	O1—C7	1.412 (6)
Br—N2	3.302 (4)	O2—C5	1.379 (6)
N1—C9	1.292 (6)	O2—C8	1.420 (5)
N1—C10	1.465 (7)	O3—C8	1.387 (5)
N2—C9	1.308 (6)	O3—C12	1.438 (6)
N2—C11	1.458 (7)	F—C1	1.350 (7)
O1—C6	1.350 (7)		

Symmetry code: (i) $1+x, y, z$.

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—HN1···Br^{i}	0.77 (5)	2.47 (5)	3.240 (4)	172 (5)
N2—HN2···Br	0.91 (5)	2.52 (5)	3.302 (4)	145 (4)

Symmetry code: (i) $x-1, y, z$.

Data collection

Nonius CAD-4 diffractometer
ω–θ scans
3134 measured reflections
1568 independent reflections (plus 1121 Friedel-related reflections)
1869 reflections with $I > 2\sigma(I)$
R_{int} = 0.024
θ_{max} = 25.95°
$h = -10 \rightarrow 10$
$k = -11 \rightarrow 11$
$l = -22 \rightarrow 22$
3 standard reflections every 100 reflections
intensity decay: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.096
S = 0.968
2689 reflections
178 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0477P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.64 e Å^{-3}
$\Delta\rho_{min}$ = −0.58 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = 0.007 (15)

H atoms attached to C atoms were treated as riding atoms (C—H = 0.93–0.97 Å). H atoms attached to N atoms were positioned from a difference Fourier map and their positions were refined. All H atoms were given a fixed U_{iso} displacement parameter of 0.05 Å^2.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: local program; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1579). Services for accessing these data are described at the back of the journal.

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