The temperature of the crystal was controlled using an Oxford Cryosystems Cryostream Cooler (Cosier & Glazer, 1986). Data were collected over a hemisphere of reciprocal space by a combination of three sets of exposures. Each set had a different φ angle for the crystal and each exposure of 10 s covered 0.3° in ω. The crystal-to-detector distance was 5.01 cm. Coverage of the unique set was over 90% complete to at least 28° in θ. Absence of crystal decay was established by repeating the initial frames at the end of the data collection and analyzing the duplicate reflections. H atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl H atoms) times the equivalent isotropic displacement parameter of the atom to which they are attached.

Data collection: *SMART* (Siemens, 1994*a*). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL/PC* (Siemens, 1994*b*). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *SHELXTL/PC*. Software used to prepare material for publication: *SHELXTL/PC*.

We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury Laboratory (Fletcher, McMeeking & Parkin, 1996) for access to the Cambridge Structural Database (Allen & Kennard, 1993).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1183). Services for accessing these data are described at the back of the journal.

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(–)-Formoterol,† a Selective β_2-Adrenoreceptor Agonist

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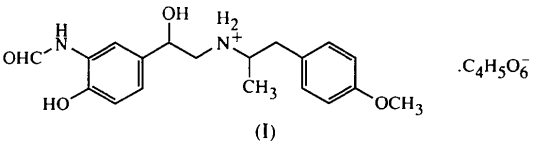
Abstract

The crystal structure of (−)-formoterol [2-hydroxy-5-(hydroxy-2-{[2-(*p*-methoxyphenyl)-1-methylethyl]-amino}ethyl)formanilide (+)-tartrate, $C_{19}H_{25}N_2O_4^+ \cdot C_4H_5O_6^-$] has been determined in order to elucidate its configuration relative to that of (+)-tartrate. The result is consistent with the configuration proposed on the basis of the chemical correlation experiments.

Comment

Formoterol, one pair of enantiomers of 2-hydroxy-5-[(1*RS*)-1-hydroxy-2-{[(1*RS*)-2-(*p*-methoxyphenyl)-1-methylethyl]amino}ethyl]formanilide, is a long-acting β_2-adrenoreceptor agonist (Ida, 1976*a*,*b*) and its fumarate (YM-08316) has been clinically used for the treatment of asthma. The pharmacological properties of formoterol have been extensively evaluated in several review papers (Faulds, Hollingshead & Goa, 1991; Anderson, 1993; Tattersfield, 1993).

In the search for selective β-adrenoreceptor-stimulating compounds, we synthesized 2-hydroxy-5-[(1*RS*)-1-hydroxy-2-{[(1*RS*)-2-(*p*-methoxyphenyl)-1-methylethyl]-amino}ethyl]formanilide, which was then separated into two racemic compounds, formoterol and the other, by selective crystallization (Murase *et al.*, 1977). Each racemate was further separated into its optical isomers using the (+) and (−) forms of tartaric acid as the resolving agents (Murase *et al.*, 1978). Among these four isomers, (−)-formoterol showed the most potent bronchodilatory activity. We have now determined the crystal structure of (−)-formoterol (+)-tartrate, (I), in order to confirm its configuration.



(I)

† Systematic name: [2-(4-methoxyphenyl)-1-methylethyl][2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethyl]ammonium tartrate.

The molecular structure of (−)-formoterol (+)-tartrate is represented in Fig. 1. The configuration of (−)-formoterol is assigned to be (*R*,*R*) on the basis of the information that the absolute configuration of (+)-tartaric acid is (2*R*,3*R*) (Klyne & Buckingham, 1978). This configuration of (−)-formoterol is consistent with the results proposed previously from chemical correlations studies (Murase *et al.*, 1978).

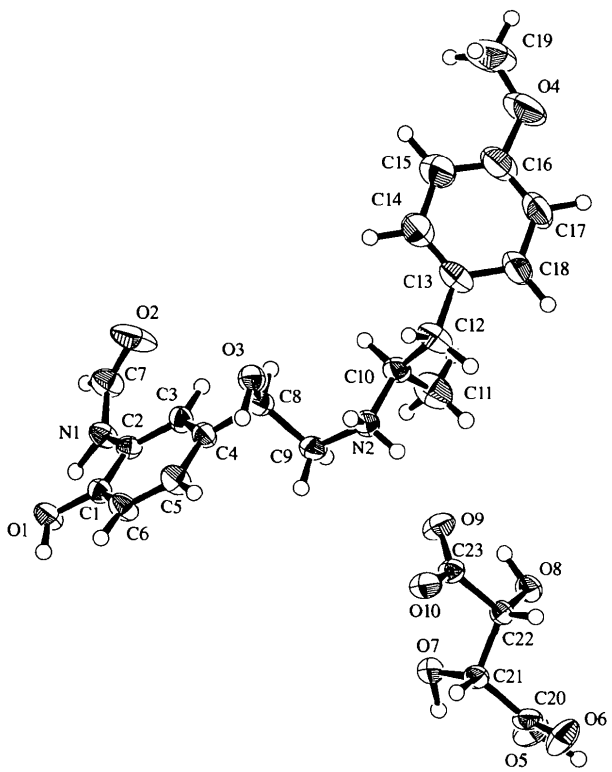


Fig. 1. The molecular structure of (−)-formoterol (+)-tartrate. Displacement ellipsoids are shown at the 50% probability level.

The N atom, N2, of (−)-formoterol is protonated and makes a salt bridge with O9 in the carboxylate of (+)-tartaric acid with an N···O distance of 2.784 (5) Å. Several other intermolecular hydrogen bonds observed in the crystalline environment are summarized in Table 1.

Experimental

(−)-Formoterol (+)-tartrate was dissolved in 1:4 methanol–ethyl acetate. Plate crystals of the compound were obtained by evaporating the solution at room temperature.

Crystal data

$C_{19}H_{25}N_2O_4^+.C_4H_5O_6^-$
M_r = 494.50
Monoclinic
$P2_1$
a = 18.965 (2) Å
b = 7.522 (2) Å
c = 8.794 (1) Å
β = 101.13 (1)°
V = 1231.0 (3) Å^3
Z = 2
D_x = 1.334 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 24 reflections
θ = 35.6–39.4°
μ = 0.892 mm^{-1}
T = 296 K
Plate
0.70 × 0.30 × 0.05 mm
Colorless

Data collection

Rigaku AFC-5*R* diffractometer
ω–2θ scans
Absorption correction: ψ scans (North, Phillips & Mathews, 1968)
T_{min} = 0.854, T_{max} = 0.995
2942 measured reflections
2772 independent reflections
2531 reflections with $I > 0.1\sigma(I)$
R_{int} = 0.025
θ_{max} = 79.74°
h = −24 → 24
k = −9 → 9
l = −9 → 11
3 standard reflections
every 150 reflections
intensity decay: −0.58%

Refinement

Refinement on F
R = 0.0662
wR = 0.0811
S = 1.197
2531 reflections
316 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o) + 0.00168|F_o|^2]$
$(\Delta/\sigma)_{max}$ = 0.009
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H11···O9	0.92	1.94	2.784 (5)	152
O3—H8···O7^{i}	1.08	1.80	2.807 (4)	153
N2—H11···O5^{i}	0.92	2.75	3.010 (5)	98
N2—H12···O8^{ii}	1.03	2.16	3.126 (5)	157
O7—H28···O2^{ii}	1.09	2.03	2.654 (5)	113
O8—H30···O3^{iii}	0.98	2.57	2.977 (4)	105
O5—H26···O10^{iii}	1.26	1.27	2.509 (6)	164
O1—H1···O10^{iv}	1.01	1.78	2.721 (4)	153
N1—H5···O3^{v}	1.09	2.18	3.054 (5)	136

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

The structure was solved by direct methods. The positions of H atoms attached to polar atoms were found using difference Fourier map and others were placed at calculated positions. All H atoms were fixed but included in the refinement. Isotropic parameters for the H atoms were set equal to 1.2 times that of the attached atom.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1992). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1995). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *TEXSAN*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: TA1149). Services for accessing these data are described at the back of the journal.

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Three 2,5-Disubstituted 9-Oxabicyclo[4.2.1]-nonanes. Transannular O-Heterocyclization Products of Cycloocta-1,5-diene

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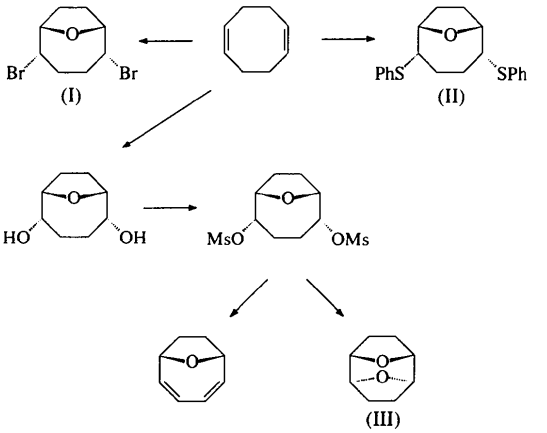
Abstract

The crystal structures of *endo,endo*-2,5-dibromo-9-oxabicyclo[4.2.1]nonane, (I), $C_8H_{12}Br_2O$, *endo,endo*-2,5-bis-(phenylthio)-9-oxabicyclo[4.2.1]nonane, (II), $C_{20}H_{22}OS_2$, and 9,10-dioxatricyclo[4.2.1.$1^{2,5}$]decane, (III), $C_8H_{12}O_2$, were determined and the conformations of these transannular O-heterocyclization products of cycloocta-1,5-diene were defined. The structure determinations reveal a tetrahydrofuran ring having an envelope conformation and an oxepane ring with a twisted-chair conformation in each of (I) and (II), with the two bulky substituents quasi-equatorial or quasi-axial, respectively, both in a *trans* position in relation to the ring O atom. The tricyclic compound (III) consists of two five-membered envelopes and a 1,4-dioxane chair. The cyclooctane moiety has a twisted-chair conformation in both (I) and (II), whereas it is a chair in (III).

Comment

Transannular O-heterocyclization of cycloocta-1,5-diene represents the easiest way to obtain disubstituted bicyclic ethers, by employing an electrophilic cascade reaction. These compounds have been designed as starting materials for syntheses of natural products and their analogues. In consecutive reactions, the conformation seems to be very important. Therefore, we determined the structures of the polycyclic tetrahydrofurans (I), (II) and (III).



Among natural products, polycycles having a tetrahydrofuran moiety are very common, especially in marine diterpenoids (Wahlberg & Eklund, 1992; Faulkner, 1996). However, no crystalline-state structures of simple synthetic building blocks for such compounds have been reported in the literature. *endo,endo*-2,5-Dibromo-9-oxabicyclo[4.2.1]nonane, (I), can be prepared using *N*-bromosuccinimide and dioxane/water (4:1) as a solvent (Haufe, 1984). The conformation in solution of (I) and the *endo*-2-bromo-*endo*-5-fluoro analogue had been assumed earlier (Kleinpeter *et al.*, 1977; Haufe *et al.*, 1978; Haufe, Alvernhe & Laurent, 1990). Based on ^{1}H NMR spectra, an envelope conformation was predicted for the five-membered ring and a chair conformation for the oxaheptane moiety. This assignment is now established by X-ray structure analysis. The same conformation is observed for *endo,endo*-2,5-bis(phenylsulfenyl)-9-oxabicyclo[4.2.1]nonane, (II). Due to the symmetry of the space group, the asymmetric unit contains only one half of the molecule. The second half