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Absolute Configuration of (+)-Ethambutol Hydrobromide

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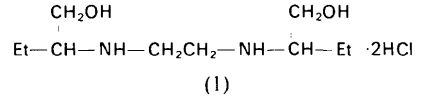
Abstract. (*S,S*)-*N,N'*-Bis(1-hydroxymethylpropyl)-ethylenediammonium bromide, $C_{10}H_{26}N_2O_2^{2+}.2Br^-$, $M_r = 366.1$, orthorhombic, $P2_12_12$, $a = 23.045$ (4), $b = 6.735$ (1), $c = 5.291$ (6) Å, $V = 821.2$ Å^3, $Z = 2$, $D_x = 1.4$ g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, μ = 48.8 cm^{-1}, $F(000) = 372$, $T = 293$ K, final $R = 0.037$ for 986 observed reflections. The cations, which are protonated at N, lie across crystallographic twofold rotation axes. In the crystal the Br anions are hydrogen bonded to the H(N) groups of two different cations and to the H(O) group of a third cation. The absolute configuration of the (+)-ethambutol cations is *S,S*.

Introduction. Ethambutol hydrochloride [(+)-2,2-(ethylenediimino)di-1-butanol dihydrochloride (1), CAS registry No. 19070-11-7] is a very important chemotherapeutic drug introduced by Lederle Laboratories as myambutol, and is used to treat tuberculosis.



(1)

The original patent (American Cyanamid Co., 1965) described the racemate. However, subsequent studies (Wilkinson, Shepherd, Thomas & Baughn, 1961; Wilkinson, Cantrall & Shepherd, 1962) showed that the (+)-enantiomer has about 12 times more antibacterial activity than the *meso* isomer, and about 200 times more activity than the (−)-enantiomer. Therefore, only the (+)-enantiomer is used clinically, and this is specified by its specific optical rotation.

Although the specific rotation of ethambutol is sufficient to define a particular enantiomer, there appears to be considerable disagreement in the literature as to the absolute stereochemistry. The *British Pharmacopeia* (1980, 1988) and the *European Pharmacopeia* (1987) define (+)-ethambutol as *R,R* in the Cahn, Ingold & Prelog (1966) notation. However, similar structures in the *United States Pharmacopeia* (1990) and in the *British Pharmacopeia* 1988 *Addendum* (1990) are designated *S*-(*R*,R**) and *S,S* respectively. The late Professor Klyne's Atlas (Klyne & Buckingham, 1974) also gives the same (+)-enantiomer as *S,S*.

The crystal and molecular structure of (1) have been reported (Hämäläinen, Lehtinen & Ahlgren, 1985), but with no determination of the absolute structure. In order to define the absolute configuration of (+)-ethambutol we have determined the crystal and molecular structure of its hydrobromide which has a larger anomalous-dispersion effect.

Experimental. Ethambutol dihydrochloride (Cyanamid batch No. 6612) was dissolved in the minimum of water and the free base precipitated with 10 *M* aqueous sodium hydroxide. The ethambutol free base was filtered off, dried, and then redissolved in tetrahydrofuran. The addition of hydrogen bromide produced a precipiate of ethambutol dihydrobromide which was recrystallized from propan-1-ol to give white needle crystals. One of these needles was cut to a suitable length and used for X-ray data collection on an Enraf–Nonius CAD-4 diffractometer.

Unit-cell parameters by least-squares fit of 25 reflections in the range $12 < 2\theta < 29°$, crystal dimensions $0.4 \times 0.08 \times 0.08$ mm, Mo $K\alpha$ radiation, graphite monochromator, θ–2θ scan mode, scan width $\Delta\theta = (0.8 + 0.35\tan\theta)°$, variable scan time between 20 and 120 s. For the data collection the cell setting was $a = 5.291$, $b = 6.735$, $c = 23.045$ Å, and 2265 reflections were measured for h 0→5, k −7→7,

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Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($Å^2 \times 10^3$)

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
Br	4203.2 (2)	2050.6 (8)	−6893.3 (10)	63 (1)
O	3750 (2)	7765 (5)	1310 (6)	74 (2)
N	4188 (1)	4869 (5)	−2013 (7)	47 (2)
C(1)	3716 (2)	8139 (8)	−1336 (9)	61 (3)
C(2)	3675 (2)	6158 (7)	−2656 (8)	50 (3)
C(3)	3133 (2)	4960 (8)	−2063 (10)	64 (3)
C(4)	2588 (2)	5920 (11)	−3113 (14)	103 (5)
C(5)	4767 (2)	5820 (7)	−2229 (9)	55 (3)

Table 2. *Intramolecular distances* (Å) *and angles* (°)

O—C (1)	1.425 (6)	O—H(O)	0.86 (6)
N—C(2)	1.505 (6)	N—C(5)	1.485 (5)
N—H(N*a*)	0.86 (5)	N—H(N*b*)	0.88 (5)
C(1)—C(2)	1.509 (7)	C(1)—H(1*a*)	1.04 (6)
C(1)—H(1*b*)	1.06 (5)	C(2)—C(3)	1.521 (6)
C(2)—H(2)	0.97 (5)	C(3)—C(4)	1.518 (8)
C(3)—H(3*a*)	1.03 (5)	C(3)—H(3*b*)	0.98 (5)
C(5)—C(5^i)	1.541 (6)	C(5)—H(5*a*)	1.04 (6)
C(5)—H(5*b*)	1.12 (6)		

C(1)—O—H(O)	107 (4)	C(2)—N—C(5)	116.1 (3)
C(2)—N—H(N*a*)	113 (3)	C(2)—N—H(N*b*)	104 (3)
C(5)—N—H(N*a*)	110 (3)	C(5)—N—H(N*b*)	108 (3)
H(N*a*)—N—H(N*b*)	105 (5)	O—C(1)—C(2)	107.6 (4)
O—C(1)—H(1*a*)	110 (3)	O—C(1)—H(1*b*)	109 (3)
C(2)—C(1)—H(1*a*)	112 (3)	C(2)—C(1)—H(1*b*)	107 (3)
H(1*a*)—C(1)—H(1*b*)	112 (4)	N—C(2)—C(1)	110.9 (4)
N—C(2)—C(3)	107.0 (4)	N—C(2)—H(2)	108 (3)
C(1)—C(2)—C(3)	115.2 (4)	C(1)—C(2)—H(2)	103 (3)
C(3)—C(2)—H(2)	112 (3)	C(2)—C(3)—C(4)	112.2 (4)
C(2)—C(3)—H(3*a*)	111 (3)	C(2)—C(3)—H(3*b*)	112 (3)
C(4)—C(3)—H(3*a*)	108 (3)	C(4)—C(3)—H(3*b*)	105 (3)
H(3*a*)—C(3)—H(3*b*)	108 (4)	N—C(5)—C(5^i)	108.5 (4)
N—C(5)—H(5*a*)	106 (3)	N—C(5)—H(5*b*)	107 (3)
C(5^i)—C(5)—H(5*a*)	115 (3)	C(5^i)—C(5)—H(5*b*)	105 (3)
H(5*a*)—C(5)—H(5*b*)	115 (4)		

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

Table 3. *Hydrogen-bond distances* (Å) *and angles* (°)

Br···H—*X*	Br···H	H—*X*	Br···H—*X*	Br···*X*
Br^i···H—O	2.38 (6)	0.86 (6)	164 (5)	3.213 (4)
Br^{ii}···H(*a*)—N	2.47 (5)	0.86 (5)	167 (5)	3.308 (4)
Br^{iii}···H(*b*)—N	2.35 (5)	0.88 (5)	163 (5)	3.205 (4)

Symmetry codes: (i) $x, 1+y, 1+z$; (ii) $x, y, 1+z$; (iii) x, y, z.

l −24→24 and $2 < \theta < 22°$. The data were changed to the standard space-group setting by the transformation (0,0,1/0,−1,0/1,0,0) which retains the right-handed axis set. Equivalent reflections were averaged ($R_{av} = 0.021$) to give 1015 unique reflections, and 986 with non-negative intensities were used in the refinement, $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{1/2}/\text{Lp}$. Three standard reflections remeasured every hour showed no significant change. Corrections were applied for Lorentz and polarization effects and for absorption (max. 1.00, min. 0.87) empirically based on ψ-scan measurements. Starting values for atom coordinates were taken from the isomorphous hydrochloride structure.

Refinement was by full-matrix least squares (on F), non-H atoms anisotropic, H atoms from a difference map, H-atom U_{iso} fixed at 1.3 times the value of U_{eq} for the parent atom, but positions refined except for those on C(4) which were fixed. $\sum w(|F_o| - |F_c|)^2$ minimized, $w = \sigma^{-2}(F)$, $R = 0.037$, $wR = 0.033$ for 986 reflections, 103 variables, $S = 0.96$, $(\Delta/\sigma)_{max} = 0.4$, $(\Delta\rho)_{max,min} = 0.55, -0.69$ e Å^{-3}. Absolute structure from refinement of the η parameter (Rogers, 1981) to 1.000 (3). As a check, a refinement fixed as the opposite absolute structure gave $R = 0.042$, $wR = 0.052$, $S = 1.47$. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV). Computer programs from the Enraf–Nonius *SDP-Plus* package (B. A. Frenz & Associates Inc., 1982).

Discussion. The final atom coordinates are given in Table 1, selected bond lengths and angles in Table 2, and hydrogen-bond details in Table 3.* The cation and its numbering scheme are shown in the *PLUTO* (Motherwell & Clegg, 1978) drawing, Fig. 1, and the unit-cell packing in Fig. 2. The dimensions of the ethambutol cation are essentially the same as those in the isomorphous hydrochloride structure. The absolute configuration of (+)-ethambutol is shown

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54148 (8 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

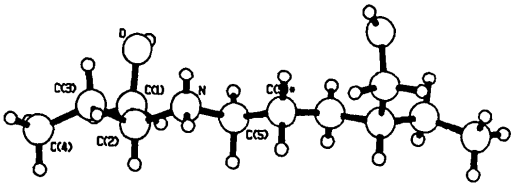

Fig. 1. The molecular structure of the (+)-ethambutol cation showing the atom numbering.

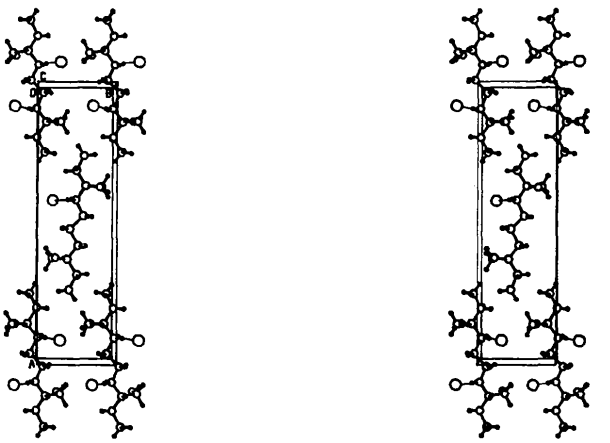

Fig. 2. A stereopair of the unit-cell contents of (+)-ethambutol hydrobromide.

to be *S,S*. This result agrees with the absolute stereochemistry of ethambutol dihydrochloride by unambiguous synthesis. (B. Blessington, personal communication).

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Structure of (+)-(*S*)-1,3-Dimethyl-6-oxiranyl-2,4-pyrimidinedione Showing Anti-ASFV Activity

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Abstract. $C_8H_{10}N_2O_3$, $M_r = 182{\cdot}18$, monoclinic, $P2_1$, $a = 6{\cdot}6405$ (7), $b = 7{\cdot}9493$ (9), $c = 8{\cdot}3662$ (9) Å, $\beta = 103{\cdot}07$ (1)°, $V = 430{\cdot}18$ (8) Å^3, $Z = 2$, $D_x = 1{\cdot}41$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 0{\cdot}879$ mm^{-1}, $F(000) = 192$, $T = 298$ K, $R = 0{\cdot}037$ for 1247 reflections with $F_o \geq 4\sigma(F_o)$. The configuration at C7 is *S*. The pyrimidine-2,4-dione ring is nearly planar [r.m.s. deviation: 0·010 (8) Å] and is antiperiplanar with respect to the epoxide ring. This arrangement is stabilized by intermolecular C—H···O interactions.

Introduction. The group of analogues of nucleic acids, the 5- and 6-substituted uracils, have recently aroused considerable interest with regard to antiviral activity (Chu & Cutler, 1986; Mijasaka, Tanaka, Baba, Hayakawa, Walker, Balzarini & De Clercq, 1989). African Swine Fever Virus (ASFV) is the agent of an important disease of wild and domestic pigs; no effective means of eradication have been found and the control of the disease is still confined to recognition, quarantine, slaughter and decontamination procedures. Here we report on the crystal and molecular structure of the title compound, which shows remarkable anti-ASFV activity (Botta, Saladino, Gambacorta & Nicoletti, 1990; Botta, Nicoletti, Saladino, La Colla, Lamba & Fabrizi, 1991).

Experimental. Transparent prismatic crystals of the title compound were grown by slow concentration of an ethyl acetate solution with the addition of few

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