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(+)-1-{(2*S*)-2-(2,4-Dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl}-1*H*-imidazole mononitrate [(+)-(*S*)-miconazole nitrate]

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.006 Å
R factor = 0.042
wR factor = 0.101
Data-to-parameter ratio = 13.9

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

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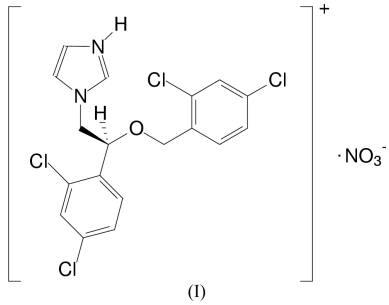
The title compound, $C_{18}H_{15}Cl_4N_2O^+\cdot NO_3^-$, (+)-miconazole nitrate, is a component of racemic miconazole nitrate, a broad spectrum antimycotic agent with antibacterial activity. It crystallizes with two protonated molecules in the asymmetric unit, both with *S* configuration, which are linked into a dimer by hydrogen bonds with the nitrate anions.

Comment

The title compound, (I), is the (+)-enantiomer of racemic miconazole nitrate, an antimycotic agent with potent, broad-spectrum activity against dermatophytes, yeast cells and gram-positive bacteria.



(I)

All antifungal azoles probably act by an identical mechanism of inhibition of the fungal cytochrome P-450 enzymes. The potency seems to be determined by the affinity of the nitrogen heterocycle for the heme iron ion and by the affinity of the non-ligand portion for the apoprotein of cytochrome P-450 (Van den Bossche *et al.*, 1988).

Liao & Li (1993) synthesized (+)- and (−)-miconazole enantioselectively. From this synthesis the absolute configuration was assigned to be (+)-(*S*)-miconazole and (−)-(*R*)-miconazole. The same paper described preliminary biological tests which showed that the levorotatory enantiomer was more active than the dextro one and the racemate against common pathogenic fungi. To check the assignment, the crystal structure and absolute configuration of (+)-miconazole has been determined.

As in the crystal structure of racemic miconazole (Peeters *et al.*, 1979), the asymmetric unit contains two independent protonated molecules. Both have the *S* configuration of the asymmetric center but differ in conformation. The main differences can be deduced from the values of the torsion angles listed in Table 1. The two independent cations are hydrogen bonded to the nitrate anions, forming a dimer (Table 2). Twofold screw-axis-related dimers are linked by C—H···O hydrogen bonds, giving rise to a two-dimensional network parallel to $(\bar{1}01)$.

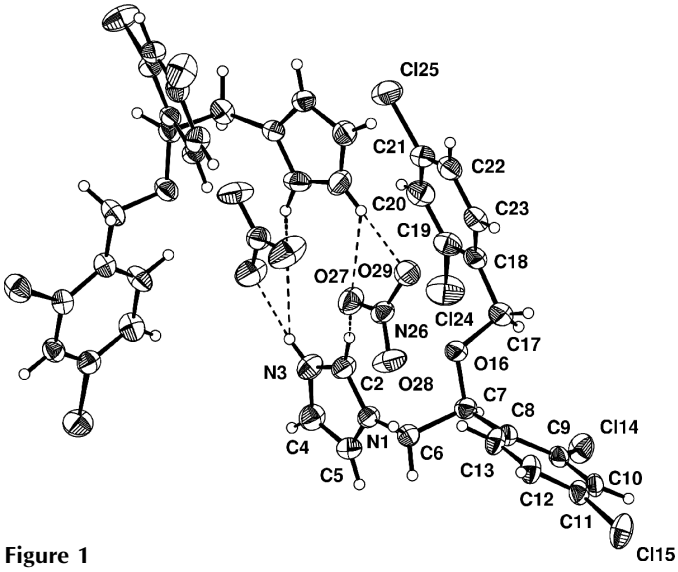


Figure 1
Perspective view of the two ion pairs in the asymmetric unit, with the atomic numbering scheme for one of them. Displacement ellipsoids are drawn at the 50% probability level.

Experimental

The title compound, (I), was synthesized as described by Godefroi & Heeres (1973). Single crystals were grown by slow evaporation of a 2-propanol/methanol solution.

Crystal data

$C_{18}H_{15}Cl_4N_2O^+\cdot NO_3^-$
M_r = 479.13
Monoclinic, $P2_1$
a = 13.23 (1) Å
b = 9.191 (7) Å
c = 18.30 (2) Å
β = 110.63 (8)°
V = 2082. (3) Å^3
Z = 4
D_x = 1.528 Mg m^{-3}
Mo Kα radiation
Cell parameters from 24 reflections
θ = 7.7–10.3°
μ = 0.60 mm^{-1}
T = 293 K
Prism, colorless
0.60 × 0.50 × 0.40 mm

Data collection

Stoe Stadi4 four-circle diffractometer
ω scans
Absorption correction: ψ scan (*EMPIR*; Stoe & Cie, 1992)
T_{min} = 0.721, T_{max} = 0.787
9914 measured reflections
7254 independent reflections
5518 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.020
θ_{max} = 25.0°
$h = -15 \rightarrow 15$
$k = -10 \rightarrow 10$
$l = -21 \rightarrow 21$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.101
S = 1.03
7254 reflections
523 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0448P)^2 + 0.4257P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}
Absolute structure: Flack (1983); 3357 Friedel pairs
Flack parameter = −0.02 (5)

Table 1
Selected torsion angles (°).

C2—N1—C6—C7	−73.6 (5)	C52—N51—C56—C57	78.1 (5)
N1—C6—C7—O16	66.5 (4)	N51—C56—C57—O66	−70.4 (4)
C6—C7—C8—C9	127.0 (4)	C56—C57—C58—C59	88.4 (5)
C6—C7—O16—C17	−167.0 (3)	C56—C57—O66—C67	−165.4 (3)
C7—O16—C17—C18	156.1 (3)	C68—C67—O66—C57	156.0 (3)
O16—C17—C18—C19	−79.3 (5)	O66—C67—C68—C69	166.5 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···O27	0.93	2.35	3.199 (6)	151
C13—H13···O28	0.93	2.39	3.287 (6)	162
C52—H52···O78	0.93	2.39	3.213 (7)	147
N3—H3···O77^{i}	0.86	1.94	2.801 (5)	174
N3—H3···O78^{i}	0.86	2.45	2.996 (6)	122
C5—H5···O28^{ii}	0.93	2.57	3.016 (6)	110
N53—H53···O27^{iii}	0.86	2.36	2.962 (5)	128
N53—H53···O29^{iii}	0.86	1.97	2.819 (5)	169
C54—H54···O79^{iv}	0.93	2.57	3.480 (7)	166
C54—H54···O77^{iv}	0.93	2.62	3.291 (6)	130
C55—H55···O79^{v}	0.93	2.54	3.088 (6)	118

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

After checking their presence in the difference map, H atoms were placed at their geometrically calculated positions (C—H = 0.93–0.98, N—H = 0.86 Å). All H atoms were allowed to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed at 1.2 U_{eq} of their parent atoms. To check the absolute configuration, data were also collected on another crystal with Cu radiation. The refinement converged to R = 0.0495 with a Flack (1983) parameter of 0.00 (2).

Data collection: *DIF*4 (Stoe & Cie, 1992); cell refinement: *DIF*4; data reduction: *REDU*4 (Stoe & Cie, 1992); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *DIAMOND* (Bergerhoff, 1996); software used to prepare material for publication: *PARST* (Nardelli, 1983).

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