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Two polymorphs of morpholin-4-ium 2-(5-methyl-1*H*-1,2,4-triazol-3-ylsulfanyl)acetate

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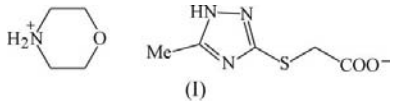
Two polymorphs of the title organic salt (a very effective medicinal preparation with the commercial name thiotriazoline), $C_4H_{10}NO^+\cdot C_5H_6N_3O_2S^-$, were obtained. The cations and anions are connected by hydrogen bonds and extend into two-dimensional networks. The main packing motifs are an $R_4^4(12)$ cluster in the monoclinic form and a chain in the orthorhombic form.

Comment

Derivatives of thiotriazole represent a class of organic compounds with a wide range of biological activity (Kim *et al.*, 1994; Gilbert *et al.*, 1995; Davydov & Shvets, 2002; Meinhardt *et al.*, 2002). The title compound, (I), is known (Mazur *et al.*, 2007) as a very effective medicinal preparation with the commercial name thiotriazoline. It shows antioxidant, membrane-stabilizing, anti-ischemic, anti-arrhythmic, immunomodulatory, antiphlogistic, hepatoprotector, cardioprotector and nephroprotector activities. It is also well known that polymorphism is very important for medical products that are produced as pills (Bernstein, 2002). In this paper, we report the results of an investigation of the molecular and crystal structures of two polymorphic modifications of the medical product thiotriazoline.



(I)

During crystallization of thiotriazoline, it was found that crystals of (I) grown from water and organic alcohols differ in shape. The X-ray diffraction study demonstrates that these represent two polymorphic modifications of thiotriazoline, namely an orthorhombic modification (OM) crystallized from aqueous solution and a monoclinic modification (MM) obtained from alcohol solution.

Analysis of the molecular structure of (I) in both modifications demonstrates that this compound is an organic salt (Figs. 1 and 2). Two H atoms on the N atom of the morpholine ring were located from electron-density difference maps, and the Csp^3—N bond lengths are very close (Tables 1 and 3) to the mean value (1.494 Å; Bürgi & Dunitz, 1994) for (Csp^3)$_2$—NH_2^+ bonds (the corresponding bond length in the unprotonated morpholine ring is 1.473 Å). Thus, it is possible to conclude that the positive charge is located on the protonated N atom of the morpholine ring. The C—O bond lengths of the carboxylate group are almost equal, and they are very close to the mean value of the bond length in the carboxylate anion (1.250 Å). This indicates the localization of the negative charge within the carboxylate group. It is noted also that the bond lengths within the cation and anion are very similar for both polymorphic modifications.

The morpholine ring adopts a chair conformation in both modifications [the puckering parameters (Zefirov *et al.*, 1990) are $S = 1.19$, $\theta = 2.8°$ and $\psi = 2.9°$ for MM, and $S = 1.20$, $\theta = 1.6°$ and $\psi = 23.5°$ for OM]. The deviations of atoms N12 and O15 from the mean-square plane of the remaining atoms of the ring are 0.644 (3) and 0.667 (2) Å, respectively, in MM, and 0.669 (1) and 0.659 (1) Å, respectively, in OM. The anion is

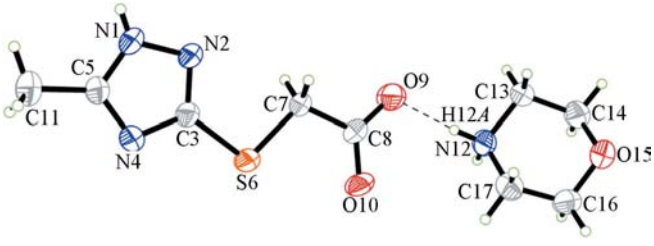


Figure 1
A view of the monoclinic polymorph of the title compound, showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level.

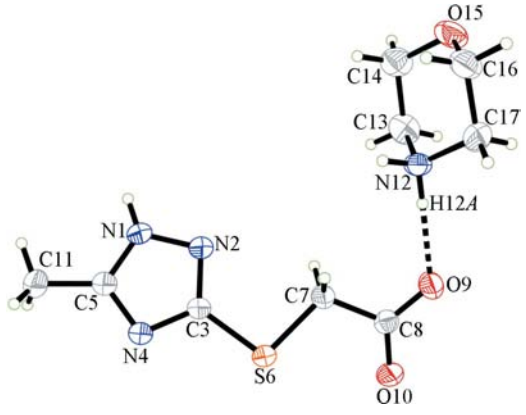


Figure 2
A view of the orthorhombic polymorph of the title compound, showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level.

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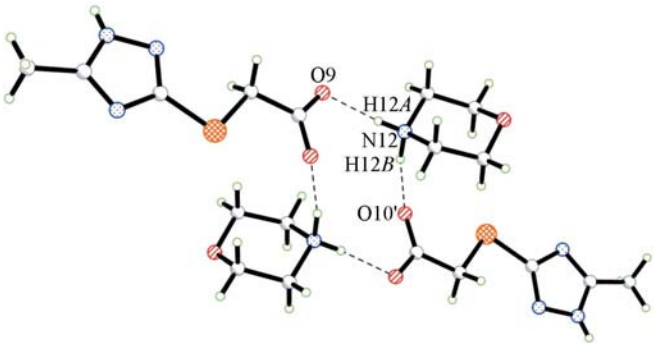

Figure 3
The $R_4^4(12)$ motif in the crystal structure of the monoclinic polymorph. Two cation–anion pairs are connected by intermolecular hydrogen bonds. [Symmetry code: (′) $-x+1, -y+1, -z$.]

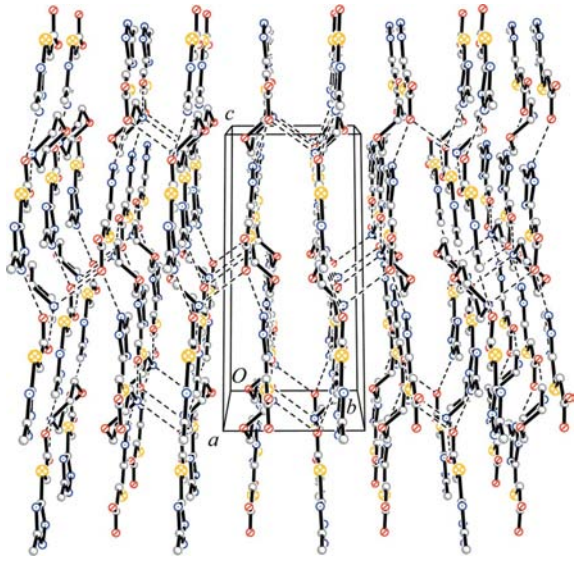

Figure 4
A view of the two-dimensional-network layer in the crystal structure of the monoclinic polymorph.

planar, in contrast to the neutral molecule of 2-(5-methyl-1*H*-1,2,4-triazol-3-ylsulfanyl)acetic acid (Zubatyuk *et al.*, 2008).

Analysis of the crystal structures of the two polymorphic modifications demonstrates the existence of hydrogen-bonded two-dimensional networks in both forms. However, the organization of these networks differs in the two polymorphs. In the crystal structure of MM, two pairs of cations and anions form an $R_4^4(12)$ cluster (Fig. 3) based on the strong N12—H12*A*···O9 and N12—H12*B*···O10($-x+1, -y+1, -z$) hydrogen bonds (Table 2). The clusters are organized in layers (Fig. 4) that are parallel to the (100) plane. The molecules within the layer are connected by weaker N1—H1N···O10($x, -y+\frac{1}{2}, z+\frac{1}{2}$) and C14—H14*A*···N4($x+1, y, z$) hydrogen bonds (Table 2). In the crystal structure of OM, the cations and anions form infinite zigzag chains (Fig. 5) along the [010] crystallographic direction owing to the formation of intermolecular N12—H12*A*···O9 and N12—H12*B*···O10($-x+\frac{1}{2}$, $y+\frac{1}{2}, z$) hydrogen bonds (Table 4). Neighbouring chains are linked by an N1—H1N···N4($x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$) hydrogen bond, forming layers parallel to (001) (Fig. 6).

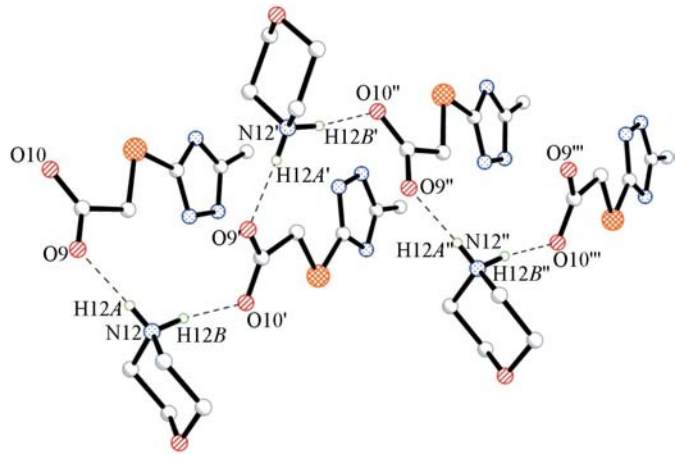

Figure 5
The infinite chains along the [010] direction in the crystal structure of the orthorhombic modification. Neighbouring cation–anion pairs are connected by intermolecular hydrogen bonds. [Symmetry codes: (′) $-x+\frac{1}{2}, y+\frac{1}{2}, z$; (″) $x, y+1, z$; (‴) $-x+\frac{1}{2}, y+\frac{3}{2}, z$.]

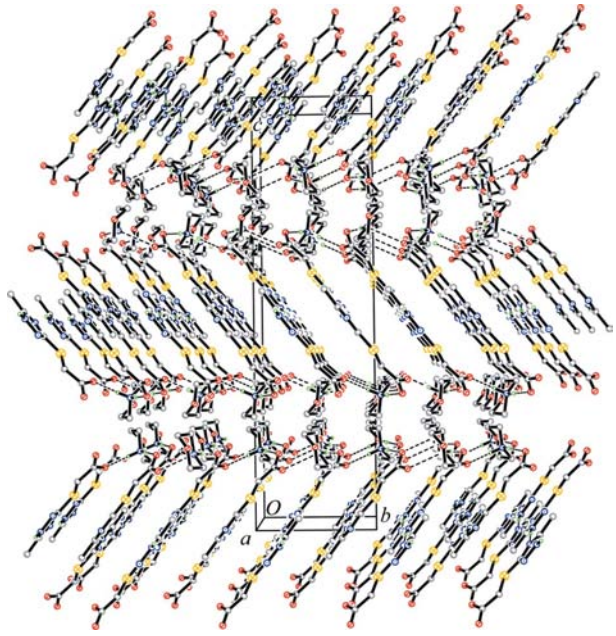

Figure 6
A view of two-dimensional-network layer parallel to (001) in the crystal structure of the orthorhombic polymorph.

Experimental

Compound (I) was prepared from a mixture of 2-(5-methyl-1*H*-1,2,4-triazol-3-ylsulfanyl)acetic acid and morpholine in an equimolar ratio. The reaction was carried out in water, ethanol or isopropanol solution. Crystals of the monoclinic polymorph were obtained from the organic alcohols, and crystals of the orthorhombic polymorph were obtained from aqueous solution.

Monoclinic polymorph

Crystal data

$C_4H_{10}NO^+\cdot C_5H_6N_3O_2S^-$
M_r = 260.32
Monoclinic, $P2_1/c$
a = 12.0500 (11) Å
b = 7.0380 (8) Å
c = 15.6547 (14) Å
β = 112.559 (11)°
V = 1226.1 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.27 mm^{-1}
T = 293 (2) K
0.20 × 0.20 × 0.20 mm

Data collection

Oxford Diffraction Xcalibur 3 diffractometer
4942 measured reflections
2086 independent reflections
1289 reflections with $I > 2\sigma(I)$
R_{int} = 0.041

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.143
S = 0.96
2086 reflections
167 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.62 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Selected bond lengths (Å) for the monoclinic polymorph.

N1—C5	1.325 (4)	S6—C7	1.802 (3)
N1—N2	1.371 (3)	C7—C8	1.515 (4)
N2—C3	1.317 (3)	C8—O9	1.232 (3)
C3—N4	1.356 (4)	C8—O10	1.251 (3)
C3—S6	1.746 (3)	N12—C17	1.481 (4)
N4—C5	1.320 (4)	N12—C13	1.493 (4)
C5—C11	1.490 (4)		

Table 2
Hydrogen-bond geometry (Å, °) for the monoclinic polymorph.

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O10^{i}	0.74 (4)	2.16 (4)	2.782 (3)	142 (4)
N12—H12A···O9	0.85 (3)	1.84 (4)	2.687 (3)	175 (3)
N12—H12B···O10^{ii}	0.98 (3)	1.90 (4)	2.864 (4)	168 (3)
C14—H14A···N4^{iii}	0.97	2.63	3.370 (4)	133

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

Orthorhombic polymorph

Crystal data

$C_4H_{10}NO^+\cdot C_5H_6N_3O_2S^-$
M_r = 260.32
Orthorhombic, $Pbca$
a = 9.6912 (2) Å
b = 8.3829 (2) Å
c = 30.1907 (8) Å
V = 2452.70 (10) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.27 mm^{-1}
T = 293 (2) K
0.40 × 0.10 × 0.10 mm

Data collection

Oxford Diffraction Xcalibur 3 diffractometer
18044 measured reflections
3481 independent reflections
2183 reflections with $I > 2\sigma(I)$
R_{int} = 0.041

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.087
S = 0.92
3481 reflections
218 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 3
Selected bond lengths (Å) for the orthorhombic polymorph.

N1—C5	1.3191 (17)	S6—C7	1.8032 (15)
N1—N2	1.3746 (16)	C7—C8	1.5155 (19)
N2—C3	1.3154 (17)	C8—O10	1.2447 (16)
C3—N4	1.3633 (16)	C8—O9	1.2531 (16)
C3—S6	1.7478 (13)	N12—C13	1.481 (2)
N4—C5	1.3328 (17)	N12—C17	1.486 (2)
C5—C11	1.486 (2)		

Table 4
Hydrogen-bond geometry (Å, °) for the orthorhombic polymorph.

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···N4^{i}	0.816 (17)	2.052 (18)	2.8566 (17)	168.4 (16)
N12—H12A···O9	0.86 (2)	1.88 (2)	2.7344 (17)	176.3 (19)
N12—H12B···O10^{ii}	0.905 (18)	1.815 (18)	2.7127 (17)	171.1 (16)

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

All H atoms in both structures were located in electron-density difference maps. The C-bound H atoms in the structure of the monoclinic modification were included in the refinement in the riding-model approximation, with U_{iso}(H) values constrained to be 1.5 times U_{eq} of the carrier atom for the methyl group and 1.2 times U_{eq} of the carrier atom for the other atoms. The N-bound H atoms were refined in isotropic approximation. In the structure of the orthorhombic modification, all H atoms were refined in isotropic approximation [C—H = 0.86 (2)–1.014 (18) Å].

For both polymorphs, data collection: *CrysAlis CCD* (Oxford Diffraction, 2007); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2007); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3272). Services for accessing these data are described at the back of the journal.

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