X-ray Structure Analysis Online

A New Polymorph of 2-Thiohydantoin

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A new polymorphic crystal of the title compound, $C_3H_4N_2OS$, belongs to space group $P\bar{1}$ with cell dimensions of a = 4.0520(9)Å, b = 6.550(1)Å, c = 9.170(2)Å, α = 100.148(4)°, β = 100.814(4)°, γ = 96.831(4)°, $R1$ = 0.069. Neighboring molecules are connected to form cyclic dimers *via* two types of hydrogen bonds, one between the thioamide groups and the other between the amide moieties, showing a distinctive difference from the hydrogen-bonding pattern of the known form.

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2-Thiohydantoin derivatives provide useful synthetic intermediates with a wide range of applications, such as therapeutics, fungicides and herbicides.[1] Polymorphism in crystal structures is a relatively common phenomenon in pharmaceutical solids. Furthermore, 2-thiohydantoins furnish an interesting feature in structural chemistry. This compound carries a thioamide and an amide group in a molecule, which provide equal numbers of the proton donor (D) and the acceptor (A) in a D-A-D-A sequence. Because of this unique structural feature, 2-thiohydantoins are expected to form intricate hydrogen bonding networks in crystals. We have been studying the crystal structures and conformations of 5-substituted-2-thiohydantoins and their derivatives.[2] During the course of a crystallization experiment, we obtained a crystal modification of 2-thiohydantoin (TH) that is different from the previously reported form.[3,4] In this paper, we report on the crystal structure of a new polymorph of TH (I, see Figs. 1 and 2). Since polymorphic crystals have different physicochemical properties, such as melting point or solubility, changes in the polymorphic forms can influence the bioavailability as well as chemical and physical stability of the drug. Thus, it is very important to control the crystal form of pharmaceuticals.

Compound I was prepared by the reaction of glycine with acetic anhydride and ammonium thiocyanate and subsequent acid hydrolysis.[5] The crude product was washed with cold water several times and purified by repeated crystallization from ethanol.

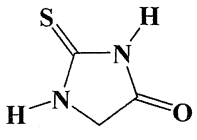

Fig. 1 Structural formula of the title compound (I).

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Single crystals of the new polymorph suitable for X-ray diffraction were grown by quickly lowering the temperature of an ethanol solution from 25°C to 4°C. Table 1 gives the crystal and experimental data. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares methods, and all hydrogen atoms were not refined. Selected bond distances, bond angles and torsion angles are listed in Table 2.

The new polymorph crystallized in the triclinic form with two molecules in a unit cell. The thiohydantoin ring is essentially planar. The molecular geometries are comparable to those reported for the known form of 2-thiohydantoin[3,4] and 5-

Table 1 Crystal and experimental data

Chemical formula: $C_3H_4N_2OS$	
Formula weight: 116.14	
Crystal system: triclinic	
Space group: $P\bar{1}$	Z = 2
a = 4.0520(9)Å	α = 100.148(4)°
b = 6.550(1)Å	β = 100.814(4)°
c = 9.170(2)Å	γ = 96.831(4)°
V = 232.41(9)Å3	
D_{calc} = 1.659 g/cm^3	
Radiation: Mo K_α (λ = 0.71070 Å)	
μ(Mo K_α) = 5.51 cm^{-1}	
F(0 0 0) = 120.00	
T = 123 K	
No. observations = 1092 ($I > 2.00\sigma(I)$)	
θ range for data collection: 3.6 to 30.1°	
No. variables = 64	
$R1$ = 0.069	
Goodness-of-fit = 1.54	
$(\Delta/\sigma)_{max}$ = 0.001	
$(\Delta\rho)_{max}$ = 1.66 e/Å^3	
$(\Delta\rho)_{min}$ = –0.55 e/Å^3	
Measurement: Rigaku/MSC Mercury CCD	
Program system: teXsan	
Structure determination: direct method (SHELXS-86)	
Refinement: full-matrix least-squares	
CCDC deposition number: 737476	

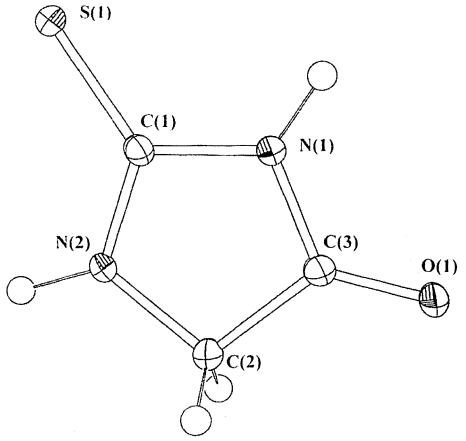

Fig. 2 Molecular structure of the title compound (I) with the labeling atoms. Thermal ellipsoids of non-H atoms are drawn at the 50% probability level. H atoms are indicated by small circles.

Table 2 Selected bond lengths (Å), bond angles (˚) and torsion angles (˚)

Atom	Atom	Atom	Atom	
S(1)	C(1)			1.664(3)
O(1)	C(3)			1.218(4)
N(1)	C(1)			1.389(4)
N(1)	C(3)			1.368(4)
N(2)	C(1)			1.332(4)
N(2)	C(2)			1.458(4)
C(2)	C(3)			1.515(4)
C(1)	N(1)	C(3)		112.3(3)
C(1)	N(2)	C(2)		112.7(3)
S(1)	C(1)	N(1)		124.3(2)
S(1)	C(1)	N(2)		128.5(3)
N(1)	C(1)	N(2)		107.2(3)
N(2)	C(2)	C(3)		101.5(2)
O(1)	C(3)	N(1)		126.0(3)
O(1)	C(3)	C(2)		127.9(3)
N(1)	C(3)	C(2)		106.1(3)
S(1)	C(1)	N(1)	C(3)	177.1(2)
S(1)	C(1)	N(2)	C(2)	-179.1(2)
O(1)	C(3)	N(1)	C(1)	-175.1(3)
O(1)	C(3)	C(2)	N(2)	176.1(3)
N(1)	C(1)	N(2)	C(2)	1.3(3)
N(1)	C(3)	C(2)	N(2)	-2.7(3)
N(2)	C(1)	N(1)	C(3)	-3.3(4)
C(1)	N(1)	C(3)	C(2)	3.7(3)
C(1)	N(2)	C(2)	C(3)	0.8(3)

substituted-2-thiohydantoin.[2] Thus, the C(1)-S(1), C(1)-N(2), C(3)-O(1) and C(3)-N(1) [1.664(3), 1.332(4), 1.218(4) and 1.368(4)Å] bond distances are in the range observed for the normal *cis*-amide moiety.[6] As shown in Fig. 3(a), in crystals of the new polymorph of TH, the amide and thioamide groups of one molecule form centrosymmetric cyclic dimers with the amide and thioamide groups, respectively, of the adjacent

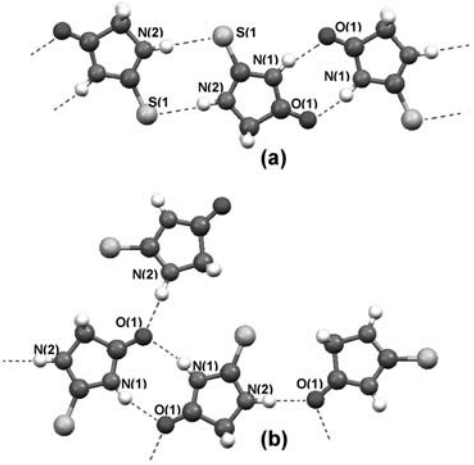

Fig. 3 Perspective views of intermolecular hydrogen bonds in (a) the new polymorph and (b) the known form.

molecules through intermolecular N–H···O and N–H···S hydrogen bonds [N(1)···O(1)$^{(i)}$ 2.828(4)Å, N(1)–H···O(1)$^{(i)}$ 164.98˚, N(2)···S(1)$^{(ii)}$ 3.351(3)Å, N(2)–H···S(1)$^{(ii)}$ 177.01˚, symmetry codes: (i) –*x*+2, –*y*+1, –*z*+2, (ii) –*x*, –*y*+1, –*z*+1]. These hydrogen bonds form an infinite sheet. On the other hand, the amide groups are linked through C=O···H–N hydrogen bonds to form cyclic dimers, and the amide C=O group is also hydrogen bonded to the thioamide N–H of a neighboring molecule in the known form (Fig. 3(b)).

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