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Synthesis and crystal structure of (*S*)-5-isopropyl-5-methyl-2-thiohydantoin

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ABSTRACT

(*S*)-5-Isopropyl-5-methyl-2-thiohydantoin was synthesized by one-pot reaction of α-methyl-*L*-valine and thiourea in the absence of solvent. The crystal structure of this compound has been determined from single crystal X-ray diffraction data. This is the first report on the crystal structure of a homochiral 5-substituted 2-thiohydantoin with the unsubstituted NH groups. This compound, $C_7H_{12}N_2OS$ crystallizes in the chiral orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell. The unit cell parameters are: a = 8.2798(12) Å, b = 8.6024(13) Å, c = 12.826(2) Å and V = 913.6(2) Å^3. In the crystals, the thioamide and amide N-H of one molecule are hydrogen-bonded to the thioamide C=S group of neighboring molecules to form rings with the $R^2_2(8)$ graph-set motif, and these rings are linked into infinite one-dimensional tapes.

1. Introduction

Hydantoins (imidazolidine-2,4-diones) are a class of 5-membered heterocycles containing two nitrogens in an ureide configuration. Due to their diverse biological and pharmacological properties, hydantoins have been used in a wide variety of therapeutic applications [1]. In particular, hydantoins substituted at the 5-position have been widely used as antiarrhythmic [2], anticonvulsant [3] and antitumoral agents [4]. Closely related analogues of hydantoins are thiohydantoins, which may have one or both of the carbonyl groups replaced by the thiocarbonyl groups. Among the known thiohydantoins, 5-substituted 2-thiohydantoins (2-thioxoimidazolidin-4-ones) are the most notable for a large number of medicinal and industrial applications [5].

This class of compounds commonly contain a thioamide and an amide group in a molecule, which provides equal number of hydrogen-bond proton donor (D) and acceptor (A) in the D-A-D-A sequence. This unique structural feature leads to the compounds with unique physicochemical and biological properties [6-7]. We have studied the crystal structures of a series of 5-substituted 2-thiohydantoins in order to get insights into the factors controlling the molecular packing in the crystal [8-13]. Crystal structure data of 5-substituted 2-thiohydantoins reported in Cambridge Structural Database (Ver. 5.34) have been mainly limited to racemic compounds. Crystal structure data of the homochiral compounds are of great importance since their physicochemical and biological properties are expected to differ from those of racemic compounds.

In this paper, we report on the synthesis and analysis of the X-ray crystal structure of (*S*)-5-isopropyl-5-methyl-2-thiohydantoin ((*S*)-IPrMTH). This is the first report on the crystal structure of a homochiral 5-substituted 2-thiohydantoin with the unsubstituted NH groups. The crystal structural features of (*S*)-IPrMTH are also discussed in comparison with those of racemic 5-isopropyl-5-methyl-2-thiohydantoin ((*rac*)-IPrMTH) previously reported [13].

2. Experimental

2.1. Instrumentation

The melting point was measured using a Shimadzu DSC-60 differential scanning calorimeter (DSC) equipment. The infrared (IR) spectra was recorded on a Horiba FT-720 Fourier transform infrared spectrometer. IR measurements were carried out by the KBr method at 64 scans per spectrum with 4 cm^{-1} resolution. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded on a JEOL JNM-ECA 500 spectrometer. The X-ray diffraction data was collected at 123(2) K by ω scan technique on a Rigaku/MSC Mercury CCD diffractometer [14] equipped with graphite-monochromatized Mo$K\alpha$ radiation (λ = 0.71070 Å). The data were corrected for Lorentz-polarization and absorption effects [15]. These structures were solved by direct methods using *SIR2008* program [16] and refined by a full-matrix least-squares calculation on F^2 using *SHELXL-97* [17]. All calculations were performed using *CrystalStructure* software package [18]. The absolute structure of (*S*)-IPrMTH has been assigned by reference to an unchanging chiral centre in the synthetic procedure [5] and confirmed by Flack parameter [19]. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms bonded to nitrogen atoms were located in a difference map and refined freely. The remaining hydrogen atoms were positioned geometrically (C–H = 0.98 or 1.00 Å) and refined using a riding model, with U_{iso}(H) = 1.2 U_{eq}(C). Structures were visualized using *ORTEP-3 for windows* [20] and *Mercury* [21]. Details on data collection and refinement are given in Table 1.

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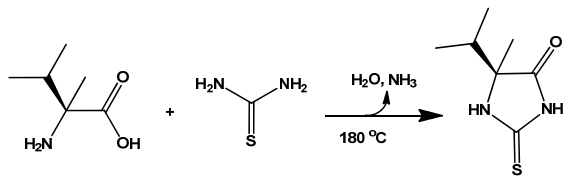
Table 1. Crystal data and structure refinement for (*S*)-IPrMTH.

Empirical formula	$C_7H_{12}N_2OS$
Formula weight	172.26
Temperature	123(2) K
Wavelength	0.71070 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.2798(12) Å
	b = 8.6024(13) Å
	c = 12.826(2) Å
Volume	913.6(2) Å^3
Z	4
Density (calcd.)	1.252 g/cm^3
Absorption coefficient	0.303 mm^{-1}
F(000)	368
Crystal size/color	0.45 × 0.30 × 0.25 mm^3/colorless
Theta range for data collection	3.18 to 27.49 °
Index ranges	$-10 \le h \le 10$
	$-11 \le k \le 11$
	$-16 \le l \le 13$
Reflections collected	9366
Independent reflections	2050 [$R_{(int)}$ = 0.0222]
Completeness to theta = 27.49 °	97.6 %
Absorption correction	Multi-scan [15]
Max. and min. transmission	0.9281 and 0.8758
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2050/0/111
Goodness-of-fit on F^2	1.079
Final R indices [I > 2sigma(I)]	R_1 = 0.0223, wR_2 = 0.0593
R indices (all data)	R_1 = 0.0231, wR_2 = 0.0597
Absolute structure parameter	Flack parameter [19] = 0.01(6), using 849 Friedel pairs
Largest diff. peak and hole	0.255 and −0.180 e Å^{-3}
Measurement	Rigaku/MSC Mercury CCD diffractometer
Program system	*Crystal Structure* [18]
Structure determination	Direct methods (*SIR2008* [16])
CCDC no	948390

2.2. Synthesis

(*S*)-5-Isopropyl-5-methyl-2-thiohydantoin was synthesized by slight modification of a literature method [5]. A 1:3 mixture of α-methyl-*L*-valine (0.20 g, 1.53 mmol, Bachem AG, Bubendorf, Switzerland) and thiourea (0.35 g, 4.57 mmol) were allowed to react directly in the absence of solvent at 180 °C for 5 h. This reaction was carried out in a 30 mL round-bottom flask under stirring using an oil bath as the heat source. After the reaction was complete, water was added while the flask was still warm. The solution was reheated to dissolve all the solids and allowed to cool to room temperature, then placed in a refrigerator for 3 h. The colorless crystals removed by vacuum filtration were further purified by flash column chromatography using hexane and ethyl acetate as eluents. Single crystals suitable for X-ray diffraction were obtained by recrystallization from aqueous solution (Scheme 1).

(S)-5-Isopropyl-5-methyl-2-thiohydantoin ((S)-IPrMTH): Colorless. Yield: 50%. M.p.: 140 °C. FT-IR (KBr, cm^{-1}): 3218 ν(NH), 3138 ν(NH), 1768 ν(C=O), 1532 ν(CN)+δ(NH). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.95 (d, J = 6.9 Hz, 3H, $(CH_3)_2$-CH), 1.04 (d, J = 6.9 Hz, 3H, $(CH_3)_2$-CH), 1.46 (s, 3H, CH_3-C), 2.07 (sep, J = 6.9 Hz, 1H, $(CH_3)_2$-CH), 8.09 (br s, 1H, N*H*-CS-NH-CO), 9.09 (br s, 1H, NH-CS-N*H*-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 181.18 (1C, *C*S), 177.69 (1C, *C*O), 70.15 (1C, CH_3-*C*), 34.86 (1C, $(CH_3)_2$-*C*H), 20.96 (1C, *C*H_3-C), 16.87 (1C, $(CH_3)_2$-CH), 16.43 (1C, $(CH_3)_2$-CH).



Scheme 1

3. Results and discussion

(*S*)-IPrMTH crystallizes in the chiral orthorhombic space group $P2_12_12_1$, which implies that (*S*)-IPrMTH was obtained in an optical pure form without racemization in the present reaction condition. (*S*)-IPrMTH molecule has two different types of NH bonds in the thioureide group. Thus, the IR spectroscopy supplies two NH stretching vibration bands at 3218 and 3138 cm^{-1}, in addition to the C=O stretching vibration band at 1768 cm^{-1}.

In ^{1}H NMR, the characteristic broad singlet appeared at 8.09 and 9.09 ppm for the thioamide proton and the amide proton of the thioureide group, respectively. The singlet proton signal due to the methyl group appeared at 1.46 ppm. Furthermore, the characteristic signals appeared at 0.95-1.04 and 2.07 ppm for the methyl and methine protons of the isopropyl group, respectively. The ^{13}C NMR spectra showed peaks at 181.18 and 177.69 ppm for the C=S and C=O of the thioureide group, respectively.

Figure 1 shows the molecular structure of (*S*)-IPrMTH with the atom-labeling scheme. Table 2 summarizes the selected geometric parameters. Figure 2 and Table 3 show the crystal packing and hydrogen-bond geometry. The 2-thiohydantoin moiety (N1/C1/S1/N2/C2/O1/C3) is nearly planar, with a maximum deviation of 0.0292 (12) Å for atom N2. The orientation of the isopropyl group, defined by the atoms C5, C6 and C7, relative to this plane is given by the torsion angles N1–C3–C5–C6 and N1–C3–C5–C7 of 58.90(13) and –65.96(12)°, respectively. The N1–C1 distance [1.3258 (15) Å] is shorter than the N2–C1 distance [1.3759 (15) Å], and the S1–C1–N1 angle [127.65 (9)°] is greater than the S1–C1–N2 angle [124.33 (9)°]. These molecular structural features are nearly identical to those observed in (*rac*)-IPrMTH previously reported [13].

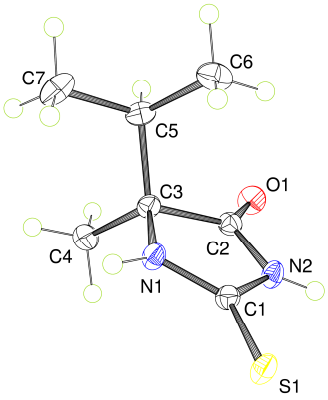


Figure 1. The molecular structure of (*S*)-IPrMTH with the atom-labeling scheme. Anisotropic displacement ellipsoids are drawn at the 50% probability level.

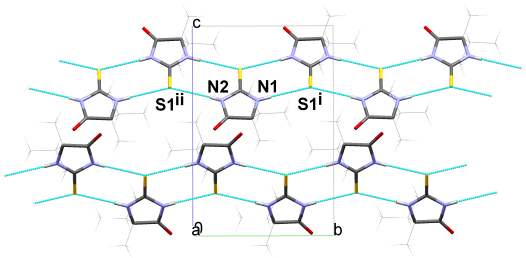


Figure 2. The crystal packing of (*S*)-IPrMTH viewed down the *a* axis, with hydrogen-bonds as dashed cyan lines (see Table 3 for details).

On the other hand, the hydrogen-bonding pattern of (*S*)-IPrMTH is quite different from that of (*rac*)-IPrMTH. In (*S*)-IPrMTH crystals (Figure 2, Table 3), the thioamide N1−H and amide N2−H of one molecule are hydrogen-bonded to the thioamide S1=C1 group of neighboring molecules to form rings with the $R^2_2(8)$ graph-set motif [22] [N1···S1^{i} 3.4036(12) Å, N1−H···S1^{i} 176.7(15) °; N2···S1^{ii} 3.3652(12) Å, N2−H···S1^{ii} 177.7(15) °; symmetry codes: (*i*) −*x*, *y*+1/2, −*z*+3/2; (*ii*) −*x*, *y*−1/2, −*z*+3/2]. The amide O1=C2 groups aren't hydrogen-bonded. These $R^2_2(8)$ rings are linked into infinite one-dimensional tapes around a two-fold screw axis along the *b* axis. In (*rac*)-IPrMTH crystals (Figure 3), the enantiomeric (*S*)- and (*R*)-molecules are connected *via* intermoleculer N−H···S hydrogen-bonds of the neighboring thioamide moieties to form centrosymmetric $R^2_2(8)$ rings. Furthermore, the other centrosymmetric $R^2_2(8)$ rings are formed *via* intermolecular N−H···O hydrogen-bonds of the neighboring amide moieties. These two different rings are linked alternately into infinite one-dimensional tapes.

Table 2. Selected geometric parameters (Å, °) for (*S*)-IPrMTH.

Bond lengths			
S1−C1	1.6732(10)	N2−C1	1.3759(15)
O1−C2	1.2088(14)	N2−C2	1.3783(16)
N1−C1	1.3258(15)	C2−C3	1.5274(14)
N1−C3	1.4722(14)		
Bond angles			
C1−N1−C3	113.22(9)	O1−C2−N2	126.37(11)
C1−N2−C2	111.91(10)	O1−C2−C3	126.96(11)
S1−C1−N1	127.65(9)	N2−C2−C3	106.67(10)
S1−C1−N2	124.33(9)	N1−C3−C2	100.16(9)
N1−C1−N2	108.02(9)		
Torsion angles			
N1−C3−C5−C6	58.90(13)	C2−C3−C5−C7	−176.34(9)
N1−C3−C5−C7	−65.96(12)	C4−C3−C5−C6	−173.51(10)
C2−C3−C5−C6	−51.48(13)	C4−C3−C5−C7	61.63(13)

Table 3. Hydrogen-bond geometry (Å, °) for (*S*)-IPrMTH (D-donor; A-acceptor; H-hydrogen) *.

D−H···A	D−H	H···A	D···A	D−H···A
N1H···S1^{i}	0.837(17)	2.566(17)	3.4036(12)	176.7(15)
N2H···S1^{ii}	0.767(17)	2.598(17)	3.3652(12)	177.7(15)

* Symmetry codes: (*i*) −*x*, *y* + 1/2, −*z* + 3/2; (*ii*) −*x*, *y* − 1/2, −*z* + 3/2

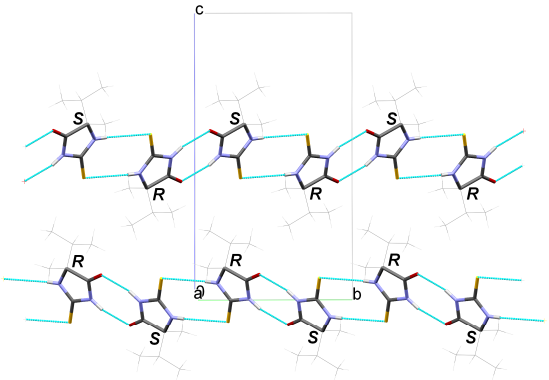


Figure 3. The crystal packing of (*rac*)-IPrMTH previously reported viewed down the *a* axis, with hydrogen-bonds as dashed cyan lines.

4. Conclusion

(*S*)-5-Isopropyl-5-methyl-2-thiohydantoin ((*S*)-IPrMTH) was synthesized by one-pot reaction of α-methyl-*L*-valine and thiourea in the absence of solvent. (*S*)-IPrMTH crystallizes in the chiral orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell. The molecular structural features in (*S*)-IPrMTH crystals are nearly identical to those in the crystals of racemic 5-isopropyl-5-methyl-2-thiohydantoin previously reported. On the other hand, the hydrogen-bonding pattern is quite different to each other. In (*S*)-IPrMTH crystals, the thioamide and amide N−H of one molecule are hydrogen-bonded to the thioamide C=S group of neighboring molecules to form rings with the $R^2_2(8)$ graph-set motif, and these rings are linked into infinite one-dimensional tapes.

Supplementary material

CCDC-948390 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

References

[1]. Mutschler, E.; Derendorf, H. Drug Actions, Basic Principles and Therapeutic Aspects, Medpharm Scientific Publishers, Stuttgart, 1995.
[2]. Knabe, J.; Baldauf, J.; Ahlhem, A. *Pharmazie* **1997**, *52*, 912-919.
[3]. Singh, G.; Driever, P. H.; Sander, J. W. *Brain* **2005**, *128*, 7-17.
[4]. Carmi, C.; Cavazzoni, A.; Zuliani, V.; Lodola, A.; Bordi, F.; Plazzi, P. V.; Alfieri, R. R.; Petronini, P. G.; Mor, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4021-4025.
[5]. Wang, Z. D.; Sheikh, S. O.; Zhang, Y. *Molecules* **2006**, *11*, 739-750.
[6]. Jha, S.; Silversides, J. D.; Boyle, R. W.; Archibald, S. J. *CrystEngComm* **2010**, *12*, 1730-1739.
[7]. Cruz-Cabeza, A. J.; Schwalbe, C. H. *New J. Chem.* **2012**, *36*, 1347-1354.
[8]. Ogawa, T.; Kitoh, S.; Ichitani, M.; Kuwae, A.; Hanai, K.; Kunimoto, K. K. *Anal. Sci. X-ray Struct. Anal. Online* **2007**, *23*, x199-x200.
[9]. Ogawa, T.; Kitoh, S.; Okagawa, M.; Ichitani, M.; Kuwae, A.; Hanai, K.; Kunimoto, K. K. *Anal. Sci. X-ray Struct. Anal. Online* **2007**, *23*, x201-x202.
[10]. Kunimoto, K.-K.; Ichitani, M.; Ogawa, T.; Kitoh, S.; Kuwae, A.; Hanai, K. *Spectrosc. Lett.* **2009**, *42*, 73-80.
[11]. Ogawa, T.; Okumura, H.; Honda, M.; Suda, M.; Fujinami, S.; Kuwae, A.; Hanai, K.; Kunimoto, K. K. *Anal. Sci. X-ray Struct. Anal. Online* **2009**, *25*, 91-92.
[12]. Taniguchi, K.; Okumura, H.; Honda, M.; Suda, M.; Fujinami, S.; Kuwae, A.; Hanai, K.; Maeda, S.; Kunimoto, K. K. *Anal. Sci. X-ray Struct. Anal. Online* **2009**, *25*, 93-94.
[13]. Ichitani, M.; Kitoh, S.; Fujinami, S.; Honda, M.; Suda, M.; Kunimoto, K. K. *Acta Cryst. E* **2013**, *69*, o953-o953.
[14]. Rigaku *CrystalClear*, Rigaku Corporation, Tokyo, Japan, 2006.
[15]. Rigaku *REQAB*, Rigaku Corporation, Tokyo, Japan, 1998.
[16]. Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Caro, L.; Giacovazzo, C.; Polidori, G.; Siliqi, D.; Spagna, R. *J. Appl. Cryst.* **2007**, *40*, 609-613.
[17]. Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112-122.
[18]. Rigaku *CrystalStructure*, Rigaku Corporation, Tokyo, Japan, 2010.
[19]. Flack, H. D. *Acta Crystallogr. A* **1983**, *39*, 876-881.
[20]. Farrugia, L. J. *J. Appl. Cryst.* **2012**, *45*, 849-854.
[21]. Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Cryst.* **2006**, *39*, 453-457.
[22]. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120-126.