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Crystal Structure of 2-Thiohydantoin-L-Isoleucine Synthesized under Solvent-Free Conditions

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The title compound with systematic name: (S)-5-secbutyl-2-thiohydantoin, is synthesized through a solvent-free reaction, crystallizes in the non-centrosymmetric space group $P2_12_12_1$. In the crystal structure, the molecules are joined by N—H···O and N—H···S hydrogen bonds, forming chains $C^2_2(10)$ and macrocycles $R^5_6(26)$ in an infinite bi-dimensional network.

Keywords Crystal structure; hydrogen bonds; thiohydantoin

1. Introduction

2-thioxoimidazolidin-4-ones, or thiohydantoins, are sulfur analogs of imidazolidine-2,4-diones, or hydantoins, and constituted by two five-member heterocyclic system with a very reactive nucleus, which provides four possible points of diversity [1, 2]. The biological activities of hydantoin and 2-thiohydantoin derivatives has been known for a long time, and are responsible for a wide variety of biological behavior, due principally to its wide range of therapeutic properties [3]. Depending on the nature and type of substitution on the heterocyclic ring, these compounds may display pharmaceutical and biological activity with a variety of applications: anti-epileptic activity, anti-tumoral, and anti-inflammatory [4], fungicidal [5], antiviral [6], herbicide [7], HIV protease inhibitor [8], hypolipidimic agent [9], and anti-hypertensive agent [10]. Recently, there has been interest in the search of new synthetic routes for the preparation of these types of compounds, via solution or solid state reactions [11–13]. We are interested in thiohydantoin derivatives of α-amino acids [14–18], and report here the structure of the 2-thiohydantoin derivative of L-isoleucine, synthesized from a solvent-free reaction.

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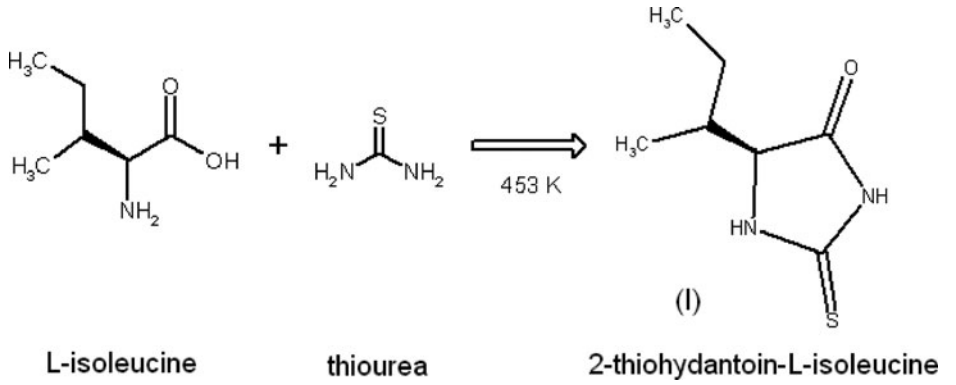

Scheme 1. Solvent-free synthesis of 2-thiohydantoin-L-isoleucine.

2. Experimental

2.1 Solvent-Free Synthesis

The title compound was synthesized using a solvent-free modified methodology previously reported, which involves the direct condensation between α-amino acids and thiourea [13]. L-isoleucine and thiourea were mixed in an agate mortar in 1:3 molar ratio. The solid mixture was placed in a reflux system and heated in an oil bath to 453 K, where thiourea melt and amino acid was dissolved in it. Reaction was maintained for 30 min and then let cool to room temperature. The resulting white solid was washed with cool water and filtered. Crystal of (I) suitable for X-ray diffraction analysis were obtained by slow evaporation of ethanol solution (Scheme 1).

Table 1. Crystal data, data collection and structure refinement

Chemical formula	$C_7H_{12}N_2OS$	CCDC	933210
Formula weight	172.26	Radiation (MoKα)	$\lambda = 0.71073$ Å
Crystal system	Orthorhombic	θ range (°)	1.5–28.1
Space group	$P2_12_12_1$	hkl range	−10, 13; −13, 14; −31, 31
a(Å)	11.279(3)	Reflections	
b(Å)	12.203(4)	Unique	7150
c(Å)	26.915(7)	Rint	0.112
V(Å^3)	3704.5(2)	With I > 2σ(I)	4102
Z	4	Refinement method	Full-matrix least-squares on F^2
dx (g cm^{-3})	1.235	Number of parameters	405
F(000)	1472	R(F^2) [I > 2σ(I)]	0.1196
μ(mm-1)	0.299	wR(F^2) [I > 2σ(I)]	0.2775
Crystal size (mm)	0.40 × 0.30 × 0.05	Goodness of fit on F^2	1.17
		Max/min $\Delta\rho$ (e Å^{-3})	0.30/−0.37

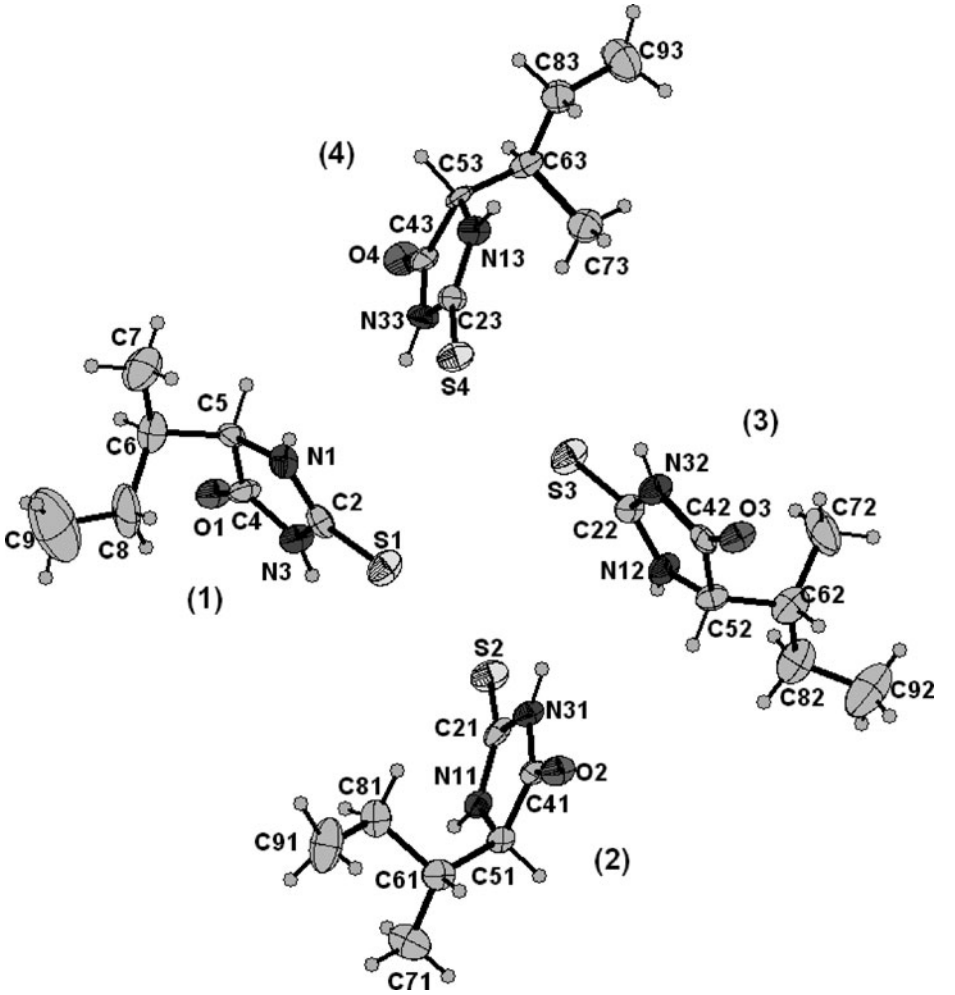

Figure 1. The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at 25% probability level. H atoms are shown as spheres of arbitrary radii.

2.2 Spectral Studies

The synthesized compound was characterized by spectroscopic data. The Fourier transform infrared spectroscopy (FT-IR) absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 model spectrometer in DMSO-d_6 solution.

FT-IR: 1174 cm^{-1} (t, C—N), 1739 cm^{-1} (t, C=O), 3152 cm^{-1} (t, N-H)].

^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.60 (s, 1H, N3H3), 10.02 (s, 1H, N1H1), 4.20 (d, 1H, C5H5), 1,78 (m, 1H, C6H6), 1.16 (m, 2H, C8H8), 0.88 (t, 3H, C7H7), 0.73 (d, 3H, C9H9).

^{13}C-NMR (100 MHz, DMSO-d_6): δ 182.71 (C2), 175.97 (C4), 64.33 (C5), 36.04 (C6), 23.50 (C8), 14.87 (C7), 13.24 (C9).

Table 2. Selected geometrical parameters (Å, °)

Molecule 12		Molecule 21	
S1-C2	1.658(8)	S2-C21	1.646(8)
O1-C4	1.224(9)	O2-C41	1.242(8)
N1-C2	1.333(13)	N11-C21	1.357(12)
N3-C2	1.386(9)	N31-C21	1.378(9)
S1-C2-N1	127.8(6)	S2-C21-N11	128.4(6)
S1-C2-N3	125.2(7)	S2-C21-N31	125.4(7)
C5-N1-C2-S1	179.2(7)	C41-N31-C21-S2	−174.8(6)
C4-N3-C2-S1	−179.5(7)	C52-N12-C22-S3	−179.7(7)
C4-C5-C6-C7	−175.4(8)	C41-C51-C61-C71	−178.0(7)
C4-C5-C6-C8	57.1(10)	C41-C51-C61-C81	54.5(9)
Molecule 33		Molecule 44	
S3-C22	1.659(8)	S4-C23	1.653(8)
O3-C42	1.242(10)	O4-C43	1.223(11)
N12-C22	1.302(12)	N13-C23	1.290(12)
N32-C22	1.418(9)	N33-C23	1.398(10)
S3-C22-N12	130.8(6)	S4-C23-N13	128.7(6)
S3-C22-N32	122.0(6)	S4-C23-N33	123.8(7)
C52-N12-C22-S3	−179.7(7)	C53-N13-C23-S4	−178.0(6)
C42-N32-C22-S3	−179.8(6)	C43-N33-C23-S4	177.6(6)
C42-C52-C62-C72	−51.6(11)	C43-C53-C63-C73	−59.1(9)
C42-C52-C62-C82	−175.5(8)	C43-C53-C63-C83	175.5(7)

2.3 X-Ray Data Collection and Structure Determination

Colorless rectangular crystal (0.40 × 0.30 × 0.05 mm) was used for data collection. Diffraction data were collected at 298(2) K by ω-scan technique on a Rigaku AFC7S Mercury diffractometer [19] equipped with graphite monochromatized MoKα radiation ($\lambda = 0.71073$ Å). The data were corrected for Lorentz-polarization and absorption effects

Table 3. Hydrogen bonds geometry (Å, °). (D-donor; A-acceptor; H-hydrogen)

D−H···A	D−H	H···A	D···A	D−H···A
N−H1···O4$^{(i)}$	0.860	2.080	2.921(9)	165.0
N13−H13···O1$^{(i)}$	0.860	2.100	2.948(8)	167.0
N1−H11···O3$^{(ii)}$	0.860	2.150	2.962(8)	159.0
N12−H12···O2$^{(ii)}$	0.860	2.040	2.874(9)	164.0
N3−H31···O1$^{(iii)}$	0.860	2.020	2.860(9)	165.0
N33−H33···O3$^{(iv)}$	0.860	2.030	2.860(9)	163.0
N32−H32···S4$^{(i)}$	0.860	2.550	3.371(8)	159.0
N3−H3···S2$^{(ii)}$	0.860	2.610	3.449(8)	164.0

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

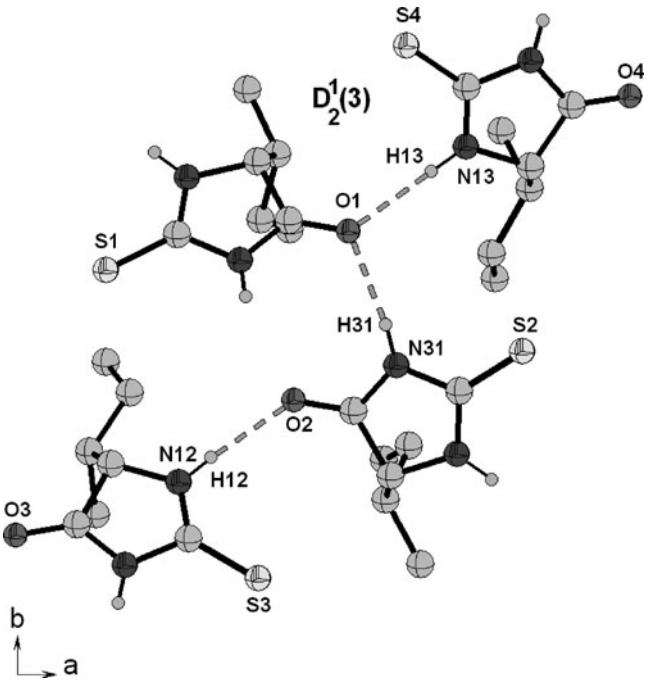

Figure 2. A partial view of the crystal packing in the *ba* plane, shown the four molecules in the asymmetric unit. H atoms not involved in hydrogen bonding have been omitted for clarity.

[19]. Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure was solved by direct methods using the SHELXS program [20] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [20].

All H atoms were placed at calculated positions and treated using the riding model, with C-H distances of 0.97–0.98 A, and N-H distances of 0.86 A. The Uiso (H) parameters were fixed at 1.2Ueq (C, N) and 1.5Ueq (methyls). All geometrical calculations were done using the program Platon [21]. Table 1 summarizes the crystal data, intensity data collection, and refinement details for the title compound.

3. Results and Discussion

The title compound (I) crystallizes as a diasteromeric mixture in the non-centrosymmetric space group $P2_12_12_1$ with four molecules in the asymmetric unit, two of these molecules have an "*RS*" configuration, while the other two present an "*SS*" configuration. Figure 1 shows the molecular structure and the atom-labeling scheme of 2-thiohydantoin-L-isoleucine. Selected geometrical parameters are presented in Table 2. All bond distances and angles are normal [22] and are in agreement with the average values found in 43 entries with thiohydantoin ring fragments, searched in the Cambridge Structural Database (CSD, version 5.34, May 2013) [22] with N1 and N3 unsubstituted and sp^3 hybridization at C5. For instance, the S1-C2 average distance value 1.654(8) Å in the four molecules, agree with the average value of 1.646 Å found in the 43 fragments, with minimal and maximum reported values of 1.519 and 1.696 Å, respectively. The thiohydantoin rings are essentially planar with a maximum deviations of +0.025(8) Å in C21 and −0.026(6)

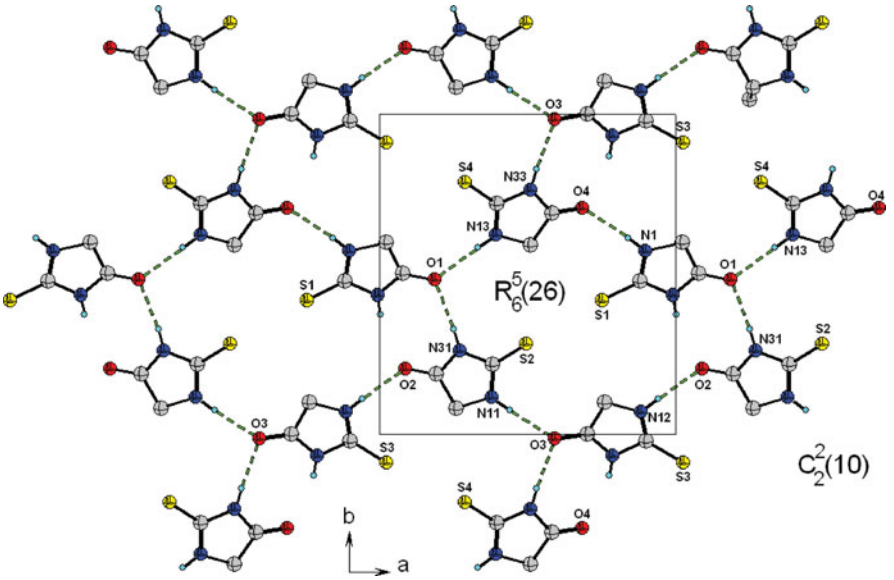

Figure 3. A portion of the crystal packing viewed in the *ba* plane. Intermolecular hydrogen bonds, N—H···O are indicated by dashed lines. C atoms of the aliphatic chain and H atoms not involved in hydrogen bonding have been omitted for clarity.

Å in N11, both in molecule 1. The S1-C2-N1 average bond angle 128.9(6)° for the four molecules is greater than S1-C2-N3, 124.1(7)°. This difference is also observed in all 43 fragments with average values of 127.7° and 125.2°, respectively. These distances and bond angles also agree with those found in the crystal structures of racemic and enantiomeric 5-isopropyl-5-methyl 2-thiohydantoin, more recently reported [23, 24].

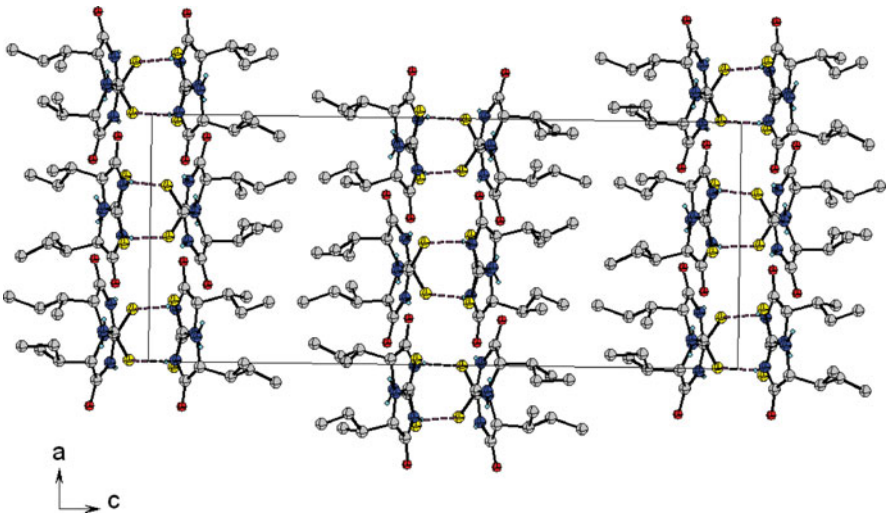

Figure 4. A partial view of the crystal packing viewed along the [010] direction. Intermolecular hydrogen bonds, N—H···S are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

The molecular structure and crystal packing of (I) are stabilized by N—H···O and N—H···S hydrogen bonds. Details of the hydrogen-bonding geometry are given in Table 3. The four molecules in the asymmetric interact through three hydrogen bonds of the type N—H···O (Fig. 2). There, the oxygen of one of the molecules acts as a bifurcated hydrogen-acceptor, forming a trimmer sub-unit, described by the graph-set $D^1_2(3)$ [25, 26].

The molecular structure and crystal packing of the title compound are stabilized by six intermolecular N—H···O hydrogen bonds, forming infinite one-dimensional chains that run along [010] direction, which can be described in graph-set notation as $C^2_2(10)$ [25, 26] (Fig. 3). Together, these hydrogen bond patterns produce a two-dimensional array parallel to the *ba* plane with the formation of a 26-atom macrocycle with graph-set $R^5_6(26)$ (Fig. 3). This graph-set is also observed in the 2-thiohydantoin structure [27]. These sheets are parallel linked through the N—H···S hydrogen bonds to form a bi-dimensional network (Fig. 4).

4. Conclusions

The title compound was synthesized by a solvent-free reaction of L-isoleucine and thiourea. The structure was unambiguously assigned by X-ray diffraction studies. The FT-IR and nuclear magnetic resonance (NMR) results were consistent with the structural results. In the crystal structure of 2-thiohydantoin-L-isoleucine, the molecules are linked by N—H···O and N—H···S hydrogen bonds, forming infinite bi-dimensional network.

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Supplementary Data

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (CCDC-933210). These data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223336033; E-mail: deposit@ccdc.cam.ac.uk.

References

[1] Avendaño López, C., & González Trigo, G. (1985). *Adv. Heter. Chem.*, *38*, 177.
[2] Meusel, M., & Gütschow, M. (2004). *Org. Prep. Proc. Int.*, *36*, 391.
[3] Mutschler, E., & Derendorf, H. (1995). *Drug Actions, Basic Principles and Therapeutic Aspects*, Medpharm Scientific Publishers: Stuttgart, Germany.
[4] Thenmozhiyal, J. C., Wong, P. T., & Chui, W.-K. (2004). *J. Med. Chem.*, *47*, 1527.
[5] Marton, J., Enisz, J., Hosztafi, S., & Timar, T. (1993). *J. Agric. Food. Chem.*, *41*, 148.
[6] Opačić, N. *et al.* (2005). *J. Med. Chem.*, *48*, 475.
[7] Hanessian, S., Sanceau, J. Y., & Chemla, P. (1995). *Tetrahedron*, *51*, 6669.
[8] Comber, R. N. *et al.* (1992). *J. Med. Chem.*, *35*, 3567.
[9] Tompkins, E. (1986). *J. Med. Chem.*, *29*, 61.
[10] Kieć-Kononowicz, K. *et al.* (2003). *Eur. J. Med. Chem.*, *38*, 555.
[11] Vázquez, J., Royo, M., & Albericio, F. (2004). *Lett. Org. Chem.*, *1*, 224.
[12] Reyes, S., & Burgess, K. (2006). *J. Org. Chem.*, *71*, 2507.
[13] Wang, Z. D., Sheikh, S. O., & Zhang, Y. L. (2006). *Molecules*, *11*, 739.

[14] Sulbaran, M. E. *et al.* (2007). *Acta Cryst.*, *C63*, o543.
[15] Uzcátegui, M. C., Delgado, G. E., Mora, A. J., González, T., & Briceño, A. (2009). *Acta Cryst.*, *E65*, o104.
[16] Delgado, G. E., Sulbaran, M. E., & Mora, A. J. (2013). *Int. J. Mater. Chem.*, *3*, 1.
[17] Seijas, L. E., Almeida, R., Mora, A. J., & Delgado, G. E. (2014). *J. Comp. Meth. Sci. Eng*., *14*, 5.
[18] Delgado, G. E., *et al.* (2014). *Av. Quím*. *9*, 3.
[19] Rigaku, (2004). *Crystal Clear, Crystal Structure*, Rigaku/MSC: Texas, USA.
[20] Sheldrick, G. M. (2008). *Acta Cryst.*, *A64*, 112.
[21] Spek, A. L., (2003). *J. Appl. Cryst.*, *36*, 7.
[22] Allen, F. H. (2002). *Acta Cryst.*, *B58*, 380.
[23] Ichitani, M. *et al.* (2013). *Eur. J. Chem.*, *4*, 350.
[24] Ichitani, M. *et al.* (2013). *Acta Cryst.*, *E69*, o953.
[25] Etter, M. C. (1990). *Acc. Chem. Res.*, *23*, 120.
[26] Etter, M. C., MacDonald, J. C., & Bernstein, J. (1990). *Acta Cryst.*, *B46*, 256.
[27] Walker, L. A., Folting, K., & Merritt, L. L. (1969). *Acta Cryst.*, *B25*, 88.