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To cite this article: Gerzon E. Delgado, Manuel O. Hernández, Asiloé J. Mora, Ali Bahsas, Robert Lobaton & Teresa González (2015) Synthesis, Spectroscopic Characterization, and Crystal Structure Analysis of rac-2-thiohydantoin-methionine, Molecular Crystals and Liquid Crystals, 616:1, 187-194, DOI: [10.1080/15421406.2014.991116](https://doi.org/10.1080/15421406.2014.991116)

To link to this article: <http://dx.doi.org/10.1080/15421406.2014.991116>



Published online: 25 Sep 2015.



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Synthesis, Spectroscopic Characterization, and Crystal Structure Analysis of *rac*-2-thiohydantoin-methionine

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In this work, we present the synthesis, FT-IR and NMR spectroscopic characterization, and X-ray single-crystal structural study of the heterocyclic compound rac-2-thiohydantoin-methionine, C₆H₁₀N₂OS₂, also known as rac-5-(2-methylthio-ethyl)-2-tioxo-imidazolidin-4-one. This material crystallize in the triclinic system, space group P-1 (N°2), Z = 4, with two independent molecules in the asymmetric unit. In the supramolecular structure, the molecules are linked by N–H...O and N–H...S hydrogen bonds forming infinite bi-dimensional chains along the [100] direction, with graph-set motif R²₂(8) and C²₂(9).

Keywords Hydrogen bonds; supramolecular chemistry; thiohydantoin; X-ray diffraction crystal structure

1. Introduction

The focus of supramolecular chemistry is the identification and study of synthons that can control the molecular assemble and thus lead to controlled supramolecular crystal architectures [1]. In molecular crystal, the combination of noncovalent interactions, such as hydrogen bonds, provides a powerful way for generating supramolecular architectures from simple building blocks [2]. Thiohydantoins and hydantoins, five-member heterocyclic systems with a very reactive nucleus, represent significant building blocks for combinatorial

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chemistry libraries [3]. The hydantoin heterocycle is present in a wide range of biologically active compounds including therapeutic drugs for the treatment of seizures and antitumor compounds [4–6]. Thiohydantoins, have also been used as anti-convulsant agents and are present in fungicides, herbicides, and natural products [7, 8]. 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 [9–11]. In our laboratory, we are interested in the study of thiohydantoin natural α -amino acids derivative compounds [12–17], therefore we report here the synthesis, spectroscopic characterization and crystal structure of a new 2-thiohydantoin derivative. The analysis of the hydrogen bond patterns is also discussed.

2. Experimental

2.1. Synthesis

L-methionine (3.0 mmol) and NH_4SCN (3.0 mmol) were dissolved in a mixture of acetic anhydride (9 mL) and acetic acid (2 mL). This solution was warmed, with agitation, to 100°C over a period of 30 min, and then cooled in ice/water and stored in a freezer overnight. The resulting white solid was collected by filtration and washed with cold water. Crystals of (I) suitable for single-crystal X-ray diffraction were obtained by slow evaporation of a 1:1 ethanol-methanol solution. Yield 42%, mp $149\text{--}150^\circ\text{C}$. This experimental procedure corresponds with a modified and improved methodology previously reported [10, 12] (see Scheme 1).

2.2. FT-IR and NMR Spectroscopic Characterization

The FT-IR absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer. ^1H and ^{13}C NMR spectra were determined on a Bruker Avance 400 model spectrometer, using DMSO-d_6 as solvent.

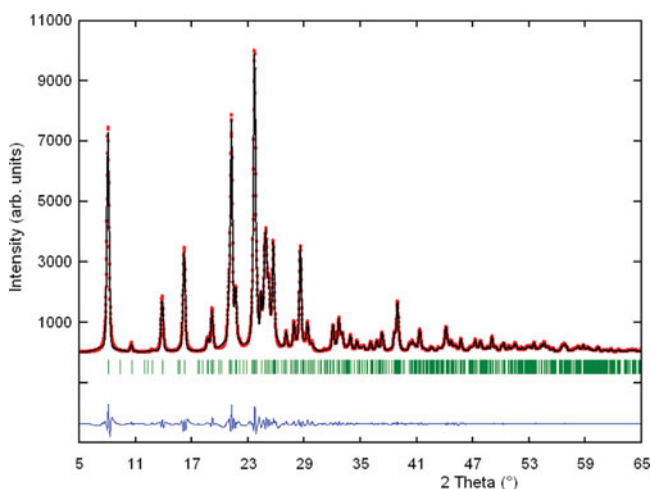


Figure 1. X-ray powder diffraction data for (I). The powder pattern was refined without structural model to confirm the unit cell parameters.

Table 1. Crystal data, data collection, and structure refinement

| | |
|-------------------------------------------------------------------|---------------------------------------------------------------|
| CCDC | 997752 |
| Chemical formula | C ₆ H ₁₀ N ₂ OS ₂ |
| Formula weight | 190.30 |
| Crystal system | Triclinic |
| Space group | P-1 (N ^o 2) |
| <i>a</i> (Å) | 8.653(2) |
| <i>b</i> (Å) | 9.790(2) |
| <i>c</i> (Å) | 11.013(3) |
| α (°) | 84.53(2) |
| β (°) | 83.97(2) |
| γ (°) | 75.61(2) |
| <i>V</i> (Å ³) | 896.4(4) |
| <i>Z</i> | 4 |
| <i>dx</i> (g cm ⁻³) | 1.410 |
| <i>F</i> (000) | 400 |
| μ (mm ⁻¹) | 0.54 |
| Crystal size (mm) | 0.50 × 0.30 × 0.20 |
| θ range (°) | 1.9–27.9 |
| hkl range | –10, 10; –12, 12; –12, 12 |
| Reflections | |
| Unique | 3381 |
| R _{int} | 0.031 |
| With <i>I</i> > 2σ(<i>I</i>) | 1539 |
| Refinement method | Full-matrix least-squares on <i>F</i> ² |
| Number of parameters | 201 |
| <i>R</i> (<i>F</i> ²) [<i>I</i> > 2σ(<i>I</i>)] | 0.059 |
| w <i>R</i> (<i>F</i> ²) [<i>I</i> > 2σ(<i>I</i>)] | 0.145 |
| Goodness of fit on <i>F</i> ² | 1.00 |
| Max/min Δρ (e Å ⁻³) | 0.38/–0.36 |

FT-IR (ν cm⁻¹): 1175 (*t*, C = S), 1410 (*t*, C-N), 1542 (*t*, N-H), 1739 (*t*, C = O), 2900 (*t*, C-H), 3152 (*t*, N-H).

¹H-NMR (400 MHz): δ 11.69 (*s*, 1H, N3H3), 10.08 (*s*, 1H, N1H1), 4.27 (*t*, 1H, C5H5), 2.52 (*t*, 2H, C7H7), 2.01 (*s*, 3H, C8H8), 1.90 (*m*, 1H, C6H6A), 1.80 (*m*, C6H6A).

¹³C-NMR (100 MHz): δ 182.5 (C2), 176.3 (C4), 59.5 (C5), 30.2 (C6), 28.6 (C7), 14.4 (C8).

2.3. X-Ray Powder Diffraction

The X-ray powder diffraction pattern of (I) was collected at room temperature in a Phillips PW-1250 goniometer using monochromatized CuKα radiation. A small quantity of compound was ground mechanically in an agate mortar and pestle and mounted on a flat holder covered with a thin layer of grease. The sample was scanned from 5–65° 2θ, with a step size of 0.02° and counting time of 10s. Silicon was used as an external standard. X-ray powder pattern of hydantoin compound is shown in Fig. 1. The 20 first measured reflections

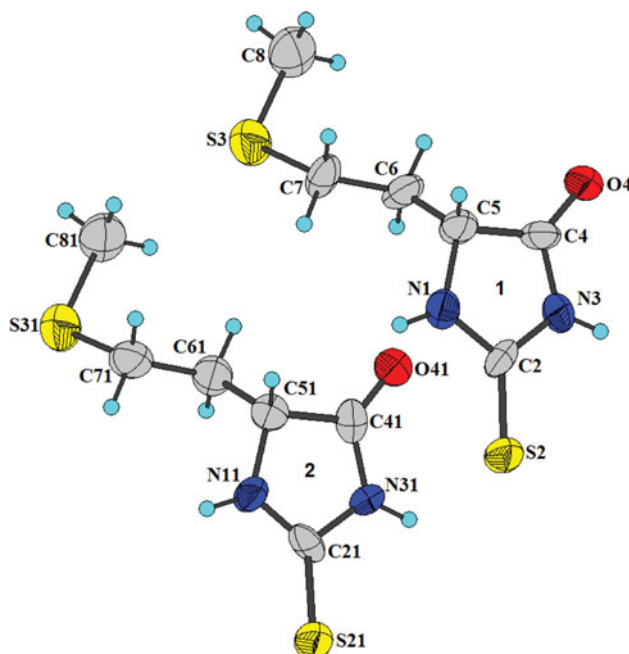


Figure 2. Asymmetric unit of 2-thiohydantoin-methionine (I) with anisotropic ellipsoid representations, together with atom labeling scheme. The ellipsoids are drawn at 50% probability level. Hydrogen atoms are depicted as spheres with arbitrary radii.

were completely indexed using the program Dicvol04 [18], which gave a unique solution in a triclinic cell with parameters $a = 8.654(2) \text{ \AA}$, $b = 9.790(2) \text{ \AA}$, $c = 11.0145(2) \text{ \AA}$, $\alpha = 84.55(1)^\circ$, $\beta = 83.99(1)^\circ$, $\gamma = 75.61(2)^\circ$ with figures of merit $M_{20} = 56.3$ [19] and $F_{20} = 121.5$ (0.0046, 36) [20]. In order to confirm the unit cell parameters, a Le Bail refinement

Table 2. Selected geometrical parameters (\AA , $^\circ$)

| Molecule 1 | | Molecule 2 | |
|-------------|-----------|-----------------|-----------|
| S2-C2 | 1.657(5) | S21-C21 | 1.668(5) |
| S3-C7 | 1.816(5) | S31-C71 | 1.771(6) |
| S3-C8 | 1.785(7) | S31-C81 | 1.780(7) |
| O4-C4 | 1.224(6) | O41-C41 | 1.212(7) |
| N1-C2 | 1.348(6) | N11-C21 | 1.313(6) |
| N3-C2 | 1.366(7) | N31-C21 | 1.391(6) |
| N3-C4 | 1.357(6) | N31-C41 | 1.364(7) |
| S2-C2-N3 | 126.4(4) | S21-C21-N31 | 121.2(3) |
| S2-C2-N1 | 127.1(4) | S21-C21-N11 | 130.5(4) |
| N1-C2-N3 | 106.5(4) | N11-C21-N31 | 108.3(4) |
| O4-C4-N3 | 124.9(5) | O41-C41-N31 | 128.4(5) |
| C5-N1-C2-S2 | -179.2(4) | C51-N11-C21-S21 | 179.1(4) |
| C4-N3-C2-S2 | -177.3(4) | C41-N31-C21-S21 | -177.6(4) |

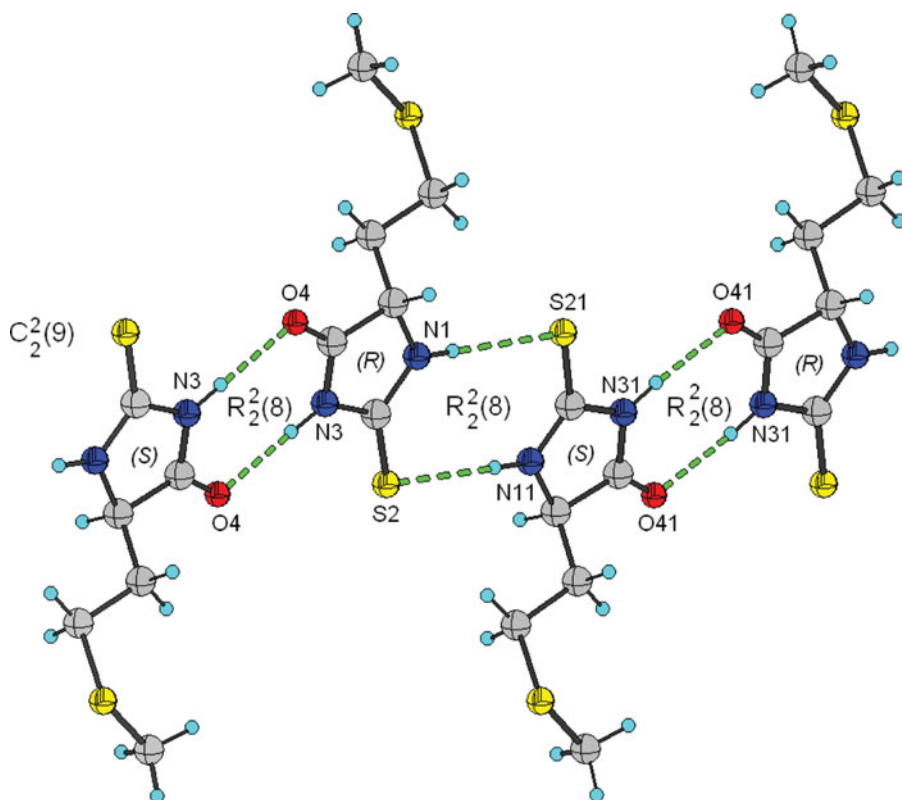


Figure 3. A portion of the crystal packing of (I) showing the hydrogen bonds pattern. Intermolecular hydrogen bonds, N–H...S and N–H...O are indicated by dashed lines.

[21] was carried out using the Fullprof program [22]. The Fig. 1 shows a very good fit between the observed and calculated patterns.

2.4. X-Ray Data Collection and Structure Determination

Single crystal data were collected at room temperature in a Rigaku AFC7S diffractometer coupled with a CCD area detector using graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å). The unit cell parameters were found by indexing of reflections from the first

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

| D–H...A | D–H | H...A | D...A | D–H...A |
|------------------------------|-------|-------|----------|---------|
| N3–H3...O4 ⁽ⁱ⁾ | 0.860 | 1.990 | 2.837(5) | 168.0 |
| N1–H1...S21 ⁽ⁱⁱ⁾ | 0.860 | 2.520 | 3.378(4) | 176.0 |
| N31–H31...O41 ⁽ⁱ⁾ | 0.970 | 2.480 | 2.854(5) | 166.0 |
| N11–H11...S2 ⁽ⁱⁱ⁾ | 0.960 | 2.700 | 3.341(5) | 177.0 |

Symmetry codes: ⁽ⁱ⁾ $-x, 1-y, 2-z$, ⁽ⁱⁱ⁾ $1-x, 1-y, 2-z$

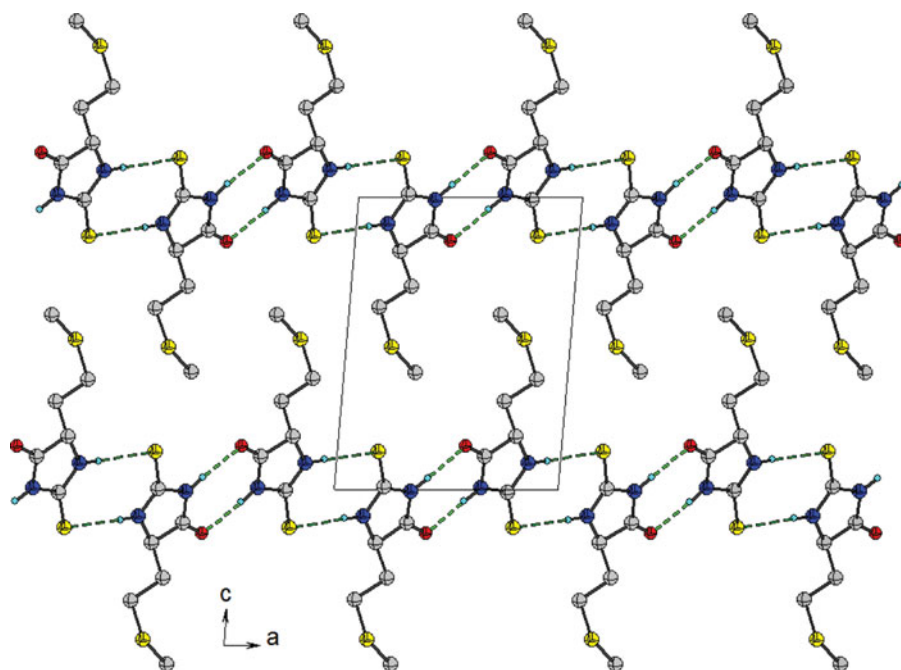
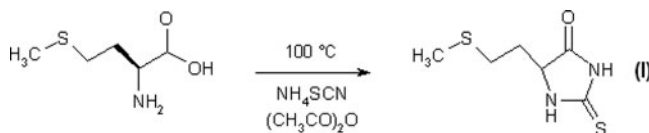


Figure 4. A packing view of (I) in the *ca* plane, showing the infinite bi-dimensional chains along the [100] direction. H atoms not involved in hydrogen bonding have been omitted for clarity.

20 frames and refined along with diffractometer constants to give the final cell parameters using the program CrystalClear [23]. Integration, scaling correction, and data reduction were accomplished using CrystalStructure [23]. Absorption corrections were performed using the multi-scan method. The structure was solved using the program SHELXS [24] and refined by the full-matrix least-squares methods in SHELXL [24]. The nonhydrogen atoms were modeled anisotropically. All H atoms were placed at calculated positions and treated using the riding model, with C-H distances of 0.97–0.98 Å, and N-H distances of 0.86 Å. The Uiso(H) parameters were fixed at 1.2Ueq (C, N) and 1.5Ueq (methyl carbon). Molecular diagrams were generated using Diamond [25]. All geometrical calculations were done using the program Platon [26]. Experimental details of the X-ray analysis are provided in Table 1.

3. Results and Discussion

Spectroscopic studies confirm the molecular skeleton of *rac*-2-thiohydantoin-methionine. From the X-ray results, the title compound (I) crystallizes in the centro-symmetric space group P-1 with two independent molecules in the asymmetric unit. In this case, *L*-methionine suffered an amino acid racemization produced by the use of acetic acid and the high temperature in the synthesis [27]. Figure 2 shows the atom labeling and molecular conformation of *rac*-2-thiohydantoin-methionine. Selected geometrical parameters are presented in Table 2. All bond distances and angles are normal [28] and are in agreement with the average values found in 43 entries with thiohydantoin ring fragments, found in the Cambridge Structural Database (CSD, version 5.35, Feb 2014) [28] with N1 and N3 unsubstituted and sp^3 hybridization at C5. For instance, the S1-C2 average distance value 1.663(5) Å in the two



Scheme 1. Synthesis of *rac*-2-thiohydantoin-methionine (I) from L-methionine.

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 $-0.030(8)$ Å in C4 and $+0.025(6)$ Å in C5 for molecule 1, and $-0.014(6)$ Å in C41 and $+0.010(5)$ Å in C51 for molecule 2. The S2-C2-N1 average bond angle $128.8(4)^\circ$ for the two molecules is greater than S2-C2-N3, $123.8(4)^\circ$. This difference is also observed in all 43 fragments with average values of 127.7° and 125.2° , respectively. The dihedral angle between the thiohydantoin ring and the plane formed by the alkyl chains is $66.51(1)^\circ$ and $65.47(1)^\circ$ for the molecules 1 and 2, respectively.

The supramolecular structure and crystal packing of (I) are stabilized by N-H...O and N-H...S hydrogen bonds, as depicted in Fig. 3. The geometrical parameters of these hydrogen bonds are summarized in Table 3.

The N3-H3...O4 and N31-H31...O41 ($1-x$, $1-y$, $2-z$) hydrogen bonds generates centro-symmetric rings parallel to the *ca* plane, described by the graph-set $R^2_2(8)$ [29,30]. This motif constituted a typical amide–amide hydrogen bond joining pairs of molecules, and is also observed in other thiohydantoins²¹. These dimers are parallel linked through the N1-H1...S21 and N11-H31...S2 ($-x$, $1-y$, $2-z$) hydrogen bonds to form a second centro-symmetric ring motif $R^2_2(8)$ type. The joining together of these rings produces $C_2(9)$ chains, in alternated (*R*) and (*S*) molecules, which run along the [100] direction. The combination of these interactions produces chains parallel to the *ca* plane in a bi-dimensional hydrogen bond network scheme (Fig. 4).

4. Conclusions

The title compound was synthesized and characterized by spectroscopy and X-ray diffraction techniques. In the supramolecular structure of *rac*-2-thiohydantoin-methionine, the molecules are linked by N-H...O and N-H...S hydrogen bonds forming a bi-dimensional network.

Supplementary Materials

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (CCDC-997752). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

Funding

This work was supported by CDCHT-ULA (grant C-1853-13-08-A) and FONACIT (grant LAB-97000821).

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