SÍNTESE LIVRE DE SOLVENTES E ESTRUTURA DE CRISTAL DE *rac*-2-TIOHIDANTOINA-VALINA

SOLVENT-FREE SYNTHESIS AND CRYSTAL STRUCTURE OF *rac*-2-THIOHYDANTOIN-VALINE

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Received 30 September 2017; received in revised form 18 October 2018; accepted 22 October 2018

RESUMO

As tiohidantoínas têm sido utilizadas na fabricação de medicamentos e em processos industriais. Dependendo da natureza e do tipo de substituição no anel heterocíclico, estes compostos podem apresentar atividade farmacêutica e biológica com uma variedade de aplicações como antiepiléptico, antitumoral, anti-inflamatório e, principalmente, para o tratamento do câncer da próstata. Neste estudo, uma nova tiohidantoína foi sintetizada a partir do aminoácido valina e estruturalmente caracterizada. O composto de fórmula $C_6H_{10}N_2O_2S$ com o nome sistemático rac-5-isopropil-2-tioxoimidazolidin-4-ona, foi sintetizado por uma síntese isenta de solvente. O composto heterocíclico foi caracterizado por técnicas de espectroscopia de infravermelho (FTIR) e ressonância magnética nuclear (RMN), análise de difração de raios X em pó e monocristal (XRD). Este material cristaliza no grupo espacial monoclínico $P2_1/c$. Na estrutura supramolecular, as moléculas são unidas pelas ligações de hidrogênio N---H···O e N---H···S, formando dímeros centrossimétricos $R^2_2(8)$ e cadeias $C^2_2(9)$ que percorrem a direção [001] em uma rede unidimensional infinita.

Palavras-chave: *tiohidantoína, síntese livre de solvente, química supramolecular, estrutura do cristal, ligações de hidrogênio*

ABSTRACT

Thiohydantoins have been used in the manufacture of medicines and in industrial processes. 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 as antiepileptic, antitumoral, anti-inflammatory, and principally for the treatment of prostate cancer. In this study, a new thiohydantoin was synthetized from the valine amino acid and structurally characterized. The title compound, $C_6H_{10}N_2O_2S$, with systematic name *rac*-5-isopropyl-2-tioxoimidazolidin-4-one, has been synthetized by a solvent-free synthesis. The heterocyclic compound was characterized by spectroscopic infrared (FTIR) and nuclear magnetic resonance (NMR) techniques, powder and single-crystal X-ray diffraction analysis (XRD). This material crystallizes in the monoclinic space group $P2_1/c$. In the supramolecular structure, the molecules are joined by N---H···O and N---H···S hydrogen bonds, forming centrosymmetric $R^2_2(8)$ dimers and $C^2_2(9)$ chains that run along the [001] direction in an infinite one-dimensional network.

DOI: 10.52571/PTQ.v16.n31.2019.353_Periodico31_pgs_347_352.pdf

Keywords: *thiohydantoin, solvent-free synthesis, supramolecular chemistry, crystal structure, hydrogen bonds*

INTRODUCTION

Thiohydantoins, or 2-thioxoimidazolidin-4-ones, or are sulfur analogs of hydantoins, or imidazolidine-2,4-diones. These compounds are five-member heterocyclic system with a very reactive nucleus, which provides four possible points of diversity (Avendaño and González, 1985; Meusel and Gütschow, 2004). 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: antiepileptic activity, antitumoral and antiinflammatory (Thenmozhiyal *et al*., 2004), fungicidal (Marton *et al*., 1993), antiviral (Opačić *et al*., 2005), herbicide (Hanessian *et al*., 1995), HIV protease inhibitor (Comber *et al*., 1992), hypolipidimic agent Tompkins, 1986), and anti-hypertensive agent (Kieć-Kononowicz *et al*., 2003). Nevertheless, the principal current interest comes from the application of thiohydantoins for the treatment of prostate cancers (Harrison, 2009; Shen and Balk, 2009).

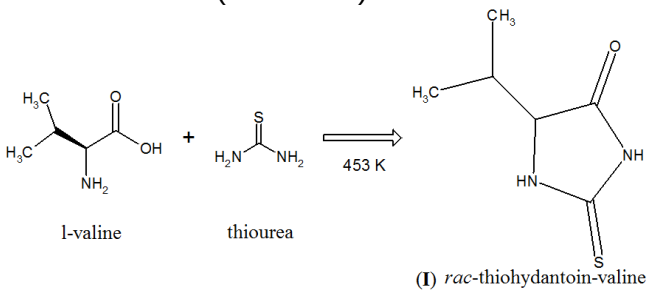
These heterocycles are commonly used as templates in combinatorial chemistry libraries, due its very reactive nucleus which provides four possible points of diversity (Park *et al*., 2001; Muccioli *et al*., 2003), and there has been an interest in the search of new synthetic routes for its preparations (Vázquez *et al*., 2004; Wang *et al*., 2006; Reyes and Burgess, 2006).

As part of our research work to explore the synthesis and structural characterization of hydantoin and thiohydantoin derivative compounds (Delgado *et al*., 2007; 2012; 2013; 2014; 2015a; 2015b; 2015c; 2016; Sulbaran *et al*., 2007; Uzcátegui *et al*., 2009; Seijas *et al*., 2010; 2014), we have investigated the synthesis, crystalline and molecular structure of *rac*-2-thiohydantoin-valine, systematic name *rac*-5-isopropyl-2-tioxoimidazolidin-4-one, synthesized from a solvent-free reaction.

MATERIALS AND METHODS

Solvent-free synthesis

All the reagents used were obtained from Sigma-Aldrich and were used without any further purification. The title compound was synthesized using a solvent-free modified methodology previously reported (Reyes and Burgess, 2006; Delgado *et al*., 2015). L-valine 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 minutes and then let cool to room temperature. The resulting white solid was washed with cool water and filtered (mp 409-410 K). Crystal of (**I**) suitable for X-ray diffraction analysis were obtained by slow evaporation of ethanol solution (Scheme 1).



Scheme 1. *Synthesis of rac-2-thiohydantoin-valine (**I**)*

Spectroscopic studies

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

FT-IR: 1175 cm^{-1} (t, C-N), 1737 cm^{-1} (t, C=O), 3150 cm^{-1} (t, N-H)].

^{1}H-NMR (400 MHz, DMSO d_6): δ 11.60 (s, 1H, N3H3), 10.00 (s, 1H, N1H1), 4.10 (d, 1H, C5H5), 1,98 (m, 1H, C6H6), 0.99 (m, 2H, C8H8), 0.83 (t, 3H, C7H7).

^{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).

Powder X-ray diffraction study

The powder pattern of (**I**) was collected at room temperature in a Phillips PW-1250 goniometer using monocromatized 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. Powder X-ray pattern of the thiohydantoin compound (**I**) is show in Figure 1. The 20 first measured reflections were completely indexed using the program Dicvol04 (Boultif and Louër, 2004), which gave a unique solution in a monoclinic cell with parameters *a*= 5.73 Å, *b*= 17.42 Å, *c*= 8.23 Å, β= 103.5°. In order to confirm the unit cell parameters, a Le Bail (Le Bail, 2005) refinement was carried out using the Fullprof program (Rodríguez-Carvajal, 2017). Figure 1 shows a very good fit between the observed and calculated patterns.

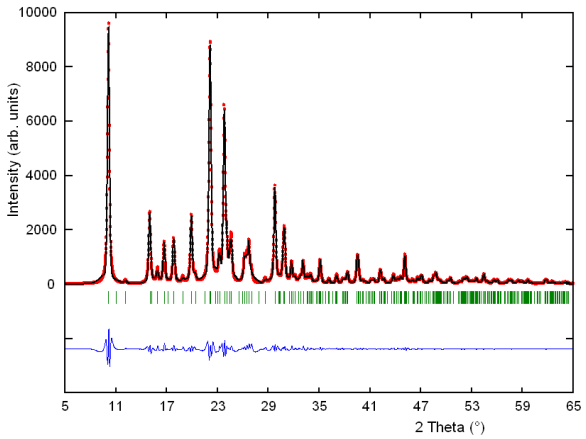


Figure 1. *X-ray powder diffraction data for (**I**). The powder pattern was refined without structural model to confirm the unit cell parameters*

X-ray data collection and structure determination

Colorless rectangular crystal (0.2 x 0.12 x 0.11 mm) was used for data collection. Diffraction data were collected at 298(2) K by ω-scan technique on a Rigaku AFC7S Mercury diffractometer, equipped with graphite monochromatized MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz-polarization and absorption effects. Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure was solved by direct methods using the SHELXS program (Sheldrick, 2008), and refined by a full-matrix least-squares calculation on F^2 using SHELXL (Sheldrick, 2015). 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). Table 1 summarizes the crystal data, intensity data collection and refinement details for the title compound. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre (CCDC-933209).

RESULTS AND DISCUSSION:

The title compound (**I**) crystallizes with one independent molecule in the asymmetric unit, in a centrosymmetric space group, which implies that L-valine suffered an amino acid racemization in the synthesis (Yoshioka, 2007). Figure 2 shows the molecular structure and the atom-labeling scheme of *rac*-2-thiohydantoin-valine. Selected geometrical parameters are presented in Table 2.

Table 1. *Crystal data, data collection and structure refinement for rac-2-thiohydantoin-valine (**I**)*

CCDC	933209
Chemical formula	$C_6H_{10}N_2O_2S$
Formula weight	158.23
Crystal system	Monoclinic
Space group	$P2_1/c$
a(Å)	5.7217(7)
b(Å)	17.410(2)
c(Å)	8.241(1)
β(°)	103.710(3)
V(Å^3)	797.6(2)
Z	4
dx (g cm^{-3})	1.318
F(000)	336
μ(mm-1)	0.341
Crystal size (mm)	0.20 x 0.12 x 0.11
θ range (°)	2.3-28.1
hkl range	-6, 7; -20, 20; -10, 1(
Reflections	
Unique	1601
Rint	0.032
With I > 2σ(I)	1303
Refinement method	Full-matrix ls on F^2

Number of parameters	94
$R(F^2)$ [I > 2σ(I)]	0.0410
$wR(F^2)$ [I > 2σ(I)]	0.1171
Goodness of fit on F	1.03
Max/min Δρ (e Å^{-3})	0.21/-0.20

Table 2. *Selected geometrical parameters (Å, º) for (**I**)*

S1-C2	1.661(2)	N1-C5	1.458(2)
O1-C4	1.217(2)	N3-C2	1.378(2)
N1-C2	1.328(2)	N3-C4	1.367(2)
S1-C2-N3	124.7(1)	S1-C2-N1	128.5(1)
N1-C2-N3	106.7(2)	O1-C4-N3	126.3(2)
C5-N1-C2-S1	-179.9(1)	C4-N3-C2-S1	179.9(1)

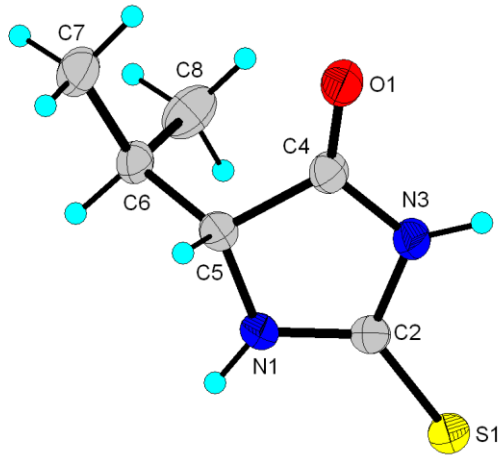


Figure 2. *The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level. H atoms are shown as spheres of arbitrary radii*

Table 3 shows the hydrogen bonding geometry for the title compound. All bond distances and angles are normal and are in agreement with the average values found in 31 entries with thiohydantoin ring fragments, searched in the Cambridge Structural Database (CSD, version 5.38, May 2017) (Groom and Allen, 2014), with N1 and N3 unsubstituted and sp^3 hybridization at C5. For instance, the S1-C2 distance value 1.661(2) Å, agree with the average value of 1.646 Å found for the 31 fragments, with minimal and maximum reported values of 1.519 and 1.696 Å, respectively. The thiohydantoin ring is essentially planar with a maximum deviations of 0.003 (2) Å in N3 and −0.004 (2) Å in C2. The S1-C2-N1, 128.5(1)° bond angle is greater than S1-C2-N3, 124.7(1)°. This difference is also observed in all 31 fragments with average values of 127.7° and 125.2°, respectively.

Table 3. *Hydrogen bonds geometry (Å, º). (D-donor; A-acceptor; H-hydrogen) for (**I**)*

D--H···A	D--H	H···A	D···A	D--H···A
N3-- H3···O1$^{(i)}$	0.860	2.030	2.866(2)	164.0
N1--H1···S1$^{(ii)}$	0.860	2.530	3.389(2)	176.0

Symmetry codes: $^{(i)}$ 1-x, -y, -z, $^{(ii)}$ -x, -y, 1-z

The molecular structure and crystal packing of (I) are stabilized by N--H···O and N--H···S hydrogen bonds (Figure 3). The N3--H3···O1 (1-x, -y, -z) hydrogen bond generates centrosymmetric rings parallel to the *bc* plane, described by the graph-set $R^2_2(8)$ (Etter, 1990). This motif constituted a typical amide-amide hydrogen bond joining pairs of molecules, and is also observed in other thiohydantoins (Groom and Allen, 2014). These dimers are parallel linked through the N1--H1···S1 (-x, -y, 1-z) hydrogen bond to form a second centrosymmetric ring motif $R^2_2(8)$ type (Figure 3). The combination of these rings produces $C^2_2(9)$ chains, which run along the [001] direction, forming infinite zig-zag chains parallel to the *bc* plane (Figure 4).

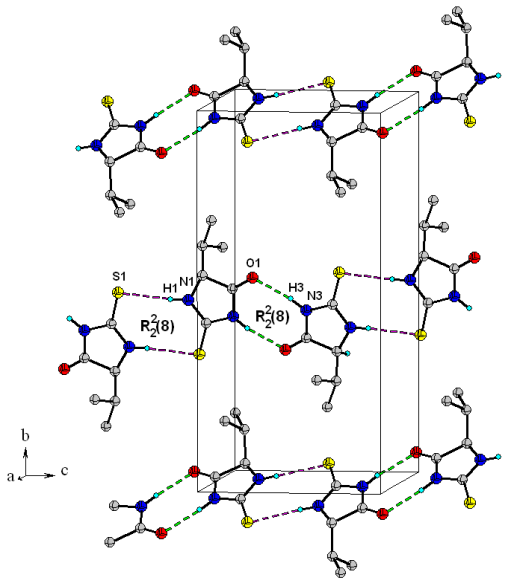


Figure 3. *A portion of the crystal packing for (**I**). Intermolecular hydrogen bonds, N--H···O and N--H···S, are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity*

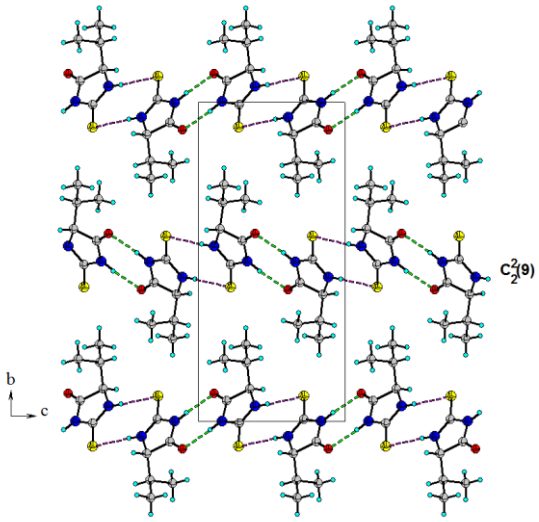


Figure 4. *Crystal packing for (**I**) viewed in the bc plane showing supramolecular structures extending along c direction forming $C^2_2(9)$ chains*

CONCLUSIONS:

The title compound, *rac*-thiohydantoin-valine, was synthesized by a solvent-free reaction of valine and thiourea and its crystal structure was characterized by X-ray diffraction analysis. In the supramolecular structure of (**I**), the molecules are linked by N---H···O and N---H···S hydrogen bonds, forming infinite one-dimensional chains with graph-set motif $C^2_2(9)$ formed by centrosymmetric rings $R^2_2(8)$.

For this new thiohydantoin compound, known its crystalline structure, its biological properties will be studied as a possible anticancer agent.

ACKNOWLEDGMENTS:

This work was supported by CDCHTA-ULA (grant C-1980-16-08-A) and FONACIT (grant LAB-97000821).

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