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Synthesis, Crystal Structure and Hydrogen-bonding Patterns in Rac-N-acetyl-2-thiohydantoin-leucine

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Abstract In this work we present the synthesis and X-ray single crystal structural characterization of the heterocyclic compound rac-N-acetyl-2-thiohydantoin-leucine. This material crystallize in the triclinic system with space group P-1 (Nº2), Z=4, with two independent molecules in the unit asymmetric. The crystal packing is governed by N--H···O hydrogen bond-type intermolecular interactions, forming infinite one-dimensional chains with graph-set motif C(6).

Keywords Thiohydantoin, Crystal Structure, Hydrogen Bonding

1. Introduction

Thiohydantoins and hydantoins are five-member heterocyclic system with a very reactive nucleus, which provides four possible points of diversity. Both heterocycles represent significant building blocks for combinatorial chemistry libraries[1-4]. 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 behaviour[5], due principally to its wide range of therapeutic properties. For instance, several applications have been reported for hydantoins: antiarrhythmic and antihypertensive[6-7], antiviral[8], antineoplastic[9], antitumoral[10] and anticonvulsant agents[11-12]. The best knwon hydantoin, phenytoin, is the most widely used antiepileptic drug[13]. Thiohydantoins are known for their uses as hypolipidemic[14], antimutagenic[15] and anticarcinogenic agents[16]. In addition, both heterocyclic compounds are used as herbicides[17] and fungicides agents[18]. Recently, there has been interest in the search of new synthetic routes for the preparation of these type of compounds, via solution or solid state reactions[19-21].

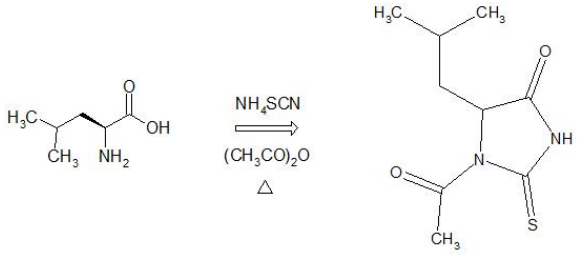
We are interested in N-carbamoyl, hydantoin and thiohydantoin derivatives of α-amino acids[22-28], and report here the structure of the N-acetylthiohydantoin derivative of the α-amino acid L-leucine.

2. Experimental

2.1. Synthesis

The title compound was synthesized from L-leucine using a modified methodology previously reported[18-19]. L-leucine (1000 mg, 7.6 mmol) and NH_4SCN (580.3 mg, 7.6 mmol) was dissolved in a 9 ml acetic anhydride - 1 ml acetic acid mixture and transferred in a 25 ml round-bottom flask. The mixture was warmed, with agitation, to 363 K over a period of 30 min. The resulting solution was cooled in a ice/water mixture and stored in a freezer overnight. The resulting white solid was filtered off and washed with cool water (m.p. 404-405 K). Crystal of (I) suitable for X-ray diffraction analysis were obtained by slow evaporation of a 1:1 ethanol-methanol solution.

$RMN^{-1}H$ (400 MHz, DMSO-d_6) δ=12.66 (H3, s), 4.71 (H5, d), 2.70 (H7, s), 1.76 (H8, H9, m), 0.85 (H10, H11, d). $RMN^{-13}C$ (100.6 MHz, DMSO-d_6) δ=182.5 (C2), 173.5 (C4), 169.7 (C6), 61.3 (C5), 38.1 (C8), 27.3 (C7), 23.7 (C9), 23.1 (C10), 21.9 (C11).



Scheme 1. Synthesis of rac-N-acetyl-2-thiohydantoin-leucine

2.2. X-Ray Crystallography

Colorless rectangular crystal (0.3, 0.3, 0.1 mm) was used for data collection. Diffraction data were collected at 298(2) K by ω-2θ scan technique on a Siemens P4 four-circle diffractometer[29] equipped with graphite monochromatized CuKα radiation (λ = 1.54178 Å). The data were corrected for Lorentz-polarization and absorption effects[29]. Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure was solved by direct

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methods using the SHELXS97 program[30] and refined by a full-matrix least-squares calculation on F^2 using SHELXL97[30].

Table 1. Crystal data, data collection and structure refinement

Chemical formula	$C_9H_{14}N_2O_2S$
Formula weight	214.28
Crystal system	Triclinic
Space group	P-1
a(Å)	7.1855(4)
b(Å)	9.7300(4)
c(Å)	16.442(1)
α (°)	101.13(1)
β(°)	94.00(1)
γ (°)	90.49(1)
V(Å3)	1125.0(1)
Z	4
dx (g cm-3)	1.265
F(000)	456
μ(mm-1)	0.27
θ range (°)	2.8-69.1
hkl range	$-1 \le h \le 8$, $-11 \le k \le 11$, $-18 \le l \le 19$
Reflections	
Collected	4921
Unique (Rint)	3991 (0.088)
With $I > 2\sigma(I)$	3003
Refinement method	Full-matrix least-squares on F^2
Number of parameters	260
$R(F^2)[I > 2\sigma(I)]$	0.0782
$wR(F^2)[I > 2\sigma(I)]$	0.1998
Goodness of fit on F^2	1.11
Max/min Δρ (e Å^{-3})	0.73/-0.71

Table 2. Selected geometrical parameters (Å, º)

Molecule A		Molecule B	
S2-C2	1.6340(3)	S21-C21	1.6480(3)
O4-C4	1.2050(4)	O41-C41	1.2070(4)
O6-C6	1.2130(4)	O61-C61	1.2190(4)
N1-C2	1.3860(4)	N11-C21	1.3860(4)
N3-C2	1.3770(4)	N31-C21	1.3650(4)
N3-C4	1.3700(4)	N31-C41	1.3780(4)
S2-C2-N1	131.5(2)	S21-C21-N11	130.8(2)
S2-C2-N3	122.8(2)	S21-C21-N31	122.6(2)
O4-C4-N3	125.5(3)	O41-C41-N31	125.8(3)
O4-C4-C5	128.2(3)	O41-C41-C51	127.9(3)
C6-N1-C2-S2	4.10(5)	C61-N11-C21-S21	-6.90(5)
C4-N3-C2-S2	-174.80(2)	C41-N31-C21-S21	176.50(2)

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...O6$^{(i)}$	0.860(i)	1.980	2.825(3)	166.6
N3-- H31...O61$^{(ii)}$	0.860(ii)	1.990	2.834(3)	167.7

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

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)

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-860694). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/perl/catreq.cgi (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam. ac.uk).

Molecular diagrams were generated using Diamond[31]. All geometrical calculations were done using the program Platon[32]. Table 1 summarizes the crystal data, intensity data collection and refinement details for the title compound. Selected geometrical parameters are presented in Table 2. Table 3 shows the hydrogen bonding geometry for the title compound.

3. Results and Discussion

N-acetyl-thiohydantoin-L-leucine crystallizes with two independent molecules in the asymmetric unit, in a centrosymmetric space group, which implies that L-leucine suffered an amino acid racemization produced by the use of acetic acid in the synthesis[33]. Figure 1 shows the atom labeling and molecular conformation of the two independent molecules of the title compound in the asymmetric unit.

All bond distances and angles are normal[34] and are in agreement with the average values found in 31 entries with 36 thiohydantoin ring fragments, searched in the Cambridge Structural Database (CSD, version 5.33; Feb, 2012) with N1 and N3 unsubstituted and sp^3 hybridization at C5. The thiohydantoin ring, in both molecules, is essentially planar with a maximum deviations of 0.034 (3) Å in C4 and −0.037 (3) Å in C4, in molecule A and 0.039(3) Å in C41 and -0.038(3) Å in C51, for molecule B.

The S2-C2-N1 bond angles are greater than S2-C2-N3 angles in both molecules. This difference is also observed in the only three 2 N-acetyl thiohydantoin compounds reported in the CSD; KOMGUO[35] with angle values 130.6° and 123.4°, NIFHIT[36] with angles 132.0° and 121.9°, and DIKWAW[28] with angles 132.2°-131.2° and 125.8°-119.0°. The average values for the same angle in the 36 fragments searched above are 127.7° and 125.2°, respectively.

The S2-C2 and S21-C21 distance values, see Table 2, agree with the average value of 1.646 Å found for the 36 fragments search in the CSD, with minimal and maximum reported values of 1.519 and 1.696 Å, respectively.

The molecular structure and crystal packing of the title compound is stabilized by intermolecular N3--H3···O4 (x, 1/2 − y, 1/2 + z) hydrogen bonds (Table 3), forming infinite one-dimensional chains that run along[100] direction, which can be described in graph-set notation as C(6)[37] (Figure 2).

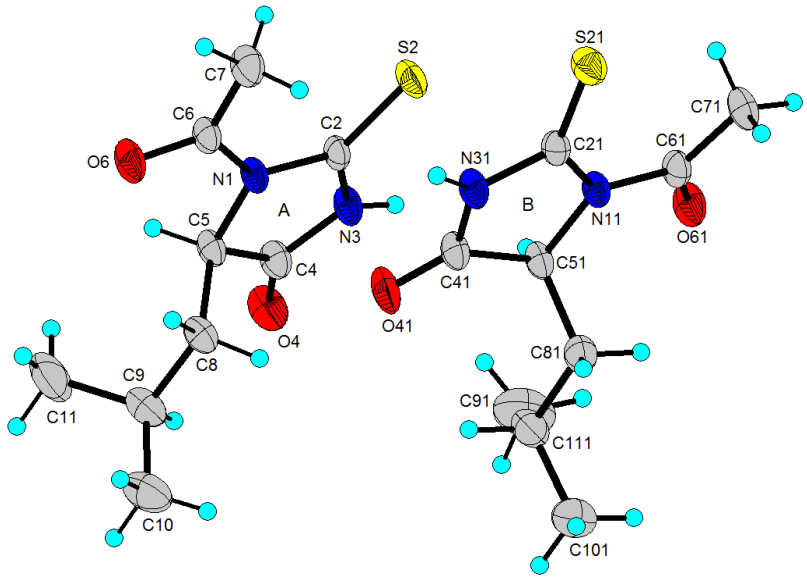

Figure 1. Asymmetric unit with anisotropic ellipsoid representations, together with atom labeling scheme. The ellipsoids are drawn at 25% probability level, hydrogen atoms are depicted as spheres with arbitrary radii

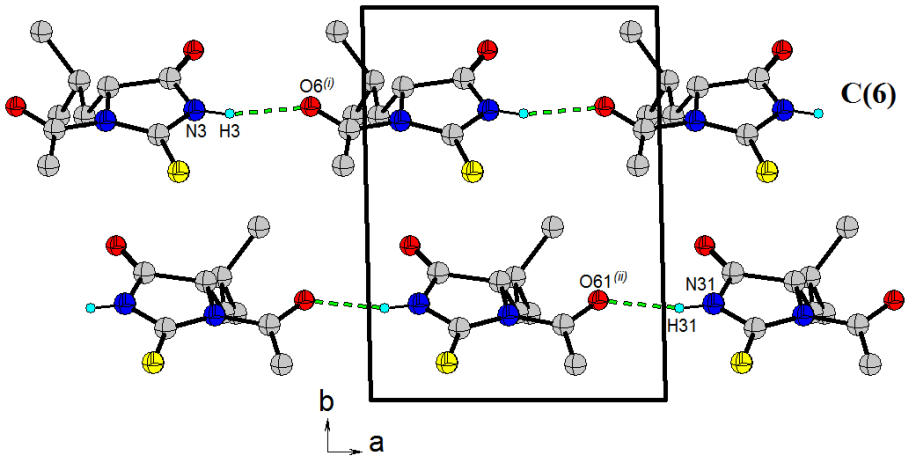

Figure 2. Packing view of 1. Intermolecular hydrogen bonds, N–H···O and O–H···O, are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity

4. Conclusions

The thiohydantoin derivative rac-N-acetyl-2-thiohydantoin-leucine was synthesized and characterized by NMR spectroscopy. This material crystallize in the triclinic system with space group P-1 (Nº2), Z=4, with two independent molecules in the unit asymmetric. In the crystal structure, the molecules are linked by N---H···O hydrogen bonds, forming infinite one-dimensional zigzag chains, running along [100] direction, with C(6) graph-set motif.

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