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Artículo científico

Synthesis, crystal and supramolecular structure of *rac*-N-acetyl-2-thiohydantoin-asparagine

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Resumen

El compuesto $C_7H_9N_3O_3S$, también conocido como *rac*-N-acetil-5-propionamida-2-tioxo-imidazolidin-4-ona, cristaliza en el sistema monoclínico con grupo espacial $P2_1/n$ (N°14), Z = 4, y parámetros de celda unidad: *a*= 9.338 (7) Å, *b*= 7.545 (5) Å, *c*= 13.212 (10) Å, β= 97.10 (2)°, V= 932.8 (12) Å^3. El plano del grupo acetil y el plano del grupo ureido forman un ángulo de 81.0 (2)°. En la estructura supramolecular, las moléculas se mantienen unidas por enlaces de hidrógeno del tipo N--H···O mediante estructuras cíclicas representadas por los grafos $R^2_2(14)$ y $R^2_2(16)$, formando una red tridimensional.

Palabras claves: tiohidantoinas; estructura cristalina; química supramolecular; enlaces de hidrógeno

Abstract

The title compound, $C_7H_9N_3O_3S$, also known as *rac*-N-acetyl-5-propionamide-2-thioxo-imidazolidin-4-one, crystallize in the monoclinic system with space group $P2_1/n$ (N°14), Z=4, and unit cell parameters *a*= 9.338 (7) Å, *b*= 7.545 (5) Å, *c*= 13.212 (10) Å, β= 97.10 (2)°, V= 932.8 (12) Å^3. The acetyl group and the mean plane of the ureido group form an angle of 81.0 (2)°. In the supramolecular structure, the molecules are joined by N--H···O hydrogen bonds into cyclic structures with graph-set $R^2_2(14)$ and $R^2_2(16)$, forming a three-dimensional network.

Keywords: thiohydantoin; crystal structure; supramolecular chemistry; hydrogen bonds

Introduction

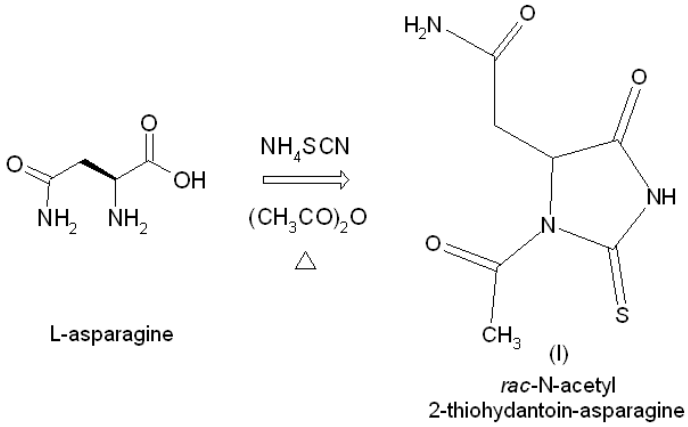
Thiohydantoins and hydantoins are five-member heterocyclic system with a very reactive nucleus, which provides four possible points of diversity. Both heterocycles represent significant building blocks for combinatorial chemistry libraries[1,2]. The biological activities of hydantoin and 2-thiohydantoin derivatives have been known for a long time[3]. For instance, several applications have been reported for hydantoins: antiarrhythmic and antihypertensive, antiviral, antineoplastic, antitumoral and anticonvulsant agents[4]. The best known hydantoin, phenytoin, is a widely used antiepileptic drug[5]. Thiohydantoins are known for their uses as hypolipidemic, antimutagenic and anticarcinogenic agents[6]. In addition, derivatives of both heterocyclic compounds are used as herbicides and fungicides agents[7]. 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[8-10]. As part of ongoing studies on thiohydantoin derivatives of α-amino acids[11-14], we report here the structure of N-acetyl-2-thiohydantoin-asparagine, which is an intermediate in the preparation of 2-thiohydantoin-asparagine.

Experimental

Synthesis

The title compound was synthesized using a modified methodology previously reported[10,11]. L-asparagine (3.4 mmol) and NH_4SCN (3.4 mmol) were dissolved in a 9 ml acetic anhydride - 1 ml acetic acid mixture and transferred in a round-bottom flask. The mixture was warmed, with agitation, to 363 K over a period of 30 min. The resulting solution was cooled in an ice/water mixture and stored in a freezer overnight. The resulting white solid was filtered off and washed with cold water. Crystal of (I) suitable for X-ray

diffraction analysis were obtained by slow evaporation of a 1:1 ethanol-methanol solution. The measured melting point of 220-222 °C is in good agreement with that reported of 224 °C[15].



Scheme 1: Synthesis of *rac*-N-acety-2-thiohydantoin-asparagine.

X-ray data collection and structure determination

Colorless rectangular crystal (0.40x0.30x0.20 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[16]. Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure was solved by direct methods using the SHELXS program and refined by a full-matrix least-squares calculation on F^2 using SHELXL[17].

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 U iso(H) parameters were fixed at 1.2Ueq (C, N) and 1.5Ueq (methyl carbon). Molecular diagrams were generated using Diamond[18]. All geometrical calculations were done using the program Platon[19]. Table 1 summarizes the crystal data, intensity data collection and refinement details for the title compound.

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-asparagine suffered an amino acid racemization produced by the use of acetic acid in the synthesis[20]. Figure 1 shows the atom labeling and molecular conformation of *rac*-N-acetyl-2-thiohydantoin-asparagine. Selected geometrical parameters are presented in Table 2.

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

CCDC	984672
Chemical formula	$C_7H_9N_3O_3S$
Formula weight	215.23
Crystal system	Monoclinic
Space group	$P2_1/n$
a(Å)	9.338(7)
b(Å)	7.545(5)
c(Å)	13.212(10)
β(°)	97.10(2)
V(Å^3)	932.8(12)
Z	4
dx (g cm^{-3})	1.548
F(000)	448
μ(mm-1)	0.34
Crystal size (mm)	0.40 x 0.30 x 0.20
θ range (°)	2.5-28.1
hkl range	-10, 10; -6, 8; -15, 15
Reflections	
Unique	1777
Rint	0.046
With I > 2σ(I)	1328
Refinement method	Full-matrix least-squares on F^2
Number of parameters	128
R(F^2) [I > 2σ(I)]	0.061
wR(F^2) [I > 2σ(I)]	0.160
Goodness of fit on F^2	1.14
Max/min Δρ (e Å^{-3})	0.21/-0.31

All bond distances and angles are normal[21]. The thiohydantoin ring is essentially planar with a maximum deviations of 0.015 (3) Å in N1 and -0.015 (2) Å in C5. The S2-C2-N1, 130.6(3)° bond angle is greater than S2-C2-N3, 123.8(2)°, which is observed in other 31 thiohydantoin fragments found in the Cambridge Structural Database (CSD, version 5.34, May 2013)[21]. The acetyl group is almost coplanar with the thiohydantoin ring and form, with the mean plane of the ureido group, an angle of 81.0(2)°. The supramolecular structure and crystal packing of (I) are stabilized by three intermolecular N--H···O hydrogen bonds, which involve the carboxyl and ureido groups in the molecule, serving as both acceptors and donors in a set of interactions, as depicted in Figure 2. The geometrical parameters of these hydrogen bonds are summarized in Table 3.

Table 2: Selected geometrical parameters (Å, º)

S2-C2	1.633(3)	N1-C5	1.481(4)
O4-C4	1.205(5)	N3-C2	1.362(5)
N1-C2	1.396(4)	N3-C4	1.374(4)
S2-C2-N3	123.8(2)	S2-C2-N1	130.6(3)
N1-C2-N3	105.6(3)	O4-C4-N3	126.4(3)
C5-N1-C2-S2	178.2(2)	C4-N3-C2-S2	-179.7(2)

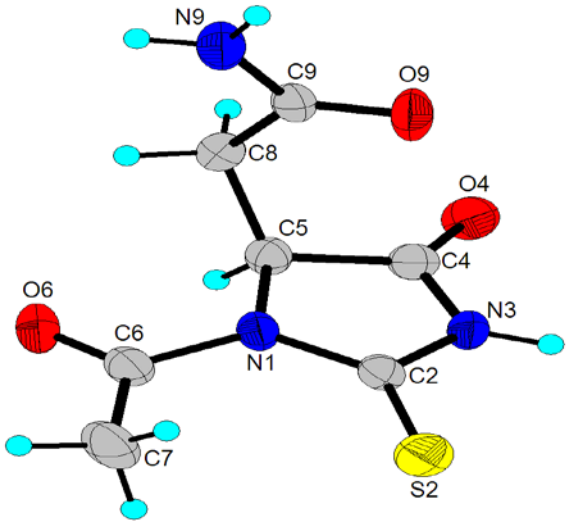


Fig. 1: The molecular structure of I, showing the atomic numbering scheme. Displacement ellipsoids are drawn at 50 % probability level. H atoms are shown as spheres of arbitrary radii.

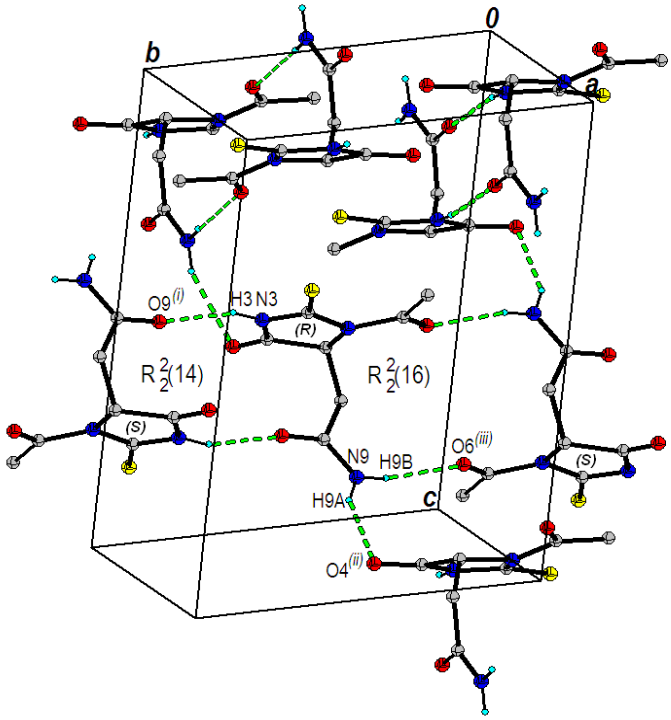


Fig. 2: A partial crystal packing view of (I). Intermolecular hydrogen bonds, N--H···O, are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity.

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

D--H···A	D—H	H···A	D···A	D--H···A
N3-- H3··O9(i)	0.860	1.960	2.782(4)	159.0
N9--H9A··O4(ii)	0.860	2.290	3.068(4)	151.0
N9--H9B···O6(iii)	0.860	2.130	2.963(4)	164.0
C7--H7B···S2	0.960	2.700	3.158(5)	110.0
C8--H8B···O6	0.970	2.480	3.019(5)	115.0
C8--H8A···O4(iv)	0.970	2.390	3.194(5)	139.0

Symmetry codes: (i)1-x, 1-y, 1-z, (ii)½-x, ½-y, ½+z, (iii)2-x, -y, 1-z, (iv)1-x, -y, 1-z

The N3--H3··O9 (1-x, 1-y, 1-z), N9--H9A··O4 (½-x, ½-y, ½+z) and N9--H9B···O6 (2-x, -y, 1-z) hydrogen bonds form rings, in alterned (*R*) and (*S*) molecules, with graph-sets notation $R^2_2(14)$ and $R^2_2(16)$[22,23] (see Figure 2). In addition to the classical hydrogen bonds, there are another two weak non-classical C--H···O and one C--H··S hydrogen bonds, which play the role of keeping the molecules together. The combination of these interactions produces a three-dimensional hydrogen bond network.

Conclusions

The title compound was synthesized by reaction of L-asparagine and thiourea in presence of anhydride acetic. In the supramolecular structure, the molecules are linked by N--H···O hydrogen bonds forming cyclic structures in a three-dimensional network.

Supplementary Materials

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (CCDC-984672). 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.

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