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# Synthesis and Structural Characterization of (S)-Tetrahydro-Pyrrol-[1,2,c]-Imidazole-1,3-Dione

**Gerzon E. Delgado*, Jines E. Contreras**

Laboratorio de Cristalografía, Departamento de Química, Facultad de Ciencias, Universidad de Los Andes, Mérida, 5101, Venezuela

**Abstract** In this work we present the synthesis and X-ray single crystal structural characterization of the heterocyclic compound (S)-tetrahydro-pyrrol-[1,2,c]-imidazole-1,3-dione. This material crystallize in the orthorhombic system with space group $P2_12_12_1$ (Nº19), Z=4, and unit cell parameters a = 7.136(1) Å, b = 8.009(2) Å, c = 11.378(2) Å. The molecular structure shows a hydantoin and pyrrolidine ring coupling forming a bicyclohydantoin. The crystal packing is governed by N--H···O hydrogen bond-type intermolecular interactions, forming infinite one-dimensional chains.

**Keywords** Hydantoin, Hydrogen Bonding, X-ray Crystal Structure

## 1. Introduction

The imidazolidine-2,4-dione, or hydantoin, is a common 5-member ring containing a reactive cyclic urea core[1,2]. This heterocycle represents a significant molecular template in combinatorial chemistry libraries[3-5], due principally to the four possible points of substitutions. The biological activities of hydantoin derivatives has been known for a long time, and are responsible for a wide variety of biological behavior[6], due principally to its wide range of therapeutic properties. For instance, several applications have been reported for hydantoins: antiarrhythmic and antihypertensive[7], antiviral[8], antineoplastic[9], antitumoral[10] and anticonvulsant agents[11]. The best knwon hydantoin, phenytoin, is the most widely used antiepileptic drug[12]. In addition, these compounds are used as herbicides[13] and fungicides agents[14]. On the other hand, the biocatalytic conversion of 5-subtituted hydantoins to amino acids has received considerable attention recently for their potential applications in the industrial productions of optically pure amino acids[15,16].

For these reasons, there has been much interest in the search of new synthetic routes for hydantoin via solution[17], or solid state reactions[18-21].

In our laboratory we are interested in the study of N-carbamoyl and hydantoin natural amino acids derivative compounds[22-26], therefore we report here the structure of (S)-tetrahydro-pyrrol-[1,2,c]-imidazole-1,3-dione, the hydantoin derivative of the natural amino acid L-proline. The analysis of the hydrogen bond patterns is also discussed.

* Corresponding author:
gerzon@ula.ve (Gerzon E. Delgado)
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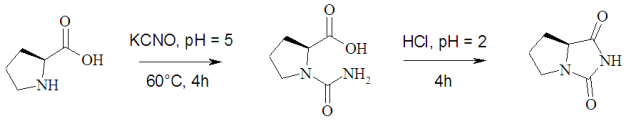
## 2. Experimental

### 2.1. Synthesis

The title compound was synthesized from L-proline using a methodology previously reported[22,23]. 500 mg (4.3 mmol) of L-proline was disolved in 20 mL of water and the solution was acidified with concentrated HCl (37 % v/v) to pH = 5. Then, 1050 mg (12.9 mmol) of KOCN was added to this solution. The mixture was warmed up, with agitation, to 60 °C, during 4 h. The resultant solution was acidified with HCl to pH = 2 and agitated during 4 h, until the precipitation of a white solid. (see scheme 1). The solid was filtered and washed with cool water. Colorless crystals of 1 suitable for X-ray diffraction analysis were grown by slow evaporation in a 1:1 methanol-water solution (m.p.: 210-212 °C). FT-IR 1757.6 $cm^{-1}$ [t, C=O], 1708.7 $cm^{-1}$ [t, C=O]. $^1$H NMR (400 MHz, DMSO-d6) δ =7.27 (H3), 4.07 (t, H5), 3.43 (q, H6A), 3.02 (q, H6B), 2.03 (s, H8A), 1.60 (s, H8B), 1.90 (m, H7A), 1.93 (H7B). $^{13}$C NMR (100.6 MHz, DMSO-d6) δ =161.0 (C2), 174.5 (C4), 64.0 (C5), 44.9 (C6), 26.7 (C8), 26.6 (C7).




**Scheme 1.** Synthesis of (S)-tetrahydro-pyrrol-[1,2,c]-imidazole-1,3-dione

### 2.2. X-ray crystallography

Colorless rectangular crystal (0.4, 0.2, 0.1 mm) was used for data collection. Diffraction data were collected at 298(2) K by ω-scan technique on a Rigaku AFC7S Mercury diffractometer [27] equipped with graphite- monochromatized MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz-polarization and absorption effects[28]. The

structure was solved by direct methods using the SHELXS program[29] and refined by a full-matrix least-squares calculation on $F^2$ using SHELXL[28]. The absolute structure was assigned from the known configuration of L-proline.

All H atoms were placed at calculated positions and treated using a riding model, with C-H distances 0.96-0.98 Å and Uiso(H) = 1.2Ueq(C)], N-H 0.86 Å and Uiso(H) = 1.2Ueq(N)].

## 3. Results and discussion

Figure 1 shows the molecular structure and the atom-labeling scheme of 1[30], and Table 1 shows the crystallographic data and structure refinement parameters.

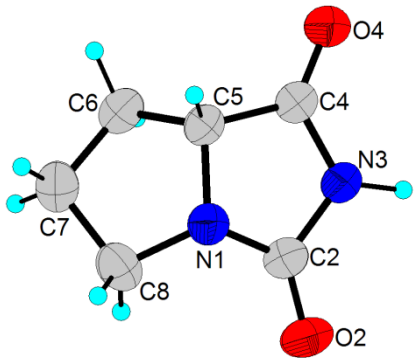



**Figure 1.** The molecular structure of 1, showing the atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level. H atoms are shown as spheres of arbitrary radii

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

| | |
|---|---|
| Chemical formula | $C_6H_8N_2O_2$ |
| Formula weight | 140.14 |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| a(Å) | 7.136(1) |
| b(Å) | 8.009(2) |
| c(Å) | 11.378(7) |
| V(Å$^3$) | 650.3(2) |
| Z | 4 |
| $d_x$ (g cm$^{-3}$) | 1.431 |
| F(000) | 296 |
| μ(mm$^{-1}$) | 0.110 |
| θ range (°) | 3.1-28.1 |
| hkl range | $-9 \le h \le 8, -9 \le k \le 9, -14 \le l \le 14$ |
| Reflections | |
| Collected | 7408 |
| Unique ($R_{int}$) | 1374 (0.026) |
| With $I > 2\sigma(I)$ | 1207 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Number of parameters | 93 |
| R($F^2$) [$I > 2\sigma(I)$] | 0.0389 |
| *w*R($F^2$) [$I > 2\sigma(I)$] | 0.1042 |
| Goodness of fit on $F^2$ | 1.09 |
| Max/min Δρ (e Å$^{-3}$) | 0.17/-0.13 |

The hydantoin ring is essentially plane with a maximal deviations of -0.049 (2) Å in N1 and 0.049 (2) Å in C2. The pyrrolidine ring shows maximal deviations to the average plane in the atoms C6 [0.225(2) Å] and C5 [0.189(2) Å].

The N1--C2--O2 bond angle 128.4(2)° is lightly greater than the N3--C2--O2 angle 124.7 (2)° (Table 2). This difference is also observed in the hydantoin molecule[31] and the others hydantoin derivative compounds found in the Cambridge Structural Database, CSD version 5.33 updates (Feb 2012)[32], including the same hydantoin structural report without hydrogen atoms[33].

The asymmetry parameter analysis of the pyrrolidine ring, [ΔCsmax= +47.1(3)°, ΔCsmin= +1.9(4)°, $\Delta C_2$max= +62.0(3)°, $\Delta C_2$min= 16.5(3)°, ΔCs(C8)=1.9(4)°, ΔCs(C6-N1) = 1.9(4)°], indicates that the same adopt an envelope conformation [34].

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

| | | | |
|---|---|---|---|
| O2-C2 | 1.215(2) | O4-C4 | 1.224(2) |
| N1-C2 | 1.352(2) | N1-C5 | 1.461(2) |
| N1-C8 | 1.468(2) | N3-C2 | 1.408(2) |
| N3-C4 | 1.356(2) | C4-C5 | 1.499(2) |
| C5-C6 | 1.522(2) | C6-C7 | 1.529(3) |
| C7-C8 | 1.529(3) | N1-C2-N3 | 106.9(1) |
| N1-C2-O2 | 128.4(2) | N3-C2-O2 | 124.7(2) |
| C2-N1-C5 | 110.9(1) | C2-N1-C8 | 123.0(1) |
| C5-N1-C8 | 111.6(1) | C2-N3-C4 | 111.9(1) |
| C5-N1-C2-O2 | -170.6(2) | C4-N3-C2-O2 | 172.1(2) |
| C8-N1-C2-O2 | -34.7(3) | C2-N3-C4-O4 | -177.5(2) |

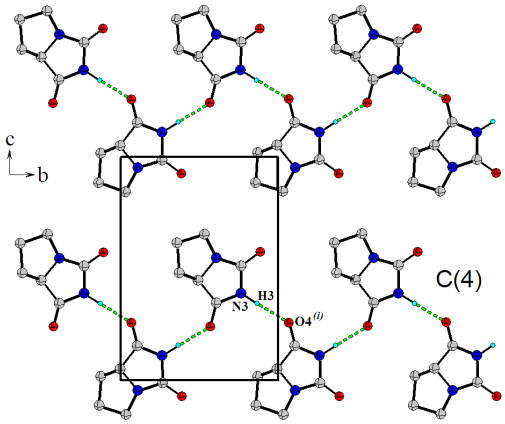



**Figure 2.** A portion of the crystal packing viewed in the cb plane. Intermolecular hydrogen bonds, N–H···O, are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity

The molecular structure and crystal packing of 1 are stabilized by intermolecular N3---3···O4 (-x, ½+y, ½-z) hydrogen bonds (Table 3), forming infinite one-dimentional zigzag chains that run along (010) direction, which can be described in graph-set notation as C(4)[35] (see Figure 2).

These chains that extend along the b axis overlap resulting in a lamellar packing type with molecules that pile up along the a direction, with average planes separated 3.57 Å.

**Table 3.** Hydrogen bonds geometry Selected (Å, º)

| D--H···A | D--H | H···A | D···A | D--H···A |
|---|---|---|---|---|
| N3--H3···O4$^{(i)}$ | 0.98 | 1.90 | 2.881 (2) | 174 |

Symmetry codes: $^{(i)}$-x, ½ + y, ½ - z

# 4. Conclusions

In the crystal structure of (S)-tetrahydro-pyrrol-[1,2,c]-imidazole-1,3-dione, the molecules are linked by N---H···O hydrogen bonds, forming infinite one-dimensional zigzag chains, running along [010] plane, with a C(4) graph-set motif.

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