ЖУРНАЛ СТРУКТУРНОЙ ХИМИИ

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CRYSTAL AND MOLECULAR STRUCTURE STUDIES OF 1′-BENZYL-8-(4-FLUOROBENZYL)-8-AZASPIRO[BICYCLO-[3.2.1]OCTANE-3,4′-IMIDAZOLIDINE]-2′,5′-DIONE

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The title compound 1′-Benzyl-8-(4-fluorobenzyl)-8-azaspiro[bicyclo[3.2.1] octane-3,4′-imidazolidine]-2′,5′-dione, $C_{23}H_{23}FN_3O_2$ is synthesized and the structure is investigated by X-ray diffraction studies. The compound crystallizes in the triclinic crystal class in the $P\bar{1}$ space group. The hydantoin ring adopts a planar conformation and is affected by the π conjugation. The pyrrolidine and piperidine rings in the bicyclo octane moiety adopt envelope and chair conformations respectively. The structure exhibits both inter- and intramolecular hydrogen bonds of the type N—H…O, C—H…O, and C—H…N. The oxygen atom in the hydantoin ring simultaneously accepts two hydrogen bonds to form a three-centered hydrogen bonding pattern.

K e y w o r d s: hydantoins, crystal structure, spiro centered, *chair* conformation, hydrogen bonding.

INTRODUCTION

In recent times hydantoins have been the subject of extensive investigations due to their biological properties. Hydantoins, 2,4-imidazolidine-diones, comprise a class of compounds that are of considerable interest. Many of these compounds possess clinically useful activities, especially as anticonvulsants (e.g., norantoin, mepheenytoin, nirvanol, and methetoin). The antiepileptic activity of 5,5-diphenyl-hydantoin has been known since 1938; it has been employed very effectively as the drug Dilantin. In addition, a number of other biological activities of hydantoin derivatives are known in their use as herbicides and fungicides. With limited improvement in diagnosis, surgical techniques, patient care, and adjuvant therapies, most of the deaths from cancer are due to metastases [1]. When cancer has metastasized, it may be treated with radio-surgery, chemotherapy, radiation therapy, biological therapy, hormone therapy or a combination of these. Angiogenesis has been described as one of the hallmarks of cancer [2]. The stimuli that promote tumor angiogenesis may be provided directly by the tumor cells themselves or indirectly by the host inflammatory cells that are attracted towards the tumor site. The inhibition of tumor angiogenesis affords attractive targets for the development of novel antitumor agents.

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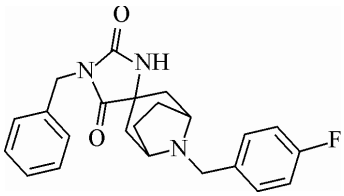
Fig. 1. Schematic diagram of the molecule



Earlier we have reported [5] the effect of novel hydantoin derivatives on the proliferation of human ovarian tumor cells such as SKOV-3, OVSAHO and murine osteosarcoma cells such as LM8 and LM8G7, which have metastatic potential to lung and liver respectively. The derivatives of hydantoin have a wide range of biological activities and therapeutic applications depending on the nature of substitution in the hydantoin ring [3]. Also, it has been reported that the structural characteristics of spirohydantoins are interesting because of their potential biological activities [4]. The title compound has exhibited antitumor property under *in vitro* conditions. This prompted us to study the molecular structure of the title compound. In continuation of our ongoing studies on hydantoins [5], herein we report the crystal structure of the title compound.

EXPERIMENTAL

Method of crystallization. After synthesis and purification [6], the resulting pure product was dissolved in ethylacetate and was left undisturbed. Due to slow evaporation of the solvent, white crystals grew after five days. A schematic diagram of the molecule is shown in Fig. 1.

Crystal Structure Determination. A single crystal of the title compound with the dimensions of 0.3×0.27×0.25 mm was chosen for an X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3 kW sealed X-ray source (graphite monochromated MoK_α). The crystal-to detector distance is fixed at 120 mm with a detector area of 441×240 mm^2. Thirty six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400 s. Successive frames were scanned in steps of 5° per min with an oscillation range of 5°. Image processing and data reduction were made using Denzo [7]. The reflections were merged with Scalepack [8]. All of the frames could be indexed using a triclinic crystal lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [9]. All of the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [9] with isotropic temperature factors for all the non-hydrogen atoms converged the residuals to 0.155. Anisotropic refinement of non-hydrogen atoms was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on their parent atoms. 263 parameters were refined with 3073 unique reflections, which converged the residuals to 0.0550. The details of crystal data and refinement are given in Table 1*.

The final atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms are listed in Table 2. Tables 3 give the list of selected bond distances and bond angles of non-hydrogen atoms respectively, which are in good agreement with the standard values. Fig. 2 represents the ORTEP [10] diagram of the molecule with thermal ellipsoids drawn at 50 % probability.

RESULTS AND DISCUSSIONS

The bond distances and bond angles in the hydantoin moiety are in good agreement with the corresponding values observed for amino-cycloalkanespiro-5-hydantoin [11]. As expected, the hydantoin ring is affected by π conjugation, which is evident from the N—C bond length values: N1—C2 = = 1.331(3) Å, N3—C2 = 1.395(3) Å and N3—C4 = 1.359(3) Å. These values are comparable with the values of 1.340(3) Å, 1.400(3) Å, and 1.370(4) Å reported previously for N-substituted nitropane spirohydantoin [12], but slightly differ from the values of 1.342(2) Å, 1.393(2) Å, and 1.362(1) Å reported for hydantoin and hydrogen-bonding patterns of hydantoin derivatives [13].

* CCDC 746774 consists of the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: +45(0)1223-336033): email:deposit@ccdc.cam.ac.uk

T a b l e 1

Crystal data and Structure Refinement

CCDC	746774
Empirical formula	$C_{23}H_{24}FN_3O_2$
Formula weight	393.45
Temperature, K	293(2)
Wavelength	0.71073
Crystal system	Triclinic
Space group	*P*1
Cell dimensions, Å, deg.	a = 9.3910(16), b = 10.836(2), c = 11.9450(9), α = 90.109(8), β = 67.664(10), γ = 66.877(6)
Volume, Å^3	1017.6(3)
Z	2
Density(calculated), Mg/m^3	1.284
Absorption coefficient, mm^{-1}	0.089
F(000)	416
Crystal size, mm	0.3×0.27×0.25
Theta range for data collection, deg.	2.6—25.0
Index ranges	$-10 \le h \le 11$, $-12 \le k \le 12$, $-13 \le l \le 14$
Independent reflections	3073
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3073 / 0 / 293
GOOF F^2	1.04
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0550, $wR2$ = 0.1592
Largest diff. peak and hole, e/Å^{-3}	0.28 and –0.18

The molecule possesses chiral centers at C7 and C9 with S and R conformations respectively. Since the molecule has crystallized in a centrosymmetric space group, we can surmise that the compound is a racemic mixture.

The hydantoin ring is almost planar with the C5 atom deviating by 0.045(3) Å from the mean plane defined by the N1, C2, N3, C4, and C5 atoms. The presence of a spiro center at C5 explains the longer C5—C4 bond distance of 1.531(3) Å in comparison with the values of 1.519(4) Å and 1.518(4) Å reported for amino-cycloalkanespiro-5-hydantoin [11]. A study of the torsion angles,

T a b l e 2

Selected bond Lengths (Å) *and bond angles* (deg.)

Atoms	Length	Atoms	Length	Atoms	Angles	Atoms	Angles
N1—C2	1.331(3)	C4—O13	1.213(3)	O14—C2—N3	122.8(2)	N3—C4—C5	107.6(2)
N1—C5	1.462(3)	C4—C5	1.531(3)	N1—C2—N3	107.9(2)	N1—C5—C4	99.9(2)
C2—O14	1.221(3)	C7—C6	1.531(3)	C4—N3—C2	111.0(2)	N1—C5—C6	114.1(2)
C2—N3	1.395(3)	C9—C10	1.527(3)	C4—N3—C15	126.1(2)	C2—N1—C5	113.1(2)
N3—C4	1.359(3)	C9—C12	1.537(4)	C2—N3—C15	122.7(2)	O14—C2—N1	129.3(2)
N3—C15	1.465(3)	C7—C11	1.542(3)	O13—C4—N3	125.6(2)	C4—C5—C6	110.3(2)
				O13—C4—C5	126.8(2)		

asymmetric parameters and least-squares plane calculations reveals that the pyrrolidine ring in the bicyclo octane moiety adopts an *envelope* conformation. The piperidine ring in the same moiety adopts a *chair* conformation with the N8 and C5 atoms deviating by –0.875(3) Å and 0.477(3) Å, respectively from the least-square plane defined by the C6, C7, C9, and C10 atoms. This is confirmed by the puckering parameters: Q = = 0.661(3) Å, $\theta = 154.7(3)°$, and φ = = 180.8(5)°. The C7—C6 and C9—C10 bonds make an angle of 12.6(2)° and 11.9(2)° respectively with the Cremer and Pople plane [14] of the piperidine ring and thus are in the axial plane of the piperidine ring. Also, the C7—C11 and C9—C12 bonds of the pyrrolidine ring make an angle of 14.7(1)° and 14.3(2)° with the Cremer and Pople plane of the piperidine ring indicating that the pyrrolidine ring lies in the axial plane of the piperidine ring. The plane of the piperidine ring is nearly perpendicular to the plane of the hydantoin ring, as evident from the dihedral angle value of 88.46(14)°. This value differs from the value of 59° reported for N-methyltropane-3-spiro-5′-hydantoin [15]. The dihedral angle between the hydantoin and phenyl rings bridged by the CH2 group is 73.97(2)°, while the flurophenyl ring makes an angle of 66.18(2)° with the piperidine ring.

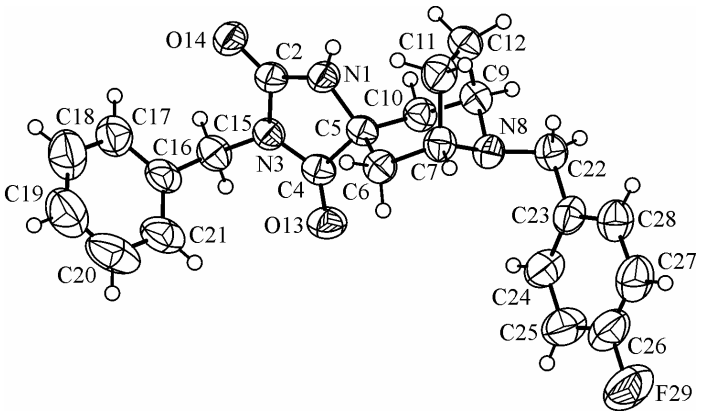


Fig. 2. ORTEP diagram of the molecule with thermal ellipsoids drawn at 50 % probability

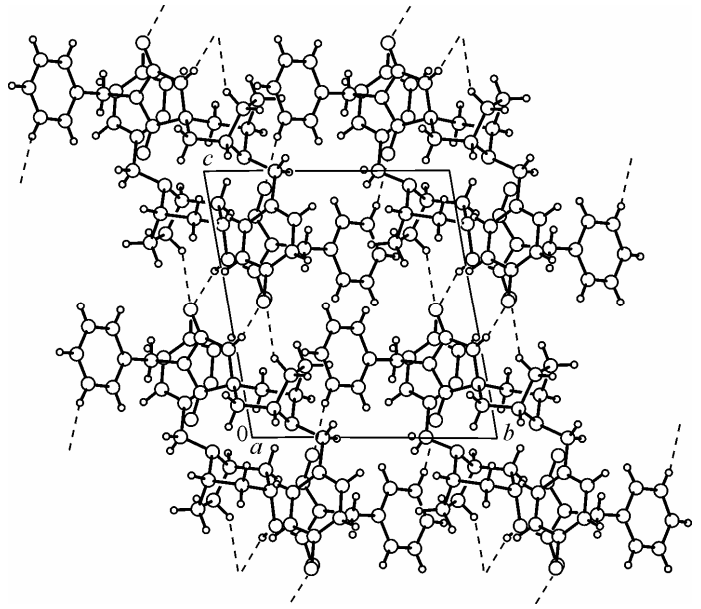


Fig. 3. Packing of the molecule when viewed along the *a*-axis. The dashed lines represent the hydrogen bonds

The molecules within the crystal lattice are separated by normal van der Waals forces. Hence, the crystal packing is due to van der Waals forces and hydrogen bondings [16]. Both oxygen atoms attached to the hydantoin rings accept the hydrogen bonds [17]. The O14oxygen atom of the keto group in the hydantoin ring simultaneously accepts two hydrogen bonds to form a three-centered hydrogen bonding pattern. The structure exhibits both inter- and intramolecular hydrogen bonds of the type N—H…O, C—H…O, and C—H…N. The intermolecular N1—H1O14 hydrogen bond has a length of 2.845(3) Å and an angle of 162°; C11—H11A…O14 has a length of 3.306(3) Å and an angle of 133°; while C20—H20…O13 has a length of 3.426(5) Å and an angle of 171° with symmetry codes –*x*, 2–*y*, 1–*z* and 1–*x*, 1–*y*, –*z* respectively. Fig. 3 shows packing of the molecules when viewed along the *a*-axis. The packing indicates that the molecules are stacked in pairs and they exhibit layered stacking.

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