Universal Journal of Physics and Application 11(2): 57-61, 2017 http://www.hrpub.org
DOI: 10.13189/ujpa.2017.110203

Crystal Structure and Theoretical Study of N,N-di[(5-chloro-2-oxo-2,3-dihydrobenzo[d]oxazole-3-yl) methyl]ethanamine

Abdullah Aydin[1,*], Zeynep Soyer[2], Mehmet Akkurt[3], Orhan Buyukgungor[4]

[1]Department of Mathematics and Science Education, Faculty of Education, Kastamonu University, Turkey
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University, Turkey
[3]Department of Physics, Faculty of Sciences, Erciyes University, Turkey
[4]Department of Physics, Faculty of Arts and Sciences, Ondokuz Mayis University, Turkey

Abstract The aim of the present work is to explore crystal and electronic structure of N,N-di[(5-chloro-2-oxo-2,3-dihydrobenzo[d]oxazole-3-yl) methyl]ethanamine. In the title compound, $C_{18}H_{15}Cl_2N_3O_4$, the two 2, 3-dihydro-1, 3-benzoxazole ring systems are almost planar and make a dihedral angle of 96.12(7) with each other. The ethyl group is disordered over two set of sites with a site-occupancy ratio of 0.766(12):0.234(12). The crystal structure contain intermolecular C—H...O hydrogen bonds which form a zigzag chains along the c-axis, C—H...π interactions and π-π stacking interactions [centroid-centroid distance = 3.5668(19) Å].

Keywords Crystal Structure, 2(3H)-Benzoxazolone, Hydrogen Bonding, π-π Stacking Interactions, AM1 Method

1. Introduction

A series N-substituted-5-chloro-2(3H)-benzoxazolone derivatives were synthesized and evaluated by [1] their acetylcholinesterase inhibitory activity. These compounds were synthesized by Mannich reaction of 5-chloro-2(3H)-benzoxazolone with the appropriated amines. The acetylcholinesterase inhibitory activity of the title compounds was determined by colorimetric Ellman\'s method. The preliminary screening results indicated that 5-chloro-2-(3H)-benzoxazolone scaffold demonstrated different inhibition range against acetylcholinesterase enzyme depending on the structural differences.

2(3H)-Benzoxazolone, as one of the most versatile heterocyclic ring, produce diverse compounds with a wide range of biological activities such as anti-HIV [2], anticancer [3], analgesic [4], anti-inflammatory [5], antinociceptive [6], antimicrobial [7], anticonvulsant [8], antimalarial [9], human leukocyte MPO clorinating inhibitor activity [10].

In this paper the title compound, $C_{18}H_{15}Cl_2N_3O_4$ was prepared and characterized using elemental analysis and FT-IR and ^{1}H-NMR spectroscopy studies. The crystal and molecular structure of the title compound was determined from single-crystal X-ray diffraction data. It crystallizes in the monoclinic space group $P2_1/c$. Semi-emprical molecular orbital calculations were carried out using the AM1 method.

2. Experimental

2.1. Synthesis and Crystallization

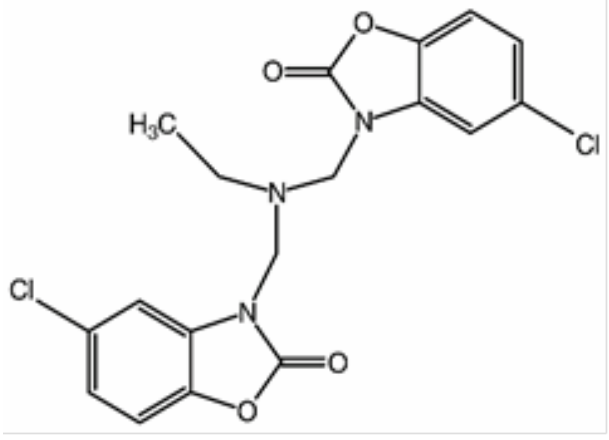

Figure 1. Schematic diagram of (I)

4-chloro-2-aminophenol (10 mmol), urea (50 mmol) and 37% HCl (2.5 ml) were irradiated (300 W, 413 K) for 15 min in a microwave oven. After completion of reaction (by monitoring with TLC), water (10 ml) was added to the reaction mixture and stirred at room temperature for 1 h. The resulting precipitate was filtered and washed with water.

After drying the precipitate was by crystallization from ethanol-water (1:1) to yield 5-chloro-2(3H)-benzoxazolone.

This compound (2 mmol) was dissolved in methanol (5 ml). Ethylamine (2 mmol) and 37% formalin (2.5 mmol) were added to this solution. The mixture was stirred vigorously for 3h. The resulting precipitate was filtered and washed with cold methanol. The crude product was crystallized from methanol-water (1:1) (Figure 1).

Yield 52%; M.p.: 420 K; MS (ESI) m/z (%): 239 (100), 241 (31), 408 (M+H, 10), 410 (M+H+2, 4), 412 (M+H+4, 1).

2.2. Crystal Structure Analysis

In this study, the crystal structure of the title compound, N,N-di[(5-chloro-2-oxo-2,3-dihydrobenzo[d]oxazole-3-yl) methyl]ethanamine, was determined by X-ray analysis. The crystal structure of the title compound was solved by direct methods and was refined by a full-matrix least-squares method on F^2. A summary of the crystallographic data is given in Table 1.

Table 1. The results of the X-ray structure analysis of the title compound

Crystal data	
CCDC no	1543745
$C_{18}H_{15}Cl_2N_3O_4$	D_x = 1.495 Mg m^{-3}
M_r = 408.23	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 7238 reflections
a = 5.7628 (7) Å	θ = 1.2–25.9°
b = 35.059 (3) Å	μ = 0.388 mm^{-1}
c = 8.9921 (11) Å	T = 296 (2) K
β = 92.948 (10)°	Prism, light yellow
V = 1814.3 (3) Å^3	0.760 × 0.313 × 0.040 mm
Z = 4	
Data collection	
STOE IPDS 2 diffractometer	1315 reflections with I > 2σ(I)
ω scans	R_{int} = 0.077
Absorption correction: integration	θ_{max} = 25.0°
T_{min} = 0.9412, T_{max} = 0.9813	h = -6 → 6
11421 measured reflections	k = -41 → 40
3098 independent reflections	l = -10 → 10
Refinement	
Refinement on F^2	Calculated weights w = $1/[\sigma^2(F_o^2) + (0.0158P)^2]$ where P = $(F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.0423	$(\Delta/\sigma)_{max}$ = 0.000
$wR(F^2)$ = 0.0529	$\Delta\rho_{max}$ = 0.163 e Å^{-3}
S = 0.806	$\Delta\rho_{min}$ = -0.163 e Å^{-3}
3098 reflections	Extinction correction: none
263 parameters	

A single crystal suitable for X-ray diffraction obtained in methanol-water was light yellow and prismatic. The data were collected using a STOE X-AREA [11], using graphite-monochromated MoKα radiation. Diffraction measurements were made at 296 K. The cell was refined on a X-AREA and the data were reducted on a X-RED32 [11]. The structure was solved by direct methods using SIR-97 [12] and refined by a full-matrix least-squares on F^2 and by using the program SHELXL-97 [13]. N-bound and C-bound H atoms were positioned geometrically [N—H = 0.86 Å, C—H = 0.93-0.97 Å] and refined using a riding model with U_{iso}(H) =1.5 U_{eq}(C) for methyl H atoms and U_{iso}(H) = 1.2U_{eq}(C, N) for the others. The software used to prepare material for publication: WinGX publication routines [14]. Empirical absorption corrections were applied by integration (XRED-32; [11]). Molecular graphics: ORTEP-3 for Windows [15]; PLATON [16] and PARST [17].

3. Result and Discussion

3.1. Spectral Studies

The synthesized compound was characterized IR and ^{1}H-NMR data. The ^{1}H-NMR data of the compound obtained in $CDCl_3$ solution were given in the experimental section and was consistent with the structural results. The significant absorption bands of the compound are given in Table 2.

Table 2. The important IR and ^{1}H-NMR signals of the title compound

IR (FT-IR/ATR, cm^{-1})	^{1}H-NMR ($CDCl_3$, δ)
2968	1.18 (3*H*, t, J=7.2 Hz, CH_2CH_3),
1769	2.92 (2*H*, q, J=7.2 Hz, CH_2CH_3)
1037	4.90 (4*H*, s, 2xCH_2)
	7.00 (2*H*, t, J=1.6 Hz, Ar-H)
	7.09-7.14 (4*H*, m, Ar-H)

3.2. Description of the Crystal Structure of $C_{18}H_{15}Cl_2N_3O_4$

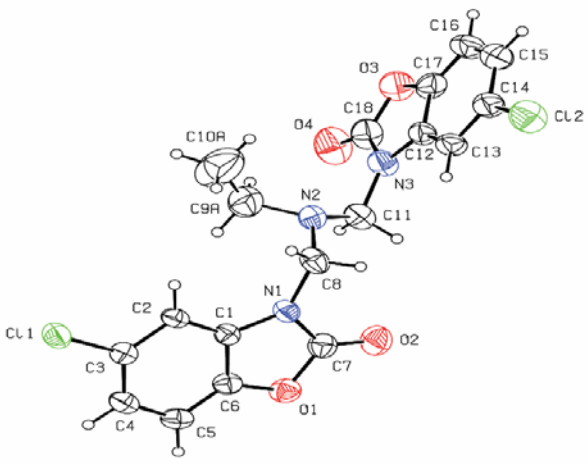

Figure 2. View of the title molecule (I) with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level. Only the major component of the disordered ethyl goup is shown.

An ORTEP drawing of the title molecule with 30 % probability displacement thermal ellipsoids and atom-labeling scheme are shown in Figure. 2. Crystal data and details for the crystal structure determination of the compound are listed in Table 1, and selected bond lengths, bond and torsion angles are given in Table 3. As the C–O and C–C distances, and O–C–C angles, geometric parameters all lie in the expected ranges [18].

In the title compound (Figure 2) the two nine-membered 2, 3-dihydro-1, 3-benzoxazole ring systems (O1/N1/C1–C7 and O3/N3/C12–C18) of the title compound (I) are essentially planar [maximum deviations = -0.033(4) for C7 and 0.005(4) Å for C18, respectively] and make a dihedral angle of 96.12(7)° with each other. The N1—C8—N2—C11 and N3—C11—N2—C8 torsion angles are 77.2(4) and 142.1(3)°. The values of all bond lengths and angles in (I) are normal and are consistent with those reported for the related compounds [19-20].

In the crystal, molecules are linked by C—H...O hydrogen bonds (Table 4 and Figure 3), forming a zigzag chains along the [001] direction. In addition, C—H... π interactions and π-π stacking interactions [$Cg1...Cg3^{iii}$ = 3.5668(19) Å, where symmetry codes: (*iii*) = 1-*x*,-*y*,-*z*; *Cg*1 and *Cg*3 are the centroids of the O1/N1/C1/C6/C7 oxazole ring and the C1—C6 benzene ring, respectively] are observed.

Table 3. Selected bond lengths (Å), angles (º) and torsion angles (º) of the title compound

Cl1—C3	1.734 (3)	N1—C1	1.393 (4)
Cl2—C14	1.734 (4)	N1—C7	1.361 (5)
O1—C6	1.380 (4)	N2—C8	1.413 (5)
O2—C7	1.196 (5)	N3-C18	1.369 (5)
C1—N1—C7	109.5 (3)	N1—C8—N2	117.9 (3)
C7—N1—C8	121.9 (3)	O3—C17—C16	128.4 (3)
C8—N2—C9A	117.9 (5)	O3—C18—N3	107.9 (4)
N1—C1—C2	133.0 (3)	Cl1—C3—C2	118.9 (3)
N1—C1—C6	105.9 (3)	Cl2—C14—C15	119.0 (3)
O1—C6—C1	109.6 (3)	N2—C9A—C10A	100.1 (8)
O1—C7—N1	107.8 (3)	C13—C14—C15	122.3 (4)
O1—C7—O2	122.5 (4)		
C7—O1—C6—C5	-178.2 (3)	C12—N3—C18—O4	-179.3 (5)
C18—O3—C17—C16	-179.5 (4)	C1—C2—C3—Cl1	179.3 (2)
C7—N1—C1—C2	177.5 (3)	Cl1—C3—C4—C5	-178.7 (3)
Cl2—C14—C15—C16	178.3 (3)	C12—C13—C14—Cl2	-178.8 (3)
C1—N1—C7—O2	-178.7 (4)	C8—N1—C7—O2	-7.7 (6)
C15—C16—C17—C2	0.3 (6)	C11—N3—C18—O4	-0.7 (7)
C11—N3—C18—O3	179.2 (3)	N3—C12—C17—O3	0.4 (4)
N1—C1—C2—C3	-179.3 (3)		

Table 4. Hydrogen-bonding geometry (Å, °)

	D—H	H...*A*	D...A	*D*—H...*A*
C15—H15...O4	0.93	2.58	3.213 (5)	126
C10B—H10D...*Cg*4	0.96	2.98	3.830 (3)	149

*Cg*4 is a centroid of the C12—C17 benzene ring.

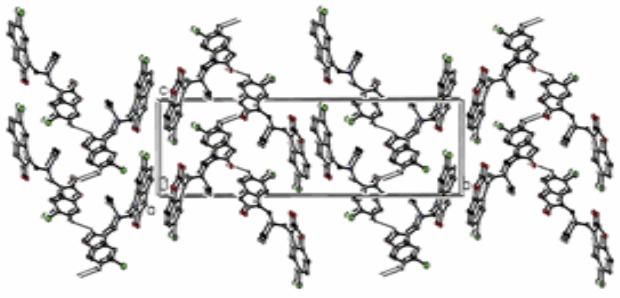

Figure 3. Packing diagram of (I), viewed down the a axis, with the hydrogen bonds (dashed lines). For clarity, H atoms not involved in hydrogen bonding and the minor component of the disordered ethyl group have been omitted.

3.3. Theoretical Study

Semi-empirical molecular orbital calculations of the title compound were carried out using the AM1 method [21] with *WinMopac*7.2 software [22]. A spatial view of the single molecule of the title compound calculated in the gas phase is shown in Figure 4. The two planar 2,3-dihydro-1,3-benzoxazole ring systems of (I) make a dihedral angle of 68.83° with each other. The conformational analysis of the molecule as theoretically obtained (Figure 4) is in a good agreement with the X-ray structure. The calculated dipole moment of (I) is 5.430 Debye. The HOMO and LUMO energy levels are -9.35210 and -.48704 eV, respectively.

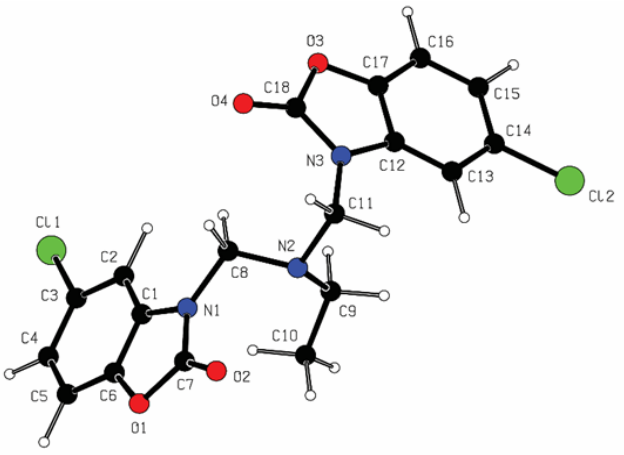

Figure 4. A spatial view of the calculated molecule of the title compound

4. Conclusions

In conclusion, $C_{18}H_{15}Cl_2N_3O_4$ has been synthesized and structurally characterized. We summarize the results from synthesis and X-ray diffraction measurements for (I) single crystal. In the molecule, the ethyl group is disordered over two positions with occupancies of 0.766(12) (for atom labelled A) and 0.234(12) (for atom labelled B). The terminal C atoms of the disordered ethyl group were refined anisotropically with the U_{ij} values restrained to behave isotropically, with the ISOR instruction [ISOR 0.010 C10A C10B].

In the crystal, molecules are linked by C—H...O hydrogen bonds forming a zigzag chains along the [001] direction. In addition, C—H... π interactions and π-π stacking interactions are observed.

According to the Semi-empirical molecular orbital calculations of the title compound with the AM1, the calculated dipole moment of (I) is 5.430 Debye. The HOMO and LUMO energy levels are -9.35210 and -.48704 eV, respectively.

Supplementary Information

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1543745 for compound N,N-di[(5-chloro-2-oxo-2,3-dihydrobenzo[d]oxazole-3-yl) methyl]ethanamine.

Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223–336–033; e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgements

The authors acknowledge the Faculty of Arts and Sciences, Ondokuz Mayis University, Turkey, for the use of the Stoe *IPDS* 2 diffractometer (purchased under grant F.279 of the University Research Fund).

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