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Research paper

Crystal structure of 2-[(2-acetoxyethoxy) methyl]-3-amino-1,2,4-triazin-5(2*H*)-one

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Abstract

The X-ray structural investigations has been carried out for the title compound, 2-[(2-acetoxyethoxy)methyl]-3-amino-1,2,4-triazin-5(2*H*)-one (1-[(2-acetoxyethoxy)methyl]-6-azaisocytosine), molecular formula $C_8H_{12}N_4O_4$, crystallizes in a monoclinic space group *P*-1 with a = 5.3124(3) Å, b = 7.3635(3) Å, c = 14.0170(8) Å, α = 81.5265(19)°, β = 85.852(2)°, γ = 76.760(2)°, V = 527.49(5) Å^3 and Z = 2, resulting in a density, D_{calc}, of 1.437 g/cm^3. The hydrogen-bonding systems assemble with N-H···O [graph set $C_1^1(6)$], N-H···N [graph set $R_2^2(8)$], and N-H···N combine with N-H···O [graph set $R_4^4(12)$]. The side chain of the molecular structure is further stabilized by short contacts formed by intermolecular C-H···O interactions.

Keywords: *1,2,4-Triazine; 1,2,4-Triazin-5(2H)-one; Acyclic Nucleoside Analogue; X-Ray Crystal Structure; Hydrogen Bonds.*

1. Introduction

9-(2-hydroxyethoxymethyl)guanine (Acyclovir®), which is a prototype of acyclic nucleosides, has been a drug of choice for the treatments of herpetic infections (Elion et al. 1977, Schaeffer et al. 1978). In Fig. 1 the title compound, 2-[(2-acetoxyethoxy)methyl]-3-amino-1,2,4-triazin-5(2*H*)-one(I), bears a (2-acetoxyethoxy)methyl side chain, which easily be deacetylation to form a 2-hydroxyethoxymethyl group, the deprotective group similar to side chain of acyclovir as a part of important pharmacophore. 1,2,4-Triazine is an aza analogue of pyrimidine, and its derivatives form an important class of heteroaromatic compounds with various interesting biochemical properties (Neunhoeffer & Wiley 1978). The aglycone, 3-amino-1,2,4-triazin-5(2*H*)-one (6-azaisocytosine, II), of title compound is an isosteric isomer of isocytosine. We expect the acyclic nucleoside of title compound and it derivate compounds have several promising biochemical properties. Previously, we had studied the crystal structure of 3-amino-1,2,4-triazin-5(2*H*)-one(II), which are linked by extensive hydrogen-bonding systems assemble with N-H···O [graph set $C_1^1(6)$] and N-H···N [graph set $R_2^2(8)$] (Hwang et al. 2002). Another compound 3-amino-2-benzyl-6-bromo-1,2,4-triazin-5(2*H*)-one have hydrogen-bonding systems assemble with N-H···O [graph set $C_1^1(6)$], N-H···N [graph set $R_2^2(8)$], and N-H···N combine with N-H···O [graph set $R_4^4(12)$] (Hwang et al. 2010, Hwang et al. 2016). In the present paper, we provide the information about the aglycone and acyclic nucleoside chain of title compound by X-ray crystallographic structure analysis.

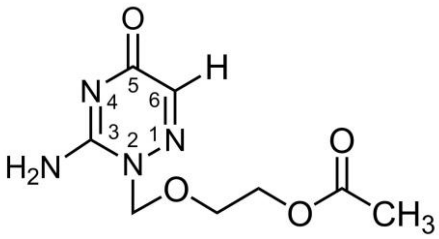

Fig. 1: Chemical Structure of the Title Compound and IUPAC Atom-Numbering Scheme.

2. Results and discussion

2.1. X-ray techniques

The title compound was prepared according to a method described by Hwang (Hwang et al. 1995). A plate colorless crystal having dimensions of 0.269 × 0.246 × 0.049 mm^3 was obtained by recrystallization from a CH_3OH/CH_2Cl_2 diffusion solvent system. The X-ray data were collected by a graphite-monochromatized Mo K_α radiation (λ = 0.71073 Å) at 200(2) K. The crystal structure was solved by direct methods using SHELXS-97, and refined by full-matrix least-squares methods on F^2 using SHELXL-2014/7. All of the non-hydrogen atoms were refined anisotropically. All hydrogen atom positions were calculated and included in the calculation using the riding atom model. The final positional parameters for all non-hydrogen atoms are given in Table 1. The final cycle of full-matrix least-squares refinement gave R_1 = 0.0545, wR_2 = 0.1424 ($w = 1/[\sigma^2(F_o^2) + (0.0515P)^2 + 0.6594P]$, where $P = (F_o^2 +$

$2F_c^2$)/3). The crystal and experimental data are given in Table 2. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1535722).

Table 1: Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3)

	x	y	z	U(eq)
N1	5650(4)	8896(2)	3524(1)	24(1)
C1’	7067(5)	6998(3)	3369(2)	27(1)
O2’	6153(3)	6334(2)	2615(1)	30(1)
C2	3393(4)	9252(3)	4068(2)	21(1)
N3	2306(3)	10969(2)	4286(1)	24(1)
C3’	7105(5)	6967(3)	1675(2)	33(1)
C4	3464(4)	12410(3)	3943(2)	24(1)
C4’	6965(5)	5523(3)	1043(2)	37(1)
O5’	9067(3)	3928(2)	1313(1)	34(1)
C5	5789(5)	11972(3)	3318(2)	31(1)
N6	6839(4)	10303(3)	3125(1)	29(1)
C6’	9110(5)	2348(4)	946(2)	34(1)
N7	2253(4)	7852(3)	4404(2)	29(1)
C7’	11389(5)	837(4)	1263(2)	40(1)
O8	2607(3)	14012(2)	4156(1)	33(1)
O8’	7470(4)	2200(3)	436(2)	64(1)

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Table 2: Crystal and Experimental Data

Formula: $C_8H_{12}N_4O_4$
Formula weight = 228.22
Crystal system: triclinic
Space group: *P*-1
a = 5.3124(3) Å
b = 7.3635(3) Å
c = 14.0170(8) Å
α = 81.5265(19)°
β = 85.852(2)°
γ = 76.760(2)°
V = 527.49(5) Å^3
Z = 2
D_{calc} = 1.437 g/cm^3
Radiation: Mo K$_\alpha$ (λ = 0.71073 Å)
μ(Mo K$_\alpha$) = 0.117 mm^{-1}
F(000) = 240
No. of reflections collected = 4444
No. of independent reflections = 2413 (R_{int} = 0.0179)
θ range for data collection: 2.868 to 27.492°
Data/Restraints/Parameters = 2413/0/146
Goodness-of-fit on F^2 = 1.078
R indices [I>2σ(I)]: R1 = 0.0545, wR2 = 0.1424
R indices (all data): R1 = 0.0683, wR2 = 0.1495
$(\Delta/\sigma)_{max}$ = < 0.001
$(\Delta\rho)_{max}$ = 0.324 eÅ^{-3}
$(\Delta\rho)_{min}$ = – 0.360 eÅ^{-3}
Measurement: Bruker APEX3
Program system: Bruker SAINT
Structure determination: Direct methods (SHELXS-97)
Refinement: full-matrix least-squares (SHELXL-2014/7)
CCDC deposition number: CCDC 1535722

2.2. Analysis of the X-ray crystallographic structure

An ORTEP drawing for the title compound is depicted in Fig. 2. From this X-ray analysis of the title compound, revealing the 1,2,4-triazine ring is slightly distorted. Obviously, the extending out acyclic nucleoside chain is located at N1 (i.e., N-2), which is compatible well to the tautomeric proton 2-H located at N-2 of the compound 3-amino-1,2,4-triazin-5(2*H*)-one (6-azaisocytosine, II), as reported by us (Hwang et al. 2002). A comparison of selected bond lengths and angles for compounds I and II in Table 3. In title molecular the N1 atom of 1,2,4-triazine ring with the acyclic nucleoside chain atom C1'-O2' makes a bond angle 113.2(2)° (N1-C1'-O2').

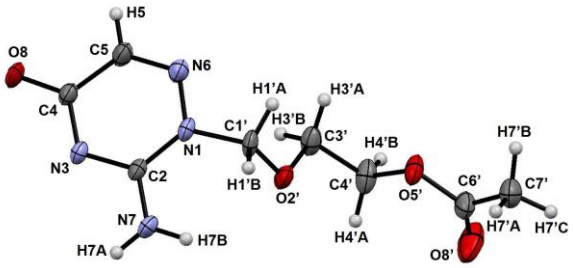

Fig. 2: ORTEP Drawing of the Title Compound with Atom Labeling, Thermal Ellipsoids Drawn at the 50% Probability Level.

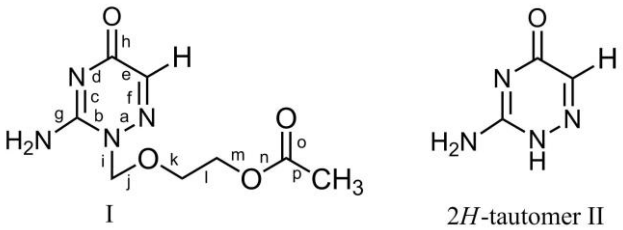

Table 3: Comparison of Selected Bond Lengths (Å) and Bond Angles (°) for I and II.

Bond Lengths & Angle	I	II*
a	1.365(3)	1.357(2)
b	1.368(3)	1.357(2)
c	1.334(3)	1.333(2)
d	1.357(3)	1.353(2)
e	1.464(3)	1.470(2)
f	1.287(3)	1.283(2)
g	1.324(3)	1.320(2)
h	1.235(3)	1.241(2)
i	1.466(3)	-
j	1.388(3)	-
k	1.428(3)	-
l	1.498(3)	-
m	1.449(3)	-
n	1.334(3)	-
o	1.200(3)	-
p	1.488(4)	-
∠ab	121.68(17)	123.20(12)
∠bc	122.13(19)	121.92(13)
∠cd	118.73(18)	117.92(12)
∠de	116.83(18)	117.68(12)
∠ef	123.7(2)	123.22(13)
∠fa	116.74(19)	116.06(12)
∠bg	119.46(18)	117.20(13)
∠cg	118.4(2)	120.89(13)
∠dh	121.5(2)	121.70(13)
∠eh	121.6(2)	120.61(13)
∠ai	114.60(18)	-
∠bi	123.63(18)	-

* Data from reference [4].

2.3. Analysis of the molecular packing

The molecular packing of the title compound are shown in Fig. 3 and Fig. 4. An analysis of the molecular packing in the unit cell reveals that each molecule is linked with three other molecules by intermolecular hydrogen bonds (Table 4 and Fig. 5). Each title molecule is linked into the $C_1^1(6)$ graph set association via N-H···O hydrogen bond interactions (Fig. 5 notation [a], [b]). Meanwhile, each molecule is linked into the $R_2^2(8)$ graph set association via two N-H···N hydrogen bond interactions (Fig. 5 notation [c], [d]). Furthermore, another type of hydrogen bond involves interactions via N-H···N combined with N-H···O that are linked into the $R_4^4(12)$ graph set association. The amino atom N7^{i} acts as a hydrogen-bond donor, via H7A^{i}, to nitrogen atom N3^{iv} at (–x, 3 – y, 1 – z) to form a N-H···N hydrogen bond interaction

(Fig. 5 notation [e]). Meanwhile, the amino atom N7^{iii} acts as hydrogen-bond donor, via H7B^{iii}, to the oxygen atom O8^{iv} to form a N-H···O hydrogen bond interaction (Fig. 5 notation [f]). Therefore, together with four hydrogen-bond [a], [c], [f], and [e] to form a $R_4^4(12)$ graph set association. It's worth noting that the acyclic nucleoside chain of the molecular is further stabilized by a short contacts formed by intermolecular C-H···O interactions, which revealed a meaningful short H5···O2'^{i} and O2'···H5^{ii} (Fig. 5 notation [g] and [h]) having the same short contact distance of 2.419(1) Å. The assignment of the H-bond descriptors is based on the graph-set theory (Bernstein et al. 1994).

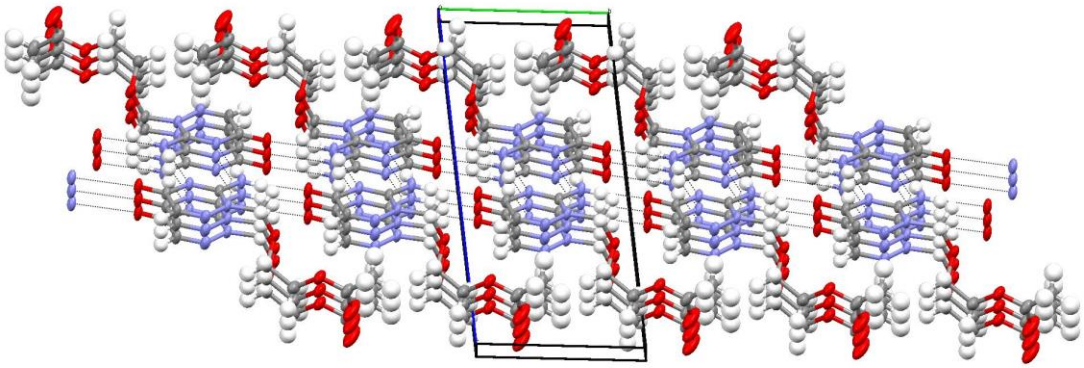

Fig. 3: A Perspective Drawing of the Packing Arrangement of the Title Compound, Showing the Molecules' Direction along the A-View with X-6°. Dashed Lines are Intermolecular N−H···O and N−H···N Hydrogen Bonds.

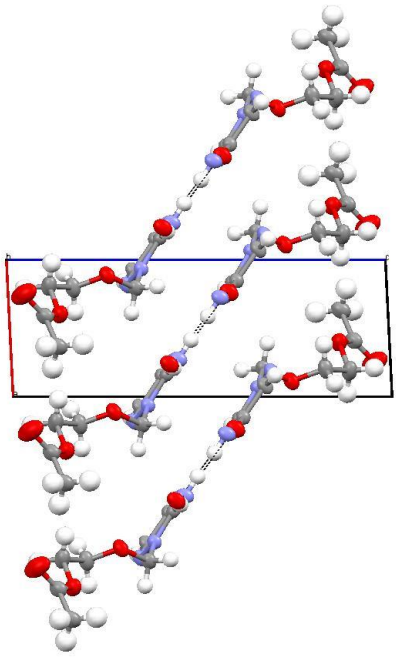

Fig. 4: A Perspective Drawing of the Packing Arrangement of the Title Compound, Showing the Molecules' Direction along the B-View. Dashed Lines are Intermolecular N−H···O Hydrogen Bonds.

Table 4: Hydrogen-Bond Geometry (Å, °)

Notation	D−H···A	D−H	H···A	D···A	D−H···A
a	N7−H7B^{i}···O8	0.88	2.062	2.862(3)	150.7
b	N7−H7B···O8^{ii}	0.88	2.062	2.862(3)	150.7
c	N7−H7A···N3^{iii}	0.88	2.109	2.975(3)	167.9
d	N7−H7A^{iii}···N3	0.88	2.109	2.975(3)	167.9

Symmetry codes: (i) x, 1 + y , z; (ii) x, –1 + y, z; (iii) –x, 2 – y, 1 – z.

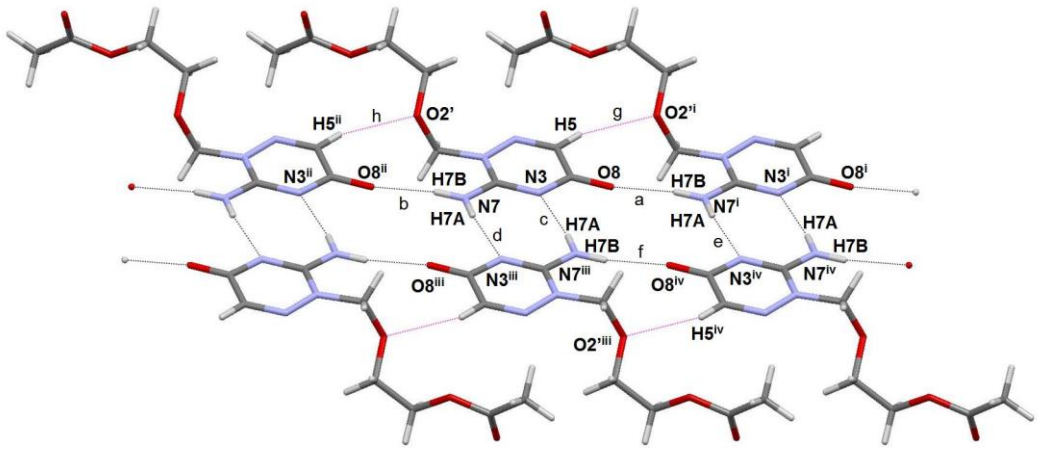

Fig. 5: Intermolecular N-H···O, N-H···N and C-H···O Contacts in the Title Compound. for the Notation and Symmetry Codes See Table 4 and in the Text.

3. Conclusion

In conclusion, from X-ray crystallographic structure analysis shows 3-amino-1,2,4-triazin-5(2*H*)-one, which contain N-H···O [graph set $C_1^1(6)$] and N-H···N [graph set $R_2^2(8)$] hydrogen-bonding systems (Hwang et al. 2002). The increase N-H···N combine with N-H···O [graph set $R_4^4(12)$] hydrogen-bonding system exit in the bearing N-2 substituted group of the title compound and 3-amino-2-benzyl-6-bromo-1,2,4-triazin-5(2*H*)-one (Hwang et al. 2010, Hwang et al. 2016).

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[8] CCDC 1535722 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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