SYNTHESIS AND CRYSTAL STRUCTURE OF 3,3,6,6-TETRAMETHYL-9-(2-HYDROXYPHENYL)-3,4,6,7,9,10-HEXAHYDROACRIDINE-1,8- DIONE

Imran Hussain, [a] Sumati Anthal, [a] M. B. Deshmukh, [b] and Rajni Kant[a]*

Keywords: Crystal structure; Acridine; Direct methods; Hydrogen bonds; Ring conformations.

The title compound 3,3,6,6-tetramethyl-9-(2-hydroxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-dione, crystallizes in the orthorhombic space group $Pna2_1$ with unit cell parameters: a = 13.669(5) Å, b = 14.753(5) Å, c = 10.043(5) Å, Z=8. The crystal structure is solved by Direct methods and refined by full matrix least squares procedure to a final R value of 0.0982 for 2602 observed reflections. The crystal structure is stabilized by N1–H1···O2, O3–H3···O1 and C13–H13···O3 hydrogen bonds.

*Corresponding Authors
Fax: +911912432051
E-Mail: rkant.ju@gmail.com
[a] X-ray Crystallography Laboratory, Department of Physics, University of Jammu, Jammu-Tawi, 180006.
[b] Department of Chemistry, Shivaji University, Kolhapur–416 004 (MS), India

Introduction

Acridine derivatives have occupied a unique position in medicinal chemistry due to their wide range of biological application[1]. The acridine derivatives containing two keto functional groups at its 2nd and 11th position give rise to acridinediones. Acridinediones and their derivatives possess a wide range of pharmaceutical activities, including antimicrobial[2], antimalarial[3], antitumor[4],anticancer[5], antibacterial[6],fungicidal[7], and DNA binding properties[8]. These derivatives have been used in chemotherapy for the treatment of cancer[9] and the treatment of cardiovascular diseases, such as angina pectoris and hypertension[10]. As a continuation of our research devoted to the development of acridine derivatives[11-13], we herein report the synthesis and the crystal structure of the title compound.

Experimental

Synthesis

The synthetic route for 3,3,6,6-tetramethyl-9-(2-hydroxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-dione (Figure 1) is presented in Scheme 1. A mixture of dimedone (2 mmol), 2-hydroxybenzaldehyde 2 (1 mmol) and ammonium acetate (1.2 mmol) in mixture of aqueous ethanol (5 ml) was stirred at RT for 5 min. To this [CMIM][HSO_4] (20 mol %) was added and the reaction mixture heated at 85 ^{0}C until completion of the reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was gradually cool to room temperature and poured on ice water under stirring, solid were precipitate out. Filter the product and dried. The crude product was recrystallized from ethanol.(M.p>300 ^{0}C, Yield: 81 %). The chemical structure of the title compound is given in Figure 1.

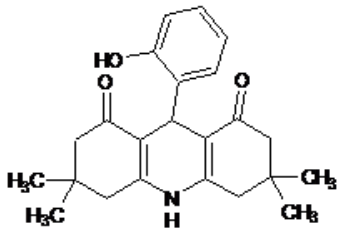

Figure 1. Chemical strcture of the 3,3,6,6-tetramethyl-9-(2-hydroxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-dione

Table 1. Crystal and experimental data for $C_{23}H_{27}NO_3$

CCDC Number	965867
Crystal description	Block
Crystal size	0.30 x 0.20 x 0.20 mm
Empirical formula	$C_{23}H_{27}NO_3$
Formula weight	365.46
Radiation, wavelength	MoK_α, 0.71073 Å
Unit cell dimensions	a= 13.669(5) Å
	b= 14.753(5) Å
	c=10.043(5) Å
Crystal system	Orthorhombic
Space group	$Pna2_1$
Unit cell volume	3328.7(5) Å^3
No. of molecules per unit cell, Z	8
Absorption coefficient	0.079 mm^{-1}
***F*(000)**	784
θ range for entire data collection	3.5986 < θ< 29.0363
Reflections collected / unique	7713 /3174
Reflections observed I > 2σ(I))	2602
Range of indices	h=-15 to 15,
	k=-16 to 16,
	l=-11 to 11
No. of parameters refined	249
Final *R*-factor	0.0982
w*R*(F_2)	0.2916
R_{int}	0.0373
R_{sigma}	0.0214
Goodness-of-fit	1.376
$(\Delta/\sigma)_{max}$	0.766
Final residual electron density	-0.308<Δρ>0.766 eÅ^{-3}

Table 2. Selected Bond Lengths and Bond angles

Bond lengths

Bond	Bond length, Å	Bond	Bond length, Å
C2-O1	1.209(7)	C11-O2	1.208(7)
C1- C2	1.476(7)	C7-C12	1.356(7)
C6- C5	1.503(8)	C19-O3	1.349(8)
C1- C6	1.350(7)	C13-C14	1.518(7)
N1-C6	1.363(7)	N1 - C7	1.373(7)
C12 -C7	1.356(7)	C12 - C11	1.450(7)
C12-C13	1.505(7)	C13-C14	1.518(7)
C18 - C17	1.344(12)	C19 - C18	1.430(9)
N1- H1	0.8600	O3- H3	0.8200

Bond Angles

Bond	Bond angle, °	Bond	Bond angle, °
C6-C1-C2	119.2(4)	C12-C13-C1	109.0(4)
C1-C6-C5	123.1(5)	N1-C7-C8	115.3(4)
O1-C2-C1	120.3(5)	C12-C7-C8	125.8(5)
O1-C2-C3	121.5(5	O2-C11-C12	121.5(5)
C1-C2-C3	118.1(5)	O2-C11-C10	121.4(6)
C5-C4-C3	113.6(6)	O3-C19-C14	122.8(5)
C23-C4-C3	114.4(6)	O3-C19-C18	117.4(6)
C1-C6-N1	120.7(4)	C14-C19-C18	119.8(6)
C12-C7-N1	118.9(5)	C15-C14-C13	122.3(5)
N1-C6-C5	116.2(5)	C19-C14- C13	121.1(5)
Torsion angles			
C1-C2-C3-C4	23.2(14)	O2-C11-C10-C9	160.6(12)
C5-C4-C3- C2	-38.1(15)	O3-C19-C18-C17	179.8(6)
C6-C1-C2-C3	-8.6(11)	C11-C12-C7-C8	-6.1(11)
C13-C1-C2-O1	-3.8(10)	C10-C9-C8-C7	-27.0(14)
C7-N1-C6-C1	14.1(11)	O1-C2-C3-C4	-159.1(8)
C7-C12-C7-N1	-3.9(9)	C21-C9-C8-C7	-172.5(9)
C21-C9-C10-C11	-73.1(12)	C23-C4-C3-C2	-173.6(9)
C23- C4- C5- C6	173.2(10)	C10-C9-C8-C7	-27.0(14)
C11-C12-C7-N1	176.8(7)	C11-C12-C7-C8	-6.1(11)
C11-C12-C13-C1	-161.5(6)	C11-C12-C13-C14	72.8(7)
C13-C12-C11-O2	5.1(11)	C13- C12 -C11- C10	-169.7(10)

Crystal structure determination and refinement

The crystallographic data are summarized in Table 1. A well-defined crystal of dimensions 0.30 x 0.20 x 0.20 mm^3 was used for data collection on *X'calibur CCD* area-detector diffractometer equipped with graphite monochromated MoK_α radiation (λ=0.71073 Å). X-ray intensity data of 24799 reflections were collected at 293(2) K and out of these reflections 3174 were found unique. The intensities were measured by ω scan mode for θ ranges 3.60° to 29.04°. 2602 reflections were treated as observed using (I>2σ(I)) as a criterion. Data were corrected for Lorentz-polarization and absorption factors. The structure was solved by direct methods using SHELXS97[14]. All non-hydrogen atoms of the molecule were located from the best E-map. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms with O-H= 0.82 Å, N-H= 0.86 Å, C-H= 0.93-0.97Å and U_{iso}= 1.2 U_{eq}(C), except for the methyl groups where U_{iso}(H) = 1.5U_{eq}(C). The final refinement cycles converged to an R-factor of 0.0979 (wR(F^2)=0.2916) for the 2602 observed reflections. Residual electron densities range from -0.308 to 0.766 eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography. The geometry of the molecule was calculated using the WinGX[15], PARST[16]and PLATON[17]softwares.

Crystallographic information has been deposited with **CCDC-965867** to Cambridge Crystallographic Data Centre. This data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and discussion

The molecular structure containing atomic labeling is shown in Figure 2 (ORTEP)[18]. The molecule consists of four rings which are labeled as ring A, ring B, ring C and ring D Figure 1. The crystallographic and refinement data of the crystal is given in Table 1.

Table 3. Geometry of Intra and Inter molecular Hydrogen bonds

D–H…A	D–H(Å)	H…A(Å)	D…A(Å)	D–H…A(º)
N1-H1…O2^{i}	0.86	2.21	2.820(6)	128
O3-H3…O1	0.82	2.10	2.668(6)	126
C13-H13…O3	0.98	2.15	2.905(6)	104

Symmetry code: (i) -1/2+x, 1/2-y, z.

Some selected bond distances, bond angles and torsion angle values are given in Table 2. The structural parameters, including bond distances and bond angles, show a normal geometry[19] and agree with the values observed for some related structures.[11-13] The O3 atom attached with the carbon atom C19 is coplanar with the ring D, indicated by the torsion angles O3-C19-C18-C17 = 179.8(6)˚ and O3-C19-C18-C17 = 178.2(5)˚, this feature can also be seen in the related structures.[11-13] The double bonds C2=O1 [1.209(7) Å] and C11=O2 [1.208(7)Å] agree with the corresponding distances in structures containing similar systems.

The central ring B (N1/C6/C1/C13/C12/C7) of the acridinedione moiety adopts a *sofa* conformation with best mirror plane passing through atoms N1 and C13 [asymmetry parameter ΔCs(N1) = 0.46]. Ring A of the title compound (C1-C6) adopts a *sofa* conformation with best mirror plane passing through atoms C1 and C4 [asymmetry parameter Cs(C1)=1.50. Whereas ring C (C7-C12) adopt *half-chair* conformations with best two fold rotation axis bisecting the bond C9-C10 [asymmetry parameter (ΔC_2 (C9-C10) = 3.98].[20] In the title molecule, some carbon atoms are thermally disordered. The thermal disorder could not be tackled and hence, it led to the large value of the R-factor.

In the crystal structure, intramolecular hydrogen bonds (O3–H3…O1 and C13–H13….O3) helps in stabilizing the molecule. Intermolecular interactions N1–H1…O2 play a crucial part in assembling the molecules in three-dimensional network Table 3. Packing of the molecules in the unit cell down the c-axis is shown in Figure 3.

Acknowledgements

Rajni Kant is thankful to the Indian Council of Medical Research and the Department of Science and Technology, New Delhi for funding under sponsored research project (No. BIC/12(14)/2012 and EMR/2014/000467).

References

[1]Wroblewska, A., Huta, O. M., Patsay, I. A., Petryshnand, R. S. and Blazejowski, J., *Anal. Chim. Acta.*, **2004,** *507*, 229. https://doi.org/10.1016/j.aca.2003.11.032

[2]Shchekotikhin, Y. M., Nikolaeva, T. G., Shub, G. M., and Kriven'ko, A. P., *Pharm. Chem.* J., **2001,** *35*, 206. https://doi.org/10.1023/A:1010484013306

[3]Kidwai, M. and Bhatnagar, D., *Tetrahedron Lett*., **2010**, 51, 2700. https://doi.org/10.1016/j.tetlet.2010.03.033

[4]Tu, S., Zhang, X., Shi, F., Li, T., Wang, Q., Zhu, X., Zhang, J., and Xu, J., *J. Heterocycl. Chem*., **2005**, *42*, 1155. https://doi.org/10.1002/jhet.5570420618

[5]Gamage, S. A., Spicer, J. A., Atwell, G. J., Finlay, G. J., Baguley, B .C and Denny, W. A., *J. Med. Chem*. **1992**, *42*, 2383. https://doi.org/10.1021/jm980687m

[6]Palani, K., Thirumalai,D., Ambalavanan, P., Ponnuswamy, M. N., and Ramakrishnan, V. T., *J. Chem. Crystallogr*., **2005**, *35***,** 751. https://doi.org/10.1007/s10870-005-3880-2

[7]Wainwright, M. J., *Antimicrob. Chemother*., **2001**, *47*, 1. https://doi.org/10.1093/jac/47.1.1

[8]Venkatesan, K., Pujari, S. S., Srinivivasan, K. V., *Synth. Commun*., **2009**, *39*, 228. https://doi.org/10.1080/00397910802044306

[9]Kidwai, M., and Bhatnagar, D., *Tetrahedron Lett*., **2010**, *51*, 2700. https://doi.org/10.1016/j.tetlet.2010.03.033

[10]Venkatesan, K., Pujari, S. S., and Srinivivasan, K. V., *Synth. Commun*., **2009**, *39*, 228. https://doi.org/10.1080/00397910802044306

[11]Kour, D., Patil, D. R., Deshmukh, M. B., Gupta, V. K. and Kant, R., *Eur. Chem. Bull*. **2014**, *3(2)*, 173-175. DOI: 10.17628/ecb.2014.3.173-175

[12]Kour, D., Patil, D. R., Deshmukh, M. B. and Kant, R., *Eur. Chem. Bull.*, **2014**, *3(6)*, 552-554. DOI: 10.17628/ecb.2014.3.552-554

[13]Kour, D., Patil, D. R., Deshmukh, M. B., Gupta, V. K. and Kant, R., *J. Crystallogr*., **2014,** Article ID 914504.

[14]Sheldrick, G. M., *Acta Cryst*.,**2008,** *A64*, 112-122. https://doi.org/10.1107/S0108767307043930

[15]Farrugia, L., *J. Appl. Crystallogr*.,**1999**, *32*, 837-838. https://doi.org/10.1107/S0021889899006020

[16]Nardelli, M., *J. Appl. Cryst*., **1995**, *28*, 659. https://doi.org/10.1107/S0021889895007138

[17]Spek, A. L., *Acta Cryst D*., **2009**, *65*, 148-155. https://doi.org/10.1107/S090744490804362X

[18]Farrugia, L. J., *J. Appl. Cryst*., **2012**, *30*, 565. https://doi.org/10.1107/S0021889897003117

[19]Allen, F. H., Kennard, O., Watson, D. G., Brammer L., Orpen, A. G., Taylor, R., *J. Chem. Soc., Perkin Trans*., **1987**, *2*, S1–19. https://doi.org/10.1039/p298700000s1

[20]Duax W. L. and Norton, D. A., *Atlas of Steroid Structures*, **1975**, Plenum Press, New York, NY, USA. https://doi.org/10.1007/978-1-4684-6150-3

Received: 28.12.2017.
Accepted: 10.01.2018.