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Crystal and Molecular Structure Analysis of Novel Bioactive Heterocyclic Compound: 7-Chloro-5-cyclopropyl-9-methyl-10-(4-nitro-benzyl)-5,10-Dihydro-4,5,6,10-Tetraaza-dibenzo [a,d] Cyclohepten-11-one

N. R. Thimmegowda [a], G. Sarala [b], C. S. Ananda Kumar [a], D. S. Prasanna [a], S. Chandrappa [a], H. Raju [a], M. A. Sridhar [b], J. Shashidhara Prasad [b] & K. S. Rangappa [a]

[a] Department of Studies in Chemistry, University of Mysore, Mysore, India

[b] Department of Studies in Physics, University of Mysore, Mysore, India

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N. R. Thimmegowda[1], G. Sarala[2], C. S. Ananda Kumar[1], D. S. Prasanna[1], S. Chandrappa[1], H. Raju[1], M. A. Sridhar[2], J. Shashidhara Prasad[2], and K. S. Rangappa[1]
[1]Department of Studies in Chemistry, University of Mysore, Mysore, India
[2]Department of Studies in Physics, University of Mysore, Mysore, India

The title compound 7-chloro-5-cyclopropyl-9-methyl-10-(4-nitro-benzyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one was synthesized and characterized spectroscopically and finally confirmed by X-ray diffraction study. The title compound crystallizes in the monoclinic space group P21/c with cell parameters $a = 11.644(8)$ Å, $b = 14.826(1)$ Å, $c = 15.919(8)$ Å, $\alpha = 90^\circ$, $\beta = 130.377(4)^\circ$, $\gamma = 90^\circ$, $V = 2093.5(2)$ Å^3, and $Z = 4$. The NO_2 group in the ring is almost in the same plane of the nitrobenzyl ring. The structure exhibits neither inter nor intra molecular hydrogen bonding.

Keywords: 4-nitrobenzylbromide; azepinone; crystal structure; heterocyclic compound

INTRODUCTION

Heterocycles play a vital role in the pharmacological, agricultural, and synthetic fields. Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities.

Azepines probably represent the most important of all structural classes in drug discovery. The azepine nucleus is a fundamental constituent of a number of natural and synthetic products with biological

Address correspondence to Prof. K. S. Rangappa, Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India. E-mail: rangappaks@gmail.com and rangappaks@chemistry.uni-mysore.ac.in

activity. The investigation of the chemistry of azepines has been, and continues to be, a particularly active area of heterocyclic chemistry [1]. Azepine derivatives have been found to be associated with diverse pharmacological activities. The anti-HIV drug Nevirapine [2], made up of azepinone nucleus, is the first human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase (RT) inhibitor to reach regulatory approval [3]. It prevents damage to the immune system and reduces the risk of developing AIDS-related illnesses [4]. The compound 7-chloro-5-cyclopropyl-9-methyl-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one is an intermediate of the potent anti-HIV drug Nevirapine. The N-alkylation of this compound by different alkyl and aryl halides leads to the novel molecules of biological interest. In continuation of our studies on the crystal structures of these compounds [5], we report herein the crystal structure study of the compound 7-chloro-5-cyclopropyl-9-methyl-10-(4-nitro-benzyl)-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one.

EXPERIMENTAL

Melting points were determined using SELACO-650 hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Jasco FTIR-4100 series. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Shimadzu AMX 400-Bruker, 400 MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard (chemical shift in δ ppm). Spin multiplets are given as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Elemental analyses (CHNS) were obtained on Vario EL III Elementar. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck made TLC plates.

Synthesis of 7-Chloro-5-cyclopropyl-9-methyl-10-(4-nitro-benzyl)-5,10-Dihydro-4,5,6,10-Tetraaza-dibenzo [a,d] Cyclohepten-11-one

To a solution of 7-chloro-5-cyclopropyl-9-methyl-5,10-dihydro-4,5,6,10-tetraaza-dibenzo [a,d] cyclohepten-11-one (0.5 g, 1.66 mmol) in 10 mL of N,N-Dimethyl formamide, were added 4-nitro benzyl chloride (0.375 g, 1.66 mmol) and anhydrous powdered potassium carbonate. The reaction mixture was heated to 60°C for 5–6 hr. The reaction scheme for the synthesis of the title compound is shown in Figure 1. The reaction mixture was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and extracted with ethyl

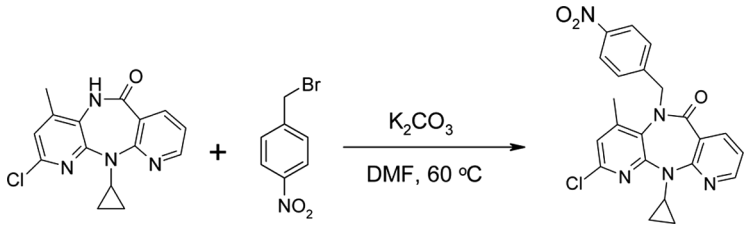

FIGURE 1 Reaction scheme.

acetate. The organic layer was dried with anhydrous sodium sulphate, the solvent was evaporated to get crude product which was purified by using silica gel (60–120 mesh) using hexane: ethyl acetate (8:2) as an eluent for column chromatography. Pure product obtained was recrystallized by slow evaporation method using acetonitrile as a solvent. The product obtained was pale yellow, Yield: 76% M. P.: 182–184°C.

IR (KBr cm^{-1}): 1660 (-C=O str), 1582 (-C=C- str), 3021 (-C-H str), 1426 (-N=O str).

^{1}H NMR: δ 8.45 (1 H, m), 8.06 (1 H, m), 7.02 (1 H, m), 7.08 (1 H, m), 8.14 (2 H, d), 7.38 (2 H, d), 2.32 (5 H, s) 1.6 (3 H, s), 4.2 (1 H, d), 5.9 (1 H, d).

Anal. Calcd. (%) for $C_{22}H_{18}ClN_5O_3$: C, 60.62; H, 4.16; N, 16.07. Found: C, 60.58; H, 4.13; N, 16.03.

CRYSTAL STRUCTURE DETERMINATION

A single crystal of the title compound with dimensions $0.3 \times 0.25 \times 0.25$ 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 MOKα). 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 minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo [6]. The reflections were merged with Scalepack [7]. All of the frames could be indexed using a primitive triclinic lattice. The structure was solved by direct methods using SHELXS-97 [8]. All the non-hydrogen atoms were revealed in the first Fourier map itself. Least-squares refinement using SHELXL-97 with isotropic temperature factors was done for all the non-hydrogen atoms. Subsequent refinements were carried out with anisotropic thermal parameters for

non-hydrogen atoms converged the residual $R_1 = 0.1287$. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms. After eight cycles of refinement the residuals converged to 0.0868. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms.

RESULTS AND DISCUSSION

The details of crystal data and refinement are given in Table 1. The final atomic coordinates and equivalent thermal parameters for all the non-hydrogen atoms are given in Table 2. The bond lengths and angles of all the non-hydrogen atoms are given in Table 3 and in Table 4 respectively, which are in good agreement with the standard values. Figure 2 represents the ORTEP diagram of the molecule with

TABLE 1 Crystal Data and Structure Refinement Table

Empirical formula	$C_{22}H_{26}N_5ClO$
Formula weight	411.93
Temperature	293(2)K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1
Cell dimensions	
	a = 8.918(7) Å
	b = 9.297(7) Å
	c = 14.184(8) Å
	$\alpha = 94.950(4)^\circ$
	$\beta = 97.466(6)^\circ$
	$\gamma = 108.439(2)^\circ$
Volume	1095.98(13) $Å^3$
Z	2
Density (calculated)	1.248 Mg/m^3
Absorption coefficient	0.197 mm^{-1}
F000	436
Crystal size	0.3 × 0.25 × 0.25 mm
Theta range for data collection	2.63° to 25.02°
Reflections collected	5906
Independent reflections	3554 [$R_{int} = 0.0241$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3554/0/263
Goodness-of-fit on F2	1.063
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0451$, w$R_2 = 0.1291$
R indices (all data)	$R_1 = 0.0514$, w$R_2 = 0.1358$
(Δ/σ)max	0.000
$(\Delta\rho)$max	0.177 e · °A^{-3}
$(\Delta\rho)$min	−0.296 e · °A^{-3}

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Non-Hydrogen Atoms

Atom	x	y	z	U_{eq}
Cl1	−0.5446(6)	0.0726(7)	0.2788(4)	0.0698(2)
C2	−0.3410(2)	0.1763(2)	0.2992(1)	0.0474(4)
N3	−0.2467(2)	0.0969(2)	0.2790(1)	0.0431(4)
C4	−0.0903(2)	0.1741(2)	0.2922(1)	0.0382(4)
N5	0.0131(2)	0.0887(2)	0.2792(1)	0.0410(3)
C6	0.1208(2)	0.0952(2)	0.3638(1)	0.0401(4)
N7	0.1152(2)	−0.0377(2)	0.3936(1)	0.0525(4)
C8	0.2131(3)	−0.0332(2)	0.4747(2)	0.0652(6)
C9	0.3185(3)	0.0985(3)	0.5274(2)	0.0639(6)
C10	0.3292(2)	0.2350(2)	0.4935(1)	0.0516(5)
C11	0.2287(2)	0.2357(2)	0.4103(1)	0.0405(4)
C12	0.2631(2)	0.3792(2)	0.3657(1)	0.0425(4)
N13	0.1385(2)	0.4133(2)	0.3187(1)	0.0429(4)
C14	−0.0255(2)	0.3319(2)	0.3211(1)	0.0393(4)
C15	−0.1273(2)	0.4103(2)	0.3479(1)	0.0462(4)
C16	−0.2901(2)	0.3285(2)	0.3365(1)	0.0504(5)
C17	−0.0561(2)	−0.0578(2)	0.2183(2)	0.0534(5)
C18	0.0474(3)	−0.0980(3)	0.1543(2)	0.0783(8)
C19	−0.0890(3)	−0.0509(3)	0.1133(2)	0.0715(7)
O20	0.4022(2)	0.4622(2)	0.3692(1)	0.0574(4)
C21	−0.0651(3)	0.5766(2)	0.3895(2)	0.0645(6)
C22	0.1769(2)	0.5315(2)	0.2539(2)	0.0503(5)
C23	0.2158(3)	0.4671(2)	0.1618(2)	0.0553(5)
N24	0.2440(2)	0.5780(2)	0.0944(1)	0.0532(4)
C25	0.4027(3)	0.6937(3)	0.1204(2)	0.0682(6)
C26	0.4300(4)	0.8145(3)	0.0537(2)	0.0809(7)
C27	0.4074(4)	0.7420(4)	−0.0487(2)	0.0902(9)
C28	0.2481(4)	0.6167(4)	−0.0744(2)	0.0985(1)
C29	0.2254(3)	0.5027(3)	−0.0029(2)	0.0769(7)

$U_{eq} = (1/3)\ \Sigma_i\ \Sigma_j U_{ij}\ (a_i^*\ a_j^*)(a_i \cdot a_j)$.

TABLE 3 Selected Bond Lengths (Å)

Atoms	Length	Atoms	Length
Cl1–C2	1.7371(2)	N13–C22	1.478(2)
C15–C21	1.504(3)	C4–N5	1.413(2)
N5–C6	1.420(2)	N5–C17	1.452(2)
C6–N7	1.329(2)	C22–C23	1.517(3)
C23–N24	1.452(3)	N24–C29	1.456(3)
C27–C28	1.502(4)	C12–O20	1.228(2)
C28–C29	1.516(4)	C12–N13	1.359(2)

TABLE 4 Selected Bond Angles (°)

Atoms	Angle	Atoms	Angle
N3–C2–Cl1	115.15(2)	C14–N13–C22	118.77(1)
C16–C2–Cl1	119.31(1)	C2–N3–C4	116.45(2)
C4–C14–N13	121.05(2)	C16–C15–C21	120.16(2)
C14–C15–C21	122.06(2)	C4–N5–C17	116.73(1)
C6–N5–C17	117.01(1)	N5–C17–C18	116.08(2)
N5–C17–C19	115.85(2)	C17–C18–C19	60.36(2)
N13–C22–C23	110.41(2)	N24–C23–C22	111.49(2)
C23–N24–C29	110.89(2)	N24–C25–C26	112.10(2)
O20–C12–N13	121.17(2)	O20–C12–C11	120.12(2)
C12–N13–C14	123.80(1)	N24–C29–C28	111.40(2)

thermal ellipsoids drawn at 50% probability. Figure 3 represents the packing of the title molecule along a axis

In 7-chloro-5-cyclopropyl-9-methyl-10-(4-nitrobenzyl)-5,10-dihydro-4,5,6,10-tetraazadibenzo [a,d] cyclohepten-11-one, the 4-nitrobenzyl ring (ring ~ 4) and the 7-chloro-5-cyclopropyl-9-methyl-5,10-dihydro-4,5,6,10-tetraazadibenzo [a,d] cyclohepten-11-one ring are linked by a CH_2 group making an angle of 113.76(3)° at the atom C22 of CH_2 group. The dihedral angle between the least squares planes of ring-1 and ring-4 is 74.09(1)° indicating that they are in *syn-clinal* conformation. Also, it is maximum with respect to other molecules of this

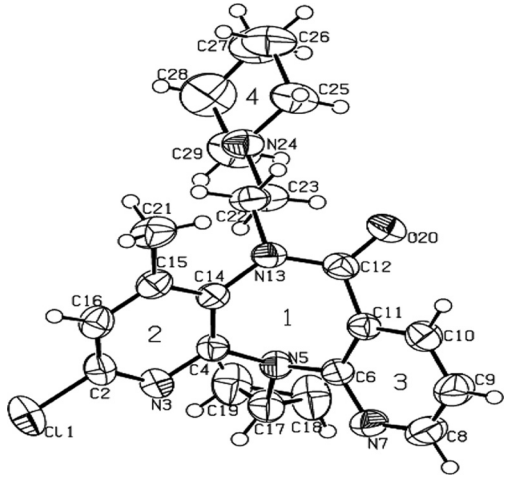

FIGURE 2 ORTEP of the title molecule with thermal ellipsoids drawn 50% probability.

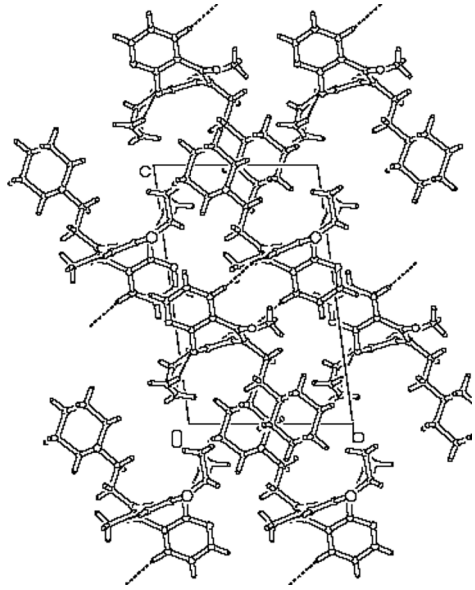

FIGURE 3 Packing of the title molecule along a axis.

class studied. The dihedral angle between least squares planes of cyclopropyl ring and the cyclohepten ring is 85.56(3)° making them to be in *equatorial* conformation. The atoms N5 and N13 where the cyclopropyl ring and 4-nitro-benzyl ring are substituted, deviate from the plane defined by the atoms N3-C2-C16-C15-C14-C13-C12-C11-C10-C9-C8-N7-C6-C5-C4 by −1.0836(2) Å and −0.9822(2) Å, respectively. The ring-puckering amplitude of the whole-base moiety, 7-chloro-5-cyclopropyl-9-methyldibenzo[a,d] cyclohepten-11-one is 2.5045(3) Å. The NO_2 group in the ring ~4 is almost in the same plane of the nitrobenzyl ring which is indicated by the torsion angle −4.2(4)° for the plane containing the atoms C25-C26-N29-O30. The bond lengths and angles in this molecule are in agreement with the standard values. The structure exhibits neither inter- nor intramolecular hydrogen bonding.

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