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Spectral Analysis and Crystal Structure of Spiro[2.2"] Acenaphthene-1"-One-Spiro[3.3']-5'-(2,3-Dichlorophenyl Methylidene)-1'-Methylpiperidin-4'-One-4-(2,3-Dichlorophenyl) Octahydroindolizine

Rakkappan Vishnu Priya[1], Janakiraman Suresh[1*], Sathiyamoorthi Sivakumar[2], Raju Ranjith Kumar[2]
[1]Department of Physics, The Madura College (Autonomous), Madurai, India
[2]Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai, India
Email: [*]ambujasureshj@yahoo.com

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ABSTRACT

The crystal structure of spiro[2.2"]acenaphthene-1"-onespiro[3.3']-5'-(2,3-dichlorophenylmethylidene)-1'-methylpiperidin-4'-one-4-(2,3-dichorophenyl) octahydroindolizine was elucidated by single crystal X-ray diffraction. The title compound $C_{37}H_{30}Cl_4N_2O_2$, crystallizes in the orthorhombic system, space group $P2_12_12_1$ with a = 8.4610(4) Å, b = 16.0926(6) Å, c = 23.8997(11) Å and Z = 4. The central piperidine ring adopts twisted conformation, the piperidine of octahydroindolizine ring is in chair conformation and the pyrrole ring is in slightly twisted envelope conformation. Details of the synthesis, NMR, crystal structure determination and intra- and intermolecular interactions of the compound are given.

Keywords: Single Crystal Structure; Conformation; Hydrogen Bond; NMR Spectra

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB), which usually infects the lungs but may also affect the other parts of the body. This is one of the most prevalent diseases responsible for the death of approximately one billion people during the last two centuries. TB remains a severe public health problem in India accounting for nearly one-third of the global burden, and it has been estimated that 3.5 million of the population are infected with TB [1]. In the past years, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB, which reflects the inherent difficulties in the discovery and clinical testing of new agents [2]. Hence, the discovery of fast-acting new drugs to effectively combat TB is imperative.

In general, spiro compounds [3,4] and nitrogen heterocycles display good antimycobacterial activities [5-7]. Recently, Perumal *et al*. reported an atom economic synthesis and evaluation of antimycobacterial activities of spiro pyrido-pyrrolizines and pyrrolidines, [8,9] which inhibited in vitro MTB and multi-drug resistant Mycobacterium tuberculosis (MDR-TB). In the course of screening to discover new compounds that could be useful for the treatment of TB, we herein report the synthesis, NMR spectra and single crystal X-ray studies of the title spiro compound.

Further it is also pertinent to note that the synthesis of biologically active indolizine derivatives continues to attract the attention of organic chemists, because of their wide spectrum of biological activity. Indolizine derivatives have been found to possess a variety of biological activities such as anti-inflammatory [10], antiviral [11], aromatase inhibitory [12], analgesic and antitumor [13] activities. A brief survey of the Cambridge Structural Database (Version 5.33; [14]) revealed a scarcity of precise crystallographic data on octahydroindolizine ring systems. Hence, this structure is presumed to be very interesting and rarely studied moieties. The chemical diagram of the title compound is shown in **Figure 1**.

2. Experimental

2.1. Synthesis of the Title Compound

1,3-Dipolar cycloaddition of azomethine ylides to exocyclic olefins constitutes a versatile protocol for the construction of poly functionalized spiro-heterocycles. In this context, we have synthesized 1-methyl-3,5-bis[(*E*)-

[*]Corresponding author.

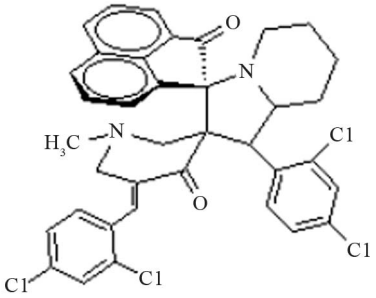

Figure 1. Chemical diagram of the molecule.

2,3-dichlorophenylmethylidene]tetrahydro-4(1H)-pyridi none, an exocyclic dipolarophile, from the reaction of 1-methyl-4-piperidone and 2,3-dichlorobenzaldehyde in ethanol in the presence of NaOH. The cycloaddition of the above dipolarophile with azomethine ylide generated *in situ* from the decarboxylative condensation of acenaphthenequinone and piperidine-2-carboxylic acid led to the formation of the title compound in excellent yield.

A mixture of 1-methyl-3,5-bis[(*E*)-2,3-dichlorophenylmethylidene]tetrahydro-4(1H)-pyridinone (1 mmol), acenaphthenequinone (1 mmol) and piperidine-2-carboxylic acid (1 mmol) was dissolved in isopropyl alcohol (15 mL) and heated to reflux for 60 min. After completion of the reaction as evident from TLC, the mixture was poured into water (50 mL), the precipitated solid was filtered and washed with water (100 mL) to obtain the product as pure yellow solid. The product was recrystallized from ethyl acetate to obtain suitable crystals for the X-ray analysis. Melting point: 494 (2) K, Yield: 94%.

2.2. Structure Determination and Refinement

For the crystal structure determination, the intensity data of the single-crystal of the compound $C_{37}H_{30}Cl_4N_2O_2$ was collected using a Bruker AXS Kappa APEX II single crystal CCD Diffractometer equipped with graphite-monochromated MoKα radiation (λ = 0.71073 Å) at room temperature with a crystal dimension of 0.35 × 0.25 × 0.20 mm^3. Accurate unit cell parameters were determined from the reflections of 36 frames measured in three different crystallographic zones. The data collection, data reduction and absorption correction were performed by APEX2, SAINT-plus and SADABS program [15]. The structure was solved by the direct method procedure and the non-hydrogen atoms were subjected to anisotropic refinement by full-matrix least squares on F^2 using SHELXL-97 program [16]. The positions of all the hydrogen atoms were identified from difference electron density map, and they were constrained to ride on the corresponding non-hydrogen atoms. Molecular graphics were drawn using PLATON [17]. The crystal data, experimental conditions and structure refinement parameters for the title compound are presented in **Table 1**.

Table 1. The crystal data, experimental conditions and structure refinement parameters of the title compound.

Empirical formula	$C_{37}H_{30}Cl_4N_2O_2$
Formula weight	676.43
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	$P2_12_12_1$, orthorhombic
Unit cell dimensions	a = 8.4610(4) Å b = 16.0926(6) Å c = 23.8997(11) Å
Volume	3254.2(2) $Å^3$
Z, Calculated density	4, 1.38 mg/m^3
Absorption coefficient	0.401 mm^{-1}
F(000)	1400
Crystal size	0.23 × 0.21 × 0.19 mm^3
Theta range for data collection	2.12 to 24.91 deg
Limiting indices	–8<= h <= 10, –18, = k <= 19 –22<= l <= 28
Reflections collected/unique	16629/5642 [R(int) = 0.032]
Completeness to theta	99.6%
Absorption correction	ω-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5642/0/407
Goodness-of-fit on F^2	1.024
Final R indices [I > 2sigma(I)]	R_1 = 0.038, wR_2 = 0.077
R indices (all data)	R_1 = 0.058, wR_2 = 0.085
Largest diff. peak and hole	0.194 and −0.203 $e \cdot A^{-3}$

3. Results and Discussion

3.1. Spectral Data

The structure of title compound has been elucidated with the help of ^1H, ^{13}C and two dimensional NMR spectroscopic studies. The H,H-COSY spectrum of the compound assigns a doublet and multiplet at 4.81 ppm (J = 9.9 Hz) and 4.00 ppm to H-4 and H-4a respectively.

Further, H-4 shows HMBC correlations with C-4', C-3, C-4a and C-5 at 195.7, 64.4, 64.5 and 25.5 ppm respectively. The signals of 5, 6, 7 and 8-CH_2 protons overlap and appear as a multiplets from 1.26 to 2.15 ppm whereas the carbon signals appear at 25.5, 24.1, 30.8 and 45.6 respectively. The multiplet in a range 1.26 - 1.30 ppm and the doublet at 2.95 ppm (J = 12.6 Hz) are assigned to 2'-CH_2 protons. The 6'-CH_2 protons appears as doublets at 2.71 and 2.48 ppm (J = 15.3 Hz). The C,H-COSY correlations assign the carbon signals at 56.9 and 55.3 to C-2' and C-6' carbons respectively. The singlet at

1.69 ppm is due to the N-CH_3 protons. The aromatic protons appear as a multiplet in a range 6.58 - 7.97 ppm. The ^1H and ^{13}C NMR chemical shifts of the title compound are shown in **Figure 2**.

It is pertinent to observe that the chemical shifts of 2'-CH_2 of the compound (2.95 ppm ~1.30 ppm) differ very much by 1.65 ppm. This suggests that probably the H-2eq is spatially proximate to the carbonyl of acenaphthylen-1(2*H*)-one shifting it downfield, while H-2ax lies in the shielding zone of the acenaphthylen-1(2*H*)-one ring shifting it downfield suggesting relative configuration at C-2 for the compound. The alternative stereochemistry with inversion of configuration at C-2 relative to that shown on the compound bringing both the carbonyls of the piperidone and acenapthene rings towards each other in spatial proximity, probably renders the transition state of the cycloaddition unstable by electrostatic repulsion. This could raise the free energy of activation (transition state B in **Figure 3**), relative to the transition state leading to the formation of the compound with both carbonyls placed far off (transition state A in **Figure 3**).

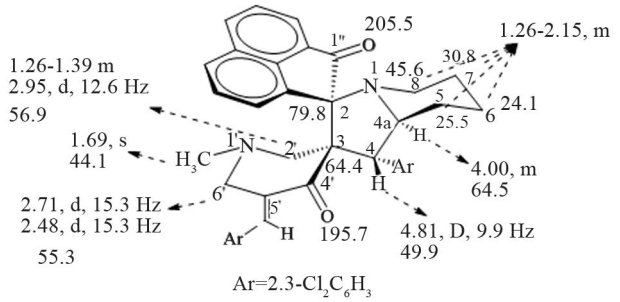

Figure 2. ^1H and ^{13}C NMR chemical shifts of the compound.

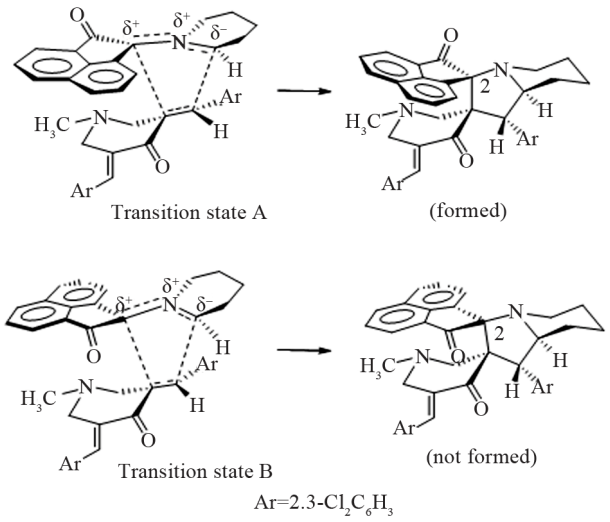

Figure 3. Stereochemistry of formation of cycloadducts differing in their configurations at C-2.

3.2. Crystal Structure

Figure 4 shows the ORTEP plot drawn at 50% probability displacement ellipsoids of title compound and the atom-numbering scheme. The six membered piperidine ring in the title compound adopts the half chair conformation as evident from puckering parameters Q = 0.561 (3) Å, θ = 136.9(3)˚ and Φ = 140.6(4)˚ [18]. The olefinic double bond in the structure has an E configuration. The piperidine of octahydroindolizine ring is in the chair conformation as evident from the puckering parameters Q = 0.574(2) Å, θ = 180(3)˚ and Φ = 69(11)˚ [18]. The pyrrole ring is in the twisted envelope conformation with atom N2 at the flap as the puckering parameters are, Q = 0.424(3) Å, and Φ = 12.2(4)˚ [18,19].

The dihedral angles between the mean plane of the piperidone ring and the aryl rings are 38.69(1)˚, 82.28(1)˚ which indicate that the aryl rings in the structure are not coplanar with the mean plane of the piperidone ring.

As a result, the torsion angle C3–C31–C32–C33 is 41.24(3)˚. This lack of coplanarity is caused by non-bonded interactions between one of the ortho H atoms in the aryl ring and the equatorial H atoms at the 2-position of the piperidone ring (H33/H2A or H2B). As a result of these steric repulsions, the bond angle C3–C31–C32 expands to 128.69 (19)˚ instead of 120˚. The dichlorophenyl rings are planar as confirmed by the values of the r.m.s. deviations 0.0186 and 0.0127 Å. The dihedral angle between the dichlorophenyl rings is 74.22 (1)˚. The di- hedral angles of these dichlorophenyl rings with acenaphthene group are 30.84 (1)˚ and 78.99 (1)˚.

The C_{sp^2}-C_{sp^2} distances in the acenaphthene group range from 1.346(3) (C19-C20) to 1.574(2) Å (C13-C14) and the C-C-C bond angles from 101.54(16)˚ (C12-C11-

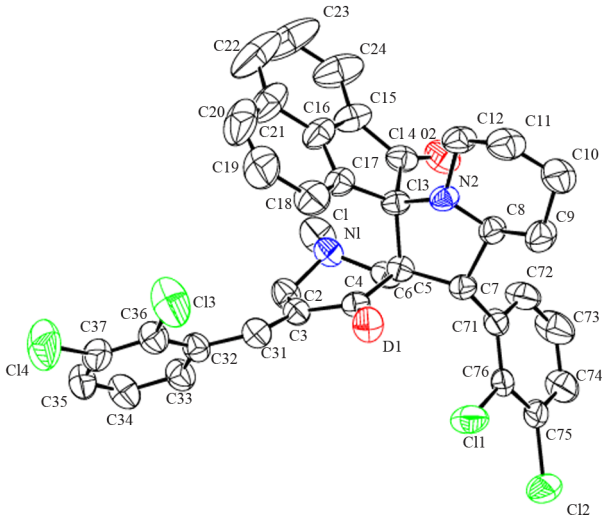

Figure 4. The molecular structure of the tittle compound showing the atom numbering scheme. Displacement ellipsoids are drawn at 50% probability level, using ORTEP 3. Hydrogen atoms are omitted for clarity.

C19) to 123.32(2)° (C16-C17-C21). These values are in agreement with related structures [20-24]. The C8-N2 bond distance being 1.450 (3) Å is comparable to the C_{sp}^2-N_{sp}^2 distances found in similar structures [25,26]. In the crystal structure some weak C—H···O intramolecular interactions have been observed (**Table 2**). A C---H...π interaction (**Table 2**) C10---H10B…Cg1, (Cg1 is the centroid of the ring C32-C37) forms, a two dimensional linear zig zag chain running parallel to the b-axis as shown in **Figure 5**.

4. Conclusion

Spiro[2.2"]acenaphthene-1"-onespiro[3.3']-5'-(2,3-dichlorophenylmethylidene)-1'-methylpiperidin-4'-one-4-(2,3-dichlorophenyl) octahydroindolizine was synthesized through 1,3-dipolar cycloaddition reaction. The single crystal of the title compound is obtained by slow evaporation method (solvent: 1:1 ethyl acetate-ethanol). The conformational features of the compound are determined in the solid phase by X-ray method and in liquid phase by NMR method. The replacements of the equatorial H atoms at the 2- and 6-positions, and the attachment of different atoms to one or two of the atoms C33, C37, C72 and C76, are likely to alter the C3-C31-C32 and C8-C7-C71 bond angles. Correlations have been established between the bond angle values and bio-activity [27]. In addition, the orientation of aryl rings will affect the alignment of these rings at a binding site and hence influence bioactivity [28]. Further studies on structure-bioactivity relationship of this compound are in progress in our research group.

Table 2. Hydrogen bonds [Å and °] of the compound.

D-H...A	d(D-H)	d(H...A)	d(D...A)	DHA
C(6)-H(6A)...O(2)	0.97	2.37	3.003(3)	122
C(7)-H(7)...Cl1(1)	0.98	2.53	3.062(3)	114
C(8)-H(8)...O(2)	0.98	2.45	3.091(3)	123
C(18)-H(18)...O(1)	0.93	2.55	3.192(4)	126
C(7)-H(7)...O(1)	0.98	2.23	2.774(3)	113
C(10)-H(10B)...Cg1[(i)]	0.93	2.88	3.675(4)	140

Symmetry transformations used to generate equivalent atoms: (i) 1 – x, 1/2 + y, 1/2 – z.

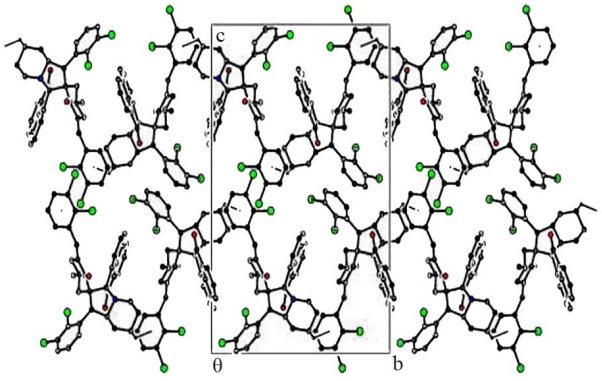

Figure 5. Partial packing diagram showing the C---H…π interaction along "b" axis.

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