



**Synthesis, Characterization Studies of a Novel Indole Derivative:
3, 3'-[(5-methylthiophen-2-yl) methanediyl]bis (1H-indole)**

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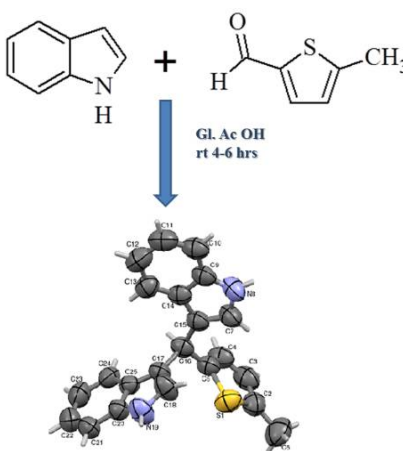
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ABSTRACT

The title compound 3, 3'-[(5-methylthiophen-2-yl) methanediyl]bis(1H-indole) was synthesized and the resultant compound was crystallized using ethanol by slow evaporation technique. The compound was characterized by FTIR, ¹H NMR and finally the structure was confirmed by single crystal X-ray diffraction studies. The title compound crystallizes in monoclinic C₂/c spacegroup with cell parameters a=26.282(4) Å, b=10.3274(14) Å, c=17.671(2) Å, β=130.254(8) and Z= 8. The indole rings are orthogonal to each other.

Graphical Abstract



Keywords: 1H-Indoles; Crystal structure; FTIR spectrum; Orthogonal conformation.

INTRODUCTION

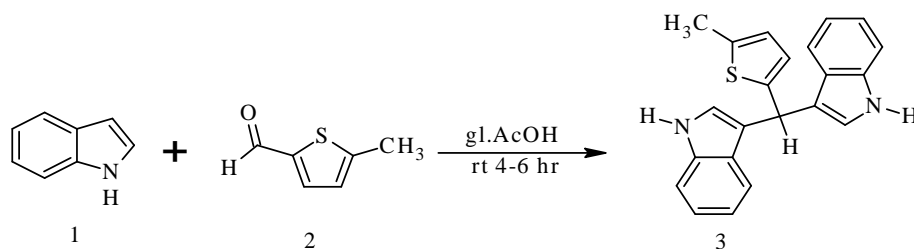
Indole nucleus has been an interesting structural subunit present in numerous biological and pharmacologically important lead molecules and also, they are present abundantly in natural products with a wide range of biological activities [1]. Development of new synthetic methods [2-9] leading to distinct indole derivatives have been attracting considerable attention due to their application in drug discovery [10-12]. A Few bisindolylmethanes (BIM's) have been reported to exhibit wide range of biological activities [13-17]. In specific to cancer, very interestingly BIM's were found to exhibit potent anticancer property towards various types of cancers [16-17]. Hence, following the broader biological and pharmacological importance of bisindolylmethanes and in continuation of our efforts to investigate novel bio active molecules [18-22], we report herein the synthesis, characterization and crystal structure studies of the title compound.

MATERIALS AND METHODS

The melting points were measured on a Boetius-Mikroheiztisch the company "VEB" weighing. Rapido Radebeul / VEB NAGEMA "measured and are uncorrected. TLC was performed by using aluminium foil fluorescent indicator from Merck KGaA (silica gel 60 F254, layer thickness 0.2 mm). Rf -values (run level relative to the solvent front). ¹H-NMR spectra were recorded on a "Gemini 2000" (400/100 MHz). The ATR spectrum was recorded on a FT-IR spectrometer "IFS 28" by "Bruker". Crystal structure was recorded by Bruker X8 Proteum Single-crystal X-ray diffractometer.

RESULTS AND DISCUSSION

The synthesis of 3,3'-[(5-methylthiophen-2-yl)methanediyl]bis(1*H*-indole) is depicted in **Scheme-1**. The 3,3'-[(5-methylthiophen-2-yl)methanediyl]bis(1*H*-indole) was obtained by reaction between commercially available indole and 5-methylthiophene-2-carbaldehyde under stirring in glacial acetic acid as catalyst and solvent. Thus the resulted crude product was purified by recrystallization using methanol as solvent to furnish 3,3'-[(5-methylthiophen-2-yl)methanediyl]bis(1*H*-indole) (**3**) as colorless crystals. The product structure was established by IR and ¹H NMR spectral analysis.



Scheme: 1 Synthesis of 3,3'-[(5-methylthiophen-2-yl)methanediyl]bis(1*H*-indole).

General procedure: In a flask containing 5 ml of glacial acetic acid and indole (2 mmol, 0.23 g) was added under stirring until all the indole was dissolved. Then 5-methylthiophene-2-carbaldehyde (1 mmol, 0.123 g) was added under vigorous stirring. The reaction mixture was allowed to stir over 4 to 6 hr, where the reaction solution turned from light yellow to light pink and then to dark red colour. The product was detected by TLC (100 % CH₂Cl₂). After, completion of the reaction, the reaction mixture was added to the ice cold water. The product separated out from the reaction mixture was filtered and washed with water. The crude product was further purified by recrystallization by using

methanol as solvent to furnish white crystals of 3,3'-[(5-methylthiophen-2-yl)methanediyl]bis(1H-indole) in good yield (80.5%). M.P=150-152⁰C.

Spectral Characterization: IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3464 (N-H), 3062 (C-H), 1237(C-N), 756 (C-S) ¹H-NMR (400 MHz, DMSO): 10.994 (s, 2H, NH), 7.448 (t, 1H), 7.301-7.334 (d, d, 2H J=4.8 HZ), 7.001-7.032 (d, d, 2H, J=2.4 HZ), 6.872-6.879 (t, 3H, J=2.8 HZ), 6.652 (d, 1H, J=2.8 HZ), 6.574(d,1H),5.954(s,1H),2.331(s,3H=CH₃).

X-ray diffraction studies: A white colored rectangle shaped single crystal of dimensions 0.29×0.26×0.25 mm of the title compound was chosen for an X-ray diffraction study. The X-ray intensity data were collected at a temperature of 296 K on a Bruker Proteum2 CCD diffractometer equipped with an X-ray generator operating at 45 kV and 10 mA, using CuK_α radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of ϕ (0° and 90°), keeping the scan width of 0.5°, exposure time of 2 s, the sample to detector distance of 45.10 mm and 2 θ value at 46.6°. A complete data set was processed using *SAINT PLUS* [23]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [24].

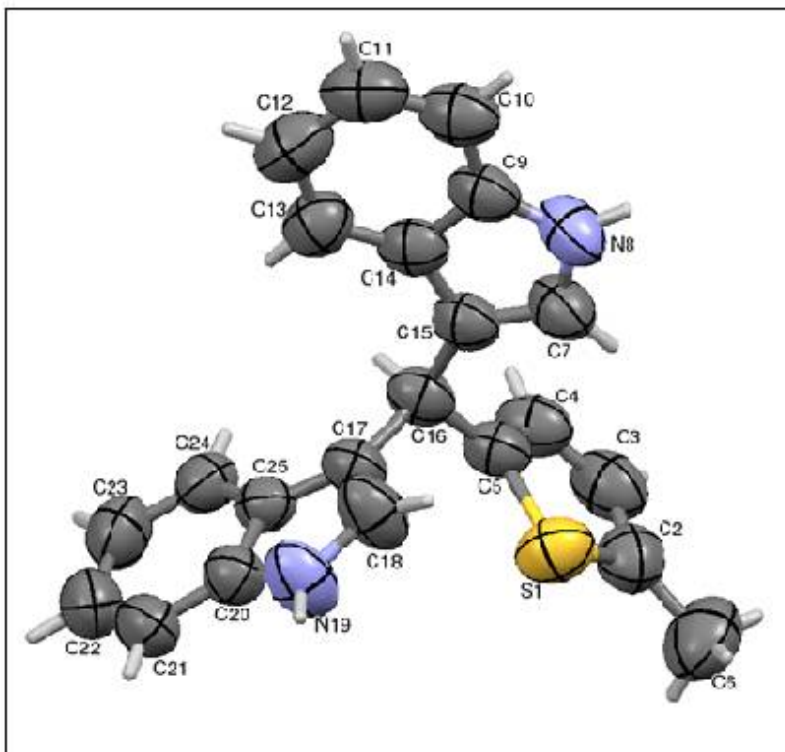


Figure 1. ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability

All the non-hydrogen atoms were revealed in the first difference Fourier map itself. All the hydrogen atoms were positioned geometrically and refined using a riding model. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residuals saturated to 0.0861. The geometrical calculations were carried out using the program *PLATON* [25]. The molecular and packing diagrams were generated using the software *MERCURY* [26]. The details of the crystal structure and data refinement are given in Table-1. The list of selected bond lengths and bond angles are given in Tables-2 and 3. Figure 1 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

Table 1. Crystal data and structure refinement details.

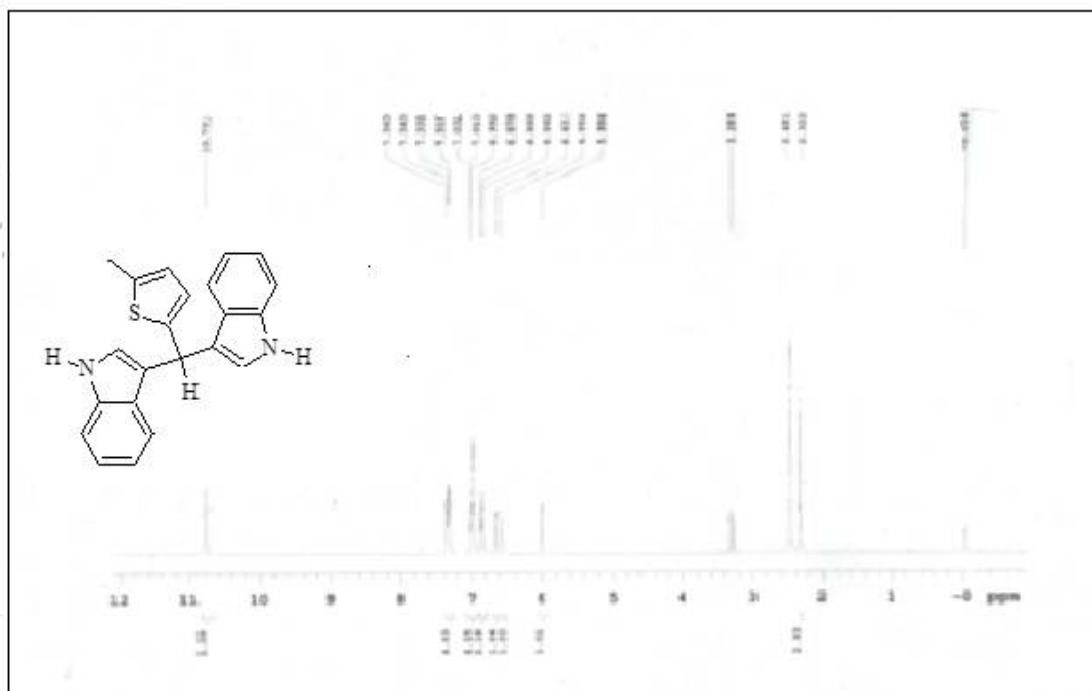
Empirical formula	C ₂₂ H ₁₈ N ₂ S
Formula weight	342.44
Temperature	296(2) K
Wavelength	1.54178 Å
Reflections for cell determination	1522
θ range for above	4.82° to 64.22°
Crystal System	Monoclinic
Space Group	C2/c
Cell dimensions	$a = 26.282(4)$ Å
	$b = 10.3274(14)$ Å
	$c = 17.671(2)$ Å
	$\beta = 130.254(8)^\circ$
Volume	3660.5(9) Å ³
Z	8
Density (calculated)	1.243 Mg m ⁻³
Absorption coefficient	1.597 mm ⁻¹
F_{000}	1440
Crystal size	0.29 x 0.26 x 0.25 mm
Index ranges	$-30 \leq h \leq 30$
	$-12 \leq k \leq 10$
	$-20 \leq l \leq 19$
Reflections collected	17067
Independent reflections	3009 [$R_{int} = 0.1332$]
Absorption correction	Multi-scan
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3009 / 0 / 228
Goodness of fit on	0.959
R indices [$I > 2\sigma(I)$]	$R1 = 0.0878$, $\omega R2 = 0.1994$
R indices (all data)	$R1 = 0.1452$, $\omega R2 = 0.2531$
Extinction coefficient	0.0050(7)
Largest diff. Peak and hole	0.591 and -0.301 e Å ⁻³

Table 2. Bond lengths (Å)

Atoms	Length	Atoms	Length
S1-C5	1.710(5)	C16-C15	1.523(6)
S1-C2	1.714(6)	C17-C18	1.342(6)
N19-C20	1.359(6)	C5-C4	1.356(6)
N19-C18	1.376(6)	C15-C7	1.361(7)
N8-C9	1.354(6)	C4-C3	1.380(7)
N8-C7	1.372(6)	C24-C23	1.381(7)
C25-C24	1.389(6)	C9-C10	1.380(7)
C25-C20	1.407(6)	C13-C12	1.381(7)
C25-C17	1.422(6)	C21-C22	1.366(8)
C14-C13	1.371(7)	C23-C22	1.392(8)
C14-C9	1.413(7)	C2-C3	1.350(8)
C14-C15	1.436(6)	C2-C6	1.491(8)
C20-C21	1.380(7)	C10-C11	1.358(8)
C16-C5	1.495(6)	C11-C12	1.405(8)
C16-C17	1.523(6)	-	-

Table 3. Bond angles (°)

Atoms	Angle	Atoms	Angle
C5-S1-C2	93.5(3)	C7-C15-C14	107.0(4)
C20-N19-C18	108.6(4)	C7-C15-C16	127.8(5)
C9-N8-C7	109.0(4)	C14-C15-C16	125.1(5)
C24-C25-C20	118.9(4)	C5-C4-C3	114.5(5)
C24-C25-C17	133.8(4)	C23-C24-C25	118.1(4)
C20-C25-C17	107.3(4)	N8-C9-C10	129.5(5)
C13-C14-C9	119.1(5)	N8-C9-C14	108.5(4)
C13-C14-C15	135.1(5)	C10-C9-C14	122.1(5)
C9-C14-C15	105.8(5)	C14-C13-C12	118.8(6)
N19-C20-C21	130.1(4)	C22-C21-C20	117.6(5)
N19-C20-C25	107.2(4)	C15-C7-C8	109.7(5)
C21-C20-C25	122.6(5)	C24-C23-C22	122.0(5)
C5-C16-C17	112.3(3)	C3-C2-C6	128.9(6)
C5-C16-C15	111.1(4)	C3-C2-S1	109.0(4)
C17-C16-C15	111.4(4)	C6-C2-S1	122.0(5)

**Figure 2.** ¹H-NMR Spectrum of 3, 3'-(5-methylthiophen-2-yl)methanediyl]bis(1H-indole)

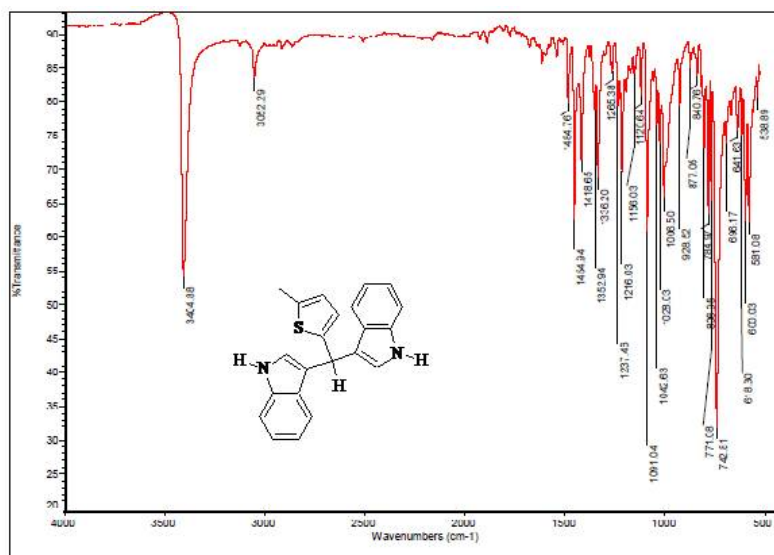
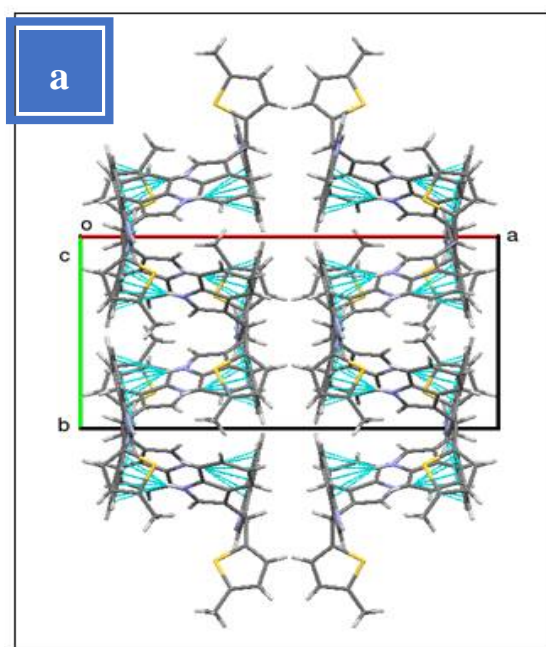


Figure 3. IR Spectrum of 3, 3'-(5-methylthiophen-2-yl)methanediyl]bis(1H-indole)

Crystal structure studies: Both the indole ring systems are essentially planar with dihedral angles of $0.97(1)^\circ$ and $2.77(1)^\circ$ between the two fused ring systems N8/C7-C15 and N19/C17-C25 respectively. These values are in good agreement with those reported for 2-[(4-chlorophenyl)(1H-indol-3-yl)methyl]-1H-indole [27]. The indole ring systems makes a dihedral angle of $89.88(19)^\circ$ with respect to each other indicating that they are orthogonal to each other. The thiophene ring is nearly perpendicular to the indole ring system N8/C7-C15 as indicated by the dihedral angle values of $86.3(3)^\circ$ whereas it makes a dihedral angle of $69.5(3)^\circ$ with the other indole ring system N19/C17-C25 respectively. The packing of the molecules when viewed down along the c axis indicate that the molecules form a tunnel like structure (**Figure 4a**) whereas when viewed down along the b axis it forms a one dimensional sheet (**Figure 4b**).



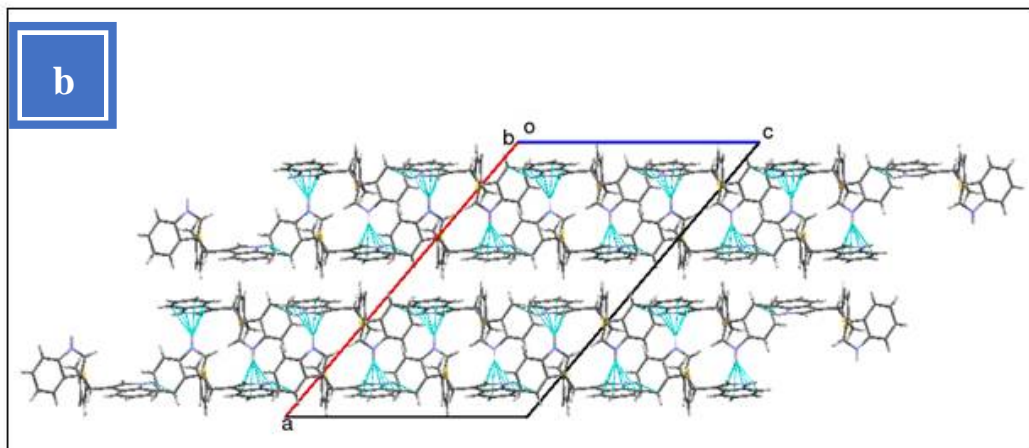


Figure 4. The packing of the molecules when viewed down along the *c* axis indicate that the molecules form a tunnel like structure (a), whereas when viewed down along the *b* axis it forms a one dimensional sheet(b).

APPLICATIONS

The structure of the compound was established by X-ray crystallographic studies. The indole ring systems makes a dihedral angle of 89.88° with respect to each other indicating that they are ortho gonial to each other. The thiophene ring is nearly perpendicular to the indole ring system N8/C7-C15 as indicated by the dihedral angle values of 86.33° where as it makes a dihedral angle of 69.53° if the other indole ring system N19/C17-C25.

CONCLUSIONS

Aqueous acetic acid (30%) was served as potential catalyst and solvent for a synthesis of 3, 3'-[(5-methylthiophen-2-yl)methanediyl]bis(1*H*-indole) with good yields. The compound obtained was characterized spectroscopically and finally the structure of the compound was established by X-ray crystallographic studies.

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