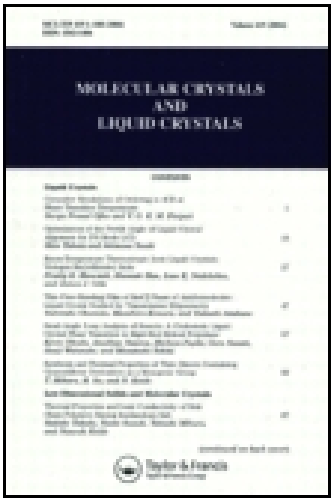

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Synthesis and Crystal Structure of [1-(Toluene-4-Sulfonyl)-Piperidin-4-yl]-Methanol

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The title compound, [1-(toluene-4-sulfonyl)-piperidin-4-yl]-methanol was synthesized by the condensation of diphenyl(piperidin-4-yl)methanol with p-toluenesulfonyl chloride in methylene dichloromethane as solvent and triethylamine as the base. The product obtained was characterized by spectroscopic techniques and the structure was investigated by X-ray crystallography. The compound crystallizes in the monoclinic crystal class in the space group $P2_1/c$ with cell parameters $a = 10.2490(13)$ Å, $b = 11.4710(9)$ Å, $c = 20.997(3)$ Å, $\beta = 116.344(3)^\circ$, $V = 2212.2(5)$ Å^3 for $Z = 4$. The structure reveals that the piperidine ring is in a chair conformation. The geometry around the S atom is comparable with the classic tetrahedral value. The structure exhibits both inter and intramolecular hydrogen bonds of the type O–H···O and C–H···O.

Keywords: chair conformation; hydrogen bonds; toluenesulfonyl chloride

INTRODUCTION

Piperidines are a class of important heterocycles, which exhibits its diverse therapeutic activities due to its conformationally flexible nature. Interest in the piperidine class of opiate analgesics continues to increase in the pharmaceutical community. The biological properties of these agents have been the subject of on going investigations [1]. The importance of the nitrogen heterocycles, especially piperidine type, as subunits of bio-active molecules stimulates the chemist for the

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development of new synthetic methods [2]. Thus piperidine derivatives are associated with diverse pharmacological significance and are thus considered as privileged scaffolds. Piperidine is a key structural component of successful anti-Parkinsons drugs [3] and displays antipsychotic [4], antiviral [5], metabolic [6], antimicrobial [7], antidepressants [8], acetylcholinesterase inhibitor [9], antimalarial [10], and anticonvulsant [11,12] properties.

In continuation of our work on the synthesis and characterization of bioactive heterocycles and their biological evaluation, the title compound was synthesized. The compound obtained was characterized by spectroscopic techniques and finally confirmed by X-ray crystallography.

EXPERIMENTAL

Melting points were determined using Veego model VMP-III 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 a Bruker AM-400 spectrometer and chemical shifts are expressed in parts per million (ppm, for d) relative to tetra methyl silane as an internal standard and DMSO-d6 as solvent. Spin multiplets are given as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Elemental (CHNS) analysis was 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. The reaction scheme is shown in Fig. 1.

Synthesis of Diphenyl-[1-(toluene-4-sulfonyl)-piperidin-4-yl]-methanol

A solution of diphenyl(piperidin-4-yl)methanol 1 (0.5 g, 1.77 mmol), in dry dichloromethane was taken and cooled to 0–5°C in an ice bath. Triethylamine (0.537 g, 5.31 mmol) was added to the cold reaction mixture and stirred for 10 minutes. Then p-toluenesulfonyl chloride (0.338 g, 1.77 mmol) was added and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally water wash was given to the organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to get a crude product which was purified by column chromatography over silica gel (60–120 mesh) using hexane:ethyl

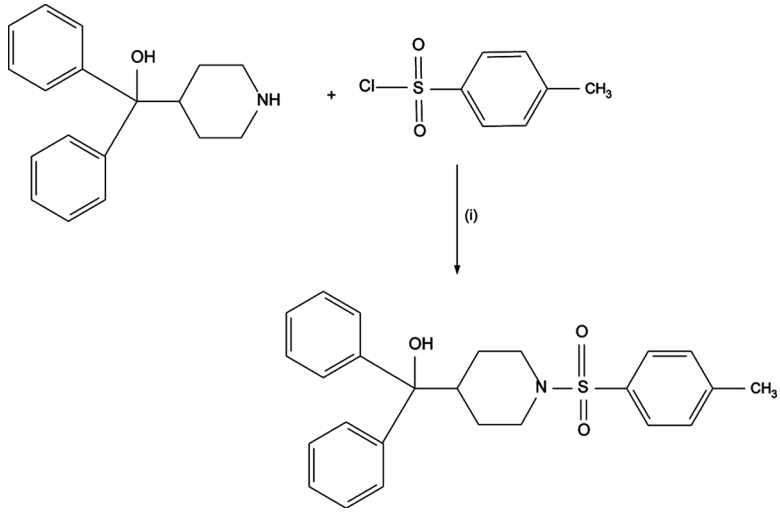

FIGURE 1 Reaction scheme. (i) *p*-toluenesulfonyl chloride, TEA, MDC, r. t., 4 hr.

acetate (8:2) as an eluent. The pale brown crystalline solid obtained was dissolved in ethyl acetate. Pure light brown crystals were obtained after four days due to the slow evaporation of the solvent. M.P.: 165–167°C, Yield 90%.

Anal. Calcd. for $C_{25}H_{27}NO_3S$ (in %): C: 71.23, H: 6.46, N: 3.32, S: 7.61. Found C: 71.20, H: 6.40, N: 3.28, S: 7.58.

^{1}H NMR (DMSO, 400 MHz): δ 7.7 (m, 4H, Ar-H), 7.48 (m, 4H, Ar-H), 7.35 (m, 4H, Ar-H), 7.18 (t, 2H, Ar-H), 3.13 (d, 2H, -CH_2), 2.65 (t, 2H, -CH_2), 2.46 (m, 1H, -CH), 2.31 (s, 3H, -CH_3), 2.2 (s,1H, -OH), 1.5 (d, 4H, -CH_2).

IR (KBr, cm^1): 3500, 2856, 1350, 1276.

MS (ESI) *m/z:* 422.17 ($M + H^+$).

CRYSTAL STRUCTURE DETERMINATION

A single crystal of the title compound with dimensions $0.27 \times 0.25 \times 0.25$ 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 MoK_α). 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 400s. 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 [13]. The reflections were merged with Scalepack [14]. All of the frames could be indexed using a primitive monoclinic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [15]. Least-squares refinement using SHELXL-97 [16] with isotropic temperature factors for all the non-hydrogen atoms converged the residual *R1* to 0.1413. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. The hydrogen atoms were allowed to ride on their parent atoms. After eight cycles of refinement the residual converged to 0.0452. The details of crystal data and

TABLE 1 Crystal Data and Structure Refinement Table

CCDC Deposition Number	CCDC 667632
Empirical formula	$C_{25}H_{27}NO_3S$
Formula weight	421.54
Temperature	293(2)K
Wavelength	0.7I073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell dimensions	$a = 10.2490(13)$ Å $b = 11.4710(9)$ Å $c = 20.997(3)$Å $\beta = 116.344(3)^\circ$
Volume	2212.2(5) Å^3
Z	4
Density (calculated)	1.266 Mg/m^3
Absorption coefficient	0.172 mm^{-1}
F_{000}	896
Crystal size	$0.27 \times 0.25 \times 0.25$ mm
Theta range for data collection	2.31° to 25.02°
Index ranges	$-11 \leq h \leq 11$ $-11 \leq k \leq 11$ $-24 \leq l \leq 24$
Reflections collected	4241
Independent reflections	2460 [R(int) = 0.0211]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2460/0 /273
Goodness-of-fit on F^2	1.108
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0452$, $wR2 = 0.1311$
R indices (all data)	$R1 = 0.0574$, $wR2 = 0.1504$
Extinction coefficient	0.014(3)
Largest diff. peak and hole	0.158 and -0.234 e·Å^{-3}

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

Atom	x	y	z	U_{eq}
N1	0.5554(3)	−0.0314(2)	0.1744(2)	0.0551(8)
C2	0.6723(4)	−0.0317(2)	0.2474(2)	0.0530(8)
C3	0.7464(4)	−0.1500(2)	0.2626(2)	0.0503(8)
C4	0.8075(4)	−0.1780(2)	0.2099(2)	0.0469(8)
C5	0.6883(4)	−0.1660(2)	0.1339(2)	0.0551(9)
C6	0.6082(5)	−0.0489(3)	0.1202(2)	0.0582(9)
S7	0.4046(1)	0.03678(6)	0.15233(5)	0.0529(3)
O8	0.3856(3)	0.0461(2)	0.2160(1)	0.0698(8)
O9	0.2939(3)	−0.0201(2)	0.0916(2)	0.0735(8)
C10	0.4206(4)	0.1792(2)	0.1262(2)	0.0475(7)
C11	0.3261(5)	0.2180(3)	0.0603(2)	0.0727(1)
C12	0.3332(6)	0.3340(3)	0.0417(3)	0.0851(2)
C13	0.4339(4)	0.4093(3)	0.0885(2)	0.0621(9)
C14	0.5306(4)	0.3674(3)	0.1538(2)	0.0606(9)
C15	0.5243(4)	0.2539(3)	0.1734(2)	0.0597(9)
C16	0.4380(7)	0.5366(3)	0.0697(3)	0.0961(2)
C17	0.8826(4)	−0.2998(2)	0.2237(2)	0.0464(8)
O18	0.7735(3)	−0.3886(2)	0.2063(1)	0.0564(6)
C19	0.9960(4)	−0.3115(2)	0.3009(2)	0.0476(8)
C20	1.1184(4)	−0.2401(3)	0.3297(2)	0.0595(9)
C21	1.2158(5)	−0.2451(3)	0.4006(2)	0.0693(1)
C22	1.1961(5)	−0.3218(3)	0.4459(2)	0.0712(1)
C23	1.0779(5)	−0.3948(3)	0.4181(2)	0.0761(1)
C24	0.9803(4)	−0.3912(3)	0.3474(2)	0.0626(9)
C25	0.9522(4)	−0.3221(2)	0.1731(2)	0.0507(8)
C26	0.9450(5)	−0.4311(3)	0.1438(2)	0.0591(9)
C27	1.0088(6)	−0.4531(4)	0.0989(2)	0.0778(1)
C28	1.0817(6)	−0.3673(4)	0.0832(2)	0.0837(1)
C29	1.0917(6)	−0.2593(4)	0.1119(3)	0.0831(1)
C30	1.0286(5)	−0.2364(3)	0.1568(2)	0.0692(1)

$U_{eq} = (1/3)\sum_i \sum_j U_{ij}(a_i^* a_j^*)(\mathbf{a_i} \cdot \mathbf{a_j})$.

refinement are given in Table 1.[†] Table 2 gives the atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles respectively which are in good agreement with the standard values. The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2.

[†]CCDC 667632 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0)1223-336033. E-mail: de-posit@ccdc.cam.ac.uk

TABLE 3 Bond Lengths (Å)

Atoms	Length	Atoms	Length
N1-C2	1.469(5)	C14-C15	1.376(4)
N1-C6	1.475(3)	C17-O18	1.435(3)
N1-S7	1.605(3)	C17-C19	1.525(5)
C2-C3	1.519(4)	C17-C25	1.540(3)
C3-C4	1.528(3)	C19-C20	1.392(5)
C4-C5	1.526(5)	C19-C24	1.398(4)
C4-C17	1.558(4)	C20-C21	1.377(6)
C5-C6	1.533(4)	C21-C22	1.375(5)
S7-O9	1.434(3)	C22-C23	1.372(6)
S7-O8	1.438(2)	C23-C24	1.374(6)
S7-C10	1.754(3)	C25-C26	1.381(4)
C10-C11	1.365(5)	C25-C30	1.390(4)
C10-C15	1.382(5)	C26-C27	1.388(4)
C11-C12	1.397(5)	C27-C28	1.362(6)
C12-C13	1.371(6)	C28-C29	1.361(6)
C13-C14	1.373(6)	C29-C30	1.386(4)
C13-C16	1.518(5)		

TABLE 4 Bond Angles (°)

Atoms	Angle	Atoms	Angle
C2-N1-C6	113.4(3)	C13-C14-C15	121.4(4)
C2-N1-S7	122.5(2)	C14-C15-C10	119.7(4)
C6-N1-S7	118.7(2)	O18-C17-C19	110.4(2)
N1-C2-C3	108.7(2)	O18-C17-C25	104.7(2)
C2-C3-C4	111.3(2)	C19-C17-C25	110.5(2)
C5-C4-C3	110.0(2)	O18-C17-C4	108.9(2)
C5-C4-C17	112.0(2)	C19-C17-C4	110.9(2)
C3-C4-C17	112.4(2)	C25-C17-C4	111.2(2)
C4-C5-C6	112.9(3)	C20-C19-C24	116.3(3)
N1-C6-C5	108.9(2)	C20-C19-C17	121.6(2)
O9-S7-O8	118.6(2)	C24-C19-C17	122.0(3)
O9-S7-N1	108.4(1)	C21-C20-C19	121.7(3)
O8-S7-N1	106.1(1)	C22-C21-C20	121.1(4)
O9-S7-C10	107.1(2)	C23-C22-C21	117.9(4)
O8-S7-C10	106.9(1)	C22-C23-C24	121.6(3)
N1-S7-C10	109.5(1)	C23-C24-C19	121.3(3)
C11-C10-C15	119.9(3)	C26-C25-C30	117.0(3)
C11-C10-S7	119.9(3)	C26-C25-C17	120.6(2)
C15-C10-S7	120.1(3)	C30-C25-C17	122.4(2)
C10-C11-C12	119.5(4)	C25-C26-C27	121.3(3)
C13-C12-C11	121.1(5)	C28-C27-C26	120.5(3)
C12-C13-C14	118.4(3)	C29-C28-C27	119.5(3)
C12-C13-C16	121.2(4)	C28-C29-C30	120.5(3)
C14-C13-C16	120.4(4)	C29-C30-C25	121.2(3)

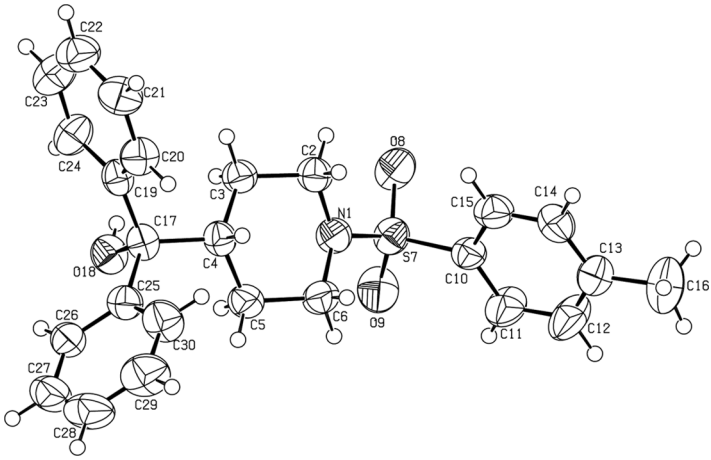

FIGURE 2 ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

A study of the torsion angles, asymmetric parameters and least-squares plane calculations reveals that the piperidine ring in the structure is in a chair conformation with the atoms N1 and C4 deviating 0.253(4) Å and − 0.211(4) Å from the Cremer and Pople plane [17] defined by the atoms C2/C3/C5/C6. This is confirmed by the puckering parameters $Q = 0.5701(40)$ Å $\theta = 4.55(40)^\circ$ and $\Phi = 40(5)^\circ$. The bonds N1-S7 and C4–C17 make an angle of 74.41(11)° and 71.0(2)°, respectively, with the Cremer and Pople plane of the piperidine ring and thus lie in the equatorial plane of the piperidine ring. The dihedral angle between the least-squares plane of the piperidine ring and the phenyl ring C19–C24 is 89.40(19)° implying that the phenyl ring is nearly perpendicular to the plane of the piperidine ring. The other phenyl ring C25–C30 makes a dihedral angle of 73.4(2)° with the least-squares plane of the piperidine ring. The dihedral angle between the two phenyl rings bridged by the alcoholic group is 65.9(2)°. The methylphenyl ring is inclined at an angle of 66.3(2)° to the sulfonyl plane. The sulfonyl O atoms O8 and O9 are oriented in *+synperiplanar* and *−synclinal* conformations as indicated by the torsion angle values of −24.8(3)° and 54.6(3)° for C2-N1-S7-O8 and C6-N1-S7-O9, respectively.

The geometry around the S atom is distorted tetrahedron, with the largest deviations observed for the O-S-O [O8-S7-O9 = 118.6(2)°] and O-S-N angles [O9 S7 Nl = 108.4(l)°. This widening of angles is due to the repulsive interaction between the two short S=O bonds.

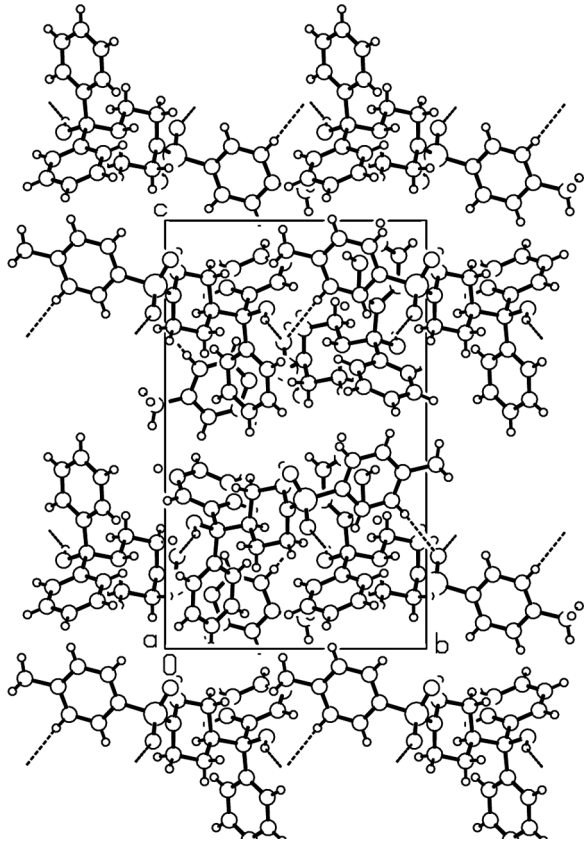

FIGURE 3 Packing of the molecules when viewed down the *a* axis. The dashed lines indicate the hydrogen bonds.

The S-N bond distance lies within the expected range of 1.60–1.69 Å. The bond angle for N1-S7-C10 = 109.5(1)° is comparable with the classic tetrahedral value of 109.47°. Similar conformation was observed in the molecule of [1-(4-chloro-2-fluoro-benzenesulfonyl)-piperidin-4-yl]-diphenyl-methanol [18]. The structure exhibits both inter and intramolecular hydrogen bonds of the type O-H ··· O and C-H ··· O. The intermolecular hydrogen bond O18-H18 ··· O8 between the alcoholic group and the sulfonyl group has a length of 2.871(4) Å and an angle of 151° with the symmetry code $1-x,\ -1/2+y,\ 1/2-z$ while the other hydrogen bond C14-H14 ··· O8 hydrogen bond between the methylphenyl ring and the sulfonyl group has a length of 3.214(4) Å and an angle of 133° with the symmetry code $-1+x,\ 1/2+y,\ 1/2-z$. The packing

of the molecules when viewed down the *a* axis indicate that the molecules are stacked in pairs and they form a one dimensional polymeric chain (Fig. 3).

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