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Synthesis and Crystal Structure of 1-Benzenesulfonyl-4-benzhydryl-piperazine

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1-Benzenesulfonyl-4-benzhydryl-piperazine was synthesized from 1-benzhydryl piperazine with benzenesulfonyl chloride. The title compound, $C_{23}H_{24}N_2O_2S$, was synthesized 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 $a = 13.2390(10)$ Å, $b = 9.1960(7)$ Å, $c = 18.5810(16)$ Å, $\beta = 110.873(3)^\circ$, and $Z = 4$. The piperazine ring in the structure is in a chair conformation. The geometry around the S atom is distorted tetrahedral. The structure exhibits an intermolecular hydrogen bond of the type C–H···O.

Keywords: chair conformation; crystal structure; piperazine

INTRODUCTION

Piperazine derivatives are important pharmacophores that can be found in biologically active compounds in a number of different therapeutic areas [1], such as antifungal [2], antibacterial, antimalarial,

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antipsychotic [3], HIV protease inhibitor [4–6], antidepressant [7], and antitumour activity against colon, prostate, breast, lung, and leukemia tumors [8]. Diphenyl piperazine derivatives possess broad pharmacological action on the central nervous system (CNS), especially on dopaminergic neuro transmission [9]. They are also reported to be potent enterovirus inhibitors [10]. Piperazine sulfonamides are among the most widely used antibacterial [11] agents in the world, chiefly because of their low cost, low toxicity, and excellent activity against common bacterial diseases. In continuation of our work on the synthesis of novel bioactive heterocycles, 1-benzenesulfonyl-4-benzhydryl-piperazine was synthesized. The structure of the compound obtained was established on the basis of Fourier Transform Infrared Spectroscopy (FTIR), ^{1}H NMR, Liquid Chromatography (LC)/ Mass Spectrometry (MS), elemental analysis, and finally confirmed by X-ray crystallography.

EXPERIMENTAL

The melting points were determined using a Veego model VMP-III melting-point apparatus and are uncorrected. The IR spectra were recorded using a Jasco FTIR-4100 series. ^{1}H NMR spectra were recorded on a Bruker AM-400 instrument, and chemical shifts (ppm, for δ) are relative to TMS as an internal standard. Spin multiplets are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Mass and purity were recorded on a LC-MSD-Trap-XCT. Elemental analyses (CHNS) were done on a Vario EL III Elementar. Silica-gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made thin-layer chromatography (TLC) plates.

A solution of 1-benzhydryl-piperazine (0.5 g, 1.98 mmol) in dichloromethane (10 ml) was taken and cooled to 0–5°C in an ice bath. Triethylamine (0.601 g, 5.94 mmol) was added to the cold reaction mixture and stirred for 10 min. Benzenesulfonyl chloride (0.349 g, 1.98 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 5 h. The reaction was monitored by TLC. On completion of the reaction, the solvent was removed under reduced pressure, and the residue was taken in water and extracted with ethyl acetate. Finally, a water wash was given to the organic layer, which was dried with anhydrous sodium sulphate, and the solvent was evaporated to get a crude product, which was purified by column chromatography over silica gel using hexane–ethyl acetate (8:2) as an eluent. The pure product obtained was dissolved in ethyl acetate. Yield was 0.621 g (80%). Because of the slow evaporation of the solvent, white crystals developed after 3 days. The synthetic method employed for synthesis is shown in Fig. 1.

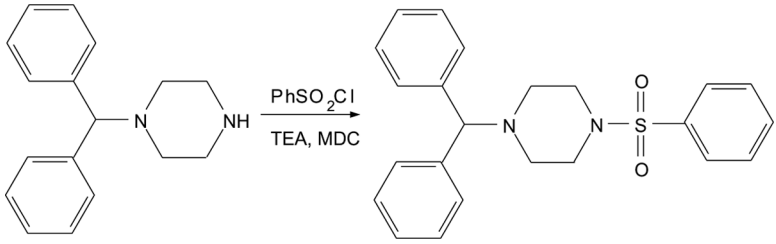

FIGURE 1 Schematic diagram.

Melting point: 159°C. ^{1}H NMR (DMSO, 400 MHz) δ: 7.48 (d, 2H, Ar−H), 7.40 (m, 6H, Ar−H), 7.27 (t, 5H, Ar−H), 7.15 (t, 2H, Ar−H), 4.26 (s, 1H, −CH−), 3.1 (t, 4H, $-CH_2-$), 2.50 (t, 4H, $-CH_2-$). IR (KBr, cm^{-1}): 3026, 2925, 2960, 1319, 1150. Anal. Calc. for $C_{23}H_{24}N_2O_2S$ (in %): C = 70.38, H = 6.16, N = 7.14, S = 8.17; found: C = 70.34, H = 6.11, N = 7.10, S = 8.15. Mass: 393.61; purity: 98.6%.

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 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 [12]. The reflections were merged with Scalepack [4]. 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 [13]. All of the nonhydrogen atoms were revealed in the first Fourier map. Full-matrix least-squares refinement using SHELXL-97 with isotropic temperature factors for all the atoms converged the residuals to 0.1961. Refinement of nonhydrogen atoms with anisotropic parameters was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on the parent atoms. Parameters (254) were refined with 3693 unique reflections, which converged the residuals to 0.0603. The details of crystal data and refinement are given in

TABLE 1 Crystal Data and Structure Refinement

Parameter	Value
CCDC number	CCDC 632236
Empirical formula	$C_{23}H_{24}N_2O_2S$
Formula weight	392.50
Temperature	293(2) K
Wavelength	0.7I073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell dimensions	$a = 13.2390(10)$ Å $b = 9.1960(7)$ Å $c = 18.5810(16)$ Å $\beta = 110.873(3)^\circ$
Volume	2113.7(3) Å^3
Z	4
Density (calculated)	1.233 Mg/m^{-3}
Absorption coefficient	0.173 mm^{-1}
F_{000}	832
Crystal size	$0.27 \times 0.25 \times 0.25$ mm
Theta range for data collection	2.34° to 25.03°
Index ranges	$-15 \le h \le 15$ $-10 \le k \le 10$ $-22 \le l \le 22$
Reflections collected	6810
Independent reflections	3693 [R(int) = 0.0244]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3693/0/254
Goodness of fit on F^2	1.186
Final R indices [$I \ge 2\sigma(I)$]	$R1 = 0.0603$, $wR2 = 0.1503$
R indices (all data)	$R1 = 0.0832$, $wR2 = 0.1838$
Extinction coefficient	0.056(5)
Largest diff. peak and hole	0.656 and −0.665 e.Å^{-3}

Table 1.[†] The final atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms are listed in Table 2. Tables 3 and 4 gives the list of bond distances and bond angles of nonhydrogen atoms respectively. The bond lengths and bond angles are in good agreement with the standard values. Figure 2 shows the ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

[†]CCDC 632236 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: deposit@ccdc.cam.ac.uk.

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Nonhydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}
N1	0.5274(2)	0.3166(2)	0.3791(2)	0.0533(5)
C2	0.4662(2)	0.2410(3)	0.4197(2)	0.0642(6)
C3	0.3482(2)	0.2788(3)	0.3848(2)	0.0673(7)
N4	0.3346(2)	0.4366(2)	0.3903(1)	0.0627(6)
C5	0.3974(2)	0.5179(3)	0.3530(2)	0.0627(6)
C6	0.5145(2)	0.4735(3)	0.3869(2)	0.0623(6)
C7	0.6431(2)	0.2786(3)	0.4103(2)	0.0582(6)
C8	0.7032(2)	0.3501(3)	0.3639(2)	0.0651(7)
C9	0.6579(2)	0.3606(3)	0.2843(2)	0.0742(7)
C10	0.7155(3)	0.4213(3)	0.2424(2)	0.0975(1)
C11	0.8183(4)	0.4702(4)	0.2793(4)	0.1160(2)
C12	0.8644(3)	0.4601(4)	0.3575(4)	0.1210(2)
C13	0.8070(2)	0.4012(3)	0.4001(2)	0.0909(1)
C14	0.6638(2)	0.1158(3)	0.4139(2)	0.0544(6)
C15	0.7397(2)	0.0558(3)	0.4797(2)	0.0649(7)
C16	0.7665(2)	−0.0877(3)	0.4826(2)	0.0756(8)
C17	0.7182(2)	−0.1771(3)	0.4214(2)	0.0785(8)
C18	0.6414(2)	−0.1204(3)	0.3555(2)	0.0749(7)
C19	0.6141(2)	0.0246(3)	0.3521(2)	0.0628(6)
S20	0.21206(5)	0.49599(8)	0.37483(4)	0.0705(3)
O21	0.1679(2)	0.4071(3)	0.4191(2)	0.1034(9)
O.22	0.2210(2)	0.6491(2)	0.3874(2)	0.0872(7)
C23	0.1358(2)	0.4671(3)	0.2771(2)	0.0569(6)
C24	0.0757(2)	0.3415(3)	0.2538(2)	0.0817(8)
C25	0.0202(3)	0.3193(4)	0.1760(3)	0.1030(2)
C26	0.0251(2)	0.4183(4)	0.1229(2)	0.0915(1)
C27	0.0834(2)	0.5415(4)	0.1452(2)	0.0862(9)
C28	0.1394(2)	0.5674(3)	0.2228(2)	0.0701(7)

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

The piperazine ring in the structure adopts a chair conformation. This has been confirmed by the puckering parameters [14] $Q = 0.5854(31)$ Å, $\theta = 176.27(29)^\circ$, and $\phi = 208(5)^\circ$ and the intra ring torsion angles for the atom sequence N1/C2/C3/N4/C5/C6. The bonds N1–C7 and N4–S20 make an angle of 73.01(19)° and 85.94(16)° respectively with the Cremer and Pople plane of the piperazine ring and thus are in the equatorial plane of the piperazine ring. The dihedral angle between the least-squares plane of the piperazine ring and the phenyl ring bridged by the sulfonyl group is 79.09°. The piperazine ring makes an angle of 71.65(16)° with the phenyl ring (C8–C13) and 72.34(16)° with the phenyl ring (C14–C19).

TABLE 3 Bond Lengths (Å)

Atoms	Length
N1–C2	1.464(3)
N1–C6	1.466(3)
N1–C7	1.475(3)
C2–C3	1.502(3)
C3–N4	1.471(3)
N4–C5	1.464(3)
N4–S20	1.637(2)
C5–C6	1.506(3)
C7–C8	1.515(4)
C7–C14	1.519(3)
C8–C13	1.381(4)
C8–C9	1.388(4)
C9–C10	1.386(4)
C10–C11	1.363(6)
C11–C12	1.364(6)
C12–C13	1.388(6)
C14–C19	1.384(3)
C14–C15	1.390(3)
C15–C16	1.363(4)
C16–C17	1.364(4)
C17–C18	1.386(4)
C18–C19	1.377(3)
S20–O21	1.425(2)
S20–O22	1.425(2)
S20–C23	1.756(3)
C23–C24	1.381(4)
C23–C28	1.381(4)
C24–C25	1.384(5)
C25–C26	1.361(5)
C26–C27	1.350(5)
C27–C28	1.386(4)

These values are less than the corresponding values of 86.32(10)° and 88.27(15)° reported for 1-benzhydryl piperazine [15]. This can be attributed to the steric hindrance caused by the bulky sulfonyl substituent at the fourth position [N4] of the piperazine ring. The dihedral angle between the two phenyl rings bridged by the carbon atom is 77.30(15)°. The geometry around the S atom is distorted from a regular tetrahedron, with the largest deviations observed for O–S–O [O21–S20–O22 = 120.1(2)°] and O–S–N [O21–S20–N4 = 106.4(2)°]. This widening of angles is due to the repulsive interaction between the two short C=O bonds and the nonbonded interactions involving the two S−O bonds. The S−N bond distance lies within the expected range of 1.63–1.69 Å. The reduction of the N4–S20–C23 angle to 107.5(2)° from the ideal tetrahedral value can be attributed to the Thorpe–Ingold

TABLE 4 Bond Angles (°)

Atoms	Angle
C2–N1–C6	108.2(2)
C2–N1–C7	112.0(2)
C6–N1–C7	109.6(2)
N1–C2–C3	110.5(2)
N4–C3–C2	109.4(2)
C5–N4–C3	111.5(2)
C5–N4–S20	116.3(2)
C3–N4–S20	117.2(2)
N4–C5–C6	109.7(2)
N1–C6–C5	111.3(2)
N1–C7–C8	110.9(2)
N1–C7–C14	113.4(2)
C8–C7–C14	109.3(2)
C13–C8–C9	118.2(3)
C13–C8–C7	120.2(3)
C9–C8–C7	121.5(2)
C10–C9–C8	120.8(3)
C11–C10–C9	120.1(4)
C10–C11–C12	120.0(4)
C11–C12–C13	120.5(4)
C8–C13–C12	120.4(4)
C19–C14–C15	118.1(2)
C19–C14–C7	122.4(2)
C15–C14–C7	119.4(2)
C16–C15–C14	121.0(3)
C15–C16–C17	120.8(2)
C16–C17–C18	119.3(2)
C19–C18–C17	120.2(3)
C18–C19–C14	120.6(2)
O21–S20–O22	120.1(2)
O21–S20–N4	107.0(2)
O22–S20–N4	106.4(2)
O21–S20–C23	107.9(2)
O22–S20–C23	107.6(2)
N4–S20–C23	107.5(2)
C24–C23–C28	119.7(3)
C24–C23–S20	120.3(2)
C28–C23–S20	119.9(2)
C23–C24–C25	118.8(3)
C26–C25–C24	120.9(3)
C27–C26–C25	120.6(3)
C26–C27–C28	119.9(3)
C23–C28–C27	120.0(3)

effect [16]. The structure exhibits an intermolecular hydrogen bond of the type C–H···O between the sulfonyl group and the substituted phenyl ring. The intermolecular hydrogen bond C25–H25···O22 has a

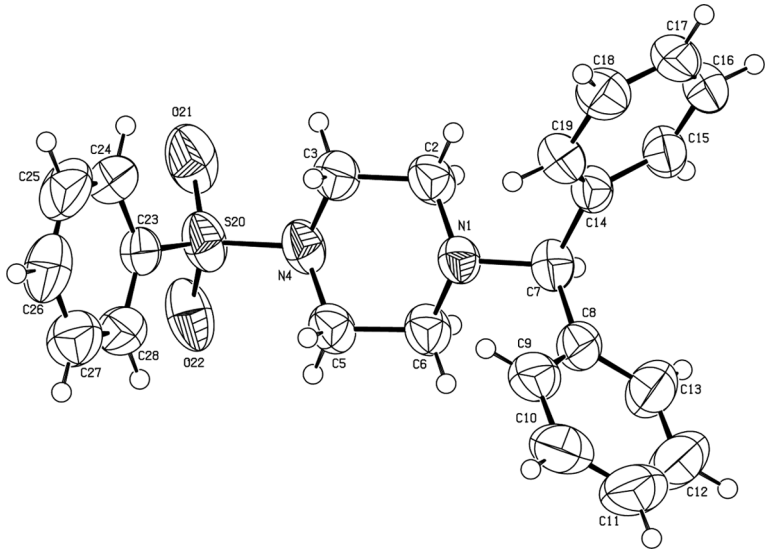

FIGURE 2 ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

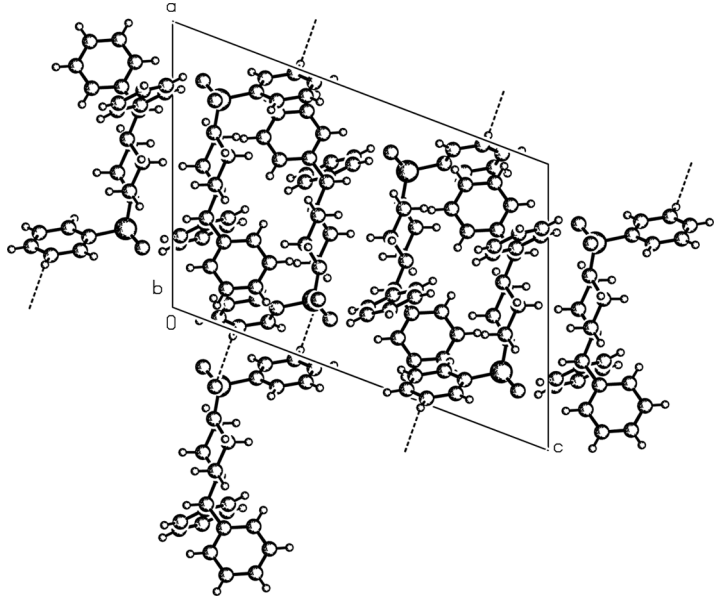

FIGURE 3 Packing of the molecules down the *b* axis. The dashed lines represent the hydrogen bonds.

length of 3.370(5) Å and an angle of 141° with symmetry code $-x, 1/2+y, 1/2-z$. The packing of the molecules when viewed down the b axis indicates that the molecules are linked by intermolecular hydrogen bonds to form a one-dimensional chain (Fig. 3).

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