Crystal Structure of a Bioactive Intermediate: 1-Benzhydrylpiperazine

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A new bioactive intermediate, 1-benzhydrylpiperazine, crystallizes in monoclinic space group $P2_1/c$ with cell parameters $a = 10.171(8)\text{\AA}$, $b = 9.599(5)\text{\AA}$, $c = 15.526(13)\text{\AA}$, $\beta = 107.861(2)^\circ$ and $Z = 4$. The piperazine ring is in the chair conformation.

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1-Benzhydrylpiperazine bearing dihydronaphthalene derivatives are found to possess excellent pharmacological activities, such as vasodilator, hypotensive and cerebral blood flow increasing actions.¹ Recently, a series of pyrazolo[3,4-d]pyrimidines were synthesized using 1-benzhydrylpiperazine, and their antiviral activity was evaluated. It was found that they are very specific for human enteroviruses, particularly coxsackieviruses at nanomolar concentrations.² We report here the single-crystal x-ray structure of the title compound, which is an intermediate for the synthesis of the antipsychotic drug. A schematic diagram of the molecule is shown in Fig. 1.

A single crystal of the title compound with dimensions of $0.25 \times 0.3 \times 0.25$ mm was chosen for an X-ray diffraction study. Measurements were made on a DIPLabo Imaging Plate system with graphite monochromated Mo K_α radiation. Thirty six frames of data were collected by the oscillation method, with each frame being exposed for 300 s. Successive frames were scanned in steps of $5^\circ/\text{min}$ with an oscillation range of 5° . Image processing and data reduction were performed using Denzo.³ All the frames could be indexed using a primitive monoclinic lattice. The reflections were merged with Scalepack.⁴ The structure was solved by direct methods using SHELXS97.⁵ All of the non-hydrogen atoms were revealed in the first map, itself. Anisotropic refinement using SHELXL97⁵ was started at this stage and the residual R_1 finally converged to 0.0621.

The hydrogen atoms were placed at chemically acceptable positions and were not refined. Details of the crystal and refinement data are given in Table 1. Table 2 gives the selected bond lengths and bond angles of the non-hydrogen atoms. The

bond lengths and bond angles are in good agreement with the standard values. An ORTEP diagram of the molecule with thermal ellipsoids at 50% probability is shown in Fig. 2.

A study of the torsion angles, asymmetric parameters and least-squares plane calculations reveals that the piperazine ring in the structure is in the chair conformation. The dihedral angles between the piperazine ring and the benzene rings (C15–C19) and (C8–C13) are $86.32(10)^\circ$ and $88.27(15)^\circ$, respectively, indicating that the benzene rings are nearly perpendicular to the piperazine ring. The dihedral angle between the two benzene rings is $81.12(11)^\circ$, which is very low when compared to 1-[(4-chlorophenyl)phenylmethyl]piperazine.⁶ The piperazine ring is in a chair conformation. This has been confirmed by the puckering parameters $q_2 = 0.008(2)\text{\AA}$, $q_3 = 0.591(2)\text{\AA}$, $Q_T = 0.592(2)$ and $\theta = 0.53(2)^\circ$. A ring puckering analysis⁷ shows that the piperazine ring has a

Fig. 1 Schematic diagram.

Table 1 Crystal and experimental data

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Empirical formula	$C_{17}H_{20}N_2$
Formula weight	252.35
Crystal system	monoclinic
Space group	$P2_1/c$ $Z = 4$
Cell dimensions	$a = 10.171(8)\text{\AA}$ $b = 9.599(5)\text{\AA}$ $c = 15.526(13)\text{\AA}$ $\beta = 107.861(2)^\circ$
Volume	$1442.8(2)\text{\AA}^3$
D_c	1.162 Mg/m^3
θ_{max}	32.51°
Independent reflections	4912 [$R(\text{int}) = 0.0232$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4912/0/173
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0621$ [2822 reflns] $wR2 = 0.1827$
$(\Delta/\sigma)_{\text{max}}$	0.001
Largest diff. peak and hole	0.320 and $-0.209\text{ e\AA}^{-3}$
Measurement	DIPLabo Kappa
Program system	Denzo
Structure determination	SHELXS-97
Refinement	full-matrix: SHELXL-97

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Fig. 2 ORTEP of the molecule at 50% probability.

Table 2 Selected bond lengths (Å) and bond angles (°)

Atoms	Length	Atoms	Length
N1-C6	1.442(2)	N4-C5	1.460(5)
N1-C2	1.452(2)	C8-C7	1.524(9)
N4-C7	1.476(7)	C7-C14	1.522(7)
N1-C2-C3	109.3(1)	N4-C7-C8	112.5(1)
N4-C7-C14	111.5(1)	C15-C14-C7	122.6(1)
C8-C9-C10	120.2(2)	C14-C19-C18	121.1(2)

weighted average ring bond distance of 1.4681(10, 108)Å and a weighted average absolute torsion angle of 59.10(8, 15)°. The

molecules when viewed down the *b* axis appear to be stacked in pairs. No hydrogen bonding between the molecules is observed.

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