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Structural and conformational studies of 1-[2-(2-benzyloxyphenyl-5-methyl)-2-oxo-ethyl]-4-dimethylamino pyridinium bromide

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ABSTRACT

The title compound crystallizes with the monoclinic space group $P2_1/c$. The dihedral angle between the central benzene and the phenyl ring is 77.74(2)˚. The dihedral angle between the planes of the pyridine moiety and the 5-methylphenyl group is 87.9(2)º. The pyridinium and dimethyl amino group are in co-planar orientation. The DMAP ring is essentially planar with an average deviation of 1.3º.The 5-methylphenyl ring and the phenyl ring of the benzyloxy group are orthogonal with the dihedral angle of 83.9(2)º.

INTRODUCTION

Pyridinium derivatives exhibit antibacterial and antifungal activities [1]. It has been demonstrated that the human peripheral mononuclear cells isolated from healthy volunteers contain traces of derivatives of pyridinium compounds. 4-Aminopyridine (4AP) has been found to be an efficient drug, affecting potassium permeability and capable of provoking membrane depolarization [2] and is also able to induce an increase in intracellular calcium influx through modulation of the activity of purinergic cationic channels [3]. This drug is also used in the treatment of neurological ailments such as multiple sclerosis (MS), with tests showing that 4AP improves motor function in MS patients [4].

In order to study and explain the behaviour of 4-dimethylamino pyridinium bromide the title compound was subjected to an X-ray crystallographic study. The chemical scheme of the molecule of the compound is given in **Fig. 1.1**

MATERIALS AND METHODS

A solution of 2-benzyloxyphenyl bromide (1.112g; 4 mmol) and DMAP (0.5g, 4 mmol) in dry acetone was refluxed for 30 min. After cooling to room temperature (303K) the solid that separated was filtered and washed with dry acetone and dried in vacuum to a stable salt with 89% of yield (m.p 236-239º C), Quality crystals were obtained using ethanol as solvent.

The chemical scheme of the title compound is shown in **Fig 1.1**

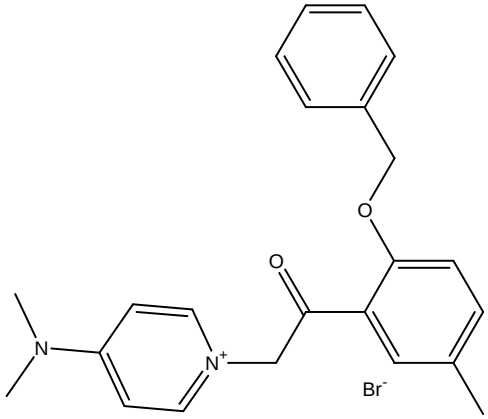

Fig. 1.1

Intensity Data Collection

X-ray data were collected on a Bruker AXS (Kappa APEX2) CCD area detector using ω and ψ scan mode. A small crystal of size 0.28 × 0.24 × 0.16 mm was chosen and its quality was checked using polarizing microscope. Cell refinement and data reduction were carried out by using APEX2/SAINT-NT [5]. Sets of two standard reflections were monitored for every one hour of exposure during the data collection and there was no noticeable change in the intensity observed. A total of 18549 reflections were collected resulting in 3292 independent reflections of which 2318 had $I > 2\sigma(I)$, were considered as observed reflections. The intensities were corrected for Lorentz and polarization effects. Absorption corrections were made with SADABS (Ver.2004/1)[6].

Structure Solutions and Refinement

The analysis over the data set revealed the following set of systematic absences:
(i) in the 0 k 0 series, the k odd reflections and
(ii) in the h 0 l series, the l odd reflections

The first set of systematic absences revealed 2_1 screw parallel to b-axis. Hence the space group monoclinic, $P2_1/c$ was unambiguously assigned. The structure was solved by direct methods using SIR92 [7] which revealed the positions of all non hydrogen atoms. All the non-hydrogen atoms were refined anisotropically using SHELXL97 [8]. At this stage, the difference Fourier map revealed all hydrogen atoms. After checking their presence in the difference map, H atoms were placed in calculated positions with [C-H=0.93Å and 0.97 Å with 1.2 U_{eq} (C) for all hydrogen atoms and U_{iso} (H)=1.5U_{eq}(C) for methyl hydrogen atoms] in the riding model approximation. The refinement was completed at R=0.0526 for 2318 reflections.

The weighting scheme [9],[10], adopted during the final cycle of refinement is

$w = 1 / [S^2 (F_o^2)+(0.0738P)^2+2.3608P]$ where $P=(F_o^2 + 2 F_c^2) / 3$.

The geometric calculations were performed using the PARST [11][Nardelli, 1983b, 1995]. The crystal data and refinement parameters are summarized in **Table 1.1**. The maximum and minimum values of the residual electron density were 0.31e $Å^{-3}$ and -0.74e $Å^{-3}$.

RESULTS AND DISCUSSION

The structure which contains dimethylamino pyridinium moiety and a benzyloxy phenyl ring connected through an oxoethyl group is shown in the Fig 1.2.

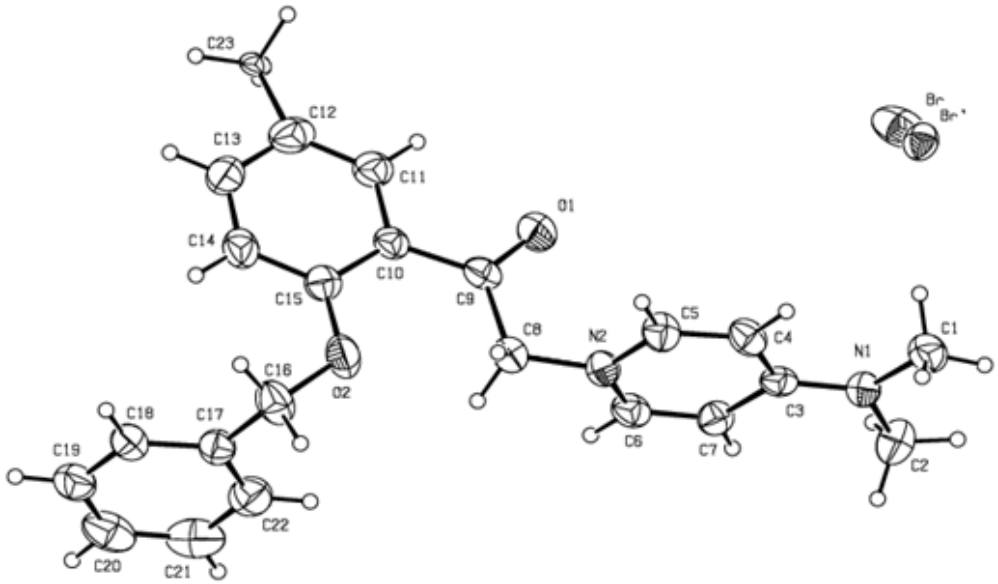

Fig. 1.2 shows the ORTEP view of the molecule drawn at 30% probability displacement ellipsoid level with atom numbering scheme

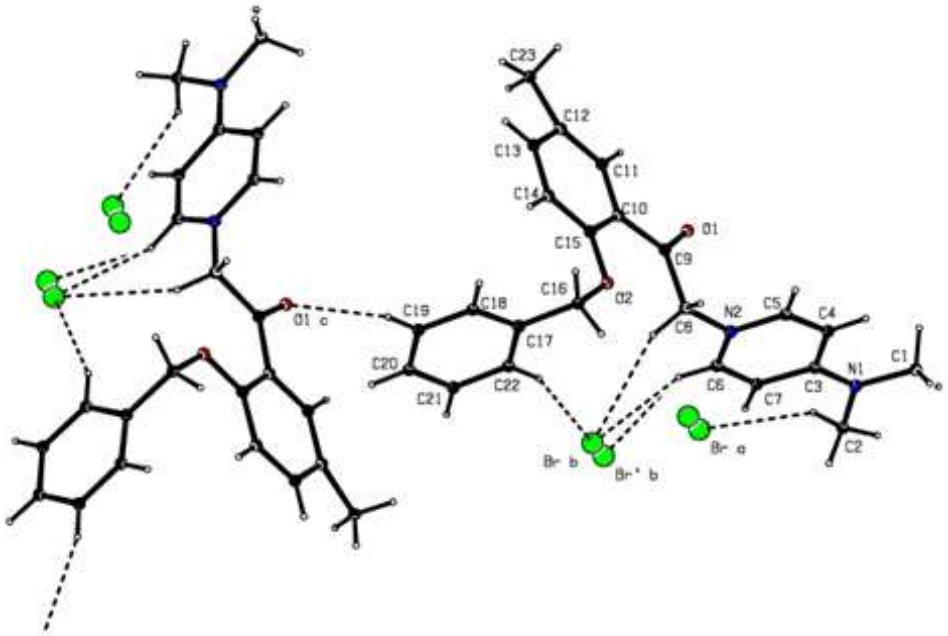

Fig 1.3. Packing diagram of title compound with C-H..Br interactions and hydrogen is bifurcated

Molecular Geometry and Conformation

The bond lengths and bond angles involving all non hydrogen atoms are presented in **Table 1.2** and **Table 1.3.**

An interesting feature of the pyridinium system is that it has a substantial degree of quinonoidal character since the bond lengths C6-C7 [1.345(7)Å] andC4-C5 [1.359(8)Å] are significantly shorter than C3-C7 [1.408(7)Å] and C3-C4 [1.405(7)Å]. The C3-N1 bond length [1.335(6)Å] is intermediate between typical C-N single and double bond distances[1.465 and 1.239Å] [12] indicating a significant conjugation of exocyclic nitrogen.

The bond lengths and bond angles of the pyridinium ring are comparable with those reported for related structures [13]. The sum of the bond angles around N1 and N2 are equal to 360º. Hence there is no evidence for sp^3 lone pair. The DMAP ring is essentially planar with an average deviation of 1.3º

The torsion angles of C9-C8-N2-C6 and C9-C8-N2-C5 are 89.8(5)º and -82.9(6)º respectively which describe the orientation of the oxoethyl group with respect to the pyridinium moiety. The torsion angles of C15-O2-C16-C17 [-74.0(7)º], C10-C15-O2-C16 [176.9(5)º] and O2-C16-C17-C22.[-49.4(8)º] confirm the orientation of the benzyloxy group. The orientation of the methyl phenyl ring with respect to oxoethyl group of pyrdinium ring is described by the torsion angles O1-C9-C10-C11 [-2.1(7)º] and C8-C9-C10-C15 [-2.5(8)º] respectively.

Table 1.4 lists the torsion angles of the title compound and **Table 1.4a** shows the dihedral angles between the planes. The dihedral angle between the planes of the pyridine moiety and the 5-methylphenyl group is 87.9(2)º. The pyridinium and dimethyl amino group are in co-planar orientation. The 5-methylphenyl ring and the phenyl ring of the benzyloxy group are orthogonal with the dihedral angle of 83.9(2)º. The packing of molecules viewed along '**b**'-axis is shown in the **Fig. 1.3.**

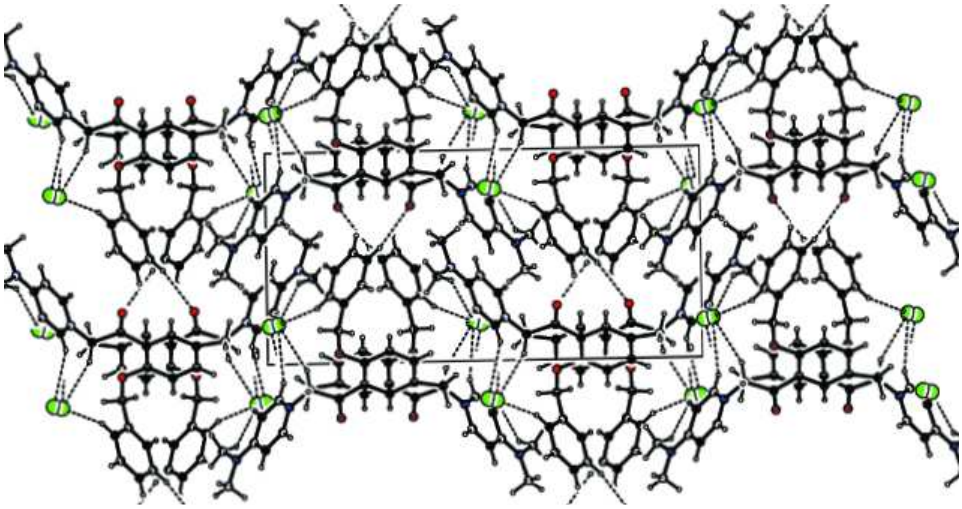

Fig 1.4 The C-H…O and C-H…Br^- hydrogen bonding interactions form a chain along bc plane

Hydrogen Bonding

The hydrogen bonding scheme is listed in **Table 1.5** The bromide ion is surrounded by either phenyl or pyridinium rings from adjacent cations forming C-H…Br contacts. The C-H…O and C-H…Br^- hydrogen bonding interactions form a chain along **bc** plane [**Fig. 1.4**]. The crystal structure is stabilized by C6-H6…Br^{i} [symmetry code i = $^3/_2$-x, $^1/_2$+y, -z] and C19-H19…$O1^{ii}$[symmetry code ii = -$^1/_2$+x, -$^1/_2$-y, -1+z] interactions and one weak intra-molecular interaction C11-H11…O1 involving atoms C11-H11-…O1-C9-C10 which forms a ring of graph set motif S(5). In this compound, C1-H1C…$Cg1^{iii}$ interaction is observed. The atom H1C is separated by a distance of 2.81Å from the centroid of the phenyl ring Cg1.[symmetry code (iii)=1-x, -y, -z; where Cg1=C17-C22]. Additionally C16-H16B…$Cg2^{iv}$ interaction is also formed where Cg2 is 5-methyl benzene ring [Cg2=C10/C11/C12/C13/C14/C15, symmetry code (iv)= -$^1/_2$+x, -$^1/_2$-y, z]. Other interactions governing the packing of the molecule are generally considered to be weak.

TABLE 1.1 Crystal data and structure refinement for 1-[2-(2-Benzyloxyphenyl-5-methyl)-2-oxo-ethyl]-4-dimethylamino pyridinium bromide

Empirical formula	C_{23} H_{25} Br N_2 O_2
Formula weight	441.36
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 9.4213(10) Å α = 90° b = 20.979(3) Å β = 96.998(5)° c = 10.2757(12) Å γ = 90°
Volume	2015.9(4) A^3
Z, Calculated density	4, 1.454 Mg/m^3
Absorption coefficient	2.061 mm^{-1}
F(000)	912
Crystal size	0.28 × 0.24 × 0.16 mm
Theta range for data collection	1.94 to 24.38 deg.
Limiting indices	-10<=h<=10, -24<=k<=24, -11<=l<=11
Reflections collected / unique	18549 / 3292 [R(int) = 0.0504]
Completeness to theta = 24.38	99.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3292 / 1 / 265
Goodness-of-fit on F^2	1.115
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1396
R indices (all data)	R1 = 0.0862, wR2 = 0.1636
Extinction coefficient	0.0044(11)
Largest diff. peak and hole	0.31e.$Å^{-3}$ and -0.740 e.$Å^{-3}$

TABLE 1.2 Bond lengths (Å) for non-H atoms of the title compound with esd's in parentheses

Atom	Distance
C1-N1	1.450(7)
C2-N1	1.458(7)
C3-N1	1.334(6)
C3-C4	1.405(7)
C3-C7	1.408(7)
C4-C5	1.359(8)
C5-N2	1.344(6)
C6-N2	1.343(6)
C6-C7	1.345(7)
C8-N2	1.463(6)
C8-C9	1.521(7)
C9-O1	1.203(6)
C9-C10	1.489(7)
C10-C11	1.375(7)
C10-C15	1.405(7)
C11-C12	1.369(9)
C12-C13	1.386(9)

C12-C23	1.510(7)
C13-C14	1.354(9)
C14-C15	1.388(8)
C15-O2	1.370(6)
C16-O2	1.435(7)
C16-C17	1.498(8)
C17-C18	1.364(8)
C17-C22	1.382(8)
C18-C19	1.359(8)
C19-C20	1.372(10)
C20-C21	1.351(11)
C21-C22	1.383(10)

TABLE 1.3 Bond angles (°) for non-H atoms of the title compound with esd's in parentheses

Atom	Angle
N1-C3-C4	122.3(5)
N1-C3-C7	122.0(5)
C4-C3-C7	115.7(5)
C5-C4-C3	120.7(5)
N2-C5-C4	121.8(5)
N2-C6-C7	122.5(5)
C6-C7-C3	120.6(5)
N2-C8-C9	110.0(4)
O1-C9-C10	119.5(5)
O1-C9-C8	118.2(5)
C10-C9-C8	122.3(5)
C11-C10-C15	117.2(5)
C11-C10-C9	117.7(5)
C15-C10-C9	125.1(5)
C12-C11-C10	122.6(6)
C11-C12-C13	119.2(6)
C11-C12-C23	130.3(7)
C13-C12-C23	109.8(6)
C14-C13-C12	120.1(6)
C13-C14-C15	120.6(6)
O2-C15-C14	123.6(5)
O2-C15-C10	116.1(5)
C14-C15-C10	120.3(5)
O2-C16-C17	113.2(5)
C18-C17-C22	117.9(6)
C18-C17-C16	120.7(5)
C22-C17-C16	121.4(6)
C19-C18-C17	122.4(6)
C18-C19-C20	119.1(7)
C21-C20-C19	120.1(7)
C20-C21-C22	120.4(7)
C17-C22-C21	120.0(6)
C3-N1-C1	121.4(5)
C3-N1-C2	121.8(4)
C1-N1-C2	116.4(5)
C6-N2-C5	118.6(5)
C6-N2-C8	120.7(4)
C5-N2-C8	120.3(4)
C15-O2-C16	118.8(4)

TABLE 1.4 Torsion angles (°) for non-hydrogen atoms of title with esd's in parentheses

Atom	Angle	Atom	Angle
N1-C3-C4-C5	178.6(5)	C9-C10-C15-C14	-178.4(5)
C7-C3-C4-C5	-0.4(7)	O2-C16-C17-C18	132.7(6)
C3-C4-C5-N2	-0.2(8)	O2-C16-C17-C22	-49.4(8)
N2-C6-C7-C3	0.5(8)	C22-C17-C18-C19	1.3(8)
N1-C3-C7-C6	-178.7(5)	C16-C17-C18-C19	179.2(5)
C4-C3-C7-C6	0.3(7)	C17-C18-C19-C20	-1.7(9)
N2-C8-C9-O1	1.3(7)	C18-C19-C20-C21	1.2(10)
N2-C8-C9-C10	-179.1(4)	C19-C20-C21-C22	-0.4(10)
O1-C9-C10-C11	-2.1(7)	C18-C17-C22-C21	-0.5(8)
C8-C9-C10-C11	178.4(5)	C16-C17-C22-C21	-178.4(6)
O1-C9-C10-C15	177.0(5)	C20-C21-C22-C17	0.0(10)
C8-C9-C10-C15	-2.5(8)	C4-C3-N1-C1	-0.6(7)
C15-C10-C11-C12	-0.3(8)	C7-C3-N1-C1	178.3(5)
C9-C10-C11-C12	178.9(5)	C4-C3-N1-C2	-174.1(5)
C10-C11-C12-C13	-0.4(9)	C7-C3-N1-C2	4.8(7)
C10-C11-C12-C23	168.5(5)	C7-C6-N2-C5	-1.2(8)
C11-C12-C13-C14	0.6(9)	C7-C6-N2-C8	-174.0(5)
C23-C12-C13-C14	-170.4(5)	C4-C5-N2-C6	1.0(8)
C12-C13-C14-C15	-0.2(9)	C4-C5-N2-C8	173.9(5)
C13-C14-C15-O2	-179.9(5)	C9-C8-N2-C6	89.8(5)
C13-C14-C15-C10	-0.5(8)	C9-C8-N2-C5	-82.9(6)
C11-C10-C15-O2	-179.9(4)	C14-C15-O2-C16	-3.7(8)
C9-C10-C15-O2	1.1(7)	C10-C15-O2-C16	176.9(5)
C11-C10-C15-C14	0.7(7)	C17-C16-O2-C15	-74.0(7)

TABLE 1.4a Dihedral angles (°) formed by LSQ-planes with e.s.d's in parentheses

Plane	Plane	Angle (s.u.)	Angle (s.u.)
1	**2**	**87.90(0.17)**	**92.10(0.17)**
1	**3**	**5.43(0.18)**	**174.57(0.18)**
2	**3**	**83.87(0.18)**	**96.13(0.18)**

TABLE 1.5 Hydrogen bonding geometry (Å, °) (D-donor; A-acceptor; H-hydrogen) for title compound

Interactions	D-H	H...A	D...A	D-H…A
Intramolecular				
C11-H11...O1	0.9300	2.4000	2.727(8)	100.00
Intermolecular				
C6-H6... Br^{i}	0.9300	2.8700	3.581(7)	134.00
C19-H19...O1^{ii}	0.9300	2.5200	3.406(7)	159.00
C1-H1C…Cg1^{iii}	0.9300	2.81	3.684(7)	152
C16-H16B...Cg2^{iv}	0.9300	2.95	3.734(6)	139

Symmetry Code: (i) = $^{3}/_{2}$ -x, ½ + y,-z ; (ii) = $^{-1}/_{2}$ + x, $^{-1}/_{2}$ -y, -1+z;
(iii) = 1 -x, -y, -z ; (iv) = $^{-1}/_{2}$ + x, $^{1}/_{2}$ -y, z.

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