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X-RAY CRYSTAL STRUCTURE AND CONFORMATIONAL FLEXIBILITY STUDY OF A N-SUBSTITUTED 2,6-DIPHENYLPIPERIDINE DERIVATIVE

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Piperidine is one of the basic skeletons in many of pharmacological active compounds derived from natural or synthetic medicaments. Substitution of various groups in the piperidine ring regulates conformational flexibility due to the nature of the substituent on the nitrogen atom. One of the N-substituted piperidine derivatives, **PMDPM**, phenyl(3-methyl-2,6-diphenyl-piperidin-1-yl)methanone, was crystallized and analysed by X-ray crystallography. The crystallographic data are: $C_{23}H_{25}NO$, $M = 355.46$, triclinic, space group $P\bar{1}$, $a = 8.2543(7)$, $b = 10.5543(8)$, $c = 12.6184(6)$ Å, $\alpha = 77.901(7)$, $\beta = 71.270(2)°$, $\gamma = 70.390(5)°$; $V = 974.3(1)$ Å^3, $Z = 2$, $d_{cal} = 1.212$ Mg/m^3, $\lambda(MoK_\alpha) = 0.71073$ Å. The core piperidine ring of **PMDPM** shows a positional disorder and adopts dual conformations as *chair* and twisted *boat*. The phenyl rings are oriented axially to the piperidine ring with the dihedral angle of 22.0(1)° between them. The packing is stabilized by C—H···O intra molecular interactions including few C—H···π and π···π weak interactions.

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K e y w o r d s: piperidine, conformation, crystallography, *chair*, twisted *boat*, dihedral angle, PMDPM, phenyl ring.

INTRODUCTION

Piperidine is one of the N-containing heterocyclic rings, which is observed in many synthetic and natural medicaments [1—3]. Piperidine derivatives are synthetic intermediates in various alkaloids and pharmaceutical products [4, 5]. Various piperidine derivatives possess pharmacological activities and form an essential moiety in the molecular structure of important drugs. For example, the piperidine ring is a characteristic feature of antihistaminic agents [6], oral anaesthetics, narcotic analgesic [7, 8] and postganglionic parasympathetic agonists [9]. Clebopride, a 1,4-disubstituted piperidine, is used clinically to prevent post-operative vomiting, to speed up gastric emptying before giving anaesthesia, to facilitate radiological evaluation and to correct a variety of disturbances of gastrointestinal function [10]. Several 2,6-disubstituted piperidine derivatives are found to be very useful as tranquillisers [11], hypotensive drugs [12]. Bacterial, fungicidal and herbicidal activities have been also reported [13]. Many piperidine derivatives form the skeleton of several alkaloids [14, 15].

The importance of these piperidine derivatives lies in the clinical use of suitably substituted groups and the different ways available for making modifications in the anticipated structure of the pharmacologically active compounds. Substitution of electron withdrawing groups (CHO, $COCH_2CH_3$, COPh, NO, etc.) at the nitrogen atom of piperidine ring causes major changes in the ring

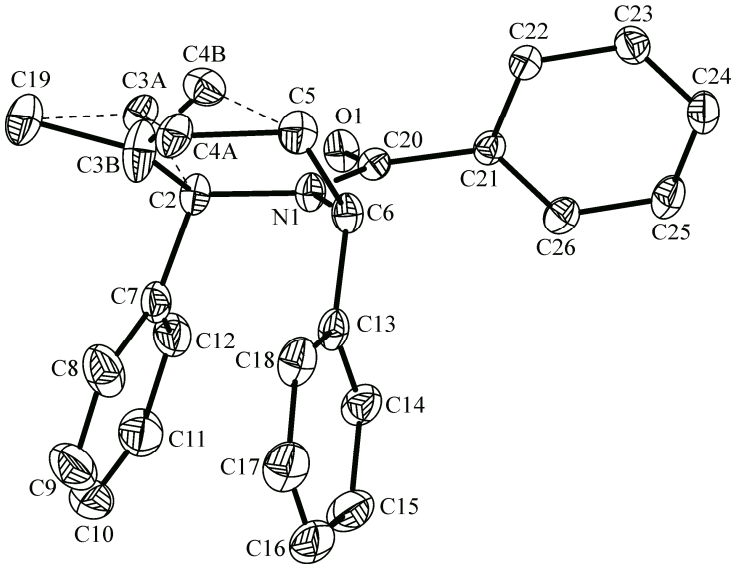
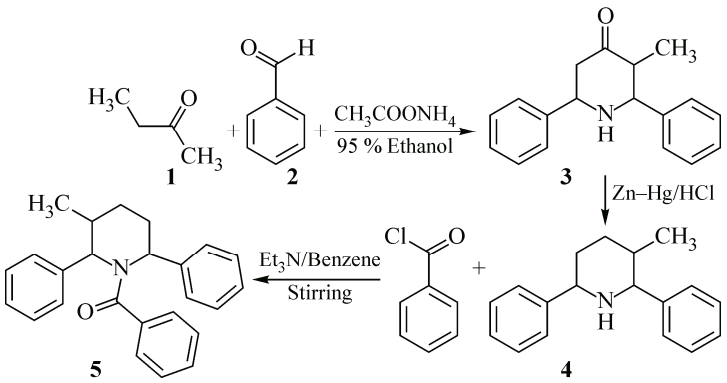


Fig. 1. **ORTEP** diagram of the molecule **PMDPM** with the atom numbering scheme. Displacement ellipsoid is drawn at 30 % probability level. Dashed lines represent the connection between the disordered atoms. Hydrogen atoms were removed for clarity

conformations [16]. In the title compound, phenyl(3-methyl-2,6-diphenylpiperidin-1-yl)methanone (**PMDPM**), the benzoyl group at the nitrogen atom shows electron delocalization through the atoms N1, C20 and O1 (Fig. 1) which causes conformationally flexible piperidine ring to adopt dual conformations as *chair* and twisted *boat*. By contrary, the compound with the $COOCH_2CH_3$ substituent at nitrogen showed only twisted *boat* conformation [16].

EXPERIMENTAL

The starting compound, 3-methyl-2,6-diphenylpiperidin-4-one (**3**) was obtained by adopting an earlier method [17], and it was reduced with amalgamated zinc in aqueous methanol solution in presence of small amount of HCl into 3-methyl-2,6-diphenylpiperidine (**4**). To a well stirred solution of **4** (2 mM) and triethylamine (4 mM) in freshly distilled benzene (50 ml), a little excess of benzoylchloride (2.2 mM) was added dropwise and the stirring was continued until the reaction was over. The reaction mixture was then poured into water and the final compound (**5**), phenyl(3-methyl-2,6-diphenylpiperidin-1-yl)methanone (**PMDPM**, scheme 1), was extracted with dichloromethane. Pale yellow **PMDPM** X-ray quality crystals of **5** were obtained by slow evaporation from ethanol.



Scheme 1. Synthetic root of the compound, **PMDPM**

Crystal data collection and reduction. A suitable-size **PMDPM** crystal was mounted on a glass fibre and used for data collection. Cell parameters and an orientation matrix for data collection were obtained by least-squares refinement of the diffraction data from 25 reflections in an ENRAF—NONIUS CAD4 automatic diffractometer [18]. Data were collected at 293(2) K using MoK_α radiation (λ = 0.71073 Å) with ω scan technique. The minimum and maximum of 2θ angle data collected for this structure are 2.722 and 33.221°, respectively. The data reduction was carried out by **XCAD4** [19] program. Out of 8836 reflections collected, 6597 reflections with $I \geq 2\sigma(I)$ were used for structure solution and refinement. The intensity data were corrected for Lorentz and polarization effects.

Structure determination. The structure of **PMDPM** was solved by direct-methods by using **SHELXS97** [20] program, which results the position of non-hydrogen atoms, and refined the structure with F^2 full-matrix least squares procedure using **SHELXL97** [20] program. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were fixed geometrically and allowed to ride over their respective parent atoms. The final refinement of **PMDPM** structure was analysed and the structural formula consists the atoms $C_{23}H_{25}NO$ with the molecular weight of 355.46. The structure was solved with triclinic system using the space group $P\bar{1}$, which contains the cell parameters a = 8.2543(7), b = 10.5543(8), c = 12.6184(6) Å, α = 77.901(7), β = 71.270(2), γ = 70.390(5)°. The crystal volume was found to be 74.3(1) Å^3 with the calculated crystal density of 1.212 Mg/m^3. The final cycle of the refinement was converged to R_1 = 0.0873 and wR_2 = 0.2067 for the observed reflections. The maximum and minimum heights in the final difference Fourier map were found to be 0.490 and –0.330 e/Å^3, respectively. The final refinement of the structure **PMDPM** was done using two restraints {isotropic U_{ij} restraint **ISOR** (C3A & C3B) and bond distance restraint **DFIX** (H3B & H8)} to converge the structure in appropriate conformation due to the presence of disordered atoms. The final goodness-of-fit of this structure was found to be 1.021, which indicates that the structure is fully converged to form stable conformation. Least-squares planes and asymmetry calculations were done using the program **PARST97** [21]. The thermal ellipsoid plot was done using **ORTEP** [22] and **PLATON** [23] programs.

Selected bond distances, bond angles and torsion angles are given in Table 1. The atomic coordinates of the non-hydrogen atoms with their equivalent thermal displacement parameters are included in the deposited material CCDC 1050050 as a complete list of bond distances and angles. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk

T a b l e 1

Selected torsion angles (deg.), *bond angles* (deg.) *and bond lengths* (Å) *for molecule* **PMDPM**

Atoms	Angle	Atoms	Angle	Atoms	Bond lengths
C3A—C4A—C5—C6	–57.6(4)	C4B—C3B—C2—C7	149.6(6)	C3A—C4A	1.599(6)
C6—N1—C2—C3A	57.2(3)	C4A—C5—C6—C13	–70.8(3)	C3A—C2	1.549(6)
C4A—C3A—C2—N1	–53.2(5)	C4B—C5—C6—C13	–105.6(4)	C3A—C19	1.479(7)
C2—C3A—C4A—C5	55.6(5)	C2—N1—C6—C13	71.6(2)	C4A—C5	1.578(5)
C4A—C5—C6—N1	55.9(3)	C6—N1—C2—C7	–89.7(2)	C3B—C4B	1.358(1)
C2—N1—C6—C5	–57.9(2)			C3B—C2	1.597(6)
C3B—C4B—C5—C6	38.8(8)	C6—N1—C2	118.0(2)	C3B—C19	1.590(7)
C6—N1—C2—C3B	33.5(4)	C20—N1—C2	118.0(2)	C4B—C5	1.427(9)
C4B—C3B—C2—N1	26.0(8)	C20—N1—C6	123.8(2)	O1—C20	1.231(2)
C2—C3B—C4B—C5	–64.7(9)	O1—C20—N1	122.4(2)		
C4B—C5—C6—N1	21.1(4)	O1—C20—C21	118.4(2)		
C4A—C3A—C2—C7	87.7(5)	N1—C20—C21	119.3(2)		

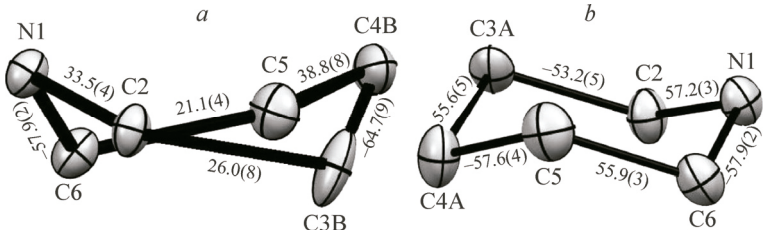


Fig. 2. Dual conformations and their respective torsion angels (°) of piperidine ring of **PMDPM**: twisted *boat* conformation (*a*), *chair* conformation (*b*)

RESULT AND DISCUSSION

The compound **5**, **PMDPM**, was crystallized in triclinic system ($P\bar{1}$ space group) using ethanol as solvent by slow evaporation method. The perspective view of ORTEP diagram of **PMDPM** is shown in Fig. 1. The central piperidine ring atoms, C3 and C4, show positional disorder which results from two ring conformations, a *chair* (N1, C2, **C3A**, **C4A**, C5 & C6; Q_T = 0.581(2) Å) and a twisted *boat* (N1, C2, **C3B**, **C4B** C5 & C6). The disordered atoms of C3A and C4A showed the occupancies 48 and 64 %, respectively, to form *chair* conformation. Similarly, the other two atoms, C3B and C4B, had the occupancies 52 and 36 %, respectively, to form a twisted *boat* conformation.

In the *chair* conformation, the atoms N1 and C4A deviate by –0.611(1) and 0.738(1) Å, respectively, from the plane atoms (C2, C3A, C5 and C6) with the phase angle of 175.6(7)°. Similarly, the twisted *boat* conformation shows puckering amplitude Q_T = 0.662(1) Å with the phase angle of 89.5(1)° [21, 24]. Conformational flexibility of this piperidine ring (*chair* and twisted *boat*) is also evidenced from the respective torsion angles which are shown in Fig. 2. A reported structure almost similar to **PMDPM**, but with of an ethyl acetate group at the nitrogen atom adopts perfect twisted *boat* conformation, and the phenyl rings at C2 and C6 occupy axial and equatorial positions [16]. Instead, the **PMDPM** structure shows conformational flexibility, adopting both *chair* and twisted *boat* conformations due to positional disorder of C3 and C4 atoms. The disorder might be caused by the presence of bulky benzoyl substituents on N1 atom, forcing both phenyl rings into the *axial* positions at C2 and C6 atoms to avoid the steric hindrance.

Axially substituted phenyl rings at C2 and C6 position of **PMDPM** are also confirmed by the torsion angles {C2—N1—C6—C13 = 71.6(2) & C6—N1—C2—C7 = –89.7(2)}, and the dihedral angle between these phenyl rings is 21.6(1)°. The dihedral angles between the phenyl rings and piperidine ring (*chair*) are 88.8(1)° (C7 through C12) and 74.1(1)° (C13 through C18). Similarly, the dihedral angles between the phenyl rings and piperidine ring (twisted *boat*) are 80.2(1)° (C7 through C12) and 82.9(1)° (C13 through C18). The methyl group substituted in the disordered C3 atom is oriented in equatorial position. All these substitutions are confirmed by the respective torsion angles (Table 1).

The benzoyl group at N1 atom is coplanar to the piperidine ring, and the respective atoms {C2, N1, C6, C20, O1, and C21} are positioned in the same plane. The co-planarity conformation is due to the existence of electron delocalization between the atoms of nitrogen from piperidine ring and carbonyl atoms from benzoyl moiety. This co-planarity is also expressed in the respective torsion angles {[C2—N1—C20—O1 =] –7.8(3)°; [C2—N1—C20—C21 =] 172.0(2)°; [C6—N1—C20—C21 =] –3.3(3)°; and [C6—N1—C20—O1 =] 176.9(2)°}. The dihedral angles between the benzoyl group and piperidine ring of *chair* and twisted *boat* are 37.7(1)° and 35.5(1)°, respectively [21, 24]. The molecule does not form classical hydrogen bonds. In addition to the van-der-Waals forces, four C—H···π {C24—H24···Cg^1, Cg^1 (C7 through C12) and C17—H17···Cg^3, C19—H19F…Cg^3 & C19—H19B…Cg^3; Cg^3 (C21 through C26)} and an intra π···π {[Cg^1···Cg^2 =] 4.04 Å; Cg^2 (C13 through C18)} weak interactions help to control the molecules in the crystal packing. The detailed geometry of the non-bonded interactions is presented in Table 2.

Table 2

Possible non-bonded interactions in the molecule of **PMDPM**

D—H···A	D—H	H···A	D···A	D—H···A
C12—H12…O1	0.93	2.50	3.180(1)	131
^{i}C24—H24···Cg^{1}	0.93	2.93	3.661	136
^{ii}C17—H17···Cg^{3}	0.93	2.81	3.607	144
^{iii}C19—H19F…Cg^{3}	0.96	2.84	3.752	158
^{iii}C19—H19B…Cg^{3}	0.96	2.99	3.752	137

Symmetry codes: ^{i} x+1, y–1, z; ^{ii} 1–x, –y, –z; ^{iii} –x, –y, 1–z.

CONCLUSIONS

A new piperidine derivative, **PMDPM**, was synthesised and its X-ray crystal structure was determined to understand the structural features and its property. The piperidine ring adopts both *chair* and twisted *boat* conformations. Most of the early reported N-substituted (with electron withdrawing groups) piperidine rings showed twisted *boat* conformations with phenyl rings substituted in C2 and C6 positions occupying *axial* and *equatorial* positions. In the **PMDPM** structure both phenyl rings occupy only *axial* positions in the piperidine ring. This structural feature might be adopted in order to avoid the steric hindrance.

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REFERENCES

1. *Daly J.W.* In the alkaloids / (Ed.) G.A. Cordell. – San Diego: Academic Press, 1998. – **50**. – P. 141 – 169.
2. *Parthiban P., Aridoss G., Rathika P. et al.* // Bioorg. Med. Chem. Lett. – 2009. – **19**. – P. 2981 – 2985.
3. *Aridoss G., Balasubramanian S., Parthiban P. et al.* // Med. Chem. Res. – 2007. – **16**. – P. 188 – 204.
4. *Wang C.-L., Wuorola M.A.* // Org. Prep. Proceed. Int. – 1992. – **24**. – P. 585 – 621.
5. *Grishina G.V., Gaidarova E.L., Zefirov N.S.* // Chem. Heterocyclic Compd. – 1994. – **30**. – P. 11 – 12.
6. *Casy A.F., Ison R.R.* // J. Pharm. Pharmacol. – 1970. – **22**. – P. 270 – 278.
7. *Reynolds A.K., Randall L.O.* In: Morphine and Allied Drugs. – Toronto: University of Toronto Press, 1957.
8. *Lu Z.Y., Zaho S.Y., Yuaw X.M., Ng Y.L.* // Chem. Abstr. – 1991. – **114**. – P. 815135.
9. *Hermons B., Van Dacle P., van der Westeringh C. et al.* // J. Med. Chem. – 1968. – **11**. – P. 797 – 800.
10. *Robinson O.P.W.* // Postgrad. Med. J. – 1973. – **49**. – P. 9 – 12.
11. *Bochringer C.F., Soehne G.M.B.H.* // Chem. Abstr. – 1961. – **55**. – P. 24796.
12. *Severs W.B., Kinnard W.J., Buckley J.P.* // Chem. Abstr. – 1965. – **63**. – P. 10538.
13. *Mobio I.G., Soldatenkov A.T., Federov V.O. et al.* // Khim Farm Zh. – 1989. – **23**. – P. 421 – 427.
14. *MacConnell J.G., Blum M.S., Fales H.M.* // Tetrahedron. – 1971. – **27**. – P. 1129 – 1139.
15. *Hootele C., Colau B., Halin F. et al.* // Tetrahedron. Lett. – 1980. – **21**. – P. 5063.
16. *Sampath N., Rita M.* // Acta Cryst. – 2011. – **E67**. – P. o1530.
17. *Sampath N., Malathy Sony S.M., Ponnuswamy M.N. et al.* // Acta Cryst. – 2003. – **C59**. – P. o346 – o348.
18. Enraf—Nonius, CAD-4 EXPRESS Program, Delft, The Netherlands, 1994.
19. *Harms K.* XCAD4 Program, University of Marburg, Germany, 1996.
20. *Sheldrick G.M.* Programs for Structure solution (SHELXS) & Refinement (SHELXL) // Acta Cryst. – 2008. – **A64**. – P. 112 – 122.
21. *Nardelli M.* PARST95 Program // J. Appl. Cryst. – 1995. – **28**. – P. 659.
22. *Farrugia L.J.* // J. Appl. Cryst. – 1997. – **30**. – P. 565.
23. *Spek A.L.* // Acta Cryst. – 2009. – **D65**. – P. 148 – 155.
24. *Cremer D., Pople J.A.* // J. Am. Chem. Soc. – 1975. – **97**. – P. 1354 – 1358.