Research Article

X-Ray Crystal Structure, Molecular Structure, Spectral And Antimicrobial Activity of *t*-(3)-Benzyl-*r*-(2),*c*-(6)-diphenylpiperidin-4-one

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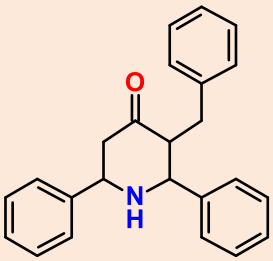
Abstract

The title compound, $C_{24}H_{23}NO$, crystallizes with two crystallographically independent molecules (A and B) in the asymmetric unit, in the monoclinic space group $P2_1/n$. In both molecules, the piperidine rings adopt a chair conformation and the phenyl rings and the benzyl group substituents are attached equatorially. Crystal data: M_r = 341.43, a = 9.8918 (5) Å, b = 30.6042 (12) Å, c = 12.3878 (6) Å, β = 92.426 (2)°, V = 3746.8 (3) Å^3, Z = 8, λ(Mo Kα) = 0.71073 Å, T = 178 K, D_x = 1.211 Mg m^{-3}, μ = 0.07 mm^{-1}, Final R[F^2> 2σ(F^2)] = 0.066, wR(F^2) = 0.150, S = 1.05. The spectra of the title compound reveal the presence of two isomers labeled as E (carbonyl carbon is *anti* to benzyl group at C3) and Z (carbonyl carbon is *syn* to benzyl group at C3) in solution and from the coupling constant values the favoured conformation for the Z- and E-isomers was found to be the normal chair conformation. The antibacterial and antifungal activities were also evaluated.



Keywords: crystal structure; piperidin-4-one; conformation; spectra; antimicrobial activity.

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Introduction

The piperidine ring is an ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson et al. asserted that during a recent 10-year period there were thousands of piperidine compounds mentioned in clinical and preclinical studies [1]. Piperidine heterocycles play an important role in the field of medicinal chemistry. Several 2,6-disubstituted derivatives of this class have been found to possess useful biological activities such as herbicidal, insecticidal, fungicidal, bactericidal, anti-inflammatory, antihistaminic, hypotensive, anticancer, CNS stimulant and depressant and nerve activities [2-9]. In the present study *syn* and *anti* isomer of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one **(1)** were synthesized and their conformational behavior was analyzed using ^{1}H and ^{13}C NMR spectroscopy. The preferred conformations were further confirmed by means of single crystal XRD measurements also [10].

Materials and Methods

Preparation of compounds

A mixture of ammonium acetate (0.1 mol, 7.71 g), benzaldehyde (0.2 mol, 20.3 ml) and benzyl acetone (0.1 mol, 15.0 ml) in distilled ethanol was heated first to boiling. After cooling, the viscous liquid obtained was dissolved in ether (200 ml) and shaken with 100 ml concentrated hydrochloric acid. The precipitated hydrochloride of t(3)-benzyl-r(2),c(6)-diphenylpiperidin-4-one was removed by filtration and washed first with 40 ml mixture of ethanol and ether (1:1) and then with ether to remove most of the coloured impurities. The base was liberated from an alcoholic solution by adding aqueous ammonia and then diluted with water. The title compound was recrystallized from ethanol to give colourless plate-like crystals (yield 2.5 g). The compound melted at 471 K. IR (cm^{-1}): 3311.58, 3031.16, 1706.07, 1584.21, 1494.98, 1453.71, 1427.78, 1275.76, 1030.25, 828.04, 758.39 and 727.70.

Recording of spectra

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400 and 100.6 MHz. Solutions were prepared by dissolving 10 mg (^{1}H) and 50 mg (^{13}C) of the compound in 0.5 mL of solvent ($CDCl_3$). All NMR measurements were made in 5 mm NMR tubes.

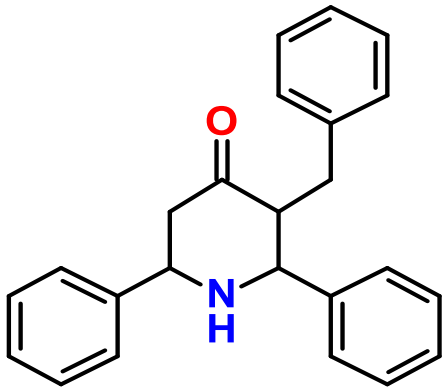
Recording of XRD

Bruker Kappa APEXIII CCD area-detector diffractometer	10617 independent reflections
Radiation source: fine-focus sealed tube	6350 reflections with $I > 2\sigma(I)$
Detector resolution: 8.3333 pixels mm^{-1}	$R_{int} = 0.078$
φ and ω scans	$\theta_{max} = 29.7°$, $\theta_{min} = 1.8°$
Absorption correction: multi-scan (SADABS; Bruker, 2015)	h = −13→13
$T_{min} = 0.81$, $T_{max} = 0.99$	k = −42→42
58653 measured reflections	l = −14→17

Results and Discussion

^{1}H NMR Analysis

The high resolution ^{1}H and ^{13}C NMR spectra of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1)** have been recorded in $CDCl_3$ and analyzed. The structure of the synthesized compound (**1)** is indicated in **Figure 1**. The ^{1}H NMR spectra of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one contained two distinct signals for each protons at room temperature. The observation of two sets of signals in (**1)** suggests the presences of two rotamers are labeled as *syn* and *anti* isomers as shown in **Figure 2**. Based on intensities and integrals, the signals for one rotamer can be easily differentiated from the other rotamer. For the compound (**1)** single crystal XRD measurements also recorded to confirm the structure and conformations. The conformation of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one is expected to be normal chair with equatorial orientation of all substituents. In the parent t(3)-benzylpiperidin-4-one H(2) resonates at upfield (lower frequency) relative to H(6) due to magnetic anisotropic effect of nearby equatorial benzyl group at C(3). Therefore, among the two sets of signals in the *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one, the set in which H(6) is considerably lower can be assigned to the *Syn* isomer [H(6) *Syn* < H(6) anti].



t(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one

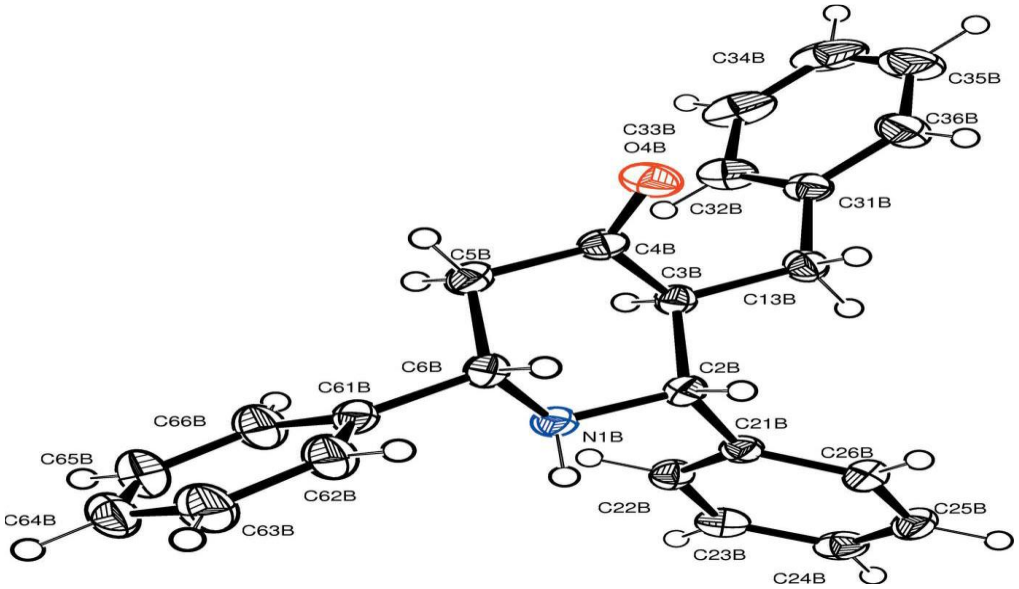
Figure 1

The ^{1}H NMR data of (**1)** is displayed in **Table 1**. From the chemical shifts, the coupling constants were extracted.

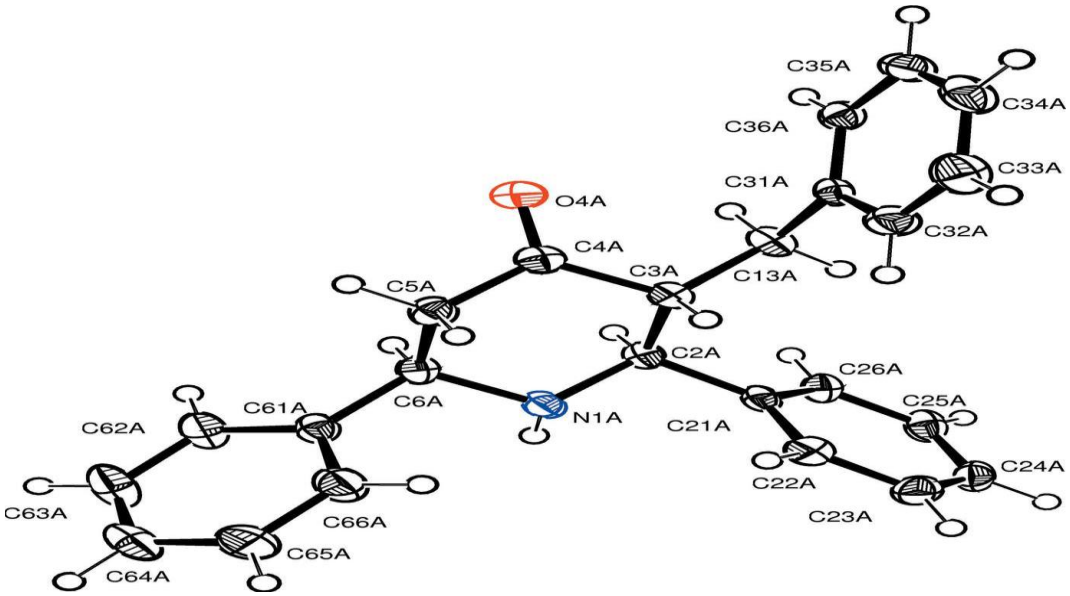
Analysis of coupling constants

The observation of one large and one small coupling about C(5)-C(6) bond and one large coupling about C(2)-C(3) bond in (**1)** reveals equatorial orientation of benzyl groups at C-3 and aryl rings at C-2 and C-6. Hence, the compound (**1)** exists in normal chair conformation with equatorial orientations of all the substituents. The coupling constants

about C(2)-C(3) bond in **(1)** is considerably lower than the trans couplings about C(5)-C(6) bond. This can be explained as follows. The benzyl group at C-3 experiences severe gauche interaction with phenyl group at C-2 and in order to avoid this gauche interaction, the ring is flattened about C(2)-C(3) bond. This flattening is responsible for lowering of the magnitude of $J_{2a,3a}$ relative to $J_{6a,5a}$ in compounds (**1**).



Syn isomer of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one



Anti isomer of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one

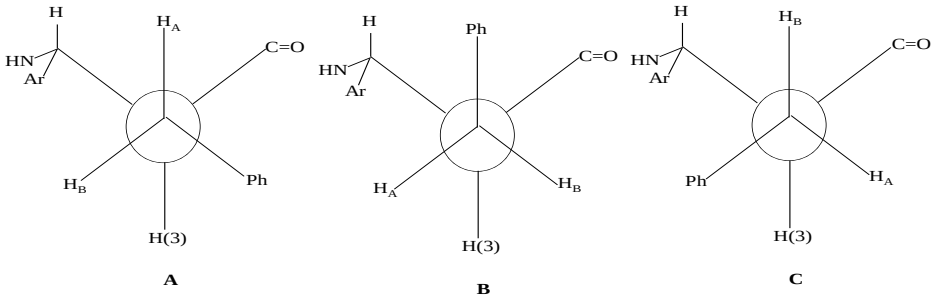
Figure 2

Table 1 ^{1}H NMR data of (**1**)

Compound		H(2)	H(3)	H(5)	H(6)	$C_6H_5CH_2$	NH	Aromatic protons
1	*Syn*	3.82	3.08	2.68, 2.52	4.12	3.02, 2.20	2.10	6.94 - 7.50
	Anti	4.52	3.08	2.68, 2.52	4.36	3.02, 2.20	2.10	

Conformation of benzyl group

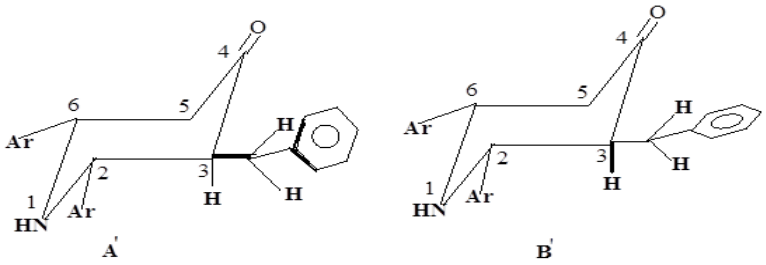
There are three possible conformations **A, B** and **C** for the benzyl group at C(3) in compound (**1)** as shown in **Figure 3**. In conformation **B** H(3) is gauche with respect to both the methylene protons of the benzyl group at C(3) and hence both the coupling constants $J_{H(3),CH_2}$ are expected to be around 3-4 Hz. However, in conformations **A** and **C** one coupling i.e., $J_{H(3),CH_2}$ is expected to be around 10-12 Hz and the other coupling is expected to be around 3-4 Hz. In 3-benzyl piperidine the couplings are 2.25 and 8.32 Hz. The former corresponds to gauche coupling and other value falls in between those for a gauche and anti-coupling. This large coupling suggests that the major conformer may be either **A** or **C**. Dreiding model reveals that in conformation **C** there will be severe interaction between phenyl ring of the benzyl group at C(3) with the phenyl ring at C(2) and hence this conformation is ruled out in the present study. Therefore, the favoured conformation of benzyl group is predicted to be **A**. In conformation **A** the large and small couplings are expected to be 10 and 3 Hz. However, the observed couplings 8.32 and 2.25 Hz suggest that a small amount of another conformer i.e., the conformation **B** may also be present in solution in addition to the major conformation **A**. Thus the conformation of benzyl group is found to be an equilibrium mixture of conformations **A** (major) and **B** (minor).



Possible conformations of benzyl group in (**1)**

Figure 3

There are two possible conformations for phenyl ring of benzyl group at C(3) as shown in **Figure 4**. In conformation A' the phenyl group prefers to be oriented in such a way that phenyl ring is parallel to C(3)-CH_2 bond. In conformation B' the phenyl ring prefers to be oriented in such a way that the phenyl ring is perpendicular to C(3)-CH_2 bond i.e., parallel for C(3)-H_{3a} bond. The conformation A' is destabilized due to severe interaction between the ortho protons of the phenyl ring with carbonyl group in conformation **A** and with the H(2) and in conformation **B**. Therefore, this conformation is not favoured in compound (**1)**. Thus, the favoured conformation of phenyl ring of benzyl group is established as in conformation B'.



Possible conformations of phenyl ring of benzyl group in (**1)**

Figure 4

Analysis of ^{13}C NMR

The aromatic carbons could be readily distinguished by their characteristic absorption above 100 ppm. Assignments for the heterocyclic ring carbons and benzylic carbons have been made on the basis of known effects of alkyl

substituents in six-membered ring compounds. The assignment of the signals in *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1**) was made as follows. In compound (**1)** the chemical shift of C-2 is greater than that of C-6. Therefore, in the anti-isomer *t*-3-benzylpiperidin-4-one**,** C-6 carbon is expected to appear at upfield when compared to C-2 carbon. The signal for one isomer can be easily differentiated from the other isomer based on intensities. The ^{13}C chemical shifts are displayed in **Table 2**.

Table 2 ^{13}C NMR data of (**1**)

Compound		C(2)	C(3)	C(4)	C(5)	C(6)	$C_6H_5CH_2$	Aromatic Carbons
1	*Syn*	67.52	58.90	207.16	51.32	61.86	30.80	142.43-125.32
	Anti	62.83	58.90	207.16	53.52	65.76	32.62	

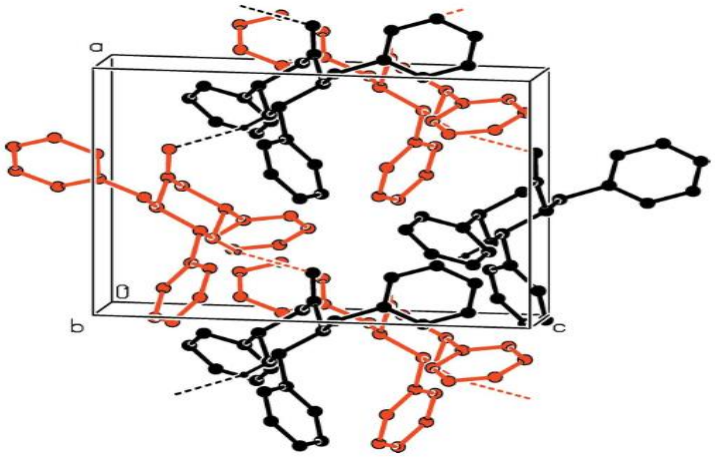
Ring conformations

The observation of one large and one small coupling about C(5)–C(6) bond and large coupling about C(2)–C(3) bond in the piperidin-4-one (**1)** reveals that the compound adopts normal chair conformation with the equatorial orientations of phenyl rings at C(2) and C(6) and benzyl group at C(3) for both *syn* and *anti* isomers. For (**1)** single crystal measurements were also made [10]. The single crystal measurements also reveal normal chair conformation with equatorial orientations of all substituents. The molecule belongs to the Monoclinic crystal system and ($P2_1/n$) space group. The crystal packing and AutoMolFit diagram of both molecules [Molecule B in red colour and Molecule A in black colour] are given in **Figure 5** and **Figure 6**.

Antimicrobial activity

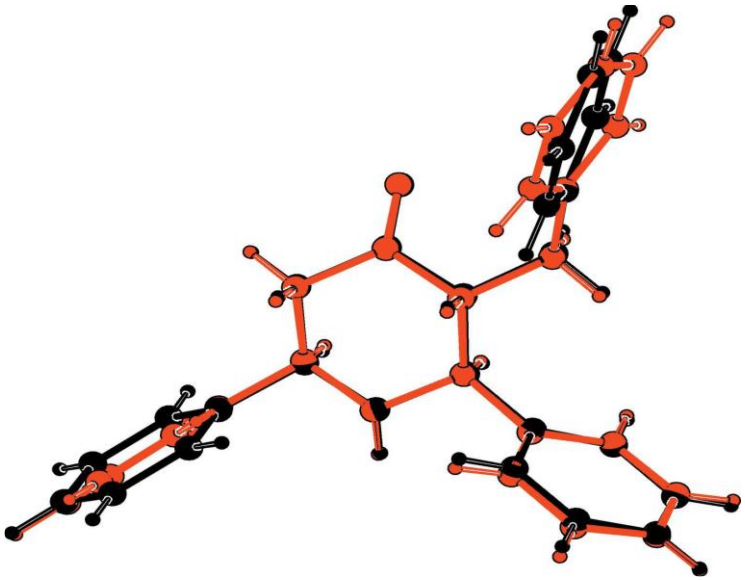
Antibacterial activity

The synthesized compound *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1**) was tested for their antibacterial activity *in vitro* against Streptococcus faecalis, Bacillus subtilis, Escherichia coliand Klebsiella pneumoniae. Ciprofloxacin was used as standard drug whose minimum inhibitory concentration values are furnished in **Table 3**. The antibacterial screening put in evidence that the synthesized *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1**) exhibited a wide spectrum of antibacterial profile *in vitro* against the tested organisms. *t*(3)-benzyl-*r*(2),*c*(6)-diphenyllpiperidin-4-one (**1**) exhibited good antibacterial activity against all the tested strains.



Crystal Packing diagram of *Syn and Anti* isomer of **(1)**

Figure 5



AutoMolFit diagram of *Syn and Anti* isomer of **(1)**

Figure 6

Crystal data

$C_{24}H_{23}NO$	F(000) = 1456
M_r = 341.43	D_x = 1.211 Mg m^{-3}
Monoclinic, $P2_1/n$	Melting point: 471 K
Hall symbol: -P 2yn	Mo Kα radiation, λ = 0.71073 Å
a = 9.8918 (5) Å	Cell parameters from 7035 reflections
b = 30.6042 (12) Å	θ = 2.6–22.8°
c = 12.3878 (6) Å	μ = 0.07 mm−1
β = 92.426 (2)°	T = 178 K
V = 3746.8 (3) $Å^3$	Plate, colourless
Z = 8	0.40 × 0.36 × 0.16 mm

Table 3 *In vitro* antibacterial activity of (**1**)

Compound	Minimum Inhibitory Concentration (MIC) in µg/ml			
	Streptococcus faecalis	**Bacillus subtilis**	**Escherichia coli**	**Klebsiella pneumoniae**
(1)	25	50	25	25
Ciprofloxacin	50	25	50	50

Antifungal activity

The *in vitro* antifungal activity of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1**) was examined against the fungal strains viz., Aspergillus niger, Candida 6, Candida 51 and Aspergillus flavus. Amphotericin B was used as standard drug whose minimum inhibitory concentration values are furnished in **Table 4**.

Table 4 *In vitro* antifungal activity of (**1**)

Compound	Minimum Inhibitory Concentration (MIC) in µg/ml			
	Aspergillus niger	**Candida 6**	**Candida 51**	**Aspergillus flavus**
(1)	25	25	50	50
Amphotericin B	25	25	25	50

Conclusion

Spectral studies reveal the presence of two rotameric forms (*syn* and *anti*) in solution for the *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1**). From the coupling constants, ^{1}H and ^{13}C chemical shift data of Compound (**1)**, the piperidine ring exist in normal chair conformation with equatorial orientation of all substituents. This result is further confirmed by XRD data. A minute examination of *in vitro* antibacterial and antifungal spectra of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1)** against the tested bacterial and fungal strains provide a better structure activity which is *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one (**1**) influence the antimicrobial properties. Thus in future this compound may be used as templates to generate better drug to fight against bacterial and fungal infections.

Acknowledgement

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