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SYNTHESIS AND SPECTRAL (IR AND NMR) STUDIES OF 3,5-DIETHYL-2*r*,6*c*-DI(*p*- LUOROPHENYL)PIPERIDIN-4-ONE PICRATE

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ABSTRACT

3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate have been synthesised and characterised by FT-IR and NMR spectral studies. NMR spectral assignments were made unambiguously by their one dimensional (^{1}H NMR and ^{13}C NMR) and two dimensional (NOESY & HSQC) NMR spectra. The difference in the chemical shifts between equatorial methylene proton and axial proton at C(5) [$\Delta = \delta eq-\delta ax$] is highly negative in compounds in contrast to the value observed for the corresponding parent piperidine-4-one and is indicative of the 1,3-diaxial interaction between the axial NH bond and axial hydrogen at C(5). The chemical shifts of the heterocyclic ring protons are influenced by the picrate anion.

Keywords:piperidin-4-one picrate, FT-IR, ^{1}H NMR, ^{13}C NMR, NOESY and HSQC spectra.

INTRODUCTION

Piperidine heterocycles play an important role in the field of medicinal chemistry. The relative chemical shift order of equatorial and axial protons in the normal chair conformation of cyclohexane and its derivatives (deq>dax) are considered as caused by magnetic anisotropic effect of the CAC single bonds. The influence of substituents on the chemical shifts of protons attached to the adjacent carbons has been studied in detail [1–3]. The effect of protonation on the ^{1}H and ^{13}C chemical shifts of 2*r*,6*c*-diarylpiperidin-4-ones and their derivatives has also been studied widely [4–9]. the effects of protonation on ^{1}H chemical shifts in

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2r,6c-diarylpiperidin-4-ones and 2r,6cdiphenylpiperidines by comparing their chemical shifts with those of their hydrochlorides [10]. The effect of protonation on the ^{1}H and ^{13}C chemical shifts in 2*r*,6*c*-diphenylpiperidin-4-one by examining carefully their picrates [11]. By investigating one picrate with the corresponding hydrochloride, they have shown that anions also could influence ^{1}H chemical shifts. However, the chemical shifts of the picrates have been determined in CDCl3 and there could be a solvent effect. Vimalraj [12] have studied the effect of protonation and co-anion on the ^{1}H and ^{13}C chemical shifts of diphenylpiperidin-4-one (NMR, antimicrobial, XRD and theoretical studies have been made on 3*t*-pentyl-2*r*,6*c*-diphenylpiperidin- 4-ones and their oximes) [13–15]. 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, hypertensive, anticancer, CNS stimulant, depressant and nerved activities [16–25]. The present study, the syntheses of picrates characterized by spectral techniques

EXPERIMENTAL

MATERIALS AND METHODS

All the solvents used were of spectral grade. The melting points of the compounds were measured in open capillaries and are uncorrected. IR spectra were recorded on an AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz on a BRUKER model using DMSO-d6 as solvent for all the compounds. Tetramethylsilane (TMS) was used as internal reference for all NMR spectra, with chemical shifts reported in d units (parts per million) relative to the standard. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q) and multiplet (m). Coupling constants are expressed in Hertz (Hz). Mass spectra were recorded in VARIAN- SASTURAN 2200 GC–MS spectrometry using electron impact technique. The sample was prepared by dissolving about 1 mg in 5 ml of methanol.

Synthesis of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one

A mixture of ammonium acetate (0.05mol), substituted *p*-fluorobenzaldehyde (0.1mol) and 4-heptanone (0.05 mol) in distilled ethanol

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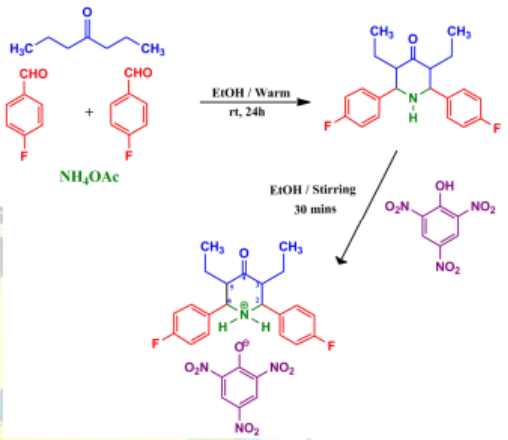
was heated to boiling. After cooling, the viscous liquid obtained was dissolved in ether (200 ml) and shaken with 10 mL concentrated hydrochloric acid, the precipitated hydrochloride of 3,5-diethyl-2*r*,6*c*-di(p-fluorophenyl)piperidin-4-one picratewas removed by filtration and washed first with a mixture 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 product was recrystallized from alcohol.

synthesis of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

The piperidinium picrate were prepared by mixing equimolar solutions of the corresponding, 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one with picric acid in ethanol and stirring the solution for 30 min. The yellowish crystals formed were filtered. The yield of the product was found to be 95%. The harvested crystals were recrystallized repeatly to get excellent quality crystals.

RESULTS AND DISCUSSION

The general schematic representation describing the routes of synthesis is furnished in **Scheme**. The structures of the synthesised compound is established on the basis of FT-IR, 1D NMR (1H and 13C NMR), 2D NMR (HSQC, NOESY) were performed to make unambiguous configurational and conformational characterisations.



Scheme. Synthetic route for 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

IR spectrum

The IR spectrum of3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate is shown in **fig 1**, the NHstretching vibration appears at 3436 cm^{-1}. The bands in the region 3085-2981 cm^{-1} are due to aromatic stretching vibrations. The bands in the region 2927-2849 cm^{-1} are attributed to aliphatic stretching vibrations. The band observed at 1716 cm^{-1} is due to C=O stretching vibration. The bands at 1562 and 1518 cm^{-1} are due to NO_2 asymmetric stretching vibrations. The bands at 1336,

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1271 and 1236 cm^{-1} are attributed to NO_2 symmetric stretching vibrations.

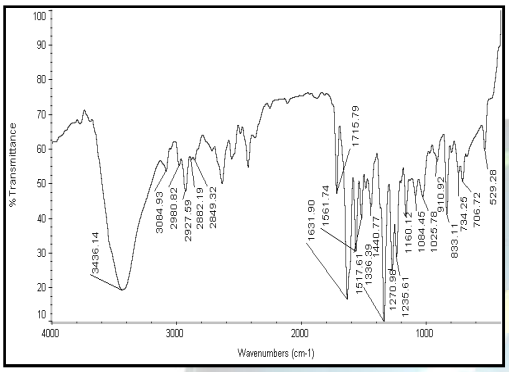

Fig. 1. IR spectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

^{1}H NMR Spectrum

The ^{1}H NMR spectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate **is** shown in **fig 2**, the two doublets at 10.04 ppm (J = 6.8 Hz) and 10.36 ppm (J = 7.6 Hz) are assigned to NH axial and equatorial protons of piperidinium ring. Equatorial NH proton undergoes geminal coupling with the axial NH proton and small vicinal couplings with H-2a and H-6a. The small couplings are not resolved. The axial NH proton undergoes geminal coupling with the equatorial NH proton and large vicinal couplings with H-2a and H-6a. The aromatic protons appear in the region 7.29-7.81 ppm with eight proton integrals. The triplet in the higher frequency region at 4.73 ppm may be assigned to the benzylic protons at H-2a and H-6a which are chemically equalent. Furthermore, a triplet observed in the lower frequency region at 3.54 ppm with two protons integral is pertinent to the axial methine protons H-3a and H-5a. The signals in the region 1.27-1.36 ppm corresponding to four protons integral should be due to methylene proton in ethyl group at C-3. There is a triplet at 0.72 ppm corresponding to six protons integral and this should be due to the methyl protons in ethyl group. In the protonated piperidine-4-one derivatives, the axial NH bond experiences severe *syn* 1, 3-diaxial interaction with the axial protons at C-5 and C-3 and due to these interactions the protons are deshielded to a greater extent than the corresponding C-3 and C-5 carbons which are shielded. All the above mentioned assignments are further confirmed by NOESY spectrum is shown in **fig. 4**.

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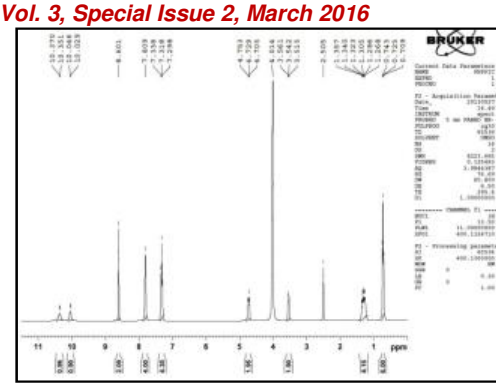

Fig. 2.[1]HNMR spectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

It is seen from fig.2 that the chemical shifts of H(2) are considerably lower than that of H(6) in compounds This also supports the equatorial orientation of alkyl group at C(3).The NMR spectral data suggest that the title compounds exist in normalchair conformation with equatorial orientation of all the substituents. In the protonated piperidine derivatives, the axial NH bond experiences severesyn 1,3-diaxial interaction with axial hydrogens at C(5), H(5a) andC(3), H(3a) and due to these interactions the protons are deshieldedto a greater extent and the corresponding carbons are shielded in **Fig. 3**.

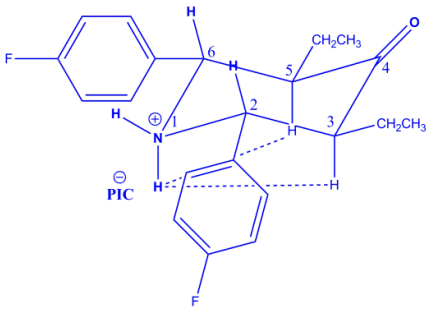

Fig. 3. Schematic representation of syn 1,3-diaxial interactions

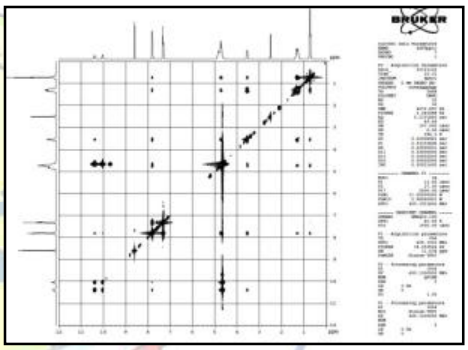

Fig. 4.NOESY spectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

[13]C NMR spectrum

The [13]C NMR spectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate **is** shown in**fig 5**, well resolved signals are obtained. The signals in the region 115.52-141.75 ppm are due to aromatic carbons. The signals appears at 204.22 ppm is due to C=O carbon. The signals in the region (downfield) at 160.70 and 163.74, 161.29 ppm are due to C-O carbon of picryl group and carbons attached with *fluoro*substitiuent at C-2

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and C-6 position of the piperidone ring. The signal at 62.11 ppm is due to benzylic carbons at C-2 and C-6. The signal at 51.86 ppm is due to C-3 and C-5 methine carbons. The signal observed at 17.79 ppm is assigned to methylene carbons of ethyl group and the most upfield signal at 10.67 ppm is assigned to methyl carbon of ethyl group. All the above mentioned assignments are further confirmed by HSQC spectrum is shown in **fig 6**.

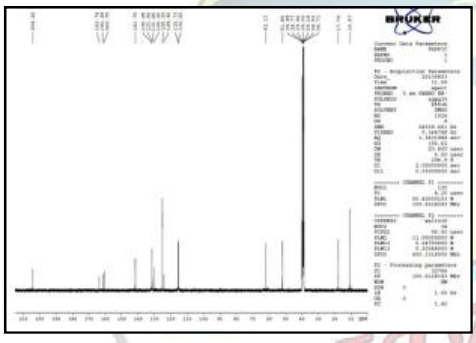

Fig. 5.^{13}Cspectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

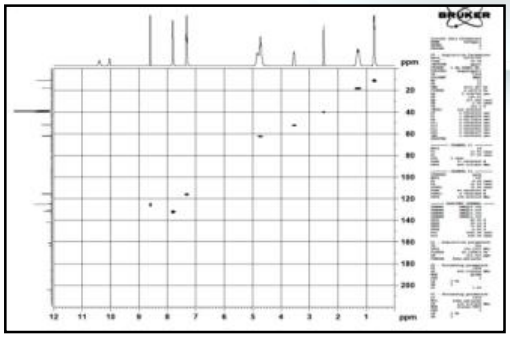

Fig. 6.HSQCspectrum of 3,5-diethyl-2*r*,6*c*-di(*p*-fluorophenyl)piperidin-4-one picrate

CONCLUSIONS

The NMR spectral datasuggest that the title compounds exist in normalchair conformation with equatorial orientation of all the substituents.Due to protonation, the axial NH bond experiences severesyn 1,3-diaxial interaction with axial hydrogens at C(3) and C(5) and due to these interactions the protons H(3a) and H(5a) are deshielded and corresponding carbons C(3) and C(5) shielded. The chemical shifts of the heterocyclic ring protons are influenced by the picrate anion. All the piperdone ring protons are deshielded whereas carbons are shielded.

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