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Synthesis, characterisation, stereochemistry and biological activity of *N*-formylpiperidin-4-ones

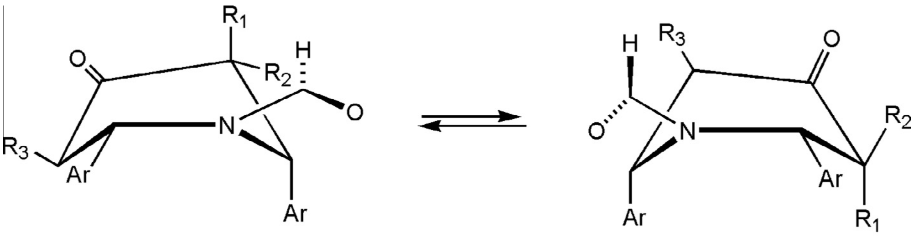
P. Sakthivel, S. Ponnuswamy *

P. G. & Research Department of Chemistry, Government Arts College (Autonomous), Coimbatore 641 018, Tamil Nadu, India

HIGHLIGHTS

- Four new compounds are characterised using IR, mass and advanced NMR techniques.
- Compounds showed doubling of all the signals due to *syn* and *anti* rotamers at RT.
- The energy barrier for *N*-CO rotation of one of the compounds was determined.
- The equilibrium observed between the *syn* rotamer of **TB1** and *anti* rotamer of **TB2**.
- All the compounds were screened for their antibacterial & antifungal activities.

GRAPHICAL ABSTRACT



TB1 *syn rotamer*

TB2 *anti rotamer*

Ar=$C_6H_4OCH_3$; R^1, R^2, R^3=CH_3, C_2H_5, H

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ABSTRACT

A new series of *N*-formyl-2,6-bis(4-methoxyphenyl)piperidin-4-ones **5**–**8** has been synthesized and characterised using IR, mass and ^{1}H, ^{13}C, DEPT and 2D (COSY and HSQC) NMR spectral techniques. The NMR spectral data indicated that the *N*-formylpiperidin-4-ones **5**–**8** prefer to exist in a conformational equilibrium between a *syn* rotamer with a twist boat conformation (**TB1**) and an *anti* rotamer with a twist boat conformation (**TB2**) in solution. The stereodynamics of these systems have been studied by recording the dynamic ^{1}H NMR spectra of compound **5**, and the energy barrier for the *N*-CO rotation was determined to be 64.3 kJ/mol. All of the synthesized compounds (**5**–**8**) were screened for their biological activity.

Introduction

The conformational equilibrium between the *syn* and *anti* rotamers based on the restricted rotation at the N—C bond in several *N*-acyl derivatives of azacycles is known to be fast at RT, and their conformations can be drastically different due to the influence of *N*-acyl functions [1–22]. Resonance stabilisation in the *N*-nitroso and *N*-acetyl derivatives of *cis*-2,6-dimethylpiperidine has been observed [23,24]. Competition between A^{1,3}-strain [25] and resonance stabilisation in these cases leads to dynamic equilibria due to restricted rotation around the N—N bond of the *N*-nitroso group or N—C bond of the *N*-acetyl group. The ring has been shown to prefer flipped chair conformation with diaxial methyl groups (Fig. 1) [23,24]. However, when the *cis*-2,6-substituents are aromatic groups, the rings prefer, twist chair, twist boat or flattened boat conformations [1–22] even though the flipped chair conformation has also been observed in a few cases in the

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* Corresponding author. Mobile: +91 9244645744.
E-mail address: kspons2001@gmail.com (S. Ponnuswamy).

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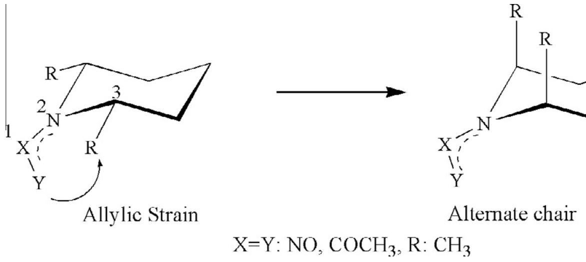

Fig. 1. Allylic strain or $A^{1,3}$ strain.

solid state [2,22,26–28]. Because the presence of *cis*-2,6-diaryl groups in *N*-acetyl and *N*-nitrosopiperidines exerts unpredictable conformational changes [1–22] in the piperidine ring, there are significant differences between the steric influences of an α-aryl group and an α-alkyl group on the conformational preferences of 2,6-disubstituted piperidines containing heteroconjugate groups (i.e., groups capable of delocalising the lone pair of electrons on nitrogen, such as NO, CHO and COMe).

A comparison of the rotational barriers of various 2,6-dimethylpiperidines containing hetero conjugate groups indicates that the rotational barrier for the *N*-CHO derivatives [23,24] was lower than that of *N*-nitroso derivatives but larger than that of any other derivatives (e.g., $COCH_3$, COPh and CONHPh) [1–19,29]. The *N*-formyl derivatives of 2,6-diphenylpiperidines were reported to favour flattened boat conformations [8].

To study the relative influences of allylic strain, torsional strain, resonance energy due to the delocalisation of the lonepair electrons on nitrogen to the carbonyl π-cloud and 1,3-diaxial strains over the preferred conformations of the piperidine ring, four new *N*-formyl-*cis*-2,6-bis(4-methoxyphenyl)piperidin-4-ones **5**–**8** were synthesized and their stereochemistry was studied using ^{1}H, ^{13}C, DEPT and 2D (COSY and HSQC) NMR spectral data and dynamic ^{1}H NMR spectra. In addition, the antibacterial and antifungal activities have also been tested.

Experimental

Materials, methods and instruments

All of the reported melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded using a SHIMADZU FT-IR 88400s spectrometer using KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution at 243 K with a Bruker AV 300 & 75 MHz, Bruker DRX 500 & 125 MHz and Bruker (Avance III) 500 & 125 MHz NMR spectrometers, and the chemical shifts were referenced to TMS. A 0.05 M solution of the sample prepared in $CDCl_3$ was used for obtaining the 2D NMR spectra. The tubes used for recording the NMR spectra were 5-mm diameter. Electron impact mass spectra were recorded using a JEOL GS mate spectrometer, and microanalyses were performed on a Carlo Erba 1108 CHN analyser. Unless otherwise stated, all of the reagents and solvents were of high grade and purchased from Sigma–Aldrich chemicals, Bangalore, India and Merck chemicals, Worli, Mumbai. All of the solvents were distilled prior to use. The parent piperidin-4-ones were prepared by following the literature procedure [30–33].

General procedure for the synthesis of compounds **5–8**

An ice-cold solution of acetic-formic anhydride was prepared from acetic anhydride (10 ml) and 85% formic acid (5 ml), and this solution was slowly added to a cold solution of piperidin-4-ones [**1**: (1.625 g, 5 mmol), **2, 3** and **4**: (1.69 g, 5 mmol)] in benzene (30 ml) to synthesize compounds **5**–**8**, respectively (see Scheme 1) The reaction mixture was allowed to stir at room temperature for 5 h. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated. The resulting product was purified by crystallisation from benzene–petroleum ether (333–335 K) in a 1:1 ratio. The analytical data of compounds **5**–**8** are reported in Table 1.

Results and discussion

In the IR spectra of the compounds **5**–**8**, the amide >C=O stretching bands were observed at approximately 1662–79 cm^{-1}. In addition, the ring carbonyl stretching band was observed at approximately 1704–1716 cm^{-1}. The NH stretching band at approximately 3300 cm^{-1} that was observed for parent compounds **1**–**4** was absent in *N*-formylpiperidin-4-ones **5**–**8** (Table 2). In the mass spectra, the presence of molecular ion peaks at *m*/*z* 353, 367, 367 and 367 for compounds **5**–**8**, respectively, and their fragmentation pattern confirmed the structures.

The RT NMR spectra showed the doubling of signals with broadening. Therefore, all of the NMR spectra were recorded at 243 K for *N*-formylpiperidin-4-ones **5**, **7** and **8**, which showed well resolved signals for each of the protons and carbons corresponding to the *syn* and *anti* rotamers. For compound **6**, a well-resolved doubling of the NMR signals was observed at 283 K. These observations indicated the existence of conformational equilibria in compounds **5**–**8**.

The ^{1}H NMR signals of *N*-formylpiperidin-4-ones **5**–**8** were assigned based on their chemical shifts, multiplicities and intensities as well as in comparison with those of parent piperidin-4-ones

Table 1
Analytical data for compounds **5**–**8**.

Compounds	Molecular formula (Mol. Wt.)	Melting point (°C)	Yield (%)	Elemental analysis found (Calcd)%		
				C	H	N
5	$C_{21}H_{23}NO_4$ (353)	106–108	84.9	71.09 (71.37)	6.61 (6.56)	3.82 (3.96)
6	$C_{22}H_{25}NO_4$ (367)	85–87	64.3	71.64 (71.91)	6.80 (6.86)	3.92 (3.81)
7	$C_{22}H_{25}NO_4$ (367)	98–100	65.3	72.12 (71.91)	6.79 (6.86)	3.75 (3.81)
8	$C_{22}H_{25}NO_4$ (367)	85–87	79.0	71.72 (71.91)	6.93 (6.86)	3.98 (3.81)

Table 2
IR spectral data for compounds **5**–**8**.

Compound	IR (cm^{-1})
5	2966, 2933, 2881, 1716(C=O stretching), 1670(amide C=O stretching), 1654, 1514, 1365, 1033, 840, 582, 682, 563
6	2954, 2933, 2835, 1704(C=O stretching), 1662(amide C=O stretching),1616, 1514, 1419, 1249, 1184, 1035, 827, 671, 514
7	2993, 2954, 2831, 1716(C=O stretching), 1666(amide C=O stretching),1610, 1514, 1251, 1024, 838, 651, 547, 491
8	2975, 2937, 2835, 1716(C=O stretching), 1679(amide C=O stretching),1654, 1514, 1247, 1178, 1033, 835, 686, 541