

CONFORMATIONAL STUDIES OF SOME *N*-ACYL-3-ETHYLPIPERIDIN-4-ONES

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ABSTRACT

The compounds *N*-acyl-3-ethyl-difurylpiperidones **1-4** were prepared and conformational studies were done based on coupling constant and torsional angle values. Based on coupling constant and torsional angle values, the compounds **1-4** shows that mixture of alternate chair form **CA** and boat form **B1** for both E and Z isomers.

Keywords: conformational studies, dihedral angles, *N*-acyl-piperidin-4-ones

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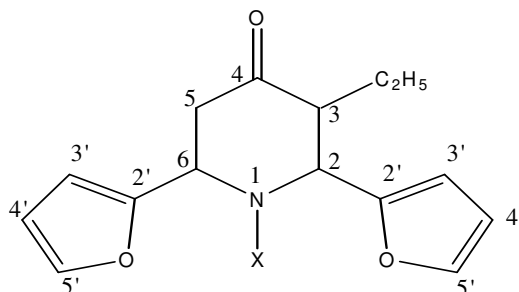
INTRODUCTION

The conformational studies of various 2,6-dimethyl, 2,6-diethyl and 2,6-diphenylpiperidone derivatives¹⁻⁹ exhibited normal chair conformation. The same type of compounds i.e., 3-isopropylpiperidin-4-one derivatives are prepared and also done conformational studies (Manimekali et al¹⁰). Conformational studies of substituted 2,6-diphenylpiperidin-4-ones exhibited a mixture of B1 and B2 conformations (Akila et al¹¹). A series of 3-heptyl-2,6-diarylpiperidin-4-ones have been synthesized and exhibited chair form (Krishnasamy et al¹²). A series of 2,6-diarylpiperidin-4-ones with a chloro substitution at C3 and dichloro substitutions at C3 and C5 have been prepared and conformational analysis was studied (Pillay et al¹³). A mixture of boat forms (B₁ and B₂) is obtained for some substituted nitrosopiperidones (Z isomer). E isomer exhibited boat form B₁ be the major conformer¹⁴. At present we discussed conformational studies of substituted *N*-acyl-3-ethyl-difuryl-piperidones.

EXPERIMENTAL

¹H, ¹³C NMR, NOESY and ¹H, ¹³C COSY spectra were recorded on NMR spectrophotometer. By using general procedure the starting compound was prepared¹⁵.

The compounds *N*-acyl-3-ethyl-difurylpiperidones **1-4** are synthesized by reference paper¹⁶. The structure of compounds as described in Fig.-1.



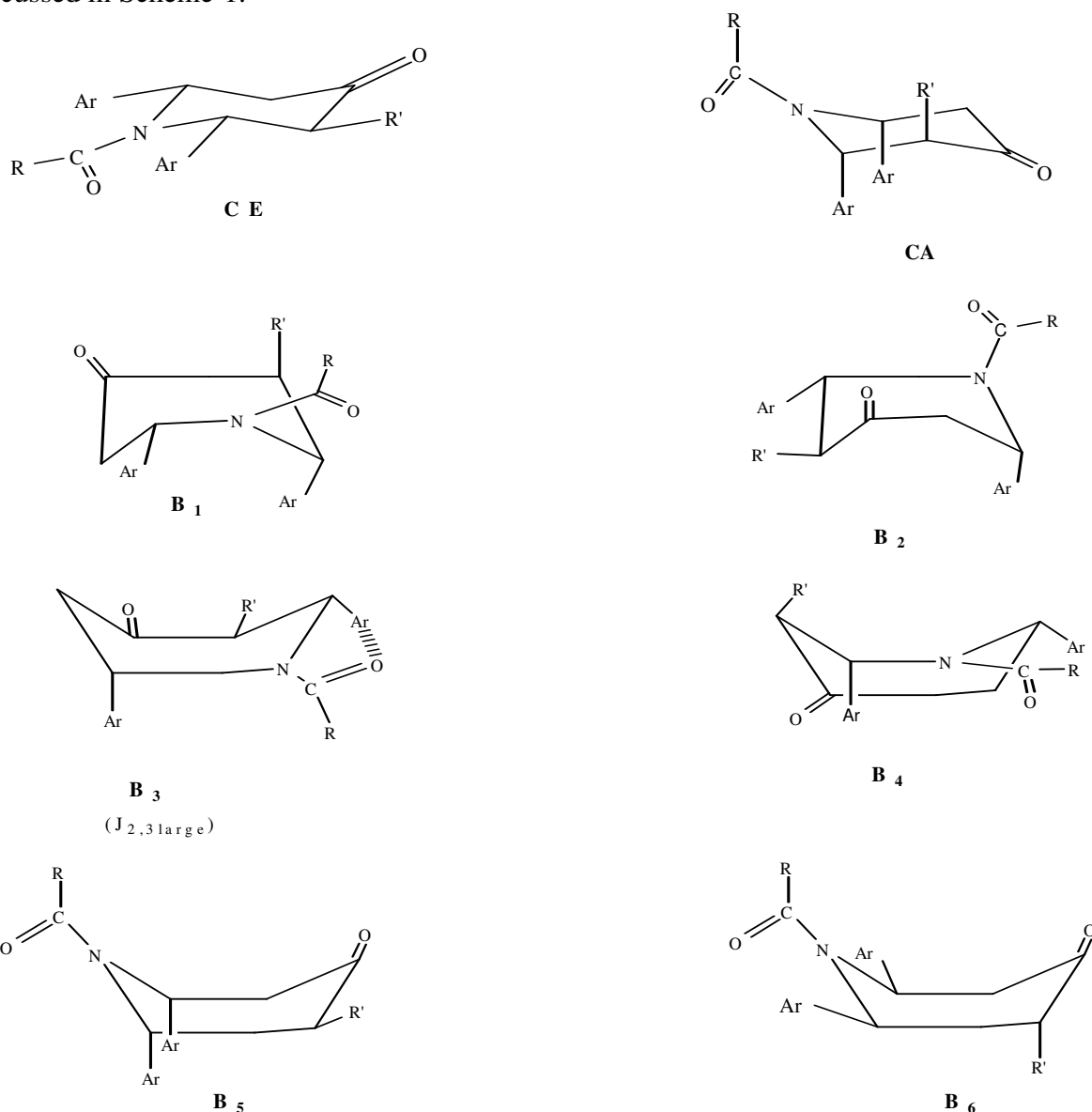
X = **1**: CHO, **2**: COCH₃, **3**: COCH₂CH₃, **4**: COC₆H₅

Fig.-1

RESULTS AND DISCUSSION

Analysis of Coupling Constants

Based on coupling constant values parent piperidones 1-4 showed normal chair form with the equatorial orientations of furfuryl group at 2nd and 6th position and alkyl groups at 3rd position. The coupling constant values in C(2)-C(3) bond in the Z isomers of N-formyl-3-alkyl derivatives 1-4 are drastically lower when compared with their parent piperidin-4-ones. The value of the coupling constant is 7 Hz about 5, 6 bonds (another coupling is very small) in N-acyl-3-alkyl derivatives 1-4. Based on these coupling constant values, N-acyl-3-alkyl derivatives 1-4 not obeyed normal chair conformation (CE) with equatorial orientations of all the substituents. The compounds 1-4 having A^{1,3} strain between N-acyl and furfuryl groups. Due to A^{1,3} strain, the derivatives 1-4 may adopt alternate chair form or boat form. The various conformations for the Z isomers are discussed in Scheme-1.



Scheme-1: Possible conformations for the Z-isomers of 1-4

In normal chair form CE, B₃ and B₆ having A^{1,3} strain so these conformations are excluded. The expected coupling constant values i.e., J_{2,3} value around 10 Hz but the actual value is around 4 Hz in N-acyl-3-alkyl derivatives 1-4. Based on literature survey¹⁴ the boat form B₄ is having higher energy. So B₄ is also ruled out. The small coupling around 4 Hz is possible for alternate chair form, B₁ and B₅. The expected coupling constant i.e., J_{5,6} values for B₁ and B₅ (trans coupling – 10 and 4 Hz and cis coupling 4 and 10 Hz). But the actual coupling constant value is 7 Hz and another coupling constant value is very small ≈ 1 Hz. So the combination of boat forms B₁ and B₅ are also excluded. So the possible conformation is an equilibrium mixture of boat form B₁ [J_{trans} ≈ 10, J_{cis} ≈ 4 Hz] and alternate chair form CA [both J_{trans} and J_{cis} ≈ 3-4 Hz]. The observation of large coupling around 7 Hz suggests that boat form B₁ contribute more to the equilibrium than alternate chair form CA.

Gdaniec *et al.*⁵ have reported that 3-alkyl piperidines adopt alternate chair conformation CA in the solid state in order to relieve the A^{1,3} strain. Molecular mechanics calculations have also shown that alternate chair form CA is having lower energy when compared to boat forms in these derivatives. So we concluded that the Z forms of compounds 1-4 exist as an equilibrium mixture of alternate chair form CA and boat form B₁.

The same arguments are made for E-isomers of 1-4. The E-isomers of 1-4 also concluded that a mixture of alternate chair form and boat form B₁ (Scheme-2).

Calculation of Torsional Angles

Torsional angles also give clue regarding the conformations of these N-formyl derivatives. Several methods to calculate the ring torsional angles from the coupling constants have surfaced. DAERM method of Slessor and Tracey¹⁷ and the equation proposed by Haasnoot¹⁸ are of considerable practical utility, since they do not require too many parameters. DAERM method requires two coupling constants [J_{trans} and J_{cis}] to evaluate torsional angles whereas torsional angles can be calculated even from one coupling constant according to the Haasnoot method. Therefore, Haasnoot equation is employed in the present investigation to calculate the torsional angles in the N-acyl derivatives 1-4.

Estimation of Dihedral Angles between Vicinal Protons using the equation of Haasnoot *et al.*

The torsional angles between vicinal protons about C(5)-C(6) bond were determined using Haasnoot equation for trisubstituted ethane system. The equation can be written as:

$$J_{\text{HH}} = 13.22 \cos^2\phi - 0.99 \cos\phi + \Sigma\Delta x_i [0.87 - 2.46 \cos^2(19.91|\Delta x_i \pm \epsilon_i \phi)] \quad (1)$$

Where, $\Sigma\Delta x_i$ is the sum of the difference in the electronegativities of all elements attached to the C-C segment and hydrogen and ϕ is the torsional angle between the two hydrogens. The value of ϵ_i in the equation 2 is taken as +1 or –1 depending upon the orientation of the substituents.

The orientations of various substituents about C(5)-C(6) bond in the normal chair conformation CE and boat form B₁ of N-acyl derivatives 1-4. The substituents N-C=O and >C=O will have negative values of ϕ as they lie beyond 180° along with the direction of measurement of ϕ_{trans} whereas aryl and H_c will have positive values of ϕ since they lie within 180° along with the direction of measurement of ϕ_{trans} . Thus, it appears that the orientation of various substituents is found to be the same irrespective of the conformations (CE and B₁) adopted by the molecules.

The torsional angles about C(2)-C(3) segment in N-acyl-3-alkyl derivatives 1-4 were determined using Haasnoot equation 2 for the tetrasubstituted ethane system:

$$J_{\text{HH}} = 13.24 \cos^2\phi - 0.91 \cos\phi + \Sigma\Delta x_i [0.53 - 2.41 \cos^2(15.51|\Delta x_i \pm \epsilon_i \phi)] \quad (2)$$

The orientation of various substituents about C(2)-C(3) bond in the normal chair conformation CE and boat forms B₁ and B₅.

Table-1: Calculated Torsional Angles using the Haasnoot equation for some N-acetylpiperidin-4-one derivatives 1-4

Compound		$J_{5,6}^{trans}$	ϕ_{trans}	$J_{2,3}^{trans}$	ϕ_{trans}
1	E	5.07	121.2°	-	-
	Z	5.84	125.5°	3.19	52.1°
2	E	7.92	137.3°	-	-
	Z	7.88	137.0°	-	-
3	E	7.52	135.0°	-	-
	Z	7.38	134.2°	-	-
4	E	6.95	131.7°	-	-
	Z	7.33	133.9°	-	-

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