Indian Journal of Chemistry
Vol. 46B, January 2007, pp. 160-169

Conformational studies of some *N*-acyl-*t*(3)-isopropyl-r(2),*c*(6)-bis-(2′-furyl)piperidin-4-ones

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Received 4 August 2005; accepted (revised) 23 August 2006

The high resolution ^{1}H and ^{13}C NMR spectra of four *N*-acyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(2′-furyl)piperidin-4-ones **1-4** have been recorded at various temperatures and analysed. The spectra reveal the presence of two rotameric forms (*E* and *Z*) in solution. ^{1}H-^{1}H COSY spectra for **1-4** and ^{1}H-^{13}C COSY spectrum for **4** have been recorded to assist the assignment of the signals for the *E* and *Z* isomers of **1-4**. Coupling constants predict an equilibrium mixture of boat form $\mathbf{B_1}$ and alternate chair form **CA** for **1-4**. The effect of varying the substituents at nitrogen on the ^{1}H and ^{13}C chemical shifts have been analysed in detail. Mass spectra have also been recorded for **1-5**.

Keywords: NMR spectra, molecular conformation, *N*-acyl-piperidin-4-ones

IPC: Int.Cl.[8] C07D

Many piperidine derivatives are found to possess pharmacological activity[1,2] and form an essential part of the molecular structures of important drugs[3,4]. Recently attention has been focussed on the application of the piperidone derivatives as prospective biophotonic materials[5,6]. Since the pharmacological properties and the reactivity depend on their stereochemistry, efforts were made for the development of new synthetic techniques leading to stereoselective piperidines and their characterization[7-10]. Most of the piperidine precursors are known to exist in chair conformation. Electron withdrawing groups (–NO, –CHO, –COR and –CONHPh) introduced at the nitrogen atom profoundly affect the conformations of the heterocyclic ring and orientation of the substituents in 2,6-dialkyl- and 2,6-diaryl substituted piperidines. Considerable work has been carried out on the conformations of several substituted 2,6-dialkyl- and 2,6-diarylpiperidine derivatives[11-17] in which severe $A^{1,3}$ strain exists in the normal chair conformation. In all these cases conformations which avoid $A^{1,3}$ strain are favoured. In an effort to create new derivatives of pharmacologically active piperidones, the present investigation was undertaken. So far only a few studies have been carried out on the conformation of piperidine derivatives in which a five membered ring is incorporated at 2 and 6 positions[18]. Moreover, there is no systematic study by varying the substituent at nitrogen on the conformations of sterically hindered piperidine derivatives. Therefore, in the present study a set of compounds has been chosen in which (i) five membered heterocyclic ring *i.e.,* 2-furyl ring is incorporated at 2 and 6 positions of piperidine ring and (ii) the substituent at nitrogen is varied (–CHO, $–COCH_3$, $–COCH_2CH_3$ and –COPh) and studied their conformational behaviour through NMR techniques.

Results and Discussion

The high resolution ^{1}H and ^{13}C NMR spectra of *N*-formyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(2′-furyl)piperidin-4-one **1**, *N*-acetyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(2′-furyl)piperidin-4-one **2**, *N*-propanoyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(2′-furyl)piperidin-4-one **3** and *N*-benzoyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(2′-furyl)piperidin-4-one **4** have been recorded in $CDCl_3$ and analysed. The spectra were also recorded at low temperatures (0, -15 and -30°C). The ^{1}H NMR spectra of *N*-acyl-*t*(3)-isopropyl derivatives **1-4** contained two distinct broad signals for each α proton at RT and the signals are well resolved at low temperatures. ^{13}C NMR spectra also reveal the presence of two isomers in solution. The observation of two sets of signals in

1-4 suggests the presence of restricted rotation around N-C bonds and establishment of equilibrium between two rotamers with coplanar orientation of acyl group in these derivatives. The two rotamers are labelled as *Z* [carbonyl oxygen is *syn* to isopropyl group at C(3)] and *E* [carbonyl oxygen is *anti* to isopropyl group at C(3)] isomers (**Figure 1**).

Based on intensities, the signals for one rotamer can be easily differentiated from the other rotamer. The identification of proton signals in the *E* and *Z* isomers was done based on the results obtained in the ^{1}H-^{1}H COSY spectra recorded for **1-4**. The assignment of the signals in ^{13}C NMR spectra have been made on the basis of known effects of alkyl and acyl substituents in six-membered rings[13b,15,19]. The assignment of these signals in **4** are further confirmed from the ^{1}H-^{13}C COSY spectrum. The chemical shifts and coupling constants derived from -30°C NMR spectra are displayed in **Table I**. **Table II** reports ^{13}C chemical shifts of **1-4** recorded at -10°C. The chemical shifts and the coupling constants of parent piperidin-4-one *i.e.,* *t*(3)-isopropyl-r(2), *c*(6)-di-2′-furylpiperidin-4-one[20] **5** are also included in these tables for comparison purpose. Mass spectra were also recorded for **1-5**.

Ring Conformations

The coupling constant about C(2)-C(3) bond is close to 0 Hz in **1-4** (only singlet is observed for H(2) signal). The observation of only one coupling around 7 Hz about C(5)-C(6) bond or total width of around 8-11 Hz for H(6) signal in **1-4** is in contrast to the values observed in the parent piperidin-4-one, **5**. These coupling constants cannot be accounted by normal chair conformation (**CE**). Moreover, in the normal chair conformation severe pseudoallylic ($A^{1,3}$) strain exists between *N*-acyl group and equatorial furfuryl rings at C(2) and C(6). In order to relieve $A^{1,3}$ strain, the *N*-acyl derivatives **1-4** may adopt alternate chair form or boat form. The possible conformations for the *Z* isomers of **1-4** are shown in **Scheme I**.

In conformations **CE**, $\mathbf{B_3}$ and $\mathbf{B_6}$ allylic strain exists between N-COR group and furfuryl rings and hence these conformations are ruled out in the present study. The conformation $\mathbf{B_2}$ is also not possible since in this conformation $J_{2,3}$ is expected to be around 10 Hz which is in contrast to the singlet observed for H(2) in **1-4**. Molecular mechanics calculations for several *N*-formyl-*trans*-3-alkyl-*cis*-2,6-diphenyl-piperidin-4-ones[19] have shown that the boat form $\mathbf{B_4}$ with alkyl group at flagpole position is having higher energy when compared to alternate chair form **CA** and boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$. Therefore, in the present study, the boat conformation $\mathbf{B_4}$ is also excluded. In alternate chair form **CA** both couplings about C(5)-C(6) bond are expected to be around 3-4 Hz whereas in boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$ they are expected to be around 10 and 4 Hz. The observation of one coupling around 7 Hz about C(5)-C(6) bond suggests that these compounds cannot exist in single conformation. They can exist as an equilibrium mixture of two or three conformers. In alternate chair form **CA** and boat form $\mathbf{B_5}$, *syn*-1,3 diaxial interaction exists between furfuryl groups at C(2) and C(6) whereas in boat form $\mathbf{B_1}$ such interaction is absent. Therefore, an equilibrium mixture of **CA** and boat form $\mathbf{B_5}$ is ruled out in the present study since in both the forms 1 and 3 interactions are present. Moreover, an equilibrium mixture of boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$ is also excluded in the present study based on the following observations.

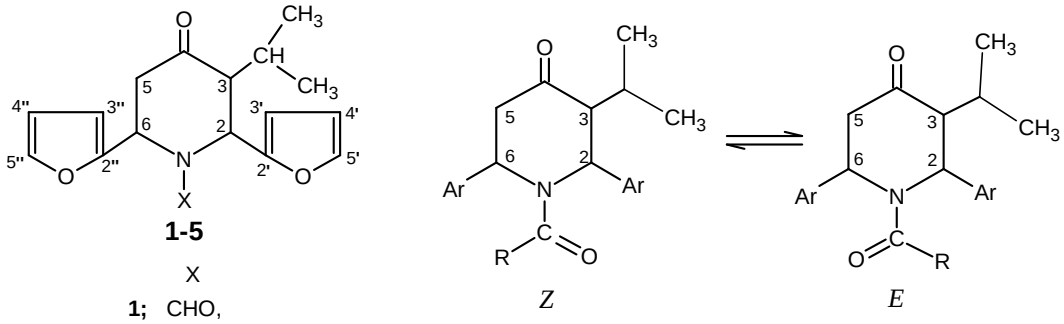


Figure 1

Table I — ^{1}H Chemical shifts (ppm) of *N*-acyl-*t*(3)-isopropylpiperidin-4-ones **1-4** and their parent compound **5**

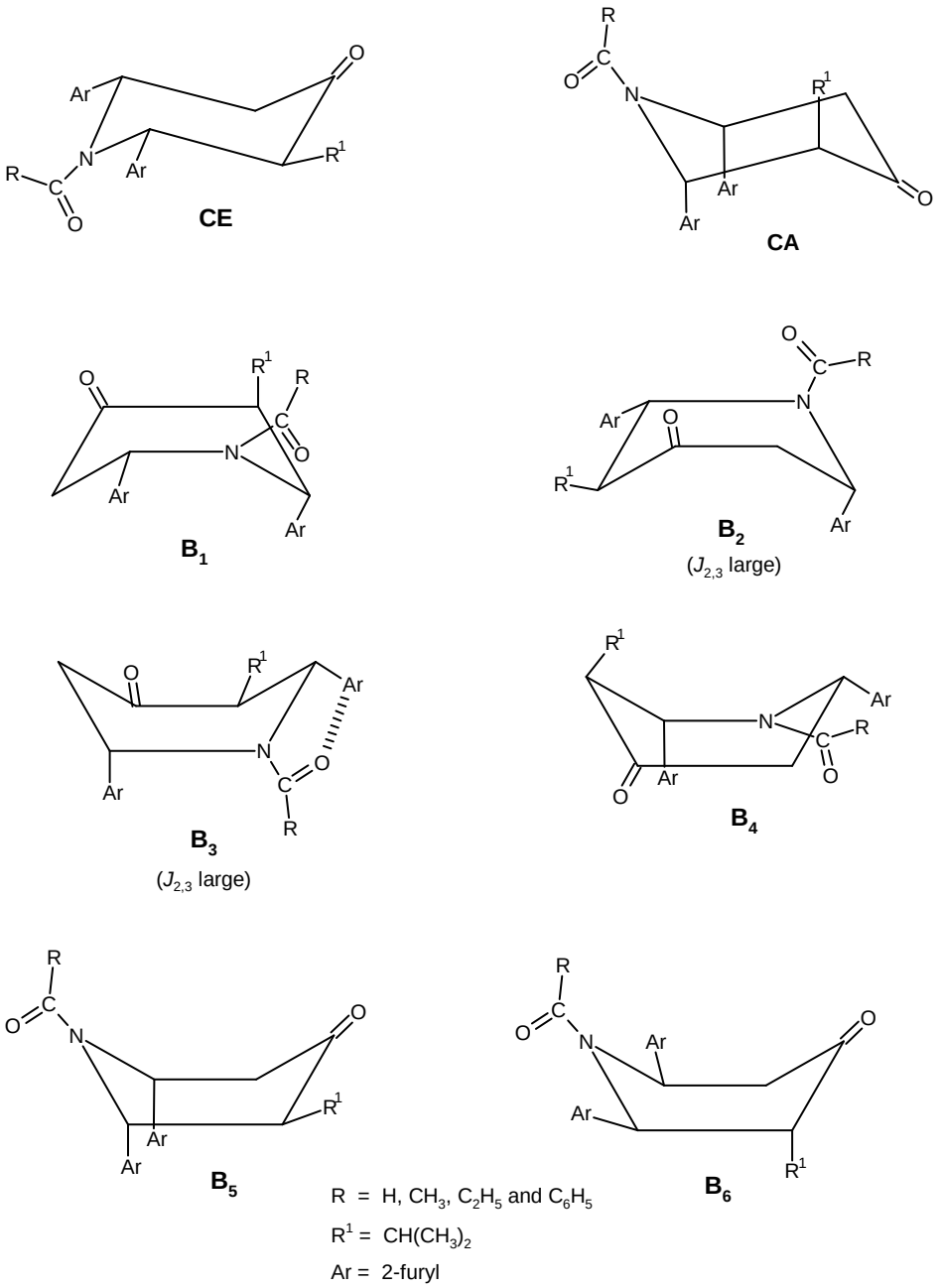
Compd		H(2)	H(3)	H(5)	H(6)	Alkyl protons	Acyl protons	Aromatic protons
1	*E*	5.11 (s)	2.56 (d, 10.00[a])	3.01 (dd, 8.28; 14.91) 2.87 – 2.93	6.19 (t, 11.55[b])	0.97 (d, 6.70) 1.13 (d, 6.47) } [CH(CH$_3$)$_2$] 1.97 – 2.10 [CH(CH$_3$)$_2$]	8.54	5.88 (2H); 5.93 (1H); 5.96 (1H) 6.03 (2H); 6.07 (2H) 7.01 (1H); 7.05 (1H); 7.07 (1H); 7.11 (1H)
	Z	6.17 (s)	2.58 (d, 10.24[a])	2.87 – 2.93	5.29 (d, 8.03)	0.94 (d, 6.71) 1.15 (d, 6.44) } [CH(CH$_3$)$_2$] 1.97 – 2.10 [CH(CH$_3$)$_2$]	8.66	
2	*E*	5.41 (s)	2.46 – 2.61	2.81 – 2.90	6.46 (d, 7.31)	0.96 (d, 6.64) 1.17 (d, 6.43) } [CH(CH$_3$)$_2$] 2.14 [CH(CH$_3$)$_2$]	2.55	5.81 (1H); 5.85 (1H); 5.89 (2H) 6.01 (2H); 6.05 (2H) 6.98 (1H); 7.11 (1H); 7.04 (2H)
	Z	6.52 (s)	2.46 – 2.61	3.01 (dd, 8.37, 14.91) 2.81 – 2.90	5.54 (d, 7.97)	0.93 (d, 6.67) 1.14 (d, 6.41) } [CH(CH$_3$)$_2$] 2.05 [CH(CH$_3$)$_2$]	2.58	
3	*E*	5.48 (s)	2.51 (d, 9.81[a])	2.84 – 2.87	6.51 (dd, 2.77, 5.82)	0.95 (d, 6.68) 1.17 (d, 6.45) } [CH(CH$_3$)$_2$] 2.11 [CH(CH$_3$)$_2$]	1.33 (t, 7.20) (COCH$_2$CH$_3$) 2.68-2.78 (COCH$_2$CH$_3$)	5.60 (1H); 5.85 (1H); 5.88 (2H) 6.00-6.02 (2H); 6.04-6.05 (2H) 6.99 (1H); 7.03 (2H); 7.09 (1H)
	Z	6.56 (s)	2.53 (d, 10.12[a])	2.91 – 2.99	5.60 (d, 7.93)	0.92 (d, 6.70) 1.15 (d, 6.43) } [CH(CH$_3$)$_2$] 2.01 [CH(CH$_3$)$_2$]	1.33 (t, 7.20) (COCH$_2$CH$_3$) 2.91 – 2.99 (COCH$_2$CH$_3$)	
4	*E*	5.38 (s)	2.40 (d, 10.56[a])	2.98 (dd, 8.43, 14.96) 2.76 (d, 14.75)	6.66 (d, 7.87)	0.61 (d, 6.35) 0.90 (d, 6.60) } [CH(CH$_3$)$_2$] 2.04 [CH(CH$_3$)$_2$]	-	-
	Z	6.59 (s)	2.63 (d, 10.33[a])	2.87 – 2.94	5.50 (d, 7.68)	0.98 (d, 6.72) 1.24 (d, 6.36) } [CH(CH$_3$)$_2$] 2.16 [CH(CH$_3$)$_2$]	-	5.84 (1H); 5.90 (1H); 5.93 (1H); 5.95 (1H) 6.01 (1H); 6.04 (1H); 6.06 (1H); 6.08 (1H) 7.07 (1H); 7.09 (2H); 7.15 (1H) 7.45-7.55; 7.65; 7.72; 7.78; 8.13 (COC$_6$H$_5$)
5		4.19 (d, 11.76)	2.79 – 2.85	2.79 – 2.85 (ax) 2.71 (eq) (dd, 3.44, 14.05)	4.22 (dd, 3.44, 12.09)	0.79 (d, 7.17) 1.05 (d, 7.06) } [CH(CH$_3$)$_2$] 1.97 [CH(CH$_3$)$_2$]	-	6.23 – 6.36 4(H) 7.29 – 7.41 2(H)

[a] $J_{H(3),H(7)}$, [b] total width

Table II — ^{13}C Chemical shifts (ppm) of *N*-acyl-*t*(3)-isopropylpiperidin-4-ones **1-4** and their parent compound **5**

Compd		C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	Acyl carbons	Aromatic carbons	
1	*E*	54.48	58.49	208.30	38.76	45.17	20.11 (CH$_3$); 21.08 (CH$_3$) 28.26 [CH(CH$_3$)$_2$]	162.86	151.19, 150.88, 150.30 142.89, 142.57, 142.31	C(2)′ and C(2)″ C(5)′ and C(5)″
	Z	47.37	58.49	208.30	39.53	51.82	20.23 (CH$_3$); 21.62 (CH$_3$) 28.59 [CH(CH$_3$)$_2$]	163.16	110.63, 110.46, 110.25, 110.10 108.81, 108.38, 108.14, 107.97	C(3)′ and C(3)″ C(4)′ and C(4)″
2	*E*	54.32	58.58	208.89	39.20	46.61	20.09 (CH$_3$); 22.03 (CH$_3$) 28.62 [CH(CH$_3$)$_2$]	22.48 (COCH$_3$) 171.63 (COCH$_3$)	152.20, 151.99, 151.70 142.52, 142.36, 142.21	C(2)′ and C(2)″ C(5)′ and C(5)″
	Z	48.49	58.70	208.89	39.39	51.76	20.26 (CH$_3$); 21.81 (CH$_3$) 28.83 [CH(CH$_3$)$_2$]	22.48 (COCH$_3$) 171.63 (COCH$_3$)	110.59, 110.41, 110.16, 110.06 108.49, 108.14, 107.90, 107.76	C(3)′ and C(3)″ C(4)′ and C(4)″
3	*E*	53.04	58.59	209.11	39.51	46.83	20.08 (CH$_3$); 22.21 (CH$_3$) 28.58 [CH(CH$_3$)$_2$]	9.64 (COCH$_2$CH$_3$) 26.67 (COCH$_2$CH$_3$) 174.31 (COCH$_2$CH$_3$)	142.34, 142.15 110.56, 110.38, 110.11, 110.03	C(2)′ and C(2)″ C(5)′ and C(5)″
	Z	48.64	58.86	209.11	39.51	50.60	20.25 (CH$_3$); 21.92 (CH$_3$) 28.83 [CH(CH$_3$)$_2$]	9.73 (COCH$_2$CH$_3$) 26.85 (COCH$_2$CH$_3$) 174.31 (COCH$_2$CH$_3$)	108.41, 108.12 107.82	C(3)′ and C(3)″ C(4)′ and C(4)″
4	*E*	55.19	59.52	208.81	39.35	47.03	20.07 (CH$_3$); 21.55 (CH$_3$) 27.96 [CH(CH$_3$)$_2$]	172.96	151.98, 151.79, 150.99, 150.81 143.08, 142.59, 142.27, 142.06, 141.60 135.45, 135.09, 133.76, 130.22, 128.91 128.77, 128.59, 127.47, 126.91 } (COC$_6$H$_5$)	C(2)′ and C(2)″ C(5)′ and C(5)″
	Z	49.16	59.19	208.81	39.83	52.99	20.41 (CH$_3$); 22.07 (CH$_3$) 29.27 [CH(CH$_3$)$_2$]	172.80	110.46, 110.33 108.98, 108.46, 108.20, 108.10	C(3)′ and C(3)″ C(4)′ and C(4)″
5		56.64	59.51	207.24	47.21	53.69	18.05 (CH$_3$); 19.97 (CH$_3$) 26.01 [CH(CH$_3$)$_2$]	–	154.61, 154.00 C(2)′ and C(2)″ ; 141.97 C(5)′ and C(5)″ 110.27, 110.22 C(3)′ and C(3)″ ; 107.51, 105.70 C(4)′ and C(4)″	

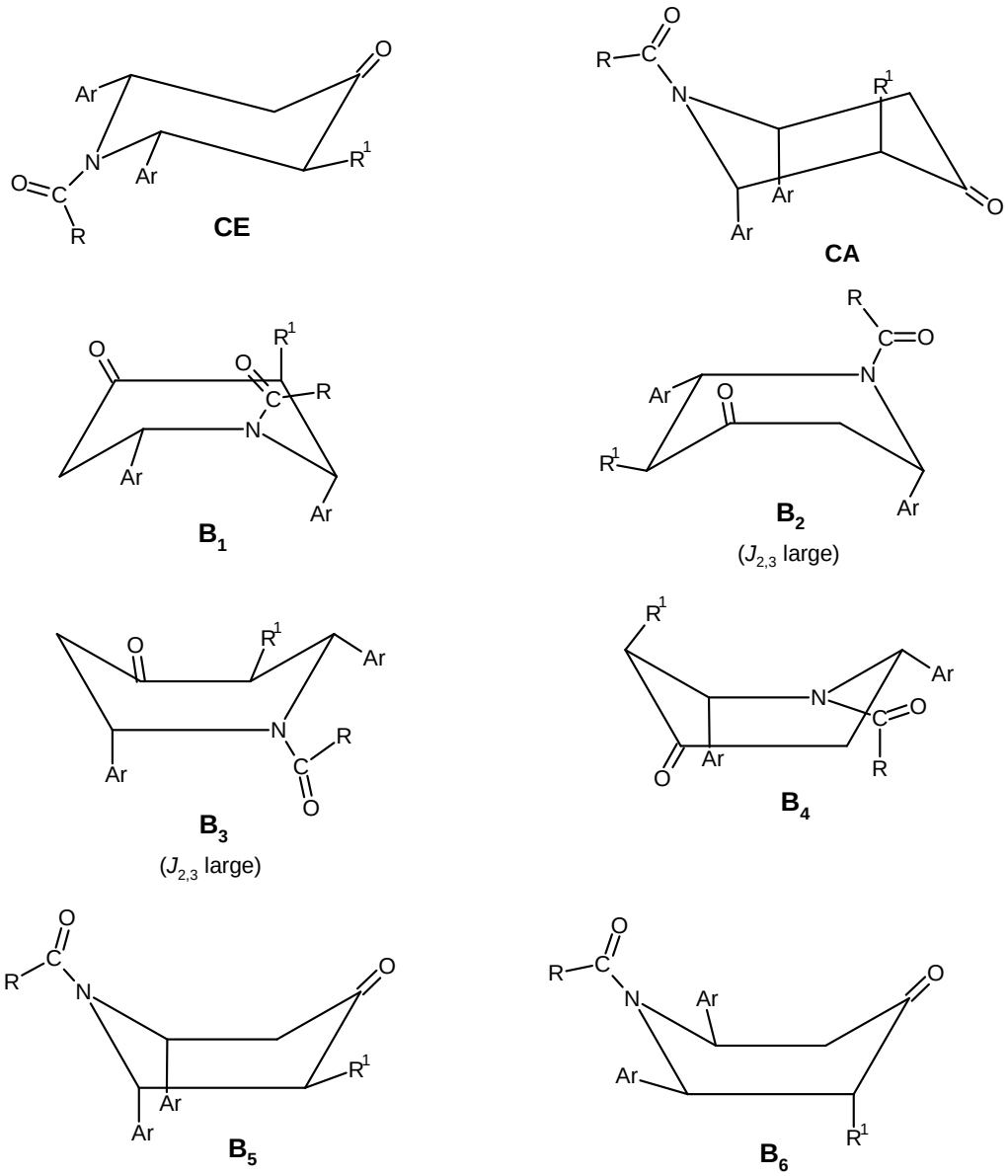
The *trans* coupling about C(5)-C(6) bond in the boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$ are expected to be around 10 and 4 Hz and the *cis* coupling are expected to be around 4 and 10 Hz respectively. An equilibrium mixture of boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$ suggests that both couplings about C(5)-C(6) bond are expected to be almost the same and in the region 5-8 Hz. However, the observation of only one coupling around 7 Hz (the other coupling is of very small magnitude ≈1 Hz) ruled out the possibility of the existence of an equilibrium mixture of boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$. Therefore, it is concluded that the *Z* isomers of *N*-



Scheme I — Possible conformations for the *Z*-isomers of **1-4**

acyl-3-isopropylpiperidin-4-ones **1-4** exist as an equilibrium mixture of boat form $\mathbf{B_1}$ and alternate chair form **CA**. Existence of such an equilibrium mixture suggests that one coupling should be small and another coupling should be around 6-8 Hz depending upon the population. The possible conformations for the *E* form of *N*-acyl-3-isopropylpiperidin-4-ones **1-4** are shown in **Scheme II**.

The normal chair conformation **CE**, and the boat forms $\mathbf{B_4}$ and $\mathbf{B_6}$ are ruled out since in these conformations $A^{1,3}$ strain exists between acyl group and equatorial furfuryl groups. The observation of singlet for H(2) [coupling close to 0 Hz] ruled out the possibility of existing in boat conformations $\mathbf{B_2}$ and $\mathbf{B_3}$. An equilibrium mixture of boat forms $\mathbf{B_1}$ and $\mathbf{B_5}$ for the *E* form of *N*-acyl-3-isopropylpiperidin-4-ones is also ruled out based on the same arguments given for *Z* form. Therefore, it is concluded that the *E* isomers of **1-4** also exist as an equilibrium mixture of boat conformation $\mathbf{B_1}$ and alternate chair form **CA** similar to *Z* forms of **1-4**.



Scheme II — Possible conformations for the *E*-isomers of **1-4**

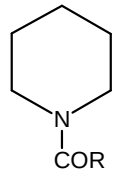
The torsional angles about C(5)-C(6) bond in **1-4** calculated according to Haasnoot equation[21] are in the range 135° and these values are abnormally lower than the ϕ_{trans} values expected in the normal chair conformation (180°) and in the boat conformation $\mathbf{B_1}$ (180°). Simple distortion cannot decrease the torsional angle from 180° to 135° and therefore, torsional angle calculations also suggest the presence of additional conformer *i.e.,* **CA** in equilibrium with the boat form $\mathbf{B_1}$ for **1-4**.

Analysis of Chemical Shifts

To determine the effect due to *N*-acylation on ^{1}H chemical shifts of α protons in normal chair conformation the chemical shifts of *N*-formylpiperidine **6** (Ref. 22), *N*-acetyl- and *N*-benzoyl-3-methylpiperidines **7** and **8** (Ref. 23) (exists in two rotameric forms) and *N*-acetyl-*t*(7)-methyldecahydroquinoline **9** (Ref. 24) are compared with their corresponding parent compounds *i.e.,* piperidine, 3-methylpiperidine and *t*(7)-methyldecahydroquinoline. From the comparison, it

is seen that in normal chair conformation the *anti* α protons (*anti* to –N–C=O bond) are deshielded to an extent of ≈ 0.6 ppm (equatorial) and ≈0.4 ppm (axial) and the *syn* equatorial α protons are deshielded to an extent of ≈1.3-1.5 ppm due to *N*-acylation. There is slight deshielding on the *syn* axial proton if equatorial hydrogen is attached to *syn* α carbon whereas the presence of equatorial alkyl group causes the *syn* axial proton to experience a deshielding magnitude of 1.2 ppm due to *N*-acylation.

The effects observed due to *N*-acylation in **1-4** are displayed in **Table III**. The deshielding magnitude observed on H(2) in the *Z* isomers (*syn* α protons) are roughly same as those observed on H(6) in the *E* isomers (*syn* α protons) and the magnitude of deshielding is ≈ 2 ppm in **1-4**. This is considerably higher than the magnitude observed for *syn* α axial protons in the normal chair conformation. Moreover, the deshielding magnitude observed on *anti* α protons [H(2) in the *E* isomer and H(6) in the *Z* isomer] is also higher (≈ 1 ppm) compared to the *anti* α axial protons in the normal chair conformation. Thus, the observed deshielding of α protons are inconsistent with the normal chair conformation **CE** thus



6-8

6; R = H

7; R = CH_3

8; R = C_6H_5

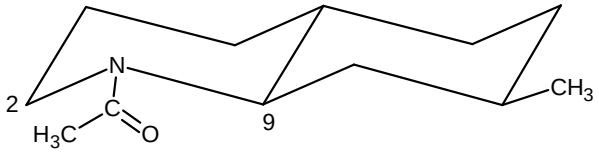


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Table III — Observed deshielding magnitude (ppm) in *N*-acylpiperidin-4-one derivatives **1-4**

Compd		H(2)	H(3)	H(5)	H(6)	Alkyl protons
1	*E*	+ 0.92	- (0.23 - 0.29)	+ (0.16 - 0.22) + (0.16 - 0.22)	+ 1.97	+ 0.18 + 0.08 } [CH(C*H*$_3$)$_2$] + 0.0 to 0.13 [C*H*(CH$_3$)$_2$]
	Z	+ 1.98	- (0.21 - 0.27)	+ (0.02 - 0.14) + (0.16 - 0.22)	+ 1.07	+ 0.15 + 0.10 } [CH(C*H*$_3$)$_2$] + 0.0 to 0.13 [C*H*(CH$_3$)$_2$]
2	*E*	+ 1.22	- (0.18 - 0.39)	- 0.04 to +0.11 + (0.10 - 0.19)	+ 2.24	+ 0.17 + 0.12 } [CH(C*H*$_3$)$_2$] + 0.17 [C*H*(CH$_3$)$_2$]
	Z	+ 2.33	- (0.18 - 0.39)	+ (0.16 - 0.22) + (0.10 - 0.19)	+ 1.32	+ 0.09 + 0.14 } [CH(C*H*$_3$)$_2$] + 0.08 [C*H*(CH$_3$)$_2$]
3	*E*	+ 1.29	- (0.28 - 0.34)	- 0.01 to +0.08 + (0.13 - 0.16)	+ 2.29	+ 0.12 + 0.16 } [CH(C*H*$_3$)$_2$] + 0.14 [C*H*(CH$_3$)$_2$]
	Z	+ 2.37	- (0.26 - 0.32)	+(0.06 - 0.20) +(0.20 - 0.28)	+ 1.38	+ 0.10 + 0.13 } [CH(C*H*$_3$)$_2$] + 0.04 [C*H*(CH$_3$)$_2$]
4	*E*	+ 1.19	- (0.39 - 0.45)	+ (0.13 - 0.19) + 0.05	+ 2.44	- 0.15 - 0.18 } [CH(C*H*$_3$)$_2$] + 0.07 [C*H*(CH$_3$)$_2$]
	Z	+ 2.40	- (0.16 - 0.22)	+ (0.02 - 0.15) + (0.16 - 0.23)	+ 1.28	+ 0.19 + 0.19 } [CH(C*H*$_3$)$_2$] + 0.19 [C*H*(CH$_3$)$_2$]

supporting an equilibrium mixture of boat conformation $\mathbf{B_1}$ and alternate chair form **CA** for **1-4**. In these conformations the *syn* α protons lie in the same plane of the N-C=O moiety and hence experience greater deshielding due to steric and magnetic anisotropic effect of N-C=O bond. The *anti* α protons are also closer to the plane of the N-C=O moiety and hence expected to experience greater magnetic anisotropic effect of the N-C=O moiety. It is also seen that replacement of *N*-formyl group by other *N*-acyl group (acyl = acetyl, propanoyl and benzoyl) increases the deshielding magnitude observed on the α protons due to *N*-acylation and the deshielding magnitude is roughly the same and independent of the nature of the R group of NCOR moiety in the *N*-acyl derivatives **2-4**.

Comparison of the chemical shifts of β protons in *N*-formylpiperidine [1.55 ppm (*syn*); 1.59 ppm (*anti*)][22] and *N*-acetylpiperidine (1.52 ppm)[25] with piperidine (1.46 ppm) reveals that there is no appreciable change in the chemical shifts of β protons due to *N*-acylation in normal chair conformation. Thus, it appears that in cases where there is no conformational change due to *N*-acylation the chemical shifts of β hydrogens are not expected to be altered significantly due to *N*-acylation.

It is very surprising to note that H(3) proton is shielded whereas H(5) proton is deshielded due to *N*-acylation in *N*-acyl-3-isopropyl derivatives **1-4**. The shielding observed on H(3) due to *N*-acylation is probably due to the different conformations of the isopropyl group in the parent piperidin-4-one **5** and its *N*-acyl derivatives **1-4**. In the chair conformation of the parent isopropylpiperidin-4-one **5** it has been previously established[20] that among the three possible conformations for isopropyl group (**Figure 2**) the favoured conformation of isopropyl group at C(3) is established as **A** in which H(3) is *gauche* to one methyl group and *anti* to the other methyl group and hence experiences shielding due to magnetic anisotropic effect of *gauche* methyl group of isopropyl moiety alone.

The possible conformations of isopropyl groups at C(3) in the boat conformation $\mathbf{B_1}$ of *N*-acyl-3-isopropyl derivatives **1-4** are shown in **Figure 3**. In conformations **A′** and **C′** only small coupling of around 4 Hz is expected for $J_{H(3),H(7)}$. The observed large $J_{H(3),H(7)}$ value (≈ 10 Hz) supports that H(3) should be *anti* to H(7) and hence predicts conformation **B′** for **1-4** in which H(3) is *gauche* to both the methyl groups. In this conformation, the H(3) proton experiences shielding due to magnetic anisotropic effect of both the methyl groups and this is the probable reason for the shielding observed on H(3) in **1-4** due to *N*-acylation.

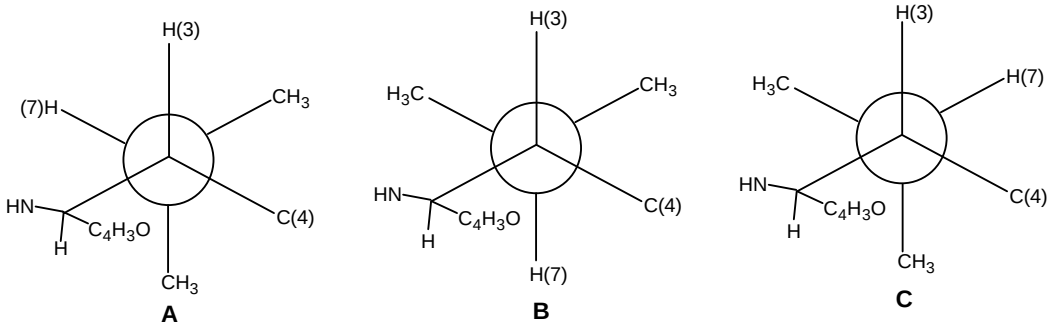

Figure 2 — Possible conformations of isopropyl group in **5**

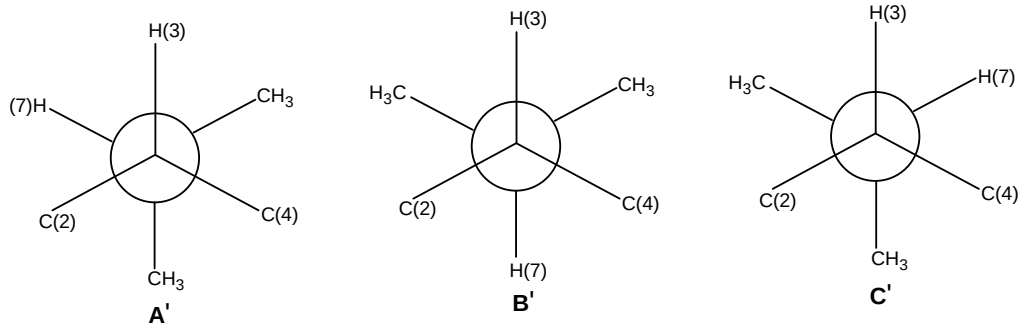

Figure 3 — Possible conformations of isopropyl group in **1-4**

With a view to determine the ^{13}C substituent parameters of the formyl, acetyl and benzoyl substituents at nitrogen in the normal chair conformation **CE** of the six-membered ring compounds, the chemical shifts of *N*-formylpiperidine[22], *N*-acetylpiperidine[26] and *N*-benzoylpiperidine[27] are compared with that of the parent piperidine and the parameters are displayed in **Table IV**. It is seen from **Table IV** that *syn* α carbons are shielded to the extent of 5-7 ppm due to *N*-acylation in normal chair conformation **CE**. The shielding observed on *anti* α, *syn* β, *anti* β and γ carbons appears to be very small (≈ 1-3 ppm) in normal chair conformation. The shielding magnitude observed due to *N*-acylation in **1-4** are also displayed in **Table IV**.

Table IV reveals that the shielding values observed on α carbons [C(2) and C(6)] in **1-4** and C(5) [β carbon] are considerably higher than the values observed in normal chair conformation **CE**. The magnitude of shielding observed on β carbon *i.e.*,

Table IV — Observed shielding magnitude (ppm) of some simple *N*-acylpiperidines and *N*-acylpiperidin-4-one derivatives **1-4**

Compd	α		β		γ
	syn	*anti*	*syn*	*anti*	
N-Formylpiperidine	40.57 (-7.33)	46.76 (-1.14)	26.66 (-1.24)	24.75 (-3.15)	25.16 (-1.04)
N-Acetylpiperidine	41.58 (-6.32)	46.66 (-1.24)	25.29 (-2.61)	26.08 (-1.82)	24.12 (-2.08)
N-Benzoylpiperidine	42.60 (-5.30)	26.11 (-1.79)	24.60 (-1.60)	26.11 (-1.79)	48.30 (+0.40)
Piperidine	47.90		27.90		26.20

		C(2)	C(3)	C(4)	C(5)	C(6)	Isopropyl group
1	*E*	- 2.16	- 1.02	+ 1.06	- 8.45	- 8.52	+ 2.06, +1.11 [CH(CH_3)$_2$] + 2.25 [CH(CH$_3$)$_2$]
	Z	- 9.27	- 1.02	+ 1.06	- 7.68	- 1.87	+ 2.18, +1.65 [CH(CH_3)$_2$] + 2.58 [CH(CH$_3$)$_2$]
2	*E*	- 2.32	- 0.93	+ 1.65	- 8.01	- 7.08	+ 2.04, +2.06 [CH(CH_3)$_2$] + 2.61 [CH(CH$_3$)$_2$]
	Z	- 8.15	- 0.81	+ 1.65	- 7.82	- 1.93	+ 2.21, + 1.84 [CH(CH_3)$_2$] + 2.82 [CH(CH$_3$)$_2$]
3	*E*	- 3.60	- 0.92	+ 1.87	- 7.70	- 6.86	+ 2.03, +2.24 [CH(CH_3)$_2$] - 2.57 [CH(CH$_3$)$_2$]
	Z	- 8.00	- 0.65	+ 1.87	- 7.70	- 3.09	+ 2.20, +1.95 [CH(CH_3)$_2$] - 2.82 [CH(CH$_3$)$_2$]
4	*E*	- 1.45	+ 0.01	+ 1.57	- 7.86	- 6.66	+ 2.02, +1.58 [CH(CH_3)$_2$] + 1.95 [CH(CH$_3$)$_2$]
	Z	- 7.48	- 0.32	+ 1.57	- 7.38	- 0.70	+ 2.36, + 2.10 [CH(CH_3)$_2$] + 3.26 [CH(CH$_3$)$_2$]

C(3) is considerably lower than that observed on C(5) indicating different conformation of isopropyl group at C(3) in *N*-acyl-3-isopropyl derivatives **1-4** compared to their corresponding parent 3-isopropyl-piperidin-4-one, **5**. For isopropyl group and C(4) carbons considerable deshielding has been observed due to *N*-acylation which also supports conformation other than normal chair conformation **CE** for these *N*-acyl-3-isopropyl derivatives **1-4**.

Comparison of shielding magnitude observed on *syn* α carbons [C(2) in *Z* isomer and C(6) in *E* isomer] and *anti* α carbons [C(6) in *Z* isomer and C(2) in *E* isomer] reveals the following order.

N-Formyl > *N*-acetyl > *N*-propanoyl > *N*-benzoyl (*syn* α carbon) *N*-Benzoyl < *N*-formyl ≈ *N*-acetyl < *N*-propanoyl (*anti* α carbon).

The bulky *N*-propanoyl group causes higher shielding magnitude on the nearby α carbon which lies on the same side of the ethyl group of the propanoyl moiety compared to other acyl groups of N-COR moiety.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400 and 100.6 MHz for ^{1}H and ^{13}C respectively. The ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY spectra were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. 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.

The compound *t*(3)-isopropyl-r(2),*c*(6)-bis(2′-furyl)piperidin-4-one, **5** was prepared according to the procedure described for the preparation of 2,6-diarylpiperidin-4-ones reported by Noller and Baliah[28]. A mixture of ammonium acetate (0.05 mol), furfuraldehyde (0.1 mol) and 4-methylpentan-2-one (0.05 mol) in distilled ethanol was heated first to boiling and then stirred under cold condition for 1 hr. To the viscous liquid obtained ether (200 mL) and concentrated hydrochloric acid (20 mL) were added. The precipitated hydrochloride 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 the addition of aqueous ammonia followed by dilution with water. It was recrystallised twice from benzene-petroleum ether mixture. Yield 9.6 g (calc. 13.65 g); m.p. 181-83°C; MS: *m/z* 273 ($M^{+\bullet}$), 258, 244, 229, 188, 174, 167, 96, 94, 85, 81, 68 and 44.

The *N*-formyl derivative **1** was prepared from **5** by adopting the general procedure described in the literature[19]. Formic acid (85%, 5 mL) was added slowly to cold acetic anhydride (10 mL) kept at about 5°C in a 50 mL round bottomed flask. After the addition was over, the mixture was heated to 60°C and then maintained at 50-60°C for 1 hr. The solution was then cooled to 5°C and added dropwise to a cold solution of the parent piperidone **5** (5 mmol) in dry benzene (50 mL) taken in a 250 mL round bottomed flask. The reaction mixture was stirred at 25°C for 8 hr after which it was poured into water. The organic layer was separated and dried over anhydrous sodium sulphate, partially concentrated and left for crystallisation. The crystals thus separated were purified by recrystallization from petroleum ether. Yield 0.8 g (calc. 1.51 g); m.p. 36-37°C; MS: *m/z* 300 $(M-1)^{+\bullet}$ 286, 273, 257, 216, 208, 174, 186, 91, 81, 68, 44 and 29.

The other *N*-acyl derivatives **2-4** were prepared by following the procedures reported in literature[29]. Equimolar amounts of acetic anhydride/ propanoic anhydride/benzoyl chloride (0.01 mol), parent piperidone **5** (0.01 mol) and triethylamine in benzene (50 mL) were refluxed for 4-10 hr. The progress of reaction was monitored by TLC. The precipitated ammonium salt was filtered off, the organic layer was washed with 2N HCl followed by water and then the solvent removed at low pressure. The *N*-acylpiperidones **2-4** obtained were purified by recrystallization from petroleum ether. **2**: Yield 2.2 g (calc. 3.15 g); m.p. 90-91°C; MS: *m/z* 315 ($M^{+\bullet}$), 300, 287, 272, 186, 174, 96, 92, 81, 66 and 43; **3**: Yield 2.1 g (calc. 3.29 g); m.p. 88-89°C; MS: *m/z*, 330 $(M-1)^{+\bullet}$ 314, 302, 285, 272, 244, 236, 174, 94, 85, 57 and 29; **4**: Yield 2.3 g (calc. 3.77 g); m.p. 60-61°C; MS: *m/z* 378 $(M+1)^{+\bullet}$ 362, 333, 300, 272, 188, 174, 105, 92, 85, 83, 44 and 29.

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