

Synthesis and spectral studies of some heteroarylpiperidin-4-ones and their derivatives

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The ^1H and ^{13}C NMR spectra have been recorded for *t*(3)-methyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **1**, *t*(3)-ethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **2**, *t*(3)-isopropyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **3**, *t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **4** and their derivatives **5-12** and analysed. The ^1H - ^1H COSY and ^1H - ^{13}C COSY spectra are recorded for *t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one oxime **8** and from the results boat conformation has been proposed for **8**. The possible conformations of ethyl group at C-3 in **2**, its oxime **6** and its hydrazone **12** have been suggested based on ^{13}C spectral data. The spectral data predict that the azine **10** exists as a pair of diastereoisomers in solution. An attempt to synthesise *t*(3)-carboxyethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **13** using ethyl acetoacetate as the ketone component has yielded an unexpected dihydropyridine namely 3,5-dicarboxyethyl-2,6-dimethyl-4-(2'-furyl)-1,4-dihydropyridine **14** (supported by spectral data) instead of the expected piperidin-4-one **13**.

Keywords: NMR data, 2,6-di-2'-furylpiperidin-4-one derivatives

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Many natural compounds and drugs contain the piperidine ring system as a structural element. As this class of compounds exhibits pharmacological properties¹ the elaboration of versatile, flexible regio- and stereo-selective synthesis of chiral piperidines is therefore of major interest to organic chemists². Since 2,6-disubstituted-4-piperidine derivatives are the constituents of a number of alkaloids which possess broad spectrum of biological activities,³ extensive studies have been made on the synthesis and stereo-dynamics of several *cis*-2,6-diphenyl-4-substituted piperidine derivatives⁴⁻¹⁰. However very few studies^{11,12} have been made on the preparation and stereochemistry of piperidines with varying ring size at 2 and 6 positions. The present investigation was focussed on the synthesis of piperidines in which 5-membered ring [furyl ring] was incorporated at 2 and 6 positions. In this paper we report the synthesis and detailed ^{13}C and ^1H NMR spectral studies of *t*(3)-methyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **1****, *t*(3)-ethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **2**, *t*(3)-isopropyl-

r(2),*c*(6)-di-2'-furylpiperidin-4-one **3**, *t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **4** and their derivatives **5-12**. An attempt to synthesise *t*(3)-carboxyethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **13** however yielded an unexpected dihydropyridine *i.e.*, 3,5-dicarboxyethyl-2,6-dimethyl-4-(2'-furyl)-1,4-dihydropyridine **14** which is confirmed by mass, ^1H , ^{13}C NMR and off-resonance spectra.

Results and Discussion

Analysis of spectra

The signals in the ^1H and ^{13}C NMR spectra were assigned based on their positions, integrals, multiplicities and on comparison with the corresponding signals observed in the closely related 3-alkyl- and 3,5-dimethyl-2,6-diphenylpiperidin-4-ones⁵ and their oximes⁷. For 3,5-dimethyl oxime **8** ^1H - ^1H COSY spectrum was also recorded to confirm the assignments. The COSY spectrum reveals that the downfield multiplet at 3.47 ppm which is unambiguously assigned to H-5 [*syn* to OH group] shows cross peak with the doublet at 3.82 ppm. Therefore, the doublet at 3.82 ppm is obviously due to H-6 only. The upfield multiplet at 2.92 ppm [H-3] shows cross

** (With reference to the substituent at the second position, the substituent at the sixth position, *i.e.*, furyl ring is *cis* and the substituent at the third position *i.e.*, methyl substituent is *trans*)

Table I — Coupling constants (Hz) of some 2,6-di-2'-furylpiperidin-4-ones **1-4** and their derivatives **5-12**

Compd	$J_{2,3}$	$J_{5,6}$	$J_{5a,5e}$	J_{H-CH_3}	$J_{H(3),H(7)}$
1	10.74	11.72 ($J_{6a,5a}$) 3.42 ($J_{6a,5e}$)	13.67	6.34	-
2	11.23	11.72 ($J_{6a,5a}$) 3.42 ($J_{6a,5e}$)	13.67	-	-
3	11.76	12.09 ($J_{6a,5a}$) 3.44 ($J_{6a,5e}$)	14.05	7.06 7.17	2.53
4	10.74	10.74	-	6.83	-
5	10.25	12.21 ($J_{6a,5a}$) 2.93 ($J_{6a,5e}$)	13.67	6.35	-
6	10.26	12.21 ($J_{6a,5a}$) 2.93 ($J_{6a,5e}$)	13.67	-	-
7	8.03	10.06 ($J_{6a,5a}$) 4.19 ($J_{6a,5e}$)	14.80	6.90 7.04	4.90
8	6.35	8.79	-	7.81 8.30	-
9	10.56	12.07 ($J_{6a,5a}$) 2.57 ($J_{6a,5e}$)	13.97	6.55	-
10	10.74 10.26	2.93 ($J_{6a,5e}$) 2.93 ($J_{6a,5e}$)	-	6.35	-
11	10.74	\approx 11.23 ($J_{6a,5a}$)	\approx 12.79	6.35	-
12	10.74	11.72 ($J_{6a,5a}$)	13.67	-	-

Table II — ^1H Chemical shifts (ppm) of some 2,6-di-2'-furylpiperidin-4-ones **1-4** and their derivatives **5-12**

Compd	H-2	H-3	H-5	H-6	Alkyl	NH	Other protons
1	3.80	2.88- 2.81	2.81-2.88 (<i>ax</i>) 2.72 (<i>eq</i>)	4.17	0.92	2.37	7.39-7.35 H(5)' and H(5)'' 6.34-6.29 H(4)' and H(4)'' 6.22 H(3)' and H(3)''
2	3.92	2.75- 2.69	2.84 (<i>ax</i>) 2.75-2.69 (<i>eq</i>)	4.16	0.80 (CH_2CH_3) 1.59; 1.28 (CH_2CH_3)	2.35	7.39-7.36 H(5)' and H(5)'' 6.34-6.29 H(4)' and H(4)'' 6.22-6.21 H(3)' and H(3)''
3	4.19	2.85- 2.79	2.85-2.79 (<i>ax</i>) 2.71 (<i>eq</i>)	4.22	0.79 (' CH_3 '); 1.05 (CH_3) 1.97 [$\text{CH}(\text{CH}_3)_2$]	1.71	7.41-7.29 2(H) 6.36-6.23 4(H)
4	3.75	2.94	2.94	3.75	0.91	2.27	7.38 H(5)' and H(5)'' 6.32 H(4)' and H(4)'' 6.27 H(3)' and H(3)''
5	3.63	2.66	2.12 (<i>ax</i>) 3.69 (<i>eq</i>)	3.90	0.90	\approx 1.7	8.77 (NOH) 7.30-7.27 H(5)' and H(5)'' 6.27-6.22 H(4)' and H(4)'' 6.18-6.17 H(3)' and H(3)''
6	3.95	2.72	2.31 (<i>ax</i>) 3.84 (<i>eq</i>)	4.07	0.98 (CH_2CH_3) 1.49; 1.69 (CH_2CH_3)	-	9.14 (NOH) 7.47-7.43 H(5)' and H(5)'' 6.42-6.39 H(4)' and H(4)'' 6.35 H(3)' and H(3)''
7	4.12	2.63- 2.58	2.63-2.58 (<i>ax</i>) 3.29 (<i>eq</i>)	4.08	0.80 (' CH_3 '); 1.06 (CH_3) 2.04 [$\text{CH}(\text{CH}_3)_2$]	1.56	6.98 (NOH) 7.31-7.26 2(H) 6.27-6.20 4(H)
8	3.88	2.92	3.47	3.82	1.22 1.20	2.17	9.16 (NOH) 7.26 H(5)' and H(5)'' 6.21 H(4)' and H(4)'' 6.16 H(3)' and H(3)''
9	3.63	2.63	2.14 (<i>ax</i>) 3.12 (<i>eq</i>)	3.93	0.92	1.88	7.33 H(5)' and H(5)'' 6.29-6.24 H(4)' and H(4)'' 6.22-6.20 H(3)' and H(3)''
10	3.67 3.65	2.70- 2.76	2.21-2.11 (<i>ax</i>) 3.36- 3.33 (<i>eq</i>)	3.86- 3.94	0.96	1.81	7.30-7.19 H(5)' and H(5)'' 6.26-6.21 H(4)' and H(4)'' 6.16-6.15 H(3)' and H(3)''
11	3.70	2.76	2.32 (<i>ax</i>) 3.08 (<i>eq</i>)	3.98	1.09	\approx 2.4	7.38-7.35 H(5)' and H(5)'' 6.33 H(4)' and H(4)'' 6.28 H(3)' and H(3)'' 7.07 H(2)''' and H(6)''' 7.24 H(3)''' and H(5)''' 6.83 H(4)'''
12	3.88	2.66	2.26 (<i>ax</i>) 3.43 (<i>eq</i>)	3.96	0.90 (CH_2CH_3) 1.77; 1.40 (CH_2CH_3)	2.16	7.36 H(5)' and H(5)'' 6.32-6.29 H(4)' and H(4)'' 6.21 H(3)' and H(3)''

Table III — ^{13}C Chemical shifts (ppm) some 2,6-di-2'-furylpiperidin-4-ones **1-4** and their derivatives **5-12**

Compd	C-2	C-3	C-4	C-5	C-6	Alkyl	Aromatic carbons
1	60.62	49.51	207.97	46.35	53.97	10.14	153.46, 154.14 [C(2)' and C(2)"] 141.99, 142.12 [C(5)' and C(5)"] 110.11, 110.05 [C(3)' and C(3)"] 107.51, 105.70 [C(4)' and C(4)"]
2	58.82	56.17	207.63	46.93	54.11	11.78 (CH_2CH_3) 18.17 (CH_2CH_3)	153.44, 154.16 [C(2)' and C(2)"] 142.06, 142.17 [C(5)' and C(5)"] 110.15 [C(3)' and C(3)"] 107.62, 105.78 [C(4)' and C(4)"]
3	56.64	59.51	207.24	47.21	53.69	19.97; 18.05 (CH_3) 26.01 [$\text{CH}(\text{CH}_3)_2$]	154.61; 154.0 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')
4	61.11	49.60	209.68	49.60	61.11	10.47	153.55 [C(2)' = C(2)"] 142.07 [C(5)' = C(5)"] 110.05 [C(3)' = C(3)"] 107.45 [C(4)' = C(4)"]
5	61.70	41.65	159.45	29.78	53.76	12.20	155.39, 154.54 [C(2)' and C(2)"] 142.32, 142.15 [C(5)' and C(5)"] 110.46, 110.41 [C(3)' and C(3)"] 107.83, 105.86 [C(4)' and C(4)"]
6	59.51	47.67	157.45	29.64	53.15	11.52 (CH_2CH_3) 19.34 (CH_2CH_3)	154.93, 154.02 [C(2)' and C(2)"] 141.92, 141.78 [C(5)' and C(5)"] 110.14 [C(3)' and C(3)"] 107.59, 105.63 [C(4)' and C(4)"]
7	56.10	50.92	157.68	30.87	51.94	20.05, 19.34 (CH_3) 27.95 [- $\text{CH}(\text{CH}_3)_2$]	155.18 C(2") and C(2') 141.69 C(5") and C(5') 110.16 C(3") and C(3') 107.03, 105.49 C(4") and C(4')
8	59.54	39.05	162.55	35.50	58.39	20.32 16.25	155.55, 155.23 [C(2)' and C(2)"] 141.95, 141.92 [C(5)' and C(5)"] 110.12, 110.06 [C(3)' and C(3)"] 106.27, 106.01 [C(4)' and C(4)"]
9	61.63	42.69	162.57	29.65	53.44	12.42	154.94, 152.53 [C(2)' and C(2)"] 141.86, [C(5)' and C(5)"] 110.10 [C(3)' and C(3)"] 107.20, 105.60 [C(4)' and C(4)"]
10	61.59 61.53	43.29 43.21	162.91 162.41	33.00 32.88	53.58 53.76	12.28	155.17, 155.23 [C(2)' and C(2)"] 141.88, 141.92 [C(5)' and C(5)"] 110.09, 110.03 [C(3)' and C(3)"] 107.31, 105.53 [C(4)' and C(4)"]
11	61.64	42.80	154.72	30.32	53.44	12.46	154.72 [C(2)' and C(2)"] 141.85 [C(5)' and C(5)"] 110.20, 110.05 [C(3)' and C(3)"] 107.24, 105.64 [C(4)' and C(4)"] 146.46, 145.85, 129.17, 119.76, 118.81 (aromatic carbons of phenyl ring)
12	59.71	49.86	161.34	33.54	53.62	12.00 (CH_2CH_3) 19.56 (CH_2CH_3)	155.23, 154.47 [C(2)' and C(2)"] 141.89 [C(5)' and C(5)"] 110.09 [C(3)' and C(3)"] 107.40, 105.43 [C(4)' and C(4)"]

peak with the doublet at 3.88 ppm and this confirms the assignment of the signal at 3.88 ppm for H-2. The assignment of the signals in the ^{13}C NMR spectrum of 3,5-dimethyloxime **8** is confirmed by recording ^1H - ^{13}C COSY spectrum.

The reaction of *t*(3)-ethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **2** with hydrazine hydrate yielded the corresponding hydrazone **12** whereas *t*(3)-methyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **1** yielded the azine **10** under the same experimental conditions instead of the expected hydrazone **9**. Probably, the hydrazone formed may be quantitatively converted into the azine **10** under the reaction conditions¹³. By altering the experimental conditions however it was

possible to prepare the expected hydrazone **9** along with a small amount of azine **10** and the signals however can be easily distinguished based on intensities and their positions. For the 3-methyl azine **10** two sets of signals were observed in the ^1H as well as in ^{13}C NMR spectra indicating the presence of two isomers in solution. The assignment of the signals for the furan ring in ^1H and ^{13}C NMR spectra were made from the multiplicities, known effect of electronegativity of oxygen atom and on comparison with that observed in 2-substituted furans^{14,15}. Further, the assignments were confirmed from the results obtained in the off-resonance spectra. The coupling constants were extracted using first order analysis and the values are

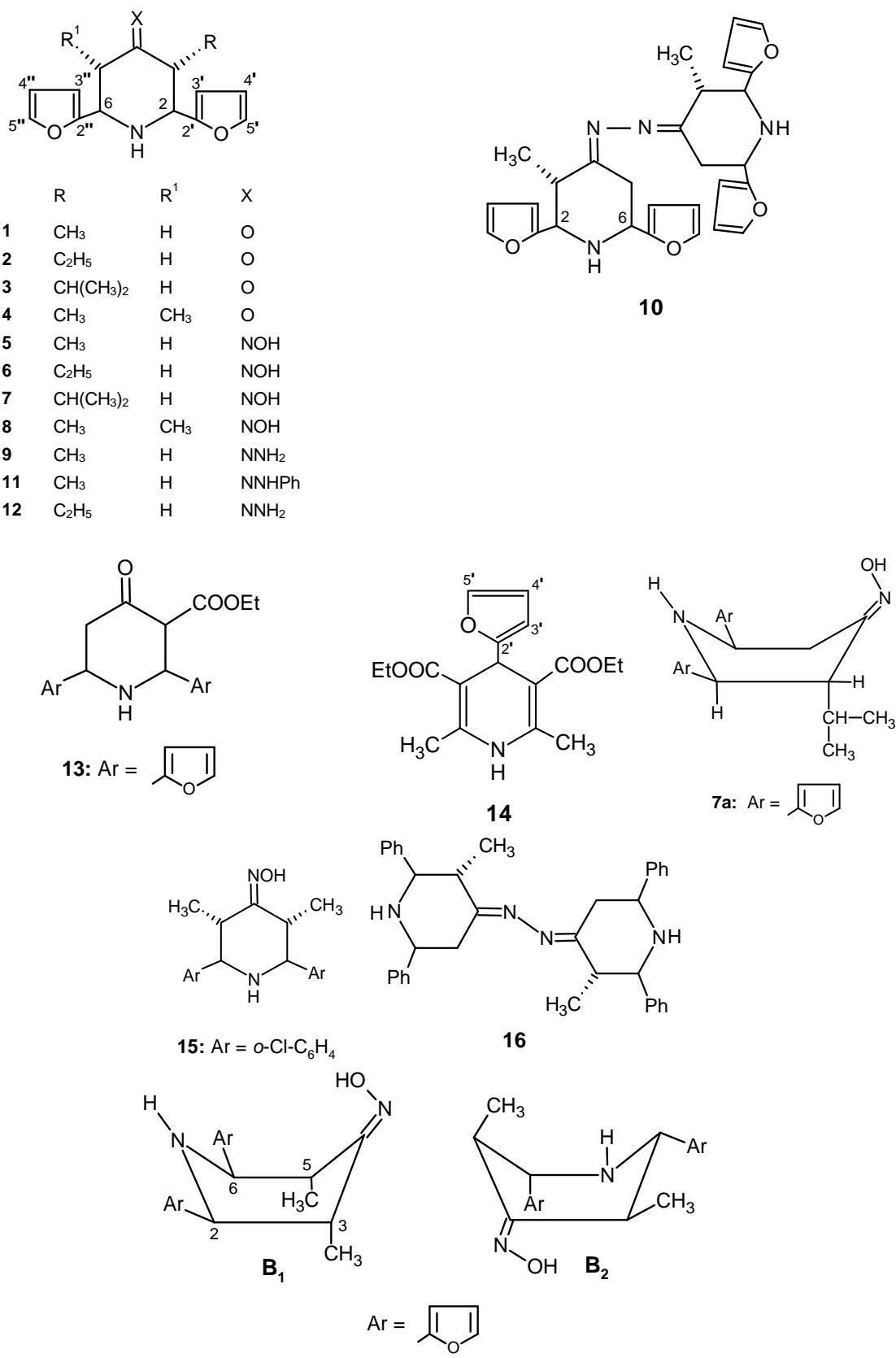


Figure 1

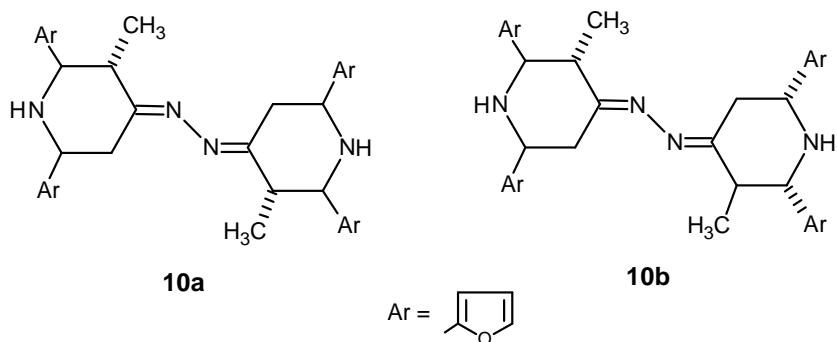


Figure 2

displayed in **Table I**. **Tables II** and **III** report ^1H and ^{13}C chemical shifts of **1-12**.

Ring conformations

The observation of large coupling about C(2)-C(3) bond in all the compounds except **8** reveals equatorial orientations of furyl rings at C-2 and alkyl groups at C-3 in these compounds. The large *trans* coupling about C(5)-C(6) bond (10-12 Hz) in **1-7** and **9, 11** and **12** also reveals equatorial orientations of furyl rings at C-6 in these derivatives. Hence, all these compounds exist in normal chair conformation with equatorial orientations of all the substituents. The coupling constants about C(2)-C(3) bond are considerably lower than the *trans* coupling about C(5)-C(6) bond [$J_{6a,5a}$] in these compounds which is in agreement with the observations already made in the closely related 2,6-diphenylpiperidine derivatives by Pandiarajan *et al.*^{5,7}. It is seen from the comparison of the coupling constants of oximes **5** and **6** and hydrazones **9** and **12** with those of **1** and **2** that oximation and hydrazone formation decreases the coupling about C(2)-C(3) bond [$J_{2a,3a}$]. The ring is probably highly flattened about C(2)-C(3) bond in 3-methyl derivatives **5** and **9** and 3-ethyl derivatives **6** and **12** compared to the corresponding piperidones **1** and **2**.

Comparison of the coupling constants about C(5)-C(6) bond in 3-isopropyl piperidone **3** with those of 3-isopropyl oxime **7** reveals that oximation increases *cis* coupling [4.19 Hz in **7**; 3.44 Hz in **3**] and decreases *trans* coupling to a greater extent [10.06 Hz in **7**; 12.09 Hz in **3**]. Moreover, the *trans* coupling about C(2)-C(3) bond is also decreased to a greater extent in 3-isopropyl oxime **7** compared with 3-isopropyl piperidone **3** [8.03 Hz in **7**; 11.76 Hz in **3**]. These observations cannot be accounted by simply flattening of the chair form since flattening affects the coupling constants to a smaller extent. The boat form **7a** may

contribute to the equilibrium significantly in 7. Similar observation has already been noted in *t*(3)-isopropyl-*r*(2),*c*(6)-diphenylpiperidin-4-one oxime by Pandiarajan *et al*¹⁶.

Comparison of the coupling constants in 3,5-dimethyl oxime **8** with those of 3-methyl oxime **5** reveals that $J_{2,3}$ is abnormally lower in **8** (6.35 Hz) relative to **5** (10.25 Hz). If 3,5-dimethyl oxime **8** adopts normal chair conformation similar to 3-methyl oxime **5** one should expect $J_{2,3}$ in **8** to be closer to that in **5**. The abnormal coupling constants suggest that the conformation of 3,5-dimethyl oxime **8** is different from normal chair conformation. In the normal chair conformation severe A^{1,3} strain exists between the oxime group and the *syn*-equatorial methyl group [C(5)-methyl] and in order to relieve the strain, the compound **8** adopts other than normal chair conformation. Pandiarajan *et al.*⁷ have reported highly distorted boat conformation for the closely related 3,5-dimethyl-2,6-diarylpiridin-4-one oxime **15** (aryl = *o*-ClC₆H₄) based on abnormal coupling constants (6.8 and 8.9 Hz) and chemical shift data. In the present study also similar distorted boat conformation **B**₁ (**Figure 1**) has been suggested for 3,5-dimethyl oxime **8**. In the undistorted boat form N-O bond will be completely eclipsed with the α (C-H) bonds and both the couplings ($J_{2,3}$ and $J_{5,6}$) and the torsional angles are expected to be 4 Hz and 120° respectively. However, to decrease the interaction between two axial like methyl groups and that between the α (C-H) and N-O bonds distortion occurs about C(5)-C(6) bond.

The observed coupling constants can also be accounted by the boat conformation **B**₂ also. In this conformation the coupling constants about C(5)-C(6) and C(2)-C(3) bonds are expected to be around 10 and 3 Hz respectively. The corresponding torsional angles are expected to be $\approx 180^\circ$ and $\approx 60^\circ$ respectively. Distortion of the boat form **B**₂ also can decrease the

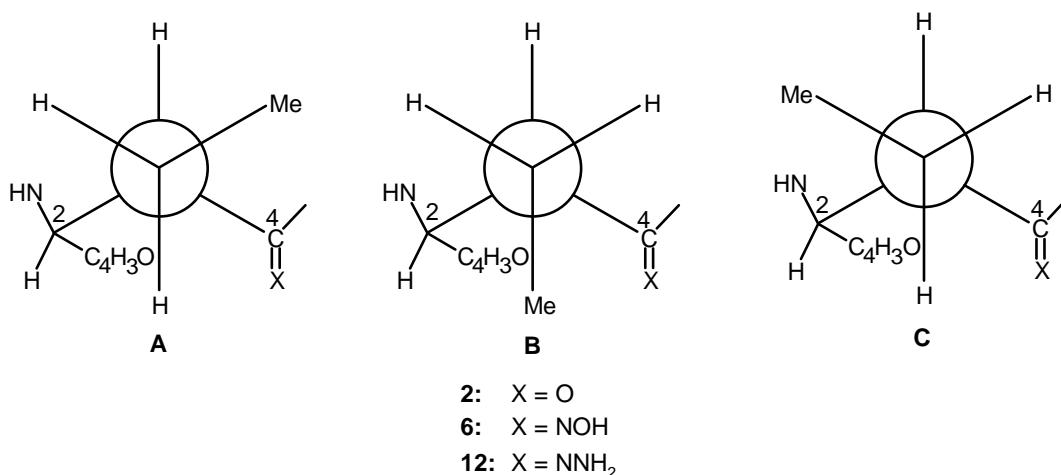
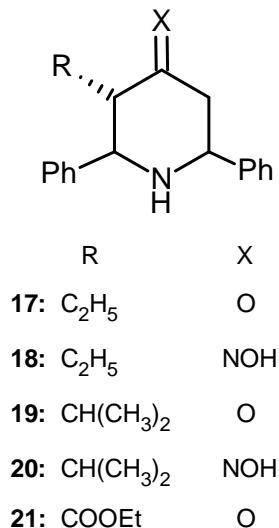


Figure 3



coupling from 10 to 8.79 Hz and increase the coupling from 3 to 6.35 Hz. To decide between these two possibilities torsional angles were calculated according to Haasnoot equation¹⁷. The torsional angles are 146.8° [$J = 8.79$ Hz] and 36.1° [$J = 6.35$ Hz] for the boat form **B**₂ and 146.8° [$J = 8.79$ Hz] and 133.5° [$J = 6.35$ Hz] for the boat form **B**₁. Simple distortion of the boat form **B**₂ cannot decrease the torsional angles from 180° to 146.8° and from 60° to 36.1°. However in the boat form **B**₁ slight distortion can easily change the torsional angle from 120° to 146.8° [$J = 8.79$ Hz] and 133.5° [$J = 6.35$ Hz]. Therefore, the favoured conformation for 3,5-dimethyl oxime **8** is predicted to be the boat form **B**₁.

In the azine **10** the observation of two sets of signals in the ^1H NMR spectrum clearly reveals the presence of two isomers. Recently Manimekalai

et al.¹⁸ have reported that the closely related heterocyclic azine **16** exists as an equilibrium mixture of diastereoisomers in solution and in both the forms the two C=N bonds are *S-trans* to each other in order to relieve A^{1,3} strain. For the azine **10** also, probably the different orientations of heterocyclic ring in space **Figure 2** are responsible for the observation of two sets of signals in the ¹H NMR spectrum. Thus, the azine **10** exists as an equilibrium mixture of diastereoisomeric forms **10a** and **10b**.

Conformations of alkyl groups

It is seen from **Table III** that replacement of methyl by ethyl group at C-3 shields both C-2 and C-4 carbons in 3-ethyl oxime **6** and 3-ethyl hydrazone **12**. However such replacement causes no change on C-4 but shields C-2 in 3-ethyl piperidone **2**. This suggests that the conformation of ethyl group at C-3 in **6** and **12** are different from that in **2**. The three possible conformations of the ethyl group at C-3 in the 3-ethyl piperidone **2** and its derivatives **6** and **12** [A, B and C] are shown in **Figure 3**.

In the conformation **B** the methyl group of the ethyl side chain is *gauche* with respect to both C-2 and C-4. The methyl group is *gauche* to C-4 and *anti* to C-2 in conformation **A** whereas it is *anti* to C-4 and *gauche* to C-2 in conformation **C**. The upfield shift observed on C-2 [-1.8 ppm] and absence of appreciable shift on C-4 carbon in **2** compared to **1** can be explained by the conformation **C** only. Therefore, **2** exists preferably in conformation **C** only. However, in **6** and **12** upfield shifts are observed on both C-2 and C-4 carbons compared to **5** and **9** thus predicting the conformation of ethyl group to be **B** in

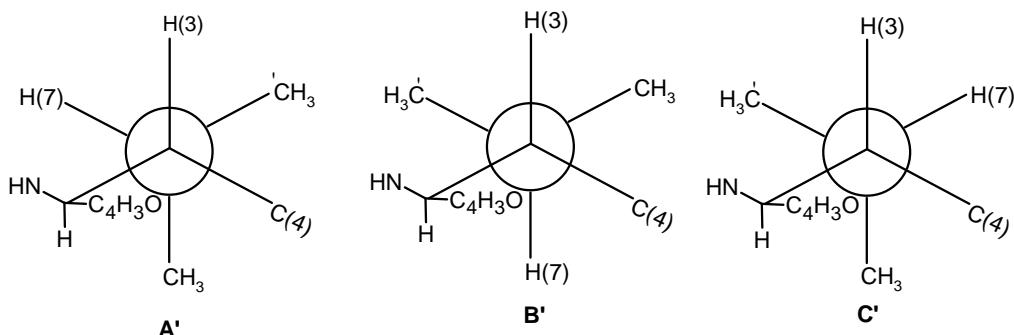


Figure 4

6 and **12**. Thus, the conformations of ethyl group in the 3-ethyl oxime **6** and 3-ethyl hydrazone **12** are different from 3-ethyl piperidone **2**. This is in contrast to the observation made in the closely related *t*(3)-ethyl-*r*(2),*c*(6)-diphenylpiperidin-4-one **17** and its oxime **18** by Pandiarajan *et al.*¹⁶ The conformation of ethyl group is predicted to be an equilibrium mixture of **A** and **B** in both **17** and **18**.

The three possible conformations **A'**, **B'** and **C'** for 3-isopropyl piperidone **3** and its oxime **7** are shown in Figure 4. In conformations **A'** and **C'** the H-7 is gauche to the methine proton at C-3 *i.e.*, H-3 and therefore, the $J_{H(7),H(3)}$ should be around 4 Hz in **A'** and **C'**. In conformation **B'**, the H-7 proton is *anti* to methine proton at C-3 and hence the $J_{H(7),H(3)}$ should be around 10-12 Hz. The observed $J_{H(7),H(3)}$ coupling constants [2.53 Hz **3**; 4.9 Hz **7**] ruled out the possibility of existing in conformation **B'**. In conformation **C'** there is severe interaction between the two methyl groups and the groups at C-2. Therefore, the preferred conformation around C(3)-CH(CH₃)₂ bond for isopropyl group should be **A'** in **3** and **7**. Similar conformation has also been reported by Pandiarajan *et al.*¹⁶ for the closely related *t*(3)-isopropyl-*r*(2),*c*(6)-diphenylpiperidin-4-one **19** and its oxime **20**.

A detailed study regarding the conformations of ethyl group in 3-ethyl-2,6-diphenylpiperidine, the corresponding piperidin-4-one and its oxime¹⁶ has shown that the conformational preference of 3-ethyl group is not influenced by the change in the functional group at C-4. However, a report from ¹³C shifts of the corresponding alcohols by Manimekalai and Rajarajan¹⁹ reveals that the orientation of hydroxyl group at C-4 influences the conformational preference of ethyl group at C-3 in epimers. The present study also supports that the conformational preference of ethyl group is influenced by nearby groups.

Chemical shifts

The H-2 protons resonate considerably at downfield in 3-ethyl piperidone **2** and its derivatives **6** and **12** compared to the 3-methyl piperidone **1** and its derivatives **5** and **9**. This is probably due to the *gauche* conformation of ethyl group at C-3 Figure 3. It is seen from Table II that oxime, hydrazone and azine formations shield all heterocyclic ring protons except H_{5e} in **5-7** and **9-12**. The shielding magnitude observed on H_{5a} in **5-7** and **9-12** are considerably greater than those observed on other protons. The equatorial protons at C-5 [H_{5e}] resonate considerably at downfield in **5** [+0.97 ppm], **6** [≈ 1.1 ppm], **7** [+0.58 ppm], **9** [+0.4 ppm], **10** [≈+0.6 ppm], **11** [+0.36 ppm] and **12** [≈+0.7 ppm] compared to the corresponding piperidones **1-3**. The observed downfield and upfield resonances of H_{5e} and H_{5a} in **5-7** and **9-12** can be explained as follows.

In hydrazone, azine and oximes severe interaction exists between N-N/N-O bond and equatorial *syn*- α (C-H) bond. Due to these interactions the equatorial *syn*- α (C-H) bond is said to be polarised. As a result of this polarisation the equatorial hydrogen acquires a slight positive charge and the *syn* α -carbon acquires a slight negative charge. Indeed ¹³C spectral data (Table III) also confirms greater shielding of *syn* α -carbon *i.e.*, C-5 due to oxime, azine and hydrazone formations. The negative charge on the *syn* α -carbon [C-5] is transmitted to *syn* α -axial hydrogen [H_{5a}] and *syn* β -carbon [C-6] to some extent. Therefore, axial hydrogen at C-5 is shielded whereas equatorial hydrogen at C-5 is deshielded due to azine, hydrazone and oxime formations. Similar explanation has been offered in some oxime and azines^{7,18} for the greater downfield resonance of H_{5e} and upfield resonance of H_{5a} due to oximation and azine formation.

Table III reveals that oximation shields all heterocyclic ring carbons except C-2. Hydrazone and azine formation also has similar effect on the heterocyclic ring carbons. The $>\text{C}=\text{N}$ group in oxime, azine and hydrazone is less polar compared to $>\text{C}=\text{O}$ group. It has been previously reported²⁰ that decrease in electronegativity is expected to shield α carbon but deshield β and γ carbons. Thus, the shielding magnitude observed on C-3 and C-5 carbons [α carbons] and deshielding observed on C-2 [β carbons] in **5-7, 9-12** relative to **1-3** are in accordance with the lower electronegativity of $>\text{C}=\text{N}$ group compared to $>\text{C}=\text{O}$ group. The shielding magnitude observed on C-5 (≈ 17 ppm) due to oximation and hydrazone formation is considerably greater than those observed on C-3 ($\approx 8\text{-}9$ ppm). The higher shielding magnitude observed on C-5 is already explained in terms of steric polarisation of oxime or azine group with the equatorial *syn* α (C-H) bond.

The ^1H and ^{13}C chemical shifts of 3,5-dimethyl oxime **8** are also in agreement with the boat conformation **B₁** for **8**. If **8** adopts chair conformation similar to the 3-methyl oxime **5** then the chemical shift of H-5 should be closer to that observed on H_{5a} in **5**. However, the observed value of H-5 in **8** [3.47 ppm] is significantly different from that of H_{5a} in **5** [2.12 ppm]. It is inferred from **Table III** that the methyl carbons at C-3 and C-5 in **8** resonate considerably at downfield (20.32, 16.25 ppm) compared to **5** [12.20 ppm]. Moreover, oximation (conversion of keto group to oxime group) also deshields these carbons to a greater extent in **8** [+9.85 ppm, +5.78 ppm] compared to **5** [+2.06 ppm]. All these observations also support boat conformation for the 3,5-dimethyl oxime **8**.

Spectral studies on dihydropyridine **14**

Ethyl acetoacetate on condensation with benzaldehyde and ammonium acetate yielded *t*(3)-carboxyethyl-*r*(2),*c*(6)-diphenylpiperidin-4-one **21** and NMR studies have shown that this piperidin-4-one exists mainly in the keto form⁸. Under the same conditions furfuraldehyde yielded an unexpected dihydropyridine *i.e.*, 3,5-dicarboxyethyl-2,6-dimethyl-4-(2'-furyl)-1,4-dihydropyridine **14** instead of the expected *t*(3)-carboxyethyl-*r*(2),*c*(6)-di-2'-furylpiperidin-4-one **13**.

The presence of two signals for methyl group, one signal for methylene group and one signal for methine group confirms that the product formed during the condensation reaction of ethyl acetoacetate with

furfuraldehyde and ammonium acetate is the 3,5-dicarboxyethyl-2,6-dimethyl-4-(2'-furyl)-1,4-dihydropyridine **14**. The spectral data of the dihydropyridine **14** are: ^1H NMR: δ 5.20 (H-4), 2.32 (CH₃) (C-2 and C-6), 4.18 (COOCH₂CH₃), 1.26 (COOCH₂CH₃), 5.94 (H-3'), 6.21 (H-4'), 7.21 (H-5') and 5.98 ppm (NH). ^{13}C NMR: δ 145.12 (C-2 and C-6), 100.59 (C-3 and C-5), 33.33 (C-4), 19.43 (CH₃) (C-2 and C-6), 59.76 (COOCH₂CH₃), 14.27 (COOCH₂CH₃), 167.45 (COOCH₂CH₃), 158.63 (C-2'), 109.04₊ (C-3') and 104.37 ppm (C-4'). Mass: m/e 319 (M⁺) 304, 390, 274, 262, 246, 174, 77 and 67.

Experimental Section

Preparation of piperidin-4-ones 1-4. The general procedure reported for the preparation of 3-alkyl- and 3,5-dialkyl-2,6-diphenylpiperidin-4-ones by Noller and Baliah⁴ was followed except the fact that furfuraldehyde is used as the aldehydic component instead of benzaldehyde and the reaction is carried out at 40°C. Recrystallisation from ethanol gave colourless crystals of **1** yield: 70%, m.p. 40°C, IR (KBr): 3317 (v_{N-H}), 1708 (v_{C=O}) and 1151 cm⁻¹ (v_{C-O-C}); **2** yield: 80%, m.p. 47°C, IR (KBr): 3293 (v_{N-H}), 1706 (v_{C=O}) and 1151 cm⁻¹ (v_{C-O-C}); **3** yield: 65%, m.p. 182°C, IR (KBr): 3287 (v_{N-H}), 1704 (v_{C=O}) and 1153 cm⁻¹ (v_{C-O-C}) and **4** yield: 70%, m.p. 57°C, IR (KBr): 3312 (v_{N-H}), 1704 (v_{C=O}) and 1151 cm⁻¹ (v_{C-O-C}).

Preparation of piperidin-4-one oximes 5-8. The general procedure reported for oximation⁷ was followed to get the oximes **5-8**. Recrystallisation from ethanol gave pure crystals of **5** yield: 70%, m.p. 112°C, IR (KBr): 3729 (v_{O-H}), 3141 (v_{N-H}), 1678 (v_{C=N}) and 937 cm⁻¹ (v_{N-O}); **6** yield: 70%, m.p. 110°C, IR (KBr): 3727 (v_{O-H}), 3150 (v_{N-H}), 1667 (v_{C=N}) and 948 cm⁻¹ (v_{N-O}); **7** yield: 70%, m.p. 198°C, IR (KBr): 3307 (v_{O-H} and v_{N-H}), 1612 (v_{C=N}) and 955 cm⁻¹ (v_{N-O}) and **8** yield: 70%, m.p. 91°C, IR (KBr): 3670 (v_{O-H}), 3275 (v_{N-H}), 1659 (v_{C=N}) and 942 cm⁻¹ (v_{N-O}).

Preparation of hydrazones and azine 9-12. The 3-methyl azine **10** and 3-methylphenylhydrazone **11** were prepared by warming **1** (2.45 g, 10 mmole) and hydrazine hydrate (0.5 g, 10 mmole)/phenylhydrazine hydrochloride (1.08 g, 10 mmole) in ethanol (30 mL) followed by stirring for 3 hr. The contents were concentrated and cooled to get colourless crystalline products. Recrystallisation from ethanol yielded colourless crystals of **10** yield: 80%, m.p. 196°C, IR (KBr): 3120 (v_{N-H}), 1635 (v_{C=N}) and 1149

cm⁻¹ (ν_{N-N}) and **11** yield, 80%, m.p. 112°C, IR (KBr): 3115 (ν_{N-H}), 1600 ($\nu_{C=N}$) and 1151 cm⁻¹ (ν_{N-N}).

The 3-methyl hydrazone **9** was prepared from **1** and hydrazine hydrate by adopting the same procedure mentioned above except the fact that the reaction was done at room temperature and stirring was done for 15 min. The product obtained as colourless crystals was purified by column chromatography and recrystallised from ethanol-chloroform (1:1) mixture. It melted at 152°C. Yield 60%, IR (KBr) 3383 (ν_{N-H}), 1634 ($\nu_{C=N}$) and 1149 cm⁻¹ (ν_{N-N}).

The 3-ethyl hydrazone **12** was prepared by warming **2** (2.59 g, 10 mmole) and hydrazine hydrate (0.5 g, 10 mmole) in ethanol (30 mL) in the presence of sodium acetate (3.28 g, 40 mmole) followed by stirring for 3 h by maintaining the temperature at 40°C. The product obtained as colourless crystals was recrystallised from ethanol. It melted at 140°C. Yield 80%, IR (KBr): 3070 (ν_{N-H}), 1618 ($\nu_{C=N}$) and 1145 cm⁻¹ (ν_{N-N}).

Preparation of dihydropyridine 14. A mixture of ethyl acetoacetate (0.88 g, 10 mmole), furfuraldehyde (1.92 g, 20 mmole) and ammonium acetate (0.77 g, 10 mmole) in distilled ethanol (30 mL) was heated to boiling and the mixture was kept aside over night. The dihydropyridine **14** separated as white needles alongwith resinous material was washed with petroleum-ether (40-60°C) several times and the dihydropyridine **14** obtained was recrystallised twice from ethanol. Yield 60%, m.p. 128°C, IR (KBr): 3346 (ν_{N-H}), 1700 ($\nu_{C=O}$), 1209 (ν_{C-O-C} of carboxyethyl group) and 1120 and 1096 cm⁻¹ (ν_{C-O-C}) of furan ring.

Spectral measurements. Proton spectra and proton decoupled ¹³C NMR spectra were recorded on a JEOL GSX-400 NMR instrument operating at 400 and 100 MHz respectively. ¹H-¹H COSY spectrum was recorded on a AMX-300 NMR spectrometer at 300 MHz using the standard pulse sequences employing the TPPI method to obtain pure absorption mode spectra. The experimental parameters are: number of scans 2; acquisition time 0.17s and spectral width 6009 Hz. ¹H-¹³C COSY spectrum was obtained on a DRX-500 NMR spectrometer using standard parameters: the number of scans 32; number of data points 2048; acquisition time 0.17s and spectral width 6009 Hz.

IR spectra were recorded on a NICOLET AVATAR 360 FT-IR spectrometer. The sample was mixed with KBr and the pellet technique was adopted to record the spectra. Mass spectrum (EI) was recorded using Finnigan Mat 8230 mass spectrometer with a sensitivity of 0.3 ng at 70 eV with a direct inlet system and the inlet temperature was maintained at 100°C.

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