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NMR spectral study of some 2r,6c-diarylpiperidin-4-one (3′-hydroxy-2′-naphthoyl)hydrazones with special reference to γ-syn effect

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ABSTRACT

^{1}H and ^{13}C NMR spectra have been recorded for 2r,6c-diarylpiperidin-4-one (3′-hydroxy-2′-naphthoyl)hydrazones **10–17** and 3,3-dimethyl-2r,6c-bis(p-methoxyphenyl)piperidin-4-one (**5**). For selected compounds 2D NMR spectra have been recorded. The spectral data along with those reported for related compounds are used to study the effect of a heteroatom X on the ^{13}C chemical shift of a γ-carbon with X C_α C_β C_γ torsional angle close to 0°, termed as γ-syn effect. Also γ-gauche and δ-effects of the alkyl groups at C-3 on the carbons of the aryl group at C-2 have been studied. The chemical shifts for the naphthalene ring are in accord with the mesomeric and steric effects of the carbonyl and hydroxy groups.

1. Introduction

Nuclear magnetic resonance spectroscopy has been widely used in the study of organic compounds [1–18] and reviews [19,20] also have appeared on this subject. ^{1}H chemical shifts are influenced by electronic, steric and magnetic anisotropic effects whereas ^{13}C chemical shifts are largely influenced by electronic and steric effects. The α, β, γ-gauche, γ-anti and δ effects of substituents on the chemical shifts of ring carbons in saturated six-membered ring compounds have been well discussed [21–23].

In cyclohexanones, adopting chair conformations, the carbon of an equatorial alkyl group attached to the ring carbon adjacent to the carbonyl group, will be at the γ-position with respect to the carbonyl oxygen. Also this carbon should be coplanar with the CC=O plane and its chemical shift should be influenced by the carbonyl oxygen. A similar effect can be expected in oximes and hydrazones with a nitrogen atom instead of the oxygen atom. Though ^{13}C NMR spectral data are available for large number of such compounds, in no study this effect has been addressed. Also the effect of substituent on a δ-carbon in close proximity, has not been studied.

The derivatives of 3-hydroxy-2-naphthoic acid hydrazide (**1**) have been found to possess valuable biological activities [24–27]. Though NMR spectral data of the derivatives of **1** have been reported [27,28] the signals of the naphthalene ring have not been assigned using 2D spectra.

In the present study, the above-mentioned aspects are investigated using the NMR spectral data of piperidin-4-one **5**, hydrazones **10–17** and related compounds reported in the literature.

2. Results and discussion

2.1. Assignments of NMR signals

The numbering of carbon atoms in **10–17** is shown in Scheme 1. Protons are numbered accordingly. Thus, the proton at C-2 is denoted as H-2 and that at C-5′ is denoted as H-5′. The atoms in **5** also are numbered accordingly.

For **5**, **13**, **16** and **17** the signals were assigned based on the correlations in the 2D spectra. For **10**, **11**, **12**, **14** and **15** the signals were assigned by comparison with **13** and using known effects [29,30] of the CH_3, OMe and Cl substituents in the aryl rings. The observed ^{1}H and ^{13}C chemical shifts are given in Tables 1 and 2, respectively. The chemical shifts of naphthalene also are given for comparison. The ^{1}H–^{1}H coupling constants are given in Table 3.

2.2. Conformation of the piperidine ring

Based on a previous study [5], piperidin-4-ones **2–9** should exist in chair conformations **2C–9C**. In these conformations the aryl groups are equatorial and the alkyl group at C-3 is equatorial in the 3t-alkyl compounds. The observed vicinal coupling constants

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Table 1
^{1}H chemical shifts (ppm) of **5** and **10–17**.

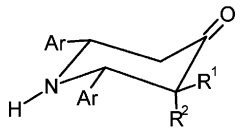
Proton	Compound									
	5	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	Naphthalene
NH, OH	–	11.46	11.45	11.63	11.42	11.44	11.48	11.48	11.46	
H-2a	3.76	3.57	3.57	3.51	3.70	3.78	3.73	3.69	3.43	
H-3a	–	2.64	2.64	2.57	–	–	–	2.51	2.55	
H-5e	2.26	3.07	3.06	3.02	2.87	2.90	2.87	3.03	2.99	
H-5a	2.84	2.33	2.32	2.27	2.41	2.38	2.41	2.30	2.39	
H-6a	3.94	3.93	3.93	3.86	3.82	3.89	3.84	3.93	4.34	
H-1′	–	8.54	8.53	8.56	8.53	8.52	8.53	8.54	8.52	(7.84)
H-4′	–	7.31	7.31	7.29	7.28	7.29	7.28	7.29	7.28	(7.84)
H-5′	–	7.73	7.73	7.70	7.72	7.73	7.72	7.71	7.71	(7.84)
H-6′	–	7.52	7.52	7.47	7.47	7.48	7.48	7.49	7.51	(7.48)
H-7′	–	7.34	7.34	7.31	7.34	7.40	7.33	7.32	7.36	(7.48)
H-8′	–	7.93	7.93	7.93	7.93	7.93	7.93	7.92	7.91	(7.84)
H-2″ and H-6″	7.35	7.51	7.50	7.38	7.36	7.49	7.34	7.49	7.48	
H-2‴ and H-6‴	7.44	7.52	7.52	7.39	7.48	7.60	7.44	7.49	7.50	
H-3″ and H-5″	6.91	7.36	7.36	6.87	6.90	7.40	7.14	7.32	7.34	
H-3‴ and H-5‴	6.91	7.38	7.38	6.91	6.92	7.43	7.17	7.37	7.35	
H-4″ and H-4‴	–	7.28	–	–	–	–	–	7.24, 7.29	7.25, 7.27	
3-Alkyl protons	0.80	0.88	0.88	0.93	1.04	1.05	1.05	1.23 (CH_2)	1.89 (CH)	
	1.06				1.13	1.12	1.13	0.83 (CH_3)	1.11, 1.05 (CH_3)	
p-OCH_3	3.77	–	–	3.75	3.75	–	–	–	–	
				3.72	3.72					
p-CH_3	–	–	–	–	–	–	2.30	–	–	

Chemical shifts of naphthalene [33] are given in the parentheses.

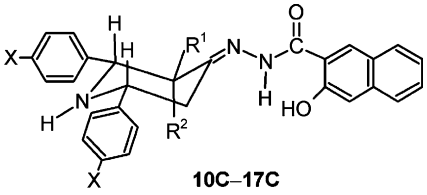
suggest that hydrazones **10–17** also must adopt such chair conformations.

2.3. Configuration about the C=N bond

Compared to **5**, in **13** H-5e is deshielded by 0.51 ppm and H-5a is shielded by 0.43 ppm. Also, C-5 is shielded by 13.7 ppm whereas C-3 is shielded only by 6.7 ppm. These observations are similar to those made in 3t-alkyl-2r,6c-diarylpiperidin-4-one oximes [3] with E configuration about the C=N bond. Obviously, in **13** the configuration about C=N bond is E. In the other hydrazones also H–5e has a higher chemical shift than H–5a and C–5 has a lower chemical shift than C–3. Hence, in all the hydrazones the configuration about the C=N bond should be E. Therefore, hydrazones **10–17** must exist in chair conformations **10C–17C**.



2C–9C



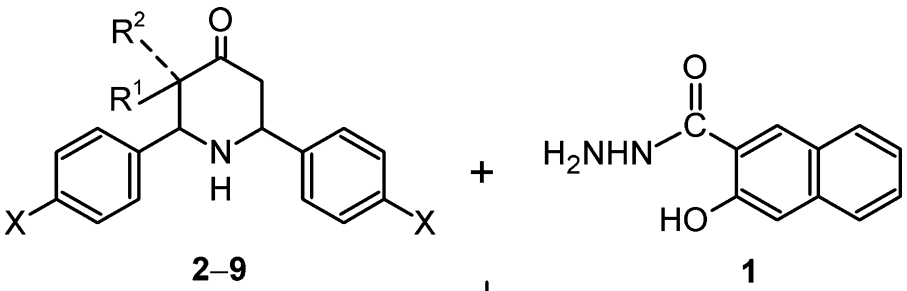
10C–17C

	R^1	R^2	X
2C;	CH_3	H	H
3C;	CH_3	H	Cl
4C;	CH_3	H	OCH_3
5C;	CH_3	CH_3	OCH_3
6C;	CH_3	CH_3	Cl
7C;	CH_3	CH_3	CH_3
8C;	CH_2CH_3	H	H
9C;	$CH(CH_3)_2$	H	H

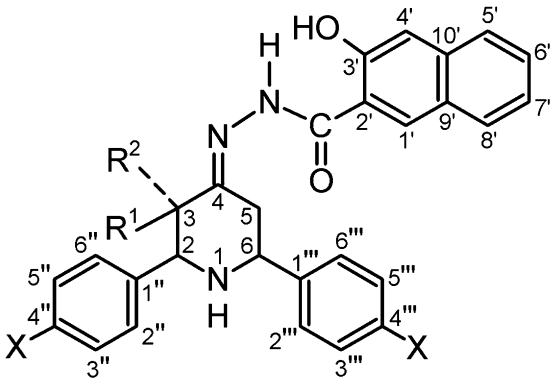
	R^1	R^2	X
10C;	CH_3	H	H
11C;	CH_3	H	Cl
12C;	CH_3	H	OCH_3
13C;	CH_3	CH_3	OCH_3
14C;	CH_3	CH_3	Cl
15C;	CH_3	CH_3	CH_3
16C;	CH_2CH_3	H	H
17C;	$CH(CH_3)_2$	H	H

2.4. Conformation of the NHCO (3′-hydroxynaphthyl) moiety

The NHCO (3′-hydroxynaphthyl) moiety in **10–17** can adopt eight conformations due to rotation about N–N, CO–NH and CO–C(2′) bonds. In related hydrazones, among the two possible rotamers about the N–N bond, the anti form (C=N and NCO bonds are anti) has been found to be stable [6,9]. The two rotamers about the CO–NH bond have been found to give rise to distinct NMR signals [9,32]. Also, in the E-forms of N-isonicotinylhydrazones [31] the equatorial methyl protons have been found to be shielded markedly by the magnetic anisotropic effect of the aromatic group attached to carbonyl group. In **10–17** such a shielding is not observed. Hence, it can be concluded that hydrazones **10–17** exist in the Z-form about the CO–NH bond in solution. Thus, two rotamers R1 and R2 may be considered for the hydrazones. In R1 there can be N–H···O intramolecular hydrogen bonding whereas in R2 there can be C=O···H–O intramolecular hydrogen bonding. In salicylamide [7] and related compounds [6,7,9] separate signals have been observed for OH and NH protons. However, only one signal is observed for NH and OH protons in **10–17**. This shows that there is a fast exchange between OH and NH protons. Hence, we suggest that, compounds **10–17** may exist as rotamer R1 rather than as rotamer R2. In R1



Methanol | Acetic acid

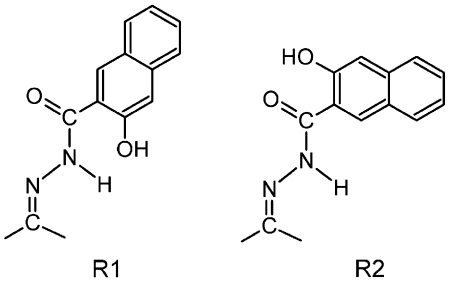


10–17

	R^1	R^2	X
2, **10**;	CH_3	H	H
3, **11**;	CH_3	H	Cl
4, **12**;	CH_3	H	OCH_3
5, **13**;	CH_3	CH_3	OCH_3
6, **14**;	CH_3	CH_3	Cl
7, **15**;	CH_3	CH_3	CH_3
8, **16**;	CH_2CH_3	H	H
9, **17**;	$CH(CH_3)_2$	H	H

Scheme 1. Synthesis of 2r,6c-diarylpiperidin-4-one (3′-hydroxy-2′-naphthoyl)hydrazones.

the exchange between OH and NH protons should be faster than in R2.



2.5. ^{13}C chemical shifts of the methyl groups at C-3

3t-Alkyl-2r,6c-diphenylpiperidines (**18–20**) have been shown to adopt chair conformations with equatorial orientations of the substituents, based on the observed vicinal coupling constants [32]. The chemical shift of the methyl carbon in **18** has been found as 18.7 ppm [32]. However, the methyl carbon appears at 13.0 ppm in **10** and 10.1 ppm in **2** [1]. Also, the chemical shift of the methyl carbon is 14.8 ppm in 2-methylcyclohexanone (**21**) [33] but 23.0 ppm in methylcyclohexane (**22**) [33]. These observations can be explained as follows.

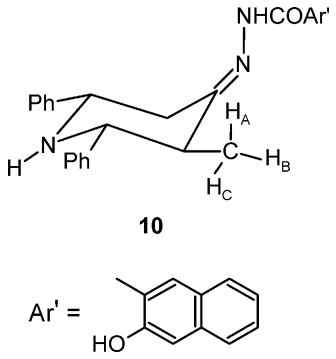
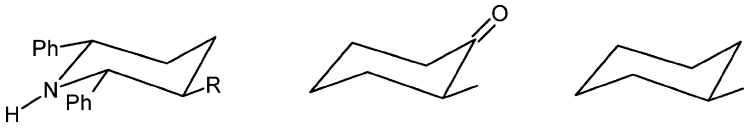


Fig. 1. Conformations of the methyl group in **2**, **10** and **18**.



18; R = CH_3
19; R = CH_2CH_3
20; R = $CH(CH_3)_2$

The conformation of the methyl group in **10** is shown in Fig. 1. It is seen that the nitrogen atom of the C=N group can polarize C–H_A and C–H_B bonds so that H_A and H_B get partial positive charges and the methyl carbon gets a partial negative charge. The negative charge on the carbon shields it. In **2** this shielding is larger due to the greater electronegativity of oxygen than nitrogen. Hence, the chemical shift of the methyl carbon increases in the order **2** < **10** < **18**. Since **21** and **22** should adopt chair conformations with equatorial methyl group the chemical shift of the methyl carbon in **21** is much less than that in **22**. It is also interesting to note that in 4-methylcyclohexanone the methyl carbon appears at 21.0 ppm [33].

In 3t,5c-dimethyl-2r,6c-diphenylpiperidine (**24**) the chemical shifts of the axial and equatorial methyl carbons have been found as 12.8 and 18.6 ppm, respectively [32]. This is because the axial methyl carbon is gauche to the nitrogen atom and the methylene carbon C-5. In ketone **5** and hydrazones **13–15** the axial methyl carbon is subjected to similar gauche interactions. In addition the equatorial methyl group exerts a β-effect on this methyl carbon. The axial methyl group exerts a similar β-effect on the equatorial methyl carbon. Based on this, one must expect that in the 3,3-dimethyl compounds **5**, **13**, **14** and **15** the axial and equatorial methyl carbons should differ in their chemical shifts by about 6.0 ppm. However, the observed difference is quite small. The CH bonds of the axial methyl group are far away from the carbonyl oxygen in the ketone or nitrogen of the C=N group in the hydrazones. Hence, the axial methyl carbon is not shielded by the interaction of the carbonyl oxygen in the ketone or the nitrogen of the C=N group in the hydrazones. The shielding experienced by the equatorial methyl carbon is almost the same as the shielding experienced by the axial methyl carbon due to the γ-gauche effects.

Table 2
^{13}C chemical shifts (ppm) of **5** and **10–17**.

Carbon	Compound									
	5	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	Naphthalene
–C=O	–	162.3	162.5	162.1	162.1	162.6	162.5	162.6	161.9	
C-2	68.4	69.0	69.0	68.3	69.1	69.3	70.0	67.2	63.7	
C-3	49.6	45.1	45.1	45.1	42.9	43.2	43.4	51.8	54.8	
C-4	212.6	162.5	162.5	162.5	165.7	165.3	165.9	161.0	160.0	
C-5	47.1	37.4	37.4	37.3	33.4	33.7	33.9	37.7	36.9	
C-6	60.4	60.4	60.4	59.8	59.6	59.8	60.5	60.4	58.1	
C-1′	–	131.9	131.9	131.9	131.3	131.8	131.9	131.9	131.5	(127.8)
C-2′	–	121.4	121.4	121.4	120.7	121.3	121.3	121.4	120.7	(125.8)
C-3′	–	153.7	153.7	154.1	153.3	153.6	153.7	153.9	153.2	(125.8)
C-4′	–	111.0	111.0	111.0	110.5	111.0	111.0	111.0	110.5	(127.8)
C-5′	–	126.1	126.1	126.1	125.6	126.2	126.1	126.2	126.7	(127.8)
C-6′	–	127.9	127.9	128.4	128.0	127.9	127.5	127.5	127.7	(125.8)
C-7′	–	124.2	124.2	124.0	123.6	124.2	124.2	124.2	123.7	(125.8)
C-8′	–	128.4	128.7	128.4	128.7	128.8	128.6	128.7	128.8	(127.8)
C-9′	–	127.1	127.5	127.4	126.9	127.5	127.2	127.8	127.2	(133.5)
C-10′	–	136.1	136.1	135.3	135.6	136.1	136.1	136.2	135.7	(133.5)
C-1″	131.0	143.4	143.5	136.2	132.4	138.8	137.9	143.5	144.4	
C-1‴	136.1	143.5	143.6	136.2	136.2	143.6	141.6	144.3	144.4	
C-2″, C-6″	130.2	128.8	128.8	129.3	129.9	131.3	129.4	128.8	128.3	
C-2‴, C-6‴	128.3	127.8	127.3	128.5	127.9	128.6	128.5	127.3	127.3	
C-3″, C-5″	113.4	128.7	127.8	114.0	112.8	129.3	128.5	128.6	128.2	
C-3‴, C-5‴	114.1	128.6	128.4	114.1	113.7	128.6	129.3	128.5	128.0	
C-4″, C-4‴	149.0	127.3	129.3	159.0	158.4	132.2	136.7	127.9	127.0	
		127.5	131.9		158.5	132.3	136.9	127.8	125.7	
3-Alkyl carbons	20.2	13.0	13.0	13.0	23.4	23.3	21.7	19.5 (CH_2)	28.5 (CH)	
	21.1				21.7	21.6	21.2	12.5 (CH_3)	21.0, 18.8 (CH_3)	
p-OCH_3	55.6	–	–	55.5	55.6	–	–	–	–	
	55.5			55.5	55.4					
p-CH_3	–	–	–	–	–	–	23.4	–	–	

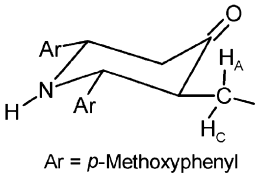
Chemical shifts of naphthalene [33] are given in the parentheses.

Table 3
^{1}H–^{1}H coupling constants (Hz) of **10–17**.

Compound	$^{3}J_{6a,5a}$	$^{3}J_{2a,3a}$	$^{2}J_{5e,5a}$	$^{3}J_{6a,5e}$	$^{3}J_{3a,alkyl}$
10	11.5	10.0	14.0	2.5	6.5
11	11.5	9.5	12.0	[a]	6.0
12	11.0	10.0	12.0	[a]	6.5
13	11.0	–	12.0	[a]	–
14	11.5	–	10.0	[a]	–
15	11.0	–	12.0	[a]	–
16[b]	11.0	10.0	11.5	[a]	3.0, 7.0
17[c]	11.7	13.0	14.8	3.2	2.0

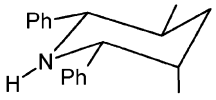
[a] H-6 and H-5a were observed only as doublets due to poor resolution.
[b] Methyl protons appeared as a triplet with a *J* value of 5.0 Hz.
[c] The methyl protons appeared as a doublet with a *J* value of 5.0 Hz.

Hence, axial and equatorial methyl carbons do not differ much in their chemical shifts in **5**, **13**, **14** and **15**.



Ar = *p*-Methoxyphenyl

23



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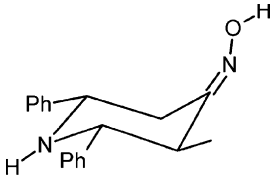

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2.6. ^{13}C chemical shifts of the ethyl group at C-3

From X-ray crystallographic study [34], it has been found that 3t-ethyl-2r,6c-bis(p-methoxyphenyl)piperidin-4-one (**23**) adopts chair conformation with equatorial orientations of all the substituents. Interestingly, the torsional angle for the segment O=CC(3)CH_2 has been found as 1°. The methyl group is gauche to C(3)–C(4) bond but anti to C(2)–C(3) bond in the solid state. However, in solution the ethyl group can adopt three different conformations **A**, **B** and **C** shown in Fig. 2. In conformation **C** there will be severe nonbonded interaction between the methyl and 2-phenyl groups, and its contribution can be ignored.

In conformation **A** one methylene proton is anti to H-3 and the vicinal coupling constant between this proton and H-3 will be around 10–12 Hz. The other methylene proton is gauche to H-3 and the coupling constant between this proton and H-3 will be around 2–4 Hz. However, in conformation **B** both the methylene protons are gauche to H-3 and both the vicinal coupling constants will be around 2–4 Hz.

In **16** the vicinal coupling constants of H-3a with the methylene protons of the ethyl group are found as 7.0 and 3.0 Hz. The observed vicinal coupling constants suggest that **16** exists as an equilibrium mixture of conformations **A** and **B**. Hence, in **16** one C–H bond will be polarized by the nitrogen atom of the C=N group. A similar conformational equilibrium has been proposed for **8** [8]. Thus, the methylene carbon should be shielded in **8** and **16** compared to **19**. Indeed, the chemical shifts of the methylene carbon in **8** and **16** are 17.8 [32] and 19.5 ppm [1], respectively, whereas in **19** the chemical shift of the methylene carbon is 25.1 ppm [32]. It is interesting to note that the chemical shift of the methylene carbon increases in the order **8** < **16** < **19**. However, the chemical shifts of the methyl carbon of the ethyl group in **8**, **16** and **19** are 12.2, 12.5 and 11.1 ppm, respectively.

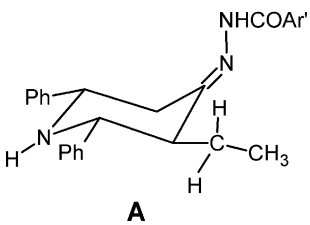
2.7. ^{13}C chemical shifts of isopropyl group at C-3

From X-ray crystallographic study [35], it has been found that **9** adopts chair conformation with equatorial orientations of all the substituents and the isopropyl group adopts a conformation so that the isopropyl methine proton is anti to C(3)–C(4) bond. From the observed NOEs and vicinal coupling constants it has been found that **9** adopts such a conformation in solution also [8]. The vicinal coupling constant between the isopropyl methine proton and H-3 is 2.0 Hz in **17** suggesting that in **17** also the isopropyl group adopts a similar conformation. Hence, the CH bond of the isopropyl group cannot interact with the oxygen in **9** or with the nitrogen of the C=N group in **17**. In **9** and **17** there may be a shielding due to the eclipsing of C=X bond with the C(3)–$CHMe_2$ bond. In **9**, **17** and **20** the chemical shifts of the isopropyl methine carbon are 25.5 [32], 28.5 and 27.1 ppm [32], respectively. It is seen that relative to the isopropyl methine carbon in **20**, in **9** it is shielded by 1.6 ppm whereas in **17** it is deshielded by 1.4 ppm. Thus, the effect due to bond eclipsing should be only small and may be +ve or −ve. The chemical shifts of one methyl carbon in **9**, **17** and **20** are 21.1, 21.0 and 21.7 ppm, respectively. The corresponding chemical shifts of the other methyl carbon are 17.8, 18.8 and 16.2 ppm, respectively.

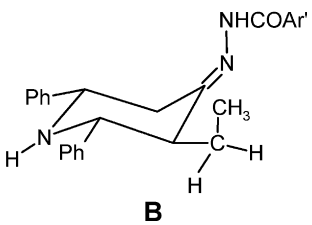
2.8. γ-Syn effect

The effect of a heteroatom X on the γ-carbon with the torsional angle X C_α C_β C_γ close to 0° may be termed as γ-syn effect. Indeed the observed shielding on C-5 in compounds **9–17** may be attributed to this effect. This is because C-5, C-4, nitrogen atom of the C=N bond and the amide nitrogen should be coplanar.

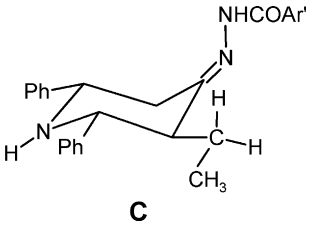
By comparing the chemical shifts of **10** with those [1] in **2** the shielding on C-3 and C-5 due to hydrazone formation are found as 6.5 and 13.5 ppm, respectively. The corresponding shieldings in 3t-methyl-2r,6c-diphenylpiperidin-4-one oxime (**25**) [3] due to oximation have been found as 8.4 and 17.1 ppm, respectively. The shielding on C-3 has been attributed to lower polarity of the C=N bond than the C=O bond [3]. The observed shielding on C-3 in **13**



A



B



C

Fig. 2. Conformations of ethyl group.

suggests that the C=N bond in the hydrazone is somewhat more polar than the C=N bond in oxime. Assuming the polar effect to be same on C-3 and C-5 the shielding on C-5 due to the γ-syn effect may be taken as 8.7 ppm (17.1–8.4) in **25**. In **10** the shielding on C-5 due to γ-syn effect comes as 7.0 ppm (13.5–6.5). The γ-syn effect is larger in oxime than in the hydrazone because in oximes the γ-syn effect is due to oxygen whereas in the hydrazone it is due to nitrogen.

2.9. γ-Gauche effect

The γ-gauche effect by an axial substituent in cyclohexanes has been well discussed [22]. Polarization of the axial C–H bond has been advocated as the major contribution to γ-gauche effect. However, this effect has been termed as syn-γ-effect in that study since the axial C–H bond, which is polarized by the substituent (or atom in the case of halogens), is parallel to the C–X bond. However, this term is not appropriate because the affected carbon is only gauche to the substituent X (or atom in the case of halogens).

By comparing **12** and **13** it is seen that the axial methyl group at C-3 shields C-5 by 3.9 ppm. This γ-gauche effect due to an axial methyl group has been found as 6.9 ppm in cyclohexanes [22]. Probably the γ-gauche effect is less on a carbon already compressed by γ-syn effect.

In **5** and **10–17** C-1″ is gauche to the alkyl groups at C-3. Thus, in all those compounds C-1″ should have a lower chemical shift than C-1‴. However, only in the 3,3-dimethyl compounds **5**, **13**, **14** and **15** the chemical shifts of C-1″and C-1‴ differ significantly. The observed shieldings on C-1″ in 5, 13, 14 and 15 suggest that γ-gauche effect may have another origin apart from polarization of a C–H bond on the γ-carbon atom.

2.10. δ-Effect

It has been found that [22] in cyclohexanes a substituent (equatorial or axial) shields the δ-carbon and this shielding has been attributed to linear electric field effect. In these cases the δ-carbons are not involved in a steric interaction with the substituents. In **10–17** the ortho carbons C-2″ and C-6″ are at δ-positions relative to the alkyl groups at C-3. In these cases there is steric interaction between the δ-carbons and the substituents. From Table 2 it is seen that the ortho carbons C-2″ and C-6″ are deshielded by the alkyl groups at C-3. The reason for this deshielding is not clear.

2.11. Chemical shifts of the naphthyl protons and carbons

Based on the mesomeric effects of the OH and CO groups one should expect that in **10–17** C-4′, C-5′, C-7′, C-9′, H-4′, H-5′ and H-7′ should be shielded and C-1′, C-6′, C-8′, C-10′, H-1′, H-6′ and H-8′ should be deshielded relative to those in naphthalene. Indeed the observed chemical sifts suggest so. However, the effects on C-5′, C-6′ and H-6′ are not significant.

Moreover, compared to the deshielding on C-1′ that on H-1′ seems to be abnormally high. Also, the shielding on C-4′ seems to be abnormally high compared to that on H-4′. These observations suggest that the C(1′)–H(1′) and C(4′)–H(4′) bonds are polarized by interaction with C=O and OH bonds, respectively. Due to this, partial positive charges are placed on H-1′ and H-4′ whereas partial negative charges are placed on C-1′ and C-4′. Thus, C-1′ is subjected to a shielding by this polarization and to deshielding by the mesomeric effect of the carbonyl group. The mesomeric effect outweighs the polarization effect causing a net deshielding on C-1′. However, H-1′ is deshielded by both these effects and the magnetic anisotropic effect of the carbonyl group. Thus, the observed deshielding on H-1′ is abnormally higher compared to the deshielding on C-1′.

Though H-4′ is shielded by the mesomeric effect of the OH group it is deshielded by the polarization effect. The mesomeric effect outweighs the polarization effect causing a shielding on H-4′. However, both these effects shield C-4′ and the shielding on C-4′ is abnormally high compared to that on H-4′.

3. Conclusion

The observed vicinal proton–proton coupling constants suggest that in hydrazones **10–17** the piperidine ring adopts chair conformation with equatorial orientations of the aryl groups. The observed chemical shifts of H-5e, H-5a and C-5 are in accord with E configuration about the C=N bond. In **10–16** the carbon of the equatorial alkyl carbon attached to C–3 is shielded by the nitrogen atoms of the C=N bond due to the interaction of the nitrogen atom with the C–H bonds of this carbon. This effect is termed as γ-syn effect. This effect is somewhat greater in the corresponding ketones. The chemical shifts for the naphthalene ring could be accounted by the mesomeric effects of the carbonyl and hydroxy groups. However, the chemical shifts of carbons adjacent to the substituents and protons on them are influenced by polarization effects also. However, the chemical shifts of carbons adjacent to the substituents and protons on them are influenced by polarization effects also.

4. Experimental

4.1. Materials

3-Hydroxy-2-naphthoic acid hydrazide was purchased from Sigma–Aldrich and was used as such. All the reagents and solvents were of laboratory grade.

4.2. Methods

The melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on an AVATAR 330 FT-IR Thermo Nicolet spectrometer in KBr pellets. Elemental analysis was performed on an Elementar Vario EL III CHNS analyser.

^{1}H NMR spectra were recorded on a Bruker DRX-500 NMR spectrometer operating at 500.03 MHz for ^{1}H with the following spectral parameters; acquisition time = around 3.0 s, number of scans = 100, number of data points = 32 K and spectral width = 10,330 Hz.

Proton decoupled ^{13}C NMR spectra were recorded on a Bruker DRX-500 NMR spectrometer operating at 125.77 MHz for ^{13}C with the following spectral parameters; acquisition time = around 0.5 s; number of scans = 1000; number of data points = 32 K; spectral width = 30,000 Hz.

^{1}H-^{1}H COSY spectrum of **13**, HSQC spectra of **5**, **13**, **16** and **17**, HMBC spectra of **13**, **16** and **17** and phase-sensitive NOESY spectrum of **13** were recorded on a Bruker DRX-500 NMR spectrometer using standard parameters. The number of data points was 1 K. For NOESY spectrum the mixing time was 800 ms.

All NMR measurements were made in 5 mm NMR tubes using solutions made by dissolving about 10 mg of the material in 0.5 mL of DMSO-d_6.

4.3. Preparation of compounds

Piperidin-4-ones **2–9** were prepared following the procedure of Noller and Baliah [36].

4.3.1. 3t-Methyl-2r,6c-diarylpiperidin-4-ones (**2–4**)

Dry ammonium acetate (100 mmol) was dissolved in ethanol and the solution was mixed with 2-butanone (100 mmol) and appropriate substituted benzaldehyde (200 mmol). The mixture was just heated to boil and allowed to stand at room temperature

Table 4
Yields, melting points, elemental analysis and IR stretching frequency of **10–17**.

Compd.	m.p. (°C)	Yield (%)	Elemental analysis						IR stretching frequencies (cm^{-1})				
			Calculated (%)			Found (%)			C=N	C=O	NH (pip)	NH (amide)	OH group
			C	H	N	C	H	N					
10	177–179	80	–	–	–	–	–	–	1627	1655	3309	3309	3419
11	222–224	90	–	–	–	–	–	–	1600	1639	3315	3271	3435
12	190–192	85	72.43	6.05	8.13	73.08	6.09	8.35	1616	1644	3315	3282	3424
13	202–204	85	73.60	6.34	8.02	73.42	6.50	8.03	1608	1649	3309	3266	3419
14	231–234	90	67.59	5.08	7.86	67.68	5.27	7.89	1600	1633	3320	3278	3402
15	221–224	78	–	–	–	–	–	–	1594	1633	3281	3281	3446
16	220–221	80	–	–	–	–	–	–	1596	1654	3306	3306	3408
17	223–224	80	–	–	–	–	–	–	1597	1652	3273	3273	3397

overnight. The reaction mixture was diluted with ether (100 mL) and treated with conc. HCl (20 mL). The precipitated hydrochloride was washed with ethanol–ether. The hydrochloride was suspended in acetone and neutralized with aqueous ammonia. Dilution with water gave the free base which was recrystallized from ethanol.

*4.3.2. 3,3-Dimethyl-2r,6c-diarylpiperidin-4-ones (**5–7**)*

Piperidin-4-ones **5–7** were prepared by condensing ammonium acetate (100 mmol), 3-methyl-2-butanone (100 mmol) and appropriate substituted benzaldehyde (200 mmol) in ethanol by following the above mentioned procedure.

*4.3.3. 3t-Ethyl-2r,6c-diphenylpiperidin-4-one (**8**)*

This was prepared by condensing ammonium acetate (100 mmol), pentan-2-one (100 mmol) and benzaldehyde (200 mmol) in ethanol by following the above mentioned procedure.

*4.3.4. 3t-Isopropyl-2r,6c-diphenylpiperidin-4-one (**9**)*

This was prepared by condensing ammonium acetate (100 mmol), 4-methylpentan-2-one (100 mmol) and benzaldehyde (200 mmol) in ethanol by following the above mentioned procedure.

*4.3.5. 2r,6c-Diarylpiperidin-4-one (3′-hydroxy-2′-naphthoyl)hydrazones (**10–17**)*

Hydrazones **10–17** were synthesized by refluxing a mixture of piperidin-4-ones (**2–9**) (25 mmol) and 3-hydroxy-2-naphthoic acid hydrazide **1** (25 mmol) in methanol (10 mL) containing a few drops of acetic acid for 1 h. The separated solid was washed with ice-cold water and was recrystallized from methanol.

The physical data for hydrazones **10–17** are given in Table 4.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.saa.2010.09.015.

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