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Research Article

Synthesis and Spectral Studies of Some 4-hydroxy-4-methylpiperidines

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Abstract

^{1}H and ^{13}C NMR spectra have been recorded for seven 4-hydroxy-4-methylpiperidines 1-7 and analysed. The methyl group at C(4) occupies axial orientation in 1 and equatorial orientations in 2-7. Effect of solvent on ^{1}H chemical shifts of 1-7 have also been studied in detail.

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Introduction

Several methods to synthesise tertiary alcohols in high yields with high levels of enantioselectivity have been reported recently [1-4]. Study of 4,4-disubstituted piperidines is of considerable interest, since these compounds have been shown to be pharmacologically active and hence they can be used in the clinical field extensively [5,6] and useful as monomer for the preparation of photoregiomaterial [7] having high transparency. The stereochemistry of several 4-substituted-4-hydroxypiperidines have also been established based on NMR measurements [8-10] and using chiral bidendate NMR solvent BMBA-*p*-Me [11]. The present investigation deals with the stereochemical behaviour of seven 4-hydroxy-4-methylpiperidines **1-7** through NMR techniques.

Experimental Section

Synthesis of 4-hydroxy-4-methylpiperidines 1-7

The 4-hydroxy-4-methylpiperidines **1-7** were synthesised from the respective parent piperidin-4-ones by following the general procedure reported in literature [23]. The tertiary alcohols thus obtained were chromatographed and recrystallised from petroleum-ether (60-80°C). The melting points are, 40-50°C (**1** and **2**); 48-49°C (**3**); 42-43°C (**4**); 44-45°C (**5**); 46-47°C (**6**) and 50-51°C (**7**).

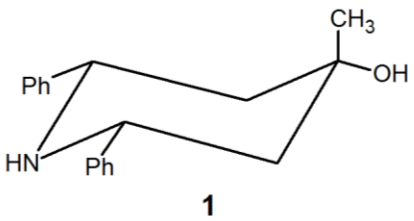
Spectral Measurements

^{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-2D phase sensitive NOESY spectrum was 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 on 5 mm NMR tubes. ^{1}H NMR spectra were also recorded in DMSO-d_6 and C_6D_6.

Results and Discussion

cis-2,6-Diphenylpiperidin-4-one on treatment with CH_3MgI gave diastereoisomeric mixture of 4-hydroxy-4-methylpiperidines **1** and **2**. Only one isomer with 100% yield was observed with other 3-alkyl-*cis*-2,6-diarylpiperidin-4-ones. The high resolution ^{1}H and ^{13}C NMR spectra of *c*(4)-hydroxy-4-methyl-r(2),*c*(6)-diphenylpiperidine (**1**), *t*(4)-hydroxy-4-methyl-r(2),*c*(6)-diphenylpiperidine (**2**), *t*(4)-hydroxy-4-methyl-*t*(3)-methyl-r(2),*c*(6)-diphenylpiperidine (**3**), *t*(4)-hydroxy-4-methyl-*t*(3)-methyl-r(2),*c*(6)-bis(*p*-chlorophenyl)piperidine (**4**), *t*(4)-hydroxy-4-methyl-*t*(3)-methyl-r(2),*c*(6)-bis(*o*-chlorophenyl)piperidine (**5**), *t*(4)-hydroxy-4-methyl-*t*(3)-methyl-r(2), *c*(6)-di-2′-furylpiperidine (**6**) and *t*(4)-hydroxy-4-methyl-*t*(3)-ethyl-

r(2),*c*(6)-diphenylpiperidine (**7**) have been recorded in $CDCl_3$ and analysed. The signals in the ^1H NMR spectra were assigned based on their positions, integrals and multiplicities. The coupling constants are determined using first-order analysis for compounds **1**, **2**, **5** and **6** and second-order analysis for compounds **3**, **4** and **7**. The various coupling constants and chemical shift values obtained in this manner are given in **Tables I** and **II** respectively. The assignment of the signals in the ^{13}C NMR spectra was done based on small intensities expected for quaternary carbon and known deshielding α and β effects of alkyl group. **Table III** reports ^{13}C spectral data for 4-hydroxy-4-methylpiperidines **1-7**.



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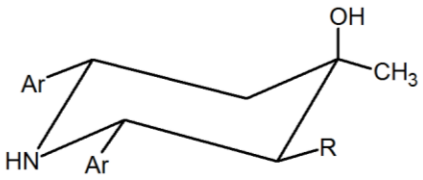

	Ar	R
2;	Ph	H
3;	Ph	CH_3
4;	*p*-ClC_6H_4	CH_3
5;	*o*-ClC_6H_4	CH_3
6;	Furyl	CH_3
7;	Ph	C_2H_5

Figure 1 Chemical structures of compounds **1-7**.

Table 1 Coupling constants (Hz) of 4-hydroxy-4-methylpiperidines **1-7** in $CDCl_3$

Compd	$J_{6a,5a}$	$J_{6a,5e}$	$J_{5a,5e}$	$J_{2a,3a}$	J_{H,CH_3} / J_{CH_2,CH_3}
1	11.61	-	-	11.61	-
2	11.58	-	-	11.58	-
3	11.77	2.38	13.40	10.26	6.86
4	11.72	2.40	13.38	10.25	6.84
5	11.54	2.30	13.32	10.43	6.89
6	10.74	3.47	-	10.58	6.78
7	11.83	2.36	13.39	10.35	7.47

Table 2 ^1H chemical shifts (ppm) of 4-hydrxy-4-methylpiperidines **1-7** in $CDCl_3$

Cd	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	Alkyl protons	NH and OH	Aromatic protons
1	3.90	Same as H(5)	1.73	1.89	3.90	1.50 (4-CH_3)	-	7.47 (t); 7.34 (t);
2	4.22	Same as H(5)	1.65	1.81	4.22	1.30 (4-CH_3)	-	7.28-7.24 (m)
3	3.79	1.71	1.80	1.88	4.22	0.71 (3-CH_3) 1.28 (4-CH_3)	1.60 (s) 2.17 (s)	7.44 (dd); 7.36-7.20 (m)
4	3.74	1.59	1.68	1.79	4.16	0.66 (3-CH_3) 1.23 (4-CH_3)	-	7.27-7.22 (m); 7.34-7.31 (m)
5	4.56	1.71	1.64	2.03	4.72	0.78 (3-CH_3) 1.29 (4-CH_3)	1.44	7.74-7.70 (dt); 7.36-7.13 (m)
6	3.95	1.85-2.08			4.32	0.77 (3-CH_3) 1.32 (4-CH_3)	-	7.32 (d); 6.16 (d); 6.23 (d); 6.29-6.27 (m)
7	3.85	1.54-1.43	1.79	1.84	4.21	1.54-1.43, 1.10 (CH_2CH_3) 0.49 (CH_2CH_3) 1.32 (4-CH_3)	1.66	7.46 (dd); 7.34-7.22 (m)

Table 3 ^{13}C chemical shifts (ppm) of 4-hydroxy-4-methylpiperidines **1-7** in $CDCl_3$

Cd	C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	Aromatic carbons
1	59.36	49.02	≈ 71.0	49.02	59.36	26.09 (4-CH_3)	145.18, 128.42, 127.32,
2	57.33	47.39	69.87	47.39	57.33	31.72 (4-CH_3)	127.14, 126.84
3	64.24	49.20	71.45	45.50	57.08	10.41 (3-CH_3)	128.34, 128.22, 127.32,
						29.29 (4-CH_3)	127.06, 126.75
4	63.38	49.13	71.21	45.52	56.36	10.42 (3-CH_3)	143.56, 142.57, 132.99,
						29.25 (4-CH_3)	132.70, 129.57, 128.54,
							128.47, 128.18
5	58.25	46.86	71.24	46.09	53.08	9.78 (3-CH_3)	141.96, 141.45, 134.45,
						29.14 (4-CH_3)	132.81, 129.42, 129.21,
							128.21, 128.02, 127.79,
							127.14
6	56.64	44.30	70.63	43.50	50.07	10.46 (3-CH_3)	156.57, 155.84, 141.63,
						29.11 (4-CH_3)	141.48, 110.04, 109.96,
							107.20, 105.01
7	63.86	52.63	72.25	49.09	57.00	29.29 (4-CH_3)	144.53, 143.30, 129.02,
						14.78 (CH_2CH_3)	128.62, 128.51, 128.36,
						19.34 (CH_2CH_3)	128.18, 127.95, 127.49,
							127.16, 126.96, 126.82

Configurational assignments at C(4) could be made based on the results obtained in the NOESY spectrum and on comparison of the signals with those of corresponding 4-hydroxypiperidines **8-11** [12] (secondary alcohols). In the major isomer of 4-hydroxy-4-methylpiperidine **2** the benzylic protons resonate at 4.22 ppm which is closer to the value observed in *t*(4)-hydroxy-r(2),*c*(6)-diphenylpiperidine **9** (4.29 ppm). Therefore, the configuration of hydroxyl group at C(4) in **2** is same as that in **9** and thus assigned as axial. Therefore in the major isomer **2** methyl group occupies equatorial orientation. Obviously in the minor isomer **1** methyl group occupies axial orientation. NOESY spectrum reveals that the signal at 1.50 ppm due to methyl group at C(4) in the minor isomer reveals cross peak with the benzylic proton signals at 3.90 ppm in the minor isomer which support that methyl group occupies axial orientation in the minor isomer **1**. Obviously in the major isomer **2** methyl group occupies equatorial orientation.

The presence of equatorial methyl group at C(3) is not expected to alter the chemical shift of H(6) provided the configuration at C(4) is same in 3-methyl tertiary alcohol **3** and 4-hydroxy-4-methylpiperidine **2**. The benzylic proton H(6) absorbs at the same field in **3** (4.22 ppm) as that of *t*(4)-hydroxy-4-methylpiperidine **2** (4.22 ppm). Thus, the configuration of methyl group at C(4) is established as equatorial in **3**. In a similar manner one can assign equatorial configuration of methyl group at C(4) for the other 4-hydroxy-4-methyl-3-alkyl-2,6-diarylpiperidines **4-7**.

The observation of one large (≈ 11 Hz) and one small coupling ≈ 2-3 Hz about C(5)-C(6) bond in **1-7** and large coupling about C(2)-C(3) bond (≈ 10 Hz) in 3-alkyl derivatives **3-7** reveals equatorial orientations of aryl rings at C(2) and C(6) and alkyl groups at C(3). Hence, all the 4-hydroxy-4-methylpiperidines **1-7** 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 **3-7**. This can be explained as follows.

The alkyl group at C(3) experiences severe *gauche* interaction with aryl group at C(2) and inorder to avoid this *gauche* interaction, the ring is flattened about C(2)-C(3) bond. This flattening is responsible for the lower magnitude of $J_{2a,3a}$ relative to $J_{6a,5a}$ in **3-7**.

Comparison of the coupling constants about C(5)-C(6) and C(2)-C(3) bonds in **4** and **5** with those of **3** reveals that the coupling constants are not affected due to the introduction of chloro substituent at the *para* position in the phenyl ring whereas such introduction in the *ortho* position slightly increases the coupling about C(2)-C(3) bond but decreases both the *trans* and *cis* couplings about C(5)-C(6) bond. This suggests that the introduction of chloro substituent at the *ortho* position of phenyl ring causes slight puckering about C(2)-C(3) bond. It is also seen from **Table 1** that there is no appreciable change in the coupling constants about C(5)-C(6) bond due to the replacement of methyl by ethyl group at C(3).

Torsional angles were calculated for 4-hydroxy-4-methylpiperidines according to DAERM method [13] and Haasnoot equation [14] and these values are given in **Table IV**. **Table IV** reveals that the ring torsional angles (ϕ_{cis}) calculated according to Haasnoot method are slightly higher when compared to DAERM method. The higher

torsional angle about C(2)-C(3) bond in 3-methyl *ortho*-chloro derivative **5** compared to 3-methyl derivative **3** supports puckered nature of C(2)-C(3) bond in **5** due to the presence of chloro substituent at the *ortho* position.

Table 4 Comparison of calculated torsional angles in some 4-hydroxy-4-methylpiperidines **1-7**

Cd	$J_{5,6}$ (*trans*)	$J_{5,6}$ (*cis*)	$\phi_{5,6}$ (*trans*)		$\phi_{5,6}$ (*cis*)		$J_{2,3}$ (*trans*)	$\phi_{2,3}$ (*trans*)	
			S-T	Haasnoot	S-T	Haasnoot		S-T	Haasnoot
1	11.61	-	-	187.2	-	-	-	-	-
2	11.58	-	-	187.6	-	-	-	-	-
3	11.77	2.38	180.2	183.3	60.2	63.6	10.26	159.3	159.8
4	11.72	2.40	180.0	185.3	60.0	63.4	10.25	159.6	159.7
5	11.54	2.30	180.4	188.1	60.4	64.3	10.43	162.2	161.6
6	10.74	3.47	172.4	197.6	52.4	54.7	10.58	169.7	161.2
7	11.83	2.36	180.4	182.9	60.4	63.8	10.35	159.6	160.9

From **Table II** it is seen that the introduction of an equatorial methyl/ethyl group at C(3) shields the benzylic proton H(2) by ≈ 0.4 ppm due to the magnetic anisotropic effect of equatorial alkyl group. Replacement of methyl by ethyl group at C(3) shields H(3) alone. It is also seen from table that there is no appreciable change in the chemical shifts of benzylic protons and methyl protons at C(3) but methine proton H(3) and both the methylene protons at C(5) [H_{5e} and H_{5a}] are shielded due to the introduction of chloro substituent in the *para* position of the phenyl ring. The introduction of chloro substituent in the *ortho* position of phenyl ring in **3** deshields the benzylic protons by 0.77 [H(2)] and 0.50 [H(6)] ppm and equatorial methylene proton at C(5) by 0.15 ppm and shields axial methylene proton at C(5). This can be explained as follows.

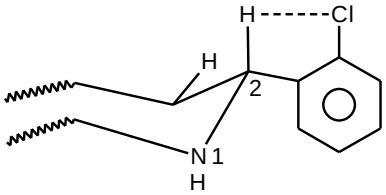

Figure 2 Syn configuration of benzylic hydrogens

The rotation of aryl group is probably restricted by the *ortho* chloro group in **5** where the chlorine atom prefers to be *syn* to the benzylic hydrogens (**Figure 1**) to avoid dipole-dipole interaction between C-Cl and C-N bonds. In this conformation the chlorine can interact with the benzylic hydrogens and adjacent equatorial methylene hydrogen. This van der Waal's interaction causes considerable deshielding on these protons. Since the chlorine atom is more closer to the benzylic hydrogen than to the equatorial methylene hydrogen at C(5), benzylic hydrogen experiences greater deshielding than equatorial methylene hydrogen at C(5). Such a van der Waal's interaction makes C(2)-H and C(6)-H bonds polar so that the hydrogens get slight positive charges and the carbons get negative charges. So benzylic hydrogens become deshielded in **5** compared to **3**. The interaction of chlorine in the *syn* orientation with the equatorial methylene proton at C(5) makes the bond slightly polar and hence the C(5) carbon gets shielded which is transmitted to the axial hydrogen attached to C(5) to some extent. Similar explanation has been offered by Pandiarajan *et al.* [15] in *trans*-3-alkyl-*cis*-2,6-bis(*o*-chlorophenyl)-piperidin-4-ones **12** due to the presence of *ortho* chloro substituent.

The chemical shift values of the heterocyclic ring protons and alkyl protons at C(3) in 4-hydroxy-4-methylpiperidines are compared with those of corresponding 4-hydroxypiperidines [12]. Such a comparison is given in **Table V**. Introduction of axial methyl group at C(4) in **8** deshields H(2)/H(6) and the nearby axial methylene proton at C(5)/C(3) [H_{5a}/H_{3a}] but shields the nearby equatorial methylene proton (H_{5e}/H_{3e}). These findings are in line with the observations already made by Booth [16] and can be explained based on the spatial *syn*-1,3-diaxial interaction and magnetic anisotropic effect of axial methyl group at C(4). The benzylic protons of *t*(4)-hydroxy-4-methylpiperidine **2** and *t*(4)-hydroxy-4-methyl-3-alkyl-2,6-diphenylpiperidines **3** and **7** absorb slightly at lower frequency compared to *t*(4)-hydroxypiperidine **9** and *t*(4)-hydroxy-3-alkyl-2,6-diphenylpiperidines **10** and **11**. It is also seen from **Table V** that both the methylene protons at C(5) and H(3) are shielded due to the introduction of equatorial methyl group at C(4). The magnetic anisotropic effect of the equatorial methyl group at C(4) is responsible for the observed shielding magnitude on H(3) and H(5) and benzylic protons H(2) and H(6) in **2**, **3** and **7**.

Table 5 Comparison of ^{1}H chemical shifts (ppm) of some 4-hydroxy-4-methylpiperidines and 4-hydroxypiperidines

Compd	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	3-Alkyl protons
1	3.90	Same as H(5)	1.73	1.89	3.90	-
8	3.85		1.56	2.16	3.85	-
2	4.22	Same as H(5)	1.65	1.81	4.22	-
9	4.29		1.81	1.92	4.29	-
3	3.79	1.71	1.80	1.88	4.22	0.71
10	3.87	1.86	1.90	2.02	4.28	0.75
7	3.85	1.54-1.43	1.79	1.84	4.21	0.49 (CH_2**CH_3**) 1.54-1.43, 1.10 (**CH_2**CH_3)
11	3.91	1.65	2.07	1.90	4.27-4.31	0.79 (CH_2**CH_3**) 1.03, 1.30 (**CH_2**CH_3)

In order to study the influence of solvent on the ^{1}H chemical shifts of 4-hydroxy-4-methylpiperidines the ^{1}H NMR spectra were recorded in C_6D_6 and DMSO-d_6. **Table VI** reports the chemical shifts of 4-hydroxy-4-methylpiperidines measured in different solvents. It is seen from **Table VI** that the chemical shifts of all the heterocyclic ring protons and alkyl protons at C(3) are shielded in DMSO-d_6 compared to $CDCl_3$. The shielding observed on H(3) and H(5) are slightly higher when compared to those observed on H(2) and H(6).

The OH group at C(4) and NH group are more solvated compared to other protons in the 4-hydroxy-4-methylpiperidines. These upfield shifts are due to specific molecular association involving intermolecular hydrogen bonding between solute and solvent molecules. Due to this specific association *syn*-1,3-diaxial interaction between hydroxyl group at C(4) and benzylic protons and *syn*-1,3-diaxial interaction between H(3) and H_{5a} are relieved and hence these protons resonate at lower frequency in DMSO-d_6 compared to that observed in $CDCl_3$. In addition magnetic anisotropic effect of S=O bond of DMSO-d_6 also may contribute to the shielding observed in these systems.

Table 6 Chemical shifts (ppm) of 4-hydroxy-4-methylpiperidines **1-7** in different solvents.

Compd	Solvent	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	3-Alkyl protons
1	$CDCl_3$	3.90	Same as H(5)	1.73	1.89	3.90	-
	DMSO-d_6	3.81		1.49	1.66-1.63	3.81	-
	C_6D_6	3.76		1.86	1.95	3.76	-
2	$CDCl_3$	4.22	Same as H(5)	1.65	1.81	4.22	-
	DMSO-d_6	4.13		1.37	1.66-1.63	4.13	-
	C_6D_6	4.32		1.69	1.81	4.32	-
3	$CDCl_3$	3.79	1.71	1.80	1.88	4.22	0.71
	DMSO-d_6	3.76	1.53	1.62	1.75	4.19	0.59
	C_6D_6	3.95	1.80	1.88-1.90		4.36	0.90
4	$CDCl_3$	3.74	1.59	1.68	1.79	4.16	0.66
	DMSO-d_6	3.71	1.43	1.51	1.70	4.14	0.55
	C_6D_6	3.76	1.56	1.66	1.73	4.16	0.78
5	$CDCl_3$	4.56	1.71	1.64	2.03	4.72	0.78
	DMSO-d_6	4.44	1.55	1.46	1.84	4.61	0.64
	C_6D_6	4.87	1.70	1.61	2.11	4.96	0.99
6	$CDCl_3$	3.95	1.85-2.08			4.32	0.77
	DMSO-d_6	3.85	1.62-1.71		1.83	4.20	0.65
	C_6D_6	4.18	1.95-2.05			4.53	0.97
7	$CDCl_3$	3.85	1.54-1.43	1.79	1.84	4.21	1.54-1.43, 1.10 (CH_2CH_3) 0.49 (CH_2CH_3)
	DMSO-d_6	3.80	1.24-1.18	1.58	1.70	4.15	1.51, 0.90 (CH_2CH_3) 0.39 (CH_2CH_3)
	C_6D_6	3.77	1.34	1.65	1.58	4.09	1.42, 1.12 (CH_2CH_3) 0.52 (CH_2CH_3)

It is seen from **Table VI** that all the heterocyclic ring protons are deshielded in 3-methyl-2,6-diphenyl derivative **3** and 3-methyl-2,6-di-2′-furyl derivative **6** which is in contrast to the shielding observed in 3-ethyl-2,6-diphenyl derivative **7** due to the variation of solvent from $CDCl_3$ to C_6D_6. In 3-methyl-*para*-chlorophenyl derivative **4** there is no appreciable change in the chemical shifts of ring protons due to the change of solvent from $CDCl_3$to C_6D_6. In 3-methyl-*ortho*-chlorophenyl derivative **5** and *t*(4)-hydroxy-4-methylpiperidine **2**, H(6) and H(2) are deshielded whereas other protons are not affected in C_6D_6 compared to $CDCl_3$. In *c*(4)-hydroxy-4-methylpiperidine **1** changing the solvent from $CDCl_3$ to C_6D_6 causes appreciable shielding of benzylic protons H(2) and H(6) and deshielding of axial methylene protons at C(5) and C(3) [H_{5a} and H_{3a}]. The methyl protons at C(3) absorb at higher frequency in C_6D_6 relative to $CDCl_3$ in **3-6**.

It has been previously reported [17] that phenol forms weak hydrogen bonding with π electrons of the benzene molecule. One can expect such OH-π interaction of C_6D_6 molecule in the present set of compounds also. The deshielding and shielding magnitude observed on heterocyclic ring protons due to the change of solvent from $CDCl_3$ to magnetically anisotropic solvent C_6D_6 can be explained based on hydrogen bonding between OH proton and aromatic solvent molecule (C_6D_6) [OH-π interaction]. Hence, the solvent molecule C_6D_6 prefers a particular orientation in which most of the heterocyclic ring protons lie in the deshielding region of the aromatic ring of the solvent C_6D_6 molecules. This is probably being the reason for the deshielding magnitude observed on heterocyclic ring protons in the magnetically anisotropic solvent C_6D_6 relative to $CDCl_3$.

It is seen from the **Table III** that the introduction of methyl group at C(3) in **2** deshields both the β-carbons C(2) and C(4). The magnitude of the β-effect observed on C(4) is somewhat lower (+ 1.58 ppm) when compared to the value observed on C(2) (+ 6.91 ppm). It has been previously reported [18] that the magnitude of the α-effect of a particular substituent is significantly reduced by the nearby substituent and it decreases as the number of *gauche* interaction increases. The presence of methyl group at C(3) significantly reduces the α-effect of both the hydroxyl and methyl groups at C(4), due to severe *gauche* interaction. This is probably be responsible for the lower deshielding magnitude observed on C(4) compared to C(2) in *t*(4)-hydroxy-4-methyl-*t*(3)-methyl-2,6-diphenylpiperidine **3**. There is no appreciable change in the chemical shifts of heterocyclic ring carbons in **4** due to the presence of chloro substituent in the *para* position of phenyl ring. Introduction of chloro substituent at the *ortho* position of the phenyl ring in **3** shields benzylic carbons C(2) and C(6) and methine carbon C(3). This has already been explained on the basis of preferred orientation (**Figure 1**) of chloro substituent (chlorine is *syn* to benzylic hydrogen).

Table 7 Comparison of ^{13}C chemical shifts (ppm) of some 4-hydroxy-4-methylpiperidines and 4-hydroxypiperidines.

Compd	C(2)	C(3)	C(4)	C(5)	C(6)	3-Alkyl carbons
1	59.4	49.0	71.0	49.0	59.4	-
	(– 0.6)	(+ 5.3)	(+ 1.1)	(+ 5.3)	(– 0.6)	
8	60.0	43.7	69.9	43.7	60.0	-
2	57.3	47.4	69.9	47.4	57.3	-
	(+ 1.3)	(+ 6.0)	(+ 3.8)	(+ 6.0)	(+ 1.3)	
9	56.0	41.4	66.1	41.4	56.0	-
3	64.2	49.2	71.5	45.5	57.1	10.4 (CH_3)
	(+ 1.8)	(+ 6.5)	(+ 1.0)	(+ 4.0)	(+ 1.5)	(– 4.1)
10	62.4	42.7	70.5	41.5	55.6	14.5
7	63.9	52.6	72.3	49.1	57.0	14.8 (CH_2**CH_3**)
	(+ 1.8)	(+ 4.7)	(+ 6.0)	(+ 6.4)	(+ 1.3)	(+ 3.6)
						19.3 (**CH_2**CH_3)
						(– 1.0)
11	62.1	47.9	66.3	42.7	55.7	11.2 (CH_2**CH_3**)
						20.3 (**CH_2**CH_3)

+ denotes deshielding; – denotes shielding.

Table VII reports the chemical shifts of heterocyclic ring carbons and alkyl carbons at C(3) in 4-hydroxy-4-methylpiperidines and 4-hydroxypiperidine [18,19]. From **Table VII** it is seen that introduction of an axial methyl group at C(4) deshields the α and β carbons by 1.1 and 5.3 ppm respectively. The deshielding

magnitude are in line with the observation already made by Grant and Dalling [20] and Schneider and Hoppen [21]. However, the shielding magnitude observed on γ carbon [C(2)/C(6)] is considerably lower (-0.6 ppm) when compared to the value (≈ -6 ppm) reported previously [20, 21]. The α effect of equatorial methyl group at C(4) in **2** and **3** are found to be 3.8 and 1 ppm respectively. The lower α effect observed in **3** is due to the *gauche* interaction between CH_3 group at C(3) with hydroxyl and methyl groups at C(4). It has been previously established [18] that *gauche* interaction decreases the substituent parameters of a particular substituent. The deshielding β and γ-effect of equatorial methyl group at C(4) is found to be 4-6.5 and 1-2 ppm respectively.

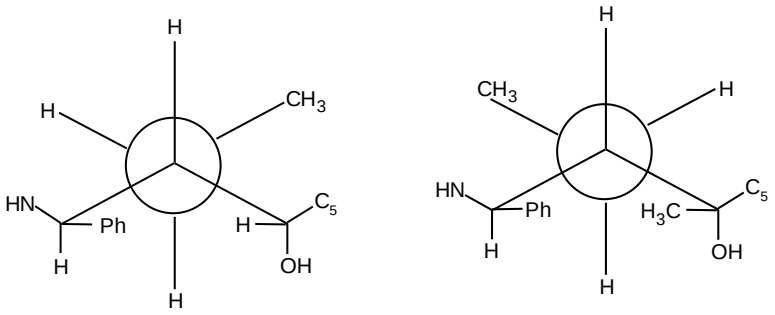

Figure 3 (a) & (b) Anti to Gauche conformations

It is interesting to note that the α effect of equatorial methyl group at C(4) in *t*(4)-hydroxy-4-methyl-3-ethylpiperidine **7** (+ 6.0 ppm) is considerably higher when compared to the value observed in **2** (+ 3.8 ppm). This can be explained based on the different conformations of the ethyl group in **7** and *t*(4)-hydroxy-3-ethyl-2,6-diphenylpiperidine **11**. Manimekalai and Rajarajan [19] have reported that the favoured conformation of the ethyl group in **11** is found to be the one in which the methyl group of the ethyl side chain should be *anti* to C(2) and *gauche* to C(4) (**Figure 3a**).

In *t*(4)-hydroxy-4-methyl-3-ethyl-2,6-diphenylpiperidine **7** one can expect the conformation of ethyl group to be same as that observed in the closely related 4-benzyl-*t*(4)-hydroxy-3-ethyl-2,6-diphenylpiperidine **13** [22]. The favoured conformation is shown in **Figure 3b** in which methyl group of ethyl side chain should be *anti* to C(4) and *gauche* to C(2). Therefore C(4) resonates considerably at lower frequency in **11** compared to **7** and hence α effect is significantly higher in **7**.

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