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BENZYL GROUP CONFORMATION IN SOME 4-BENZYL-4-HYDROXYPIPERIDINES

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The high resolution ^{1}H and ^{13}C NMR spectra of eight 4-benzyl-4-hydroxypiperidines **1—8** have been recorded in $CDCl_3$ and analyzed. In **2**, the conformation of the equatorial benzyl group at C(4) was established as an equilibrium mixture of **A** [phenyl group is gauche with respect to OH and C(5)] and **B** [phenyl group is gauche with respect to OH and C(3)], whereas in 3-alkyl-4-benzyl-4-hydroxypiperidines **3—8** the favored conformation of the benzyl group at C(4) is **A**. In **1**, the axial benzyl group at C(4) adopts the gauche conformations **A′** [phenyl group is gauche with respect to OH and C(3)] and **B′** [phenyl group is gauche with respect to OH and C(5)] in which the phenyl ring of the benzyl group is gauche with respect to OH group. Hybrid HF/DFT B3LYP/6-3G* calculations of model systems **1′—3′** also support these conformations. ^{13}C data reveal that the equatorial methyl group at C(3) exerts a shielding influence on the methyl-bearing carbon and the magnitude of α-effect was found to be approximately –1.5 ppm. The ^{13}C substituent parameters for the benzyl group reveal that the α-effect of the equatorial benzyl group is considerably higher in 3-ethyl tertiary alcohol **7** than in 3-methyl tertiary alcohol **3** and 4-benzyl-t(4)-hydroxypiperidine **2**. This may be explained taking into account different conformations of ethyl group in t(4)-hydroxy-3-ethyl-2,6-diphenylpiperidine **12** and 3-ethyl tertiary alcohol **7**.

K e y w o r d s : 4-Benzyl-4-hydroxypiperidines; ^{1}H NMR, ^{13}C NMR; configuration; conformation.

INTRODUCTION

Several methods of the synthesis of tertiary alcohols with high yields and high levels of enantioselectivity have been recently reported [1—6]. The stereochemistry of several 4-substituted-4-hydroxypiperidines have also been established from NMR measurements [7—10] and using chiral bidendate NMR solvent BMBA-p-Me (bis-1,3-methylbenzylamine-2-methylpropane) [11]. Study of 4,4-disubstituted piperidines is of considerable interest since these compounds have been shown to be pharmacologically active and, therefore, they can be extensively used in the clinical field [12—16] and as monomers in the preparation of photoregiomaterials [17] with high transparency. Different orientations of phenyl ring in the diastereoisomeric 1,3-dimethyl-4-phenylpiperidin-4-ols [18], cis-1-(p-bromophenyl)-4-tert-butylcyclohexane [19], 2-phenyl-1,3-dioxane [20] and 1-methyl-1-phenylcyclohexane [21] have been reported in the literature. Conformations of some crowded piperidines [22] and a piperidine alkaloid N-methylalbine [23] were also studied in detail. However, little information is available regarding the conformation of benzyl group [24—26]. This prompted us to undertake the present investigation devoted to the conformational behavior of eight 4-benzyl-4-hydroxypiperidines.

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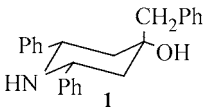

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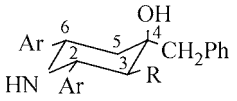


	Ar	R
2	Ph	H
3	Ph	CH_3
4	*p*-ClC_6H_4	CH_3
5	*p*-$CH_3OC_6H_4$	CH_3
6	Furyl	CH_3
7	Ph	C_2H_5
8	*p*-ClC_6H_4	C_2H_3

RESULTS AND DISCUSSION

cis-2,6-Diphenylpiperidin-4-one yielded diastereoisomeric mixture of 4-benzyl-4-hydroxypiperidines on treatment with $PhCH_2MgCl$. However, with 3-methyl- and 3-ethyl-2,6-diarylpiperidin-4-ones, only one isomer was observed in 100 % yield. The high resolution ^1H and ^{13}C NMR spectra of 4-benzyl-*c*(4)-hydroxy-r(2), *c*(6)-diphenylpiperidine* (**1**), 4-benzyl-*t*(4)-hydroxy-r(2), *c*(6)-diphenylpiperidine (**2**), 4-benzyl-*t*(4)-hydroxy-*t*(3)-methyl-r(2), *c*(6)-diphenylpiperidine (**3**), 4-benzyl-*t*(4)-hydroxy-*t*(3)-methyl-r(2), *c*(6)-bis(*p*-chlorophenyl)piperidine (**4**), 4-benzyl-*t*(4)-hydroxy-*t*(3)-methyl-r(2), *c*(6)-bis(*p*-methoxyphenyl)piperidine (**5**), 4-benzyl-*t*(4)-hydroxy-*t*(3)-methyl-r(2), *c*(6)-di-2′-furylpiperidine (**6**), 4-benzyl-*t*(4)-hydroxy-*t*(3)-ethyl-r(2), *c*(6)-diphenylpiperidine (**7**) and 4-benzyl-*t*(4)-hydroxy-*t*(3)-ethyl-r(2), *c*(6)-bis(*p*-chlorophenyl)piperidine (**8**) (Scheme 1) have been recorded in $CDCl_3$ and analyzed. The assignment of the signals in the ^{13}C NMR spectra was based on the results obtained in ^1H—^{13}C COSY spectra recorded for all the compounds. The signals in the 1H NMR spectra were assigned based on their positions, integrals and multiplicities. The coupling constants were determined using second-order analysis for **3—6** and **8** and first-order analysis for the remaining compounds. The various coupling constants and chemical shift values (^1H and ^{13}C) obtained in this manner are given in Tables 1—3.

Configurational assignments at C(4) in the diastereoisomeric mixture of 4-benzyl-4-hydroxypiperidines **1** and **2** could be based on the results obtained from the NOESY spectrum. A signal at 3.16 ppm which corresponds to methylene protons of benzyl group at C(4) in the minor isomer **1** reveals considerable NOE with the signal of the benzyl protons H(2) and H(6) at 4.15 ppm.

T a b l e 1

Coupling constants (Hz) *of* 4-*benzyl*-4-*hydroxypiperidines* **1—8** *in* $CDCl_3$

Compound	$J_{6a,5a}$	$J_{6a,5e}$	$J_{5a,5e}$	$J_{2a,3a}$	J_{CH_2Ph}	J_{H,CH_3}/ J_{CH_2,CH_3}
1 (Minor isomer)	11.95	a	12.64	11.95	–	–
2 (Major isomer)	10.69	2.95	a	10.69	–	–
3	11.65	2.10	13.43	10.22	13.30	6.75
4	12.19	1.77	13.44	10.21	13.32	6.76
5	11.60	2.12	13.36	9.90	13.30	6.76
6	11.84	2.30	13.46	10.53	14.32	6.76
7	11.47	2.27	13.53[b]	10.41	13.29	7.58
8	11.60	2.35	13.48	10.39	13.32	7.59

[a] Could not be determined due to overlapping.
[b] Calculated from 500 MHz spectrum.

* With respect to the second substituent, *i.e.* phenyl ring, the hydroxy substituent at C(4) is *cis* and the phenyl substituent at C(6) is *cis*.

Table 2

^{1}H *chemical shifts* (ppm) *of* 4-*benzyl*-4-*hydroxypiperidines* **1—8** *in* $CDCl_3$

Compound	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	Alkyl protons	CH_2Ph	NH and OH	Aromatic protons
1 (Minor isomer)	4.15	Same as H(5)	1.76—1.66	1.92	4.15	–	3.16	1.40 1.26	7.45 (d); 7.34-7.29 (m); 7.25 (t); 7.20 (d); 7.17 (s) 7.19 (d); 7.36–7.23 (m)
2 (Major isomer)	4.19	Same as H(5)	1.76—1.66		4.19	–	2.79		
3	3.86	1.83	1.75	1.62	4.10	0.86	3.06 2.69	1.37	7.43 (d); 7.36–7.17 (m)
4	3.84	1.75	1.66	1.57	4.08	0.84	3.04 2.68	2.17	7.16 (d); 7.36 (dd); 7.24 (t); 7.30-7.26 (m)
5	3.79	1.78	1.71	1.57	4.04	0.85 3.80 (OCH_3) 3.76 (OCH_3)	3.04 2.69	1.26 1.34	7.33 (d); 7.18 (d); 6.85 (d); 6.80 (d); 7.28-7.23 (m)
6	4.02	2.01	1.87	1.71	4.18	0.92	2.73 3.07	1.28	7.34 (t); 7.31 (d), 7.27 (dd); 7.21 (dd); 6.23 (d); 6.08 (d); 6.30-6.29 (m)
7	3.92	1.58[a]	1.78[b]	1.63[b]	4.06	1.21, 1.80[a] (**CH_2**CH_3) 0.52 (CH_2**CH_3**)	3.15 2.66	1.31	7.50 (d); 7.36–7.24 (m); 7.20 (dd)
8	3.91	1.47	1.64	1.53	4.03	1.75, 1.17 (**CH_2**CH_3) 0.55 (CH_2**CH_3**)	2.64 3.13	1.29 1.26	7.44 (d); 7.36 (s); 7.18 (t); 7.31–7.21 (m)

[a] Calculated from 500 MHz spectrum.

Table 3

^{13}C *chemical shifts* (ppm) *of some* 4-*benzyl*-4-*hydroxypiperidines* **1—8**

Compound	C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	CH_2Ph	Aromatic carbons
1 (Minor isomer)	58.83	46.45	71.99	46.45	58.83	–	43.51	144.44, 136.09, 127.37, 126.74
2 (Major isomer)	57.17	45.84	71.39	45.84	57.17	–	50.35	147.15, 145.15, 130.66, 128.43, 127.19
3	64.38	44.26	73.24	45.97	56.88	10.80	47.07	145.08, 144.26, 136.77, 130.67, 128.29, 127.36, 127.07, 126.88, 126.58
4	63.53	44.27	72.97	46.01	56.17	10.68	46.96	143.44, 142.61, 136.47, 133.07, 132.75, 130.59, 129.58, 128.47, 128.18, 127.77, 126.71
5	63.74	44.36	73.30	46.02	56.24	10.77	47.13	158.93, 137.36, 136.87, 136.56, 130.65, 129.15, 128.32, 127.85, 126.52, 113.70
6	56.96	42.35	72.57	41.54	49.99	10.83	46.91	156.82, 156.19, 141.60, 141.40, 136.49, 130.64, 128.48, 126.77, 109.97, 107.16, 104.90
7	64.18	52.27	74.11	46.28	56.83	19.62 (**CH_2**CH_3) 14.83 (CH_2**CH_3**)	46.91	145.14, 143.96, 136.61, 130.82, 128.68, 128.38, 128.19, 127.44, 127.07, 126.88, 126.61
8	63.27	52.21	73.85	46.27	56.11	19.54 (**CH_2**CH_3) 15.00 (CH_2**CH_3**)	46.72	143.52, 142.37, 136.29, 133.14, 132.74, 130.78, 129.97, 128.52, 127.80, 126.78

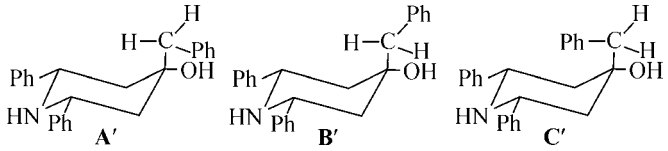


Fig. 1. Possible conformations of axial benzyl group in **1**

Therefore, in the minor isomer **1** benzyl group at C(4) occupies the axial position. Obviously, in the major isomer **2** the benzyl group at C(4) adopts equatorial configuration which is further confirmed by the absence of NOE between H(2) and H(6) with benzyl group at C(4). In 3-methyl tertiary alcohol **3**, the axial orientation of the hydroxy-group at C(4) is confirmed by the cross peak between hydroxyl group (1.37 ppm) and benzyl protons H(2) (3.86 ppm) and H(6) (4.10 ppm) in the NOESY spectrum. For the other 3-alkyl-4-benzyl-4-hydroxy-2,6-diarylpiperidines **4—8**, one can also expect similar orientations.

Conformational studies. The observation of one large (≈12 Hz) and one small (≈2 Hz) couplings about C(5)— C(6) bond in **1—8** and large coupling about C(2)—C(3) bond (≈10 Hz) in 3-alkyl derivatives **3—8** reveals normal chair conformation with equatorial orientations of aryl rings at C(2) and C(6) and alkyl groups at C(3).

There are three possible conformations (Figure 1) for the axial benzyl group at C(4) in **1**. In the conformations **A′** and **B′**, the phenyl ring of the benzyl group is gauche with respect to OH group, whereas in conformation **C′** the phenyl ring of the benzyl group is anti with respect to OH group and, moreover, only in this conformation it is directed inside the ring. The conformation **C′** is destabilized due to strong interaction of the phenyl ring of the benzyl group with hydrogens at C(2) and C(6) and hence it is not favored. Similar explanation has already been offered for the case of *cis*-1-benzyl-4-methylcyclohexane [13, 24, 25]. Therefore, the two gauche conformers **A′** and **B′** are equally populated in **1**. In both these conformations the phenyl ring of the benzyl group prefers to be oriented in such a way that the ring is perpendicular to the axial C(4)—CH_2 bond (parallel to the C(4)—O bond). The other orientation, in which the phenyl ring of the benzyl group lies in the same plane as the axial C(4)—CH_2 bond, is destabilized due to strong interaction of ortho protons of the phenyl ring of the benzyl group at C(4) with neighboring equatorial methylene protons at C(3)/C(5) and between ortho protons and hydroxyl group at C(4) and, therefore, not favored.

The conformation of the equatorial benzyl group in *cis*-1-benzyl-4-methylcyclohexane (**13**) (exists as an equilibrium mixture of conformations **13A** and **13B**) and in *trans*-1-benzyl-4-methylcyclohexane (**14**) has already been established [24, 25] as an equilibrium mixture of **A** and **B** with little contribution from C where the phenyl group is gauche to two carbon-carbon bonds (Figure 2). The three possible conformations for the equatorial benzyl group at C(4) in **2—8** are shown in Figure 3. In conformations **A** and **B**, the phenyl group is *gauche* with respect to OH group, whereas in conformation **C** it is *anti* to OH group. In all the three conformations the phenyl ring of the benzyl group at C(4) prefers to be oriented in such a way that the ring is roughly parallel to C(4)—O bond. Another orientation in which the phenyl ring lies in the same plane of the equatorial C(4)—CH_2 bond is destabilized due to the interaction of *ortho* protons of the phenyl ring of the benzyl group with the axial hydrogens at C(3) and C(5) in conformation C and with equatorial protons at C(5) and C(3) in conformations **A** and **B**, respectively. One can expect an equilibrium mixture of **A** and **B** in 4-benzyl-

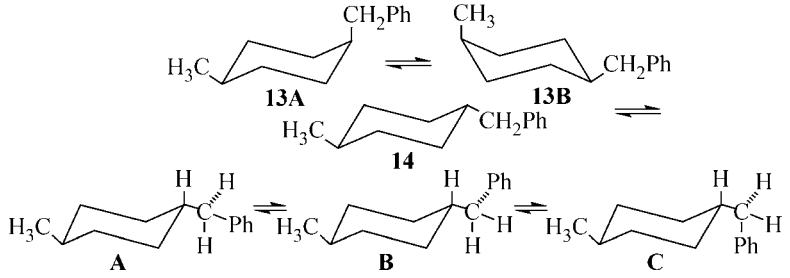


Fig. 2. Possible conformations of the equatorial benzyl group

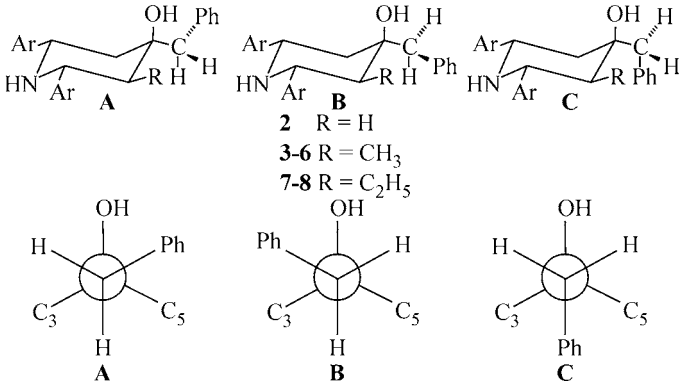


Fig. 3. Possible conformations of the equatorial benzyl group in **2**—**8**

t(4)-hydroxy-2,6-diphenylpiperidine **2** as well. However, in **3**—**8** the conformations **B** and **C** are destabilized due to strong interaction between alkyl group at C(3) and the phenyl ring of the benzyl group at C(4). Therefore, the favored conformation of 3-alkyl derivatives **3**—**8** has been determined as **A**.

Conformational search for the different conformers proposed in the present article has been carried out using hybrid HF/DFT methods, B3LYP/6-31*. The systems considered were models **1′**—**3′**. Frequency calculations at the same level have been carried out for all the structures (Figure 4)

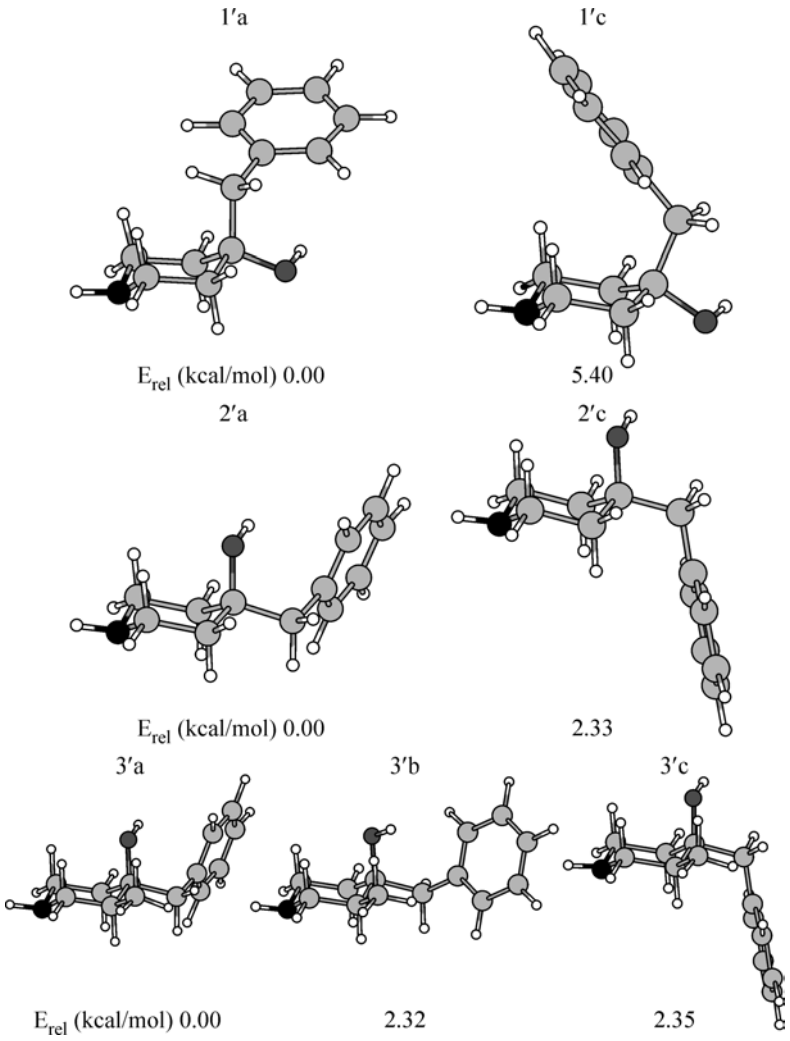


Fig. 4. Optimized structures of the model compounds

Table 4

Relative energy (kcal/mol) *of the energetic minima found for models* **1′—3′** *calculated at the* B3LYP/6-31G* *computational level*

1′a	**1′c**	**2′a**	**2′c**	**3′a**	**3′b**	**3′c**
0.00	5.40	0.00	2.33	0.00	2.32	2.35

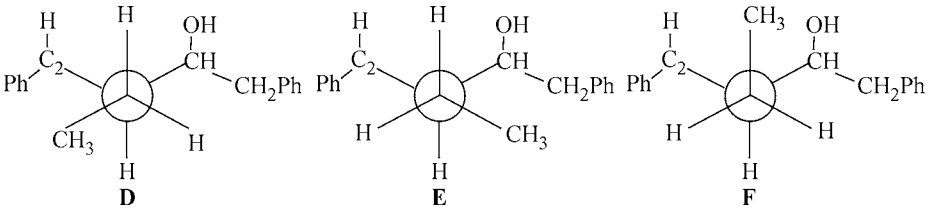
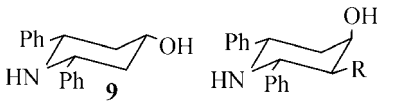


Fig. 5. Possible conformations of the ethyl group at C(3) in **7** and **8**

to confirm their correspondence to energetic minima (Table 4). In these cases the favored conformation was in agreement with the conformations as proposed in Figures 1 and 3 for **1—8**.

The three possible conformations for the ethyl group at C(3) in **7** and **8** are shown in Figure 5. The conformation **E** is destabilized due to strong interaction between methyl protons of the ethyl group at C(3) and methylene protons of the benzyl group at C(4) and hence this conformation was ruled out. In conformation **F**, there would be strong syn-1,3-diaxial interaction of the methyl protons of the ethyl group at C(3) with the benzyl proton H(2) and hydroxyl group at C(4) and hence the conformation is not favored. Therefore, the favored conformation of the ethyl group at C(3) in **3** and **7** was predicted to be **D**. This is further confirmed by **E** relative values calculated according to DFT method (E relative = 0.00 (**D**); 0.82 (**E**) and 1.26 (**F**) kcal/mol).

Analysis of chemical shifts. The chemical shift values of the heterocyclic ring protons and alkyl protons at C(3) in 4-benzyl-4-hydroxypiperidines (**1—3** and **7**) were compared with those of the corresponding 4-hydroxypiperidines [27], *i.e*. *c*(4)-hydroxy-r(2), *c*(6)-diphenylpiperidine (9), *t*(4)-hydroxy-r(2), *c*(6)-diphenylpiperidine (**10**), *t*(4)-hydroxy-t(3)-methyl-r(2), *c*(6)-diphenylpiperidine (**11**) and *t*(4)-hydroxy-*t*(3)-ethyl-r(2), *c*(6)-diphenylpiperidine (**12**) (Scheme 2). The comparison is given in Table 5.



10 R = H
11 R = CH_3
12 R = C_2H_5

The effects due to the introduction of an axial benzyl group at C(4) are in line with the observations already made by Booth [28]. The benzyl protons H(2) and H(6) of 4-benzyl-*t*(4)-hydroxypiperidine **2** absorb slightly at lower frequency as compared with t(4)-hydroxypiperidine **10**. These protons probably lie in the shielding region of the phenyl ring of the benzyl group at C(4) in the gauche conformations **A** and **B** (Figure 3), respectively, in **2**. In 3-alkyl-4-benzyl-*t*(4)-hydroxypiperidines **3** and **7**, the equatorial benzyl group at C(4) shields H(6) and causes no change in the chemical shifts of H(2) and H(3). In 3-alkyl derivatives **3—8**, the *gauche* conformation **B** is destabilized and hence there is no appreciable change in the chemical shifts of H(2) due to the presence of an equatorial benzyl group at C(4), whereas the shielding observed on H(6) can be explained by the gauche conformation **A**.

The shielding magnitude observed on the equatorial methylene proton at C(5), H_{5e}, is somewhat higher then for the axial methylene proton at C(5), H_{5a}, due to the presence of an equatorial benzyl group at C(4) in **3** and **7**. In gauche conformation **A**, the equatorial methylene proton at C(5) lies closer to the shielding region of the phenyl ring of the benzyl group at C(4) as compared with the axial

T a b l e 5

Comparison of ^{1}H *chemical shifts* (ppm) *for* 4-*benzyl*-4-*hydroxypiperidines* **1—3**, **7** *and* 4-*hydroxypiperidines* **9—11**

Compound	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	Alkyl protons
1	4.15	Same as H(5)	1.76—1.66	1.92	4.15	–
9	3.85	Same as H(5)	1.56	2.16	3.85	–
2	4.19	Same as H(5)	1.76—1.66		4.19	–
10	4.29	Same as H(5)	1.81	1.92	4.29	–
3	3.86	1.83	1.75	1.62	4.10	0.86
11	3.87	1.86	1.90	2.02	4.28	0.75
7	3.92	1.58	1.78	1.63	4.06	1.80, 1.21 (**CH_2**CH_3) 0.52 (CH_2**CH_3**)
12	3.91	1.65	1.90	2.07	4.27—4.31	1.03, 1230 (**CH_2**CH_3) 0.79 (CH_2**CH_3**)

methylene proton at C(5). Therefore, the shielding observed on H_{5e} is greater than that on H_{5a} due to the presence of the equatorial benzyl group at C(4) in 4-benzyl-4-hydroxypiperidines.

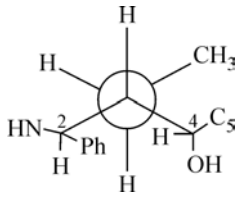
It is interesting to note that the methyl protons at C(3) in **3** and methylene protons of the ethyl group at C(3) in **7** are deshielded due to the presence of an equatorial benzyl group at C(4). The methyl protons at C(3) in **3** and methylene protons of the ethyl group at C(3) in **7** are γ-*gauche* with respect to the benzyl group at C(4). The steric polarization interaction between the methylene part of the benzyl group at C(4) and methyl/methylene protons of the alkyl group at C(3) is responsible for the observed deshielding in **3** and **7**. Indeed, in ^{13}C spectra the corresponding carbons are shielded due to the introduction of the equatorial benzyl group at C(4). On the other hand, the methyl protons of the ethyl group are shielded due to the presence of the equatorial benzyl group at C(4). In the favored conformation **D** for the ethyl group (Figure 5), the methyl protons of the ethyl group lie in the shielding region of the aryl ring at C(2), *i.e*. the methyl protons of the ethyl group are shielded due to a magnetic anisotropic effect from the aryl ring at C(2).

It is highly surprising that, as seen from Table 3, the chemical shifts of C(3) in **3—5** are slightly lower than that of C(5) and the α-effect from the equatorial methyl group was found to be approximately –1.5 ppm. Pandiarajan and Manimekalai [29] have shown that the α-effect of the equatorial methyl is +5.7±0.6 ppm in cases where there is no close substituents and it is reduced even more, to +1.1 ppm, due to *gauche* interaction, *i.e*. the magnitude of the α-effect of a particular substituent is significantly reduced by another, neighboring substituent and it decreases as the number of *gauche* interactions increases. In the present study we demonstrate that even the sign of α-effect of the equatorial methyl group is changed due to the presence of neighboring substituents. The methyl group experiences three strong gauche interactions with the neighboring substituents and hence the sign of α-effect of methyl group is changed. To our knowledge, this is the first observation of an equatorial methyl group exerting shielding influence on a methyl-bearing carbon. Moreover, the magnitude of the β-effect of the equatorial methyl group is somewhat lower (+1.85 ppm) on C(4) as compared with C(2) (+7.21) in **3**. A similar effect has also been observed in 7 due to the presence of ethyl group at C(3). The number of *gauche* interactions is greater on C(4) than on C(2) and, as a result, the α-effects of both the hydroxyl and benzyl groups at C(4) are reduced. This is probably a reason for the lower deshielding magnitude observed on C(4) as compared with C(2) in **3** and **7**.

In order to determine the substituent parameters of the benzyl group, the ^{13}C data for 4-benzyl-4-hydroxypiperidines (tertiary alcohols) were compared with those for the corresponding 4-hydroxypiperidines (secondary alcohols) [29, 30]; the substituent parameters are displayed in Table 6. The substituent parameters derived from 4-benzylpiperidine [31] are also included in this Table for comparison.

The α-effect of the equatorial benzyl group in **17** is considerably higher than in **2** which, in turn, is higher than in **3**. However, the α-effect of the benzyl group observed in 3-ethyl tertiary alcohol **7** is

Fig. 6. Favored conformation of the ethyl group in **12**



significantly higher than in **2** and **3**. This can be explained taking into account different conformations of the ethyl group in **12** and **7**. The favored conformation of the ethyl group in **12** is the one in which the methyl group of the ethyl side chain is anti to C(2) and gauche to C(4) (Figure 6), as was found by Manimekalai and Rajarajan [30]. Among three possible, the favored conformation in 3-ethyl tertiary alcohol **7** may be predicted as the one in which the methyl group of the ethyl side chain is *anti* to C(4) and *gauche* to C(2) (**D** in Figure 5). Therefore, the C(4) carbon resonates more considerably at lower frequency in **12** than in **7** and hence α-effect is considerably higher in **7** in comparison with the other compounds.

CONCLUSION

The conformation of the equatorial benzyl group at C(4) in **2** was established as an equilibrium mixture of **A** and **B**, whereas in 3-alkyl-4-benzyl-4-hydroxypiperidines **3—8** the favored conformation of benzyl group at C(4) was established to be **A**. In **1**, axial benzyl group at C(4) adopts the *gauche* conformations **A′** and **B′**. The α-effect of equatorial methyl group was found to be –1.5 ppm and this shielding magnitude may be explained by a strong gauche interaction. The conformation of ethyl group in **7** was found to be different from that in **12**.

EXPERIMENTAL

Synthesis of 4-benzyl-4-hydroxypiperidines 1—8. The 4-benzyl-4-hydroxypiperidines **1—8** were prepared from the corresponding parent piperidin-4-ones by adopting the general procedure reported in the literature [32]. The tertiary alcohols obtained were purified by chromatography and recrystallization from a benzene — petroleum ether mixture.

The melting points were as follows: 124—125 °C (**1**); 112—120 °C (**2**); 198—199 °C (**3**); 148—149 °C (**4**); 168—169 °C (**5**); 154—155 °C (**6**); 190—191 °C (**7**) and 182—183 °C (**8**).

Spectra. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AMX 400 NMR spectrometer operating at 400 and 100.6 MHz for ^{1}H and ^{13}C, respectively. The ^{1}H spectrum had the following experimental parameters: spectral width 5682 Hz; number of scans 32; acquisition time 2.88 s. The ^{13}C spectrum had the following experimental parameters: spectral width 29412 Hz; number of scans 54; acquisition time 0.56 s. ^{1}H—2D phase sensitive NOESY and ^{1}H—^{13}C COSY spectra were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. Samples were prepared by dissolving 10 mg (^{1}H) or 50 mg (^{13}C) of a compound in 0.5 ml of $CDCl_3$. All NMR measurements were performed using 5 mm NMR tubes.

Computational methods. Different conformations of the models **1′—3′** have been optimized at the B3LYP/6-31* computational level [33—35] using Gaussian-03 package [36]. Frequency calculations at the same level have been carried out to confirm that the geometries obtained corresponded to energetic minima on the energy surfaces.

T a b l e 6

Substituent parameters (ppm) *of the benzyl group in some* 4-*benzyl*-4-*hydroxypiperidines*

Compound	α	β	γ	Alkyl
1	+ 2.1	+ 2.75	– 1.17	–
2	+ 5.29	+ 4.44	+ 1.17	–
3	+ 2.74	+ 1.56 [C(3)] + 4.47 [C(5)]	+ 1.98 [C(2)] + 1.28 [C(6)]	– 3.70 (CH_3)
7	+ 7.81	+ 4.37 [C(3)] + 3.58 [C(5)]	+ 2.08 [C(2)] + 1.13 [C(6)]	– 0.68 (**CH_2**CH_3) + 3.63 (CH_2**CH_3**)
4-Benzylpiperidine	+ 12.19	+ 5.51	– 1.33	–

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