Synthesis and NMR study of the stereochemistry of r(2),c(6)-diaryl-c(3)-chloropiperidin-4-ones

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r(2),c(6)-Diaryl-c(3)-chloropiperidin-4-ones have been obtained by the epimerization of r(2),c(6)-diaryl-t(3)-chloropiperidin-4-ones by treatment with ammonia in DMF. The $^1$H and $^{13}$C NMR spectra of these piperidones were measured in CDCl$_3$ at 360 and 90 MHz respectively and the chemical shifts assigned unambiguously employing one dimensional $^1$H and $^{13}$C and two-dimensional $^1$H-$^1$H-COSY, $^1$H-$^{13}$C-COSY and NOESY NMR spectra. NMR spectroscopic parameters of the epimeric pair of chloropiperidones have been compared and the differences rationalized in terms of stereochemical features.

Experimental Section

The melting points reported in this work are uncorrected. The $^1$H and $^{13}$C NMR spectra were recorded in a Bruker NMR instrument at 360 and 90 MHz respectively in CDCl$_3$ or DMSO-$d_6$ solvent. All the spectra were measured employing standard Bruker software and the chemical shifts are referenced with respect to tetramethylsilane. The precursors, r(2),c(6)-diaryl-t(3)-chloropiperidin-4-ones 1a-e employed in the synthesis of the c(3)-chloropiperidones 3 were prepared according to literature method.

Preparation of c(3)-chloro-r(2),c(6)-diphenyl-piperidin-4-one 3a: A General procedure. To a solution of t(3)-chloro-r(2),c(6)-diphenylpiperidin-4-one (1.4 g; 5 mmole) in dimethylformamide (50 mL), ammonia (20 mL, 25% solution) was added and the solution kept for two days at room temperature. Then, the reaction mixture was poured into crushed ice, extracted with chloroform and dried over calcium chloride. The residue obtained after removal of the solvent was subjected to column chromatographic purification over silica gel using pet. ether-ethyl acetate mixture [5:1 (v/v)] as an eluent, yield 64%; m.p. 98°C. Anal. Caled for C$_{17}$H$_{16}$ClNO: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.40; H, 5.68; N, 4.93%.

c(3)-Chloro-r(2),c(6)-bis(4-methylphenyl)-piperidin-4-one 3b: Yield 66%; m.p. 70°C. Anal. Caled for C$_{19}$H$_{20}$ClNO: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.65; H, 6.48; N, 4.41%.

c(3)-Chloro-r(2),c(6)-bis(4-methoxyphenyl)-piperidin-4-one 3c: Yield 70%; m.p. 82°C. Anal. Caled for C$_{19}$H$_{20}$ClNO$_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 66.07; H, 5.85; N, 4.01%.
Results and Discussion

The r(2),c(6)-diaryl-t(3)-chloropiperidin-4-ones (1a: Ph; 1b: 4-MeC₆H₄; 1c: 4-MeOC₆H₄) required for the present study were obtained by a literature method.7 The piperidones 1, upon treatment with ammonia in dimethylformamide underwent epimerization to afford the axial diastereomers (3a: Ph; 3b: 4-MeC₆H₄; 3c: 4-MeOC₆H₄). The products were purified by column chromatography. It is pertinent to note that only ¹H NMR spectroscopic study was made for 1 in the previous study, wherein the chemical shifts were assigned only tentatively.7 In the present work, the ¹H and ¹³C NMR spectra of these compounds were measured and assigned unambiguously employing one-dimensional ¹H and ¹³C NMR and two-dimensional NMR spectra such as H,H-COSY, C,H-COSY, HMBC and NOESY to gain insight into the stereochemical aspects and their influence on the chemical shifts.

Assignment of chemical shifts of piperidones 1. The ¹H chemical shifts of piperidones 1a-c were assigned in the present work unambiguously employing one and two-dimensional ¹H NMR spectroscopic methods.7 For instance, the chemical shifts assigned for a representative example 1a are: 2.30 (s, NH); 2.75 (m, 1H, H-5ax); 2.81 (m, 1H, H-5eq); 4.60 (d, J=10 Hz, 1H, H-3); 4.14 (dd, J=10 and 5 Hz, 1H, H-6); 4.00 (d, J=10 Hz, 1H, H-2); 7.25–7.55 (m, 10H, Ph). These chemical shifts and the C,H-COSY correlations helped in the complete unambiguous assignment of the ring carbons of the piperidones. The carbon chemical shifts for the piperidones 1a-c are listed in Table I.

Relative stabilities of the epimeric chloropiperidones 1 and 3. The epimerization of equatorial chloro to axial chloropiperidones (viz., 1 to 3) under basic conditions indicates that axial isomers are thermodynamically more stable products and this may be explained in the following manner. While the equatorial chloropiperidones 1 may be destabilised by electrostatic interaction and the eclipsing interactions between the carbonyl and the C-Cl bonds, the diastereomeric axial chloropiperidones may suffer from the diaxial interaction between the axial chlorine and H-5ax as depicted in Figure 1. On the other hand, some attractive interaction between the NH proton and the axial chlorine is also possible in the case of axial epimer (Figure 1), when the NH proton adopts an axial orientation in one of the invertomers (3I). Thus, it seems that the total interactions in the axial isomer are not as destabilising as that in the equatorial isomer and this explains the formation of axial piperidones. The epimerization may be represented as shown in Figure 2.

¹H NMR study of r(2),c(6)-diaryl-c(3)-chloropiperidin-4-ones 3. The chemical shift assignment of these piperidones is illustrated taking 3a as a representative example. The ¹H NMR spectrum of 3a has one AMX and one AX spin system for the heterocyclic ring protons. The AMX spin system consisting of H-6, H-5ax and H-5eq affords three doublets of doublets at 4.67, 3.08 and 2.33 ppm. Among these, the signal at 3.08 ppm with two large coupling constants (19 and 9 Hz) is assigned to H-5ax as this proton has one geminal coupling (J) with H-5eq and one diaxial coupling (J) with H-6. Another doublet of doublets at 4.67 ppm with coupling constants of 9 and 2.4 Hz is assigned to H-6 as these coupling constants are ascribable to J_{H6,H5eq} and J_{H6,H5ax} respectively. The other signal at 2.33 ppm with J values of 19 and 2.4 Hz can be attributed to H-5eq.

The NOESY spectrum of 3a reveals that H-6 is proximate to the doublet at 3.27 ppm (J = 2.3 Hz) (Figure 3) ascribable to H-2, as H-6 is proximate only to H-2 and not to H-3. The other remaining doublet at 2.81 ppm (J = 2.3 Hz) is therefore due to H-3. Both H-2 and H-3 constitute the AX spin system. The proton chemical shifts of 3 are listed in Table II.

The ¹³C NMR spectra of other piperidones 3 showed similar features and the spectroscopic data of these compounds are presented in Table II. The ¹³C NMR spectra of r(2),c(6)-diaryl-t(3)-chloropiperidin-4-ones 3. The proton noise decoupled ¹³C NMR spectra of the compounds were measured in
The assignment of the carbon signals of the piperidones is discussed for c(3)-chloro-r(2),c(6)-diphenylpiperidin-4-one 3a. The assignment of the signals due to the heterocyclic ring carbons is readily achieved from the proton chemical shifts and C,H-COSY correlations. The C,H-COSY spectrum shows that the diastereotopic protons at C-5 are attached to the carbon at 39.6 ppm. The C,H-COSY correlations lead to the assignments: C-2: 45.3, C-3: 52.8 and C-6: 63.4 ppm for 3a. The carbon chemical shifts assigned for 3b and 3c are also furnished in Table III.

Proton and carbon chemical shifts of the epimeric chloropiperidones – A comparison. The proton and carbon chemical shifts of the epimeric chloropiperidones (1a and 3a, Ar = Ph) are compared in Table IV to assess the influence of the orientation of the chlorine atom on the chemical shifts. An examination of the proton chemical shifts reveals the following important differences between the epimers.

1. The H-2 in the equatorial isomer 1a is deshielded by 0.73 ppm relative to the corresponding

Table II — ¹H NMR spectroscopic data of r(2),c(6)-diaryl-c(3)-chloropiperidin-4-ones ³

<table>
<thead>
<tr>
<th>Piperidone (Ar)</th>
<th>(¹H NMR δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a (Ph)</td>
<td>2.33 (dd, J = 19 and 2.4 Hz, 1H, H-Seq), 2.81 (d, J = 2.3 Hz, 1H, H-3), 3.08 (dd, J = 19 and 9 Hz, 1H, H-Sax), 3.27 (d, J = 2.3 Hz, 1H, H-2), 4.67 (dd, J = 9 and 2.4 Hz, 1H, H-6), 7.20 - 7.40 (m, 10H, Ph)</td>
</tr>
<tr>
<td>3b (4-MeC₆H₄)</td>
<td>2.31 (dd, J = 19 and 2.3 Hz, 1H, H-Seq), 2.35 and 2.37 (singlets, 3H each, Me), 2.77 (d, J = 2.3 Hz, 1H, H-3), 3.06 (dd, J = 19 and 9 Hz, 1H, H-Sax), 3.24 (d, J = 2.3 Hz, 1H, H-2), 4.62 (dd, J = 9 and 2.3 Hz, 1H, H-6), 7.14 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H) and 7.31 (d, J = 8 Hz, 2H) [aryl]</td>
</tr>
<tr>
<td>3c (4-MeOC₆H₄)</td>
<td>2.28 (dd, J = 19 and 2.2 Hz, 1H, H-Seq), 2.72 (d, J = 2.3 Hz, 1H, H-3), 3.03 (dd, J = 19 and 9 Hz, 1H, H-Sax), 3.21 (d, J = 2.3 Hz, 1H, H-2), 3.77 and 3.79 (singlets, 3H each, OMe), 4.59 (dd, J = 9 and 2.2 Hz, 1H, H-6), 6.83 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 7.21 (d, J = 9 Hz, 2H) and 7.28 (d, J = 9 Hz, 2H) [aryl]</td>
</tr>
</tbody>
</table>

The spectra of 3a and 3b were measured in CDCl₃, while for 3c DMSO-d₆ was used; NH proton signal was not seen in all the cases.

Table III — ¹³C NMR chemical shifts of r(2),c(6)-diaryl-c(3)-chloropiperidin-4-ones ³

<table>
<thead>
<tr>
<th>Piperidone (Ar)</th>
<th>(¹³C NMR δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a (Ph)</td>
<td>39.6 (C-5), 45.3 (C-2), 52.8 (C-3), 63.4 (C-6), 126.1, 126.4, 127.5, 127.9, 128.4, 128.7, 136.5, 143.7 (aryl), 209.1 (CO)</td>
</tr>
<tr>
<td>3b (4-MeC₆H₄)</td>
<td>39.4 (C-5), 45.3 (C-2), 52.7 (C-3), 63.1 (C-6), 126.0, 126.2, 129.1, 129.3, 133.5, 137.0, 137.6, 140.8 (aryl), 209.5 (CO), 21.1, 21.0 (Me)</td>
</tr>
<tr>
<td>3c (4-MeOC₆H₄)</td>
<td>39.5 (C-5), 45.2 (C-2), 52.7 (C-3), 62.9 (C-6), 113.9, 114.1, 127.3, 127.5, 128.5, 136.1, 158.9, 159.4 (aryl), 209.6 (CO), 55.2 (both OMe)</td>
</tr>
</tbody>
</table>

²For 3a and 3b, CDCl₃ and for 3c, DMSO-d₆ employed for spectroscopic measurements.
proton in the axial epimer 3a. This can be ascribed to (i) gauche interaction between C-Cl and H-2 in 1a deshielding H-2 and (ii) variation in the orientation of the 2-phenyl group in 1a and 3a. Molecular mechanics calculations show that in 3a both the rings take up almost similar orientations with the dihedral angle between each aryl group and its benzylic C-H almost the same, ~40°, while in the case of 1a, the aryl at C-2 and the C-2-H are almost coplanar.

2. The signal of H-3 in the equatorial epimer 1a occurs deshielded by 1.79 ppm compared to H-3 in 3a. This could probably be attributed to the overlap of the axial C-3-H σ bond with the carbonyl π-bond in 1a resulting in deshielding of H-3, while the stereochemical relationship would preclude such an interaction of the equatorial C-3-H σ bond with the carbonyl π-bond in 3a.

3. The signal of H-5ax occurs 0.33 ppm deshielded in 3a relative to the corresponding proton in the epimer 1a. This is ascribable to van der Waals and diaxial interaction between the axial chlorine and H-5ax in 3a shifting electron density from H-5 towards C-5, which could also increase the electron density at H-5eq. This is also supported by the fact that the signal of H-5eq, on the other hand, is shielded in 3a relative to the corresponding proton in 1a by 0.48 ppm.

4. It is surprising to note that H-6 in 3a deshielded by 0.53 ppm relative to H-6 in 1a as this proton is far away from the C-3 carbon wherein the orientation of the chlorine is changed. Probably, 3a, which can exist in the form of two conformations interconvertible by nitrogen inversion, prefers the hydrogen-bonded conformation (Figure 4) wherein the equatorially oriented lone pair of nitrogen can deshield H-6. The above features are observed in the case of other epimeric piperidones also.

A comparison of the carbon chemical shifts of the heterocyclic rings of 1a and 3a reveals the following information:

1. The signals of C-2, C-3 and C-5 of 3a are shielded (by 23.0, 15.9, and 10.9 ppm respectively) relative to the signals of the corresponding carbons in 1a. This is explicable by the steric interaction between the axial chlorine and the C-5 syn-axial hydrogen in 3a resulting in a steric shielding shift.

2. On the other hand, the carbonyl carbon in 1a appears shielded by 10.0 ppm relative to that of 3a. This can be attributed to the fact the carbonyl group and the chlorine atom in 1a are sterically interacting resulting in shielding, besides dipole repulsion.

3. The C-6 carbon in 1a appearing at 60.7 ppm is only marginally shielded by 2.7 ppm relative to that in 3a, ascribable to the difference in the geometry of the heterocyclic rings in these diastereomers arising from the difference in the configuration at C-3 and the steric interactions.

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References

PERUMAL et al.: SYNTHESIS AND NMR STUDY OF SUBSTITUTED CHLOROPIPERIDIN-4-ONES