

Conformational studies on some 3-chloro-2,6-diaryl- piperidin-4-ones by ^1H NMR spectra

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A series of 2,6-diarylpiperidin-4-ones **1-10** with a chloro substitution at C3 and dichloro substitutions at C3 and C5 have been prepared. Based on the ^1H NMR data, the compounds are assigned the chair conformation in which aryl and chloro substituents are equatorially disposed. The presence of chloro group(s) on the piperidinone ring does not affect the nature of ring conformation. However, the coupling constant data of the compounds reveal that in few cases there is a flattening of the piperidinone ring. The ^1H NMR data of the compounds are substantiated by the dihedral angles estimated by the DAERM method.

The 2,6-disubstituted piperidines are biologically important compounds owing to their pharmacological activities and their presence in a variety of alkaloids¹. Although 2,6-diphenylpiperidin-4-ones with various substituents at 3- and 5-positions of the ring have been prepared earlier^{2a-c}, the 3-chloro substituted 2,6-diarylpiperidin-4-one derivatives were recently reported by us³. In continuation of our work, we report herein the preparation of few more new 3-chloro- and 3,5-dichloro-piperidin-4-ones (**3**, **4**, **6** and **10**) based on the available methods³. Since the conformational features of these compounds are yet to be studied, this work has a focus primarily on the conformational study using ^1H NMR data.

Results and Discussion

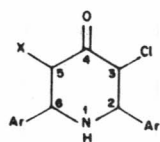
The ^1H NMR signal assignments have been made (cf. Table I) based on the earlier studies³. All the compounds gave analysable *ABX* spectra for the ring protons. In cases where the signals of C5 axial proton overlap with C5 equatorial, the coupling constants could be derived from the less complicated portion of the signal. Moreover, the C6 proton signal also gave the required information in place of C5 methylene protons. The ring protons in compound **10** forms only *AX* system and the coupling constant could be very easily extracted. The value of its coupling constant (10 Hz) and the signal assignments help the spectral analysis of other compounds (**1-9**).

Table I— ^1H NMR chemical shift data of compounds **1-10**

Compd	H(2) _{ax}	H(3) _{ax}	H(5) _{ax}	H(5) _{eq}	H(6) _{ax}	NH proton	Aromatic protons	Other protons
1	4.01	4.61	→ 2.85 →		4.16	1.62	7.54-7.26	
2	4.74	4.74	2.71 3.04		4.68	1.62	7.72-7.21	
3	4.72	4.72	2.66 3.04		4.62	2.26	7.69-7.13	
4	4.38	4.73	→ 2.82 →		4.38	1.72	7.69-7.17	2.45 and 2.38 ^a
5	4.32	5.01	→ 2.97 →		4.37	1.64	7.39-6.87	3.91 and 3.88 ^b
6	3.99	4.53	→ 2.81 →		4.14	1.62	7.52-7.02	
7	3.98	4.52	→ 7.79 →		4.13	1.59	7.48-7.26	
8	3.96	4.59	→ 2.82 →		4.11	1.72	7.41-7.15	2.36 and 2.34 ^a
9	3.94	4.56	→ 2.80 →		4.09	1.63	7.44-6.87	3.81 and 3.80 ^b
10	4.03	4.72	→ 4.72 →		4.03	1.58	7.83-7.26	

^aMethyl protons in the aromatic ring.

^bMethoxy protons in the aromatic ring.



- 1 Ar = Phenyl; X = H
- 2 Ar = *o*-Chlorophenyl; X = H
- 3 Ar = *o*-Bromophenyl; X = H
- 4 Ar = *o*-Methylphenyl; X = H
- 5 Ar = *o*-Methoxyphenyl; X = H
- 6 Ar = *p*-Fluorophenyl; X = H
- 7 Ar = *p*-Chlorophenyl; X = H
- 8 Ar = *p*-Methylphenyl; X = H
- 9 Ar = *p*-Methoxyphenyl; X = H
- 10 Ar = Phenyl; X = Cl

In the ^1H NMR spectra of the compounds **1-9**, the C6 proton gives rise to a doublet of doublet due to coupling with adjacent methylene protons. The two coupling constants, $\cong 10$ Hz and $\cong 4$ Hz are respectively due to a diaxial (J_{aa}) coupling and an axial-equatorial (J_{ae}) coupling (Table II). The C2 or C3 proton gives simply a doublet with a coupling constant of 10.18 to 10.51 Hz. In compound **10**, the C2 and C6 protons absorb at δ 4.01 with a coupling constant of 10.0 Hz. All these observations are in favour of the chair conformation to the compounds **1-10** with the equatorial orientation of the aryl and chloro substituents. The UV and IR spectral data also point out the equatorial disposition of the chloro substituent as follows. The UV spectrum of simple 2,6-diphenylpiperidin-4-one shows a λ_{max} of 292.0 nm for the carbonyl function. A λ_{max} of the same wavelength (290.0 nm) is observed for compound **1**. Had the chloro substituent been in axial position, the λ_{max} value would be shifted 22 nm to the

higher wavelength region⁴. Therefore, the absence of a bathochromic shift indicates the equatorial orientation of the chloro substituent. The IR spectra of the compounds **1-10** (cf. Table III) show the carbonyl absorptions in the range 1725-1741 cm^{-1} whereas the simple 2,6-diphenylpiperidin-4-one shows the same absorption at 1720 cm^{-1} . In cyclic α -haloketones if α -halogen is placed in equatorial position there will be a shift in the absorption to the extent of 10-20 cm^{-1} towards the high frequency region⁴. The observation of such a shift in these compounds prove the equatorial disposition of the α -chloro substituent. This orientation is favourable whenever the steric repulsion between axial halogen and the axial nitrogen lone pair exceeds the dipole repulsion between the carbonyl function and the adjacent equatorial α -halogen⁵ (Figure 1).

Coupling Constants. Inspection of coupling constants (cf. Table II) of the compounds reveals that

Table II—Vicinal and geminal coupling constants (Hz) of piperidinones **1-10**

Compd	$^3J_{2a3a}$	$^3J_{6a5a}$	$^3J_{6a5e}$	$^2J_{5a5e}$
1	10.265	9.546	4.904	8.908
2	a	11.770	2.746	13.615
3	a	11.570	2.710	13.670
4	10.358	11.102	3.131	13.498
5	10.515	8.982	6.388	7.347
6	10.187	10.386	4.044	13.045
7	10.314	10.726	3.712	14.421
8	10.388	9.104	5.297	8.375
9	10.192	8.613	5.744	7.550
10	10.000	10.000	—	—

^a = J values could not be determined as the signals are found merged.

Table III—Some physical data on the piperidinones

Compd*	m.p. °C	Mol. formula	Found (%) (Calcd)		
			N	C	H
1	108-9	C ₁₇ H ₁₆ ONCl	4.96 (4.90)	71.73 (71.44)	5.70 (5.64)
2	138-40	C ₁₇ H ₁₄ ONCl ₃	3.97 (3.95)	58.07 (57.57)	3.99 (3.97)
3	128-29	C ₁₇ H ₁₄ ONClBr ₂	3.08 (3.15)	46.13 (46.03)	3.12 (3.18)
4	129-30	C ₁₉ H ₂₀ ONCl	4.50 (4.46)	72.50 (72.71)	6.35 (6.42)
5	140-42	C ₁₉ H ₂₀ O ₃ NCl	4.30 (4.05)	66.19 (65.98)	5.90 (5.83)
6	135-37	C ₁₇ H ₁₄ ONClF ₂	4.32 (4.35)	63.42 (63.45)	4.35 (4.38)
7	180-82	C ₁₇ H ₁₄ ONCl ₃	3.92 (3.95)	57.92 (57.57)	4.06 (3.97)
8	147-48	C ₁₉ H ₂₀ ONCl	4.62 (4.46)	72.96 (72.71)	6.51 (6.41)
9	138-39	C ₁₉ H ₂₀ O ₃ NCl	4.15 (4.05)	65.81 (65.98)	5.75 (5.83)
10	162-64	C ₁₇ H ₁₅ ONCl ₂	4.48 (4.37)	63.28 (63.76)	4.65 (4.72)

* $\nu\text{C}=\text{O}$ at 1723-1741 and νNH at 3300-3354 cm^{-1}

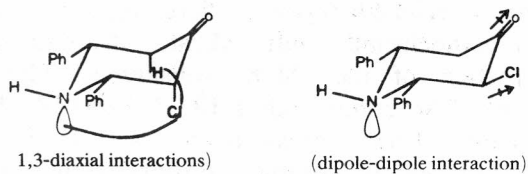


Figure 1

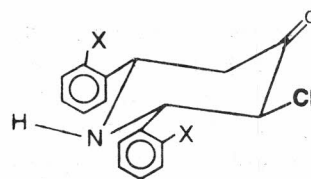
while the vicinal coupling (J_{2a3a}) values are fairly a constant, the J_{6a5a} values are found to have slight variations. This may be due to the fact that the aryl groups have greater rotational freedom at C6-C5 bond compared to C2-C3 (Cl) bond in the cases of unsubstituted compound **1** and *para*-substituted phenyl compounds **6-9**. Another observation is that for the majority of the compounds J_{2a3a} is almost equal to J_{6a5a} indicating a normal chair form for these compounds. However, for the methyl and methoxy substituted phenyl compounds **4**, **5**, **8** and **9** the differences between J_{2a3a} and J_{6a5a} values are significant. Hence, these compounds (**4**, **5**, **8** and **9**) should have a slightly flattened chair conformation. The slight deformation may be the result of electronegativity difference in the piperidinone ring, arising out of the introduction of mesomerically electron donating group (methyl or methoxy) bearing phenyl at C2 and the electron withdrawing chlorine at C3.

Since the J_{2a3a} values are constant, the dihedral angles ϕ_{2a3a} also should be constant for the compounds. However, the J_{6a5a} values which have slight variations are expected to reflect on the dihedral angles ϕ_{6a5a} and ϕ_{6a5e} . Hence, the dihedral angles to hydrogen adjacent to methylene function have been calculated based on DAERM method suggested by Slessor and Tracey⁶ (Table IV). Accordingly, the coupling constants are substituted in a modified Karplus equation⁶ and a complete solution for the angles ϕ_1 and ϕ_2 is arrived at by setting a program in FORTRAN 77 in IBM 486 DX computer. The best solutions are chosen based on the magnitudes of Karplus constants.

Table IV—Dihedral angles (deg.) based on DAERM method

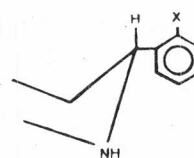
Compd	J_{aa}	J_{ac}	ϕ_{ac}	ϕ_{aa}
1	9.54	4.90	51.07	171.07
2	11.77	2.74	66.58	186.58
3	11.75	2.71	66.75	186.75
4	11.10	3.13	63.56	183.56
5	8.98	6.38	42.44	162.44
6	10.38	4.04	57.45	177.45
7	10.72	3.71	59.84	179.84
8	9.10	5.29	47.91	167.91
9	8.61	5.74	44.21	164.21

The dihedral angles thus derived are produced in Table IV. For compounds **5**, **8** and **9** for which $J_{6a5a} < J_{2a3a}$, the dihedral angles are found decreased appreciably, i.e. if a perfect ϕ_{ac} is considered 60° and ϕ_{aa} as 180° , then the decrease in the angle with respect to $H(6)_{ax}-H(5)_{eq}$ as well as $H(6)_{ax}-H(5)_{ax}$ is in the range $12.1-17.6^\circ$. Flattening of the ring becomes significant when there is a deviation in the dihedral angle by 7° in a regular chair form⁷. Hence, the compounds **5**, **8** and **9** should have flattening of the ring around C(6)-C(5) bond. Although the compound **4** has a difference between J_{2a3a} and J_{6a5a} values, it is only J_{2a3a} value which is lower by 0.744 Hz (cf. Table II)



X = Cl or Br

Figure 2



X = Cl, Br, Me or OMe

Figure 3

than J_{6a5a} value, and this is not expected to affect the C(6)-C(5) side, as it is the case, of the ring. In all the other cases (**1**, **2**, **3**, **6** and **7**), the deviations from the perfect ϕ_{aa} and ϕ_{ac} angles are not so high and hence they should have regular chair form. Thus, the estimated dihedral angles substantiate the observed 1H NMR data.

Chemical shifts. Some interesting observations have been made from the chemical shift data (cf. Table I) of the compounds. In compounds **2** and **3**, the signals due to H(2) and H(3), axial protons are found merged owing to the same magnetic environment as a result of halogen proximity around these protons (Figure 2). The nature of substitution on the aromatic ring produces two kinds of effects—shielding and deshielding on the benzylic protons. While the substitution in the *para*-position of the aromatic ring (as in compounds **6-9**) produces a slight shielding effect, the substitution in the *ortho*-position (as in compounds **2-5**) produces a deshielding effect (cf. Table I). The shielding order is *p*-methoxyphenyl > *p*-methylphenyl > *p*-chlorophenyl > *p*-fluorophenyl, whereas the deshielding order is *o*-chlorophenyl > *o*-bromophenyl > *o*-methylphenyl > *o*-methoxyphenyl. The values of deshielding produced by *ortho*-substituents on benzylic protons are substantial. This deshielding may not be due to the electronic effects of the

substituents, in that case the same substituent at *para*-position should cause the same deshielding. Further, it has been shown⁸ that the *ortho*-substituents, when adapt *syn*-orientation with benzylic proton can interact with the benzylic C-H bond creating polarity in such a way as to get the benzylic hydrogen deshielded. By considering significant deshielding on the benzylic hydrogens of the compounds **2** to **5**, the *ortho*-substituents of these compounds may be assigned the *syn*-orientation with the benzylic hydrogens (Figure 3). Another interesting observation is that in the cases of *o*-chloro and *o*-bromo substituted compounds (**2** and **3**), the equatorial protons at C5 are found deshielded compared to the axial protons (Table I). This may be attributed to the fact that the lone pair of electrons on the *o*-chloro and *o*-bromo substituent should deshield the equatorial methylene protons in these compounds (Figure 2). The deshielding produced on equatorial methylene protons by the lone pairs of *ortho*-substituents has been reported⁹ in the case of 1,4-oxathian-4,4-dioxides. This is also in favour of *syn*-orientation of the *ortho*-substituents with the benzylic hydrogens (Figure 3). However, such a deshielding is not observed in the *o*-methoxy compound **5** although the methoxy group contains lone pairs. This may be due to the slightly deformed chair configuration of the compound **5** as discussed earlier and because of it, the lone pair on the *o*-methoxy group is not properly rendered in a position to deshield the equatorial methylene protons at C5. Hence in that case, the *o*-methoxy group must be slightly tilted away from the *syn*-orientation with the benzylic hydrogens.

Experimental Section

¹H NMR spectra were recorded on a 270 MHz instrument. IR spectra were recorded on an FT-IR spectrophotometer and UV on a Hitachi U 3410 instrument.

The compounds were prepared according to the available methods³. All melting points (Table III) were determined on an electrically heated apparatus and are uncorrected.

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