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Papers

Stereochemistry and stereodynamics of *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones - NMR studies and semi-empirical molecular orbital calculations

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The preferred conformations of *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** have been determined using NMR spectral techniques, X-ray crystallography and semi-empirical molecular orbital calculations (AM1 method). The NMR spectral data indicates that the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** are found to exist in conformational equilibrium between the *syn* rotamer of boat conformations **B1** and *anti* rotamer of boat conformations **B2** in solution. The preferred conformation of **12** obtained through X-ray crystallography is found to be the *syn* rotamer of boat conformation **B1** with C2 and C5 occupying the prow and stern positions. The barriers for the N-CO rotation determined using variable temperature ^{1}H NMR spectral studies for the *N*-chloroacetyl derivatives **8** and **12** are 54.2 and 50.3 kJ mol^{-1}, respectively. The semi-empirical calculations (AM1 method) for the *N*-chloroacetyl derivatives **8-14** also support the conformational equilibrium between *syn* rotamer of boat conformations **B1** and *anti* rotamer of boat conformations **B2**.

Keywords: *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-one, NMR spectra, semiempirical MO calculation, boat conformation, *syn* and *anti* rotamers, variable temperature ^{1}H NMR spectra, energy barrier

The conformational equilibrium between the *syn* and *anti* rotamers due to the restricted rotation at N-C bond in several *N*-acyl derivatives of azacycles is known to be fast at RT and their ring conformations have been changed drastically due to the influence of *N*-acyl functions[1-7]. With a view to studying the relative influence of allylic strain, torsional strain, resonance energy due to the delocalisation of the lone-pair of electrons on nitrogen into the *N*-$COCH_2Cl$ group and 1,3-diaxial strains over the preferred conformations of the piperidine ring, certain *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** were synthesized and their stereochemistry was studied with the help of ^{1}H and ^{13}C NMR spectral data, dynamic ^{1}H NMR spectra, X-ray crystal structure determination and semi-empirical molecular orbital calculations (AM1 of MOPAC 6).

Results and Discussion

The *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** were prepared[1e] by the action of chloroacetyl chloride on the corresponding *r*-2,*c*-6-diarylpiperidin-4-ones **1-7** in dry benzene using triethylamine as a catalyst (**Scheme I**).

In the IR spectra of the compounds **8-14**, the amide >C=O stretching bands were observed around 1650 cm^{-1} in addition to the carbonyl stretching band around 1720 cm^{-1}. In the mass spectra, the presence of molecular ion peaks at *m/z* 327, 341, 355, 369, 355, 424 and 367 for the compounds **8-14**, respectively, and the fragmentation patterns confirmed their structures. The ^{1}H and ^{13}C NMR spectral signals of the *N*-chloroacetyl derivatives **8-14** were assigned by comparison with those of the *r*-2,*c*-6-diaryl-piperidin-4-ones **1-7** (ref. 7b,8) **(Table I)**. The SEFT (Spin Echo Fourier Transform) and SFORD (Single Frequency Off Resonance Decoupled) spectra were also used for the assignments.

Analysis of the ^{1}H and ^{13}C NMR spectra of the *N*-chloroacetyl derivatives **8-14** revealed the isochronous nature of proton and carbon signals, respectively, at RT. The signals of the benzylic protons appeared broad at RT. The broadening might have resulted from the coalescence of signals corresponding to the *syn* and *anti* rotamers involved in an equilibrium. The ^{1}H NMR spectra recorded at 213 K for all the *N*-chloroacetyl derivatives showed

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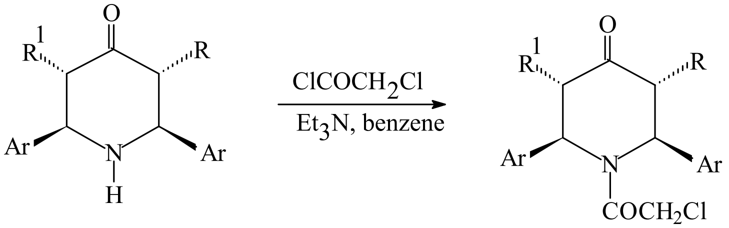


1	Ar = Ph; R = R^1 = H	**8**
2	Ar = Ph; R = Me; R^1 = H	**9**
3	Ar = Ph; R = Et; R^1 = H	**10**
4	Ar = Ph; R = i-Pr; R^1 = H	**11**
5	Ar = Ph; R = Me; R^1= Me	**12**
6	Ar = *p*-Cl-C_6H_4; R = Me; R^1 = Me	**13**
7	Ar = Thienyl; R = Me; R^1 = Me	**14**

Scheme I

doubling of all the signals for each of the protons corresponding to the *syn* and *anti* rotamers. The observation of broad signals at RT and doubling of all the proton signals at low temperature indicated the existence of conformational equilibrium in these *N*-chloroacetyl derivatives **8-14**.

Orientation of chloroacetyl group

If the delocalisation of the lone-pair of electrons on the nitrogen of the compounds **8-14** is sufficient to create a partial double bond character along the N-CO bond, the adjacent carbons and protons may give rise to anisochronous signals as in the case of *N*-nitroso-*r*-2,*c*-6-diarylpiperidines[8c,9]. The absence of anisochronous signals in the NMR spectra (at RT) of these *N*-chloroacetyl derivatives indicated that the N-CO moiety might adopt a coplanar orientation with the C2-N1-C6 plane with very low N-CO rotational barrier ($\Delta G^{\#}$).

In order to confirm the presence of restricted rotation around the N-CO bond, variable temperature ^{1}H NMR studies[10] have been carried out on the *N*-chloroacetyl derivatives **8** and **12** and the energy barriers for N-CO rotation ($\Delta G^{\#}$) were calculated from dynamic ^{1}H NMR spectra (**Charts 1** and **2**) using modified Eyring equation[10,11].

The change in the shapes of the signals of the benzylic protons was followed (**Charts 1** and **2**) for both the *N*-chloroacetyl derivatives **8** and **12** to calculate the energy barriers for the N-CO rotation. In both the cases the *syn* and *anti* rotamers have equal population. The chemical shift difference was plotted against the temperature and the chemical shift difference ($\delta\nu$) at coalescence temperature (T_c) was determined by extrapolating the plot. The T_c and $\delta\nu$ were found to be 284 K and 446.6 Hz, respectively, for **8** and the T_c and $\delta\nu$ were found to be 263.5 K and 468 Hz, respectively, for **12**. The energy barriers for the N-CO rotation for the compounds **8** and **12** were calculated as 54.2 and 50.3 kJ mol^{-1}, respectively. The observation of two signals for each of the protons at low temperature (213 K) in the chloroacetyl derivatives **8-14** revealed that the restricted rotation around the N-CO bond is the cause for the anisochronous nature of signals at this temperature and the orientation of N-CO would be co-planar.

Identification of s*yn* and a*nti* proton signals

In the case of *N*-chloroacetyl derivatives **8-14**, when N-C=O is *syn* to C2 carbon it is designated as a *syn* rotamer and when N-C=O is *anti* to C2 carbon it is designated as an *anti* rotamer (**Figure 1**). In the *syn* rotamer, H2 proton is *syn* to N-C=O group and H6 proton is *anti* to N-C=O group. In the *anti* rotamer, H6 proton is *syn* to N-C=O function and H2 proton is *anti* to N-C=O function. In the case of *N*-chloroacetyl derivatives **8** and **12-14** (symmetrical, H2 = H6), the H2 proton of *syn* rotamer and H6 proton of *anti* rotamer are chemical shift equivalent. Similarly the H6 proton of *syn* rotamer and H2 proton of *anti* rotamer are identical. Hence only two signals are expected for H2 and H6 protons of the *syn* and *anti* rotamers provided the ring conformation is symmetrical. In the case of *N*-chloroacetyl derivatives

Table I — Spectral characterization data of compounds **8-14**

Compd	IR	^{1}H NMR (CDCl$_3$, δ, ppm)	^{13}C NMR (CDCl$_3$, δ, ppm)	MS (M$^+$)
8	1640 (COCH$_2$Cl) & 1725 (C=O)	At RT: 2.78 (dd, H3-eq & H5-eq), 3.07 (dd, H3-ax & H5-ax), 3.94 (s, COCH$_2$), 5.89 (s, br, H2 & H6), 6.98- 7.48 (m, aromatic) At 213 K: 2.53 (dd, *J* = 17.4 and 4.5 Hz), 2.75 (dd, *J* = 17.4 and 11.4 Hz), 2.85 (dd, *J* = 18.7 and 5.7 Hz), 3.21 (dd, *J* = 18.6 and 2.9 Hz), H3 and H5 corresponding both *syn* and *anti* rotamers, 5.17 (dd, *J* = 11.4 and 4.5 Hz, H2-*anti* and H6-*syn*), 6.36 (s, br, H2-*syn* and H6-*anti*)	42.7 (CH$_2$ of COCH$_2$), 44.0 (C3 & C5), 55.0 (C2 & C6), 126.3,127.9, 128.9 (aromatic), 140.6 (ipso), 168.5 (COCH$_2$), 206.4 (C4)	327
9	1645 (COCH$_2$Cl) & 1720 (C=O)	At RT: 1.06 (d, CH$_3$ at C3), 2.85 (dd, H5-eq), 3.07 (t, H3-ax), 3.19 (dd, H5-ax), 3.92 (dd, COCH$_2$), 5.40 (s, br, H2), 5.93 (s, br, H6), 7.14-7.37 (aromatic) At 213 K: 4.75 (d, *J* = 10.8 Hz, H2-*anti*), 5.41 (s, br, H6-*syn*), 5.89 (s, br, H2-*syn*), 6.60 (s, br, H6-*anti*)	13.5 (CH$_3$ at C3), 42.6 (CH$_2$ of COCH$_2$), 42.8 (C5), 46.0 (C3), 54.5 (C2), 61.6 (C6), 126.5-129.1 (aromatic) 140.5, 140.7 (ipso), 168.8(COCH2),, 208.6 (C4)	341
10	1635 (COCH$_2$Cl) & 1720 (C=O)	At RT: 1.06 (t, CH$_3$ of ethyl), 1.71 (m, CH$_2$ of ethyl), 2.72 (dd, H5-eq), 2.93 (dd, H5-ax), 3.06 (dd, H3-ax), 3.94 (dd, COCH$_2$), 5.53 (s, br, H6), 6.14 (s, br, H2), 7.07-7.31 (aromatic) At 213 K: 5.08 (s, br, H2-*anti*), 5.28 (s, br, H6-*syn*), 6.33 (s, br, H6-*anti*), 6.46 (s, br, H2-*syn*)	11.7 (CH$_3$ of ethyl), 22.9 (CH$_2$ of ethyl), 42.4 (CH$_2$ of COCH$_2$), 44.5 (C5), 52.1 (C3), 56.5 (C2 & C6), 126.0-129.1 (aromatic), 140.6, 141.1 (ipso), 169.0 (COCH$_2$), 208.7 (C4)	355
11	1650 (COCH$_2$Cl) & 1725 (C=O)	At RT: 1.08 (d, CH$_3$ of isopropyl), 1.14 (d, CH$_3$ of isopropyl), 2.13 (m, CH of isopropyl), 2.73 (dd, H5-eq), 2.84 (m, merged, H3-ax & H5-ax), 3.93 (s, br) & 4.05 (d) COCH$_2$, 5.44 (s, br, H6), 6.49 (s, br, H2), 7.00-7.32 (m, aromatic) At 213 K: 5.34 (s, br, H6-*syn*) 5.38 (s, br, H2-*anti*), 6.34 (s, br, H6-*anti*), 6.58 (s, br, H2-*syn*).	20.5 & 21.3 (CH$_3$' s of isopropyl), 28.5 (CH of isopropyl), 42.5 (CH$_2$ of COCH$_2$), 44.7 (C5), 54.6 (C6), 57.2 (C2), 57.7 (C3), 125.9-129.0 (aromatic), 140.8 (ipso), 168.7 (COCH$_2$), 208.5 (C4)	369
12	1650 (COCH$_2$Cl) & 1705 (C=O)	At RT: 1.11 (d, CH$_3$ at C3 & C5), 3.16 (m, H3 and H5-ax), 3.91 (s, COCH$_2$), 5.49 (s, br, H2 & H6), 7.19-7.37 (aromatic) At 213 K: 4.81 (d, *J* = 10.3, H2- *anti* and H6-*syn*), 6.19 (s, br, H2-*syn* and H6-*anti*)	14.1 (CH$_3$ at C3 and C5), 42.6 (CH$_2$ of COCH$_2$), 45.4 (C3 & C5), 61.1 (C2 & C6), 128.0-128.9 (aromatic), 140.8 (ipso), 169.3 (COCH$_2$), 210.7 (C4)	355
13	1655 (COCH$_2$Cl) & 1720 (C=O)	At RT: 1.09 (d, CH$_3$ at C3 & C5), 3.07 (m, H3 and H5-ax) 3.90 (s, COCH$_2$), 5.42 (s, br, H2 & H6), 7.12-7.35 (aromatic) At 213 K: 4.88 (d, *J* = 9.5, H2- *anti* and H6-*syn*), 6.01 (s, br, H2-*syn* and H6-*anti*)	14.0 (CH$_3$ at C3 and C5), 42.3 (CH$_2$ of COCH$_2$), 45.3 (C3 & C5), 60.5 (C2 & C6), 128.7, 129.2 (aromatic), 134.1, 139.0 (ipso), 169.1 (COCH$_2$), 209.7 (C4)	424
14	1655 (COCH$_2$Cl) & 1705 (C=O)	At RT: 1.16 (d, CH$_3$ at C3 & C5), 3.26 (m, H3 and H5-ax) 4.07 (s, COCH$_2$), 5.59 (s, br, H2 & H6), 7.12-7.35 (aromatic) At 213 K: 5.25 (s, br, H2- *anti* and H6-*syn*), 5.94 (d, *J* = 4.1, H2-*syn* and H6-*anti*)	14.2 (CH$_3$ at C3 and C5), 42.1 (CH$_2$ of COCH$_2$), 46.9 (C3 & C5), 57.6 (C2 & C6), 126.0, 126.5 126.7 (aromatic), 144.0 (ipso), 168.2 (COCH$_2$), 209.0 (C4)	367

9-11 (unsymmetrical, H2 ≠ H6), H2 proton of *syn* rotamer and H6 proton of *anti* rotamer are not identical. Similarly the H6 proton of *syn* rotamer and H2 proton of *anti* rotamer are not identical. Hence four signals are expected corresponding to the H2 and H6 protons of *syn* and *anti* rotamers.

In general, as a result of the introduction of the –N-X=Y groups at nitrogen of the heterocyclic systems, the benzylic proton which is *syn* to the N-C=O function would be observed at downfield[1-3,4b,12-14] compared to the *anti* one on the basis of the Paulsen and Todt's model for anisotropy of amides and, on this basis, the signals corresponding to the H2 proton of *syn* rotamer (H2 is *syn* to N-C=O), H2 proton of *anti* rotamer (H2 is *anti* to N-C=O), H6 proton of *syn* rotamer (H6 is *anti* to N-C=O) and H6 proton of *anti* rotamer (H6 is *syn* to N-C=O) for the *N*-chloroacetyl derivatives **8-14** were assigned and presented in **Table I**.

Conformational analysis of *n*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones, 8-14

The possible ring conformations of the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** are shown in **Figure 2**. The *N*-chloroacetyl derivatives **8-14** may adopt any one of the conformations in which

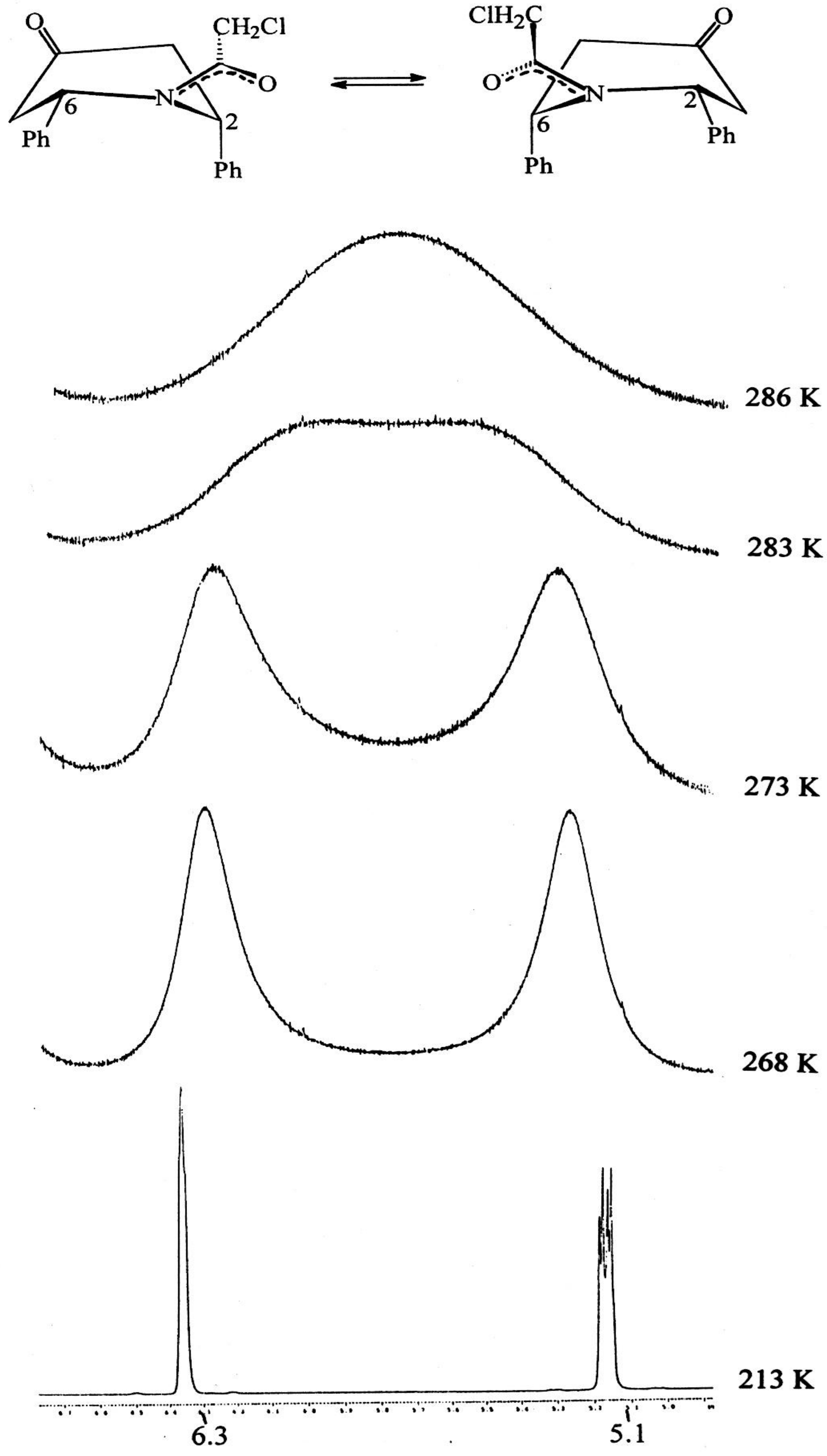


Chart 1 – Dynamic ^{1}H NMR spectra of **8**

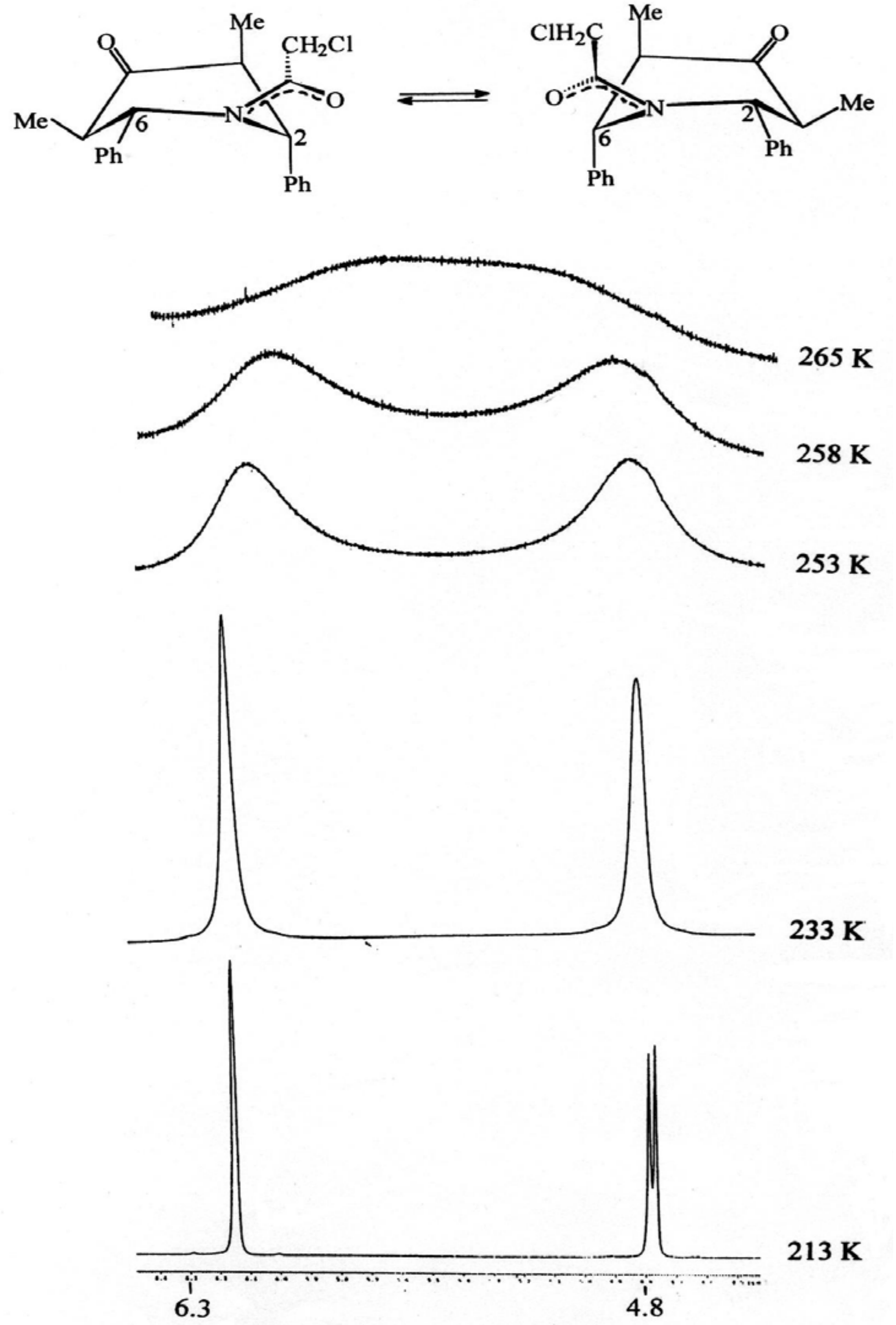
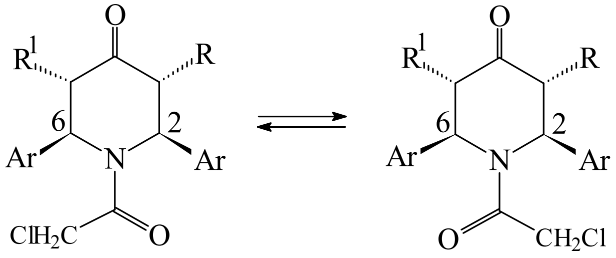


Chart 2 – Dynamic ^{1}H NMR spectra of **12**

the destabilizing strain factors such as $A^{1,3}$-strain, torsional strain and 1,3-diaxial interactions are minimum while retaining the coplanar N-C=O function which gives the maximum resonance energy to the molecule.

The preferred conformation of the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** was arrived at on the basis of the following factors. (i) The relative strain factors involved in each of the possible conformations (**Figure 2**), (ii) The observed vicinal coupling constant data (**Table II**), (iii) Orientation of protons deduced from the anisotropic influence of the chloroacetyl groups (by applying Paulsen and Todt's model[12] for the anisotropy of the amides, **Table III**),



Ar = Ph, p-ClC$_6$H$_4$, Thienyl; R, R^1 = H, Me, Et, i-Pr

Syn rotamer	*Anti* rotamer
N-C=O is *syn* to C2	N-C=O is *anti* to C2
H2 is *syn* to -C=O H6 is *anti* to -C=O	H2 is *anti* to -C=O H6 is *syn* to -C=O

Figure 1— Designation of *Syn* and *Anti* rotamers of **8-14**

(iv) Shielding of C2 and C6 carbons (**Table IV**) and (v) The relative stability of the conformations predicted on the basis of the semi-empirical molecular orbital calculations using the AM1 method available in MOPAC-6[15] (**Table V**).

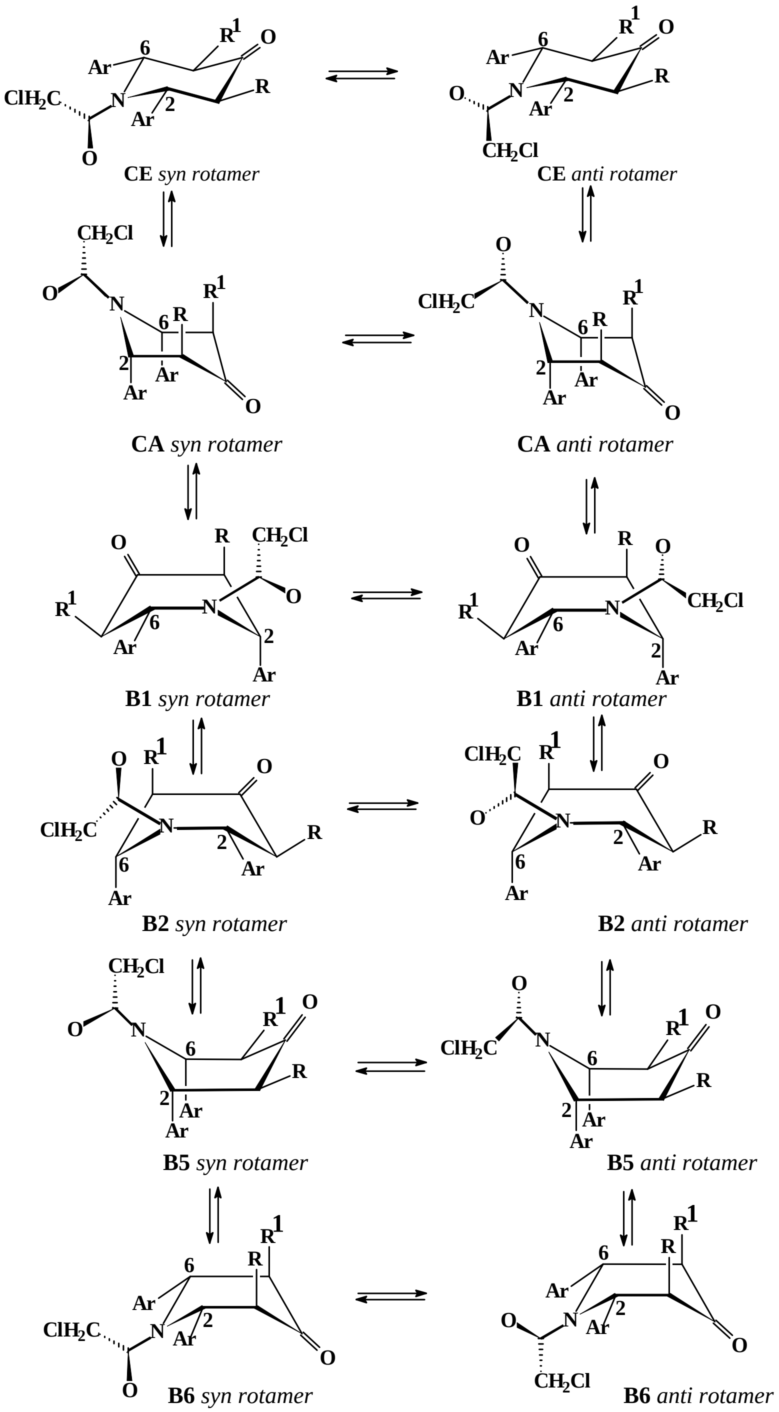
N-Chloroacetyl-*r*-2,*c*-6-diphenylpiperidin-4-one, 8

The variable temperature ^{1}H NMR spectral studies carried out for the *N*-chloroacetyl derivative **8** indicated that the broad signal for the benzylic protons H2 and H6 at δ 5.89 ppm (at RT) was split into two signals corresponding to *syn* and *anti* rotamers at 213 K (**Table I**). The signal which appeared broad at δ 6.36 ppm was assigned to H2 of *syn* rotamer (= H6 of *anti* rotamer) and the signal which appeared as doublet of doublet ($^3J_{2H3HA}$ = 11.4 Hz and $^3J_{2H3HB}$ = 4.5 Hz) at δ 5.17 ppm was assigned to H2 of *anti* rotamer (= H6 of *syn* rotamer). Since the signal for H2 proton of *syn* rotamer at δ 6.36 ppm was broad, the *trans* and *cis* vicinal coupling constants for H2 proton of *syn* rotamer were calculated from the corresponding coupling partners at C3 ($^3J_{2H3HA}$ = 5.7 Hz and $^3J_{2H3HB}$ = 2.9 Hz).

If the molecule assumes an equilibrium between the chair conformations **CE** (*syn* and *anti* rotamers)**,** the expected *trans* and *cis* coupling constants would be around 10-12 Hz and 2-4 Hz, respectively. However, the observed vicinal coupling constants $^3J_{2H3HA}$ = 5.7 Hz and $^3J_{2H3HB}$ = 2.9 Hz for the H2 of *syn* rotamer (= H6 of *anti* rotamer) and $^3J_{2H3HA}$ = 11.4 Hz and $^3J_{2H3HB}$ = 4.5 Hz for the H2 of *anti* rotamer (= H6 of *syn* rotamer) ruled out the possibility of the chair conformations **CE**. In the chair conformations **CE,** the benzylic protons at C2 and C6 are in the axial “out of plane” (shielding) region. The observed deshielding of the H2 (Δδ = 2.29 ppm) of *syn* rotamer (= H6 of *anti* rotamer) and of the H2 (Δδ = 1.10 ppm) of *anti* rotamer (= H6 of *syn* rotamer) from those of the parent cannot be convincingly explained on the basis of the model proposed by Paulsen and Todt for the anisotropic effect of the amides[12]. Hence the possibility of an “equilibrium” between the chair conformations **CE** (*syn* and *anti* rotamers) was ruled out.

In the flipped chair conformations **CA** (*syn* and *anti* rotamers), the A^{1,3}-strain is completely relieved since the phenyl groups are in axial position. But the 1,3-diaxial interaction between the two phenyl groups at C2 and C6 positions would destabilize the conformations. In these conformations, the benzylic protons H2 and H6 are at equatorial orientations and the J_{trans} and J_{cis} coupling constants are expected in the range of 2-4 Hz. Though the observed deshielding can be reasonably explained on the basis of the Paulsen and Todt’s model[12], the observed vicinal coupling constant $^3J_{2H3HA}$ = 11.4 Hz for the H2 of *anti* rotamer (= H6 of *syn* rotamer) ruled out the possibility of an “equilibrium” between the flipped chair conformations **CA** (*syn* and *anti* rotamers)**.**

In the boat conformations **B5** (*syn* and *anti* rotamers), though the A^{1,3}-strain is relieved, the 1,3-diaxial interaction between the phenyl groups would destabilize the conformations. The vicinal coupling



Ar = Ph, *p*-ClC_6H_4, Thienyl; R, R^1 = H, Me, Et, *i*-Pr

Figure 2— Possible conformations of *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-one

constants between H2 and H3 protons (= H5 and H6 protons) are expected to be around 8 Hz and 4 Hz but the observed vicinal coupling constant $^3J_{\mathrm{H2H3HA}}$ = 11.4 Hz for the H2 of *anti* rotamer (= H6 of *syn* rotamer) ruled out the possibility of an "equilibrium" between the boat conformations **B5** (*syn* and *anti* rotamers).

The boat conformations **B6** (*syn* and *anti* rotamers) are destabilized by the $A^{1,3}$-strain and bond eclipsing interactions. The vicinal coupling constants between H2 and H3 protons (= H5 and H6 protons) are expected to be around 8 Hz and 4 Hz but the observed vicinal coupling constant $^{3}J_{2H3HA}$ = 11.4 Hz for the H2 of *anti* rotamer (= H6 of *syn* rotamer) eliminated the possibility of an "equilibrium" between the boat conformations **B6** (*syn* and *anti* rotamers)**.**

In the boat conformations **B1** (*syn* and *anti* rotamers), the benzylic protons at C2 and C6 occupy equatorial and axial orientations, respectively. The benzylic protons H2 and H6 are not chemical shift equivalent. If an equilibrium is assumed between the boat conformations **B1** (*syn* and *anti* rotamers) four signals would be expected for the benzylic protons H2 and H6 (two signals for H2 and two signals for H6). The observation of only two signals for the benzylic protons, H2 and H6, ruled out the possibility of an "equilibrium" between the boat conformations **B1** (*syn* and *anti* rotamers). In the boat conformations **B2** (*syn* and *anti* rotamers), the benzylic protons at C2 and C6 occupy axial and equatorial orientations, respectively. Similar to the boat conformations **B1** (*syn* and *anti* rotamers), here also, the benzylic protons H2 and H6 are not identical. Hence, the observation of only two signals for the benzylic protons H2 and H6 eliminated the possibility of an "equilibrium" between the boat conformations **B2** (*syn* and *anti* rotamers).

Table II — Vicinal coupling constants (in Hz) of the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** compared with *r*-2,*c*-6-diarylpiperidin-4-ones **1-7**

Compd	C-2 (H)		C-6 (H)	
	syn rotamer	*anti* rotamer	*syn* rotamer	*anti* rotamer
8	5.7,2.9	11.4,4.5	11.4, 4.5	5.7, 2.9
1	9.9,4.5		9.9,4.5	
9	-----a	10.8	------a	------a
2	10.3		11.4,3.2	
10	-----a	10.8	------a	------a
3	10.4		11.8,2.8	
11	-----a	-----a	------a	------a
4	10.5		11.3,3.4	
12	-----a	10.3	10.3	-----a
5	10.3		10.3	
13	-----a	9.5	9.5	------a
6	10.4		10.4	
14	4.1	-----a	-----a	4.1
7	10.2		10.2	

[a]The value could not be determined due to the broadening of the signal

The observation of only two signals for the benzylic protons H2 and H6 and the observed vicinal coupling constants $^{3}J_{2H3HA}$ = 5.7 Hz and $^{3}J_{2H3HB}$ = 2.9 Hz for the H2 of *syn* rotamer (= H6 of *anti* rotamer) and $^{3}J_{2H3HA}$ = 11.4 Hz and $^{3}J_{2H3HB}$ = 4.5 Hz for the H2 of *anti* rotamer (= H6 of *syn* rotamer) could only be accounted by considering an "equilibrium" between the *syn* rotamer of boat conformation **B1** and the *anti* rotamer of boat conformation **B2**. The benzylic

Table IV — ^{13}C NMR chemical shift differences between the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** and the corresponding *r*-2,*c*-6-diarylpiperidin-4-ones **1-7** (in δ ppm)

Compd	C2	C3	C4	C5	C6
8	-6.0	-6.2	-1.3	-6.2	-6.0
9	-6.8	-5.6	-1.0	-8.1	-7.0
10	-10.2	-6.3	-0.4	-7.1	-5.3
11	-9.4	-0.4	-----	-6.4	-7.1
12	-7.7	-6.6	-0.4	-6.6	-7.7
13	-7.5	-6.6	-0.5	-6.6	-7.5
14	-5.9	-6.1	-0.3	-6.1	-5.9

Table III — Magnitude of deshielding (in δ ppm) of protons in the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** from the *r*-2,*c*-6-diarylpiperidin-4-ones **1-7**

Compd	H2	H3a	H3e	H5a	H5e	H6	H2		H6	
							syn rotamer	*anti* rotamer	*syn* rotamer	*anti* rotamer
			at RT				at 213 K			
8	1.82	1.82	0.47	0.18	0.47	0.18	2.29	1.10	1.10	2.29
9	1.78	1.84	----	0.39	0.51	0.17	2.27	1.13	1.32	2.51
10	2.41	1.46	----	0.38	0.25	0.04	2.73	1.35	1.21	2.26
11	2.50	1.35	----	0.17	0.17	0.17	2.59	1.39	1.25	2.25
12	1.88	1.88	----	0.37	----	0.37	2.58	1.20	1.20	2.58
13	1.85	1.85	----	0.38	----	0.38	2.44	1.31	1.31	2.44
14	1.64	1.64	----	0.53	----	0.53	1.99	1.30	1.30	1.99

Table V — Calculated relative heats of formation (kcal mol^{-1}) of various conformations of *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** by AM1 method

		Relative heats of formation (kcal mol^{-1}) Conformations						
Compd	Rotamers	CE	CA	B1	B2	B3	B4	B5
8	*syn*	6.60	4.49	0.00	3.43	6.01	------	------
	anti		2.57	3.43	0.00	-----	4.58	5.01
9	*syn*	7.37	2.48	0.00	4.00	7.01	4.56	-----
	anti		2.77	3.72	0.65	-----		5.01
10	*syn*	7.74	2.54	0.00	4.22	9.11	4.64	-----
	anti		2.02	3.97	0.97			5.07
11	*syn*	10.88	1.61	0.00	3.99	4.71	4.08	5.64
	anti		1.16	4.11	0.83	------		5.96
12	*syn*	7.42	4.65	0.00	3.66	6.41	4.66	4.53
	anti		3.25	3.66	0.00	------		4.77
13	*syn*	7.40	4.21	0.00	3.53	6.28	4.58	6.37
	anti		2.96	3.53	0.00	------		4.74
14	*syn*	10.86	5.22	0.00	1.62	13.71	14.29	5.14
	anti		6.66	1.62	0.00		------	5.14

protons at C2 in the boat conformation **B1** (*syn* rotamer) and at C6 in the boat conformation **B2** (*anti* rotamer) are equatorial (deshielding region). The observed deshielding of the H2 ($\Delta\delta$ =2.29 ppm) of *syn* rotamer (= H6 of *anti* rotamer) from those of the parent piperidin-4-one **1** (**Table III**) can be convincingly explained on the basis of the model proposed by Paulsen and Todt for the anisotropic effect of the amides[12].

The dihedral angles between the proton at C2 and the protons at C3 in *syn* rotamer of **B1** (= between the proton at C6 and the protons at C5 in *anti* rotamer of **B2)** are expected to be around 60°, respectively. However, the observed vicinal coupling constants, $^3J_{2H3HA}$ = 5.7 Hz and $^3J_{2H3HB}$ = 2.9 Hz, for the H2 of *syn* rotamer of **B1** ($^3J_{6H5HA}$ = 5.7 Hz and $^3J_{6H5HB}$ = 2.9 Hz, for the H6 of *anti* rotamer of **B2**) indicated that one of the dihedral angles is greater than 60° and the other dihedral angle is less than 60°. This could be explained by a twist along C6-N1-C2-C3 part of the *syn* rotamer of **B1** and a twist along C2-N1-C6-C5 part of the *anti* rotamer of **B2 (Figure 3)**.

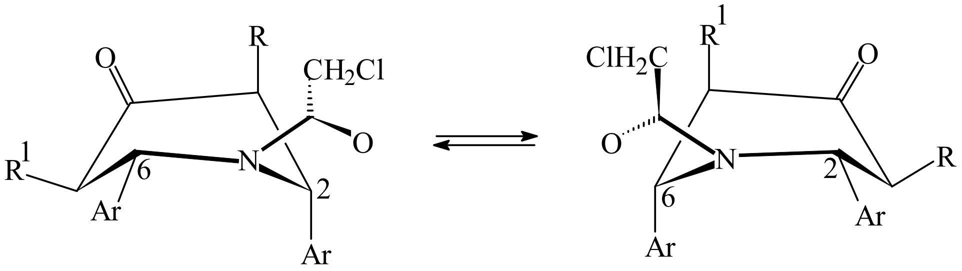
In the *N*-chloroacetyl derivative **8,** the benzylic carbons C2 and C6 were shielded by 6.0 ppm (**Table IV**) compared with the corresponding piperidin-4-one **1.** The shielding of C2 and C6 carbons may be due to the Γ-eclipsing interaction between the –C=O and N-C2/N-C6 bonds.

The results from semi-empirical molecular orbital calculations (AM1 of MOPAC 6) also support the conformational equilibrium between the *syn* rotamer of boat conformation **B1** and the *anti* rotamer of boat conformation **B2** (**Table V**). The relative energy difference between *syn* and *anti* rotamers of boat conformation **B1** is 3.43 kcal mol^{-1}. If an equilibrium between *syn* and *anti* rotamers of boat conformation **B1** is considered, then the population of *anti* rotamer is expected to be very less. On the other hand, the relative energy difference of 0 kcal mol^{-1} between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2** suggests that the equilibrium is between *syn* rotamer of **B1** and *anti* rotamer of **B2**.

Thus, on the basis of the coupling constant data, shielding/deshielding of benzylic carbons and protons and results from semi-empirical calculations, the *N*-chloroacetyl derivative **8** exists in conformational equilibrium between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2 (Figure 3)**.

N-Chloroacetyl-*r*-2,*c*-6-diphenyl-*t*-3-methylpiperidin-4-one, 9

In the *N*-chloroacetyl derivative **9**, two broad signals were observed for the benzylic protons H2 and H6 at δ 5.40 and 5.93 ppm, respectively (at RT). When the temperature was lowered to 213 K four



B1 *syn rotamer* **B2** *anti rotamer*

Ar = Ph, *p*-chlorophenyl, Thienyl ; R, R^1 = H, Me, Et, *i*-Pr

Figure 3 Conformational equilibrium between *Syn* and *Anti* rotamers of **8-14**

signals were observed for the benzylic protons H2 and H6 at δ 5.89, 4.75, 5.41 and 6.60 ppm corresponding to the *syn* and *anti* rotamers (**Table I**). The signals at δ 5.89, 5.41 and 6.60 ppm were not resolved well even at 213 K and the signal at δ 4.75 ppm appeared as a doublet. The signals at δ 5.89 (b) and 4.75 ppm (d, 10.8 Hz) were assigned to H2 proton of *syn* rotamer (H2 is *syn* to C=O) and H2 proton of *anti* rotamer (H2 is *anti* to –C=O), respectively. Similarly, the signals at δ 5.41 (b) and 6.60 (b) ppm were assigned to H6 proton of *syn* rotamer (H6 is *anti* to -N-C=O) and H6 proton of *anti* rotamer (H6 is *syn* to –N-C=O), respectively.

The calculation of coupling constants for the H2 proton of *syn* rotamer and H6 protons of *syn* and *anti* rotamers was not possible since the signals appeared broad. The calculation of the coupling constants from the coupling partners at C3 and C5 was also difficult because of the appearance of broad multiplets for the H3 and H5 protons. The coupling constant for the H2 proton of the *anti* rotamer was 10.8 Hz (**Table II**).

On the basis of the discussion made for the *N*-chloroacetyl derivative **8**, if an equilibrium between the *syn* rotamer of **B1** conformation and *anti* rotamer of **B2** conformation is considered, the following observations could be expected:

i) The signals for the H2 proton in the *syn* rotamer of **B1** and the H2 proton in the *anti* rotamer of **B2** would appear as doublets with vicinal coupling constants around 2-4 Hz and 10-12 Hz, respectively, and the signals for the H6 proton in the *syn* rotamer of **B1** and the H6 proton in the *anti* rotamer of **B2** would appear as doublet of doublets with vicinal coupling constants around 10-12 and 2-4 Hz and, 2-4 and 2-4 Hz, respectively.

ii) The signals corresponding to the H2 proton of *syn* rotamer (H2 is *syn* to C=O) and H6 proton of *anti* rotamer (H6 is *syn* to –N-C=O) are to be more deshielded.

The observation of coupling constant 10.8 Hz for H2 proton of *anti* rotamer and deshielding of H2 (Δδ =2.27 ppm) proton in *syn* rotamer and H6 proton (Δδ =2.51 ppm) in *anti* rotamer (**Table III**) support the conformational equilibrium between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2 (Figure 3)**.

In the case of *N*-chloroacetyl derivative **8,** the benzylic carbons C2 and C6 were shielded by 6.8 and 7.0 ppm, respectively (**Table IV**) compared with the corresponding piperidin-4-one **2**. This observation indicates that the Γ-eclipsing interaction between the C-O and N-C2 may be slightly less compared to the C-O and N-C6 bonds.

The relative energy difference of 0.65 kcal mol^{-1} between the *syn* rotamer of boat conformation **B1** and the *anti* rotamer of boat conformation **B2** from semi-empirical calculations for the *N*-chloroacetyl derivative **8** also suggests that the equilibrium is between *syn* rotamer of **B1** and *anti* rotamer of **B2 (Table V)**.

N-Chloroacetyl-*r*-2,*c*-6-diphenyl-*t*-3-ethylpiperidin-4-one, 10 and *N*-Chloroacetyl-*r*-2,*c*-6-diphenyl-*t*-3-isopropylpiperidin-4-one, 11

In the *N*-chloroacetyl derivatives **10** and **11** the signals for the H2 and H6 protons of *syn* and and *anti* rotamers were not resolved even at 213 K. The deshielding of benzylic protons and results from semi-empirical calculations were similar to *N*-chloroacetyl derivative **9.** Hence the *N*-chloroacetyl derivatives **10** and **11** also exist in conformational equilibrium between *syn* rotamer of boat conformations **B1** and *anti* rotamer of boat conformations **B2 (Figure 3)**.

N-Chloroacetyl-*r*-2,*c*-6-diphenyl-*t*-3,*t*-5-dimethylpiperidin-4-one, 12

In the case of *N*-chloroacetyl derivative **12**, a broad signal was observed for the benzylic protons H2 and H6 at δ 5.49 ppm (at RT). When the temperature was lowered to 213 K two signals were observed for the benzylic protons H2 and H6 at δ 6.19 and 4.81 ppm corresponding to the *syn* and *anti* rotamers (**Table I**). The signal at δ 6.19 ppm was not resolved well at 213 K and the signal at δ 4.81 ppm appeared as a doublet. The signals at δ 6.19 (b) and 4.81 ppm (d, 10.3 Hz) were assigned to H2 proton of *syn* rotamer (= H6 proton of *anti* rotamer) and H2 proton of *anti* rotamer (= H6 of *syn* rotamer), respectively. The coupling constant for the H2 proton of *syn* rotamer (= H6 proton of *anti* rotamer) could not be calculated since the signal appeared broad. The coupling constant for the H2 proton of the *anti* rotamer (= H6 proton of *syn* rotamer) was 10.3 Hz (**Table II**).

On the basis of the discussion made for the *N*-chloroacetyl derivative **8**, if an equilibrium between the *syn* rotamer of **B1** conformation and *anti* rotamer of **B2** conformation is considered for the compound **12**, the following observations would be expected:

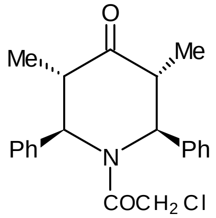
(i) The signals for the H2 proton in the *syn* rotamer of **B1** (= H6 proton in the *anti* rotamer of **B2)** and the H2 proton in the *anti* rotamer of **B2** (= H6 proton in the *syn* rotamer of **B1)** should appear as doublets with vicinal coupling constants around 2-4 Hz and 10-12 Hz, respectively.

(ii) The signal corresponding to the H2 proton of *syn* rotamer (= H6 proton of *anti* rotamer) is to be more deshielded.

The observation of coupling constant 10.3 Hz for H2 proton of *anti* rotamer (= H6 proton of *syn* rotamer) and deshielding of H2 (Δδ =2.58 ppm, **Table III**) proton in *syn* rotamer (= H6 proton of *anti* rotamer) support the conformational equilibrium between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2 (Figure 3)**.

The X-ray crystal structure of **12** (**Figure 4**) also corresponds to the *syn* rotamer of boat conformation **B1** with a twist along C6-N1-C2-C3 part[16].

The relative energy difference of 0 kcal mol^{-1} between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2** from semi-empirical calculations also suggests that the equilibrium is between *syn* rotamer of **B1** and *anti* rotamer of **B2 (Table V)**.



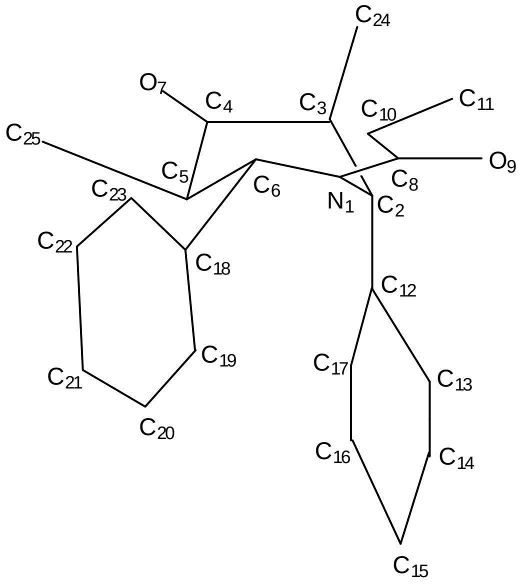


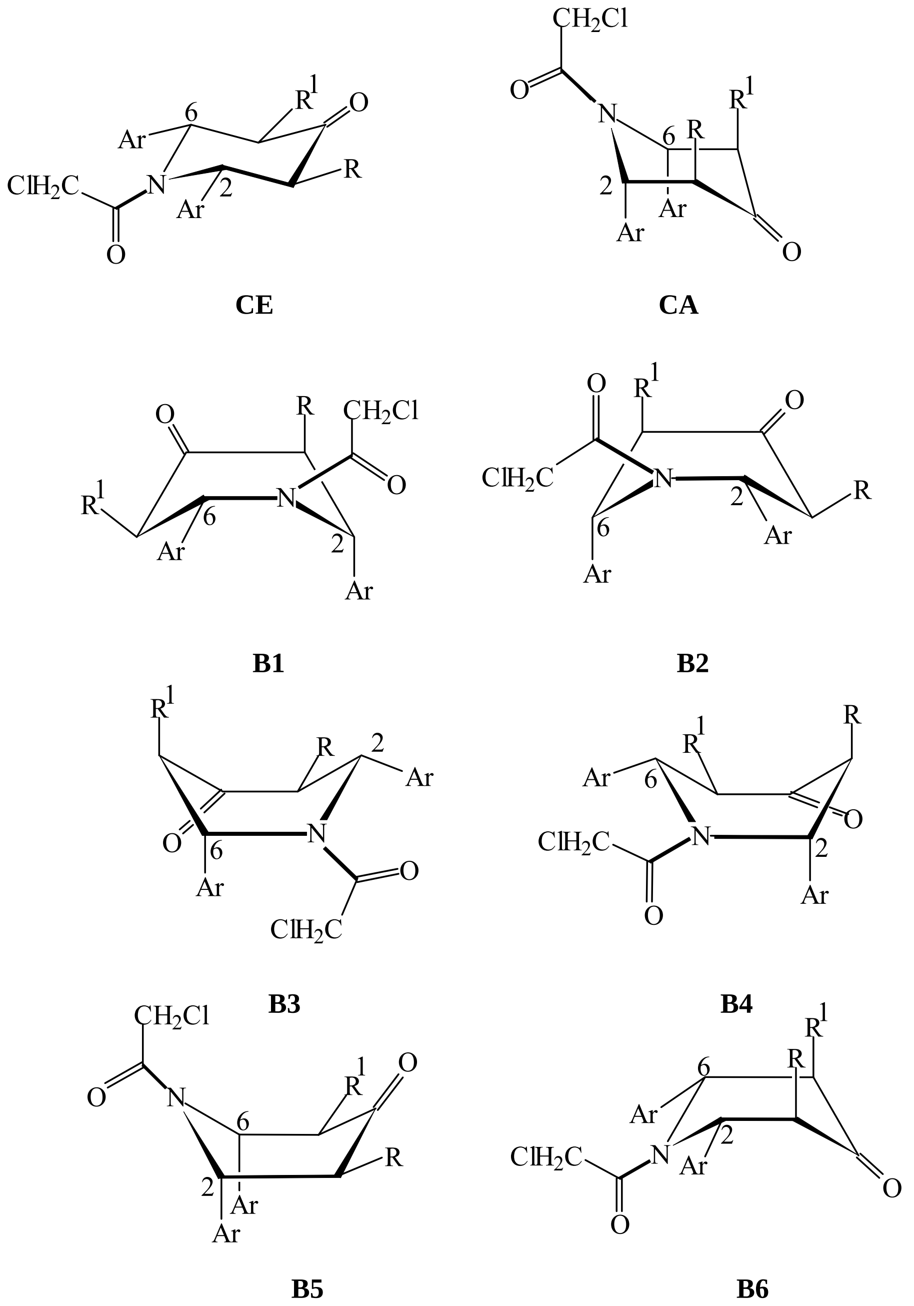
Figure 4 — ORTEP plot of **12**

N-Chloroacetyl-*r*-2,*c*-6-di(*p*-chlorophenyl)-*t*-3,*t*-5-dimethylpiperidin-4-one, 13

The observation of coupling constant 9.5 Hz (**Table II**) for H2 proton of *anti* rotamer (= H6 proton of *syn* rotamer), deshielding of H2 (Δδ =2.44 ppm, **Table III**) proton in *syn* rotamer (= H6 proton of *anti* rotamer) and the results from semi-empirical calculations for the *N*-chloroacetyl derivative **13** were similar to those of **12.** Thus the compound **13** exists in the conformational equilibrium between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2 (Figure 3)**.

N-Chloroacetyl-*r*-2,*c*-6-di(thienyl)-*t*-3,*t*-5-dimethylpiperidin-4-one, 14

In the case of compound **14**, the signal at δ 5.94 ppm for H2 proton of *syn* rotamer (= H6 proton of *anti* rotamer) appeared as a doublet with vicinal coupling constant value of 4.1 Hz and the signal at δ



CE CA

B1 B2

B3 B4

B5 B6

Ar = Ph, *p*-chlorophenyl, Thienyl; R, R^1 = H, Me, Et, *i*-Pr

Figure 5 — Input structures for *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14**

5.25 ppm for H2 proton of the *anti* rotamer (= H6 proton of *syn* rotamer) was not well resolved even at 213 K (**Table I**).

The observation of coupling constant 4.1 Hz (**Table II**) for H2 proton of *syn* rotamer (= H6 proton of *anti* rotamer) and deshielding of H2 ($\Delta\delta$ =1.99 ppm, **Table III**) proton in *syn* rotamer (= H6 proton of *anti* rotamer) support the conformational equilibrium between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2** (**Figure 3**). The relative energy difference of 0 kcal mol^{-1} between *syn* rotamer of boat conformation **B1** and *anti* rotamer of boat conformation **B2** from semi-empirical calculations also suggests that the equilibrium is between *syn* rotamer of **B1** and *anti* rotamer of **B2** **(Table V)**.

X-ray crystallography

In the case of a few *N*-nitroso-*r*-2,*c*-6-diarylpiperidines[13a] and *N*-ethoxycarbonyl-*r*-2,*c*-6-diphenylpiperidines[3] the preferred conformations in the solid state were different from the solution state. The *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** exist in conformational equilibrium between the *syn* rotamer of boat conformations **B1** and the *anti* rotamer of boat conformations **B2** in solution state. The crystal structure for one of the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones was determined to study the preferred conformation in the solid state. The ORTEP plot (**Figure 4**) of the molecule **12** showed the *syn* rotamer of boat conformation **B1** for the piperidine ring with a twist along C6-N1-C2-C3 part[16]. The phenyl group at C2 occupies axial orientation while that at C6 is at equatorial position. The bond lengths (N1-C8 = 1.37 Å; C8-O9 = 1.21 Å), bond angles (C6-N1-C2 = 118.68°; C6-N1-C8 = 123.07°) and dihedral angles (C2-N1-C8-O9 = - 10.34°; C6-N1-C8-O9 = -177.54°) clearly indicate the coplanar orientation of the *N*-chloroacetyl group.

Semi-empirical calculations

In order to know the preferred conformations of the *N*-chloroacetyl derivatives in an isolated environment, semi-empirical molecular orbital calculations[15] have been carried out. The heats of formation of various conformations of the *N*-chloroacetyl-*r*-2, *c*-6-diarylpiperidin-4-ones **8-14** were calculated using AM1 method available in MOPAC 6 program. For each *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-one all possible ring conformations (**Figure 5**), such as, a chair conformation (**CE**), a flipped chair form (**CA**), four boat forms (**B1-B4**) with C2 and C5 occupying prow and stern positions and two boat forms (**B5** and **B6**) with N1 and C4 occupying stern and prow positions, were considered as input structures. The optimization of these conformations was carried out by varying the torsion angle C2-N1-C=O within the possible range in 10° increments and the results are summarized in **Table V**.

The results obtained by changing the dihedral angle C2-N1-C=O in all the forms indicated that the chloroacetyl group was found to be coplanar with respect to the C2-N1-C6 plane. The N-C bond length was found to be around 1.39 Å, which is close to the average *sp*^{2} N-C bond length (1.38 Å) rather than the *sp*^{3} N-C bond length (1.47 Å). The shortening of the N-C bond showed the presence of a partial double bond character in the N-C bond in the coplanar orientation. In the case of **CE** conformations the nitrogen was found to be more of pyramidal type.

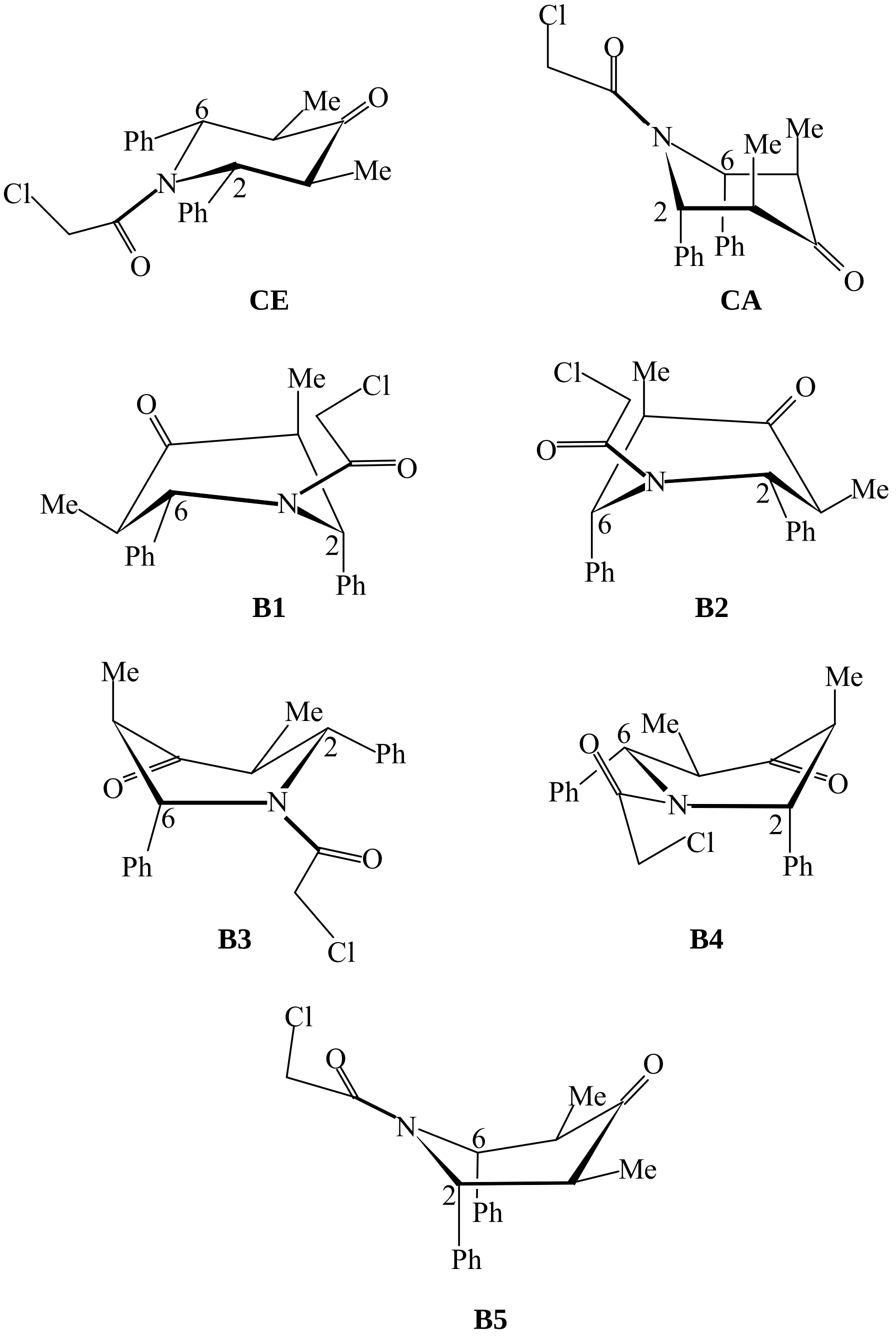
The relative formation energies of various conformations of the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** indicate that the *N*-chloroacetyl derivatives **8-14** exist in conformational equilibrium between *syn* rotamer of boat conformations **B1** and *anti* rotamer of boat conformations **B2**. AM1 optimized structures for various conformations of **12** are given in **Figure 6** as a representative example.

The chair forms **CE** with all equatorial substituents have higher energy. This observation shows that the A^{1,3}-strain operating between the alpha aryl groups and the N-C=O group causes destabilization of the **CE** conformation.

The **B6** form was found to be highly unstable, due to a combination of factors, the A^{1,3}-strain, bond eclipsing interactions and 1,3 Me-Me diaxial interactions. The energy difference between the **B1** and **CA** conformations seems to arise primarily from the 1,3-diaxial interaction of the two phenyl groups in the **CA** form though both the conformations are completely relieved from the A^{1,3}-strain.

In *syn* rotamer of boat conformation **B1** and in *anti* rotamer of boat conformation **B2** of the compound **12**, a typical case, the non-bonded distance between the oxygen of the chloroacetyl group and the alpha hydrogen (H2 in *syn* rotamer of **B1** and H6 in *anti* rotamer of **B2**) is 2.25 Å which is less than the sum of van der Waals' radii. The hydrogen bond type of attraction between the electron rich oxygen atom of N-C=O group and the electron deficient hydrogen at α-position (H2 in *syn* rotamer of **B1** and H6 in *anti* rotamer of **B2**) makes the *syn* rotamer of **B1** conformation and the *anti* rotamer of **B2** conformation more stable (in addition to other factors) than the others. The hydrogen bond type of attraction between α-CH and C=O is further supported by an elongated C2-H bond in the X-ray structure of the chloroacetyl derivative **12**. The elongation of C2-H bond due to a hydrogen bond type of interaction between α-CH and C=O (or N=O) in X-ray crystal structures of many *N*-acyl and *N*-nitroso derivatives of 2,6-diarylpiperidines was also reported[2-4,9,13a].

Thus it was concluded that the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14** exist in conformational equilibrium between boat conformations (*syn* rotamer of **B1** and *anti* rotamer of **B2, Figure 3**) in solution and in gaseous states. The X-ray crystal structure of **12** also showed the *syn* rotamer of boat



CE CA

B1 B2

B3 B4

B5

Figure 6 —AM1 optimized sttructures of **12**

conformation **B1**. These results indicate that the $A^{1,3}$-strain has a larger influence over other factors in determining the preferred conformations of the *N*-chloroacetyl-*r*-2,*c*-6-diarylpiperidin-4-ones **8-14**.

Experimental Section

All the melting points were determined using an electrically heated block with a calibrated thermometer and are uncorrected. Infrared spectra were recorded on a Shimadzu IR-435 spectrometer as KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on a Jeol GSX-400 MHz, Bruker AMX-400 MHz and Bruker DRX-500 MHz spectrometers in $CDCl_3$ solution using TMS as internal reference. Dynamic ^1H NMR spectra were recorded in $CDCl_3$ for the compounds **8** and **12** using Bruker DRX-500 MHz

Table VI —Physical characterization data of compounds **8-14**

Compd	m.p (°C)	Yield (%)	Mol.formula	Calcd/(Found) %		
				C	H	N
8	88-89	75.6	$C_{19}H_{18}NO_2Cl$	69.72	5.50	4.28
				(69.94	5.71	4.43)
9	112-13	83.5	$C_{20}H_{20}NO_2Cl$	70.38	5.87	4.11
				(70.63	6.12	4.35)
10	105-06	76.4	$C_{21}H_{22}NO_2Cl$	70.99	6.20	3.94
				(71.21	6.42	4.11)
11	85-86	84.8	$C_{22}H_{24}NO_2Cl$	71.54	6.50	3.79
				(71.27	6.34	4.02)
12	160-61	82.0	$C_{21}H_{22}NO_2Cl$	70.99	6.20	3.94
				(70.76	6.38	4.06)
13	138-39	85.8	$C_{21}H_{20}NO_2Cl_3$	59.43	4.72	3.30
				(59.76	4.54	3.56)
14	101-02	87.0	$C_{17}H_{18}NO_2ClS_2$	55.59	4.90	3.81
				(55.75	4.68	3.96)

spectrometer. Mass spectra were recorded on a Jeol JMS-D 300 spectrometer operating at 70 eV. The *r*-2,*c*-6-diaryl-piperidin-4-ones **1-7**[9,17] were prepared according to the reported procedures.

Computational details

The AM1 and PM3 methods available in MOPAC 6.1 version were used to perform the calculations on Pentium personal computers. The optimization of the conformations was performed by using an analytic gradient minimization method (BFGS, Precise option). Furthermore, eigenvector (EF option) procedure was used to lower the mean gradient up to values below 0.01 kcal mol^{-1}.

General procedure for the synthesis of *N*-chloroacetyl derivatives, 8-14

To a solution of the corresponding *r*-2,*c*-6-diaryl-piperidin-4-one (2.5 mmole) in anhyd. benzene (50 mL) was added triethylamine (1.4 mL, 10 mmole). The solution was cooled to 0-5°C and chloroacetyl chloride (0.8 mL, 10 mmole) in anhyd. benzene (20 mL) was added dropwise for a period of 30 min. After the addition was over, the reaction mixture was stirred at RT and the course of the reaction-mixture was monitored by TLC (silica, $CHCl_3$ as eluent). The reaction mixture was cooled, washed with sodium bicarbonate solution (10%), water and dried over anhyd. sodium sulfate. Evaporation of the solvent and purification by recrystallization from ethanol afforded the colourless crystals of *N*-chloroacetyl derivative. The yields and melting points are given in **Table VI**.

Acknowledgement

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