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Synthesis and NMR spectral studies of *N*-chloroacetyl-2,6-diarylpiperidin-4-ones

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Abstract

A series of 2,6-diarylpiperidin-4-ones having electron withdrawing chloroacetyl group at the heterocyclic nitrogen were synthesized. Unambiguous characterizations of the synthesized compounds were achieved by one-dimensional (^{1}H NMR and ^{13}C NMR) and two-dimensional (HOMOCOSY, NOESY and HSQC spectra for compounds **8** and **9** and HOMOCOSY spectrum only for **10**) NMR spectroscopic data. The conformational preferences of *N*-chloroacetyl-2,6-diarylpiperidin-4-ones with and without alkyl substituent at C-3 and C-5 (**8**–**14**) have also been discussed using the spectral studies. The spectral data and extracted coupling constant values suggest that the compounds **8**, **12** and **14** adopt flattened boat conformation whereas the remaining compounds exist in twist-boat conformations in solution with coplanar orientation of the chloroacetyl moiety present at the heterocyclic nitrogen. The substituent parameters for the chloroacetyl moiety on the heterocyclic ring carbons have also been derived and discussed elaborately on the basis of their steric, electronic and γ-eclipsing interaction. This substituent at the nitrogen causes a substantial change on the chemical shifts of ring carbons and the associated protons.

Keywords: ^{1}H NMR; ^{13}C NMR; 2D techniques; Conformation; Substituent effect; 2,6-Diarylpiperidin-4-ones; Chloroacetylation

1. Introduction

NMR spectroscopy is a versatile tool for providing information about the structural diagnosis of most of the heterocyclic compounds. It also finds its frequent use in the conformational analysis and in understanding the influence of electronic and conformational effects on chemical shifts and coupling constants. ^{1}H and ^{13}C NMR technique have been extensively applied in deriving stereochemical information about a wide variety of systems. Vicinal coupling constant values have been used in conformational analysis as it can give clue about the orientation of the substituent [1,2]. Substituted 2,6-diarylpiperidin-4-ones synthesized by Noller and Baliah [3] have been subjected to quite a large number of synthetic [4] and physico-chemical studies [5–8].

2,6-Diarylpiperidin-4-ones normally adopt chair conformation with equatorial orientation of all the substituents. However, introduction of certain heteroconjugate groups such as –NO, –CHO, $–COCH_3$, $–COC_6H_5$, etc., at the ring nitrogen of 2,6-disubstituted piperidine ring system have reported to cause a major change in ring conformation, chemical shifts of carbons and associated protons and also orientation of the substituents [9–13]. Further it has also been well documented by Johnson and Malhotra [14] that in N–NO, *N*-acyl, *N*-sulphonyl derivatives of 2-methylpiperidine and *r*-2, *c*-6-dimethylpiperidine, the methyl groups occupy axial position due to $A^{1,3}$ strain operated by the various type of substituents present at nitrogen on the equatorial methyl group (at both the α-positions). Hence, the change in ring conformation is mainly ascribed to an extensive delocalization of the lone pair of electrons on the nitrogen with the π-electron orbital of –COR function [9–13,15]. Owing to this, –N–CO acquires partial double bond character, which in turn leads to restricted rotation around this bond and consequently affects the conformation of the ring and chemical shifts of carbons and the attached protons.

In six-membered heterocyclic compounds, ^{13}C chemical shifts are very much affected by electronic effects due to heteroatom, γ-eclipsing effect operated by the substituent at 'N' and conformation of the ring [16].

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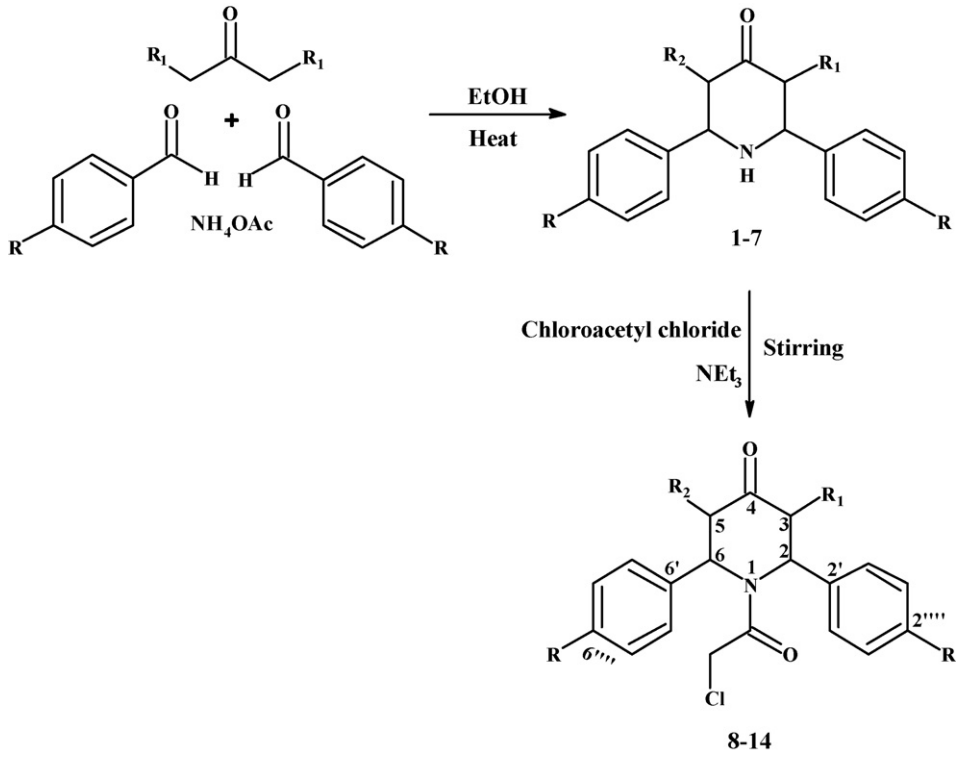
Though conformational analyses of 2,6-diarylpiperidin-4-ones having some electron withdrawing groups, viz. N–NO, N–COR, etc., at the heterocyclic nitrogen have been made already, no extensive study has been carried out on the NMR studies and conformational analysis of *N*-chloroacetyl-2,6-diarylpiperidin-4-ones. This prompted us to undertake a detailed NMR study on a series of synthesized compounds **8–14**, and to understand the change in ring conformation and its consequences on the chemical shift of ring carbons and attached protons due to the replacement of hydrogen by relatively bulkier chloroacetyl moiety at the heteroatom site.

In continuation of our earlier work on the spectral [17] and biological [18] studies of variously substituted 2,6-diarylpiperidin-4-ones, we report herein the synthesis and spectral studies of *N*-chloroacetyl-2,6-diarylpiperidin-4-ones with a view to assign its ^{1}H and ^{13}C NMR signals unambiguously and compare its stereochemical aspects with that of its parent compounds. Besides the effect of chloroacetyl substituent on the ring carbons resonances is also studied extensively.

2. Results and discussion

Variously substituted *N*-chloroacetyl-2,6-diarylpiperidin-4-ones were synthesized by electrophilic substitution reaction of chloroacetyl chloride with the corresponding parent piperidones in the presence of NEt_3 as base and benzene as solvent (Scheme 1). The yields, melting points and elemental analysis are furnished in Table 1. ^{1}H NMR chemical shifts of the synthesized compounds **8–14** are furnished in Table 2, while coupling constant values are given in Table 3. For the complete analysis of the compounds **8–14**, ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. Besides, HOMOCOSY, NOESY and HSQC spectra were also recorded for compounds **8** and **9** while for compound **10**, HOMOCOSY spectrum only was recorded.

IR spectra of all the compounds **8–14** (Table 4) reveal that the stretching band due to NH group disappeared while a new signal significant for the amide carbonyl stretching appeared at around 1660–1633 cm^{-1}. This confirms the complete conversion of NH into N-$COCH_2Cl$. Furthermore, it is obvious from Table 1 that chemical ionization mass spectrum of the compound



Scheme 1.

Compound	R	R_1	R_2
1	H	H	H
2	H	Me	H
3	H	*i*-Pr	H
4	Cl	Me	H
5	Cl	Me	Me
6	OMe	Me	H
7	OMe	Me	Me

Table 1
Physical data for compounds **1–9**

Compound	mp (°C)	Yield (%)	Elemental analysis					
			Calculated (%)			Found (%)		
			C	H	N	C	H	N
8	120–122	84	69.59	5.54	4.27	69.60	5.52	4.27
9[a]	131	94	70.25	5.90	4.09	70.28	5.91	4.1
10	102	89	71.41	6.54	3.79	71.41	6.55	3.8
11	169	82	58.45	4.42	3.41	58.46	4.42	3.4
12	159	80	59.34	4.75	3.29	59.32	4.74	3.29
13	128	83	65.72	6.02	3.49	65.73	6.01	3.5
14	108–110	80	66.39	6.30	3.37	66.40	6.30	3.37

[a] From the mass spectrum, molecular mass was found to be 342 $(M+H)^+$ for 2, which is consistent with the proposed molecular formula.

Table 2
Proton chemical shifts (δ, ppm) of compounds **8–14** and their parent compounds **1–3** and **5**

Compound	H_2 (s)	H_{3a} (m)	H_{3e} (dd)	H_{5a} (dd)	H_{5e} (dd)	H_6 (s)	Aromatic (m)	*p*-OCH_3 (s)	CH_3 (d)	CH (m)	CH_2Cl (m)
8	5.88	3.08 (dd)	2.78	3.08	2.78	5.88	6.99–7.30	–	–	–	3.90 (s)
9	5.39	3.04–3.07	–	3.17	2.83	5.92	7.11–7.36	–	1.06	–	3.86–3.95
10	6.45	2.82	–	2.85	2.72	5.43	6.98–7.30	–	1.13/1.07	2.08–2.16	3.89–4.05
11	5.35	2.95–2.98	–	3.11	2.87	5.86	7.02–7.33	–	1.06	–	3.91–3.97
12	5.42	3.03–3.09	–	3.03–3.09 (m)	–	5.42	7.11–7.35	–	1.09	–	3.89 (s)
13	5.30	3.00–3.04	–	3.15	2.80	5.87	7.01–7.16	3.78/3.81	1.03	–	3.87–3.96
14	5.39	3.09–3.13	–	3.12 (m)	–	5.39	6.84–7.10	3.81	1.08	–	3.90 (s)
1	4.09 (dd)	2.35–2.75 (m)				4.09 (dd)	7.26–7.49	–	–	–	–
2	3.63 (d)	2.68	–	2.74	2.83	4.10 (dd)	7.24–7.48	–	0.84	–	–
3	3.99 (d)	2.67	–	2.67	2.55	4.09 (dd)	7.22–7.47	–	0.8/1.02	1.66	–
5	3.63 (d)	2.69	–	2.69	–	3.63 (d)	7.26–7.38	–	[a]	–	–

[a] Not available.

9 shows $(M+H)^+$ ion at 342 and also peaks characteristic for the fragmentation pattern are obtained.

2.1. ^1H NMR spectra of symmetrically substituted N-chloroacetyl-2,6-diarylpiperidin-4-ones 8, 12 and 14

^1H NMR spectrum of symmetrically substituted compound **8** shows a multiplet in the most downfield region of about 6.99–7.30 ppm. This is due to aromatic protons at C-2 and C-6 positions of heterocyclic ring. Further, there are two double doublets each resonating at 3.08 ppm and 2.78 ppm respectively and a sharp singlet with maximum intensity at 3.93 ppm. Apart from this, there is also a broad singlet centered at 5.88 ppm. The double doublets centered at 3.08 ppm and 2.78 ppm has one large and one small couplings respectively at 17.44/6.24 Hz and 17.64/5.52 Hz. From the magnitude of coupling constants and on the basis of HOMOCOSY correlations (these two have cross peaks with each other Table 5) we can assign these two double doublets to methylene protons at C-3 and C-5. Here the large coupling constant is due to geminal coupling of H-3a/H-5a protons with H-3e/H-5e protons while the small coupling constant is due to the coupling of each of the methylene protons at C-3 and C-5 (H-3a/H-5a and H-3e/H-5e) with benzylic protons at C-2 and C-6.

Table 3
Vicinal and geminal coupling constants (Hz) of compounds (**8–14**) and parent piperidones (**1–5**)

Compound	$^3J_{2a,3a}$	$^3J_{2a,3e}$	$^2J_{3a,3e}$	$^2J_{5a,5e}$	$^3J_{5a,6a}$	$^3J_{5e,6a}$
8	6.24	5.52	17.54	17.54	6.24	5.52
9	7.01	–	–	18.22	6.10	5.91
10	1.50	–	–	17.02	9.50	6.00
11	6.90	–	–	18.15	5.46	6.02
12	6.71	–	–	–	6.71	–
13	6.99	–	–	18.35	5.59	6.01
14	6.78	–	–	–	6.78	–
1	9.96	4.47	–	–	9.96	4.47
2	10.36	–	–	–	11.85	2.83
3	10.51	–	–	–	11.67	3.03
5	10.36	–	–	–	10.36	–

NOE spectrum of compound **8** (Table 5) gives useful information about the assignments of ring protons and side chain methylene protons. Among the two double doublets, the one at 3.08 ppm has strong NOE with aromatic protons *ortho* to the phenyl *ipso* carbon than the other at 2.78 ppm. From this, it is concluded that the former one is due to H-3a and H-5a protons since these are spatially close to *ortho* protons while the later one is due to H-3e and H-5e protons. It has also been previously reported by Pandiarajan et al. [19] that the aromatic protons *ortho* to the *ipso* carbons show strong NOE with the adjacent axial proton.

A broad singlet centered at 5.88 ppm is unambiguously assigned for benzylic protons at C-2 and C-6. This assignment is evident from the NOESY spectrum of **8**, wherein this broad sin-

Table 4
IR and mass spectroscopic data **8–14**

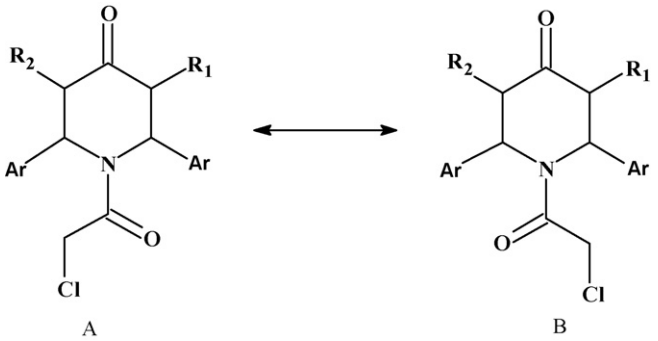
Compound	IR (cm^{-1})	M.S. *m/z*
8	3059; 3028; 2949; 2912; 2853(C–H stretching); 1723 (C=O stretching); 1633(N–C=O stretching); 1569; 1497; 1453; 1391; 1358; 1247; 1119; 1023; 947; 781; 702; 596; 480; 424	
9	3077; 3057; 3028; 2971; 2937; 2886(C–H stretching); 1721 (C=O stretching); 1651 (N–C=O stretching); 1495; 1453; 1386; 1323; 1253; 1199; 1116; 1079; 1027; 931; 855; 784; 744; 704; 607; 529; 405	$(M+H)^+$ 342 (base peak); 249; 238; 182; 149; 131; 119; 105; 91; 77
10	3082; 3044; 3028; 2984; 2962; 2924; 2897; 2869 (C–H stretching); 1718 (C=O stretching); 1648 (N–C=O stretching); 1494; 1454; 1383; 1263; 1216; 1137; 1105; 1031; 993; 931; 764; 701; 627; 518	
11	3071; 3044; 2981; 2929; 2869 (C–H stretching); 1723 (C=O stretching); 1658 (N–C=O stretching); 1492; 1433; 1401; 1342; 1302; 1263; 1130; 1093; 1013; 942; 834; 735; 670; 585; 543; 499; 448	
12	3010; 2983; 2938; 2872 (C–H stretching); 1717 (C=O stretching); 1652 (N–C=O stretching); 1492; 1386; 1335; 1258; 1206; 1091; 1014; 836; 788; 652	
13	3060; 3006; 2968; 2831 (C–H stretching); 1714 (C=O stretching); 1646 (N–C=O stretching); 1610; 1512; 1463; 1389; 1306; 1252; 1179; 1116; 1029; 930; 870; 848; 787; 662; 553; 411	
14	3021; 3015; 3000; 2973; 2962; 2935; 2902; 2836 (C–H stretching); 1713 (C=O stretching); 1658 (N–C=O stretching); 1609; 1513; 1458; 1388; 1289; 1252; 1180; 1110; 1029; 974; 886; 838; 809; 722; 586; 542	

Table 5
Correlations in the HOMOCOSY and NOESY spectra of compounds **8–10** [δ (ppm)]

Compound	Signal	Correlations in the HOMOCOSY spectrum	Correlations in the NOESY spectrum
8	7.19 (s, 4H)	No	5.88, 3.93, 3.08, 2.78
	5.88 (bs, 2H)	2.78	7.19, 3.93, 3.08, 2.78
	3.93 (s, 2H)	No	7.19, 5.88, 2.78
	3.08 (dd, 2H)	2.78	7.19, 5.88, 2.78
	2.78 (dd, 2H)	5.88, 3.08	7.19, 5.88, 3.08
9	7.24 (d, 2H)	No	5.92, 3.93, 3.88, 3.17, 3.06
	7.12 (d, 2H)	No	5.39, 3.93, 3.88, 3.17,1.06
	5.92 (bs, 1H)	3.17, 2.83	7.24, 3.93, 3.88, 3.17, 2.83,
	5.39 (bs, 1H)	3.06	7.12, 3.93, 3.88, 3.06, 1.06
	3.93, 3.88 (2d, 2H)	No	7.24, 7.12, 5.92, 5.39
	3.17 (dd, 1H)	5.92	7.24, 7.12, 5.92, 3.06
	3.06 (t, 1H)	5.39, 1.06	7.24, 7.12, 5.39, 1.06
	2.83 (dd, 1H)	5.92	7.24, 5.92, 2.83
	1.06 (d 3H)	3.06	7.12, 3.06
10	5.51 (bs, 1H)	2.91; 2.69	–
	2.91 (dd, 1H)	2.69	–
	2.69 (dd, 1H)	5.51; 2.91	–
	3.02–3.04 (m, 1H)	1.66–1.75	–
	1.66–1.75 (m, 2H)	3.02–3.04	–
	1.05 (t, 3H)	1.66–1.75	

glet shows strong NOE with the signals for methylene protons at C-3/C-5 and aromatic protons *ortho* to the *ipso* carbon. A more intense signal centered at 3.93 ppm shows strong NOE with the signals due to H-3e/H-5e, H-2a/H-6a and aromatic *ortho* protons. Hence, it can be conveniently assigned to methylene protons of chloroacetyl moiety at the heterocyclic nitrogen site. Since methylene protons of chloroacetyl moiety have strong NOE with the benzylic protons at C-2 and C-6, there is a possibility for the existence of two rotamers **2A** and **2B** (Scheme 2) arising out of restricted rotation of N–CO bond. However, only an average ^{1}H NMR spectrum was obtained in our case. This indicates that the two rotamers undergo interconversion at a faster rate on NMR time-scale.

^{1}H NMR spectrum of compounds **12** (having *p*-chloro phenyl at C-2 and at C-6) and **14** (having *p*-methoxy phenyl at C-2 and at C-6) having equatorial methyl substituent at C-3 and C-5



Scheme 2.

positions shows multiplet for the methine proton at the corresponding positions in the region of 3.03–3.18 ppm. Furthermore, a doublet in the region of about 1.09 ppm is assigned to methyl protons at C-3 and C-5. Unlike **8**, in **12** and **14**, two sets of signals were observed corresponding to two kind of aromatic protons (*ortho* and *meta* protons with respect to substituent at the *para* position). An additional sharp singlet appears at 3.81 ppm in **14** is due to methoxy protons present at the *para* position of phenyl groups at C-2 and C-6. The ^{1}H NMR assignments for the remaining signals are similar to that of corresponding signals in compound **8**.

2.2. ^{1}H NMR spectral analysis of unsymmetrically substituted N-chloroacetyl-2,6-diarylpiperidin-4-ones *9*, *10*, *11* and *13*

In compound **9** having equatorial methyl group at C-3, there are two double doublets centered respectively at 3.17 ppm ($^3J_{5a,6a}$ = 6.10 Hz, $^2J_{5a,5e}$ = 18.22 Hz) and 2.83 ppm ($^3J_{5a,6a}$ = 5.91 Hz, $^2J_{5a,5e}$ = 18.22 Hz). These are assigned respectively to H-5a and H-5e on the basis of its ^{1}H NMR, HOMOCOSY and NOESY spectra.

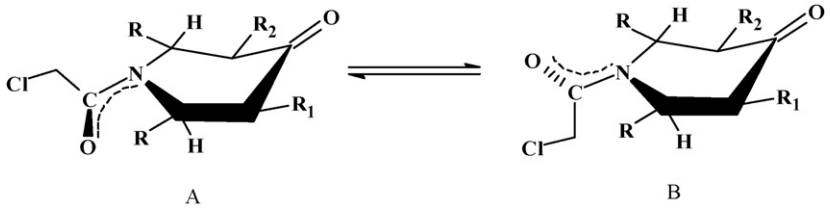
From the NOE (Table 5), it is pertinent to note that a triplet centered at 3.06 ppm has strong NOE with methyl protons signal at 1.06 ppm. Hence, the triplet is due to methine proton at C-3. Two broad singlets are observed for the benzylic protons H-2 and H-6 at 5.39 ppm and 5.92 ppm, respectively. A striking observation from NOE is that among the two, the upfield signal shows strong NOE with methyl protons signal at 1.06 ppm, methine proton signal at 3.06 ppm and aromatic protons *ortho* to the phenyl *ipso* carbon at 7.12 ppm whereas downfield one to two double doublets centered at 3.17 ppm and 2.83 ppm and also aromatic protons *ortho* to the phenyl *ipso* carbon at 7.24 ppm. Therefore two singlets at 5.39 ppm and 5.92 ppm are unambiguously assigned to H-2 and H-6 protons, respectively. Akin to compound **8**, the upfield double doublet at 2.83 ppm is assigned to H-5e while the downfield one at 3.17 ppm to H-5a by considering HOMOCOSY and NOESY correlations (Table 5). It is very interesting to note that the methylene protons of chloroacetyl moiety appears as two sets of closely spaced doublet at 3.88 ppm and 3.93 ppm unlike in compound **8** due to its anisochronous nature rather than isochronous, i.e. these protons become diastereotopic in nature due to the loss of symmetry by the methyl group introduction at C-3. In a similar manner, assignments of the ring and side chain protons are also made for **11** and **13**.

In the case of compound **10**, among the two benzylic proton signals, the one in the downfield region is assigned unambiguously to H-6 proton whereas the upfield one to H-2 proton on the basis of its HOMOCOSY correlations (Table 5) and with the supports of the magnitude of observed coupling constants. The HOMOCOSY spectrum of **10** correlates the broad singlet at 5.43 ppm with the two double doublets for C-5 protons at 2.72 ppm and 2.82 ppm thereby rendering the distinct assignment of this signal to H-6 proton. Hence, the other singlet at 6.45 ppm is due to H-2 proton.

2.3. Conformational analysis based on the coupling constant values

It is pertinent to note that the introduced chloroacetyl moiety at heterocyclic nitrogen can adopt either a coplanar or perpendicular orientation with respect to reference plane of the piperidone ring system. If chloroacetyl moiety is in energy minimum of planar conformation, the π-electron orbital of the amide carbonyl group overlaps with the orbital of the lone pair of electrons on the nitrogen there by stabilizes the planar conformation [20]. Further the signal due to benzylic protons is broadened instead of getting multiplicities in their signal (as observed for parent piperidones). Hence, the broadening of benzylic signal at room temperature strongly suggests the existence of restricted rotation about N-CO bond in the molecule due to high-energy barrier [20]. Furthermore, it is also obvious from the NMR study that such line broadening is possible only if we visualize coplanar orientation of chloroacetyl moiety to that of dynamically averaged plane of piperidone ring and is also confirmed by X-ray studies in the case of *N*-phenylcarbamoyl [11a] and *N*-benzoyl [11c] derivatives. Thus the prediction of coplanarity of chloroacetyl moiety is also supported by Lunazzi et al. [21] who have stated that perpendicular orientation does not bring about the said line broadening. Despite the restricted rotation of N-CO group in the molecules, we get only one set of signals for the ring protons instead of getting two set of signals corresponding to two rotamers **2A** and **2B** (Scheme 2) arising out of restricted rotation. Thus, the obtained one is only an average ^{1}H NMR spectrum for the compounds **8**–**14**. This may be due to the fact that the two rotomers undergo interconversion at a faster rate on NMR time scale.

In all the cases, the benzylic protons appear as a broad singlet while the ring methylene protons (at C-3 and C-5 in **8** and C-5 in **9**, **10**, **11** and **13**) appear as double doublet. A close survey of Table 2 reveals that incorporation of chloroacetyl moiety at the heterocyclic nitrogen makes the ring protons to deshield significantly compared to the corresponding parent piperidones. The deshielding magnitude of benzylic protons at C-2 and C-6 is in the range of 1.34–2.46 ppm. By comparing the coupling constant values of parent piperidones [7] a rigid chair conformation could not be offered for these molecules **8**–**14**, since the coupling constant values are abruptly changed from the parent compounds **1**–**7**. As reported earlier by Johnsons and Malhotra [14], in the case of *N*-substituted-2,6-dimethylpiperidines, the preferred conformation was found to be the one with axial methyl groups in order to avoid the severe 1,3 diaxial interaction ($A^{1,3}$) between the methyl groups. Hence, in this series of molecules also, there may be allylic ($A^{1,3}$) strain between the carbonyl group of chloroacetyl moiety with the α-phenyl groups. In order to avoid this, the normal conformation for these compounds **8**–**14** is ruled out and a non-chair conformation is proposed. To support this, the vicinal coupling constant values are also very much reduced in compounds **8**–**14** compared to their parents **1**–**7**. Therefore, it is more appropriate to note that the decrease in coupling constant values in these compounds may be due to increased electronegativity of 'N' owing to the existence of conjugation between nitrogen lone pair and p-electrons of carbonyl



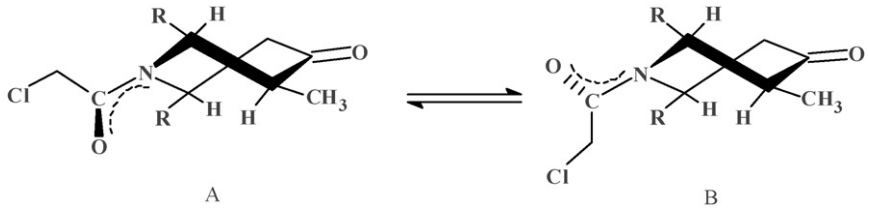
Scheme 3.

Compound	R_1	R_2	R
8	H	H	Ph
12	CH_3	CH_3	Ph (*p*-Cl)
14	CH_3	CH_3	Ph (*p*-OCH_3)

group. Also as the extracted coupling constant values are in close proximity with the one reported earlier for *N*-phenylcarbamoyl [11a] and *N*-benzoyl [11c] derivatives of 2,6-diarylpiperidin-4-ones, we may also propose similar kind of conformation for the chloroacetyl derivatives too, wherein the said $A^{1,3}$ strain is very minimum. Thus the compound **8** may exist in equilibrium between half boat conformations **3A** and **3B** (Scheme 3). In this proposed conformation, the ring becomes flattened appreciably at the nitrogen end and consequently the benzylic protons get into the planar region of chloroacetyl moiety. Inspite of this, the benzylic protons are deshielded by about 1.79 ppm compared to the parent piperidone **1** as they lie in the deshielding region of the amide plane (on the basis of the model proposed by Paulson and Todt [22] for the anisotropic effect of amides) [23]. Since the compounds **12** and **14** are symmetrically substituted by methyl group at C-3 and C-5, we may offer similar kind of conformation **3A** and **3B** for these compounds also. However, the benzylic protons are shielded by about 0.46 ppm and 0.49 ppm respectively compared to **8**. Also a striking observation in this molecule is that the vicinal coupling values are increased by about 0.8 Hz compared to the compound without methyl substitution at C-3 and C-5 (compound **7**). This reveals that flattening of the ring at the nitrogen is lowered slightly in conformations **3A** and **3B** for **12** and **14** thereby decreases their "in plane" nature of the benzylic protons. This consequently shields the H-2 and H-6 protons of **12** and **14** by about 0.46 ppm and 0.49 ppm respectively compared to **8**.

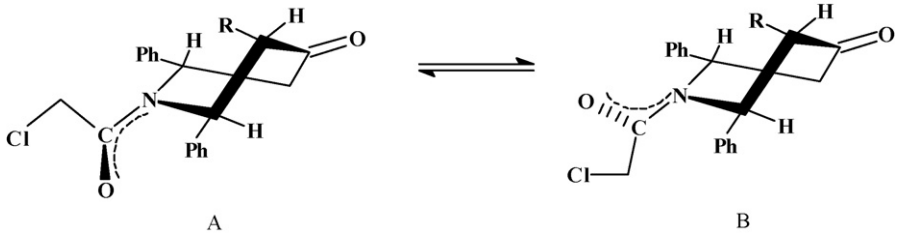
In the case of compound **9** having equatorial methyl group at C-3 position, the benzylic protons H-2 and H-6 are deshielded by about 1.76 ppm and 1.82 ppm respectively compared to its parent compound **2**. However, the magnitude of deshielding is not changed appreciably from compound **8** but, $^3J_{2a,3a}$ value is higher than that of **8**. Thus, in order to account for the observed difference in chemical shift and coupling constant values, an equilibrium mixture of twist-boat conformers **4A** and **4B** (Scheme 4) is proposed for compound **2**. In this conformation, the ring of **9** is puckering about C(2)-C(3) and C(5)-C(6) bonds compared to **8**. Similarly compounds **11** and **13** respectively bearing *p*-chloro and *p*-methoxy phenyl groups at C-2 and C-6 instead of phenyl groups also adopt similar conformation (i.e. **4A** and **4B**) as the difference in chemical shift and coupling constant value are not significant from **9**.

In the case of compound **10** having bulkier isopropyl group at C-3 deshields the C-2 benzylic proton significantly (H-2 = 6.45 ppm) compared to **9** (H-2 = 5.39 ppm). This may be due to the increased bulkiness of the substituent at C-3 which forced the C-2 benzylic proton more to lie "in plane" with chloroacetyl moiety. As a result of this C-2 benzylic proton is deshielded greatly than C-6 proton. Furthermore, there is a substantial decrease in $^3J_{2a,3a}$ value in **10** compared to **9**. Thus in **10**, the ring is further flattened about C(2)–C(3) bond and prefers to be in equilibrium mixture of the conformations **5A** and **5B**. In all the cases (**8**–**14**), the benzylic protons are deshielded significantly compared to their parents. Due to coplanarity of



Scheme 4.

Compound	R
9	Ph
11	Ph (*p*-Cl)
13	Ph (*p*-OCH_3)



Scheme 5.

Compound	R
10	*i*-Pr

chloroacetyl moiety, the C–H(2)/C–H(6) bonds get polarized by amide carbonyl group, which in turn develops fractional positive charge over protons and negative charge over the carbon, which bears the corresponding proton. As a result of this, resonances of carbons are shielded while the attached protons are deshielded (Scheme 5).

2.4. ^{13}C NMR spectral analysis of N-chloroacetyl-2,6-diarylpiperidin-4-ones

In the ^{13}C NMR spectrum of this series of compounds, there are two signals in the region of 206–210 ppm and 168–169 ppm. These are characteristic for ring carbonyl group at C-4 and amide carbonyl carbon at the heterocyclic nitrogen respectively. The signals in the region of 114–159 ppm are due to aromatic carbons. Among this, the less intense signals with higher chemical shift values in the region of 132–159 ppm are characteristic for *ipso* carbons. In compounds **11** and **12**, the chlorine bearing *ipso* carbons show resonance at around 134 ppm while in **13** and **14** the methoxy bearing *ipso* carbons appear at about 159 ppm due to the effect of substituent present at the corresponding carbons.

The heterocyclic ring carbon signals appear in the range of 42–62 ppm can be assigned more precisely with the help of HSQC spectra recorded for compounds **1** and **2**. The chemical shift values of compounds **8**–**14** and their parent compounds **1**–**7** are listed in Tables 6 and 7, respectively.

From the HSQC spectrum of compound **8** (Table 8), it is evident that benzylic protons at C-2 and C-6 have cross peaks with the low intensity signal at 55.36 ppm. Thus, it is due to benzylic carbons at C-2 and C-6. Similarly, as the signal at 44.06 ppm shows cross peaks with methylenic protons at C-3 and C-5, it corresponds to methylenic carbons at C-3 and C-5. A signal with double the intensity to that of C-3 and C-5 signal is ascribed to methylenic carbon of side chain chloroacetyl moiety, since it has cross peak with –$\underline{CH_2}$Cl protons signal. It is pertinent to note that, shielding of C-2 and C-6 carbons may perhaps be due to flattening of the ring at the 'N' site and also due to the known electronic and γ-eclipsing interaction.

From the ^{13}C NMR spectrum of compound **9**, the assignments for the C-2, C-6 and C-3 carbons are made and are further confirmed from its HSQC (Table 8) spectrum. However, there are two signals resonating very closely at 42.98 ppm and 42.73 ppm in **9**. The assignment of this signal is made unambiguously with the help of HSQC, wherein the signal at 42.98 ppm has cross peak with methylene protons at C-5 while the other at 42.73 ppm with side chain –$\underline{CH_2}$Cl protons. Therefore, among the two, the former one is assigned more precisely to C-5 carbon and the

Table 6
^{13}C chemical shifts (δ, ppm) of compounds **8**–**14**

Compound	C-2	C-3	C-4	C-5	C-6	CH_3	CH	N–C=0	CH_2Cl	Aromatic
8	55.36	44.06	206.33	44.06	55.36	–	–	168.66	42.68	140.79 (C-2′,C-6′), 126.57–129.11 (other aryl carbons)
9	61.85	46.14	208.61	42.98	54.73	13.63	–	168.94	42.73	140.65 (C-2′), 140.92 (C-6′), 126.66–129.21 (other aryl carbons)
10	57.77	54.94	208.37	44.64	57.19	20.40/21.28	28.56	168.64	42.41	140.89 (C-2′,C-6′), 125.894–128.99 (other aryl carbons).
11	61.26	46.12	207.69	42.48	54.34	13.75	–	168.71	42.33	138.82 (C-2′), 138.99 (C-6′), 134.31 (C-6′′′), 134.19 (C-2′′′), 128.05–129.40 (other aryl carbons)
12	60.73	45.51	209.76	45.51	60.73	14.14	–	169.30	42.38	139.20 (C-2′, C-6′), 134.35 (C-2′′′,C-6′′′), 128.81 and 129.32 (other aryl carbons)
13	61.44	46.35	208.77	43.06	54.19	13.59	–	168.76	42.67	159.35 (C-6′′′), 159.28 (C-2′′′), 132.78 (C-2′), 132.98 (C-6′), 114.25-128.73 (other aryl carbons)
14	60.68	45.64	210.81	45.64	60.68	14.03	–	169.17	42.59	159.24 (C-2′′′, C-6′′′), 132.92 (C-2′, C-6′), 114.24–128.59 (other aryl carbons)

Table 7
^{13}C chemical shifts of parent piperidin-4-ones **1–3** and **5**

Compound	C-2	C-3	C-4	C-5	C-6	CH_3	CH_2	CH	Aromatic
1	61.0	50.2	207.8	50.2	61.5	–	–	–	142.60 (C-2′, C-6′), 126.40–128.60 (other aryl carbons)
2	68.4	51.6	209.50	50.90	61.50	10.10	–	–	141.80 (C-2′), 142.7(C-6′), 126.50–128.60 (other aryl carbons)
3	66.6	58.1	209.0	51.1	61.7	12.0	–	17.8	141.9 (C2′), 142.9 (C6′), 126.4-128.5 (others)
5	68.0	51.9	210.1	51.9	68.0	[a]	–	–	140.3 (C-2′, C-6′), 133.6 (C-2′′′′, C-6′′′′), 128.6, 128.9 (other carbons)

[a] Not available.

Table 8
Correlations in the HSQC spectra of compounds **1** and **2** [δ (ppm)]

Compound	Signal	Correlations in the HSQC spectrum
8	126.11–140.79	6.99–7.30 (aromatic protons)
	55.36	5.88 (H-2a, H-6a)
	44.06	2.78 (H-3a,H-5a and H-3e, H-5e)
	42.68	3.93 (chloroacetyl)
9	126.66–140.92	7.11–7.36 (aromatic protons)
	61.85	5.39 (H-2a)
	54.73	5.92 (H-2a)
	46.14	3.06 (H-3a)
	42.98	2.83 and 3.17 (H-5a, H-5e)
	42.73	3.88, 3.93 (chloroacetyl)
	13.63	1.06 (methyl)

latter one to $-CH_2Cl$ carbons. However, these two protons are interchangeable.

Similarly assignments for rest of the compounds **10–14** are also made unambiguously by comparing the assignments made for **8** and **9**.

2.5. *Effect of chloroacetyl substituent on the ring carbons chemical shifts*

In order to study the effect of chloroacetyl substituent on the heterocyclic ring carbons chemical shift, the substituent parameters are derived and discussed here. The substituent parameters furnished in Table 9 are obtained by subtracting the chemical shifts of **1–3** and **5** from the corresponding shifts in compounds **8–10** and **12** and are discussed in terms of α, β and γ effects.

A perusal of the data in Table 9 reveals that the magnitude of α and β effects are much higher than the expected value. Pople-Gordon [23] have suggested that through-bond inductive effect exhibit an alteration in magnitude of polarity in saturated heterocyclic systems having different groups at the heteroatom site and consequently exert different effect on the ring carbon chemical shifts. Further, due to coplanar orientation of chloroacetyl moiety at 'N' site with the plane of the ring, it would induce different charge densities at α, β and γ carbons in the proposed conformations and consequently shield or deshields the same differently. However, the marked shielding effect observed with the ring carbon chemical shifts may not be explained on the basis of electronic effect only. Instead, it would have also been explained on the basis of the steric interactions and conformational distortions arising out of the substituent at the nitrogen site.

Earlier reports [11a,c] stated that remarkable shielding of α, β and γ carbons of the heterocyclic ring are primarily controlled by the orientation of substituent at the 'N' site. The observed shielding of ring carbons resonances by chloroacetyl introduction is explained primarily on the basis of steric and γ-eclipsing effect as it has been made for *N*-phenylcarbamoyl [11a] and *N*-benzoyl [11c] derivatives of 2,6-diarylpiperidin-4-ones.

2.5.1. *α-Effect*

In all the *N*-chloroacetyl derivatives (compounds **8–14**), α carbons (C-2 and C-6) are shielded significantly over a wide range, i.e. about 6–10 ppm compared to their parent piperidones due to the substitution of chloroacetyl moiety.

Coplanarity of chloroacetyl moiety in **8–14** with the plane of the ring is established well by ^{1}H NMR studies. As stated already such situation arises only if π electrons of chloroacetyl carbonyl group delocalize with p-electrons of 'N' and effecting rehybridisation with diminished electron density at the nitrogen. Thus, irrespective of the various conformations, which the heterocyclic ring adopts in order to avoid various strain energies, the atoms such as N, C-2, C-6 and CO of chloroacetyl moiety lie in the same plane. Therefore, in all the cases γ-eclipsing interaction exists between C–O (of *N*-substituent) and N–C(2)/N–C(6). Owing to this γ-eclipsing interaction, C-2 and C-6 carbons are shielded to a greater extent in all the compounds compared to their parent compounds. However, in compound **9**, an additional shielding of about 0.91 ppm and 1.13 ppm are observed for C-2 and C-6 carbons respectively compared to **8**. Though this shielding magnitude is not significant, it warrants explanation. If we closely look at its conformations **3A** and **3B** (Scheme 3), the

Table 9
Chloroacetyl substituent parameters for compounds **8–10** and **12**

Compound	C-2(α)	C-3(β)	C-4(γ)	C-5(β)	C-6(α)	C-2′(β)	C-6′(β)	CH_3(γ)	CH_2(γ)	CH(γ)
8–1	−5.64	−6.14	−1.47	−6.14	−5.64	−1.81	−1.81	–	–	–
9–2	−6.55	−5.46	−0.89	−7.92	−6.77	−1.15	−0.78	+3.53	–	–
10–4	−8.83	−3.16	−0.63	−6.46	−4.51	−1.01	−2.01	–	–	+10.76
12–5	−7.27	−6.39	−0.34	−6.39	−7.27	−1.1	−1.1	+3.74	–	–

+: denotes deshielding; –: denotes shielding.

C(6)–C(5) and C(4)–C(3) bonds are comparatively eclipsed. Hence, it explains the slight increase in shielding magnitude of C(2) and C(6) carbons.

In compound **10**, C-2 (8.83 ppm) and C-6 (4.51 ppm) carbons are shielded markedly than the corresponding carbons in its parent **3**. However, the shielding magnitude of C-2 carbon in **10** is increased by about 3.19 ppm than the corresponding carbon in **8**. This can be explained satisfactorily by considering again γ-eclipsing interaction between C(2)–C(3) and C(4)–C(5) bonds in the molecule. Therefore, C-2 carbon is shielded markedly than rest of the carbons in the molecule **10**.

Among the two symmetrically substituted compounds **8** and **12**, the shielding effect experienced by the α-carbons (C-2 and C-6) of 12 is relatively high. This can be explained by the fact that in addition to γ-eclipsing interaction, there is a considerable non-bonded interaction between benzylic protons at C-2 and C-6 and methyl groups at C-3 and C-5. This in turn may increase the electron density around C-2 and C-6 and consequently shields more. This may be the reason for the shielding of C-2 and C-6 carbons in **12** by 1.63 ppm compared to **8**.

It is interesting to point out here that there also exist electronic interaction between amide carbonyl group and benzylic C–H bond. In the preferred conformations of all the compounds, the amide carbonyl N, C-2 and C-6 are "in plane" with each other. Hence, the amide carbonyl function may polarize the C–H bond at C-2 and C-6. In spite of this, carbons of C-2 and C-6 acquire a fractional negative charge there by shield much. It is known from the NMR studies that in **10**, the ring is flattened about C(2)–C(6) bond which in turn may increases the extent of polarization there by shields C-2 carbon significantly than C-6 carbon. It is also in corroboration with the earlier studies on piperidones [16].

2.5.2. β-Effect

The chloroacetyl group shields β carbons also to a considerable extent. But the magnitude of shielding is less in **9**–**10** but it is high for compound **8** compared to α-effect.

C-3 and C-5 carbons of **8** are shielded by 6.14 ppm when compared to **1**. It is quite obvious from the proposed conformations **3A** and **3B** that γ-eclipsing interactions noted in between C(2)–N and C(6)–C(5) bonds and between C(6)–N and C(2)–C(3) bonds may be responsible for the observed shielding effect on C-3 and C-5 carbons. Besides, higher β-effect in **8** compared to α-effect may perhaps be due to the electronic interaction prevailing between the C(3)–H/C(5)–H and the C(4)–O bonds.

In **12**, β-effect is higher than that of compound **8**. This is explained similar to α-effect that the existence of steric interaction between benzylic protons (at C-2/C-6) and methine protons (at C-3/C-5), will in turn paved a way to perturb the electron density around C-3 and C-5 in **12** thereby shields it well. In unsymmetrically substituted compounds **9** and **10**, the shielding characteristic observed with C-3 and C-5 carbons are different due to difference in assumed conformation. In this set of compounds, C-5 carbon is shielded much than C-3 carbon. This may be explained on the grounds of electronic interaction between C(5)–H and C(4)–O bonds in addition to steric interaction between the substituents in the assumed conformations of the molecule.

Due to chloroacetyl substitution, chemical shifts for the phenyl *ipso* carbons (C-2′ and C-6′) of **8**–**10** and **12** are also moved to upfield magnitude (shielding) of about 1–2 ppm compared to their parent compounds **1**–**3** and **5**.

2.5.3. γ-Effect

The shielding of carbonyl carbon has been noticed in most of the heterocyclic compounds bearing substituent at the N. In compounds such as N–Cl, N–CH_3 and *N*-SO_2Ph-2,6-diarylpiperidin-4-ones, the carbonyl carbon is shielded in the range of 4–6 ppm compared to the corresponding parent compounds [24] whereas in N–$COCH_3$, N–COPh [25], N–CONHPh [11a], the shielding magnitude is very negligible. However in the present set of compounds, the γ-carbonyl carbon in **9**, **10** and **12** is shielded by less than 1 ppm, while for **8**, it is about 1.47 ppm compared to the corresponding carbon in their parents. The magnitude of shielding indicates that it is not a significant one when compared to 4–6 ppm observed in the analogues compounds. The decreased γ-effect may perhaps be due to increase in electronegativity at the 'N' site by the chloroacetyl incorporation. The γ-anti carbon of **9** (methyl) and **10** (methine carbon of isopropyl group) are deshielded by 3.53 ppm and 10.76 ppm respectively compared to their parents **2** and **3**. Hence, deshielding of anti carbon in these molecules may be owing to the fact that, if nitrogen has lone pair of electrons it can shield the carbons anti periplanar to it through hyperconjugative interaction as reported by Eliel et al. [26]. But in compounds under study such interaction is absent due to the loss of lone pair of electrons by chloroacetyl substitution at 'N', which in turn deshields the anti carbon (alkyl carbon) at C-3 with respect to heterocyclic 'N'.

Furthermore, the deshielding parameters noticed in **9**, **10** and **12** may also be due to the interactions arising out of major conformational change compared to the corresponding parent piperidones (**2**, **3** and **5**).

Comparison of ^{13}C chemical shifts of *p*-chloro and *p*-methoxy phenyl substituted compounds **11**, **13** and **14** indicates that replacement of phenyl groups present at C-2 and C-6 of heterocyclic ring by *p*-chlorophenyl or *p*-methoxyphenyl would not bring about a significant change in chemical shifts of ring carbons. Therefore, we may expect similar kind of α, β and γ effects from these set of compounds too.

It is of interesting to note that, the detected α, β and γ effects strongly agree with our suggestion of coplanarity of the chloroacetyl moiety at the 'N' site and also proposed conformations for the heterocyclic ring with and without alkyl substituent at C-3 and C-5 positions.

3. Conclusion

Replacement of 'H' by electron withdrawing chloroacetyl group at the heterocyclic nitrogen is known to exert a major change in chemical shifts of ring carbons and associated protons. Besides, the coupling constants values are also affected markedly by the incorporation of this group. Similarly, α and β carbons are shielded significantly, whereas the shielding magnitude of γ-carbon (carbonyl carbon) is very less. However, the

γ-anti carbon is deshielded remarkably due to increase in electronegativity of the heterocyclic nitrogen by the introduction of chloroacetyl moiety. Therefore, in order to substantiate the abrupt change in coupling constant values and chemical shift values from the corresponding parent piperidones we have proposed different conformations such as flattened boat (for **8**, **12** and **14**) and twist-boat forms (for **9**, **10**, **11** and **13**) for the compounds under study.

4. Experimental

All the reported melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only noteworthy absorption levels (reciprocal centimeters) are listed. ^{1}H NMR spectra were recorded at 400 MHz on BRUKER AMX 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz on BRUKER AMX 400 MHz spectrophotometer in $CDCl_3$. ^{1}H-^{1}H COSY, phase-sensitive NOESY and one-bond ^{1}H–^{13}C correlations spectra were recorded on BRUKER DRX 500 NMR spectrometer using standard parameters. 0.05 M solutions of the sample prepared in $CDCl_3$ were used for recording 2D NMR spectra. The tubes used for recording NMR spectra are of 5 mm diameter. Mass spectra were recorded on Jeol SX-102 (EI) and microanalyses were performed on Heraeus Carlo Erba 1108 CHN analyzer. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Fluka and Merck. All the solvents were distilled prior to use.

All the parent 2,6-diarylpiperidin-4-ones were prepared by the literature precedent of Noller and Baliah [3].

4.1. Synthesis of N-chloroacetyl-2,6-diphenylpiperidin-4-one ***8***

To a well-stirred solution of respective 2,6-diphenylpiperidin-4-one (**1**) (0.005 mol) and triethylamine (0.005 mol) in benzene, chloroacetyl chloride (0.005 mol) in benzene was added in drop wise for about half an hour. Stirring was continued with mild heating (30–35 °C) using a magnetic stirrer. After the completion of reaction, it was poured into water and extracted with ether. The collected ether extracts were then washed well with 3% sodium bicarbonate solution and dried over anhydrous sodium sulphate. This upon evaporation afforded the compound (**8**) in good yield. The obtained compound is recrystalized from ethanol. The compounds **9**–**14** were also synthesized similarly.

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