Fast Equilibrium in *N*-(Ethoxycarbonyl)-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones in Flattened Boat Conformations

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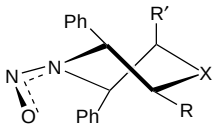
The preferred conformations of three *N*-ethoxycarbonyl derivatives of *r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **9**−**11** have been studied using NMR spectral techniques. The N^1,N^4-bis(ethoxycarbonyl)-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **9** and **10** were found to prefer flattened boat conformations with fast equilibrium between two N−CO rotamers while 4-(ethoxycarbonyl)-*t*-3-isopropyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (**11**) was found to prefer a chair conformation with the N−COOEt group locked in one rotameric state. Dynamic ^{1}H NMR studies have been carried out on the N^1,N^4-bis(ethoxycarbonyl) derivatives **9** and **10**, and the barriers for the N−CO rotation were found to be 49.9 and 58.0 kJ mol^{-1}, respectively. These barriers are much lower than those observed for *N*-nitroso- and *N*-formyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones (90.0 and 84.4 kJ mol^{-1}, respectively), indicating a fast equilibrium in **9** and **10** at room temperature.

Introduction

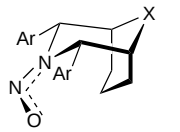
The relative influences of the allylic strain ($A^{1,3}$-strain), torsional strain, resonance energy (due to the delocalization of the lone pair of electrons on nitrogen into the carbonyl group), and 1,3-diaxial strain, etc., over the conformational preferences of *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines **1a**−**j**,[1a,d] *N*-nitroso-3-azabicyclo[3.3.1]nonanes



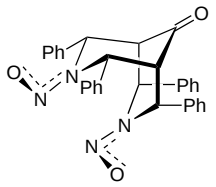
	R	R′	X
1a	H	H	CO
b	Me	H	CO
c	Et	H	CO
d	*i*–Pr	H	CO
e	Me	Me	CO
f	H	H	CH_2
g	Me	H	CH_2
h	Et	H	CH_2
i	*i*–Pr	H	CH_2
j	Me	Me	CH_2

2a−**c** and **3a**,**b**,[1d,2a,b] *N*-nitroso- and *N*-formyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **4a**−**j**,[3a−c] and N^1,N^4-dinitroso-*r*-2,*c*-7-diphenylhexahydrodiazepines **5a**−**c**,[3c,d] have been studied in our laboratory.

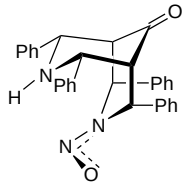
The *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines **1a**−**j**[1a,d] prefer twist-boat conformations and the *N*-nitroso-*r*-2,*c*-4-diphenyl-3-azabicyclo[3.3.1]nonanes (**2a**−**c**)[1d,2] preferred twin-chair conformations. The *N*-nitroso- and *N*-formylhexahydro-1,4-diazepin-5-ones[3a−c] were shown to prefer flattened boat conformations while the dinitroso derivatives[3c,d] preferred twist-chair conformations. In all the dinitroso compounds (**5a**−**c**), of the two sets of twist-chair conformations, the population of four equilibrating major rotamers was about 95% while the minor set of four rotamers accounted for the other 5%.



	Ar	X
2a	Ph	CO
b	Ph	CH_2
c	*p*–anisyl	CO



3a



3b

All these nitroso derivatives were found to exist in an equilibrium between *syn* and *anti* rotamers at room temperature with coplanar orientation of the nitroso group.[1−4] The delocalization of the nitrogen lone pair into the double bond of the N−N=O system results in restricted rotation about the N−N bond (Figure 1) leading to a gain in resonance energy[5] (60−95 kJ mol^{-1}) while the allylic strain[5,6] between the coplanar nitroso group and the equatorial substituents at the α-carbon tends to destabilize the conformation. In order to relieve the allylic strain the molecule may flip over to the

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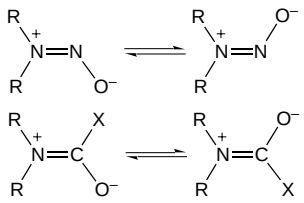
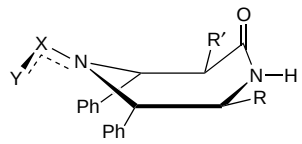


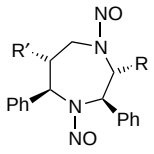
Figure 1. N−N and N−C rotational equilibria.

alternate chair,[5,7] twist-chair[1a,8] conformations or flattened boat conformations with pseudo-axial phenyl groups,[3a−c] etc., retaining the planar C2(C6)−N−N=O function.

In this paper we report the results of similar stereochemical investigations on the *N*-ethoxycarbonyl derivatives of *r*-2,*c*-7-diphenylhexahydrodiazepin-5-ones. These derivatives prefer flattened boat conformations with fast equilibrium between two N−CO rotamers (Figure 1) with energy barriers of 50−58 kJ mol^{-1}. In contrast, the energy barriers for N−NO rotation in *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines **1a**−**j**,[1a,d] *N*-nitroso-*r*-2,*c*-4-diphenyl-3-azabicyclo[3.3.1]nonanes, (e.g., **2a**−**c**,[1d], *N*-nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **4a**−**d**,[3a,c] and N−CO rotation in *N*-formyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **4f**−**j**[3c] are about 70−90 kJ mol^{-1}.



	R	R′	—X═Y
4a	H	H	NO
b	Me	H	NO
c	Et	H	NO
d	*i*-Pr	H	NO
e	Me	Me	NO
f	H	H	CHO
g	Me	H	CHO
h	Et	H	CHO
i	*i*-Pr	H	CHO
j	Me	Me	CHO

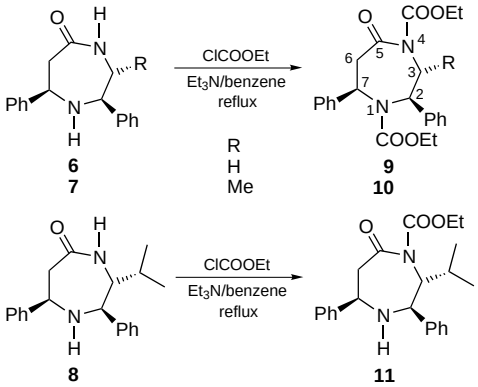


	R	R′
5a	Me	H
b	*i*-Pr	H
c	Me	Me

Results and Discussion

The reaction of ethyl chloroformate with the hexahydrodiazepines **6** and **7** in dry benzene and triethylamine at reflux temperature yielded the diethoxycarbonylated products **9** and **10** (Scheme 1). When the reaction was carried out at controlled conditions, a product believed to be the monoethoxycarbonyl derivative was formed during the reaction. However, these products could not be isolated by column chromatography.

Scheme 1



In the IR spectra of the N^1,N^4-bis(ethoxycarbonyl)-hexahydro-1,4-diazepin-5-ones **9** and **10**, both the amine and amide NH stretching bands were absent. The compounds **9** and **10** showed IR absorption bands at 1760, 1720, and 1680 cm^{-1} and 1765 and 1680 cm^{-1}, respectively. In the mass spectra, the molecular ion peaks observed at *m*/*z* 410 and 424 and the fragmentation pattern agreed with the structures of the bis(ethoxycarbonyl) compounds **9** and **10**, respectively.

The 3-isopropylhexahydrodiazepin-5-one **8** was treated with ethyl chloroformate in the presence of dry benzene and triethylamine (Scheme 1). The product was found to be imido ester **11** since, in the IR spectra, the amide NH stretching band at 3200 cm^{-1} disappeared while the amine NH band at 3300 cm^{-1} was retained. In the ^{1}H NMR spectrum of the compound **11** the amide NH signal (∼6.0 ppm) was absent while the amine NH signal (∼1.7 ppm) was present, indicating that the reaction has taken place at the amide nitrogen site. In the mass spectrum, the molecular ion peak was observed at *m*/*z* 380. The bis(ethoxycarbonyl) derivative could not be isolated.

Orientation of N1−COOEt. A broad peak for the H7 proton was observed in the room temperature spectrum of **10** while the corresponding signal for **9** was sharp. In addition the CH_2 and CH_3 protons of the ethoxycarbonyl moiety of N1 in **10** showed a broad signal at room temperature. At 50 °C, the ^{1}H NMR signals of **10** became sharp.

On lowering the temperature down to −55 °C, doubling of the signals for benzylic protons at C2 and C7 as well as those for CH_2 and CH_3 protons of carbethoxy group at N1 was observed. The doubling of signals at low temperature indicates that the carbethoxy group at N1 position may adopt a coplanar orientation with respect to the C2−N1−C7 plane of the molecule[9] with weaker N−CO conjugation than in N−NO of the *N*-nitroso derivatives.[1−4]

The coplanar orientation of the N1−COOEt in the compounds **9** and **10** has been further confirmed from the following observations: (i) the greater deshielding of H2 and H7 benzylic protons[10,11] ($\Delta\delta$ =1.8 and 2.03 ppm for **9** and **10**, respectively) compared to the parent diazepines[3a] (Tables 1 and 5) (ii) the greater shielding of

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Table 1. ^{1}H NMR Chemical Shift Data of *N*-(Ethoxycarbonyl)diazepin-4-ones 9−11 Compared with Those of the Parent diazepin-4-ones 6−8, Respectively (in δ)

compd	H_2	H_{3ax}	H_{3eq}	H_{6ax}	H_{6eq}	H_7
9	5.83	4.20	4.67	3.73	3.12	6.17
6	4.03	3.65	3.14	3.14	2.66	4.14
10	5.95	4.91		3.36	2.97	5.75
7	3.70	3.83		3.14	2.65	4.13
11	3.87	4.66		3.24	2.73	4.26
8	3.86	3.71		3.14	2.65	4.12

Table 2. ^{13}C NMR Chemical Shift Data of *N*-(Ethoxycarbonyl)diazepin-4-ones 9−11 Compared with Those of the Parent Diazepin-4-ones 6−8, Respectively (in δ)

compd	C2	C3	C5	C6	C7
9	56.2	46.9	170.1	40.9	52.6
6	65.3	50.8	174.4	47.7	59.4
10	60.9	51.0	171.9	41.8	53.4
7	71.0	54.7	175.7	47.4	59.5
11	67.4	59.8	172.9	45.4	65.7
8	68.6	63.4	176.2	47.4	59.6

C2 and C7 benzylic carbons[7,11a,12] ($\Delta\delta$ = −9.1 and −6.8 ppm for **9** and −10.1 and −6.1 for **10**) in ^{13}C NMR spectra (Tables 2 and 6).

Orientation of N4−COOEt. The dynamic ^{1}H NMR studies[13] carried out for the compounds **9** and **10** indicated that even at −55 °C the signals due to the axial proton at C3 and CH_2 and CH_3 protons of the carbethoxy group at N4 did not show doubling. This observation may indicate the absence of dynamic equilibrium at N4 due to the rotation about N−CO. In the case of **9** the equatorial proton at C3 was deshielded by 1.53 ppm. If the orientation of the C═O group is *syn* to C3 (*endo* orientation), the observed deshielding may be explained on the basis of the model proposed by Paulsen and Todt for the anisotropic effect of amides.[10] In the *endo* orientation of the carbethoxy group at N4, the C3 equatorial proton would fall into the deshielding region of the amide plane and thereby get deshielded.[10,11] In addition, the *syn* orientation of C═O with reference to C3 would result in an eclipsing interaction between N4−C3 and C−O bonds and the C3 carbon is expected to be shielded.[7,11a,12] In the compounds **9** and **10** the C3 carbons were shielded by −3.9 and −3.7 ppm (Table 6), respectively, supporting the *endo* orientation of C═O. Hence the ethoxycarbonyl group at N4 may prefer an *endo* orientation exclusively.

^{1}H NMR Spectra. The variable temperature ^{1}H NMR studies[13] carried out for the compounds **9** and **10** indicated that the signals for the benzylic protons were resolved into two at −60 °C while the other ring proton signals did not double. The signal due to the benzylic proton at C2 in the compound **9** showed two double doublets (at −60 °C) at 5.90 and 5.65 ppm corresponding to two rotamers with the coupling constants of 12.5 and 6.6 and 11.2 and 6.4 Hz, respectively. Among these coupling constants, the higher values (12.5 and 11.2 Hz) may be assigned to the *trans* coupling ($J_{2,3(a)}$) and the lower values (6.6 and 6.4 Hz) to the *cis* coupling ($J_{2,3(e)}$).

Table 3. Vicinal and Geminal Coupling Constants (in Hz) of the *N*-(Ethoxycarbonyl)diazepin-4-ones 9−11 Compared with Those of the Parent Diazepin-4-ones 6−8, Respectively

compd	$^3J_{2(a),(3a)}$	$^3J_{2(a),3(e)}$	$^3J_{3(a),3(e)}$	$^3J_{7(a),6(a)}$	$^3J_{7(a),6(e)}$	$^3J_{6(a),6(e)}$
9	12.0	6.5	15.6	11.0	8.8	13.7
6	9.0	0.0		10.3	0.0	14.5
10	7.6			10.9	5.6	15.0
7	7.8			10.5	0.0	14.2
11	5.9			7.5	2.6	14.2
8	8.3			10.6	0.0	13.9

Table 4. Dihedral Angles (in degrees) of the *N*-(Ethoxycarbonyl)diazepin-4-ones 9−11 Compared with Those of the Parent Diazepin-4-ones 6−8, Respectively, Estimated Using DAERM

compd	$\phi_{2(a),3(e)}$	$\phi_{2(a),3(a)}$	$\phi_{7(a),6(e)}$	$\phi_{7(a),6(a)}$
9	42	162	33	153
6	80	160	81	−159
10			43	163
7			81	−159
11			51	171
8			81	−159

In the case of compound **10**, the signal due to the benzylic proton at C2 appeared as two doublets (at −35 °C) at 6.03 and 5.85 ppm corresponding to two rotamers with coupling constants ($J_{2H,3H}$) of 8.8 and 8.3 Hz, respectively. This pattern would be possible only if there is an equilibrium between two conformers or rotamers that do not involve any ring flipping such as chair-chair and chair-boat interconversions. Such a type of interconversion will convert the axial hydrogens into equatorial hydrogens and vice versa which result in a drastic difference in the coupling constants within each pair. The coupling constants between the H7 and H6e protons in the case of parent diazepinones **6** and **7** were zero, indicating that the dihedral angles were close to 90° (ca. 81°).[3a] But in the case of carbamates **9** and **10**, $J_{7,6(e)}$ values were found to be 8.8 and 5.6 Hz, respectively (Table 3). There was an increase in the coupling constant from zero in both the cases, suggesting a decrease in the dihedral angle from 90° between the H7 and H6e protons. The angles were found to be 33° and 43° for the compounds **9** and **10** (Table 4), respectively, calculated using DAERM[14] (dihedral angle estimation by ratio method). This observation may be explained from coplanar orientation of the ethoxycarbonyl group. The flattening at C3−C2−N1−C7−C6 part of the ring would decrease the dihedral angles between the C2−N1−C(O) and N1−C2−Ph and C7−N1−C(O) and N1−C7−Ph planes. As a consequence, the $A^{1,3}$-strain between phenyl groups and the carbonyl group becomes significant.[6,11a]

The chair conformation with equatorial phenyl groups **IA** and **IB** (Figure 2) is destabilized by $A^{1,3}$-strain.[6] The chair form also requires a *cis* dihedral angle (between H6e and H7a) of at least 60°. The calculated dihedral angles ($\phi_{2(a),3(e)}$ = 42°, $\phi_{6(e),7(e)}$ = 33° for the compound **9** and $\phi_{6(e),7(a)}$ = 43° for the compound **10**) eliminate the possibility of chair conformations **IA** and **IB** (Table 4).

In the alternate chair conformations **IIA** and **IIB** with axial phenyl groups, the $A^{1,3}$-strain is absent but the two phenyl groups would exhibit a 1,3-diaxial interaction (Figure 2). Since the α-hydrogens are at equatorial positions the $J_{2H(e),3H(e)}$ coupling constants are expected to be around 2−5 Hz. But the observed values were

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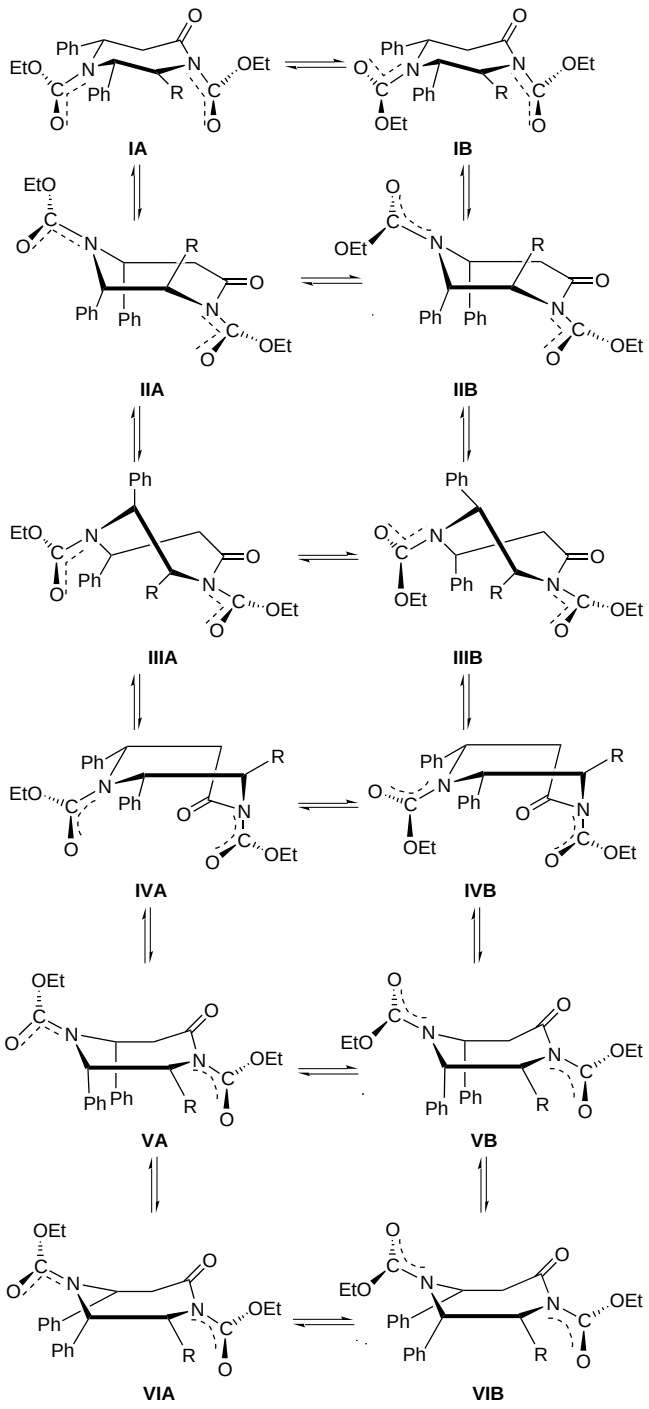


Figure 2. Possible conformations for the *N*-(ethoxycarbonyl)-diazepines 9 and 10.

around 10.0 Hz (Table 3), excluding the possibility of chair conformations **IIA** and **IIB**.

In the twist conformations **IIIA** and **IIIB** (Figure 2) the $A^{1,3}$-strain is relieved if the coplanar carbonyl group orients toward the axial phenyl group.[8] Equilibrium between the twist conformations **IIIA** and **IIIB** involves pseudorotation which converts axial hydrogens into equatorial hydrogens (and vice versa) and one of the benzylic hydrogens to occupy the equatorial orientation. But the values observed were 12.0 and 11.0 Hz in the case of compound **9** and 7.6 and 10.9 Hz for compound **10** (Table 3). Hence, it eliminates the possibility for twist conformations **IIIA** and **IIIB**.

The approximate dihedral angles can be calculated using the models which show that the boat conformations **IVA** and **IVB** require approximate *cis* and *trans* angles of 30° and 90°, respectively. Therefore, one of the coupling constants *cis* or *trans* might be very low or zero. In addition, these forms would also be destabilized by the $A^{1,3}$-strain[6] due to the presence of α-equatorial phenyl groups. Thus the possibility of boat conformations **IVA** and **IVB** with equatorial phenyl groups was not considered on the basis of the above points.

The approximate dihedral angles calculated using the models show that the alternate boat conformations **VA** and **VB** require an approximate *cis* (H−C7−C6−He) and *trans* (H−C7−C6−Ha) angles of 0−10° and 120−130°, respectively. The *cis* and *trans* angles calculated using ^{1}H NMR data were 33° and 153° and 43° and 163° for the compounds **9** and **10**, respectively (Table 4). The calculated angles agree to the forms **VA** and **VB** with flattening at C3−C2−N1−C7−C6 part of the ring (as shown in **VIA** and **VIB**).

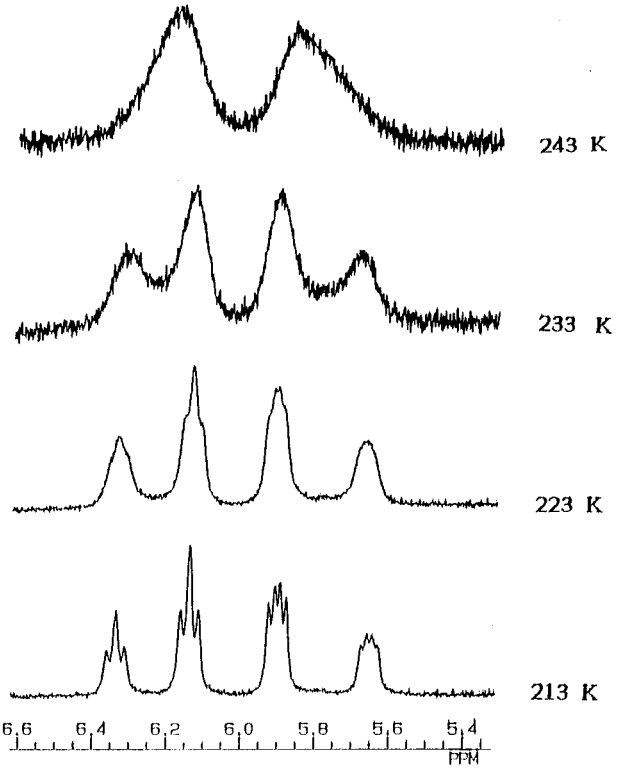
Thus, the observed dihedral angles and other observations can be well accommodated by assuming a boat conformation with flattening at the C3−C2−N1−C7−C6 part of the ring with quasiaxial phenyl groups **VIA** and **VIB**.

The *cis* dihedral angle between H6e and H7 was found to decrease from 81° for both the parent compounds (**6** and **7**) to 33° for **9** and 43° for **10** upon substituting the carbethoxy group at N1 site (Table 4). Such a large decrease in dihedral angle may presumably arise from the coplanar orientation of the carbethoxy group leading to flattening at the C3−C2−N1−C7−C6 part of the ring. In order to alleviate from $A^{1,3}$ strain, the C7−N1−C2 end of the ring undergoes flipping to boat form, leading to a decrease in the dihedral angles between the C6e and C7 hydrogens. The flattening would also result in γ-eclipsing interactions[7,11a,12] between the C−O and N1−C2/N1−C7 bonds which appears to be responsible for the shielding of C2 and C7 α-carbons ($\Delta\delta = -6$ to -10 ppm) compared to their parent diazepin-5-ones[3a] (Table 6).

The *syn* and *anti* designations for the α-proton are with reference to the carbonyl oxygen of the planar delocalized N−COOR group. In the flattened boat conformations, the benzylic protons occupy quasi-equatorial orientations and the *syn* α-protons are expected to lie within the plane of the deshielding cone (in-plane region) of the carbonyl group and they would experience relatively higher deshielding compared to the *anti* α-hydrogens.[10,11] Also, in the case of *N*-nitrosohexahydrodiazepin-5-ones,[3a] the *syn* α-protons were reported to be deshielded compared to the anti α-protons. Thus, of the two observed resonances for each α-hydrogen in the compounds **9** and **10**, the downfield one was assigned to the *syn* α-proton and the other to *anti* α-proton [i.e., for the compound **9** (at −60 °C), $H2_{syn} = 6.03$, $H2_{anti} = 5.85$, $H7_{syn} = 5.90$, $H7_{anti} = 5.68$ ppm and for the compound **10** (at −35 °C) $H2_{syn} = 5.90$, $H2_{anti} = 5.65$, $H7_{syn} = 6.35$, $H7_{anti} = 6.15$ ppm].

The variable temperature ^{1}H NMR studies[13] have been carried out for compounds **9** and **10**. The lowering of the temperature to −60 °C resulted in doubling of the signals for H2 and H7 protons corresponding to the *syn* and *anti* forms of **9** and **10** with the population ratio of 65:35. The energy barrier for the N−CO rotation was estimated using the modified Eyring equation derived by Shanon-Atidi and Bar-Eli for the rotamers of unequal popula-

Chart 1



tion[15] (eqs 1 and 2)

$$\Delta G^{\#}_{AB} = 4.57T_c[10.62 + \log X/2\pi(1 - \Delta p) + \log T_c/\Delta\nu] \text{ cal mol}^{-1} \quad (1)$$

$$\Delta G^{\#}_{BA} = 4.57T_c[10.62 + \log X/2\pi(1 + \Delta p) + \log T_c/\Delta\nu] \text{ cal mol}^{-1} \quad (2)$$

where $\Delta G^{\#}$ is the free energy of activation, T_c is the coalescence temperature, $\Delta\nu$ is the chemical shift difference in hertz at T_c, Δp is the population difference between the rotamers, X is the value defined by $\Delta p = ((X^2 - 2)/3)^{3/2}/X$, and $\Delta G^{\#}_{AB}$ and $\Delta G^{\#}_{BA}$ are the energy barriers for the interconversion of rotamer A to B and B to A, respectively.

For compound **9**, the change in shapes of the signals of the benzylic proton at C7 was followed (Chart 1) to calculate the energy barrier for the N−CO rotation. The T_c and $\Delta\nu$ were found to be 243 K and 56 Hz, respectively, and the calculated energy barriers for the N−CO rotations $\Delta G^{\#}_{AB}$ and $\Delta G^{\#}_{BA}$ were 50.5 and 49.2 kJ mol^{-1}, respectively, with an average barrier of 49.9 kJ mol^{-1}. Similarly, for compound **10**, the change in the shapes of the signals of the benzylic proton at C2 was followed (Chart 2) and T_c and $\Delta\nu$ were found to be 283 K and 67.0 Hz, respectively. The calculated energy barriers for the N−CO rotation $\Delta G^{\#}_{AB}$ and $\Delta G^{\#}_{BA}$ were 58.7 and 57.3 kJ mol^{-1}, respectively, with an average barrier of 58.0 kJ mol^{-1}.

The observation of broad signals at room temperature in the ^{1}H NMR spectrum for carbamate **10** and sharp signals in the case of **9** shows that the energy barrier for N1−C(O) rotation of **10** may be larger than that of **9**. On the basis of the dynamic ^{1}H NMR studies, the barrier for the compound **10** was found to be 8.1 kJ mol^{-1} higher than that for the carbamate **9**.

All the ring protons in the compounds **9** and **10** were found to be deshielded when compared to those of the parent compounds (Tables 1 and 5). The benzylic hydrogens at C2 and C7 were deshielded by about 1.62 to 2.25 ppm. This may be explained using the model proposed by Paulsen and Todt for the anisotropic effect of amides.[10] According to this model, in the flattened boat conformation the quasi-equatorial α-protons are closer

(15) Shanon-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961.

Chart 2

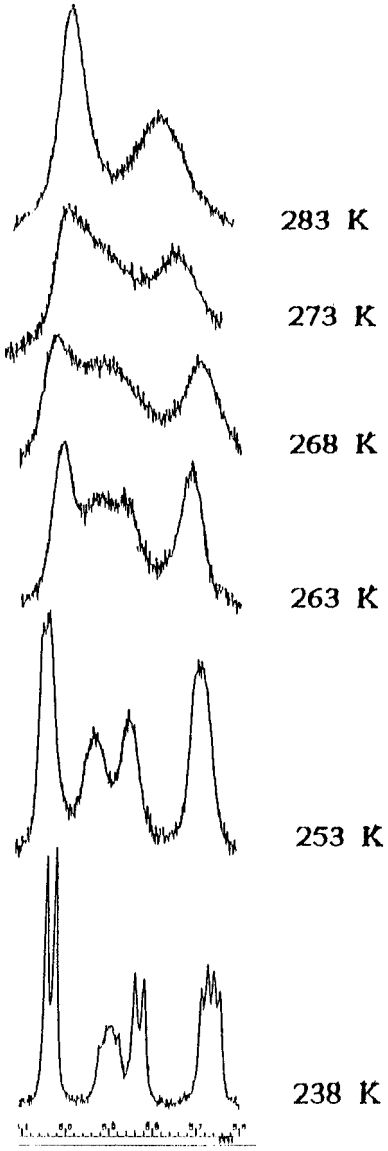


Table 5. Magnitude of Deshielding (in δ) of Protons in the *N*-(Ethoxycarbonyl)diazepin-4-ones 9−11 from the Corresponding Parent Diazepin-4-ones 6−8

compd	H_2	H_{3ax}	H_{3eq}	H_{6ax}	H_{eq}	H_7
9	1.8	0.55	1.53	0.59	0.46	2.03
10	2.25	1.08		0.22	0.32	1.62
11	0.01	0.95		0.10	0.08	0.14

Table 6. ^{13}C NMR Chemical Shift differences (in δ) between the *N*-(Ethoxycarbonyl)diazepin-4-ones 9−11 and the Corresponding Parent Diazepin-4-ones 6−8

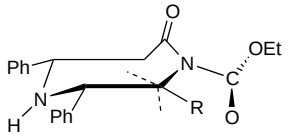
compd	C_2	C_3	C_5	C_6	C_7
9	−9.1	−3.9	−4.6	−6.8	−6.8
10	−10.1	−3.7	−3.8	−5.6	−6.1
11	−1.2	−3.6	−3.3	−2.0	6.1

to amide plane and they are within the deshielding cone (in-plane region) of the amide and thereby get deshielded.

Thus it was concluded that the N^1,N^4-bis(ethoxycarbonyl)hexahydrodiazepin-5-ones **9** and **10** prefer to adopt flattened boat conformations with coplanar ethoxycarbonyl groups at both N1 and N4 positions and that there is an equilibrium between two rotamers at N1 while the COOEt at N4 is exclusively in the *endo* form.

4-(Ethoxycarbonyl)-*t*-3-isopropyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (11). Analysis of ^{1}H NMR data (Table 1) revealed that the H2 and H7 protons of **11** appeared at the same region as that of the parent diazepine **8**.[3a] Only the H3 axial proton was found to be deshielded by 0.95 ppm (Table 5). The magnitude of shielding of C3 carbon for the compound **11** ($\Delta\delta = -3.6$ ppm) was comparable to that of the compounds **9** ($\Delta\delta = -3.9$ ppm) and **10** ($\Delta\delta = -3.7$ ppm) which indicated that the orientation of the carbethoxy group at N4 may be *syn* to C3 (*endo* orientation) similar to that of compounds **9** and **10**. The *endo* orientation would result in an eclipsing interaction between C−O and N4−C3 bonds and may result in a shielding effect on C3.[7,11a,12] The *endo* orientation of the carbethoxy group would also result in an $A^{1,3}$-strain[6] between the carbonyl group and the α-equatorial isopropyl group. The $A^{1,3}$-strain may be partly relieved by a twist along the C3−N4 bond which would move the isopropyl group away from the amide plane bringing the H_{3ax} into the amide plane. Hence, on the basis of the Paulsen and Todt model,[10] a deshielding effect is expected on the H_{3ax} proton. The H_{3ax} proton was deshielded by 0.95 ppm when compared with that of the parent **8** which supports the above argument.

Analysis of the Dreiding model indicated that the dihedral angles between the H_{2a}, H_{3a} ($\phi_{2a,3a}$) and H_{7a}, H_{6a}/H_{6e} ($\phi_{7a,6a}$ and $\phi_{7a,6e}$) would be changed due to the twist along C3−N4 bond. The angles $\phi_{7a,6a}$ and $\phi_{7a,6e}$ in the parent were found to be −159° and 81°, respectively, calculated using DAERM.[14] The approximate dihedral angles calculated using the models show that the twist along the C3−N4 bond would shift the *cis* and *trans* angles by about 25−35° and an approximate *cis* and *trans* angles of 45−55° and 165−175° would be required. The *cis* and *trans* angles calculated using ^{1}H NMR data were 51° and 171°, respectively (Table 4). Thus the calculated angles can be achieved by considering a twist along the C3−N4 bond (to alleviate $A^{1,3}$-strain). In addition the angles ϕ_{trans} (171°) and ϕ_{cis} (51°) were characteristic of a chair conformation indicating that the conformation of the ring may be chair (**12**).



12, R = *i*-Pr

Hence, on the basis of the above observations, it was concluded that the 4-(ethoxycarbonyl)-*t*-3-isopropyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (**11**) may prefer to adopt a chair conformation with *endo* orientation of the carbethoxy group at the N4 position and a slight twist along the C3−N4 bond (**12**).

Thus, the bis(ethoxycarbonyl) compounds **9** and **10** prefer flattened boat conformations (**VIA, VIB**) with fast equilibrium between the two N−CO rotamers. In the case of monoethoxycarbonyl compound **11** the preferred conformation is chair with *endo* orientation of carbethoxy group. The energy barriers for N−CO rotation in the compounds **9** and **10** (49.9 and 58.0 kJ mol^{-1}, respectively) are lower than those observed for the *N*-nitroso- and *N*-formyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones indicating a much weaker N−CO double bond character in **9** and **10**. Hence the equilibrium is fast in **9** and **10**.

Experimental Section

The melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-435 infrared spectrophotometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 MHz spectrometer in $CDCl_3$ solution using TMS as internal reference. Dynamic ^{1}H NMR spectra were recorded in $CDCl_3$ solution using a Jeol GSX-400 MHz NMR spectrometer. The *r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **6**−**8** were prepared according to the reported procedures.[3a,16]

***N*^{1},*N*^{4}-Bis(ethoxycarbonyl)hexahydro-*r*-2,*c*-7-diphenyl-5*H*-1,4-diazepin-5-one (9).** To an ice-cold solution of hexahydro-*r*-2,*c*-7-diphenyl-1,4-diazepin-5-one (**6**) (0.67 g, 2.5 mmol) in anhydrous benzene (60 mL) were added triethylamine (4.2 mL, 30 mmol), and ethyl chloroformate (4.0 mL, 41.6 mmol). The reaction mixture was allowed to reflux on a water bath for 5 h, and the course of the reaction was monitored by TLC [silica, $CHCl_3$:CH_3COOEt (9:1) as eluent]. The precipitated ammonium salt was filtered off, and the filtrate was washed with water (4 × 25 mL). The organic layer was dried (anhydrous Na_2SO_4), passed through a short column of silica (eluent: CH_2Cl_2), and evaporated. The oily mass was crystallized by being dissolved in hot petroleum ether (boiling range 60−80 °C) and slowly cooled to 0 °C to yield 0.65 g (63.4%) of **9**: mp 85−86 °C; IR (KBr): 1760, 1720 (−C(O)−N4−CO), 1680 cm^{-1} (N1−C=O); ^{1}H NMR δ (in ppm) 1.25 (3H, t, CH_3 at N4), 1.37 (3H, t, CH_3 at N1), 4.36 (2H, m, CH_2 at N4), 4.2 (3H, m, CH_2 at N1 and C3-axial), 3.12 (1H, dd, C6-equatorial), 5.83 (1H, dd, C2-axial), 3.73 (1H, dd, C6-axial), 4.67 (1H, dd, C3-equatorial), 6.17 (1H, unsym t, C7-axial), 6.88−7.25 (10H, m, aromatic); ^{13}C NMR δ (in ppm) 14.3, 14.5 (CH_3 at N1 and N4), 40.9 (C6), 46.9 (C3), 52.6 (C7), 56.2 (C2), 62.6, 63.6 (CH_2 at N1 and N4), 127.1, 127.4, 127.5, 127.9, 128.1 (aromatic), 137.6, 138.6 (ipso), 153.3 (−C(=O)O− at N4), 157.5 (−C(=O)O− at N1), 170.1 (C5); MS *m*/*z* 410 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.39; N, 6.83. Found: C, 67.52; H, 6.53; N, 6.85.

***N*^{1},*N*^{4}-Bis(ethoxycarbonyl)hexahydro-*t*-3-methyl-*r*-2,*c*-7-diphenyl-5*H*-1,4-diazepin-5-one (10).** The procedure described for compound **9** was followed for the ethoxycarbonylation of hexahydro-*t*-3-methyl-*r*-2,*c*-7-diphenyl-5*H*-1,4-diazepin-5-one (**7**) (0.7 g, 2.5 mmol). The oily mass was crystallized from petroleum ether (60−80 °C) to yield 0.64 g (60.4%) of **10**: mp 113−115 °C; IR (KBr) 1765 (−C(O)N4−CO), 1680 cm^{-1} (N1−C=O); ^{1}H NMR (at 50 °C) δ (in ppm) 1.19 (3H, t, CH_3 at N1), 1.39 (3H, t, CH_3 at N4), 1.40 (3H, d, CH_3 at C3), 2.97 (1H, dd, C6-equatorial), 3.36 (1H, dd, C6-axial), 4.20 (2H, q, CH_2 at N1), 4.41 (2H, q, CH_2 at N4), 4.91 (1H, m, C3-axial), 5.75 (1H, dd, C7-axial), 5.95 (1H, d, C2-axial), 6.98−7.26 (aromatic); ^{13}C NMR δ (in ppm) 14.2, 14.4 (CH_3 at N1 and N4), 18.2 (CH_3 at C3), 41.8 (C6), 51.0 (C3), 53.4 (C7), 60.9 (C2), 62.5, 63.9 (CH_2 at N1 and N4), 126.3, 126.9, 127.5, 127.7, 128.1, 128.4, 128.7, 128.9 (aromatic), 138.3, 140.8 (ipso), 154.5 (N4−CO), 157.8 (N1−CO), 171.9 (C5); MS *m*/*z* 424 (M^+). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.60; H, 6.43; N, 6.28.

4-(Ethoxycarbonyl)hexahydro-*t*-3-isopropyl-*r*-2,*c*-7-diphenyl-5*H*- 1,4-diazepin-5-one (11). To an ice-cold solution of hexahydro-3-isopropyl-*r*-2,*c*-7-diphenyl-1,4-diazepin-5-one (**8**) (0.308 g, 1 mmol) in anhydrous benzene (40 mL) were added triethylamine (0.7 mL, 5 mmol) and ethyl chloroformate (0.5 mL, 5mmol). The reaction mixture was allowed to reflux

(16) Baliah, V.; Lakshmanan, MR.; Pandiarajan, K. *Indian J. Chem.* **1978**, *16B*, 72.

on a water bath for 2 h, and the reaction was monitored by TLC (silica, $CHCl_3$ as eluent). The precipitated ammonium salt was filtered off, and the filtrate was washed with water (4 × 25 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, passed through a short coloumn of silica (eluent: CH_2Cl_2), and evaporated. The oily mass was crystallized by being dissolved it in boiling petroleum ether (boiling range 60−80 °C) and cooled to 0 °C slowly, yielding 0.24 g (63.2%) of **11**: mp 79−81 °C; IR (KBr) 3300 (N4−H), 1710 cm^{-1} (−C(O)−N4−CO); ^1H NMR δ (in ppm) 0.89, 0.98 (2 × 3H, 2t, 2 × CH_3 of C3-isopropyl), 1.38 (3H, t, CH_3 at N4), 1.65 (b, N1-H), 2.10 (1H, m, CH of C3-isopropyl), 2.73 (1H, dd, C6-equatorial), 3.24 (1H, dd, C6-axial), 3.87 (1H, d, C2-axial), 4.26 (1H, dd, C7-axial), 4.38 (2H, q, CH_2 at N4), 4.66 (1H, dd, C3-axial), 7.22−7.46 (aromatic); ^{13}C NMR δ (in ppm) 14.4 (CH_3 at N4), 20.1, 21.2 (2 × CH_3 of C3-isopropyl), 33.4 (CH of C3-isopropyl), 45.4 (C6), 59.8 (C3), 63.1 (CH_2 at N4), 65.7 (C7), 67.4 (C2), 127.0, 127.7, 127.9, 128.6, 129.0 (aromatic), 143.1, 144.9 (ipso), 156.2 (N4-CO), 172.9 (C5); MS *m*/*z* 380 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.82; H, 7.51; N, 7.21.

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