Chemistry of N-Nitroso Compounds. 3. Synthesis and Conformational Analysis of N-Nitrosohexahydro-1,4-diazepin-5-ones[1]

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A comparison of the barrier to N-X rotation in a series of compounds with various N—X=Y systems has shown that the *N*-nitrosamines, some of which have been found to be highly carcinogenic, exhibit the highest rotation barrier. All the other systems which, to date, have not been found to be carcinogenic have lower barriers. With a view to studying the influence of the *N*-nitroso group on the conformations of *N*-nitrosodiazepinones, several 1-nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **16–20** were synthesized from the corresponding *r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-ones **11–15** and their conformations in deuterated solvents were studied. The *N*-nitrosodiazepinones **16–20** were found to prefer *boat* conformations, with some flattening at the nitroso end of the ring and with quasi-axial phenyl groups. As shown earlier, *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines prefer *partially twisted chair* conformations with equatorial phenyl groups and *r*-2,*c*-6-dimethyl-*N*-nitrosopiperidine prefers a *chair* conformation with 1,3-diaxial methyl groups. The title compounds **16–20** exist in conformational equilibria involving syn and anti orientations of the coplanar nitroso group in an approximate syn–anti ratio of 60:40 (observed from ^{1}H NMR spectroscopic studies). The ^{13}C NMR spectra of these compounds show that the carbons syn to the nitroso group are shifted upfield by about 11–15 ppm compared to the precursor compounds **11–15**, while the anti carbons were shifted by less than 1 ppm in either direction. It was observed that all of the syn α-protons are more deshielded than the anti α-protons while for the β-protons the reverse is true. The N—N=O rotational barriers for these compounds could not be determined precisely since they start decomposing above 150 °C in DMSO-d_6 solutions. A rough estimate of the energy barrier for the isopropyl derivative **19** shows that the barrier is at least 21.5 kcal mol^{-1}.

Introduction

Extensive studies have been made on the carcinogenicity and mutagenicity of many *N*-nitrosamines and *N*-nitrosamides.[2a–e] In addition, some *N*-nitrosoureas are found to be anticancer agents.[2f–g] These *N*-nitroso compounds have been found to exist as syn and anti rotamers[3] due to N-N restricted rotation as a result of nitrogen lone-pair delocalization (Figure 1). This delocalization causes the hydrogens at the α-carbons to become acidic as evidenced by their base-catalyzed reactions, such as exchange with deuterium,[4a,c] stereoselective α-alkylation with alkyl iodide,[4a,b] and isomerization at the α-position.[4b] The α-carbons of nitrosamines undergo enzymatic hydroxylation followed by oxidative cleavage leading to the formation of alkyldiazo hydroxides, alkyldiazonium ions and alkyl cations.[2e,5a] These cations are postulated to initiate the process of carcinogenesis in some cases by alkylating the bases of DNA.[5]

Table I. Energy Barriers to N-X Rotation in Related Systems[a]

N—X=Y	energy barriers to N-N rotation (kcal mol^{-1})	refs
Me_2N—N=O	23.3 (19.4)	3a, 6b (6b)
Me_2N—N=CH_2	<6.0 (7.0)	7a,b (7a)
Me_2N—N=CMe_2	<6.0	7a,b
Me_2N—CHO	21.0 (16.4)	6a,b (6b)
Me_2N—$COCH_3$	17.4 (13.8)	6a,b (8b, 6b)
Me_2N—COPh	15.3 (12.1)	6a,b (8b, 6b)
Me_2N—N=S=O	10.5 (8.0)	8c (8a)
Me_2N—N=CHPh	(7.0)	(7a)
Me_2N—N=NPh	13.8 (10.8)	9 (9)
Me_2N—C(Me)=NPh	(10.9)	(9, 8b)

[a] Values in parentheses are for the corresponding *cis*-2,6-dimethylpiperidine derivatives.

In spite of the extensive studies on structure–activity relationships over a large variety of *N*-nitroso compounds, there is still a need to examine further molecular properties which may play a role in carcinogenesis initiated by *N*-nitrosamines. In particular, there is a paucity of information regarding the relationship between the conformation of these compounds and carcinogenicity. It is of interest to note that among the several known N—X=Y systems in which Y is an atom or a group that permits access to a 1,3-dipole by withdrawing the pair of electrons on nitrogen (X = Y = $COCH_3$,[6] CHO,[6a,b] COPh,[6a–c] N=O,[7b–d] N=CR_2,[7a,b] N=CH_2,[7a,b] N=S=O,[8a,c] N=NAr,[9]

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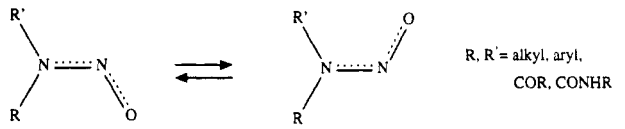
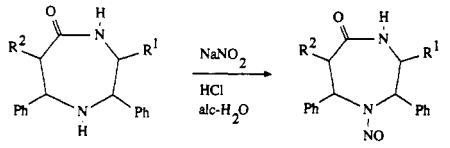


Figure 1. N–N restricted rotation in *N*-nitrosamines.

Scheme I



	R^1	R^2
16	H	H
17	Me	H
18	Et	H
19	i-Pr	H
20	Me	Me

SO_2CH_3,[6b] C(Me)=NAr,[7a,8b] etc.), only compounds with the N—N=O group are carcinogenic. All the other N—X=Y systems, which have lower barriers[10,11] to syn–anti interconversion (Table I), are not reported to be carcinogenic.

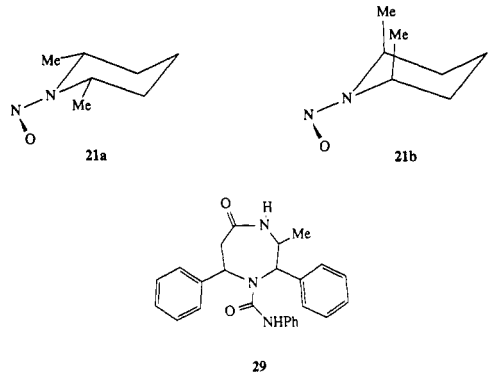
The carcinogenicity of cyclic *N*-nitroso compounds varies greatly depending upon the number and nature of α-substituents.[2d,12] These α-substituents are, in general, forced to occupy *axial* orientations.[6b] As a result, the *spatial distance* between the nitroso oxygen and the α-hydrogen is expected to increase due to twisting of the ring in order to relax the axial steric strain. This increase in distance would make the intramolecular proton abstraction process difficult. With a view to investigating a possible correlation of the relative carcinogenicity with the spatial distance between the nitroso oxygen and the α-hydrogen, we have been involved in stereochemical analysis of *N*-nitroso derivatives[1a] of cyclic amines where the rings are conformationally homogeneous. This homogeneity of the ring conformation freezes simple substituents in one particular orientation or the other, thereby fixing the spatial distance.

We have prepared five mononitrosodiazepinones **16–20** from the corresponding diazepinones **11–15** using sodium nitrite and HCl in an ethanol–water mixture (Scheme I).

The diazepinones were prepared from the requisite diphenylpiperidinones **1–5** after converting them to the hydrochlorides **6–10**. We have also attempted to synthesize the corresponding *N,N'*-dinitrosodiazepinones. However, only mononitrosation was observed under all the conditions employed. In all the compounds obtained (**16–20**) the nitroso group was found to be present only at the amine nitrogen as evidenced by IR and NMR data.

Results and Discussion

The delocalization of the nitrogen lone pair over the double bond of the N—N=O system results in restricted rotation about the N–N bond (Figure 1) with barriers to rotation as high as 23.3 kcal mol^{-1}.[3a,6b] In the case of cyclic nitrosamines such as *r*-2,*c*-6-dimethyl-*N*-nitrosopiperidine (**21**), the energy barrier is controlled by several factors



including steric interaction between the coplanar nitroso group and the α-substituents. Similar interactions have been observed and correlated with stereochemistry[6b,13b] in a variety of piperidine derivatives as well as in oximes of cyclic ketones. This kind of steric strain that arises in a conjugated planar group with the α-equatorial substituents of a 5-, 6-, or 7-membered ring system has been termed $A^{1,3}$-strain (allylic strain).[13] This allylic strain is an important factor in determining the energy barriers for rotational equilibria. Other factors which affect the stereochemistry include 1,3-diaxial interaction between the α-substituents in the appropriate conformation (as in the case of **21b**), resonance energy due to lone pair delocalization, and ring size. For example, in the case of **21** the steric strain energy ($A^{1,3}$-strain) between the coplanar nitroso group and the equatorial methyl substituents at the 2 and 6 positions (conformer **21a**) is greater than the 1,3-diaxial methyl interaction energy (conformer **21b**), and thus the ring exists exclusively in conformation **21b**.[6b]

The stereodynamics of several 2,6-diaryl-*N*-nitrosopiperidines and piperidin-4-ones have been studied and the results presented in previous papers.[1] While the orientation of the α-substituents in the *r*-2,*c*-6-dialkyl-*N*-nitrosopiperidines was axial,[6b] in the *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones the phenyl groups were found to be equatorial.[1a] In this paper the effects of conformational equilibria on the ^1H NMR and ^{13}C NMR spectra of some seven-membered analogs are described.

The parent diazepinones **11–15** exist in the chair conformation in which the phenyl groups and the alkyl substituents are in the equatorial orientation as evidenced by a single-crystal X-ray diffraction study on one of the derivatives (**14**).[14] These diazepinones exhibit *vicinal* diaxial coupling constants[15] of 8–9 and 10–11 Hz for the benzylic

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(10) (a) While the $\Delta G^{\ddagger}$ for NCHO (of Me_2NCHO) rotation appears to be comparable to that for the N—N=O system, only the latter is expected to give the alkyl cation on enzymatic decomposition. In the nitroso compound the intermediate RNHNO is unstable, decomposing to R^+ and N_2. The corresponding intermediate RNHCHO is known to be very stable, i.e.

$$RNHNO \rightleftarrows RN{=}N{-}OH \rightarrow R^+ + N_2 + OH^-$$

$$RNHCHO \rightleftarrows RN{=}C{-}OH$$

(b) It is noted that while carcinogenic *N*-nitrosamines have barriers of ca. 22 kcal/mol, many nitrosamines with similar barriers are not carcinogenic.

(11) One might expect the N—CHO system to have a higher rotational barrier than the N—N=O system since the carbonyl group is more polarizable than N=O. However, the transition state (perpendicular orientation) for syn/anti interconversion is destabilized for the N—N=O group due to an additional lone pair–lone pair repulsion. Thus, although the expected resonance energy is higher in N—CH=O than for the N—N=O, the rotational barrier is higher for the N—N=O system (Figure 5).

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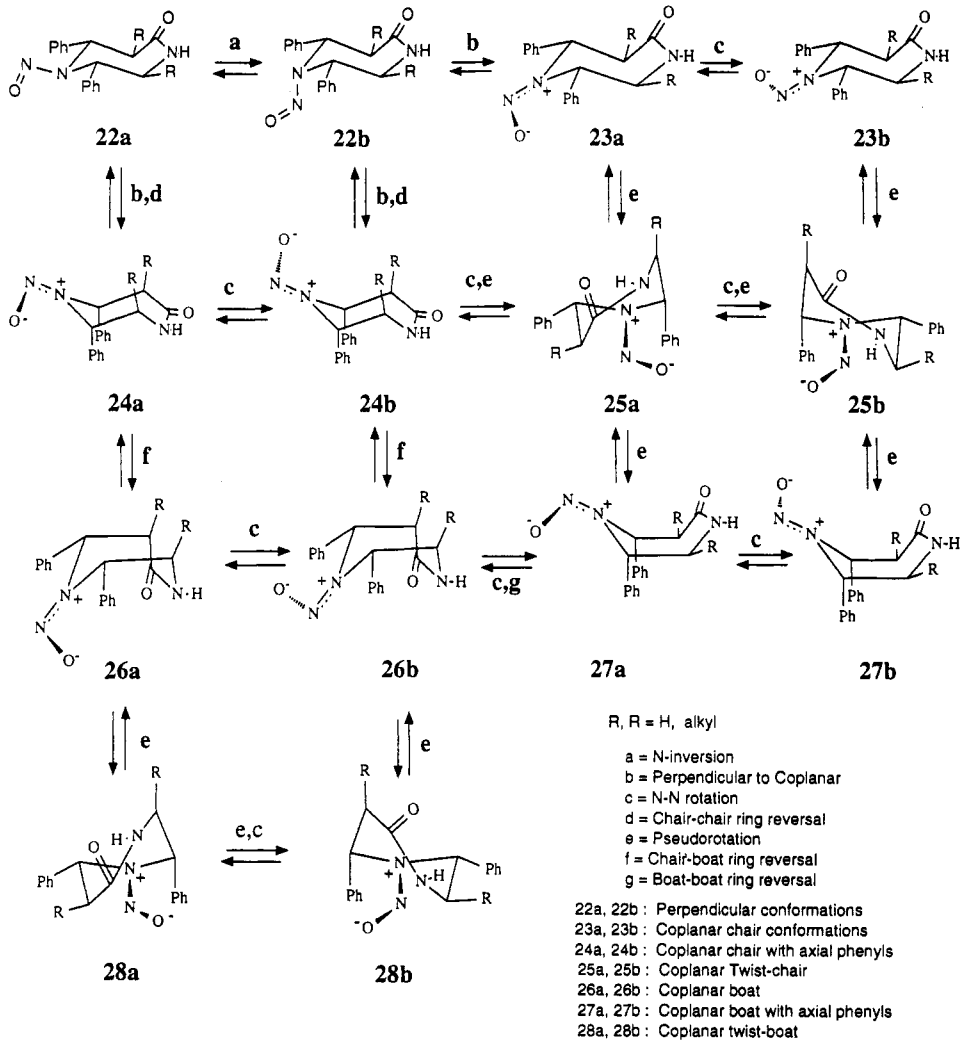

Figure 2. Possible conformations for the *N*-nitrosodiazepinones **16–20.**

hydrogens at C-2 and C-7, respectively. The cis coupling constant of 0 Hz observed for H-7_{ax} with H-6_{eq} in the parent diazepinones **11–14** suggests a dihedral angle of ca. 90°.[15] Also, weak Bohlmann bands observed in the region 2700–2800 cm^{-1} indicate that both benzylic hydrogens are axial but one of them is not exactly antiperiplanar to the nitrogen lone pair (Bohlmann bands arise due to the interaction of the nitrogen lone pair in its axial orientation with at least two antiperiplanar α-hydrogens).[16]

On the basis of elemental analysis, IR, NMR, and mass spectral data, compounds **16–20** were confirmed to be mononitroso derivatives. The absence of Bohlmann bands in the IR spectra of these nitroso compounds (region 2700–2800 cm^{-1}) suggests that the amine nitrogen is the one that has been nitrosated. Complementary evidence for the position of the nitroso group at the amine nitrogen came from the disappearance of the IR peak at 3300 cm^{-1} and the retainment of the peak at 3200 cm^{-1} due to the amide NH, after nitrosation. This conclusion was further confirmed from the ^1H NMR spectra in which the peak at ca. δ 2.5 ppm due to the amine NH disappeared on nitrosation while that near δ 6.0 ppm, due to the amide NH, was retained and disappeared on D_2O exchange.

The possible conformations for the *N*-nitrosodiazepinones **16–20** are given in Figure 2. The amide group in the seven-membered ring exerts a strong torsional constraint due to its partial double-bond character (the C–N rotational barrier is likely to be close to the 18 kcal mol^{-1} observed for dimethylacetamide[17a]). The ring is therefore likely to be somewhat rigid with chair, twist-boat, or boat conformations possible as observed for cycloheptenes, ε-caprolactams, and 1,4-benzodiazepines.[17] In these conformations, if $A^{1,3}$-strain, 1,3-diaxial interaction, etc., are of higher magnitude than the amide rotation barrier, then the C–N bond (of CONH) could lose its partial double-bond character and the torsional constraint would be lost. In such a case the ring could adopt a twist-chair conformation.

The nitroso group can adopt either a coplanar or a perpendicular conformation[7b] with respect to the dynamically averaged plane of the diazepine ring (e.g., **23a** and **22a**, respectively). Though the coplanar conformation is stabilized by the resonance energy due to lone-pair delocalization with the nitroso group, it is destabilized by severe $A^{1,3}$-strain between the coplanar nitroso group and the

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Table II. ^{1}H NMR Chemical Shifts of the α- and β-Protons (δ ppm) in Compounds 16–20[a]

	C(2)-H		C(3)-H_{ax}		C(6)-H_{ax}		C(6)-H_{eq}		C(7)-H	
compd	syn	anti	syn	anti	syn	anti	syn	anti	syn	anti
16	6.29	6.26	4.09	4.28	3.56	3.77	2.81	3.00	6.50	6.47
17	6.00	5.90	4.35	4.55	3.60	3.81	2.98	3.24	6.73	6.57
18	6.16	5.96	4.10	4.31	3.57	3.78	2.99	3.25	6.72	6.56
19	6.42	6.14	4.17	4.36	3.55	3.75	2.98	3.23	6.69	6.52
20	5.96	5.77	4.47	4.72	3.75	3.98			6.34	6.02

[a] Syn and anti refer to the direction of orientation of the nitroso group with respect to the hydrogen under study.

equatorial phenyl groups. If the resonance energy is higher than the $A^{1,3}$-strain energy, the nitroso compounds prefer chair conformations (**23a** and **23b**) with equatorially oriented phenyl groups. On the other hand, if the $A^{1,3}$-strain energy exceeds the resonance energy, conformations **23a** and **23b** become unfavorable and the ring could flip to the other chair conformation in which the phenyl groups occupy axial positions (**24a**). In this chair conformation there will not be any $A^{1,3}$-strain but the two axial phenyl groups would exhibit a 1,3-diaxial interaction. If the 1,3-diaxial interaction energy is less than the resonance energy, **24a** and **24b** will exist in equilibrium. If the 1,3-diaxial interaction is also greater than the resonance energy, then the chair conformations **24a** and **24b** are destabilized.

If the ring is destabilized in all of the chair conformations (**23a–24b**), it could adopt twist-chair conformations **25a** and **25b** where one of the phenyl groups is axial and the other equatorial. In each conformer (**25a** or **25b**), the copolanar nitroso group is oriented syn to the axial phenyl group so as to avoid the $A^{1,3}$-strain. Thus, the molecule avoids the allylic strain while gaining the resonance energy due to lone-pair delocalization over the nitroso group. A serious problem in these twist-chair conformations is that the C–N bond in the amide group loses its double-bond character, and thus, the molecule has to sacrifice the resonance energy due to lone pair delocalization in the *amide* group. Destabilization can also result from the axial disposition of one of the phenyl groups.

Alternatively, the ring may flip to the boat conformation with equatorial phenyl groups (**26a** and **26b**). If the molecule cannot tolerate the $A^{1,3}$-strain and the bond opposition energies, the ring may flip to the other boat conformation with axial phenyl groups (**27a** and **27b**) to avoid the $A^{1,3}$-strain while still retaining the coplanar orientation of the nitroso group. The stability of this conformation depends on the relative magnitudes of the resonance energy and the 1,3-diaxial interaction energy. If the diaxial interaction energy is higher than the resonance energy, the ring could flip to the twist-boat conformations **28a** and **28b** with one of the phenyl groups being axial in each conformer. In contrast to the twist-chair conformations discussed earlier, the amide C–N bond is allowed to have double-bond character in these twist-boat conformations, and the molecule gains resonance energy due to the nitrogen lone-pair delocalization in the CONH moiety. If these conformations are also disfavored due to the torsional strains and the axial orientation of one of the phenyl groups, the resonance energy can compensate neither $A^{1,3}$-strain nor 1,3-diaxial strain energy nor ring torsional strain in any of the coplanar conformations of the nitroso group. As a result, the nitroso group would adopt a perpendicular conformation in which it can either be at an equatorial or an axial orientation (**22a** or **22b**).

^{1}H NMR Spectra. The chemical shifts of the ring protons of the nitroso compounds **16–20** are given in Table II. The ^{1}H NMR spectra of these *N*-nitrosodiazepinones exhibit pairs of multiplets (e.g., absorptions at δ 1.79 and 1.96, 2.98 and 3.23, 3.55 and 3.75, 4.17 and 4.36, 5.72 and 5.95, 6.14 and 6.42, 6.52 and 6.69 ppm, etc. for **19**) having very similar splitting patterns (Figure 3) and nearly the same coupling constants (Table III). This pattern can arise only if there are two conformers existing in an equilibrium which *does not* involve any ring flipping such as chair–chair, chair–boat, or boat–boat interconversion.

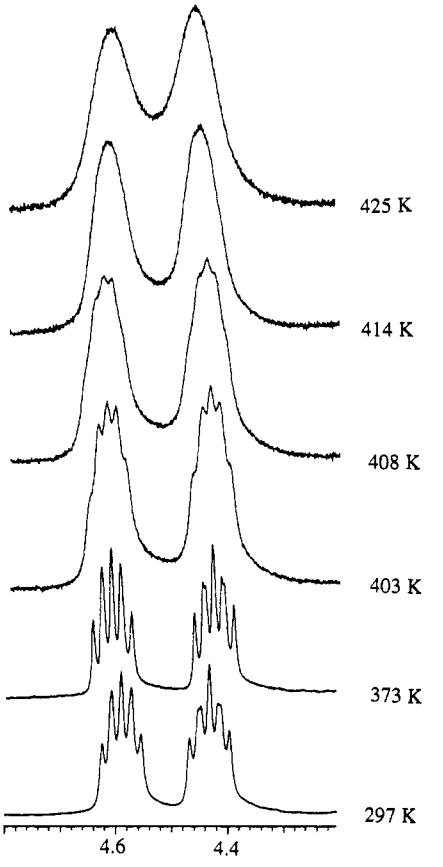

Figure 3. Variable-temperature ^{1}H NMR spectrum of the isopropyl derivative **19**.

Table III. Vicinal Coupling Constants (Hz) for the α- and β-Protons in 16–20[a]

	$J_{2H,3Ha}$		$J_{2H,3He}$		$J_{6Ha,7H}$		$J_{6He,7H}$	
compd	syn	anti	syn	anti	syn	anti	syn	anti
16	9.6	9.5	5.3	6.1	10.2	10.1	6.5	7.1
11	(9.0)		(0.0)		(10.3)		(0.0)	
17	10.8	10.5			12.3	11.7	7.0	8.3
12	(7.8)				(10.5)		(0.0)	
18	10.8	10.5			12.4	11.7	7.1	7.8
13	(7.8)				(10.6)		(0.0)	
19	10.0	10.7			12.4	11.8	6.7	7.8
14	(8.3)				(10.6)		(0.0)	
20	11.2	10.6			11.0	10.4		
15	(8.1)				(8.8)			

[a] Values in parentheses are the corresponding coupling constants in the parent diazepinones **11–15**.

If such an interconversion were occurring then the equatorial hydrogens become axial and vice versa resulting in drastic differences in coupling constants within each pair. Thus, it is concluded that of the seven pairs of possible conformers (**22a–28b**), only one pair exists in equilibrium. The question is to decide which of the pairs of conformations is adopted by the nitrosodiazepinones.

Perpendicular Orientation. The observation of a pair of absorptions for each hydrogen and the examination of the dynamic NMR spectra recorded up to 150 °C eliminate the possibility of a perpendicular orientation for the nitroso group (**22a–22b**). Conformational equilibrium due to ring-nitrogen inversion (with a perpendicular nitroso group) would give rise to two conformers of which one would have axial and the other equatorial nitroso groups. Since nitrogen inversions are known to be very fast at room temperature,[18] each conformer could not give separate signals in the NMR spectrum at room temperature and only the averaged signal for the conformers would be obtained. In the case of **16–20** the pair of multiplets for each hydrogen did not coalesce even at 150 °C indicating that the equilibrium involves the coplanar, and not the perpendicular, orientation of the nitroso group.

The coupling constants between the H-7 and the H-6_{eq} protons (in compounds **16–19**) were found to be ca. 7.4 ± 0.9 Hz, whereas in the case of the parent diazepinones **11–14** they were zero. This increase in coupling constant from 0 to 7.4 Hz, on nitrosation, suggests a decrease in dihedral angle from 90° to ca. 30° between H-7 and H-6_{eq}. Such a twisting can be visualized with a coplanar nitroso group. The coplanar orientation, which is a consequence of the lone-pair delocalization, causes the ring nitrogen (N—N=O) to attain sp^2 hybridization resulting in a flattening at the C7–N1–C2 end of the ring. As a result of this flattening, the consequent $A^{1,3}$-strain between the phenyl groups and the nitroso group is so severe that it could bring twisting of the ring.

Twist-Chair Conformations. Equilibrium between the twist-chair conformations **25a** and **25b** involves pseudorotation which converts axial hydrogens into equatorial and vice versa. Thus, as with ring-flipping, an equilibrium involving pseudorotation also lacks support from the spectral data. However, even without pseudorotation, an equilibrium could occur where the two rotamers have the same ring-backbone as in **25a**, but with two orientations of the coplanar nitroso group. These conformations can be ruled out with the help of the ^{13}C NMR data for the carbonyl carbon as follows: The twist-chair conformations do not favor a double-bond character at the amide C–N bond[17] and, thus, in the ^{13}C NMR spectra, the carbonyl carbon is expected to behave like a ketone carbon rather than an amide carbon. In other words, the carbonyl carbon is expected to be deshielded compared to the parent compound. Since the carbonyl carbon is in fact *shielded* by about 3 ppm, the twist-chair conformations can be ruled out.

Observaton of a W-coupling with J = 1.5 Hz between the amide NH proton and H-6_{eq}, in addition to a coupling of J = 4–7 Hz between the NH proton and H-3_{ax}, suggests that compounds **16–19** exist in dimeric form holding the NH in the hydrogen-bonded form thus preventing a fast exchange of the NH and permitting the NH to couple with the C-6 equatorial hydrogen. Such a W-coupling is possible only when H-6_{eq}, C-6, C-5, N-4, and N(4)-H lie almost in a plane, thereby providing a convenient geometric disposition for the amide lone-pair delocalization. All the foregoing evidence confirms that the title compounds avoid twist-chair conformations.

Table IV. ^{13}C Chemical Shifts of the α- and β-Carbons in 16–20[a,b]

	C-2		C-7		C-3		C-6	
compd	syn	anti	syn	anti	syn	anti	syn	anti
16	54.2	64.7	48.6	60.7	41.1	41.6	36.1	36.7
11	(65.4)		(59.4)		(50.7)		(47.7)	
17	59.0	71.9	48.1	59.8	48.3	48.9	36.4	36.5
12	(71.1)		(59.6)		(54.7)		(47.5)	
18	56.8	70.2	48.4	59.8	54.2	55.0	36.5	36.5
13	(70.1)		(60.5)		(59.6)		(47.4)	
19	53.8	67.7	48.6	59.9	57.1	57.7	36.4	36.5
14	(68.6)		(59.7)		(63.5)		(47.5)	
20	58.6	70.5	53.6	67.0	46.5	46.9	37.4	37.5
15	(71.0)		(64.9)		(54.2)		(45.9)	

[a] The values in parentheses correspond to the parent diazepinones. [b] The designations α and β are made with reference to the amine nitrogen (N_1).

Twist-Boat Conformations. In conformation **28a** the phenyl group at C-2 and the alkyl group at C-3 are axial. In its equilibrium counterpart **28b** the orientation of these groups is equatorial. As a result, the ^{13}C chemical shifts of the C-3 carbon (as well as those of the C-3 alkyl substituent) in the two conformers are expected to be separated well apart. However, the experimental observation is that the C-3 carbon, as well as the C-3 alkyl groups, in the two conformers have very similar ^{13}C resonances (Table IV). Hence, on this basis the twist-boat conformations are ruled out.

The dihedral angles of the C(6)-hydrogens with the C(7)-H were calculated using the DAERM method (dihedral angle estimation by ratio method)[19a] and are listed in Table V. This method is based on the assumption that, although the magnitude of the Karplus constants k_1 and k_2 vary, the ratio of k_1 to k_2 is a constant. The ratio of k_1 (k_{cis}) to k_2 (k_{trans}), which is employed for the estimation of the dihedral angles, was calculated using the dihedral angles (from the crystal structure data) and H–H coupling constants[19b] of the analogous *N*-phenylcarbamoyl derivative of *t*-3-methyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (**29**). For the nitroso compounds **16–20**, the cis angle varies from 29° to 36° and the trans angle from 149° to 156°, suggesting an outward twisting of the C-7 hydrogen.

Chair Conformations. It was discussed earlier that the chair conformations having equatorial phenyl groups (**23a, 23b**) are destabilized by an $A^{1,3}$-strain. The calculated dihedral angles (Table V) exclude the possibility of chair conformations **23a** and **23b** as the chair form requires a cis dihedral angle (between H-6_{eq} and H-7_{ax}) of at least 60°.

Chair conformation **24a** contains axially oriented phenyl and alkyl groups. If this were the actual conformation, both the α- and β-hydrogens (C-2 and C-3 hydrogens of **17–20**) would be equatorial and the coupling constants ($J_{e,e}$) would be ca. 2–3 Hz. The corresponding observed $J_{2H,3H}$ values (Table III) were 10.8 ± 0.4 Hz, indicating that the title compounds do not adopt conformations **24a** and **24b**.

Boat Conformations. In the boat conformations **26a** and **26b** the orientations of the alkyl substituents (at C-3 and C-6) in compound **20** are axial. As the bulkiness of

(18) (a) Crabb, T. A.; Katritzky, A. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1984; Vol. 36, p 34. (b) Katritzky, A. R.; Patel, R. C.; Riddell, F. G. *Angew. Chem.* **1981**, *20*, 521 and references cited therein.

(19) (a) Slessor, K. N.; Tracey, A. S. *Can. J. Chem.* **1971**, *49*, 2874. (b) Krishna Kumar, R. Ph.D. Thesis, Bharathidasan University, India, 1990.

Table V. Calculated Dihedral Angles Using the DAERM Method[a]

	$J_{6He,7H}$		$J_{6Ha,7H}$		cis angle (deg) H_{eq}–C6–C6–H		trans angle (deg) H_{ax}–C6–C6–H	
compd	syn	anti	syn	anti	syn	anti	syn	anti
16	6.5	7.1	10.2	10.1	32	29	152	149
17	7.0	8.3	12.3	11.7	34	29	154	149
18	7.1	7.8	12.4	11.7	34	31	154	151
19	6.7	7.8	12.4	11.8	36	31	156	151

[a] The ratio K_1/K_2 used in this method has been calculated from the X-ray crystal structure and ^{1}H NMR data[19b] of the protons in the C6–C7 fragment in *t*-3-methyl-*r*-2,*c*-7-diphenyl-1-(phenylcarbamoyl)-1,4-diazepin-5-one (**29**).

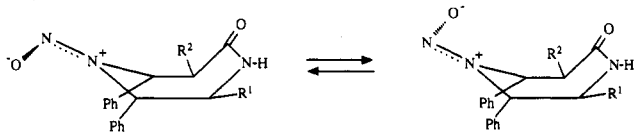

Figure 4. Flattened boat conformations for *N*-nitrosodiazepinones **16–20**.

the alkyl group at C-3 is increased on moving from **17** to **19** (Me, Et, i-Pr), the 1,4-diaxial hydrogen–alkyl interaction also increases. Obviously, the alkyl groups (of **17–20**) will be pushed outward so as to relax the axial strain. Consequently, the dihedral angles between the vicinal hydrogens at C-2 and C-3 would increase resulting in a decrease of $J_{a,e}$. However, on substituting a methyl group (**16** → **17**) the observed value of $J_{3H,2H}$ was found to increase from 9.5 to 10.5 Hz. A further increase in the size of the alkyl group (**17** → **18** → **19**) has no effect on the coupling constant. The highest value of 11.2 Hz ($J_{3H,2H}$) was observed for **20**, even though it contains alkyl groups at both C-3 and C-6. Thus, all of the observations are the reverse of what could be expected for a boat conformation with equatorial phenyl groups, and therefore conformations **26a** and **26b** are not considered further.

It was mentioned earlier that, on nitrosation, the dihedral angle between H-6_{eq} and H-7 decreased from 90° to ca. 30°. The driving force for the large change in the dihedral angle presumably arises from the coplanar orientation of the nitroso group leading to flattening at the nitrogen end (N_1) of the ring and a resulting $A^{1,3}$-strain of the nitroso group with the phenyl groups. Since the seven-membered ring is more flexible than the six-membered analog, the C7–N1–C2 end of the ring apparently undergoes flipping so as to give the boat form and relax the $A_{1,3}$ interaction as the phenyl groups are pushed away from the equatorial positions. This leads to the decrease in the dihedral angles between the hydrogens at C-6 and C-7. The calculations using models show that the boat conformations (**27a** and **27b**) require approximate cis (H–C7–C6–H_{eq}) and trans (H–C7–C6–H_{ax}) angles of 0–10° and 120–130°, respectively. The corresponding calculated angles (Table V) using ^{1}H NMR data were ca. 32° and 152°, respectively. Therefore it is concluded that the title compounds exist in the *boat conformation flattened at the nitroso end* of the ring with quasi-axial phenyl groups (Figure 4).

In the conformations depicted in Figure 4 the syn α-hydrogens are found to lie within the plane of the deshielding cone[20] of the nitroso moiety and thus experience deshielding relative to the anti α-hydrogens. Thus, of the two observed resonances for each α-hydrogen, the downfield one is assigned to the syn proton and the other to the anti proton (Table II).

All of the alkyl protons were found to be shifted *downfield* from the corresponding proton signals in the parent

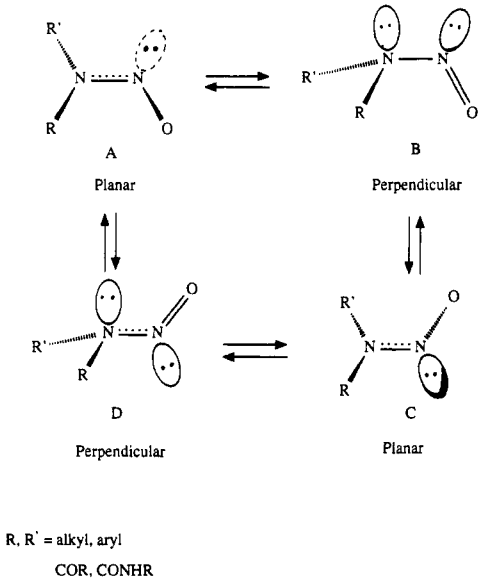

Figure 5. Ground-state and transition-state conformations for *N*-nitrosamines.

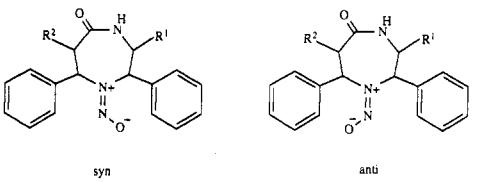

Figure 6. Designation of conformers in **16–20**.

compounds. While the α-hydrogens were shifted *downfield* by ca. 2 ppm, the aromatic hydrogens were, as a whole, shifted *upfield* by ca. 0.5 ppm from the corresponding protons in the parent diazepinone, thus confirming the existence of N—N=O as $^+$N=N—O$^-$. This upfield shift could arise from a repulsive interaction between the O$^-$ of the nitroso group and the phenyl ring π-cloud leading to a decrease in the diamagnetic ring current of the latter.

^{13}C NMR Spectra. In the ^{13}C NMR spectra also two signals appear for each carbon, thus confirming the presence of two conformations. Two methods were followed in assigning the ^{13}C NMR signals for compound **16**. In the first method, the series of nitrosodiazepinones with varying substituents at C-3 were considered in sequence. On varying the equatorial alkyl substituents at the C-3 position (i.e., compounds **16–19**) the peaks corresponding to those at δ 36.1, 36.7, 48.6, and 60.7 ppm of **16** were affected very little and thus they were assigned to the C-6 and C-7 carbons in the two conformations.[21] The peaks at δ 36.7 and 36.1 ppm in **16** were assigned to the C-6 carbon in the anti and syn conformers,[22] respectively (in the corre-

(20) Harris, R. K.; Spragg, R. A. *J. Mol. Spectrosc.* **1967**, *23*(2), 158.

(21) It is assumed that the equatorial alkyl substituents will not have a major effect on the ^{13}C chemical shifts of carbons 6 and 7.

(22) The syn conformer refers to the one with the nitroso group oriented in the direction of N4 (Figure 6).

Table VI. ^{13}C Chemical Shift of the Ipso Carbons of the Phenyl Groups of 16–20[a]

compd	Ipso carbons[b] at C-2	at C-7
16	136.5, 135.2	137.7, 136.6
11	(142.2)	(144.7)
17	135.2, 134.2	137.4, 136.0
12	(142.1)	(144.7)
18	135.2, 134.1	137.3, 135.9
13	(142.0)	(144.8)
19	135.3, 134.1	137.4, 136.0
14	(141.7)	(144.7)
20	134.7, 134.2	135.4, 134.9
15	(142.2)	(143.2)

[a] The values in parentheses correspond to the parent diazepinones. [b] Since the difference in chemical shifts is very small (ca. 1 ppm) no syn and anti assignments have been made.

sponding parent diazepinones 11–14, the C-6 carbons absorb at δ 47.7 ppm). Of the two remaining absorptions in this group, the one at δ 48.6 ppm was assigned to the C-7 carbon syn to the coplanar nitroso group and the peak at δ 60.7 ppm was assigned to the C-7 carbon anti to the nitroso group. The assignments for C_6 and C_7 are made based on C_7 being downfield because of the influence of the phenyl and positive N groups. Assignments in the other nitroso derivatives were made in a similar manner.

In the second method, peak assignments were made by comparing them with the ^{13}C NMR spectral data of the parent diazepinones (11–15). Precise estimation of chemical shift values using known structural additivity parameters was difficult owing to the large range of shift effects brought about by the nitroso group.

The chemical shifts of the α- (C-2 and C-7) and β-carbons (C-3 and C-6) for the nitrosodiazepinones 16–20 and their parent diazepinones 11–15 are summarized in Table IV. The α-carbons syn to the nitroso group have absorptions that are shifted upfield by about 11–15 ppm from those in the parent compounds whereas the anti carbon absorptions are affected by less than 1 ppm. The high upfield shift can be understood with the aid of models which show (i) steric shielding over the syn α-carbon as a result of the γ eclipsed conformation of the N–O bond with respect to the syn C–N bond and (ii) partial eclipsing interactions between the N1–C7 and C2–C3 bonds as well as between the N1–C2 and C7–C6 bonds due to the small dihedral angle (ca. 30°) arising out of the sp^2 hybridization achieved by the ring nitrogen. However, the anti carbon is not very much affected as the electronic effect due to the anti-oriented nitroso group is nearly compensated for by the partial eclipsing interaction discussed above.

The effect of coplanar orientation of the nitroso group is felt almost to the same extent at the two β-carbons (C-3 and C-6) in both the syn and anti forms. The β-carbons of both syn and anti forms experience an upfield shift of about 5–11 ppm compared to the corresponding carbons in the parent compounds. This upfield shift may be ascribed to the decrease in dihedral angle between the C2–N1–C7 and N1–C7–C6 planes as well as the C7–N1–C2 and N1–C2–C3 planes as discussed above.

The chemical shifts of the ipso carbons of the phenyl moieties of the nitroso compounds 16–20 and the corresponding parent diazepinones are listed in Table VI. The ipso carbons of the phenyl groups of 16–20 in both syn and anti conformations are also found to be shifted upfield by about 7 ppm compared to those in the parent diazepinone. This *upfield* shift can be attributed to (i) the decrease in C–N1 bond length and (ii) the decrease in the dihedral angle between the N(O)–N1–C2 and N1–C2–C_{ipso} (as well as the N(O)–N1–C7 and N1–C7–C_{ipso}) planes. These two factors are the consequences of sp^2 character attained by the ring-nitrogen on lone-pair delocalization in the coplanar conformation.

By integrating the proton spectra the ratio of syn to anti conformers was found to be 60:40 for 16–19 and 68:32 for 20. A variable-temperature NMR study up to 150 °C (Figure 3) did not result in the coalescence of peaks, and thus the coalescence temperature lies above this temperature. A further increase in temperature led to the decomposition of the compounds. However, a rough estimation (see Experimental Section) of the energy barrier for the isopropyl derivative 19 could be made which showed that the barrier is at least 21.5 kcal mol^{-1}, a value considerably higher than those (18.4–19.3 kcal mol^{-1})[1a] for the six-membered analogs, viz. *N*-nitroso-*r*-2,*c*-6-diphenylpiperidones.

Experimental Section

General Methods. All mp's were determined using an electrically heated block with a calibrated thermometer and are uncorrected. IR spectra were recorded in KBr pellets. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions with TMS as an internal standard using a 300-MHz spectrometer. All chemical shifts are reported in δ units and described as being either singlet (s), broad singlet (bs), doublet (d), quartet (q), septet (sep), or multiplet (m). Mass spectra were recorded on a commercial EI spectrometer at 70 eV. Dynamic ^1H NMR spectra were recorded for compound 19 in DMSO-d_6 solution up to 150 °C, above which the decomposition of the nitroso compounds began. The coalescence temperature (T_c) was determined by extrapolating the plot of temperature against the ratio of height of the valley (between the equilibrating resonances) to the average height of the two equilibrating resonances. The chemical shift difference at T_c was determined by extrapolating the plot of temperature against the chemical shift difference at that temperature. The free energy of activation was calculated by substituting the coalescence temperature (T_c) and the chemical shift difference at T_c into the Eyring equation.[23]

***r*-2,*c*-6-Diphenylpiperidin-4-ones 1–5** were prepared by literature methods[24,25] as described in the previous paper.[1a]

***r*-2,*c*-6-Diphenylpiperidin-4-one Hydrochloride (6).** Powdered dry *r*-2,*c*-6-diphenylpiperidin-4-one (1) (10 g, 39.8 mmol) was dissolved in ether (200 mL) in a conical flask. HCl gas was passed through the solution until precipitation of the white solid was complete (5–10 min). The solid was then separated by filtration through a Buchner funnel, washed with ether, and dried. Recrystallization from ethanol afforded colorless crystals of 6 (yield 96%); mp 216–217 °C dec (lit.[24] mp 217 °C dec).

***t*-3-Methyl-*r*-2,*c*-6-diphenylpiperidin-4-one Hydrochloride (7).** The procedure described for 6 was used except using ethanol–water as solvent. Powdered *t*-3-methyl-*r*-2,*c*-6-diphenylpiperidin-4-one (2) (10 g, 37.7 mmol) was converted to pure 7 (yield 89%); mp 225–226 °C (lit.[25] mp 224–226 °C).

***t*-3-Isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one hydrochloride (9)** was prepared from *t*-3-isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one (4) in a manner described for 6 and recrystallized from 1:1 EtOH–H_2O; mp 192–193 °C (lit.[25] mp 192–194 °C).

***t*-3,*t*-5-Dimethyl-*r*-2,*c*-6-diphenylpiperidin-4-one hydrochloride (10)** was prepared from *t*-3,*t*-5-dimethyl-*r*-2,*c*-6-diphenylpiperidin-4-one (5) as described above and recrystallized from aqueous EtOH; mp 227–229 °C (lit.[25] mp 228–230 °C).

***r*-2,*c*-7-Diphenylhexahydro-1,4-diazepin-5-one (11).** In a typical reaction dry, powdered 6 (10 g, 37.59 mmol) was added, in portions, to cold concd H_2SO_4 (50 mL) in a conical flask equipped with a magnetic stirrer. After the dissolution of 6 was

(23) Oki, M. *Application of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Florida, 1985; Chapter 1.
(24) Baliah, V.; Ekambaram, A.; Govindarajan, T. S. *Curr. Sci.* **1954**, *23*, 264.
(25) Noller, C. R.; Baliah, V. *J. Am. Chem. Soc.* **1948**, *70*, 3853.

complete, the temperature of the solution was allowed to rise to 25 °C. NaN_3 (3 g, 46.15 mmol) was added in portions of 0.1 g, with vigorous stirring. After the addition was over, the solution was poured into crushed ice and stirred well with a glass rod. Cold NaOH solution (2 N) was added slowly with stirring until the pH was 8. A white solid separated out. After keeping the mixture at room temperature overnight the solid was separated by filtration through a Buchner funnel, washed free of NaOH, and dried. The dried solid was dissolved in benzene and filtered through a fluted filter paper and the solution concentrated. The solution was kept aside for crystallization. The crystals obtained were separated and then recrystallized from ethanol (yield 85%): mp 171–172 °C; IR (KBr) 3300 (NH), 3200 (CONH), 1670 (CO); ^{1}H NMR ($CDCl_3$) δ 2.11 (s, amine NH), 2.67 (d, J = 13.9 Hz, 1 H, H-6_{eq}), 3.13 (d, J = 14.9 Hz, 1 H, H-3_{eq}), 3.14 (dd, J = 10.5 and 14.3 Hz, 1 H, H-6_{ax}), 3.65 (ddd, J = 4.2, 9.1 and 14.7 Hz, 1 H, H-3_{ax}), 4.03 (d, J = 9.0 Hz, 1 H, H-2_{ax}), 4.14 (d, J = 10.3 Hz, 1 H, H-7_{ax}), 6.25 (bs, CO*NH*), 7.25–7.46 (aromatic protons); ^{13}C NMR ($CDCl_3$) δ 47.7 (C-6), 50.7 (C-3), 59.4 (C-7), 65.4 (C-2), 142.2 and 144.7 (ipso carbons), 176.7 (carbonyl carbon), 126.4, 126.7, 127.7, 128.0 and 128.7 (aromatic carbons). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.64; H, 6.84; N, 10.50.

***t*-3-Methyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (12)**: mp 184–185 °C (lit.[26] mp 183 °C); IR (KBr) 3300 (NH), 3200 (CONH), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3 H, CH_3), 2.07 (bs, amine NH), 2.65 (d, J = 14.1 Hz, 1 H, H-6_{eq}), 3.14 (dd, J = 10.6 and 14.1 Hz, 1 H, H-6_{ax}), 3.70 (d, J = 7.8 Hz, 1 H, H-2_{ax}), 3.82 (ddq, J = 7.0, 7.6 and 4.0 Hz, 1 H, H-3_{ax}), 4.13 (d, J = 10.5 Hz, 1 H, H-7_{ax}), 5.75 (bs, CO*NH*), 7.23–7.43 (aromatic protons); ^{13}C NMR ($CDCl_3$) δ 19.8 (CH_3), 47.5 (C-6), 54.7 (C-3), 59.6 (C-7), 71.1 (C-2), 142.1 and 144.7 (ipso carbons), 175.7 (carbonyl carbon), 126.4, 127.7, 128.0 and 128.6 (aromatic carbons).

***t*-3-Ethyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (13)**: mp 200–201 °C mp mp 202 °C); IR (KBr) 3310 (NH), 3210 (CONH), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.4 Hz, 3 H, CH_3), 1.12 (m, J = 7.4 and 7.8 Hz, 2 H, CH_2 at C-3), 2.03 (s, amine NH), 2.65 (d, J = 14.0 Hz, 1 H, H-6_{eq}), 3.15 (dd, J = 10.7 and 14.1 Hz, 1 H, H-6_{ax}), 3.65 (m, J = 4.5, 8.0 and 7.5 Hz, 1 H, H-3_{ax}), 3.77 (d, J = 7.8 Hz, 1 H, H-2_{ax}), 4.14 (d, J = 10.6 Hz, 1 H, H-7_{ax}), 5.77 (bs, CO*NH*), 7.20–7.44 (aromatic protons); ^{13}C NMR ($CDCl_3$) APT spectrum δ 10.1 (CH_3), 25.6 (CH_2CH_3), 47.4 (C-6), 59.6 (C-3), 60.5 (C-7), 70.1 (C-2), 142.0 and 144.8 (ipso carbons), 176.1 (carbonyl carbon), 126.4, 127.6, 127.7, 127.8, 128.5 (aromatic carbons).

***t*-3-Isopropyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (14)**: mp 188–189 °C (lit.[26] mp 188 °C); IR (KBr) 3305 (NH), 3200 (CONH), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ 0.85 (2d, J = 6.8 and 7.1 Hz, 6 H, 2 CH_3), 1.5 (d sep, J = 2.4 and 6.9 Hz, 1 H, C*H*Me_2), 1.96 (s, amine NH), 2.65 (d, J = 13.9 Hz, 1 H, H-6_{eq}), 3.20 (dd, J = 10.6 and 14.1 Hz, 1 H, H-6_{ax}), 3.70 (ddd, J = 2.2, 8.3, and 3.7 Hz, 1 H, H-3_{ax}), 3.85 (d, J = 8.3 Hz, 1 H, H-2_{ax}), 4.15 (d, J = 10.6 Hz, 1 H, H-7_{ax}), 5.68 (bs, CO*NH*), 7.23–7.40 (aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3, 20.8 (CH_3), 28.5 ($CHMe_2$), 47.5 (C-6), 59.7 (C-7), 63.5 (C-3), 68.6 (C-2), 141.7 and 144.7 (ipso carbons), 176.3 (carbonyl carbon), 126.3, 127.6, 127.8 and 128.5 (aromatic carbons).

***t*-3,*t*-6-Dimethyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (15)**: mp 180–181 °C; IR (KBr) 3300 (NH), 3200 (CO*NH*), 1660 (CO); ^{1}H NMR ($CDCl_3$) δ 0.70 (d, J = 7.1 Hz, 3 H, CH_3 at C-6), 0.79 (d, J = 6.7 Hz, 3 H, CH_3 at C-3), 2.06 (s, amine NH), 3.08 (dq, J = 7.1 and 8.8 Hz, 1 H, H-6_{ax}), 3.65 (d, J = 8.1 Hz, 1 H, H-2_{ax}), 3.79 (d, J = 8.8 Hz, 1 H, H-7_{ax}), 3.86 (ddq, J = 5.1, 6.7 and 7.6 Hz, 1 H, H-3_{ax}), 5.75 (bd, CO*NH*), 7.20–7.40 (aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3 at C-6), 19.6 (CH_3 at C-3), 45.9 (C-6), 54.2 (C-3), 64.9 (C-7), 71.0 (C-2), 142.2 and 143.2 (ipso carbons), 178.4 (carbonyl carbon), 126.7, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5 and 128.7 (aromatic carbons). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 77.61; H, 7.58; N, 9.50.

1-Nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (16). Dry, powdered 11 (2 g, 7.52 mmol) was dissolved in ether (150 mL), and HCl was passed through the solution until precipitation of the hydrochloride of 11 was complete. The solid was separated by filtration, washed with a 1:1 ether–alcohol mixture (100 mL), and dried. The powdered hydrochloride of 11 was added, in portions, to a water–alcohol mixture (water 20 mL; alcohol 10 mL) at 0–10 °C in a two-necked round-bottom flask equipped with a thermometer and magnetic stirrer. The contents were stirred well until the solid dissolved. While stirring, a solution of $NaNO_2$ (2 g, 29 mmol) in water (10 mL) was added dropwise from a dropping funnel over a period of 1 h at 0–10 °C. To this mixture was added 25 mL of water and stirring continued for another 10 min. The precipitated white solid was filtered through a Buchner funnel, washed well with 50% aqueous alcohol, and dried. Recrystallization from ethanol gave colorless needles of **16** (yield 88%): mp 202–204 °C; IR (KBr) 3200 (CO*NH*), 1680 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ syn conformer[20,22] 3.00 (dd, J = 7.1 and 14.6 Hz, 1 H, H-6_{eq}), 3.65 (overlapped ddd, J = 15.7 and 5.5 Hz, 1 H, H-3_{eq}), 3.77 (dd, J = 10.2 and 14.5 Hz, 1 H, H-6_{ax}), 4.09 (ddd, J = 6.8, 9.6 and 15.9 Hz, 1 H, H-3_{ax}), 6.12 (dd, J = 5.3 and 9.6 Hz, 1 H, H-$_{2ax}$), 6.47 (dd, J = 7.1 and 10.1 Hz, 1 H, H-7_{ax}), 7.9 (t, J = 5.8 Hz, 1 H, NH); anti conformer 2.81 (dd, J = 6.5 and 14.0 Hz, 1 H, H-6_{eq}), 3.56 (dd, J = 10.2 and 14.1 Hz, 1 H, H-6_{ax}), 3.84 (overlapped ddd, J = 15.6 and 6.0 Hz, 1 H, H-3_{eq}), 4.28 (ddd, J = 6.1, 9.5 and 15.6 Hz, 1 H, H-3_{ax}), 6.18 (dd, J = 6.1 and 9.5 Hz, 1 H, H-2_{ax}), 6.50 (dd, J = 6.5 and 10.2 Hz, 1 H, H-7_{ax}), 8.1 (t, J = 5.8 Hz, 1 H, NH), 6.7–7.3 (aromatic signals corresponding to both syn and anti conformers); ^{13}C NMR (DMSO-d_6) δ syn conformer 36.7 (C-6), 41.1 (C-3), 54.2 (C-2), 60.7 (C-7), 135.2 and 137.7 (ipso carbons at C-2 and C-7), 172.3 (carbonyl carbon); anti conformer 36.1 (C-6), 41.6 (C-3), 48.6 (C-7), 64.7 (C-2), 136.5 and 136.6 (ipso carbons at C-2 and C-7), 172.5 (carbonyl carbon), 127.1, 127.2, 127.6, 127.7, 127.8, 127.9 and 128.1 (aromatic carbon signals other than ipso carbons corresponding to both syn and anti conformers); MS m/z (relative intensity) 295 (M^+), 278 (4.6), 277 (11.7), 265 (16.1), 251 (21.5), 248 (3), 206 (4.6), 104 (100). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.90; H, 5.98; N, 13.95.

***t*-3-Methyl-1-nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (17)**. The same procedure as for **16** was followed. Dry, powdered **12** (1.0 g, 3.51 mmol) was converted to colorless crystals of **17** (yield 80%): mp 196–198 °C; IR (KBr) 3200 (CO-*NH*), 1670 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ syn conformer 1.21 (d, J = 6.4 Hz, 3 H, CH_3), 3.24 (ddd, J = 1.5, 8.3 and 13.7 Hz, 1 H, H-6_{eq}), 3.81 (dd, J = 11.7 and 13.5 Hz, 1 H, H-6_{ax}), 4.35 (ddq, J = 6.3 and 11.0 Hz, 1 H, H-3_{ax}), 6.0 (d, J = 10.8 Hz, 1 H, H-2_{ax}), 6.57 (dd, J = 8.3 and 11.7 Hz, 1 H, H-7_{ax}); anti conformer 1.40 (d, J = 6.4 Hz, 3 H, CH_3), 2.98 (ddd, J = 1.5, 7.2 and 13.2 Hz, 1 H, H-6_{eq}), 3.60 (dd, J = 13.2 and 12.6 Hz, 1 H, H-6_{ax}), 4.55 (ddq, J = 6.0 and 10.5 Hz, 1 H, H-3_{ax}), 5.9 (d, J = 10.5 Hz, 1 H, H-2_{ax}), 6.73 (dd, J = 7.0 and 12.3 Hz, 1 H, H-7_{ax}), 6.8–7.4 (aromatic protons of both syn and anti conformers); ^{13}C NMR ($CDCl_3$) δ syn conformer 18.4 (CH_3), 36.5 (C-6), 48.3 (C-3), 59.0 (C-2), 59.8 (C-7), 134.2 and 137.4 (ipso carbons at C-2 and C-6), 172.6 (carbonyl carbon); anti conformer 18.8 (CH_3), 36.4 (C-6), 48.1 (C-7), 48.9 (C-3), 71.9 (C-2), 135.2, 136.0 (ipso carbons at C-2 and C-6), 172.7 (carbonyl carbon), 126.1, 126.3, 127.2, 127.8, 128.0, 128.1, 128.3, 128.5 and 128.6 (aromatic signals other than ipso carbons corresponding to both syn and anti conformers); MS m/z (relative intensity 309 (M^+), 292 (1.4), 279 (42), 265 (8.5), 236 (13.4), 206 (5), 132 (100). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.93; H, 6.49; N, 13.42.

***t*-3-Ethyl-1-nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (18)**. The same procedure as for **16** was followed. Powdered **13** (1.0 g, 3.40 mmol) was converted to colorless needles (yield 78%) of **18**: mp 225–226 °C; IR (KBr) 3200 (CO*NH*), 1675 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ syn conformer 1.00 (t, J = 7.5 Hz, 3 H, CH_3), 1.41 (m, 1 H, CH of CH_2), 1.60 (m, 1 H, CH of CH_2), 3.25 (ddd, J = 1.4, 8.0 and 13.6 Hz, 1 H, H-6_{eq}), 3.78 (dd, J = 11.8 and 13.4 Hz, H-6_{ax}), 4.10 (m, 1 H, H-3_{ax}), 6.16 (d, J = 10.8 Hz, 1 H, H-2_{ax}), 6.56 (dd, J = 7.8 and 11.7 Hz, 1 H, H-7_{ax}); anti conformer 1.09 (t, J = 7.6 Hz, 3 H, CH_3), 1.64 (m, 1 H, H of CH_2), 1.78 (m, J = 3.4, 7.6 and 14.7 Hz, 1 H, H of CH_2), 2.99 (ddd, J = 1.5, 6.9 and 13.2 Hz, 1 H, H-6_{eq}), 3.57 (dd, J = 12.7 Hz, 1 H, H-6_{ax}), 4.31 (m, 1 H, H-3_{ax}), 5.96 (d, J = 10.5 Hz, 1 H, H-2_{ax}), 6.72 (dd, J = 7.1 and 12.4 Hz, 1 H, H-7_{ax}), 6.26 (bd, 1 H, CO*NH* of both syn and anti conformers), 6.8–7.1 (aromatic protons corresponding to both syn and anti conformers); ^{13}C NMR ($CDCl_3$)

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APT spectrum δ syn conformer 10.8 (CH_3), 25.5 (CH_2 of C_2H_5 group), 36.5 (C-6), 54.2 (C-3), 56.8 (C-2), 59.8 (C-7), 134.1 and 137.3 (ipso carbons attached to C-2 and C-6), 172.8 (carbonyl carbon); anti conformer 11.0 (CH_3), 26.1 (CH_2 of C_2H_5 group, 36.5 (C-6), 48.4 (C-7), 55.0 (C-3), 70.2 (C-2), 135.2 and 135.9 (ipso carbons attached to C-2 and C-6), 173.0 (carbonyl carbon), 126.0, 126.2, 127.0, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4 and 128.5 (aromatic carbon signals other than ipso carbons for both syn and anti conformers); MS *m/z* (relative intensity 323 (M^+), 305 (2.0), 295 (1.9), 294 (17.4), 293 (71.3), 132 (100). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.54; N, 12.99. Found: C, 70.63; H, 6.61; N, 12.92.

***t*-3-Isopropyl-1-nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (19).** The same procedure as that for **17** was followed using **14** (2.1 g, 6.82 mmol) which was converted to colorless needles of **19** (yield 75%): mp 215–218 °C; IR (KBr) 3220 (CO*NH*), 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ syn conformer 0.94 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.79 (d sep, *J* = 3.4 and 6.8 Hz, 1 H, C*H*Me_2), 3.23 (ddd, *J* = 1.5, 7.8, and 13.5 Hz, 1 H, H-6_{eq}), 3.75 (dd, *J* = 12.0 and 13.4 Hz, 1 H, H-6_{ax}), 4.17 (m, *J* = 3.4, 6.6 and 10.7 Hz, 1 H, H-3_{ax}), 5.72 (bs, NH), 6.42 (d, *J* = 10.7 Hz, 1 H, H-2_{ax}), 6.52 (dd, *J* = 7.8 and 11.8 Hz, 1 H, H-7_{ax}); anti conformer 1.06 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.08 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.96 (d sep, *J* = 3.7 and 6.9 Hz, 1 H, C*H*Me_2), 2.98 (ddd, *J* = 1.5, 6.7 and 13.2 Hz, 1 H, H-6_{eq}), 3.55 (dd, *J* = 12.9 and 12.7 Hz, 1 H, H-6_{ax}), 4.36 (m, *J* = 3.7, 5.9 and 10.0 Hz, 1 H, H-3_{ax}), 5.95 (bs, NH), 6.14 (d, *J* = 10.0 Hz, 1 H, H-2_{ax}), 6.69 (dd, *J* = 6.7 and 12.4 Hz, 1 H, H-7_{ax}), 6.8–7.4 (aromatic protons corresponding to both syn and anti conformers); ^{13}C NMR ($CDCl_3$) APT Spectrum δ syn conformer 15.9 and 20.6 (methyl groups), 29.0 ($CHMe_2$), 36.5 (C-6), 53.8 (C-2), 57.1 (C-3), 59.9 (C-7), 134.1 and 137.4 (ipso carbons at C-2 and C-7), 172.6 (carbonyl carbon); anti conformer 15.4 and 20.6 (methyl groups), 28.3 ($CHMe_2$), 36.4 (C-6), 48.6 (C-7), 57.7 (C-3), 67.7 (C-2), 135.3 and 136.0 (ipso carbons at C-2 and C-7), 172.6 (carbonyl carbon), 126.0, 126.1, 127.1, 127.7, 127.8, 127.9, 128.1, 128.5 and 128.6 (aromatic carbons other than ipso carbons corresponding to both syn and anti conformers); MS *m/z* (relative intensity) 337 (M^+), 307 (50.74), 293 (15.3), 250 (5.8), 132 (100). Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.93; H, 6.83; N, 12.37.

***t*-3,*t*-6-Dimethyl-1-nitroso-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepin-5-one (20).** The same procedure as for **16** was followed. Powdered crystals of **15** (2.0 g, 6.80 mmol) were converted to colorless needles of **20** (yield 85%): mp 217–218 °C; IR (KBr) 3200 (CO*NH*), 1675 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ syn conformer 1.23 (d, *J* = 6.4 Hz, 3 H, CH_3 at C-6), 1.42 (d, *J* = 6.4 Hz, 3 H, CH_3 at C-3), 3.98 (m, *J* = 6.4 and 10.6 Hz, 1 H, H-6_{ax}), 4.47 (m, *J* = 6.5, 10.9, and 4.5 Hz, 1 H, H-3_{ax}), 5.96 (d, *J* = 11.2 Hz, 1 H, H-2_{ax}), 6.02 (d, *J* = 10.4 Hz, 1 H, H-7_{ax}), 6.28 (NH); anti conformer 1.21 (d, *J* = 6.4 Hz, 3 H, CH_3 at C-6), 1.46 (d, *J* = 6.4 Hz, 3 H, CH_3 at C-3), 3.75 (m, *J* = 6.4 and 11.3 Hz, 1 H, H-6_{ax}), 4.72 (m, *J* = 6.4, 4.6 and 10.7 Hz, 1 H, H-3_{ax}), 5.77 (d, *J* = 10.6 Hz, 1 H, H-2_{ax}), 6.34 (d, *J* = 11.0 Hz, 1 H, H-7_{ax}), 6.22 (NH), 6.8–7.3 (aromatic protons corresponding to both syn and anti conformers); ^{13}C NMR ($CDCl_3$) δ syn conformer 14.8 (CH_3 at C-6), 18.4 (CH_3 at C-3), 37.5 (C-6), 46.5 (C-3), 58.6 (C-2), 67.0 (C-7), 134.2 and 135.4 (ipso carbons attached to C-2 and C-7), 173.9 (carbonyl carbon); anti conformer 14.2 (CH_3 at C-6), 18.9 (CH_3 at C-3), 37.4 (C-6), 46.9 (C-3), 53.6 (C-7), 70.5 (C-2), 134.7 and 134.9 (ipso carbons attached to C-2 and C-7), 174.1 (carbonyl carbon), 127.3, 127.5, 127.5, 127.6, 128.0, 128.1, 128.2, 128.3 and 128.5 (aromatic signals other than ipso carbons corresponding to both the syn and anti conformers); MS *m/z* (relative intensity) 323 (M^+), 293 (20.8), 279 (6.5), 264 (5), 250 (17.9), 132 (100), 127 (95). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.34; H, 6.82; N, 12.69.

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N-Substituted 2,2,2-Trifluoroethanimidic Acid 1-Methylethylidene Hydrazides as Synthetic Blocks for Trifluoromethylated Nitrogen Heterocycles: Syntheses and Oxidative Cyclizations

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N-Substituted 2,2,2-trifluoroethanimidic acid 1-methylethylidene hydrazides have been prepared and allowed to react wtih *tert*-butyl hypochlorite in CH_2Cl_2. N-Aryl-, N-alkyl-, and *N*-(methoxycarbonyl)amidrazones **2–4** undergo three types of cyclizations via the initially formed *N*-chloro intermediates leading to 3-(trifluoromethyl)-1,2,4-benzotriazines **5**, 3-(trifluoromethyl)-5-alkyltriazoles **8** and **9**, and 3-chloro-3-(trifluoromethyl)-4-*N*-(methoxycarbonyl)-5,5-dimethyltriazoline (**11**), respectively. Reaction mechanisms for the cyclizations are discussed.

Trifluoromethylated compounds have received an increasing amount of attention because of their unique nature for biological activities and high-performance material science.[1] Functionalized trifluoromethylated building blocks are subjects of active investigation.[2] Among them, trifluoromethylated C_2 blocks such as trifluoroacetonitrile,[3] 2,2,2-trifluoroethyl tosylate,[4] trifluoroacetaldehyde ethyl

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