Chemistry of *N*-Nitroso Compounds. 7.[1] Conformational Preferences of Hexahydro-N^1,N^4-dinitroso-*r*-2,*c*-7-diphenyl-*1H*-1,4-diazepines: Use of Modified 1D HOHAHA and NOE Techniques

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Modified HOHAHA and NOE experiments on three *N,N'*-dinitrosohexahydrodiazepines, at temperatures ranging from −50 °C to +120 °C, indicated that each of the title compounds exists as an equilibrium mixture of two families of conformations, the major family consisting of four rotamers and the minor consisting of, possibly, four rotamers resulting from two parallel dynamic processes viz., the restricted N−N rotation at two N−NO bonds and the pseudorotation of the seven-membered ring. The 3-isopropyl derivative **10**, at +50 °C, exhibited only four resonances for each kind of proton/carbon, indicating that the rate of pseudorotation is fast compared to the NMR time scale. The ^{1}H resonances, broad at room temperature, became decoalesced at −50 °C as a result of the slow pseudorotation process. In all the three dinitroso compounds, of the two sets of twist-chair conformers, the major rotamers (~95%) have the alkyl group (at C3) axially disposed while the minor rotamers have quasiequatorial alkyl groups. On the other hand, the alkyl group at C6 of the 3,6-dimethyl derivative **11** adopts equatorial orientation in all its conformers.

Introduction

As a part of a program on the determination of dynamic equilibria in cyclic *N*-nitrosamines,[2a-g] the ^{1}H and ^{13}C NMR spectral investigations on *N*-nitrosopiperidines (**1a–j**),[2a] *N*-nitrosoazabicyclo[3.3.1]nonanes (**2a–c, 3a,b**),[2b,d,e,h] *N*-nitrosohexahydro-1,4-diazepines (**4–8**),[2c,f,g] etc., were undertaken. The aryl substituents are *cis* to each other in both the parent amines[3] as well as the *N*-nitrosamines **1–8**.[2] While the parent piperidines prefer chair conformations[3] with equatorial phenyl groups the *N*-nitrosopiperidines **1a–j** preferentially adopt unsymmetrically twisted chair conformations[2a] with one of the α phenyl groups in pseudoaxial orientation and the other in pseudoequatorial position (Figure 1). Several crystal structure determinations[2b,d,f-h] have been performed revealing the wide variation in the conformational preferences as well as, in a few cases, the dual positions of the nitroso oxygen.[2h] For instance, 3-isopropyl-*N*-nitroso-2,6-diphenylpiperidin-4-one (**1b**) was shown to adopt a chair conformation in which all the substituents occupy axial orientations.[2h]

Due to the restricted rotation around N−N bond, an equilibrium between rotational isomers has been encountered in several nitrosamines.[4-7] In the case of cyclic nitrosamines the nitroso group is found to be coplanar

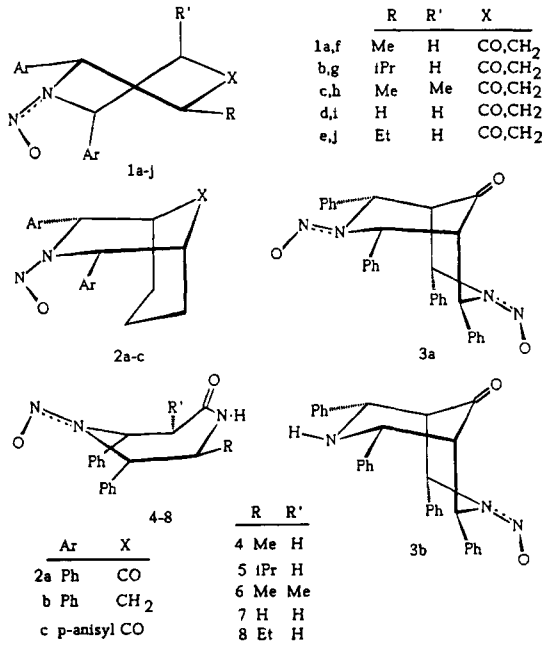

Figure 1. Conformational preferences of α,α'-diaryl cyclic nitrosamines.

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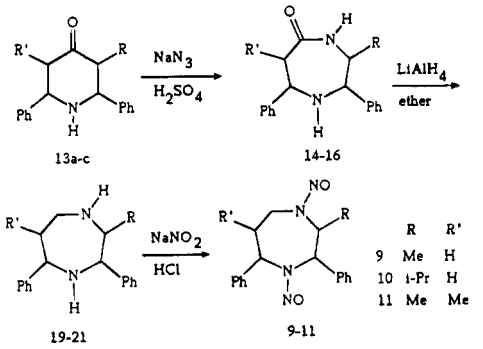
Scheme 1



to the dynamically averaged plane of the ring system so as to facilitate delocalization of the lone-pair of electrons on nitrogen over N—N=O linkage. The delocalization brings about considerable stability to the molecule (60–95 kJ/mol) while the allylic strain ($A^{1,3}$-strain)[8,9] between the *coplanar* nitroso group and the *equatorial* substituents at α-carbons tends to destabilize the conformation. In such cases the molecule flips to alternate chair or twist-chair conformations where the allylic strain can be relieved. The seven-membered rings, *N*-nitrosohexahydro-1,4-diazepines **4–8**, were found to prefer flattened boat conformations with the phenyl groups at pseudoaxial orientations (Figure 1).[2c] X-ray crystallographic analysis revealed the flattened boat conformation of the nitrosohexahydrodiazepinones **4–8** in solid state also.[2f,g]

While the conformations of mononitrosamines containing alkyl substituents have been studied extensively in a number of cases,[4–6] to our knowledge, no work has been done on the conformational aspects of dinitrosohexahydrodiazepines, probably due to the complexity of the NMR spectrum caused by the different relative orientations of all the nitroso groups. In this paper, we report the synthesis of *N,N'*-dinitrosohexahydrodiazepines **9–11** and discuss the stereochemistry of these dinitroso compounds in solutions.

Results and Discussion

The title compounds were synthesized from *r*-2,*c*-6-diphenylpiperidin-4-ones **13a–c** as shown in Scheme 1. The coupling constants J_{2H-3H} (~10 Hz) and $J_{H7-H6ax}$ (~10 Hz) and the calculation of the dihedral angles employing energy minimization methods and DAERM method (dihedral angle estimation by ratio method),[10] led to the conclusion that the hexahydrodiazepinones **14–16** prefer chair conformation with equatorial substituents as in the piperidones **13a–c**. In addition, the proposed conformation of **15** was confirmed by X-ray crystal structure study which indicated the *cis* and *trans* torsional angles H7–C7–C6–H6eq and H7–C7–C6–H6ax to be 79° and 159°, respectively.[11] In each of the mononitrosohexahydrodiazepinones **4–6**, where the amide group in the ring enforces conformational rigidity, the ring was found to adopt a flattened boat conformation with pseudoaxially oriented phenyl groups.[2c]

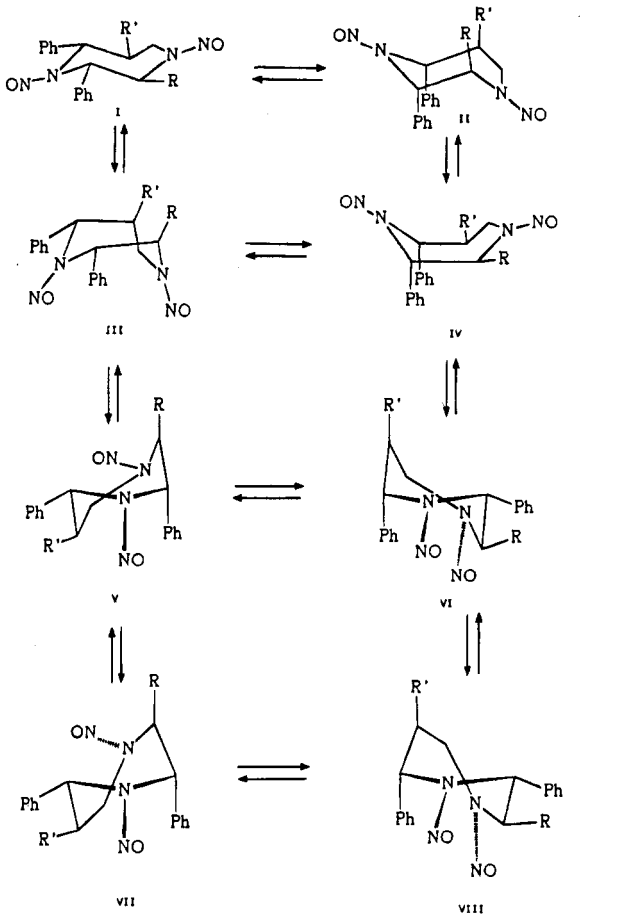


Figure 2. Chair, twist-chair, boat, and twist-boat forms of the dinitrosohexahydro-1,4-diazepines **9–11**.

Conformational Analysis of the Dinitrosohexahydrodiazepines 9–11. In the IR spectra of the dinitroso compounds **9–11** Bohlmann bands[12] in the region 2700–2850 cm^{-1} were found to be absent. This implies that the lone-pairs of electrons on both *N1* and *N4* were involved in resonance and not available for enrichment of the electron density of the antiperiplanar C–H bonds suggesting coplanar conformation for the nitroso group (Bohlmann bands arise due to the interaction of the lone pair of electrons with the α hydrogens which are in antiperiplanar arrangement[12]).

In contrast to the hexahydrodiazepin-5-ones **14–16**[2c,11] and their mononitroso derivatives **4–6**,[2c] which have *restricted torsional freedom* due to the presence of the amide linkage in the ring, the dinitrosohexahydrodiazepines **9–11** have *torsional freedom* allowing the molecule to possess flexible conformations; however, the presence of *cis*-2,7-diphenyl groups minimizes the flexibility of the ring system.

The dinitrosohexahydrodiazepines **9–11** may prefer one or more of the molecular conformations such as chair, twist-chair, boat and twist-boat forms as shown in Figure 2. The chair form **I** has severe allylic strain as a result of equatorial orientation of all the α-substituents (adjacent to planar N–NO group) while the other chair form **II** has 1,3-diaxial Ph/Ph and 1,4-diaxial R/R' interactions.

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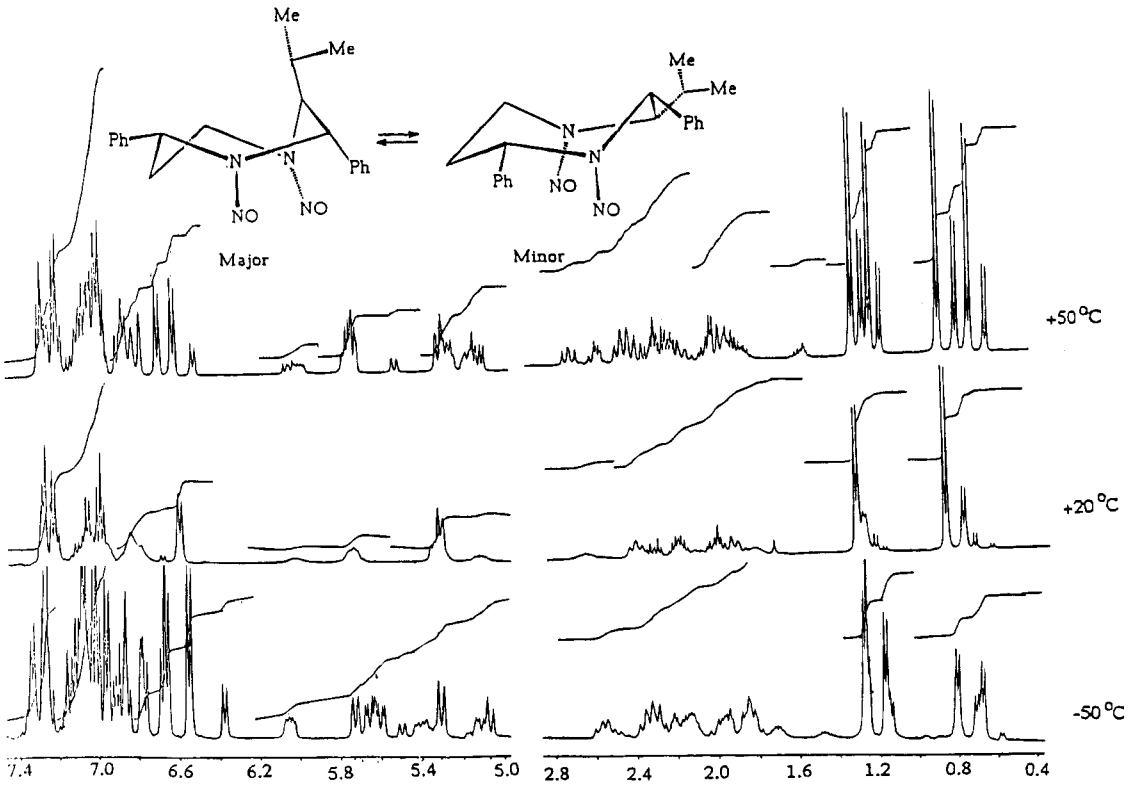

Figure 3. ^{1}H NMR spectra of the dinitrosamine **10** at −50, +20, and +50 °C.

In the case of the two boat forms **III** and **IV**, the alkyl group at C3 of **III** is axial while the phenyl groups at C2 and C7 of IV are axial.

In the chair (**I** and **II**) and boat forms (**III** and **IV**) one of the torsional angles is nearly 0[13a] leading to the destabilization of these conformers, as observed in the case of cycloheptane and azacycloheptane derivatives.[13] On the other hand, introduction of a double bond in the ring, as in the case of cycloheptene,[14] benzocycloheptene,[14] tetrahydrobenzodiazepines,[15] or a partial double bond, as in ϵ-caprolactam,[16] demands one of the torsional angles to be 0 permitting the ring to adopt chair conformations.[13] In the case of dinitrosohexahydrodiazepines **9**−**11** which do not have either a double bond or an amide group, the chair and boat forms (**I**−**IV**) are not preferred, unless they serve to alleviate the allylic strains imposed by the two nitroso groups.

In the twist-boat forms **VII** and **VIII**, the torsional strain is relieved partially. In the flexible twist-chair forms **V** and **VI**, the molecule can avoid the allylic strain at one of the nitrogen sites through pseudorotation. The molecule may prefer one of the several intermediate twist-chair forms. The preferred conformation of the molecule is expected to have the lowest possible allylic and torsional strains while retaining the resonance at the N−NO groups.

^{1}H NMR Spectral Analysis of the Isopropyldinitrosohexahydrodiazepine 10. The ^{1}H NMR spectra of the dinitrosoisopropylhexahydrodiazepine **10** at +20 °C and +50 °C contained eight methyl doublets for the isopropyl group (Figure 3). The two diastereotopic methyl groups of the isopropyl moiety generally exhibit separate signals. The isopropylhexahydrodiazepinone **15** and the isopropylpiperidone **13b**[3] exhibit two methyl signals, and the corresponding mononitroso hexahydrodiazepinone **5** exhibits four methyl signals owing to an equilibrium between two rotamers.[2c]

The signals for all the other protons of the dinitroso compound **10** appear as sets of multiplets each set containing four clusters, indistinguishable in the 1D NMR spectrum, which however, could be edited into subspectra using the modified 1D HOHAHA experiment[17] and classified into individual groups of peaks by a combination of 1D and 2D NMR techniques (Table 1). A typical subspectrum is shown in Figure 4. The observation of four major sets for the dinitroso derivative **10** suggests the presence of restricted rotation around N−N bonds of both the nitroso groups yielding *four* atropisomers with *syn-syn*, *syn-anti*, *anti-syn*, and *anti-anti* nitroso groups (the designations *syn* and *anti* represent the orientations of the nitroso group with respect to C2; Figure 5).

The reasonably well-resolved signals observed at +50 °C gradually became broad on increasing the temperature to +120 °C indicating the existence of an *equilibrium* between these conformers through N−N rotation. The actual coalescence temperature should be above +120 °C which, however, could not be determined due to certain complications in the measurement at high temperatures for this particular case. Interestingly, on decreasing the temperature to +20 °C the signals became broad again

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Table 1. Selected ^{1}H NMR Data (δ) of the Dinitroso Compounds 9–11[a]

	chemical shifts in the											
	conformer **A**			conformer **B**			conformer **C**			conformer **D**		
protons	**9**	**10**	**11**	**9**	**10**	**11**	**9**	**10**	**11**	**9**	**10**	**11**
H2	6.32	6.85	6.35	6.41	6.80	6.31	6.47	–	6.33	6.84	7.12	6.52
H3	5.85	5.35	5.92	6.23	5.77	6.16	5.65	5.20	5.73	6.00	5.56	5.92
H5a	4.80	5.33	4.74	5.12	5.15	4.87	4.94	5.31	4.73	5.17	5.25	4.91
H5b	3.00	2.46	2.63	3.80	3.73	3.65	3.15	2.71	2.76	3.98	3.90	3.90
H6a	2.45		2.31	2.40		2.69	2.30		2.58	2.60		2.93
H6b	2.15			2.30			2.15			2.15		
H7	5.72	5.79	5.67	5.82	5.78	5.63	6.02	6.03	5.60	6.08	6.09	5.92
CH<		2.22			1.91			1.85			1.55	
Me′	1.64	1.33	1.65	1.23	1.23	1.23	1.44	1.28	1.43	1.01	1.18	1.15
Me″		0.90	0.86		0.74	0.90		0.81	1.08		0.65	0.99

[a] For **11**, Me″ is Me6; for **9** and **11**, Me′ is Me3.

indicating a different dynamic process that might involve the interconversion between ring-backbone conformations, possibly through pseudorotation. Further lowering of the temperature to −50 °C resulted in the sharpening of ^{1}H resonances as well as the appearance of new small methyl doublets suggesting that the dynamic behavior at room temperature could be due to the interconversion between the *ring* conformations. Possibly each of the four major conformers observed at −50 °C is in dynamic equilibrium with a single or eventually more minor conformers, which have the same orientation of the nitroso group but different backbone conformations. The population of the four conformers which form the major set was found to be ~95% while that of the minor set was ~5%.

NOE experiments were carried out at +50 °C using methyl and other selected proton signals as targets and the results of the analysis are collected in the Table 2. Modified 1D NOE measurements,[18] and modified 1D HOHAHA[17,19] using multiselective excitation and simultaneous acquisition were employed. Since the set of minor isomers is populated feebly, detailed analysis regarding their conformational nature was not carried out but significant results on their conformations were derived. Assignment of the NMR resonances (Table 1) and calculation of coupling constants (Table 3) were made with the help of COSY, HETCOR, and 1D HOHAHA data.

The large *vicinal* coupling constants of about 10–11 Hz observed between H3 and CH< of the isopropyl group (Table 3) in all the four conformers of the dinitrosohexahydrodiazepine **10** indicate (i) an antiperiplanar arrangement between the two and (ii) the isopropyl group has *static* orientation (does not rotate freely). Examination of models for the chair form **I** did not favor such an arrangement since it would bring an intolerable steric compression between the isopropyl and the phenyl groups. The high value of the coupling constant (10–11 Hz) is rather unusual since the corresponding coupling constant was found to be around 3–5 Hz in both the hexahydrodiazepinone **15** and the mononitroso derivative **5**, which exist, respectively, as chair and flattened boat forms, the H3 and CH< being in *gauche* arrangement with the *equatorial* isopropyl group.[2a,c,3] Though this antiperiplanar arrangement is admitted in the chair form **II** (Figure 2) which has all substituents in axial orientations the appearance of H2 signals of all the four conformers as singlets excluded the possibility of the chair conformer **II**. The boat conformers **III** and **IV** (Figure 2) were excluded on the ground that the J_{H2-H3} is 0. The coupling constants of 0 Hz were also observed between (i) H5a and H6b, and (ii) H5b and H6a. The torsional angles between the hydrogens at C5, C6, and C7 were estimated using DAERM[10] and the results are listed in Table 4.

One of the methyl groups of the isopropyl group in the dinitrosohexahydrodiazepine **10** (Me″ in Table 2) exhibited NOE with one of the hydrogens at C5 (H5b in Table 2) while the other methyl group (Me′) did not. This observation confirmed that the isopropyl group *does not* rotate freely in all the four conformers. Further it was inferred that the equilibrium does not involve the flipping or pseudorotation of the ring. It was therefore concluded that all the four conformers have the same backbone conformations except for differences in the orientation of the two nitroso groups, and the question that remained to be answered was which of the backbone conformations the molecule was preferred.

Observation of NOE between H7 and H5b as well as between H7 and Me″ suggested that H7, H5b, and the isopropyl group are axial in all the four conformers. If the molecule were in a twist-boat conformation **VII** or **VIII**, NOE would not have been observed between the isopropyl group and H5b since the distance between them would be too large to produce any detectable NOE. The summarized results of NOE studies indicated that the molecule exists in an equilibrium containing four twist-chair forms **17a–d** which have an axial isopropyl group; the phenyl group at C7 adopts an equatorial orientation while that at C2 orients pseudoequatorially in all the four conformers (Figure 6).

***Syn* and *Anti* Protons α to the Nitroso Group.** The determination of spacial orientation of α protons involves a comparison of the chemical shifts of a proton in a pair of conformers which *differ* only in the orientation of the adjacent nitroso group. Thus the four signals of each proton need to be differentiated with respect to the orientation of both the nitroso groups. Though the HOHAHA spectra allow the identification of a set of four signals corresponding to each proton, information regarding which ^{1}H signal correspond to which *conformer* could not be derived using the ASIS (aromatic solvent-induced shift study)[7] as it resulted in (i) merging of α-proton signals with the signals due to aromatic as well as other protons, and (ii) unusual "downfield" ASIS shifts of protons in certain cases raising questions about the applicability of ASIS technique which predicts only "upfield" shifts. Therefore, the chemical shifts of *syn* and *anti* protons were deduced using a new method which

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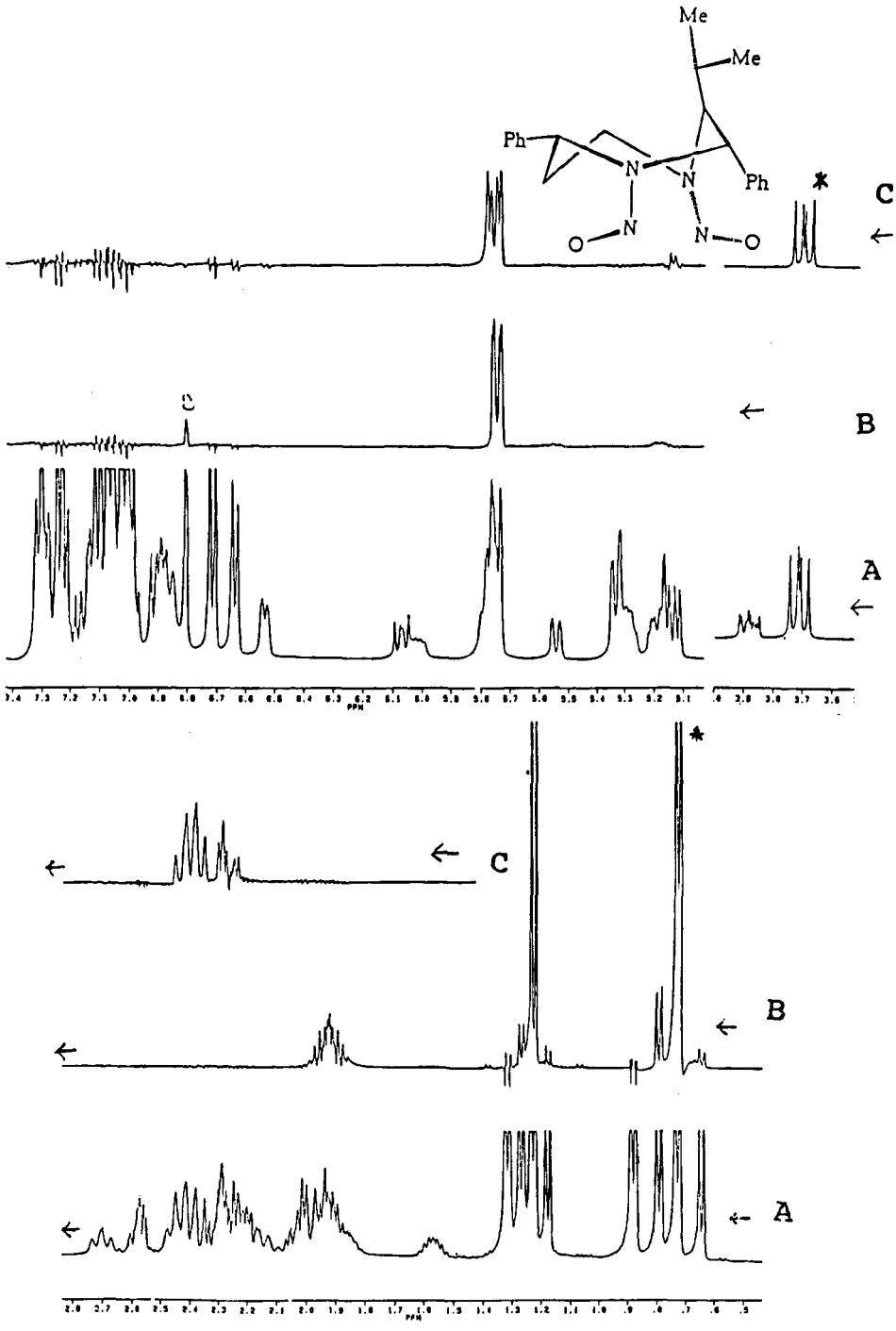

Figure 4. Trace A: Normal spectrum of **10**. Traces B and C: HOHAHA subspectra for one conformer of **10**. * Targets for HOHAHA.

uses HETCOR spectra and certain generalizations discussed in the next section.

$^{1}H-^{13}C$ HETCOR Spectral Analysis of the Isopropyldinitrosohexahydrodiazepine 10. The assignments of ^{13}C resonances of **10** were made with the help of $^{13}C-^{1}H$ HETCOR spectrum as well as by comparing the chemical shifts with those of the hexahydrodiazepinones **14–16** (Table 5). We make use of the generalizations that (i) the α-carbons in nitrosamines appear, in general,[20] upfield (up to a maximum of 17 ppm) if the nitroso group is *syn* to them than when it is *anti* and (ii) the nitroso group does not exhibit anisotropic shift on the β-carbons leading to almost identical chemical shifts for both the *syn* and *anti* β-carbons.

The orientation of the nitroso group in each conformer was determined by making use of the anisotropic effect of the nitroso group over the ring carbons. In the ^{13}C NMR spectra, C7 gives four signals which can be grouped into two pairs on the basis of their proximity to each other. The C7 signals of the conformers **A** and **B** (δ 59.77

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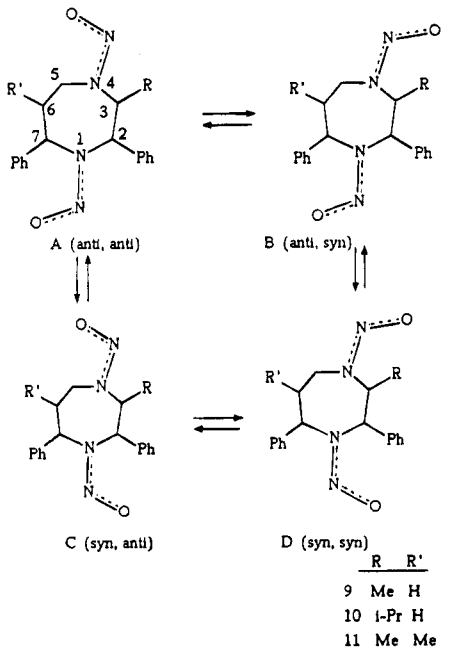

Figure 5. N–N Restricted rotation and the relative orientations of the two nitroso groups.

Table 2. Selected NOE Data of the *N,N'*-Dinitrosohexahydrodiazepines 9–11[a]

compd	proton	H2	H5b	H7	CH<	Me″	Me3	H5a
9	H5b		0	ABCD			ABCD	
	H7		ABD	0			A	
	Me3	ABC	ABCD	ABD			0	
	H2	0					AB	
10	H5b		0	BD	ABCD	ABCD		
	H7		ABCD	0	B			
	CH<	ABD	ABCD	ABD	0			
	Me′	ABD						
	Me″		ABCD	ABCD		0		
11	H2	0					A	
	H5b		0	ABCD			ACD	
	Me3	ABC	ABCD				0	
	Me6			ABCD				ABCD

[a] NOEs detected are indicated by the entries A, B, C, D which correspond to the four conformers in Figure 5.

Table 3. Vicinal and geminal H–H Coupling Constants (Hz) in the Isopropyldinitrosohexahydrodiazepine 10[a]

H–H	A	B	C	D
Me′–CH<	6.3	6.4	6.3	6.3
H3–CH<	10.4	11.1	10.5	10.6
CH<–Me″	–	6.5	–	6.7
H7–H6a	4.8	5.2	5.9	7.2
H7–H6b	12.5	13.0	12.6	11.7
H5b–H5a	14.3	14.7	14.3	–
H5b–H6b	11.6	10.7	10.9	–
H6b–H5a	–	0.0	0.0	–
H6b–H6a	–	16.9	15.5	–
H5b–H6a	–	0.0	–	–
H5a–H6a	–	–	6.4	–

[a] *J* values were calculated wherever possible from the expansions of 1D HOHAHA subspectra.

and 60.56) are close to each other and those of **C** and **D** (δ 66.85 and 66.85) are identical (Table 5). Since the chemical shift difference of C7 signals within each pair is very small or 0, the orientation of the N^1-nitroso group that is α to C7 might be the same (Figure 5). The difference in the chemical shifts, though small, arises from the two orientations of the N^4-nitroso group that is at a γ-position from C7.

Table 4. Dihedral Angles Estimated for the Dinitroso Compound 10 Using the DAERM Method

conformer	vicinal protons[a]	vicinal *J* (Hz) *cis*	vicinal *J* (Hz) *trans*	*cis* (deg)	*trans* (deg)
A	H7 and H6a,b[b]	4.8	12.5	49	169
B	H7 and H6a,b	5.2	13.0	48	168
C	H7 and H6a,b	5.9	12.6	45	165
D	H7 and H6a,b	7.2	11.7	39	159
B	H5a and H6a,b	0.0	6.4	80	40
D	H5a and H6a,b	0.0	6.4	80	40
B	H5b and H6a,b	0.0	10.7	81	201
D	H5b and H6a,b	0.0	10.9	81	201

[a] H6a,b refers to the two protons at C6 (H6a and H6b). [b] *cis* and *trans* angles are H7–C7–C6–H6a and H7–C7–C6–H6b, respectively.

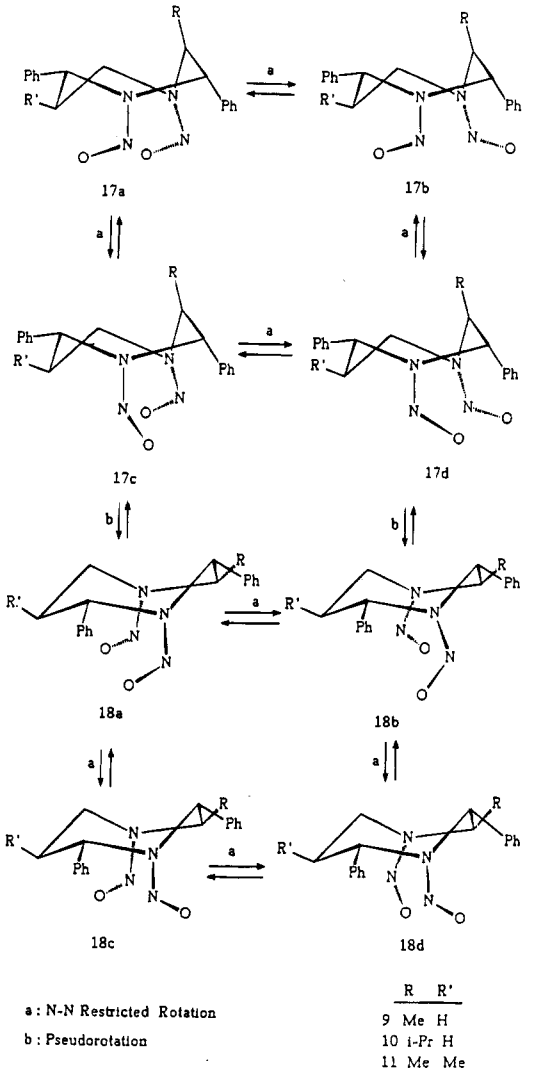

Figure 6. Equilibrium of the eight conformers of dinitrosohexahydrodiazepines **9–11**.

Further, the *downfield* appearance of the C7 signals of **C–D** pair with respect to those of the **A–B** pair indicated that in the former set of rotamers the N^1-nitroso group is *anti* to C7 while in the latter it is *syn* to C7 (Table 6).

Among the four ^{13}C chemical shifts of the C3 carbon, the resonances due to the conformers **A** and **C** form a proximal pair (δ 69.24 and 68.63, respectively) while those of **B** and **D** form another pair (δ 56.17 and 56.17, respectively). Since the chemical shift difference of C3 signals within each pair of conformers is negligible (<1

Table 5. ^{13}C Chemical Shift (δ; +50 °C) Assignments for the Dinitrosohexahydrodiazepine 10[a]

carbons	A	B	C	D
C2	64.59	64.95	*b*	51.66
C3	69.24	56.17	68.63	56.17
C5	36.31	49.18	36.45	48.73
C6	28.77	31.63	28.04	30.50
C7	59.77	60.56	66.85	66.85
CH<	27.80	27.40	28.50	28.04
Me′	20.20	19.85	20.88	20.70
Me″	19.48	18.55	19.37	18.44

[a] **A**, **B**, **C**, and **D** are the four conformers of **10**. [b] C2 signal is not observable.

Table 6. Orientation of the α Nitroso Groups in the Four Conformers of the Isopropyldinitrosohexahydrodiazepine 10

conformer	C7	C2	C3	C5
A	*syn*	*anti*	*anti*	*syn*
B	*syn*	*anti*	*syn*	*anti*
C	*anti*	*a*	*anti*	*syn*
D	*anti*	*syn*	*syn*	*anti*

[a] Though the C2 signal is not observable, the orientation may be derived as *syn* to C2 as it is *anti* to C7 in conformer **C**.

ppm), the conformers in each pair are suggested to have the same orientation of the N^4-nitroso group.

The ^{13}C signals of C3 in the **A**–**C** pair appear considerably downfield compared to those of **B**–**D** pair, indicating that the N^4-nitroso group is *syn* to C3 in the latter set of conformers while it is *anti* in the former set (Table 6). Similar anlaysis using ^{13}C spectral data of C2 and C5 signals afforded the results shown in the Table 6.

The assignment of *syn* and *anti* ^{13}C signals made were used for the determination of *syn* and *anti* proton signals employing the HETCOR spectrum.

Orientations of α Protons in the Isopropyldinitrosohexahydrodiazepine 10. The orientations of the α-protons were deduced by comparing the chemical shifts of α-protons within a pair of rotamers which differ *only in the orientation of the adjacent nitroso group* (the second farther nitroso group being in the same orientation in both the rotamers). For example, the chemical shift of H7 proton in the conformer **A** was compared with that in the conformer **C** since (i) the orientation of the N^1-nitroso group is *syn* to H7 in the former while in the latter it is *anti*, and (ii) the N^4-nitroso group has the same orientation in both the conformers. The resonance of H7 in the conformer **A** (δ 5.79) appears *upfield* compared to that in the conformer **C** (δ 6.03) indicating that, in both the cases, the H7 is away from the deshielding cone of the nitroso group. In other words, the H7 is axial and not equatorial (Table 7). Comparison of the chemical shift of H7 proton in the conformer **B** with that in the conformer **D** showed that H7 is axial in these conformers also. Similar comparison of the chemical shifts of H2 proton showed that, in contrast to the axially oriented H7, the H2 prefers in-plane geometry having the pseudoequatorial orientation. By employing similar comparative analysis of the conformers A and B (as well as **C** and **D**) which differ only in the orientation of the N^4-nitroso group, the CH< and Me were found to prefer the out-of-plane geometry while H3 was found to prefer in-plane geometry. Comparison of the 1D NMR resonances of the protons H7 and H5b, which prefer out-of-plane geometry, showed that the anisotropic shift (Table 7) for the former is very low (~−0.24, −0.31 vs ~−1.27, −1.19). This suggests that the H7 is tilted slightly from the perfect axial orientation while H5b is not. All the results (Table 7) are in line with the twist-chair conformations **17a**–**d** (Figure 6).

Table 7. Comparison of the Chemical Shifts of Protons Which Differ only in the Orientation of the α Nitroso Group in 10[a]

protons	conformers compared	δ (*syn*)[b]	δ (*anti*)	$\Delta\delta$ (*syn* − *anti*)	orientation[c] of the proton
H7	**A** and **C**	5.79 (**A**)	6.03 (**C**)	−0.24	out-of-plane
H7	**B** and **D**	5.78 (**B**)	6.09 (**D**)	−0.31	out-of-plane
H2	**D** and **B**	7.12 (**D**)	6.80 (**B**)	+0.32	in-plane
H2	**C** and **A**	− (**C**)	6.85 (**A**)	−	H2 of **C** not known
H3	**B** and **A**	5.77 (**B**)	5.35 (**A**)	+0.42	in-plane
H3	**D** and **C**	5.56 (**D**)	5.20 (**C**)	+0.36	in-plane
H5b	**A** and **B**	2.46 (**A**)	3.73 (**B**)	−1.27	out-of-plane
H5b	**C** and **D**	2.71 (**C**)	3.90 (**D**)	−1.19	out-of-plane
H5a	**A** and **B**	5.33 (**A**)	5.15 (**B**)	+0.18	in-plane
H5a	**C** and **D**	5.31 (**C**)	5.25 (**D**)	+0.06	in-plane
CH<	**B** and **A**	1.91 (**B**)	2.22 (**A**)	−0.31	out-of-plane
CH<	**D** and **C**	1.55 (**D**)	1.85 (**C**)	−0.30	out-of-plane

[a] **A**, **B**, **C**, and **D** indicate the conformers depicted in Figure 5. [b] The α nitroso group is *syn* to the proton under consideration. [c] Orientation of the proton with respect to the plane of N–N–O group.

Table 8. Anisotropic Influence of the Nitroso Groups over Carbon Resonances of the Isopropyldinitrosohexahydrodiazepine 10[a,c]

carbon	$\Delta\delta$ (α-shift)	$\Delta\delta$ (β-shift)	$\Delta\delta$ (γ-shift)
C2	*−13.29* (**D**–**B**)	+0.36 (**B**–**A**)	–
C2[b]	–	–	–
C3	−13.07 (**B**–**A**)	*−0.61* (**C**–**A**)	–
C3	−12.46 (**D**–**C**)	*0.00* (**D**–**B**)	–
C5	−12.87 (**A**–**B**)	–	*−0.14* (**A**–**C**)
C5	−12.28 (**C**–**D**)	–	*+0.45* (**B**–**D**)
C7	*−7.08* (**A**–**C**)	–	−0.79 (**A**–**B**)
C7	*−6.29* (**B**–**D**)	–	0.00 (**C**–**D**)
C6	–	*+0.73* (**A**–**C**)	–
C6	–	*+1.13* (**B**–**D**)	–
C6	–	−2.86 (**A**–**B**)	–
C6	–	−2.46 (**C**–**D**)	–
C<	–	−0.40 (**B**–**A**)	*+0.70* (**C**–**A**)
C<	–	−0.46 (**D**–**C**)	*+0.64* (**D**–**B**)
Me′	–	–	−0.35 (**B**–**A**)
Me′	–	–	−0.18 (**D**–**C**)
Me″	–	–	−0.93 (**B**–**A**)
Me″	–	–	−0.93 (**D**–**C**)

[a] The anisotropic shift differences were calculated by subtracting the *anti* carbon signal from the *syn* carbon signal ($\Delta\delta = \delta(syn) - \delta(anti)$). [b] C2 signal of the conformer **C** is not visible. [c] The anisotropic shifts due to the N^1-nitroso group are italicized to differentiate from those due to the N^4-nitroso group.

Rotamer Populations. The rotamer populations were found to have a direct correlation with the magnitude of anisotropic shifts of the carbon resonances in the ^{13}C NMR spectrum. The magnitudes of the anisotropic shifts of carbon signals which are α-, β-, and γ- to each nitroso group are listed in Table 8. In the case of α-carbons the upfield shifts were found to be in the order C2 > C3 > C5 > C7, indicating a decreasing order of steric compression by the *syn* oriented nitroso group. This observation suggested that the conformer **D** in which the both the nitroso groups are *syn* to C2 and C3 has the maximum strain while the conformer **A** in which the nitroso groups are *syn* to C5 and C7 has the minimum strain; the conformers **C** and **B** with intermediate nitroso orientations (*syn* to C2 and C5; *syn* to C3 and C7, respectively) can have an intermediate energy. Thus the relative strain energies of the conformers decrease in the order **D** > **C** > **B** > **A** which may be expected to be the reverse when the population of the conformers is con-

sidered. In agreement with these predictions, the order of relative populations of the conformers was found to be **A** > **B** > **C** > **D**. The populations were calculated to be within ±5% from the integrations of methyl resonances in the ^{1}H NMR spectrum recorded in $CDCl_3$ at +50 °C.

The relative populations of the rotamers **A**, **B**, **C**, and **D** at +50 °C were estimated as 35, 31, 21, and 13%, respectively. The rotamer populations were found to be sensitive to the temperature. At lower temperature the equilibrium was shifted toward more stable conformers. Thus, on decreasing the temperature the population of the conformer **A** was increased at the expense of **C** and **D** while the population of **B** remained the same. The relative populations at +20 °C (in $CDCl_3$) were estimated as 61% (**A**), 31% (**B**), 6% (**C**), and 2% (**D**).

By applying a similar strategy, the relative populations of the conformers **A**, **B**, **C**, and **D** of the 3-methyl (**9**) and 3,6-dimethyl compounds (**11**) were estimated to be 34, 30, 22, and 14% and 31, 27, 26, and 16%, respectively, being in the same order as that of the 3-isopropyl analog **10** at 50 °C. The rotamer ratio for **9** and **11**, unlike the isopropyl derivative **10**, was found not to vary much while lowering the temperature to 20 °C.

β-Shifts of Ring Carbons. While all the carbons in the ring experience very small β-shifts, the C6 has been found to be shifted by 2.46 and 2.86 ppm due to the N^4-nitroso group (Table 8). These large β-shifts are rather unusual in the sense that, in the case of several nitrosamines, the β-carbons were found to have almost the same chemical shifts whether the nitroso group is oriented *syn* or *anti*.[2a,c,20] This observation suggested a spatial proximity of the N^4-nitroso group to C6 when it is oriented *syn* to C5 side. The possibility of a change in ring backbone conformation, specifically with changes at the C5–C6 region (leading to a decrease in torsional angle C6–C5–N4–N), when the N^4-nitroso group reverts to the side of C5 was ruled out since such a change would be reflected in the β-shifts of C2 and CH< as well as in H–H coupling patterns.

3-Methyl and 3,6-dimethyl-1,4-dinitrosohexahydrodiazepines (9 and 11). In the ^{1}H NMR spectrum of the dinitrosamine **9**, four doublets for the 3-methyl group were observed owing to the presence of four rotamers in equilibrium. The assignment of the ^{1}H resonances for the 3-methyl compound **9** (Table 1) using the COSY spectrum indicated that the peak positions and coupling patterns of hydrogens at C5, C6, and C7 are similar to those of the 3-isopropyldinitrosohexahydrodiazepine **10**.

In the ^{1}H NMR spectrum of 3,6-dimethyl-1,4-dinitrosohexahydrodiazepine **11**, eight methyl doublets were observed corresponding to four rotamers. The methyl resonances were classified first by making use of the large shift difference between the protons H3 and H6. The signals of the H6 proton appear at an upfield region (δ 2–3) while those of H3 appear at a downfield region (δ 5–6) since the latter is α to nitrogen. The four methyl doublets which have cross peaks with the *downfield* resonances (corresponding to H3) in the region δ 5–6 were assigned to the methyl group at C3 while the other four which have cross peaks with the *upfield* signals in the region δ 2–3 were assigned to the methyl group at C6.

Among the four signals of the methyl group in **9** and **11**, one of the doublets was slightly broad as observed in the case of the isopropyl analog **10**. In addition, the signals of H2 protons of the four conformers of **9** and **11** appear as singlets as in the isopropyl analog **10**, indicating a similar conformational nature in all the cases.

Table 9. Δδ (*syn* − *anti*) of α Protons in 3-Me, 3-iPr, and 3,6-Dimethyl Derivatives 9–11

protons	conformers compared	Δδ (*syn* − *anti*) in 9	10	11	Orientation of α-protons[a]
H7	**A** and **C**	−0.30	−0.24	−0.07	out-of-plane
H7	**B** and **D**	−0.26	−0.31	−0.29	out-of-plane
H2	**D** and **B**	+0.43	+0.32	+0.31	in-plane
H2	**C** and **A**	+0.15	–	−0.02	–
H3	**B** and **A**	+0.38	+0.42	+0.24	in-plane
H3	**D** and **C**	+0.35	+0.36	+0.19	in-plane
H5b	**A** and **B**	−0.80	−1.27	−1.02	out-of-plane
H5b	**C** and **D**	−0.83	−1.19	−1.14	out-of-plane
H5a	**A** and **B**	−0.32	+0.18	−0.13	out-of-plane[b]
H5a	**C** and **D**	−0.23	+0.06	−0.18	out-of-plane[b]
Me3	**B** and **A**	−0.41	−0.31	−0.42	out-of-plane
Me3	**D** and **C**	−0.43	−0.30	−0.28	out-of-plane

[a] Orientation with respect to the plane of the nitroso group. [b] H5a prefers in-plane orientation in **10**.

The relative conformational dispositions of the methyl groups and various protons in **9** and **11** were determined by recording the NOE (Table 2) and comparing the NOEs with those of the isopropyl analog **10**. The C3-Me group of **9** and **11** exhibit NOE with the H5b as in the case of **10**. The similar NOEs among the dinitrosamines **9**–**11** suggested that these compounds have almost the same conformational preferences.

It is of interest to note that the signals for H5b proton in two of the major rotamers appeared as doublet of doublets in **9**–**11** irrespective of the presence or absence of the methyl group at C6. In both the compounds, H5b appeared as doublet of doublets (around δ 3.8 and 3.9) as a result of the *geminal* coupling with H5a and the *vicinal* coupling with the axial proton at C6. The coupling constant of H5b with the second hydrogen attached to C6 in the case of **9** and **10** was found to be nearly 0. These observations indicated that (i) H5b couples with an axial-like hydrogen at C6, (ii) the presence of the methyl group at C6 does not alter the conformation of the hexahydrodiazepine, and (iii) the C6-Me group, of the dimethyl compound **11**, is therefore in equatorial orientation. This view was also supported by NOE experiments which showed only a weak NOE with H5b, but medium effects with H5a, H6, and H7, as expected for this orientation. Further it appears that the C6-Me group is nearly orthogonal to H5b since the replacement of methyl group by a hydrogen has no effect on the coupling pattern of H5b. In contrast to the 3-alkyl derivatives **9** and **10**, no NOE was observed between the alkyl substituent at C3 (i.e., Me) and H7 in the dimethyl derivative **11**. Therefore the alkyl group at C3 was considered to be slightly twisted out of the axial orientation.

The orientations of the α-protons were determined by comparing their chemical shifts in a pair of conformers which *differ* in the orientation of the α-nitroso groups (Table 9). The results indicated that H2 and H3 lie in the plane of the nitroso groups while H7, H5b, and Me3 lie out of the plane, being in line with the observations made for the 3-isopropyl compound **10**. All the foregoing results indicated that the mono- and dimethyl derivatives **9** and **11** also adopt twist-chair conformation.

While the signs of shifting of the resonances for each kind of proton are almost the same for all the dinitrosamines **9**–**11** (Table 9), the sign of shifting experienced

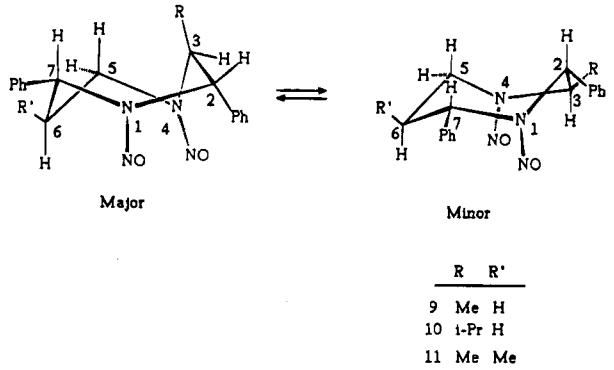

Figure 7. Pseudorotation-driven equilibrium between the ring conformations of **9**–**11**.

by H5a is positive for **10** and negative for **11**. This observation suggests that H5a is in the plane of the nitroso group in the former while in the latter it is slightly tilted out of the plane.

Minor Conformers. As indicated earlier in the case of the isopropyl compound **10**, on decreasing the temperature from +50 °C to +20 °C, broadening of the ^{1}H resonances was observed. Further lowering of the temperature to −50 °C resulted in relatively well-resolved multiplets and the appearance of new weak methyl doublets. These observations indicated the presence of a new set of minor conformers which exist in equilibrium with the major set of twist-chair conformers. Though the signals of the minor conformers are relatively very weak, certain basic conclusions about their stereochemistry have been made. The detailed conformational aspects are, however, somewhat speculative owing to the weak intensity of the signals.

In the case of the 3-methyl and 3,6-dimethyl derivatives, **9** and **11**, respectively, the increase in temperature from +20 °C to +50 °C increases the resolution of the ^{1}H NMR spectra. However, the signals are still broad compared to those of the isopropyl analog **10** what may be ascribed to the relatively higher pseudorotation barrier. Thus a decrease in the size of the C3-alkyl group increases the pseudorotation barrier, indicating an inverse relationship between the two. The increase in the barrier on decreasing the size of the C3-alkyl group suggests a decrease in the ground state energy level. The C3-alkyl group which is *axial* in the set of major conformers flips to the *quasiequatorial* position in the corresponding minor conformers (Figure 7). It is therefore suggested that the set of major conformers are in twist-chair conformations **17a**–**d** (Figure 6) with *axial* 3-alkyl groups while the set of minor conformers are in partially twisted chair conformations **18a**–**d** (Figure 6) with quasiequatorially oriented 3-alkyl groups. Since in the case of both **9** (3-methyl compound) and **11** (3,6-dimethyl compound) the temperature behavior of the ^{1}H NMR spectra were nearly similar, the part of the ring containing C5, C6, and C7 does not vary significantly. Thus the methyl group at C6 is at equatorial orientation in both sets of conformers.

It is essential to mention that X-ray crystallographic studies[21] on the 3-isopropyl derivative **10** revealed that the dinitroso compound adopts partially twisted chair conformation with quasiequatorial orientation of the isopropyl as well as the phenyl substituents. This conformation is analogous to one of the conformers in the minor set (~5%) indicating that it is a minor conformer, one among **18a**–**d**, that crystallizes preferentially.

On the basis of a combination of multipulse experiments and variable temperature NMR spectra recorded from −50 °C to +120 °C, it has been shown that the introduction of the nitroso groups at N^1 and N^4 nitrogens results in a conformational equilibrium of major and minor sets of twist-chair conformers, the interconversion between the two being driven by pseudorotation. The major set is comprised of four rotamers resulting from the restricted rotation along the N–N bond. The substituents at C2 (phenyl) and C3 (alkyl) prefer axial/pseudoaxial positions while those at C7 (Ph) and C6 (Me in **11**) prefer equatorial positions in all the dinitroso compounds (**9**–**11**) studied. The alkyl group at C3 was found to be in axial orientation in the major set of conformers while it was quasiequatorial in the minor set.

***Caution:* The nitrosamines reported in this paper are believed to be potent carcinogens. Precautionary handling is required.**

Experimental Section

General Methods. As described elsewhere.[2a,c]

Hexahydro-*t*-3-methyl-*r*-2,*c*-7-diphenyl-5*H*-1,4-diazepin-5-one (14). To a mixture of ethanol (100 mL) and dilute hydrochloric acid (110 mL, 9%) was added powdered *t*-3-methyl-*r*-2,*c*-6-diphenylpiperidin-4-one[2a,22] (**13a**) (10.0 g, 37.7 mmol) slowly, and the mixture was heated to 65–70 °C on a water bath. The solution was immediately filtered through cotton under hot condition, and the filtrate was kept aside at 25 °C for 3 h and then at 0–5 °C overnight. The crystals that appeared were separated by filtration through a Buchner funnel, washed slightly with cold aqueous alcohol (50%; 10 °C), and dried to get pure hydrochloride of **13a** (yield 89%); mp 225–6 °C (lit.[22a] mp 224–6 °C).

Dry, powdered hydrochloride of **13a** (10.0 g, 37.59 mmol) was added, in portions, to cold concd sulfuric acid (50 mL; 5 °C) in a conical flask equipped with a magnetic stirrer. When all the solid has dissolved, the temperature of the solution was allowed to rise to 25 °C. Sodium azide (3.0 g, 46.15 mmol) was added slowly in portions of about 0.1 g with vigorous stirring. Nitrogen gas evolution was observed during each addition. The addition was continued for 1 h. After the addition was over, the solution was poured into crushed ice and stirred well with a glass rod. Cold sodium hydroxide solution (2 N) was added slowly with stirring until the pH was 8. A white solid precipitated out. After keeping the mixture at 25 °C overnight the solid was separated by filtration through a Buchner funnel, washed with water until free of sodium hydroxide, and dried. The dried solid was dissolved in benzene and filtered through a fluted filter paper, and the solution was concentrated. The solution was kept aside for crystallization. The crystals obtained were separated and recrystallized from ethanol (yield 85%); mp 184–5 °C (lit.[23] mp 183 °C). IR (KBr): 3300 (NH), 3200 (CO*NH*), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ 0.81 (d, J = 6.8 Hz, 3H), 2.07 (bs), 2.65 (d, J = 14.1 Hz), 3.14 (dd, J = 10.6, and 14.1 Hz), 3.70 (d, J = 7.8 Hz), 3.82 (ddq, J = 7.0, 7.6, and 4.0 Hz), 4.13 (d, J = 10.5 Hz), 5.75 (bs), and 7.23–7.43; ^{13}C NMR ($CDCl_3$) δ 19.8, 47.5, 54.7, 59.6, 71.1, 142.1, 144.7, 175.7, 126.4, 127.7, 128.0, and 128.6.

Hexahydro-*t*-3-isopropyl-*r*-2,*c*-7-diphenyl-5*H*-1,4-diazepin-5-one (15). *t*-3-Isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one hydrochloride was prepared from *t*-3-isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one (**13b**)[2a] in a manner described above and recrystallized from 60% aqueous ethanol; yield 92%; mp 192–3 °C (lit.[22a] mp 192–4 °C). The same procedure as described for **14** was followed using the hydrochloride of

(21) Priya, V.; Viswamitra, M. A.; Shamala, N.; Senthilkumar, U. P.; Jeyaraman, R. (unpublished).

(22) (a) Noller, C. R.; Baliah, V. *J. Am. Chem. Soc.* **1948**, *70*, 3853. (b) Baliah, V.; Ekambaram, A.; Govindarajan, T. S. *Curr. Sci.* **1954**, *23*, 264.

3-isopropylpiperidone **13b**; yield 86%; mp 188–9 °C (lit.[23] mp 188 °C); IR (KBr) 3305 (NH), 3200 (CO*NH*), 1665 (CO); ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H), 1.5 (d sep, J = 2.4, and 6.9 Hz), 1.96 (s), 2.65 (d, J = 13.9 Hz), 3.20 (dd, J = 10.6, and 14.1 Hz), 3.70 (ddd, J = 2.2, 8.3 and 3.7 Hz), 3.85 (d, J = 8.3 Hz), 4.15 (d, J = 10.6 Hz), 5.68 (bs), and 7.23–7.40; ^{13}C NMR ($CDCl_3$) δ 14.2, 20.8, 28.5, 47.5, 59.7, 63.5, 68.6, 141.7, 144.7, 176.3, 126.3, 127.6, 127.8, and 128.5.

Hexahydro-*t*-3,*t*-6-dimethyl-*r*-2,*c*-7-diphenyl-5*H*-1,4-diazepin-5-one (16). *t*-3,*t*-5-Dimethyl-*r*-2,*c*-6-diphenylpiperidin-4-one hydrochloride was prepared from *t*-3,*t*-5-dimethyl-*r*-2,*c*-6-diphenylpiperidin-4-one (**13c**) as described above and recrystallized from aqueous ethanol; yield 85%; mp 227–9 °C (lit.[22a] mp 228–30 °C). The procedure described for **14**, followed using the hydrochloride of the 3,5-dimethylpiperidone **13c**, afforded **16** in 82% yield; mp 180–1 °C; IR (KBr) 3300 (NH), 3200 (CONH), 1660 (CO); ^{1}H NMR ($CDCl_3$) δ 0.70 (d, J = 7.1 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H), 2.06 (s), 3.08 (dq, J = 7.1, and 8.8 Hz), 3.65 (d, J = 8.1 Hz), 3.79 (d, J = 8.8 Hz), 3.86 (ddq, J = 5.1, 6.7, and 7.6 Hz), 5.75 (bd), and 7.20–7.40; ^{13}C NMR ($CDCl_3$) δ 14.6, 19.6, 45.9, 54.2, 64.9, 71.0, 142.2, 143.2, 178.4, 126.7, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5, and 128.7.

Hexahydro-*t*-3-methyl-1,4-dinitroso-*r*,2,*c*-7-diphenyl-1*H*-1,4-diazepine (9). Into a dry 500-mL round-bottomed flask was added **14** (4.04 g, 14.4 mmol). Dry ether (200 mL) was added under nitrogen atmosphere. Lithium aluminum hydride (1.09 g, 28.7 mmol) was added slowly in portions of 0.1 g. After the addition was over the reaction mixture was heated under reflux for 1 h and stirred at 25 °C for 12 h. Then, the reaction mixture was transferred into a 1 L beaker. Just sufficient drops of water were added until the excess LAH was destroyed (addition of excess water or NaOH or NH_4Cl solution is not desirable since the product is soluble in water). The clear ether solution was filtered through a fluted paper. The jel-like precipiate was extracted with chloroform five times (150 mL × 5). The combined organic solutions were dried over sodium sulfate, filtered and evaporated. The resulting oily product **19** was dissolved in dry ether, and hydrogen chloride was passed through the solution. The hydrochloride **19a** which precipitated out was separated by filtration through a Buchner funnel, washed with a little dry ether, and dried; yield 47%.

Into a 500-mL round-bottomed flask containing water (25 mL) was added **19a** (1.09 g, 3.22 mmol). To the homogeneous solution was added sodium nitrite (0.52 g, 7.53 mmol) in aqueous alcohol (50%; 10 mL) slowly while stirring the solution at 10–15 °C. After the addition was over, the reaction mixture was stirred at 25 °C for 1 h and poured into ice-cold water (0–5 °C). The precipitated solid was separated by filtration through a Buchner funnel, washed with water (200 mL) and dried. Recrystallization from alcohol afforded yellow crystals of **9** in 86% yield; mp 154–5 °C; ^{1}H NMR ($CDCl_3$), 50 °C: Conformer A: δ 1.64 (d, J = 6.89 Hz, Me3), 2.15 (m, H6b), 2.45 (m, H6a), 3.0 (bs, H5b), 4.8 (bs, H5a), 5.72 (b, H7); 5.85 (bs, H3), 6.32 (bs, H2); Conformer B: δ 1.23 (d, J = 6.83 Hz, Me3), 2.30 (m, H6b), 2.40 (m, H6a), 3.80 (dd, J = 10.94 and 14.79 Hz, H5b), 5.12 (dd, J = 7.02 and 14.80 Hz, H5a), 5.82 (dd, J = 4.91 and 12.96 Hz, H7), 6.23 (qd, J = 6.76 and 1.53 Hz, H3), 6.41 (d, J = 1.86 Hz, H2); Conformer C: δ 1.44 (d, J = 6.89 Hz, Me3), 2.15 (bs, H6b), 2.30 (m, H6a), 3.15 (ddd, J = 14.29, 10.27, and 2.40 Hz, H5b), 4.94 (ddd, J = 14.54, 5.52, and 1.96 Hz, H5a), 5.65 (bs, H3), 6.47 (bs, H2); Conformer D: δ 1.01 (d, J = 6.87 Hz, Me3), 2.15 (m, H6b), 2.60 (m, H6a), 3.98 (ddd, J = 15.45, 11.70, and 2.03 Hz, H5b), 5.17 (ddd, J = 15.41, 5.24 and 2.62 Hz, H5a), 6.00 (qd, H3), 6.08 (dd, J = 11.76 and 6.98 Hz, H7), and 6.84 (s, H2). MS *m/z* (relative intensity), 324 (M^+; 0.51), 294 (3.2), 264 (3.4), 208 (5.4), 195 (30.4), 174 (8.8), 163 (9.8), 146 (21.1), 132 (9.7), 118 (100). Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27%. Found: C, 66.38; H, 6.41; N, 17.01%.

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Hexahydro-*t*-3-isopropyl-1,4-dinitroso-*r*-2,*c*-7-diphenyl-1*H*-1,4-diazepine (10). By following the procedure described for **19a**, the hydrochloride of *t*-3-isopropyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepine, **20a**, was prepared in 41% yield by the LAH reduction of the diazepin-5-one **15**. The hydrochloride **20a** (0.79 g, 2.16 mmol) was dissolved in water (40 mL) and cooled to 5–10 °C. To the stirred solution was added sodium nitrite (0.45 g, 6.52 mmol) in water (10 mL) in drops for a period of 1 h. After the addition was over, the reaction mixture was stirred at 25 °C for 1 h. Excess water (100 mL) was added, and the precipitated solid was separated, washed with water, and dried. Recrystallization from alcohol afforded yellow needles of **10** in 82% yield; mp 143–4 °C; ^{1}H NMR ($CDCl_3$), +50 °C: Conformer A: δ 0.90 (d, Me″), 1.33 (d, Me′), 2.22 (m, CH<), 5.35 (m, H3), 6.85 (s, H2), 2.46 (m, H5b), 5.33 (m, H5a), 5.79 (H7); Conformer B: δ 0.74 (d, Me″), 1.23 (d, Me′), 1.91 (m, CH<), 5.77 (m, H3), 6.80 (s, H2), 3.73 (dd, H5b), 5.15 (dd, H5a), 5.78 (dd, H7); Conformer C: δ 0.81 (d, Me″), 1.28 (d, Me′), 1.85 (m, CH<), 5.20 (m, H3), 2.71 (m, H5b), 5.31 (m, H5a), 6.03 (m, H7); Conformer D: δ 0.65 (d, Me″), 1.18 (d, Me′), 1.55 (m, CH<), 5.56 (d, H3), 7.12 (s, H2), 3.90 (m, H5b), 5.25 (m, H5a), and 6.09 (dd, H7). MS: *m/z* (relative intensity) 352 (M^+; 7.5), 322 (64.5), 291 (12.6), 249 (12.5), 208 (17.0), 195 (57.4), 174 (21.5), 163 (28.0), 146 (100), 131 (39.0). Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90%. Found: C, 68.35; H, 7.01; N, 16.24%.

Hexahydro-*t*-3,*t*-6-dimethyl-1,4-dinitroso-*r*-2,*c*-7-diphenyl-1*H*-1,4-diazepine (11). In a similar manner as described for **19a**, *t*-3,*t*-6-dimethyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepine hydrochloride was prepared in 38% yield by the LAH reduction of the diazepin-5-one **16**. To a stirred solution of *t*-3,*t*-6-dimethyl-*r*-2,*c*-7-diphenylhexahydro-1,4-diazepine (1.03 g; 3.68 mmol) in aqueous alcohol (90%, 40 mL) was added conc hydrochloric acid (1 mL), and the mixture was cooled to 10 °C. A solution of sodium nitrite (1.51 g, 21.8 mmol) in 50% aqueous alcohol (10 mL) was added to the reaction mixture, in portions, for a period of 1 h, and the mixture was stirred at 25 °C for 6 h. The reaction was followed by TLC analysis. Further quantities of hydrochloric acid (2 mL) and sodium nitrite solution (2 g in 10 mL of 50% aqueous alcohol) were added, and the stirring was continued for another 6 h. After the reaction was over, the reaction mixture was poured into water. The precipitated solid was separated by filtration through a Buchner funnel, washed with aqueous alcohol, and dried. Repeated recrystallizations from alcohol afforded **11** in 40% yield; mp 223–4 °C; ^{1}H NMR ($CDCl_3$), 50 °C: Conformer A: δ 0.86 (d, J = 6.72 Hz, Me6), 1.65 (d, J = 6.83 Hz, Me3), 2.31 (m, H6), 2.63 (m, H5b), 4.74 (d, J = 14.29 Hz, H5a), 5.67 (d, J = 11.61 Hz, H7), 5.92 (m, H3); Conformer B: δ 0.90 (d, J = 7.62 Hz, Me6), 1.23 (d, J = 6.81 Hz, Me3), 2.69 (m, H6), 3.65 (dd, J = 9.67 Hz, H5b), 4.87 (d, J = 14.50 Hz, H5a), 5.63 (d, J = 11.86 Hz, H7), 6.16 (q, J = 6.81 Hz, H3); Conformer C: δ 1.08 (d, J = 6.26 Hz, Me6), 1.43 (d, J = 6.87 Hz, Me3), 2.58 (m, H6), 2.76 (m, H5b), 4.73 (d, J ~ 14.0 Hz, H5a); Conformer D: δ 0.99 (d, J = 6.85 Hz, Me3), 1.15 (d, J = 6.77 Hz, Me6), 2.93 (m, H6), 3.90 (dd, J = 13.49 and 9.89 Hz, H5b), 4.91 (d, J = 13.08 Hz, H5a), and 5.92 (m, H3). **MS**, *m/z* (relative intensity, %), 338 (M^+; 12.5), 308 (43.0), 296 (5.9), 277 (18.0), 269 (11.8), 263 (10.0), 249 (5.5), 235 (16.9), 222 (100), 108 (9.1), 206 (9.0). Anal. Calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56%. Found: C, 67.64; H, 6.34; N, 16.72%.

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