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Competing $A^{1,3}$-strain and Ph:Ph diaxial repulsion in oximes and semicarbazones of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones

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The effect of $A^{1,3}$-strain introduced by N-NO group in N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones on the selectivity in the formation of oximes **14-18** and semicarbazones **19-22** has been studied. In general, the oximes and semicarbazones formed are the *E* isomers, exclusively, except in the cases of the oximation of 3-methyl-N-nitrosopiperidin-4-one and 3,5-dimethyl-N-nitrosopiperidin-4-one which have produced a mixture of *E* and *Z* isomeric oximes. Oximation of 3,5-dimethyl-N-nitrosopiperidin-4-one yields a mixture of two isomers **17** and **18** differing in the relative configurations of methyl group due to epimerization at C5. The configurations and preferred conformations of the oximes **14-18** and semicarbazones **19-22** of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones have been determined using NMR spectral experiments and are found to prefer twist-boat conformations with an equilibrium between two rotameric states due to restricted rotation around N-NO bond. The semiempirical MO calculations performed on the nitrosamines **14-22** have also shown the preference of twist-boat conformations.

Keywords: $A^{1,3}$-strain, N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones, oximes, semicarbazones, conformation, configuration, epimerization, NMR spectra, semiempirical MO calculation, twist-boat

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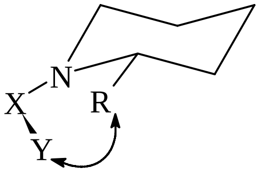
The NMR spectral studies on 2,6-disubstituted N-nitrosopiperidines[1] and related compounds[2] **1-5** showed that the $A^{1,3}$-strain[3] (**Figure 1**) arising due to coplanar orientation of the N-nitroso group plays an important role in determining the preferred conformations of such heterocycles. In addition, the hindered rotation about the N-N bond results in interesting stereodynamics between two or more conformers in each of these compounds[2].

The relative preferences among the various conformers in the conformational equilibria in N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones **6-9** (Refs 1,2) and N-nitroso-*r*-2,*c*-4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones (*e.g.* **5**) (Ref. 2) have been studied. Most of the N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones **6-9** (Ref.1) prefer twist-boat/twist-chair conformations. It is also interesting to note that certain N-nitroso compounds have been reported to possess anti-cancer activities[2]. Geneste and others[4] studied the stereochemistry of *r*-2,*c*-6-diphenylpiperidin-4-one oximes **10-13** and proposed chair conformations with all the ring substituents in equatorial orientation.

It was anticipated that the introduction of $A^{1,3}$-strain at more than one site, at both N1 and C4 ends, in N-nitroso-*r*-2,*c*-6-diarylpiperidines might have significant effect on the conformational preferences. With a view to investigating this, stereochemical analysis of the oximes **14-18** and semicarbazones **19-22** of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones was carried out and the results are reported herein. In addition, the anti-cancer activities of compounds **14-17** were examined.



R = alkyl or aryl

Figure 1 — Allylic strain

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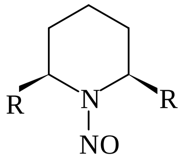
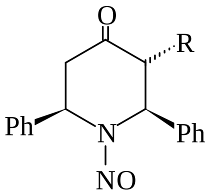


1a R = CH_3

1b R = Ph



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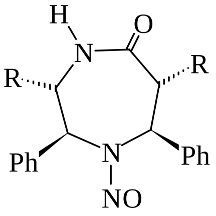
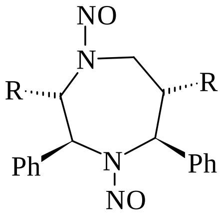


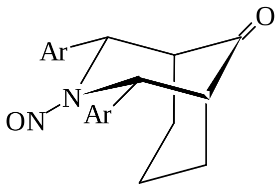
R = alkyl

3



R = alkyl

4



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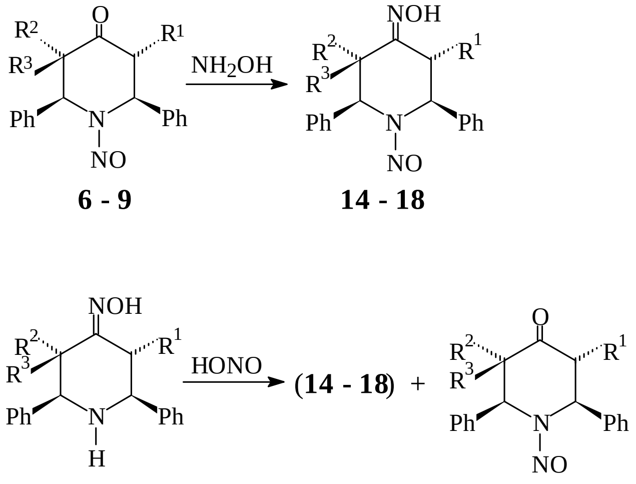


6 - 9

14 - 18

10 - 13

6 - 9

	R^1	R^2	R^3
6, 10, 14	H	H	H
7, 11, 15	Me	H	H
8, 12, 16	*i*-Pr	H	H
9, 13, 17	Me	Me	H
18	Me	H	Me

Scheme I

Results and Discussion

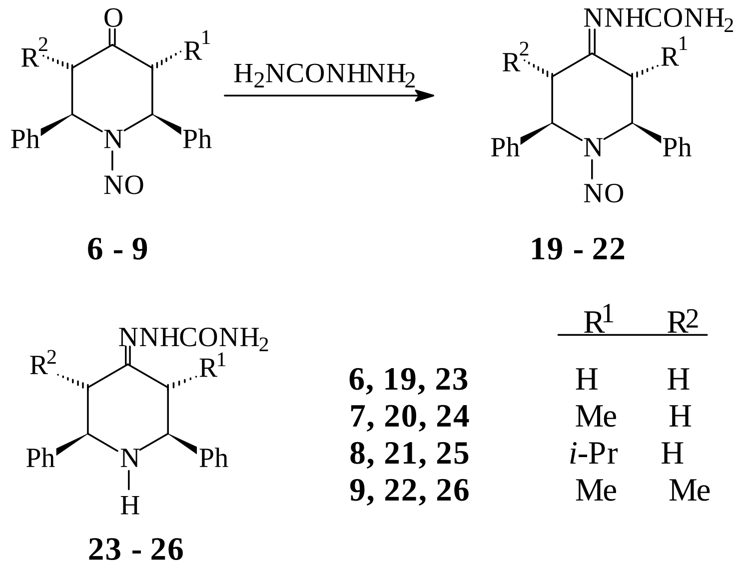
Two complementary methods were considered for the preparation of the nitrosopiperidin-4-one oximes **14-18** (**Scheme I**). Employing the first route, the N-nitrosopiperidin-4-ones **6-9** were treated with hydroxylamine to obtain the nitrosopiperidin-4-one oximes. The complementary route involving the nitrosation of the piperidin-4-one oximes **10-13** resulted in the partial hydrolysis of the oximes leading to a mixture of the corresponding nitrosopiperidin-4-ones **6-9** and nitrosopiperidin-4-one oximes **14-18**. Since the composition of the mixture of products varied over a wide range on repeating the experiments, this method was not studied in detail. The semicarbazones **19-22** of nitrosopiperidin-4-ones were prepared by the reaction of the N-nitrosopiperidin-4-ones **6-9** with semicarbazide (**Scheme II**). The stereochemistry of the title compounds was investigated by analyzing their ^{1}H and ^{13}C NMR spectral data (**Tables I-V**).

Orientation of the N-NO group

The N-N-O plane in these compounds can be either coplanar, or perpendicular with respect to the C2-N1-C6 plane of the ring. Out of these two possibilities for the N-NO orientation, the coplanar orientation was found to be preferred as revealed by the presence of two (anisochronous) signals for each magnetic nucleus in their NMR spectra which is due to equilibrium between *syn* and *anti* rotamers (**Figure 2**). The terms *syn* and *anti* refer to the orientation of nitroso group with reference to C2 carbon.

Possible conformations

Various possible isomers of the N-nitrosamines, differing in the relative orientation of the nitroso and oxime functions are shown in **Figure 3**. The nitrosopiperidin-4-one oximes **14** and **16** were obtained as single products. Observation of anisochronous signals in the NMR spectra of these compounds indicated an equilibrium between the rotamers **A** and **B**. On the other hand, two isomers were obtained during the oximation of 3-methylnitrosopiperidin-4-one **7** and 3,5-dimethylnitrosopiperidin-4-one **9**. Out of the two isomers, the major one was separated by fractional crystallization. Isolation of the minor isomers could not be achieved in either case due to isomerisation and decomposition during the chromatographic separation process using either alumina or silica gel. However, conclusions regarding the conformations and the ratio of the isomers formed in each case were derived from the ^{1}H and ^{13}C NMR spectral data of the mixtures. The NMR signals due to the minor isomers could be picked up from the NMR spectra of the mixtures by eliminating the signals due to the pure major isomers. Analysis of ^{13}C NMR spectra revealed that the two isomers obtained in the case of the 3-methylnitrosopiperidin-4-one oxime **15** differ in the configuration around >C=N bond as in isomers **A** and **C** (**Table I**). Anisochrony of signals in the ^{1}H and



6 - 9

19 - 22

23 - 26

	R^1	R^2
6, 19, 23	H	H
7, 20, 24	Me	H
8, 21, 25	*i*-Pr	H
9, 22, 26	Me	Me

Scheme II

Table I — Spectral data of compounds **17-25**

Compd	IR(KBr)	^{1}H NMR ($CDCl_3$, δ, ppm)	^{13}C NMR ($CDCl_3$, δ, ppm)	MS (M^+, m/z)
17	1630 (C=N) 3340 (OH)	syn conformer 3.77 (dd, H5eq, *J*=3.2 and 18.9 Hz), 5.58 (dd, H2, *J*=6.0 and 9.7 Hz), 6.43 (dd, H6, *J*=3.2 and 6.6 Hz); anti conformer 3.29 (m, H3eq, *J*=6.0 Hz), 6.13 (t, H2, *J*=6.0 Hz), 6.34 (dd, H6, *J*=4.5 and 6.8 Hz), 6.8-7.4 (aromatic), 7.74 (s, -OH)	syn conformer 28.1(C4), 34.0(C3), 56.5(C2), 59.3(C5), anti conformer 26.8(C4), 31.0(C3), 50.3(C5), 61.0 (C2), 126.4, 126.5, 127.4, 127.6, 128.0, 128.3, 128.4, 128.5, 128.9 (aromatic), 138.1, 138.2, 138.6(ipso)	295
18	1620 (C=N) 3300 (OH)	E syn conformer 0.97 (d, CH_3, *J*=7.6 Hz), 3.80 (d, H5eq, *J*=2.1Hz), 5.20 (d, H2, *J*=9.3Hz), 6.49 (dd, H6, *J*=2.1 and 7.2 Hz), 8.19 (s, -OH); anti isomer 1.23 (d, CH_3, *J* =7.0 Hz), 2.93 (d, H5ax, *J*=6.7 Hz), 3.52 (q, H3ax, *J*=4.9 Hz), 5.83 (d, H2, *J*=4.9Hz), 6.09 (dd, H2, *J*=2.1 and 6.7 Hz), 7.96 (s, -OH); Z syn isomer 1.35 (d, CH_3, *J*=7.0 Hz), 6.01 (dd, H6, *J*=6.6 and 6.7 Hz), 6.14 (m, H2); anti isomer 1.26 (d, CH_3, *J*=3.3 Hz), 5.52 (dd, H6, *J*=7.7 and 8.4 Hz), 6.50 (m, H2), 6.89-7.42 (aromatic)	E syn conformer 14.2(CH_3), 27.0(C4), 37.1(C3), 58.9(C5), 62.5(C2), 156.89 (C4) anti conformer 17.6(CH_3), 25.9 (C4), 36.7(C3), 51.4(C5), 66.9(C2), 157.3(C4) Z syn conformer 16.88 (CH_3), 30.3(C3), 32.2(C4), 55.2(C2), 61.3(C5) anti conformer 16.2(CH_3), 31.8(C3), 33.1(C4), 56.0(C5), 65.9 (C2), 126.5, 127.4, 127.6, 127.9, 128.1, 128.4, 128.6, 128.8 (aromatic), 137.1, 138.3, 138.4(ipso)	309
19	1640 (C=N) 3300 (OH)	syn conformer 1.09 (d, CH_3, *J*=9.3 Hz), 1.17 (d, CH_3, *J*=6.5 Hz), 2.67 (dd, H5ax, *J*=7.3 and 16.1 Hz), 3.04 (d, H3ax, *J*=10.0 Hz), 3.91 (dd, H5eq, *J*=3.5 and 16.0 Hz), 6.76 (s, H2), 7.91 (s, -OH); anti conformer 0.95 (d, CH_3, *J*=6.7 Hz), 1.01 (d, CH_3, *J*=3.2 Hz), 1.81 (m, 1H of >CH), 2.54 (dd, H5ax, *J*=7.7 and 9.5 Hz), 2.83 (s, H3ax), 3.42 (dd, H5eq, *J*=4.9 and 16.8 Hz), 6.20 (dd, H6, *J*=4.9 and 7.7 Hz), 6.37 (s, H2), 7.96 (s, -OH), 6.85-7.31 (aromatic)	syn conformer 20.3(CH_3), 25.0(C4), 28.7(>CH), 48.9(C3), 51.1(C2), 60.5 (C5), anti conformer 20.8, 21.7(CH_3's) 24.6(C4), 29.1(>CH), 49.3(C5), 50.6 (C5), 62.1(C2), 126.8, 127.0, 127.5, 127.8, 127.9, 128.0 (aromatic), 137.6, 137.9, 138.3 (ipso)	337
20	1660 (C=N) 3250 (OH)	E syn conformer 0.86 (d, CH_3, *J*=6.4 Hz), 1.31 (d, CH_3, *J*=7.2 Hz) 2.79 (m, H3ax, *J*=13.0 Hz), 4.30 (m, H5ax) 4.75 (m, H2, *J*=13.0 Hz), 6.10 (d, H6, *J*=1.6 Hz), 7.80 (s, -OH); anti conformer 0.96 (d, CH_3, *J*=6.6 Hz), 1.28 (d, CH_3, *J*=7.3 Hz), 2.99 (m, H3ax, *J*=11.4 Hz), 4.19 (m, H5ax), 5.25 (d, H2, *J*=11.4 Hz), 4.19 (m, H5ax), 5.25 (d, H2, *J*=11.4 Hz), 6.39 (d, H6ax, *J*=0.9 Hz), 7.74 (m, -OH); Z syn conformer 5.88 (d, H2, *J*=6.4 Hz), 6.21 (s, H6), 3.22 (m); anti conformer 3.47 (m), 5.46 (d, H2, *J*=7.2 Hz), 6.49 (m, H6), 7.00-7.40 (aromatic)	E syn conformer 13.2, 16.0(CH_3's), 32.0(C4), 37.2(C3), 63.9(C2), 65.0 (C5) anti conformer 13.89, 16.58 (CH_3's), 31.0 (C4), 37.9(C3), 54.8 (C5), 68.1(C2), Z syn conformer 34.1 (C4), 34.7(C3), 59.3(C2), 67.0(C5), anti conformer 10.9, 12.6, 14.7(CH_3's), 28.4(C4), 55.2(C5), 67.5 (C5), 160.7 (C4), 126.4, 127.5, 127.7, 127.8, 128.0, 128.1, 128.5, 128.7, 128.9 (aromatic), 137.8, 138.3, 139.5(ipso)	323
22	1570 (C=N) 1680 (C=O) 3450 (NH)	syn conformer 5.56 (t, H2, *J*=5.9 and 6.0), 6.20 (dq, H6, *J*=5.5 and 7.3 Hz), 9.18 (s, >NH); anti conformer 6.02 (t, H6, *J*=5.2 and 5.3 Hz), 6.10 (q, H2, *J*=5.9, 6.0 Hz), 9.41 (s, >NH), 7.14-7.49 (aromatic)	syn conformer 32.7(C4), 37.4(C3), 57.3 (C2), 59.9(C5), 144.6(C=N), anti conformer 29.8(C4), 52.4(C5), 61.6 (C2), 145.1(C=N), 126.0, 126.2, 127.4 127.7, 128.4, 128.8, 129.0, 129.2, 129.3, 139.4, 139.7(aromatic), 140.2, 141.4, 143.4, 144.1(ipso), 157.5 (carbonyl)	337
23	1560 (C=N) 1680 (C=O) 3450 (NH)	syn conformer 0.89 (d, CH_3, *J*=6.6 Hz), 5.04 (d, H2, *J*=9.4 Hz), 6.47 (dd, H6, *J*=3.3 and 6.5 Hz), 9.30 (s, >NH); anti conformer 0.99 (d, CH_3, *J*=6.8 Hz), 5.79 (m, H2, *J*=7.5 Hz), 5.84 (dd, H6, *J*=6.1 and 6.5), 9.33 (s, >NH), 6.70-7.50 (aromatic)	syn conformer 15.0(CH_3), 30.1(C4) 59.0 (C2), 63.5(C5), anti conformer 16.6(CH_3), 29.6(C4), 53.0(C5), 67.1 (C2), 126.2, 127.7, 128.1, 128.2, 128.5, 128.8, 129.0, 129.2, 129.3(aromatic), 146.6, 147.1(ipso), 157.7(carbonyl)	351

—*Contd*

Table I — Spectral data of compounds **17-25**—*Contd*

Compd	IR(KBr)	^{1}H NMR ($CDCl_3$, δ, ppm)	^{13}C NMR ($CDCl_3$, δ, ppm)	MS (M^+, m/z)
24	1560 (C=N) 1670 (C=O) 3450 (NH)	syn conformer 0.92 (d, CH_3, J=6.6 Hz), 0.97 (d, CH_3, J=6.7 Hz), 1.74 (m, >CH), 2.74 (d, H3, J=10.1 Hz), 2.96 (dd, H5eq, J=6.16 and 18.14 Hz), 3.15 (dd, H5ax, J=8.36 and 17.78 Hz), 6.04 (dd, H6, J=7.6 and 7.6 Hz), 6.29 (s, H2), 9.41 (s, -NH); anti conformer 1.01 (d, CH_3, J=6.45 Hz), 1.07 (d, CH_3, J=6.6 Hz), 1.84 (m, >CH), 2.53 (dd, H5eq, J=7.6 and 17.7 Hz), 2.91 (dd, H3ax, J=1.82 and 9.39 Hz), 5.67 (dd, H6, J=7.6 Hz), 6.37 (m, H2), 9.43 (s, >NH), 6.99-7.40 (aromatic)	syn conformer 20.7, 20.9(CH_3's), 30.8 (C4), 51.0(C3), 54.1(C2), 60.2(C5), anti conformer 21.2, 21.7(CH_3's), 29.8 (C4), 53.1(C3), 54.0(C5), 62.2(C2), 126.5, 126.9, 127.2, 127.5, 128.0, 128.2, 128.4, 128.7, 128.9 (aromatic), 145.3, 145.5(ipso), 157.7 (carbonyl)	379
25	1560 (C=N) 1670 (C=O) 3450 (NH)	syn conformer 0.82 (d, CH_3, J=6.5 Hz), 1.13 (d, CH_3, J=5.8 Hz), 2.55 (m, H3, J=12.0 Hz), 4.36 (m, H5), 4.80 (d, H2, J=12.0 Hz), 6.28 (m, H6), 9.65 (s, >NH); anti conformer 0.86 (d, CH_3, J=8.6 Hz), 1.13 (d, CH_3, J=5.8 Hz), 2.74 (m, H5), 4.24 (m, H3, J=12.2 Hz), 5.54 (d, H2, J=12.0 Hz), 6.20 (m, H6), 9.72 (s, >NH), 7.05-7.64 (aromatic)	syn conformer 13.5, 14.7(CH_3's), 32.5 (C4), 64.5(C2), 64.9(C5), anti conformer 32.3(C3), 56.1(C5), 67.6 (C2), 126.4, 127.5, 127.7, 128.2, 128.4, 128.9, 129.1, 129.5(aromatic), 138.9, 139.0, 139.5(ipso), 149.6(C=N), 157.8 (carbonyl)	365

Table II — The vicinal coupling constants (in Hz) and estimated dihedral angles of nitroso oximes **14-18** and piperidin-4-one oximes **10-13**

Compd	Coupling constant (Hz)				Dihedral angles (°)			
	2a3e	2a3a	5e6a	5a6a	5e6a	5a6a	2a3e	2a3a
14A	6.0	9.7	3.2	6.6	44	164	39	159
14B	6.0	6.0	4.5	6.8	37	157	27	147
10	2.9	11.5	2.9	11.7	57	177	57	177
15A	-	9.3	2.1	7.2	54	174	-	-
15B	-	4.9	6.2	6.7	29	149	-	-
15C	-	-[a]	6.6	6.7	28	148	-	-
15D	-	-[a]	7.7	8.4	30	150	-	-
11	-	10.1	2.9	11.8	57	177	-	-
16A	-	0.0	3.5	7.3	44	164	-	-
16B	-	0.0	4.9	7.7	38	158	-	-
12	-	8.8	3.9	11.2	51	171	-	-
17A	-	13.0	1.6	-	-	-	-	-
17B	-	11.4	0.9	-	-	-	-	-
18A	-	6.4	0.0	-	-	-	-	-
18B	-	7.2	0.0	-	-	-	-	-
13A	-	10.5	3.5	-	-	-	-	-
13B	-	5.8	9.2	-	-	-	-	-

[a] The value could not be determined since NMR signal of H2 proton of rotamers **C** and **D** merged with those of rotamers **A** and **B**.

^{13}C NMR spectra of each of the isomers indicated that there is an equilibrium between the rotamers **A** and **B** and another between the rotamers **C** and **D**. The ^{1}H NMR spectral analysis of the mixture of products formed from 3,5-dimethylnitrosopiperidin-4-one indicated that the products differ in the configuration of the methyl group at C5 position (**17** and **18**). The ratio of the *E* and *Z* isomers of the 3-methylnitrosopiperidin-4-one oxime was found to be 85:15 and that of the isomers **17** and **18** of the 3,5-dimethylnitrosopiperidin-4-one oxime was 80:20.

Assignment of signals

An attempt was made to assign the ^{1}H NMR signals

Table III — The vicinal coupling constants (in Hz) and estimated dihedral angles of nitroso semicarbazones **19-22** and semicarbazones **23-26** of piperidin-4-ones

Compd	Coupling constant (Hz)				Dihedral Angles (°)			
	2a3e	2a3a	5e6a	5a6a	5e6a	5a6a	2a3e	2a3a
19A	5.9	6.0	5.5	7.3	34	154	28	158
19B	4.4	8.6	5.2	5.3	28	148	43	163
23	2.4	9.3	2.9	11.4	57	177	56	176
20A	-	9.4	3.3	6.5	43	163	-	-
20B	-	7.5	6.1	6.5	29	149	-	-
24	-	10.2	-a	11.7	-b	-b	-	-
21A	-	0.0	6.4	8.0	32	152	-	-
21B	-	0.0	7.6	7.6	27	147	-	-
25	-	8.8	3.7	11.5	53	173	-	-
22A	-	12.0	-	0.0	-	-	-	-
22B	-	12.2	-	0.0	-	-	-	-
26	-	2.9	-	10.7	-	-	-	-

[a] The value could not be determined

[b] The value is not estimated since $J_{5e,6a}$ is not available

Table IV — Aromatic Solvent Induced Shifts (ASIS) of *syn* and *anti* protons of the nitroso oxime **14** and nitroso semicarbazones **20-22** of nitrosopiperidin-4-ones

Compd	Proton	*syn*			*anti*		
		solvent[a]	Solvent + C_6D_6	δ[b]	solvent[a]	Solvent + C_6D_6	δ[b]
14	H2	5.58	5.54	+0.04	6.13	6.03	+0.10
	H6	6.34	6.27	+0.07	6.43	6.31	+0.12
20	H2	5.04	5.03	+0.01	5.79	5.78	+0.01
	H6	5.84	5.93	-0.09	6.47	6.50	-0.03
21	H2	6.29	6.42	-0.13	6.37	6.40	-0.03
	H6	5.67	5.69	-0.02	6.04	6.05	-0.01
22	H2	4.80	4.77	+0.03	5.54	5.50	+0.04
	H6	6.20	6.24	-0.04	6.28	6.22	+0.06

[a] Solvent is $CDCl_3$ for compound **14** and DMSO-d_6 for compounds **20-22**

[b] Is the change in chemical shift on adding C_6D_6 for compounds **14** and **20-22**

by Aromatic Solvent Induced Shift (ASIS) measurements similar to earlier studies[5]. The results are given in **Table IV**. Examination of chemical shift differences (Δδ) between the signals in the ^{1}H NMR spectra of nitrosopiperidin-4-one oxime **14** recorded using $CDCl_3$ and $CDCl_3$ + C_6D_6 showed that signals of H2 and H6 protons, which are *anti* to the nitroso oxygen, experienced slightly more upfield shifts (δ 0.10, 0.12 ppm) than the corresponding *syn* protons (δ 0.04, 0.07 ppm) as observed in many nitrosamines[2]. However, unlike earlier cases, the differences were only marginal. The results of ASIS studies on the nitroso semicarbazones **19-22** revealed that, in most of the cases, ^{1}H NMR signals of the benzylic protons have been shifted to a downfield region after the addition of C_6D_6 to DMSO-d_6. This observation contradicted the results from the ASIS studies on oximes[5] and nitrosamines[2]. In cases where the ^{1}H NMR signals were shifted to a higher field region (after the addition of C_6D_6), there was no significant difference between the ASIS of protons, which are *syn* and *anti* with respect to the nitroso group. Hence, the ASIS results were not relied upon heavily. The signals in the ^{1}H and ^{13}C NMR spectra of the title compounds were assigned using SEFT (Spin Echo Fourier Transform) experiments and ^{1}H-^{13}C HETCOR analysis.

The reported observations[6] that α-carbons of several oximes and nitrosamines are shielded when they are *syn* to the oxime/nitroso function were

Table V — C3-C5 values of the compounds with substituents at C3 position

Compd	Rotamer **A**	Rotamer **B**	Rotamer **C**	Rotamer **D**
15	10.1	10.8	-1.9	-1.3
16	23.9	24.7	-	-
20	+*	+*	-	-
21	20.2	23.3	-	-
24	8.29			
25	18.17			

*The exact value could not be determined since the signal of C3 was found to mingle with the solvent signals. However, the value was found to be positive since the solvent signals appeared at lower field than that of C5 carbon.

utilized to find out the configuration around >C=N bond. The ^{13}C NMR spectral data indicate that the C5 carbon is more shielded than C3 carbon, in all the cases (**Table V**) except the minor isomer of 3-methylnitrosopiperidin-4-one oxime (**C** and **D**, **Figure 3**). Hence, the compounds **15-18** (except the minor isomer of 3-methylnitrosopiperidin-4-one oxime **15**, **C** and **D**) are *E*-isomers. On the other hand, C3 was more shielded than C5 in the minor isomer of 3-methyl-nitrosopiperidin-4-one oxime (**C/D**) indicating that it is a *Z* isomer in which the substituent on the imino nitrogen is oriented towards the C3 carbon (**A, B, C** and **D** are illustrated in **Figure 3**).

The ^{1}H NMR data of the nitrosopiperidin-4-one oximes **14-18** and semicarbazones **19-22** of nitrosopiperidin-4-ones were compared with those of the piperidin-4-one oximes **10-13** and semicarbazones **23-26**, respectively. The dihedral angles between the protons of the CH-CH$_2$ fragments in these compounds (**Tables II** and **III**) were estimated from the vicinal coupling constants using Dihedral Angle Estimation by Ratio Method (DAERM)[7]. In **Tables II** and **III A**, **B, C** and **D** are isomers as represented in **Figure 3**.

Ring conformations

The parent piperidin-4-one oximes **10-12** prefer chair conformation with all the ring substituents in the equatorial orientation[4]. However, 3,5-dimethyl-piperidin-4-one oxime **13** is an equilibrium mixture of two isomers **A** and **B** of which **A** prefers chair conformation with C5 methyl (*syn* to the oxime group) in axial orientation (after epimerisation at C-5) while the isomer **B** prefers twist-boat conformation[8].

Though the stereochemistry of the semicarbazones **23** and **26** of piperidin-4-ones was already reported by analyzing the NMR spectra recorded using CDCl$_3$ as solvent[9], NMR spectra of these samples were recorded again in DMSO-d_6 with and without D$_2$O for comparison. Examination of NMR spectral data revealed that the piperidine ring in all the semicarbazones prefers chair conformation. The magnetic non-equivalence of the methyl groups in semicarbazone **26** of 3,5-dimethylpiperidin-4-one, as revealed by the presence of two signals for the methyl group in the ^{1}H NMR spectrum, and widely differing $J_{H2,H3}$ (10.7 Hz indicating diaxial coupling) and $J_{H5,H6}$ (2.9 Hz indicating axial-equatorial coupling) values indicated the epimerisation of the methyl group at C5 (*syn* to the semicarbazone function).

The *J* and estimated ϕ values of the nitrosamines were found to be quite different from those of the piperidin-4-one oximes **10-13** and semicarbazones **23-26**. Hence, the possibility of chair conformation with equatorial substituents (CE) in **Figure 4** is ruled out. Moreover, the *J* and estimated ϕ values do not correspond to any of the conformations in **Figure 4** except **TB**. The twist-boat conformation **TB** in which the phenyl groups occupy pseudo-equatorial position and the substituents at C3 and C5 occupy pseudo-axial orientation best explains the observed values.

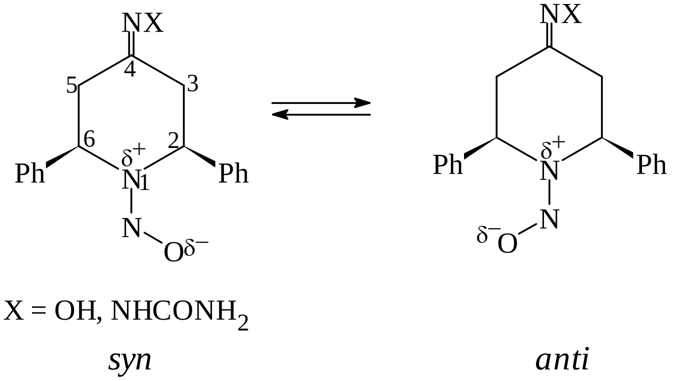
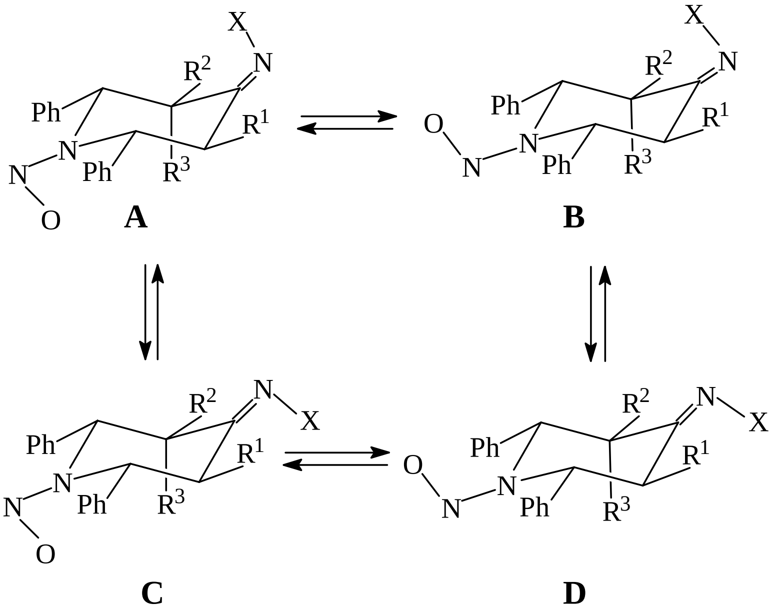


Figure 2 — Coplanar orientations of N-nitroso group



A and **B** = ***E*** isomer   **C** and **D** = ***Z*** isomer

X = OH

Figure 3 — Relative orientation of N-nitroso and oxime functions in N-nitroso oximes

In all the oximes and semicarbazones of nitrosopiperidin-4-ones except those with substituents at both C3 and C5 (**14-16** and **19-21**), the estimated $\phi_{e,a}$ and $\phi_{a,a}$ values (**Tables II** and **III**) were found to be lower than those of the respective piperidin-4-one oximes and semicarbazones. Consequently, the $J_{e,a}$ values were found to be higher and $J_{a,a}$ values lower than the corresponding values of piperidin-4-one oximes and semicarbazones. For instance, the dihedral angles $\phi_{2a,3e}$ and $\phi_{5e,6a}$ are lowered to 39° and 44°, respectively, and $\phi_{2a,3a}$ and $\phi_{5a,6a}$ are lowered to 159° and 164°, respectively, in rotamer **A** of the nitrosopiperidin-4-one oxime **14** from the corresponding values ($\phi_{2a,3e} = \phi_{5e,6a} = 57°$ and $\phi_{2a,3a} = \phi_{5a,6a} = 177°$) of the piperidin-4-one oxime 10. **A** similar observation ($\phi_{2a,3e} = 27°$; $\phi_{2a,3a} = 147°$; $\phi_{5e,6a} = 37°$; $\phi_{5a,6a} = 157°$) was also made for the rotamer **B** of the nitrosopiperidin-4-one oxime **14**. These changes indicate that the piperidine ring in these compounds has undergone twisting across both C2-C3 and C5-C6 bonds resulting in a conformation similar to twist-boat (**Figure 4, TB**).

Interestingly, in compounds **16** and **21** having isopropyl group at C3, singlets were obtained for the H2 protons showing the absence of coupling between H2 and H3 protons. Moreover, ^{1}H NMR signals due to H2 and H6 protons appeared at a lower field when they are *syn* to the nitroso function than when they are *anti*. For example, ^{1}H NMR signal of H2 proton in rotamer **A** (*syn* to nitroso function of compound **16**) appeared at a lower field (δ 6.76 ppm) compared to that of rotamer **B** in which H2 proton is *anti* to nitroso function (δ 6.37 ppm). These observations indicated that the piperidine rings of **16** and **21** are twisted across C2-C3 bond to a larger extent than the other compounds. The C2-H and C3-H bonds in compounds **16** and **21** are nearly orthogonal and the torsional angle between H2 and H3 protons approaches 90° resulting in singlets for the H2 protons. Twisting of the ring across the C2-C3 bond brings the H2 proton of rotamers **A** of **16** and **21** into the deshielding plane of the N-N-O linkage. Therefore, H2 proton signals of rotamers **A** of **16** and **21** appear at a lower field region than those of their rotamers **B**. Twisting of this type results in a conformation in which the phenyl group at C2 and the isopropyl group at C3 positions occupy axial position as in **16 A**. Such a preference for axial orientation by

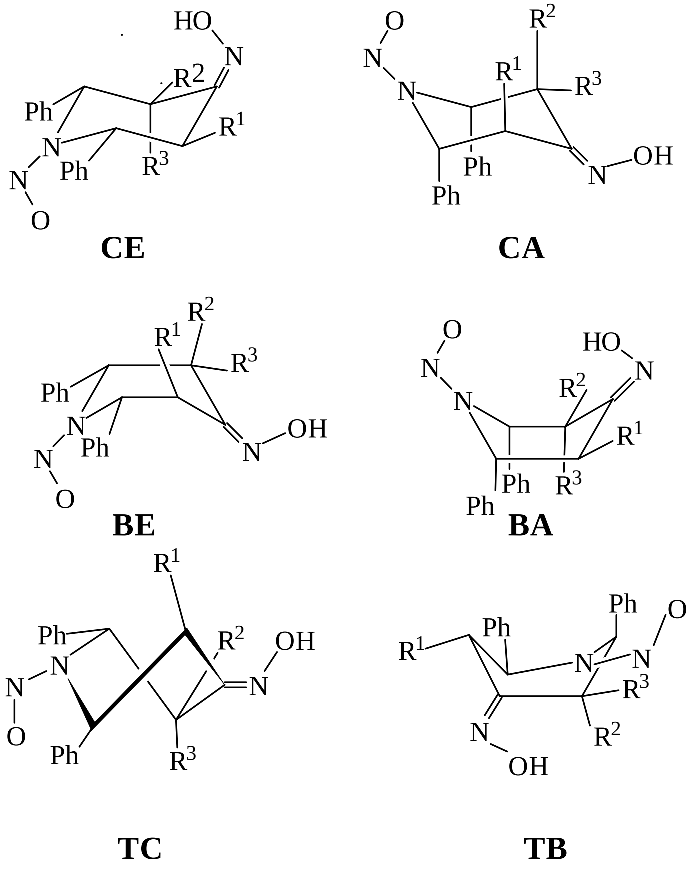


Figure 4 — Possible conformations of N-nitroso oximes **14-18**

isopropyl group was reported in 1,2,3,4,5,6-hexaisopropyl-cyclohexane also[10].

The methyl groups in the dimethylnitrosopiperidin-4-one oxime **17** and semicarbazone **22** of dimethylnitrosopiperidin-4-one (methyl groups *cis* to each other) gave rise to four ^{1}H NMR spectral signals indicating the non-equivalence of methyl groups at C3 and C5. In addition, the vicinal coupling constants of the H2 and H6 protons were found to be significantly different. The $J_{2H,3H}$ values (13.0 and 11.4 Hz) for the rotamers **A** and **B** of **17** and **22** (12.0 and 12.2 Hz) corresponded to nearly perfect orientations with a diaxial dihedral angle of about 180° while the $J_{5H,6H}$ values (1.6, 0.9 Hz for compound **17** and 0 Hz for compound **22**) were found to be low. Hence, it was inferred that the part of the ring around C2-C3 bond in the dimethyl compounds **17** and **22** resembles that of the perfect chair conformation while the part around C5-C6 linkage has undergone significant twisting. The twisting might be due to the $A^{1,3}$-interaction between the C5-methyl group and the substituents present on the imino nitrogen.

Though twisting has been reported[8] for the *cis*-3,5-dimethylpiperidin-4-one oxime **13**, on the basis of unequal $J_{2H,3H}$ (5.8 Hz) and $J_{5H,6H}$ (9.2 Hz) values, the extent of twisting was found to be less when compared to the *cis*-3,5-dimethylnitrosopiperidin-4-one oxime **17**.

The information that twisting of the ring has taken place about C5-C6 linkage (and not about C2-C3 bond) was derived from decoupling and ^{1}H-^{13}C HETCOR experiments performed on compound **17**. Among the signals of C3 and C5 carbons in the ^{13}C NMR spectra, those at higher field were assigned to the C5 carbons, since they are *syn* to the oxime hydroxyl function. From the ^{1}H-^{13}C HETCOR spectrum, the corresponding H5 proton signals were assigned. The decoupling studies carried out on this compound showed that the protons coupling with the H5 protons, *i.e.* the H6 protons, gave rise to the doublet with lower coupling constant. Hence, twisting has taken place on the side *syn* to the oxime hydroxyl group *i.e.* about C5-C6 linkage.

In the isomeric nitrosopiperidin-4-one oxime **18** (methyl groups *trans* to each other) also, the two methyl groups were found to be non-equivalent.

Furthermore, $J_{5H,6H}$ value was found to be zero in both the rotamers while $J_{2H,3H}$ was found to be 6.4 and 7.2 Hz. These values could be accounted for by considering a twist-boat conformation **18TB** in which the methyl group at C5 (*syn* to the oxime hydroxyl group), has epimerised to axial position during oximation. If the compound prefers chair conformation, there would be an interaction between C5-C7 and C3-C4 bonds. To avoid this interaction, the ring undergoes twisting about C5-C6 bond. As a result, the torsional angle between H5 and H6 protons approaches 90°, thereby, making the $J_{5H,6H}$ value to be zero. In addition, twisting about C2-C3 bond lowers the $J_{2H,3H}$ values to 6.4 and 7.2 Hz from the corresponding values (13.0 and 11.4 Hz) of compound **17**. The X-ray crystallographic studies on the compounds **17** also showed a twist-boat conformation with twisting along C5-C6 bond[11].

Anti-cancer activity

The anti-cancer activities of the oximes **14-17** of nitrosopiperidin-4-ones were examined along with a number of other N-nitrosamines[2]. Among the compounds screened, the D$\underline{H}$ values of the nitrosopiperidin-4-one oximes **14** and **17** were found to be 85.58 and 76.83, respectively, suggesting selective activity against cancer cells. (The selectivity expressed in terms of D$\underline{H}$ values is statistically significant when D$\underline{H}$ > 75).

Semiempirical MO Calculations

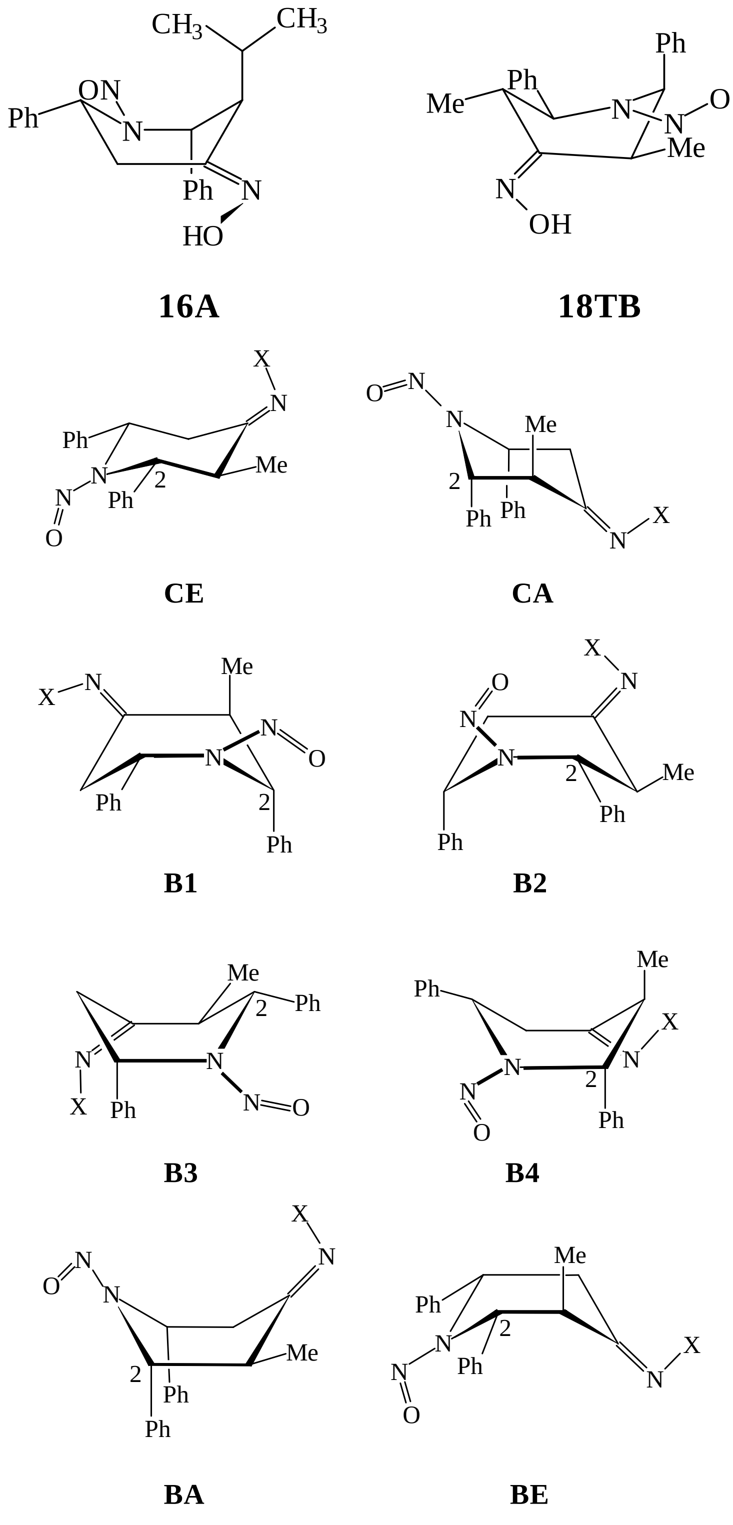
Semiempirical MO calculations were performed on oximes (**14-18**) and semicarbazones (**19-22**) of N-nitrosopiperidin-4-ones with the MOPAC package (version 6.01)[12] on a Pentium personal computer, using AM1 Hamiltonian in order to know the contributions of various conformations and rotational states in *isolated gaseous environment* and to compare the results with those obtained for the solution and solid states (NMR and X-ray studies, respectively). The criteria for optimization were increased by using PRECISE option and the optimizations were controlled by applying the key word GNORM = 0.1 of the EF routine. The key word MMOK was added in the case of semicarbazones to include the molecular mechanics correction. With the use of Dreiding model all the possible orientations of the piperidine ring were considered for the input and classified as eight conformationally different entities (**CE, CA, BA, BE** and **B1-B4, Figure 5**). Since the *E* and *Z* forms of the oximes and semicarbazones are configurationally different, they were considered individually for optimization.

The energy of the various preferred conformations of the ring was first calculated by changing the relative orientation of N-NO group with reference to the C2-N1-C6 plane. The results showed the preferred orientation as the one with dihedral angle either 0° (as in the *syn* conformer) or 180° (as in the *anti* conformer). The heats of formation values were calculated by varying the C2-N1-N-O angle smoothly from 0 to 180° with an increment of 5° each time while retaining the input ring geometry by applying minimum number of constraints at selected dihedral angles. Thereafter the output geometries were allowed to relieve to its nearest stationary points by removing all the constraints. The resulting conformationally stable points, in other words, local minima, were again classified into various conformations as in the case of input geometries. Their relative formation energies were given in **Tables VI** and **VII**.

The global minimum corresponds to the distorted boat forms over other conformations in all the compounds studied. The conformations with equatorial phenyl substituents (**CE** and **BE**) are energetically far away from the distorted boat forms showing that significant $A^{1,3}$-strain drives the molecules to prefer boat forms. These observations were in accordance with the NMR spectral results that the piperidine ring in all these compounds prefers the distorted boat conformations. For the nitrosopiperidin-4-one oximes **14** and **17**, due to the symmetric arrangement of ring substituents, *E-syn* rotamer of the one of the similar conformational pairs **B1** and **B2**, **B3** and **B4**, **CE**, **CA** is equivalent to the *Z-anti* rotamer. Thus

$\mathrm{CE}_{ES} = \mathrm{CE}_{ZA}$ $\mathrm{CE}_{EA} = \mathrm{CE}_{ZS}$
$\mathrm{CA}_{ES} = \mathrm{CA}_{ZA}$ $\mathrm{CA}_{EA} = \mathrm{CE}_{ZS}$
$\mathrm{B1}_{ES} = \mathrm{B2}_{ZA}$ $\mathrm{B1}_{EA} = \mathrm{B2}_{ZS}$
$\mathrm{B2}_{ES} = \mathrm{B1}_{ZA}$ $\mathrm{B2}_{EA} = \mathrm{B1}_{ZS}$
$\mathrm{B3}_{ES} = \mathrm{B4}_{ZA}$ $\mathrm{B3}_{EA} = \mathrm{B4}_{ZS}$
$\mathrm{B4}_{ES} = \mathrm{B3}_{ZA}$ $\mathrm{B4}_{EA} = \mathrm{B3}_{ZS}$

Among the possible conformations, **B1/B2** forms were found to be the most favoured for nitroso oxime **14** and **17**. Other conformations (**B1, B2, B3** and **B4**) were found to have slightly larger heats of formation. Therefore, the contribution to the equilibrium is predominant (≈47%) by the above two forms only.



16A **18TB**

CE **CA**

B1 **B2**

B3 **B4**

BA **BE**

X = OH, $NHCONH_2$

Figure 5

Table VI — Calculated relative formation energies of ($\Delta\Delta H_f$ in kcal mol^{-1}) various conformers of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one oximes **14-18** by the AM1 Method

Compd	Conformer	*E* isomer *syn*	*E* isomer *anti*	*Z* isomer *syn*	*Z* isomer *anti*
14	CE	2.50	2.58	2.58	2.50
	CA	2.51	2.55	2.55	2.51
	B1	0.34	2.05	0.00	1.61
	B2	1.61	0.00	2.05	0.34
	B3	3.60	0.94	3.63	0.87
	B4	0.87	3.63	0.94	3.60
15	CE	3.88	3.61	4.99	4.68
	CA	2.30	2.35	2.60	2.57
	B1	0.00	1.83	0.00	1.85
	B2	2.49	1.10	4.32	2.86
	B3	4.94	2.15	5.02	2.15
	B4	1.08	5.30	1.12	----
	BE	----	----	----	5.74
16	CE	5.34	4.90	----	8.09
	CA	1.09	1.16	0.97	0.95
	B1	0.63	2.34	0.04	2.02
	B2	----	----	6.50	5.26
	B3	5.48	3.81	5.31	3.19
	B4	0.00	2.78	0.00	2.74
	BA	5.42	4.55	----	----
	BE	----	3.74	----	----
17	CE	5.00	5.01	5.01	5.00
	CA	2.20	2.24	2.24	2.22
	B1	1.32	2.89	0.00	1.56
	B2	1.56	0.00	2.89	1.32
	B3	----	1.25	3.85	1.52
	B4	1.52	3.85	1.25	----
	BA	----	4.73	5.29	4.52
	BE	----	3.99	----	4.14
18	CE	2.00	2.48	3.54	4.10
	CA	1.82	1.89	1.34	1.42
	B1	0.00	3.10	----	6.51
	B2	2.22	0.64	3.40	1.54
	B3	3.37	0.59	2.76	0.00
	B4	4.23	4.32	0.68	3.83
	BA	----	5.13	----	----
	BE	----	----	----	4.60

Table VII — Calculated relative formation energies of ($\Delta\Delta H_f$ in kcal mol^{-1}) the various conformers of semicarbazones **19-22** of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones by the AM1 Method

Compd	Conformer	*E* isomer *syn*	*E* isomer *anti*	*Z* isomer *syn*	*Z* isomer *anti*
19	CE	2.98	2.98	2.98	2.98
	CA	2.95	3.07	3.07	2.95
	B1	0.62	2.58	0.00	1.38
	B2	1.38	0.00	2.58	0.62
	B3	3.27	0.67	3.79	0.93
	B4	0.96	3.78	0.67	3.27
20	CE	4.42	4.06	7.76	7.19
	CA	2.48	2.60	3.78	3.68
	B1	0.00	2.07	0.00	1.50
	B2	2.25	1.02	7.84	6.10
	B3	4.85	1.98	4.88	2.01
	B4	0.95	3.67	3.43	----
	BA	----	4.10	----	----
	BE	6.74	5.08	6.97	----
21	CE	6.20	5.79	13.78	----
	CA	1.28	1.39	3.25	3.13
	B1	0.86	2.70	0.00	1.60
	B2	3.54	2.43	11.56	10.57
	B3	4.23	1.86	5.31	2.51
	B4	0.00	2.84	1.93	4.64
	BA	3.37	5.35	8.64	8.32
	BE	5.88	3.41	6.84	3.41
22 *trans*	CE	9.24	6.82	6.82	----
	CA	3.26	3.40	3.40	3.26
	B1	----	----	0.00	1.36
	B2	1.36	0.00	----	----
	B3	4.67	2.29	3.88	1.48
	B4	1.48	3.88	2.29	4.67
	BA	4.90	6.87	6.61	4.90
	BE	4.75	5.23	5.23	4.75
cis	CE	1.25	2.13	6.75	6.86
	CA	5.20	5.28	2.80	2.76
	B1	----	6.07	----	3.72
	B2	2.50	1.03	7.69	----
	B3	6.53	3.72	2.80	0.00
	B4	0.00	3.23	1.26	7.13
	BA	3.15	3.88	----	7.39
	BE	9.00	----	6.07	----

When a substituent is present at C3 position the molecule becomes unsymmetrical and therefore all the considered conformers/rotamers are different from each other. For 3-methyl substituted piperidin-4-one oxime **15**, **B1** conformation is the preferred for both *E* and *Z* oximes.

The 3-isopropyl substituted oxime **16** prefers the **B4** conformation for both *E* and *Z* isomers. However, in the case of *E* oxime the contribution from other forms to equilibrium is low compared with that of the *Z* isomer where the relative formation energy between the preferred conformer and the next higher energy form is low. Hence, the contribution from the **B1** form is significant (≈39%) in *Z* oxime while it is less (≈21%) in *E* oxime. The dimethyl N-nitroso-piperidin-4-one oxime **18** prefer the **B1** conformation for its *E* isomer (≈63%) while its *Z* isomer prefers the

B3 form over other conformations (≈62%). Like in the cases of oximes **14** and **17**, the **B1/B2** form is found to be the most favoured conformation for semicarbazones **19** and for the *trans* isomer of **22**. The semicarbazones **19** and **21** prefer the boat conformation **B1** as the most stable conformation.

Both the *E* and *Z* isomers of the 3-methyl substituted semicarbazone **20** prefer the distorted boat conformation **B1**. The presence of isopropyl group at C3 forces the ring to prefer **B4** form (in which one of the phenyl groups occupies the equatorial position while the other phenyl group staying away from the 3-isopropyl group thereby reducing the Ph:Ph repulsion) for its *E* isomer and **B3** form for its *Z* isomer. The AM1 optimized structures of **15** and **20** are given in **Figure 6** and **Figure 7**, respectively, as representative examples.

The torsion angle C2-N1-N-O for all the N-nitrosopiperidin-4-one oximes and semicarbazones were found to be either 0 or 180 ± 8° indicating the preference of the coplanar orientation for the nitroso group. The distorted boat conformations predicted from the NMR spectral studies for the oximes **14-18** and semicarbazones **19-22** of nitrosopiperidin-4-ones were found to be retained in the *isolated gaseous environment* also.

Experimental Section

All melting points were determined using an electrically heated block with a calibrated thermometer and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrometer in KBr pellets. Mass spectra were recorded on a Jeol JMS-D 300 spectrometer operating at 70 eV. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker WH-270 or Jeol GSX-400 or Bruker AMX-400 instruments using $CDCl_3$, DMSO-d_6, or acetone-d_6 solutions. The NMR spectra of the nitrosopiperidin-4-one oximes[13] **14-18** were recorded using $CDCl_3$ as solvent and those of semicarbazones **19-22** of nitrosopiperidin-4-ones[13] were recorded in DMSO-d_6 since the solubilities of semicarbazone compounds were found to be very low in $CDCl_3$ and C_6D_6. Column chromatography was performed using silica gel 60-120 mesh (Qualigens) and analytical thin-layer chromatography was performed using silica gel-G (Qualigens). The compounds **6-9** and **23** and **26** were prepared using the reported procedures[1,9].

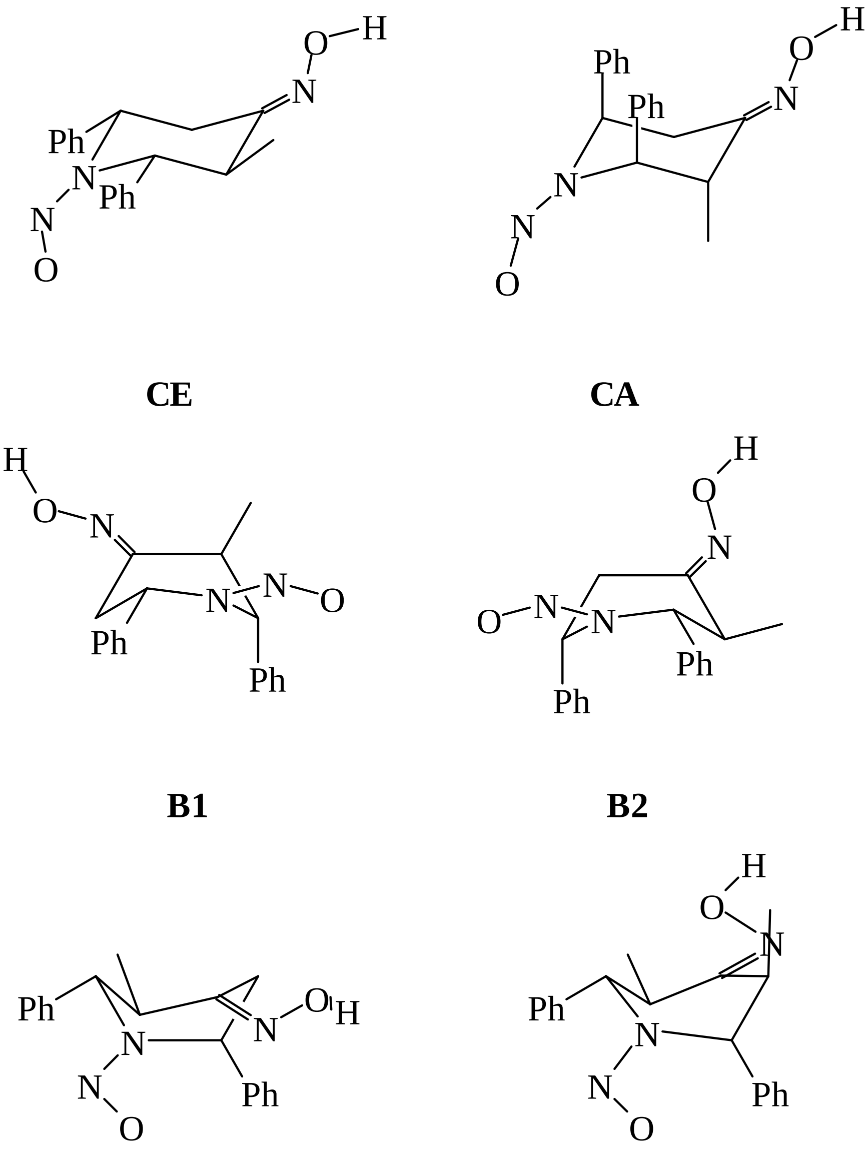
N-Nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one oxime, 14. Hydroxylammonium hydrochloride (2.46 g, 35.68 mmol) and sodium acetate trihydrate (10.85 g, 71.42 mmol) were dissolved in methanol (400 mL) and the NaCl formed was filtered off. The filtrate was added to a solution of the nitrosamine **6** (5.01 g, 17.90 mmol) in methanol (200 mL) and the mixture was allowed to reflux for 2h, cooled, concentrated and poured into water (300 mL). The solid separated out was filtered, washed with water and purified by recrystallization from ethanol to give **14** as colourless crystals (4.59 g, 87% yield). m.p. 193-95°C.

***t*-3-Methyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one oxime, 15**. Oximation of *t*-3-methyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**7**, 5.11 g, 17.39 mmol) was carried out with hydroxylamine (prepared from hydroxylammonium hydrochloride (2.3 g, 33.68 mmol) and sodium acetate trihydrate (10.59 g, 69.71 mmol). The reaction resulted in the mixture of *E* and *Z* isomers. The ratio of *E* and *Z* isomers was found to be 85:15 from the NMR spectrum. Out of the two isomers formed, 4.73 g (88% yield) of major one was separated by fractional recrystallization from ethanol. m.p. 178-80°C.

***t*-3-Isopropyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one oxime, 16**. By following the method described for compound **14**, the nitrosamine **8** (5.22 g, 15.50 mmol) was converted to the compound **16** by treatment with hydroxylammonium hydrochloride (2.14 g, 31.13 mmol) and sodium acetate trihydrate (9.43 g, 62.08 mmol) and purification by recrystallization from ethanol yielded 4.87 g (89% yield) of **16**. m.p. 132-34°C.

***t*-3,*t*-5- and *t*-3, *c*-5-Dimethyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one oximes, 17 and 18**. Compounds **17** and **18** were prepared from *t*-3,*c*-5-dimethyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**9**, 1.13 g, 3.68 mmol) with hydroxyl-ammonium hydrochloride (0.51 g, 7.41 mmol) and sodium acetate (1.44 g, 14.73 mmol) by following the procedure for the preparation of compound **14**. The product was found to be a mixture of **17** and **18** in the ratio 78:22 (1.02 g, 84% yield). Fractional recrystallization from ethanol yields **17** as colourless crystals. m.p. 214-16°C.

Semicarbazone, 19, of N-nitroso-*r*-2, *c*-6-diphenylpiperidin-4-one. Semicarbazide hydrochloride (2.46 g, 22.09 mmol) and sodium acetate trihydrate (6.71 g, 44.18 mmol) were dissolved in methanol (50 mL) and the NaCl formed was filtered off. The filtrate was added to the solution of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**6**, 3.09 g,



CE **CA**

B1 **B2**

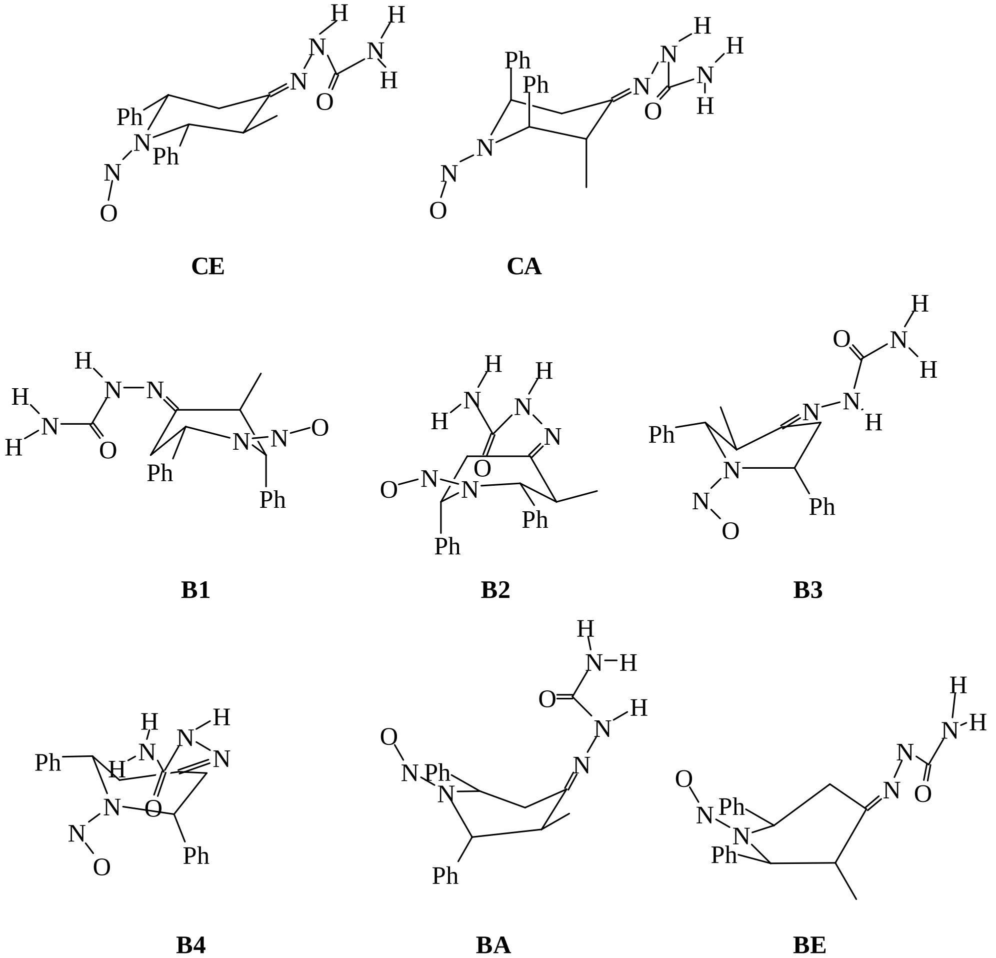
B3 **B4**

Figure 6 — AM1 optimized structures of **15**

11.05 mmol) in methanol (200 mL) and the mixture was heated under reflux for 4 h. The reaction mixture was concentrated and poured into water (300 mL). The solid separated was filtered, washed with water and purified by recrystallization from a mixture of ethanol and benzene (9:1) as colourless crystals. (2.75 g, 74%). m.p. 129-31°C.

Semicarbazone of *t*-3-methyl-N-nitroso-*r*-2, *c*-6-diphenylpiperidin-4-one, 20. Compound **20** was prepared from *t*-3-methyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (7, 5.07 g, 17.30 mmol), semicarbazide hydrochloride (3.80 g, 34.12 mmol), and sodium acetate trihydrate (10.35 g, 68.15 mmol) using the procedure described for the preparation of compound **19**. Recrystallization from ethanol and benzene (9:1) yields 4.86 g (80% yield) of the product as colourless crystals. m.p. 202-04°C.

Semicarbazone of *t*-3-isopropyl-N-nitroso-*r*-2, *c*-6-diphenylpiperidin-4-one, 21. Isopropylnitrosopiperidin-4-one 8 (4.99 g, 15.50 mmol) was converted to the corresponding semicarbazone **21** by the reaction with semicarbazide hydrochloride (3.47 g,



CE CA

B1 B2 B3

B4 BA BE

Figure 7 - AM1 optimized structures of **20**

31.13 mmol) and sodium acetate trihydrate (9.44 g, 62.12 mmol) by following the procedure for the preparation of compound **19**. The product obtained was purified by recrystallization from a mixture of benzene and petroleum ether (1:9) to yield 4.52 g (77% yield) of **21** as colourless crystals. m.p. 203-05°C.

Semicarbazone of *t*-3,*t*-5-dimethyl-N-nitroso-*r*-2, *c*-6-diphenylpiperidin-4-one, 22. Compound **22** was prepared from *t*-3,*t*-5-dimethyl-N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**9**, 4.99 g, 16.23 mmol), semicarbazide hydrochloride (3.68 g, 32.03 mmol) and sodium acetate (6.34 g, 64.79 mmol) by following the procedure described for the preparation of the compound **19**. The product formed was purified by recrystallization from a mixture of ethanol and benzene (9:1) to yield 4.67 g (79% yield) of **22** as colourless crystals. m.p. 167-70°C.

Semicarbazone of *t*-3-methyl-*r*-2, *c*-6-diphenylpiperidin-4-one, 24. Semicarbazide hydrochloride (0.82 g, 7.41 mmol) and sodium acetate trihydrate (2.25 g, 14.81 mmol) were dissolved in methanol (50 mL) and the NaCl formed was filtered off. The filterate was added to the solution of *t*-3-methyl-*r*-2,*c*-6-diphenylpiperidin-4-one (0.98 g, 3.70 mmol) in methanol (100 mL) and the mixture was heated under reflux for 4 h. The reaction mixture was concentrated and poured into water (200 mL). The solid separated was filtered, washed with water and purified by recrystallization from ethanol. (0.87 g, 73% yield) m.p. 205-07°C.

Semicarbazone of *t*-3-isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one, 25. Compound **25** was prepared from *t*-3-isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one

(1.20 g, 3.49 mmol), semicarbazide hydrochloride (0.78 g, 6.99 mmol), semicarbazide hydrochloride (0.78 g, 6.99 mmol) and sodium acetate trihydrate (2.12 g, 13.97 mmol) using the procedure given for compound **24**. The product formed was purified by recrystallization from ethanol as colourless solid. (0.90 g, 75% yield) m.p. 212-14°C.

Conclusion

The $A^{1,3}$-strain at two sites forces the oximes **14-18** and semicarbazones **19-22** of N-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones to prefer twist-boat conformations. The N-NO group assumes a coplanar orientation with the C2-N1-C6 plane of the piperidine ring which ultimately results in the existence of *syn* and *anti* rotamers. The nitroso oximes and nitroso semicarbazones with substituents at C3 position were found to be exclusively *E* isomers except in oximes **15, 17** and **18** where the mixture of both *E* and *Z* isomers was formed. The nitrosopiperidin-4-one oximes **17** and **18** were found to differ in the relative orientation of the methyl group at C5 due to epimerisation. The results of NMR spectral studies and semiempirical MO calculations indicate that the twisting of the ring, for stability, occurs around C2-C3 and C5-C6 bonds when there is a 3-alkyl group. Thus, in general, the competing influence of the $A^{1,3}$-strain at two sites forces the rings to prefer twist-boat (**TB**) conformations.

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References

1 (a) Chow Y L, Colon C J & Tam J N S, *Can J Chem*, 46, **1968**, 2821; (b) Ravindran T, Jeyaraman R, Murray R W & Singh M, *J Org Chem*, 56, **1990**, 4833; (c) Jeyaraman R, Thenmozhiyal J C, Murugadoss R & Muthukumar M, *J Indian Chem Soc*, 76, **1999**, 527.

2 (a) Senthilkumar U P, Jeyaraman R, Murray R W & Singh M, *J Org Chem*, 57, **1992**, 6006; (b) Senthilkumar U P, Jeyaraman R & Bigler P, *J Org Chem*, 60, **1995**, 7461; (c) Ravindran T, *Synthesis, Stereodynamics and Reactivity of N-nitroso-piperidines and N-nitrosoazabicyclo[3.3.1]nonanes*, Ph.D. thesis, Bharathidasan University, India, **1993**.

3 Johnson F & Malhotra S K, *J Am Chem Soc*, 87, **1965**, 5492.

4 (a) Pandiarajan K, Mohan R T S & Ul Hasan M, *Magn Reson Chem*, 24, **1986**, 312; (b) Geneste P, Kamenka J M & Brevard C, *Org Magn Reson*, 10, **1977**, 31.

5 Karabatsos G J & Hsi N, *Tetrahedron* 24, **1968**, 3347.

6 Hawkes G E, Herwig K & Roberts J D, *J Org Chem*, 39, **1974**, 1017.

7 Slessor K N & Tracey A S, *Can J Chem*, 49, **1971**, 2874.

8 (a) Geneste P, Kamenka J M, Hugon I & Graffin P, *J Org Chem*, 41, **1976**, 3637; (b) Roques P R, Declercq J P, Germain G, Graffin P, Kamenka J M & Geneste P, *Acta Crystallogr*, B37, **1981**, 712.

9 (a) Haller R & Ziriakus W, *Arch Pharm*, 305, **1972**, 541; (b) Haller R & Ziriakus W, *Tetrahedron* 28, **1972**, 2863; (c) Haller R & Ziriakus W, *Arch Pharm*, 28, **1972**, 741.

10 Goren Z & Biali S E, *J Am Chem Soc*, 112, **1990**, 893.

11 Sukumar N, Ponnusamy M N, Vijayalakshmi R & Jeyaraman R, *Z Kristallogr*, 209, **1994**, 823.

12 (a) Dewar M J S, Zoebisch E G, Healy E F & Stewart J J P, *J Am Chem Soc*, 107, **1985**, 3902; (b) Stewart J J P, *J Comput Aided Mol Des*, 4, **1990**, 1.

13 Vijayalakshmi R, *Studies on the Stereochemistry and Reactions of Piperidines having Heteroconjugate Groups*, Ph.D. thesis, Bharathidasan University, India, **1994**.