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# Conformational Analysis of Substituted *N*-Nitroso-*trans*-decahydroquinolin-4-ones

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**$^1$H and $^{13}$C NMR resonance assignments and conformational assignments were carried out for four *N*-nitroso-2-phenyl-*trans*-decahydroquinolin-4-ones. In addition to conventional 1D NMR methods, 2D shift-correlated NMR techniques ($^1$H–$^1$H COSY, $^1$H–$^1$H NOESY and $^1$H–$^{13}$C HETCOR) were used for the signal assignments. At room temperature the title compounds exist in two isomeric forms. The preferred conformations of both the isomers of nitrosamines were determined by a comparison of the spectral data with those for the parent amines, and with the aid of substituent parameters. Molecular strain in nitrosamines is minimized by partial escape of the piperidine moiety into non-chair conformation.** 

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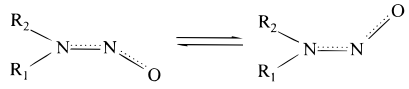
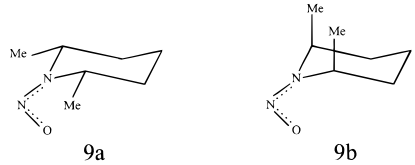
## INTRODUCTION

Extensive studies have been carried out on the carcinogenicity and mutagenicity of many *N*-nitrosamines and *N*-nitrosamides.[1–3] In addition, some *N*-nitrosoureas have been found to be anticancer agents.[4,5] These *N*-nitroso compounds exist as *syn* and *anti* rotamers[6–8] due to N—N restricted rotation as a result of delocalization of the nitrogen lone pair over the double bond of the N—N=O system with barriers to rotation as high as 23.3 kcal mol$^{-1}$ (kcal = 4.184 kJ).[7,9]



$R_1 = R_2$ = alkyl, aryl, COR, CONHR

In the case of cyclic nitrosamines, the energy barrier is controlled by several factors, including steric interaction between the coplanar nitroso group and the α-substituents. This kind of steric strain that arises in a conjugated planar group with the α-equatorial substituents of five-, six- or seven-membered ring system has been termed $A^{1,3}$ strain (allylic strain).[10,11] Other factors which affect the stereochemistry include 1,3-diaxial interaction between the α-substituents in the appropriate conformation, resonance energy due to lone pair delocalization and ring size. $A^{1,3}$ interactions have been observed and correlated with stereochemistry[6,9] in a variety of piperidine derivatives and oximes of cyclic ketones. For example, in the case of *r*-2,*c*-6-dimethyl-*N*-nitrosopiperidine the steric strain energy ($A^{1,3}$ strain) between the coplanar nitroso group and the equatorial methyl substituents at the 2- and 6-positions (conformer **9a**) is greater than the 1,3-diaxial methyl–methyl interaction energy (conformer **9b**) and thus the ring exists exclusively in conformation **9b**.[9]



9a 9b

While the orientation of the α-substituents in the *r*-2, *c*-6-dialkyl-*N*-nitrosopiperidines is diaxial, in the *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones the phenyl groups are found to be diequatorial.[12] Generally one can expect a complex situation in a *trans*-fused bicyclic system involving $A^{1,3}$ strain between the substituent at nitrogen and the equatorial α-substituents, since the system is rigid when compared with piperidine derivatives. For example, in *N*-nitroso-2-methyl-*trans*-decahydroquinolines (methyl group equatorially orientated) the molecular strain ($A^{1,3}$ strain) is minimized by partial escape of the piperidine moiety into a non-chair conformation.[13] There is no detailed report on conformational study of *N*-nitroso-*trans*-decahydroquinoline derivatives using coupling constants, 2D COSY techniques and x-ray data. In this paper, the effect of $A^{1,3}$ strain on the conformation of some substituted *N*-nitroso-2-phenyl-*trans*-decahydroquinolin-4-ones investigated through $^1$H and $^{13}$C NMR data is described.

## RESULTS AND DISCUSSION

The nitrosamines **5–8** were prepared from the respective parent amines **1–4** by reaction with sodium nitrite and HCl in ethanol–water (Scheme 1). $^1$H and $^{13}$C NMR

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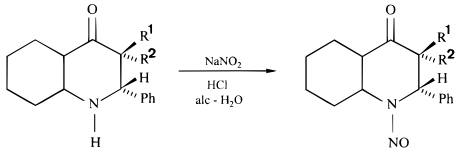
spectra were recorded for **5–8** and the spectral data are summarized in Tables 1–3.




| | | | |
|---|---|---|---|
| 1 | $R_1 = R_2 = H$ | 5 |
| 2 | $R_1$ = Me ; $R_2 = H$ | 6 |
| 3 | $R_1$ = Et ; $R_2 = H$ | 7 |
| 4 | $R_1 = R_2$ = Me | 8 |

**Scheme 1**

The assignments of the $^1$H NMR chemical shifts are based on the coupling constants (Table 1) and on $^1$H–$^1$H shift correlation experiments. The $^1$H NMR spectra of all these nitrosamines exhibit pairs of signals for every proton having very similar splitting patterns. The conformer ratios were determined by averaging integrations of more than three pairs of corresponding signals obtained in the $^1$H NMR spectra.

In the $^1$H NMR spectrum of **5** the major conformer signals appear at 6.28, 4.38, 3.17, 3.15 and 2.92 ppm. The doublet at 6.28 ppm and the multiplet (doublet of double doublets) at 4.38 ppm are assigned to H-2 and H-9, respectively. The two doublet of doublets at 3.15 and 2.92 ppm are assigned to H-3(ax) and H-3(eq). The remaining signal at 3.17 ppm is assigned to one of the H-8 protons. In a similar manner, the signals at 6.55, 4.02, 3.56, 2.96 and 2.55 ppm in the minor conformer are assigned to H-2, H-9, H-3, H-3 and H-8, respectively. This assignment is further confirmed by the results obtained in the $^1$H COSY spectrum of **5**. The signals of the remaining compounds **6–8** were assigned in an analogous manner.

The deshielding effect due to *N*-nitrosation is much pronounced on H-2 than on H-9 (Table 2), indicating that the nitroso group is *anti* to C-9. The observed deshielding magnitude suggests that the benzylic hydrogen (H-2) should lie in the same plane of the nitroso group.

It is seen from Table 1 that both the minor and major forms have nearly the same coupling constants. This pattern can arise only when there are two forms similar in conformation with no ring flip such as chair–chair or chair–boat interconversion between them. If such interconversion occurs then the equatorial hydrogens become axial and *vice versa*, resulting in a large change in coupling constants within each pair. There is no appreciable change in the vicinal coupling constants about the C(9)—C(10) bond in nitrosamines **5–8** compared with the parent amines **1–4**.

**Table 1. Vicinal and geminal coupling constants (Hz) of *N*-nitroso-*trans*-decahydroquinolin-4-ones and *trans*-decahydroquinolin-4-ones**

| Compound | Conformer | *J*(2,3) | *J*(3,3) | *J*(9,8) | *J*(9,8)[a] | *J*(9,10)[a] |
|---|---|---|---|---|---|---|
| **5** | Major | 5.86, 1.96 | 17.58 | 4.27 | 11.48[a] | 11.36[a] |
| | Minor | 6.35, 1.71 | 19.29 | 9.05 | 12.21[b] | 10.62[b] |
| **1** | — | 11.88, 3.01 | 19.43 | 2.93 | 10.74 | 10.74 |
| **6** | Major | 1.47 | — | 2.93 | 11.67[c] | 10.74[c] |
| | Minor | 1.47 | — | 3.91 | 12.45[d] | 10.99[d] |
| **2** | — | 10.25 | — | 2.93 | 10.98 | 10.98 |
| **7** | Major | 1.47 | — | 2.93 | 12.20[e] | 10.75[e] |
| | Minor | 1.47 | — | 3.91 | 11.47 | 11.47 |
| **3** | — | 10.75 | — | 3.42 | 10.99 | 10.99 |
| **8** | Major | — | — | 3.91 | 12.20[f] | 10.75[f] |
| | Minor | — | — | — | — | — |
| **4** | — | — | — | 3.46 | 10.52 | 10.52 |

[a] Values having the same superscript may be interchanged.

**Table 2. $^1$H NMR chemical shifts (ppm) of *N*-nitroso-*trans*-decahydroquinolin-4-ones and *trans*-decahydroquinolin-4-ones**

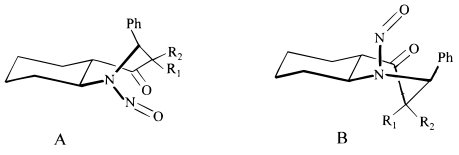
| Compound | Conformer (%) | H-2 | H-3 | H-8 | H-9 | $CH_3$ |
|---|---|---|---|---|---|---|
| **5** | Major (65) | 6.28 | 3.15, 2.92 | 3.17 | 4.38 | — |
| | Minor (35) | 6.55 | 3.56, 2.93 | 2.55 | 4.02 | — |
| **1** | — | 4.02 | 2.60, 2.53 | — | 2.63 | — |
| **6** | Major (57) | 6.17 | 3.54 | 2.57 | 3.95 | 1.23[a] |
| | Minor (43) | 6.30 | 3.29 | 3.06 | 4.35 | 1.23[a] |
| **2** | — | 3.53 | 2.65 | — | 2.65 | 0.76 |
| **7** | Major (54) | 6.33 | 3.02 | 2.59 | 3.92 | 1.08 |
| | Minor (46) | 6.42 | 3.24 | 3.07 | 4.32 | 1.02 |
| **3** | — | 3.63 | 2.54 | — | 2.60 | 0.72 |
| **8** | Major (76) | 5.87 | — | 2.54 | 4.48 | 1.22, 1.10 |
| | Minor (23) | 6.03 | — | 3.08 | 3.94 | 1.50, 1.05 |
| **4** | — | 3.71 | — | — | 2.54 | 1.09, 0.89 |

[a] Overlaid methyl protons.

**Table 3. $^{13}$C NMR chemical shifts (ppm) of *N*-nitroso-*trans*-decahydroquinolin-4-ones and *trans*-decahydroquinolin-4-ones**

| Compound | Conformer | C-2 | C-3 | C-4 | C-8 | C-9 | C-10 | $CH_3$ | Other carbons | Aromatic carbons |
|---|---|---|---|---|---|---|---|---|---|---|
| **5** | Major | 51.9 | 42.7 | 205.5 | 32.9 | 60.6 | 50.2 | — | 25.3, 24.8, 24.6, 24.5, 24.3 24.1 | 138.1, 137.5, 129.3, 129.0 128.4, 127.7, 126.0, 125.3 |
| | Minor | 58.9 | 41.8 | 206.4 | 30.9 | 59.5 | 49.3 | — | | |
| **1** | — | 61.8 | 5.6 | 209.7 | 33.9 | 61.7 | 55.4 | — | 25.0, 24.6, 23.4 | 142.6, 128.7, 128.5, 126.5 |
| **6** | Major | 65.6 | 44.8 | 208.9 | 30.7 | 58.0 | 48.7 | 16.3 | 25.0, 24.6, 24.4, 24.3, 24.2 | 138.4, 137.9, 129.2, 129.1, 128.3, 127.7, 126.0, 125.5 |
| | Minor | 56.3 | 46.0 | 208.5 | 34.7 | 60.4 | 49.3 | 17.3 | | |
| **2** | — | 69.2 | 51.5 | 211.1 | 33.9 | 62.1 | 55.6 | 10.4 | 25.0, 24.5, 23.6 | 141.9, 128.6, 127.9, 127.6 |
| **7** | Major | 62.4 | 53.6 | 207.8 | 30.7 | 57.8 | 48.7 | 11.7 | 25.1, 24.7, 24.6, 24.5, 24.4, 24.2, 23.4 | 138.6, 138.1, 129.2, 139.1, 128.3, 127.7, 126.1, 125.5 |
| | Minor | 53.6 | 52.1 | 208.3 | 34.5 | 60.3 | 49.3 | 12.1 | | |
| **3** | — | 67.7 | 58.8 | 210.7 | 33.9 | 62.4 | 56.2 | 12.3 | 24.0, 24.6, 23.6 | 141.8, 128.6, 127.9, 127.7 |
| **8** | Major | 63.1 | 47.5 | 210.4 | 33.9 | 60.9 | 50.6 | 22.8 | 25.5, 24.9, 26.3, 25.9, 25.3, 25.1, 24.4, 24.9 | 137.0, 129.1, 128.7, 128.5, 128.4, 128.3, 127.9 |
| | Minor | 70.0 | 48.4 | 210.2 | 30.7 | 58.5 | 49.2 | 22.1 | | |
| **4** | — | 70.2 | 49.8 | 214.9 | 34.0 | 62.1 | 51.2 | 20.4 20.9 | 251, 24.5, 23.9 | 139.5, 128.9, 127.7 127.6 |

There is a drastic change in the vicinal coupling constants (Table 1) about the C(2)—C(3) bond in nitrosamines **5**–**8**. The vicinal coupling constants about the C(2)—C(3) bond in **5** are 5.86 and 1.96 Hz (major) and 6.35 and 1.71 Hz (minor). These values are considerably lower than those observed in the corresponding parent amine **1** (11.88 and 3.01 Hz). The geminal coupling constant *J*(3a,3e) is also varied in **5** [17.58 Hz (major) and 19.29 Hz (minor)] compared with **1** (13.43 Hz). The *J*(2, 3) values in **6** (1.47 Hz) and **7** (1.47 Hz) are also very much lower than those in the parent amines **2** and **3** (*ca.* 10.5 Hz). The smaller values of vicinal coupling constants about the C(2)—C(3) bond in nitrosamines suggest a considerable change in dihedral angles, which in turn reveals a conformational change in the heterocyclic ring. Interestingly, the *J*(2,3) values in **5**, **6** and **7** are very close to those in *N*-acetyl-2-phenyl- (6.35 and 1.47 Hz), *N*-acetyl-3-methyl-2-phenyl- (1.46 Hz) and *N*-acetyl-3-ethyl-2-phenyl-*trans*-decahydroquinolin-4-one (1.91 Hz), for which twist–boat conformation was proposed for the heterocyclic ring by dihedral angle calculation using *J*(2,3) coupling constants.[14] A similar non-chair conformation was reported previously in *N*-nitroso-2-methyl-*trans*-decahydroquinolines.[13] Hence a twist–boat conformation is probable for the heterocyclic ring in both the forms of the nitrosamines. The preference for non-chair conformation is presumably due to the $A^{1,3}$ strain between the nitroso group and the α-phenyl group in the chair conformation. Further, this suggestion is supported by the solid-state conformation of *N*-nitroso- 3,3-dimethyl-2- phenyl-*trans*- decahydroquinolin-4-one (**8**), which adopts a twist–boat conformation (heterocyclic ring) as revealed by an x-ray study.[15] Thus, the observed coupling constants about the C(2)—C(3), C(8)—C(9) and C(9)—C(10) bonds suggest a chair conformation for the carbocyclic ring and a twist–boat conformation with axial orientation of the phenyl and alkyl groups for the heterocyclic ring in all the nitrosamines **5**–**8**.




In conformation **5A** there is interaction between the phenyl group with C-10 hydrogen but the C-8–NO interaction is relieved. However, in conformation **5B** the phenyl–C-10 interaction is relieved whereas a C-8–NO interaction is reintroduced. Dreiding models of the conformers **6A** and **7A** show interaction between C-10 and the phenyl group with the relief of the alkyl–C-9 interaction, whereas in the conformers **6B** and **7B** the phenyl–C-10 interaction is somewhat relieved but alkyl–C-9 strain is reintroduced. Both the forms allow the nitroso group to retain its partial double bond character. A similar twist–boat conformation could be assumed for the two forms of *N*-nitroso-3,3-dimethyl-2-phenyl-*trans*-decahydroquinolin-4-one (**8A** and **8B**) also. The proposed twist–boat conformation (heterocyclic ring) is further confirmed by the results obtained from the $^1$H–$^1$H NOESY spectrum of **6**. The absence of an NOE between H-2 and H-9 protons and between methyl protons and phenyl ring protons excludes the possibility of chair conformation for the heterocyclic ring. Moreover, the strong NOE between H-2 and H-3, H-2 and methyl protons, H-3 and aromatic protons and H-9 and methyl protons in both the forms is also inconsistent with the chair form. However, in the twist–boat conformation a number of protons are in close proximity and are expected to give a significant NOE.

In the $^{13}$C NMR spectra also two signals appear for each carbon, thus confirming the presence of two conformers. The signals for the two conformers are identified by the relative intensities. The assignments of various signals for **6** and **7** were made with the use of $^1$H–$^{13}$C HETCOR spectra. The signals of the other compounds were assigned from the multiplicities of signals in the off-resonance spectra and by comparison of the observed spectral data with those for **6** and **7**.

It can be seen from Table 3 that in **5**–**8** the ring carbons (C-2, C-3, C-9 and C-10) are shielded compared with the respective parent amines **1**–**4**. However, the alkyl carbons in **6**–**8** are deshielded. These effects may be due to the various γ-eclipsing interactions possible in the twist–boat conformation. The shielding magnitude

observed on C-2 carbons are considerably higher (3.5–14.0 ppm) than that observed on C-9 carbons (1.0–3.5 ppm) in both the major and minor forms. The greater shielding magnitude observed on C-2 relative to C-9 supports the *anti* configuration of the nitroso group with respect to the C-9 carbon. Similar shifts are also observed in *N*-nitroso-2$\beta$-methyl-*trans*-decahydroquinolines.[13] The high upfield shift of C-2 can be understood with the aid of a model which shows (i) steric shielding over the *syn* $\alpha$-carbon (C-2) as a result of the $\gamma$-eclipsed conformation of the N—O bond with respect to the *syn* C—N bond and (ii) partial eclipsing interactions between the N(1)—C(9) and C(2)—C(3) bonds due to the small dihedral angle arising out of the $sp^2$ hybridization achieved by the ring nitrogen.

The effect of a coplanar orientation of the nitroso group is felt almost to the same extent at C-3 in both the major and minor forms in **5–8**. The $\beta$-carbons of both the major and minor forms experience an upfield shift of about 4–8 ppm compared with the corresponding carbon (C-3) in the parent amines **1–4**. This upfield shift may be ascribed to the decrease in the dihedral angle between the C(9)—N(1)—C(2) and N(1)—C(2)—C(3) planes.

The *ipso* carbons of the phenyl group of **5–8** in both the major and minor conformations are also found to be shifted upfield by about 5.0 ppm with respect to the parent amines. This upfield shift can be attributed to (i) the decrease in the C—N(1) bond length and (ii) the decrease in the dihedral angle between the N(0)—N(1)C(2) and N(1)—C(2)—$C_{ipso}$ planes. These two factors are the consequence of the $sp^2$ character attained by the ring nitrogen on lone pair delocalization in the coplanar conformation. Thus, the shielding and deshielding magnitude (C-2, C-3, *ipso* carbons and methyl carbon signals) supports the twist–boat conformation for the heterocyclic ring in both forms of nitrosamines **5–8**.

## CONCLUSION

This NMR study of substituted *N*-nitroso-2-phenyl-*trans*-decahydroquinolin-4-ones indicates a chair conformation for the carbocyclic ring and a twist–boat conformation with axial orientation of the phenyl and alkyl groups for the heterocyclic ring in the two forms of the nitrosamines.

## EXPERIMENTAL

### Materials

Nitrosamines **5–8** were prepared according to a published procedure.[12] A mixture of ketones **1–4** (0.5–0.7 g, 0.0075 mol) and concentrated hydrochloric acid (12 ml) was dissolved in 1:1 ethanol–water (25 ml). The temperature of the solution was kept at 25 °C and, while stirring, a solution of sodium nitrite (7.9 g, 1.15 mol) in 1:1 ethanol–water (25 ml) was added dropwise over a period of 1.5 h. The stirring was continued for another 3 h. The reaction mixture was extracted four times with chloroform (100 ml) and the extract was washed with water several times. The chloroform layer was dried over anhydrous sodium sulphate. After removal of chloroform the crude product was recrystallized twice from ethanol and provided pure **5**, **6**, **7** and **8** with melting points of 74–75, 77–78, 90–91 and 99–100 °C, respectively. These compounds were characterized by their elemental analyses: **5** ($C_{15}H_{18}N_2O_2$), calculated C 69.8, H 7.0, N 10.9, found C 69.7, H 6.8, N 10.6%; **6** ($C_{16}H_{20}N_2O_2$), calculated C 70.6, H 7.4, N 10.3, found C 70.3, H 7.1, N 10.7%; **7** ($C_{17}H_{22}N_2O_2$), calculated C 72.0, H 8.0, N 9.3, found C 71.8, H 7.7, N 9.5%; **8** ($C_{17}H_{22}N_2O_2$), calculated C 71.3, H 7.6, N 9.8, found C 69.8, H 7.3, N 9.5%.

### Spectra

All one- and two-dimensional experiments were recorded on a Jeol GSX-500 FT NMR spectrometer operating at 500.00 and 125.00 MHz for $^1H$ and $^{13}C$, respectively. Spectra were recorded at a constant temperature of 297 K. Chemical shifts are referred to TMS as internal standard. Data acquisition and processing of 2D NMR were performed under similar conditions according to Jeol standard pulse programmes (RSX system). $^1H$–$^1H$ COSY and NOESY: spectral width, 4000 Hz; data points, 1024: FID, 512; pulse repetition time, 1–2 s. $^1H$–$^{13}C$ HETCOR: spectral width, 22 723 Hz; data points, 2048; FID, 256; pulse repetition time, 1.2–1.55 s.

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## REFERENCES

1. D. Hoffmann and S. S. Hecht, *Cancer Res*. **45**, 935 (1985).
2. S. E. Murphy and R. Heiblum, *Carcinogenesis* **11**, 1663 (1990).
3. J. W. Lown, S. M. S. Chauhan, R. R. Koganty and A. M. Sapse, *J. Am. Chem. Soc*. **106**, 6401 (1984).
4. A. M. Sapse, E. B. Allen and J. W. Lown, *J. Am. Chem. Soc*. **110**, 5671 (1988).
5. T. P. Johnston, C. L. Carter, J. L. Frye, N. R. Lomax, J. Plowman and V. L. Narayanan, *J. Med. Chem*. **27**, 1422 (1984).
6. S. Mihara and T. Shibamoto, *J. Magn. Reson*. **38**, 41 (1980).
7. C. E. Looney, W. D. Phillips and E. J. Reilly, *J. Am. Chem. Soc*. **79**, 6136 (1957).
8. J. E. Haky, J. E. Saavedra and B. D. Hilton, *Org. Magn. Reson*. **21**, 79 (1983).
9. Y. L. Chow, C. J. Colon and J. N. S. Tam, *Can. J. Chem*. **46**, 2821 (1968).
10. F. Johnson, *Chem. Rev*. **68**, 375 (1968).
11. R. Haller and W. Ziriakus, *Tetrahedron* **28**, 2863 (1972).
12. T. Ravindran, R. Jeyaraman, R. Murray and M. Singh, *J. Org. Chem*. **56**, 4833 (1991).
13. F. W. Vierhapper, *J. Org. Chem*. **45**, 3111 (1980).
14. D. Natarajan, N. Bhavani and A. Manimekalai, *Bull. Chem. Soc. Jpn*. submitted for publication.
15. A. Thiruvalluvar, V. Parthasarathi, D. Natarajan, N. Bhavani and M. Bhadbhade, *Acta Crystallogr*. in press.

 