using $MeOH/CH_2Cl_2$ (3:2), 115 mg (0.1% from frozen sponge).

Discodermide (1): mp ~200 °C dec; $[\alpha]_D$ 97.5° (c 0.2, $CHCl_3$/MeOH (1:1); UV λ_{max} (MeOH) 313 (ε 9650), 238 (16 500) nm; IR (KBr) 3350, 2910, 2460, 1665, 1600, 1465, 1227, 995, 840 cm^{-1}; ^1H and ^{13}C NMR, Table I; HRFABMS (Thio) m/z 505.2312, Δ 0.7 μm for $C_{27}H_{34}N_2O_6Na$ (MNa^+); LRFABMS (Thio) m/z (relative intensity) 505 (58), 313 (17), 239 (23), 217 (100), 181 (34).

Acetylation of Discodermide. A solution of discodermide (25 mg) in pyridine (2 mL) and acetic anhydride (0.5 mL) was stirred overnight. The solvents were removed in vacuo and the resulting gum was purified on a reversed-phase amino Sep-Pak with 20% H_2O/MeOH to give discodermide acetate, 22 mg.

Discodermide acetate (2): colorless gum; $[\alpha]_D$ 77.5° (c 0.17, MeOH); UV λ_{max} (MeOH) 312 (ε 9660), 238 (16 500) nm; IR (KBr) 3360, 2900, 2500, 1724, 1655, 1600, 1465, 1240 cm^{-1}; ^1H and ^{13}C NMR, Table I; HRFABMS (mb) m/z 547.2304, Δ 0.9 μm for $C_{29}H_{36}N_2O_7Na$ (MNa^+); LRFABMS (Thio) m/z (relative intensity) 547 (100, MNa^+), 525 (25, MH^+), 505 (20), 487 (55), 469 (15), 429 (18), 319 (34).

Acknowledgment. We thank Dan Pentek, Yale University, New Haven, for mass spectral data. We are also grateful to Drs. S. A. Pomponi for identification of the sponge and N. S. Burres for P388 assays. This is Harbor Branch Oceanographic Institution, Inc., Contribution No. 841.

Registry No. 1, 134458-00-7.

Supplementary Material Available: ^1H and ^{13}C NMR spectra, COSYRCT, COSY, C-H correlations, HMBC, and NOE experimental reference spectrum for 2 (17 pages). Ordering information is given on any current masthead page.

Chemistry of *N*-Nitroso Compounds. 1. Synthesis and Stereodynamics of *N*-Nitrosopiperidines and *N*-Nitrosopiperidin-4-ones

Thiruvenkadam Ravindran and Ramasubbu Jeyaraman*

Department of Chemistry, Bharathidasan University, Tiruchirapalli-620 024, India

Robert W. Murray* and Megh Singh

Department of Chemistry, University of Missouri-St. Louis, St. Louis, Missouri 63121

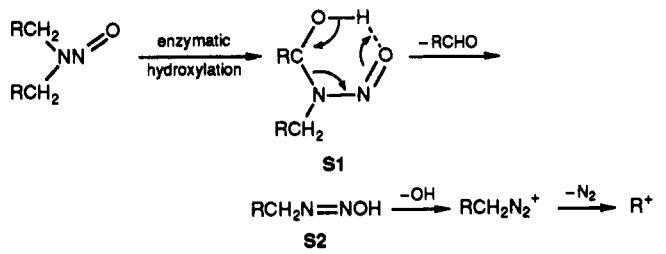
Received January 17, 1991

The stereochemistry of a series of *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones (**10–15**) and *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines (**16–18**) in solution has been investigated by ^1H NMR, ^{13}C NMR, and dynamic ^1H NMR spectroscopic studies. Unlike the *r*-2,*c*-6-dialkyl-*N*-nitrosopiperidines, which have diaxial alkyl groups, these *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines (**16–18**) and *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones (**10–15**) have diequatorial phenyl groups even though the nitroso group is coplanar to the dynamically averaged plane of the piperidine ring. The rotamer populations of the N–NO orientations in the nitrosamines were derived from continuous wave ^1H NMR spectral data and are correlated with the steric bulk of the substituents present at the C-3 and C-5 positions. *N*-Nitroso-*r*-2,*c*-6-diphenylpiperidine-4-one (**10**) was found to have a higher rotational barrier than *N*-nitroso-*r*-2,*c*-6-diphenylpiperidine (**16**). We attribute this difference to a greater degree of coplanarity (C_3–C_2–N_1–C_6–C_5) in **10** than in **16**. The rotational barriers in **10** were found to decrease as the bulk of the substituents at C_3 and C_5 increased. The rotational barrier in *N*-nitroso-*r*-2,*c*-6-diphenylpiperidine (**16**) was found to be lower than the reported rotational barriers of *N*-nitroso-*r*-2,*c*-6-dimethylpiperidine and *N*-nitroso-2,2,6,6-tetramethylpiperidine.

Introduction

Many nitrosamines are known to be carcinogenic.[1] It has also been shown that blocking of the positions α to the ring nitrogen atom by methyl groups in cyclic nitrosamines reduces the carcinogenic activity.[2] The alkyl cation formed from the nitrosamine (Scheme I) is believed to be responsible for the initial step in the process of carcinogenesis by alkylating cellular components and DNA bases.[3,4] The first step in the formation of this alkyl cation involves the enzymatic hydroxylation of an α carbon to give **S1** (Scheme I). The hydroxylation also appears to depend on the acidity of the α proton. Thus, in the case of *N*-nitrosonornicotine, where the sterically free methylenic

Scheme I



α-position is available for α-hydroxylation, the hydroxylation actually occurs at the more hindered but more acidic C-2 α-position.[5] This acidity, in turn, may also depend on the extent of electron delocalization in the N–N–O group.[6] The second step in the process leading to the

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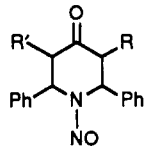
(6) It is noted that of the several NX=Y systems known including *N*-acylamines, *N*-ketiminylamines, and *N*-sulfinylhydrazines, only the *N*-nitroso compounds are known to be carcinogenic. It is also the case that the *N*-nitroso compounds have significantly higher rotational barriers (ca. 20–25 kcal/mol) than do members of these other groups (barriers of ca. 10–15 kcal/mol). The extensive delocalization in the *N*-nitroso compounds is responsible for the higher barriers. At the same time this delocalization would be expected to increase the acidity of the α hydrogens.

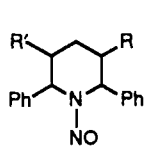
0022-3263/91/1956-4833$02.50/0

required cation is intramolecular abstraction of the hydroxylic proton by the nitroso oxygen. This step is followed by an elimination of a carbonyl compound to give **S2** (Scheme I). This step will depend on the proximity of the hydroxyl proton to the nitroso oxygen, which, in turn, may depend on the conformation of the ring in a cyclic nitrosamine. While no DNA alkylation has been observed with cyclic nitrosamines, *N*-nitrosomorpholine is known to produce a carbocation after α-hydroxylation.[7]

It is also interesting to note that certain *N*-nitroso ureas are antitumor agents or antibiotics.[8] A large number of nitrosamines are often encountered in a variety of environmental samples.[9] In view of the general interest in the utility and reactivity of *N*-nitroso compounds, several *N*-nitrosopiperidines and *N*-nitrosopyrrolidines have been synthesized and their conformations studied.[10] The conformations of the 2-alkyl- and *r*-2,*c*-6-dialkyl-*N*-nitrosopiperidines have been analyzed critically.[11] On the other hand, conformational analyses of the *r*-2,*c*-6-diaryl-*N*-nitrosopiperidines apparently have not been described. In this paper the syntheses of the *r*-2,*c*-6-diphenyl-*N*-nitrosopiperidin-4-ones **10–15** and the *r*-2,*c*-6-diphenyl-*N*-nitrosopiperidines **16–18** are described as well as the stereochemistry and conformational analysis of these compounds.



R	R′
10, H	H
11, CH_3	H
12, C_2H_5	H
13, $CH(CH_3)_2$	H
14, CH_3	CH_3
15, Ph	Ph



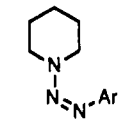
R	R′
16, H	H
17, CH_3	H
18, CH_3	CH_3

The presence of partial N–N double-bond character in nitrosamines, due to an extensive delocalization of the lone pair of electrons on nitrogen with the hetero π electron system, has been established by NMR spectroscopy.[12] In *N*-nitroso, *N*-acyl, and N-sulfonyl derivatives of 2-methylpiperidine and *r*-2,*c*-6-dimethylpiperidine, the methyl groups occupy axial positions due to $A^{1,3}$ strain[13] exhibited by the nitroso or acyl groups on the equatorial methyl group.[11] The axial preference of the methyl groups can be rationalized by comparing the 1,3-diaxial CH_3–CH_3 interaction [3.5 kcal mol^{-1}][11b] with that of the energy due to resonance in the N–N–O [or N–X–Y] linkage [15 to 20 kcal mol^{-1}].[11b]

Lunazzi et al. have studied the stereochemistry of the *N*-nitroso, *N*-imino, and *N*-acyl derivatives of piperidine, *r*-2,*c*-6-dimethylpiperidine, and 2,2,6,6-tetramethylpiperidine.[14] They found that, of the two possible orientations of the substituents at nitrogen, namely, planar and perpendicular, that adopted by the substituents in *N*-nitrosopiperidines and piperidyltriazines **19** is planar regardless of the number of substituents in the 2 and 6 positions.

Evidence for their argument came from NMR studies. If the orientation of the substituent at the piperidinyl nitrogen is perpendicular, then the C-2 and C-6 protons will be equivalent as will the C-3 and C-5 protons. The same is true for the C-2, C-6 and C-3, C-5 carbons. If the orientation is coplanar to the dynamically average plane of the piperidine ring, these same protons and carbons become nonequivalent. Another way of distinguishing the copolanar and perpendicular orientations of a piperidinyl nitrogen substituent is by the use of dynamic NMR. If the substituent is coplanar, then the rotational barrier is expected to decrease as the substituent at the piperidinyl nitrogen increases in size, since the ground state (coplanar) is destabilized. In the perpendicular structure, however, the bulkiness of the substituent destabilizes the transition state (coplanar) and hence an increase in rotational barrier will be observed.

The *N*-acylpiperidines **20** also adopt the coplanar conformation.[15] Piperidinyl hydrazones **21** with no substituents at the 2 and 6 positions adopt a coplanar conformation, but 2,2,6,6-tetramethylpiperidine hydrazone exists in the perpendicular conformation. When there is only one methyl at the 2 and 6 positions, there exists an equilibrium between the planar (**22a**) and perpendicular (**22b**) conformations. The piperidyl sulfinylhydrazines **23** adopt coplanar conformations regardless of the number of substituents at the 2 and 6 positions.



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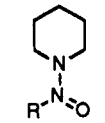

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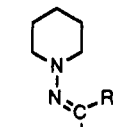

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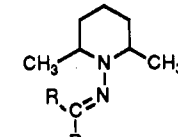
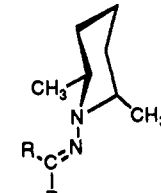
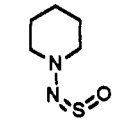


22a



22b



23

Results and Discussion

The *r*-2,*c*-6-diphenylpiperidin-4-ones **1–6** were prepared by condensing benzaldehyde, ammonia, and the appropriate aliphatic ketone. The *r*-2,*c*-6-diphenylpiperidines

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Table I. ^{1}H NMR Spectral Data for Nitrosopiperidines and Nitrosopiperidinones[a]

compd	C-2 (H) syn	C-2 (H) anti	C-6 (H) syn	C-6 (H) anti	syn/anti ratio
10	5.99 (t, 7.2 Hz)	6.45 (t, 5.4 Hz)			1:1
11	5.21 (d, 10.2 Hz)	5.92 (d, 6.3 Hz)	6.05 (t, 6.6 Hz)	6.64 (dd, 6.6 and 2.4 Hz)	0.9:1
12	6.07 (d, 6.1 Hz)	6.36 (d, 3.1 Hz)	5.83 (dd, 9.3 and 6.8 Hz)	6.45 (dd, 6.8 and 4.4 Hz)	0.7:1
13[b]	6.56 (d, 0.3 Hz)		6.05 (t, 7.5 Hz)	6.39 (dd, 7.2 and 3.0 Hz)	0.7:1
14	5.22 (d, 10.0 Hz)	6.16 (d, 3.0 Hz)			1:1
15	6.15 (d, 7.7 Hz)	6.31 (d, 6.4 Hz)			1:1
16[c]					
17	5.28 (d, 7.8 Hz)	5.57 (d, 5.4 Hz)	5.78 (t, 6.6 Hz)	6.14 (dd, 7.2 and 4.0 Hz)	0.9:1
18	5.27 (d, 7.6 Hz)	6.02 (d, 6.1 Hz)	5.52 (d, 5.9 Hz)	5.79 (d, 6.1 Hz)	0.6:1

[a] Chemical shifts on the δ scale. [b] In compound 13 one of the doublets merged with the aromatic signals. [c] Separate syn and anti signals could not be observed.

Table II. ^{13}C Chemical Shifts of Benzylic Carbons (in ppm) of Nitrosopiperidines and Nitrosopiperidinones

compd	C-2 syn	C-2 anti	C-6 syn	C-6 anti
10	53.8	60.3		
11	59.6	66.7	53.1	62.2
12	56.3	63.6	54.3	60.4
13	58.4	62.6	57.8	61.2
14	61.7	65.9		
15	59.2	66.0		
16	51.9	60.4		
17	60.3	68.1	54.2	62.0
18	58.7	66.8	55.4	66.6

Table III. Rotational Barriers of *N*-Nitrosopiperidines and *N*-Nitrosopiperidinones

compd	coalescence temp (°C)	rotational barrier (kcal mol^{-1})
10	123	19.3
14	110	19.1
15	81	18.4
16	80	18.1
DMPNO[a]	100	19.4[b]
TMPNO[c]		19.6[b]

[a] DMPNO = *r*-2,*c*-6-dimethyl-*N*-nitrosopiperidine (24). [b] From ref 14. [c] TMPNO = 2,2,6,6-tetramethyl-*N*-nitrosopiperidine (25).

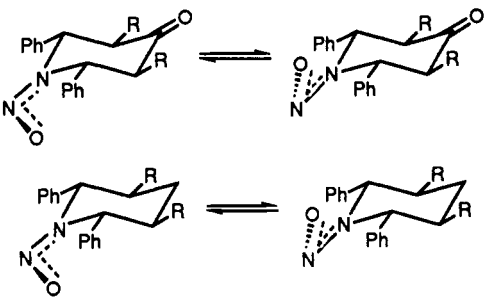
7–9 were prepared by the Wolff–Kishner reduction of the corresponding piperidin-4-ones. On treatment with nitrous acid, these piperidines and piperidin-4-ones[16] gave rise to the *N*-nitroso derivatives.

The ^{1}H NMR and ^{13}C NMR spectra were recorded for the *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones **10–15** and *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines **16–18**. The spectral data of these compounds are summarized in Tables I and II. The dynamic ^{1}H NMR spectra were recorded for selected nitrosamines (**10**, **14**, **15**, and **16**) and the data obtained are given in Table III.

***N*-Nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones.** The preferred conformation of all the piperidine and piperidone precursors (**1–9**) has been shown to be chair, with a slight flattening or distortion of the ring depending upon the positions and size of the substituents.[17] In the current studies, determining the conformations of the nitroso derivatives is the main goal since introduction of the *N*-nitroso group exerts a large influence on these conformations and the orientations of ring substituents. We have made use of NMR techniques to achieve this goal.

Two different benzylic carbon signals and two different methylene carbon signals were observed in the ^{13}C NMR spectrum of the *N*-nitrosopiperidin-4-one **10**. This nonequivalence arises due to the syn and anti orientations of the nitroso group. Moreover, the syn carbon is shielded by 7.19 ppm compared to the parent amine. Therefore, **10** exists as an equilibrium mixture of conformers as shown in Scheme II.

Scheme II



In the ^{1}H NMR spectrum of **10** the benzylic (C-2, C-6) protons give two triplets with coupling constants of 7.2 and 5.4 Hz. Two doublet of doublets and a multiplet (the multiplet is revealed to be a combination of two doublet of doublets by computer simulations studies) were observed for the methylene (C-3, C-5) protons. A perfect chair conformation for this compound would give rise to a doublet of doublets for the benzylic protons with two different coupling constants, a larger axial–axial coupling (ca. 11 Hz) and a smaller axial–equatorial coupling (ca. 4 Hz). On the other hand, if **10** exists in a twist conformation, then the axial and equatorial methylene protons would become equivalent and one would observe two triplets for the benzylic protons (one syn and one anti). The observation of two triplets for the benzylic protons and four doublet of doublets for the methylene protons suggests that the compound exists neither in a perfect chair conformation nor in a completely twisted conformation, but rather in a partially twisted chair conformation. The observation of two signals for each benzylic proton indicates that the nitroso group is coplanar to the dynamically averaged plane of the piperidine ring with significant hindrance to N–N rotation.

In *t*-3-methyl-*N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**11**), which, unlike **10**, is an unsymmetrical nitrosamine, two sets of signals were observed. There were two doublets for the methyl group. The benzylic protons (C-2 H and C-6 H) showed four absorptions: two doublets, one triplet, and one doublet of doublets. One of the doublets has a coupling constant of 10.2 Hz, indicating diaxial coupling, and hence the phenyl groups are equatorially oriented. The splitting patterns for the syn C-6 and anti C-6 protons are different. One signal is a triplet and the other is a doublet of doublets. The triplet appears upfield relative to the doublet of doublets. The triplet is assigned to the syn C-6 proton and the doublet of doublet is assigned to the anti C-6 proton. Shielding of the syn α protons in cyclic nitrosamines has been previously observed.[18] Thus

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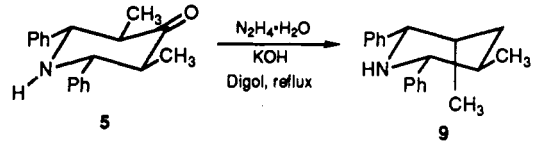
Scheme III



it appears that the syn orientation of the nitroso group leads to a twisting of the piperidine ring on the syn side only. When the nitroso group is anti to C-6, the twisting relaxes and now the C-6 proton signal appears as a doublet of doublets due to splitting by the axial and equatorial protons at C-5. The same observation is made for the syn and anti C-6 protons in *N*-nitrosopiperidin-4-ones **12** and **13**. One of the benzylic doublets in **13** merged with the aromatic signals as demonstrated by use of the irradiation technique. The isopropyl group of nitrosamine **13** gives four methyl signals due to the diastereotopicity of the methyl groups and the syn–anti orientation of the nitroso group.

The ^{13}C NMR spectra of the *N*-nitrosopiperidin-4-ones **11**, **12**, and **13** show two signals for each carbon. The syn and anti conformers of these compounds have different energies, thus leading to unequal populations. The more populated rotamers show lines of higher intensities than the less populated rotamers.

The ^1H NMR spectrum of *t*-3,*t*-5-dimethyl-*r*-2,*c*-6-diphenyl-*N*-nitrosopiperidin-4-one (**14**) shows two different signals for the methyl groups and two doublets were observed for the benzylic protons. The ^{13}C NMR shows two signals for each carbon. Thus N–N restricted rotation exists in this compound. The same observation was made for *N*-nitroso-*r*-2,*t*-3,*t*-5,*c*-6-tetraphenylpiperidin-4-one (**15**).

***N*-Nitroso-*r*-2,*c*-6-diphenylpiperidines.** The ^1H NMR spectrum of *N*-nitroso-*r*-2,*c*-6-diphenylpiperidine (**16**) is complex compared to those of the other *N*-nitrosopiperidines in this series. The chemical shift difference between the syn and anti benzylic protons in **16** is very low (0.05 ppm), while this difference ranges from 0.3 to 1.2 ppm in the other nitrosamines (**10–15**, **17–18**). Moreover, two doublet of doublets overlapped and gave a multiplet centered at 6.03 ppm. The exact coupling constants could not be determined. The possibility that the two phenyl groups might have gone to the axial positions was ruled out by an analysis of the ^{13}C NMR spectrum. If the two phenyl groups were at the axial positions, then the C-4 carbon would experience two γ-gauche effects, which would force C-4 to resonate at less than 10 ppm. The observed value is 17.34 ppm, indicating that the phenyl groups cannot be axial. Moreover, the ^{13}C NMR shows the syn benzylic carbon at 51.9 ppm and the anti at 60.4 ppm. Syn-β and anti-β carbon signals were also observed separately. These observations indicate the coplanar orientation of the nitroso group.

In the 3-methyl derivative **17**, the methyl group shows two doublets. Two doublets, one triplet, and one doublet of doublets were observed for the benzylic protons. The doublet of doublets appeared downfield compared to the triplet as in the case of the carbonyl analogue **11**. In the ^{13}C NMR also each carbon shows two signals that are due to syn and anti forms.

The Wolff–Kishner reduction of *t*-3,*t*-5-dimethyl-*r*-2,*c*-6-diphenylpiperidin-4-one (**5**) gave *t*-3,*c*-5-dimethyl-*r*-2,*c*-6-diphenylpiperidine (**9**) (Scheme III), i.e., a methyl group has isomerized. Isomerization during the Wolff–Kishner reduction of this ketone has not been reported previously. A similar isomerization in ketone **5** was observed, however, when it was converted to its oxime and semicarbazide derivatives.[19] This result has been attributed to the $A^{1,3}$ strain exerted by the oxime or semicarbazide moiety on the equatorial α-methyl group.[19] Since the formation of the hydrazone is the first step in the Wolff–Kishner reduction of **5** and the hydrazone is expected to exert an $A^{1,3}$ strain similar to that of the oximes and semicarbazides, isomerization to give **9** may have taken place during hydrazone formation. Nitrosation of piperidine **9** gave the nitrosamine **18**. The ^1H NMR spectrum of **18** showed four methyl signals and four doublets for the benzylic hydrogens. The ^{13}C NMR spectrum gave 14 different carbon signals due to the equilibrium between syn and anti forms.

The syn and anti rotamer populations of all of the nitrosamines (**10–18**) were derived from the continuous wave ^1H NMR integration data (Table I). These data indicate that as the substituent at C-3 gets larger, the percentage of the syn isomer decreases presumably because of a steric influence.

Dynamic ^1H NMR Spectra. The dynamic ^1H NMR spectra were recorded for four nitrosamines, namely, **10**, **14**, **15**, and **16**, and the activation free energy, $\Delta G^{\ddagger}$, was calculated by substituting the coalescence temperature (T_c) and chemical shift difference at coalescence temperature ($\Delta\nu$) into the Eyring equation (Table III). The stereodynamics in these *N*-nitrosopiperidines may in principal be due either to ring flipping of the piperidine ring or to restricted rotation along the N–N–O bond. The observation of an upfield shift in the ^{13}C chemical shifts for the benzylic carbons of the nitroso compounds compared to their parent amines is consistent only with the latter possibility.

The effect of temperature on the benzylic proton signals of **10**, **16**, **14**, and **15** is shown in Figures 1, 2, 3, and 4, respectively. At 20 °C the benzylic protons of the *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**10**) appeared as two triplets at 5.99 and 6.45 ppm. The triplet multiplicity is not observed at 90 °C and the signals coalesced at 123 °C. At 20 °C, the benzylic protons of the piperidine **16** showed a multiplet centered at 6.03 ppm that coalesced at 80 °C. The rotational barriers in piperidin-4-one **10** and piperidine **16** were compared in order to determine the effect of C-4 hybridization on the N–N rotational barrier. Piperidin-4-one **10** has a rotational barrier of 19.3 kcal mol^{-1} while piperidine **16** has a barrier of 18.1 kcal mol^{-1}.

The higher energy barrier for the carbonyl compound may be explained in the following way. The energy barrier is proportional to the extent of N–N–O delocalization in the *N*-nitroso group. The degree of delocalization will be higher when the dihedral angle between the N–N–O plane and the C_2–N_1–C_6 plane is closer to 0°. That is, flattening of the piperidine ring should cause an increase in N–N–O delocalization and a consequent increase in rotational barrier. Since *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**10**) is more coplanar at the C_2–N_1–C_6 end compared to *N*-nitroso-*r*-2,*c*-6-diphenylpiperidine (**16**), the former has a higher rotational barrier. Another way of rationalizing this trend is to note that the ground states of both compounds have a coplanar nitroso group, while in the excited states the nitroso group lies in the plane perpendicular to the dynamically averaged plane of the piperidine ring. In the ground state the piperidinyl nitrogen has partial sp^2 character and the C_2–N_1–C_6 angle is nearly 120°. Because

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(19) Geneste, P.; Kamenka, J. M.; Hugon, I.; Graffin, P. *J. Org. Chem.* **1976**, *22*, 3637.

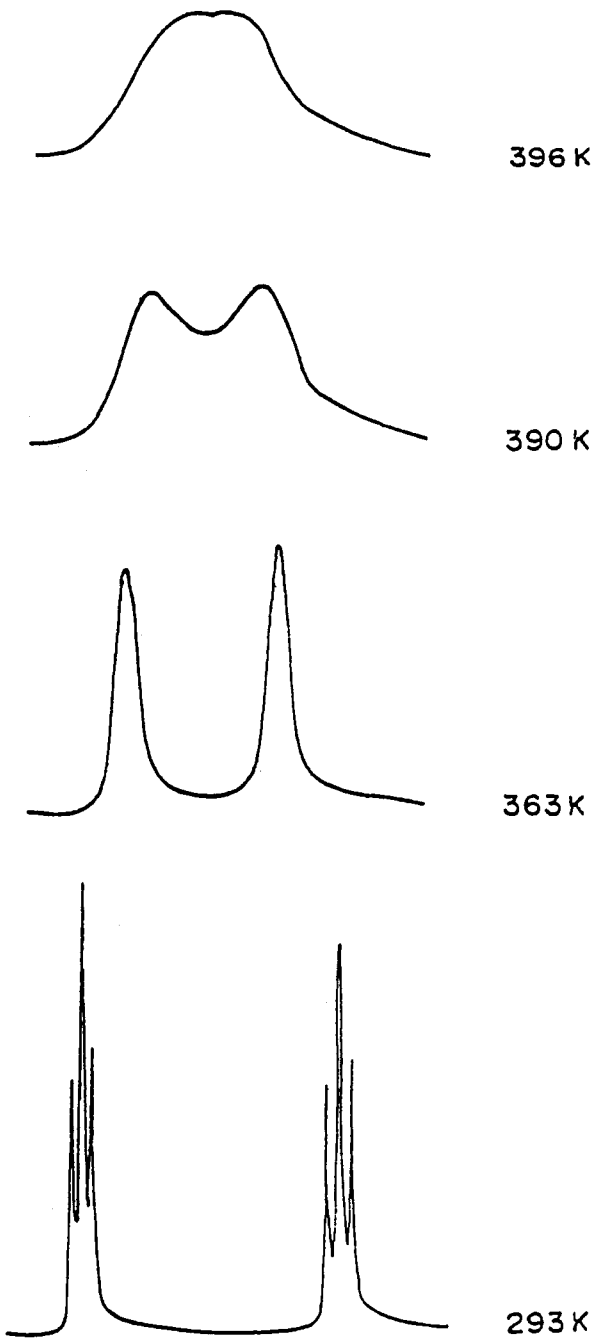

Figure 1. Dynamic ^1H NMR spectra of *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**10**).

of this increase in the C_2–N_1–C_6 angle, the C_3–C_4–C_5 angle will decrease in piperidine **16**. Such a contraction is not possible in ketone **10** since C-4 is already sp^2 hybridized. The contraction in **16** will bring carbons 3 and 5 in closer proximity, leading to a greater 1,3-diaxial H,H interaction. Thus ground state **16** is less stable than **10**. The higher ground-state energy in **16** leads to a lower energy barrier.

The effect of increasing bulk in the substituents at C-3 and C-5 in the piperidinones was determined by comparing the barriers in **14** and **15** with that in **10**. The syn and anti benzylic proton signals of nitrosamine **14** coalesced at 110 °C, indicating a rotational barrier of 19.1 kcal mol^{-1}. The benzylic proton signals of nitrosamine **15** coalesced at 81 °C and the rotational barrier is 18.4 kcal mol^{-1}. Thus as the size of the substituents at C-3 and C-5 increases, the rotational barrier decreases. Increasing the size of the substituents present at C-3 and C-5 distorts the chair conformation of the piperidine ring such that coplanarity between the C_2–N_1–C_6 plane and the N–N–O plane will be decreased. Therefore increasing substituent size at C-3 and C-5 is expected to decrease the rotational barrier.

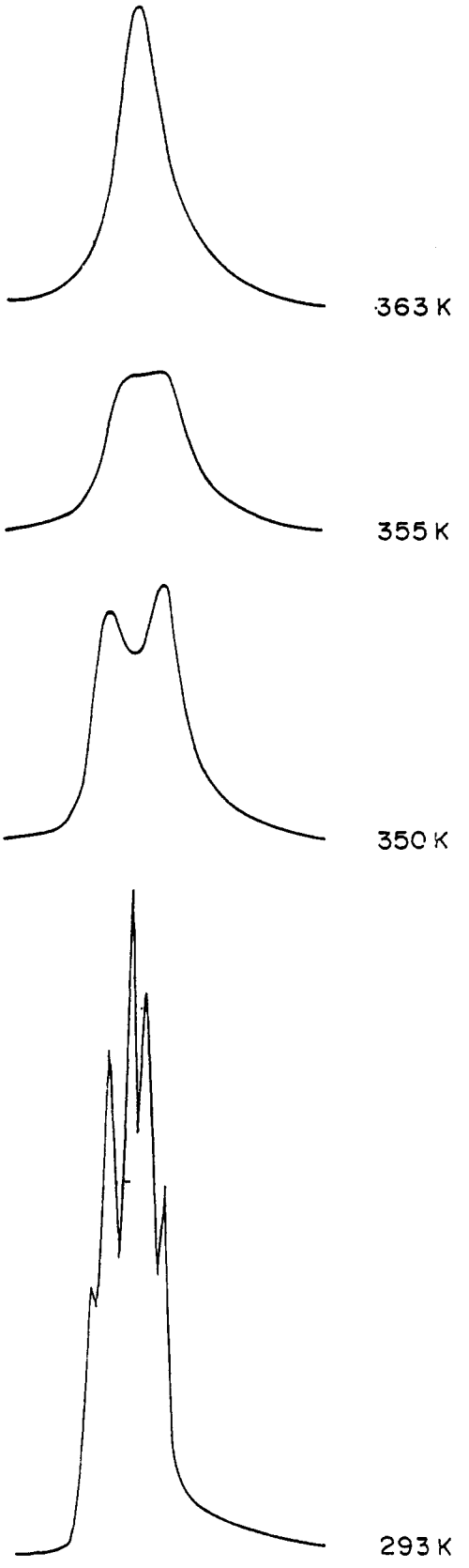

Figure 2. Dynamic ^1H NMR spectra of *N*-nitroso-*r*-2,*c*-6-diphenylpiperidine (**16**).

The rotational barrier in *N*-nitroso-*r*-2,*c*-6-diphenylpiperidine (**16**) was compared with those reported[14] for *r*-2,*c*-6-dimethyl-*N*-nitrosopiperidine (**24**) and 2,2,6,6-tetramethyl-*N*-nitrosopiperidine (**25**) (Table III). These

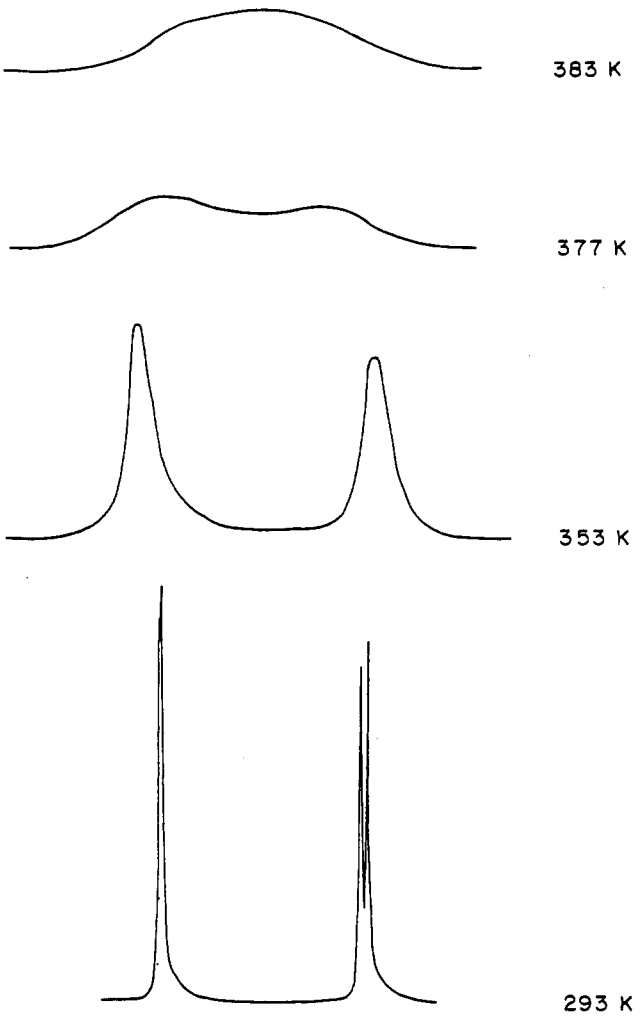

Figure 3. Dynamic ^1H NMR spectra of *t*-3,*t*-5-dimethyl-*N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (**14**).

results indicate that an increase in the number of methyl groups at the α positions from two to four did not greatly affect the rotational barrier. However, when the methyl groups are replaced by phenyl groups, there is a considerable decrease in rotational barrier (e.g., **16** vs **24**). Nitrosamine **24** does not have any $A^{1,3}$ strain because of the diaxial orientation of the methyl groups. On the other hand, the tetramethyl counterpart **25** should experience an $A^{1,3}$ strain, but this difference causes no significant change in rotational barrier. When the methyl groups of **24** are replaced by phenyl groups, there is a considerable change in the conformation of the ring and this change decreases the rotational barrier by about 1.3 kcal mol^{-1}. These results suggest that the change in conformation has a more pronounced effect on rotational barriers in *N*-nitrosopiperidines than can be explained by the presence or absence of $A^{1,3}$ strain.

Conclusions

A literature survey on the conformations of *r*-2,*c*-6-dialkyl-*N*-nitrosopiperidines and related compounds suggested the following possibilities regarding the conformations of *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines: (1) the phenyl groups might have to occupy the axial positions due to $A^{1,3}$ strain, with the nitroso group coplanar to the dynamically averaged plane of the piperidine ring, or (2) the phenyl groups could occupy the equatorial positions and the nitroso group would then have to adopt a perpendicular orientation to avoid $A^{1,3}$ strain. If the conformations

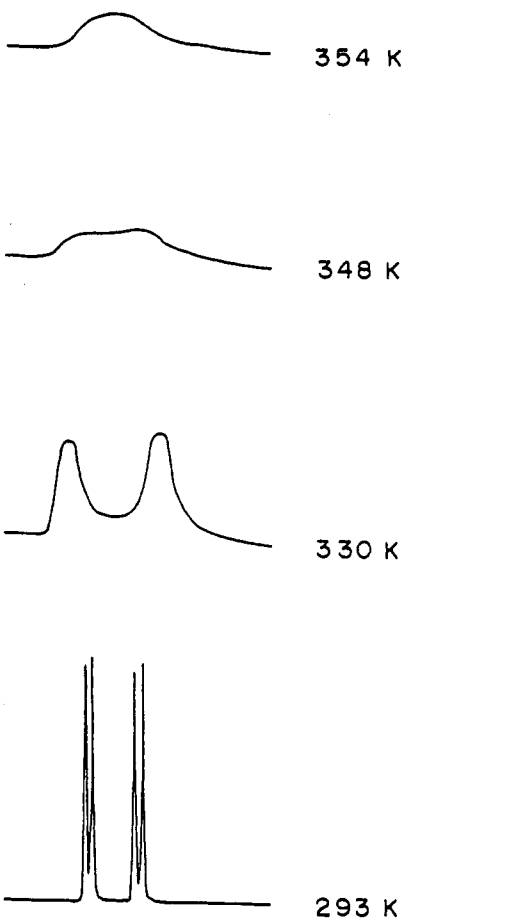

Figure 4. Dynamic ^1H NMR spectra of *N*-nitroso-*r*-2,*t*-3,*t*-5,*c*-6-tetraphenylpiperidin-4-one (**15**).

fell into category 1, then these nitrosamines would form a conformationally important group of compounds with two 1,3-diaxial phenyl groups. The results reported here indicate that, quite unexpectedly, the orientation of the phenyl groups is diequatorial despite the coplanar orientation of the nitroso group. The rotational barriers in these *N*-nitrosodiphenylpiperidines are comparable with those reported for other nitrosamines.

All of the α,α-disubstituted nitrosamines studied to date are noncarcinogenic. There apparently are no reports on the carcinogenicity of cyclic nitrosamines containing aryl groups at both α positions, however. In contrast to alkyl groups that decrease the acidity of the α protons in cyclic nitrosamines, aryl groups increase the acidity of these protons. Nitrosamines having aryl groups at the α-positions might therefore be expected to be more easily hydroxylated at the α-position in metabolism studies. As with the case of *N*-nitrosonornicotine,[5] the steric effect of the phenyl groups may not be the controlling factor. Predictions regarding the carcinogenicity of these compounds based on what is known about other 2,6-disubstituted *N*-nitrosopiperidines may not be warranted.

Experimental Section

General. All melting points were taken on an electrically heated block with a calibrated thermometer and are uncorrected. IR spectra were recorded on a IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a 300-MHz instrument in $CDCl_3$ solution with TMS as internal standard. Mass spectra were recorded by using a direct injection probe at 70 eV. Preparation of the *r*-2,*c*-6-diphenylpiperidin-4-ones and *r*-2,*c*-6-diphenylpiperidines followed the literature methods.[17] The *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines **10**, **14**, and **16** were also previously

reported.[20d-f] Dynamic ^1H NMR spectra were recorded at 270 MHz in DMSO-d_6 solution. Free energies of activation were obtained by substituting coalescence temperatures (T_c) and chemical shift differences at the coalescence temperature ($\Delta\nu$) into the Eyring equation.[21]

***r*-2,*c*-6-Diphenylpiperidin-4-one (1).** Ammonium acetate (7.7 g, 100 mmol), benzaldehyde (21.1 mL, 200 mmol), and acetone (14.5 mL, 200 mmol) were dissolved in 95% ethanol (20 mL) and the solution heated on a hot plate with gentle swirling until the color of the mixtures changed to orange. The mixture was cooled under running tap water and poured into ether (100 mL). The ether-insoluble 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (mp 235–236 °C, lit.[20b] mp 234–236 °C) was filtered off and concentrated HCl (14 mL) was added to the filtrate. The precipitated *r*-2,*c*-6-diphenylpiperidin-4-one hydrochloride was collected by filtration and recrystallized from ethanol–ether by dissolving it in the minimum amount of ethanol and then adding dry ether until turbidity appeared in the cold solution. The hydrochloride (mp 215–216 °C, lit.[20c] mp 217 °C) was dispersed in acetone (50 mL) and concentrated aqueous ammonia was added dropwise until a clear solution was obtained. The clear solution was poured into cold water (500 mL) and the solid precipitate was collected and crystallized from ethanol: yield 6.25 g (25%); mp 102–103 °C, lit.[20c] mp 105 °C.

***t*-3-Methyl-*r*-2,*c*-6-diphenylpiperidin-4-one (2).** Ammonium acetate (7.7 g, 100 mmol) was dissolved in 95% ethanol (80 mL) by heating. Benzaldehyde (21.1 mL, 200 mmol) and butan-2-one (9 mL, 100 mmol) were added to this solution and the mixture was heated until the color of the solution changed to yellow. The solution was stored at room temperature for about 5 h. The solid that precipitated was filtered off, washed with ethanol, and recrystallized from ethanol: yield 16 g (60.3%); mp 87 °C, lit.[20a] mp 86–87 °C.

***t*-3-Ethyl-*r*-2,*c*-6-diphenylpiperidin-4-one (3).** The general method described for 2 was followed. The solid precipitate was filtered off, washed with ethanol, and recrystallized from ethanol: yield 14.5 g (52%); mp 90–92 °C. Anal. ($C_{19}H_{21}NO$) C, H, N.

***t*-3-Isopropyl-*r*-2,*c*-6-diphenylpiperidin-4-one (4).** The general method described for 2 was followed. The solid precipitated was filtered off, washed with ethanol, and recrystallized from ethanol: yield 17.5 g (60%); mp 127 °C, lit.[20a] mp 125–126 °C.

***t*-3,*t*-5-Dimethyl-*r*-2,*c*-6-diphenylpiperidin-4-one (5).** The general method described for 2 was followed. The solution was kept at room temperature for about 5 h. The solid precipitate was filtered off, washed with ethanol, and recrystallized from ethanol: yield 19.5 g (70%); mp 132–133 °C, lit.[20a] mp 131–133 °C.

***r*-2,*t*-3,*t*-5,*c*-6-Tetraphenylpiperidin-4-one (6).** The general method described for 2 was followed. The solid precipitate was filtered off, washed with ethanol, and recrystallized from ethanol: yield 2.6 g (64%); mp 206–207 °C, lit.[20a] mp 205–206 °C.

***r*-2,*c*-6-Diphenylpiperidine (7).** A mixture of 1 (2.51 g, 10 mmol) and 80% hydrazine hydrate (3.1 mL, 50 mmol) in diethylene glycol (100 mL) was heated on a steam bath for 2 h. Potassium hydroxide pellets (2.8 g, 50 mmol) were added to the mixture and the contents were refluxed vigorously on a heating mantle for another 2 h. The reaction mixture was cooled and poured into ice-cold water (500 mL). The mixture was extracted with three 50-mL portions of ether and the combined ether layers were washed thoroughly with water. Concentrated HCl (5 mL) was added dropwise to the ether solution while stirring. The piperidine hydrochloride that precipitated out was filtered off and crystallized from the ethanol–ether mixture (mp 310–312 °C, lit.[20b] mp 310–311 °C). The *r*-2,*c*-6-diphenylpiperidine hydrochloride was dispersed in acetone (25 mL), and an ammonia solution was added to it drop by drop until a clear solution was obtained. The clear solution was poured into water (250 mL) and the precipitated solid was filtered and recrystallized from ethanol: yield 1.7 g (71%); mp 69–71 °C, lit.[20b] mp 73–74 °C.

***t*-3-Methyl-*r*-2,*c*-6-diphenylpiperidine (8).** Wolff–Kishner reduction of 2 (2.65 g, 10 mmol) was carried out by following the same procedure as described for compound 7. The *t*-3-methyl-*r*-2,*c*-6-diphenylpiperidine hydrochloride was recrystallized from ethanol (mp 326–327 °C, lit.[20b] mp 324–326 °C). The corresponding piperidine was also recrystallized from ethanol: yield 1.65 g (65%); mp 71–72 °C, lit.[20b] mp 75–76 °C.

***t*-3,*c*-5-Dimethyl-*r*-2,*c*-6-diphenylpiperidine (9).** By following the general procedure 5 (2.79 g, 10 mmol) was also converted to the corresponding piperidine hydrochloride (mp 336–337 °C, lit.[20b] mp 332–334 °C) and then to the piperidine (yield 1.25 g (47%); mp 55–56 °C, lit.[20b] mp 56–57 °C).

***N*-Nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (10).** A mixture of 1 (0.75 g, 2.98 mmol) and concentrated HCl (0.4 mL) was dissolved in a 1:1 ethanol–water mixture (25 mL). The temperature of the solution was kept at 65–70 °C, and while stirring, a solution of $NaNO_2$ (0.21 g, 3.0 mmol) in a 1:1 ethanol–water mixture (15 mL) was added dropwise over a period of 1 h. The heating and stirring was continued for another 2 h. The reaction mixture was extracted 4 times with ether (100 mL) and the extracts were washed with water several times. The combined ethereal layer was dried over anhydrous Na_2SO_4. After removal of ether, the crude product was recrystallized twice from ethanol to give pale yellow crystals. 10: yield 0.55 g (65.9%); mp 105–107 °C, lit.[20f] mp 107–108.5 °C; IR (KBr) 1720, 1300, 1180, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (dd, J = 17.1 and 6.3 Hz, 1 H), 2.9–3.05 (m, 2 H), 3.33 (dd, J = 17.7 and 5.1 Hz, 1 H), 5.99 (t, J = 7.2 Hz, 1 H), 6.45 (t, J = 5.4 Hz, 1 H) 6.8–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 43.1, 43.4, 53.8, 60.3, 126.1, 127.2, 127.5, 128.4, 128.5, 128.9, 137.7, 137.8, and 204.9; MS m/z 280, 263, 250, 236, 235, 208, 194, 176, 165, 145, 131, 118, 105, 104, 103, 91, 89, 78, 77, 65, 57, and 51. Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

***t*-3-Methyl-*N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (11).** Nitrosation of 2 (0.80 g, 3.02 mmol) followed that described for 1. The crude *N*-nitroso compound was crystallized twice from ethanol. 11: yield 0.62 g (69.8%); colorless, spongy solid; mp 124–125 °C; IR (KBr) 1720, 1310, 1180, 1170, and 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (d, J = 5.4 Hz, 1.5 H), 1.13 (d, J = 7.2 Hz, 1.5 H), 2.79–3.57 (m, 3 H), 5.21 (d, J = 10.2 Hz, 0.45 H), 5.92 (d, J = 6.3 Hz, 0.55 H), 6.05 (t, J = 6.6 Hz, 0.45 H), 6.64 (dd, J = 6.6 and 2.4 Hz, 0.55 H), and 6.74–7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.1, 14.2, 41.3, 42.2, 45.9, 46.1, 53.1, 59.6, 62.2, 66.7, 126.2, 127.4, 127.6, 127.7, 127.8, 128.2, 128.5, 128.7, 128.9, 129.1, 137.2, 137.8, 138.1, 206.9, and 207.7; MS m/z 294, 277, 265, 249, 207, 194, 176, 165, 160, 119, 118, 104, 103, 78, 77, 71, and 57. Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

***t*-3-Ethyl-*N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (12).** Compound 12 was synthesized from 3 (0.80 g, 2.86 mmol) by the same procedure as used for 11. 12: yield 0.42 g (47.6%); colorless crystals; mp 86–88 °C; IR (KBr) 1720, 1300, 1180, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, J = 7.5 Hz, 1.3 H), 1.07 (t, J = 7.4 Hz, 1.7 H), 1.44–1.6 (m, 2 H), 2.7–3.4 (m, 3 H), 5.83 (dd, J = 8.3 and 6.8 Hz, 0.65 H), 6.07 (d, J = 6.1 Hz, 0.35 H), 6.36 (d, J = 3.1 Hz, 0.65 H), 6.45 (dd, J = 6.8 and 4.4 Hz, 0.35 H), and 6.8–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 11.1, 11.2, 21.9, 23.3, 41.8, 42.6, 52.2, 52.3, 54.3, 56.3, 60.4, 63.6, 126.3, 127.2, 127.4, 127.5, 127.55, 127.6, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 137.1, 137.7, 137.9, 138.0, 207.5, and 207.7; MS m/z 308, 263, 221, 204, 132, 117, 104, 91, and 77. Anal. ($C_{19}H_{20}N_2O_2$): C, H, N.

***t*-3-Isopropyl-*N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (13).** The crude product obtained by the nitrosation of 4 (0.9 g, 3.07 mmol) was crystallized twice from ethanol. 13: yield 0.72 g (72.8%); pale yellow crystals; mp 119–120 °C; IR (KBr) 1720, 1440, 1340, 1180, and 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.9 Hz, 1.5 H), 1.03 (d, J = 6.6 Hz, 1.5 H), 1.05 (d, J = 6.6 Hz, 1.5 H), 1.13 (d, J = 6.6 Hz, 1.5 H), 1.7–2.05 (m, 1 H), 2.7–3.25 (m, 3 H), 6.05 (t, J = 7.5 Hz, 0.5 H), 6.39 (dd, J = 3.0 and 7.2 Hz, 0.5 H), 6.56 (d, J = 0.3 Hz, 0.5 H), 6.7–7.3 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.8, 20.1, 21.4, 28.4, 28.8, 41.7, 42.1, 52.3, 53.3, 57.8, 58.4, 61.2, 62.6, 126.5, 127.1, 127.2, 127.3, 127.4, 127.8, 128.1, 128.15, 128.2, 128.6, 137.1, 137.7, 137.8, 137.9, 207.8, 208.2; MS m/z 322, 308, 293, 278, 235, 218, 208, 194, 179, 176, 146, 131, 104, 97, 91, 77, 69, and 57. Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

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t-3,t-5-Dimethyl-N-nitroso-r-2,c-6-diphenylpiperidin-4-one (14). Nitrosation of **5** (0.80 g, 2.86 mmol) was performed by the same procedure as used for **11**. **14**: yield 0.65 g (73.8%); colorless spongy solid; mp 164–166 °C, lit.[20e] mp 166–167 °C; IR (KBr) 1720, 1440, 1180, 1160, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 3 H), 1.22 (d, J = 7.3 Hz, 3 H), 3.03 (m, 1 H), 3.52 (m, 1 H), 5.22 (d, J = 10.01 Hz, 1 H), 6.16 (d, J = 3.0 Hz, 1 H), and 6.7–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.4, 15.7, 44.5, 45.4, 61.7, 65.9, 127.5, 127.7, 128.4, 128.7, 129.1, 137.3, 138.2, and 209.5; MS m/z 308, 291, 264, 263, 207, 194, 190, 160, 134, 132, 118, 117, 104, 91, 89, 77, 65, and 57. Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

N-Nitroso-r-2,t-3,t-5,c-6-tetraphenylpiperidin-4-one (15). A mixture of **6** (1.1 g, 2.72 mmol) and concentrated HCl (0.4 mL dissolved in a 1:1 ethanol–water mixture (75 mL)) was prepared. The nitrosation was carried out by the addition of a $NaNO_2$ solution (0.21 g in 15 mL of a 1:1 ethanol–water mixture) as in the previous cases. The crude product was crystallized twice from ethanol. **15**: yield 0.85 g (72.3%); colorless crystals; mp 169–171 °C; IR (KBr) 1715, 1330, 1180, 1170, and 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (d, J = 7.7 Hz, 1 H), 4.54 (d, J = 6.4 Hz, 1 H), 6.15 (d, J = 7.7 Hz, 1 H), 6.32 (d, J = 6.4 Hz, 1 H), and 6.8–7.3 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 57.6, 58.0, 59.2, 66.0, 126.7, 127.8, 128.0, 128.3, 128.5, 128.6, 128.7, 129.0, 133.3, 135.5, 137.0, 138.0, and 205.4; MS m/z 432, 402, 222, 194, 179, 165, 152, 107, 105, 97, 91, and 77. Anal. ($C_{29}H_{24}N_2O_2$) C, H, N.

N-Nitroso-r-2,c-6-diphenylpiperidine (16). Nitrosation of **7** by the above procedure (0.70 g, 2.95 mmol) yielded **16**. The product was recrystallized twice from ethanol. **16**: yield: 0.45 g (57.3%); pale yellow crystals; mp 68–69 °C, lit.[20d] mp 66.5–67.5 °C; IR (KBr) 1490, 1430, 1350, 1190, 1160, and 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72–1.92 (m, 2 H), 2.03–2.30 (m, 3 H), 2.50–2.62 (m, 1 H), 6.00–6.07 (m, 2 H), 6.75–7.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) 17.3, 26.9, 27.0, 51.9, 60.4, 126.7, 126.8, 127.3, 127.4, 127.9, 128.1, 138.4, and 139.1; MS m/z 266, 249, 236, 221, 194, 165, 145, 131, 117, 104, 91, 77, 65, and 51. Anal. ($C_{17}H_{18}N_2O$) C, H, N.

t-3-Methyl-N-nitroso-r-2,c-6-diphenylpiperidine (17). The crude product obtained by nitrosating **8** (0.75 g, 2.98 mmol) was crystallized twice from ethanol. **17**: yield 0.38 g (45.5%); pale yellow crystals; mp 62–64 °C; IR (KBr) 1490, 1440, 1340, 1190, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 8.1 Hz, 1.35 H), 1.12 (d, J = 8.4 Hz, 1.65 H), 1.4–1.6 (m, 1 H), 2.1–2.8 (m, 4 H), 5.28 (d, J = 7.8 Hz, 0.45 H), 5.57 (d, J = 5.4 Hz, 0.55 H), 5.78 (t, J = 6.6 Hz, 0.55 H), 6.14 (dd, J = 4.0 and 7.2 Hz, 0.45 H), 6.8–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.1, 20.5, 24.2, 25.7, 25.9, 26.2, 31.4, 31.9, 54.2, 60.3, 62.0, 68.1, 126.4, 126.7, 126.8, 127.4, 127.6, 127.7, 127.8, 128.0, 128.1, 128.4, 138.4, 139.1, 139.6, and 140.1; MS m/z 280, 263, 250, 235, 194, 156, 145, 131, 117, 104, 91, 77, 65, and 51. Anal. ($C_{18}H_{20}N_2O$) C, H, N.

t-3,c-5-Dimethyl-N-nitroso-r-2,c-6-diphenylpiperidine (18). Nitrosation of **9** (0.75 g, 2.83 mmol) was carried out by the same procedure as described above. The crude product was crystallized twice from ethanol. **18**: yield 0.54 g (62.5%); pale yellow crystals; mp 76–77 °C; IR (KBr) 1460, 1420, 1380, 1350, 1230, 1180, 1170, and 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 1 H), 0.98 (d, J = 6.9 Hz, 0.5 H), 1.08 (d, J = 6.6 Hz, 1 H), 1.14 (d, J = 6.6 Hz, 0.5 H), six multiplets at 1.54, 1.7, 2.06, 2.4, 2.7, and 2.92 account for 4 protons, 5.27 (d, J = 7.6 Hz, 0.6 H), 5.52 (d, J = 5.9 Hz, 0.4 H), 5.79 (d, J = 6.1 Hz, 0.6 H), 6.02 (d, J = 6.1 Hz, 0.4 H), and 6.6–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 18.1, 18.7, 18.8, 19.7, 28.3, 29.9, 30.2, 31.8, 33.2, 33.6, 55.4, 58.7, 66.6, 66.8, 126.7, 127.1, 127.2, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.6, 128.8, 128.9, 129.6, 136.2, and 139.0; MS m/z 294, 277, 264, 194, 172, 159, 145, 131, 117, 105, 91, 77, 65, and 51. Anal. ($C_{19}H_{22}N_2O$) C, H, N.

Acknowledgment. We are grateful to DST, New Delhi, for support of this work and CSIR, New Delhi, for fellowship to T.R. R.W.M. and M.S. thank the NIH (grant No. ES01984). The Varian XL-300 NMR spectrometer was purchased with support from the National Science Foundation. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Electrochemical and Chemical Reduction of Furopyrazines, Thienopyrazines, Furoquinoxalines, and Thienoquinoxalines

Joseph Armand,*[†] Christian Bellec,[‡] Line Boulares,[†] Patrick Chaquin,[§] Daniel Masure,[§] and Jean Pinson[⊥]

Laboratoire de Physicochimie des Solutions, ENSCP 75231 Paris, Cedex 05 (URA 403) France, Laboratoire de Chimie des Hétérocycles and Laboratoire de Chimie Organique Théorique (URA 506), Université Pierre et Marie Curie, 4 Place Jussieu, 75252 Paris, Cedex 05, France, and Laboratoire d'Electrochimie Moléculaire (URA 438), Université Paris VII, 2 Place Jussieu, 75251 Paris, Cedex 05, France

Received January 23, 1991

The electrochemical reduction of furopyrazines, thienopyrazines, furoquinoxalines, and thienoquinoxalines was investigated in protic and aprotic mediums. The thieno[2,3-*b*]pyrazines and the thieno[3,4-*b*]pyrazines both lead, in aqueous medium, to a dihydro compound where the two nitrogen atoms of the pyrazine ring are hydrogenated. These primary reduction products isomerize in different ways: in the [2,3-*b*] series the thiophene ring is reduced while in the [3,4-*b*] series the pyrazine ring is reduced. These results can be rationalized on the basis of quantum calculations of the energies of the different isomers. These calculations also permit the explanation of the different reducibility between the two series of compounds.

The electrochemical reduction in protic medium of heterocyclic compounds containing a pyrazine ring has been shown[1-9] to lead to 1,4-dihydro derivatives. Some dihydro compounds, where the two pyrazine nitrogen are hydrogenated, are stable. This is, for example, the case with 7,8-dimethylpyrido[2,3-*b*]quinoxaline[9] (**1**) and with

[†] Laboratoire de Physicochimie des Solutions.
[‡] Laboratoire de Chimie des Hétérocycles.
[§] Laboratoire de Chimie Organique Théorique.
[⊥] Laboratoire d'Electrochimie Moléculaire.

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