Photoreactions of Nitroso Compounds in Solution.[1] XXI. Stereochemical Course of Photoaddition of Nitrosamines to some Cyclic Olefins and Conformational Isomers Generated by $A^{1,3}$-Interaction

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The results of the photoadditions of *N*-nitrosopiperidine and *N*-nitrosodimethylamine to three substituted cyclohexenes are discussed in terms of an "electrophilic" free radical attack of the aminium radicals generated from the photolysis of the nitrosamines. The photoaddition to 4-*t*-butylcyclohexene gave all four possible oximes; the axial approach of the aminium radical was preferred over the equatorial approach. The photoadditions to 3-methylcyclohexene are highly stereoselective giving oxime pairs **1**–**2** and **4**–**5**. Both oximes in each pair have 2-amino and 6-methyl substituents in *trans*-relation; but locked in the alternative conformations through $A^{1,3}$ interaction of the oximino group. In this addition the aminium radical almost exclusively approaches the C-1 carbon of the most stable conformer from the axial side. The steric hindrance to all possible axial and equatorial approaches to conformers of olefins have been compared. Piperidinium radicals, however, abstract an allylic hydrogen from $\Delta^{9,10}$-octaline since the steric hindrance in the addition process is too great to overcome. The hydrogen abstraction process leads to an intermolecular hydrogen–nitroso group exchange reaction which is similar to that in the photolysis of nitrosamides. A pathway is suggested to account for the generation, *in situ*, of the heteroannular diene **28** from which oxime **17** could be derived by photoaddition in 1,4-mode.

On discute les résultats de photoadditions de *N*-nitrosopipéridine et de *N*-nitrosodiméthylamine à trois cyclohexènes substitués en termes d'une attaque par radical "électrophile" des radicaux aminium provenant de la photolyse des nitrosamines. La photoaddition au 4-*t*-butylcyclohexène a donné les quatre oximes possibles; l'approche axiale du radical aminium avait priorité sur l'approche équatoriale. Les photoadditions au 3-méthylcyclohexène sont très stéréosélectives, donnant les paires d'oxime **1**–**2** et **4**–**5**. Les deux oximes dans chaque paire ont les substituants 2-amino et 6-méthyle en relation *trans*; par contre ils sont figés dans des conformations alternatives par interaction $A^{1,3}$ du groupe oximino. Dans cette addition, le radical aminium approche presque exclusivement le carbone C-1 du conformère le plus stable par son côté axial. On a comparé l'empêchement stérique à toutes les approches axiales et équatoriales possibles sur des conformères d'oléfines. Toutefois, les radicaux pipéridinium enlèvent un hydrogène allylique au $\Delta^{9,10}$-octaline puisque l'empêchement stérique dans le procédé d'addition est trop important pour l'empêcher. Ce procédé d'abstraction d'un hydrogène nous amène à une réaction intermoléculaire d'échange de groupe hydrogène–nitroso, qui est semblable à celle qu'on rencontre dans la photolyse des nitrosamides. On suggère un mécanisme qui tient compte de la formation, *in situ*, du diène **28** hétéroannulaire à partir duquel l'oxime **17** pourrait être dérivé par photoaddition par un mode 1,4.

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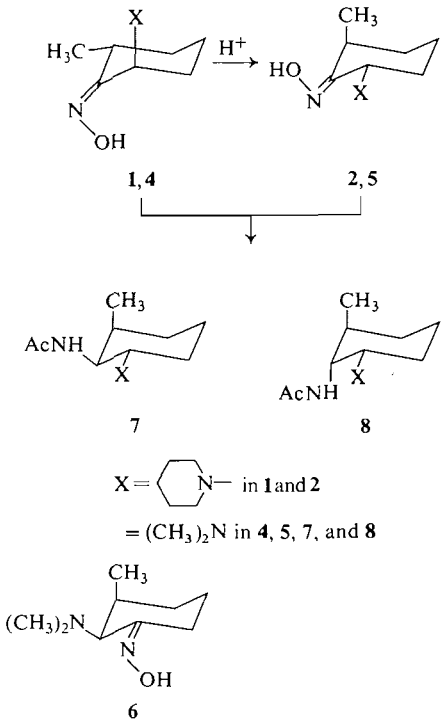
Introduction

Photoaddition of a nitrosamine to a carbon–carbon double bond is an extraordinary reaction in that both acid-catalysis and photoenergy are required (2–4). The photoaddition occurs with a short chain process as suggested by the quantum yield of $2 \sim 3$. On the other hand, it is neither retarded by the presence of air (2) in the solution, nor in the presence of a quencher such as a diene (5). Recent work from this laboratory by the technique of flash excitation has established that the primary photoprocess is the decay of a singlet excited nitrosamine to aminium radical which initiates the addition to a double bond (6). Due to the cationic charge, an aminium radical is expected to be a very strong electrophilic species. The reactivity of the latter is, however, expected to be strongly under the influence of steric factors since even the smallest aminium radical, dimethylamino radical, is equivalent in size to isopropyl radical. In order to evaluate the steric factors controlling the stereochemical course of the photoadditions to olefins, photoaddition to 3-methyl- and 4-*t*-butylcyclohexenes and $\Delta^{9,10}$-octaline were studied.

Results

The conditions of the photoaddition have been described and discussed in our previous publications (2–4) and, in the present case, are also outlined in the Experimental. When a

[1]For paper XX of this series, see ref. 1.



SCHEME 1

methanol solution containing equimolar quantities of *N*-nitrosopiperidine and 3-methylcyclohexene was irradiated in the presence of hydrochloric acid, two photoadducts, *syn,trans*-2-piperidino-6-methylcyclohexanone oxime[2] (**1**) and *anti,trans*-2-piperidino-6-methylcyclohexanone oxime (**2**), were obtained in 13 and 16% yield, respectively. In addition a small amount of *N*-piperidinoformamide (**3**) (1) was also isolated; but the amount of the neutral product was very small. In the presence of an excess of *N*-nitrosopiperidine and irradiation with a uranium glass filter, the yields of oximes **1** and **2** rose to 21 and 50%, respectively. Again no appreciable amount of the neutral product was obtained.

Both oxime **1** and **2** had the correct elemental analysis for the molecular formula of a 1:1 adduct, and exhibited characteristic i.r. absorption for the oxime group (7). The *anti*-oxime **2** dissolved readily in an aqueous solution of cupric sulfate (10%) to give a deep green solution indicating that chelation of the cupric ion had occurred[3] (8, 9). The blue color of cupric sulfate was, however, not affected when a methanol solution of the *syn*-oxime **1** was added. The presence of the *anti*-configuration in **2** and the *syn*-configuration in **1** were thus indicated.

The n.m.r. spectra provide information with regard to the configuration and conformation of the adducts and the relevant results are summarised in Table 1. The assignments of the lower field signals to C-2 and -6 protons are facilitated by the fact that the C-6 proton is coupled to the C—CH_3 group. The triplet ($J = 3.5$ Hz) at τ 6.18 in the spectrum of **1** is readily assigned to the C-2 equatorial proton while the C-6 proton is located at about τ 7.6 and partially hidden by the α-methylene signal of the piperidine ring. The chemical shift of the C-6 axial proton is comparable to that of the *anti*-α-axial proton of 4-*t*-butylcyclohexanone oxime (τ 7.95) (10) supporting the assignment of the axial orientation. The double doublet at τ 6.83 in the spectrum of **2** is assigned to the C-2 axial proton on the basis of the coupling constant. The broad multiplet at τ 6.35 ($w_{1/2} = 25$ Hz) is assigned to the equatorial proton at C-6 on the basis of the chemical shift value.[4] The orientations of the methyl group, equatorial in **1** and axial in **2**, are further supported by the observation that the coupling constant of the methyl group with the C-6 methine proton is larger for **2** (7 Hz) than for **1** (6.5 Hz); the coupling constant of an axial methyl proton with the vicinal methine proton in cyclohexane derivatives has been shown to be generally larger than that of the alternative conformation (11). Thus oximes **1** and **2** both possess piperidine and methyl groups oriented in a 1,3-*trans* relation and as the consequence of the $A^{1,3}$ interaction due to the oximino group (12, 13), the conformation of the ring is locked in the alternative orientations as shown. In agreement with this, oxime **1** was readily isomer-

[2]The *syn–anti* notation refers to the configuration of the oximino group and *cis–trans* notation is reserved for the configuration of the ring system. For the definition of *syn–anti* configuration, see ref. 2.

[3]So far, cupric sulfate tests of other *syn–anti* isomers have been successful, except in one bicyclic case. The *syn*-isomer of 2-*exo*-dimethylaminobicyclo[2,2,1]heptan-2-one oxime gave green coloration (unpublished results from this laboratory).

[4]The unpublished results from our laboratory show that the chemical shifts of the *syn*,equatorial proton at C-2 in various cyclohexanone oximes are as follows: 4-*t*-butylcyclohexanone oxime, τ 6.64; *cis*-3,5-dimethylcyclohexanone oxime, τ 6.68; 3-*t*-butylcyclohexanone oxime, τ 6.68.

TABLE 1. The n.m.r. data of the photoadducts to 3-methylcyclohexene*

	1	2	4	5
		Chemical shift (τ-value)		
OH	1.00(b)	1.54(b)	0.30(b)	1.06(b)
C-2	6.18(t)	6.83(dd)	6.23(t)	6.77(m)
N-CH_3	—	—	7.83(s)	7.60(s)
C-6	~7.6(m)	6.35(m)	7.25(m)	6.34(m)
C-CH_3	8.92(d)	8.87(d)	8.95(d)	8.86(d)
		Coupling constant (Hz)		
$J_{2,3e}$	~3.5	~4	3	4
$J_{2,3a}$	~3.5	~10	3	11
$J_{5e,6}$			2.5	~3
$J_{5a,6}$			10	~3
J_{6,CH_3}	6.5	7	6.5	7

*The spectra of oximes **4** and **5** were recorded with a Varian HA-100.

ized to **2** in the presence of hydrochloric acid; while the reverse isomerization did not take place. This is to be expected as piperidine ring is "bulkier" than methyl group.

The photoaddition of *N*-nitrosodimethylamine to 3-methylcyclohexene was run with a Rayonet photochemical reactor. The major photoadducts were *syn,trans*-2-dimethylamino-6-methylcyclohexanone oxime (**4**) and *anti,trans*-2-dimethylamino-6-methylcyclohexanone oxime (**5**) in 15 and 20% yield, respectively. A small amount (2%) of what appeared to be *anti,trans*-2-dimethylamino-3-methylcyclohexanone oxime (**6**) was also isolated. The proof of the structures and conformations of oximes **4** and **5** follows the same arguments as those used in the cases of **1** and **2**. In the present case the assignments of the protons and the configurations of the oximes were placed on a firmer basis by decoupling experiments; the relevant results and some examples of the decoupling are given in Table 1 and Figs. 1 and 2.

In both cases, the decoupling experiments (Figs. 1 and 2) related not only the signals of the C-6 proton and the *C*-methyl protons; but also located the signal due to the C-3 proton. The chemical shifts and the coupling patterns of the C-2 proton in **4** and **5** confirmed beyond any doubt their orientation as equatorial and axial, respectively. The narrow triplet, due to the C-6 proton in **5**, when decoupled from the *C*-methyl group, clearly indicates that the proton was equatorially oriented (Fig. 2*b*). The same decoupling operation in **4**, however, did not afford a clear coupling pattern. Judging from the width

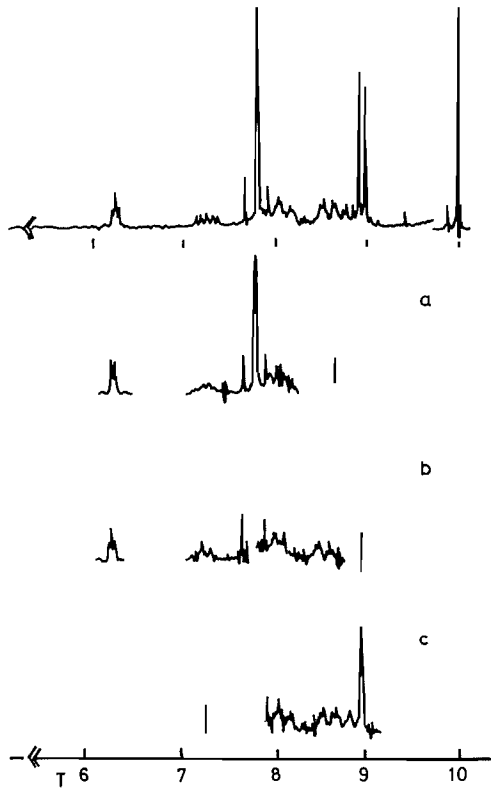


FIG. 1. The n.m.r. spectrum (100 MHz) of *syn,trans*-2-dimethylamine-6-methylcyclohexanone oxime (**4**) in pyridine: (*a*) irradiation at τ 8.78, (*b*) irradiation at τ 8.95, and (*c*) irradiation at τ 7.25.

at half-height of the decoupled signal, an axial orientation of the C-6 proton was indicated.

The n.m.r. data shown in Table 1 and the decoupling results described above firmly placed

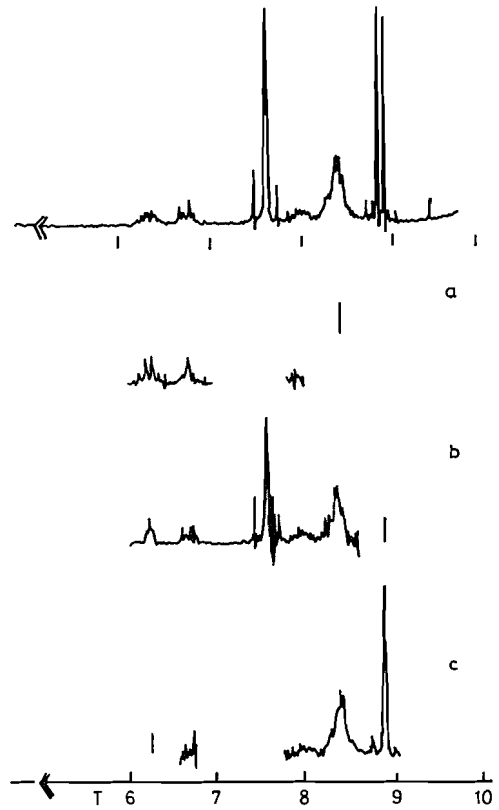


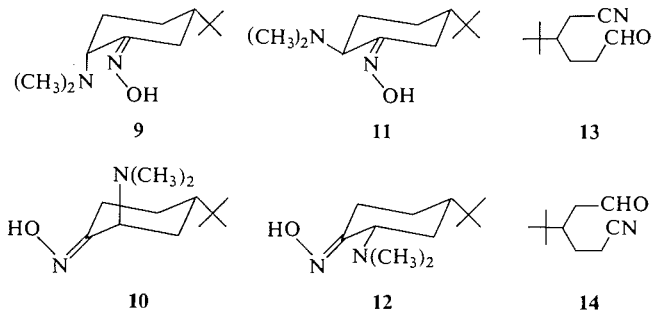
FIG. 2. The n.m.r. spectrum (100 MHz) of *anti,trans*-2-dimethylamino-6-methylcyclohexanone oxime (**5**) in pyridine: (*a*) irradiation at τ 8.35, (*b*) irradiation at τ 8.86, and (*c*) irradiation at τ 6.34.

the configuration and conformation of oximes **4** and **5** as shown. This is similar to the relation of oximes **1** and **2**; where they are forced to assume the alternative conformation though possessing the common *trans*-configuration at 2-amino-6-methyl groups. Further corroboration that oxime **5** possessed the *anti,trans*-configuration was given by the appearance of a deep green color on treatment with a copper sulfate solution.

The third isomer in the photoaddition of *N*-nitrosodimethylamine to 3-methylcyclohexene was obtained in a small quantity and was suggested to have the structure **6** on the basis of the following evidence. The *anti*-configuration of the oximino group was indicated according to the positive copper sulfate test (8, 9) exhibited by the compound.[3] The superimposed n.m.r. signal at τ 7.25 ~ 7.15 was integrated to be equivalent to two protons. One of these was clearly due to the C-6 equatorial proton as shown by a doublet ($J = 14$ Hz), each portion of which was further broadened. The remaining signals could be interpreted as a doublet with coupling constant of 2–3 Hz. The orientation of the equatorial 2-amino group and the axial 3-methyl group were suggested on the basis of the conformational energy of the substituents, which should have the *cis*-relation as indicated by the coupling constant of the methine protons. The structure **6** was also favored on consideration of the steric course of the approach of the reactant (*vide infra*).

In order to relate the configuration of oximes **1** and **2**, both compounds were reduced separately with lithium aluminum hydride followed by acetylation. From both operations the crude acetamide was shown to contain the same major and minor products; although the ratio from each preparation was slightly different. Both major and minor product acetamides showed i.r. absorption characteristic of the acetamido group, and an appropriate mass spectral pattern. The major product acetamide was shown to be 1-acetamido-2-*trans*-piperidino-6-*cis*-methylcyclohexane (**7**) and the minor one 1-acetamido-2-*cis*-piperidino-6-*trans*-methylcyclohexane (**8**).

The major product acetamide **7** exhibited n.m.r. signals at τ 3.35 and 6.30, the latter of which was sharpened to a double doublet ($J = 11$ and 4 Hz) when the former was removed by D_2O exchange. These results indicated that the τ 6.30 signal was due to the C-1 proton, oriented axially. The n.m.r. spectrum of the deuteriochloride of **7** exhibited the axial C-1 methine proton at τ 5.85 as a double doublet and the axial C-2 methine proton at τ 6.55 as a triplet each of which was further split to a doublet ($J = 11$ and 4.5 Hz). The orientations of the substitutions around the cyclohexane ring were such that both the 1-acetamido and 2-amino groups were equatorial and the 6-methyl was axial. The shifts of both the C-1 and -2 protons downfield as the consequences of the protonation of **7** were unusual. The minor acetamide **8** was obtained in impure state and showed a triplet n.m.r. signal at τ 5.98 ($J = 5.5$ Hz), indicating that the C-1 methine proton was equatorial. Although the signal due to the C-2 methine proton could not be observed clearly,



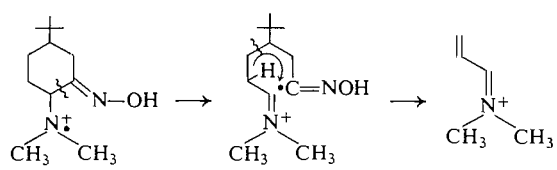
the configuration of **8** was provisionally assigned on the basis of the mechanism of the reduction.

The photoaddition of *N*-nitrosodimethylamine to 4-*t*-butylcyclohexene under the usual conditions afforded four isomeric oximes, *anti*, *cis*-2-dimethylamino-5-*t*-butylcyclohexanone oxime (**9**), *anti,trans*-2-dimethylamino-4-*t*-butylcyclohexanone oxime (**10**), *anti,trans*-2-dimethylamino-5-*t*-butylcyclohexanone oxime (**11**), and *anti-cis*-2-dimethylamino-4-*t*-butylcyclohexanone oxime (**12**), in that order of decreasing yield. The last two compounds were obtained in semi-pure state; each of which was contaminated by a small amount of the other. All four oximes **9**–**12** were shown to possess the *anti*-configuration as evidenced by positive cupric sulfate tests (8, 9). This was in agreement with the exclusive formation of the *anti*-oxime in the photoaddition to cyclohexene (2).

Oximes **9** and **11** were both transformed to 5-cyano-4-*t*-butyl-pentanal (**13**) through the Beckmann cleavage reaction (14–16). Pentanal **13** was characterized as 2,4-dinitrophenylhydrazone (2,4-DNPH, m.p. 127–128°). In the same manner, oxime **10** was cleaved to afford a different compound, 5-cyano-3-*t*-butylpentanal (2,4-DNPH, m.p. 125–126°). Due to the limited quantity available, oxime **12** was not cleaved in the same manner. While the i.r. and n.m.r. spectra of the two pentanals were distinctly different, it was not possible to establish the position of the *t*-butyl group unambiguously. This information enabled us to conclude that oximes **9** and **11** were the epimeric pair at the C-2 position having the same arrangement of the substituents around the cyclohexane ring. It is also clear that oxime **10** had a different arrangement of the substituents than oximes **9** and **11**. Oxime **10** was perhaps epimeric to oxime **12**.

The i.r. spectra of oxime **9** and **11** exhibit the C=N stretching band at 1650 and 1647 cm^{-1}, respectively, whereas the corresponding bands of **10** and **12** appear at 1670 and 1675 cm^{-1}, respectively, indicating their structural similarity (7). The mass spectra of oximes **9**–**10** determined under identical conditions are shown in Fig. 3 and unequivocally demonstrate that oximes **9** and **11** are one epimeric pair, while oximes **10** and **12** are the other. The significant feature of the mass spectra of oximes **9** and **11** is the most intense mass peak at *m/e* 84 which has been shown to correspond to the $C_5H_{10}N^+$ ion (**9***c*, 84.0812); but not to the $C_6H_{12}^+$ ion (84.0936) by exact mass determination (Found: 84.0811). A fragmentation scheme of oxime **9** or **11** to give **9***c* via **9***b* is proposed (see Scheme 2). This demands that the dimethylamino group must be related to the *t*-butyl group in a 1,4-orientation on the cyclohexane ring. The most intense mass peak at *m/e* 137 in the mass spectra of oxime **10** and **12** has been shown to correspond to the $C_9H_{15}N^+$ ion (**10***d*, 137.1204) by an exact mass determination (Found: 137.1178). This ion of *m/e* 137 is probably related to the ion of *m/e* 97 as proposed in Scheme 3. This scheme suggests that the *t*-butyl and the oximino groups are related in 1,4-fashion.

It is our aim now to ascertain the relative position of the *t*-butyl group in the respective pair of oximes. For this purpose, n.m.r. spectroscopy is shown to be the less ambiguous method.



SCHEME 2

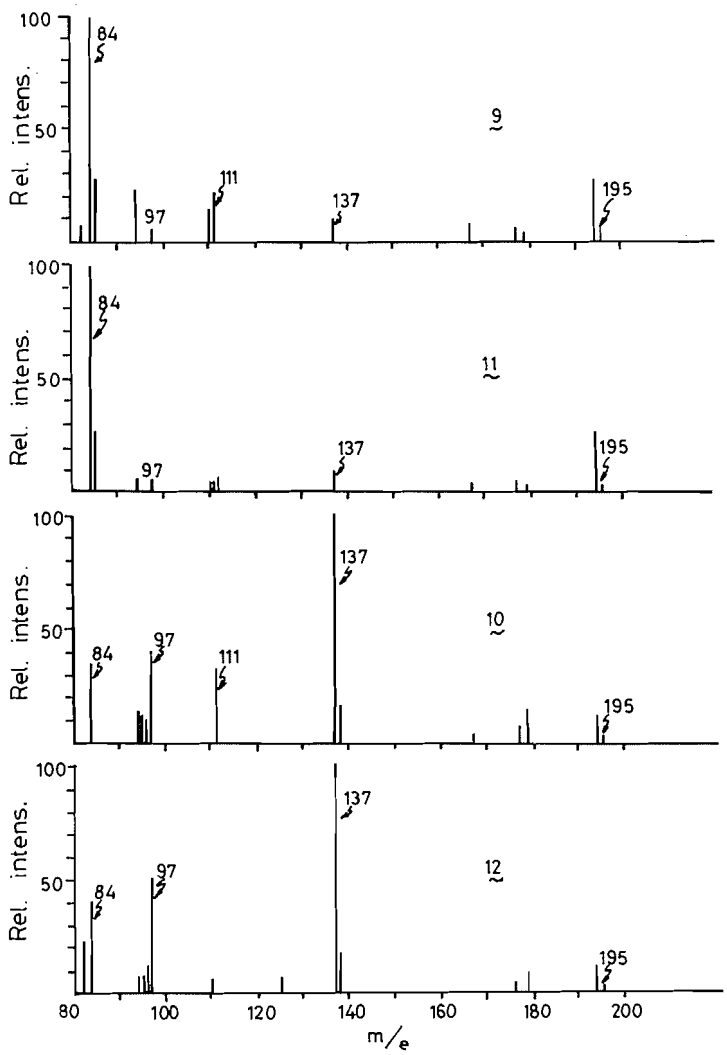
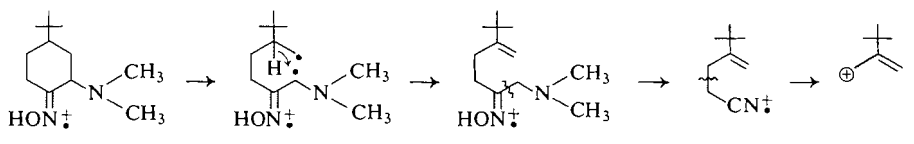


FIG. 3. Mass spectra (80 eV) of isomeric oximes **9**, **10**, **11**, and **12**.



SCHEME 3

The n.m.r. results for these four oximes are summarized in Table 2 in which both the chemical shifts and coupling constants of oxime **9** have been confirmed by decoupling experiments. In all four n.m.r. spectra, the signals due to C-6 equatorial[4] and C–2 protons were readily identified in the range τ 6.25–6.45 and τ 7.25–6.79, respectively (Table 2). The C-2 proton in oxime **9** was equatorially oriented and that in oxime **11** axially, as shown by the coupling

TABLE 2. The n.m.r. data (100 MHz) of oximes **9**–**10** taken in pyridine solution

	9*	**10**	**11**†	**12**
		Chemical shift (τ-value)		
C-2	7.5(*t*)	7.16(t)	6.95(dd)	6.79(dd)
C-6e	6.25(d)	6.32(d)	6.42(d)‡	6.45(dt)
N-CH_3	7.82(s)	7.82(s)	7.47(s)	7.42(s)
C-CH_3	9.11(s)	9.20	9.15(s)	9.18(s)
		Coupling constant (Hz)		
$J_{2,3e}$	~3	3	5	4.5
$J_{2,3a}$	~3	3	10	10
$J_{5a,6a}$	12	—	11	
$J_{6a,6e}$	12.5	12	13	13

*The decoupling experiments also show that the chemical shifts of C-3 equatorial and C-6 axial are at τ 7.73 and 8.18, respectively.

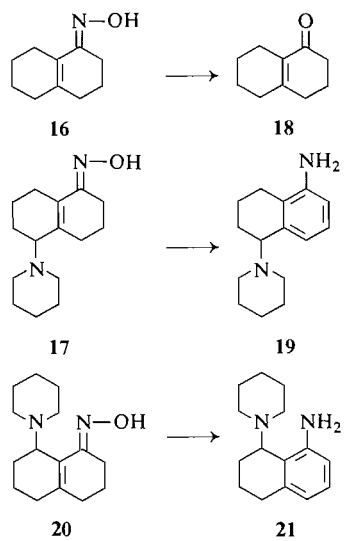
†The decoupling experiments also show that the chemical shift of the C-6 axial proton is at τ 8.38.

‡The doublet is further broadened by small couplings.

patterns of the proton. The former is shown as a narrow triplet and the latter as a double doublet with a large and a small coupling constant. On the same grounds the C-2 proton of oxime **10** was assigned to the equatorial orientation and that of oxime **12** to the axial orientation. It was noted that in both pairs the chemical shifts of the axial protons (**11** and **12**) appeared at lower field than those of the equatorial protons (**9** and **10**). A similar reversal of the relative chemical shift positions for axial and equatorial protons was also found in α-bromocyclohexanones (17) and could be related to the conformation of the ring with respect to the anisotropic effects of the π-bond system.

The C-6 equatorial proton in all four oximes resonated in the expected range, in agreement with *syn*-α-equatorial protons of substituted cyclohexanone oximes with "frozen" conformations.[4] In all four oximes this proton signal was split to a doublet by the C-6 axial proton by a large geminal coupling constant. In oximes **9** and **11**, each signal was further broadened to the unresolved doublet by a small coupling (2–3 Hz) with C-5 (the carbon carrying the *t*-butyl group) axial proton. In the corresponding pair of oximes **10** and **12**, each signal of the doublet was weakly coupled (*ca.* 3 Hz) with the two C-5 protons as shown by the broad signal in **10** and the unresolved triplet in **12**. Furthermore, by the decoupling experiments, the C-6 axial proton in oximes **9** and **11** was shown to be a triplet and a double doublet, respectively, exhibiting large coupling constants (12 and 11 Hz, respectively) with the C-5 axial proton. This evidence allows us to place the *t*-butyl group at C-5 position for oximes **9** and **11** and at C-4 position for oximes **10** and **12**.

Photoaddition of *N*-nitrosopiperidine to Δ^9-octaline (**15**) was investigated under the standard photolysis conditions from which Δ^9-decalone-1 oxime (**16**, 30%) and 5-piperidino-Δ^9-decalone-1 oxime (**17**, 9%) were isolated. The isolation of these anomalous products was accompanied by a small yield of *N*-piperidinoformamide (3). For oxime **16**, the C=N stretching absorption at 1640 cm^{-1} and the u.v. absorption maximum at 237 nm indicated the presence of the con-



SCHEME 4

jugated enone oxime chromophor. Since the n.m.r. spectrum of oxime **16** did not show signal below τ 6, except the broad OH signal at τ 0.5, the tetra-substituted double bond was established. The identity of oxime **16** was established by the trans-oximation reaction with levulinic acid to give Δ^9-decalone, which was characterized by formation of its 2,4-DNPH. The melting points of oxime **16** and its derivatives are identical with those reported by Hückel and Blohm (18) and those by Campbell and Harris (19).[5] The configuration of oxime **16** must have the OH portion of the oximino group oriented *anti* to the olefinic bond since the alternative configuration would cause severe $A^{1,3}$ interaction (12, 13). The partially resolved triplet at τ 7.38 ($J = 6.5$ Hz) was assigned to two C-2 protons and the multiplet at τ 7.84 to the six allylic protons. The former assignment was justified in view of the similarity of the chemical shift to that of the α-*cis* protons of cyclohexanone oxime (τ 7.54). The magnetic equivalence of these C-2 protons also indicated that oxime **16** was flexible and rapidly interchanging among various conformations.

The basic oxime **17** contained a piperidine ring and the basic skeleton of oxime **16** as shown by i.r. (1633 cm^{-1}) and u.v. (237 nm) absorptions and the elemental analysis. The n.m.r. spectrum was not readily analyzable due to extensive overlapping of the signals (with the exception of the multiplet signal at τ 6.85 due to the tertiary allylic proton adjacent to the piperidino ring). Oxime **17** was transformed under the conditions of Semmler and Hofmann (20) to 1,2,3,4-tetrahydro-1-piperidino-5-aminonaphthalene (**19**), which exhibited appropriate mass peaks at *m/e* 230, 216, and 145 corresponding to the ions of M^+, $(M\text{-}NH_2)^+$ and $(M\text{-}C_5H_{10}N)^+$. The conclusion that the two amino groups were oriented in the 1,5-relation was supported by the comparable u.v. absorption curves of **19** and its dihydrochloride with those of 1-amino-5-di-(2′-chloroethylamino)-1,2-3,4-tetrahydronaphthalene and its dihydrochloride (21).[6] Structures **20** and **21**, the alternative possibilities to oxime **17** and aniline **19**, were not rigorously excluded. In view of the failure of the oxime and the aniline derivative to form Cu^{2+} or Ni^{2+} complexes (22), structures **20** and **21** could not be considered probable structures. From the mechanistic considerations (*vide infra*), no logical pathway could be formulated to arrive at structure **20**.

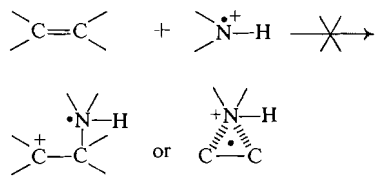
[5]The structure **16** was first suggested by Hückel and Blohm; but Campbell and Harris later erroneously reassigned the same compound to $\Delta^{8,9}$-decalone-1 oxime.

[6]The authors are grateful to the Director, Institute of Chemical-Pharmaceutical Research, Bucharest, Romania for the authentic samples.

Discussion

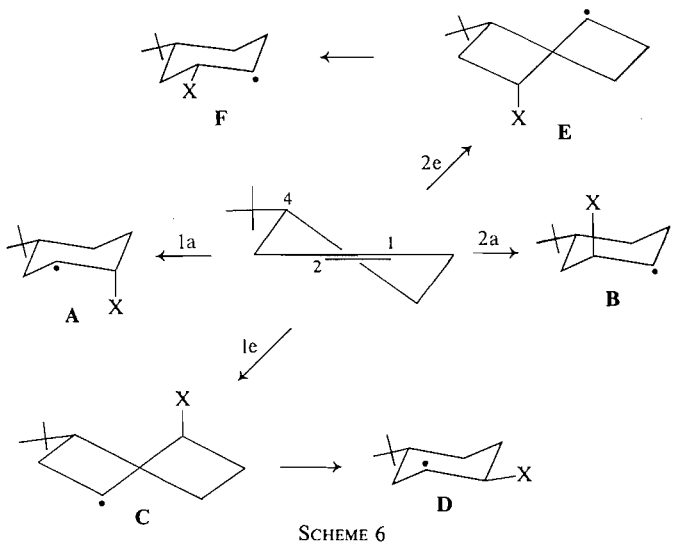
We have demonstrated that the primary photoprocess of a nitrosamine, in the presence of an acid, is the generation of the corresponding aminium radical from the singlet excited state of a nitrosamine–acid association complex (16). Further we have shown that piperidinium radical reacts with cyclohexene with a bimolecular rate constant of 2.4×10^7 M^{-1} s^{-1} (6). Although the aminium radical may be considered as an electrophilic species, it attacks a carbon–carbon double-bond by a purely free radical mechanism (see Scheme 5). However, it does not behave as an electrophilic reagent since a purely electrophilic attack would result in an electronic configuration of the nitrogen outer shell in excess of the limit imposed by the octet rule (see **22**). Further, a bridged aminium radical, such as **23**, cannot be rationally proposed as an intermediate on the same basis. The following discussion is based on free-radical addition of the aminium radical.

The investigation of the photoaddition to 4-*t*-butylcyclohexene, a conformationally "frozen" cyclohexene, affords an insight into the steric course of the initial attack of an aminium radical on the olefinic bond (Scheme 6). Although a more complex mixture of adducts has been obtained from the addition to this cyclohexene, the process is mechanistically less complicated since the olefinic bond is relatively free from a direct steric influence of the remote 4-*t*-butyl group. The isolation of all four possible oximes **9**–**12** indicates that the attack of the



22 **23**

SCHEME 5

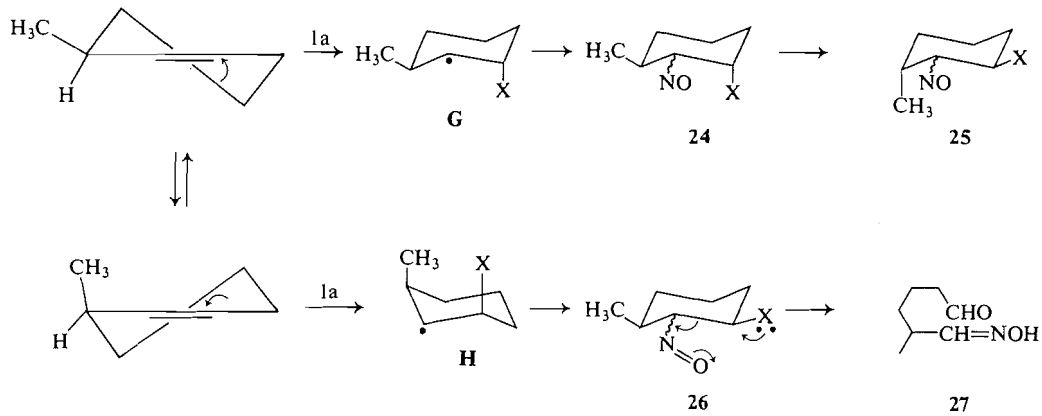


SCHEME 6

dimethylaminium radical is not stereospecific; but is stereoselective. Thus the aminium radical initiates the addition by preferentially attacking the C-1 position over the C-2 position. Between two available approaches to the respective carbon atom of the double-bond, it prefers to take the axial approach at both C-1 and -2 positions to give the intermediates **A** and **B**, respectively. The axial approach of the aminium radical at C-1 position (**A**) involves a nonbonded interaction from the C-5 axial hydrogen while that at C-2 (**B**) involves a similar interaction from the C-4 axial hydrogen. The latter is clearly more severe than the fomer due to compression from the 4-*t*-butyl group in **B**. The equatorial approaches[7] of the aminium radical at the C-1 and -2 positions led to the energetically unfavorable boat conformations **C** and **E**, respectively, that invert to chair conformations **D** and **F**. During the inversion of the boat conformation in **C** and **E**, the amino group would encounter eclipsing strain from the neighboring axial hydrogens. The total energies required in these two cases are apparently greater than those required in the axial approaches. It is not difficult to understand that the steric strain exerted by the C-3 axial hydrogen in **E** is more severe, owing to compression of the 4-*t*-butyl group. The same order of selectivity has been observed in the addition of methylthiyl radical to 4-*t*-butylcyclohexene (23). A similar steric effect has been shown in the light-induced addition of methane- and ethanethiol to *trans*-Δ^2-octaline to give a mixture in which the axial attack predominates over the equatorial one by a factor of *ca.* 10–1 (24). Since the "bulk" of the dimethylaminium radical is expected to be somewhat greater than that of the thiyl radicals, the lower selectivity observed in the present addition signifies that the aminium radical is more aggressive toward electrophilic attack, causing less stereochemical discrimination.

In the photoaddition to 3-methylcyclohexene (Scheme 7), the conformational equilibrium of the initial-state conformations has to be taken into account and the unknown steric strain imposed by the C-3 methyl group on various approaches of aminium radical has to be considered. It has been shown by a gas phase equilibrium (25), and supported by the recent theoretical calculation (26), that 3-methylcyclohexene exists mainly (85–90%) in the conformation with the methyl group at pseudoequatorial orientation. The conformer with the methyl group in pseudoaxial orientation, however, is also present in significant concentration. An attack of an aminium radical at the C-2 position in both conformations is considered to be severely restricted by compression of the C-3

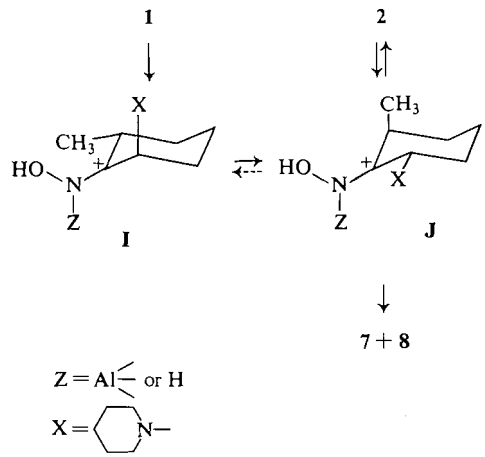
[7]Strictly speaking, the mode of the attack leading to **C** and **E** is not precisely equatorial in conformational definition. If the attack and the inversion of the ring take place in a rapid succession, the net result and energetics can be approximated as an equatorial approach.



SCHEME 7

methyl group. The less hindered approaches at C-1 position in both conformations are visualized to follow the lowest energy pathways with axial approaches, for reasons similar to those stated in the previous case, leading to two possible intermediates with 1,3-*trans* (**G**) and 1,3-*cis* orientation (**H**). The latter intermediate appears less likely to form due to the 1,3-diaxial interaction between the amino and the methyl groups. The isolation of isomeric oximes (**1**–**2** and **4**–**5**) with two substituent groups (methyl and amino) solely in *trans*-orientation is in full accord with this argument. In both cases, the oxime pair is derived from tautomerization of the single *C*-nitroso compound in different conformations (**24** and **25**). The ratio in each pair is controlled by the rate of inversion, in competition with the rate of tautomerization. A small amount of the minor product **6** obtained in the photoaddition of *N*-nitrosodimethylamine apparently arises from an attack of dimethylaminium radical at the C-2 position. In accordance with the preferred axial approach of dimethylaminium radical, the *trans*-orientation of the substituents is assigned to **6**. Since piperidinium radical is "bulkier" than dimethylaminium radical, it is not surprising that the possible corresponding minor product in the photoaddition of *N*-nitrosopiperidine is not found.

The isomeric pairs of oximes (**1**–**2** and **4**–**5**) are interesting cases in which the 2-dimethylamino and 6-methyl groups, though in *trans*-relation in both cases, are locked in the alternative conformation by severe $A^{1,3}$ interactions generated by the oximino group (12, 13). The



SCHEME 8

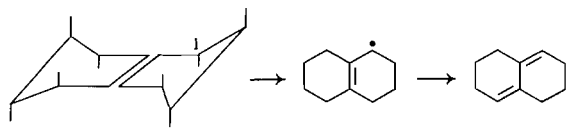
ready isomerization of oxime **1** to oxime **2** in an acidic solution is a good proof of the isomeric pair and apparently occurs through an intermediate such as the protonated species **I** (Scheme 8). The latter has been relieved of the $A^{1,3}$ interaction of the oximino group and rapidly inverts to more stable **J**; followed by deprotonation of **J** to give **2**. The result of the lithium aluminum hydride reduction of **1** and **2** can be explained on the same grounds. In both reductions the product-forming step, with hydride attack at the C-1 position, takes place from the common intermediate **J** to afford the observed configurational isomers **7** and **8**.

It is speculated that *C*-nitroso compound **26** (derived from **H**), though not a favored product, may also be formed in small quantity during photoaddition to 3-methylcyclohexene. The

tautomerization of **26** is certainly unlikely, since this process would entail a prior inversion to the 2,6-diaxial conformation of the substituents; the energy barrier of which appears to be too great to overcome (12). Among various other alternative decomposition routes, the cleavage pathway to **27** may be possible in analogy to the similar cleavage reaction observed previously (4). It is suspected that aldehyde **27** may have undergone various aldol condensations leading to a tarry material under the conditions of the experiment.

The photolysis of *N*-nitrosopiperidine in the presence of $\Delta^{9,10}$-octaline does not lead to the formation of a regular addition product. The failure of the addition can be traced to the 1,3-diaxial interactions due to the axial and pseudo-axial hydrogens. These hinder the approaches of piperidinium radical to the carbon–carbon double-bond. Since the addition pathway is sterically blocked, *N*-nitrosopiperidine undergoes an intermolecular hydrogen–nitroso group exchange reaction. The latter reaction is a process similar to Hofmann–Löffler–Freytag reaction (27), and is related to nitrosamide photolysis (28). Formation of oxime **16** must have taken place via hydrogen abstraction by the piperidinium radical to give **K**, which scavenges a nitroso group to afford the precursor to **16**. Such a hydrogen-abstraction process has been shown to take place between the piperidinium radical and methanol (1) although the rate is slower by 5000 times than its addition to cyclohexene according to flash excitation studies (6). This process also has been proposed as the initial step in Hofmann–Löffler–Freytag reaction (27). Indeed *N*-piperidinoformamide and *N*-dimethylaminoformamide, photoreaction products between the nitrosamines and methanol (1), have been isolated in these cases and also during other photoadditions. The present intermolecular hydrogen–nitroso group exchange reaction with an allylic hydrogen is so far the first instance observed in the photoreaction of nitrosamines.

The minor product of oxime **17** in this photoreaction can be derived from the photoaddition to a diene such as **28** in analogy to the established photoaddition pattern to dienes (5, 29). Since the olefin **15** used in this experiment has been shown, by v.p.c., to be completely free of diene **28**, this diene must be generated *in situ* during the photolysis. It is suggested that a hydrogen atom acceptor interacts with intermediate **K** to provide the heteroannular diene **28** (Scheme 9).



15 **K** **28**

SCHEME 9

Experimental

Unless specified otherwise the i.r. spectra were recorded with a Perkin–Elmer 457 spectrometer in Nujol mulls or in liquid film, the mass spectra with an Hitatchi RMU-6E mass spectrometer (80 eV), and the n.m.r. spectra with a Varian A56/60 spectrometer in $CDCl_3$ solution using TMS as the internal standard. The decoupling experiments of n.m.r. spectroscopy were carried out with a Varian HA-100 spectrometer through the kind assistance of Professor K. R. Kopecky, The University of Alberta, Edmonton, Alberta. The melting points were measured with a Fisher–Johns hotstage and were corrected. The microanalyses were performed by Dr. A. Bernhardt, Elbach, West Germany.

Addition of N-Nitrosopiperidine to 3-Methylcyclohexene

(*a*) A methanol solution (320 ml) of *N*-nitrosopiperidine (4.75 g, 41.5 mmol), 3-methylcyclohexene (4.0 g, 41.5 mmol, Aldrich Chemical Co.), and concentrated hydrochloric acid (4.4 ml, 48 mmol) was irradiated with a 200 W Hanovia medium pressure mercury lamp (654A-36) for 2 h. The solvent was distilled off under reduced pressure, and the residue was treated with water (20 ml) and extracted with ether (30 ml × 3). The ether extract was dried ($MgSO_4$) and evaporated, leaving a light brown liquid (242 mg). Chromatography of this liquid on a silicic acid column (12 g) eluting with chloroform gave, after recrystallization from petroleum ether, *N*-piperidinoformamide (**3**), m.p. 70–72°, whose i.r. and n.m.r. were identical with those of an authentic sample (1).

The aqueous solution of the photolysate was then made basic with a saturated Na_2CO_3 solution. The white precipitate formed from the basic solution was filtered, dried in a desiccator to give crude crystals (4.03 g) which contained two compounds as indicated by t.l.c. analysis. One gram of this mixture was chromatographed on basic alumina (35 g). Elution with benzene (500 ml) gave *syn,trans*-2-piperidino-6-methylcyclohexanone oxime (**1**, 258 mg); m.p. 164–166° (dec.); i.r. 3350, 1670, 1135, 935, 740 cm^{-1}.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.71; H, 10.43; N, 13.37.

Elution with 50% chloroform in benzene (100 ml) gave a mixture of **1** and isomer **2** (254 mg) in a ratio of *ca.* 1:10. Subsequent fractions from the same eluent (400 ml) contained *anti,trans*-2-piperidino-6-methylcyclohexanone oxime (**2**, 124 mg); m.p. 156–158° (dec.); i.r. 3250, 1670, 960, 880, and 800 cm^{-1}.

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.71; H, 10.43; N, 13.37.

The total yields of **1** and **2** were 13 and 16%, respectively. When a mixture of **1** and **2** was irradiated under the same

conditions of the photoaddition, the ratio of **1** to **2** was not changed.

(*b*) A methanol solution (200 ml) of 3-methylcyclohexene (2.0 g, 20.8 mmol), *N*-nitrosopiperidine (4.75 g, 41.5 mmol), and concentrated hydrochloric acid (4.4 ml, 52 mmol) was irradiated with a 200 W Hanovia lamp using a uranium glass filter. After complete disappearance of the nitrosamine absorption ($6\frac{1}{2}$ h), the photolysate was worked-up in the similar manner as described above. The acidic extract gave a mixture (220 mg) of recovered nitrosamine and amide **3** as indicated by i.r. spectroscopy and t.l.c. The yellowish basic extract was chromatographed to give oxime **1** (940 mg, 21.4%) and **2** (2.2 g, 50%).

Isomerization of syn,trans-2-Piperidino-6-methylcyclohexanone oxime (1)

A solution of oxime **1** (340 mg, 16 mmol) and hydrochloric acid (0.5 ml, 6 mmol) in methanol (40 ml) was stirred at 60° for 6 h. The resultant solution was worked-up in the usual manner to give a solid (320 mg) whose n.m.r. showed two pairs of doublets at τ 8.87 ($J = 7$ Hz) and 8.92 ($J = 6.5$ Hz), due to oximes **2** and **1** respectively, with an integration ratio of *ca.* 1:3. Silicic acid t.l.c. of this mixture eluted with 25% methanol in chloroform exhibited two spots at R_f 0.87 and 0.56, corresponding to oxime **1** and **2**, respectively. This mixture was chromatographed on a basic alumina column (10 g) to give pure oxime **2** (32 mg) together with recovered compound **1**.

Addition of N-Nitrosodimethylamine to 3-Methylcyclohexene

In a manner similar to the previous photolysis, a methanol solution (360 ml) of *N*-nitrosodimethylamine (3.08 g, 40.5 mmol), the olefin (4 g, 41.5 mmol) and concentrated hydrochloric acid (4 ml, 48 mmol) was irradiated using a single Rayonet RPR 3500 Å lamp. The photolysis was complete after 12 h. The methanol was removed under vacuum leaving a crude mixture which was treated with acetone to give a crystalline precipitate. The crystals were removed by filtration to give the hydrochloride of *anti,cis*-2-dimethylamino-3-methylcyclohexanone oxime (**6**) (400 mg). The hydrochloride was treated with saturated $NaHCO_3$ solution (20 ml) to give a suspension, which was filtered to give the free base (**6**, 159 mg, 2.3%). Recrystallization once from methanol and sublimation gave an analytical sample of **6**; m.p. 110–111.5°; i.r. 3230, 1655, 960, 925, and 885 cm^{-1}; n.m.r. τ 0.05 (s, 1H, D_2O exchangeable), 6.75–7.15 (m, 2H), 7.7 (m, superimposed, 1 H), 7.75 (s, 6H), 9.10 (d, $J = 7$ Hz, 3H).

Anal. Calcd. for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45. Found: C, 63.44; H, 10.52; N, 16.28.

After removal of **6**, the filtrate was worked-up in the usual manner to give a basic fraction (3.2 g) which was chromatographed on a basic alumina column (100 g). A solid eluted with benzene was identified as *syn,trans*-2-dimethylamino-6-methylcyclohexenone oxime (**4**, 1.05 g, 15.2%), which was sublimed to give a pure compound; m.p. 121–122°; i.r. 3360, 2800, 1670, 995, 935 cm^{-1}.

Anal. Calcd. for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45. Found: C, 64.61; H, 10.74; N, 17.07.

Further elution with 10% methanol in chloroform gave a solid, which was recrystallized from isopropanol to give *anti,trans*-2-dimethylamino-6-methylcyclohexanone oxime (**5**, 1.4 g, 20%); m.p. 105.5–107°; i.r. 3250, 3100, 1655, 1505, 960, and 900 cm^{-1}.

Anal. Calcd. for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45. Found: C, 63.42; H, 10.96; N, 16.22.

Photoaddition of N-Nitrosodimethylamine to 4-t-Butylcyclohexene

4-*t*-Butylcyclohexene was prepared from an isomeric mixture of 4-*t*-butylcyclohexanols (Aldrich) according to the method of Sicher and co-workers (30).

Photoaddition of *N*-nitrosodimethylamine to 4-*t*-butylcyclohexene was carried out using a single Rayonet RPR 3500 Å lamp. A solution of the nitrosamine (2.22 g, 30 mmol), the olefin (4.15 g, 30 mmol), and concentrated hydrochloric acid (2.6 ml, 31 mmol) in methanol (300 ml) was photolyzed to completion (3 h). The photolysate was concentrated, neutralized ($NaHCO_3$ solution), and cooled to furnish a crystalline precipitate (500 mg). The crystals were removed by filtration, and shown by t.l.c. to contain exclusively one compound. Recrystallization twice from ethanol gave *anti,cis*-2-dimethylamino-5-*t*-butylcyclohexanone oxime (**9**); m.p. 200–201°; i.r. 3170, 3060, 1650, 1365, 962, 942, and 905 cm^{-1}.

Anal. Calcd. for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.86; H, 11.18; N, 13.16.

The aqueous filtrate was basified (Na_2CO_3) and extracted with CH_2Cl_2 (40 ml × 3), dried (Na_2SO_4), and evaporated to dryness. The gummy residue was chromatographed on a basic alumina column (100 g) in which 100 ml fractions were collected. Fractions 1–10 eluted with benzene gave a trace of a liquid which was not investigated. Fractions 11–14 eluted with $CHCl_3$ gave a mixture of two compounds. These fractions were combined for further purification. Fractions 15–18 gave exclusively one crystalline compound (283 mg). A small portion was sublimed to furnish pure *anti,trans*-2-dimethylamino-5-*t*-butylcyclohexanone oxime (**11**); m.p. 169–172°; i.r. 3160, 1647, 1367, 1040, 986, 932 cm^{-1}.

Fractions 19–22 from 5% methanol in $CHCl_3$ gave a resinous substance (336 mg) which on treatment with methanol afforded a crystalline solid (100 mg). Sublimation yielded pure *anti,cis*-2-dimethylamino-4-*t*-butylcyclohexanone oxime (**12**), m.p. 161–163°; i.r. 3200, 1675, 1367, 1060, 962, and 930 cm^{-1}. The last fraction eluted with 10% methanol in $CHCl_3$ gave a resin. Attempts to purify this substance were unsuccessful.

Fractions 11–14 obtained above were further chromatographed on a silicic acid column (50 g). The first fraction eluted with $CHCl_3$ (1 l) was *anti,trans*-2-dimethylamino-4-*t*-butylcyclohexanone oxime (**10**, 443 mg), recrystallized from ethyl acetate; m.p. 130–132°; i.r. 3200, 3100, 1670, 984, 960, 928, 918 cm^{-1}.

Anal. Calcd. for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.84; H, 11.17; N, 13.09.

Further elution with $CHCl_3$ (200 ml) gave a mixture of **9** and **10** (60 mg). Elution with 1% methanol in chloroform (700 ml) gave a single compound **9** (285 mg). The total yields of oximes **9**, **10**, **11**, and **12** were 13, 7.3, 4.5, and 1.6%, respectively.

Beckmann Cleavage of Oximes 9 and 11

A solution of oxime **9** (340 mg, 1.6 mmol) in a mixture of dioxane (30 ml) and water (5 ml) was placed in a 50 ml beaker, in which p*H* electrodes were immersed. The beaker was set in a water bath regulated at 45° on a magnetic stirrer. To the stirred solution, finely pulverized *p*-toluenesulfonylchloride (610 mg, 3.2 mmol) was added portionwise and subsequently neutralized with 2 *N* NaOH solution to

p*H* 7 after each addition so as not to bring the p*H* of the solution below 6. When all of the *p*-toluenesulfonylchloride had been introduced, the solution was allowed to cool to room temperature, then poured onto ice flakes (50 g). The ether extracts were dried (Na_2CO_3) and evaporated to give a liquid mixture (333 mg), which was purified on a silicic acid column (16 g). Elution with benzene gave *N,N*-dimethyltoluenesulfonamide (98 mg). The next fraction eluted from the same solvent gave a mixture (71 mg). Subsequent fractions gave a liquid, exhibiting a single spot on t.l.c. This liquid was tentatively assigned as 5-cyano-4-*t*-butylpentanal **13** (50 mg): i.r. 2880, 2715, 2250, 1725, and 1168 cm^{-1}; n.m.r. τ 0.34 (t, $J = 1$ Hz, 1H), 6.35 (m, 2H), 7.67 (m, 2H), 8.0 (m, 1H), 8.5 (m, 2H), and 9.02 (s, 9H). The 2,4-DNPH derivative of **13** was prepared in the usual manner to afford a yellow precipitate which was recrystallized from ethanol; m.p. 127–128° (dec.); n.m.r. τ −0.9 (s, 1H), 1.0 (d, $J = 2.5$ Hz, 1H), 1.75 (dd, $J = 2.5$ and 9.5 Hz, 1H), 2.45 (t, $J = 4.5$ Hz, 1H), 7.35–7.75 (m, 4H), 8.00 (m, 1H), 8.35–8.60 (m, 2H), 9.00 (s, 9H); *m/e* 345(14), 224(14), 206(23), 91(28), and 57(100).

A solution of oxime **11** (91 mg, 0.43 mmol) in a mixture of water (1 ml) and dioxane (10 ml) was similarly reacted as described above with *p*-toluenesulfonylchloride (82 mg, 0.86 mmol). The reaction mixture was worked-up to give 5-cyano-4-t-butylpentanal which was identical with that obtained from oxime **9**.

Cleavage of Oxime ***10***

In a similar fashion, oxime **10** (260 mg, 1.25 mmol) in dioxane (4.0 ml) and water (1.0 ml) was treated with *P*-toluenesulfonylchloride (466 mg, 2.5 mmol) giving a mixture of the sulfonamide and a ω-cyanoaldehyde; the latter was purified by chromatography to give 5-cyano-3-t-butylpentanal (**14**, 102 mg): i.r. 2885, 2720, 2260, 1725, 1095 cm^{-1}; n.m.r. τ −0.15 (t, $J = 1.5$ Hz, 1H), 7.40–7.80 (m, 4H), 8.10 (m, 2H), 8.60 (m, 1H), and 9.10 (s, 6H). The 2,4-DNPH derivative was prepared by the usual method to give the hydrazone of **14**: m.p. 125.5–126.5°; *m/e* 347(100), 224(16), 206, 152(52), and 83(74).

Preparation of $\Delta^{9,10}$*-Octalin (***15***)*

Crude $\Delta^{9,10}$-octalin was prepared according to Dauben and co-worker (31). Isomeric 2-decanol (Aldrich) (47.7 g, 310 mmol) was dehydrated with boric acid (19.5 g, 87 mmol) and isomerized with phosphorus pentoxide (12.3 g) to give a mixture of octalins, b.p. 190–196° (28.9 g, 69%). The crude product contained 73% of **15** as indicated by v.p.c. analysis. This mixture was fractionally distilled on a spinning band column to give 7.3 g (25%) of **15**, which showed single peak on v.p.c. (SE 30% column at 225°) analysis and whose n.m.r. spectrum exhibited two superimposed multiplets at τ 8.25 and 8.42 of 1 : 1 integration ratio. The i.r. showed three main absorptions at 2920, 1445, and 1161 cm^{-1}.

Addition of N-Nitrosopiperidine to $\Delta^{9,10}$*-Octalin*

A methanol solution (170 ml) of *N*-nitrosopiperidine (1.66 g, 14.5 mmol), $\Delta^{9,10}$-octalin (2.0 g, 14.7 mmol), and concentrated hydrochloric acid (1.4 ml, 17 mmol) was photolyzed in a Rayonet photoreactor using a 350 mμ lamp. After completion of the photolysis (3 h), the photolysate was concentrated, treated with water (10 ml), and extracted with ether (30 ml × 3). The ether solution was dried ($MgSO_4$) and evaporated to give a solid (760 mg, 30%). This solid was recrystallized from methanol and sublimed to give an analytical sample of Δ^9-decalone-1 oxime (16); m.p. 146–147° (lit. m.p. 147° (18)); i.r. 3300, 1640, 1025, and 960 cm^{-1}; n.m.r. τ −0.5 (s, 1H, D_2O exchangeable), 7.38 (t, $J = 6.5$ Hz, 2H), 7.84 (m, 6H); *m/e* 165(50), 148(100), 131(25), 119(25).

After work-up in the usual manner, the basic extracts gave a viscous liquid (895 mg), which was treated with methanol to give a crystalline precipitate. Recrystallization once from methanol yielded colorless needles of 5-piperidino-Δ^9-decalone oxime (**17**); m.p. 178–180°; i.r. 3230, 1633, 980, and 943 cm^{-1}; n.m.r. τ 0.3 (s, 1H, D_2O exchangeable), 6.85 (m, 1H), 7.30–7.90 (m, 10H), and 8.20–8.65 (m, 12H); *m/e* 248(18), 231(43), 148(51), 86(100).

Anal. Calcd. for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.74; H, 9.59; N, 11.13.

The mother liquor after removal of **17** was chromatographed on a silicic acid column (40 g). A solid (84 mg) eluted with $CHCl_3$ was identified as *N*-piperidinoformamide by direct comparisons with an authentic sample prepared from *N*-aminopiperidine and formic acid (1). The subsequent eluate from 5% methanol in $CHCl_3$ was found to be **17** (122 mg). The last fraction eluted with 10% methanol in $CHCl_3$ gave a gummy substance (50 mg), from which no pure compound could be isolated. Total yield of **17** was 402 mg (9%).

Deoximation of ***16***

Oxime **16** (100 mg, 0.6 mmol) was mixed with levulinic acid (2.7 ml) and 1.2 *N* hydrochloric acid (0.3 ml). The mixture was heated under reflux for 3 h. The resultant solution was then basified with saturated Na_2CO_3 solution, extracted with CH_2Cl_2 (30 ml × 3). The extracts were washed with water, dried (Na_2SO_4), and evaporated to give an impure substance (100 mg). The liquid ketone **18** (72 mg, 79%), i.r. 2930, 2865, 1660, 1632 cm^{-1}, was obtained by chromatography through a silicic acid column (35 g) eluting with $CHCl_3$. The 2,4-DNPH derivative of ketone **18** was obtained as a red solid and was recrystallized from ethanol to give crimson crystals; m.p. 265–266°, (lit. m.p. 264.5–265.5° (32)); i.r. 3330, 1620, 1585, 1330 cm^{-1}; *m/e* 331(21), 330(100), 119(21), 91(25).

Aromatization of ***17***

The oxime **17** (140 mg, 5.7 mmol) in acetic anhydride (0.2 ml) and acetic acid (1 ml) was placed in a two-necked pear-shaped flask equipped with a gas inlet and a condenser whose exit was attached to a calcium chloride tube. The mixture was saturated with anhydrous hydrogen chloride for 2 h at room temperature and then heated on a water bath for an additional 4 h. The resultant dark brown solution was evaporated to dryness under vacuum. The residue was treated with isopropanol to give 1,2,3,4-tetrahydro-1-piperidino-5-aminonaphthalene dihydrochloride (**19**, 92 mg, 61%) which was recrystallized from isopropanol m.p. 214–217° (dec.); i.r. 3410, 3315, 2525, 1625, 1600, 795, 720 cm^{-1}; n.m.r. (D_2O) τ 2.30–2.55 (m, 3H), 6.40–6.66 (m, 5H), 6.70 (t, $J = 6$ Hz, 2H); u.v. (MeOH) 210 and 250 nm.

The free base of **19** (53 mg) was obtained by dissolving the hydrochloride (80 mg) in saturated Na_2CO_3 solution and extracting with $CHCl_3$ (20 ml × 3). Sublimation of the crude product in a sealed tube gave a colorless liquid, 1,2,3,4-tetrahydro-1-piperidino-5-aminonaphthalene; i.r. 3460, 3370, 1640, 1575, 1325, 795 cm^{-1}; n.m.r. τ 1.90–2.40 (m, 2H), 2.63 (t, unresolved, $J = 6.5$ Hz, 1H), 6.70 (s, 2H,

D_2O exchangeable), 7.60 (m, 6H); u.v. (MeOH) 212 nm (ε 1.86×10^3), 235 (ε 11.5×10^2), 287 (ε 2.5×10^2); *m/e* 230(1), 146(12), 145(22), 130(100). The absorption spectra (in H_2O; 190–450 nm) of arylamine **19** were unaffected in the presence of Cu^{2+} or Ni^{2+} ion.

The u.v. absorption maxima of 1-amino-5-di(2-chloroethylamino-1,2,3,4-tetrahydro) naphthalene were at 209, 235, and 285 nm and its dihydrochloride at 208 and 235 nm.

Lithium Aluminum Hydride Reduction of Oxime **2** *and* **1**

To a suspension of LAH (164 mg, 3.2 mmol) in anhydrous tetrahydrofuran (THF, 10 ml), a solution of oxime **2** (300 mg, 1.4 mmol) in THF (10 ml) was added dropwise with stirring. The grey suspension was stirred for 1 h at room temperature and subsequently heated under reflux for 4 h. The resultant reaction mixture was decomposed with water, and magnesium sulfate was added to aid the coagulation of aluminum hydroxide. The solid was filtered and washed with THF. The THF solution was evaporated to give crude amines as colorless liquid (202 mg, 72%), i.r. 3400, 1590, 1165, and 110 cm^{-1}.

The crude amine mixture was acetylated with acetic anhydride and fused sodium acetate. After the usual work-up the crude acetamide exhibited two pairs of n.m.r. signals at 8.00 and 9.13 in one hand and τ 7.95 and 9.00 on the other: the ratio of the former pair to the latter pair was 3.5:1. The crude product was chromatographed on a silicic acid column to give two compounds. The less polar compound was contaminated by acetamide **7** and was the minor product 1-acetamido-2-*cis*-piperidino-6-*trans*-methylcyclohexane (**8**): i.r. 3300, 1645, and 1540 cm^{-1}; n.m.r. τ 5.98 (t, $J = 5.5$ after D_2O exchange), 7.95 (s, 3H), and 9.00 (d, $J = 7$ Hz). The major product (more polar) was sublimed to give 1-acetamido-2-*trans*-piperidino-6-*cis*-methylcyclohexane (**7**); m.p. 130–132°; i.r. 3250, 1635, 1555, and 1280 cm^{-1}; n.m.r. ($CDCl_3$) τ 3.35 (broad, 1H, D_2O exchangeable), 6.30 (m, $W_{1/2}$ *ca.* 20 Hz after D_2O exchange, 1H), 7.5 (m, 5H), 8.00 (s, 3H), and 9.13 (d, $J = 7$ Hz, 3H); n.m.r. (D_2O–DCl) τ 5.80 (dd, $J = 4$ Hz and 11 Hz), 6.65 (m, 5H); *m/e* 238(4), 179(13), 164(12), 124(100), and 84(31). The hydrochloride of **7** was recrystallized from 2-propanol; m.p. 254–256° (dec.); i.r. 3170, 2650, 1670, 1555, and 1290 cm^{-1}; n.m.r. ($CDCl_3$) τ 5.85 (dd, $J = 11$ and 4 Hz, 1H), 6.55 (dt, $J = 11$ and 4.5 Hz, 1H), 7.85 (s, 3H) and 8.79 (d, $J = 7$ Hz, 3H).

Oxime **1** (358 mg, 1.7 mmol) was reduced with LAH (196 mg, 5.2 mmol) and acetylated in the similar manner as described above. The crude acetamide showed similar n.m.r. spectra as that obtained above but the ratio of **7** to **8** was 5:1. On chromatograph of the mixture on alumina, acetamide **7** and the corresponding hydrochloride were obtained. The hydrochloride of **7** was readily soluble in chloroform and could be sublimed. The acetamide **8** was isolated in semi-pure state.

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