Reverse Cope Elimination Reactions. 1. Mechanism and Scope[1-3]

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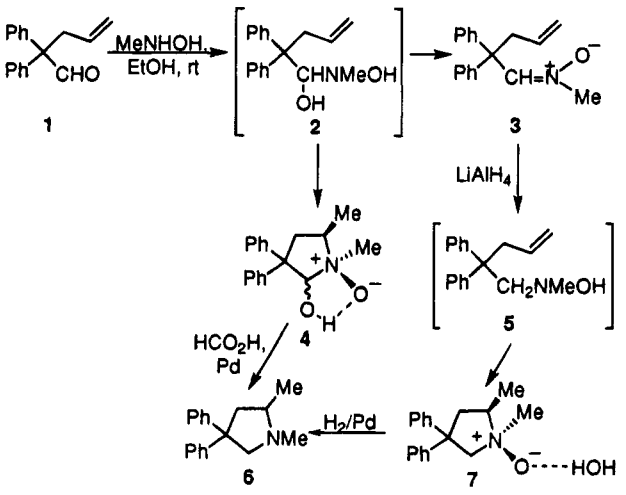
N-4-Pentenyl- and *N*-5-hexenyl-*N*-methylhydroxylamine cyclized under mild conditions in a reverse Cope elimination reaction to give 1,2-dimethylpyrrolidine *N*-oxide and 1,2-dimethylpiperidine *N*-oxide, respectively. The reaction was shown to be concerted and thermodynamically controlled. The scope of this novel cyclization is discussed, and comparisons are made with the closely related and previously reported cyclization of monosubstituted alkenylhydroxylamines to give cyclic hydroxylamines.

Introduction

The thermolysis of a tertiary amine *N*-oxide to give an olefin and an *N,N*-disubstituted hydroxylamine was first described by Mamlock and Wolffenstein[5] at the turn of the century, but the reaction remained unused until Cope and co-workers, starting in 1947, explored the scope and mechanism of this alternative to the Hofmann elimination reaction for the conversion of tertiary amines into olefins. It is now known as the Cope elimination reaction.[6] The reverse reaction, formation of a tertiary amine *N*-oxide from an olefin and an *N,N*-disubstituted hydroxylamine, has received little attention. The products of the reaction of *N,N*-dimethylhydroxylamine with terminal olefins in a closed system at elevated temperatures have been proposed to arise from intermediate, but not isolated, tertiary amine *N*-oxides,[7] and a reverse Cope elimination reaction was postulated as one of a series of steps in the reaction of 2-allylcyclohexanone with *N*-methylhydroxylamine to give 8a-hydroxy-2,3-dimethyloctahydro-2*H*-1,2-benzoxazine.[8] Our own involvement in this area stems from the chance observation that reaction of 2,2-diphenyl-4-pentenal (**1**) with *N*-methylhydroxylamine in ethanol at room temperature gave 1,5-dimethyl-3,3-diphenyl-2-pyrrolidinol 1-oxide (**4**) in 51% yield in addition to the desired nitrone **3** (45%; Scheme 1). The

Scheme 1



^{1}H NMR spectrum of *N*-oxide **4** indicated the presence of a small amount of an isomer, believed to be the C-2 epimeric alcohol. *N*-Oxide **4** could be sublimed under vacuum at 160 °C without decomposition; this remarkable thermal stability is probably a consequence of the existence of an intramolecular hydrogen bond between the oxygen and the neighboring hydroxyl group as shown. This was corroborated by its behavior on silica gel chromatography where it was eluted by a less polar solvent mixture than nitrone **3** and by the fact that unlike all the other *N*-oxides isolated in this study, *N*-oxide **4** crystallized without one molecule of water. The structure of *N*-oxide **4** was confirmed by catalytic transfer hydrogenation which led to 1,5-dimethyl-3,3-diphenylpyrrolidine (**6**). *N*-Oxide **4** is the product of a formal reverse Cope elimination reaction of the intermediate α-hydroxyhydroxylamine **2**. To confirm this hypothesis, nitrone **3** was reduced with lithium aluminum hydride at 0 °C to give a single *N*-oxide **7** which crystallized from acetonitrile as the monohydrate. Its structure was determined by X-ray crystallography which showed the two methyl groups to be *trans*. The water molecule was attached to the *N*-oxide oxygen by a hydrogen bond of 1.646 Å. The O–H–O bond angle was 177.4°. There was no evidence in the crude product for the presence of the intermediate unsaturated hydroxylamine **5**, which must have undergone a reverse Cope elimination reaction at or below room

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(1) Preliminary communication: Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007.

(2) This and the accompanying second paper in this series (Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803) are dedicated to the memory of Arthur C. Cope.

(3) The name for this reaction was chosen for its descriptive property and to distinguish it from the Cope rearrangement. However, since it was criticized as lacking elegance by one of the reviewers of the preliminary communication,[1] we suggest the term *EPOC reaction* as an alternative. The general designation "1,3-azaprotio cyclotransfer" (APT) has been introduced to encompass all additions of hydroxylamines and oximes to unsaturated systems: Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929.

(4) Current address: 121 Spring House Way, Kennett Square, PA 19348.

(5) Mamlock, L.; Wolffenstein, R. *Ber.* **1900**, *33*, 159.

(6) For reviews see: (a) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317. (b) Astles, P. C.; Mortlock, S. V.; Thomas, E. J. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 1011.

(7) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

(8) Takahashi, S.; Kusumi, T.; Sato, Y.; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1777.

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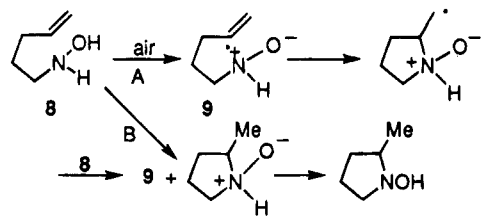
Scheme 2

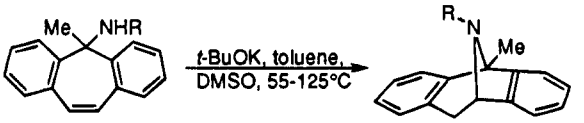


temperature. Catalytic hydrogenation of *N*-oxide **7** gave pyrrolidine **6** (Scheme 1).

Mechanism

The Cope elimination reaction is concerted and proceeds via a planar five-membered transition state involving the *syn* hydrogen.[9] It was thus reasonable to assume that the reverse reaction follows the same mechanism. However, in 1976 House and co-workers[10,11] reported the cyclization of *N*-(4-pentenyl)- and *N*-(5-hexenyl)hydroxylamines to 1-hydroxy-2-methylpyrrolidines and 1-hydroxy-2-methylpiperidines, respectively, and suggested the radical-chain mechanism depicted as path A in Scheme 2. Even though it was later shown that this transformation is not affected by radical inhibitors,[12] we felt it desirable to determine the mechanism of the reverse Cope elimination more rigorously. To this end we carried out the reactions shown in Scheme 3. Alkylation of diphenylacetonitrile with a number of unsaturated halides followed by reduction of the intermediates **10** gave the aldehydes **11**, which on treatment with *N*-methylhydroxylamine furnished the nitrones **12**. Reduction of nitrones **12a**, **12b**, and **12d** with lithium aluminum hydride at 0 °C gave the pyrrolidine *N*-oxides **14a**, **14b**, and **14d**, respectively. When nitrone **12a** was similarly reduced except that deuterium oxide containing ca. 5% H_2O was used to quench the reaction, a single diastereotopomer of *N*-oxide **14a**-*d* was obtained in addition to a small amount of the undeuterated *N*-oxide **14a** as an internal standard as shown by ^1H MNR spectroscopy (see supporting information).[13] This finding strongly militates against a radical mechanism for the transformation **13a**-*d* → **14a**-*d* which should result in the introduction of deuterium into both positions of the diastereotopic benzyl group. Remarkably, **13a**-*d* and **14a**-*d* are in rapid equilibrium at room temperature (see below), indicating that deuterium transfer is 100% specific in both directions and that the *Z*-isomer of **13a**-*d* is not involved. The dependence of the cyclization rate of hydroxylamines **13** on the substitution pattern of the double bond also supports a concerted mechanism. Thus, hydroxylamine **13d** with a methyl group on the nonterminal carbon of the double bond cyclized rapidly at or below room temperature; such a substitution pattern is known to slow down radical cyclization dramatically and to increase the proportion of the 6-*endo* products.[14] Cyclization of hydroxylamine **13c** with two terminal methyl groups was slow and never went to completion; however, cyclization of the corresponding nitrogen radical is also slow and has a rate comparable to that of the reverse reaction.[15] Finally, all reverse Cope elimination reactions described in this and the subsequent paper resulted in the formation of a single isomer with respect to the position of the *N*-oxide oxygen relative to the newly formed neighboring alkyl group which in the case of *N*-oxide **7** was shown to have the stereochemistry expected for a concerted reaction.

On the basis of these results, we suggested[1,16] that the cyclization of monosubstituted hydroxylamines reported by House and co-workers[10] also is a concerted reverse Cope elimination reaction (path B in Scheme 2) leading to a secondary amine *N*-oxide which irreversibly rearranges to the observed product. This has since been shown to be correct,[17] although there may be exceptions. Thus, cyclization of the hydroxylamine **16a** is strongly



16a R=OH **16d** R=NHCOPh
16b R=OMe **16e** R=H
16c R=NH_2

catalyzed by base, as expected for the first step of the radical cyclization mechanism (Scheme 2, path A).[18] However, the observation that the *O*-methylhydroxylamine **16b**, the hydrazines **16c** and **16d**, and even the primary amine **16e** cyclize under these conditions may suggest a base-catalyzed Michael type mechanism for this special case.

Scope

(a) Ring Size of the Cyclization Products. Since the reverse Cope elimination reaction is reversible (see below), it is not surprising that hydroxylamines **17** and **18**, prepared by addition of vinyl- and allylmagnesium bromide to *N*-benzylidenemethanamine *N*-oxide, failed to cyclize. The possibility that the reaction may succeed with the corresponding substrates having two geminal phenyl groups has not been investigated. Reduction of nitrone **19** with lithium aluminum hydride produced a single isomer of 1,2-dimethylpyrrolidine 1-oxide (**21**) in essentially quantitative yield. On the basis of the results discussed above, the stereochemistry is almost certainly that shown. Oxidation of 1,2-dimethylpyrrolidine with hydrogen peroxide gave a 4:1 mixture of *N*-oxide **21** and the isomeric *cis*-1,2-dimethylpyrrolidine 1-oxide. On distillation, *N*-oxide **21** partially reverted to hydroxylamine **20**, but on standing at room temperature complete

(9) Cram, D. J.; McCarthy, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740. Bach, R. D.; Andrzejewski, D.; Dubold, L. R. *J. Org. Chem.* **1973**, *38*, 1742. Chiao, W.-B.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2802. Kwart, H.; Brechbiel, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 4650.

(10) (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

(11) The reaction was discovered independently by: Oppolzer, W.; Siles, S.; Snowden, R.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, 4391, footnote 5. Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.

(12) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317.

(13) We thank Prof. Barry M. Trost for suggesting this experiment.

(14) Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 1980.

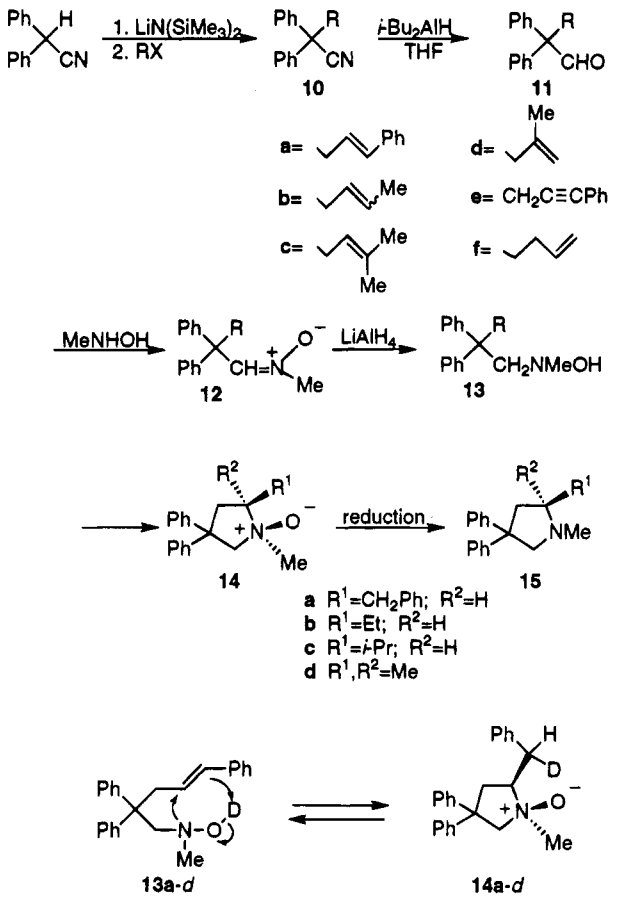
(15) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528.

(16) cf. also Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *Tetrahedron Lett.* **1992**, *33*, 7421; *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379.

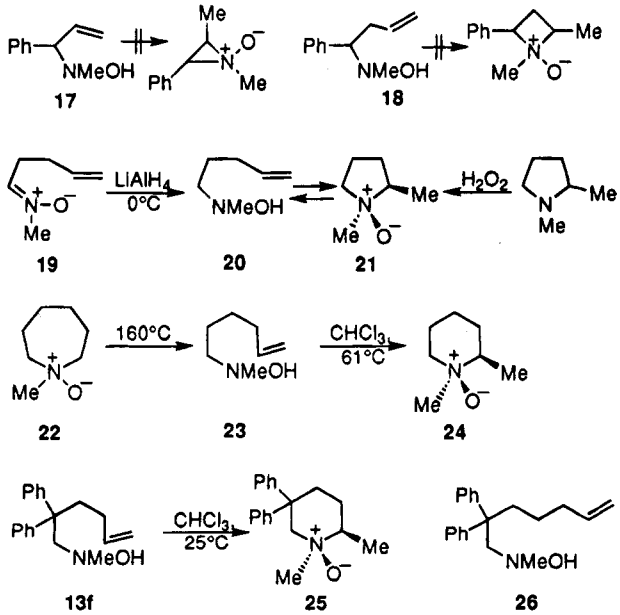
(17) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

(18) (a) Lamanec, T. R.; Bender, D. R.; DeMarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* **1988**, *53*, 1768. (b) Karady, S.; Corley, E. G.; Abramson, N. L.; Weinstock, L. M. *Tetrahedron Lett.*, **1989**, *30*, 2191. cf. also: Christy, M. E.; Anderson, P. S.; Britcher, S. F.; Colton, C. D.; Evans, B. E.; Remy, C.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3117.

Scheme 3



recyclization took place. Because of steric restraints, 1-methylpiperidine 1-oxide does not undergo Cope elimination to give hydroxylamine **20**.[19] The more flexible 1-methylhexahydroazepine 1-oxide (**22**), on the other hand, does furnish hydroxylamine **23** on pyrolysis.[19] The

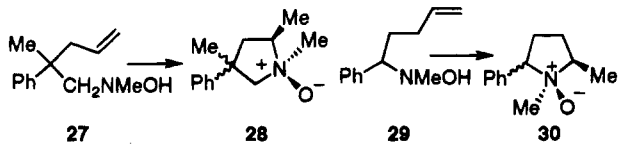


latter cyclized slowly at room temperature, more rapidly at reflux in chloroform, to give *N*-oxide **24** in 63% yield.[20] *N*-oxide **22** was absent in the crude cyclization mixture. Oxidation of 1,2-dimethylpiperidine with hydrogen peroxide gave *N*-oxide **24** and its *cis* isomer in a ratio of 3:2.

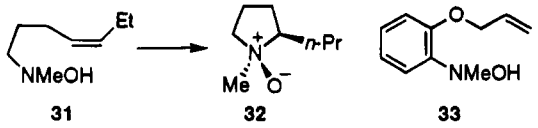
(19) Cope, A. C.; Lebel, N. A. *J. Am. Chem. Soc.*, **1960**, *82*, 4656.

Due to the buttressing effect of two geminal phenyl groups, hydroxylamine **13f** cyclized much more readily with a half-life at room temperature of about 5 h. The homologous hydroxylamine **26** failed to cyclize, indicating that the reverse Cope elimination reaction may be limited to the formation of five- and six-membered rings.

(b) Diastereoselectivity. Cyclization of hydroxylamine **27** produced the two epimeric pyrrolidine *N*-oxides **28** in a ratio of 3:2; for the reaction **29** → **30**, the ratio was the same. The diastereoselectivity of the reverse Cope elimination reaction thus is poor in these simple systems. Some cyclizations discussed in the second paper of this series, however, are more selective.



(c) Substituent Effects. As discussed in the Mechanism section, a substituent on the nonterminal carbon of the olefin does not preclude cyclization; the same is true for a single substituent on the terminal carbon. If that substituent is a methyl group, it appears to make no difference whether it is *Z* or *E*, since hydroxylamine **13b** (*E*:*Z* = 85:15) cyclized completely to *N*-oxide **14b** even though one isomer of **13b**, presumably the *Z-isomer*, disappeared more slowly (Scheme 3). If that substituent is larger, as in (*Z*)-hydroxylamine **31**, then cyclization is fairly slow. However, a direct comparison with hydroxylamine **14b** cannot be made since the latter bears the two rate-enhancing geminal phenyl groups. Hydroxylamine **33** failed to cyclize, probably because of the reduced basicity of the nitrogen bearing a phenyl group. Replacement of the methyl group on nitrogen by an isopropyl group also slows down the reaction, probably for steric reasons (see section d).



(d) Solvent Effects on Rates and Equilibria. The influence of solvents on the rate of the reverse Cope elimination reaction was briefly studied using hydroxylamine **23**. At room temperature, the cyclization half-life was about 63 h in $CDCl_3$, 250 h in CD_3CN, and 750 h in $(CD_3)_2CO$. The rates in D_2O and MeOD were even slower. Addition of 0.6 mol equiv of trifluoroacetic acid to the chloroform solution brought the cyclization to a stop, whereas pyridine-d_5 (3.5 mol equiv) caused only a

(20) It is of historical interest that Cope and LeBel[19] observed this reaction without apparently realizing it. They noted that distillation of hydroxylamine **23** always resulted in considerable loss of material and attributed it to polymerization rather than formation of the much less volatile *N*-oxide **24**. They also reported that pure *N*-oxide **24** could be isolated by partially pyrolyzing mixtures of *N*-oxide **24** and the isomeric *cis*-1,2-dimethylpiperidine 1-oxide (obtained by oxidation of 1,2-dimethylpiperidine) and selectively extracting the *trans* isomer **24** into pentane. Since it is very unlikely that an *N*-oxide is soluble in a hydrocarbon, the pentane-soluble hydroxylamine **23** must have cyclized to *N*-oxide **24** during isolation. The authors were aware of the possibility of reverse reactions since they stated that no *N*-oxide **24** was formed in the pyrolysis of *N*-oxide **22**. However, they accomplished the feat, remarkable for those pre-NMR days, of observing the spontaneous dehydrogenation of hydroxylamine **23** to the corresponding nitrone and intramolecular cycloaddition of the latter to a bicyclic isoxazolidine, thus discovering the first nitrone–olefin cycloaddition and the first intramolecular 1,3-dipolar cycloaddition.

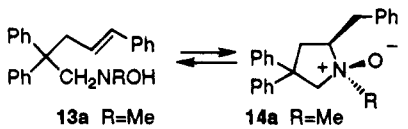
Table 1. Solvent Dependence of the Equilibria 13a/14a and 34/35 at 25 °C

solvent	% 13a	% 14a	% 34	% 35
CD_3OD	0	100	0	100
$CDCl_3$	0	100	23	77
$(CD_3)_2CO$	<5	>95		
CD_3CN	15	85	68	32
C_6D_6[a]	44	56		
$(CD_3)_2SO$	55	45	>90	<10
$(CD_3)_2SO + CF_3CO_2H$	0	100		
THF-d_6	60	40	>90	<10
$(CD_3)_2NCDO$	67	33	>90	<10
pyridine-d_5	74	26		

[a] These numbers may not represent the true equilibrium since **14a** started to precipitate before the ^1H NMR spectrum could be determined for a second time.

slight reduction in rate ($t_{0.5}$ about 94 h). Chloroform thus appears to be the solvent of choice.

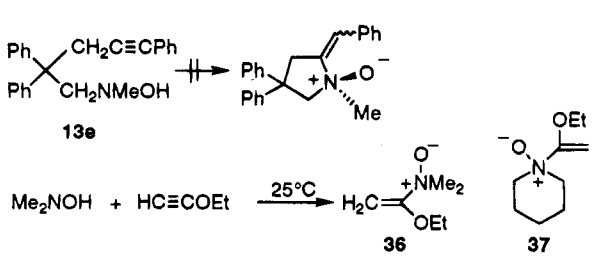
The effect of solvents on equilibria was studied with the system **13a/14a** and the corresponding pair carrying an isopropyl group in place of the methyl group on nitrogen (**34/35**). The data are collected in Table 1. The



13a R=Me **14a** R=Me
34 R=*i*-Pr **35** R=*i*-Pr

position of the equilibria correlates roughly with the hydrogen bond donor and acceptor capacities of the solvents. Thus, solvents that are hydrogen bond donors (methanol and chloroform) favor the *N*-oxides **14a** and **35** whereas the hydrogen bond acceptors dimethyl sulfoxide, tetrahydrofuran, dimethylformamide, and pyridine favor the hydroxylamines **13a** and **34**. However, with acetone and acetonitrile this correlation breaks down. The above-mentioned observation that hydroxylamine **23** cyclizes faster in chloroform, acetone, and acetonitrile than in methanol or water further muddies the picture. Interestingly, the rates of Cope elimination reactions are faster by 4–6 orders of magnitude in dimethyl sulfoxide or tetrahydrofuran as compared to water, and this effect has been ascribed to removal of the solvation envelope by these solvents.[21] The data in Table 1 are internally consistent with respect to the effect of the substitutent on nitrogen: a bulky substituent shifts the equilibrium toward the open-chain hydroxylamine.

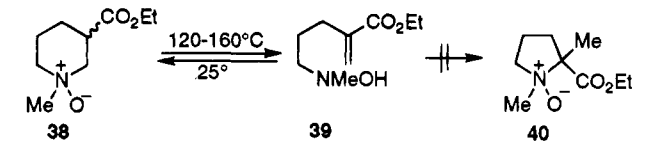
(e) Additions to Acetylenes. The acetylenic hydroxylamine **13e** slowly disappeared on standing in chloroform solution, but no products could be isolated from the complex reaction mixture. The anticipated product was an enamine *N*-oxide. Representatives of this unstable class of compounds are known,[22] and intramolecular additions of *mono*substituted hydroxylamines to acetylenes, both in the 5-*exo* and 6-*endo* modes, have been reported.[16,23] The secondary enamine *N*-oxides formed as unobserved intermediates in these reactions rearranged to the more stable cyclic nitrones. We have observed a formal *inter*molecular reverse Cope elimination reactions in the formation of the enamine *N*-oxides **36** and **37** by reaction of ethoxyacetylene with dimethylhydroxylamine and 1-hydroxypiperidine, respectively.[24]



13e

36 **37**

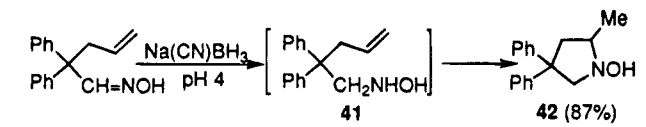
(f) Competition with Michael Additions. As mentioned above, 1-methylpiperidine *N*-oxide does not undergo a Cope elimination reaction on pyrolysis because it cannot attain the planar five-membered transition state.[19] However, we found that the 3-carbethoxy analog **38** does furnish hydroxylamine **39** on heating, probably by a change of mechanism. On standing at room temperature, hydroxylamine **39** reverted completely to the starting material, most likely by a Michael addition. The



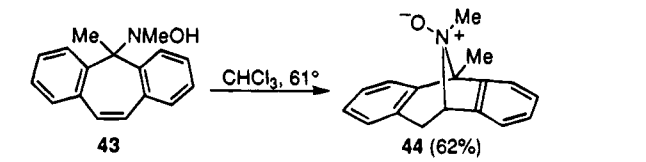
38 **39** **40**

transition state for a concerted 6-*endo* cyclization is very strained, and we did not encounter this cyclization mode in the close analog **20**. *N*-Oxide **40** was absent within detectability by ^1H NMR spectroscopy. The reverse Cope elimination thus cannot compete with a Michael reaction, at least not in this one case.

(g) Comparison of the Cyclizations of Mono- and Disubstituted Hydroxylamines. Reduction of 2,2-diphenyl-4-pentenal oxime with sodium cyanoborohydride at 25 °C and pH 4[26] gave the cyclic hydroxylamine **42** directly by cyclization of hydroxylamine **41**. Since the disubstituted hydroxylamine analog **5** (Scheme 1) also cyclized at or below room temperature, a direct comparison is not possible. We have studied only one case where a direct comparison of the two variants of the reverse Cope elimination reaction is possible.



41 **42** (87%)



43 **44** (62%)

Heating hydroxylamine **43** under reflux in chloroform for 2 h gave *N*-oxide **44** in essentially quantitative conversion; the lower yield shown in the equation is the result of loss during isolation. The corresponding monosubstituted hydroxylamine **16a** was recovered unchanged

(21) Cram, D. J.; Sahyun, M. R. V.; Knox, G. R. *J. Am. Chem. Soc.* **1962**, *84*, 1734. Sahyun, M. R. V.; Cram, D. J. *J. Am. Chem. Soc.* **1963**, *85*, 1264.

(22) Winterfeld, E.; Krohn, W. *Chem. Ber.* **1969**, *102*, 2336. Krouwer, J. S.; Richmond, J. P. *J. Org. Chem.* **1978**, *43*, 2464. Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1989**, *54*, 2862.

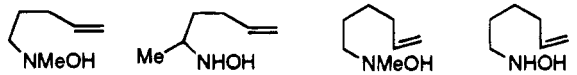
(23) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

(24) These experiments, carried out in 1969, were inspired by the report[25] that acetylene reacts with trimethylamine in water to give ethenyltrimethylammonium hydroxide by a reverse Hofmann elimination. Reaction of dimethylhydroxylamine with acetylene in water led to a complex mixture.

(25) Reppe, W.; Mitarbeiter (sic). *Liebigs Ann. Chem.* **1956**, *601*, 81.

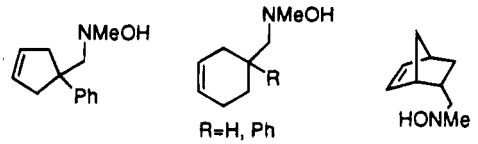
(26) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

under these conditions. That the reverse Cope elimination reaction of disubstituted hydroxylamines to give cyclic *N*-oxides may in most if not all cases be faster than that of monosubstituted hydroxylamines to give cyclic hydroxylamines is hinted at by the fact that *N*-methyl-*N*-(4-pentenyl)hydroxylamine **20** cyclized at room temperature whereas the closely related monosubstituted hydroxylamine **45** required heating to 60 °C;[10b] similarly, the next higher homolog **23** cyclized at 60 °C as compared to 145 °C for the monosubstituted hydroxylamine **46**.[10b]



20 **45** **23** **46**

(h) Unsuccessful Cyclizations. In addition to the examples already mentioned, hydroxylamines **47**–**49** failed to cyclize, probably for thermodynamic reasons.



47 **48** **49**

Conclusions

We have shown that *N,N*-disubstituted hydroxylamines connected to olefinic groups by three- or four-membered tethers give pyrrolidine and piperidine *N*-oxides by a concerted reverse Cope elimination reaction. It proceeds at lower temperatures than the corresponding cyclization of monosubstituted hydroxylamines that leads to cyclic hydroxylamines, but unlike the latter it is reversible and thus subject to thermodynamic control. In addition, cyclic hydroxylamines are much more readily converted into secondary amines than cyclic *N*-oxides. Nevertheless, the reverse Cope elimination reaction of *N,N*-disubstituted hydroxylamines is of some synthetic utility, especially for the preparation of pyrrolizidines and indolizidines which are not accessible by the cyclization of monosubstituted hydroxylamines. Examples are given in the accompanying second paper in this series.

Experimental Section

General. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Melting points were measured in unsealed capillary tubes and are uncorrected. Mass spectra were obtained by chemical ionization (NH_3 or CH_4) or by electron ionization.

Materials. Starting materials were obtained from Janssen Chimica or Aldrich Chemical Co. The THF used was EM Science anhydrous grade (stored over 4A sieves). $MgSO_4$ was used throughout for drying solutions in organic solvents.

2,2-Diphenyl-4-pentenal (1). A mixture of 10.0 g (51 mmol) of diphenylacetaldehyde, 0.5 g (3 mmol) of *p*-toluenesulfonic acid, 15 mL (12.8 g, 220 mmol) of allyl alcohol, and 25 mL of benzene (**CAUTION**: suspected carcinogen) was heated under reflux for 4 h; a Dean–Stark trap was used to collect the water formed. The benzene solution was washed with 10 mL of 10% aqueous Na_2CO_3, dried, and concentrated. The residue was dissolved in 100 mL of *p*-xylene, and the solution was heated under reflux for 6 h. Removal of the solvent and short-path distillation of the residue at 130–160 °C bath temperature (0.002 mm) gave 11.03 g (91%) of aldehyde **1** of about 90% purity as judged by its ^{1}H NMR spectrum: δ 9.8 (s, 1 H), 7.2–7.5(m, 10 H), 5.5–5.7 (m, 1 H), 4.9–5.0 (m, 2 H), 3.1 (d, J = 7 Hz, 2 H). This material was used without further purification.

***N*-(2,2-Diphenyl-4-pentenylidene)methanamine *N*-Oxide (3) and 1,5-Dimethyl-3,3-diphenyl-2-pyrrolidinol 1-Oxide (4).** A mixture of 7.69 g (32.4 mmol) of aldehyde **3**, 6.0 g (72 mmol) of *N*-methylhydroxylamine hydrochloride, 9.0 g (111 mmol) of anhydrous NaOAc, and 25 mL of EtOH was stirred at room temperature for 2.25 h. Aqueous Na_2CO_3 (10%, 120 mL) was added, and the mixture was extracted with 200 and 2 × 40 mL of warm $CHCl_3$. Removal of the solvent from the dried extracts left 8.80 g of a semisolid which on crystallization from 30 mL of toluene gave 3.60 g of title compound **4**, mp 195–196 °C, unchanged on recrystallization from DMF. Another 0.65 g of this product was obtained on crystallization of the concentrated mother liquors from 15 mL of cyclohexane. Combined yield: 4.25 g (51%). This material was recovered unchanged on sublimation at 160 °C bath temperature (0.001 mm): ^{1}H NMR δ 7.1–7.4 (m, 10 H), 5.9 (s, 1 H), 3.9 (br, 1H),2.5–2.8 (m + s, 5H), 2.2 (d, J = 13 Hz, 1 H), 1.1 (d, J = 7 Hz, 3H); an additional weak singlet at δ 5.4 indicated the presence of a small amount of the C-2 epimer. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.00; H, 7.21; N, 5.11.

Chromatography of the mother liquors on silica and elution with EtOAc gave a small amount of additional *N*-oxide **4**; the nitrone **3** (3.48 g, 45%) was eluted with 9:1 EtOAc–MeOH: ^{1}H NMR δ 7.2–7.4 (m, 11 H), 5.5–5.6, (m, 1 H), 5.1 (d, J = 16 Hz, split further, 1 H), 5.0 (d, J = 8 Hz, split further, 1 H), 3.8 (s, 3 H), 3.4 (d, J = 7 Hz, 2H); high-resolution MS calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1466.

1,2-Dimethyl-4,4-diphenylpyrrolidine 1-Oxide (7). To a solution of 1.31 g (4.9 mmol) of nitrone **3** in 10 mL of THF was added below 0 °C 4 mL (4.0 mmol) of 1 M $LiAlH_4$ in THF. The mixture was stirred in an ice bath for 1 h, and a solution of 1.0 mL of H_2O in 10 mL of THF was added slowly below 0 °C. Methylene chloride and $MgSO_4$ were added, and the mixture was stirred for 15 min and filtered. The solids were washed several times with CH_2Cl_2, and the filtrates were concentrated under vacuum at 25 °C to give 1.17 g (89%) of essentially pure title compound: ^{1}H NMR δ 7.1–7.4 (m, 10 H), 4.6 (d, J = 12 Hz, 1 H), 4.4 (d, J = 12 Hz, 1 H), 3.5 (m, 1 H), 3.2 (s, 3 H), 2.8–3.0 (m, 2 H), 3.9 (d, J = 7 Hz, 3 H). A sample crystallized from MeCN contained one molecule of H_2O, mp 130–131 °C. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 76.11; H, 8.12; N, 4.81. The crystal for X-ray structure determination was obtained by slow evaporation of a solution of *N*-oxide **7** in MeCN.

1,2-Dimethyl-4,4-diphenylpyrrolidine (6). A. From *N*-Oxide 4. A mixture of 2.74 g of *N*-Oxide **4** and 25 mL of formic acid was treated under N_2 with 0.84 g of 10% Pd/C, heated under reflux for 95 min, and concentrated under vacuum. Water was added to the residue, and the catalyst was removed by filtration. The filtrate was washed with toluene and made basic with 15% aqueous NaOH. Extraction with CH_2Cl_2 followed by short-path distillation (120–150 °C bath temperature, 0.001 mm) gave 2.02 g (83%) of the title compound: ^{1}H NMR δ 7.1–7.3 (m, 10 H), 3.8 (d, J = 10 Hz, 1 H), 2.8 (d, J = 10Hz + m, 2 H), 2.5 (m, 1 H), 2.4 (s, 3 H), 2.2 (d/d, J =12/8 Hz, 1 H), 1.1 (d, J = 7 Hz, 3 H). The fumarate, mp 192–193 °C, was obtained in 59% overall yield from *N*-oxide **4** after crystallization from 90% aqueous *n*-PrOH. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.86; H, 6.96; N, 3.76.

B. From *N*-Oxide 7. A solution of 0.40 g of *N*-oxide **7** in 5 mL of HOAc was hydrogenated at room temperature and ambient pressure in the presence of 0.37 g of 10% Pd/C for 70 min. The filtered mixture was made basic with NH_4OH and extracted with CH_2Cl_2 to give 0.33 g (88%) of the title compound, identical by ^{1}H NMR and IR spectroscopy with the sample obtained from *N*-oxide **4**.

***(E)*-2,2,5-Triphenyl-4-pentenenitrile (10a). General Procedure.** To a mixture of 12.59 g (65.2 mmol) of diphenylacetonitrile and 60 mL of THF was added slowly 80 mL (80 mmol) of 1 M $LiN(SiMe_3)_2$ in THF. After being heated under reflux for 0.5 h the cooled mixture was treated with a solution of 14.3 g (72.6 mmol) of cinnamyl bromide in 20 mL of THF, and heating under reflux was resumed for 0.5 h. Water (100 mL) was added, and the product was extracted into ether and crystalllized from EtOAc to give 14.60 g (73%) of the title

compound in two crops, mp 99–100 °C: ^{1}H NMR δ 7.2–7.5 (m, 15 H), 6.6 (d, J = 16 Hz, 1 H), 6.1 (d/t, J = 16/7 Hz, 1 H), 3.3 (d, J = 7 Hz, 2H). Anal. Calcd for $C_{23}H_{19}N$: C, 89.28; H, 6.19; N, 4.53. Found: C, 89.37; H, 5.99; N, 4.38.

2,2,5-Triphenyl-4-pentenal (11a). General Procedure. To a solution of 5.01 g ((16.2 mmol) of nitrile **10a** in 25 mL of dry THF was added below −50 °C 22 mL (33mmol) of 1.5 M i-Bu_2AlH in toluene. The cooling bath was removed, and the mixture was stirred for 75 min. Ethanol (5 mL) was added at −55 °C, followed by 30 mL of 10% HCl; the temperature was kept below 0 °C. The product was extracted into toluene, and the extracts were washed with 10% HCl and 10% Na_2CO_3. The mixture had to be filtered at this point to remove a solid. Removal of the solvent from the dried toluene solution and short-path distillation of the residue at 180–230 °C bath temperature (0.005 mm) gave 4.14 g (82%) of the title compound: ^{1}H NMR δ 9.9 (s, 1 H), 7.1–7.4 (m, 15 H), 6.2 (d, J = 16 Hz, 1 H), 5.9 (d/t, J = 16/7 Hz, 1 H), 3.2 (d, J = 7 Hz, 2 H). The spectrum indicated the presence of small amounts (<5%) of impurities; this product was used without further purification.

***N*-((*E*)-2,2,5-Triphenyl-4-pentenylidene)methanamine *N*-Oxide (12a). General Procedure.** The procedure given for the preparation of products **3** and **4** was followed except that the nitrone was isolated by extraction into CH_2Cl_2 at room temperature and the crude products were purified by chromatography on silica, using EtOAc as the eluent. The fractions were concentrated at rt to avoid intramolecular 1,3-dipolar cycloadditions: yield 70%; ^{1}H NMR δ 7.1–7.3 (m, 16 H), 6.4 (d, J = 16 Hz, 1 H), 5.9 (d/t, J = 16/7 Hz, 1 H), 3.7 (s, 3 H), 3.6 (d, J = 7 Hz, 2 H); high-resolution MS calcd for $C_{24}H_{23}NO$ 341.1780, found 341.1781.

The nitrones **12** were reduced with $LiAlH_4$ in THF at 0 °C for 1 h as described for the preparation of N-oxide **7**.

2-Benzyl-4,4-diphenyl-1-methylpyrrolidine 1-Oxide (14a). The product obtained on removal of the solvent (98% yield) was >90% pure as judged from the NMR data: ^{1}H δ 7.1–7.4 (m, 15 H), 4.7 (d, J = 12 Hz, 1 H), 4.4 (d, J = 12 Hz, 1 H), 3.6 (m, 1 H), 3.2–3.4 (m + s, 5 H), 2.8–2.9 (m, 2 H). The sample used for microanalysis and equilibrium studies was obtained, with great loss, by crystallization from EtOAc and drying at 25 °C (0.001 mm), mp 116–118 °C: high-resolution MS calcd for $C_{24}H_{25}NO$ 343.1936, found 343.1941. Anal. Calcd for $C_{24}H_{27}NO_2$ (monohydrate) C, 79.74; H, 7.53; N, 3.87. Found: C, 79.35; H, 7.55; N, 3.72. To make assignments and to determine the coupling constants, the ^{1}H NMR spectrum of the title compound was obtained in $CDCl_3$ containing CF_3CO_2H which caused better separation of the signals; 5 mg of N-oxide **14a** was dissolved in 1.0 mL of 3% (w/v) CF_3CO_2H in $CDCl_3$. The benzylic H are designated H-6a and H-6b: δ 7.1–7.4 (m 15 H), 5.3 (d, J = 12 Hz, H-5a), 6.4 (d, J = 12 Hz, H-5b), 3.8 (m, H-2, $J_{2,6a}$ = 9 Hz, $J_{2,6b}$ = 5.6 Hz, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 13.0 Hz), 3.5 (s, 3 H), 3.42 (d/d, H-6b, $J_{6a,6b}$ = 13.9 Hz), 3.17 (d/d, H-6a), 3.12 (d/d, $J_{3a,3b}$ = 14.0 Hz, H-3a), 2.88 (d/d, H-3b). For the equilibrium studies (Table 1), 5 mg of N-oxide **14a** was dissolved in 1.0 mL of solvent, and ^{1}H NMR spectra were determined at intervals until the **13a/14a** ratios remained constant; the ratios were measured by electronic integration of the three vinylic H in **13a** *vs* the H-5 AB quartet of **14a**. N-Oxide **14a** was insoluble in C_6D_6; to prepare a supersaturated solution, it was dissolved in CH_2Cl_2, the solvent was removed at 25 °C, and the residual oil was dissolved in C_6D_6; N-oxide **14a** started to precipitate after the first spectrum had been determined. The ^{1}H NMR of hydroxylamine **13a** in THF-d_8 had, among others, δ 6.3 (J = 15 Hz, 1 H), 5.9 (d/t, J = 15/7 Hz, 1 H), 3.2 (s, 3 H).

2-(Monodeuteriobenzyl)-4,4-diphenyl-1-methylpyrrolidine 1-Oxide (14a-*d*). A sample of 0.46 g (1.35 mmol) of nitrone **12a** was reduced with 1.5 mL (1.5 mmol) of 1 M $LiAlH_4$ in THF at 0 °C as described above and quenched with 0.3 mL of D_2O containing ca. 5% H_2O in 6 mL of THF to give 0.47 g of the title compound. For the ^{1}H NMR (400 MHz; see supporting information), 5 mg of N-oxide **14a**-*D* was dissolved in 1.0 mL of 3% (w/v) CF_3CO_2H in $CDCl_3$, and H-2 was irradiated to cause the benzyl group of N-oxide **14a**, present to the extent of ca. 5%, to become an AB quartet (d at δ 3.42 and 3.16). The spectrum of N-oxide **14a**-*D* showed the appearance of a new broadened singlet at δ 3.16; no such signal was observed in the δ 3.4 region.

4,4-Diphenyl-2-ethyl-1-methylpyrrolidine 1-Oxide (14b). The crude product was a mixture of 76% of the title compound and 24% of the hydroxylamine **13b** (single isomer, presumably Z). After being allowed to stand in CH_2Cl_2 for 16 h, the product had completely cyclized: ^{1}H NMR δ 7.1–7.4 (m, 10 H), 4.6 (d, J = 12 Hz, 1 H), 4.4 (d, J = 12 Hz, 1 H), 3.3 (m, 1 H), 3.2 (s, 3 H), 3.1 (d/d, J = 12/4 Hz, 1 H), 2.8 (t, presumably d/d, J = 12 Hz, 1 H), 2.0, m, 2 H), 1.0 (t, J = 7 Hz, 3 H). This product was reduced to pyrrolidine **15b** without further purification.

***N*-(2,2-Diphenyl-5-methyl-4-hexenyl)-*N*-methylhydroxylamine (13c) and 4,4-Diphenyl-1-methyl-2-(1-methylethyl)pyrrolidine *N*-Oxide (14c).** Crude product, 1.57 g (from 1.35 g of nitrone **12c**), still containing some THF: ^{1}H NMR δ 7.1–7.3 (m, 10 H), 4.7 (t, J = 7 Hz, 1 H), 3.4 (s, 2 H), 3.0 (d, J = 7 Hz, 2 H), 2.5 (s, 3 H), 1.6 (s, 3 H), 1,5 (s, 3 H); HRMS calcd for $C_{20}H_{25}NO$ 295.1936, found 295.1933.

A sample of hydroxylamine **13c**, dissolved in $CHCl_3$, stood at 25 °C for 18 days. Removal of the solvent at 25 °C left a product containing 22% of uncyclized **13c**, 48% of N-oxide (**14c**), the remainder being unidentified products. ^{1}H NMR of N-oxide **14c**: δ 4.6 (AB quartet, J = 12 Hz, 2H), 3.7 (m, 1 H), 3.2 (s, 3 H), 3.1 (m, 1 H), 2.8 (t, presumably d/d, J = 12 Hz, 1 H), 2.6 (m, 1 H), 1.1 (t, 6 H) among others; on addition of CF_3CO_2H, the latter became 2 d, J = 7 Hz. No further cyclization occurred on standing at rt for 2 months.

4,4-Diphenyl-1,2,2-trimethylpyrrolidine *N*-Oxide (14d). Crude product, 2.26 g from 2.04 g of nitrone **12d**: ^{1}H NMR δ 7.1–7.4 (m, 10 H), 4.7 (d, J =12 Hz, 1 H), 4.5 (d, J = 12 Hz, 1 H), 3.2 (d, J = 13 Hz, 1 H), 3.1 (s, 3 H), 3.0 (d, J = 13 Hz, 1 H), 1.5 (s, 3 H), 1.3 (s, 3 H); no signals due to hydroxylamine **13d** were present. The product was reduced directly to pyrrolidine **15d**.

***N*-(2,2,5-Triphenyl-4-pentynyl)-*N*-methylhydroxylamine (13e):** ^{1}H NMR δ 7.1–7.4 (m, 15 H), 3.6 (s, 2 H), 3.4 (s, 2 H), 2.6 (s, 3 H). A solution in $CDCl_3$ turned yellow on standing at 25 °C for 2.5 days. Hydroxylamine **13e** had completely disappeared; there were at least three products which were not identified.

4,4-Diphenyl-2-ethyl-1-methylpyrrolidine (15b). A mixture of crude N-oxide **14b**, obtained from 2.70 g (9.8 mmole) of nitrone **12b**, 20 mL of AcOH, and 0.92 g of 10% Pd/C, was shaken at 41 psi initial pressure for 100 min, and the product was isolated as described for the preparation of pyrrolidine **6** to give 2.01 g (78% from nitrone **12b**) of the title compound, distilling at a bath temperature of 140–150 °C (0.001 mm): ^{1}H NMR δ 7.1–7.4 (m, 10 H), 3.8 (d, J = 10 Hz, 1 H), 2.8–2.9 (m+d, J = 10 Hz, 2 H), 2.4 (s, 3 H), 2.2–2.4 (m, 2 H), 1.6–1.8 (m, 1 H), 1.2 (m, 1 H), 0.9 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 86.16; H, 8.67; N, 5.33. The fumarate had mp 149–152 °C (i-PrOH). Anal. Calcd $C_{23}H_{27}NO_4$: C, 72.42; H, 7.26; N, 3.53. Found: C, 72.44; H, 7.26; N, 3.53.

4,4-Diphenyl-1,2,2-trimethylpyrrolidine (15d): yield from nitrone **12d**, 75%, boiling at a bath temperature of 130–160 °C (0.001 mm); ^{1}H NMR δ 7.1–7.3 (m, 10 H), 3.4 (s, 2 H), 2.6 (s, 2 H), 2.3 (s, 3 H), 1.0 (s, 6H). The fumarate (67% from nitrone **12d**) had mp 197–198 °C dec. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.28; H, 7.06; N, 3.55.

***trans*-1,2-Dimethylpyrrolidine 1-Oxide (21). A. By Cyclization of *N*-Methyl-*N*-(4-pentenyl)hydroxylamine (20).** A mixture of 2.01 g (23.9 mmol) of 4-pentenal,[27] 3.98 g (47.4 mmol) of N-methylhydroxylamine hydrochloride, 4.18 g (51.0 mmol) of anhydrous NaOAc, and 7 mL of EtOH was stirred at room temperature for 1 h. Aqueous 10% Na_2CO_3 (50 mL) was added, and the mixture was extracted with CH_2Cl_2. Removal of the solvent at 25 °C gave 2.24 g (83%) of N-(4-pentenylidene)methanamine N-oxide (**19**): ^{1}H NMR δ 6.7 (t, J = 5 Hz, 1 H), 5.8 (m, 1 H), 5.1 (m, 2 H), 3.7 (s, 3 H), 2.6 (m, 2 H), 2.3 (m, 2 H). To a solution of 2.20 g (19.5 mmol) of nitrone **19** in 10 mL of dry THF was added below 0 °C 10 mL

(27) Wu, Z.; Mootoo, D. R.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 6549.

(10 mmol) of 1 M $LiAlH_4$ in THF. The mixture was stirred in an ice bath for 1 h, and a solution of 1.9 mL of H_2O in THF was added below 0 °C. Methylene chloride and $MgSO_4$ were added, and the mixture was stirred for 15 min and filtered. Removal of the solvent at 25 °C gave 2.02 g (90%) of crude *N*-oxide **21**: ^1H NMR δ 3.6 (m, 1 H), 3.2–3.4 (m, 2 H), 3.1 (s, 3 H), 2.3 (m, 1 H), 2.0 (m, 2 H), 1.8 (m, 1 H), 1.3 (d, J = 6 Hz, 3 H); there was a small amount (<10%) of uncyclized hydroxylamine **20**. Short-path distillation (120 °C bath temperature, 0.001 mm) gave 1.00 g of *N*-oxide **21** containing very little hydroxylamine **20**. From the liquid nitrogen trap there was recovered 0.74 g of an 83:17 mixture of *N*-oxide **21** and hydroxylamine **20**. ^1H NMR spectrum of hydroxylamine **20**: δ 5.8 (m, 1 H), 4.9 (m, 2 H), 2.5 (m + s, 5 H), among others. On standing in $CHCl_3$ for 24 h, hydroxylamine **20** was completely converted into *N*-oxide **21**: yield 1.74 g (78%); high-resolution MS calcd for $C_6H_{13}NO$ 115.0997, found 115.1004. The picrate had mp 214–216 °C dec after crystallization from 95% EtOH. Anal. Calcd for $C_{12}H_{16}N_4O_8$: C, 41.86; H, 4.68; N, 16.28. Found: C, 41.91; H, 4.68; N, 16.21.

B. From 1,2-Dimethylpyrrolidine. A mixture of 1.71 g (17.3 mmol) of 1,2-dimethylpyrrolidine,[28] 5 mL of MeOH and 5 mL of 30% H_2O_2 stood at room temperature for 16 h. The excess peroxide was decomposed with Pt black,[6a] and the solution was filtered and concentrated to give 1.95 g of an oil consisting of *N*-oxide **21** and its *cis* isomer in the ratio of 80:20. Short-path distillation of 1.63 g of this product (125 °C bath temperature, 0.8 mm) gave 1.34 g (81%) of a mixture containing 67% of *N*-oxide **21**, 17% of the *cis*-isomer, and 16% of hydroxylamine **20**. On standing in $CDCl_3$ for 3 days the the latter disappeared completely. The neat product partially crystallized. The supernatant was removed with a pipette, and the needles were pressed between filter paper. The sample of *N*-oxide **21** so obtained still contained 6% of the *cis*-isomer; otherwise the ^1H NMR spectrum was identical with the product obtained by procedure A. The IR spectra of the two samples were identical.

***trans*-1,2-Dimethylpiperidine *N*-Oxide (24). A. From *N*-Methyl-*N*-(4-hexenyl)hydroxylamine (23).** A solution of 0.86 g of hydroxylamine **23**[19] in 15 mL of $CHCl_3$ was heated under reflux for 16 h. Removal of the solvent left 0.86 g of *N*-oxide **24** as a solid: ^1H NMR δ 3.2 (d, J = 8 Hz, split further, 1 H), 3.0–3.2 (m + s, 5H), 2.4 (m, 1 H), 2.1 (m, 1 H), 1.8 (m, 1 H), 1.3–1.6 (m + d, J = 7 Hz, 6 H). The *cis* isomer[19] and *N*-oxide **22**[19] were absent within the limits of detection. A sample (0.21 g) was converted into the picrate (0.37 g, 63% after crystallization from EtOH), mp 219 °C (lit.[19] mp 211–215 °C dec). Anal. Calcd for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64. Found: C, 43.80; H, 4.91; N, 15.90. For the cyclization rate determinations in different solvents, 25 mg of *N*-oxide **22** was dissolved in 1 mL of solvent, and ^1H NMR spectra were determined after 3, 24, 95, and 193 h. In another set of experiments, three solutions of 37 mg of *N*-oxide **22** in 1 mL of $CDCl_3$ each were treated with 22 mg of CF_3CO_2H (0.67 mol equiv) and 82 mg (3.5 mol equiv) of pyridine-d_5, respectively. The third solution was used as standard. ^1H NMR spectra were determined after 22, 70, and 161 h.

B. From 1,2-Dimethylpiperidine. Oxidation of 1,2-dimethylpiperidine[19] as described for the preparation of *N*-oxide **21** gave a 3:2 mixture of *N*-oxide **24** and its *cis* isomer. In the ^1H NMR, the latter had δ 2.8 and 1.3 for the *N*-Me and *C*-Me, respectively; the corresponding values for the *trans* isomer **24** were 3.0 and 1.3.

***N*-(2,2-Diphenyl-5-hexenyl)-*N*-methylhydroxylamine (13f) and 1,2-Diphenyl-5,5-diphenylpiperidine 1-Oxide (25).** Reduction of 1.20 g (6.6 mmol) of nitrone **12f** gave 1.06 g (87%) of a mixture of 92% of hydroxylamine **13f** and 8% of *N*-oxide **25**: ^1H NMR δ 7.1–7.3 (m, 10 H), 5.7–5.8 (m, 1 H), 4.8–5.0 (m, 2 H), 3.4 (s, 2 H), 2.5 (s, 3 H), 2.4 (m, 2 H), 1.8 (m, 2 H). A solution of this mixture in $CDCl_3$ stood at rt for 22 h at which point cyclization was 88% complete; heating under reflux for 3.5 h completed the cyclization: ^1H NMR δ 7.1–7.4 (m, 10 H), 4.4 (d, J = 12 Hz, 1 H), 4.0 (d, J = 12 Hz, 1 H), 3.4 (m, 1 H), 2.9 (s, 3 H), 2.4 (m, 2 H), 2.0–2.3 (m, 2 H), 1.5 (d, J = 7 Hz, 3 H). The picrate had mp 220–222 °C dec. Anal. Calcd for $C_{25}H_{26}N_4O_8$: C, 58.82; H, 5.13; N, 10.98. Found: C, 58.89; H, 5.01; N, 10.91.

2-Methyl-2-phenyl-4-pentenal. A mixture of 134 g (1 mol) of 2-phenylpropanal, 62 g (1.07 mol) of allyl alcohol, 25 mL of benzene, and 0.5 g (3 mmol) of *p*-toluenesulfonic acid was heated under reflux using a 30-cm Vigreux column fitted with a Dean-Stark water collector for 16 h. Distillation gave 121.1 g (70%) of 2-methyl-2-phenyl-4-pentenal, bp 130 °C (25 mm): ^1H NMR δ 9.5 (s, 1 H), 7.2–7.5 (m, 5 H), 5.5 (m, 1 H), 5.0 (m, 2 H), 2.6 (m, 2 H), 1.5 (s, 3 H).

***N*-(2-Methyl-2-phenyl-4-pentenylidene)methanamine *N*-oxide:** yield of crude product 97%; ^1H NMR δ 7.2–7.4 (m, 5 H), 6.8 (s, 1 H), 5.5 (m, 1 H), 5.0–5.1 (m, 2 H), 3.7 (s, 3 H), 2.9 (d/d, J = 13/7 Hz, 1 H), 2.6 (d/d, J = 13/7 Hz, 1H), 1.6 (s, 3 H).

1,2,4-Trimethyl-4-phenylpyrrolidine 1-oxide (28): yield of crude product 98%; ^1H NMR δ 7.7 (2 d, 1 H), 7.2–7.4 (m, 4 H), 3.4–4.2 (m, 3 H), 3.2 (s, 1H), 3.1 (s, 2 H), 2.0–2.9 (m, 2 H), 1.8 (s, 2 H), 1.6 (s, 1 H), 1.4 (two d, ratio 65:35, 3 H). Short-path distillation (160 °C bath temperature, 0.001 mm) of 0.74 g of this product gave 0.61g (79% from 2-methyl-2-phenylpropanal) of purified material: HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1483.

1,2,4-Trimethyl-4-phenylpyrrolidine. A solution of 0.93 g (4.5 mmol) of *N*-oxide **28** in 10 mL of formic acid was treated under N_2 with 0.36 g of 10% Pd/C, and the mixture was heated under reflux for 1 h and concentrated. The residue was dissolved in H_2O, and the catalyst was removed by filtration. The filtrate was washed with toluene, and the aqueous phase was made basic with 15% aqueous NaOH and extracted with CH_2Cl_2 to give 0.67 g of the crude title compound. Short-path distillation (100 °C bath temperature, 0.001 mm) gave 0.65 g of purified material: ^1H NMR δ 7.1–7.4 (m, 5 H), 3.5 (d, J = 10 Hz, 0.4 H), 3.1 (d, J =10 Hz, 0.6 H), 1.6–2.6 (m + 2s, 7 H), 1.5 (s, 1.8 H),1.4 (s, 1.2 H), 1.2 (d, J = 7 Hz, 1.8 H), 1.1 (d, J = 7 Hz, 1.2 H); ^{13}C NMR δ 18.4, 19.7, 29.9, 32.6, 40.3, 40.5, 42.9, 43.7, 48.5, 51.0; 61.1, 62.3, 71.0, 72.0,125.4, 125.5, 125.7, 125.9, 128.1, 128.2, 150.5, 151.4; HRMS calcd for $C_{13}H_{19}N$ 189.1518, found 189.1522. Anal. Calcd for $C_{13}H_{19}N$: C, 82.40; H, 10.12; N, 7.40. Found: C, 82.12; H, 9.95; N, 7.30.

***cis*-1,2-Dimethyl-5-phenylpyrrolidine *N*-Oxide (30).** A Grignard reagent was prepared from 4.30 g (32 mmol) of freshly distilled 4-bromo-1-butene and 1.00 g (37 mmol) of Mg in 35 mL of ether and then added slowly at 0 °C to a solution of 2.68 g (19.8 mmol) of benzylidenemethanamine *N*-oxide (prepared from benzaldehyde and *N*-methylhydroxylamine) in 10 mL of THF. The mixture was stirred at rt for 1 h. Addition of 40 mL of 20% aqueous NH_4Cl solution followed by extraction with ether gave 4.12 g of the title compound which was reduced without further purification: ^1H NMR δ 7.6 (m, 1H), 7.0 (m, 4 H), 4.8 (d/d, J = 7/3 Hz, 0.6 H); 4.2 (d/d, J = 11/6 Hz, 0.4 H), 3.6 (m, 1 H), 2.9 (m, 0.6 H), 2.8 (s, 1.2 H), 2.6 (s, 1.8 H), 2.6 (m, 0.4 H), 2.0–2.4 (m, 3 H), 1.4 (t, J = 7 Hz, 3 H).

1,2-Dimethyl-5-phenylpyrrolidine. Deoxygenation of crude *N*-oxide **30** (4.05 g) with formic acid and Pd/C as described above followed by short-path distillation (120 °C bath temperature, 0.3 mm) gave 2.64 g of a product consisting of about 90% of a ca. 1:1 mixture of the two isomers of the title compound (70% from benzylidenemethanamine *N*-oxide): ^1H NMR δ 3.7 (d/d, J = 7/6 Hz, 0.5 H), 3.1 (t, J = 8 Hz, 0.5 H), 2.1 (2 s, 3 H), 1.2 (d, J = 7 Hz, 1.5 H), 1.0 (d, J = 7 Hz, 1.5 H), among others; high-resolution MS calcd for $C_{12}H_{17}N$ 175.1361, found 175.1360.

***cis*-4-Heptenylidenemethanamine *N*-oxide** was prepared in quantitative yield from *cis*-4-heptenal (Pfaltz and Bauer): ^1H NMR δ 6.7 (t, J = 5 Hz, 1H), 5.3–5.5 (m, 2 H), 3.7 (s, 3 H), 2.6 (m, 2 H), 2.3 (m, 2 H), 2.1 (m, 2 H), 1.0 (t, J = 7 Hz, 3 H).

***N*-(*cis*-4-Heptenyl)-*N*-methylhydroxylamine (31).** Yield from *cis*-4-heptenal, 78%, containing a trace of *N*-oxide **32** after short-path distillation at 100 °C bath temperature (0.001 mm): ^1H NMR δ 5.3–5.5 (m, 2 H), 2.6 (m + s, 5H), 2.0 (m, 4 H), 1.6 (m, 2 H), 1.0 (t, J = 7 Hz, 3H); high-resolution MS calcd for $C_8H_{17}NO$ 143.1310, found 143.1312.

***trans*-1-Methyl-2-propylpyrrolidine *N*-Oxide (32).** On standing at room temperature, a neat sample of hydroxylamine **31** slowly cyclized to give the title compound with a half-life

(28) Franzen, V.; Kuntze, H. *Liebigs Ann. Chem.* **1959**, *627*, 15.

of about 115 days: ^{1}H NMR δ 3.6 (t, J = 7 Hz, split further, 1 H), 3.4 (q, J = 9 Hz, 1 H), 3.2 (s, 3 H), 3.1 (m, 1 H), 2.4 (m, 1 H), 1.2–2.1 (m, 7 H), 1.0 (t, J = 7 Hz, 3 H).

***N*-(2,2,5-Triphenyl-4-pentenylidene)-1-methylethanamine *N*-oxide** was prepared in quantitative yield as discribed for nitrone **12a** except that *N*-isopropylhydroxylamine hydrochloride was used: ^{1}H NMR δ 7.4 (s, 1 H), 7.2–7.3 (m, 15 H), 6.4 (d, J = 15 Hz, 1 H), 6.0 (d/t, J = 15/7 Hz, 1 H), 4.1 (septet, J = 6 Hz, 1 H), 3.6 (d, J = 7 Hz, 2 H), 1.6 (broadened s, 1 H), 1.4 (d, J = 6 Hz, 6H). An analytical sample (EtOAc) had mp 130–131 °C. Anal. Calcd for $C_{26}H_{27}NO$: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.48; H, 7.29; N, 3.77.

***N*-(2,2,5-Triphenyl-4-pentenyl)-*N*-(methylethyl)hydroxylamine (34) and 2-Benzyl-4,4-diphenyl-1-(methylethyl)pyrrolidine 1-Oxide (35).** $LiAlH_4$ reduction of 0.32 g of *N*-(2,2,5-triphenyl-4-pentenylidene)-1-methylethanamine *N*-oxide gave 0.32 g of material. The ^{1}H NMR of hydroxylamine **34** was determined after standing in pyridine-d_5 for 2 h: δ 7.1–7.4 (m, 15 H), 6.6 (d, J = 15 Hz, 1 H), 6.4 (d/t, J = 15/7 Hz, 1 H), 3.8 (s, 2 H), 3.6 (d, J = 7 Hz, 2 H), 2.8 (septet, J = 6 Hz, 1 H), 1.2 (d, J = 6 Hz, 6 H). The ^{1}H NMR of *N*-oxide **35** was determined after standing in CD_3OD for 2 d: δ 7.1–7.4 (m, 15 H), 4.7 (d, J = 12 Hz, 1 H), 4.2 (d, J = 12 Hz, 1 H), 3.8 (m, 1 H), 3.6 (septet, J = 6 Hz, 1 H), 2.9–3.2 (m, 4 H), 1.5 (d, J = 6 Hz, 3 H), 1.1 (d, J = 6 Hz, 3 H). The equilibrium studies were carried out as described for the pair **13a/14a**.

***N,N*-Dimethyl(1-ethoxyethenyl)amine *N*-Oxide (36).** To a cooled solution of 5.06 g (82.9 mmol) of anhydrous *N,N*-dimethylhydroxylamine in 30 mL of THF was added slowly with cooling 11.68 g of a 60:40 mixture of ethoxyacetylene and hexane (6.91 g, 98.7 mmol). Removal of the solvent after 3 d at rt and short-path distillation of the residue at 70–90 °C bath temperature/0.001 mm gave 8.43 g (76%) of the title compound: n^{25}_D 1.4620; ^{1}H NMR (60 MHz, neat) δ 5.6 (d, J = 3 Hz, 1 H), 4.2 (d, J = 3 Hz, 1 H), 4.0 (q, J = 6 Hz, 2 H), 3.4 (s, 6 H), 1.4 (t, J = 6 Hz, 3 H); IR (neat) 3170, 3050, 1675 (vs) cm^{-1} among others; UV (H_2O) no maximum, only weak end absorption with a shoulder at 270 nm (ϵ 55). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.97; H, 10.08; N, 10.97.

1-(1-Ethoxyethenyl)piperidine 1-oxide (37) was prepared as above from 1.02 g (12 mmol) of 1-hydroxypiperidine to give 1.62 g of the crude title compound as a tan, hygroscopic solid: ^{1}H NMR δ 5.7 (d, J = 3 Hz, 1 H), 4.2 (d, J = 3 Hz, 1 H), 4.0 (q, J = 6 Hz, 2 H), 3.9–1.0 (m + t, 13 H).

Ethyl 1-Methylpiperidine-3-carboxylate 1-Oxide (38). A mixture of 1.71 g (10 mmol) of ethyl 1-methylpiperidine-3-carboxylate, 2.0 g (11.5 mmol) of *m*-chloroperoxybenzoic acid, and 10 mL of $CHCl_3$ stood at rt for 2 h, 10 mL of solvent was added, and the mixture was filtered. The filtrates were stirred with 3.0 g of K_2CO_3 for 24 h, filtered, and concentrated to give 1.75 g (93%) of the title compound as a single isomer: ^{1}H NMR δ 4.2 (q, J = 6 Hz, 2 H), 3.4–3.5 (m, 2 H), 3.6 (s + m, 4 H), 3.0–3.2 (m, 2 H), 2.5 (m, 1 H), 2.2 (m, 1 H), 1.8 (m, 1 H), 1.4 (m, 1 H), 1.2 (t, J = 6 Hz, 3 H). The picrate had mp 136–137 °C. Anal. Calcd for $C_{15}H_{20}N_4O_{10}$: C, 43.27; H, 4.84; N, 13.46. Found: C, 43.36; H, 4.69; N, 13.46.

***N*-(4-Carbethoxy-4-pentenyl)-*N*-methylhydroxylamine (39).** A sample of 0.47 g of *N*-oxide **38** was evacuated to 0.5 mm and slowly heated in an oil bath. It started to melt at 125 °C and completely liquefied at ca. 160 °C. The product (0.28 g) was a mixture of 88% of the title compound and 12% unreacted starting material: ^{1}H NMR of the former: δ 6.2 (s, 1 H), 5.6 (s, 1 H), 4.2 (q, J = 7 Hz, 2 H), 2.6 (s + m, 5 H), 2.4 (t, J = 6 Hz, 2 H), 1.8 (m, 2 H), 1.3 (t, J = 7 Hz, 3 H). On standing at rt in $CDCl_3$, hydroxylamine **39** completely reverted to *N*-oxide **38**; no signal attributable to ethyl 1,2-dimethylpyrrolidine-2-carboxylate 1-oxide (**40**) were observed in the ^{1}H NMR.

4,4-Diphenyl-2-methyl-1-pyrrolidinol (42). A mixture of 30 g (0.127 mol) of 2,2-diphenyl-4-pentenal (**1**), 18 g (0.257 mol) of hydroxylamine hydrochloride, 18 g (0.209 mol) of NaOAc, and 90 mL of EtOH was stirred at rt for 3 h, 450 mL of 10% aqueous Na_2CO_3 was added, and the mixture was extracted several times with CH_2Cl_2. The crude product was crystallized from 30 mL of *i*-PrOH to give 20.1 g (59%) of 2,2-diphenyl-4-pentenal oxime. To a stirred mixture of 12.5 g (47 mmol) of the oxime, 9.0 g (173 mmol) of $Na(CN)BH_3$, 30 drops of 0.01% methyl orange in EtOH, and 100 mL of MeOH was added at 20–25 °C a mixture of 32 mL of concd HCl and 168 mL of MeOH at a rate to keep the indicator pink; 95 mL was used during 3 h. The mixture was made strongly basic with 15% NaOH and extracted several times with CH_2Cl_2 to give 12.5 g of essentially pure title compound as an oil: ^{1}H NMR δ 7.1–7.3 (m, 10H), 4.0 (d, J = 10 Hz, 1 H), 3.5 (d, J = 10 Hz, 1 H), 3.2 (m, 1 H), 2.8 (d/d, J = 13/7 Hz, 1 H), 2.2 (d/d, J = 13/10 Hz, 1 H), 1.3 (d, J = 6 Hz, 3 H). The hydrochloride (56% from the oxime) had mp 194–196 °C dec. Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70.45; H, 6.96; N, 4.83. Found: C, 70.48; H, 7.00; N, 4.80.

4,4-Diphenyl-2-methylpyrrolidine. A mixture of 4.93 g of crude hydroxylamine **42**, 2.2 g of 10% Pd/C, and 50 mL of HOAc was shaken under 50 psi initial H_2 pressure for 6 h, made basic with NaOH, and extracted with CH_2Cl_2. Short-path distillation of the crude product at 100–140 °C/0.002 mm gave 4.13 g (89% from 2,2-diphenyl-4-pentenal oxime) of the title compound: ^{1}H NMR δ 7.1–7.4 (m, 10 H), 3.6 (d/d, J = 11/1 Hz, 1 H), 3.4 (d, J = 11 Hz, 1 H), 3.3 (m, 1 H), 2.7 (d/d, J = 13/7 Hz, 1 H), 2.0 (d/d, J = 13/9 Hz, 1 H), 1.9 (s, 1 H), 1.2 (d, J = 6 Hz, 3 H); ^{13}C NMR δ 22.372, 47.059, 53.010, 57.250, 57.909, 125.906, 126.941, 127.005, 128.232, 128.260, 128.562, 147.095, 147.100. Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: 85.94; H, 7.84; N, 5.86.

***N*-[5-(5-Methyl-5*H*-dibenzo[*a,d*]cycloheptenyl)]-*N*-methylhydroxylamine (43).** The procedure of ref 18a was adapted: a mixture of 17 mL of CH_2Cl_2, 17 mL of chloroacetic acid, and 10.7 g of NaOAc was stirred for 15 min, 10.0 g (119 mmol) of *N*-methylhydroxylamine hydrochloride was added, and stirring was continued for 90 min. A solution of 7.2 g (32.4 mmol) of 5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5-ol[18a] in 17 mL of CH_2Cl_2 was added, and the mixture was stirred for 45 min. Concentrated NH_4OH (70 mL) was added, followed by 100 mL of H_2O. Extraction with CH_2Cl_2 gave 8.55 g of an oil. This was dissolved in toluene, and the solution was extracted with 5% HCl. The aqueous extracts were washed with ether and made basic with NH_4OH. Extraction with CH_2Cl_2 gave 1.99 g (24%) of the title compound: ^{1}H NMR δ 7.6 (d, J = 7 Hz, 2 H), 7.2–7.4 (m, 6 H), 7.0 (s, 2 H), 3.8 (br, 1 H), 2.2 (s, 3 H), 2.1 (s, 3 H). The hydrochloride decomposed to 5-methylene-5*H*-dibenzo[*a,d*]cycloheptene on drying at 80 °C.

5,12-Dimethyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine 12-Oxide (44). A solution of 0.56 g of crude hydroxylamine **43** in 5 mL of $CHCl_3$ was heated under reflux for 2.5 h. Removal of the solvent left 0.55 g of the title compound as a solid: ^{1}H NMR δ 7.0–7.4 (m, 8 H), 4.6 (d, J = 5 Hz, 1 H), 4.2 (d/d, J = 16/5 Hz, 1 H), 3.2 (s, 3 H), 2.8 (d, J = 16 Hz, 1 H), 2.1 (s, 3 H). The hydrochloride (0.40 g, 62%) had mp 233 °C dec after crystallization from EtOH: ^{1}H NMR (in D_2O) δ 6.8–7.3 (m, 8 H), 5.2 (d, J = 5 Hz, 1 H), 3.6 (d/d, J = 16/5 Hz, 1 H), 3.2 (s, 3 H), 2.9 (d, J = 16 Hz, 1 H),2.0 (s, 3 H). Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 71.08; H, 6.13; N, 4.67.

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Supporting Information Available: Physical and spectral data for nitriles **10b–10f**, aldehydes **11b–11f**, and nitrones **12b–12f**. ^{1}H NMR spectra of new compounds **3**, **12a–12f**, **14a**, **14a–*d***, **31**, **31/32**, **34**, **35**, **39**, **43**, *N*-(2-methyl-2-phenyl-4-pentenylidene)methanamine *N*-oxide, and 1,2-dimethyl-5-phenylpyrrolidine, for which elemental analyses were not obtained (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

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