Chemistry of Four-Membered Cyclic Nitrones. 3. Reaction with Nucleophilic Reagents and Stereospecific Conversion into 1-Hydroxyazetidines[1]

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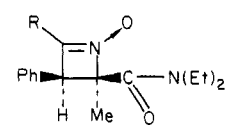
Four-membered cyclic nitrones (1) react with a variety of nucleophiles (MeMgI, CN^-, OH^-, MeO^-, and H^-) by stereospecific addition to the C=N bond. Reaction of **1a** with potassium cyanide and with methylmagnesium iodide yields the 1-hydroxyazetidines **2a** and **2b**, respectively. Reduction of **1b** with lithium aluminum hydride and with sodium borohydride affords the 1-hydroxyazetidine derivatives **3** and **4**, respectively. Sodium hydroxide in methanol–water reacts with **1a** to give a mixture of two isomeric 5-hydroxyisoxazolidines **5a** and **5b**, but under similar reaction conditions **1b** and **1c** rearrange to the oximes **6** and **7**. In acetic acid at room temperature **6a** cyclizes to the 6*H*-1,2-oxazin-6-one derivative **8**, whereas **6b** yields 5-methyl-3,4-diphenylisoxazole (**9**) after being refluxed in acetic acid, probably by carbon monoxide elimination from the intermediate oxazin-6-one derivative. Reaction of **1a** with sodium hydroxide for 2 min gives exclusively the 1-hydroxy-4-methoxyazetidine **13a**, whereas prolonged reaction gives the isomeric azetidine **13b** together with **5** (mixture of **5a** and **5b** in a ratio 4:1). Single-crystal X-ray analysis of **13b** reveals that all three relatively bulky substituents at C-2, C-3, and C-4 are on the same face of the azetidine ring. Treatment of **13b** with acetic acid at room temperature gives the 5-methoxyisoxazolidine **15**. The 1-hydroxyazetidines **2–4** are oxidized with yellow mercury(II) oxide to the corresponding four-membered cyclic nitrones **1b**, **16**, and **17**.

Nitrones belong to a class of compounds that has been the subject of intensive research throughout the past decades.[2-5] Several cyclic members of this class of compounds have been reported, including five-[6] and six-membered[7] cyclic nitrones. In 1974 Black et al.[8] reported the first four-membered cyclic nitrone, synthesized by cyclization of a β-tosyloxy oxime. They characterized this nitrone only by IR and ^1H NMR spectroscopy and described the compound as an unstable oil. Recently another four-membered cyclic nitrone was obtained as one of the products of the oxidation of the corresponding dihydroazete derivative by Harnisch and Szeimies.[9]

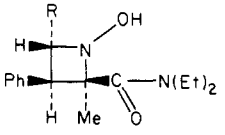
We have described a more general synthesis of a number of relatively stable four-membered cyclic nitrones by the reaction of 1-nitro(cyclo)alkenes with ynamines,[10] and we are currently investigating their reactivity. In part 2 of this series we have described the 1,3-dipolar cycloaddition reactions of these nitrones with electron-deficient acetylenes, and those reactions showed a remarkable reactivity of the four-membered azetidine ring.[11] In addition to these 1,3-dipolar cycloaddition reactions, nitrones react with a variety of nucleophiles because the C=N bond is chemically equivalent to a carbonyl function. Therefore nitrones generally react in a fashion similar to ketones or aldehydes.[2-5] In this paper we describe the results of the reactions of four-membered cyclic nitrones 1 with several nucleophilic reagents.[12]

Results and Discussion

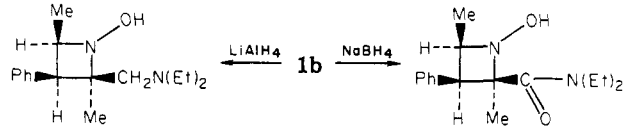
Reactions with Carbon Nucleophiles and Complex Metal Hydrides. Reaction of nitrone **1a** with potassium cyanide in methanol occurred smoothly at room temperature and gave a crystalline product in a yield of 75%. According to mass spectrometry and elemental analysis this product was formed by the addition of hydrogen cyanide to nitrone **1a**. On the basis of the two doublets



1a, R = H
b, R = Me
c, R = Ph



2a, R = CN
b, R = Me



3 **4**

at δ 3.67 and 4.39 (J = 3.4 Hz) in the ^1H NMR spectrum and the absorptions in the ^{13}C NMR spectrum, we could prove the 4-cyano-1-hydroxyazetidine structure **2a** with a stereochemistry as shown (Table I). Strong evidence for this stereochemistry is the relatively small coupling constant of 3.4 Hz of the hydrogen atoms at C-3 and C-4, which points toward trans substitution.[13]

(1) Part of the forthcoming thesis of M.L.M.P.
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(8) Black, D. St. C.; Brown, R. F. C.; Dunstan, B. F.; Sternhell, S. *Tetrahedron Lett.* **1974**, 4283.
(9) Harnisch, J.; Szeimies, G. *Chem. Ber.* **1979**, *112*, 3914.
(10) Chemistry of Four-Membered Cyclic Nitrones. 1: Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816.
(11) Pennings, M. L. M.; Okay, G.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.*, previous paper in this issue.
(12) Some of these results have been described in a preliminary publication: Pennings, M. L. M.; Reinhoudt, D. N. *Tetrahedron Lett.* **1982**, *23*, 1003.
(13) A molecular model of the azetidine ring shows that the dihedral angle between the hydrogen atoms at C-3 and C-4 in the trans configuration can vary between ~90° and ~150°, which means that the coupling constant can have values between ~0 and ~10 Hz. In the cis configuration this dihedral angle can vary between ~−30° and ~+30°, which results in a coupling constant of ~8–10 Hz. This observation explains why both in the cis- and the trans-substituted 1-hydroxyazetidines, with different substituents at C-4, different coupling constants are observed (see Table I).

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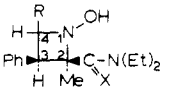
Table I. Characteristic ^1H and ^{13}C NMR Chemical Shifts of 1-Hydroxyazetidines 2-4 and 13



	^1H NMR ($CDCl_3$)				^{13}C NMR ($CDCl_3$), δ				
compd	δ(H-3)	δ(H-4)	$J_{3,4}$, Hz	δ(R)	C-2 (s)	C-3 (d)	C-4 (d)	R (q)	Me (q)
2a	3.67 (d)	4.39 (d)	3.4		77.8	50.6	60.3	117.4 (s)	18.5
2b	2.85 (d)	4.21 (m)	8.8	1.29 (d)	75.2	53.1	68.4	18.7	25.0
3	3.21 (d)	4.13 (m)	9.5	1.04 (d)	72.2	50.9	65.1	14.1	18.2
4	3.39 (d)	3.97 (m)	9.0	0.90 (d)	74.0	51.6	63.0	14.6	16.9
13a	3.16 (d)	5.09 (d)	6.6	3.46 (s)	68.8	52.1	98.6	55.7	25.2
13b	3.62 (d)	4.82 (d)	8.0	3.40 (s)	68.9	52.9	93.8	56.0	18.4

Generally, in the reactions of potassium cyanide with *C,N*-diaryl-substituted nitrones described in the literature, the intermediate hydroxylamine derivatives could not be isolated because of a fast rearrangement to the corresponding cyano and methoxy imines.[14] Hitherto only in the reaction of *C*-alkyl-*N*-(1-cyanoalkyl)nitrones with hydrogen cyanide the corresponding hydroxylamines could be isolated.[15] Reaction of hydrogen cyanide with several pyrroline 1-oxides gave the corresponding 2-cyano-1-hydroxypyrrolidines in yields of 70–80%.[16,17]

Reaction of nitrone **1a** with methylmagnesium iodide in diethyl ether at room temperature gave a crystalline product in a yield of 76%. The ^1H NMR spectrum of this product showed a methyl doublet at a relatively high field (δ 1.29) and two coupled signals at δ 2.85 and 4.21, respectively. From these data and comparison of other spectroscopic data with those of **2a**, we have assigned structure **2b** to this product (Table I). The vicinal coupling constant of the hydrogen atoms at C-3 and C-4 does not unambiguously prove the stereochemistry shown, because of its relatively large value of 8.8 Hz.[13] However, more definite proof for structure **2b** was obtained by comparison of the spectroscopic data of the product obtained by reduction of nitrone **1b** with sodium borohydride (vide infra).

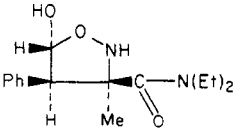
Similar Grignard reactions with pyrroline 1-oxides and oxazoline *N*-oxides, which lead to the formation of the corresponding 2-alkyl-1-hydroxypyrrolidines and 2-alkyl-*N*-hydroxyoxazolidines, respectively, have been reported.[6,16,18]

Reduction of nitrone **1b** with $LiAlH_4$ in tetrahydrofuran at room temperature gave a crystalline product in a yield of 61%. Mass spectrometry and elemental analysis clearly showed that besides the reduction of the nitrone moiety, reduction of the amide function had occurred. Comparison of the ^1H and ^{13}C NMR data with those of **2a** and **2b** clearly proved structure **3** (see Table I).

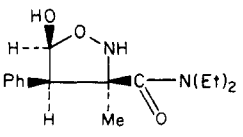
In addition to the reduction with $LiAlH_4$, which has been reported for acyclic nitrones[19] and a four-membered cyclic nitrone,[9] nitrones can be reduced to the corresponding hydroxylamine derivatives by sodium or potassium borohydride.[6,16,20] Reaction of nitrone **1b** with sodium borohydride in methanol at room temperature gave a crystalline product in a yield of 92%. Mass spectrometry and elemental analysis showed that reduction of **1b** to the corresponding 1-hydroxyazetidine **4**, which has a stereochemistry that is different from **2b**, had taken place. Although the vicinal coupling constant of H-3 and H-4 of both isomers is almost the same (8.8 vs. 9.0 Hz), comparison of the ^1H and ^{13}C NMR data of **2b** and **4** (see Table I) clearly proves the stereochemistry of both products; the absorption of the methyl group at C-4 in **4** is at a higher field (δ 0.90) than in **2b** (δ 1.29), due to the shielding of the cis-substituted phenyl group.

From these results it can be seen that four-membered cyclic nitrones are easily converted into 1-hydroxyazetidines either by reaction with carbon nucleophiles or by reduction with metal hydrides in almost quantitative yields. The four-membered cyclic nitrones **1a** and **1b** are obviously extremely crowded on one face of the almost flat four-membered ring, and therefore both the addition of the nucleophiles and the addition of the hydride take place in a stereospecific fashion from the sterically less hindered side. The 1-hydroxyazetidines **2–4**, which give a dark red color with a basic triphenyltetrazolium chloride (TTC) solution in butanol,[21] a characteristic reaction for hydroxylamines, belong to a class of virtually unknown heterocycles[22] and were further characterized by oxidation to the corresponding four-membered cyclic nitrones (vide infra).

Reactions with Oxygen Nucleophiles. Reaction of nitrone **1a** with 5 equiv of sodium hydroxide in a mixture of methanol and water gave two isomeric species in a ratio of 4:1. The major isomer exhibited a doublet at δ 5.50 and 3.61 with a coupling constant of ~1.0 Hz, whereas the minor isomer gave a doublet at δ 5.70 and 3.50 with a coupling constant of 6.0 Hz. By use of these data together with low-field absorptions in the ^{13}C NMR spectrum at δ 106.4 for the major and δ 100.5 for the minor isomer, which are characteristic for an sp^3 carbon atom adjacent to a nitrogen and an oxygen atom,[24] we assigned the 5-hydroxyisoxazolidine structures **5a** and **5b** to these isomers.



5a



5b

The configuration of both isomers is evident from the small coupling constant of H-4 and H-5 of the trans-substituted isomer (**5a**) and the larger value for the cis-substituted isomer (**5b**).

(14) Bellativa, V. *Gazz. Chim. Ital.* **1940**, *70*, 584.
(15) Masui, M.; Yijima, C. *J. Chem. Soc. C* **1967**, 2022.
(16) Bonnet, R.; Brown, R. F. C.; Clark, V. M.; Sutherland, I. O.; Todd, A. *J. Chem. Soc.* **1959**, 2094.
(17) An elegant way to obtain the cyanohydroxylamine derivatives from *C*-aryl-*N*-phenylnitrones is the reaction with trimethylsilyl cyanide, followed by hydrolysis of the resulting trimethylsilylated hydroxylamine: Tsuge, O.; Urano, S.; Iwasaki, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 485.
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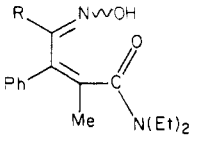
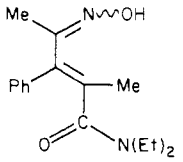
(20) Lamchen, M.; Mittag, T. W. *J. Chem. Soc. C* **1967**, 2300.
(21) Snow, G. A. *J. Chem. Soc.* **1954**, 2588.
(22) Other examples of 1-hydroxyazetidines have been prepared by reduction of a four-membered cyclic nitrone[9] and by reaction of hydroxylamine with methyl 2,4-dibromobutyrate.[23]
(23) Kostyanovskii, R. G.; Prosyanik, A. V.; Markov, V. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, 956; *Chem. Abstr.* **1974**, *81*, 25476.
(24) Abou-Gharbia, M. A.; Joullie, M. M. *Heterocycles* **1978**, *9*, 457.

Reaction of **1b** with sodium hydroxide in methanol gave the two isomeric oximes **6a** and **7** in yields of 40% and 34%, respectively. Mass spectrometry and elemental analysis revealed that the molecular formula of these products was identical with that of the starting material.



6a, R = Me
b, R = Ph



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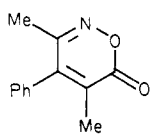
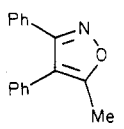
The similar reaction of **1c** with sodium hydroxide in a refluxing mixture of methanol and water gave only one oxime (**6b**) in a yield of 78%. Comparison of the spectroscopic data with those of **6a** and **7** clearly proved the oxime structure **6b**.

We assume that the stereochemistry of oximes **6** and **7** is as shown, on the basis of their chemical behavior. When oxime **6a** was dissolved in glacial acetic acid at room temperature, a cyclization reaction took place, and we isolated a white solid in a yield of 61%. According to mass spectrometry and elemental analysis this product was formed by the loss of diethylamine, and ^{1}H NMR and ^{13}C NMR clearly proved the 6*H*-1,2-oxazin-6-one structure **8**. Mass



8



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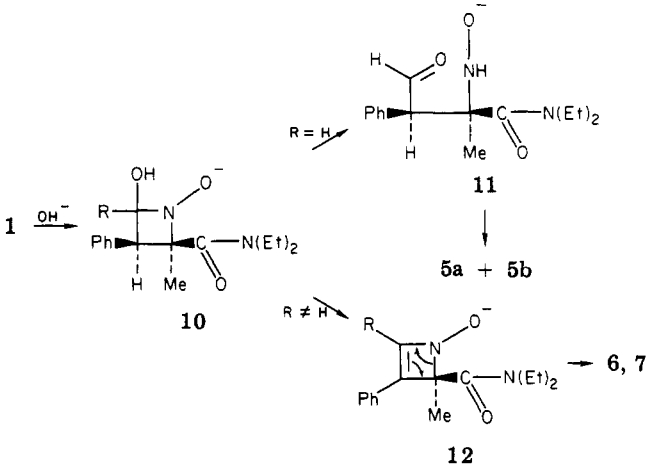
spectrometry showed a characteristic fragmentation pattern ($M^{+\cdot}$ – NO, $M^{+\cdot}$ – NO – CO), which has been reported for 6*H*-1,2-oxazin-6-ones.[25] When oxime **6b** was dissolved in acetic acid at elevated temperatures reaction did take place, and after reflux of the mixture for 5 h, we isolated a crystalline product (mp 96.5–97.5 °C) that according to ^{1}H NMR had lost the diethylamino group. Mass spectrometry showed that this product was not the expected 6*H*-1,2-oxazin-6-one but 5-methyl-3,4-diphenylisoxazole (**9**) that is probably formed from the oxazinone by elimination of carbon monoxide. Compound **9** showed a melting point, ^{1}H NMR data, and fragmentation pattern in the mass spectrum identical with those reported in the literature for 5-methyl-3,4-diphenylisoxazole.[26] All attempts to convert **7** into **8** failed, even in refluxing acetic acid.

From these results we conclude that in both **6a** and **6b** the carbonyl function and the oximino group must be cis substituted, since the formation of the oxazinones occurs via a nucleophilic attack of the hydroxy oxygen atom at the amide carbonyl, followed by elimination of diethylamine. In the case of trans substitution as in **7** such a cyclization reaction is impossible. The stereochemistry of the oximino group remains unclear, since it might be possible that the *E* isomer, which cannot undergo a cyclization reaction, is under the reaction conditions in equilibrium with the *Z* isomer which undergoes cyclization to the corresponding 1,2-oxazin-6-one.[27] Similar cyclization reactions of in situ generated oximes of γ-keto acids

Scheme I



or esters to give 6*H*-1,2-oxazin-6-ones have been reported.[28]

The formation of both type of products from the reactions of nitrones **1a–c** with sodium hydroxide can be rationalized in terms of addition of the hydroxide anion to the C=N bond of the nitrones to yield an intermediate of the type **10** (Scheme I). Similar "nitrone hydrates" have been reported by Kröhnke[29] as intermediates in the conversion of nitrones into amides which undergo a fast elimination of water across the C–N bond. However, in the reaction of **1a** (R = H) this intermediate rearranges via rupture of the C–N bond to the aldehyde **11**, which under the reaction conditions cyclizes to give the 5-hydroxyisoxazolidines **5a** and **5b**; a reaction that is formally a base-induced hydrolysis of a nitrone to a carbonyl component and a hydroxylamine derivative.[2-5] Similar cyclizations of β-iminoxy ketones have been reported to afford 5-hydroxyisoxazolines, which in some cases are in equilibrium with the starting compounds.[30]

When R = Me or Ph (**1b** or **1c**), ring opening does not occur, but instead water is eliminated to give the 2-azetine derivative **12**, which upon ring opening yields the oximes **6** or **7**. The two isomeric oximes **6a** and **7** are not interconvertible under the reaction conditions, which shows that both products must have been formed by a different mode of ring opening of the 2-azetine derivative **12** (R = Me). Monocyclic 2-azetine derivatives have been postulated as intermediates,[31] and to our knowledge only one "stable" 2-azetine has been reported.[32] Recently, Snyder predicted on the basis of MO calculations that the activation energy of the concerted conrotatory and disrotatory mode of ring opening of 2-azetines will probably be the same,[33] and therefore it will be difficult to predict the stereochemistry of the ring-opened products. A second effect which makes it difficult to predict the stereochemistry of the ring-opened oximes is the possibility of inversion of the substituent on nitrogen, both in the intermediate 2-azetines and in the oximes.

Reaction of nitrone **1a** with sodium hydroxide in *methanol* for 1 h gave in addition to the 5-hydroxyisoxazolidine **5** (61%) a second crystalline product, in a

(25) Abramovitch, R. A.; Shinkai, I.; Cue, B. W. Jr.; Ragan, F. A., Jr.; Atwood, J. L. *J. Heterocycl. Chem.* **1976**, *13*, 415.
(26) (a) Bravo, P.; Gaudiano, G.; Ticozzi, C. *Gazz. Chim. Ital.* **1972**, *102*, 395. (b) Bellec, C.; Bertin, D.; Colau, R.; Deswarte, S.; Maitte, P.; Viel, C. *J. Heterocycl. Chem.* **1979**, *16*, 1657.
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(28) (a) Kohler, E. P.; Goodwin, R. C. *J. Am. Chem. Soc.* **1927**, *49*, 219. (b) Lutz, R. E.; Hill, F. B., Jr. *J. Org. Chem.* **1941**, *6*, 175.
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(33) Snyder, P. J. *J. Org. Chem.* **1980**, *45*, 1341.

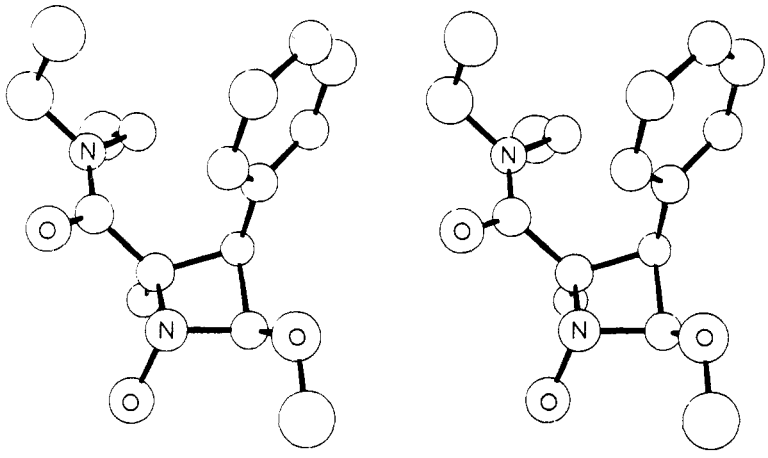
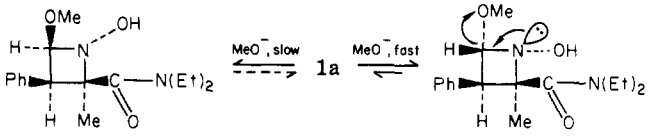


Figure 1. Stereoscopic view of the 1-hydroxy-4-methoxyazetidine **13b**.

Scheme II



13b **13a**

yield of 13%. According to mass spectrometry and elemental analysis this product must have been formed by the addition of methanol to nitrone **1a**, and ^{1}H NMR spectroscopy clearly showed the absorption of a methoxy singlet at δ 3.40 and two doublets at δ 3.62 and 4.82. Single-crystal X-ray analysis of this product showed the 1-hydroxy-4-methoxyazetidine structure **13b**. The crystal structure of **13b** contains two independent molecules, one of which is shown in Figure 1. The overall conformation of both molecules is the same, except for differences in the diethylamino moiety. Compound **13b** must have been formed by methoxide addition from the sterically most hindered side, and obviously **13b** is the thermodynamically less stable isomer because the three most bulky groups are on one face of the azetidine ring. The reaction of nitrone **1a** with sodium methoxide in methanol (Scheme II) for 1 h also gave a mixture of the 1-hydroxy-4-methoxyazetidine **13b** (58%) and the 5-hydroxyisoxazolidine **5** (15%), which probably has been formed by traces of water present.[34]

However, when nitrone **1a** was reacted with sodium hydroxide in methanol under identical conditions for 2 min, it was quantitatively converted into a 1:1 addition product with methanol, which was different from **13b**. We assigned structure **13a** to this product on the basis of the presence in the ^{1}H NMR spectrum of a methoxy singlet at δ 3.46 and the presence of two doublets at δ 3.16 and 5.09. Comparison of the ^{13}C NMR data clearly proved the isomeric structures **13a** and **13b** (Table I).

We can rationalize these results by assuming that in both the reaction with sodium hydroxide and sodium methoxide in methanol, the methoxide anion reacts under conditions of kinetic control via a fast addition to the C=N bond of nitrone **1a** *from the sterically less hindered side* to give **13a**. It is likely that in this medium an equilibrium exists between **13a** and **1a**, since the methoxide anion can easily be eliminated by a trans type of elimination process, through participation of the lone pair at nitrogen (Scheme II). At a prolonged reaction time the nitrone **1a** from the equilibrium mixture reacts by hydroxide addition to give **5** and by methoxide addition *from the sterically most hindered side* to give **13b**. This reaction, which gives **13b**, is irreversible since **13b** is stable under the reaction conditions. To our knowledge the adducts of methanol and nitrones have not been isolated previously.[2-5] Therefore, we think that the reason why **13b** can be isolated is hindered nitrogen inversion, which makes methoxide elimination via a trans type of elimination process impossible, because the nitrogen lone pair and the methoxy group are cis substituted. In the case of a fast nitrogen inversion in **13b**, the formation of **13b** would also have been reversible, and the reaction of **1a** with both sodium hydroxide and sodium methoxide would exclusively have given the irreversibly formed hydroxide addition products, the 5-hydroxyisoxazolidines **5a** and **5b**.

Hindered nitrogen inversion in cyclic amines is known;[35] however, the rate of inversion of 1-hydroxyazetidines has never been studied. It is possible to estimate a $\Delta G^{\ddagger}$ value of $\sim$16 kcal mol^{-1} by using the known $\Delta G^{\ddagger}$ values for the rate of nitrogen inversion in 1-chloroazetidines, pyrrolidines, and 1-hydroxypyrrolidines.[36] In unsymmetrically substituted azetidines like **13b** this value of 16 kcal mol^{-1} will be increased by a certain amount, because nitrogen inversion in **13b** will lead to very strong steric interactions of the hydroxy group with the three other substituents. Therefore, it can be expected that the rate of nitrogen inversion is rather slow and that the configuration of the nitrogen atom is strongly in favor of the one as shown in **13b**.

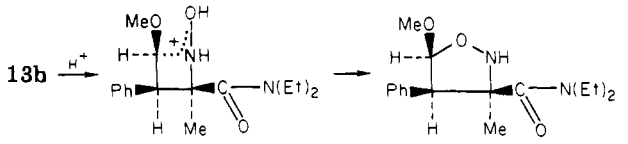
More evidence for the hindered inversion of the nitrogen atom was obtained by treating both 1-hydroxy-4-methoxyazetidines with acid. When **13a** was dissolved in $CDCl_3$ and a catalytic amount of *p*-toluenesulfonic acid was added to this solution, ^{1}H NMR spectroscopy revealed complete polymerization within 10 min. All signals became very broad except the methoxy signal which was present as a sharp singlet at δ 3.42. Most likely **13a** undergoes an acid-catalyzed elimination of methanol to give nitrone **1a**, which is known to undergo both thermal and acid-cata-

(34) In reactions of **1a** with sodium methoxide in methanol (distilled from sodium) under absolute anhydrous conditions no 5-hydroxyisoxazolidine **5** was isolated; however, the yield of 1-hydroxy-4-methoxyazetidine **13b** was not improved.

(35) (a) Lehn, J. M.; Wagner, J. *J. Chem. Soc., Chem. Commun.* **1968**, 148. (b) Lehn, J. M.; Wagner, J. *Tetrahedron* **1970**, *26*, 4227. (c) Lehn, J. M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311. (d) Riddell, F. G. *Tetrahedron* **1981**, *37*, 849.

(36) The $\Delta G^{\ddagger}$ values for 1-chloro- and 1-hydroxypyrrolidine are 9.0 and 13.0 kcal mol^{-1}, respectively:[35c] substitution of a chlorine by an oxygen atom increases the $\Delta G^{\ddagger}$ value by 4 kcal mol^{-1}. The $\Delta G^{\ddagger}$ value reported for 1-chloroazetidine (12 kcal mol^{-1}) increased by 4 kcal mol^{-1} gives the $\Delta G^{\ddagger}$ value for the corresponding 1-hydroxyazetidine, 16 kcal mol^{-1}.

Scheme III



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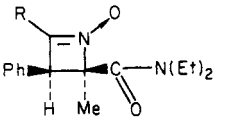
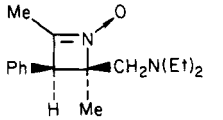
lyzed polymerization.[10] 1-Hydroxy-4-methoxyazetidine **13b** is stable when treated with acid under similar conditions, which proves also that in this case a trans type of methanol elimination is not possible. Reaction of **13b** in glacial acetic acid for 12 days gave a crystalline product in a yield of 25%, which according to mass spectrometry and elemental analysis was isomeric with **13b**. On the basis of the methoxy singlet at δ 3.31 and the two doublets at δ 5.12 and 3.46 in the ^{1}H NMR spectrum and the characteristic C sp^3 absorption in the ^{13}C NMR spectrum at δ 107.0 we assigned the 5-methoxyisoxazolidine structure **15** to this product. The cis substitution at C-4 and C-5 is quite obvious from the value of 5.4 Hz for the vicinal coupling constant of H-4 and H-5, which is almost identical with the coupling constant of H-4 and H-5 ($J \approx 6.0$ Hz) of the 5-hydroxyisoxazolidine **5b**. It should be noted that in **15** the methoxy group and the two bulky substituents at C-3 and C-4 are on the same side of the five-membered ring, which obviously represents the thermodynamically less stable configuration. Therefore, the formation of **15** can most likely be explained by assuming that the nitrogen atom of **13b** is protonated, followed by ring opening to give an intermediate of the type **14** in which rotation around the C-4,C-5 bond is not possible. Ring closure by attack of the hydroxy oxygen atom at the electrophilic carbon atom accounts for the stereospecific formation of **15** (Scheme III).[37,39]

Oxidation of the 1-Hydroxyazetidines with HgO. A general route for the synthesis of nitrones comprises the oxidation of the corresponding hydroxylamine derivatives. Several oxidative reagents including lead oxide, potassium ferricyanide, potassium permanganate, yellow mercury(II) oxide and hydrogen peroxide have been used.[3] Thesing and Sirrenberg,[6] for instance, have reported the oxidation of 1-hydroxypyrrolidine to pyrroline 1-oxide with yellow mercury(II) oxide under very mild conditions. Since we are interested in the synthesis of four-membered cyclic nitrones via other pathways than the reaction of 1-nitroalkenes with ynamines,[10] we are currently investigating the possibility of using 1-hydroxyazetidines as starting materials. The 1-hydroxyazetidines obtained by reaction of the nitrones 1 with nucleophiles and hydrides seemed to be attractive model compounds for this study.

Reaction of both **2b** (for 3 h) and **4** (for 5 h) with a suspension of HgO in dry dichloromethane at room temperature gave the known nitrone **1b** in yields of 76% and 73%, respectively. Reaction of **2a** under similar conditions at 30 °C for 24 h gave the 4-cyano-2,3-dihydroazete 1-oxide **16** in a yield of 80%. The ^{1}H NMR spectrum of **16** showed a singlet at δ 4.35 for the hydrogen atom at C-3, and the ^{13}C NMR spectrum showed the presence of two ring sp^3 carbon atoms (δ 94.0 and 52.5) and of absorptions at δ 118.2 (C=N) and 108.2 (C≡N). Reaction of the 1-hydroxyazetidine **4** with HgO in dry dichloromethane for 5 h afforded the four-membered cyclic nitrone **17** as a pale yellow oil in a yield of 83%. Very characteristic is the H-3 signal at δ 3.80 in the ^{1}H NMR spectrum, which shows a homoallylic coupling with the methyl group at C-4 (J = 1.7 Hz). All attempts to oxidize the 1-hydroxy-4-methoxyazetidine **13b** yielded complex mixtures according to TLC and ^{1}H NMR spectroscopy, from which no cyclic nitrone could be isolated.



1b, R = Me
16, R = CN



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These results show that C-4 alkyl substituted 1-hydroxyazetidines **2–4** can be oxidized to the corresponding four-membered cyclic nitrones under very mild conditions in almost quantitative yields. The advantage of this method for the preparation of four-membered cyclic nitrones above the known methods is the greater flexibility of the substitution pattern since this method seems applicable to a wide range of 1-hydroxyazetidines. Furthermore, the mild conditions (room temperature, neutral aprotic solvent) make it possible to isolate the generally rather unstable four-membered cyclic nitrones in almost quantitative yields.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 or a Bruker WP-80 spectrometer, and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian Mat 311 A spectrometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry, TNO, The Netherlands, under the supervision of W. J. Buis. Preparative TLC on silica gel was performed by using precoated plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}). Petroleum ether refers to the fraction boiling at 60–80 °C. Dry methanol refers to molecular sieve dried methanol (≤0.5% water), and glacial acetic acid refers to $CuSO_4$-dried acetic acid. Nitrones **1a–c** were prepared according to ref 10.

***N*,*N*-Diethyl-4-cyano-1-hydroxy-2-methyl-3-phenyl-2-azetidinecarboxamide (2a).** Nitrone **1a** (0.52 g, 2 mmol) was added to a solution of KCN (0.65 g, 10 mmol) in 15 mL of methanol. After being stirred for 1 h, the solution was quenched with a saturated NH_4Cl solution (50 mL) and extracted with chloroform (3 × 20 mL). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. The remaining solid was triturated with diisopropyl ether to give **2a** as a white solid: yield 75%; mp 173–175 °C dec (chloroform/petroleum ether); see Table I for NMR data; mass spectrum, m/e 287.165 (M^+; calcd 287.163).

Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.77; H, 7.43; N, 14.62.

***N*,*N*-Diethyl-1-hydroxy-2,4-dimethyl-3-phenyl-2-azetidinecarboxamide (2b).** A methylmagnesium iodide solution in ether (4 mL, 8 mmol), which was prepared from magnesium and methyl iodide, was added dropwise and in an atmosphere of nitrogen to a stirred solution of nitrone **1a** (0.78 g, 3 mmol) in 20 mL of dry benzene. After 0.3 h the solution was hydrolized by the addition of a saturated NH_4Cl solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with benzene (2 × 20 mL). The combined extracts were dried and filtered, and the benzene was removed under reduced pressure. After a longer period of storing the residue solidified and was triturated with diisopropyl ether to give **2b** as a white solid: yield 76.5%; mp 119–120.5 °C dec (diisopropyl ether); see

(37) This mechanism shows some similarity with the ring opening of cyclic quaternary ammonium ions by the action of anionic reagents.[38]
(38) Cospito, G.; Illuminati, G.; Lillocci, C.; Petride, H. *J. Org. Chem.* **1981**, *46*, 2944.
(39) Alternatively, the formation of **15** can be explained by assuming protonation at nitrogen, followed by an S_Ni type of substitution by the hydroxy oxygen atom, which would involve a highly strained bicyclic transition state.

Table I for NMR data; mass spectrum, m/e 276.184 (M^+; calcd 276.184).

Anal. Calcd for $C_{16}N_{24}N_2O_4$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.37; H, 8.73; N, 10.01.

Reduction of Cyclic Nitrone 1b with $LiAlH_4$. 2-[(Diethylamino)methyl]-1-hydroxy-2,4-dimethyl-3-phenylazetidine (3). Nitrone **1b** (0.82 g, 3 mmol) was added in small portions at 0 °C and in an atmosphere of nitrogen to a suspension of $LiAlH_4$ (0.23 g, 6 mmol) in 30 mL of freshly distilled tetrahydrofuran. After the mixture was stirred for 5 h, the excess $LiAlH_4$ was destroyed by the dropwise addition of a 2 N NaOH solution, after which the solution was filtered. The tetrahydrofuran was removed under reduced pressure, and the remaining solid was triturated with petroleum ether to give **3** as a white solid: yield 61%; mp 127–129 °C (petroleum ether); see Table I for NMR data; mass spectrum, m/e 262.204 (M^+; calcd 262.204).

Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.04; H, 10.04; N, 10.55.

Reduction of Cyclic Nitrone 1b with $NaBH_4$. Nitrone **1b** (0.55 g, 2 mmol) was added to a solution of $NaBH_4$ (0.3 g, 8 mmol) in 10 mL of methanol. After the mixture was stirred for 2 h, water (50 mL) was added, and this solution was extracted with chloroform (3 × 20 mL). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. The remaining solid was triturated with petroleum ether to give the azetidine **4** as a white solid: yield 92%; dec >135 °C (diisopropyl ether); see Table I for NMR data; mass spectrum, m/e 276.183 (M^+; calcd 276.184).

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.35; H, 8.57; N, 10.04.

***N,N*-Diethyl-5-hydroxy-3-methyl-4-phenyl-3-isoxazolidinecarboxamide (5).** Nitrone **1a** (0.52 g, 2 mmol) was added to a solution of NaOH (0.4 g, 10 mmol) in 30 mL of methanol–water (3:1 v/v). After being stirred for 1 h, the solution was worked up as described for **2a**. The remaining solid was triturated with diisopropyl ether to give **5** as a mixture of two isomers: yield 85%; mp 124.5–125.5 °C (toluene/petroleum ether). The ratio of both isomers remained unchanged upon recrystallization. **5a**: 80%; ^1H NMR δ 5.50 (d, 1 H, $J \approx 1.0$ Hz, H-5), 3.61 (d, 1 H, $J \approx 1.0$ Hz, H-4), 1.80 (s, 3 H, CH_3), 1.05 and 0.40 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 106.4 (d, C-5), 71.3 (s, C-3), 65.6 (d, C-4). **5b**: 20%; ^1H NMR δ 5.70 (d, 1 H, $J \approx 6.0$ Hz, H-5), 3.50 (d, 1 H, $J \approx 6.0$ Hz, H-4), 1.70 (s, 3 H, CH_3), 0.86 and 0.79 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 100.5 (d, C-5), 70.7 (s, C-3), 64.6 (d, C-4); mass spectrum, m/e 278.163 (M^+; calcd 278.163).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.70; H, 7.96; N, 10.06. Found: C, 65.00; H, 8.01; N, 9.94.

***(Z,?)*-*N,N*-Diethyl-4-(hydroxyimino)-2-methyl-3-phenyl-2-pentenamide (6a).** Nitrone **1b** (0.82 g, 3 mmol) was added to a solution of NaOH (0.6 g, 15 mmol) in 20 mL of methanol. After being stirred for 5 h the solution was worked up as described above. The remaining sticky solid was triturated with diisopropyl ether to give **6a** as a white solid: yield 40%; mp 181.5–183 °C (chloroform/petroleum ether); ^1H NMR δ ~8.7 (br s, 1 H, OH), 7.5–7.2 (m, 5 H, Ph H), 3.6–3.2 (m, 4 H, NCH_2), 1.89 and 1.82 (s, 6 H, CH_3), 1.18 and 1.14 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 171.4 (s, C=O), 156.4 (s, C=N), 136.7 (s), 135.3 (s) and 133.4 (s) (C=C and Ph C-1); mass spectrum, m/e 274.168 (M^+; calcd 274.168).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.01; H, 8.14; N, 10.16.

The filtrate of **6a** was concentrated under reduced pressure and stored at −20 °C. After a longer period crystalline material was formed that was triturated with cold diisopropyl ether to give ***(E,?)*-*N,N*-diethyl-4-(hydroxyimino)-2-methyl-3-phenyl-2-pentenamide (7)** as a white solid: yield 34%; mp 113.5–115 °C (toluene/petroleum ether); ^1H NMR δ ~10.5 (br s, 1 H, OH), 7.5–7.2 (m, 5 H, Ph H), 3.8–2.3 (m, 4 H, NCH_2), 2.10 and 1.85 (s, 6 H, CH_3), 0.79 and 0.80 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 170.9 (s, C=O), 156.5 (s, C=N), 136.4 (s), 134.0 (s) and 133.4 (s) (C=C and Ph C-1); mass spectrum, m/e 274.168 (M^+; calcd 274.168).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.11; H, 7.91; N, 10.21.

***(Z,?)*-*N,N*-Diethyl-4-(hydroxyimino)-2-methyl-3,4-diphenyl-2-butenamide (6b).** Nitrone **1c** (0.67 g, 2 mmol) was added to a solution of NaOH (0.4 g, 10 mmol) in 25 mL of methanol–water (3:1 v/v), and this solution was refluxed for 1 h, after which it was worked up as described above. The remaining solid was triturated with diisopropyl ether to give **6b** as a white solid: yield 76%; mp 169–171 °C dec (chloroform/ethyl acetate); ^1H NMR (Me_2SO-d_6) δ ~11.5 (br s, 1 H, OH), 7.8–7.0 (m, 10 H, Ph H), 3.7–2.7 (m, 4 H, NCH_2), 1.99 (s, 3 H, CH_3), 0.76 (t, 6 H, $NCCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 169.7 (s, C=O), 152.4 (s, C=N), 137.4 (s), 134.5 (s), 133.3 (s) and 131.9 (s) (C=C and Ph C-1); mass spectrum, m/e 336.183 (M^+; calcd 336.184).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.96; H, 7.27; N, 8.25.

3,5-Dimethyl-4-phenyl-6*H*-1,2-oxazin-6-one (8). A solution of oxime **6a** (0.274 g, 1 mmol) in 3 mL of glacial acetic acid was stirred for 3 h, after which the acetic acid was removed under reduced pressure. To the residue was added a dilute $NaHCO_3$ solution (25 mL), and this mixture was extracted with chloroform (3 × 15 mL). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. The residue solidified upon the addition of diisopropyl ether and was triturated with a minimal amount of cold diisopropyl ether to give **8**: yield 62%; mp 137–139.5 °C dec (toluene/petroleum ether); ^1H NMR δ 7.6–7.1 (m, 5 H, Ph H), 2.01 and 1.96 (s, 6 H, CH_3); ^{13}C NMR δ 165.3 (s, C=O), 153.4 (s, C=N), 142.0 (s), 133.2 (s) and 132.1 (s) (C=C and Ph C-1); mass spectrum, m/e 201.080 (M^+; calcd 201.080).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.79; H, 5.52; N, 6.94.

5-Methyl-3,4-diphenylisoxazole (9). A solution of oxime **6b** (0.5 g, 1.5 mmol) in 5 mL of glacial acetic acid was refluxed for 5 h, after which the acetic acid was removed under reduced pressure, and the residue was worked up as described above. The resulting oil was separated by preparative TLC (silica gel, chloroform). From the fraction at R_f ~0.6 was isolated the isoxazole **9** as a white solid after trituration with petroleum ether: yield 40%; mp 96.5–97.5 °C dec (ethanol) (lit.[26b] mp 94 °C); ^1H NMR δ 7.5–7.1 (m, 10 H, Ph H), 2.43 (s, 3 H, CH_3); ^{13}C NMR δ 166.3 (s, C-5), 161.0 (s, C-3), 115.5 (s, C-4), 11.6 (q, CH_3); mass spectrum, m/e 235.100 (M^+; calcd for $C_{16}H_{13}NO$ 235.100).

Reaction of Sodium Hydroxide with Nitrone 1a in Dry Methanol. *N,N*-Diethyl-1-hydroxy-4-methoxy-2-methyl-3-phenyl-2-azetidinecarboxamide (13a). Nitrone **1a** (0.26 g, 1 mmol) was added to a solution of NaOH (0.12 g, 3 mmol) in 10 mL of dry methanol. After being stirred for 2 min, the solution was worked up as described for **2a**. According to ^1H NMR spectroscopy the resulting oil consisted of the ~95% pure azetidine **13a**, yield 90%. Compound **13a** could not be purified because of its extreme instability[40] (see Table I); mass spectrum, m/e 292.178 (M^+; calcd for $C_{16}H_{24}N_2O_3$ 292.179).

Similarly, nitrone **1a** (0.52 g, 2 mmol) was added to a solution of NaOH (0.4 g, 10 mmol) in 20 mL of dry methanol. After being stirred for 1 h, the solution was worked up as described above. The resulting oil was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 1:3 v/v). From the fraction at R_f ~0.2 was isolated the 5-hydroxyisoxazolidine **5** (61%), while from the fraction at R_f ~0.5 was isolated the isomeric 4-methoxy-1-hydroxyazetidine **13b** as a white solid after trituration with cold diisopropyl ether: yield 13%; mp 134–135 °C dec (diethyl ether/petroleum ether); see Table I for NMR data; mass spectrum, m/e 292.179 (M^+; calcd 292.179).

Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.82; H, 8.37; N, 9.61.

Reaction of Sodium Methoxide with Nitrone 1a in Dry Methanol. Nitrone **1a** (0.52 g, 2 mmol) was added to a solution of Na (0.46 g, 20 mmol) in 20 mL of dry methanol. After being stirred for 1 h, the solution was worked up as described above. The resulting oil was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 1:3 v/v). The slowly eluted fraction yielded the 5-hydroxyisoxazolidine **5** (15%), and from the more rapidly eluted fraction was isolated the 4-methoxy-1-hydroxyazetidine **13b** (58%).

***N,N*-Diethyl-5-methoxy-3-methyl-4-phenyl-3-isoxazolidinecarboxamide (15).** The azetidine **13b** (0.58 g, 2 mmol) was dissolved in 20 mL of glacial acetic acid, and this solution was stirred for 12 days, after which the solution was worked up as

(40) In duplicate experiments **13a** was partially contaminated either with nitrone **1a** or with products of continued reaction (**5** and **13b**).

described for 8. The residue was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 1:2 v/v). From the fraction at $R_f \sim 0.5$ was isolated the isoxazolidine **15** as a white solid after trituration with cold diisopropyl ether: yield 25%; mp 113–114 °C (diisopropyl ether); partial decomposition during TLC accounts for the low yield; ^{1}H NMR $\delta \sim 7.5$ (br s, 1 H, NH), 7.22 (s, 5 H, Ph H), 5.12 (d, 1 H, J = 5.4 Hz, H-5), 3.46 (d, 1 H, J = 5.4 Hz, H-4), 3.31 (s, 3 H, OCH_3), 3.3–2.7 and 2.2–1.8 (m, 4 H, NCH_2), 1.69 (d, 3 H, J = 1.2 Hz, CH_3), 0.83 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 170.5 (s, C=O), 107.0 (d, C-5), 70.5 (s, C-3), 64.9 (d, C-4); mass spectrum, m/e 292.178 (M^+; calcd 292.179).

Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.78; H, 8.30; N, 9.56.

General Procedure for the Oxidation of 1-Hydroxyazetidines to Four-Membered Cyclic Nitrones 1b, 16, and 17 with HgO. The 1-hydroxyazetidine (1 mmol) was added to a suspension of yellow HgO (0.43 g, 2 mmol) in 10 mL of dry dichloromethane. This suspension was stirred at 25 °C for 3 h in the case of **2b** and for 5 h in the case of **3** and **4**. Oxidation of azetidine **2a** was carried out at 30 °C for 24 h. After the reaction was complete, Hyflo was added to the mixture, and the solution was filtered. The dichloromethane was removed under reduced pressure, and the residue was dissolved in acetone (**2b** and **4**) or ethyl acetate (**2a** and **3**) and filtered through Florisil to remove any traces of mercury salts. The filtrate was concentrated under reduced pressure, and in the case of **2b** and **4** the residue was triturated with diisopropyl ether to yield the known cyclic nitrone **1b** in yields of 76% and 73%, respectively.

***N*,*N*-Diethyl-4-cyano-2,3-dihydro-2-methyl-3-phenyl-2-azetecarboxamide 1-oxide (16)** was prepared according to the general procedure from **2a**. The residue was triturated with diisopropyl ether to give **16** as a white solid: yield 80%; mp 119.5–121.5 °C (chloroform/petroleum ether); ^{1}H NMR δ 7.37 (s, 5 H, Ph H), 4.35 (s, 1 H, H-3), 3.5–2.1 (m, 4 H, NCH_2), 2.00 (s, 3 H, CH_3), 0.88 and 0.63 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 163.5 (s, C=O), 118.2 (s, C=N), 108.2 (s, C≡N), 94.0 (s, C-2), 52.5 (d, C-3); mass spectrum, m/e 285.147 (M^+; calcd 285.148).

Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.29; H, 6.64; N, 14.70.

2-[(Diethylamino)methyl]-2,3-dihydro-2,4-dimethyl-3-phenylazete 1-oxide (17) was prepared according to the general procedure from **3** and isolated as a pale yellow oil in a purity of >95%: yield 83%; ^{1}H NMR δ 7.5–7.0 (m, 5 H, Ph H), 3.80 (q, 1 H, J = 1.7 Hz, H-3), 2.60 and 2.33 (AB, 2 H, J = 14.6 Hz, CH_2), 2.3–2.0 (m, 4 H, NCH_2), 2.07 (d, 3 H, J = 1.7 Hz, CH_3), 1.64 (s, 3 H, CH_3), 0.72 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 146.0 (s, C=N), 86.4 (s, C-2), 54.5 (d, C-3), 53.8 (t, CH_2N); mass spectrum, m/e 261.196 ($M^+ + 1$, calcd for $C_{16}H_{25}N_2O$ 261.197).

X-ray Crystal Structure Analysis of 13b. The crystals of **13b** are monoclinic, space group $P2_1/c$. The unit cell dimensions are a = 17.647 (5) Å, b = 14.358 (4) Å, c = 13.943 (4) Å, β = 111.99 (3)°. With eight molecules in the unit cell the calculated density is 1.19 g cm^{-3}. Reflexions were measured by using Mo Kα radiation (Philips PW1100 diffractometer, graphite monochromator, $3 < \theta < 20°$, θ–2θ scan mode, scan speed 0.025° s^{-1}, scan width (θ) 1.3°, total number of reflexions measured 3212). The unit cell contains two independent molecules. The crystal structure determination and refinement was based on 2191 reflexions having a net intensity greater than the standard deviation from counting statistics. The structure was determined by MULTAN[41] and refined by ORFLS.[42] The parameters refined were the scale factor, isotropic extinction parameter, and positional and isotropic thermal parameters of the nonhydrogen atoms (total number of parameters 170). The final R factor was 13.7%. Figure 1 was prepared by ORTEP.[43]

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Supplementary Material Available: Lists of cell parameters, atomic coordinates, thermal parameters, bond distances, and bond angles (4 pages). Ordering information is given on any current masthead page.

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Selective Preparation. 37. Bromination of 2,2′-Dihydroxy-3,3′,5,5′-tetra-*tert*-butylbiphenyl and Preparation of Hydroxydibenzofurans[1]

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Treatment of 2,2′-dihydroxy-3,3′,5,5′-tetra-*tert*-butylbiphenyl (**3**) with excess bromine in alcohols afforded the 2-alkoxy-1-bromo-4,6,8-tri-*tert*-butyldibenzofurans **6a,b** in 68% and 44% yields, respectively. When compound **6a** was treated with $AlCl_3$ in boiling toluene, 2-hydroxydibenzofuran (**14**) was obtained in 79% yield together with bromotoluenes (**15**) and *tert*-butyltoluenes (**10**). However, at room temperature, this reaction afforded 1-bromo-2-methoxy-4-*tert*-butyldibenzofuran (**16**) in 74% yield. Furthermore, it was found that $AlCl_3$–CH_3NO_2-catalyzed reaction of **6a** in toluene gave 1-bromo-2-methoxy-4,6-di-*tert*-butyldibenzofuran (**17**) in 71% yield together with **10**. From **6a** were obtained 1,2,8-trihydroxy- (**26**) and 1,2,7,8-tetrahydroxydibenzofuran (**27**) in several steps.

It has been previously reported that[3] although oxidation of 2-bromo-4,6-di-*tert*-butylphenol with potassium hexacyanoiron(III) afforded 1,4-dihydro-4-bromo-2,4,6,8-tetra-*tert*-butyl-1-oxodibenzofuran similar oxidation of the

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