84118-28-5; **11a**, 49678-72-0; **11b**, 49678-79-7; **11c**, 72011-34-8; **11d**, 49678-66-2; **11e**, 49678-81-1; **15a**, 72011-35-9; **15bA** (isomer 1), 84171-42-6; **15bA** (isomer 2), 84171-43-7; **15bB** (isomer 1), 84171-44-8; **15bB** (isomer 2), 84171-45-9; **15c**, 72011-38-2; **15d**, 84118-17-2; **16a**, 72011-39-3; **17aA** (isomer 1), 84171-46-0; **17aA** (isomer 2), 84171-47-1; **17aB** (isomer 1), 84234-86-6; **17aB** (isomer 2), 84171-48-2; **17bA**, 84118-18-3; **17bB**, 84118-19-4; **19a**, 32417-96-2; **19b**, 63066-09-1; **20**, 32418-03-4; **21**, 2940-19-4; **22a**, 72011-41-7; **22b**, 72011-42-8; **22e**, 84118-20-7; **23a**, 72011-43-9; **23b**, 72011-44-0; **24b**, 84118-23-0; **24e**, 84118-22-9; **25**, 84118-21-8; **27**, 84118-24-1; **28a**, 84118-25-2; **28b**, 84118-26-3; **28c**, 84118-27-4; **29b**, 84130-26-7; dimethyl acetylenedicarboxylate, 762-42-5; *tert*-butyl isocyanide, 7188-38-7; 1,1,33-tetramethylbutyl isocyanide, 14542-93-9; cyclohexyl isocyanide, 931-53-3; isopropyl isocyanide, 598-45-8; hydrazine, 302-01-2.

Supplementary Material Available: Table containing mass spectral data of azetidines **4**, **8–10**, **15a–c**, and **17b** and azadienes **22** (1 page). Ordering information is given on any current masthead page.

Chemistry of Four-Membered Cyclic Nitrones. 4. Reaction with Electrophilic Reagents and Conversion into β-Lactam Derivatives[1]

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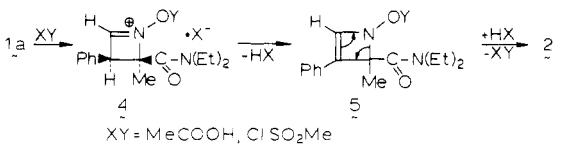
The conversion of the four-membered cyclic nitrone **1a** into a β-lactam has been investigated by using several electrophilic reagents. With methanesulfonyl chloride or with acetic acid, **1a** reacts to give the oxime **2**. In acetic acid this oxime undergoes cyclization at room temperature to yield the 6*H*-1,2-oxazinone **3**. Reaction of nitrones **1a** and **1b** with acetyl chloride at 0 °C, followed by an aqueous workup leads to the formation of the aldehyde **8a** and ketone **8b**, respectively. Aldehyde **8a** is rather unstable and rearranges in chloroform solution at room temperature via the aziridine **9** to the 2,5-dihydrooxazole **12**. Reaction of both **8a** and **8b** with sodium hydroxide causes saponification of the acetoxy group and subsequent cyclization to give the 5-hydroxyisoxazolidines **14a** and **14b**, respectively. Reaction of the nitrones **1b** and **1c** with acetyl chloride at room temperature gives the 3-chloroazetidine **15** and the 3-chlorodihydroazete **16**, respectively. The structure of **16** has been elucidated with single-crystal X-ray analysis. Oxidation of nitrone **1a** with 1 equiv of lead tetraacetate in benzene yields the 1-acetoxy-2-azetidinone **26a** which can be converted into the 1-hydroxy-2-azetidinone **26b** either by hydrolysis with aqueous sodium carbonate or catalytic reduction with palladium on charcoal catalyst. Reduction of **26b** with titanium(III) chloride in tetrahydrofuran–water gives the β-lactam derivative **27**. 1-Acetoxy-2-azetidinone **26a** is also prepared by oxidation of the corresponding 1-hydroxyazetidine **28**, obtained by reduction of **1a** with sodium borohydride, with *2 equiv* of lead tetraacetate.

Recently we described the synthesis of a number of four-membered cyclic nitrones (2,3-dihydroazete 1-oxides) by the reaction of nitro(cyclo)alkenes with ynamines.[2] Since these four-membered cyclic nitrones belong to a class of virtually unknown heterocycles,[3] we are currently investigating the chemical reactivity of the nitrone moiety of these compounds. In previous papers we have described the 1,3-dipolar cycloadditions[4] of these nitrones and their reactions with nucleophiles.[5]

Since four-membered cyclic nitrones are isomeric with β-lactams, a heterocyclic ring system that is present in a number of biologically important compounds like cephalosporins and penicillins,[6] we have investigated the possibility of converting these four-membered cyclic nitrones into β-lactams. In general, the conversion of nitrones into amides is a well-known reaction and can be achieved by a number of electrophilic reagents such as acetyl chloride, phosphorus chlorides, acetic anhydride, and thionyl chloride.[7-12] In this paper we describe the results of reactions of four-membered cyclic nitrones **1** with several of these electrophilic reagents.[13]

Scheme I



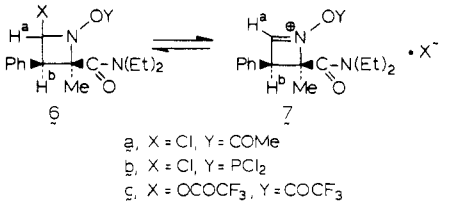
Results and Discussion

Reaction of **1a** with mesyl chloride gave a product isomeric with **1a** in 40% yield which was shown, by com-

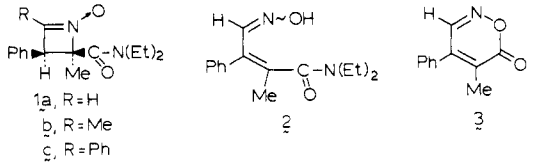
(1) Part of the forthcoming thesis of M.L.M.P.
(2) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816.
(3) Other examples of four-membered cyclic nitrones: Black, D. St. C.; Brown, R. F. C.; Dunstan, B. F.; Sternhell, S. *Tetrahedron Lett.* **1974**, 4283. Harnisch, J.; Szeimies, G. *Chem. Ber.* **1979**, *112*, 3914.
(4) Pennings, M. L. M.; Okay, G.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1982**, *47*, 4413.
(5) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1982**, *47*, 4419.
(6) (a) Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731. (b) Heusler, K. "Cephalosporins and Penicillins, Chemistry and Biochemistry"; Flynn, E. H., Ed.; Academic Press: New York, 1972; p 255.
(7) Rundel, W. In "Methoden der Organischen Chemie (Houben-Weyl)"; Mueller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1968; Vol. X/4, p 310.
(8) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.
(9) Delpierre, G. R.; Lamchen, M. *Q. Rev., Chem. Soc.* **1965**, *19*, 329.
(10) Korte, F. Ed. "Methodicum Chimicum"; Georg Thieme Verlag: Stuttgart, 1974; Vol. 6, p 341.
(11) Kröhnke, F. *Justus Liebigs Ann. Chem.* **1957**, *604*, 203 and references cited therein.
(12) Breuer, E. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Interscience: New York, 1982; Supplement F, Part 1, p 459.
(13) Some of these results have been described in a preliminary publication: Pennings, M. L. M.; Reinhoudt, D. N. *Tetrahedron Lett.* **1981**, *22*, 1153.

0022-3263/83/1948-0486$01.50/0

Scheme II



parison of its spectra with those of products obtained from nitrones **1b** and **1c**,[5] to be the oxime **2**. The oxime was also



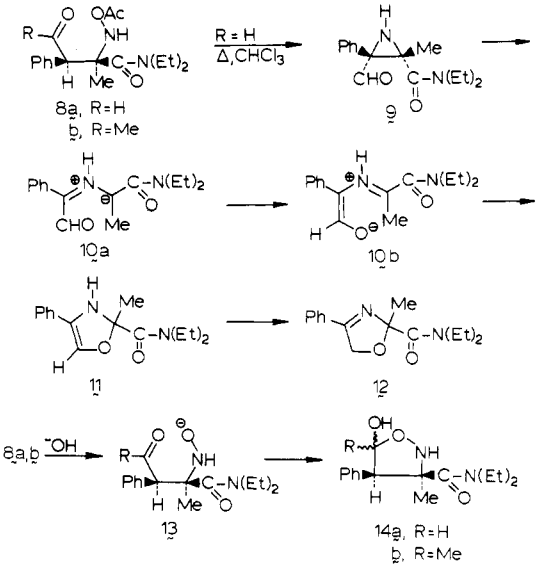
obtained from **1a** in 15% yield in acetic acid; prolonged reaction gave the oxazinone **3**. Similarly, when oxime **2** was dissolved in acetic acid, it cyclized with the elimination of diethylamine to give the oxazinone **3**.

The formation of **2** can be explained by the reaction sequence shown in Scheme I. The 2-azetine **5** may undergo a thermal cyclobutene to 1,3-butadiene type of ring opening to give the oxime **2**. Similar 2-azetines have been proposed as the intermediates in the formation of oximes by reaction of nitrones **1b** and **1c** with base.[5] Evidence in favor of the stereochemistry shown is the fact that **2** undergoes a cyclization reaction to give the oxazinone derivative **3**.[5] We attribute the relatively low yields in the formation of **2** from nitrone **1a** to a concurring polymerization reaction of nitrone **1a** because of an increased electrophilicity of the C=N carbon atom of compound **4**.

Previously Black et al.[14] have reported that mesyl chloride converts 3,3,5,5-tetramethyl-1-pyrroline 1-oxide into the corresponding γ-lactam, and acetic acid has been reported to convert an indolenine 1-oxide into the corresponding bicyclic γ-lactam.[15]

Refluxing a solution of nitrone **1a** in acetic or trifluoroacetic anhydride leads to decomposition and/or polymerization, just as does refluxing of nitrone **1a** in chloroform with the above reagents or with phoshorus trichloride, thionyl chloride, and acetyl chloride. In order to study reactions of four-membered cyclic nitrone **1a** with these electrophilic reagents at lower temperatures, we have monitored these reactions in deuteriochloroform solution by ^{1}H NMR spectroscopy. When 1 equiv of acetyl chloride was added to a solution of nitrone **1a** in $CDCl_3$ at 0 °C, the ^{1}H NMR spectrum showed two doublets at δ 5.97 and 3.88 (J = 8.3 Hz) corresponding to H^a and H^b in the undissociated form **6a** (Scheme II).[16] With 1 equiv of PCl_3 a similar spectrum was obtained, with H^a at δ 5.98 and H^b at δ 3.91 (J = 8.3 Hz),[17] indicating the presence of **6b**. Nitrone **1a** did not react with acetic anhydride under these conditions, but according to ^{1}H NMR spectroscopy trifluoroacetic anhydride and **1a** yielded the iminium salt **7c**. The two signals at δ 6.21 and 3.73 that show a very small coupling of 0.9 Hz, which is comparable with that in the starting nitrone (J = 1.5 Hz), are in agreement with structure **7c** (Scheme II).

Scheme III



As described above, the attempts to convert nitrone **1a** into a β-lactam by thermal rearrangement of **6** or **7** failed because of decomposition. Therefore, we tried to generate β-lactams by reacting **6** or **7** with water. However, nearly all these reactions lead to decomposition and to very complex reaction mixtures. Only the reaction of nitrone **1a** with acetyl chloride to give **6a**, followed by reaction with water, yielded a crystalline solid in a yield of 58%. Mass spectrometry and elemental analysis revealed that this product was composed of one molecule of nitrone **1a** and one molecule of acetic acid. On the basis of the presence of doublets at δ 10.00 and 4.45 (J = 2.3 Hz) and an absorption corresponding to an acetoxy methyl group (δ 2.13) in the ^{1}H NMR spectrum, we have assigned structure **8a** to this product.

We have subsequently also reacted the 4-methyl and 4-phenyl nitrones **1b** and **1c** with acetyl chloride. Upon reaction of the nitrone **1b** with acetyl chloride in chloroform at 0 °C for 10 min followed by an aqueous workup, we obtained a crystalline product in a yield of 76%. ^{1}H and ^{13}C NMR spectroscopy revealed that this compound was of the same type as the product obtained by reaction of **1a** and acetyl chloride, and therefore we assigned structure **8b** to this product.

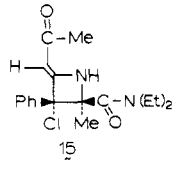
More evidence for structures **8a** and **8b** was obtained from their chemical reactivity. We found that **8a** rearranged slowly in chloroform solution, and after 10 days at 30 °C a crystalline product was obtained in a yield of 42%. Mass spectrometry and elemental analysis showed that this compound was formed by the elimination of acetic acid. On the basis of a singlet absorption in the ^{1}H NMR spectrum at δ 5.06 which corresponds to two hydrogens[19] and the relatively low-field C sp^3 absorption in the ^{13}C NMR spectrum at δ 110.9, we assigned structure **12** to this compound. The first step in the conversion of **8a** into **12** is the cyclization to the aziridine **9**, which could be observed by ^{1}H NMR spectroscopy (δ_{CHO} 9.56, Scheme III). Subsequently the aziridine **9** will undergo electrocyclic ring opening to a 1,3-dipolar intermediate, the azomethin ylide

(14) Black, D. St. C.; Davis, V. C. *Aust. J. Chem.* **1977**, *30*, 1573.
(15) Nour El-Din, A. M. Ph.D. Thesis, Kaiserslautern University, 1979, and references cited therein.
(16) Similar 2-methoxy-1-hydroxyazetidines showed coupling constants of 8–9 Hz. The structure of one of these compounds has been proven by X-ray analysis.[5]
(17) The two doublets showed a second coupling due to interaction with the phosphorus nucleus: J_{P,H^a} = 1.0 Hz, J_{P,H^b} = 1.2 Hz; values of 1.2–0.6 Hz have been reported for P–N–C–C–H long-range coupling constants.[18]
(18) Kaplan, F.; Singh, G.; Zimmer, H. *J. Phys. Chem.* **1963**, *67*, 2509.
(19) Obviously the two hydrogen atoms are magnetically equivalent, and therefore a singlet signal is observed. However, the ^{1}H NMR spectrum in deuteriobenzene shows an AB pattern due to the unequivalence of the two hydrogen atoms in this solvent (see Experimental Section).

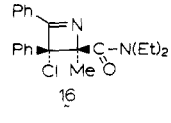
10a. Since the 1,3-dipole in **10a** is conjugated with a carbonyl group, it can react as a 1,5-dipole (**10b**) via a 1,5-dipolar electrocyclization to give the oxazole derivative **11**. Finally, a hydrogen shift accounts for the formation of **12**. Similar transformations of aziridines into oxazoles have been reported previously.[20] Under identical conditions **8b** is stable, probably because of the decreased nucleophilic character of the benzylic carbon atom.

Reaction of both **8a** and **8b** with NaOH in aqueous methanol yielded crystalline products in yields of 25% and 67%, respectively. The product of the reaction of **8a** was shown to be the 5-hydroxyisoxazolidine **14a**, which is also formed by the reaction of nitrone **1a** with NaOH under the same conditions.[5] Comparison of the spectroscopic data with those of **14a** clearly proved structure **14b**, which consists, like **14a**, of a mixture of two diastereoisomers. The structure of the major isomer (75%) with the methyl group at C-5 trans with the phenyl group was evident from the difference of the chemical shift of the C-5 methyl group in the ^{1}H NMR spectrum as compared with that of the other isomer (25%; δ 1.52 vs. 1.06). The formation of both isoxazolidines is explained by assuming that saponification of the acetoxyamino group is followed by cyclization of the intermediate **13** (Scheme III). The same type of intermediate (**13a**) has been proposed in the formation of **14a** by reaction of nitrone **1a** with NaOH.[5] When **8a** was reacted with sodium methoxide in dry methanol, a mixture of aziridine **9** and 5-hydroxyisoxazolidine **14a** was obtained, the latter being formed by transesterification of the acetoxyamino group followed by cyclization. Aziridine **9** is rather unstable and could not be obtained in a pure state. ^{1}H NMR spectroscopy showed a methyl singlet at relatively high field (δ 1.13), which proves the stereochemistry of **9**, since an aziridine in which the phenyl and methyl group are trans substituted has been reported to exhibit a methyl absorption at $\delta \sim 1.7$.[4]

Reaction of nitrone **1b** with acetyl chloride at 0 °C, followed by stirring at room temperature for 1 h and an aqueous workup, gave a crystalline product that was different from **8b** in a yield of 31%. Mass spectrometry and elemental analysis revealed that the addition of acetyl chloride to nitrone **1b** to give an intermediate of the type **6** must have been followed by the elimination of water. In the ^{1}H NMR spectrum of this product a doublet at δ 4.44 is present, which shows coupling with, most likely, an N–H proton, corresponding to the broad absorption at $\delta \sim 5.5$ (J = 2.7 Hz). Surprisingly, only two, instead of three, methyl signals were observed at δ 2.18 and 2.06. Considering this together with the vinylic enamine absorptions in the ^{13}C NMR spectrum at δ 151.7 and 91.2, we have tentatively assigned the azetidine structure **15** to this compound.



15



16

Nitrone **1c** is less reactive toward acetyl chloride, but reaction for 2 h with 1 equiv of acetyl chloride at 0 °C gave a crystalline product that could be isolated in a yield of 45%. X-ray analysis showed that this product was the 2,3-dihydroazete derivative **16** (Figure 1). The ^{13}C NMR spectrum of **16** shows a low-field absorption of the C=N

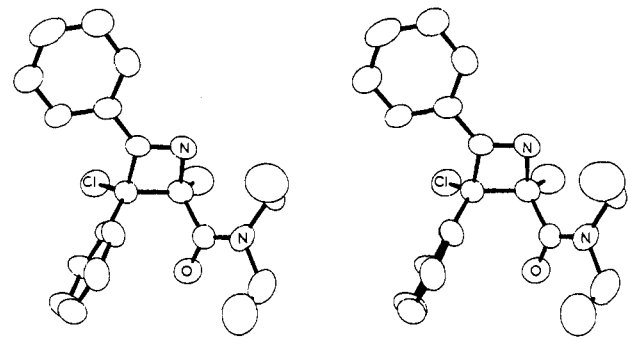
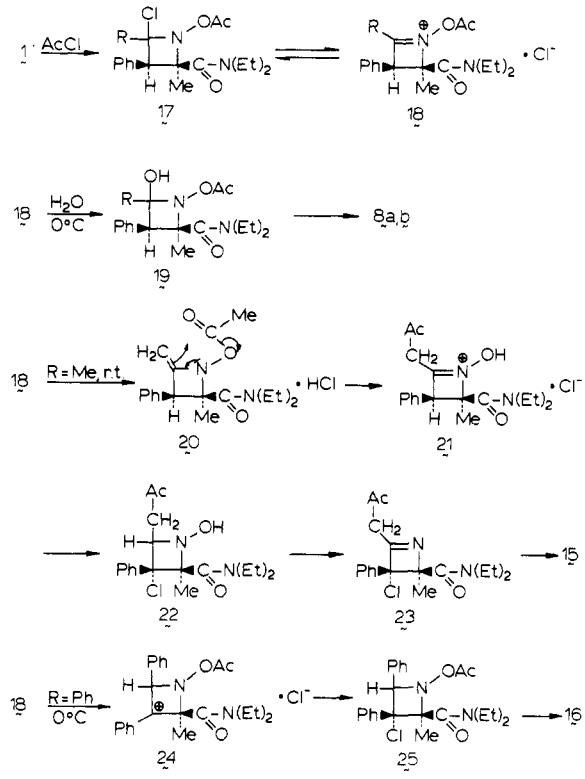


Figure 1. Stereoscopic view of the 2,3-dihydroazete derivative **16**.

Scheme IV



carbon atom at δ 180.8 and the presence of two sp^3 carbon atoms, the chemical shifts of which are almost the same as those of the azetidine **15** (δ 80.1 and 74.4). This provides additional support for the structure **15**. Because of the instability of **16**, which is probably caused by ring opening and decomposition of the resulting azabutadiene,[21] the X-ray analytical work was performed at −25 °C.

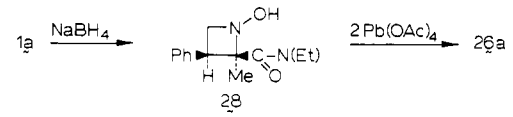
The formation of the reaction products (**8**, **15**, and **16**) of acetyl chloride and the nitrones **1a–c** can be explained when we assume that acylation of the nitrone oxygen is the first step (Scheme IV). In the case of R = H or Me (**1a** and **1b**) this intermediate, **17**, possibly present as an equilibrium mixture with the iminium salt **18**, can be intercepted at 0 °C by the addition of water. Water acts as a nucleophile and reacts with the iminium salt **18** to give **19**, a type of product which is known to be unstable.[22] Upon ring opening, the (acetyloxy)amino aldehyde and ketone **8a** and **8b** are formed, respectively. In the case R = Me the equilibrium at room temperature is obviously

(20) (a) Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325. (b) Niklas, K. J. Ph.D. Thesis, Muenchen University, 1975.

(21) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 7570 and references cited therein.

(22) A similar 2-hydroxyazetidine has been postulated as the intermediate in the formation of **14a** from nitrone **1a**.[5]

Scheme V

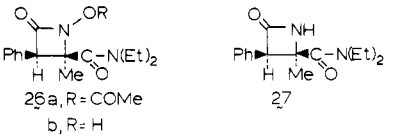


in favor of the iminium salt **18**, and deprotonation occurs to give **20**. Subsequent rearrangement as shown in Scheme IV accounts for the formation of **15**.[23] In the case of **1c** (R = Ph) the initial adduct with acetyl chloride could not be intercepted by reaction with water, probably because the equilibrium **17** ⇄ **18** at 0 °C is in favor of the iminium salt **18**, which will be stabilized by the presence of the phenyl group. Therefore, a fast rearrangement of **18** can occur which leads to the formation of the 2,3-dihydroazete **16** (see Scheme IV).

To our knowledge, **6a,b** and **7c** are the first relatively stable examples of addition products of electrophilic reagents and nitrones. Previously Kröhnke[11] had proposed that the conversion of nitrones into amides by reaction with acetic anhydride occurs via the elimination of acetic acid from a postulated intermediate of the type **6**, followed by deacylation of the O-acylated amide by the acetate anion. Recently Heine et al.[24] showed that the conversion of nitrones into amides by reaction with acid chlorides proceeds in three steps. Elimination of acid from an intermediate of the type **7** to give a nitrilium ion is followed by recombination of the nitrilium ion with the carboxylate anion to give the O-acylated amide which is deacylated by the chloride ion to the amide. In view of this elimination reaction, leading to the formation of a C=N or even a C≡N bond, it can be understood that such a reaction will be unfavorable in the case of a four-membered ring. Furthermore, almost all isomerizations of nitrones to amides seem to proceed smoothly only when a phenyl group is present at the electrophilic carbon atom, possibly because this lowers the activation energy for the generation of a C=N or C≡N bond.

The reactions of nitrones **1** with electrophilic reagents clearly, show in the case of acetyl chloride, the formation of an acylated intermediate **17**, which can be observed by ^{1}H NMR spectroscopy in the case of **1a**. The above results show that **17** is in equilibrium with its iminium salt and that the position of this equilibrium is determined both by the substituent R and by the nature of the electrophilic reagents, viz., in the case of trifluoroacetic anhydride. Furthermore, the elimination of HOY, a reaction step which seems to be necessary in the conversion of nitrones into amides, is in the case of intermediates of the type **6** a process of high energy and therefore prevents a facile conversion of the four-membered cyclic nitrones into β-lactams.

In 1970 Gutteridge and McGillan[25] reported the oxidation of a pyrroline 1-oxide to the corresponding 1-acetoxypyrrolidone which represents an example of the conversion of a nitrone into an N-acetylated amide, viz., a hydroxamic acid derivative.[26] Reaction of nitrone **1a** with lead tetraacetate in benzene gave a crystalline solid in a yield of 51%. IR spectroscopy showed three carbonyl absorptions at 1820, 1780, and 1630 cm^{-1}. On consideration of this together with the absorptions in the ^{13}C NMR spectrum at δ 167.4, 167.1, and 162.4, we assigned the 1-acetoxy-2-azetidinone structure **26a** to this product.



Hydrolysis of the acetoxy group in **26a** was achieved with Na_2CO_3 in a mixture of methanol and water and gave the 1-hydroxy-2-azetidinone **26b** in a yield of 86%. Attempts to catalytically reduce the N–O bond of **26a** with palladium on charcoal in ethanol failed but gave the 1-hydroxy-2-azetidinone **26b** in a yield of 91%. From duplicate experiments under similar conditions in the absence of hydrogen was recovered the starting azetidinone quantitatively, which shows that **26b** must have been formed by reduction of the acetoxy group and not by hydrolysis by traces of water present. Recently $TiCl_3$ has been reported to reduce the N–O bond of 1-hydroxy-2-azetidinones to give the corresponding β-lactams.[27] Thus, when **26b** was reacted with 2 equiv of $TiCl_3$ in a two-phase system of water and THF, the 2-azetidinone **27** was isolated in a yield of 71%.

In part three of this series we have reported the formation of four-membered cyclic nitrones by oxidation of the corresponding 1-hydroxyazetidines with yellow mercury(II) oxide.[5] Since 2-azetidinone **26a** can be obtained by the oxidation of four-membered cyclic nitrone **1a**, we were interested if it would be possible to oxidize 1-hydroxyazetidines directly to the corresponding azetidinones by using 2 equiv of the oxidizing agent. Reduction of nitrone **1a** with $NaBH_4$ in methanol[5] gave the 1-hydroxyazetidine **28** in a yield of 93%. Oxidation of this 1-hydroxyazetidine with 2 equiv of lead tetraacetate in benzene gave the 1-acetoxy-2-azetidinone **26a** in a yield of 44% (Scheme V).

These results show that a direct conversion of four-membered cyclic nitrones into β-lactams via the methods that are usually employed for the conversion of nitrones into amides is not possible because of decomposition or polymerization of the intermediate products. However, four-membered cyclic nitrone **1a** can be converted into the corresponding 1-acetoxy-2-azetidinone by oxidation with lead tetraacetate. Furthermore, 1-hydroxyazetidines, which have been shown to be precursors of four-membered cyclic nitrones,[5] can be converted into similar 1-acetoxy-2-azetidinones by oxidation with *2 equiv* of lead tetraacetate, which implies a more direct and convenient route to these heterocycles than the oxidation of the generally rather unstable four-membered cyclic nitrones.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with Varian XL-100 and Bruker WP-80 spectrometers, 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 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of W. J. Buis. Preparative TLC on silica gel was performed by using precoated plates (Merck

(23) The hydrochloric salt of nitrone **1b**, which is quite similar to compound **21**, is a very unstable product, which can be explained if we assume that it undergoes the same reaction as **21** to give the 4-methyl derivative of the 2,3-dihydroazete **16**. This 4-methyl derivative will be much more unstable toward ring opening, and therefore decomposition, than **16**.[2,21]

(24) Heine, H. W.; Zibuck, R.; VandenHeuvel, W. J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3693.

(25) Gutteridge, N. J. A.; McGillan, F. J. *J. Chem. Soc. C* **1970**, 641.

(26) The mechanism of the lead tetraacetate oxidation of nitrones has been discussed in detail in a recent review on nitrones.[12]

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DC-Fertigplatten Kieselgel 60 F_{254}). Petroleum ether refers to the fraction boiling at 60–80 °C. Nitrones **1a–c** were prepared according to ref 2.

(*Z*,?)-*N*,*N*-Diethyl-4-(hydroxyimino)-2-methyl-3-phenyl-2-butenamide (2). A solution of nitrone **1a** (0.52 g, 2 mmol) in 4 mL of glacial acetic acid was stirred for 0.5 h, after which the solution was neutralized with $NaHCO_3$ and extracted with chloroform (3 × 15 mL). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. The resulting oil was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 2:1 v/v). From the fraction at R_f ~0.5 was isolated oxime **2** after trituration with diisopropyl ether: yield 15%; mp 183–184 °C (chloroform/petroleum ether); ^{1}H NMR δ ~9.0 (br s, 1 H, OH), 7.90 (s, 1 H, HC=N), 7.6–7.0 (m, 5 H, Ph H), 3.7–3.2 (m, 4 H, NCH_2), 1.78 (s, 3 H, CH_3), 1.20 and 1.18 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 170.0 (s, C=O), 149.9 (d, C=N), 138.8 (s), 135.2 (s) and 132.5 (s) (C=C and Ph C-1); mass spectrum, *m/e* 260.154 (M^+; calcd 260.153).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.84; H, 7.76; N, 10.56.

Methanesulfonyl chloride (156 μL, 2 mmol) was added to a stirred solution of nitrone **1a** (0.52 g, 2 mmol) in 20 mL of dry dichloromethane. After 3 h the solution was washed with a dilute aqueous $NaHCO_3$ solution (3 × 10 mL). The dichloromethane was dried and filtered, and the solvent was removed under reduced pressure, after which the residue was dissolved in ethyl acetate and filtered through Florisil. The solvent was removed under reduced pressure, and the residue was triturated with ethyl acetate to give **2** as a white solid; yield 40%.

5-Methyl-4-phenyl-6*H*-1,2-oxazin-6-one (3). A solution of nitrone **1a** (0.52 g, 2 mmol) in 4 mL of glacial acetic acid was stirred for 4 h, after which the solution was worked up as described above, and the resulting oil was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 2:1 v/v). From the fraction at R_f ~0.3 was isolated the oxazinone **3** as a white solid after trituration with diisopropyl ether: yield 9%; mp 110–111 °C dec (toluene-/petroleum ether); IR (KBr) 1715 (C=O), 1640 cm^{-1} (C=N); ^{1}H NMR δ 8.17 (s, 1 H, HC=N), 7.7–7.3 (m, 5 H, Ph H), 2.20 (s, 3 H, CH_3); ^{13}C NMR δ 165.0 (s, C=O), 147.3 (s, C=N), 139.1 (s), 132.7 (s) and 131.3 (s) (C=C and Ph C-1); mass spectrum, *m/e* 187.063 (M^+; calcd 187.063).

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.70; H, 4.99; N, 7.37.

A solution of oxime **2** (0.26 g, 1 mmol) in 4 mL of glacial acetic acid was stirred for 3 h, after which the solution was worked up as described above. The remaining solid was triturated with diisopropyl ether to give oxazinone **3** in a yield of 65%.

***N*,*N*-Diethyl-2-[(acetyloxy)amino]-2-methyl-4-oxo-3-phenylbutanamide (8a).** Acetyl chloride (150 μL, 2 mmol) was added at 0 °C to a stirred solution of nitrone **1a** (0.52 g, 2 mmol) in 10 mL of dry dichloromethane. After 10 min, 30 mL of water was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined extracts were dried and filtered, and the dichloromethane was removed under reduced pressure. The residue solidified upon the addition of diisopropyl ether and was triturated with diisopropyl ether to give **8a** as a white solid: yield 58%; mp 102.5–105 °C dec (diisopropyl ether); ^{1}H NMR δ 10.00 (d, 1 H, *J* = 2.3 Hz, CHO), 7.34 (s, 5 H, Ph H), 6.80 (br s, 1 H, NH), 4.45 (d, 1 H, *J* = 2.3 Hz, CHPh), 4.0–3.0 (m, 4 H, NCH_2), 2.13 (s, 3 H, $COCH_3$), 1.49 (s, 3 H, CH_3), 1.13 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 197.6 (d, HC=O), 169.6 (s) and 168.6 (s) (OC=O and NC=O), 71.7 (s, C-2), 59.1 (d, C-3); mass spectrum, *m/e* 320.175 (M^+; calcd 320.174).

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.64; H, 7.55; N, 8.68.

***N*,*N*-Diethyl-2-[(acetyloxy)amino]-2-methyl-4-oxo-3-phenylpentanamide (8b)** was prepared from nitrone **1b** (0.55 g, 2 mmol) and acetyl chloride (150 μL, 2 mmol) as described above: yield 76%; mp 90.5–92 °C (diisopropyl ether); ^{1}H NMR δ 7.5–7.1 (m, 5 H, Ph H), 6.62 (br s, 1 H, NH), 4.67 (s, 1 H, CHPh), 4.5–2.9 (m, 4H, NCH_2), 2.25 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $OCOCH_3$), 1.56 (s, 3 H, CH_3), 1.10 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 195.5 (s, C=O), 169.8 (s) and 168.6 (s) (OC=O and NC=O), 70.3 (s, C-2), 59.5 (d, C-3); mass spectrum, *m/e* 334.193 (M^+; calcd 334.189).

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.78; H, 7.89; N, 8.29.

***N*,*N*-Diethyl-3-chloro-2-methyl-4-(2-oxopropylidene)-3-phenyl-2-azetidinecarboxamide (15).** Acetyl chloride (375 μL, 5 mmol) was added at 0 °C to a stirred solution of nitrone **1b** (1.10 g, 4 mmol) in 20 mL of dry dichloromethane. After 10 min the mixture was allowed to reach room temperature and was stirred for 1 h, after which the solution was washed with a dilute aqueous $NaHCO_3$ solution (3 × 10 mL). The dichloromethane was dried and filtered, and the solvent was removed under reduced pressure, after which the residue was dissolved in ethyl acetate and filtered through Florisil. The solvent was removed under reduced pressure, and the resulting solid was triturated with diisopropyl ether to give **15** as a white solid: yield 31%; mp 165–168 °C dec (diisopropyl ether); ^{1}H NMR δ 7.8–7.2 (m, 5 H, Ph H), ~5.5 (br s, 1 H, NH), 4.44 (d, 1 H, *J* = 2.7 Hz, =CH), 2.18 and 2.06 (s, 6 H, CH_3), 1.01 and 0.37 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 170.5 (s, NC=O), 166.4 (s, C=O), 151.7 (s, =C-N), 91.2 (d, =CH), 81.4 (s, C-3), 74.7 (s, C-2); mass spectrum, *m/e* 334.144 (M^+; calcd 334.145).

Anal. Calcd for $C_{18}H_{23}N_2O_2Cl$: C, 64.56; H, 6.92; N, 8.37. Found: C, 64.78; H, 7.04; N, 8.34.

***N*,*N*-Diethyl-3-chloro-2,3-dihydro-2-methyl-3,4-diphenyl-2-azetecarboxamide (16).** Acetyl chloride (150 μL, 2 mmol) was added at 0 °C to a stirred solution of nitrone **1c** (0.67 g, 2 mmol) in 10 mL of dry dichloromethane. After 2 h at 0 °C the mixture was worked up as described above. The resulting oil was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 2:1 v/v). From the fraction at R_f ~0.4 was isolated **16** as a white solid after trituration with diisopropyl ether: yield 45%; mp 116.5–118 °C (diisopropyl ether); ^{1}H NMR δ 7.9–7.1 (m, 10 H, Ph H), 3.6–2.6 (m, 4 H, NCH_2), 1.87 (s, 3 H, CH_3), 1.05 and 0.51 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 180.8 (s, C=N), 168.2 (s, C=O), 80.1 (s, C-3), 74.4 (s, C-2); mass spectrum, *m/e* 354.150 (M^+; calcd 354.150).

Anal. Calcd for $C_{21}H_{23}N_2OCl$: C, 71.07; H, 6.53; N, 7.89. Found: C, 71.26; H, 6.70; N, 7.85.

***N*,*N*-Diethyl-2,5-dihydro-2-methyl-4-phenyl-2-oxazolecarboxamide (12).** A solution of **8a** (0.64 g, 2 mmol) in 20 mL of dry chloroform was kept at 30 °C for 10 days, after which it was washed with 10 mL of a dilute aqueous $NaHCO_3$ solution and 10 mL of water. The chloroform solution was dried and filtered, the solvent was removed under reduced pressure, and the resulting oil was separated by preparative TLC (silica gel; chloroform–ethyl acetate, 1:1 v/v). From the fraction at R_f ~0.3 was isolated **12** as a white solid after trituration with diisopropyl ether: yield 42%; mp 105.5–107 °C (diisopropyl ether); ^{1}H NMR δ 7.9–7.4 (m, 5 H, Ph H), 5.06 (s, 2 H, CH_2), 4.0–3.1 (m, 4 H, NCH_2), 1.74 (s, 3 H, CH_3), 1.16 (t, 6 H, $NCCH_3$); ^{1}H NMR (C_6D_6) δ 4.68 (AB, 2 H, *J* = 14 Hz, $\Delta\delta_{AB} \approx 6$ Hz, CH_2); ^{13}C NMR δ 168.9 (s) and 167.5 (s) (C=O and C=N), 110.9 (s, C-2), 73.1 (t, C-5); mass spectrum, *m/e* 260.153 (M^+; calcd 260.153).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.40; H, 7.85; N, 10.73.

***N*,*N*-Diethyl-5-hydroxy-3-methyl-4-phenyl-3-isoxazolidinecarboxamide (14a).** Compound **8a** (0.32 g, 1 mmol) was added to a solution of NaOH (0.2 g, 5 mmol) in 10 mL of methanol–water (3:1 v/v). After being stirred for 1 h, the solution was quenched with a saturated aqueous ammonium chloride solution (50 mL) and extracted with chloroform (3 × 10 mL). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. 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 the 5-hydroxyisoxazolidine **14a** was isolated as a white solid after trituration with diisopropyl ether: yield 25%. Compound **14a** was obtained as a mixture of two isomers and was identical with the product obtained from the reaction of **1a** with sodium hydroxide.[5]

***N*,*N*-Diethyl-5-hydroxy-3,5-dimethyl-4-phenyl-3-isoxazolidinecarboxamide (14b).** Compound **8b** (0.33 g, 1 mmol) was added to a solution of NaOH (0.2 g, 5 mmol) in 10 mL of methanol–water (3:1 v/v). After being stirred for 1 h, the solution was worked up as described above. The remaining solid was triturated with diisopropyl ether to give **14b** as a white solid: yield 67%; mp 150–151.5 °C dec (chloroform/diisopropyl ether); the ratio of the two isomers (3:1) did not change upon recrystallization.

Isomer 1: 75%; ^{1}H NMR δ 3.22 (s, 1 H, H-4), 1.71 and 1.52 (s, 6 H, CH_3); ^{13}C NMR δ 107.1 (s, C-5), 71.1 (s, C-3), 69.2 (d, C-4). Isomer 2: 25%; ^{1}H NMR δ 3.57 (s, 1 H, H-4), 1.89 and 1.06 (s, 6 H, CH_3); ^{13}C NMR δ 108.5 (s, C-5), 72.3 (s, C-3), 67.3 (d, C-4); 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, 65.47; H, 8.24; N, 9.52.

Reaction of 8a with Sodium Methoxide in Methanol. Compound **8a** (0.66 g, 2 mmol) was added to a solution of sodium (0.12 g, 5 mmol) in 10 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, ethyl acetate). From the slowly eluted fraction at R_f ~0.3 was isolated the 5-hydroxyisoxazolidine **14a** (10%) while, from the fraction at R_f ~0.6 was isolated. ***N,N*-Diethyl-3-formyl-2-methyl-3-phenyl-2-aziridinecarboxamide (9)** as a contaminated pale yellow oil: yield ~40%; ^{1}H NMR δ 9.56 (s, 1 H, CHO), 7.6–7.1 (m, 5 H, Ph H), 3.7–3.0 (m, 4 H, NCH_2), ~3.0 (br s, 1 H, NH) 1.30 and 1.13 (t, 6 H, $NCCH_3$), 1.13 (s, 3 H, CH_3); because of its instability, **9** could not be obtained ina pure state.

***N,N*-Diethyl-1-(acetyloxy)-4-methyl-3-phenyl-2-azetidinone-4-carboxamide (26a).** Nitrone **1a** (0.52 g, 2 mmol) was added in small portions at 10 °C to a solution of lead tetraacetate (0.88 g, 2 mmol) in 15 mL of dry benzene. After stirring for 1 h at 10 °C, the precipitated lead diacetate was filtered off, the benzene solution was washed with 10 mL of water, dried, and filtered, and the benzene was removed under reduced pressure. The resulting oil was separated by preparative TLC (silica gel; chloroform-ethyl acetate, 1:1 v/v). From the fraction at R_f ~0.4 was isolated the azetidinone **26a** as a white solid after trituration with diisopropyl ether: yield 51%; mp 113–115 °C dec (chloroform/petroleum ether); IR (KBr) 1820 ($COCH_3$), 1780 (C=O), 1630 cm^{-1} (C=O, amide); ^{1}H NMR δ 7.34 (s, 5 H, Ph H), 4.08 (s, 1 H, H-3), 3.6–2.3 (m, 4 H, NCH_2), 2.30 (s, 3 H, $COCH_3$), 1.82 (s, 3 H, CH_3), 0.76 and 0.66 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 167.4 (s) and 167.1 (s) (OC=O and NC=O), 162.7 (s, C-2), 74.3 (s, C-4) 63.1 (d, C-3); mass spectrum, m/e 318.159 (M^+; calcd 318.158).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.96; N, 8.80. Found: C, 63.91; H, 6.93; N, 8.78.

***N,N*-Diethyl-1-hydroxy-4-methyl-3-phenyl-2-azetidinone-4-carboxamide (26b). By Hydrolysis of 26a.** Azetidinone **26a** (0.32 g, 1 mmol) was added to a solution of Na_2CO_3 (0.27 g, 2.5 mmol) in 10 mL of methanol–water (2:1). After being stirred for 2 h, the solution was worked up as described for **14a**. The remaining solid was triturated with petroleum ether to give the azetidinone **26b** as a white solid: yield 86%; mp 186–189 °C dec (chloroform/petroleum ether); IR (KBr) 1775 (C=O), 1625 cm^{-1} (C=O amide); ^{1}H NMR δ 7.28 (s, 5 H, Ph H), 3.94 (s, 1 H, H-3), 3.6–2.2 (m, 4 H, NCH_2), 1.83 (s, 3 H, CH_3), 0.78 and 0.76 (s, 6 H, $NCCH_3$); ^{13}C NMR δ 170.0 (s, C=O), 162.7 (s, C-2), 72.3 (s, C-4), 63.4 (d, C-3); mass spectrum, m/e 276.148 (M^+; calcd 276.147).

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.29; N, 10.14. Found: C, 64.79; H, 7.26; N, 9.98.

By Catalytic Reduction of 26a. Azetidinone **26a** (0.16 g, 0.5 mmol) was dissolved in 10 mL of absolute ethanol and hydrogenated in the presence of 100 mg of Pd on charcoal catalyst (5%) at atmospheric pressure. After 24 h, the reaction mixture was filtered through Hyflo, the solvent was removed under reduced pressure, and the remaining solid was triturated with petroleum ether to give 1-hydroxyazetidinone **26b** in a yield of 91%.

***N,N*-Diethyl-4-methyl-3-phenyl-2-azetidinone-4-carboxamide (27).** 1-Hydroxyazetidinone **26b** (0.14 g, 0.5 mmol) was dissolved in 10 mL of freshly distilled THF in an atmosphere of nitrogen. A solution of sodium acetate (0.49 g, 6 mmol) in 5 mL of water was added followed by the dropwise addition of a 15% $TiCl_3$ solution (0.8 mL, 1 mmol) in water. After being stirred for 2 h, the suspension was poured into 25 mL of ethyl acetate, the aqueous layer was separated, and the organic layer was washed with a 0.1 N NaOH solution (2 × 10 mL) and 10 mL of brine. The ethyl acetate was dried and filtered, and the solvent was removed under reduced pressure. The remaining solid was triturated with diisopropyl ether to give **27** as a white solid: yield 71%; mp 185–186 °C dec (diisopropyl ether); IR (KBr) 1760 (C=O) 1620 cm^{-1} (C=O, amide); ^{1}H NMR δ 7.26 (s, 5 H, Ph H), ~6.7 (br s, 1 H, NH), 4.12 (d, 1 H, J = 0.7 Hz, H-3), 3.6–2.1 (m, 4 H, NCH_2), 1.77 (s, 3 H, CH_3), 0.78 and 0.74 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 169.5 (s, C=O), 166.4 (s, C-2), 66.8 (d, C-3), 63.4 (s, C-4); mass spectrum, m/e 260.154 (M^+; calcd 260.153).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.14; H, 7.74; N, 10.54.

***N,N*-Diethyl-1-hydroxy-2-methyl-3-phenyl-2-azetidinecarboxamide (28).** Nitrone **1a** (0.52 g, 2 mmol) was added in small portions to a solution of $NaBH_4$ (0.3 g, 8 mmol) in 10 mL of methanol. After the mixture was stirred for 1 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 **28** as a white solid: yield 93%; mp ~141 °C dec (petroleum ether); ^{1}H NMR δ 7.5–7.1 (m, 5 H, Ph H), ~6.2 (br s, 1 H, OH) 4.0–3.2 (ABX, 3 H, H-3 and H-4), 3.6–2.3 (m, 4 H, NCH_2), 1.69 (s, 3 H, CH_3), 0.82 and 0.65 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 172.3 (s, C=O), 77.1 (s, C-2), 61.3 (t, C-4), 46.8 (d, C-3); mass spectrum, m/e 262.167 (M^+; calcd 262.168).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.90; H, 8.43; N, 10.53.

Oxidation of 1-Hydroxyazetidine 28 with 2 Equiv of Lead Tetraacetate in Benzene. Azetidine **28** (0.39 g, 1.5 mmol) was added in one portion at 6 °C to a solution of lead tetraacetate (1.33 g, 3 mmol) in 10 mL of dry benzene. After being stirred for 2 h at 6 °C, the solution was worked up and purified as described for **26a**. After preparative TLC, azetidinone **26a** was isolated in a yield of 44%.

X-ray Crystal Structure Analysis of 16. The crystals of **16** obtained belong to the monoclinic space group $P2_1/n$, with cell constants a = 15.709 (4) Å, b = 9.718 (2) Å, c = 12.647 (2) Å, and β = 97.71 (2)°. With four molecules in the unit cell the calculated density is 1.23 g cm^{-3}. Data were collected at 248 (2) K by using a Philips PW1100 diffractometer (Mo Kα radiation, λ = 0.7107 Å; graphite monochromator; θ – 2 θ scan mode, 2 < θ < 20°; scan speed (θ), 0.05° s^{-1}; scan width (θ), (1.3 + tan θ)°; number of reflexions measured, 1882). The determination and refinement of the crystal structure is based on 1512 reflexions with $I > \sigma(I)$. The structure was solved by direct methods[28] and refined by full-matrix least-squares methods.[29] The parameters refined were the scale factor, extinction parameter, and positional and anisotropic thermal parameters of the nonhydrogen atoms. In the last cycles of refinement the positions of the hydrogen atoms of the phenyl rings and their isotropic thermal parameters were also refined. The final R factor was 6.6%. A number of the remaining hydrogen atoms were found in the final difference Fourier synthesis. Inclusion of these hydrogen atoms, however, gave rise to some unacceptable bond angles involving these hydrogen atoms. The drawing (Figure 1) was made by ORTEP.[30]

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Supplementary Material Available: Lists of atomic coordinates, thermal parameters, bond distances, bond angles, and observed and calculated structure factors (15 pages). Ordering information is given on any current masthead page.

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