150 (16.5), 149 (10.1), 148 (17.7), 147 (30.0), 145 (8.0), 138 (15.3), 137 (100), 136 (12.8), 135 (24.8), 134 (7.3), 133 (17.6), 132 (13.1), 131 (14.9), 129 (7.7); M_r calcd for $C_{15}H_{18}O_3$ 246.1251, found, (MS) 246.1253.

The third fraction (**3**, 42 mg) was recrystallized from benzene–EtOAc: mp 121–123 °C; IR (KBr) 1778, 1752, 1740, 1642, 1190, 1020, 1002, 960 cm^{-1}; ^1H and ^{13}C NMR spectra in Tables I and II; $[\alpha]_D$ +147.9° (*c* 0.126, MeOH); CD curve (MeOH) $[\theta]_{310}$ −3760 (negative max), $[\theta]_{288}$ 0, $[\theta]_{235}$ +20500 (max), mass spectrum, *m/z* (relative intensity) 248 (M^+, 92.0), 233 (4.1), 220 (5.7), 219 (8.9), 203 (4.7), 202 (5.0), 192 (4.4), 190 (4.8), 187 (5.5), 177 (9.3), 176 (17.7), 175 (100), 174 (40.9), 173 (8.4), 161 (19.5), 160 (7.4), 159 (20.3), 157 (9.0), 150 (15.5), 194 (21.1), 148 (50.9), 147 (53.0), 146 (24.9), 145 (21.4), 137 (8.3), 136 (15.3), 135 (27.4), 134 (14.7), 133 (54.9), 132 (14.7), 131 (28.9); M_r calcd for $C_{15}H_{20}O_3$ 248.1412, found, (MS) 248.1434.

(B) A solution of 25 mg of achalensolide in 15 mL of acid-free EtOAc containing 10 mg of 5% $Pd/CaCO_3$ catalyst was hydrogenated at atmospheric presure for 2 h, at which time reduction was complete. Filtration, removal of solvent at reduced pressure, and preparative TLC of the residue (C_6H_6–EtOAc, 1:1, multiple development) afforded as the first band 5 mg of lactone **4** and as the second band 13 mg of lactone **3**.

X-Ray Analysis of Achalensolide. Single crystals of **1** were prepared by slow crystallization from benzene–EtOAc. The crystals were orthorhombic, space group $P2_12_12_1$ with a = 7.449 (5) Å, b = 7.574 (3) Å, c = 22.44 (1) Å, and d_{calcd} = 1.292 g cm^{-3} for Z = 4 ($C_{15}O_3H_{18}$, M_r = 246.3). The intensity data were measured on a CAD4 diffractometer (Mo radiation, monochromated, θ–2θ scans). The size of the crystal used for data collection was approximately 0.3 × 0.3 × 0.3 mm^3. No absorption correction was necessary (μ = 0.829). A total of 1331 reflections were measured for $\theta \leq 25.0°$, of which 1115 were considered to be observed [$I \geq 3\sigma$]. The structure was solved by direct methods using MULTAN 78[36] and refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. Methyl hydrogen atoms were located from a difference Fourier map; the remaining hydrogen-atom parameters were calculated assuming idealized geometry. Hydrogen-atom contributions were included in the structure factor calculations; but their parameters were not refined. The final discrepancy, indices were R = 4.1 and R_w = 4.3% for the 1115 observed reflections. The final difference Fourier map was essentially featureless with no peaks greater than 0.3 e A^{-3}.

Registry No. **1**, 87302-42-9; **2**, 13447-58-0; **3**, 87206-13-1; **4**, 87174-96-7.

Supplementary Material Available: Tables III–VI listing final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound **1** (5 pages). Ordering information is given on any current masthead page.

(36) Main, P. "MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data"; Department of Physics, University of York, York, England.

Chemistry of Four-Membered Cyclic Nitrones. 5. Synthesis and Oxidation of 1-Hydroxyazetidines

Marcel L. M. Pennings and David N. Reinhoudt*

Laboratory of Organic Chemistry, Twente University of Technology, Enschede, The Netherlands

Received March 24, 1983

1-(Benzyloxy)azetidines **9** are prepared by reductive cyclization of the corresponding *O*-benzyl oximes (**6**) that have a leaving group at the β-position. Reduction of the unprotected oxime **6a** with sodium cyanoborohydride in acetic acid affords 3,4,4-trimethylisoxazolidine (**8**) in a yield of 61%. The azetidines **9** are catalytically debenzylated with Pd/C, H_2 in acetic acid to give the 1-hydroxyazetidines **10a** and **10b** in yields of 71% and 61%, respectively. A study of the nitrogen inversion process in azetidines **9b** and **10b** shows that the barrier is dependent on both the substituent at oxygen and the solvent. Oxidation of 1-hydroxyazetidine **10a** with active lead(IV) oxide quantitatively gives a mixture of the two isomeric nitrones, **11a** and **11b**, and oxidation of **10b** affords four-membered cyclic nitrone **12**, which is characterized by reaction with dimethyl acetylenedicarboxylate. Reaction of 1-hydroxyazetidine **10a** with 3 equiv of lead tetraacetate gives 1,4-bis(acetyloxy)-3,3,4-trimethyl-2-azetidinone (**19**) in a yield of 71%, whereas oxidation of **10b** with lead tetraacetate results in a mixture of the 1,4-bis(acetyloxy)-2-azetidinone **22** and the 1,4,4-tris(acetyloxy)-2-azetidinone **25**.

Introduction

Recently we have described the synthesis of four-membered cyclic nitrones by reaction of 1-nitroalkenes and 1-aminoacetylenes (ynamines).[1] Since four-membered cyclic nitrones are structural isomers of β-lactams, we have studied a number of reactions under which nitrones are converted into amides. Reactions with both nucleophiles[2] and electrophiles[3] failed in this respect, but reaction with lead tetraacetate resulted in the formation of 1-acetyloxy β-lactams.[3]

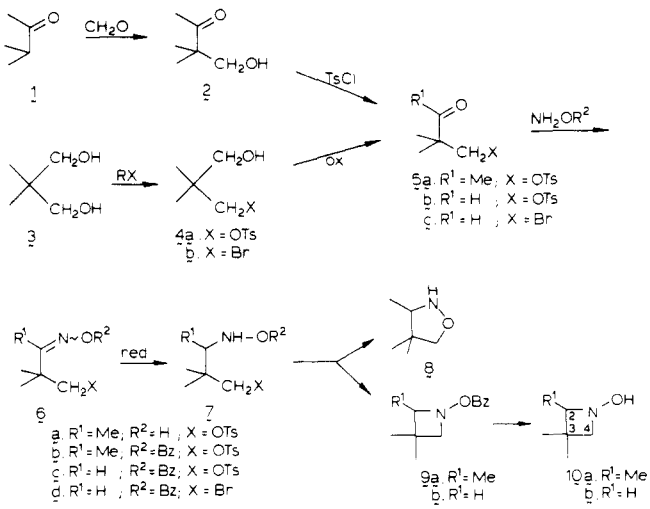
Since in addition to the aforementioned nitrones only two other four-membered cyclic nitrones have been reported[4,5] by using synthetic methods that have also a very limited scope, a wider application of this novel β-lactam synthesis requires a more general synthesis of four-membered cyclic nitrones.

In the course of our studies on the reactivity of four-membered cyclic nitrones with nucleophiles we obtained 1-hydroxyazetidines, and we have shown that these compounds can be oxidized to the corresponding four-membered cyclic nitrones with yellow mercury(II) oxide.[2] Furthermore, it revealed that 1-hydroxyazetidines that are unsubstituted at C-4 can be oxidized with *2 equiv* of lead tetraacetate to the corresponding 1-(acetyloxy)-2-azetidinones via the in situ generated four-membered cyclic nitrones. This result, viz., the oxidation of 1-hydroxy-

(1) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816.
(2) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1982**, *47*, 4419.
(3) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1983**, *48*, 486.
(4) Black, D. St. C.; Brown, R. F. C.; Dunstan, B. T.; Sternhell, S. *Tetrahedron Lett.* **1974**, 4283.
(5) Harnisch, J.; Szeimies, G. *Chem. Ber.* **1979**, *112*, 3914.

0022-3263/83/1948-4043$01.50/0

Scheme I



azetidines to β-lactam derivatives, opens a new and more direct route for the synthesis of 2-azetidinones having an oxygen substituent at nitrogen.

However, 1-hydroxyazetidines belong to a class of virtually unknown heterocycles and besides the reduction of four-membered cyclic nitrones,[2] only one other route has been reported, which comprises the reaction of methyl 2,4-dibromobutyrate with hydroxylamine to give the 1-hydroxyazetidine in a yield of 10%.[6] In this paper we wish to report the results of a study toward the synthesis and reactivity of 1-hydroxyazetidines, in order to allow a further study of the scope of the β-lactam synthesis via oxidation of 1-hydroxyazetidines.[7]

Results and Discussion

Synthesis. We anticipated that 1-hydroxyazetidines might be synthesized by cyclization of hydroxylamine derivatives of the type **7**, which in turn might be prepared by reduction of the corresponding oximes **6**. For this purpose we started from carbonyl compounds **5** having a leaving group at the β-position (Scheme I). Compound **5a** was prepared according to a known procedure,[8] via the aldol of 3-methyl-2-butanone and formaldehyde and subsequent tosylation. Both **5b** and **5c** were obtained from the alcohols **4a**[9] and **4b**[10] by oxidation with pyridinium chlorochromate in yields of 82% and 72%, respectively. Oximation of **5a–c** according to a standard procedure gave the oximes **6a–d** in yields of 87%–96%. Several methods, including BH_3/THF,[11] BH_3/pyridine,[12] and $NaCNBH_3$ in methanol/HCl,[13] have been employed to reduce oximes. We have used the reduction with $NaCNBH_3$ in acetic acid,[14] a relatively mild method that has recently been applied for the reduction of O-acetyl oximes.

Reaction of oxime **6a** with $NaCNBH_3$ in acetic acid at room temperature for 16 h gave a liquid compound, in a yield of 61%, that according to mass spectrometry and elemental analysis contained no tosylate group. On the basis of the ^1H NMR spectrum, which showed signals at δ ~4.6 (NH), 3.70 and 3.58 (AB, CH_2O), and 3.02 (q, CHN), that are characteristic for isoxazolidines,[15] we have assigned the trimethylisoxazolidine structure **8** to this compound.[16] When the *O*-benzyl oxime **6b** was reacted with $NaCNBH_3$ at 35 °C for 16 h, a colorless liquid was obtained in a yield of 63%. This compound was also formed by elimination of *p*-toluenesulfonic acid, and both ^1H NMR [δ 3.35 and 3.02 (AB), 3.27 (q)] and ^{13}C NMR spectroscopy [δ 73.8 (d, C-2), 68.3 (t, C-4), 30.4 (s, C-3)] clearly revealed the azetidine structure **9a**. In both reactions the intermediate hydroxylamine derivatives **7a** and **7b** could not be isolated, because they underwent a rapid cyclization by intramolecular alkylation at the oxygen and nitrogen atom, respectively. It is noteworthy that in **7a** alkylation occurs at oxygen and not at nitrogen; therefore the oxygen atom needs to be protected to produce the four-membered azetidine ring (**9a**).

Attempted catalytic debenzylation of **9a** with palladium on charcoal (5%) in ethanol failed, and no reaction occurred. However, hydrogenation of **9a** in acetic acid at atmospheric pressure for 7 h using the same catalyst gave the corresponding 1-hydroxyazetidine **10a** in a yield of 71%, after distillation at reduced pressure.

Reaction of both **6c** and **6d** with $NaCNBH_3$ in acetic acid at room temperature for 7 h quantitatively gave the corresponding hydroxylamine derivatives **7c** and **7d**. Prolonged reaction of **6c** at elevated temperatures caused decomposition of the hydroxylamine derivative **7c**. Both hydroxylamines **7c** and **7d** are quite stable liquids, which were characterized as the corresponding solid hydrochlorides. The fact that **7b** obviously very easily undergoes cyclization under the reaction conditions compared to **7c** must be due to the repulsion of the methyl groups at the α- and β-position of **7b**. This repulsion will lead to a decreased nitrogen γ-carbon atom distance, and therefore the rate of cyclization will be enhanced.[17]

Because of the low acidity of the N–H hydrogen atom in **7c** and **7d** the cyclization of these compounds required strongly basic conditions. Cyclization of **7c** was achieved by the rapid addition of a *n*-butyllithium solution in hexane to a solution of **7c** in diethyl ether to give the corresponding azetidine **9b** in a yield of 53%. Hydroxylamine **7d** was cyclized in refluxing pyridine and **9d** was isolated in yield of 61%. Debenzylation of azetidine **9b** in acetic acid (Pd/C, H_2, 7 h) afforded 3,3-dimethyl-1-hydroxyazetidine (**10b**) in a yield of 61%.

Hindered Nitrogen Inversion. In a previous paper we have reported the formation of two isomeric 4-methoxy-1-hydroxyazetidines that showed a significant difference in chemical reactivity.[2] The relative stability of one of these compounds was explained by assuming a very slow nitrogen inversion that prevents a trans type of elimination of methanol through participation of the lone pair at nitrogen.

Although nitrogen inversion in cyclic (hydroxyl)amines has been extensively studied,[18–21] no data are available of

(6) Kostyanovskii, R. G.; Prosyanik, A. V.; Markov, V. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1974**, 956; *Chem. Abstr.* **1974**, *81*, 25476v.
(7) Pennings, M. L. M.; Kuiper, D.; Reinhoudt, D. N. *Tetrahedron Lett.* **1983**, *24*, 825.
(8) Lumma, W. C., Jr.; Ma, O. H. *J. Org. Chem.* **1970**, *35*, 2391.
(9) Dolby, L. J.; Meneghini, A.; Koizumi, T. *J. Org. Chem.* **1968**, *33*, 3060.
(10) Searles, S., Jr.; Nickerson, R. G.; Witsiepe, W. K. *J. Org. Chem.* **1959**, *24*, 1839.
(11) Feuer, H.; Vincent, B. F., Jr.; Bartlett, R. S. *J. Org. Chem.* **1965**, *30*, 2877.
(12) Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 643.
(13) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(14) Sternbach, D. D.; Jamison, W. C. L. *Tetrahedron Lett.* **1981**, *22*, 3331.
(15) Takeuchi, Y.; Furusaki, F. *Adv. Heterocycl. Chem.* **1977**, *21*, 207 and references cited therein.
(16) When a solution of **6a** in acetic acid was stirred for 16 h at room temperature, the starting material was recovered quantitatively, which proves the *E* configuration of the oximino group[4] and which reveals that cyclization occurs after reduction of the C=N bond.
(17) A similar effect was observed in the formation of epoxides by the base-induced cyclization of chlorohydrins: Eliel, E. L. In "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New Yok, 1963; p 61 and references cited therein.
(18) Lehn, J. M.; Wagner, J. *J. Chem. Soc., Chem. Commun.* **1968**, 148.

Table I. Spectral Data and $\Delta G^{\ddagger}$ Values

compd	solvent	sign	T_c, °C	$\Delta\nu$, Hz	J_{AB}, Hz	$\Delta G^{\ddagger}$,[a] kcal mol^{-1}
9b	$CDCl_3$	CH_3	13	10.5		14.9
		CH_2	20	18	8.3	14.7
	CD_3OD	CH_3	9	8		14.8
		CH_2	15	13	8	14.6
10b	$CDCl_3$	CH_3	28	4.6		16.3
		CH_2	44	17.5	6.7	16.1
	CD_3OD	CH_3	26	7		15.9
		CH_2	~40	[b]		
	CD_3COCD_3	CH_3	18	9.1		15.3
		CH_2	32	17.5	6.7	15.4
	D_2O	CH_3	<0			
		CH_2	82	29	8.3	17.8

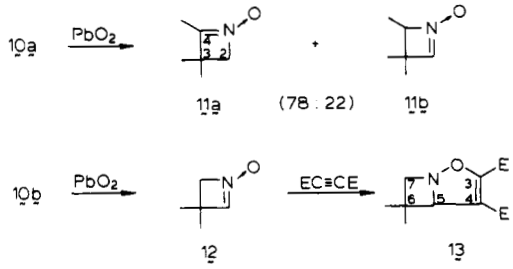
[a] Because the CH_2 signal was treated as an AB spectrum the calculated values are less accurate. [b] Signal collapses at lower temperatures.

the nitrogen inversion process in azetidines that have an oxygen atom linked to the nitrogen atom. Using known substituent effects on the rate of nitrogen inversion we were able to estimate a $\Delta G^{\ddagger}$ value of ~16 kcal mol^{-1} for the nitrogen inversion process in 1-hydroxyazetidines. The availability of the symmetrical 1-oxyazetidines **9b** and **10b** made it now possible to study the rate of nitrogen inversion in these compounds by variable-temperature ^{1}H NMR spectroscopy in order to determine experimentally the activation parameters of this process. In the spectrum of **10b** in $CDCl_3$ at higher temperatures, both the NCH_2 and CH_3 protons exhibit a singlet absorption, revealing the magnetic equivalence of these groups on both sides of the azetidine ring, due to a fast inversion of the substituent at nitrogen. At lower temperatures the protons above and below the azetidine ring become unequal and give rise to an AA'BB' pattern (NCH_2) and two singlets for the methyl groups, indicating that the nitrogen inversion is slow on the ^{1}H NMR time scale. From the chemical shift differences $\Delta\nu$, and in the case of the NCH_2 absorption J_{AB}, and the temperature at which the signals coalesce to give a singlet (T_c), the free activation energy $\Delta G^{\ddagger}$ was calculated (see Table I and Experimental Section).

Table I shows a value of 16.3 kcal mol^{-1} for the activation energy of the nitrogen inversion process in 1-hydroxyazetidine **10b** in deuterochloroform solution. Furthermore it can be seen that in the 1-benzyloxy analogue **9b** this value is decreased by 1.4 kcal mol^{-1} to a $\Delta G^{\ddagger}$ value of 14.9 kcal mol^{-1}. The reason for the faster nitrogen inversion in **9b** is most likely the steric interaction of the benzyl group with one of the methyl groups at C-3, which favors the planar transition state, and therefore the activation energy of the inversion process is lowered.

The solvent effect on the rate of nitrogen inversion of cyclic hydroxylamine derivatives has never been systematically studied, and therefore we have determined the $\Delta G^{\ddagger}$ values of the nitrogen inversion process in **10b** in different polar and protic solvents (Table I). When the solvent polarity is increased, viz., in the case of acetone, the rate of nitrogen inversion increases and a $\Delta G^{\ddagger}$ value of 15.3 kcal mol^{-1} is found. However, a comparison of aprotic polar solvents like acetone with polar protic solvents such as methanol and water shows that the rate of nitrogen inversion decreases, particularly in the case of water ($\Delta G^{\ddagger}$ = 17.8 kcal mol^{-1}).

Scheme II



The fact that polar nonprotic solvents tend to decrease the activation energy for nitrogen inversion has also been found in the case of *N*-methoxy-*N*-(phenylmethyl)-methylamine, and this was attributed to the fact that the planar transition state of hydroxylamines is more polar then the pyramidal ground state.[22] Unlike the simple alkyl-substituted amines, which show a decrease of the rate of nitrogen inversion in more polar solvents, amines substituted with an electron-withdrawing atom show an increase of the dipole moment going from the pyramidal ground state to the planar transition state. The second effect that is observed in protic solvents, an increase in activation energy, is due to hydrogen bonding of the solvent with the basic nitrogen atom, which causes a decrease in ground-state energy.

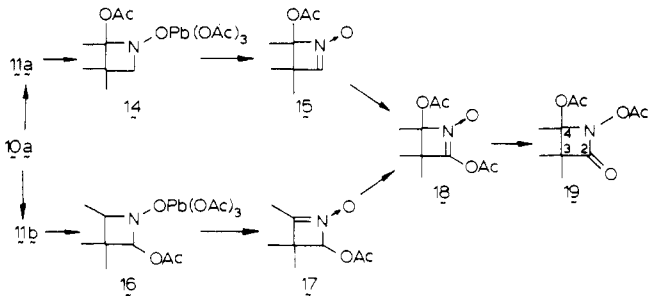
Whereas in alkyl-substituted amines both polar and protic solvents lower the rate of nitrogen inversion,[20] our results demonstrate that in the case of hydroxylamine derivatives polar solvents tend to incrase the rate of inversion and protic solvents lead to a decreased rate of inversion. In polar protic solvents these two effects, which are of opposite magnitude, can either lead to an increase of the rate of inversion (methanol) or a decrease of the rate of nitrogen inversion (water).

Oxidation. Oxidation of 1-hydroxyazetidine **10a** with yellow mercury(II) oxide in dichloromethane for 2 h gave an oil that according to ^{1}H NMR spectroscopy consisted of about 30% of 3,3,4-trimethyl-2,3-dihydroazete 1-oxide (**11a**). Nitrone **11a** was prepared previously by Black et al. by cyclization of **6a**, and the absorptions in the ^{1}H NMR spectrum at δ 1.32 (s), 1.93 (t, J = 1.95 Hz), and 3.96 (q, J = 1.95 Hz) are in good agreement with those reported by Black.[4] Obviously this method of oxidation is rather drastic since the formation of nitrone **11a** is accompanied with products that arise from decomposition or polymerization. Oxidation of **10a** with freshly prepared "active lead(IV) oxide",[23] which has been used for the preparation of sensitive and unstable nitrones, gave a mixture of two isomeric four-membered cyclic nitrones in quantitative yield (Scheme II). According to ^{1}H NMR spectroscopy, in addition to **11a** (78%), a second nitrone (**11b**) was formed (22%), which showed a very characteristic absorption for C-4 unsubstituted nitrones at δ 6.74 (s, CH=N). Obviously there is competition between hydrogen abstraction at C-2 and C-4; for energetic reasons abstraction at C-2 will be favored, whereas abstraction at C-4 is sterically more facile. This competition has also been observed in the dehydrogenation of 1-hydroxypyrrolidine and piperidine derivatives to give the corresponding five- and six-membered cyclic nitrones.[24]

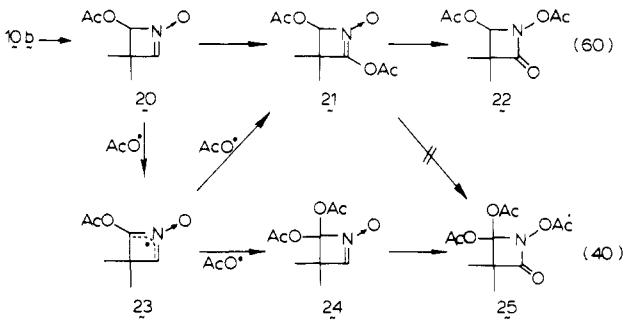
Oxidation of 1-hydroxyazetidine **10b**, in which there is only one possible way of hydrogen abstraction, gives an oil that contained about 70% 3,3-dimethyl-2,3-dihydro-

(19) Lehn, J. M.; Wagner, J. *Tetrahedron* **1970**, *26*, 4227.
(20) Lehn, J. M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311.
(21) Riddell, F. G. *Tetrahedron* **1981**, *37*, 849.
(22) Griffith, D. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4089.
(23) Kuhn, R.; Hammer, I. *Chem. Ber.* **1950**, *83*, 413.
(24) Thesing, J.; Sirrenberg, W. *Chem. Ber.* **1959**, *92*, 1748 and references cited therein.

Scheme III



Scheme IV



azete 1-oxide (**12**), as is evident from the ^1H NMR spectrum (δ 6.86). Nitrone **12** could not be purified, and was characterized by reaction with dimethyl acetylenedicarboxylate to give the more stable cycloadduct **13**. The structure of **13** was proven by comparison of the ^1H NMR and ^{13}C NMR spectroscopic data with those of similar cycloadducts described previously.[25]

These results show that the dehydrogenation of 1-hydroxyazetidines to four-membered cyclic nitrones is a quite general reaction that, in the case of 1-hydroxyazetidines having hydrogen atoms at both the 2- and 4-position, can lead to a mixture of two isomeric nitrones.

Reaction of 1-hydroxyazetidine **10a** with lead tetraacetate revealed that 3 equiv of the oxidizing agent is consumed to give a white solid in a yield of 71%. On the basis of absorptions in the IR spectrum at 1810, 1785, and 1745 cm^{-1} and absorptions in the ^{13}C NMR spectrum at δ 169.0, 168.3, 167.1, and 97.2, we have assigned the 1,4-bis(acetyloxy)-2-azetidinone structure **19** to this product.

The mechanism of the formation of **19** is shown in Scheme III. Most likely the first step involves oxidation of the 1-hydroxyazetidine **10a** to a mixture of nitrones **11a** and **11b**. 1,3-Addition of the oxidizing reagent to the nitrone moiety followed by oxidative elemination of lead(II) acetate and acetic acid gives **15** and **17**, respectively. Again 1,3-addition of lead tetraacetate followed by oxidative elimination occurs to give **18**, in which acyl migration to the nitrone oxygen atom accounts for the formation of the 2-azetidinone **19**. A similar mechanism was proposed in the oxidation of *N,N*-dibenzylhydroxylamine with lead tetraacetate.[26,27]

A somewhat different course of reaction was observed when 1-hydroxyazetidine (**10b**) was reacted with lead tetraacetate, and according to ^1H NMR spectroscopy, a mixture of two compounds was formed. The major product (60%) exhibited a rather low-field signal in the ^1H NMR spectrum at δ 5.93 and together with the absorptions in the ^{13}C NMR spectrum, which were in good agreement with those of **19**, we have assigned structure **22** to this compound. The minor product (40%), which could be isolated in a pure state as a white solid (yield 31%), exhibited absorptions in the ^1H NMR spectrum corresponding to three acetyloxy groups. The elemental analysis and the extreme low-field absorption in the ^{13}C NMR spectrum at δ 109.1 point toward the 1,4,4-tris(acetyloxy)-2-azetidinone structure **25**.[28] Again **10b** is oxidized to nitrone **12**, which undergoes a transformation to **21** and subsequent acyl migration to give the 2-azetidinone **22** (Scheme IV). We can exclude that **21** is also an intermediate in the formation of **25**. The intramolecular acyl migration is a first-order reaction, whereas the 1,3-addition of lead tetraacetate to **21** that would have given **25** follows second-order kinetics, and since we found no concentration effect on the product ratio (**22**:**25**), compound **25** must have been formed via an alternative pathway.

Besides 1,3-addition of lead tetraacetate to nitrone **20**, there is a second possibility of reaction, viz., hydrogen abstraction by an acetyloxy radical to give the azaallylic radical **23**. This radical can recombine with a second acetyloxy radical to give **21** or nitrone **24**, the latter giving rise to the formation of **25**. The formation of the tris(acetyloxy) compound from the oxidation of the hydroxylamine **10b** with lead tetraacetate, a type of reaction that to our knowledge is unprecedented, reveals that the oxidation of 1-hydroxyazetidines unsubstituted at C-2 and C-4 at least partially proceeds via an azaallylic radical of the type **23**.

Unlike the 1-hydroxyazetidines blocked at one of the α-positions, which give 1-(acetyloxy)-2-azetidinones upon oxidation with lead tetraacetate, the 1-hydroxyazetidines described in this paper give rise to the formation of 1,4-bis(acetyloxy)-2-azetidinones. 2-Azetidinones with an acetyloxy group at the 4-position are well-known and easily accessible starting materials for the synthesis of biologically important β-lactam derivatives,[29] because of the ease of substitution of the acetyloxy group.[30] Therefore the synthesis of 1,4-bis(acetyloxy)-2-azetidinones via oxidation of 1-hydroxyazetidines seems to open a route to an unknown and interesting class of β-lactam derivatives.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra ($CDCl_3$) were recorded with 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 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 supervision of G. J. Rotscheid.

Materials. Sodium cyanoborohydride (Aldrich), pyridinium chlorochromate (Aldrich), dimethyl acetylenedicarboxylate (Merck), and lead tetraacetate (Merck) are commercially available. Lead tetraacetate was washed with diethyl ether immediately before use to remove the acetic acid. Petroleum ether refers to the fraction boiling at 60–80 °C and glacial acetic refers to $CuSO_4$ dried acetic acid. The starting materials **4a**,[9] **4b**,[10] and **5a**[8] were

(25) Pennings, M. L. M.; Okay, G.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1982**, *47*, 4413.
(26) Neiman, L. A.; Zhukova, S. V.; Tyurikov, V. A. *Tetrahedron Lett.* **1973**, 1889.
(27) For a review see: Breuer, E. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Interscience: New York, 1982; Supplement F, Part 1, p 459.
(28) Azetidinone **22** could not be oxidized to the tris(acetyloxy)azetidinone **25**; the ratio of **22**:**25** only was slightly dependent of the reaction temperature (T = −15 °C, **22**:**25** = 70:30).
(29) Clauss, K.; Grimm, D.; Prossel, G. *Justus Liebigs Ann. Chem.* **1974**, 539.
(30) See, for instance: Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379.

prepared according to the literature from 1,3-propanediol (Aldrich) and 3-methyl-2-butanone, respectively.

Preparation of 5b and 5c. A solution of alcohol **4** (60 mmol) in 75 mL of dry dichloromethane was added in one portion to a suspension of pyridinium chlorochromate (19.5 g, 90 mmol) in 75 mL of dry dichloromethane. After being stirred for 7 h, the solution was diluted with 700 mL of dry diethyl ether, and the supernatant liquid was filtered through Florisil. The remaining sticky solid was washed 3 times with 100 mL of dry diethyl ether, and the combined liquids were filtered through Florisil. The remaining solution was concentrated under reduced pressure to give **5b** and **5c**. Compound **5b**: yield 82% after trituration with diisopropyl ether; mp 67–69 °C dec (diisopropyl ether) (lit.[31] mp 61.3 °C). Compound **5c**: yield 72% after distillation; bp 62–63 °C (22 mm); n^{20}_D 1.4636 (lit.[32] bp 60–70 °C (80 mm); lit.[33] bp 73 °C (0.5 mm); n^{20}_D 1.5485).

Preparation of Oximes 6a–d. A solution of the hydrochloride of hydroxylamine or *O*-benzylhydroxylamine (20 mmol) in 25 mL of methanol was neutralized by the addition of NaOH (0.8 g, 20 mmol), after which compound **5** (20 mmol) was added to this solution. After being stirred for 4 h, the solution was diluted with 150 mL of water. In the case of **6a** and **6b** the formed solids were filtered off, and in the case of **6c** and **6d** the aqueous solution was acidified with 2 N HCl and extracted with chloroform (3 × 30 mL). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. The resulting oil could be purified by distillation in the case of **6d**.

(*E*)-3,3-Dimethyl-4-[[(4-methylphenyl)sulfonyl]oxy]-2-butanone oxime (6a):[34] yield 92%; mp 119.5–121.5 °C (diisopropyl ether); ^{1}H NMR δ 8.2 (br s, 1 H, OH), 7.78 and 7.33 (AB, 4 H, SO_2Ar H), 3.96 (s, 2 H, CH_2O), 2.44 (s, 3 H, $ArCH_3$), 1.77 (s, 3 H, $CH_3C{=}N$), 1.10 (s, 6 H, CH_3); mass spectrum, *m/e* 285.103 (M^+; calcd for $C_{13}H_{19}NO_4S$, 285.103).

3,3-Dimethyl-4-[[(4-methylphenyl)sulfonyl]oxy]-2-butanone *O*-(phenylmethyl)oxime (6b): yield 96%; mp 83–84.5 °C (diisopropyl ether); ^{1}H NMR δ 7.78 and 7.30 (AB, 4 H, SO_2Ar H), 7.30 (s, 5 H, Ph H), 4.99 (s, 2 H, CH_2Ph), 4.00 (s, 2 H, CH_2O), 2.43 (s, 3 H, $ArCH_3$), 1.74 (s, 3 H, $CH_3C{=}N$), 1.08 (s, 6 H, CH_3); mass spectrum, *m/e* 375.149 (M^+; calcd 375.150).

Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 64.12; H, 6.73; N, 3.56.

2,2-Dimethyl-3-[[(4-methylphenyl)sulfonyl]oxy]-1-propanone *O*-(phenylmethyl)oxime (6c): yield 93%; oil, used without further purification; ^{1}H NMR δ 7.76 and 7.30 (AB, 4 H, SO_2Ar H), 7.31 (s, 5 H, Ph H), 7.24 (s, 1 H, =CH), 4.99 (s, 2 H, CH_2Ph), 3.88 (s, 2 H, CH_2O), 2.42 (s, 3 H, $ArCH_3$), 1.08 (s, 6 H, CH_3); mass spectrum, *m/e* 361.135 (M^+; calcd for $C_{19}H_{23}NO_4S$, 361.135).

3-Bromo-2,2-dimethyl-1-propanone *O*-(phenylmethyl)oxime (6d): yield 87%; bp 94–96 °C (0.05 mm); n^{20}_D 1.5326; ^{1}H NMR δ 7.41 (s, 1 H, =CH), 7.34 (s, 5 H, Ph H) 5.07 (s, 2 H, CH_2Ph), 3.38 (s, 2 H, CH_2Br), 1.22 (s, 6 H, CH_3); mass spectrum, *m/e* 190.123 (M^+ – Br; calcd for $C_{12}H_{16}NO$, 190.123).

Reduction of Oximes 6a–d. $NaCNBH_3$ (1.1 g, 18 mmol) was added in portions to a solution of the oxime **6** (15 mmol) in 40 mL of glacial acetic acid. After the reaction was complete, the acetic acid was removed under reduced pressure and the residue was neutralized with a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (3 × 40 mL). The combined extracts were dried and filtered and the chloroform was removed under reduced pressure.

3,4,4-Trimethylisoxazolidine (8) from 6a. After being stirred for 16 h at room temperature, the mixture was worked up as described above and distilled to give the isoxazolidine **8**: yield 61%; bp 62–64 °C (13 mm); n^{20}_D 1.4444; ^{1}H NMR δ 4.6 (br s, 1 H, NH), 3.70 and 3.58 (AB, 2 H, *J* = 7.3 Hz, H-5), 3.02 (q, 1 H, H-3), 1.03 (d, 3 H, CH_3), 1.11 and 0.97 (s, 6 H, CH_3); ^{13}C NMR δ 82.6 (t, C-5), 64.3 (d, C-3), 44.6 (s, C-4); mass spectrum, *m/e* 115.100 (M^+; calcd 115.100). **8·HCl**: white solid that decomposes at temperatures above 120 °C (chloroform/ethyl acetate).

Anal. Calcd for $C_6H_{13}NO{\cdot}HCl$: C, 47.53; H, 9.31; N, 9.24. Found: C, 47.74; H, 9.32; N, 9.64.

2,3,3-Trimethyl-1-(phenylmethoxy)azetidine (9a) from 6b. After being stirred for 16 h at 35 °C, the mixture was worked up as described above and distilled to give the azetidine **9a**: yield 63%; bp 62–64 °C (0.5 mm); n^{20}_D 1.4909; ^{1}H NMR δ 7.30 (s, 5 H, Ph H), 4.65 (s, 2 H, CH_2Ph), 3.27 (q, 1 H, H-2), 3.35 and 3.02 (AB, 2 H, *J* = 7 Hz, H-4), 1.04 (s, 6 H, CH_3), 1.00 (d, 3 H, CH_3); ^{13}C NMR δ 75.5 (t, OCH_2), 73.8 (d, C-2), 68.3 (t, C-4), 30.4 (s, C-3); mass spectrum, *m/e* 205.146 (M^+; calcd 205.147).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.93; H, 9.42; N, 6.79.

***N*-(Phenylmethoxy)-2,2-dimethyl-3-[[(4-methylphenyl)sulfonyl]oxy]-1-propanamine (7c) from 6c.** After being stirred at room temperature for 7 h, the mixture was worked up as described above to give **7c**: yield 95% (oil); ^{1}H NMR δ 7.76 and ~7.3 (AB, 4 H, SO_2Ar H), 7.29 (s, 5 H, Ph H), ~5.1 (br s, 1 H, NH), 4.55 (s, 2 H, CH_2Ph), 3.81 (s, 2 H, CH_2O), 2.76 (s, 2 H, CH_2N), 2.42 (s, 3 H, $ArCH_3$), 0.90 (s, 6 H, CH_3); mass spectrum, *m/e* 363.148 (M^+; calcd 363.150). **7c·HCl**: white solid, mp 110–119 °C (chloroform/diisopropyl ether).

Anal. Calcd for $C_{19}H_{25}NO_4S{\cdot}HCl$: C, 57.06; H, 6.55; N, 3.50. Found: C, 57.10; H, 6.49; N, 3.47.

***N*-(Phenylmethoxy)-3-bromo-2,2-dimethyl-1-propanamine (7d) from 6d.** After being stirred at room temperature for 7 h, the mixture was worked up as described above to give **7d** as a colorless oil: yield 91%; ^{1}H NMR δ 7.32 (s, 5 H, Ph H), ~5.3 (br s, 1 H, NH), 4.66 (s, 2 H, CH_2Ph), 3.36 (s, 2 H, CH_2Br), 2.89 (s, 2 H, CH_2N), 1.02 (s, 6 H, CH_3); mass spectrum, *m/e* 271.055 (M^+; calcd 271.057). **7d·HCl**: white solid, mp ~110 °C dec (chloroform/diisopropyl ether).

Anal. Calcd for $C_{12}H_{18}NOBr{\cdot}HCl$: C, 46.70; H, 6.20; N, 4.54. Found: C, 46.53; H, 6.22; N, 4.41.

3,3-Dimethyl-1-(phenylmethoxy)azetidine (9b) from 7c. To a solution of **7c** (2.9 g, 8 mmol) in 50 mL of dry diethyl ether was rapidly added in an atmosphere of nitrogen and at room temperature a solution of *n*-butyllithium in hexane (5.4 mL, 8.1 mmol). After being stirred for 15 min the solution was filtered. This procedure was repeated with another two portions of **7c**. The combined etheral solutions were concentrated under reduced pressure, and the residue was distilled to give **9b**: yield 53%; bp 62–64 °C (0.6 mm); n^{20}_D 1.4960; ^{1}H NMR δ 7.31 (s, 5 H, Ph H), 4.62 (s, 2 H, CH_2Ph), ~3.3 (br s, 4 H, NCH_2), 1.17 (s, 6 H CH_3); ^{13}C NMR δ 74.6 (t, OCH_2), 70.3 (t, NCH_2), 28.5 (s, C-3); mass spectrum, *m/e* 191.131 (M^+; calcd 191.130).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found C, 75.31; H, 9.23; N, 7.13.

From 7d. A solution of **7d** (4.1 g, 15 mmol) in 70 mL of dry pyridine was heated at 100 °C for 6 h. The solution was cooled, diluted with 70 mL of water, and acidified with a 6 N HCl solution. The aqueous mixture was extracted with chloroform (3 × 50 mL) and the combined extracts were dried and filtered. The chloroform was removed under reduced pressure and the residue was dissolved in chloroform and passed through a small silica gel column. The resulting solution was concentrated under reduced pressure and distilled to give **9b**: yield 61%.

Debenzylation of 1-(Phenylmethoxy)azetidines 9a and 9b. A solution of the azetidine **9** (20 mmol) in 40 mL of glacial acetic acid was hydrogenated at atmospheric pressure in the presence of 0.7 g of palladium on charcoal catalyst (5%). After being stirred for 7 h, the reaction mixture was filtered over Hyflo and the acetic acid was removed under reduced pressure at 30 °C. The residue was neutralized with a saturated aqueous $NaHCO_3$ solution and extracted with chloroform (5 × 20 mL in the case of **9a** and 10 × 20 mL in the case of **9b**). The combined extracts were dried and filtered, and the chloroform was removed under reduced pressure. The remaining liquid was distilled under reduced pressure to give the pure 1-hydroxyazetidines **10a** and **10b** in yields of 71% and 61%, respectively.

1-Hydroxy-2,3,3-trimethylazetidine (10a): bp 58–60 °C (5 mm); n^{20}_D 1.4363; ^{1}H NMR δ 6.9 (br s, 1 H, OH), 3.37 and 3.06 (AB, 2 H, *J* = 7.3 Hz, H-4), 3.25 (q, 1 H, H-2), 1.08 (d, 3 H, CH_3),

(31) Nerdel, F.; Frank, D.; Lengert, H.-D.; Weyerstahl, P. *Chem. Ber.* **1968**, *101*, 1850.

(32) Lucas, K.; Weyerstahl, P.; Marschall, H.; Nerdel, F. *Chem. Ber.* **1971**, *104*, 3607.

(33) Temnikova, T. I.; Oshueva, N. A. *Zh. Obshch. Khim.* **1963**, *33*, 2464. The authors describe this compound as extreme unstable, but in our hands it proved to be quite stable and could be stored at room temperature for several months.

(34) This compound has been described in the literature, but spectral and physical data were not reported.[4]

1.09 and 1.03 (s, 6 H, CH_3); ^{13}C NMR δ 74.7 (d, C-2), 69.3 (t, C-4), 30.7 (s, C-3); mass spectrum, m/e 115.099 (M^+; calcd for $C_6H_{13}NO$, 115.100).[35]

1-Hydroxy-3,3-dimethylazetidine (10b): bp 56–58 °C (5 mm); n^{20}_D 1.4359; mp ~10 °C; ^1H NMR δ ~7.6 (br s, 1 H, OH), ~3.4 (br AB, 4 H, NCH_2), 1.19 (s, 6 H, CH_3); ^{13}C NMR δ 71.3 (t, NCH_2), 28.1 (s, C-3); mass spectrum, m/e 101.084 (M^+; calcd for $C_5H_{11}NO$, 101.084).[35]

Oxidation of 1-Hydroxyazetidines 10a and 10b with Lead(IV) Oxide. 1-Hydroxyazetidine **10** (1 mmol) was added to a suspension of PbO_2 (0.36 g, 1.5 mmol) in 5 mL of dry dichloromethane. After being stirred for 45 min, $MgSO_4$ was added, and the mixture was filtered over Hyflo. The solvent was removed under reduced pressure to give an oil that could not be further purified. According to ^1H NMR spectroscopy, oxidation of **10a** gave a mixture of nitrone **11a** and nitrone **11b** (95%, **11a**:**11b** = 78:22), and oxidation of **10b** gave an oil that consisted for about 70% of nitrone **12**.

3,3,4-Trimethyl-2,3-dihydroazete 1-oxide (11a):[4] ^1H NMR δ 3.96 (q, 2 H, J = 1.95 Hz, H-2), 1.93 (t, 3 H, J = 1.95 Hz, $=CCH_3$), 1.32 (s, 6 H, CH_3).

2,3,3-Trimethyl-2,3-dihydroazete 1-oxide (11b): ^1H NMR δ 6.74 (s, 1 H, =CH), 4.14 (q, 1 H, H-2), 1.42 (d, 3 H, CH_3), 1.36 and 1.23 (s, 6 H, CH_3).

3,3-Dimethyl-2,3-dihydroazete 1-oxide (12): ^1H NMR δ 6.86 (s, 1 H, =CH), 4.04 (s, 2 H, H-2), 1.39 (s, 6 H, CH_3).

Dimethyl 6,6-Dimethyl-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4-dicarboxylate (13). The crude oil containing **12** (0.1 g) was dissolved in 5 mL of dry dichloromethane and reacted with DMAD (91 μL, 0.75 mmol) at 0 °C for 30 min, after which the solvent was removed under reduced pressure. The residue was dissolved in chloroform and passed through a small Florisil column, to give pure **13** after removal of the solvent under reduced pressure: yield 145 mg (oil that solidifies at −20 °C); ^1H NMR δ 4.82 (t, 1 H, J ~ 1 Hz, H-5), 3.91 and 3.75 (s, 6 H, OCH_3), 3.79 and 3.62 (d AB, 2 H, J = 10 Hz, J ~ 1Hz, H-7), 1.45 and 1.14 (s, 6 H, CH_3); ^{13}C NMR δ 154.0 (s, C-3), 108.0 (s, C-4), 81.2 (d, C-5), 72.0 (t, C-7), 39.8 (s, C-6); mass spectrum, m/e 241.094 (M^+; calcd for $C_{11}H_{15}NO_5$, 241.095).

Oxidation of 1-Hydroxyazetidines 10a and 10b with Lead Tetraacetate. A solution of the 1-hydroxyazetidine **10** (3 mmol) in 5 mL of dry toluene was added, in an atmosphere of nitrogen and at 0 °C, to a stirred solution of lead tetraacetate (4.0 g, 9 mmol in the case of **10a** and 4.43 g, 10 mmol in the case of **10b**) in 40 mL of dry toluene. After being stirred for 30 min at 0 °C, the mixture was filtered and the filtrate was washed with brine (2 × 10 mL). The toluene solution was dried and filtered and the solvent was removed under reduced pressure, after which the residue was worked up as described below.

1,4-Bis(acetyloxy)-3,4,4-trimethyl-2-azetidinone (19) was prepared according to the above procedure from **10a**. The resulting oil was dissolved in chloroform and passed through a small Florisil column. The chloroform was removed under reduced pressure to give an oil that solidified upon storage at −20 °C. The azetidinone **19** was isolated as white solid after trituration with petroleum ether: yield 71%; mp 68.5–70 °C (petroleum ether); IR (KBr) 1810 ($NOCOCH_3$), 1785 (C=O), and 1745 cm^{-1} ($OCOCH_3$); ^1H NMR δ 2.19 and 2.07 (s, 6 H, $COCH_3$), 1.78 (s, 3 H, CH_3), 1.36 (s, 6 H, CH_3); ^{13}C NMR δ 169.0 (s), 168.3 (s), 167.1 (s), (C=O and OC=O), 97.2 (s, C-4), 55.0 (s, C-3); mass spectrum, m/e 230.103 (M^+ + 1; calcd 230.103).

Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.51; H, 6.66; N, 6.08.

1,4,4-Tris(acetyloxy)-3,3-dimethyl-2-azetidinone (25) was prepared according to the above procedure from **10b**. The resulting oil solidified and was triturated with diisopropyl ether/petroleum ether (1:1 v/v) to give **25** as a white solid: yield 31%; mp 127.5–128.5 °C (diisopropyl ether): IR (KBr) 1825 ($NOCOCH_3$), 1790 (C=O) and 1760 cm^{-1} ($OCOCH_3$); ^1H NMR δ 2.17 (s, 3 H, $NOCOCH_3$), 2.12 (s, 6 H, $COCH_3$), 1.40 (s, 6 H, CH_3); ^{13}C NMR δ 167.1 (s, C=O), 109.1 (s, C-4), 57.4 (s, C-3); mass spectrum, m/e 214.073 (M^+ − OAc; calcd 214.072).

Anal. Calcd for $C_{11}H_{15}NO_7$: C, 48.35; H, 5.56; N, 5.13. Found: C, 48.54; H, 5.61; N, 5.23.

The filtrate was concentrated under reduced pressure, dissolved in chloroform, and passed through a small Florisil column. The solvent was removed under reduced pressure to give an oil (0.17 g) that consisted of 10% of **25** and 80% of **1,4-bis(acetyloxy)-3,3-dimethyl-2-azetidinone (22)**, from which compound **22** could not be isolated in a pure state: ^1H NMR δ 5.93 (s, 1 H, H-4), 2.17 and 2.14 (s, 6 H, $COCH_3$); 1.46 and 1.27 (s, 6 H, CH_3); ^{13}C NMR δ 170.1 (s), 168.6 (s) and 167.7 (s), (C=O and OC=O), 87.7 (d, C-4), 51.6 (s, C-3); mass spectrum, m/e 215.079 (M^+; calcd for $C_9H_{13}NO_5$, 215.079).

Kinetic Study of the Nitrogen Inversion Process in 3,3-Dimethylazetidines 9b and 10b. Variable-temperature ^1H NMR spectra of **9b** and **10b** (2 mmol) in 0.4 mL of a deuterated solvent were obtained with a Bruker WP-80 spectrometer equipped with a Bruker B-VT-1000 temperature unit (temperature in the tube ±0.25 °C). The coalescence temperature (T_c) of both the NCH_2 and CH_3 signals was determined by changing the temperature of the sample in steps of 1 °C. Cooling the samples to temperatures ≤0 °C allowed an accurate determination of the chemical shift differences ($\Delta\nu$) of the coalescing signals and the coupling constant of the NCH_2 hydrogen atoms (J_{AB}), the signal of which is treated as an AB spectrum. The free activation energies ($\Delta G^\ddagger$) of the nitrogen inversion process were calculated by using the equation $\Delta G^\ddagger = 4.57T_c\,[9.97 + (\log T_c)/(\Delta\nu^2 + 6J^2_{AB})^{1/2}]$ (see table).

Acknowledgment. We thank D. Kuiper for carrying out parts of the experimental work and are indebted to T. W. Stevens for recording the mass spectra and to J. L. M. Vrielink and J. M. Visser for recording the NMR and IR spectra. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

Registry No. **4a**, 21651-04-7; **4b**, 40894-00-6; **5a**, 24706-89-6; **5b**, 18516-19-3; **5c**, 34795-31-8; (*E*)-**6a**, 87070-46-0; **6b**, 86043-95-0; **6c**, 86043-98-3; **6d**, 87070-47-1; **7c**, 86043-99-4; **7d**, 87070-48-2; **8**, 86043-94-9; **9a**, 86043-96-1; **9b**, 86044-00-0; **10a**, 86043-97-2; **10b**, 86044-01-1; **11a**, 55386-66-8; **11b**, 86044-02-2; **12**, 86044-03-3; **13**, 86044-04-4; **19**, 86044-05-5; **22**, 87070-50-6; **25**, 87070-49-3; DMAD, 762-42-5.

(35) This compound could not be obtained analytically pure, even upon repeated distillation.