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Reaction of four-membered cyclic nitrones with acetyl chloride[α]. X-Ray crystal structures of 2-[(acetyloxy)amino]-*N,N*-diethyl-2-methyl-4-oxo-3-phenylpentanamide and 1-acetyl-3-chloro-*N,N*-diethyl-2-methyl-4-methylene-3-phenyl-2-azetidinecarboxamide

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Abstract. Reactions of the four-membered cyclic nitrones **1** with acetyl chloride differ strongly from those of other (cyclic) nitrones. In the presence of water, the nitrones **1** yield the 2-[(acetyloxy)-amino]-*N,N*-diethylalkanamides **4**. The structure of **4b** was confirmed by X-ray analysis. In the absence of water, the *N,N*-diethyl-4-methylene-2-azetidinecarboxamides **5** or the *N,N*-diethyl--2,3-dihydro-2-azetecarboxamides **6** were obtained. X-ray analysis elucidated the structure of **5a**. Under acidic conditions, compounds **5a** yielded the 2-oxa-5-azabicyclo[2.1.1]hexan-3-one derivative **13**. Acid hydrolysis of **6a** gave the α-chloroketone derivative **18** and the 2-oxopropanamide derivative **19**.

Introduction

We are currently investigating the synthesis and reactivity of four-membered cyclic nitrones. The four-membered cyclic nitrones are prepared via a (4 + 2) cycloadditon of the electron-deficient nitroalkenes and electron-rich ynamines[1,2]. Recently, we have reported reactions of four-membered cyclic nitrones with 1,3-dipolarophiles[3] and with nucleophiles[4-6] and also the synthesis of the potentially biologically active 6*H*-1,2-oxazin-6-ones[7] starting from four-membered cyclic nitrones. We have also published some preliminary results on the reactivity of four-membered cyclic nitrones towards electrophiles in relation to our work on the synthesis of β-lactams by isomerization of four-membered cyclic aldonitrones[8].

In general, nitrones are susceptible to electrophilic attack, due to the nucleophilic character of the oxygen atom[9,10]. The products formed depend on the amount of electrophile present and on the structure of the nitrone[11]. Upon reaction of the nucleophilic oxygen atom with the electrophile (XY), the carbon atom of the nitrone moiety becomes even more electron-deficient. One of the possible reactions is an attack of the nucleophilic anion (X^-) at the electrophilic carbon atom, which results in the formation of hydroxylamine derivatives. Elimination of XOY gives imine derivatives. The conversion of nitrones into amides is a well-known reaction and can be achieved using a variety of electrophilic reagents such as acetyl chloride, phosphorus chlorides, acetic anhydride and thionyl chloride[12-15]. Such isomerization reactions require only a catalytic amount of the electrophile[13]. The final product of this isomerization is identical with the amide obtained upon *Beckmann* rearrangement of ketoximes[16]. However, the mechanism of formation is believed to be different. In the classical *Beckmann* rearrangement, one substituent shifts from carbon to nitrogen, whereas in the nitrone isomerization reaction, as suggested by *Kroehnke*[12], the electrophile acts as an oxygen acceptor and subsequently as an oxygen donor. The conversion of *aldo*nitrones to the corresponding amides in the absence of oxygen donors seems to follow a different route. In their study on the reaction of *C,N*-diarylnitrones with ^{18}O-labelled benzoyl chloride and triethylamine, *Heine* et al. proposed the presence of a planar nitrilium cation as the key intermediate. This intermediate could explain the formation of amides in the absence of base, and also the formation of *N,N*-diacylamines in the presence of base[13]. The presence of α-methyl(ene) protons at the nitrone moiety can give rise to the formation of α-halo- or α-acyloxy-substituted imine derivatives.

As expected, on the basis of the results reported by *Heine* et al., we have shown previously that the isomerization of a *four-membered cyclic aldonitrone* into a β-lactam derivative could not be achieved under the generally applied isomerization conditions, since the formation of a planar nitrilium cation will be sterically impossible in a four-membered ring. Only by reaction with lead tetraacetate did we succeed in preparing 1-(acetyloxy)-2-azetidinone derivatives[17].

In this paper a systematic study of the reactions of four-membered cyclic nitrones with one electrophile, *viz.* acetyl chloride, is described. The conversion into 2-[(acetyloxy)-amino]-*N,N*-diethylalkanamides (**4**), *N,N*-diethyl-4-methylene-2-azetidinecarboxamides (**5**) and *N,N*-diethyl-2,3-dihydro-2-azetecarboxamides (**6**) is also discussed.

[α] Part of the thesis of *P. J. S. S. v. Eijk.*

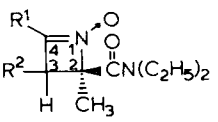
Results and discussion

We have found that, upon reaction of the nitrones **1** with acetyl chloride in the presence of water or under anhydrous conditions, different products are obtained. Reaction of the four-membered cyclic nitrones (**1**) with acetyl chloride results in an equilibrium between the acylated intermediates **2** and **3** (Scheme 1) which can be observed by ^{1}H NMR spectroscopy.

When the nitrones **1a-1q** were dissolved in chloroform *in the presence of one equivalent of water*, subsequent reaction with a slight excess of acetyl chloride gave the 2-[(acetyloxy)-amino]-*N,N*-diethylalkanamides **4a-4m**. However, in the case of the nitrones **1i**, **1n** and **1p**, we were unable to isolate the corresponding compounds **4** satisfactorily from the reaction mixture. The formation of these compounds **4** can be explained by addition of water to the iminium moiety of **3** and subsequent ring opening of the four-membered ring (Scheme 1). The downfield shifts of the hydrogen atoms in the ^{1}H NMR spectra at C-3 ($\delta \approx 4.62$)), as compared to the corresponding four-membered cyclic nitrones[2] ($\delta \approx 3.84$), are caused both by the influence of the carbonyl moiety at C-4 and by the carbamoyl function at C-2[18]. The chemical shift of H-3 in the ^{1}H NMR spectra of the compounds **4d**, **4k** and **4m** is influenced by the various substituents in the same way as in the ^{13}C NMR absorptions of C-3 *(vide infra)*. In the ^{13}C NMR spectra of the compounds **4**, the carbon atoms C-2 and C-3 absorb at $\delta \approx 70$ and $\delta \approx 59$, respectively (Table I). The highfield absorption of C-3 (δ 51.2) of compound **4d** is caused by the 2-methoxy substituent in the aryl group R^2. For the compounds **4k** (δ 54.4) and **4m** (δ 61.4), the deviation is caused by the R^1 group, *i.e.* a phenyl and a phenylthio group, respectively.

For compound **4f**, the slight differences in the ^{1}H and ^{13}C NMR data, as compared with the data of the other compounds **4**, can be attributed to the different stereochemistry at C-3 in this compound[2]. The structure of **4b** was confirmed by single crystal X-ray analysis (Fig. 1).

The compounds **4** can be regarded as functionalized and protected *N*-hydroxy amino acid derivatives[19]. *N*-Hydroxy amino acids may play a role as intermediates in the biogenetic pathway that converts L-amino acids into "uncommon" amino acids, such as α,β-dehydroamino acids, α- and β-functionalized α-amino acids and D-amino acids. These uncommon amino acids are generally found in fungal metabolites and they sometimes possess interesting biological properties, *e.g.* penicillin and sparsomycin.

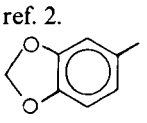


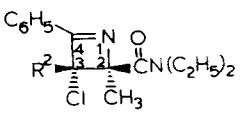
1

Compound[a]	R^1	R^2
1a	H	Ph
1b	Me	Ph
1c	Me	3-Pyridinyl
1d	Me	2-MeO-C_6H_4
1e	Me	4-Cl-C_6H_4
1f	Me	3,4-dioxyMe-C_6H_3[b]
1g	Me	2,4,6-$(Me)_3$-C_6H_2
1h	Me	3-Br-C_6H_4
1i	Me	2-MeO-Naphth
1j	Et	Ph
1k	Et	4-Cl-C_6H_4
1m	$PhCH_2$	Ph
1n	Ph	Ph
1p	Ph	4-Cl-C_6H_4
1q	PhS	Ph

[a] Except for **1g** and **1i**, *all* nitrones have the *cis* stereochemistry, see ref. 2.

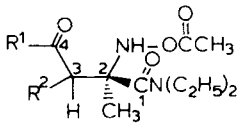
[b] 3,4-dioxyMe-C_6H_3 =





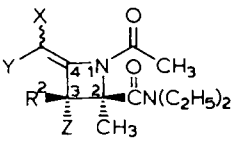
6

	R^2
6a	Ph
6b	4-Cl-C_6H_4



4

Compound	R^1	R^2
4a	H	Ph
4b	Me	Ph
4c	Me	3-Pyridinyl
4d	Me	2-MeO-C_6H_4
4e	Me	4-Cl-C_6H_4
4f	Me	3,4-dioxyMe-C_6H_3
4g	Me	2,4,6-$(Me)_3$-C_6H_2
4h	Me	3-Br-C_6H_4
4i	Et	Ph
4j	Et	4-Cl-C_6H_4
4k	Ph	4-Cl-C_6H_4
4m	PhS	Ph



5

	X	Y	Z	R^2
5a	H	H	Cl	Ph
5b	H	H	Cl	4-Cl-C_6H_4
5c	H	H	Cl	3-Br-C_6H_4
5d	H	H	Cl	2-MeO-Naphth
5e	Me	H	Cl	Ph
5f	Ph	Cl	H	Ph

Chart 1

Table I Spectral data of the compounds **4**[a].

Comp.	^{1}H NMR ($CDCl_3$): δ						^{13}C NMR ($CDCl_3$): δ								MS (*m/z*)	
	NH	H-3 (s)	R^1 (s)	$OCOCH_3$ (s)	R^3 (s)	$NCCH_3$ (t)	C-4	OC=O/NC=O (s)	C-2 (s)	C-3 (d)	R^1 (q)	R^3 (q)	$OCOCH_3$ (q)	$NCCH_3$ (br q)	(calcd.) exp.	formula
4a	6.80	4.45 (d)[b]	10.00 (d)[b]	2.13	1.49	1.13	197.6 (d)	169.6 168.6	71.7	59.1	–	17.8	19.1	13.7 12.4	(320.174) 320.175	$C_{17}H_{24}N_2O_4$
4b	6.62	4.67	2.25	2.12	1.56	1.10	195.5 (s)	169.8 168.6	70.3	59.5	31.3	17.0	19.2	13.2	(334.189) 334.193	$C_{18}H_{26}N_2O_4$
4c	6.71	4.66	2.27	2.13	1.53	1.10	205.7 (s)	169.6 168.8	71.0	56.9	31.6	17.1	19.2	13.9 12.4	(335.185) 335.190	$C_{17}H_{25}N_3O_4$
4d	7.02	5.21	2.18	2.08	1.63	1.11	206.4 (s)	170.2 169.0	70.8	51.2	31.1	17.7	19.2	13.8 12.2	(364.200) 364.198	$C_{19}H_{28}N_2O_5$
4e	6.66	4.63	2.25	2.12	1.53	1.10	206.0 (s)	169.7 168.8	70.5	58.6	31.5	16.8	19.3	13.9 12.2	(368.150) 368.143	$C_{18}H_{25}ClN_2O_4$
4f	6.57	4.57	2.27	2.12	1.55	1.10	206.5 (s)	169.8 169.0	70.1	58.3	31.4	16.4	19.4	13.9 12.1	(378.179) 378.183	$C_{19}H_{26}N_2O_6$
4g	9.04	4.62	2.04	1.96	1.70	0.86	208.0 (s)	169.7 169.6	72.3	60.9	29.6	20.7	19.0	13.3 11.9	(376.236) 376.236	$C_{21}H_{32}N_2O_4$
4h	6.64	4.62	2.27	2.14	1.54	1.10	205.8 (s)	169.6 168.9	70.4	58.6	31.7	16.6	19.3	13.9 12.2	(412.100) 412.106	$C_{18}H_{25}BrN_2O_4$
4i	6.73	4.64	[c,d]	2.11	1.57	1.08	209.0 (s)	169.9 168.9	70.2	59.1	[e]	17.2	19.3	13.9 12.2	(348.205) 348.207	$C_{19}H_{28}N_2O_4$
4j	6.76	4.60	[c,f]	2.11	1.54	1.08	208.8 (s)	169.7 168.9	70.4	58.4	[g]	17.2	19.2	13.9 12.3	(382.166) 382.168	$C_{19}H_{27}ClN_2O_4$
4k	7.40	5.49	[h]	2.13	1.65	1.07	197.8 (s)	169.5 169.0	70.7	54.4	[h]	18.1	19.3	13.9 12.2	(330.091) 330.091	$C_{18}H_{17}ClNO_3$ ($M^+ - C_5H_{10}NO$)
4m	6.68	4.80	[h]	2.10	1.54	1.09	196.3 (s)	169.1 168.9	70.2	61.4	[h]	17.6	19.2	13.8 12.3	(319.166) 319.164	$C_{17}H_{23}N_2O_4$ ($M^+ - C_6H_5S$)

[a] The stereochemistry of the compounds **4** at C-2 and C-3 is determined by the stereochemistry of the starting four-membered cyclic nitrones **1**. [b] *J* 2.3 Hz. [c] CH_2 quartet coincides with multiplet at δ 4.5–2.1 (NCH_2). [d] δ 0.98 (t, 3H, CH_3). [e] δ 36.8 (t, C-5), 8.0 (q, C-6). [f] δ 0.99 (t, 3H, CH_3). [g] δ 36.9 (t, C-5), 7.9 (q, C-6). [h] Phenyl absorptions.

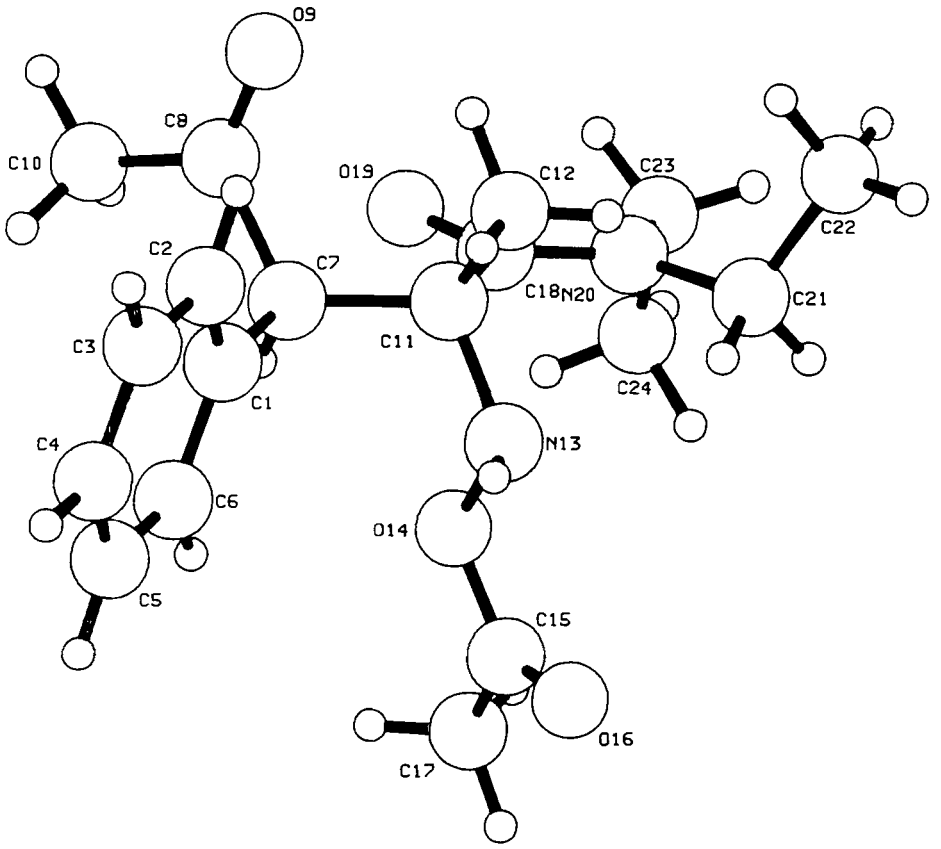


Fig. 1. Crystal structure of **4b**.

In *the absence of water*, prolonged reaction of the nitrones **1b**, **1e**, **1h-1j** and **1m** with acetyl chloride did not give the 2-[(acetyloxy)amino]-*N,N*-diethylalkanamides (**4**), but rather yielded different products, *viz.* the *N,N*-diethyl-4-methylene--2-azetidinecarboxamides **5** (Scheme 1). In the ^{1}H NMR spectrum of **5a**, which is representative of the compounds **5a–5d** (X = Y = H), one of the vinylic protons gives a doublet at δ 4.44 (*J* 2.7 Hz), whereas the other hydrogen atom gives a broad singlet at δ ≈ 5.5. Line broadening is also found for one of the methyl groups (δ 2.15) and for one of the amide methyl groups (δ 0.34). The absorptions at δ 74.2 and δ 81.1 in the ^{13}C NMR spectrum were assigned

Table II Positional parameters and their estimated standard deviations of compound **4b**.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
C1	0.9445(2)	0.4822(2)	0.2504(2)	H3	0.965(3)	0.789(2)	0.099(2)
C2	0.8938(3)	0.6219(2)	0.1814(2)	H4	1.252(3)	0.674(2)	0.147(2)
C3	1.0062(3)	0.6921(3)	0.1429(2)	H5	1.336(3)	0.435(2)	0.262(2)
C4	1.1703(3)	0.6239(3)	0.1737(2)	H6	1.147(2)	0.317(2)	0.322(2)
C5	1.2231(3)	0.4858(3)	0.2408(2)	H7	0.883(2)	0.326(2)	0.360(1)
C6	1.1112(3)	0.4155(3)	0.2793(2)	H10A	0.616(3)	0.596(2)	0.498(2)
C7	0.8257(2)	0.4022(2)	0.2981(2)	H10B	0.707(3)	0.425(3)	0.520(2)
C8	0.6807(2)	0.5090(2)	0.3493(2)	H10C	0.807(3)	0.530(3)	0.484(2)
O9	0.5595(2)	0.5910(2)	0.2942(1)	H12A	0.665(2)	0.379(2)	0.052(2)
C10	0.7041(3)	0.5139(2)	0.4723(2)	H12B	0.588(3)	0.505(2)	0.130(2)
C11	0.7781(2)	0.3224(2)	0.2123(2)	H12C	0.759(2)	0.481(2)	0.061(2)
C12	0.6874(3)	0.4287(2)	0.1048(2)	H13	0.981(4)	0.246(4)	0.134(3)
N13	0.9248(2)	0.2198(2)	0.1687(1)	H17A	1.296(3)	−0.191(3)	0.327(2)
O14	1.0074(2)	0.1111(2)	0.2699(1)	H17B	1.217(3)	−0.075(3)	0.409(2)
C15	1.1346(3)	0.0016(2)	0.2434(2)	H17C	1.120(3)	−0.160(3)	0.369(2)
O16	1.1870(3)	0.0041(2)	0.1505(2)	H21A	0.755(2)	0.135(2)	0.081(2)
C17	1.1981(3)	−0.1166(3)	0.3467(3)	H21B	0.698(2)	−0.002(2)	0.123(2)
C18	0.6739(2)	0.2327(2)	0.2793(2)	H22A	0.529(3)	0.164(3)	−0.042(2)
O19	0.6342(2)	0.2510(2)	0.3773(1)	H22B	0.421(3)	0.132(2)	0.069(2)
N20	0.6293(2)	0.1379(2)	0.2325(2)	H22C	0.454(3)	0.283(3)	0.038(2)
C21	0.6599(3)	0.1056(2)	0.1165(2)	H23A	0.463(3)	0.118(2)	0.356(2)
C22	0.5071(3)	0.1711(3)	0.0394(2)	H23B	0.482(3)	0.022(3)	0.259(2)
C23	0.5420(3)	0.0516(3)	0.3077(2)	H24A	0.598(3)	−0.139(3)	0.428(2)
C24	0.6583(4)	−0.0811(3)	0.3836(3)	H24B	0.750(3)	−0.148(3)	0.338(2)
H2	0.780(2)	0.668(2)	0.163(2)	H24C	0.726(3)	−0.059(3)	0.431(2)

to the ring carbon atoms C-2 and C-3, respectively. Previously[8], the *N,N*-diethyl-3-chloro-2-methyl-4-(2-oxopropylidene)-3-phenyl-2-azetidinecarboxamide structure has been assigned to **5a**. However, the ^{1}H NMR spectrum did not change upon addition of deuterium oxide. In addition, the ^{13}C NMR spectrum exhibits a very broad triplet at δ 91.2, which points to the presence of a $=CH_2$ moiety. As previously reported, the mass spectrum of this compound pointed to a 1:1 adduct of the nitrone and acetyl chloride with loss of water[8]. Finally, single-crystal X-ray analysis elucidated the methyleneazetidine structure for this compound (**5a**; 1-acetyl-3-chloro-*N,N*-diethyl-2-methyl-4--methylene-3-phenyl-2-azetidinecarboxamide[20]; Fig. 2). The four-membered ring in **5a** is almost planar with a torsional angle (C1–C2–N3–C4) of 1.4° and the *N*-acetyl moiety is coplanar with the methylene double bond. This indicates substantial conjugation, which is also expressed in the bond length of the C4–N3 bond. The C4–N3 bond length (0.1391 nm) is comparable with the bond length reported for the C(sp^2)–N bond (0.136 nm) of formamide[21]. The

Table III Positional parameters and their estimated standard deviations of compound **5a**.

Atom	*x*	*y*	*z*
Cl5	0.90989(7)	0.26063(5)	0.02407(4)
O13	0.9538(2)	0.6081(1)	−0.1728(1)
O20	1.3260(2)	0.4982(2)	−0.0994(2)
N3	1.1055(2)	0.4484(2)	−0.0906(1)
N14	0.7541(2)	0.5085(2)	−0.1702(1)
C1	0.9393(2)	0.4104(2)	−0.0127(1)
C2	0.9628(2)	0.4144(2)	−0.1110(1)
C4	1.0895(2)	0.4428(2)	−0.0054(1)
C6	0.8387(2)	0.4973(2)	0.0254(1)
C7	0.8749(3)	0.6183(2)	0.0302(2)
C8	0.7830(3)	0.6997(3)	0.0628(2)
C9	0.6573(3)	0.6636(3)	0.0910(2)
C10	0.6217(3)	0.5452(3)	0.0861(2)
C11	0.7109(3)	0.4618(3)	0.0542(2)
C12	0.8885(2)	0.5193(2)	−0.1536(1)
C15	0.6855(3)	0.6133(2)	−0.2070(2)
C16	0.6435(4)	0.7029(3)	−0.1436(2)
C17	0.6630(2)	0.4113(2)	−0.1438(2)
C18	0.6094(3)	0.3389(3)	−0.2150(2)
C19	1.2202(2)	0.4748(2)	−0.1355(2)
C21	1.2087(3)	0.4728(4)	−0.2280(2)
C22	1.1702(3)	0.4592(3)	0.0586(2)
C23	0.9552(3)	0.2965(2)	−0.1592(2)
H7	0.969(3)	0.647(2)	0.004(2)
H8	0.812(3)	0.782(3)	0.065(2)
H9	0.602(4)	0.719(3)	0.116(2)
H10	0.543(4)	0.509(3)	0.104(2)
H11	0.679(3)	0.367(2)	0.048(2)
H15A	0.598(4)	0.590(3)	−0.238(2)
H15B	0.738(3)	0.642(2)	−0.249(2)
H16C	0.598(4)	0.773(3)	−0.164(2)
H16A	0.727(4)	0.728(3)	−0.120(2)
H16B	0.575(4)	0.663(3)	−0.103(3)
H17B	0.583(3)	0.441(3)	−0.114(2)
H17A	0.712(3)	0.364(2)	−0.106(2)
H18A	0.531(4)	0.288(3)	−0.195(2)
H18B	0.578(3)	0.387(2)	−0.254(2)
H18C	0.682(3)	0.299(2)	−0.244(2)
H21A	1.249(5)	0.390(3)	−0.241(4)
H21B	1.235(8)	0.556(5)	−0.238(6)
H21C	1.128(4)	0.449(3)	−0.245(3)
H22B	1.131(4)	0.441(3)	0.113(2)
H22A	1.262(4)	0.487(3)	0.043(2)
H23A	1.026(4)	0.246(2)	−0.139(2)
H23C	0.952(3)	0.312(3)	−0.221(2)
H23B	0.875(4)	0.253(2)	−0.146(2)

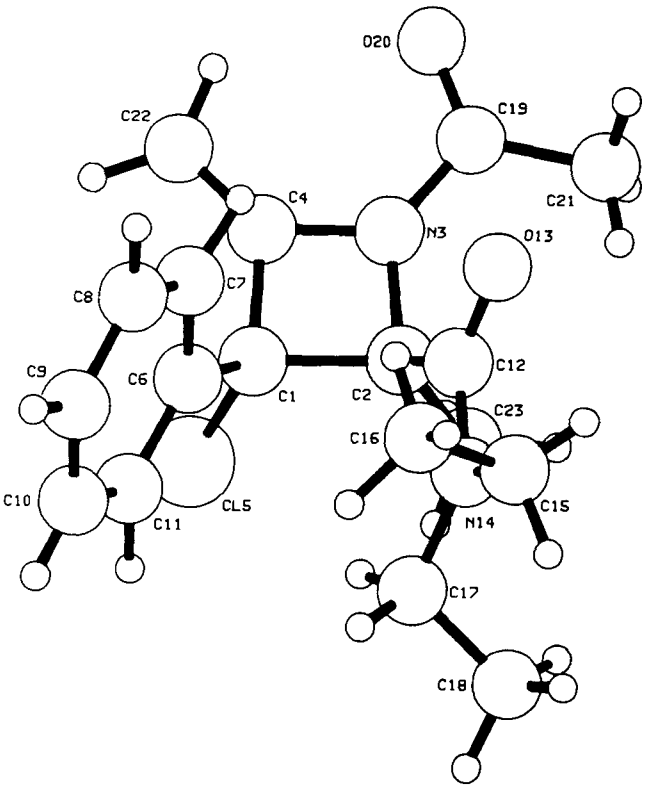
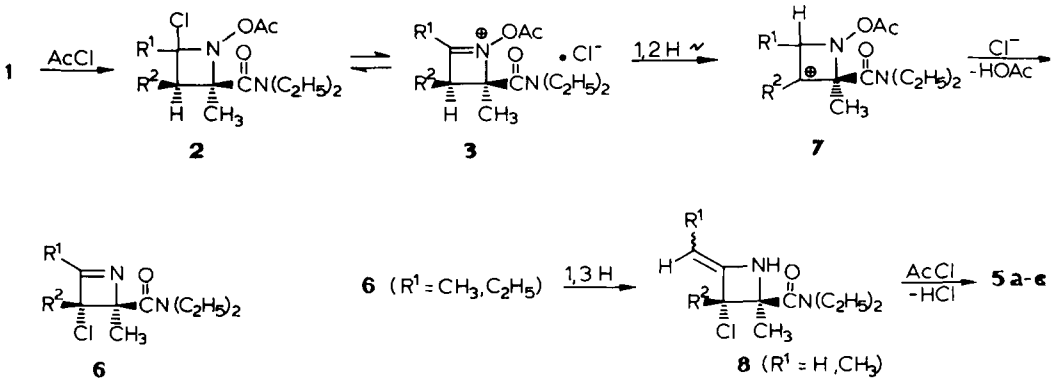


Fig. 2. Crystal strucuture of **5a**.

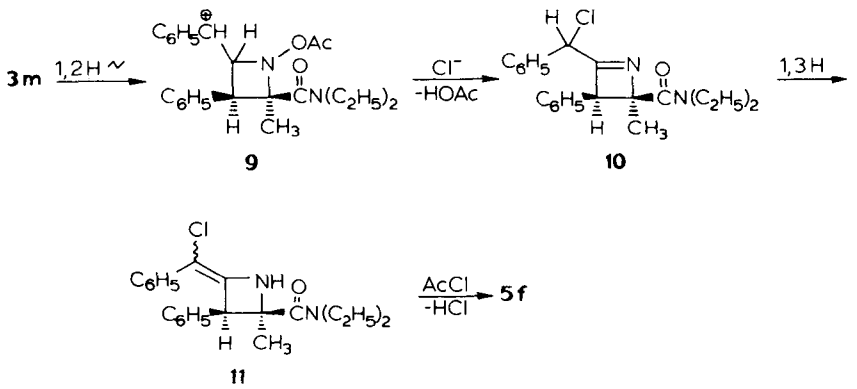
C2–C3 bond (0.1610 nm) is longer than an average C(sp^3)–C(sp^3) bond (0.150 nm)[21].

When the four-membered cyclic nitrone **1j** (R^1 = ethyl) was reacted with acetyl chloride under similar anhydrous conditions, a mixture of two stereoisomers was obtained in a 2:1 ratio. The ^{1}H NMR spectrum shows two broad quartets for vinylic hydrogen atoms at δ ≈ 6.25 and δ ≈ 5.05. The ^{13}C NMR spectrum exhibits one doublet at δ 104.4. Since, for both isomers, the mass spectrum pointed to the expected molecular composition of a methylenazetidine derivative (**5**), we concluded that the reaction of the nitrone **1j** with acetyl chloride yields a mixture of two stereoisomers (**5e**) (Scheme 1).

Reaction of the nitrone **1m** (R^1 = benzyl) with acetyl chloride under anhydrous conditions also yielded a mixture of two products in a 3:1 ratio. According to mass spectrometry, both compounds had the overall composition $C_{24}H_{27}ClN_2O_2$. In the ^{1}H NMR spectrum, singlets are present at δ 4.26 and δ 4.13 and the corresponding doublets in the ^{13}C NMR spectrum at δ 58.8 and δ 57.5. These data exclude the presence of vinylic hydrogen atoms, but point to the presence of a benzylic proton in the ring (Scheme 2). Therefore, on the basis of both NMR and MS data, we have assigned the azetidine structure (**5f**) to these isomers. The formation of a product with a structure similar to **5a**, *viz.* 1-acetyl-3-(acetyloxy)-4,4-dimethyl-2-methylenepyrrolidine, has been reported by *Barton* and co-workers[22]. This compound was obtained from the reaction of 2,4,4-trimethyl-1-pyrroline 1-oxide with acetic anhydride in carbon tetrachloride at −20°C. Acylation of the nitrone oxygen atom, followed by a deprotonation at C-3 and a 1,3-acetate shift to the C-3 position, results in the formation of an imine. This imine is susceptible to a second acylation and subsequent deprotonation of the methyl group at C-2 would account for the formation of the methylenepyrrolidine. *Breuer* reviewed this reaction[23] and explained the formation



Scheme 1



Scheme 2

of the product via a tandem hetero-*Cope* type rearrangement reaction. The reaction of *N*-oxides with acetic anhydride is known as the *Polonovski*[24] reaction, which involves a deprotonation, followed by a sigmatropic shift of an acetate group. This *Polonovski*-type rearrangement reaction has been reported to be *non-concerted* for *C*-phenylbenzazepin *N*-oxides[25,26]. The formation of 9-(acetyloxy)-acridine by rearrangement of the acetylated acridine 1-oxide was explained by an intramolecular shift of the acetate group, via a cyclic or a "gliding" mechanism, from the N-1 to the C-9 position[27].

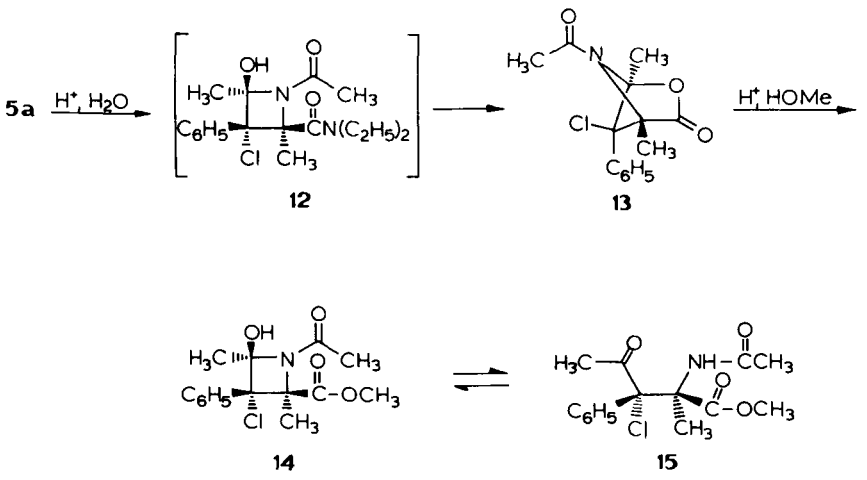
In our case, the reaction does occur with acetyl chloride. The benzylic carbocation at C-3 in the compound **7**, which is formed by a 1,2-hydride shift from C-3 to C-4, is attacked by an anion present in solution. In our case, this will be the chloride anion since it is a better nucleophile than the acetate anion. Subsequent acetic acid elimination gives the imine **6** (Scheme 1). Tautomerization of one of the α-methyl(ene) protons gives the methyleneazetidine intermediate **8**. Acetylation of **8**, followed by deprotonation, gives the compounds **5**.

In **3m**, there are two types of benzylic protons. The hydride shift takes place to give the energetically favourable exocyclic carbocation, since this route avoids the more strained carbocation **7m** (Scheme 1). The stereochemistry at C-2 and C-3 of **5f**, obtained as a mixture of two isomers, has not changed. This can be concluded by comparison of the H-3 absorptions in the ^{1}H NMR spectra of both isomers of **5f** with those of the starting nitrone **1m** and the *trans*-four-membered cyclic nitrones **1g** and **1i**. The H-3 absorptions of **5f** are present at δ 4.26 and δ 4.13, $\delta_{H\text{-}3}$ of **1m** 3.72, and $\delta_{H\text{-}3,trans} \approx 5.30$. Thus, the lower field absorption of H-3 is not caused by a *cis* relationship of H-3 with a carbamoyl moiety.

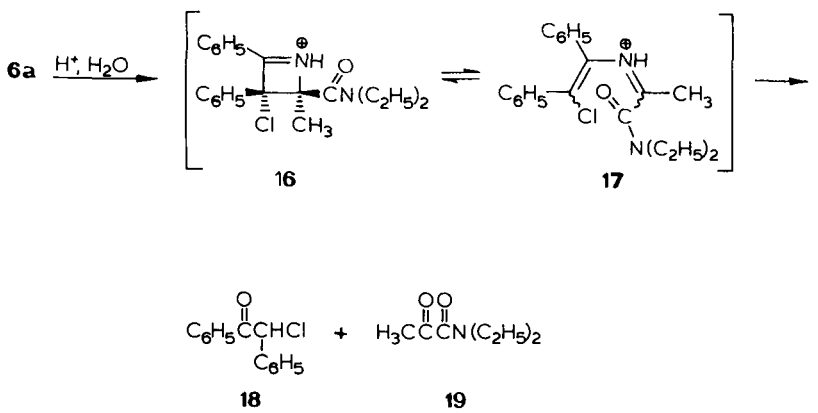
Prolonged reaction of the nitrones **1c-1d** and **1f-1g** with acetyl chloride under the same reaction conditions did not give rise to the corresponding compounds **5**. It is possible that reaction of the four-membered cyclic nitrone **1c** (R^2 = 3-pyridinyl) with acetyl chloride may also lead to an acetylation of the pyridinyl moiety. Due to the positive charge introduced in the pyridinyl ring, the aryl group will not stabilize the carbocation at C-3. In the nitrones **1d** and **1g**, the aryl *ortho* substituents of R^2 may hinder the aryl moiety sterically to become coplanar with the carbocation at C-3. Upon reaction of the *trans* four-membered cyclic nitrone **1i** with acetyl chloride under anhydrous conditions, we obtained compound **5d** in a yield of 2%. Mass spectrometry showed the expected molecular composition. However, ^{1}H NMR data point to a 2:1 mixture in which the *cis* isomer is the major component. This proves that in the reaction sequence the aryl moiety becomes planar with the carbocation. In this case, the products result from a chloride anion attack at either side of the ring.

When the four-membered cyclic nitrones **1n** and **1p** (R^1 = phenyl) were reacted with acetyl chloride, the reaction stopped to yield the 2,3-dihydroazete derivatives **6** (Scheme 1)[28]. Obviously this dihydroazete is not susceptible to further acylation due to the absence of a methylene hydrogen atom at the α-position, which is necessary to form an exocyclic double bond prior to acetylation *(vide supra)*.

Reaction of the exocyclic double bond of the compounds **5** with oxidizing agents seemed very interesting, since cleavage of the exocyclic double bond would lead to β-lactams. However, neither ozonolysis nor oxidation with



Scheme 3



Scheme 4

sodium periodate or oxidation with osmium tetroxide satisfactorily oxidized this double bond.

Upon reaction of compound **5a** with *p*-toluenesulfonic acid hydrate in dichloromethane at room temperature, a dramatic change in the NMR spectra was observed. The ^{1}H NMR spectrum shows only phenyl protons and three methyl absorptions. The diethylamino signals of the carbamoyl moiety had disappeared, which was confirmed by ^{13}C NMR spectroscopy. The absorption at 1815 cm^{-1} in the IR spectrum points to a strained lactone derivative. Protonation of the exocyclic double bond of **5a** creates a positive charge on C-4, which is susceptible to addition of water. Elimination of the protonated diethylamino moiety, achieved by an intramolecular attack[29] of the hydroxyl group at C-4 (**12**) on the carbamoyl moiety, gives the lactone **13** (Scheme 3). The observation that the compound **5a** gives the lactone derivative **13** can be explained in terms of the diminishing of ring strain. In the bicyclic compound **13**, the steric hindrance is minimized by the puckering conformation of the azetidine ring and the envelope conformation of the lactone ring. Treatment of the lactone derivative **13** with acidified methanol yielded the pentanecarboxylic ester **15**, which may be formed via compound **14** (Scheme 3). The absorptions in the IR spectrum of **15** at 3280 and 3220 cm^{-1} point to a secondary amide, whereas the absorptions at 1750, 1720 and 1640 cm^{-1} point to the presence of three C=O moieties. In the ^{13}C NMR spectrum, the carbonyl absorption at δ 203.4 definitively proves the presence of a ketone moiety which is not present in the compound **14**.

Hydrolytic cleavage of the C=N double bond of compound **6a** would lead to an α-chloro β-amino ketone derivative, which can be regarded as interesting starting material for the preparation of aziridines[30]. In the literature, a few examples of the hydrolysis of 2,3-dihydroazetes to yield amino ketones have been reported[31]. However, treatment of **6a** with diluted HCl under the same reaction conditions did not give the expected amino ketone. Instead, ring opening of the protonated 2,3-dihydroazete derivative **16** and subsequent hydrolysis of the azabutadiene derivative **17** account for the compounds 2-chloro-1,2-diphenylethanone (**18**)[32] and *N,N*-diethyl-2-oxopropanamide (**19**)[33] which were obtained (Scheme 4). In his theoretical study on the ring opening of (aza)cyclobutenes, *Snyder* discussed the possibility of ring opening of protonated azacyclobutenes[34].

Conclusions

Due to the four-membered ring, the products obtained from the reaction of four-membered cyclic nitrones with acetyl chloride are different from those which are usually obtained upon reaction with cyclic nitrones. Firstly, due to the small four-membered cyclic ring, the generally observed isomerization reaction giving lactams does not occur. Secondly, the presence of a benzylic hydrogen atom in the ring of the

four-membered cyclic nitrone leads to the incorporation of chloride in the product.

Our results show that a direct conversion of the four-membered cyclic nitrones (**1**) into *N*-hydroxy amino acid derivatives[19], *i.e.* the 2-[(acetyloxy)amino]-*N,N*-diethyl-alkanamides (**4**), upon reaction with acetyl chloride *in the presence of water*, is a facile and useful reaction. Moreover, the C-2 position might also be functionalized, since the ynamine substituents can be easily varied[2]. However, the nitrone substitution pattern has a slight influence on this process. In the case of the nitrones **1** with R^1 = Ph, the hydrolysis of the $PhC{=}N^+$ bond is dependent on the substitution pattern in R^2. The four-membered cyclic nitrone **1p** (R^2 = 4-ClC_6H_4) is converted into the corresponding amide **4k**, whereas the four-membered cyclic nitrone **1n** (R^2 = Ph) did not react in the same way.

The synthesis of the methyleneazetidines **5** by reaction of four-membered cyclic nitrones with acetyl chloride under *anhydrous conditions* is restricted by the substitution pattern of the nitrone and, in addition, the presence of an alkyl group at C-4 of the nitrone is required. Furthermore, the substitution pattern of the aryl moiety at C-3, *i.e.* R^2, limits the scope of the reaction. The presence of a 3-pyridinyl group (**1c**), or the presence of one or two *ortho* substituents in the aryl group R^2 (**1d**, **1g** and **1i**), prevents the formation of the compounds **5**. This can be explained by the inability of the aryl group to stabilize the carbocation on electronical (**1c**) or on steric grounds (**1d**, **1g** and **1i**). Unfortunately, the attempted oxidation of the exocyclic double bond, in order to obtain β-lactam derivatives, failed. The presence of acid resulted in a hydrolysis of the carbamoyl moiety under *mild conditions* of **5a** to give the bicyclic product **13**.

Reaction of the four-membered cyclic nitrone **1n** with acetyl chloride under anhydrous conditions yielded the 2,3-dihydroazete derivative **6a**. Treatment of this compound with acid resulted in a ring opening reaction of the protonated azacyclobutene derivative (**16**) in agreement with *Snyder*'s calculations on azacyclobutenes[34]. The compounds **18** and **19** are the result of a hydrolysis of the initially formed 2-azabutadiene derivative **17**.

Experimental

Melting points were determined using a Reichert melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Bruker WP-80 spectrometer and a Nicolet NT 200-WB spectrometer, respectively. The NMR spectra were recorded in $CDCl_3$ using tetramethyl silane (TMS) as an internal standard. Mass spectra were obtained using a Varian MAT 311A spectrometer and IR spectra using a Perkin-Elmer 257 spectrophotometer. X-Ray data were obtained using an Enraf-Nonius CAD4 diffractometer. Elemental analyses were carried out by *E. Hoogendam* of the Laboratory of Chemical Analysis at the University of Twente. The four-membered cyclic nitrones **1** were prepared as described in refs. 1 and 2. The synthesis, the analytical and the spectral data of the 2-[(acetyloxy)amino]-*N,N*-diethyl-alkanamides **4a** and **4b**, the *N,N*-diethyl-4-methylene-2-azetidine-carboxamide **5a** and the *N,N*-diethyl-2,3-dihydro-2-azetecarboxamide **6a** are described in ref. 8. All reactions were carried out under a nitrogen atmosphere. Petroleum ether refers to the fraction boiling at 60 – 80°C. Mass spectra were calculated for ^{79}Br and ^{35}Cl.

General procedure for the synthesis of compounds **4**

The four-membered cyclic nitrone **1** (1.0 mmol) was dissolved in dichloromethane (15 ml) and water (1.0 mmol) was added to the solution. Acetyl chloride (1.1 mmol) was added at 0°C and the reaction mixture was stirred for a further 5–10 min. After addition of water (40 ml), the organic layer was separated. The aqueous layer was extracted with chloroform (3 × 20 ml). The organic layers were collected, dried and the solvent evaporated under vacuum. Pure compound **4** was obtained by purification of the crude reaction products by column chromatography (silica gel; petroleum ether/diethyl ether mixtures) or directly upon trituration with diisopropyl ether or petroleum ether. NMR and MS data of the compounds **4** are given in Table I.

2-[(Acetyloxy)amino]-N,N-*diethyl-2-methyl-4-oxo-3-(3-pyridinyl)-pentanamide* (**4c**) was prepared from nitrone **1c** (0.62 g, 2.0 mmol) and acetyl chloride (150 µl, 2.1 mmol) as described above. The crude reaction mixture was triturated with diisopropyl ether which gave a white solid, yield 72%; m.p. 115–117°C dec (diisopropyl ether). IR: 3220 (NH), 1780, 1750 (OC=O), 1710 (C=O), 1620 (NC=O) cm^{-1}. Anal. calcd. for $C_{17}H_{25}N_3O_4$ (335.41): C 60.88, H 7.51, N 12.53; found: C 61.13, H 7.78, N 12.41.

2-[(Acetyloxy)amino]-N,N-*diethyl-3-(2-methoxyphenyl)-2-methyl-4-oxopentanamide* (**4d**) was prepared from nitrone **1d** (0.31 g, 1.0 mmol) and acetyl chloride (75 µl, 1.1 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the eluent polarity was gradually increased by addition of pure diethyl ether). After trituration of the main component with a diisopropyl ether/petroleum ether mixture, a white solid was isolated: yield 27%; m.p. 124–126°C dec (diisopropyl ether). IR: 3240 (NH), 1750 (OC=O), 1700 (C=O), 1625 (NC=O) cm^{-1}. Anal. calcd. for $C_{19}H_{28}N_2O_5$ (364.44): C 62.62, H 7.74, N 7.69; found: C 62.63, H 7.78, N 7.69.

2-[(Acetyloxy)amino]-3-(4-chlorophenyl)-N,N-*diethyl-2-methyl-4-oxopentanamide* (**4e**) was prepared from nitrone **1e** (0.92 g, 3.0 mmol) and acetyl chloride (225 µl, 3.2 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the eluent polarity was gradually increased by addition of pure diethyl ether). After trituration of the main component with diisopropyl ether, a white solid was isolated: yield 52%; m.p. 110–120°C (diisopropyl ether). IR: 3220 (NH), 1770, 1750 (OC=O), 1705 (C=O), 1620 (NC=O) cm^{-1}. Anal. calcd. for $C_{18}H_{25}ClN_2O_4$ (368.86): C 58.61, H 6.83, N 7.59; found: C 58.73, H 6.87, N 7.58.

2-[(Acetyloxy)amino]-3-(1,3-benzodioxol-5-yl)-N,N-*diethyl-2-methyl-4-oxopentanamide* (**4f**) was prepared from nitrone **1f** (0.95 g, 3.0 mmol) and acetyl chloride (225 µl, 3.2 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the polarity of the eluent was gradually increased to a ratio of petroleum ether/diethyl ether 2:3 v/v). After trituration of the main component with diisopropyl ether, a white solid was isolated: yield 57%; m.p. 126–128°C dec (chloroform/diisopropyl ether/petroleum ether). IR: 3220 (NH), 1740 (OC=O), 1710 (C=O), 1620 (NC=O) cm^{-1}. Anal. calcd. for $C_{19}H_{26}N_2O_6$ (378.43): C 60.30, H 6.93, N 7.40; found: C 60.22, H 7.05, N 7.17.

2-[(Acetyloxy)amino]-N,N-*diethyl-2-methyl-3-(2,4,6-trimethylphenyl)-4-oxopentanamide* (**4g**) was prepared from nitrone **1g** (0.63 g, 2.0 mmol) and acetyl chloride (150 µl, 2.1 mmol) as described above. Compound **4g** was obtained after column chromatography (silica gel, petroleum ether/diethyl ether 1:1 v/v) in a yield of 52%; m.p. 111–114°C (after trituration with diisopropyl ether). IR: 3220 (NH), 1740 (OC=O), 1705 (C=O), 1610 (NC=O) cm^{-1}.

2-[(Acetyloxy)amino]-3-(3-bromophenyl)-N,N-*diethyl-2-methyl-4-oxopentanamide* (**4h**) was prepared from nitrone **1h** (1.06 g, 3.0 mmol) and acetyl chloride (225 µl, 3.2 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v). After trituration of the main component with a diisopropyl ether/petroleum ether mixture, **4h** was obtained as a white solid, yield 57%; m.p. 88–90°C (after trituration with diisopropyl ether). IR: 3220 (NH), 1775 (OC=O), 1720 (C=O), 1640 (NC=O) cm^{-1}.

2-[(Acetyloxy)amino]-N,N-*diethyl-2-methyl-4-oxo-3-phenylhexanamide* (**4i**) was prepared from nitrone **1j** (0.86 g, 3.0 mmol) and acetyl chloride (225 µl, 3.2 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the polarity of the eluent was gradually increased by addition of pure diethyl ether). After trituration of the main component with diisopropyl ether, a white solid was isolated: yield 77%; m.p. 86–87°C (diisopropyl ether/

petroleum ether). IR: 3220 (NH), 1775, 1750 (OC=O), 1705 (C=O), 1625 (NC=O) cm^{-1}. Anal. calcd. for $C_{19}H_{28}N_2O_4$ (348.44): C 65.49, H 8.10, N 8.04; found: C 65.68, H 8.34, N 7.97.

2-[(Acetyloxy)amino]-3-(4-chlorophenyl)-N,N-*diethyl-2-methyl-4-oxohexanamide* (**4j**) was prepared from nitrone **1k** (0.97 g, 3.0 mmol) and acetyl chloride (225 µl, 3.2 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the polarity of the eluent was gradually increased by addition of pure diethyl ether). After trituration of the main component with petroleum ether, a white solid was isolated: yield 58%; m.p. 82–85°C (chloroform/diisopropyl ether/petroleum ether). IR: 3225 (NH), 1775, 1750 (OC=O), 1710 (C=O), 1630 (NC=O) cm^{-1}. Anal. calcd. for $C_{19}H_{27}ClN_2O_4$ (382.89): C 59.60, H 7.11, N 7.32; found: C 59.94, H 7.23, N 7.36.

2-[(Acetyloxy)amino]-3-(4-chlorophenyl)-N,N-*diethyl-2-methyl-4-oxo--4-phenylbutanamide* (**4k**) was prepared from nitrone **1p** (1.11 g, 3.0 mmol) and acetyl chloride (225 µl, 3.1 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the polarity of the eluent was gradually increased by addition of pure diethyl ether). After trituration of the main component with petroleum ether, a white solid was isolated: yield 39%; m.p. 141–143°C dec (after trituration with diisopropyl ether). IR: 3240 (NH), 1770 (OC=O), 1675 (C=O), 1620 (NC=O) cm^{-1}.

3-[(Acetyloxy)amino]-3-[(diethylamino)carbonyl]-2-phenylbutanethioic acid S-phenyl ester (**4m**) was prepared from nitrone **1q** (0.37 g, 1.0 mmol) and acetyl chloride (225 µl, 3.2 mmol) as described above. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether 60–80/diethyl ether, 1:1 v/v; gradually increasing the polarity of the eluent by addition of pure diethyl ether). After trituration of the main component with a diisopropyl ether/petroleum ether mixture, a white solid was isolated, yield 35%; m.p. 125–127°C (tetrachloromethane/petroleum ether). IR: 3220 (NH), 1745 (OC=O), 1705 (C=O), 1630 (NC=O) cm^{-1}. Anal. calcd. for $C_{23}H_{28}N_2O_4S$ (428.55): C 64.46, H 6.59, N 6.54; found: C 64.42, H 6.75, N 6.43.

General procedure for the synthesis of compounds **5b-5f**

Dry dichloromethane (2 ml) and acetyl chloride (2 ml; freshly distilled) were transferred into the reaction flask. The solution was cooled to −78°C and the nitrone **1** (2 mmol) added in one portion. The reaction mixture was allowed to reach room temperature and was stirred for a further 2 h. The reaction was quenched by the addition of ice water (100 ml). The organic layer was separated and the water phase was extracted with chloroform (4 × 20 ml). The organic layers were collected, dried and the solvent evaporated under vacuum. Pure **5** was obtained by purification of the crude reaction products by column chromatography (silica gel; petroleum ether/diethyl ether mixtures) or upon trituration with diisopropyl ether.

1-Acetyl-3-chloro-3-(4-chlorophenyl)-N,N-*diethyl-2-methyl-4-methylene-2-azetidinecarboxamide* (**5b**) was prepared from nitrone **1e** (0.62 g, 2.0 mmol). The crude reaction mixture was triturated with diisopropyl ether to give compound **5b** in a yield of 52%; m.p. 135–138°C dec (diisopropyl ether). IR: 1690 (C=C−N), 1680, 1645 (NC=O) cm^{-1}. ^1H NMR: δ 7.61 and 7.28 (AB, 4H, *J* 8.8 Hz, ArH), 5.48 (br s, 1H, =CH), 4.42 (d, 1H, *J* 2.7 Hz, =CH), 3.6–2.2 (m, 4H, NCH_2), 2.18 and 2.05 (s, 6H, CH_3 and CH_3C-2), 1.04 and 0.45 (t, 6H, $NCCH_3$). ^{13}C NMR: δ 170.5 (s, NC=O), 166.5 [s, (C=O)N-1], 151.5 (s, C-4), 135.1 (s, ArC-4), 131.8 (s, ArC-1), 91.4 (d, $=CH_2$), 81.4 (s, C-3), 74.1 (s, C-2), 41.7 and 39.7 (t, NCH_2), 23.6 and 23.2 (br q, CH_3 and CH_3C-2), 13.3 and 10.7 (q, $NCCH_3$). MS: accurate mass theor. 368.106; exp. 368.100. Anal. calcd. for $C_{18}H_{22}Cl_2N_2O_2$ (369.29): C 58.54, H 6.01, N 7.59; found: C 58.16, H 5.99, N 7.47.

1-Acetyl-3-(3-bromophenyl)-3-chloro-N,N-*diethyl-2-methyl-4-methylene-2-azetidinecarboxamide* (**5c**). For the preparation of **5c** the general procedure was slightly modified. Acetyl chloride (100 µl, 1.4 mmol) was dissolved in dry dichloromethane (2 ml). At a temperature of −60°C, nitrone **1h** (0.35 g, 1.0 mmol) was added to the solution. After dissolution of the solid, the reaction vessel was transferred to a bath having a temperature of 60°C and the solution was refluxed for 2 min. According to the method described above, the reaction products were isolated. The crude reaction mixture was separated by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v) to give both compounds **4h** and **5c** as an oil, in 44% and 49% yield, respectively. Compound **5c** solidified upon addition of diisopropyl ether and petroleum ether, m.p. 100–105°C (after trituration with diisopropyl ether/petroleum ether). IR: 1695 (C=C−N), 1675, 1640 (NC=O) cm^{-1}. ^1H NMR: δ 7.9–7.1 (m, 4H, PhH), 5.55 (br s, 1H, =CH), 4.44 (d, 1H, *J* 2.9 Hz, =CH), 3.6–2.2 (m, 4H, NCH_2), 2.18 and 2.06 (s, 6H, CH_3 and CH_3C-2), 1.05 and 0.43 (t, 6H, $NCCH_3$). ^{13}C NMR: δ 170.8 (s, NC=O), 166.2 [s, (C=O)N-1], 151.0 (s, C-4), 138.9 (s, ArC-3), 121.8 (s, ArC-1), 91.7 (d, $=CH_2$), 81.4 (s, C-3), 73.8 (s, C-2), 41.2 and 39.6 (t, NCH_2), 24.0 and 23.2 (br q, CH_3, and CH_3C-2), 13.4 and 10.8 (q, $NCCH_3$). MS: accurate mass theor. 412.055 for $C_{18}H_{22}BrClN_2O_2$; exp. 412.049.

1-Acetyl-3-chloro-N,N-*diethyl-2-methyl-3-(2-methoxynaphthalenyl)-4--methylene-2-azetidinecarboxamide* (**5d**). Compound **5d** was prepared as described for **5c**. The crude reaction mixture was separated by column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; and the polarity of the eluent was slowly increased by the addition of diethyl ether) to give compound **5d** as a white solid upon trituration with diisopropyl ether, yield 2%. According to the ^1H NMR spectrum, this compound appeared to be a 2:1 mixture of the *cis* and *trans* isomer. The data of the minor compound are shown in parentheses. ^1H NMR (200 MHz): δ 8.20 and [8.05] (d, 1H, *J* 8.6 Hz, ArH-8), 7.9–7.15 (m, 5H, ArH), 6.76 and [6.66] (d, 1H, *J* 2.6 Hz, =CH), 5.47 and [5.05] (d, 1H, *J* 2.6 Hz, =CH), 4.02 and [3.79] (s, 3H, OCH_3), 3.5–1.8 (m, 4H, NCH_2), [2.28] and 2.26 (s, 3H, $COCH_3$), 2.08 and [2.06] (s, 3H, CH_3C-2), [0.81], 0.71, [0,18] and −0.10 (t, 6H, $NCCH_3$). MS: accurate mass theor. 414.171 for $C_{23}H_{27}ClN_2O_3$; exp. 414.168.

1-Acetyl-3-chloro-N,N-*diethyl-2-methyl-3-phenyl-4-propylidene-2-azetidinecarboxamide* (**5e**) was prepared from nitrone **1j** (0.58 g, 2.0 mmol). The crude reaction mixture was purified by column chromatography (silica gel, petroleum ether/diethyl ether 3:7 v/v), yield 73%; m.p. 139–143°C (diisopropyl ether). (The spectroscopic data are obtained from a 2:1 mixture of the isomers.) IR: 1695 (C=C−N), 1650, 1640 (NC=O) cm^{-1}. ^1H NMR: δ 7.8–7.5 (m, 2H, PhH), 7.5–7.1 (m, 3H, PhH), 6.20 (br q, 1H, =CH), 5.05 (br q, 1H, =CH), 3.6–2.1 (m, 4H, NCH_2), 2.11 and 2.05 (s, 6H, CH_3 and CH_3C-2), 1.33 (d, 3H, *J* 7.6 Hz, $=CCH_3$), 1.01 and 0.37 (t, 6H, $NCCH_3$). ^{13}C NMR: δ 170.2 (s, NC=O), 166.8 [s, (C=O)N-1], 143.4 (s, C-4), 130.3 (s, PhC-1), 104.4 (d, =CH), 80.8 (s, C-3), 75.0 (s, C-2), 41.5 and 39.5 (t, NCH_2), 23.3 (q, CH_3 and CH_3C-2), 11.2 (q, $=CCH_3$), 13.3 and 10.8 (q, $NCCH_3$). MS: accurate mass theor. 348.160; exp. 348.159. Anal. calcd. for $C_{19}H_{25}ClN_2O_2$ (348.87): C 65.41, H 7.22, N 8.03; found: C 65.30, H 7.39, N 7.89.

1-Acetyl-4-(chlorophenylmethylene)-N,N-*diethyl-2-methyl-3-phenyl-2-azetidinecarboxamide* (**5f**) was prepared from nitrone **1m** (0.35 g, 1.0 mmol) and acetyl chloride (1 ml) in dry dichloromethane (2 ml), according to the general procedure. The crude reaction mixture was purified by column chromatography (silica gel; petroleum ether/diethyl ether 3:7 v/v) to give **5f** in a yield of 44%. M.p. 150–180°C dec (after trituration with diisopropyl ether). IR: 1680 (C=C−N), 1640, 1630 (NC=O) cm^{-1}. From the ^1H NMR spectrum, **5f** appeared to be a 3:1 mixture of stereo isomers. Spectral data are given for both compounds, with those for the minor compound, if separately visible, in parentheses. ^1H NMR: δ 7.5–7.0 (m, 10H, PhH), 4.26, [4.13] (s, 1H, H-3), 3.7–2.5 (m, 4H, NCH_2), [2.36], 2.17 and 2.06 (s, 6H, CH_3 and CH_3C-2), 0.93 and 0.67 (t, 6H, $NCCH_3$). ^{13}C NMR: δ [168.6], 168.0, 176.4 and [167.1] [s, NC=O and (C=O) N-1], 150.0 and [149.8] (s, C-4), 137.8, [137.7], [137.4] and 137.3 (s, PhC-1), 107.1 [br s, =C(Ph)Cl], [75.9] and 74.9 (s, C-2), [58.8] and 57.5 (d, C-3), 41.7, [41.3], 39.8 and [39.6] (t, NCH_2), 25.4 and [25.1] (q, CH_3), 23.6 and [22.9] (q, CH_3C-2), [13.3], 13.2, 11.4 and [11.2] (q, $NCCH_3$), MS: accurate mass theor. 410.176 for $C_{24}H_{27}ClN_2O_2$; exp. 410.176.

3-Chloro-3-(4-chlorophenyl)-N,N-*diethyl-2,3-dihydro-2-methyl-4-phenyl-2-azetecarboxamide* (**6b**)

Nitrone **1p** (1.11 g; 3.0 mmol) was added to a mixture of dry dichloromethane (3 ml) and acetyl chloride (3 ml) at −60°C. The temperature was allowed to rise to 0°C, at which temperature the reaction mixture was stirred for an additional 2 h. The reaction

mixture was worked up according to the method described for compounds **5**. Compound **6b** was obtained after column chromatography (silica gel; petroleum ether/diethyl ether, 1:1 v/v; the polarity of the eluent was gradually increased by the addition of pure diethyl ether to a 2:3 v/v mixture), yield 65%; m.p. 125–129°C (after trituration). IR: 1620, 1600 (C=N) and (NC=O) cm^{-1}. ^1H NMR: δ 7.8–7.6 (m, 2H, PhH-2,6), 7.55–7.1 (m, 7H, PhH and ArH), 3.6–2.6 (m, 4H, NCH_2), 1.87 (s, 3H, CH_3), 1.09 and 0.61 (t, 6H, $NCCH_3$). ^{13}C NMR (DMSO-d_6): δ 181.2 (C=N), 168.3 (s, C=O), 134.7 (s, PhC-4), 82.1 (s, C-3), 75.3 (s, C-2), 42.1 and 41.0 (t, NCH_2), 25.2 (q, CH_3C-2), 14.9 and 12.3 (q, $NCCH_3$). MS: accurate mass theor. 388.111 for $C_{21}H_{22}Cl_2N_2O$; exp. 388.108.

5-Acetyl-6-chloro-1,4-dimethyl-6-phenyl-2-oxa-5-azabicyclo[2.1.1]-hexan-3-one (**13**)

To a solution of the methyleneazetidine derivative **5a** (1.02 g, 3.0 mmol) in chloroform (12 ml), *p*-toluenesulfonic acid·H_2O (0.6 g, 3.0 mmol) was added. After 1 h, the solution turned cloudy and the reaction mixture was stirred for an additional 2 h. The salts formed were removed by passing the reaction mixture directly through a small column (silica gel). Following the use of chloroform (10 ml) as eluent, diethyl ether was used to complete the elution. Compound **13** (R_f 0.75) was obtained as a sweet smelling white solid, yield 54%; m.p. 137–143°C (crude crystals). IR: 1815 (strained lactone), 1640 (NC=O) cm^{-1}. ^1H NMR: δ 7.8–7.3 (m, 5H, PhH), 2.12 (s, 3H, CH_3(C=O)N), 1.58 (s, 3H, CH_3C-4), 1.30 (s, 3H, CH_3C-1). ^{13}C NMR: δ 171.1 and 161.6 (s, OC=O and NC=O), 133.9 (s, PhC-1), 106.2 (s, C-1), 74.0 (s, C-6), 65.7 (s, C-4), 20.7 (q, CH_3), 17.8 (q, CH_3C-1), 15.3 (q, CH_3C-4). MS: accurate mass theor. 279.066 for $C_{14}H_{14}ClNO_3$; exp. 279.068.

Methyl 2-(acetylamino)-3-chloro-2-methyl-4-oxo-3-phenylpentanoate (**15**)

To a mixture of the bicyclic lactone **13** (0.40 g; 1.5 mmol) in methanol (10 ml) four drops of concentrated sulfuric acid were added. The mixture was stirred overnight. The solvent was removed under vacuum and water (50 ml) was added to the residue. After extraction with chloroform (3 × 10 ml), the combined organic layers were washed with a saturated sodium bicarbonate solution (10 ml). After evaporation of the organic solvent under vacuum and column chromatography of the residue (silica gel; diethyl ether), **15** was obtained as an oil, yield 64%. IR: 3280 and 3220 (sec. amide), 1750, 1740 (α-haloketone), 1720 (C=O), 1640 (NC=O) cm^{-1}. ^1H NMR: δ 7.5–7.2 (m, 5H, PhH), 6.58 (br s, 1H, NH), 3.58 (s, 3H, OCH_3), 2.30 (s, 3H, $COCH_3$), 1.95 (s, 3H, CH_3), 1.76 (s, 3H, CH_3C-2). ^{13}C NMR: δ 203.4 (s, C-4), 169.8 (s), 169.0 (s, OC=O and NC=O), 133.5 (s, PhC-1), 82.2 (s, C-3), 67.0 (s, C-2), 52.3 (q, OCH_3), 28.5 (q, C-5), 24.0 (q, CH_3), 21.7 (q, CH_3C-2). MS: accurate mass theor. 312.107 for $C_{15}H_{19}ClNO_4$ ($M^+ + 1$); exp. 312.100.

X-Ray crystal structure analysis of **4b** *and* **5a**

Crystals of **4b** belong to the triclinic space group $P\bar{1}$, with cell constants: a = 8.659(4), b = 9.859(6), c = 11.891(6) Å, α = 78.41(4), β = 87.25(5), γ = 70.03(5)°, Z = 2, d_c = 1.189 g·cm^{-3}. Data were collected at 293(2) K, MoKα radiation, graphite monochromator, θ–2θ scan, $3 < \theta < 25°$, scan width (ω) 1.3 + 0.34 tgθ. The refinement of the crystal structure is based upon 2470 reflections with $I > 3\sigma(I)$. The final weighted R factor is 3.7% for 322 variables.

Crystals of **5a** belong to the orthorhombic space group $P2_12_12_1$, with cell constants: a = 9.766(3), b = 11.166(2), c = 16.198(3) Å, Z = 4, d_c = 1.214 g·cm^{-3}. Data were collected at 293(2) K, MoKα radiation, graphite monochromator, θ–2θ scan, $3 < \theta < 27.5°$, scan width (ω) 1.1 + 0.34 tgθ. The refinement of the crystal structure is based upon 1893 reflections with $I > 3\sigma(I)$. The final weighted R factor is 6.0% for 300 variables.

The X-ray structures were solved by direct methods[35]. Calculations were carried out using the SDP package[36]. Parameters refined were scale factor, extinction parameter, positional and anisotropic thermal parameters for the non hydrogen atoms; positional and anisotropic thermal parameters for the hydrogen atoms. Hydrogen atom positions were found from difference Fourier synthesis.

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