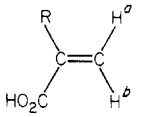
solution prepared from 37% aqueous formaldehyde (1.39 mL, 18.5 mmol), morpholine (2.39 mL, 27.4 mmol), water (100 mL), and TFA (1.38 mL, used to adjust the pH to 4.2). After 20 min the solution became turbid. The solvents were removed in vacuo, and the residue was dissolved in 50 mL of 50% aqueous DMF. After 2 h the solvent was removed in vacuo, and the resulting oil was triturated with 20 mL of 5% citric acid solution. The resulting powder was washed with an additional 5 mL of citric acid and with water and dried to yield 17: 1.02 g (72.4% based on 15); mp 215-217.5 °C dec; $[\alpha]^{25}_D$ +21.4° (c 1.0 MeOH); ^{1}H NMR (Me_2SO-d_6) δ 5.62 (s, 1 H, H^a of I), 5.64 (s, 1 H, H^a of I), 6.08 (s,



I

2 H^b of I); ^{13}C NMR (Me_2SO-d_6) δ 136.03 (s, C=CH_2), 136.64 (s, C=CH_2), off-resonance decoupled spectrum. Amino acid analysis of an acid hydrolysate of 17 indicated MGlu and "Asp" as the only ninhydrin-positive components.

Anal. Calcd for $C_{21}H_{24}O_9N_2$: C, 56.25; H, 5.39; N, 6.25. Found: C, 56.03; H, 5.37; N, 6.19.

Acknowledgment. This study was supported in part by grants from the National Institutes of Health (HL-20161 and HL-23881). Purchase of the NMR instrument was made possible by NSF Instrument Grants GU-2059 and GP-37602 and by NIH Grant 5S05RR07072. H.D.B. gratefully acknowledges the support of NIH Grant AM-07386-02; N.T.B., NIH Grant T32-HL-07255.

Registry No. D-1, 60686-52-4; L-1, 60686-50-2; **2a**, 601-75-2; **2b**, 616-75-1; **3a**, 80954-38-7; **3b**, 24643-58-1; **5**, 80954-39-8; **6**, 80954-40-1; **7**, 66513-60-8; **8**, 80954-41-2; **9**, 80954-42-3; **10**, 56618-30-5; **11**, 78746-71-1; **12**, 80954-43-4; **13**, 81024-46-6; **14**, 80954-44-5; **15**, 80963-05-9; **16**, 74201-25-5; **17**, 80954-45-6; tosylate leucine benzyl ester, 1738-77-8; *N*-(*tert*-butoxycarbonyl)-L-alanine *N*-hydroxysuccinimide, 3401-36-3.

Chemistry of Four-Membered Cyclic Nitrones. 1. Synthesis and Thermal Isomerization of 2,3-Dihydroazete 1-Oxides[1]

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Nitroalkenes (1) react with ynamines (1-aminoacetylenes, 2) to yield nitrocyclobutenes 3 and four-membered cyclic nitrones (2,3-dihydroazete 1-oxides, 5); in one case the open-chain isomer (4) of a four-membered cyclic nitrone was isolated. Nitrones 5 isomerize thermally to yield the corresponding *N*-vinylnitrones 4. Kinetic studies and X-ray analysis indicate that this reaction is a concerted conrotatory ring opening analogous to the ring opening of cyclobutenes. Only in the reaction of 1-nitrocyclopentene (**1d**) with **2b** has the initially formed nitronic ester **6** been isolated. The thermal ring contraction of **6** does not yield the corresponding four-membered cyclic nitrone but the isoxazoline derivative **7**. Compound **6** was further characterized by reaction with DMAD and with methyl propiolate to give the tricyclic products **8a** and **8b**, respectively. The mechanism of the stereospecific formation of the nitrones is discussed in terms of a concerted 1,3 sigmatropic shift.

As part of our work on [2 + 2] cycloadditions,[2,3] we have reported the reactions of electron-rich acetylenes (ynamines) with 3-nitrobenzo[*b*]thiophenes.[4] These reactions gave two products, cyclobutenes and *N*-(heteroaryl)-*C*-carbamoyl nitrones. The formation of the [2 + 2] cycloadducts, although it involves the reaction of the aromatic thiophene nucleus as a 2-π-electron moiety, is not surprizing since ynamines generally react with electron-deficient alkenes.[5] Moreover, nitroalkenes and nitroacetylenes react with electron-rich alkenes (enamines) to form nitrocyclobutanes[6] and nitrocyclobutenes,[7] respectively. The formation of the nitrones was the more surprizing result because it requires the participation of the nitro group and a transfer of oxygen from the nitro group to the C-1 carbon atom of the acetylene. An investigation into the scope of this reaction with nitro (hetero) aromatics revealed that several (hetero) aromatic compounds did not react and also that 3-nitrobenzofuran reacted in a completely different fashion. Mixtures of 1-benzoxepin, benzofuran[3,2-*c*]isoxazole, and quinoline *N*-oxide derivatives were obtained.[8,9]

These results, indicating that a reactive "nitroalkene" moiety is needed, have prompted us to investigate reactions of simple nitroalkenes with ynamines, although Nielsen and Archibald have reported that (*E*)-2-nitro-1-phenylpropene fails to react with 1-(diethylamino)-2-phenylacetylene.[10] The present paper describes the results of this investigation.[11]

Results

The acyclic 1-nitroalkenes **1a-c**, which are the thermodynamically most stable isomers, prepared by condensation

(1) Part of the forthcoming thesis of M.L.M.P.
(2) (a) Reinhoudt, D. N.; Volger, H. C.; Kouwenhoven, C. G.; Wijnberg, H.; Helder, R. *Tetrahedron Lett.* **1972**, 5269. (b) Hall, R. H.; den Hertog, H. J., Jr.; Reinhoudt, D. N., submitted for publication.
(3) (a) Reinhoudt, D. N.; Okay, G.; Trompenaars, W. P.; Harkema, S.; van den Ham, D. M. W.; van Hummel, G. J. *Tetrahedron Lett.* **1979**, 1529. (b) Reinhoudt, D. N.; Geevers, J.; Trompenaars, W. P.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1981**, *46*, 424.
(4) Reinhoudt, D. N.; Kouwenhoven, C. G. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 67.
(5) For a recent review on ynamines see: Ficini, J. *Tetrahedron* **1976**, *32*, 1449.
(6) Kuehne, M. E.; Foley, L. *J. Org. Chem.* **1965**, *30*, 4280.
(7) Jaeger, V.; Viehe, H. G. *Angew. Chem.* **1970**, *82*, 836.
(8) de Wit, A. D.; Trompenaars, W. P.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *Tetrahedron Lett.* **1980**, 1779.
(9) de Wit, A. D.; Trompenaars, W. P.; Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1981**, *46*, 172.
(10) Nielsen, A. T.; Archibald, T. G. *Tetrahedron* **1970**, *26*, 3475.
(11) Some of these results have been described in preliminary communications: (a) de Wit, A. D.; Pennings, M. L. M.; Trompenaars, W. P.; Reinhoudt, D. N.; Harkema, S.; Nevestveit, O. *J. Chem. Soc., Chem. Commun.* **1979**, 993. (b) Pennings, M. L. M.; Reinhoudt, D. N. *Tetrahedron Lett.* **1980**, 1781. (c) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 7570.

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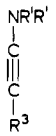
Table I. Yields and Characteristic NMR Absorptions of Four-Membered Cyclic Nitrones 5

compd	% yield: petroleum ether	% yield: acetonitrile	^{1}H NMR ($CDCl_3$), δ: R^1	R^3	[H-3]	^{13}C NMR ($CDCl_3$), δ: C-2	C-3	C-4	C=O	R^3
5a	25	35	6.90 (d)	2.02 (s)	4.02 (d)	90.8	51.5	136.3	165.0	20.3
5b	31		6.99 (d)	*a*	4.84 (d)	96.0	46.1	136.5	163.0	*a*
5c	30	61	1.98 (d)	1.98 (s)	3.94 (q)	88.8	54.7	147.2	165.4	19.9
5d	23		2.06 (d)	*a*	4.84 (q)	94.3	49.1	147.9	163.5	*a*
5e	<5	32	2.01 (d)	2.39 (s)	4.00 (q)	93.2	54.0	147.1	161.9	*b*
5f	33	63	*a*	2.05 (s)	4.27 (s)	88.4	52.6	146.2	165.5	20.6
5g	58	52	*a*	2.40 (s)	4.40 (s)	92.7	51.7	145.8	161.8	13.0
5h	35	43	*c*	1.84 (s)	2.7-3.0 (m)	84.7	49.1	155.1	166.7	21.2
5i	15	45	*c*	1.70 (s)	*d*	88.0	41.3	152.6	168.3	16.0

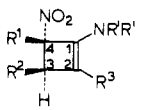
[a] Phenyl absorptions. [b] SMe and C-4 Me absorptions at δ 12.9 and 13.0. [c] Methylene absorptions. [d] Coincides with multiplet from δ 2.7 to 3.1.

of nitroalkanes with benzaldehyde, reacted at room temperature with ynamines **2a–c** in solvents of different po-

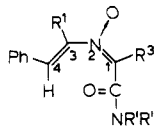
1a, R^1 = H; R^2 = Ph (*E*)
b, R^1 = Me; R^2 = Ph (*E*)
c, R^1 = R^2 = Ph (*Z*)
d, R^1 = R^2 = $(CH_2)_3$
e, R^1,R^2 = $(CH_2)_4$
f, R^1,R^2 = $(CH_2)_6$
g, R^1 = Me; R^2 = Ph (*Z*)



2a, R^3 = Me; R′ = R′ = Et
b, R^3 = Ph; R′,R′ = $(CH_2)_4$
c, R^3 = SMe; R′ = R′ = Et



3a, R^1 = H; R^2 = R^3 = Ph; R′,R′ = $(CH_2)_4$
b, R^1 = Me; R^2 = R^3 = Ph; R′,R′ = $(CH_2)_4$
c, R^1,R^2 = $(CH_2)_3$; R^3 = Ph; R′,R′ = $(CH_2)_4$
d, R^1 = R^3 = Me; R^2 = Ph; R′ = R′ = Et



4a, R^1 = H; R^3 = Ph; R′,R′ = $(CH_2)_4$
b, R^1 = R^3 = Me; R′ = R′ = Et
c, R^1 = H; R^3 = SMe; R′ = R′ = Et
d, R^1 = Me; R^3 = SMe; R′ = R′ = Et

larity.[12] Three different types of 1:1 reaction products were obtained. Compounds of the first type were easily identified as 4-nitrocyclobutenes, isolated in two cases (**3a,b**) as orange crystalline compounds and in one case (**3d**) as an unstable orange oil.[13] The absorptions of the nitro group at ~1540 and ~1345 cm^{-1} in the infrared spectra and typical enamine absorptions in the ^{13}C NMR spectra at ~136 and ~110 ppm together with other spectroscopic data unambiguously proved the cyclobutene structure. In the ^{1}H NMR spectrum, compound **3a** showed two singlets at δ 5.16 (H-4) and 4.28 (H-3) which clearly shows the trans substitution at C-3 and C-4. The absorption in the ^{1}H

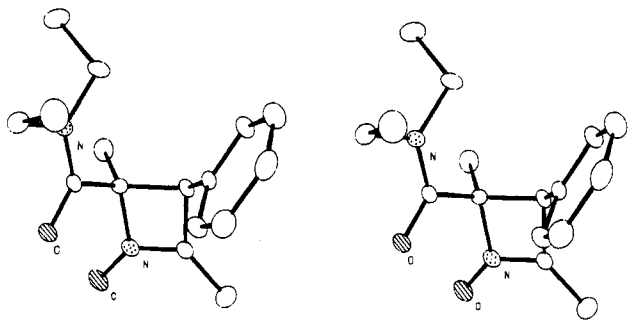


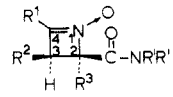
Figure 1. Stereoscopic view of the four-membered cyclic nitrone **5c**.

NMR spectra of the methyl group at C-4 of **3b** (δ 1.42) and **3d** (δ 1.28) also clearly shows that the methyl group (R^1) and phenyl group are cis substituted since a methyl group which is not shielded by the aromatic nucleus would give rise to an absorption at much lower field as for instance in **5c** (δ 2.02). The second type of product was only obtained from the reaction of **1a** and **2c**. The structure of the product, the *N*-vinyl nitrone **4c**, was assigned by the usual spectroscopic data (the ^{1}H NMR spectrum shows an AB pattern at δ 7.65 and 7.23, J_{AB} = 13.2 Hz, for the hydrogen atoms at C-3 and C-4) and by comparison of the ^{13}C NMR data with those of a similar nitrone (**4b**), the structure of which was determined by X-ray analysis (vide infra, Table II). The major reaction products belong to the third type, isolated as white crystalline compounds in yields of 5–35% when the reactions were carried out in petroleum ether. The IR spectra of these compounds did not show the absorptions of a nitro group, and the presence in the ^{1}H and ^{13}C NMR spectra of absorptions of a >C–H group at δ 4–5 and of two sp^3 carbon atoms at δ ~90 and 50 ruled out the *N*-vinyl-*C*-carbamoyl nitrone structure **4**. Single-crystal X-ray analysis of the reaction product of **1b** and **2a** showed the four-membered cyclic nitrone structure (*N*,*N*-diethyl-2,3-dihydro-2,4-dimethyl-3-phenyl-2-azetecarboxamide 1-oxide, **5c**; Figure 1).[11a] Structures for compounds **5a,b,d–g** were assigned by comparison of the spectroscopic data with **5c**. (Table I). In all cases only one of the two possible diastereoisomers is formed, which in the case of **5c** is the thermodynamically less favorable isomer with the two more bulky substituents, the *N*,*N*-diethylcarbamoyl and the phenyl group, on the same fact of the almost flat four-membered ring. The ^{13}C NMR spectra of **5a,b,d–g** point to the same stereochemistry as in **5c** because of the great similarity of the spectroscopic data of R^3 and of the carbamoyl group.

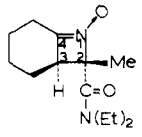
These four-membered cyclic nitrones represent the first "stable" examples of these heterocycles. Only Black et al.[14]

(12) The rate of reaction between nitroalkenes and ynamines is higher in polar solvents like acetonitrile and chloroform than in less polar solvents such as petroleum ether. Often, however, reactions were carried out in a low-polarity solvent, viz., petroleum ether, because under these conditions the reactive and sometimes unstable cyclic nitrones precipitate and can easily be isolated. Experiments in a more polar solvent, viz., acetonitrile, gave higher yields of cyclic nitrones **5** and lower yields of cyclobutenes **3** than the corresponding reactions in apolar solvents (Table I).

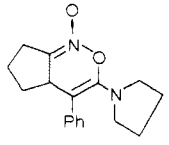
(13) Due to the thermal instability and the instability toward chromatography reagents like silica gel or alumina, attempts to isolate the nitrocyclobutenes often failed.



5a, R^1 = H; R^2 = Ph; R^3 = Me; R′ = R′ = Et
b, R^1 = H; R^2 = R^3 = Ph; R′,R′ = $(CH_2)_4$
c, R^1 = R^3 = Me; R^2 = Ph; R′ = R′ = Et
d, R^1 = Me; R^2 = R^3 = Ph; R′,R′ = $(CH_2)_4$
e, R^1 = Me; R^2 = Ph; R^3 = SMe; R′ = R′ = Et
f, R^1 = R^2 = Ph; R^3 = Me; R′ = R′ = Et
g, R^1 = R^2 = Ph; R^3 = SMe; R′ = R′ = Et
h, R^1,R^2 = $(CH_2)_6$; R^3 = Me; R′ = R′ = Et



5i



6

have previously described a four-membered cyclic nitrone, obtained by reaction of a β-(tosyloxy)ketoxime with base, as an oil that decomposes at room temperature. A second four-membered cyclic nitrone was reported by Harnisch and Szeimies[15] when we published the preliminary results of this investigation.[11a] They obtained 3,3-dichloro-4-phenyl-2,3-dihydroazete 1-oxide in 19% yield by oxidation of the corresponding 2,3-dihydroazete with 3-chloroperbenzoic acid.

Reaction of (*Z*)-2-nitro-1-phenylpropene (**1g**), prepared photochemically from **1b**, and ynamine **2a** in petroleum ether yielded the 4-nitrocyclobutene **3d** and the four-membered cyclic nitrone **5c** both with the same stereochemistry as the products formed by reaction of **2a** and the *E* isomer **1b**. We observed that the ratio in which the 4-nitrocyclobutene **3d** and the cyclic nitrone **5c** are formed is about 0.3 in the case of the *Z* isomer and ~2.3 in the case of the *E* isomer. In chloroform in which both the reactants are well soluble and the rates of reaction of the *E* and *Z* isomers could be accurately studied by NMR spectroscopy, we found that the *Z* isomer reacts slower than the *E* isomer and also that in this solvent the *Z* isomer gave exclusively the cyclic nitrone **5c** while the *E* isomer gave the 4-nitrocyclobutene and the cyclic nitrone in approximately equal amounts.

The 1-nitro*cyclo*alkenes **1e,f**, prepared by nitration of the corresponding cycloalkenes were reacted with the ynamine **2a**. They showed the same type of reactivity, and the corresponding cyclic nitrones **5i** and **5h** were obtained in yields of 15% and 35%, respectively (petroleum ether). ^{13}C NMR spectroscopy of **5i** showed a different stereochemistry, with the *N*,*N*-diethylcarbamoyl group and the hydrogen atom at C-3 on the same face of the four-membered ring. In this configuration the amide carbonyl absorption is 1.6 ppm more downfield from Me_4Si than that in the corresponding nitrone **5h**, and the methyl group at C-2 shows an absorption at δ 16.0 which is 5.2 ppm more upfield than in **5h** (Table I). 1-Nitrocyclopentene (**1d**) reacted with **2b** and gave in addition to the bicyclic nitrocyclobutene **3c** a tan solid that precipitated from the reaction mixture. The solid was hardly soluble in a variety of solvents, and the presence of radical species made it impossible to obtain high-resolution NMR spectra. Because of the fast thermal isomerization and on the basis of reactions with electron-deficient acetylenes, this reaction product was assigned the cyclic nitronic ester structure **6**. In dilute chloroform solution, and even in the solid state

Table II. Characteristic ^{13}C NMR Data ($CDCl_3$) of Nitrones 4

compd	shift, ppm C-1	C-3	C-4	C=O
4a	141.5	*a*	*a*	162.4
4b	143.1	142.0	125.1	164.1
4c	146.2	*b*	*b*	158.7
4d	144.6	141.3	*c*	158.8

[a] In aromatic region 127.7-131.3 ppm. [b] In aromatic region 123.3-129.0 ppm. [c] In aromatic region 126.9-128.8 ppm.

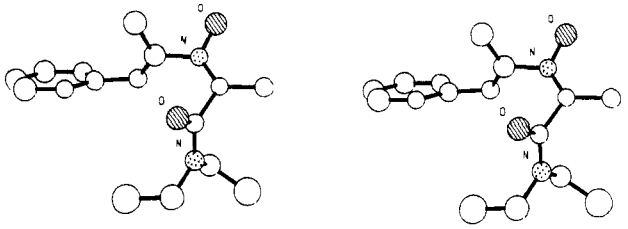
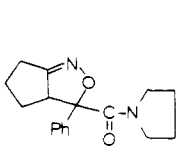
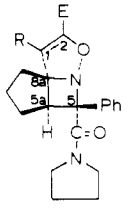


Figure 2. Stereoscopic view of the *N*-vinyl-*C*-carbamoylnitrone **4b**.

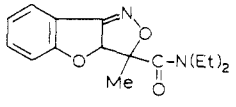
the cyclopent[*c*][1,2]oxazine 1-oxide **6** isomerized to 1-[(3a,4,5,6-tetrahydro-3-phenyl-3*H*-cyclopent[*c*]isozazol-3-yl)carbonyl]pyrrolidine (**7**) which was isolated in a yield



7



8a, R = E = COOMe
b, R = H; E = COOMe



[9]

of 70%. The structure of **7** was evident from its NMR spectroscopic data. In the ^1H NMR spectrum the absorption at δ 4.91, which shows coupling with two nonequivalent hydrogen atoms, and absorptions in the ^{13}C NMR spectrum at δ 167.4 (C=N) and 94.4 (C-3) are in good agreement with the absorptions of the corresponding 3,3a-dihydrobenzofuro[3,2-*c*]isoxazoles formed in the reactions of ynamines **2a** and **2b** with 3-nitrobenzofuran. The structure of one of these isoxazolines, *N*,*N*-diethyl-3,3a-dihydro-3-methylbenzofuro[3,2-*c*]isoxazole-3-carboxamide (**9**) has been elucidated by single-crystal X-ray analysis.[8]

Further support for the cyclopent[*c*][1,2]oxazine 1-oxide structure **6** was obtained when the crude reaction product was reacted with dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate.[16] We isolated white crystalline products in yields of 83% and 85%, respectively, composed of one molecule of 1-nitrocyclopentene, one molecule of ynamine, and one molecule of the acetylene. Both ^1H and ^{13}C NMR spectroscopic data are in agreement with the tricyclic structures **8a** and **8b**. Comparison of the ^{13}C NMR spectroscopic data of **8a** and **8b** with those of the

(14) Black, D. St. C.; Brown, R. F. C.; Dunstan, B. F.; Sternhell, S. *Tetrahedron Lett.* **1974**, 4283.
(15) Harnisch, J.; Szeimies, G. *Chem. Ber.* **1979**, *112*, 3914.
(16) Nitronic esters are known to react as 1,3-dipoles with alkenes or acetylenes see: Nielsen, A. T. In "The Chemistry of the Nitro and Nitroso Groups"; H. Feuer, Ed.; Wiley: New York, 1969; Part I, p 349.

Table III. Rate Constants for the Ring Opening of 5c and 5e

5c		5e	
temp, °C	10^5k, s^{-1}	temp, °C	10^5k, s^{-1}
51.5	0.48 ± 0.01	25.8	4.8 ± 0.2
61.1	1.50 ± 0.01	35.9	15.3 ± 0.8
71.9	5.71 ± 0.2	47.0	52.7 ± 2.0

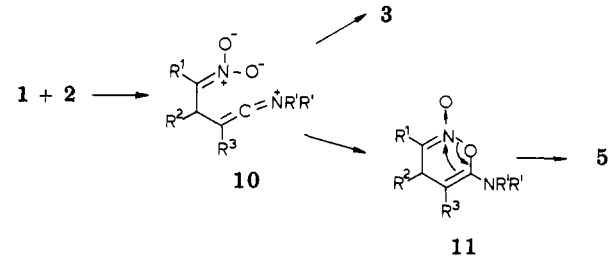
1,3-dipolar adducts of the four-membered cyclic nitrones **5** and the same electron-deficient acetylenes[11b,17] provides conclusive evidence for structures **8a** and **8b**. The stereochemistry of **8a** and **8b** is most likely such that the phenyl substituent and the cyclopentane ring are on the same face of the azetidine ring. A molecular model shows that in this configuration the rotation around the Ph–C-5 bond is restricted which explains the nonequivalence of the ortho protons of the phenyl ring in the ^{1}H NMR spectrum.

We observed that the cyclic nitrones **5b** and **5e** underwent a rearrangement in chloroform. Within several hours, even at room temperature, they were converted into isomeric species as was shown by mass spectrometry and elemental analysis. Signals in the ^{1}H NMR spectrum at δ 7.92 and 7.68 (AB pattern) and at δ 6.81 (s) showed that the reaction products were the corresponding *N*-vinyl-*C*-carbamoyl nitrones **4a** and **4d**, respectively. The ^{13}C NMR absorptions were compared with those of **4b** that was obtained in 40% yield by heating a solution of **5c** in chloroform at reflux (Table II). A single-crystal X-ray analysis of **4b** proved the *N*-vinyl-*C*-carbamoyl structure and also showed the *E,E* stereochemistry of **4b** (Figure 2).[11c] The kinetics of these isomerization reactions were studied in detail by heating **5c** and **5e** in chloroform at temperatures between 51.5 and 71.9 °C and between 25.8 and 47.0 °C, respectively. The reactions were followed by ^{1}H NMR spectroscopy, and the rate of ring opening of **5c** was determined by monitoring the decrease of the intensity of the H-3 signal of the starting compound by using the phenyl signal as an internal standard.[18] The rate of ring opening of **5e** was determined from both the decrease of the H-3 signal of the starting compound and the increase of the H-4 signal of the product **4d**. Both reactions fit first-order kinetics, and from plots of log k vs. T^{-1} the activation parameters were calculated (Table III). For the isomerization of **5c** to **4b**, values of $\Delta H^{\ddagger}$ = 26.0 ± 1.0 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −2 ± 3 eu were found, and for the isomerization of **5e** to **4d** these values are $\Delta H^{\ddagger}$ = 20.9 ± 1.0 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −8 ± 3 eu.

Discussion

The formation of the four different reaction products that were isolated from the reactions of 1-nitro(cyclo)alkenes and ynamines can be rationalized in terms of a nucleophilic addition of the electron-rich acetylene to the nitroalkene, yielding the 1,4-dipolar intermediate **10** as the first step (Scheme I). This 1,4-dipolar species can react further by formation of a second carbon–carbon bond to yield the 4-nitrocyclobutenes (**3**). In the literature a similar two-step process has been proposed for reactions of nitroalkenes with enamines, and in these reactions the 1,4-dipole has actually been intercepted by reaction with a second molecule of nitroalkene.[6] Similar 2:1 adducts were not obtained from the reactions of nitroalkenes and ynamines. This points to either a fast ring closure of the 1,4-dipolar intermediate or to a concerted formation of the nitrocyclobutenes. Previously we have proposed that thermal [2 + 2] cycloaddition reactions of strongly polarized alkenes and acetylenes with opposite electron densities might proceed in a concerted [$_\pi2_s$ + $_\pi2_n$] fashion.[19] By reacting both the *E* and *Z* isomer of 2-nitro-1-phenylpropene with ynamine **2a** we had hoped to obtain 4-nitrocyclobutenes of different stereochemistry, thus proving the concertedness of the [2 + 2] cycloaddition. Unfortunately the relatively fast reaction of the *Z* isomer in chloroform gives exclusively the cyclic nitrone **5c**, and the slower reaction of the *Z* isomer in petroleum ether gave a mixture of **5c** and the same 4-nitrocyclobutene **3d** as obtained by reaction of the *E* isomer. However, this 4-nitrocyclobutene might as well have been formed by reaction of the *E* isomer since we have detected this isomer by ^{1}H NMR spectroscopy in the reaction mixture after 148 h of reaction. It is well-known that isomerization of the (*Z*)-nitroalkenes to the thermodynamically more stable *E* isomers is catalyzed by base.[20] Therefore, it remains unclear whether the formation of the 4-nitrocyclobutenes is a concerted process or a two-step reaction via the 1,4-dipolar intermediate **10**.

Scheme I



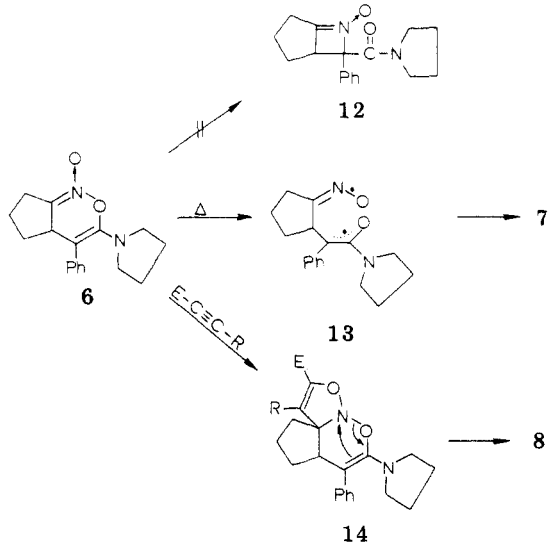
The 1,4-dipole **10** can also react further by formation of a carbon–oxygen bond to give the nitronic ester **11**. In this reaction the nitroalkene formally reacts as a heterodiene in a [4 + 2] cycloaddition reaction. A similar reactivity of nitroalkenes has been observed previously in reactions with enamines,[10,21] and *nitroso*alkenes react also with olefins and electron-rich heterocycles via a [4 + 2] cycloaddition.[22] The nitronic esters could generally not be isolated because the [4 + 2] cycloaddition is in nearly all cases followed by a fast ring-contraction reaction, which involves the cleavage of a weak N–O bond and simultaneous formation of a carbonyl function. The latter is the driving force since it will compensate for the formation of the strained four-membered ring. In the analogous five-membered heterocycles, viz., 5-alkoxyisoxazoles, a similar ring contraction, in that case to yield 1-azirine-3-carboxylates, is well documented.[23] The exception to this general reactivity of the cyclic nitronic esters **11** is the relative stability of the [4 + 2] cycloadduct **6** obtained from the reaction of 1-nitrocyclopentene (**1d**) and ynamine **2b**. In this case the ring contraction would lead to a compound (**12**) in which the cyclic nitrone moiety is fused to a cyclopentane ring (Scheme II). This is obviously unfavorable; the reactivity of the cyclic nitronic ester is lowered, and when reaction takes place, still at room temperature,

(17) Full details of the cycloaddition reactions of cyclic nitrones **5** will be published in part 2 of this series.

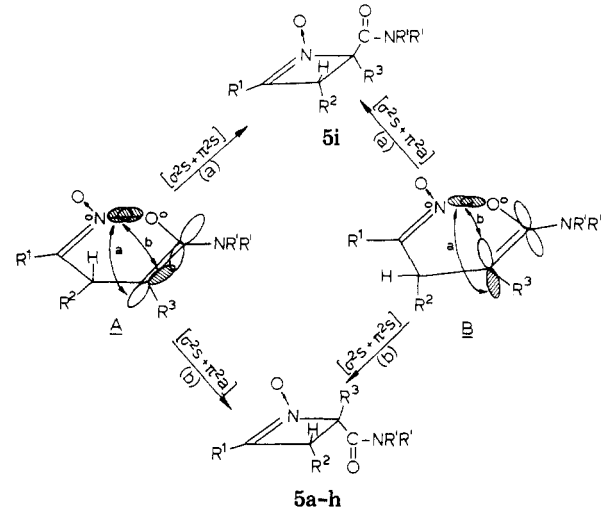
(18) Due to partial decomposition of the formed open isomer (**4b**) at the reaction temperatures, the reaction had to be monitored by following the decrease of the starting compound with an internal standard as a reference.

(19) Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Reinhoudt, D. N.; Harkema, S; van Hummel, G. J. *Tetrahedron* **1981**, *37*, 3525.
(20) Miller, D. B.; Flanagan, P. W.; Shechter, H. *J. Org. Chem.* **1976**, *41*, 2112.
(21) Pitacco, G.; Valentin, E. *Tetrahedron Lett.* **1978**, 2339.
(22) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 249.
(23) Nishiwaki, T.; Kitamura, T.; Nakano, A. *Tetrahedron* **1970**, *26*, 453.

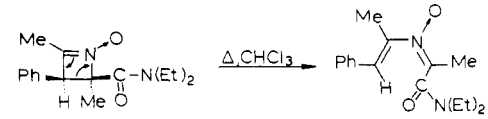
Scheme II



Scheme III



Scheme IV



an isoxazoline derivative **7** is formed as the result of O–C rather than N–C bond formation.[24] A similar type of reaction product (**9**) had been obtained previously from reaction of the ynamine **2a** and 3-nitrobenzofuran.[8] In that case the alternative formation of a fused four-membered cyclic nitrone would also have led to a highly strained heterocyclic ring system. It is interesting to note that a ring contraction in the usual fashion (**11** to **5**) does take place in the 1,3-dipolar adducts of **6** and acetylenic esters. The 1,3-dipolar adducts **14** are not even observed, and the tricyclic compounds **8** are isolated (Scheme II). Obviously the fusion of a cyclopentane ring with an azetidine ring is less unfavorable than with a 2,3-dihydroazete 1-oxide ring system.

The X-ray analysis of nitrone **5c** showed that the two most bulky substituents, the carbamoyl and the phenyl group, are on the same face of the four-membered ring. In other cases there is spectroscopic evidence that only one isomer is formed, most likely of the same stereochemistry. This strongly suggests that ring contraction occurs in a stereospecific fashion. Grêe and Carrié[25] have shown that the analogous ring contraction of isoxazolidines to 2-acetylaziridines probably represents a concerted 1,3-sigmatropic shift of the nitrogen atom, either via a symmetry-allowed $[_\sigma 2_s + _\pi 2_s]$ process or via a symmetry-forbidden $[_\sigma 2_s + _\pi 2_s]$ pathway, with the exclusion of biradical intermediates. There are two possible ways of explaining the stereospecific ring contraction of the nitronic esters **11**, depending on the conformation of the six-membered ring (Scheme III).

(A) Substituent R^2 in the Equatorial Position. In order to account for the formation of nitrones **5a–h**, in which the substituent R^2 and the carbamoyl group are cis, from the corresponding nitronic esters **11**, the nitrogen atom has to undergo a $[_\sigma 2_s + _\pi 2_a]$ 1,3 sigmatropic reaction (b) which is a symmetry-allowed process according to the Woodward–Hoffmann rules.[26] On the other hand, only a symmetry-forbidden $[_\sigma 2_s + _\pi 2_s]$ process (a) would lead to nitrone **5i** in which the hydrogen atom and the carbamoyl group are on the same face of the four-membered ring.

(B) Substituent R^2 in the Axial Position. In this case the formation of nitrones **5a–h** would proceed through a symmetry-forbidden $[_\sigma 2_s + _\pi 2_s]$ process (b) whereas the stereochemistry of **5i** requires a $[_\sigma 2_s + _\pi 2_a]$ allowed pathway (a).

In the cyclic nitronic esters **11**, except when R^1 and R^2 are part of the cyclohexane ring (in the formation of **5i**), the substituent R^2 will occupy the axial position since in that conformation the interaction of substituents R^1, R^2, and R^3 will be minimal. Therefore, in these cases the ring contraction proceeds via a concerted $[_\sigma 2_s + _\pi 2_s]$ process. The steric situation is different when the 4*H*-1,2-oxazine is fused with a cyclohexane ring. The cyclohexane ring will prefer the chair conformation and forces R^2 in an equatorial position. Again a concerted $[_\sigma 2_s + _\pi 2_s]$ process accounts for the observed stereochemistry of the nitrone **5i** which is different from the other nitrones. The ring contraction of the tricyclic 1,3-dipolar adducts (**14**) of the nitronic ester **6** and electron-deficient acetylenes differs from the reaction of **11**. The migrating nitrogen atom is an *N*-alkoxy-substituted sp^3-hybridized nitrogen atom, and therefore the reaction is very similar to the ring contraction of 4-isoxazolines. We assume that the most stable conformation of the six-membered ring in **14** corresponds to situation B in the monocyclic series (R^2 is in the axial position) since the interaction of the phenyl group and the cyclopentane ring will be in this case the least unfavorable. Consequently, the resulting azetidine derivatives **8** must be formed via a symmetry-allowed $[_\sigma 2_s + _\pi 2_a]$ process.[27] Although the concerted $[_\sigma 2_s + _\pi 2_s]$ pathway is the sym-

(24) It was not possible to characterize **6** by the usual NMR spectroscopic data; the ^1H NMR spectrum only showed very broad peaks, while in the ^{13}C NMR spectrum only signals could be obtained which belonged to the rearranged product **7** that was formed in small amounts during the measuring experiment. Probably **6** is in equilibrium with a diradical species (**13**) which causes the difficulties in recording decent NMR spectra. Attempts to obtain conclusive evidence by ESR spectroscopy failed although distinct signals were recorded.

(25) Grêe, R.; Carrié, R. *J. Am. Chem. Soc.* **1977**, *99*, 6667.

(26) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Academic Press: New York, 1970.

(27) Besides these two possible 1,3 sigmatropic processes there is the possibility of a $[_\sigma 2_a + _\pi 2_s]$ process which is allowed and often observed.[28] However, it is very unlikely that the ring contraction of the nitronic esters would proceed in that way because in both ring systems (**11** vs. **14**) there is no possibility of rotation around the C–N bond in order to achieve such a $[_\sigma 2_a + _\pi 2_s]$ process.

(28) Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406.

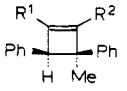
Table IV. Thermal Ring Opening of the Four-Membered Cyclic Nitrones 5 in Chloroform Solution at 61 °C

compd	time, h	% conversion
5a	3	*a*
5b	<0.2	100
5c	24	~65
5d	3	~65[b]
5e	~0.5	100
5f	90	0
5h	90	0
5i	90	0

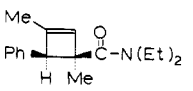
[a] Within 3 h complete polymerization of nitrone 5a took place. [b] Attempts to separate the noncyclic nitrone from the starting nitrone (5d) failed because of decomposition.

metry-forbidden process, this process cannot a priori be excluded since in the case heteroatoms (in this case an sp^2-hybridized nitrogen atom) are involved the occurrence of forbidden pathways is not unusual.[25] Our results are in agreement with those of Grêe and Carrié except that they found competition between the [$_\sigma 2_s$ + $_\pi 2_a$] and [$_\sigma 2_s$ + $_\pi 2_s$] modes of the 1,3 sigmatropic reactions of 4-isoxazolines.

The thermal isomerization of the four-membered cyclic nitrones **5** to the corresponding *N*-vinyl-*C*-carbamoyl nitrones **4** occurs in a stereospecific way. The formation of **4b** by heating **5c** in chloroform to yield exclusively the *E,E* isomer is in agreement with a concerted symmetry-allowed conrotatory ring opening of the 1-azacyclobutene 1-oxide ring (Scheme IV).[29] This result represents the first experimental support for a prediction made recently by Snyder, on the basis of semiempirical MO calculations on 1-azacyclobutenes, that the latter will undergo ring opening in a concerted conrotatory way.[30] The activation parameters obtained for the isomerization of **5c** to **4b** ($\Delta H^\ddagger$ = 26.0 ± 1.0 kcal mol^{-1} and $\Delta S^\ddagger$ = −2 ± 3 eu) and of **5e** to **4d** ($\Delta H^\ddagger$ = 20.9 ± 1.0 kcal mol^{-1} and $\Delta S^\ddagger$ = −8 ± 3 eu) are in agreement with those expected for the corresponding hydrocarbon analogues. The activation enthalpy of cyclobutene **15b** has been reported ($\Delta H^\ddagger$ = 23.4 kcal mol^{-1}),[31]



15a, $R^1 = R^2$ = H
b, $R^1 = R^2$ = Ph
c, R^1 = Me; R^2 = H



[16]

and since the effects of substituents on the cyclobutene ring on the activation enthalpy of isomerization are known, the expected value of $\Delta H^\ddagger$ for the isomerization of the unknown cyclobutene **16** was calculated ($\Delta H^\ddagger$ = 27–28 kcal mol^{-1}).[32] Therefore, we conclude that substitution of an sp^2-hybridized carbon atom of a cyclobutene ring by an N–O group has only a small effect. A further study on the effect of various substituents on the 2,3-dihydroazete 1-oxide ring on the rate of isomerization revealed the same tendency as in the corresponding cyclobutenes (Table IV). From heating various cyclic nitrones in chloroform solution it can be seen that substitution at C-4 stabilizes the four-membered cyclic nitrones in the order H < Me < Ph and that substitution at C-2 stabilizes the nitrones in the order SMe < Ph < Me. Further, it is clear that annelation of the four-membered ring (**5h,i**) also leads to a stabilization toward ring opening, probably partly due to the absence of the phenyl group at C-3.

In view of the present results it is very likely that 3-nitrobenzo[*b*]thiophene and 4-nitroisothiazole also react via a [4 + 2] cycloaddition to give the corresponding *N*-(heteroaryl)-*C*-carbamoyl nitrones and not via the previously proposed [2 + 2] cycloaddition.[4,34]

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with Varian XL-100 and Bruker WP-80 spectrometers, and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian Mat 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under supervision of W. J. Buis.

Materials. 1-(Diethylamino)propyne (**2a**, Fluka), methyl propiolate (Fluka), and dimethyl acetylenedicarboxylate (Merck) are commercially available. 1-Phenyl-2-(1-pyrrolidinyl)acetylene (**2b**),[4] 1-(diethylamino)-2-(methylthio)acetylene (**2c**),[35] (*E*)-1-nitro-2-phenylethene (**1a**),[36] (*E*)-2-nitro-1-phenylpropene (**1b**),[37] (*Z*)-1-nitro-1,2-diphenylethene (**1c**),[38] 1-nitro-cyclopentene (**1d**),[39] 1-nitrocyclohexene (**1e**),[39] and 1-nitrocyclooctene (**1f**)[40] were prepared according to the literature. Petroleum ether refers to the fraction boiling at 60–80 °C.

(*Z*)-2-Nitro-1-phenylpropene (1g).[20] A solution of **1b** (4.0 g, 25 mmol) in 450 mL of petroleum ether (bp 40–60 °C) was irradiated at 15–20 °C in a nitrogen atmosphere with a Hanau high-pressure mercury lamp. After 1.5 h the solvent was removed under reduced pressure. ^{1}H NMR spectroscopy revealed that the residue contained an ~1:1 mixture of the starting material (**1b**) and the product (**1g**), which was separated by column chromatography (SiO_2; petroleum ether (bp 40–60 °C)/diethyl ether, 10:1). The fast-eluted fraction contained the pure starting material (36%), while from the more slowly eluted fraction was isolated **1g** as a yellow solid: yield 45%; mp 45–46 °C (petroleum ether) (lit.[20] mp 43–44 °C); ^{1}H NMR δ 7.4–7.1 (m, 5 H, Ph H), 6.45 (br s, 1 H, =CH), 2.33 (d, 3 H, J = 1.2 Hz, CH_3).

General Procedure for the Reaction of Nitroalkenes 1 with Ynamines 2 in Petroleum Ether. A solution of the ynamine (**2**, 5.5 mmol) in 10 mL of dry petroleum ether was added dropwise at 15 °C and in a nitrogen atmosphere to a stirred suspension or solution of the nitroalkene **1** (5 mmol) in 10 mL of dry petroleum ether. After the reaction was completed, the precipitate was filtered off and purified.

(29) Due to steric interactions in the transition state, the formation of the *E,E* isomer is obviously favored over the also permitted formation of the *Z,Z* isomer of **4b**.

(30) Snyder, J. P. *J. Org. Chem.* **1980**, *45*, 1341.

(31) Wilcott, M. R.; Cargill, R. L.; Sears A. B. *Prog. Phys. Org. Chem.* **1972**, *9*, 25 and references cited therein.

(32) The $\Delta H^\ddagger$ value for the isomerization of cyclobutene **16** was calculated by assuming $\Delta H^\ddagger$ (**15a**) ≈ $\Delta H^\ddagger$ (**15b**) ≈ 23.4 kcal mol^{-1}, $\Delta H^\ddagger$ (**15c**) ≈ $\Delta H^\ddagger$ (**15a**) + 2.5 ≈ 25.9 kcal mol^{-1} [$\Delta\Delta H^\ddagger$ (Me) ≈ 2.5 kcal mol^{-1}], and $\Delta H^\ddagger$ (**16**) ≈ $\Delta H^\ddagger$ (**15c**) + 1–2 kcal mol^{-1} [$\Delta\Delta H^\ddagger$(CON(Et)$_2$) ≈ $\Delta\Delta H^\ddagger$ (COOMe) ≈ 1–2 kcal mol^{-1}].[31,33] The quantitative effect of *S*-alkyl substituents on the rate of isomerization of cyclobutenes is not known, but qualitatively we have observed a substantial enhancement of the rate of isomerization of 2-thiabicyclo[3.2.0]heptadienes compared to the corresponding hydrocarbon systems.[3]

(33) The increase in activation energy for the ring opening of cyclobutenes caused by $COOCH_3$ substitution relative to phenyl substitution at C-3 or C-4 we calculated to be 1–2 kcal mol^{-1}. See: Dalrymple, D. L.; Russo, W. B. *J. Org. Chem.* **1975**, *40*, 492.

(34) This mechanism was proposed in analogy to the [2 + 2] cycloaddition of enones with ynamines: Ficini, J.; Besseyre, J.; Krief, A. *Bull. Chim. Soc. Fr.* **1976**, 987.

(35) Verboom, W.; Bos, H. J. T. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 559.

(36) Worrall, D. E. *Org. Synth.* **1929**, *9*, 66.

(37) Hass, H. B.; Susie, A. G.; Heider, R. L. *J. Org. Chem.* **1950**, *15*, 8.

(38) Robertson, D. N. *J. Org. Chem.* **1960**, *25*, 47.

(39) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294.

(40) Seifert, W. K. *Org. Synth.* **1970**, *50*, 84.

(41) In duplicate experiments, **4b** could not be solidified, and therefore no elemental analysis was obtained; the oil obtained (~95%) exhibited spectroscopic (^{1}H and ^{13}C NMR) data and a mass spectrum identical with those of the solid material used for the single-crystal X-ray analysis.

***N,N*-Diethyl-2,3-dihydro-2-methyl-3-phenyl-2-azetecarboxamide 1-Oxide (5a) from 1a and 2a.** After the mixture of **1a** and **2a** was stirred for 24 h, the precipitate was filtered off. The solid that was obtained contained some amorphous material which was removed by filtration of a hot benzene solution: mp 118.5–120.5 °C dec (benzene/diisopropyl ether); mass spectrum, *m/e* 260.152 (M^+; calcd 260.152).

Anal. Calcd for $C_{15}H_{20}N_2O_2$ (mol wt 260.34): C, 69.20; H, 7.74; N, 10.76. Found: C, 69.29; H, 7.88; N, 10.84.

1-[(2,3-Dihydro-2,3-diphenyl-2-azetyl)carbonyl]pyrrolidine *N*-Oxide (5b) from 1a and 2b. After the mixture of **1a** and **2b** was stirred for 2 h, the yellow precipitate was filtered off and washed with diisopropyl ether. The remaining white solid contained some amorphous material which was removed by filtration of a chloroform solution of the precipitate. This nitrone (**5b**) could not be purified because of its thermal instability: mp ~105 °C dec; mass spectrum, *m/e* 320.152 (M^+; calcd for $C_{20}H_{20}N_2O_2$ 320.152).

The yellowish filtrate from the diisopropyl ether washings yielded upon concentration under reduced pressure **1-(4-nitro-2,3-diphenyl-1-cyclobuten-1-yl)pyrrolidine (3a)** as an orange solid: yield 31%; mp 101–102 °C dec (methanol); IR (KBr) 1650 (C=C), 1535 and 1345 cm^{-1} (NO_2); ^1H NMR δ 7.6–7.0 (m, 10 H, Ph H), 5.16 (s, 1 H, H-4), 4.28 (s, 1 H, H-3), 3.6–3.1 (m, 4 H, pyrr H(α)), 2.1–1.6 (m, 4 H, pyrr H(β)); ^{13}C NMR δ 139.3 (s) and 135.6 (s) (C-1 and Ph C-1), 111.2 (s, C-2), 86.7 (d, C-4), 49.3 (d, C-3); mass spectrum, *m/e* 320.154 (M^+; calcd 320.152).

Anal. Calcd for $C_{20}H_{20}N_2O_2$ (mol wt 320.39): C, 74.97; H, 6.29; N, 8.74. Found: C, 74.52; H, 6.34; N, 8.66.

***N,N*-Diethyl-2-[(2-phenylethenyl)imino]-2-(methylthio)acetamide *N*-Oxide (4c) from 1a and 2c.** After the mixture of **1a** and **2c** was stirred for 24 h, the precipitate was filtered off, dissolved in chloroform, and filtered to remove the amorphous solid: yield 70%; mp 130–131.5 °C dec (chloroform/diisopropyl ether); ^1H NMR δ 7.65 and 7.23 (AB, 2 H, J_{AB} = 13.2 Hz, HC=CH), 7.35 (s, 5 H, Ph H), 3.8-3.1 (m, 4 H, NCH_2), 2.33 (s, 3 H, SCH_3), 1.20 and 1.18 (t, 6 H, $NCCH_3$); mass spectrum, *m/e* 292.125 (M^+; calcd 292.124).

Anal. Calcd for $C_{15}H_{20}N_2O_2S$ (mol wt 292.43): C, 61.61; H, 6.89; N, 9.58. Found: C, 61.50; H, 6.89; N, 9.52.

***N,N*-Diethyl-2,3-dihydro-2,4-dimethyl-3-phenyl-2-azetecarboxamide 1-Oxide (5c) from 1b and 2a.** After the mixture of **1b** and **2a** was stirred for 72 h, the precipitated nitrone was filtered off: mp 126–128 °C dec (benzene/diisopropyl ether); mass spectrum, *m/e* 274.170 (M^+; calcd 274.168).

Anal. Calcd for $C_{16}H_{22}N_2O_2$ (mol wt 274.37): C, 70.04; H, 8.08; N, 10.21. Found: C, 69.64; H, 8.26; N, 10.02.

The filtrate was concentrated under reduced pressure and yielded ***N,N*-diethyl-2,4-dimethyl-4-nitro-3-phenyl-1-cyclobuten-1-amine (3d)** as a slightly contaminated orange oil, yield ~65%; because of decomposition of the labile cyclobutene, attempts to purify the latter failed: IR (neat) 1680 (C=C), 1535 and 1340 cm^{-1} (NO_2); ^1H NMR δ 7.5–7.0 (m, 5 H, Ph H), 3.82 (s, 1 H, H-3), 3.05 (q, 4 H, NCH_2), 1.82 (s, 3 H, $=CCH_3$), 1.28 (s, 3 H, CH_3), 1.10 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 141.3 (s) and 137.6 (s) (C-1 and Ph C-1), 105.6 (s, C-2), 90.8 (s, C-4), 55.9 (d, C-3); mass spectrum, *m/e* 274.168 (M^+; calcd for $C_{16}H_{22}N_2O_2$ 274.168).

From 1g and 2a. After the mixture of **1g** and **2a** was stirred for 6 days in the dark, the nitrone **5c** was filtered off, yield 65%. The filtrate yielded upon concentration under reduced pressure an oil that contained a mixture of the starting nitroalkene (**1g**), its isomer **1b**, and the cyclobutene **3d** (~15–20%).

1-[(2,3-Dihydro-4-methyl-2,3-diphenyl-2-azetyl)carbonyl]pyrrolidine *N*-Oxide (5d) from 1b and 2b. After the mixture of **1b** and **2b** was stirred for 72 h in the dark, the precipitate was filtered off: mp 156–158 °C dec (fractionated elution with diethyl ether); mass spectrum, *m/e* 334.173 (M^+; calcd 334.168).

Anal. Calcd for $C_{21}H_{22}N_2O_2$ (mol wt 334.42): C, 75.42; H, 6.63; N, 8.37. Found: C, 74.93; H, 6.71; N, 8.31.

The filtrate was concentrated under reduced pressure, and after it was stored at −20 °C for a longer period, **1-(4-methyl-4-nitro-2,3-diphenyl-1-cyclobuten-1-yl)pyrrolidine (3b)** was isolated upon trituration with diethyl ether: yield 37%; mp ~95 °C dec (because of the thermal instability of **3b** it could not be further purified); IR (KBr) 1660 (C=C), 1540 and 1340 cm^{-1} (NO_2); ^1H NMR δ 7.4–7.0 (m, 10 H, Ph H), 4.44 (s, 1 H, H-3), 3.5–3.1 (m, 4 H, pyrr H(α)), 2.1–1.7 (m, 4 H, pyrr H(β)), 1.42 (s, 3 H, CH_3); ^{13}C NMR δ 140.1 (s) and 137.1 (s) (C-1 and Ph C-1), 109.3 (s, C-2), 90.5 (s, C-4), 53.9 (d, C-3); mass spectrum, *m/e* 334.167 (M^+; calcd for $C_{21}H_{22}N_2O_2$ 334.168).

***N,N*-Diethyl-2,3-dihydro-4-methyl-3-phenyl-2-(methylthio)-2-azetecarboxamide 1-Oxide (5e) from 1b and 2c.** After the mixture of **1b** and **2c** was stirred for 72 h, a sticky precipitate had formed. Trituration of this oily substance with diisopropyl ether yielded the cyclic nitrone **5e**: mp ~90 °C dec (because of the thermal instability **5e** could not be further purified); mass spectrum, *m/e* 306.143 (M^+; calcd for $C_{16}H_{22}N_2O_2S$ 306.140).

***N,N*-Diethyl-2,3-dihydro-2-methyl-3,4-diphenyl-2-azetecarboxamide 1-Oxide (5f) from 1c and 2a.** After the mixture of **1c** and **2a** was stirred for 24 h, the precipitate was filtered off: mp 197–200 °C dec (benzene/diisopropyl ether); mass spectrum, *m/e* 336.184 (M^+; calcd 336.184).

Anal. Calcd for $C_{21}H_{24}N_2O_2$ (mol wt 336.44): C, 74.97; H, 7.19; N, 8.33. Found: C, 75.05; H, 7.21; N, 8.32.

***N,N*-Diethyl-2,3-dihydro-3,4-diphenyl-2-(methylthio)-2-azetecarboxamide 1-Oxide (5g) from 1c and 2c.** Compound **1c** (5.0 mmol) was dissolved in 10 mL of petroleum ether/diethyl ether (2:1). After the mixture of **1c** and **2c** was stirred for 72 h, the precipitate was filtered off: mp 176–178.5 °C dec (chloroform/diisopropyl ether); mass spectrum, *m/e* 368.157 (M^+; calcd 368.156).

Anal. Calcd for $C_{21}H_{24}N_2O_2S$ (mol wt 368.50): C, 68.45; H, 6.56; N, 7.60. Found: C, 68.50; H, 6.61; N, 7.55.

***N,N*-Diethyl-10-methyl-9-azabicyclo[6.2.0]dec-8-ene-10-carboxamide 9-Oxide (5h) from 1f and 2a.** After the mixture of **1f** and **2a** was stirred for 24 h, the precipitate was filtered off: mp 129–132 °C dec (benzene/diisopropyl ether); mass spectrum, *m/e* 266.199 (M^+; calcd 266.199).

Anal. Calcd for $C_{15}H_{26}N_2O_2$ (mol wt 266.39): C, 67.63; H, 9.84; N, 10.52. Found: C, 67.21; H, 10.00; N, 10.54.

***N,N*-Diethyl-8-methyl-7-azabicyclo[4.2.0]oct-6-ene-8-carboxamide 7-Oxide (5i) from 1e and 2a.** After the mixture of **1e** and **2a** was stirred for 48 h, the solution was stored at −20 °C. After one night, white crystals of **5i** were filtered off: mp 92.5–94 °C dec (petroleum ether); mass spectrum, *m/e* 238.169 (M^+; calcd 238.169). Compound **5i** slowly decomposes upon standing at room temperature.

Anal. Calcd for $C_{13}H_{22}N_2O_2$ (mol wt 238.34): C, 65.51; H, 9.30; N, 11.75. Found: C, 64.71; H, 9.41; N, 11.64.

4a,5,6,7-Tetrahydro-4-phenyl-3-(1-pyrrolidinyl)cyclopent[*c*][1,2]oxazine 1-Oxide (6) from 1d and 2b. After the mixture of **1d** and **2b** was stirred for 24 h, the tan precipitate was filtered off: yield 28%; mp 128–129 °C dec (because of its thermal instability it could not be further purified); IR (KBr) 1640 cm^{-1} (C=N and C=C); NMR spectra could not be taken because of the radical species present; mass spectrum, *m/e* 284.156 (M^+; calcd 284.152).

Anal. Calcd for $C_{17}H_{20}N_2O_2$ (mol wt 284.36): C, 71.80; H, 7.08; N, 9.85. Found: C, 71.02; H, 7.15; N, 9.74.

The filtrate was concentrated under reduced pressure and triturated with ethanol to give **1-(5-nitro-7-phenylbicyclo[3.2.0]hept-6-en-6-yl)pyrrolidine (3c)** as an orange solid: yield 40%; mp 80–81 °C (methanol); IR(KBr) 1635 (C=C), 1530 and 1350 cm^{-1} (NO_2); ^1H NMR δ 7.4–6.9 (m, 5 H, Ph H), 3.55 (dd, 1 H, J = 5.0 Hz, J = 1.5 Hz, H-1), 3.5–3.0 (m, 4 H, pyrr H(α)), 2.7–1.4 (m, 10 H, pyrr H(β) and $(CH_2)_3$); ^{13}C NMR δ 136.1 (s, C-6), 108.8 (s, C-7), 94.3 (s, C-5), 51.5 (d, C-1); mass spectrum, *m/e* 284.153 (M^+; calcd 284.152).

Anal. Calcd for $C_{17}H_{20}N_2O_2$ (mol wt 284.36): C, 71.80; H, 7.08; N, 9.85. Found: C, 71.59; H, 7.27; N, 9.73.

General Procedure for the Preparation of 5a,c,e–i and 6 in Acetonitrile. A solution of the ynamine **2** (5.5 mmol) in 10 mL of dry acetonitrile was added dropwise at 0 °C and in a nitrogen atmosphere to a solution of the nitroalkene **1** (5 mmol) in 10 mL of dry acetonitrile. After the mixture was stirred for 3 h at 15–20 °C, the solvent was removed under reduced pressure, and in the case of formation of **5a**, this was preceeded by filtration of the solution over Hyflo. Trituration of the residue with diisopropyl ether gave the nitrones **5** in yields given in Table I. In the reaction of 1-nitrocyclopentene (**1d**) with 1-phenyl-2-(1-pyrrolidinyl)acetylene (**2b**) the nitronic ester **6** precipitated from

the reaction mixture and was filtered off; yield 52%.

1-[(3a,4,5,6-Tetrahydro-3-phenyl-3*H*-cyclopent[*c*]isoxazol-3-yl)carbonyl]pyrrolidine (7). Nitronic ester **6** (0.57 g, 2 mmol) was dissolved in 10 mL of chloroform and heated at reflux for 3 h. The color of the solution changed from dark red to yellow. The solvent was removed under reduced pressure, and elution on an Al_2O_3 column first with petroleum ether followed by diethyl ether afforded **7** after trituration with petroleum ether: yield 70%; mp 109.5–110.5 °C (petroleum ether); ^1H NMR δ 7.36 (s, 5 H, Ph H), 4.91 (dd, 1 H, J = 11 Hz, J = 8 Hz, H-3a), 3.8–3.4 (m, 3 H) and 2.9–2.6 (m, 1 H, pyrr H(α)), 2.6–14 (m, 10 H, pyrr H(β) and $(CH_2)_3$); ^{13}C NMR δ 171.2 (s, C=O), 167.4 (s, C-6a), 94.4 (s, C-3), 63.2 (d, C-3a); mass spectrum, m/e 284.153 (M^+; calcd 284.152).

Anal. Calcd for $C_{17}H_{20}N_2O_2$ (mol wt 284.36): C, 71.80; H, 7.08; N, 9.85. Found: C, 71.83; H, 7.16; N, 9.87.

Dimethyl 5a,6,7,8-Tetrahydro-5-phenyl-5-[(1-pyrrolidinyl)carbonyl]-5*H*-cyclopent[2,3]azeto[1,2-*b*]isoxazole-1,2-dicarboxylate (8a). A solution of DMAD (0.42 g, 3 mmol) in 5 mL of dry chloroform was added dropwise and in a nitrogen atmosphere to a solution of nitronic ester **6** (0.8 g, 2.8 mmol) in 10 mL of dry chloroform. After the mixture was stirred for 1.5 h, the solvent was removed under reduced pressure, and the remaining solid was triturated with cold diisopropyl ether to give **8a**: yield 83%; mp 140–142 °C (benzene/petroleum ether); IR (KBr) 1755 and 1715 ($COOCH_3$), 1660 and 1640 cm^{-1} (C=C and N—C=O); ^1H NMR δ 8.1–7.8 and 7.0–6.7 (m, 2 H, Ph *o*-H), 7.5–7.2 (m, 3 H, Ph H), 4.66 (dd, 1 H, J = 8.0 Hz, J = 1 Hz, H-5a), 3.88 and 3.76 (s, 6 H, OCH_3), 3.6–3.1 (m, 4 H, pyrr H(α)), 2.3–1.4 and 1.1–0.8 (m, 10 H, pyrr H(β) and $(CH_2)_3$); ^{13}C NMR δ 153.3 (s, C-2), 110.1 (s, C-1), 84.7 (s, C-5), 82.1 (s, C-8a), 50.9 (d, C-5a); mass spectrum, m/e 426.180 (M^+; calcd 426.179).

Anal. Calcd for $C_{23}H_{26}N_2O_6$ (mol wt 426.48): C, 64.77; H, 6.14; N, 6.57. Found: C, 64.93; H, 6.25; N, 6.45.

Methyl 5a,6,7,8-Tetrahydro-5-phenyl-5-[(1-pyrrolidinyl)carbonyl]-5*H*-cyclopent[2,3]azeto[1,2-*b*]isoxazole-2-carboxylate (8b). Methyl propiolate (170 μL, 2 mmol) was added in a nitrogen atmosphere to a solution of **6** (0.41 g, 1.8 mmol) in 10 mL of dry chloroform. After the mixture was stirred for 4 h, the solvent was removed under reduced pressure and the remaining solid was triturated with cold diisopropyl ether to give **8b**: yield 85%; mp 124–126 °C (petroleum ether); IR (KBr) 1735 ($COOCH_3$), 1635 cm^{-1} (N—C=O and C=C); ^1H NMR δ 8.2–7.9 and 7.0–6.7 (m, 2 H, Ph *o*-H), 7.6–7.1 (m, 3 H, Ph H), 6.00 (s, 1 H, H-1), 4.58 (dd, 1 H, J = 8.0 Hz, $J \approx$ 1.0 Hz, H-5a), 3.80 (s, 3 H, OCH_3), 3.7–3.2 (m, 4 H, pyrr H(α), 2.3–0.8 (m, 10 H, pyrr H(β) and $(CH_2)_3$); ^{13}C NMR δ 147.1 (s, C-2), 112.4 (d, C-1), 85.1 (s, C-5), 81.4 (s, C-8a), 51.9 (d, C-5a); mass spectrum, m/e 368.173 (M^+; calcd 368.174).

Anal. Calcd for $C_{21}H_{24}N_2O_4$ (mol wt 368.44): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.51; H, 6.64; N, 7.57.

Thermal Ring Opening of Four-Membered Cyclic Nitrones 5b,c,e. 1-[Phenyl[(2-phenylethenyl)imino]acetyl]-pyrrolidine *N*-Oxide (4a). Nitrone **5b** (0.32 g, 1 mmol) was dissolved in 10 mL of dry chloroform. After one night the solution was filtered, and the solvent was removed under reduced pressure. Trituration of the residue with diisopropyl ether afforded **4a**: yield 81%; mp 124.5–125.5 °C dec (benzene/diisopropyl ether); ^1H NMR δ 7.92 and 7.68 (AB, 2 H, J_{AB} = 13 Hz, HC=CH), 8.5–8.3 and 7.7–7.1 (m, 10 H, Ph H), 3.9–3.1 (m, 4 H, pyrr H(α)), 2.1–1.6 (m, 4 H, pyrr H(β)); mass spectrum, m/e 320.154 (M^+; calcd 320.152).

Anal. Calcd for $C_{20}H_{20}N_2O_2$ (mol wt 320.39): C, 74.97; H, 6.29; N, 8.74. Found: C, 74.98; H, 6.32; N, 8.78.

(*E*,*E*)-*N*,*N*-Diethyl-2-[(1-methyl-2-phenylethenyl)imino]propanamide *N*-Oxide (4b). Nitrone **5c** (0.55 g, 2 mmol) was dissolved in 20 mL of dry chloroform and refluxed for 24 h. The chloroform was removed under reduced pressure, and the residue was separated by column chromatography (Al_2O_3, activity IV; chloroform; $R_f \sim 0.5$) to give **4b**: yield 40%; mp 117–120 °C dec (benzene/diisopropyl ether);[41] ^1H NMR δ 7.4–7.2 (m, 5 H, Ph H), 6.58 (s, 1 H, =CH), 3.39 and 3.34 (q, 4 H, NCH_2), 2.32 (s, 6 H, $=CCH_3$) 1.23 and 0.98 (t, 6 H, $NCCH_3$); mass spectrum, m/e 274.169 (M^+; calcd for $C_{16}H_{22}N_2O_2$ 274.168).

***N*,*N*-Diethyl-2-[(1-methyl-2-phenylethenyl)imino]-2-(methylthio)acetamide *N*-Oxide (4d).** Nitrone **5e** (0.31 g, 1 mmol) was dissolved in 10 mL of dry chloroform. After one night the chloroform was removed under reduced pressure, and the residue was separated by column chromatography (Al_2O_3, activity IV, chloroform, $R_f \sim 0.6$) to give **4d** as a colorless oil: yield 80%; ^1H NMR δ 7.5–7.1 (m, 5 H, Ph H), 6.81 (br s, 1 H, =CH), 3.7–3.2 (m, 4 H, NCH_2), 2.34 (s, 3 H, SCH_3), 2.30 (d, 3 H, $=CCH_3$), 1.23 and 1.05 (t, 6 H, $NCCH_3$); mass spectrum, m/e 306.143 (M^+; calcd for $C_{16}H_{22}N_2O_2S$ 306.140).

Kinetic Study of the Ring Opening of 5c and 5e. For 5c. A sealed NMR tube containing a solution of the nitrone (**5c**, 0.2 mmol) in 0.4 mL of $CDCl_3$ was heated in a thermoregulated oil bath (± 0.1 °C) and withdrawn at regular intervals for ^1H NMR analysis. The decrease of the H-3 signal at δ 3.94 was followed by using the phenyl absorption as an internal standard. The rate constants were determined in duplicate at 51.5, 61.1, and 71.9 °C.

For 5e. A sealed NMR tube containing a solution of the nitrone (**5e**, 0.2 mmol) in 0.4 mL of $CDCl_3$ was thermostated in a Bruker WP 80 spectrometer equipped with a Bruker B-VT-1000 temperature unit (temperature in the tube ±0.25 °C). The reaction was followed at 25.8, 35.9, and 47.0 °C from the ratio of the signal of H-3 of the starting nitrone (**5e**, δ 4.00) and the signal of H-4 of the open isomer (**4d**, δ 6.81), and the rate constants were determined in duplicate. The obtained results of both reactions fit first-order kinetics, and a plot of ln K vs. T^{-1} gave a straight line from which $E_a^{\ddagger}$ could be calculated. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated by using the following equations: $E_A^{\ddagger} = \Delta H^{\ddagger} + RT$; $\Delta S^{\ddagger}/4.756 = \log k - 10.753 - \log T + E_A^{\ddagger}/4.576T$.

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Registry No. (*E*)-**1a**, 5153-67-3; (*E*)-**1b**, 18315-84-9; (*Z*)-**1c**, 15341-31-8; **1d**, 22987-82-2; **1e**, 2562-37-0; **1f**, 1782-03-2; (*Z*)-**1g**, 58321-79-2; **2a**, 4231-35-0; **2b**, 54494-80-3; **2c**, 26437-82-1; **3a**, 80954-46-7; **3b**, 80954-47-8; **3c**, 73227-50-6; **3d**, 80954-48-9; **4a**, 75909-36-3; **4b**, 75909-34-1; **4c**, 80954-49-0; **4d**, 80954-50-3; **5a**, 78602-07-0; **5b**, 75909-33-0; **5c**, 75909-31-8; **5d**, 75909-32-9; **5e**, 80954-51-4; **5f**, 80954-52-5; **5g**, 80954-53-6; **5h**, 80954-54-7; **5i**, 80954-55-8; **6**, 76504-08-0; **7**, 76504-09-1; **8a**, 80996-35-6; **8b**, 80996-36-7; DMAD, 762-42-5; methylpropiolate, 922-67-8.