Chemistry of Four-Membered Cyclic Nitrones. 2. 1,3-Dipolar Cycloaddition Reactions with Electron-Deficient Acetylenes and Conversion of the 1,3-Dipolar Adducts into Pyridine Derivatives[1]

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The four-membered cyclic nitrones (2,3-dihydroazete 1-oxides) **1a–d** react with dimethyl acetylenedicarboxylate by 1,3-dipolar cycloaddition to give the dihydroazeto[1,2-*b*]isoxazole derivatives **2a–d**; cyclic nitrone **1e** reacts in a similar way via the not isolated intermediate **2e** to give the 1-azabicyclo[5.1.0]octane derivative **4e**. Upon being heated, cycloadduct **2b** rearranges to the aziridine derivative **4b**, the structure of which is elucidated by single-crystal X-ray analysis. Irradiation of nitrone **1b** yields the 5-oxa-1-azabicyclo[2.1.0]pentane derivative **5**, which upon prolonged irradiation rearranges to the aziridine **6**. Reactions of the nitrones **1a–c** with methyl propiolate yield two isomeric dihydroazeto[1,2-*b*]isoxazoles (**7a–c** and **8a–c**). Hydrogenation of the 1,3-dipolar adducts **2** and **7** in the presence of palladium on charcoal (5%) gives the pyridine derivatives **9** or **10**.

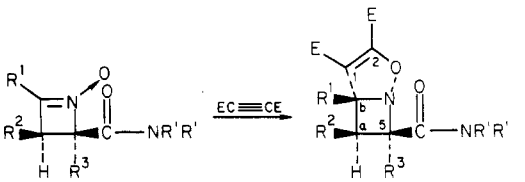
Recently we described the synthesis of four-membered cyclic nitrones (**1**, 2,3-dihydroazete 1-oxides) by the reaction of 1-nitroalkenes and ynamines.[2] Since compounds **1** represent a virtually novel class of heterocycles,[3] and since nitrones are very useful synthons in organic chemistry, we are currently exploring the reactivity of these four-membered cyclic nitrones.

Preliminary results of reactions of these four-membered cyclic nitrones with nucleophilic reagents indicate the extreme reactivity of the C=N bond.[4] This is most probably due to relief of strain upon the conversion of a dihydroazete into an azetidine ring system.

One interesting reaction of nitrones, the 1,3-dipolar cycloaddition reaction, has been extensively reviewed,[5] and this chemistry has generated special interest because of the applications in the synthesis of natural products.[6] In this paper we describe the results of 1,3-dipolar cycloaddition reactions involving the 1,3-dipolar moiety of four-membered cyclic nitrones **1** and some reactions of these cycloadducts.

Results and Discussion

Reaction of the cyclic nitrones **1a–d** with electron-deficient dimethyl acetylenedicarboxylate (DMAD) in chloroform at room temperature gave 1:1 adducts, as was proven by mass spectrometry and elemental analysis, in yields of 69–82%. We assigned structures **2a–d** to these compounds on the basis of the absorptions in the ^{13}C NMR



1 E = COOMe **2**

a, R^1 = H; R^2 = Ph; R^3 = Me; R′ = R′ = Et
b, R^1 = R^3 = Me; R^2 = Ph; R′ = R′ = Et
c, R^1,R^2 = $(CH_2)_6$; R^3 = Me; R′ = R′ = Et
d, R^1 = Me; R^2 = R^3 = Ph; R′,R′ = $(CH_2)_4$

spectra at δ 150–155 and 110–117 (C-2 and C-1, respectively) and other spectroscopic data (Table I). Since the four-membered cyclic nitrones **1a–d** have two relatively bulky substituents on the same face of the four-membered ring, it is rather likely that the acetylene reacts from the sterically less hindered side which results in the configuration shown (**2a–d**).[7] Evidence for this configuration is the small coupling constant (J = 3.9 Hz) of the hydrogen atoms at C-6 and C-6a of adduct **2a**, while in the ^1H NMR spectra of both **2b** and **2d** the methyl group at C-6a shows an absorption at a rather high field (1.15 and 1.25 ppm, respectively) due to the shielding of the cis-substituted phenyl group.

When compound **2b** was heated just above its melting point for a few minutes, the formation of a solid was observed. From this solid we isolated a compound of the same molecular composition as **2b**, as was proven by mass spectrometry and elemental analysis, in a yield of 80%. In the ^1H NMR spectrum a broad singlet at δ ~3.2 was observed, which probably corresponds to an ester methoxy group. At elevated temperatures the signal sharpened, but the spectrum never showed a sharp singlet as normally observed. X-ray analysis of a single crystal of this compound showed the aziridine structure **4b** (Figure 1). The fact that isoxazoline derivatives, which are formed by reaction of nitrones with DMAD, are often unstable and sometimes not even observed was first reported by Baldwin

(1) Part of the forthcoming thesis of M.L.M.P.
(2) (a) Chemistry of Four-Membered Cyclic Nitrones. 1: Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816. (b) 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.
(3) For two examples of four-membered cyclic nitrones see: (a) Black, D. St. C.; Brown, R. F. C.; Dunstan, B. F.; Sternhell, S. *Tetrahedron Lett.* **1974**, 4283. (b) Harnisch, J.; Szeimies, G. *Chem. Ber.* **1979**, *112*, 3914.
(4) Pennings, M. L. M.; Reinhoudt, D. N. *Tetrahedron Lett.* **1981**, *22*, 1153.
(5) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, *7*, 205.
(6) (a) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1978**, *100*, 6291. (b) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Asrof, Ali, S. *Ibid.* **1979**, *101*, 2435. (c) Tufariello, J. J.; Lee, G. E.; Senaratne, P. A.; Al-Nuri, M. *Tetrahedron Lett.* **1979**, 4359. (d) Padwa, A.; Koehler, K. F.; Rodriquez, A. *J. Am. Chem. Soc.* **1981**, *103*, 4974.
(7) We have shown that both methyl and cyano nucleophiles add in a stereospecific way to nitrone **1a** from the sterically less hindered side: Pennings, M. L. M.; Reinhoudt, D. N. *Tetrahedron Lett.* **1982**, *23*, 1003.

0022-3263/82/1947-4413$01.25/0

Table I. Physical and Spectral Properties of DMAD and Methyl Propiolate Cycloadducts 2, 7, and 8a

compd	% yield	mp, °C (solvent)[a]	^{1}H NMR ($CDCl_3$), δ H-a	R-b	^{13}C NMR ($CDCl_3$), δ C-1	C-2	C-5	C-a	C-b	MS, M$^+$ m/e found, formula (M$^+$ m/e calcd)
2a	69	78-80 (diisopropyl ether)[b]	3.91	4.84	110.5	155.2	80.9	57.2	73.3	402.180, $C_{21}H_{26}N_2O_6$ (402.179)
2b	82	114-116 (toluene/hexane)	4.12	1.15	115.4	154.2	77.0	59.6	74.8	416.194, $C_{22}H_{28}N_2O_6$ (416.195)
2c	72	76-78 (diisopropyl ether)	c	d	117.7	151.3	76.2	53.2	76.2	408.226, $C_{21}H_{32}N_2O_6$ (408.226)
2d	75	142-144 (diethyl ether)[b]	5.19	1.25	115.4	152.9	82.6	51.6	76.5	476.192, $C_{27}H_{28}N_2O_6$ (476.194)
7a	45	dec >135 (diisopropyl ether)	3.84	4.72	111.6	156.0	79.6	56.6	71.2	344.173, $C_{19}H_{24}N_2O_4$ (344.174)
7b	75	103-105 (diisopropyl ether)	4.02	1.04	116.4	155.4	75.8	59.0	72.3	358.189, $C_{20}H_{26}N_2O_4$ (358.189)
7c	65	83.5-85.5 (diisopropyl ether)	2.80	d	116.1	156.6	74.9	52.0	73.4	350.220, $C_{19}H_{30}N_2O_4$ (350.220)
8a	41	e	3.81	4.77	111.6	148.7	80.3	57.8	73.9	344.174, $C_{19}H_{24}N_2O_4$ (344.174)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all compounds in the table except for 2a. [b] Purified by fractional elution. [c] Coincides with the multiplet at δ 2.9-3.8. [d] Coincides with ring methylene proton absorptions. [e] Compd 8a could not be solidified, and therefore no elemental analysis was obtained.

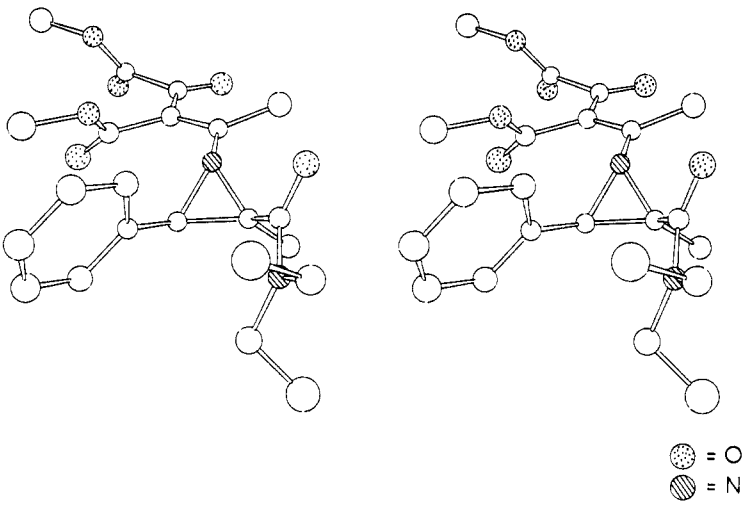
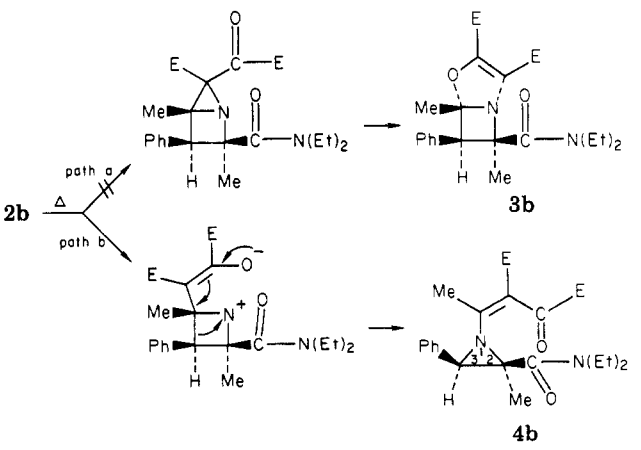


Figure 1. Stereoscopic view of aziridine 4b.

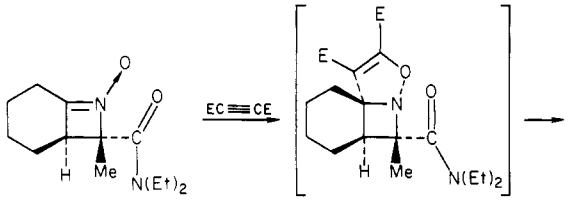
et al..[8] A concerted [1,3]sigmatropic shift of the nitrogen atom accounts for the observed ring contraction of the isoxazolines to aziridine derivatives, which rearrange to form oxazoline derivatives (compare path a, Scheme I).[9,10] The driving force of this reaction is the cleavage of the weak N–O bond with the simultaneous formation of a carbonyl function. However, the formation of a highly strained bicyclic aziridine derivative (path a) is obviously very unfavorable, and the isoxazoline **2b** rearranges via a nonconcerted diradical or dipolar pathway as shown by cleavage of the N–O bond to yield the aziridine **4b** (path b, Scheme I). From the X-ray analysis it can be seen that during this rearrangement the stereochemistry at C-2 and C-3 is preserved. The relatively short exocyclic carbon–nitrogen bond distance in **4b** of 1.365 (3) Å is nearly the same as the C–N distance of the amide group at C-2 (1.346 (4) Å), and this indicates a partial double bond character through participation of the nitrogen lone-pair electrons. This partial double bond character possibly results in a hindered rotation around the exocyclic C–N bond which explains the broadening in the ^{1}H NMR spectrum of one of the methoxy signals at δ ~3.2.

Scheme I

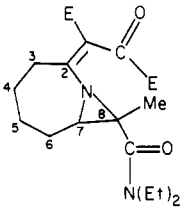


Reaction of nitrone **1e**, with a stereochemistry that is different from that in **1a–d**, with DMAD also yielded a crystalline 1:1 adduct according to mass spectrometry and elemental analysis. By comparison of the ^{13}C NMR spectrum of this compound with those of **2a–d** and **4b** it was quite obvious that the product was not the isoxazoline

(8) Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325.
(9) Grêe, R.; Carrié, R. *J. Am. Chem. Soc.* **1977**, *99*, 6667.
(10) We have also proposed a [1,3]sigmatropic shift of the nitrogen atom in the ring contraction of six-membered cyclic nitronic esters to four-membered cyclic nitrones (see ref 2a).



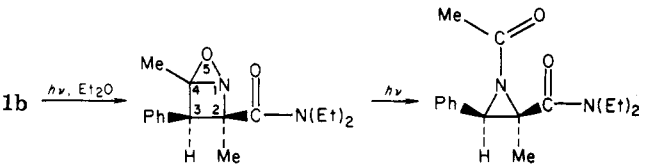
1e 2e



4e

derivative **2e** but the bicyclic aziridine **4e** (see Table I and the Experimental Section). We assume that **1e** and DMAD give first a 1,3-dipolar cycloadduct (**2e**), in which the conformation is most likely the one as shown, because in the other configuration the cyclohexane ring would be trans fused to the azetidine ring, which would lead to a highly strained molecule. It is possible that in this 1,3-dipolar adduct (**2e**) the N–O bond is weakened by the repulsion of the oxygen atom of the carbamoyl group and the isoxazoline oxygen, because these groups are now on the same face of the azetidine ring.[11] This weakening of the N–O bond leads to a decrease in activation energy for the rearrangement to the aziridine derivative **4e**.

An analogous example of the rearrangement that takes place in the formation of the aziridines **4b** and **4e**, was observed upon irradiation of nitrone **1b**. After irradiatioan for 7.5 min, according to ^{1}H NMR spectroscopy, nitrone **1b** was converted into **5** in about 60%.[14,15] The oxaziridine



5 **6**

5 was isolated in a yield of 40% as a white solid that liberated iodine from an acidic potassium iodide solution, a reaction that is characteristic for oxaziridines.[16] Oxaziridine **5** is a quite stable solid, but upon prolonged irradiation it was converted into the aziridine **6**. The ^{13}C NMR spectrum clearly showed the presence of two carbonyl functions (δ 179.4 and 166.2) and the two absorptions

(11) The fact that electronegative substituents at the 2-position of pyranes preferentially occupy the axial position, which is called the anomeric effect, is among others explained in terms of repulsion of the electron-rich substituent and the ring oxygen atom.[12] Oxygen–oxygen repulsion also plays an important role in the complexing abilities of macrocyclic polyethers and spherands.[13]

(12) Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933 and references cited therein.

(13) (a) Cram, D. J.; Kaneda, T.; Lein, G. M.; Helgeson, R. C. *J. Chem. Soc., Chem. Commun.* **1979**, 948. (b) Reinhoudt, D. N.; de Jong, F.; van de Vondervoort, E. M. *Tetrahedron* **1981**, *37*, 1753.

(14) (a) Kaminsky, L. S.; Lamchen, M. *J. Chem. Soc. C.* **1966**, 2295. (b) Black, D. St. C.; Blackman, N. A.; Boscacci, A. B. *Tetrahedron Lett.* **1978**, 175.

(15) For other examples of 5-oxa-1-azabicyclo[2.1.0]pentane derivatives formed by MCPBA oxidation of the corresponding azetines, see ref 3b and: Thomas, D.; Aue, D. H. *Tetrahedron Lett.* **1973**, 1807.

(16) Oxaziridines belong to a class of active oxygen compounds which are therefore able to liberate iodine from a potassium iodide solution; a reaction that can be used for the quantitative determination of oxaziridines: Horner, L.; Juergens, E. *Chem. Ber.* **1957**, *90*, 2184.

Table II. Characteristic ^{1}H NMR ($CDCl_3$) Chemical Shifts and Ratios of Methyl Propiolate Cycloadducts 7 and 8

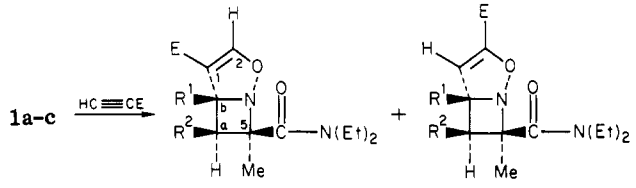
nitrone	7, δ(H-2)	8, δ(H-1)	ratio of 7/8[a]
1a	7.57 (d, J = 1.8 Hz)	6.15 (d, J = 2.4 Hz)	50:50
1b	7.52 (s)	6.11 (s)	86:14
1c	7.46 (s)	6.19 (s)	87:13

[a] Ratios were determined by ^{1}H NMR (accuracy ±3%).

of the aziridine carbon atoms. The conversion into the aziridine **6** also proceeds in a stereospecific way with retention of configuration as can be seen from the ^{1}H NMR spectrum: the signal of the methyl group at C-2 (δ 1.67), which is almost identical with that of **4b** (δ 1.66), is at relatively low field, since a methyl group cis substituted with a phenyl group at an aziridine ring would give rise to an absorption at $\delta \sim 1.0$.[17]

Photochemical and thermal rearrangement reactions of similar bicyclic oxaziridines, prepared from pyrroline 1-oxides, to 1-acetoxyazetidines have been reported previously,[14,18] and diradical and dipolar pathways have been proposed. The fact that in our work in both cases the aziridine formation occurs with retention of the thermodynamically less stable configuration suggests that both reactions might proceed via a heterolytic cleavage of the N–O bond, followed by a concerted [1,2]-C shift in the resulting nitrenium ion.[19]

The corresponding cycloaddition reactions of nitrones **1a–c** with methyl propiolate required longer reaction times and in the case of **1b** and **1c** even refluxing in dichloromethane. In all reactions, mixtures of isomeric isoxazoline derivatives **7** and **8** are formed. From these mixtures the



7 **8**

a, R^1 = H; R^2 = Ph
b, R^1 = Me; R^2 = Ph
c, R^1,R^2 = $(CH_2)_6$

isoxazolines **7** were isolated as crystalline solids in yields of 45–75%. Comparison of the ^{13}C NMR data with those of the cycloadducts with DMAD (**2**) clearly proved structures **7** (Table I). We assume that cycloadducts **7** have a configuration that is identical with that of adducts **2**. Evidence for this configuration is the small coupling constant (J = 3.9 Hz) of the hydrogen atoms at C-6 and C-6a of adduct **7a** and the relative high-field absorption of the C-6a methyl group of **7b** (δ 1.04) due to the shielding of the cis-substituted phenyl group. The ^{1}H NMR spectra of compounds **7** show an absorption (H-2) at a much lower field than the isomeric species **8** (H-1), of which only **8a** could be isolated in a pure state (oil). From the intensities of the signals of both **7** and **8** in the ^{1}H NMR spectra, the relative ratios in the crude reaction mixtures were determined (Table II). As can be seen from Table II, **1a** gives with methyl propiolate a 1:1 mixture of the two regioi-

(17) *N,N*-Diethyl-3-formyl-2-methyl-3-phenyl-2-aziridinecarboxamide, in which the methyl group is cis substituted with the phenyl group, shows an absorption at δ 1.13: unpublished results from these laboratories.

(18) Kaminsky, L. S.; Lamchen, M. *J. Chem. Soc. C* **1967**, 2128.

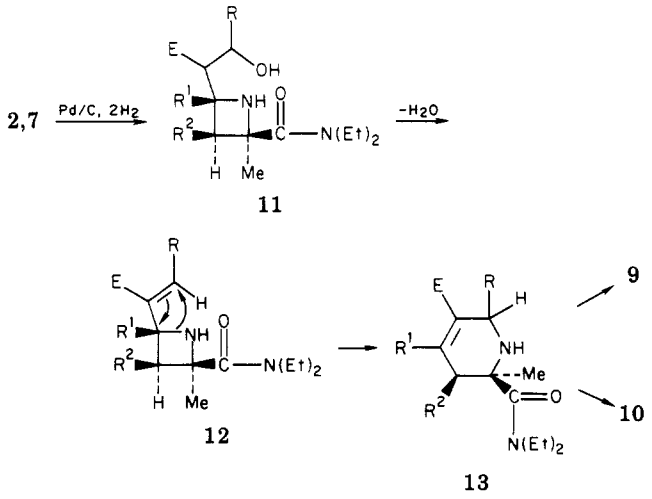
(19) Gilchrist, T. L.; Storr, R. C. "Organic Reactions and Orbital Symmetry"; Cambridge University Press: London, 1972; p 204.

Table III. Characteristic ^{13}C NMR ($CDCl_3$) Chemical Shifts of Pyridine Derivatives 9 and 10

compd	shift, δ				
	C-2	C-3	C-4	C-5	C-6
9a	143.6 (s)	91.7 (s)	26.4 (t)	52.7 (d)	59.6 (s)
9b	140.2 (d)	92.0 (s)	25.9 (t)	41.9 (d)	59.2 (s)
9c	142.2 (s)	98.0 (s)	35.4 (s)	52.5 (d)	59.7 (s)
9d	140.8 (d)	97.6 (s)	27.9 (d)	51.0 (d)	60.4 (s)

compd	shift, δ					
	C-3	C-4	C-4a	C-10a	C-1	C-5
9e	140.7 (d)	96.5 (s)	28.9 (d)	34.5 (d)	61.0 (s)	
10a	130.4 (s)	107.8 (s)	128.8 (s)	37.2 (d)	59.2 (s)	127.2 (d)
10b	139.6 (d)	94.8 (s)	127.6 (s)	37.3 (d)	59.9 (s)	123.9 (d)

Scheme II



somers (**7a** and **8a**), whereas the reactions of **1b** and **1c** give predominantly the isoxazoline **7b** and **7c**, respectively.

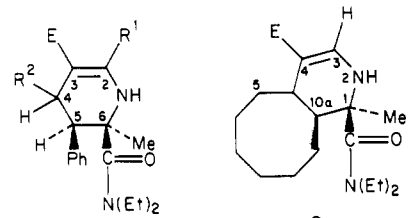
The regioselectivity of cycloaddition reactions of nitrones with electron-deficient dipolarophiles has long been an unexplained phenomenon. Houk[20] recently discussed the regioselectivity of these cycloaddition reactions in terms of the frontier molecular orbital (FMO) theory.

When the hydrogen atom at the nitrone moiety in **1a** is replaced by an electron-donating alkyl group as in **1b** and **1c**, according to Houk[21] the contribution of the LUMO(nitrone)–HOMO(dipolarophile) becomes less important and therefore the preference for isoxazolines **8**, which correspond to 5-substituted isoxazolines, decreases. A second effect of an electron-donating substituent is the increased coefficient on the oxygen atom of the HOMO(nitrone), which favors the formation of 4-substituted isoxazolines. Both effects will lead to an increased formation of 4-substituted isoxazoline derivatives (**7b** and **7c**).

We have also tried to react the four-membered cyclic nitrones **1** with several other dipolarophiles like phenyl isocyanate, dimethyl fumarate, dimethyl maleate, and aminoacetylenes, but we found that the four-membered cyclic nitrones did not react at room temperature with these dipolarophiles. At elevated temperatures the nitrones decomposed (in the case of **1a**) or underwent ring opening to form *N*-vinyl-*C*-carbamoylnitrones.[2a] Therefore, this thermal instability restricts a further investigation into the scope of 1,3-dipolar cycloaddition reactions of compounds **1**.

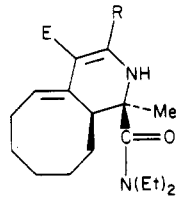
Tufariello et al.[6c] recently reported the formation of (bicyclic) β-lactams from several cycloadducts of nitrones with methyl crotonate in two steps, viz., by hydrogenolytic cleavage of the N–O bond, followed by ring closure on the ester carbonyl function. Since we are currently investigating routes for the synthesis of β-lactams starting from four-membered cyclic nitrones,[4] we have investigated the hydrogenolysis of the cycloadducts **2** and **7**.

Hydrogenation of the cycloadduct of DMAD and nitrone **1a**, the dihydroazeto[1,2-*b*]isoxazole **2a**, in the presence of palladium on charcoal (5%) gave a white crystalline product in a yield of 82%. Mass spectrometry and elemental analysis showed that the product corresponds to addition of two molecules of hydrogen and loss of a molecule of water. On the basis of the ^{13}C NMR spectrum of this product, which showed the presence of typical enamine absorptions at δ 143.6 and 91.7, we assigned the tetrahydropyridine structure **9a** to this reaction product. More



9a, R^1 = E; R^2 = H
b, R^1 = R^2 = H
c, R^1 = E; R^2 = Me
d, R^1 = H; R^2 = Me

9e



10a, R = E
b, R = H

evidence for this tetrahydropyridine structure was obtained by hydrogenatioin of adducts **2b** and **7a–c**; products (**9b–e**) with spectroscopic data similar to those for **9a** were obtained in yields of 45–82% (Table III). In the ^1H NMR spectra of **9b,d,e** absorptions of a vinylic hydrogen atom (δ ~7.6) and a broad absorption of the N–H proton were observed, which showed a coupling of ~6 Hz.

Hydrogenation of **2c** yielded a pale yellow oil after separation by preparative TLC, which was different from the pyridine derivatives **9**. Mass spectrometry showed that the product was formed by the additional loss of one molecule of hydrogen as compared with structures **9**, and in the ^1H NMR spectrum a triplet (J = 8.3 Hz) at δ 5.94 was observed. On the basis of this evidence together with the four vinylic absorptions in the ^{13}C NMR spectrum, we assigned structure **10a** to this compound (Table III).

The formation of both types of products that are obtained in these reactions can be rationalized in terms of hydrogenation of the double bond together with reductive cleavage of the N–O bond to yield the azetidine derivative **11** (Scheme II). Elimination of water yields **12**, which rearranges by nucleophilic attack of the nitrogen atom at the electron-deficient carbon–carbon double bond and subsequent ring opening of the azetidine ring to yield the tetrahydropyridine **13**. A hydrogen shift accounts for the formation of **9**. Seidl et al.[22] reported the hydrogenation

(20) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.
(21) Houk, K. N.; Bimanand, A.; Mukherjee, D.; Sims, J.; Chang, Y.-M.; Kaufman, D. C.; Domelsmith, L. N. *Heterocycles* **1977**, *7*, 293.

of isoxazoline derivatives from ethyl propiolate and 3,4-dihydroisoquinoline *N*-oxide in the presence of Raney nickel. They also found that hydrogenation of the double bond and cleavage of the N–O bond occurs to yield an alcohol of the type **11**. Upon distillation a compound was isolated that was formed by water elimination followed by a hydrogen shift. The formation of **10a** can be explained by assuming a dehydrogenation reaction of a compound of type **9** or of the intermediate **13**. In order to decide between the two pathways, we tried to convert **9e** into **10b**, but all attempts to dehydrogenate **9e** in ethanolic solution by means of palladium on charcoal failed. However, when the methyl propiolate cycloadduct **7c** was hydrogenated in the presence of a double amount of palladium catalyst, the octahydrocycloocta[*c*]pyridine derivative **10b** was isolated instead of **9e**, in a yield of 84%. The structure of **10b** was proven by elemental analysis and ^{1}H NMR spectroscopic data (t, δ 6.87, J = 8.2 Hz). From these results we conclude that the formation of both **10a** and **10b** most likely occurs via the tetrahydropyridine derivative **13** by means of a palladium on charcoal catalyzed dehydrogenation reaction.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 and a Bruker WP-80 spectrometer, and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as the internal standard). Mass spectra were obtained with a Varian Mat 311 A spectrometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry, TNO, Utrecht, The Netherlands, under supervision of W. J. Buis. Preparative TLC on silica gel was performed by using precoated plates (Merck DC-Fertigplatten Kieselgel 60 F_{254}) while TLC on Al_2O_3 was performed by using self-coated plates (Merck aluminum oxide 60 PF_{254} (Type E)) which were activated immediately before use. Dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate refer to Merck and Fluka reagents, respectively, and were distilled before use. All nitrones were prepared according to ref 2a.

General Procedure for the Reactions of Nitrones 1a–d with DMAD. Preparation of the Cycloadducts 2a–d. Dimethyl acetylenedicarboxylate (DMAD, 2.1 mmol) was added to a solution of the nitrone **1** (2 mmol) in 10 mL of dry chloroform. The solution was stirred for 24 h (in the case of **1a** for 4 h), after which the solvent was removed under reduced pressure. The solids that were obtained by addition of diisopropyl ether to the residue were triturated with cold diisopropyl ether to yield the pure products that could be recrystallized from an appropriate solvent (see Table I).

Thermolysis of 2b. Dimethyl 2-[[2-[(Diethylamino)carbonyl]-2-methyl-3-phenyl-1-aziridinyl]ethylidene]-3-oxobutanedioate (4b). Compound **2b** (0.291 g, 0.7 mmol) was heated at 125 °C. After 10 min crystallization started, and if it did not, crystallization was achieved by means of scratching. After 0.5 h the solid formed was triturated with diisopropyl ether to give **4b**: yield 80%; mp 153.5–155 °C (chloroform/hexane); ^{1}H NMR δ 7.30 (s, 5 H, Ph H), 3.76 (s, 3 H, OCH_3), 3.62 (s, 1 H, H-3), 3.5–2.4 (m, 4 H, NCH_2), ~3.2 (br s, 3 H, OCH_3), 2.73 (s, 3 H, $=CCH_3$), 1.66 (s, 3 H, CH_3), 0.73 and 0.76 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 182.8 (s, C=O), 169.9 (s), 166.8 (s), 165.5 (s) and 164.6 (s) (ester C=O, amide C=O, and =C—N), 109.1 (s, =C—E), 53.0 (s, C-2), 54.7 (d, C-3); mass spectrum, m/e 416.195 (M^+; calcd 416.195).

Anal. Calcd for $C_{22}H_{28}N_2O_6$ (mol wt 416.48): C, 63.44; H, 6.78; N, 6.73. Found: C, 63.25; H, 6.78; N, 6.73.

Dimethyl 2-[8-[(diethylamino)carbonyl]-8-methyl-1-azabicyclo[5.1.0]oct-2-ylidene]-3-oxobutanedioate (4e) was prepared according to the general procedure from **1e** and DMAD: yield 62% mp 123–124.5 °C (benzene/hexane); ^{1}H NMR δ 3.85 and 3.69 (s, 6 H, OCH_3), 4.0–3.0 (m, 4 H, NCH_2), 2.87 (dd, 1 H, J = 10, 3 Hz, H-7), 2.4–0.8 (m, 8 H, $(CH_2)_4$), 1.32 (s, 3 H, CH_3), 1.14 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 183.2 (s, C=O), 170.6 (s), 168.8 (s), 166.6 (s) and 164.7 (s) (ester C=O, amide C=O, and =C—N), 108.2 (s, =C—E), 53.2 (s, C-8), 46.8 (d, C-7); mass spectrum, m/e 380.194 (M^+; calcd 380.195).

Anal. Calcd for $C_{19}H_{28}N_2O_6$ (mol wt 380.45): C, 59.98; H, 7.42; N, 7.36. Found: C, 60.03; H, 7.45; N, 7.42.

Irradiation of 1b. *N,N*-Diethyl-2,4-dimethyl-3-phenyl-5-oxa-1-azabicyclo[2.1.0]pentane-2-carboxamide (5). Nitrone **1b** (0.5 g, 1.8 mmol) was dissolved in 400 mL of dry diethyl ether and irradiated in an atmosphere of nitrogen with a Hanau high-pressure mercury lamp (quartz) for 7.5 min. The diethyl ether was removed under reduced pressure, and the residue, which contained about 40% starting material, was dissolved in ethyl acetate and passed through a small silica gel column. Removal of the ethyl acetate under reduced pressure and trituration of the residue with diisopropyl ether gave the oxaziridine **5** as a white solid: yield 40%; mp 110–111 °C (diisopropyl ether); ^{1}H NMR δ 7.30 (s, 5 H, Ph H), 3.63 (s, 1 H, H-3), 3.5–2.9 (m, 4 H, NCH_2), 1.62 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 0.85 and 0.73 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 169.8 (s, C=O), 82.9 (s, C-4), 73.4 (s, C-2), 58.0 (d, C-3); mass spectrum, m/e 274.169 (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, 70.24; H, 8.14, N, 10.23.

Similarly, a solution of **1b** in diethyl ether was irradiated for 20 min, after which the diethyl ether was removed under reduced pressure. The residue was separated by preparative TLC (silica gel, ethyl acetate) into two fractions. Oxaziridine **5** was isolated from the fraction at R_f ~0.6 (36%), while from the fraction at R_f ~0.4 ***N,N*-diethyl-1-acetyl-2-methyl-3-phenyl-2-aziridinecarboxamide (6)** was isolated as a white solid after trituration with diisopropyl ether: yield 14%; mp 115.5–117 °C (toluene/diisopropyl ether); ^{1}H NMR δ 7.28 (s, 5 H, Ph H), 3.54 (s, 1 H, H-3), 3.8–2.8 (m, 4 H, NCH_2), 2.27 (s, 3 H, $COCH_3$), 1.67 (s, 3 H, CH_3), 0.95 and 0.83 (t, 6 H, $NCCH_3$); ^{13}C NMR δ 179.4 (s, O=CCH_3), 166.2 (s, C=O), 52.3 (s, C-2), 49.3 (d, C-3); mass spectrum, m/e 274.169 (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, 70.35; H, 8.23; N, 10.12.

General Procedure for the Reactions of Nitrones 1a–c with Methyl Propiolate. Preparation of the Cycloadducts 7a–c and 8a. Methyl propiolate (5 mmol) was added to a solution of the nitrone **1** (2 mmol) in 10 mL of dry dichloromethane. The solution was stirred for 24 h at room temperature (**1a**) or refluxed for 24 (**1b**) or 48 h (**1c**). The solvent was removed under reduced pressure, and in the case of **1a** and **1c** the residue was dissolved in ethyl acetate and passed through a small silica gel column. Removal of the ethyl acetate under reduced pressure and addition of diisopropyl ether to the residue yielded the adducts **7a** and **7c** as white solids after trituration with cold diisopropyl ether. In the case of **1b** the residue was separated by preparative TLC (Al_2O_3, chloroform; the plates were eluted three times). The fraction at R_f ~0.7 yielded after trituration with cold diisopropyl ether **7b**. The filtrate of **7c** and the more slowly eluted fraction in the case of **7b** contained the strongly contaminated isomers **8c** and **8b**, respectively according to ^{1}H NMR, while from the filtrate of **7a**, **8a** was isolated in a purity >95% as a pale yellow oil (Table I).

General Procedure for the Hydrogenation of the Isoxazoline Derivatives 2 and 7. Synthesis of Pyridine Derivatives 9 and 10. The isoxazoline derivative **2** or **7** (2 mmol) was dissolved in 40 mL of absolute ethanol and hydrogenated in the presence of 200 mg of Pd on charcoal catalyst (5%) at atmospheric pressure. After 4 mmol of hydrogen had been taken up, the reaction mixture was filtered over Hyflo, the solvent was removed under reduced pressure and the residue was worked up as described below.

Dimethyl 6-[(Diethylamino)carbonyl]-1,4,5,6-tetrahydro-6-methyl-5-phenyl-2,3-pyridinedicarboxylate (9a). Hydrogenation of **2a** was carried out for 16 h. After a work up in the usual way the residue was solidified by addition of a few drops of ethanol. Trituration with ethanol yielded **9a** as a white solid: yield 82%; mp 130–132 °C (ethanol); ^{1}H NMR δ 7.16 (s, 5 H, Ph H), 6.68 (br s, 1 H, NH), 3.89 and 3.69 (s, 6 H, OCH_3), 3.47 (dd, 1 H, J = 2.3, 5.8 Hz, H-5), 3.9–2.6 (m, 6 H, NCH_2 and H-4), 1.55

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(s, 3 H, CH_3), 1.1–0.7 (m, 6 H, $NCCH_3$); mass spectrum, m/e 388.201 (M^+; calcd 388.200).

Anal. Calcd for $C_{21}H_{28}N_2O_5$ (mol wt 388.47): C, 64.92; H, 7.26; N, 7.21. Found: C, 64.69; H, 7.32; N, 7.06.

Methyl 6-[(Diethylamino)carbonyl]-1,4,5,6-tetrahydro-6-methyl-5-phenyl-3-pyridinecarboxylate (9b). Hydrogenation of **7a** was carried out for 72 h. After a workup in the usual way the residue was purified by preparative TLC (Al_2O_3, chloroform). The solid that was obtained (R_f ~0.8) was triturated with diisopropyl ether to give **9b** as a white solid: yield 80%; mp 124–126 °C (toluene/petroleum ether, bp 60–80 °C); ^1H NMR δ 7.65 (d, 1 H, J = 6.3 Hz, H-2), 7.14 (s, 5 H, Ph H), ~6.61 (d, 1 H, J = 6.3 Hz, NH), 3.66 (s, 3 H, OCH_3), 3.8–2.4 (m, 7 H, NCH_2, H-4 and H-5), 1.53 (s, 3 H, CH_3), 1.1–0.6 (m, 6 H, $NCCH_3$); mass spectrum, m/e 330.194 (M^+; calcd 330.194).

Anal. Calcd for $C_{19}H_{26}N_2O_3$ (mol wt 330.43): C, 69.06; H, 7.93; N, 8.47. Found: C, 68.83; H, 7.99; N, 8.29.

Dimethyl 6-[(Diethylamino)carbonyl]-1,4,5,6-tetrahydro-4,6-dimethyl-5-phenyl-2,3-pyridinedicarboxylate (9c). Hydrogenation of **2b** was carried out for 16 h. After a workup in the usual way the residue was separated by preparative TLC (Al_2O_3, chloroform). Compound **9c** (R_f ~0.5) was isolated as a white solid after trituration with diisopropyl ether: yield 45%; mp 126–128 °C (toluene/petroleum ether, bp 60–80 °C); ^1H NMR 7.3–7.0 (m, 5 H, Ph H), 6.66 (br s, 1 H, NH), 3.90 and 3.65 (s, 6 H, OCH_3), 3.35 (s, 1 H, H-5), 2.81 (q, 1 H, H-4), 3.9–2.8 (m, 4 H, NCH_2), 1.67 (s, 3 H, CH_3), 1.45 (d, 3 H, CH_3), 1.1–0.5 (m, 6 H, $NCCH_3$); mass spectrum, m/e 402.218 (M^+; calcd 402.216).

Anal. Calcd for $C_{22}H_{30}N_2O_5$ (mol wt 402.50): C, 65.64; H, 7.52; N, 6.96. Found: C, 65.66; H, 7.68; N, 6.87.

Methyl 6-[(Diethylamino)carbonyl]-1,4,5,6-tetrahydro-4,6-dimethyl-5-phenyl-3-pyridinecarboxylate (9d). Hydrogenation of **7b** was carried out for 40 h. After a workup in the usual way the residue was triturated with diethyl ether to give **9d** as a white solid: yield 78%; mp 170 °C dec (toluene/petroleum ether, bp 60–80 °C); ^1H NMR δ 7.66 (d, 1 H, J = 6 Hz, H-2), 7.3–7.0 (m, 5 H, Ph H), ~6.55 (d, 1 H, J = 6 Hz, NH), 3.66 (s, 3 H, OCH_3), 3.23 (s, 1 H, H-5), 4.0–2.5 (m, 5 H, NCH_2 and H-4), 1.55 (s, 3 H, CH_3), 1.00 (d, 3 H, CH_3), 1.4–0.5 (m, 6 H, $NCCH_3$); mass spectrum, m/e 358.226 (M^+; calcd 358.226).

Anal. Calcd for $C_{21}H_{30}N_2O_3$ (mol wt 358.48): C, 69.73; H, 8.19; N, 8.13. Found: C, 69.52; H, 8.28; N, 7.96.

Methyl 1-[(Diethylamino)carbonyl]-1,2,4a,5,6,7,8,9,10,10a-decahydro-1-methyl-cycloocta[*c*]pyridine-4-carboxylate (9e). Hydrogenation of **7c** was carried out for 6 h. After a workup in the usual way the residue was solidified by the addition of petroleum ether (bp 60–80 °C), and after trituration with the same solvent, **9e** was isolated as a white solid: yield 82%; mp 109–110 °C (petroleum ether, bp 60–80 °C); ^1H NMR δ 7.46 (d, 1 H, J = 6.3 Hz, H-3), 6.23 (d, 1 H, J = 6.3 Hz, NH), 3.63 (s, 3 H, OCH_3), 4.0–2.1 (m, 6 H, NCH_2, H-4a and H-10a), 1.8–0.7 (m, 12 H, CH_2), 1.32 (s, 3 H, CH_3), 1.19 (t, 6 H, $NCCH_3$); mass spectrum, m/e 336.240 (M^+; calcd 336.241).

Anal. Calcd for $C_{19}H_{32}N_2O_3$ (mol wt 336.48): C, 67.82; 9.59; N, 8.33. Found: C, 67.84; H, 9.53; N, 8.19.

Dimethyl 1-[(Diethylamino)carbonyl]-1,2,6,7,8,9,10,10a-octahydro-1-methylcycloocta[*c*]pyridine-3,4-dicarboxylate (10a). Hydrogenation of **2c** was carried out for 6 h. After a workup in the usual way the residue was separated by preparative TLC (silica gel; ethyl acetate/chloroform, 4:1). Compound **10a** (R_f ~0.5) was isolated as a pale yellow oil, yield 82%. Attempts to characterize **10a** via its hydrochloric salt or picrate failed: ^1H NMR δ 6.36 (br s, 1 H, NH), 5.94 (t, 1 H, J = 8.3 Hz, H-5), 3.79 and 3.78 (s, 6 H, OCH_3), 3.8–3.0 (m, 4 H, NCH_2), 2.5–0.7 (m, 11 H, CH_2 and H-10a), 1.32 (s, 3 H, CH_3), 1.25 (t, 6 H, $NCCH_3$); mass spectrum, m/e 392.233 (M^+; calcd 392.231).

Methyl 1-[(Diethylamino)carbonyl]-1,2,6,7,8,9,10,10a-octahydro-1-methylcycloocta[*c*]pyridine-4-carboxylate (10b). Compound **7c** (87.5 mg, 0.25 mmol) was dissolved in 10 mL of absolute ethanol and hydrogenated in the presence of 50 mg of Pd on charcoal (5%). After 65 h the mixture was worked up in the usual way, and the residue was triturated with petroleum ether (bp 60–80 °C) to give **10b**: yield 84%; mp 126–128 °C dec (petroleum ether, bp 60–80 °C); ^1H NMR δ 7.46 (d, 1 H, J = 6.3 Hz, H-3), 6.87 (t, 1 H, J = 8.2 Hz, H-5), ~6.6 (d, 1 H, NH), 3.68 (s, 3 H, OCH_3), 3.9–3.0 (m, 4 H, NCH_2), 2.5–0.8 (m, 17 H, H-10a, CH_2 and $NCCH_3$), 1.33 (s, 3 H, CH_3); mass spectrum, m/e 334.226 (M^+; calcd 334.226).

Anal. Calcd for $C_{19}H_{30}N_2O_3$ (mol wt 334.46): C, 68.23; H, 9.04; N, 8.38. Found: C, 68.39; H, 9.14; N, 8.35.

X-ray Crystal Structure Analysis of 4b. The crystals of **4b** have triclinic symmetry, space group $P\bar{1}$. The unit cell dimensions are a = 12.034 (2) Å, b = 10.878 (2) Å, c = 9.181 (2) Å, α = 112.31 (2)°, β = 103.08 (1)°, and γ = 88.96 (2)°. With two molecules in the unit cell the calculated density is 1.285 g cm^{-3}. Data [141 (2)K] were collected by using a Philips PW1100 diffractometer (Mo K_α radiation, λ = 0.7107 Å, graphite monochromator, θ–2θ scan mode, scan speed 0.025°/s, scan width (θ) 1.8°, scan range $2 < \theta < 22.5°$, total number of reflections measured 2626, number of reflections used in refinement ($I > \sigma(I)$) 2133). The structure was solved by direct methods (MULTAN78)[23] and refined by the full-matrix least-squares method (ORFLS).[24] The drawing was made by ORTEP.[25] The positions of all hydrogen atoms were found from difference Fourier syntheses. The refinement converged to a final R factor of 3.8% (parameters refined were the scale factor, extinction parameter, positional parameters of all atoms, anisotropic thermal parameters for non-H atoms, and isotropic thermal parameters for H atoms; the total number of parameters was 384).

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Supplementary Material Available: Tables of cell parameters, atomic coordinates, thermal parameters, bond distances, and bond angles (6 pages). Ordering information is given on any current masthead page.

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