Full papers

Recl. Trav. Chim. Pays-Bas 107, 27–39 (1988) 0165–0513/88/0227–13$3.75

Stereoselective synthesis of *cis* and *trans* four-membered cyclic nitrones[1]

Peter J. S. S. van Eijk[a], Cor Overkempe[a], Willem P. Trompenaars[a], David N. Reinhoudt[a]*, Lauri M. Manninen[b], Gerrit J. van Hummel[b] and Sybolt Harkema[b]

[a] *Laboratory of Organic Chemistry,* [b] *Laboratory of Chemical Physics, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands*
(Received July 27th, 1987)

Abstract. Nitroalkenes **3–5** react with ynamines (1-aminoacetylenes) **6** to yield four-membered cyclic nitrones (2,3-dihydroazete 1-oxides) **7–13**. The nitroalkenes **3** and **5c** give the *cis* four-membered cyclic nitrones **7–11**, whereas **4** and **5b** yield the *trans* four-membered cyclic nitrones **12–13** upon reaction with **6**. Nitroalkene **4i** reacts with **6c** to give a 1:1 mixture of the *cis* and *trans* four-membered cyclic nitrones **9g** and **13i**. The *trans* stereochemistry of *trans*-*N,N*-diethyl-2,3-dihydro--3-(2-methoxynaphthalenyl)-2-methyl-4-phenyl-2-azetecarboxamide 1-oxide (**13k**) was elucidated by means of X-ray analysis. Only from the reaction of 1-nitrocyclopentene (**5a**) with **6c**, the initially formed (4 + 2) cycloadduct, the nitronic ester **17** has been isolated. The thermal ring contraction of **17** yields 3a,4,5,6-tetrahydro-*N,N*-dimethyl-3-phenyl-3*H*-cyclopent[*c*]isoxazole-3-carboxamide (**19**), the structure of which was established by X-ray analysis. The *trans* four-membered cyclic nitrones are thermally relatively stable compared with the *cis* nitrones. The mechanism of the stereoselective formation of the nitrones is related to the conformation of the (4 + 2) cycloadduct **16**, which could be correlated with Chem-X and MNDO calculations.

Introduction

Cyclic and acyclic nitrones have proven to be useful building blocks in the synthesis of heterocycles[2-4]. Four-membered cyclic nitrones represent a relatively new class of heterocycles with an extremely reactive nitrone moiety. We have published recently the synthesis of a variety of compounds, such as 5-hydroxyisoxazolines[5], β-lactams[6] and 6*H*-1,2-oxazin-6-ones starting from four-membered cyclic nitrones[7]. Representative members of all these classes of compounds have been found biologically active.

Two incidental syntheses of four-membered cyclic nitrones were reported by *Black* and co-workers[8] and by *Harnisch* and *Szeimies*[9]. Simultaneously we reported the synthesis of a series of four-membered cyclic nitrones by reaction of nitroalkenes **3** and **5** with ynamines **6** in acetonitrile in acceptable yields[10,11]. Recently, *Marcelis* et al. were able to apply our methodology successfully to 5-nitropyrimidines[12].

The cycloaddition reaction of ynamines and nitroalkenes proceeds stereoselectively. In addition to the (2 + 2) cycloadducts (*i.e.* the *N,N*-dialkyl-4-nitro-1-cyclobuten--1-amines **14**[11,13]) four-membered cyclic nitrones (**7–11**) that have the *cis* configuration, were the only products we obtained. Hence, in these four-membered cyclic nitrones, the two bulky groups, *i.e.* the carbamoyl moiety and the phenyl group are *cis* oriented. We have proposed that the initially formed intermediate (4 + 2) cycloadduct, *i.e.* the cyclic nitronic ester **16** undergoes a concerted stereoselective ring contraction to give *cis* four-membered cyclic nitrones (Scheme 1).

Only in one case the formation of a *trans* four-membered cyclic nitrone was observed[11]. Reaction of 1-nitrocyclohexene (**5b**) and *N,N*-diethyl-1-propyn-1-amine (**6c**) gave the corresponding *trans* nitrone **12**. This result was explained in terms of ring strain in the intermediate cyclic nitronic ester, due to the annelated 6-membered ring[11].

Our work on alternative routes revealed that oxidation of *N*-hydroxyazetidines with HgO[5] or PbO_2[6] gave also four-membered cyclic nitrones. However, general routes to *N*-hydroxyazetidines turned out to be difficult[14,15].

We have further investigated the scope and limitations of the (4 + 2) cycloaddition of ynamines and nitroalkenes. We have studied systematically the effects of substituent variation in the ynamines and in the nitroalkenes.

In this paper the synthesis of a series of four-membered cyclic nitrones is described of which the stereochemistry, *i.e. cis* or *trans*, can be controlled by a proper choice of the starting nitroalkenes **3–5**. The thermal stability of *trans* four-membered cyclic nitrones has been compared with the stability of *cis* four-membered cyclic nitrones.

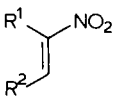
Results and discussion

In order to investigate the effect of the substitution pattern of the nitrone molecule on the yield and the stereochemistry we have systematically varied the substituents R^1 and R^2 of the nitroalkene and the substituents R^3 and NR^4R^5 of the ynamine.

Preparation of nitroalkanes, nitroalkenes and ynamines

The nitroalkenes **3** and **4** (Chart 1), with different substituents R^1 and R^2 were prepared by a condensation reaction of the corresponding nitroalkanes **1** and aldehydes **2**. The nitroalkanes **1a-c** are commercially available and nitroalkanes **1d**[16] and **1e**[17,18] were prepared according to the literature.

The nitroalkenes used in this work can be divided in three groups. Firstly, the 1-aryl-2-nitro-1-alkenes **3** in which none or only one of the *ortho* positions of the aryl group R^2 is substituted. Secondly, the 1-aryl-2-nitro-1-alkenes **4** in which minimally *both ortho* positions of the aryl group R^2 are substituted and thirdly the 1-nitro*cyclo*alkenes **5**. The nitroalkenes **3a** and **4a-d** were prepared by reaction of the corresponding aldehydes and nitromethane in an aqueous sodium hydroxide solution. The acyclic nitroalkenes **3b-p** and **4e-k** were prepared by reaction of the corresponding aldehyde with *n*-butylamine in benzene, and subsequent reaction of the resulting *Schiff* base with the appropriate nitroalkane **1** in glacial acetic acid[20,21]. The 1-nitro*cyclo*alkenes **5** were prepared from the corresponding cycloalkenes by nitromercuration[22] (**5a** and **5b**), or by reaction

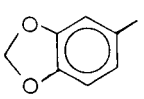


3-5

Nitroalkenes **3**
(R^2 = non- or monosubstituted aryl)

Compound	R^1	R^2		Ref.
3a	H	Ph	(*E*)	19
3b	Me	Ph	(*E*)	20
3c	Me	3-pyridinyl	(*E*)	42
3d	Me	2-OMe-C_6H_4	(*E*)	35
3e	Me	4-Cl-C_6H_4	(*E*)	43
3f	Me	CH_2O_2-C_6H_3[a]	(*E*)	36
3g	Me	3-Br-C_6H_4	(*E*)	35
3h	Et	Ph	(*E*)	37
3i	Et	4-Cl-C_6H_4	(*E*)	36
3j	Ph	Ph	(*E*)	21
3k	Ph	4-Me-C_6H_4	(*E*)	21
3m	Ph	4-Cl-C_6H_4	(*E*)	21
3n	Ph	CH_2O_2-C_6H_3[a]	(*E*)	21
3p	PhS	Ph	(*Z*)	–

[a] CH_2O_2-C_6H_3 =



Nitroalkenes **4**
(R^2 = *ortho*-disubstituted or polysubstituted aryl)

Compound	R^1	R^2		Ref.
4a	H	2,4,6-$(Me)_3$-C_6H_2	(*E*)	–
4b	H	2-F,6-Cl-C_6H_3	(*E*)	38
4c	H	2,6-$(Cl)_2$-C_6H_3	(*E*)	38
4d	H	2-MeO-Napht.	(*E*)	–
4e	Me	2-F,6-Cl-C_6H_3	(*E*)	–
4f	Me	2,6-$(Cl)_2$-C_6H_3	(*E*)	39
4g	Me	2-MeO-Napht.	(*E*)	40
4h	Ph	2,4,6-$(Me)_3$-C_6H_2	(*E*)	21
4i	Ph	2-F,6-Cl-C_6H_3	(*E*)	–
4j	Ph	2,6-$(Cl)_2$-C_6H_3	(*E*)	21
4k	Ph	2-MeO-Napht.	(*E*)	–

Nitro*cyclo*alkenes **5**

compound	-(R^1-R^2)-	Ref.
5a	$-(CH_2)_3-$	22
5b	$-(CH_2)_4-$	22
5c	$-(CH_2)_6-$	23

Nitroalkanes **1**

$R^1CH_2NO_2$

1

Compound	R^1
1a	H
1b	Me
1c	Et
1d	Ph
1e	PhS

Ynamines **6**

NR^4R^5-C≡C-R^3

6

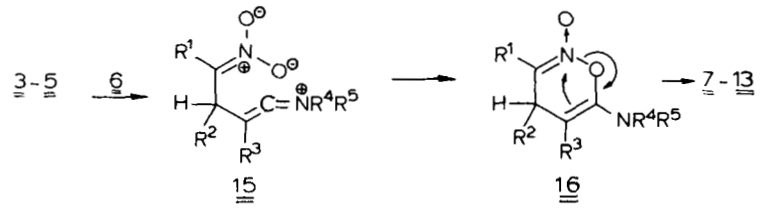
Compound	R^3	NR^4R^5
6a	H	N(Me)CH_2Ph
6b	H	$N(CH_2CH_2)_2O$
6c	Me	$N(Et)_2$
6d	Me	N(Me)Ph
6e	Et	$N(Et)_2$
6f	Et	$N(CH_2)_2C(CH_3)_2$
6g	Ph	$N(Me)_2$
6h	Ph	$N(Et)_2$
6i	Ph	$N(CH_2CH_2)_2O$

Chart 1

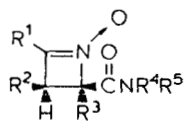
with dinitrogen tetroxide[23] (**5c**). The nitroalkenes **3p**, **4a,d,e,i,k** have not been reported previously in the literature. They were obtained in acceptable yields. The ynamines **6** were prepared according to the methods described by *Brandsma*[24] and *Ficini*[25a].

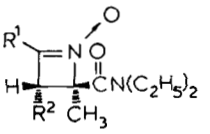
The (4 + 2) cycloaddition reaction of nitro(cyclo)alkenes and ynamines; characterization of the reaction products

Since the mode of cycloaddition of ynamines and nitroalkenes is solvent dependent, the reactions of the nitro(cyclo)alkenes **3–5** and the ynamines **6** were carried out in



15 16





cis four-membered cyclic nitrones **7–11**

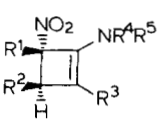
Compound	R^1	R^2	R^3	NR^4R^5
7	H	Ph	Ph	$N(CH_2CH_2)_2O$
8a[a]	Me	Ph	Me	$N(Et)_2$
8b	Me	3-pyridinyl	Me	$N(Et)_2$
8c	Me	2-MeO-C_6H_4	Me	$N(Et)_2$
8d	Me	4-Cl-C_6H_4	Me	$N(Et)_2$
8e	Me	CH_2O_2-C_6H_3	Me	$N(Et)_2$
8f	Me	3-Br-C_6H_4	Me	$N(Et)_2$
8g	Me	Ph	Me	N(Me)Ph
8h	Me	Ph	Et	$N(Et)_2$
8i	Me	Ph	Ph	$N(Me)_2$
8j	Me	Ph	Ph	$N(Et)_2$
8k	Me	2-MeO-C_6H_4	Ph	$N(Et)_2$
8m	Me	Ph	Ph	$N(CH_2CH_2)_2O$
8n	Et	Ph	Me	$N(Et)_2$
8p	Et	4-Cl-C_6H_4	Me	$N(Et)_2$
9a	Ph	Ph	H	$N(CH_2CH_2)_2O$
9b	Ph	Ph	H	$N(Me)CH_2Ph$
9c[a]	Ph	Ph	Me	$N(Et)_2$
9d	Ph	4-Me-C_6H_4	Me	$N(Et)_2$
9e	Ph	4-Cl-C_6H_4	Me	$N(Et)_2$
9f	Ph	CH_2O_2-C_6H_3	Me	$N(Et)_2$
9g	Ph	2-F,6-Cl-C_6H_3	Me	$N(Et)_2$
9h	Ph	Ph	Et	$N(CH_2)_2C(CH_3)_2$
9i	Ph	Ph	Ph	$N(Me)_2$
9j	Ph	Ph	Ph	$N(Et)_2$
9k	Ph	Ph	Ph	$N(CH_2CH_2)_2O$
10a	PhS	Ph	H	$N(CH_2CH_2)_2O$
10b	PhS	Ph	Me	$N(Et)_2$
10c	PhS	Ph	Me	N(Me)Ph
10d	PhS	Ph	Ph	$N(Me)_2$
11a[a]		$-(CH_2)_6-$	Me	$N(Et)_2$
11b		$-(CH_2)_6-$	Ph	$N(Me)_2$

[a] For spectroscopic data, see ref. 11.

trans four-membered cyclic nitrones **12** and **13**

Compound	R^1	R^2
12[a]	$-(CH_2)_4-$	
13a	H	2,4,6-$(Me)_3$-C_6H_2
13b	H	2-F,6-Cl-C_6H_3
13c	H	2,6-$(Cl)_2$-C_6H_3
13d	H	2-MeO-Napht.
13e	Me	2-F,6-Cl-C_6H_3
13f	Me	2,6-$(Cl)_2$-C_6H_3
13g	Me	2-MeO-Napht.
13h	Ph	2,4,6-$(Me)_3$-C_6H_2
13i	Ph	2-F,6-Cl-C_6H_3
13j	Ph	2,6-$(Cl)_2$-C_6H_3
13k	Ph	2-MeO-Napht.

[a] For spectroscopic data, see ref. 11.



14

Scheme 1

Table I Physical and spectral properties of the cis *four-membered cyclic nitrones* **7–11**[a,b].

	Yield (%) CH_3CN	M.p.[b] (°C)	^1H NMR ($CDCl_3$) δ				^{13}C NMR ($CDCl_3$) δ							MS (*m/z*)		
			H-3[c]	R^1 [c] (d)	R^3 (s)	$NCCH_3$ (t)	C-2 (s)	C-3 (d)	C-4 (s)	C=O (s)	R^1 (q)	R^3 (q)	$NC\underline{C}H_3$ (q)	(Calcd.)	Exp.	Formula
7	14	103–105	4.83(d)[d]	7.03[d]	[f]	–	95.6	47.1	131.3	163.0	–	[f]	–	(336.147)	336.147	$C_{20}H_{20}N_2O_3$
8b	60	145–147	3.94(q)	2.01	1.99	1.00 + 0.66	89.2	52.0	146.7	165.3	13.5	20.1	11.8 + 10.0	(275.163)	275.165	$C_{15}H_{21}N_3O_2$
8c	59	135–136	4.46(q)	2.00	1.96	0.90 + 0.60	89.0	46.7	147.5	165.9	13.5	19.8	11.6 + 10.0	(304.179)	304.180	$C_{17}H_{24}N_2O_3$
8d	57	145–148	3.83(q)	1.99	1.96	0.93 + 0.66	89.1	54.2	147.6	165.5	13.5	20.1	11.7 + 9.9	(308.129)	308.129	$C_{16}H_{21}ClN_2O_2$
8e	59	142–143	3.76(q)	1.99	1.94	0.96 + 0.76	89.2	54.8	[h]	165.8	13.5	20.1	11.8 + 9.9	(318.158)	318.160	$C_{17}H_{22}N_2O_4$
8f	55	118–120	3.84(q)	2.01	1.97	0.94 + 0.70	89.0	54.2	147.2	163.5	13.4	20.1	11.7 + 10.0	(352.079)	352.080	$C_{16}H_{21}BrN_2O_2$
8g	28	137–140	3.73(q)	2.00	1.62	–	89.9	55.1	148.1	165.4	10.1	20.5	–	(308.153)	308.152	$C_{19}H_{20}N_2O_2$
8h	24[g]	134–138	3.88(q)	2.00	[e]	0.88 + 0.68	93.0	50.3	148.0	165.6	13.4	[i]	11.7 + 8.1	(288.184)	288.184	$C_{17}H_{24}N_2O_2$
8i	14	107–114	4.68(q)	2.10	[f]	–	94.0	50.9	148.5	165.0	10.1	[f]	–	(308.153)	308.153	$C_{19}H_{20}N_2O_2$
8j	43	131–134	4.74(q)	2.03	[f]	0.57 + 0.11	94.1	49.2	147.3	164.6	10.0	[f]	11.5 + 11.2	(336.184)	336.183	$C_{21}H_{24}N_2O_2$
8k	33	118–121	5.39(q)	2.03	[f]	0.51 + 0.05	94.2	40.8	147.5	164.9	10.2	[f]	11.2	(366.194)	366.194	$C_{22}H_{26}N_2O_3$
8m	10	106–107.5	4.71(q)	2.08	[f]	–	93.5	50.3	148.5	164.1	10.1	[f]	–	(350.163)	350.166	$C_{21}H_{22}N_2O_3$
8n	50	144–145	3.90(t)	[e]	1.97	0.87 + 0.68	88.2	53.7	151.9	165.8	[j]	20.2	13.3 + 11.7	(288.184)	288.185	$C_{17}H_{24}N_2O_2$
8p	44	81–83.5	3.85(t)	[e]	1.95	0.93 + 0.73	88.3	52.9	151.7	165.7	[k]	20.3	13.5 + 11.8	(322.145)	322.146	$C_{17}H_{23}ClN_2O_2$
9a	54	235–236	4.65(d)	[f]	5.72(d)	–	78.6(d)	42.8	150.1	161.7	[f]	–	–	(336.147)	336.148	$C_{26}H_{24}N_2O_3$
9b	21	208–210	4.69(d)	[f]	5.74(d)	–	78.5(d)	42.5	149.9	163.0	[f]	–	–	(370.168)	370.168	$C_{24}H_{22}N_2O_2$
9d	40	158–159.5	4.21(s)	[f]	2.03	0.94 + 0.66	88.5	52.3	146.4	165.7	[f]	20.6	13.4 + 11.6	(350.199)	350.207	$C_{22}H_{26}N_2O_2$
9e	58	195–200	4.23(s)	[f]	2.04	1.00 + 0.69	88.5	51.7	146.0	165.4	[f]	20.7	13.6 + 11.6	(370.145)	370.145	$C_{21}H_{23}ClN_2O_2$
9f	68	203.5–205	4.17(s)	[f]	2.02	1.00 + 0.76	88.6	52.4	[n]	165.7	[f]	20.5	13.5 + 11.7	(280.174)	280.175	$C_{22}H_{24}N_2O_4$
9g	85[p]	129–132	4.90(d)[q]	[f]	2.08	1.08 + 0.83	88.7	46.8	146.9	165.7	[f]	22.6	14.3 + 12.0	(388.135)	388.133	$C_{21}H_{22}ClFN_2O_2$
9h	45	186–188	4.34(s)	[f]	[r]	–	90.8	47.6	148.1	165.4	[f]	[s]	–	(362.199)	362.199	$C_{23}H_{25}N_2O_2$
9i	56[g]	207.5–209	5.08(s)	[f]	[f]	–	93.4	48.5	146.6	164.9	[f]	[f]	–	(370.168)	370.168	$C_{24}H_{22}N_2O_2$
9j	45	234–235	5.17(s)	[f]	[f]	0.58 + 0.14	93.5	46.8	146.3	164.6	[f]	[f]	11.4 + 11.2	(398.199)	398.196	$C_{26}H_{26}N_2O_2$
9k	48	162–166	5.12(s)	[f]	[f]	–	93.2	46.1	146.8	164.1	[f]	[f]	–	(412.179)	412.178	$C_{26}H_{24}N_2O_3$
10a	33	187–188	4.26(d)	[f]	5.65(d)	–	78.9(d)	44.7	143.5	161.5	[f]	–	–	(368.120)	368.121	$C_{20}H_{20}N_2O_3S$
10b	44	104–106	3.83(s)	[f]	1.96	0.83 + 0.66	88.8	55.3	139.6	165.2	[f]	20.3	13.2 + 11.6	(368.156)	368.156	$C_{21}H_{24}N_2O_2S$
10c	13	140–142	3.72(s)	[f]	1.59	–	90.0	55.5	142.5	165.0	[f]	20.6	–	(402.140)	402.143	$C_{24}H_{22}N_2O_2S$
10d	23	115–121	4.64(s)	[f]	[f]	–	94.1	51.6	139.8	164.7	[f]	[f]	–	(372.143)	372.142	$C_{24}H_{22}NOS$ ($M^+ - 30$)
11b	33	158.5–160	3.60(d)	[m]	[f]	–	89.7	45.0	154.5	166.4	[m]	[f]	–	(300.184)	300.187	$C_{18}H_{24}N_2O_2$

[a] Note 1. [b] Satisfactory elemental analyses (%C ± 0.4) were only obtained for **8b-e,h,j,k,n**, **9a,b,e,g,j** and **10a-c**, due to the thermal instability of the four-membered cyclic nitrones. Compounds **8b-d,h,j,k,n**, **9a,b,e,g,j** and **10a,c** were recrystallized from chloroform/petroleum ether, **8e** from chloroform/ethyl acetate/petroleum ether, **9h** from chloroform/petroleum ether (b.p. 40–60°C), and **10b** from tetrachloromethane/chloroform/petroleum ether mixtures, respectively. The melting points of the remaining nitrones were obtained after trituration of the crude solid with diisopropyl ether. Compounds **9k** and **10d** were slightly contaminated with the corresponding nitroalkenes. [c] *J* 1.7 ± 0.1 Hz. [d] *J* 1.5 ± 0.1 Hz. [e] Ethyl absorptions: coincide with NCH_2 signal at δ 3.5–2.1. [f] Phenyl absorptions. [g] The reaction was performed in petroleum ether. [h] δ 148.0, 147.8 and 147.4 (s, C-4, ArC-3 and ArC-4). [i] 25.8 (t, CH_2), 9.5 (q, CH_3). [j] 17.8 (t, CH_2), 9.1 (q, CH_3). [k] 17.8 (t, CH_2), 9.2 (q, CH_3). [m] = methylene absorptions. [n] 148.0 (s), 147.8 (s), 146.2 (s, C=N, ArC-3 and ArC-4). [p] 1:1 mixture of **9g** and **13i**. [q] J_{HF} 1.8 ± 0.1 Hz. [r] 2.43 (br q, 2H, $C\underline{H}_2CH_3$), 1.15 (t, 3H, $CH_2C\underline{H}_3$). [s] 26.0 (t, $\underline{C}H_2CH_3$), 7.6 (q, $CH_2\underline{C}H_3$).

acetonitrile[11]. Generally, in apolar media the (2+2) cycloadducts, *i.e.* the *N,N*-dialkyl-4-nitro-1-cyclobuten--1-amines **14** are the major reaction products[13], whereas in a non-protic polar solvent, *viz.* acetonitrile, (4+2) cycloaddition predominates. The (4+2) cycloadducts, *i.e.* the nitronic esters **16**, which generally can neither be isolated nor detected, undergo a ring contraction to yield the four-membered cyclic nitrones **7–13** (Scheme 1). The introduction of a phenyl group as R^3 normally leads to a decrease in yields of the four-membered cyclic nitrones. This can be attributed to the destabilizing effect of a phenyl group at the sp^3-hybridized atom of the (aza)cyclobutene[26]. From earlier work in our laboratories it was known that the substituents R^1 and R^3 have a large influence on the stability of the four-membered cyclic nitrones. They are stabilized by R^1 in the order Ph > Me > H and by R^3 in the order Me > Ph > SMe[11].

All the new compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and in the case of crystalline materials by elemental analyses. However, in a number of cases it was not possible to obtain satisfactory elemental analysis data due to the thermal instability. For this reason the nitrones **7** and **8e,f,i,m,p** were characterized as the 1,3-dipolar cycloadducts of dimethyl acetylenedicarboxylate (DMAD)[27].

From previous work it was apparent that the *cis* four-membered cyclic nitrones (R^3 = Me; $NR^4R^5 = NEt_2$) exhibit a number of characteristic spectroscopic features[11]. The protons of the methyl groups of the diethylamino group ($NCCH_3$) are present as *two triplets* in the ^1H NMR spectrum. The double bond character of the *C–N* bond of the carbamoyl group is demonstrated by the absorption of the NCH_2 protons over a wide range (δ 4.5–2.0). Secondly, in the ^{13}C NMR spectra the *C=O of the carbamoyl* moiety absorbs at δ 163.0 ± 3.0 and *the methyl group at C-2* at δ 20.0 ± 0.5. These spectroscopic probes were used to determine the configuration of the four-membered cyclic nitrones **7–13** (Tables I and II).

The *first* group of nitroalkenes (**3**), which have different R^1 groups and in which R^2 is always an aryl group in which at least one of the *ortho* positions is unsubstituted, yielded the nitrones **7**, **8a-p**, **9a-k** and **10a-d** (Scheme 1 and Table I). The fact that *aldo*nitrones, compared to *keto*nitrones, are more reactive species that easily polymerize[2-4], and that the thermal stability of four-membered cyclic *aldo*nitrones decreases as compared to four-membered cyclic *keto*nitrones, explains the low yield of the aldonitrone **7**. Alkyl or phenyl substitution at C-4, *i.e.* the nitrones **8** and **9**, stabilizes the four-membered cyclic nitrones and higher yields are obtained. The reaction of the ynamines **6** and the nitro-

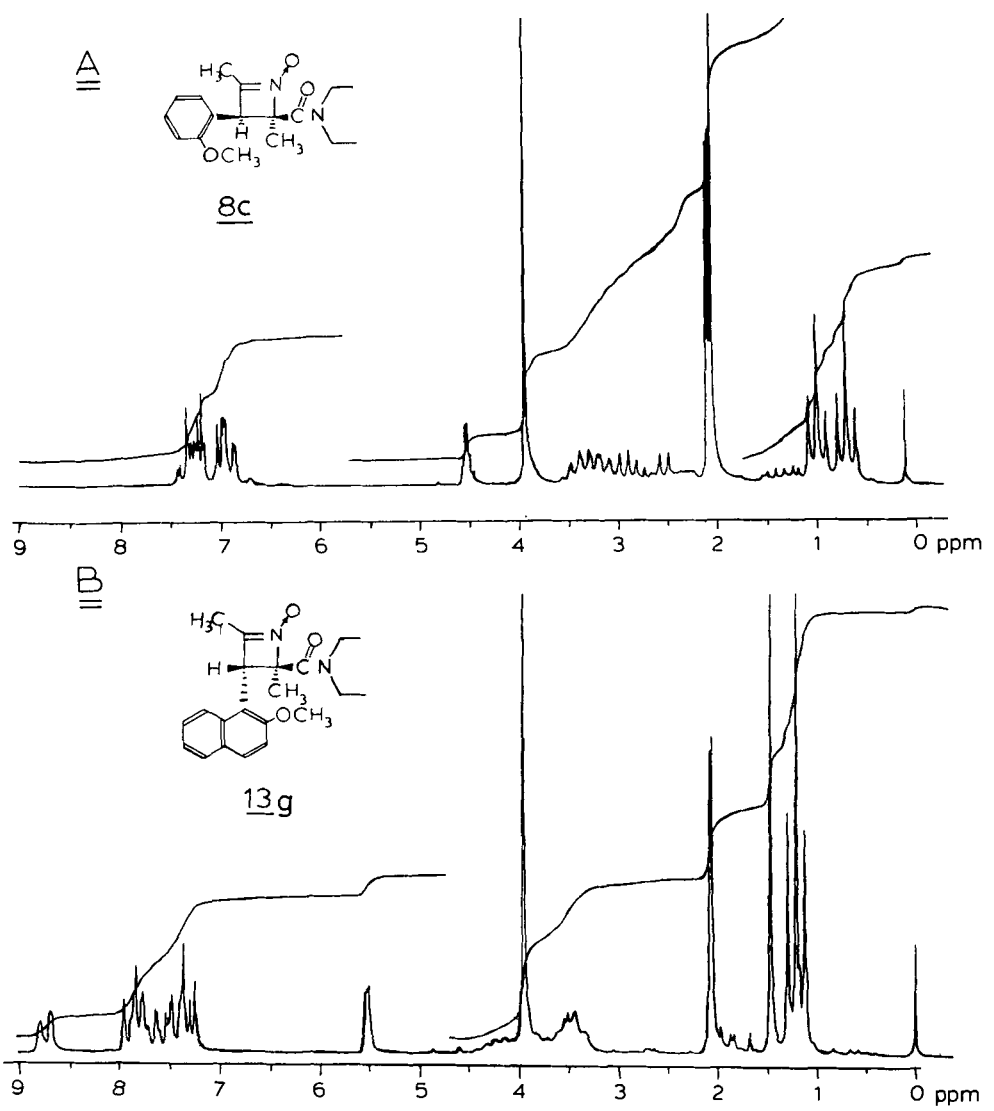


Fig. 1. A. ^1H *NMR spectrum of* **8c**.
B. ^1H *NMR spectrum of* **13g**.

Table II Physical and spectral properties of the trans *four-membered cyclic nitrones* **13**[a].

Comp.	M.p.[a] (°C)	Yield (%) CH_3CN	^1H NMR ($CDCl_3$) δ				^{13}C NMR ($CDCl_3$) δ							MS *(m/z)*		
			R^{1b}	H-3[b]	R^3 (s)	$NCCH_3$ (t)	C=O (s)	C-4 (s)	C-2 (s)	C-3 (d)	R^3 (q)	R^1 (q)	$NC\underline{C}H_3$ (q)	(Calcd.)	Exp.	Formula
13b	124–126	73	7.08(m)	5.17(t)[c]	1.59	1.20	166.1	138.6(d)	89.8	42.2	17.0	–	13.6 (br q)	(312.104)	312.103	$C_{15}H_{18}ClFN_2O_2$
13c	100–103.5	60	7.16(d)[c]	5.35(d)[c]	1.58	1.20	165.9	139.5(d)	88.5	44.9	16.2	–	14.4 + 12.4	(328.075)	328.077	$C_{15}H_{18}Cl_2N_2O_2$
13d	131.5–133	70	7.30(d)[c]	5.51(d)[c]	1.44	1.21	167.3	143.1(d)	89.8	42.0	16.7	–	14.4 + 12.5	(340.179)	340.179	$C_{20}H_{24}N_2O_3$
13e	115–125	66	2.07(m)	5.16(m)	1.55	1.19	167.0	149.7	88.0	45.4	16.0	11.3[d]	14.4 + 12.7	(326.120)	326.123	$C_{16}H_{20}ClFN_2O_2$
13f	125–129	53	2.10(d)	5.40(q)	1.59	1.19	167.1	150.1	88.1	47.9	14.7	12.9	14.4 + 12.9	(342.090)	342.087	$C_{16}H_{20}Cl_2N_2O_2$
13g	152–159	80	2.05(d)	5.50(q)	1.46	1.20	168.1	154.1	88.1	45.0	15.8	11.8	14.5 + 12.6	(354.194)	354.193	$C_{21}H_{26}N_2O_3$
13h	115–117	73	[f]	5.46(s)	1.51	1.19	167.1	148.2	87.7	45.5	15.0	[f]	14.6 + 12.5	(378.231)	378.233	$C_{24}H_{30}N_2O_2$
13i	131–135	85	[f]	5.55(d)[e]	1.66	1.19	167.1	148.2	87.5	43.4	16.2	[f]	14.3 + 12.6	(371.133)	371.135	$C_{21}H_{21}ClFN_2O$ ($M^+ - 17$)
13j	130–132	83	[f]	5.80(s)	1.70	1.19	167.1	148.2	87.7	45.5	15.0	[f]	14.5 + 12.5	(404.106)	404.106	$C_{21}H_{22}Cl_2N_2O_2$
13k	160–162	86	[f]	5.90(s)	1.57	1.22	167.8	151.6	88.0	42.6	16.0	[f]	14.5 + 12.6	(416.210)	416.215	$C_{26}H_{28}N_2O_3$

[a] Note 1; Satisfactory elemental analyses (%C ± 0.4) were obtained for **13b,e-k**. Compounds **13b,e,f,i** were recrystallized from chloroform/petroleum ether, **13g** from tetrachloromethane/diisopropyl ether, **13h** from diisopropyl ether/petroleum ether, **13j** from tetrachloromethane/petroleum ether mixtures and **13k** from diisopropyl ether, respectively. The melting points of the remaining nitrones were obtained after trituration of the crude solid with diisopropyl ether. [b] J 1.7 ± 0.1 Hz. [c] J 1.5 ± 0.1 Hz. [d] dq, J_{CF} 4.2 Hz. [e] J_{HF} 1.9 Hz. [f] Phenyl absorptions.

alkene **3p** in which a phenylthio moiety is present at the same carbon atom of the double bond as the nitro group, could be performed at −50°C, whereas normally the cycloaddition reaction in acetonitrile is performed at 0°C. The high reactivity of this nitroalkene might be due to the captodative properties[28]. Generally mono-substitution of the aryl group R^2 at the *ortho* position did not change the chemical yield of the corresponding four-membered cyclic nitrones.

The spectroscopic data of the nitrones **7**, **8a-p**, **9a-k**, **10a-d** are in accord with the above mentioned criteria for the *cis* stereochemistry. The coupling constant of 5.5 ± 0.1 Hz in the nitrones **9a,b** and **10a** between the protons at C-2 and C-3 is of a similar magnitude to that reported for protons in a *cis* relationship in 3-nitrocyclobutenes[13,29]. In addition, the upfield or downfield shifts caused by the variation of the substitution pattern can be used to assign the nitrone stereochemistry. The chemical shift of the proton at C-3 (H-3) of the *cis* four-membered cyclic nitrone **8a**[11] (R^1 = Me) is observed at δ 3.94. If R^1 is a phenyl group *i.e.* in the nitrone **9c**[11], the H-3 absorption is present at δ 4.27, which means a difference (Δδ) of +0.33 ppm. If R^1 is a phenylthio moiety, *i.e.* in the nitrone **10b**, the H-3 absorption is observed at δ 3.83, Δδ −0.11 ppm. These differences reflect the influence of the substituent R^1 (Me → Ph → PhS) on the chemical shift of H-3 of a four-membered cyclic nitrone in which R^2, R^3 and NR^4R^5 are not changed simultaneously. It is possible to compare the nitrones **8i**, **9i** and **10d** and the nitrones **8m** and **9k**, in a similar way. If the Δδ differences appear to be similar to those for **8a**, **9c** and **10b** then the stereochemistry is likely to be the same, because both **8i** and **8m** have the *cis* configuration as deduced from the NMR data of the corresponding DMAD cycloadducts[27]. The differences in the chemical shifts when the methyl group is substituted for a phenyl group or a methyl for a phenylthio moiety are for: **8i-9i**, Δδ +0.40; **8i-10d**, Δδ −0.04; **8m-9k**, Δδ +0.41 ppm. From these differences and the amide C=O absorptions in the ^{13}C NMR spectra *(vide supra)* we conclude that the nitrones **9i,k** and **10c** have the *cis* stereochemistry. As a representative of the four-membered cyclic nitrones with the *cis* stereochemistry, the ^1H NMR spectrum of compound **8c** is depicted in Fig. 1A.

The *second* group of nitroalkenes (**4**) that have different R^1 groups and in which R^2 is always an aryl group in which at least both *ortho* positions are substituted, yielded upon reaction with the ynamine **6c** the nitrones **13b-k** (Table II) in surprisingly high yields (53–86%). The reaction of **4a** and **6c** gave a complex mixture, from which the corresponding four-membered cyclic nitrone **13a** could not be isolated pure.

No (2 + 2) cycloadducts were obtained from these reaction mixtures. It is possible that the (2 + 2) cycloaddition might be hindered by the bulky R^2 group of the nitroalkene, which is probably perpendicular to the double bond, and thus might prohibit a transition state in which the double bond of the nitroalkene and the triple bond of the ynamine occupy perpendicular positions, necessary for a maximal orbital overlap to give a concerted (2 + 2) cycloaddition[30]. The formation of the six-membered nitronic ester ring is probably no problem, since the approach of the ynamine to the nitroalkene in a (4 + 2) cycloaddition is less sterically hindered, or the bond formation occurs via a stepwise process[11].

Mass spectrometry of the compounds **13** shows a parent peak with the expected composition of a 1:1 adduct of nitroalkene and ynamine. However, the ^1H NMR spectra of the compounds **13** are different from those of the corresponding four-membered cyclic nitrones **7–10**, also prepared from the ynamine **6c**, *i.e.* R^3 = Me, $NR^4R^5 = NEt_2$. Firstly, the protons of the carbamoyl methyl groups ($NCCH_3$) for the compounds **13** give a *single* triplet, whereas these groups for the four-membered cyclic nitrones **7–10** are always present as a double triplet (Fig. 1A). Secondly, the absorption of the methyl group at C-2 in the compounds **13** is shifted upfield with 0.5 ± 0.08 ppm compared with the *cis* nitrones prepared from ynamine **6c**. Thirdly, the proton at C-3 absorbs at low field (δ 5.16 – 5.90) compared with the H-3 absorptions for the nitrones **8b-f**, **8n,p**, **9d-g** and **10b** (δ 3.76–4.90). These observed differences in chemical shifts were tentatively explained by a different stereochemistry of the substituents at C-2 and C-3. The shielding effect of the aryl group may cause the observed upfield shift of the methyl group at C-2 and the deshielding effect of the carbamoyl moiety might be the reason for the large downfield shift of H-3. In the ^{13}C NMR spectra of compounds **13** the ring atoms C-2, C-3 and C-4 are observed at δ 87.5–89.8, δ 42.0–47.9 and δ 138.6–154.1, respectively. The chemical shifts of the carbamoyl and the methyl group at C-2 are present at δ 165.9–168.7 and δ 14.7–17.0, respectively.

Substantial evidence for the *trans*-stereochemistry of compounds **13** was provided by Nuclear Overhauser Enhancement (NOE) experiments with compounds **9a**, **9c**, **13g** and **13k**. The NOE effects of the R^3 substituent on H-3 were 1.15, 1.12, 1.05 and 1.06, respectively, which is an indication that in the first two compounds the magnetic influence of the substituent at C-2 on the proton at C-3 through space is larger than for the other two nitrones, therefore in the compounds **9a** and **9c** the substituent at C-2 is closer to H-3 than in the compounds **13g** and **13k**.

Ultimate proof for the *trans*-configuration of the nitrones **13** was obtained by the X-ray analysis of compound **13k** (Fig. 2 and Table III); the naphthalenyl moiety is at the same face of the ring as the methyl group at C-2. The bond angles of the four-membered ring N-1 (N19), C-2 (C20), C-3 (C11) and C-4 (C12), are for compound **8a**[10] 95.1°, 84.6°, 85.1° and 94.6° and for **13k** 95.1°, 84.0°, 85.8° and 94.8°, respectively. In both the four-membered cyclic nitrones the ring is nearly planar, *i.e.* a torsional angle (N19–C12–C11–C20) of 0.8° and 4.5° for **8a** and **13k** is found. In compound **13k** a torsional angle (C13–C12–N19–O) of 7.1° is found. The torsional angle of the phenyl ring at C-4 with the C=N double bond (C18–C13–C12–N19) is 4.3°. This indicates that there is substantial conjugation between the phenyl groups and the nitrone bond. In the *cis*-nitrone **8a** the torsional angle [H_3C–(C-4)–(N-1)–O] is 3.1°. As a representative of the four-membered cyclic nitrones with the *trans* stereochemistry, the ^1H NMR spectrum of compound **13g** is depicted in Figure 1B.

Hence, the four-membered cyclic nitrones **7–10** have the *cis* stereochemistry, and the compounds **13** are four-membered cyclic nitrones in which the substituents at C-2 and C-3 have a *trans* relationship.

Reaction of the *third* group of nitroalkenes **5** with ynamines **6** yielded bicyclic products, the structures of which depend on the ring size of the starting nitroalkenes (Chart 1 and Scheme 1). The reaction of 1-nitrocyclo*hexene* (**5b**) with *N,N*-diethyl-1-propyn-1-amine (**6c**) gave the four-membered cyclic nitrone **12**. The NMR data of **12** were different from those of the nitrone **11a** obtained from the reaction of the same ynamine with 1-nitrocyclo*octene* (**5c**)[11]. The ^{13}C NMR values for the amide C=O and the methyl group at C-2 are present at δ 168.3 and δ 16.0 for compound **12** and at δ 166.7 and δ 21.2 for compound **11a**, respectively. These ^{13}C NMR data of **11a** are in accord with the corresponding absorptions reported for **8a** (δ 165.4 and δ 19.9)[10,11]. On the basis of the X-ray data and the nearly identical ^{13}C NMR data of the amide C=O and the methyl group at C-2 we

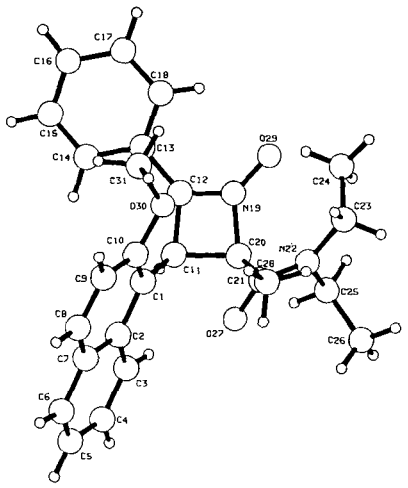


Fig. 2. X-Ray crystal structure of **13k**.

concluded that the nitrone **11a** has a *cis* configuration, whereas the nitrone **12**, annelated with the six-membered ring, has the *trans* configuration. For the nitrones **11a**[11] ($\delta_{H\text{-}3}$ 2.7–3.0) and **11b** ($\delta_{H\text{-}3}$ 3.60) a chemical shift difference ($\Delta\delta$) of 0.6–0.9 ppm, was found which is comparable with the chemical shift difference $\Delta\delta = 0.74$ of the *cis* four-membered cyclic nitrones **8a**; ($\delta_{H\text{-}3}$ 3.94) and **8i** ($\delta_{H\text{-}3}$ 4.68). The ^{13}C absorption of amide C=O of the nitrone **11b** is present at δ 166.4, which is within the range of the amide C=O absorptions of all the nitrones that have *cis* stereochemistry.

Marcelis et al.[12] also isolated *trans* four-membered cyclic nitrones upon reaction of *N,N*-diethyl-1-propyn-1-amine (**6c**) and nitropyrimidine derivatives.

Reaction of 1-nitrocyclo*pentene* (**5a**) with ynamine **6g** in petroleum ether did not give a four-membered cyclic nitrone. The solid that precipitated from the reaction mixture could not be characterized by ^1H NMR spectroscopy, because of very broad lines. This compound was refluxed in chloroform for 3 h and the isoxazoline derivative **19** was isolated in 65% yield. We attribute the formation of isoxazoline **19** to a homolytic cleavage of the N–O bond in the intermediate (4 + 2) cycloadduct **17** (Scheme 2)[11]. In the ^1H NMR spectrum of **19** the absorption at δ 4.91, which shows coupling with two non-equivalent hydrogen atoms (J 11 and 8 Hz), and absorptions in the ^{13}C NMR spectrum at δ 169.1 (C=N) and δ 94.7 (C-3) are in good agreement with the reported absorptions of 3,3a-dihydrobenzofuro[3,2-*c*]-isoxazoles and 3a,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isoxazoles formed in similar reactions of ynamines **6** with 3-nitrobenzofuran[10] and 1-nitrocyclopentene[11], respectively. The stereochemistry of **19** was established by X-ray analysis. The unit cell contains two independent molecules with the same conformation (Fig. 3 and Table IV).

The isoxazoline that is formed is the thermodynamically most stable compound, *i.e.* the annelated ring and the large carbamoyl moiety are *trans*. The average torsional angles between H-3a (H1 and H21) and the protons at C-4 (C2 and C22) are −160° and −42°. These values lead to coupling constants of 8.5 and 3.0 Hz upon substitution in the *Karplus* equation[31].

Ring contraction of the (4 + 2) cycloadduct

As expected the initially formed (4 + 2) cycloadduct, *i.e.* the nitronic esters **16**, could generally not be isolated because in nearly all cases the (4 + 2) cycloaddition is followed immediately by ring contraction, which involves the cleavage of a weak N–O bond and simultaneous formation of a carbonyl group. The latter is the driving force since it will compensate for the formation of the strained four-membered ring. The concerted stereoselective formation of *cis* or *trans*

Table III Positional parameters and their estimated standard deviations of compound **13k**.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
O27	0.7171(2)	0.02194(7)	0.3559(3)	C31	0.8850(3)	0.2598(1)	0.2891(5)
O29	0.9867(2)	0.13637(8)	0.6485(3)	H3	0.630(3)	0.057(1)	0.079(3)
O30	0.8252(2)	0.21324(7)	0.3073(3)	H4	0.454(3)	0.030(1)	−0.131(4)
N19	0.9230(2)	0.12366(8)	0.5027(3)	H5	0.332(3)	0.084(1)	−0.312(4)
N22	0.8236(2)	0.02397(8)	0.6262(3)	H6	0.379(3)	0.169(1)	−0.277(4)
C1	0.7160(2)	0.14700(9)	0.1571(3)	H8	0.502(3)	0.234(1)	−0.132(4)
C2	0.6111(3)	0.1293(1)	0.0283(3)	H9	0.668(2)	0.261(1)	0.084(3)
C3	0.5803(3)	0.0799(1)	0.0044(4)	H11	0.810(2)	0.0855(8)	0.202(3)
C4	0.4783(3)	0.0644(1)	−0.1195(4)	H14	0.981(3)	0.136(1)	0.036(4)
C5	0.4009(3)	0.0974(2)	−0.2253(4)	H15	1.165(3)	0.170(1)	−0.061(4)
C6	0.4271(3)	0.1448(1)	−0.2081(4)	H16	1.349(3)	0.201(1)	0.127(4)
C7	0.5313(3)	0.1624(1)	−0.0817(4)	H17	1.348(3)	0.202(1)	0.418(4)
C8	0.5561(3)	0.2119(1)	−0.0598(4)	H18	1.160(3)	0.168(1)	0.518(4)
C9	0.6517(3)	0.2286(1)	0.0670(4)	H23A	0,870(2)	0.0831(9)	0.771(3)
C10	0.7315(3)	0.1964(1)	0.1757(3)	H23B	0.843(2)	0.037(1)	0.872(3)
C11	0.8088(3)	0.11187(9)	0.2650(3)	H24A	1.074(4)	0.053(1)	0.936(5)
C12	0.9435(3)	0.1300(1)	0.3479(3)	H24B	1.042(3)	0.002(1)	0.834(4)
C13	1.0565(3)	0.1503(1)	0.2889(4)	H24C	1.074(4)	0.052(1)	0.737(5)
C14	1.0595(3)	0.1503(1)	0.1162(4)	H25A	0.882(3)	−0.040(1)	0.727(4)
C15	1.1660(3)	0.1686(1)	0.0564(4)	H25B	0.806(3)	−0.045(1)	0.528(4)
C16	1.2733(3)	0.1875(2)	0.1683(5)	H26A	0.668(3)	−0.077(1)	0.700(5)
C17	1.2716(3)	0.1881(2)	0.3385(5)	H26B	0.665(4)	−0.025(2)	0.807(5)
C18	1.1645(3)	0.1694(1)	0.4005(4)	H26C	0.595(3)	−0.029(1)	0.606(4)
C20	0.7870(3)	0.10010(9)	0.4500(3)	H28A	0.673(3)	0.161(1)	0.481(4)
C21	0.7766(3)	0.0453(1)	0.4772(4)	H28B	0.593(3)	0.112(1)	0.459(4)
C23	0.8886(3)	0.0476(1)	0.7813(4)	H28C	0.684(3)	0.124(1)	0.638(4)
C24	1.0361(4)	0.0378(2)	0.8249(5)	H31A	0.964(3)	0.259(1)	0.381(4)
C25	0.8014(4)	−0.0283(1)	0.6398(4)	H31B	0.910(3)	0.266(1)	0.177(4)
C26	0.6714(4)	−0.0402(1)	0.6909(6)	H31C	0.818(3)	0.287(1)	0.312(4)
C28	0.6762(3)	0.1267(1)	0.5138(4)				

four-membered cyclic nitrones is most likely governed by the stereochemistry of the initial (4 + 2) cycloadduct. Ring contraction will give either *cis* four-membered cyclic nitrones, as the kinetic products, or *trans* four-membered cyclic nitrones, which are the thermodynamically most stable compounds. This supposition is supported by the observation that homolytic N–O bond scission, followed by diradical recombination gave the *trans* isoxazoline derivatives *(vide supra).*

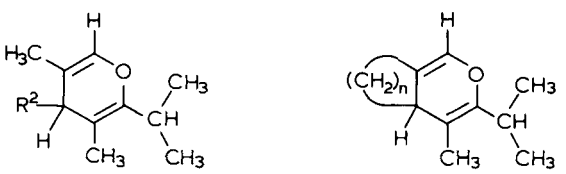
Previously[11] we explained the stereoselective ring contraction of the nitronic esters **16** to yield the four-membered cyclic nitrones in terms of the *Woodward–Hoffmann* symmetry rules. In view of our new results we prefer to explain the stereoselective ring contraction of the intermediate cyclic nitronic ester **16** in a simpler way. The heteroatoms in **16** render it difficult for us to predict the nodal planes of the molecular orbitals that are involved in a concerted process. The fact that the conformation of the nitronic ester depends on the size of R^2, depicted in a simple way in Scheme 3, was supported by molecular mechanics calculations in simple model systems.

(a) Boat conformation. Substituted 1,4-cyclohexadienes prefer a boat conformation[32]. Therefore, if the nitronic ester also prefers a boat conformation, R^2 will be in the axial position at the *same* face of the ring as the ring oxygen atom. Ring contraction, *i.e.* C–N bond formation from the *sterically less hindered bottom side of the ring*, and extrusion of the ring oxygen atom by an S_N2 type of substitution, will yield *cis* four-membered cyclic nitrones.

(b) Envelope conformation. If in R^2 the aryl ring is substituted at both *ortho* positions, it is possible that in a boat conformation the *Vander Waals* radii of the *ortho* substituents enter the *Vander Waals* sphere of the ring oxygen atom. This will cause repulsion, and the oxygen is pushed in the plane of the ring to give an envelope-type conformation. Due to the fact that the oxygen atom is in the planar part of the envelope conformation, ring contraction might result in an extrusion of the oxygen atom in such a way that both *cis* or *trans* four-membered cyclic nitrones can be formed. In this case the energy content of the product will govern the concerted ring contraction and the thermodynamically more stable *trans* four-membered cyclic nitrones will be formed.

In order to obtain some information about the stereochemistry of the nitronic ester intermediate **16** we have performed Chem-X calculations (MM2P)[33]. Since the program did not contain all parameters of the heteroatomic bonds and torsional angles we have simplified the structure; calculations were performed on the substituted 4*H*-pyran derivatives **20** and **21**. These calculations revealed that the conformation of the pyran ring depends on the substitution pattern of the phenyl ring. Firstly, if R^2 = phenyl (**20a**), the boat conformation is preferred over a chair conformation. Secondly, the phenyl group prefers a pseudo-axial position over a pseudo-equatorial position, to minimize steric hindrance with both the methyl groups at C-3 and C-5.

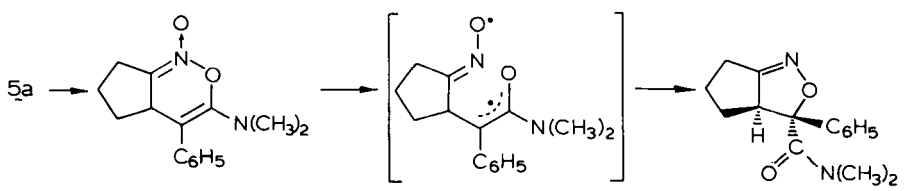
When R^2 = 2,6-dimethylphenyl (**20b**), the calculations show that also in this case the aryl moiety prefers a pseudo-axial position, but the *ortho*-methyl substituents of the aryl moiety push the ring oxygen atom out of the boat conformation coplanar with the double bonds of the ring (envelope conformation). The same is observed when an eight- or a six-



20a $R^2 = C_6H_5$ 21a n = 6

20b $R^2 = 2,6\text{-}(CH_3)_2C_6H_3$ 21b n = 4

Chart 2



17 18 19

Scheme 2

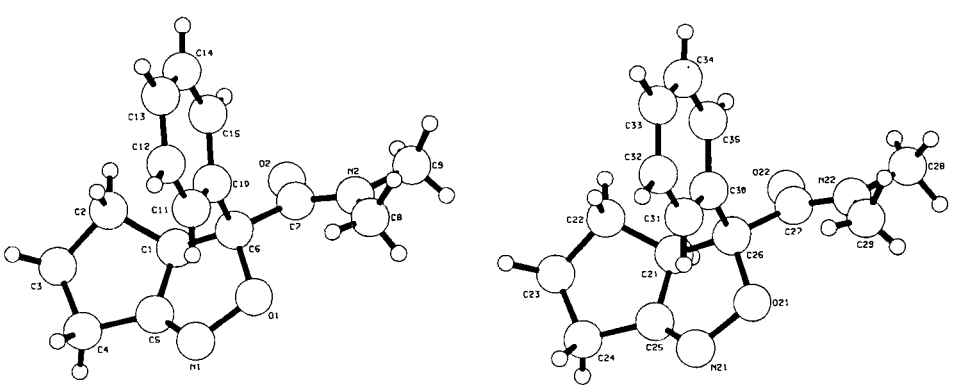


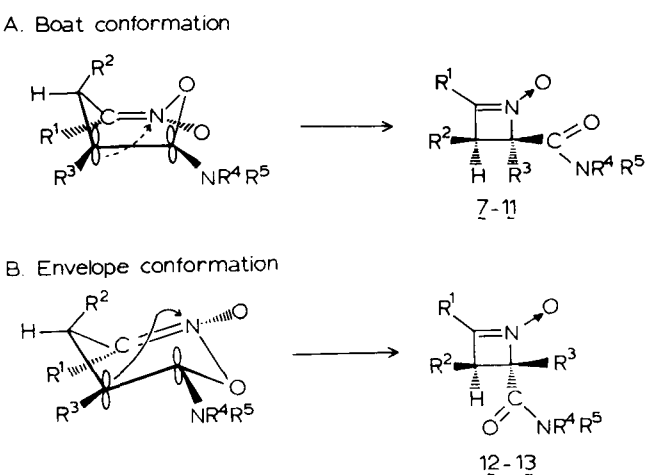
Fig. 3. X-Ray crystal structure of **19**.

Table IV Positional parameters and their estimated standard deviations of compound **19**.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
O1	0.9434(1)	0.1059(2)	0.3724(1)	C35	0.3552(2)	0.2961(3)	0.3090(2)
O2	1.0652(1)	0.3297(2)	0.4781(1)	H1	1.054(1)	0.267(2)	0.324(2)
O21	0.3104(1)	−0.0281(2)	0.3399(2)	H2A	0.913(2)	0.386(3)	0.226(2)
O22	0.1637(1)	0.1626(2)	0.2397(1)	H2B	0.999(2)	0.448(3)	0.259(2)
N1	0.9441(2)	0.0724(2)	0.2787(2)	H3A	0.964(1)	0.363(2)	0.094(2)
N2	0.9843(2)	0.2209(3)	0.5495(2)	H3B	0.056(2)	0.333(3)	0.151(2)
N21	0.3135(2)	−0.0664(3)	0.4327(2)	H4A	0.576(2)	0.666(3)	0.394(2)
N22	0.2544(2)	0.0884(3)	0.1637(2)	H4B	0.483(2)	0.635(3)	0.375(2)
C1	0.9964(2)	0.2679(3)	0.3026(2)	H8A	0.430(2)	0.432(3)	0.072(2)
C2	0.9729(2)	0.3713(3)	0.2354(2)	H8B	0.618(2)	0.634(3)	0.003(2)
C3	0.9951(2)	0.3224(3)	0.1476(2)	H8C	0.385(2)	0.322(4)	−0.902(3)
C4	0.9766(2)	0.1861(3)	0.1460(2)	H9A	0.920(2)	0.692(3)	0.368(2)
C5	0.9735(2)	0.1604(3)	0.2434(2)	H9B	0.553(2)	0.318(3)	0.169(2)
C6	0.9534(2)	0.2380(3)	0.3808(2)	H9C	0.001(3)	0.706(4)	0.322(3)
C7	1.0063(2)	0.2647(3)	0.4745(2)	H11	0.694(1)	0.666(2)	0.193(2)
C8	0.9155(2)	0.1444(4)	0.5525(2)	H12	0.813(2)	0.763(3)	0.216(2)
C9	1.0332(2)	0.2505(4)	0.6382(2)	H13	0.677(2)	0.468(3)	0.326(2)
C10	0.8727(2)	0.2997(3)	0.3698(2)	H14	0.799(2)	0.560(3)	0.405(2)
C11	0.8028(2)	0.2441(3)	0.3268(2)	H15	0.917(2)	0.456(3)	0.430(2)
C12	0.7314(2)	0.3081(4)	0.3118(2)	H21	0.187(2)	0.110(3)	0.390(2)
C13	0.7292(2)	0.4260(4)	0.3380(2)	H22A	0.317(2)	0.251(3)	0.486(2)
C14	0.7984(2)	0.4811(4)	0.3813(2)	H22B	0.221(2)	0.292(3)	0.462(2)
C15	0.8696(2)	0.4184(3)	0.3978(2)	H23A	0.776(2)	0.290(4)	0.127(2)
C21	0.2444(2)	0.1165(3)	0.4124(2)	H23B	0.823(3)	0.840(6)	0.433(4)
C22	0.2591(2)	0.2199(4)	0.4808(2)	H24A	0.826(2)	0.494(4)	0.107(3)
C23	0.2445(3)	0.1635(5)	0.5692(2)	H24B	0.735(2)	0.522(4)	0.085(3)
C24	0.2703(2)	0.0319(4)	0.5676(3)	H28A	0.326(2)	0.531(4)	0.445(3)
C25	0.2761(2)	0.0117(3)	0.4695(2)	H28B	0.343(2)	0.674(4)	0.421(3)
C26	0.2877(2)	0.1006(3)	0.3328(2)	H28C	0.271(2)	0.635(4)	0.464(2)
C27	0.2299(2)	0.1186(3)	0.2400(2)	H29A	0.133(2)	0.534(3)	0.290(2)
C28	0.2003(2)	0.1110(4)	0.0773(2)	H29B	0.176(3)	0.464(4)	0.368(3)
C29	0.3307(2)	0.0308(4)	0.1585(3)	H29C	0.141(3)	0.580(5)	0.384(3)
C30	0.3622(2)	0.1788(3)	0.3420(2)	H31	0.060(2)	0.560(2)	0.090(2)
C31	0.4363(2)	0.1391(3)	0.3876(2)	H32	0.945(2)	0.681(3)	0.067(2)
C32	0.5025(2)	0.2154(4)	0.4007(2)	H33	0.545(2)	0.388(3)	0.379(2)
C33	0.4948(2)	0.3313(4)	0.3676(2)	H34	0.411(2)	0.450(3)	0.296(2)
C34	0.4213(2)	0.3713(3)	0.3217(2)	H35	0.305(2)	0.423(3)	0.277(2)

membered ring is annelated to the pyran moiety, *i.e.* the compounds **21a** and **21b**. In **21a** the pyran ring prefers the boat conformation, but annelation with the six-membered ring in **21b** forces the pyran oxygen in the plane of the pyran double bonds to give the envelope conformation, whereas the cyclohexane ring prefers a chair conformation. Hence, the results of these molecular mechanics calculations on these simple models support the proposed conformations of the nitronic ester **16** (Scheme 3).

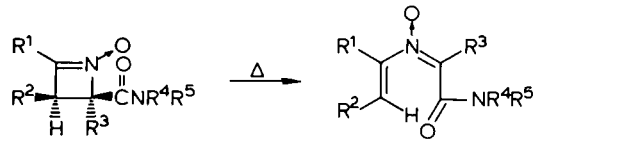
In order to estimate the limits of the effect of the *ortho* substituents in R^2 we prepared the nitroalkenes **4b**, **4e** and **4i** in which the aryl group is *ortho* substituted by Cl and F. Reaction of **4b** and **4e** with **6c** yielded the *trans* four-membered cyclic nitrones **13b** and **13e**, respectively. However, from the reaction of **4i** and **6c** both of the *cis* four-membered cyclic nitrone **9g** and the *trans* four-membered cyclic nitrone **13i** were obtained in a 1:1 ratio. The stereochemistry of the compounds was assigned on the basis of the NMR criteria mentioned above.



Scheme 3

Thermal isomerization of the trans *four-membered cyclic nitrones* **13**

Previously[34], we observed that the *cis* four-membered cyclic nitrones underwent a thermal rearrangement reaction to yield *N*-vinyl-*C*-carbamoylnitrones **22** (Scheme 4). The *trans* four-membered cyclic nitrones **13** appeared to be far more stable. The ^{1}H NMR spectrum of the *trans* four-membered



7-10 22 R^1 = H; R^2 = R^3 = C_6H_5; NR^4R^5 = $N(CH_2CH_2)_2O$

Scheme 4

cyclic nitrone **13f** does *not* change even upon heating for 6 d at 80°C, whereas the *cis* four-membered cyclic nitrone **8a** rearranges to the extent of 65% within 24 h at 0°C. The thermal ring opening of the azacyclobutene system of the *cis* four-membered cyclic nitrones only affords isomer **22** as a result of an outward rotation of the phenyl moiety (R^2) and the R^3 substituent. The *trans* four-membered cyclic nitrones might be more stable due to the *trans* relationship of the bulky R^2 group and the large carbamoyl moiety.

Conclusions

The stereochemistry of the four-membered cyclic nitrones **7–13** obtained from the reaction of the nitroalkenes **3–5** and the ynamines **6** depends on the substitution pattern in R^2 or on the ring size of the starting nitroalkenes. Generally, di-*ortho* substitution in R^2 leads to the formation of *trans* four-membered cyclic nitrones (**13**), whereas in the other cases *cis* four-membered cyclic nitrones (**7–10**) are obtained. The only exception to this rule that we have found is the reaction of the ynamine **6c** and the nitroalkene **4i** in which R^2 is a 2-F, 6-Cl-C_6H_3 moiety, which yielded a 1:1 mixture of *cis* and *trans* four-membered cyclic nitrones **9g** and **13i**.

Experimental

The melting points were determined using a Reichert melting point apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded using a Bruker WP-80 spectrometer and a Nicolet NT 200-WB spectrometer, respectively. The NMR spectra were recorded in $CDCl_3$ and using tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained using a Varian MAT 311A spectrometer and IR spectra using a Perkin-Elmer 257 spectrophotometer. X-Ray data of **13k** and **19** were obtained using an Enraf-Nonius CAD4 and a Philips PW1100 diffractometer, respectively. Elemental analyses were carried out by *E. Hoogendam* and *A. Christenhusz* of the Laboratory of Chemical Analysis at the University of Twente.

Materials

Nitroalkanes **1d**[16] and **1e**[17,18] were prepared according to the literature. The nitroalkenes (R^1 = H) were prepared according to ref. 19. The nitroalkenes (R^1 = alkyl, benzyl and phenyl) were prepared upon addition of the corresponding nitroalkane **1** to the *n*-butyl *Schiff* base of the corresponding aldehyde in glacial acetic acid, according to refs. 20 and 21. For specific literature references on nitroalkenes **3–5**, see Chart 1. The ynamines **6** were prepared according to the reports of *Brandsma*[24] and *Ficini*[25a]. Petroleum ether refers to the fraction boiling at 60–80°C. Mass spectra were calculated for ^{35}Cl and ^{79}Br, respectively.

1-Aryl-2-nitro-1-alkenes **3p** *and* **4**

(Z)-[2-Nitro-2-(phenylthio)ethenyl]benzene (**3p**). To a solution of [(nitromethyl)thio]benzene[18] (32 g, 0.19 mol) in glacial acetic acid (25 ml; dried over $CuSO_4$) *N*-(phenylmethylene)-1-butanamine (32 g, 0.20 mol) was added dropwise at 0°C. The reaction mixture was stirred for about 1 h, then the mixture was poured onto crushed ice (500 ml). The water phase was extracted with chloroform (3 × 150 ml). The combined organic layers were dried, filtered and **3p** was obtained as a yellow solid after evaporation of the solvent under vacuum; yield 56%. M.p. 65–67°C. IR (KBr): 1600 (C=C), 1520 (NO_2) cm^{-1}. ^{1}H NMR: δ 8.57 (s, 1H, CH), 8.1–7.9 (m, 2H, PhH-2,6), 7.5–7.2 (m, 8H, PhH). ^{13}C NMR: δ 144.9 (s, CNO_2), 142.6 (d, =CH), 132.1 and 130.1 (s, PhC-1 and SPh–C1). MS: accurate mass theor. 257.051 for $C_{14}H_{11}NO_2S$; exp. 257.044.

(E)-1,3,5-Trimethyl-2-(2-nitroethenyl)benzene (**4a**) was obtained in a yield of 67%. M.p. 123.5–125°C dec (methanol). IR (KBr): 1500, 1345 (NO_2) cm^{-1}. ^{1}H NMR: δ 8.26 [d, 1H, *J* 13.9 Hz, H(NO_2)C=], 7.28 (d, 1H, *J* 13.9 Hz, =CH), 6.94 (s, 2H, ArH), 2.38 and 2.30 (s, 9H, CH_3C-1, CH_3C-3 and CH_3C-5). ^{13}C NMR: δ 140.8 (s, C-1 and C-3), 139.6 (d, CNO_2), 138.4 (s, C-5), 136.4 (d, =CH), 129.9 (d, ArCH), 125.7 (s, C-2), 21.5 and 21.2 (q, $\underline{C}H_3$C-1, $\underline{C}H_3$C-3 and $\underline{C}H_3$C-5). MS: accurate mass theor. 191.095; exp. 191.093. Anal. calcd. for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32; found: C 69.04, H 6.75, N 7.21%.

(E)-2-Methoxy-1-(2-nitroethenyl)naphthalene (**4d**). Yield 62%. M.p. 142–145°C (diethyl ether/petroleum ether). IR (KBr): 1560, 1315 (NO_2). ^{1}H NMR: δ 8.77 [d, 1H, *J* 13.3 Hz, H(NO_2)C=], 8.08 (d, 1H, *J* 13.3 Hz, =CH), 8.1–7.1 (m, 6H, ArH), 4.06 (s, 3H, OCH_3). ^{13}C NMR: δ 158.9 (s, C-2), 140.1 [d, H(NO_2)$\underline{C}$=], 1343 (d, =CH), 133.3 and 128.9 (s, C-4a and C-8a), 111.5 (s, C-1), 56.2 (q, OCH_3). MS: accurate mass theor. 229.074; exp. 229.075 Anal. calcd. for $C_{13}H_{11}NO_3$ (229.24): C 68.11, H 4.84, N 6.11; found: C 67.94, H 4.79, N 6.04%.

(E)-1-Choro-3-fluoro-2-(2-nitro-1-propenyl)benzene (**4e**). Yield 53%. M.p. 49–52°C. IR (KBr): 1520, 1340 (NO_2) cm^{-1}. ^{1}H NMR: δ 7.82 (br s, 1H, =CH), 7.6–6.9 (m, 7H, PhH and ArH), 2.18 (dd, 3H, J_{HF} 2.8 Hz and J_{HH} 1.0 Hz). ^{13}C NMR: δ 159.5 (d, J_{CF} 275.9 Hz, C-3), 151.5 (s, CNO_2), 135.0 (d, J_{CF} 4.4 Hz, C-1), 131.5 (dd, J_{CF} 13.7 Hz, C-5), 125.7 (dd, J_{CF} 3.8 Hz, =CH), 124.5 (d, C-6), 120.2 (dd, J_{CF} 18.0 Hz, C-2), 114.7 (dd, J_{CF} 22.5 Hz, C-4), 14.7 (dq, J_{CF} 4.7 Hz). MS: accurate mass theor. 215.015 for $C_9H_7ClFNO_2$; exp. 215.014.

(E)-1-Chloro-3-fluoro-2-(2-nitro-2-phenylethenyl)benzene (**4i**). Yield 72%. M.p. 113–115°C subl. (methanol). IR (KBr): 1530, 1330 (NO_2) cm^{-1}. ^{1}H NMR: δ 7.96 (s, 1H, =CH), 7.5–7.0 (m, 7H, PhH and ArH), 7.0–6.6 (m, 1H, ArH-4). ^{13}C NMR: δ 159.2 (d, *J* 254.8 Hz, C-3), 154.7 (s, CNO_2), 134.3 (d, *J* 5.5 Hz, C-1), 131.1 (dd, *J* 13.7 Hz, C-5), 120.6 (d, *J* 13.7 Hz, C-2), 114.2 (dd, *J* 21.7 Hz, C-4). MS: accurate mass theor. 277.031 for $C_{14}H_9ClFNO_2$; exp. 277.027. Anal. calcd. for $C_{14}H_9ClFNO_2$ (277.68): C 60.56, H 3.27, N 5.04; found: C 60.30, H 3.27, N 4.89%.

(E)-2-Methoxy-1-(2-nitro-2-phenylethenyl)naphthalene (**4k**) was prepared in a yield of 92%. M.p. 99–114°C (ethanol). IR (KBr): 1520, 1320 (NO_2) cm^{-1}. ^{1}H NMR: δ 8.45 (s, 1H, CH), 7.85–6.90 (m, 11H, ArH), 3.52 (s, 3H, OCH_3). ^{13}C NMR: δ 154.2 (s, C-2), 153.1 (s, CNO_2), 131.8 (d, =CH), 131.2, 129.7 and 128.0 (s, PhC-1, C-4a and C-8a), 114.3 (s, C-1), 55.4 (q, OCH_3). MS: accurate mass theor. 305.105; exp. 305.104. Anal calcd. for $C_{19}H_{15}NO_3$ (305.33): C 74.74, H 4.95, N 4.59; found: C 74.99, H 5.17, N 4.46%.

1-(1-Butynyl)-3,3-dimethylazetidine (**6f**)

Addition of the lithium salt of 3,3-dimethylazetidine[41] to 1-ethoxy-1-butyne as described for the synthesis of **6e** by *Brandsma* and co-worker[24], yielded **6f** in a yield of 40%; b.p. 50–53°C (5 mmHg); n_D^{23} 1.4580. ^{1}H NMR: δ 3.52 (s, 4H, NCH_2), 2.22 (q, 2H, *J* 7.3 Hz, $C\underline{H}_2CH_3$), 1.22 (s, 6H, CH_3), 1.09 (t, 3H, *J* 7.3 Hz, $CH_2C\underline{H}_3$). ^{13}C NMR: δ 87.0 (s, N–C≡), 69.1 (t, NCH_2), 62.1 (s, ≡$\underline{C}$–CH_2CH_3), 32.3 (s, C-3), 26.5 (q, CH_3), 15.6 (q, $CH_2\underline{C}H_3$), 12.9 (t, $\underline{C}H_2CH_3$).

General procedure for the synthesis of the four-membered cyclic nitrones **7–13**

A solution of the ynamine **6** (5.5 mmol) in dry acetonitrile (10 ml), was added dropwise to a stirred solution of the nitroalkenes **3–5** (5.0 mmol) in the same solvent (10 ml) at 0°C in a nitrogen atmosphere. After the addition of the ynamine solution was complete the reaction mixture was stirred for an additional hour at 0°C, and subsequently allowed to reach room temperature. In most cases the reaction was complete after an additional 3–5 h stirring at room temperature. The reaction mixture was concentrated under reduced pressure at a temperature <25°C. Usually the four-membered cyclic nitrones crystallized from the reaction mixture spontaneously. Otherwise the nitrones solidified upon addition of diisopropyl ether. The four-membered cyclic nitrones **7–13** were purified by trituration with diisopropyl ether. In some cases the nitrocyclobutenes **14** were isolated from the filtrate[13]. The yields, the ^{1}H-, ^{13}C-NMR, and MS data of the four-membered cyclic nitrones **7–11**, and **13** are given in Tables I and II, respectively. X-Ray data of the nitrone **13k** are presented in Table III.

*4a,5,6,7-Tetrahydro-*N,N*-dimethyl-4-phenylcyclopent[c][1,2]oxazine-3-amine 1-oxide* (**17**)

After the mixture of **5a** (1.13 g, 10.0 mmol) and **6g** (1.60 g, 11.0 mmol) was stirred for 5 h in tetrachloromethane the tan precipitate formed, was filtered off, yield 38%. M.p. 110–113°C (crude crystals). Because of thermal instability **17** could not be purified further. IR (KBr): 1640, (C=N) and (C=C) cm^{-1}. NMR spectra could not be taken because of the radical species present. MS: accurate mass theor. 258.127 for $C_{15}H_{18}N_2O_2$; exp. 258.135.

*3a,4,5,6-Tetrahydro-*N,N*-dimethyl-3-phenyl-3*H*-cyclopent[c]isoxazole-3-carboxamide* **19**)

Nitronic ester **17** (0.47 g, 3.0 mmol) was dissolved in chloroform (15 ml) and refluxed for 3 h. The colour of the solution changed from dark red to yellow. Subsequently, the solvent was removed under reduced pressure and the residue was purified by column chromatography (Al_2O_3; petroleum ether, the polarity of the eluent was gradually increased by the addition of diethyl ether) affording **19**, yield 65%. M.p. 99–100°C (petroleum ether). IR (KBr): 1640 (C=O), 1400 (N–O) cm^{-1}. ^{1}H NMR: δ 7.3 (s, 5H, PhH), 4.90 (dd, 1H, *J* 11 Hz, *J* 8 Hz, H-3a), 2.96 and 2.76 [s, N(CH_3)$_2$], 2.7–1.5 (m, 6H, CH_2). ^{13}C NMR: δ 171.7 (s, C=O), 169.1 (s, C=N), 137.7 (s, Ph C-1), 94.7 (s, C-3), 63.9 (d, C-3a), 37.8 and 36.9 [q, N(CH_3)$_2$], 28.6, 25.7 and 21.5 (t, CH_2). MS: accurate mass theor. 258.137 for $C_{15}H_{13}N_2O_2$; exp. 258.135.

4-[Phenyl[(2-phenylethenyl)imino]acetyl]morpholine N*-oxide* (**22**)

The ^{1}H- and ^{13}C NMR spectra of *(cis)-4-[(2,3-dihydro-2,3-diphenyl-2-azetyl)carbonyl]morpholine* N*-oxide* (**7**) were recorded in chloroform-*d*. This solution was left overnight at room temperature to afford **22**. M.p. 152–155°C (benzene/diisopropyl ether). IR (KBr): 1540 cm^{-1}. ^{1}H NMR: δ 7.33 and 7.08 (AB, 2H, J_{AB} 13 Hz, HC=CH), 7.5–7.2 (m, 10H, PhH), 3.6–3.0 (m, 8H, CH_2). ^{13}C NMR: δ 159.0 (s, C=O), 137.7 (s, C=N), 135.7 and 133.9 (s, PhC-1), 130.8 (d, PhCH), 115.8 (d, =CH), 65.8 (t, OCH_2), 47.8 (t, NCH_2). MS: accurate mass theor. 336.147; exp. 336.147. Anal. calcd. for $C_{20}H_{20}N_2O_3$ (336.39): C 71.41, H 5.99, N 8.33; found: C 71.26, H 5.91, N 8.21%.

X-Ray crystal structure analysis of **13k** *and* **19**

Crystals of **13k** belong to the monoclinic space group $P2_1/c$, with cell constants: a = 10.200(5), b = 27.625(8), c = 8.014(5) Å, β = 100.45(5)°, Z = 4, d_c = 1.240 g·cm^{-3}. Data were collected at 293(2) K, MoKα radiation, graphite monochromator, θ–2θ scan, 3 < θ < 25°, scan width (θ) 1.3 + 0.3 tgθ. The refinement of the crystal structure is based upon 1895 reflections with $I > 3\sigma(I)$.
Crystals of **19**, containing two independent molecules in the unit cell belong also to the monoclinic space group $P2_1/c$, with cell constants: a = 16.944(7), b = 11.079(6), c = 14.976(7) Å, β = 101.21(6)°, Z = 8, d_c = 1.312 g·cm^{-3}. Data were collected at 293(2) K, MoKα radiation, graphite monochromator, θ–2θ scan, 3 < θ < 25°, scan width (θ) 1.4°. The refinement of the crystal structure is based upon 2298 reflections with $I > 3\sigma(I)$.
The X-ray structures were solved by direct methods[44]. Calculations were done using the SDP package[45]. Parameters refined were scale factor, extinction parameter, positional and anisotropic thermal parameters for the non hydrogen atoms; positional and isotropic thermal parameters for the hydrogen atoms. Hydrogen atom positions were found from difference Fourier synthesis. The final weighted R factors were 3.6% for 393 variables for **13k** and 3.7% for 487 variables for **19**, respectively.

Acknowledgements

We are indebted to Dr. *R. Visser* for recording the N.O.E. experiments and Dr. *P. D. J. Grootenhuis* for his advise concerning Chem-X calculations. We also wish to thank Mr. *T. W. Stevens* for recording the mass spectra and Mrs. *J. M. Visser* and Mrs. *J. L. M. Vrielink* for recording the NMR and IR spectra. This investigation was supported by the Netherlands Technology Foundation [STW, Future Technology Science Branch of the Netherlands Organisation for the Advancement of Pure Research (ZWO)].

References and Notes

[1] According to the IUPAC rules the presented four-membered cyclic nitrones **7–10** and **13** are referred to as 2,3-dihydro-2-azetecarboxamide 1-oxides. However, if NR^{4}R^5 is part of a cyclic amine (*viz.* pyrrolidine, morpholine) the nomenclature changes to [(2,3-dihydro-1-oxido-2-azetyl)carbonyl]amines.
[2] *E. Breuer*, Ch. 13 in "Chemistry of Amines, Nitroso, Nitro Compounds. Their Derivatives", *S. Patai*, Ed., Wiley, Chichester, 1982, p. 459.
[3] *G. R. Delpierre* and *M. Lamchen*, Quart. Rev. Chem. Soc. 329 (1965).
[4] *D. St. C. Black*, *R. F. Crozier* and *V. C. Davis*, Synthesis 205 (1975).
[5] *M. L. M. Pennings*, *D. N. Reinhoudt*, *S. Harkema* and *G. J. van Hummel*, J. Org. Chem. **47**, 4419 (1982).
[6] *M. L. M. Pennings*, *D. N. Reinhoudt*, *S. Harkema* and *G. J. van Hummel*, J. Org. Chem. **48**, 486 (1983).
[7a] *P. J. S. S. van Eijk*, *D. N. Reinhoudt*, *S. Harkema* and *R. Visser*, Recl. Trav. Chim. Pays-Bas **105**, 103 (1986);
[b] *P. J. S. S. van Eijk*, *D. N. Reinhoudt*, *S. Harkema* and *G. J. van Hummel*, "Bio-Organic Heterocycles 1986 – Synthesis, Mechanisms and Bioactivity", *H. C. van der Plas*, *M. Simonyi*, *F. C. Alderweireldt* and *J. A. Lepoivre*, Eds., Elsevier, 1986, p. 177.
[8] *D. St. C. Black*, *R. F. C. Brown*, *B. F. Dunstan* and *S. Sternhell*, Tetrahedron Lett. 4283 (1974).
[9] *J. Harnisch* and *G. Szeimies*, Chem. Ber. **112**, 3914 (1979).
[10] *A. D. de Wit*, *M. L. M. Pennings*, *W. P. Trompenaars*, *D. N. Reinhoudt*, *S. Harkema* and *O. Nevestveit*, J. Chem. Soc., Chem. Commun. 993 (1979).
[11] *M. L. M. Pennings* and *D. N. Reinhoudt*, J. Org. Chem. **47**, 1816 (1982).
[12] *A. T. M. Marcelis*, *H. C. van der Plas* and *S. Harkema*, J. Org. Chem. **50**, 270 (1985).
[13] The (2 + 2) cycloadducts formed were detected in the ^{1}H NMR spectra of the crude reaction mixtures. The isolation, characterization and the thermal ring opening of these *N,N*-dialkyl-4-nitro-1-cyclobuten-1-amines (**14**) is discussed in an accompanying paper.
[14] *M. L. M. Pennings*, *D. Kuiper* and *D. N. Reinhoudt*, Tetrahedron Lett. **24**, 825 (1983).
[15] *P. A. van Elburg* and *D. N. Reinhoudt*, Tetrahedron Lett. **26**, 2809 (1985).
[16] *N. Kornblum*, *H. O. Larson*, *R. K. Blackwood*, *D. D. Mooberry*, *E. P. Oliveto* and *G. E. Graham*, J. Am. Chem. Soc. **78**, 1497 (1956).
[17] *D. Seebach* and *F. Lehr*, Helv. Chim. Acta **62**, 2239 (1979).
[18] Phenyl sulfenyl chloride was prepared according to *P. B. Hopkins* and *P. L. Fuchs*, J. Org. Chem. **43**, 1208 (1978).
[19] *D. E. Worrall*, Org. Synth. **9**, 66 (1929).
[20] *H. B. Hass*, *A. G. Susie* and *R. L. Heider*, J. Org. Chem. **15**, 8 (1950).

[21] *D. N. Robertson*, J. Org. Chem. **25**, 47 (1960).
[22] *E. J. Corey* and *H. Estreicher*, J. Am. Chem. Soc. **100**, 6294 (1978).
[23] *W. K. Seifert*, Org. Synth. **50**, 84 (1970).
[24a] *L. Brandsma*, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971;
[b] *L. Brandsma* and *H. D. Verkruysse*, "Synthesis of Acetylenes, Allenes and Cumulenes", Elsevier, Amsterdam, 1981.
[25] For reviews on ynamines see:
[a] *J. Ficini*, Tetrahedron **32**, 1449 (1976);
[b] *J. Collard-Motte* and *Z. Janousek*, Topics in Current Chemistry, Springer Verlag, Berlin, 1986, p. 89.
[26] *D. N. Epiotis*, Angew. Chem., Int. Ed. Engl. **13**, 751 (1974).
[27] The stereochemistry at C-3 of four-membered cyclic nitrones determines the products formed upon reaction with DMAD. The dipolarophile always enters from the sterically less hindered side at C-3. The reaction of *cis* and *trans* four-membered cyclic nitrones yields 1,3-dipolar cycloadducts with a different stereochemistry. The ^{1}H NMR spectra of the 1,3-dipolar cycloadducts of *trans* four-membered cyclic nitrones (**13**), show that the substituents R^1 and R^3 are shielded by the aryl moiety R^2, whereas in the cycloadducts of *cis* four-membered cyclic nitrones only the substituent R^1 is in the shielding zone of the R^2 group. The reactivity of *cis* and *trans* four-membered cyclic nitrones towards dipolarophiles are discussed in: *P. J. S. S. van Eijk*, *W. Verboom*, *F. C. J. M. van Veggel*, *D. N. Reinhoudt* and *S. Harkema*, Recl. Trav. Chim. Pays-Bas, accepted for publication.
[28] *H. G. Viehe*, *R. Merenyi*, *L. Stella* and *Z. Janousek*, Angew. Chem. **19**, 982 (1979).
[29] A coupling constant of similar magnitude ($J \approx 5.4$ Hz) was found for the protons at C-3 and C-4 in *cis*-1,3-dinitro-2,4-diphenylcyclobutene whereas in the corresponding *trans* compound the coupling constant for the *trans*-substituted ring protons appeared to be much smaller, *i.e.* $J \approx 1.2$ Hz. *D. B. Miller*, *P. W. Flanagan* and *H. Shechter*, J. Org. Chem. **41**, 2112 (1976).
[30] *D. B. Miller*, *P. W. Flanagan* and *H. Shechter*, J. Am. Chem. Soc. **94**, 3919 (1972).
[31] *Karplus* equation: $J = 4.22 - 0.5\cos(x) + 4.5\cos(2x)$ was used; *H. Günther*, NMR spectroskopie, Georg Thieme Verlag, Stuttgart, 1983, p. 105.
[32] *P. W. Rabideau*, Acc. Chem. Res. **11**, 141 (1978).
[33] Chem X: Incorporated in the ChemGraf suite, by *E. K. Davies* (1985), distributed by Chemical Design Ltd., Oxford. MNDO: *T. Clark*, Ch. 3 and Ch. 4 in "A Handbook of Computational Chemistry", J. Wiley & Sons, New York, 1985, pp. 93–232.
[34] *M. L. M. Pennings*, *D. N. Reinhoudt*, *S. Harkema* and *G. J. van Hummel*, J. Am. Chem. Soc. **102**, 7570 (1980).
[35] *K. Binovic*, *S. Vrancea*, *D. Grandet*, *J. M. Lebourg* and *R. Porquet*, Chim. Ther. **3**, 313 (1968); Chem. Abstr. **70**, 87171y (1969).
[36] *M. Koremura*, *H. Oku*, *T. Shono* and *T. Nakanishi*, Takamine Kenkyusho Nempo **13**, 198 (1961); Chem. Abstr. **57**, 16451b (1962).
[37] *M. Pianka*, J. Sci. Food. Agr. **14**, 48 (1963).
[38] *Z. Eckstein* and *D. Rusek*, Przem. Chem. **58**, 235 (1979); Chem. Abstr. **91**, 174970k (1979).
[39] *H. L. Holmes*, Structure–Activity Relations of Some Conjugated Heteroenoid Compounds, Catechol Monoethers Morphine Alkaloids **2**, 625 (1975); Chem. Abstr. **85**, 46109a (1976).
[40] *S. N. Karmarkar*, *S. L. Kelkar* and *M. S. Wadia*, Synthesis 510 (1985).
[41] *J. B. Hendrickson* and *R. Sufrin*, Tetrahedron Lett. 1513 (1973).
[42] *R. G. Hunt* and *S. T. Reid*, J. Chem. Soc., Perkin Trans. I 2462 (1977).
[43] *A. Burger*, *L. Stein* and *J. Clements*, J. Org. Chem. **22**, 143 (1957).
[44] *G. Germain*, *P. Main* and *M. M. Woolfson*, Acta Crystallogr., Sect. **B26**, 274 (1970); *P. Main* in "Computing in crystallography", *H. Schenk*, Ed., Delft University Press, Delft, The Netherlands, 1978.
[45] *B. A. Frenz & Associates Inc.* (1983), Structure Determination Package, College Station, Texas, and Enraf-Nonius, Delft.