*Tetrahedron* Vol 44, No. 20, pp 6491 to 6504, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00


# 1,3-Dipolar Cycloaddition of Nitrones with Nitriles. Scope and Mechanistic Study

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(*Received in UK 5 July* 1988)

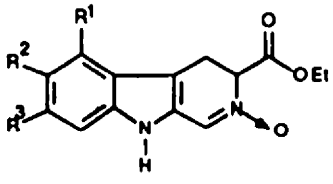
*Abstract:* 1,3-Dipolar cycloadditions of nitrones **1-6** with nitriles **14-16**, proceeded under thermal as well as under high pressure conditions with complete regioselectivity to give $\Delta^4$-1,2,4-oxadiazolines **17-19**. In general, the cycloaddition seemed to be controlled by a HOMO(nitrone)- LUMO(nitrile) interaction. However, a crossover in the orbital control is probable observed with nitrile **16c**. Nitrone-nitrile cycloadditions are normal type II cycloadditions so that the nitriles have a U-shaped reactivity curve. Kinetic study on solvent polarity and Hammett equation demonstrated that mechanistically the nitrone-nitrile cycloaddition is consistent with nitrone-alkene cycloaddition.

The [3+2] cycloaddition reactions of nitriles with 1,3-dipoles containing an orthogonal double bond (nitrilium betaines, diazonium betaines) are well documented[1] and afford useful synthetic routes to a variety of five-membered heterocyclic ring systems. In contrast, relatively few examples of the cycloaddition of nitriles to 1,3-dipoles lacking a double bond (the class of azomethinium betaines) are known.[1] Recently we reported[2] that **1**, a nitrone derived from N-hydroxytryptophane as well as several other nitrones underwent cycloaddition to *geminal* dinitriles with complete regioselectivity to give $\Delta^4$-1,2,4-oxadiazolines.

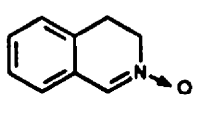
In general the knowledge and understanding of the reaction scale of 1,3-dipoles and dipolarophiles are intimately connected with mechanistic questions. It is generally accepted that 1,3-dipolar cycloadditions of nitrones to alkenes are single-step concerted four-center reactions.[3] However, it is suggested[1] that polarized dipolarophiles (*e.g.* nitriles) may undergo concerted but not necessarily synchronous cycloadditions. We now report an extensive investigation of the scope as well as a mechanistic study of the nitrone-nitrile cycloaddition.

## Synthetic Scope

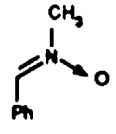
The nitrones **1-6** were used as 1,3-dipoles in this investigation. The new nitrones **3** and **4** were



**1**: $R^1$=$R^2$=$R^3$=H
**2**: $R^1$=$R^2$=H, $R^3$=OMe
**3**: $R^1$=Cl, $R^2$=$R^3$=H
**4**: $R^1$=$R^3$=H, $R^2$=Cl



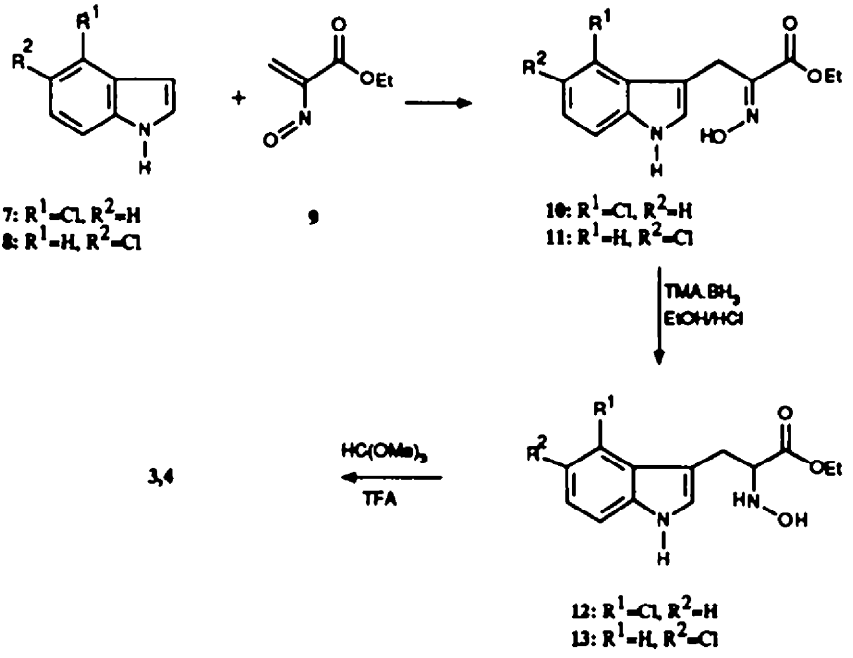
**5**



**6**

prepared in analogous fashion as 1[2,4] and 2.[2,5] Conjugate addition of 4-chloroindole[6] (7) or 5-chloroindole[6] (8) to the transient nitroso olefin (9)[7] gave the oximes 10 and 11 in 67% and 70% yield, respectively (Scheme I). Reduction with borane-trimethylamine complex afforded 12 (73%) and 13 (94%), which were converted with trimethyl orthoformate into the nitrones 3 (56%) and 4 (67%). The nitrones 5[8] and 6[9] were prepared according to known procedures.

Scheme I



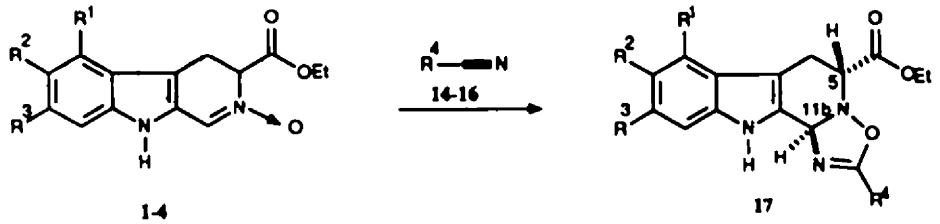

A survey of the nitriles used in this study is given in Table 1. They are divided into three classes based on structural characteristics, *viz.*, 2-substituted-2-cyanopropanes (14), ylidenemalononitriles (15) and directly substituted cyano derivatives (16). The results of the

Table 1. Survey of nitriles divided into three classes.

| 14 | | | 15 | | | | 16 | |
|---|---|---|---|---|---|---|---|---|
| | Y | Ref. | | $x^1$ | $x^2$ | Ref. | | R |
| a | $NO_2$ | 10 | a | H | $C_6H_5$ | 14 | a | $CCl_3$ |
| b | CN | 11 | b | H | p-Cl-$C_6H_4$ | 15 | b | COOEt |
| c | COOEt | 12 | c | H | 2-furanyl | 14 | c | $N(Me)_2$ |
| d | $C_6H_5$ | 13 | d | Ph | $C_6H_5$ | 14 | d | $C_6H_5$ |
| e | $CH_3$ | 6 | e | SMe | SMe | 14 | e | $CH_3$ |

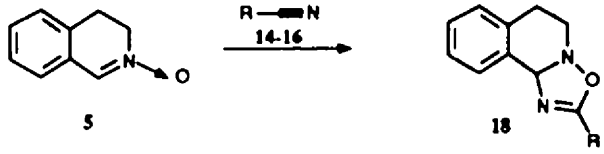
cycloaddition reactions of nitrones 1-4, 5 and 6 with nitriles 14-16 to give cycloadducts 17, 18 and 19, respectively, are listed in Table 2.

Table 2. Reactions of nitrones (1-6) with nitriles (14-16) (1.5 equivalents) in toluene.



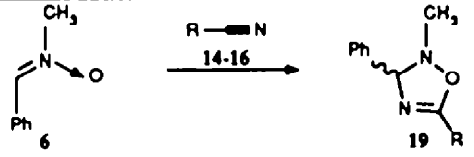
1-4 17

| Entry | Nitrone | Nitrile | Reaction conditions | product | Yield[a](%) |
|---|---|---|---|---|---|
| 1 | 1 | 14a | 80°C, 2h. | 17a | 97 |
| 2 | | 14b | 80°C, 1.5h. | 17b[b] | 99 |
| 3 | | 14c | 80°C, 7d. | 17c | 26 |
| 4 | | | 50°C, 12kbar, 28h.[c] | | 75 |
| 5 | | 14d | 80°C, 7d. | 17d | 11 |
| 6 | | | 50°C, 12kbar, 2d.[c] | | 56 |
| 7 | | 14e | 80°C, 6d. | 17e | 12 (48)[d] |
| 8 | | | 50°C, 12kbar, 3d.[c] | | 87[d] |
| 9 | 1 | 15a | 80°C, 33h. | 17f[b] | 78 |
| 10 | 2 | | 60°C, 7h. | 17g[b] | 95 |
| 11 | 3 | | 80°C, 7h. | 17h | 72 |
| 12 | 4 | | 80°C, 7h. | 17i | 72 |
| 13 | 1 | 15b | 80°C, 3h. | 17j | 97 |
| 14 | | 15c | 80°C, 1.5h. | 17k | 100 |
| 15 | | 15d | 80°C, 1d. | 17l | 11 |
| 16 | | | RT, 12kbar, 1d.[c] | | 84 |
| 17 | | 15e | RT, 12kbar, 1d.[c] | 17m | 78 |
| 18 | | 16a | 80°C, 2 minutes | 17n | 100 |
| 19 | | 16b | 80°C, 1.5h. (80°C, 0.5h.)[d] | 17o | 85 (98)[d] |
| 20 | | 16c | 80°C, 20h. (80°C, 3,5h.)[d] | 17p | 93 (100)[d] |
| 21 | | 16d | 80°C, 2d. | 17q | 87[d] |
| 22 | | 16e | refluxing acetonitrile | no reaction | |
| 23 | | | RT, 12 kbar, 3d.[c] | no reaction | |



5 18

| | | | | | |
|---|---|---|---|---|---|
| 24 | 5 | 14b | 100°C, 1h. | 18a | 100[d] |
| 25 | | 16a | 100°C, 2 minutes | 18b | 100[d] |
| 26 | | 16d | 100°C, 5d. | 18c | 56[d] |



6 19

| | | | | | |
|---|---|---|---|---|---|
| 27 | 6 | 14b | 110°C, 10d. | 19a[b] | 85[d] |
| 28 | | 16a | 110°C, 2 minutes | 19b | 100[d] |
| 29 | | 16d | 110°C, 10d. | 19c | 57[d] |

a) based on isolated products b) see reference 2 c) reaction in DMF d) ten-fold excess of dipolarophile

*Reactivity scale of nitriles.*

Within the series of reactions of **1** with nitriles **14-16** (entries 1-9 and 13-23) it is possible to study the reactivity scale of the nitriles. In the series of 2-substituted-2-cyanopropanes (**14**) (entries 1-8) we studied exclusively the inductive influence of the substituent on the reactivity of the nitrile function. Under thermal conditions the nitriles **14a** and **14b**[2] react smoothly and give cycloadducts **17a,b** in nearly quantitative yields , whereas **14c-e** react sluggishly giving **17c-e** in low yields. The yield of **17e** could be improved by the use of a ten-fold excess of the dipolarophile. Acceptable yields of **17c-e** were accomplished, when high pressure conditions (12 kbar) were used. It is apparent that the reactivity of the nitriles decreases with decreasing electron withdrawing ability of the substituent *e.g.* $NO_2$~CN > COOEt > $C_6H_5$~alkyl.

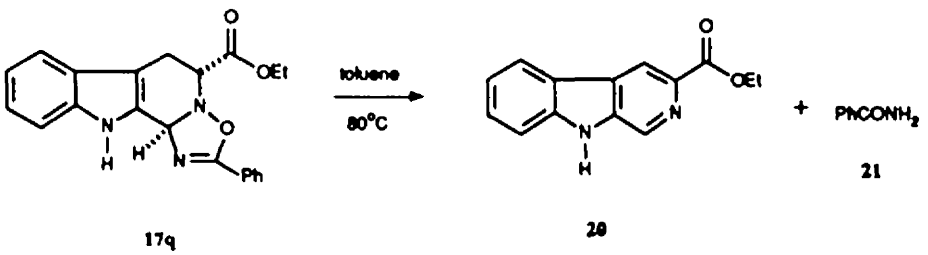
Monosubstituted ylidene malononitriles **15a-c** react easily with **1** (entries 9, 13 and 14). Remarkable is the higher reactivity of **15b** and **c** versus **15a**. The disubstituted ylidene malononitriles such as **15d** react very sluggishly under thermal conditions and gave low yields of cycloadducts **17**.(Entry 15) High pressure conditions solved this problem (Entries 16 and 17).

For the directly substituted cyano derivatives **16**, the reactivity decreases in the order **16a>16b>16c>16d** (entries 18-21). Nitrile **16e** did not react under thermal or under high pressure conditions (Entries 22 and 23). These results demonstrate that both electron withdrawing and strongly electron donating groups facilitate the reaction.

Cycloaddition reactions of nitriles with nitrones **1-4** proceeded with complete stereoselectivity -*viz.* C(5) and C(11b) substituents have an *trans* orientation- which is similar to earlier observed cycloadditions of these nitrones.[2] This was adjudged on account of the shifts of the H(5) and H(11b) protons, which are not very different[16] from analogous shifts of the *trans* compounds **17b** and **17f** (see reference 2). The *trans* orientation of the C(5) and C(11b) substituents is ascribed to steric hindrance of the ethoxycarbonyl function in the transition state. Furthermore, in the case of the ylidenemalononitriles **15a-c**, only the less sterically hindered of the two diastereotopic nitrile functions adds to the 1,3-dipole, which is in agreement with earlier results.[2] Confirmation of the influence of steric hindrance was found in the low reactivity of the disubstituted ylidenemalononitriles **15d** and **e**.

As mentioned earlier[2], β-carboline carboxyethylester (β-CCE) (**20**) was formed up to 10% yield when the cycloaddition reactions were allowed to stand for days under thermal conditions. We found that cycloaddition product **17q** partially decomposed to give **20** and benzamide (**21**) (Scheme II) when it was kept under cycloaddition reaction conditions for 2 days. This problem

Scheme II




17q 20 21

could be overcome by the use of a ten-fold excess of dipolarophile or high pressure conditions. (see Table 2)

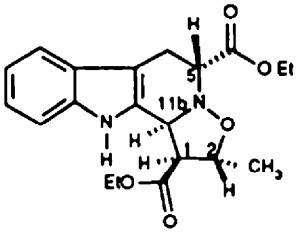
*Reactivity scale of nitrones.*

The nitrones **1-4** made it possible to study the influence of indole substitution on the reactivity of the 1,3-dipole in cycloaddition to nitriles. Reaction of nitrile **15a** with **1-4** (entries 9-12) clearly demonstrate that **2** is the most reactive nitrone as a result of the electron donating effect of the methoxy substituent.[2] The chloro substituents of **3** and **4** showed no clear effect on the reactivity with regard to the unsubstituted nitrone **1**. With regard to nitrones **5** and **6**, **1** is more reactive as shown by reaction of **5** and **6** with a few nitriles. (Entries 24-29) With the enormously reactive nitrile **16a** it is not possible to make a distinction between the reactivity of these nitrones. However, the less reactive **14b** and **16d** demonstrate that the order of reactivity is **1** > **5** > **6**, which is in agreement with our earlier results.[2]

**Kinetics**

Pseudo-first-order reaction rates were determined in 2-methoxyethanol, by using nitrone **1** and a tenfold excess of the dipolarophile and a dilatometer to monitor the progress of the reaction.[17] The results are presented in Table 3.

We studied the reactivity of **14b** and ethyl crotonate in order to compare the nitrile cycloaddition with the well-known analogous cycloaddition of alkenes. (Table 3, entries 1 and 2) Only a small difference in rate ($k_{ethyl\ crotonate}$ / $k_{dimethylmalononitrile}$=2.7) was found. Extrapolation for the $k_2$-value of ethyl crotonate from 85°C to 100°C occurred *isoentropic*.[18] Noteworthy is the




**22**

complete regio- and stereoselectivity of the cycloaddition of ethyl crotonate with **1** to give isoxazolidine **22**. Structure assignment was made in analogy with other cycloadditions of **1**,[4] *viz.*, C(5) and C(11b) substituents have an *trans*-orientation (*vide-supra*), electron withdrawing substituents on C(1) favours *endo*-[19] and alkyl substituents on C(2) *exo*-orientation. The proton coupling constant $J_{11b,1}$=9.9 Hz also supports the relative stereochemistry as depicted in **22**.[19,20]

The reaction of *para*-substituted benzonitriles was studied in order to determine a Hammett plot (Table 3 , entries 3-9). The reactivity differences made it necessary to determine the reaction rates at two temperatures. The more reactive nitriles (entries 3-7) were measured at 85°C, and the remaining nitriles (entries 8 and 9) at 110°C. Extrapolation of the $k_2$-values of the nitriles of entries 8 and 9 from 110°C to 85°C occurred *isoentropic*. The necessary activation parameters are obtained from benzonitrile, entry 7 ($\Delta S^{\ddagger}$=-23.6 cal/mol.deg and $\Delta H^{\ddagger}$=20.1 kcal/mol). The Hammett plot

Table 3. Dilatometric $k_2$-values for cycloadditions of 1 with dipolarophiles in 2-methoxyethanol.

| Entry | dipolarophile | $10^5 k_2$ (l/mol.sec) 85°C | 90°C | 100°C | 110°C | Product |
|---|---|---|---|---|---|---|
| 1 | dimethylmalononitrile | | | 553 | | 17b |
| 2 | ethyl crotonate | 584 | | 1517[a] | | 22 |
| 3 | p-nitrobenzonitrile | 21.2 | | | | 17r |
| 4 | p-cyanobenzaldehyde | 9.20 | | | | 17s |
| 5 | p-cyanobenzoic acid | 6.28 | | | | 17t |
| 6 | p-chlorobenzonitrile | 5.35 | | | | 17u |
| 7 | benzonitrile | 3.02 | 4.48 | 8.52 | 21.10 | 17q |
| 8 | p-tolunitrile | 2.60[b] | | | 17.60 | 17v |
| 9 | anisonitrile | 2.03[b] | | | 14.00 | 17w |

a) Extrapolation from 85°C to 100°C, with correction factor 2.7 (Huisgen, see ref. 3b)
b) Extrapolation from 110°C to 85°C, isoentropic ($\Delta S^{\ddagger}$=-23.6 cal/mol.deg)

showed an excellent linear correlation between the log k-values and the substituent constants ($\sigma$-values)[21], *viz.*, $\rho$=0.96 (corr.coeff. = 0.995).

Because of the insolubility of nitrone **1** in most solvents we studied the influence of solvent polarity upon the reaction rate with the better soluble but the less reactive **5**. The reaction of **5** with dimethylmalononitrile (**14b**) was studied at 100°C in three solvents covering a wide range of $E_T$ values[22] (Table 4). There is a notoriously small effect of solvent polarity. In agreement with

Table 4. Rates in various solvents for reaction of **5** with **14b** at 100°C

| solvent | $10^3 k_2$ l/mol.sec. | $E_T$ kcal/mol |
|---|---|---|
| toluene | 15.1 | 33.9 |
| phenetole | 11.5 | 36.4 |
| 2-methoxyethanol | 1.44 (1.38)[a] | 52.3 |

a) normal second-order experiment

Huisgen's[3b] study of the cycloaddition of nitrones with alkenes we found an inverse influence of solvent polarity ($k_{toluene}/k_{2\text{-methoxyethanol}}$=10.5).

## Discussion

The regioselective formation of the $\Delta^4$-1,2,4-oxadiazoline ring in the cycloaddition of nitriles **14-16** with nitrones **1-6**, can be rationalized by using Frontier Molecular Orbital (FMO) theory.[23] In our previous report[2] we suggested that the regioselectivity of the reaction depends on a favourable HOMO(nitrone)-LUMO(nitrile) interaction. This would imply that the reactivity will increase if nitrones become more electron-rich and nitriles more electron-deficient.[2] The results of this study of the synthetic scope are in line with this assumption.

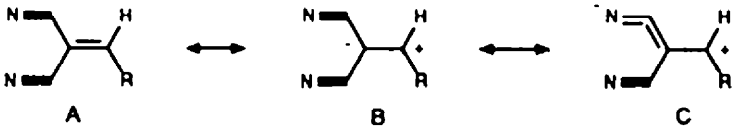
A measure for the electron richness of conjugated nitrones is the weighted average of the first two ionization potentials. The values for **1**[24], **5**[24] and **6**[24] are 8.40, 8.46 and 8.56 eV, respectively. This is in agreement with the reactivity order **1**>**5**>**6**. The enhanced reactivity of **2** suggests an average IP-value lower than 8.40 eV, as a result of the electron donating effect of the methoxy substituent.

In the case of 2-substituted-2-cyanopropanes (**14**) and directly substituted cyano derivatives **16**

we found an increas in reactivity of the nitrile function with increasing electron withdrawing ability of the substituent, *viz.*, reaction order for **14** $NO_2$~CN>COOEt>$C_6H_5$~$CH_3$ and for **16** $CCl_3$>COOEt>$C_6H_5$.

In the 1,3-dipolar cycloadditions with ylidenemalononitriles (**15**) the nitrones selectively add to the nitrile function[25], whereas the reactivity still strongly depends on the nature of the β-substituent. The influence of β-substituents has already been demonstrated in [2+2][26] cycloadditions of the alkene moiety of **15**. Generally, electron withdrawing substituents will decrease the conjugate resonance stabilization (Scheme III) and therefore make the alkene function

**Scheme III**




more reactive. Although the nitrile function is further away from the β-substituent, we observed a similar, and even stronger substituent effect. This may be attributed to the diminished contribution of resonance structure C in the order 2-furanyl<<4-Cl-$C_6H_4$<<$C_6H_5$.

The reactivity of the nitrile **16c** with the strongly electron donating dimethylamino group is the result of a crossover in the frontier orbital control, so that the regiochemistry will now depend on a favourable HOMO(nitrile)-LUMO(nitrone) interaction. This is in agreement with the classification by Sustmann[27] that nitrone cycloadditions are type II processes, in which both HOMO-LUMO interactions contribute to the stabilization of the transition-state. A U-shaped reactivity curve of dipolarophiles is a necessary consequence. In both HOMO-LUMO interactions, overlap of orbitals with comparable terminal coefficients, *i.e.* orbitals of the nitrogen and the carbon atoms of the nitrile with the carbon and oxygen of the nitrone, respectively will lead to the $\Delta^4$-1,2,4-oxadiazoline ring.

The inverse influence of the solvent polarity is an indication of a slight decrease of the polarity in the TS versus the polarity of the reactants. This supports the concerted nature of this 1,3-dipolar cycloaddition and is in agreement with an early TS.

The term *concerted* does not necessarily imply that the two new σ-bonds are developed in the TS to precisely the same extent. If in the cycloaddition of nitrones with a polarized dipolarophile -such as the nitrile- the making of one bond lays behind the closure of the other σ-bond in the TS, partial charges at the centers of the weak incipient bond can be stabilized. Therefore, a Hammett plot of the cycloaddition of nitrone **1** with p-substituted benzonitriles was determined. The excellent linear correlation between the log k-values and substituent constants (σ-values),[21] shows that all the p-substituted benzonitriles are far away from the crossover in the U-shape reactivity curve. The found ρ=0.96 is slightly higher than the analogous value found by Huisgen[3b] (ρ=0.77) in the cycloaddition of the nitrone **6** with p-subtituted styrenes. The higher ρ-value is not necessarily a result of a more polar transition state for the nitrile cycloadditions. It may also be a reflection of a smaller energy gap between HOMO(nitrone) and LUMO(nitrile) compared to HOMO(nitrone) and LUMO(alkene).[28]

In conclusion, it can be said that the results of this study are consistent with Huisgen's[3b] earlier

kinetic study of the 1,3-dipolar cycloaddition of nitrones with alkenes. Such comparisons indicate that nitrone-nitrile cycloadditions should not be considered mechanistically different from nitrone-alkene cycloadditions.

## Experimental Section

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model Lambda 5. Proton magnetic resonance spectra were measured on a Bruker WH-90 spectrometer. Chemical shifts are reported as δ-values relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, or $Cl_2$-TDM.[29] For high-performance liquid column chromatography (Jobin Yvon) Merck silica gel H (type 60) was used. Solvent systems used are, A: ($MeOH/CHCl_3$, 1/99, v/v), B: ($MeOH/CHCl_3$, 3/97, v/v), C:($MeOH/CHCl_3$, 5/95, v/v), D: ($MeOH/CHCl_3$, 7/93, v/v)

### Synthesis of Nitrones 3 and 4.

**Ethyl α-(Hydroxyimino)-β-(4-chloroindol-3-yl)propanate (10).** Ethyl α-hydroxyimino--β-bromopropanoate[7] (2.3 g., 11 mmol) in $CH_2Cl_2$ (40 mL) was added dropwise to a stirred solution of 7[6] (5.0 g., 33 mmol) and a suspension of $Na_2CO_3$ (2.4 g., 23 mmol) in $CH_2Cl_2$ (30 mL) at room temperature under argon. Stirring was continued at room temperature for 22h. The mixture was then filtered through a thin layer silica gel (60) and concentrated to dryness. The residue was subjected to column chromatography (silica gel 60H, EtOAc/n-hexane,1/2,v/v) to yield 6.3 g. of crystalline **10**, 67%. It was recrystallized from $CH_2Cl_2$/n-hexane: mp 166-171°C; Rf 0.35 (solvent system C); UV (MeOH) $\lambda_{max}$ 224, 284 nm, $\lambda_{min}$ 253 nm; EIMS (70 eV) m/z 282 ($[M+2]^+$, 12%)· 280 ($M^+$, 34%), 265 ($[M+2-OH]^+$, 21%), 263 ($[M-OH]^+$,56%), 192 ($[C_{10}H_7N_2Cl]^+$, 28%), 190 ($[C_{10}H_7N_2Cl]^+$, 81%), 166 ($[C_9H_7NCl]^+$, 33%), 164 ($[C_9H_7NCl]^+$, 100%); $^1H$ NMR δ 8.76 (br s, 1H, NH), 7.27-6.98 (m, 3H, indole C(5)-C(7)H), 6.84 (s, 1H, indole C(2)H), 4.45 (s, 2H, indole C(3)-$CH_2$), 4.26 (q, 2H, $OCH_2CH_3$), 1.23 (t, 3H, $OCH_2CH_3$); Anal.Calc. for $C_{13}H_{13}ClN_2O_3$ (MW 280.713): C, 55.62; H,4.67; N, 9.98. Found: C, 55.25; H, 4.67; N, 9.91.

**Ethyl α-(Hydroxyimino)-β-(5-chloroindol-3-yl)-propanoate (11).** Identical procedure with 5-choroindole 8[6] gave **11**, yield 70%. Recrystallized from $CH_2Cl_2$/n-hexane: mp 164-166°C; Rf 0.30 (solvent system C); UV (MeOH) $\lambda_{max}$ 224, 290 nm, $\lambda_{min}$ 253 nm; EIMS (70 eV) m/z 282 ($[M+2]^+$, 14%)· 280 ($M^+$, 41%), 265 ($[M+2-OH]^+$, 22%), 263 ($[M-OH]^+$,64%), 192 ($[C_{10}H_7N_2Cl]^+$, 34%), 190 ($[C_{10}H_7N_2Cl]^+$, 77%), 166 ($[C_9H_7NCl]^+$, 34%), 164 ($[C_9H_7NCl]^+$, 100%); $^1H$ NMR ($CDCl_3$ / $CD_3OD$,95/5,v/v) δ 7.70 (d, 1H, indole C(7)H), 7.30-6.98 (m, 3H, indole C(2)H,C(4)H and C(6)H), 4.23 (q, 2H, $OCH_2CH_3$), 3.98 (s, 2H, indole C(3)-$CH_2$), 1.27 (t, 3H, $OCH_2CH_3$); Anal.Calc. for $C_{13}H_{13}ClN_2O_3$ (MW 280.713): C, 55.62; H,4.67; N, 9.98. Found: C, 55.42; H, 4.67; N, 9.95.

**Ethyl α-(Hydroxyamino)-β-(4-chloroindol-3-yl)-propanoate (12).** A solution of HCl in ethanol (13 mL of a 7N solution) was added dropwise to a stirred solution of **10**(2.0 g., 7.2 mmol) and $(CH_3)_3N.BH_3$ (Aldrich Chemical Co; 590 mg, 8.1 mmol) in EtOH (25 mL) at room temperature and in argon atmosphere. Stirring was continued for 2.5 h. The mixture was then concentrated to near dryness. The residue dissolved in $CH_2Cl_2$. This solution was neutralized with $NaHCO_3$ and filtered. The filtrate was washed with 0.1 N HCl and dried over $Na_2SO_4$. Evaporation of the solvent in vacuo and recrystallization of the residue from $CH_2Cl_2$/MeOH/n-hexane gave 1.48 g. **12** (73%): mp 138-140°C; Rf 0.25 (solvent system D); UV (MeOH) $\lambda_{max}$ 224, 289 nm, $\lambda_{min}$ 251 nm; EIMS (70 eV) m/z 284 ($[M+2]^+$, 0.5%)· 282 ($M^+$, 1.7%), 166 ($[C_9H_7NCl]^+$, 34%), 164 ($[C_9H_7NCl]^+$, 100%); $^1H$ NMR ($CDCl_3$/$CD_3OD$,95/5,v/v) δ 7.35-7.00 (m, 4H, indole C(2)H,C(5)H-C(7)H), 4.17 (q, 2H,$^3J$ 7.1 Hz, $OCH_2CH_3$), 4.01 (X part of ABX spectrum, 1H,$^3J$ 5.3 Hz, $^3J$ 8.9 Hz, indole C(3)-$CH_2$-CH),3.40 and 3.23 (AB part of ABX spectrum, 2H,$^2J$ 14.2 Hz, $^3J$ 5.3 Hz, $^3J$ 8.9 Hz, indole C(3)-$CH_2$), 1.19 (t, 3H, $OCH_2CH_3$).

**Ethyl α-(Hydroxyamino)-β-(5-chloroindol-3-yl)-propanoate (13).** Identical procedure with **11** gave **13**, yield 94%. Recrystallized from $CH_2Cl_2$/MeOH/n-hexane:mp 188-190°C; Rf 0.26 (solvent system D); UV (MeOH) $\lambda_{max}$ 224, 289 nm, $\lambda_{min}$ 251 nm; EIMS (70 eV) m/z 284 ($[M+2]^+$, 1.3%)· 282 ($M^+$, 4.7%), 166 ($[C_9H_7NCl]^+$, 31%), 164 ($[C_9H_7NCl]^+$, 100%); $^1H$ NMR

($CDCl_3/CD_3OD$,95/5,v/v) δ 11.34 (br s, 1H, NH), 7.61-7.04 (m, 4H, indole C(2)H,C(4)H and C(6)-C(7)H), 4.28 (X part of ABX spectrum, 1H,$^3$J 3.9 Hz, $^3$J 9.6 Hz, indole C(3)-$CH_2$-CH), 4.07 (q, 2H,$^3$J=7.1 Hz, $OCH_2CH_3$), 3.46 and 3.23 (AB part of ABX spectrum, 2H,$^2$J 14.4 Hz, $^3$J 3.9 Hz, $^3$J 9.6 Hz, indole C(3)-$CH_2$), 0.97 (t, 3H, $^3$J=7.1 Hz, $OCH_2CH_3$).

**2-Oxo-3-(ethoxycarbonyl)-5-chloro-3,4-dihydro-β-carboline (3).** Trifluoracetic acid (0.45 mL) was added dropwise to a stirred solution of **12** (1.0 g., 3.6 mmol) in $HC(OMe)_3$ (10 mL) at room temperature and in argon atmosphere. Stirring was continued for 2.5 h. The solution was then concentrated to near dryness, dissolved in $CH_2Cl_2$ and concentrated again. The residue was dissolved in $CH_2Cl_2$ and washed with $NaHCO_3$ and water and dried over $Na_2SO_4$. Evaporation of the solvent gave crystalline **3**, which was recrystallized ($CH_2Cl_2$/MeOH/n-hexane) to yield 0.78 g. (75%) **3**: mp 173°C (decomposes); Rf 0.28 (solvent system D); UV (MeOH) $\lambda_{max}$ 218, 362, 367 nm, $\lambda_{min}$; EIMS (70 eV) m/z 294 ([M+2]$^+$, 16%)· 292 (M$^+$, 27%), 276 ([$C_{14}H_{11}ClN_2O_2$]$^+$, 8%), 274 ([$C_{14}H_{11}ClN_2O_2$]$^+$,14%), 221 ([$C_{11}H_8ClN_2O$]$^+$, 41%), 219([$C_{11}H_8ClN_2O$]$^+$, 72%), 204 ([$C_{11}H_7N_2Cl$]$^+$, 46%), 202 ([$C_{11}H_7N_2Cl$]$^+$, 100%); $^1$H NMR ($CDCl_3/CD_3OD$,95/5,v/v) δ 8.01 (s, 1H, C(1)H), 7.32-7.00 (m, 3H, indole C(6)-C(8)H), 4.88 (X part of ABX spectrum, 1H,$^3$J 3.2 Hz, $^3$J 8.2 Hz, C(3)H), 4.22 (q, 2H,$^3$J=7.1 Hz, $OCH_2CH_3$), 4.11-3.72 (AB part of ABX spectrum, 2H,$^2$J 17.7 Hz, $^3$J 3.2 Hz, $^3$J 8.2 Hz, C(4)H), 1.21 (t, 3H, $^3$J 7.1 Hz, $OCH_2CH_3$).

**2-oxo-3-(ethoxycarbonyl)-6-chloro-3,4-dihydro-β-carboline (4).** Identical procedure with **13** gave **4**, yield 67%. recrystallized from $CH_2Cl_2$/MeOH/n-hexane: mp 208°C (decomposes); Rf 0.19 (solvent system D); UV (MeOH) $\lambda_{max}$ 218, 362, 367 nm, $\lambda_{min}$; EIMS (70 eV) m/z 294 ([M+2]$^+$, 16%)· 292 (M$^+$, 27%), 276 ([$C_{14}H_{11}ClN_2O_2$]$^+$, 8%), 274 ([$C_{14}H_{11}ClN_2O_2$]$^+$,14%), 221 ([$C_{11}H_8ClN_2O$]$^+$, 41%), 219([$C_{11}H_8ClN_2O$]$^+$, 72%), 204 ([$C_{11}H_7N_2Cl$]$^+$,46%), 202 ([$C_{11}H_7N_2Cl$]$^+$, 100%); $^1$H NMR ($CDCl_3/CD_3OD$,95/5,v/v) δ 7.96 (s, 1H, C(1)H), 7.44-7.09 (m, 3H, indole C(5)H and C(7)-C(8)H), 4.94-4.82 (X part of ABX spectrum, 1H, C(3)H), 4.21 (q, 2H,$^3$J 7.1 Hz, $OCH_2CH_3$), 3.59-3.53 (AB part of ABX spectrum, 2H, C(4)H), 1.24 (t, 3H, $^3$J 7.1 Hz, $OCH_2CH_3$).

**General Procedure Cycloadditions.**

**Thermal Reaction Conditions.** A solution of nitrone (0.5 mmol) and nitrile (0.75 mmol) in dry toluene (10 mL) was kept at the appropriate temperature (see Table 2). The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue subjected to flash chromatography. Recrystallization was always accomplished from $CH_2Cl_2$ / MeOH / n-hexane. Spectroscopical data cycloadducts, see Table 5.

**High-Pressure Reaction Conditions.** The nitrone (0.5 mmol) and the nitrile (0.75 mmol) were dissolved in dry DMF (1.5 mL) and brought into a Teflon high-pressure vessel, which was placed in a high-pressure apparatus. Pressure was raised to 12 kbar and to the appropriate temperature (see Table 2). After completion of the reaction the solvent was evaporated and the residue subjected to flash chromatography. Recrystallization was always accomplished from $CH_2Cl_2$ / MeOH / n-hexane. Spectroscopical data cycloadducts, see Table 5.

**Decomposition of cycloadduct 17q**

A solution of **17q** (361 mg, 1.0 mmol) in dry toluene (15 mL) was kept at 80°C for two days under argon atmosphere. After evaporation of the solvent the residue was subjected to flash chromatography (silica gel 60H, eluens $CHCl_3$/MeOH, 99/1, v/v) to give 310 mg (86%) of **17q**, 34 mg (14%) of **20** and 18 mg (14%) of benzamide (**21**).

**Compound 20**: Spectroscopical data are identical with earlier published results.[4]

**Kinetic Experiments.**

*Equipment:*The dilatometer was made according to a literature method.[30] The important features of this design are: a) The coil had a capacity of about 20 ml. b) The precision capillary was 25 cm long and its inner diameter was 0.35 mm. A microprocessor controlled constant temperature bath Tamson TMV 70, filled with ethylene glycol (70 L) was used. Temperature fluctuations in the bath were less than 0.004°C.

*Execution:*Although all the reactions obeyed the second-order rate law, pseudo-first-order reaction rates were determined, by using a tenfold excess of dipolarophile.[17] The concentration of nitrone was in all the experiments 0.116M. Further, standard procedure was followed.[3b] Rate constants were calculated on a IBM XT personal computer, using a non-linear regression fit program based on the Gauss method.[31] Second-order rate constants were reproducible within 5%.

**Acknowledgement**

This work was supported by the Technology Foundation of the Netherlands (STW).

Table 5. Spectroscopic data of cycloadducts 17, 18, 19 and 22.

| Product | mp (°C) | Rf (Solv.Sys.) | UV(MeOH) λ max (nm) | IR ν(cm$^{-1}$) | Mass Spectrum | $^1$H NMR δ (ppm) |
|---|---|---|---|---|---|---|
| 17a[a] | 176-181 | 0.62 (A) | 222, 277 | 1732 (C=O) 1675 (C=N) 1556 ($NO_2$) | EIMS (70 eV) m/z 372 ($M^+$, 21%), 258 ([$C_{14}H_{14}N_2O_3$]$^+$, 25%), 185 ([$C_{11}H_{10}N_2$]$^+$, 100%), 169 (59%) | 8.36 (br s, 1H, NH), 7.52-7.02 (m, 4H, C(7)-C(10)H), 6.19 (s, 1H, C(11b)H), 4.31 and 4.29 (2q, 2H,diastereotopic protons, $OCH_2CH_3$), 3.93 (X part of ABX spectrum, 1H, $^3J$ 3.6 Hz, $^3J$ 11.8 Hz, C(5)H), 3.20 and 3.01 (AB part of ABX spectrum, 2H, $^2J$ 15.6 Hz, $^3J$ 3.6 Hz, $^3J$ 11.8 Hz, C(6)$H_2$), 1.88 (s, 6H, 2x$CH_3$), 1.32(t, 3H, $OCH_2CH_3$) |
| 17c[a] | 141-144 | 0.55 (A) | 222, 274 | 1740 (C=O) 1665 (C=N) | CIMS (100 eV) m/z 400 ([M+1]$^+$, 12%), 243 ([$C_{14}H_{14}N_2O_2$+1]$^+$, 22%), 142 ([$C_7H_{11}NO_2$+1]$^+$, 73%), 114 ([$C_6H_{10}O_2$]$^+$, 100%) | 8.98 (br s, 1H, NH), 7.49-7.00 (m, 4H, C(7)-C(10)H), 6.14 (s, 1H, C(11b)H), 4.31 (q, 2H, $OCH_2CH_3$),4.16 and 4.14 (2q, 2H, $OCH_2CH_3$), 3.88 (Xpart of ABX spectrum, 1H, $^3J$ 3.9 Hz, $^3J$ 12.3 Hz, C(5)H), 3.17 and 3.00 (AB part of ABX spectrum, 2H, $^2J$ 15.4 Hz, $^3J$ 3.9 Hz, $^3J$ 12.3 Hz, C(6)$H_2$), 1.50 (s, 6H, 2x$CH_3$), 1.34 (t, 3H, $OCH_2CH_3$), 1.23 (t, 3H, $OCH_2CH_3$) |
| 17d | oil | 0.53 (A) | 220, 272 280 (sh) 289 (sh) | 3400 (NH) 1740 (C=O) 1660 (C=N) | EIMS ( 70 eV) m/z 403 ($M^+$, 7%), 330 ([M-COOEt]$^+$, 2%), 258 ([$C_{14}H_{14}N_2O_3$]$^+$, 68%), 185 ([$C_{11}H_{10}N_2O$]$^+$, 86%), 71 (100%) | 8.80 (br s, 1H, NH), 7.46-6.96 (m, 9H, C(7)-C(10)H and Ph), 6.11 (s, 1H, C(11b)H), 4.17 (q, 2H, $OCH_2CH_3$), 3.61 (X part of ABX spectrum, 1H, $^3J$ 2.6 Hz, $^3J$ 12.3 Hz, C(5)H), 3.08 and 2.95 (AB part of ABX spectrum, 2H, $^2J$ 15.6 Hz, $^3J$ 2.6 Hz, $^3J$ 12.3 Hz, C(6)$H_2$), 1.61 (s, 6H, 2x$CH_3$), 1.21 (t, 3H, $OCH_2CH_3$) |
| 17e[a] | 169-172 | 0.78 (B) | 220, 272 280 (sh) 289 (sh) | 3370 (NH) 1735 (C=O) 1680 (C=N) | EIMS (70 eV) m/z 341 ($M^+$, 12%), 284 ([$C_{15}H_{14}N_3O_3$]$^+$, 22%), 258 ([$C_{14}H_{14}N_2O_3$]$^+$, 40%), 241 ([$C_{14}H_{13}N_2O_2$]$^+$, 11%), 185 ([$C_{11}H_{10}N_2O$]$^+$, 100%), 169 ([$C_{11}H_{10}N_2$]$^+$, 38%) | 8.93 (br s, 1H, NH), 7.52-7.00 (m, 4H, C(7)-C(10)H), 6.10 (s, 1H, C(11b)H), 4.36 and 4.34 (2q, 2H, $OCH_2CH_3$), 3.76 (X part of ABX spectrum, 1H, $^3J$ 3.3 Hz, $^3J$ 12.0 Hz, C(5)H), 3.15 and 3.04 (AB part of ABX spectrum, 2H, $^2J$ 15.5 Hz, $^3J$ 3.3 Hz, $^3J$ 12.0 Hz, C(6)$H_2$), 1.36(t, 3H, $OCH_2CH_3$), 1.25 (s, 9H, $C(CH_3)_3$) |
| 17h[a] | 172-174 | 0.66 (A) | 225, 300, 306 | 2236 (nitrile) 1730 (C=O) 1640 (C=N) | EIMS ( 70 eV) m/z 448 ([M+2]$^+$,0.9%), 446 ($M^+$,1.6%), 294 ([$C_{14}H_{13}ClN_2O_3$]$^+$, 5%), 292 ([$C_{14}H_{13}ClN_2O_3$]$^+$, 14%), 204 ([$C_{11}H_7ClN_2$]$^+$, 46%), 202 ([$C_{11}H_7ClN_2$]$^+$, 100%) | 9.03(br s, 1H, NH), 7.98-7.01 (m, 9H, C(8)-C(10)H, CHPh, Ph), 6.46 (s, 1H, C(11b)H), 4.40 (q, 2H, $OCH_2CH_3$), 3.92 (X part of ABX spectrum, 1H, $^3J$ 3.7 Hz, $^3J$ 11.2 Hz, C(5)H), 3.72 and 3.27 (AB part of ABX spectrum, 2H, $^2J$ 15.7 Hz, $^3J$ 3.7 Hz, $^3J$ 11.2 Hz, C(6)$H_2$), 1.36 (t, 3H, $OCH_2CH_3$) |
| 17i[a] | 179-182 | 0.67 (A) | 228, 303 | 2230 (nitrile) 1730 (C=O) 1640 (C=N) | EIMS (70 eV) m/z 448 ([M+2]$^+$, 0.1%), 446 ($M^+$, 0.3%), 294 ([$C_{14}H_{13}ClN_2O_3$]$^+$, 2%), 292 (6%), 276 ([$C_{14}H_{11}ClN_2O_2$]$^+$, 8%), 274(21%), 204 ([$C_{11}H_7ClN_2$]$^+$, 35%), 202 (100%) | 8.80 (br s, 1H, NH), 7.98-7.82 (m, 3H, C(9)C(10)H and C=CH-Ph), 7.53-7.11 (m, 6H, C(7)H and Ph) 6.41 (s, 1H, C(11b)H), 4.37 (q, 2H, $OCH_2CH_3$), 3.89 (X part of ABX spectrum, 1H, $^3J$ 2.7 Hz, $^3J$ 11.1 Hz, C(5)H), 3.17 and 3.04 (AB part of ABX spectrum, 2H, $^2J$ 16.4 Hz, $^3J$ 2.7 Hz , $^3J$ 11.1 Hz, C(6)$H_2$), 1.36 (t, 3H, $OCH_2CH_3$) |
| 17j[a] | 177-180 | 0.73 (A) | 221, 293(sh) 318 | 2238 (nitrile) 1717 (C=O) 1642 (C=N) | FABMS (7 kV at 1.4 mA) m/z 449 ([M+3]$^+$, 2%), 447 ([M+1]$^+$, 4%), 243 ([$C_{14}H_{14}N_2O_2$+1]$^+$, 100%) | 8.40 (br s, 1H, NH), 7.91-7.11 (m, 9H, C(7)-C(10)H and C=CH-, and $C_6H_4Cl$), 6.38 (s, 1H, C(11b)H), 4.36 (q, 2H, $OCH_2CH_3$), 3.88 (X part of ABX spectrum, 1H, $^3J$ 4.0 Hz, $^3J$ 9.9 Hz, C(5)H), 3.23 and 3.06 (AB part of ABX spectrum, 2H, $^2J$ 15.1 Hz, $^3J$ 4.0 Hz, $^3J$ 9.9 Hz, C(6)$H_2$), 1.37 (t, 3H, $OCH_2CH_3$) |

a) Satisfactory micro analyses were obtained for these compounds (C±0.5%, H±0.2%, N±0.4%)

Table 5. Spectroscopic data of cycloadducts 17, 18, 19 and 22.

| Product | mp (°C) | Rf (Solv.Sys.) | UV (MeOH) λmax (nm) | IR ν(cm⁻¹) | Mass Spectrum | ¹H NMR δ (ppm) |
|---|---|---|---|---|---|---|
| 17k[a] | 167-171 | 0.51 (B) | 222, 282, 345 | 2235 (nitrile) 1730 (C=O) 1650 (C=N) | EIMS (70 eV) m/z 402 ($M^+$, 1.5%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 35%), 144 ($[C_8H_4N_2O]^+$, 100%) | 200 MHz δ 5.4 (s, 1H, NH), 7.75 (d, 1H,C(α')H), 7.63 (s, 1H, =CH-), 7.50 (d, 1H, C(7)H), 7.40 (d, 1H, C(10)H, 7.35 (d, 1H, C(β)H), 7.24 and 7.14 (2xm, 2H, C(8) and C(9)H), 6.67 (dd, 1H,C(β')H), 6.38 (s, 1H, C(11b)H), 4.39 and 4.36 (2q, 2H, $OCH_2CH_3$), 3.86 (X part of ABX spectrum, 1H, $^3J$ 3.0 Hz, $^3J$ 11.1 Hz, C(5)H), 3.22 and 3.06 (AB part of ABX spectrum, 2H, $^2J$ 15.9 Hz, $^3J$ 3.0 Hz, $^3J$ 11.1 Hz, C(6)$H_2$), 1.38 (t, 3H, $OCH_2CH_3$) |
| 17l[a] | 148-152 | 0.29 (A) | 209, 221 273(sh), 282 290, 310 | 2220 (nitrile) 1742 (C=O) 1655 (C=N) | EIMS (70 eV) m/z 488 ($M^+$, 1%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 11%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 38%), 168 (100%) | 8.69 (br s, 1H, NH), 7.55-7.07 (m, 14H, C(7)-C(10)H and 2xPh), 6.06 (s, 1H, C(11b)H), 4.18 (q, 2H, $OCH_2CH_3$), 3.80 (X part of ABX spectrum, 1H, $^3J$ 3.8 Hz, $^3J$ 10.9 Hz,C(5)H) 3.18 and 2.94 (AB part of ABX spectrum, 2H, $^2J$ 15.5 Hz, $^3J$ 3.8 Hz, $^3J$ 10.9 Hz, C(6)$H_2$), 1.29 (t, 3H, $OCH_2CH_3$) |
| 17m[a] | 143-146 | 0.72 (B) | 222, 263 339 | 2220 (nitrile) 1710 (C=O) 1620 (C=N) | EIMS (70 eV) m/z 428 ($M^+$, 7%), 355 ($[M-COOEt]^+$, 12%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 23%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 35%), 185 (34%), 170 ($[C_6H_6N_2S_2]$, 100%), 169 (56%) | 8.46 (br s, 1H, NH), 7.53-7.04 (m, 4H, C(7)-C(10)H), 6.32 (s, 1H, C(11b), 4.35 (q, 2H, $OCH_2CH_3$), 3.92 (X part of ABX spectrum, 1H, $^3J$ 3.7 Hz, $^3J$ 11.6 Hz, C(5)H), 3.20 and 3.05 (AB part of ABX spectrum, 2H, $^2J$ 15.7 Hz, $^3J$ 3.7 Hz, $^3J$ 11.6 Hz, C(6)$H_2$, 2.69 (s, 3H, $SCH_3$), 2.57 (s, 3H, $SCH_3$), 1.30 (t, 3H, $OCH_2CH_3$) |
| 17n[a] | 159-162 | 0.75 (B) | 209 (sh) 223, 273 280 (sh) 289 (sh) | 3359 (NH) 1720 (C=O) 1666 (C=N) | EIMS (70 eV) m/z 405 ($[M+4]^+$, 1.2%), 403 ($[M+2]^+$, 3.3%), 401 ($M^+$, 3.5%), 284 ($[C_{18}H_{14}N_2O_3]^+$, 13%), 240 (7%), 185 (11%), 168 (43%), 106 (97%), 44 (100%) | 8.46 (br s, 1H, NH), 7.56-7.04 (m, 4H, C(7), C(10)H, 6.44 (s, 1H, C(11b(H), 4.36 and 4.34 (2q, 2H, $OCH_2CH_3$), 4.01 (X part of ABX spectrum, 1H, $^2J$ 3.6 Hz, $^3J$ 11.0 Hz, C(5)H), 3.26 and 3.06 (AB part of ABX spectrum, 2H, $^2J$ 15.4 Hz, $^3J$ 3.6 Hz, $^3J$ 11.0 Hz, C(6)$H_2$), 1.35 (t, 3H, $OCH_2CH_3$) |
| 17o[a] | 84-88 | 0.67 (B) | 204 (sh) 220, 272 280 (sh) 289 (sh) | 3320 (NH) 1745 (C=O) 1706 (C=O) 1654 (C=N) | EIMS (70 eV) m/z 357 ($M^+$, 1%), 284 ($[C_{15}H_{14}N_3O_3]^+$, 2%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 2%), 185 ($[C_{11}H_{10}N_2O]^+$, 5%), 169 ($[C_{11}H_9N_2]^+$, 16%), 54 (100%) | 8.63 (br s, 1H, NH), 7.53-7.02 (m, 4H, C(7)-C(10)H), 6.40 (s, 1H, C(11b)H), 4.38 (q, 2H, $OCH_2CH_3$), 4.33 (q, 2H, $OCH_2CH_3$), 3.95 (X part of ABX spectrum, 1H, $^3J$ 6.6 Hz, $^3J$ 8.1 Hz, C(5)H), 3.24 and 3.03 (AB part of ABX spectrum, 2H, $^2J$ 15.4 Hz, $^3J$ 6.6 Hz, $^3J$ 8.1 Hz, C(6)$H_2$), 1.33 (2xt, 6h, $2xOCH_2CH_3$) |
| 17p[a] | 73-77 | 0.38 (B) | 208 (sh) 223, 273 280 289 (sh) 318 | 1738 (C=O) 1665 (C=N) | EIMS (70 eV) m/z 328 ($M^+$, 65%), 284 ($[C_{15}H_{16}N_4O_2]^+$, 100%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 15%), 210 ($[C_{12}H_8N_2O_2]^+$, 95%), 185 (42%), 168 (30%) | 9.71 (br s, 1H, NH), 7.61-6.96 (m, 4H, C(7)-C(10)H), 6.21 (s, 1H, C(11b)H), 4.38 (q, 2H, $OCH_2CH_3$), 4.07 )X part of ABX spectrum, 1H, C(5)H), 3.47-2.90 (AB part of ABX spectrum, 2H, C(6)$H_2$), 2.90 (s, 6H, $N(CH_3)_2$), 1.36 (t, 3H, $OCH_2CH_3$) |
| 17q[a] | 174-176 | 0.69 (A) | 207(sh) 222, 269, 273(sh), 281(sh) 290(sh) | 3290 (NH) 1734 (C=O) 1652 (C=N) | EIMS (70 eV) m/z 361 ($M^+$, 6%), 288 ($[C_{18}H_{14}N_3O]^+$, 5%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 10%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 7%), 185 (21%), 168 (38%), 103 ($[C_7H_6N]^+$, 100%) | 8.81(br s, 1H, NH), 7.96-7.85 (m, 2H, C(2')-Ph-ortho-H), 7.54-7.04 (m, 7H, C(7)-C(10)H and C(2')Ph-meta,para-H), 6.36 (s, 1H, C(11b)H), 4.40 (q, 2H, $OCH_2CH_3$), 3.94 (X part of ABX spectrum, 1H, $^3J$ 2.5 Hz, $^3J$ 11.8 Hz, C(5)H), 3.22 and 3.11 (AB part of ABX spectrum, 2H, $^2J$ 15.5 Hz, $^3J$ 2.5 Hz, $^3J$ 11.8 Hz, C(6)$H_2$), 1.40 (t, 3H, $OCH_2CH_3$) |

a) Satisfactory micro analysis for these compounds were obtained (C±0.5%, H±0.2%, N±0.4%).

Table 5. Spectroscopic data of cycloadducts 17, 18, 19 and 22.

| Product | mp (°C) | Rf (Solv.Sys.) | UV (MeOH) λmax (nm) | IR ν (cm$^{-1}$) | Mass Spectrum | $^1$H NMR δ(ppm) |
|---|---|---|---|---|---|---|
| 17r[a] | 168-172 | 0.32 (A) | 222<br>276 | 1730 (C=O)<br>1650 (C=N)<br>1354 ($NO_2$) | EIMS (70 eV) m/z 406 ($M^+$, 1%), 333 ($[C_{18}H_{13}N_4O_3]^+$, 1%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 8%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 12%), 185 (16%), 168 ($[C_{11}H_8N_2]^+$, 61%), 148 ($[C_7H_4N_2O_2]^+$, 100%) | 8.23 and 8.02 (AB spectrum, 4H, $^3J$ 9.4 Hz, $C_6H_4NO_2$), 7.57-7.09 (m, 4H, C(7)-C(10)H), 6.41 (s, 1H, C(11b)H), 4.40 (q, 2H, $OCH_2CH_3$), 3.91 (X part of ABX spectrum, 1H, $^3J$ 2.9 Hz, $^3J$ 11.9 Hz, C(5)H, 3.23 and 3.11 (AB part of ABX spectrum, 2H, $^2J$ 15.6 Hz, $^3J$ 2.9 Hz, $^3J$ 11.9 Hz, C(6)$H_2$), 1.38 (t, 3H, $OCH_2CH_3$) |
| 17s[a] | 165-169 | 0.49 (A) | 220, 267<br>280 (sh)<br>289 (sh) | 3260 (NH)<br>1742 (C=O)<br>1700 (C=O)<br>1650 (C=N) | EIMS (70 eV) m/z 389 ($M^+$, 1%), 316 ($[C_{19}H_{14}N_2O_2]^+$, 1%), 258 (20%), 240 (31%), 185 (42%), 169 (100%), 131 ($[C_8H_5NO]^+$, 58%) | 10.06 (s, 1H, CHO), 8.74 (br s, 1H, NH), 8.05 and 7.93 (AB spectrum, 4H, $^3J$ 8.4 Hz, $C_6H_4CHO$), 7.56-7.00 (m, 4H, C(7-)C(10)H), 6.40 (s, 1H, C(11b)H), 4.39 (q, 2H, $OCH_2CH_3$), 3.92 (X part of ABX spectrum, 1H, $^3J$ 2.5 Hz, $^3J$ 12.8 Hz, C(5)H), 3.21 and 3.11 (AB part of ABX spectrum, 2H, $^2J$ 15.7 Hz, $^3J$ 2.5 Hz, $^3J$ 12.8 Hz, C(6)$H_2$), 1.39 (t, 3H, $OCH_2CH_3$) |
| 17t[a,b] | 167-170 | 0.71 (B) | 220, 253<br>282 (sh)<br>289.(sh) | 3370 (NH)<br>1731 (C=O)<br>1715 (C=O)<br>1653 (C=N) | EIMS (70 eV) m/z 419 ($M^+$, 1%), 346 ([M-COOEt]$^+$, 1%), 258 (7%), 240 (13%), 161 ($[C_9H_7NO_2]^+$, 100%) | 8.60 (br s, 1H, NH), 8.12 and 8.00 (AB spectrum, 4H, $^3J$ 9.2 Hz, $C_6H_4$-$COOCH_3$), 7.59-7.09 (m, 4H, C(7)-C(10)H), 6.40 (s, 1H, C(11b)H), 4.41 (q, 2H, $OCH_2CH_3$), 3.95 (s, 3H, $OCH_3$), 3.93 (X part of ABX spectrum, 1H, $^3J$ 2.5 Hz, $^3J$ 13.1 Hz, C(5)H), 3.23 and 3.13 (AB part of ABX spectrum, 2H, $^2J$ 15.5 Hz, $^3J$ 2.5 Hz, $^3J$ 13.1 Hz, C(6)$H_2$), 1.35 (t, 3H, $OCH_2CH_3$) |
| 17u[a] | 164-167 | 0.78 (A) | 219<br>249 | 3395 (NH)<br>1750 (C=O)<br>1645 (C=N) | EIMS (70 eV) m/z 397 ([M+2]$^+$, 3%), 395 ($M^+$, 9%), 324 (M+2-COOEt]$^+$, 5%), 322 ([M-COOEt]$^+$, 14%), 258([$C_{14}H_{14}N_2O_3$]$^+$, 21%), 240 ($[C_{14}H_{12}N_2O_2]^+$, 14%), 185 ($[C_{11}H_{10}N_2O]^+$, 44%), 168 (100%) | 8.62 (br s, 1H, NH), 7.87-7.03 (m, 8H, C(7)C(10)H and $C_6H_4Cl$), 6.35 (s, 1H, C(11b)H), 4.40 (q, 2H, $OCH_2CH_3$), 3.91 (X part of ABX spectrum, 1H, $^3J$ 3.0 Hz, $^3J$ 12.0 Hz, C(5)H) 3.22 and 3.10 (AB part of ABX spectrum, 2H, $^2J$ 15.8 Hz, $^3J$ 3.0 Hz, $^3J$ 12.0 Hz, C(6)$H_2$) 1.38 (t, 3H, $OCH_2CH_3$) |
| 17v[a] | 164-168 | 0.42 (A) | 222<br>247<br>267 | 1738 (C=O)<br>1658 (C=N) | EIMS (70 eV) m/z 375 ([$M^+$, 8%), 302 ([M-COOEt]$^+$, 8%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 24%), 169 ($[C_{11}H_{10}N_2]^+$, 29%), 117 (100%) | 8.86 (br s, 1H, NH), 7.84-7.04 (m, 8H, C(7)C(10) and $C_6H_4$-$CH_3$), 6.36 (s, 1H, C(11b)H), 4.39 (q, 2H, $OCH_3CH_2$) 3.91 (X part of ABX spectrum, 1H, $^3J$ 1.9 Hz, $^3J$ 12.4 Hz, C(5)H), 3.19 and 3.09 (AB part of ABX spectrum, 2H, $^2J$ 15.1 Hz, $^3J$ 1.9 Hz, $^3J$ 12.4 Hz, C(6)$H_2$), 2.38 (s, 3H, $C_6H_4$-$CH_3$), 1.39 (t, $OCH_3CH_2$) |
| 17w[a] | 178-182 | (A) | 216<br>270 | 1733 (C=O)<br>1657 (C=N) | EIMS (70 eV) m/z 391 ($M^+$, 9%), 318 ([M-COOEt]$^+$, 7%), 258 ($[C_{14}H_{14}N_2O_3]^+$, 36%), 185 ($[C_{11}H_{10}N_2O]^+$, 61%), 169 ($[C_{11}H_{10}N_2]^+$, 44%), 133 ($[C_8H_7NO]^+$, 100%) | 9.27 (br s, 1H, NH), 7.84 and 6.89 (AB spectrum, 4H, $^3J$ 9.0 Hz, C(2)-$C_6H_4$-$OCH_3$), 7.55-7.02 (m, 4H, C(7)C(10)H), 6.37 (s, 1H, C(11b)H), 4.40 (q, 2H, $OCH_2CH_3$), 3.93 (Xpart of ABX spectrum, $^3J$ 2.4 Hz, $^3J$ 12.4 Hz, C(5)H), 3.81 (s, 3H, $C_6H_4$-$OCH_3$), 3.21 and 3.11 (AB part of ABX spectrum, 2H, $^2J$ 15.6 Hz, $^3J$ 2.4 Hz, $^3J$ 12.4 Hz, C(6)$H_2$), 1.39 (t, 3H, $OCH_2CH_3$) |
| 18a | oil | 0.75 (B) | 214<br>258 (sh)<br>264, 271<br>286,<br>307 (sh) | 2240 (nitrile)<br>1669 (C=N) | EIMS (70 eV) m/z 241 ($M^+$, 4%), 173 ($[C_{10}H_9N_2]^+$, 14%), 147 ($[C_9H_9NO]^+$, 100%) | 7.55-7.03 (m, 4H, C(7)-C(10)H), 5.96 (s, 1H, C(10b)H), 3.48-2.63 (m, 4H, C(5)-C(6)$H_2$), 1.67 (s, 6H, 2x$CH_3$) |

a) Satisfactory micro analysis were obtained for these compounds (C±0.5%, H±0.2%, N±0.4%) b) Esterfied to methoxycarbonyl with thionyl chloride in methanol.

Table 5. Spectroscopic data of cycloadducts 17, 18, 19 and 22.

| Product | mp (°C) | Rf (Solv.Sys.) | UV (MeOH) λmax (nm) | IR ν ($cm^{-1}$) | Mass Spectrum | $^1$H NMR δ (ppm) |
|---|---|---|---|---|---|---|
| 18b | oil | 0.66 (B) | 214, 256 (sh) 263, 270 286 307 (sh) | 1660 (C=N) | EIMS (70 eV) m/z 296 ([M+6]$^+$, 0.3%), 294 ([M+4]$^+$, 2.8%), ([M+2]$^+$, 8.4%), 290 (M$^+$, 8.4%), 173 ([$C_{10}H_9N_2O$]$^+$, 20%), 147 ([$C_9H_9NO$]$^+$, 100%) | 7.61-7.06 (m, 4H, C(7)-C(10)H), 6.20 (s, 1H, C(10b)H), 3.60-2.67 (m, 4H, C(5)-C(6)$H_2$) |
| 18c | oil | 0.82 (B) | 205, 237, 283 (sh), 271 (sh) | 1645 (C=N) | EIMS (70 eV) m/z 250 (M$^+$, 6%), 173 ([$C_{10}H_9N_2O$]$^+$, 10%), 147 ([$C_9H_9NO$]$^+$, 100%), 77 (58%) | 8.02-7.90 (m, 2H, C(2)Ph-ortho-H's), 7.58-7.07 (m, 7H, C(7)-C(10)H and C(2)Ph-meta, para-H), 6.13 (s, 1H, C(10b)H), 3.74-2.67 (m, 4H, C(5)-C(6)$H_2$) |
| 19b | oil | 0.90 (B) | 204 238 | 1662 (C=N) | EIMS (70 eV) m/z 284 ([M+6]$^+$, 0.3%), 282 ([M+4]$^+$, 3.1%), 280 ([M+2]$^+$, 9.2%), 278 (M$^+$, 9.6%), 161 ([$C_9H_9N_2O$]$^+$, 5%), 134 ([$C_8H_8NO$]$^+$, 100%), 77 (33%) | 7.34 (s, 5H, Ph), 5.73 (s, 1H, C(3)H), 2.97 (s, 3H, N-$CH_3$) |
| 19c | oil | 0.76 (B) | 204 238 | 1680 (C=N) | EIMS (70 eV) m/z 238 (M$^+$, 24%), 193 ([$C_{14}H_{11}N$]$^+$, 5%), 135 ([$C_9H_9NO$]$^+$, 100%), 77 ([$C_6H_5$]$^+$, 60%) | 8.04-7.93 (m, 2H, C(5)-Ph-ortho-H's), 7.50-7.24 (m, 8H, C(3)-Ph and C(5)-Ph-meta,para-H's), 5.77 (s, 1H, C(3)H), 2.98 (s, 3H, N-$CH_3$) |
| 22[a] | 187-189 | 0.26 (B) | 222, 273 280 290 (sh) | 3200 (NH) 1740 (C=O) 1721 (C=O) | EIMS (70 eV) m/z 372 (M$^+$, 39%), 299 ([M-COOEt]$^+$, 38%), 185 ([$C_{11}H_{10}N_2O$]$^+$, 100%), 169 ([$C_{11}H_9N_2$]$^+$, 42%) | 8.03 (br s, 1H, NH), 7.48-6.98 (m, 4H, C(7)-C(10)H), 5.11 (d, 1H, $^3$J=8.9 Hz, C(11b)H), 4.93 and 4.85 (2xq, 1H, $^3$J 7.3 Hz, $^3$J 8.0 Hz, C(2)H), 4.43 (X part of ABX spectrum, 1H, $^3$J 6.6 Hz, $^3$J 6.8 Hz, C(5)H), 4.27 (q, 2H, $OCH_2CH_3$), 3.83 (q, 2H, $OCH_2CH_3$), 3.76 (2xd, 1H, $^3$J 7.3 Hz and $^3$J 9.9 Hz, C(1)H), 3.61 and 3.52 (AB part of ABX spectrum, 2H, $^2$J 15.3 Hz, $^3$J 6.6 Hz, $^3$J 6.8 Hz, C(6)$H_2$), 1.35 (d, 3H, $^3$J 8.0 Hz, C(2)$CH_3$), 1.33 (t, 3H, $OCH_2CH_3$), 0.87 (t, 3H, $OCH_2CH_3$). |

a) Satisfactory micro analysis were obtained for these compounds (C±0.5%, H±0.2%, N±0.4%).

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