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Cycloadducts of Ethene with 2(1*H*)-Pyrazinones and their conversion into 2,5-Diazabicyclo[2.2.2]octane-3,6-diones.

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Abstract: Cycloaddition of variously substituted 2(1*H*)-pyrazinones with ethene and subsequent hydrolysis of the adducts **2** provides a general and efficient route to the title compounds **3** Compound **3m** was used as a building block for a structural analogue of gliotoxin

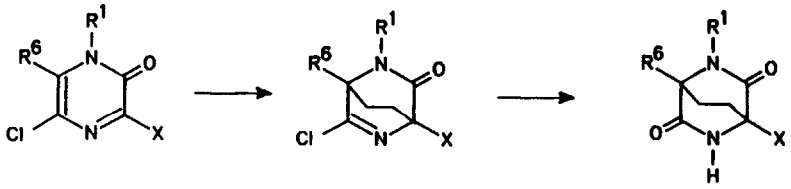
The easily accessible[1,2] 2(1*H*)-pyrazinones **1** react with acetylenic compounds to form, upon cycloreversion of the initial adducts, pyridones and/or pyridines [2,3] The reactivity of the azadiene system **1** towards ethene[4] and the cycloaddition of cyclopentene to a 5-ethoxy substituted pyrazinone[5] has been reported Now we describe in more detail the reactions of ethene with variably substituted systems **1**
Interest in the cycloadducts **2** formed in this reaction centers around their conversion, via hydrolysis of the iminochloride function, into variously substituted 2,5-diazabicyclo[2 2 2]octane-3,6-diones **3** These compounds are useful among others in peptide conformation mimetics [6]

Compounds containing the 2,5-diazabicyclo[2 2 2]octane-3,6-dione skeleton were isolated by trapping pyrazine-2,5-dione mesomeric betaines[7] or by reacting 2,5-dihydroxy-1,4-diazines[5] with some olefins Available synthetic methods for 2,5-diazabicyclo[2 2 2]octane-3,6-diones **3**, starting from α,α'-diamino adipates,[8-10] lack versatility in varying the substitution pattern on the nitrogen atoms or in the bridgehead positions 1 and 4 A lithiation-alkylation technique has been developed, aiming at the introduction of alkyl groups on the bridgehead positions of a symmetrically N,N'-disubstituted dione [11] Dione **5** was obtained as a side product in the conversion of the epoxide **4** with NH_3 [12]

In order to examine the scope of the cycloaddition with ethene, various 3-X-substituents were introduced into the pyrazinone system, in addition to the R^1 and R^6 groups determined by the choice of the starting amine and aldehyde Displacement of the 3-chloro substituent with thiocyanate proceeded in the way described for cyanide and methoxide [3] The 3-methyl substituted compound **1i** was obtained indirectly through substitution with methylenetriphenylphosphonium ylide and subsequent hydrolysis Grignard reactions with PhMgBr and *t*-BuMgBr afforded compounds **1k,l**

The cycloaddition reaction of compounds **1a-m** with ethene (25 atm) in toluene at 110°C is quite general The presence of unmodified adducts **2** (X = Cl, CN, SCN) was demonstrated by immediate spectral analysis of the Diels-Alder reaction mixture The sensitivity to air moisture observed for adducts **2** (X = aryl or alkyl) prevented their identification From the approximate reaction time needed for

SCHEME 1.



1 2 3

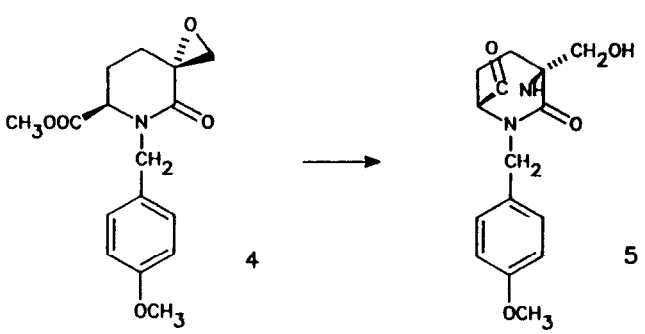
	R^1	R^6	X		R^1	R^6	X
a	Ph	H	Cl	h	Ph	H	CN
b	$PhCH_2$	H	Cl	i	$PhCH_2CH_2$	H	Me
c	$PhCH_2CH_2$	H	Cl	j	Ph	H	OMe
d	Ph	Ph	Cl	k	$PhCH_2$	H	Ph
e	Et	Ph	Cl	l	$PhCH_2$	H	*t*-Bu
f	$PhCH_2$	Ph	Cl	m	*p*-MeC_6H_4	H	SCN
g	$PhCH_2$	Et	Cl				

TABLE 1. Reaction conditions and yields of compounds 3 obtained after hydrolysis (NaOH in aqueous dioxane) of adducts 2 from 2(1*H*)-pyrazinones and ethene (25 atm.) in toluene at 110°C.

pyraz	reaction time[a] h	yield 3 %	pyraz.	reaction time[a] h	yield 3 %
1a	16	86	1h	12	82
1b	16	77	1i	24	73[b]
1c	18	76	1j	240	58[b,c]
1d	48	64	1k	24	83[b]
1e	48	80	1l	40	64[b]
1f	48	72	1m	16	82
1g	48	68			

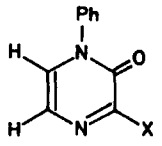
(a) approximate values corresponding to complete disappearance of the starting pyrazinone on TLC
(b) immediate hydrolysis due to air moisture
(c) incomplete reaction, ethene pressure 40 atm

SCHEME 2



4 5

complete disappearance of compounds **1a-m** (table 1) it can be deduced that the cycloaddition proceeds more easily when X is an electron withdrawing group Reaction of **1j** (X = OCH_3) required a high ethene pressure and a prolonged reaction time (more than 10 days), whereas for **1h** addition was complete within 12 hours The results obtained for **1d-g** also show a reduced reaction rate for substituents R^6 different from H Moreover, the 5-chloro substituent of **1** appears to be essential for the cycloaddition of ethene to the 2(1*H*)-pyrazinone system no reaction was observed for compounds **1n,o**



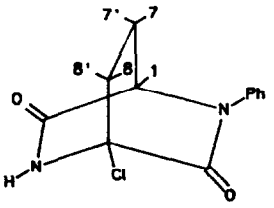
1n : X = Cl
1o X = CH_3

Hydrolysis of the iminochloride group of the crude adducts **2** with aqueous NaOH and chromatographic purification afforded the crystalline bislactams **3** in good yields (table 1)

The structures of compounds **3** were secured by spectral data. Their proton NMR-spectra show a complex coupling pattern in the region between 3 5 and 2 ppm (in $CDCl_3$), due to the presence of two mutually coupled pairs of diastereotopic protons on the bridge An even more complex pattern is observed for compounds **3a-c** and **3h-m** having an extra proton in the bridgehead position This is well illustrated by the ^{1}H-NMR data of compound **3a** listed in table 2 Assignment of the signals to protons H-8 or H-8' and H-7 or H-7' is based on their characteristic coupling pattern and J values [13]

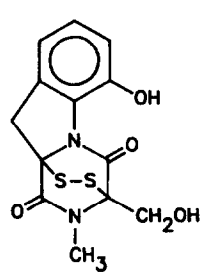
The two carbonyl groups for these compounds are observed in the ^{13}C-NMR spectrum as two low field absorptions at about δ 169 for CONH and δ 166 for CONR The intense IR-absorption band around 1700 cm^{-1} and important fragment ions corresponding to $[M - CONH]^+$ and $[M - CONR]^+$ in the electron-impact mass spectra also confirm the presence of the lactam functions

TABLE 2. Proton-NMR spectrum of compound 3a (in DMSO-d_6)



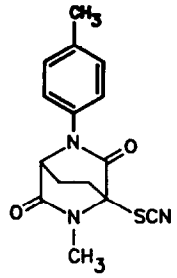
9 8	br s	1H	NH	
7 5-7 2	m	5H	Ar-H	
4 5	dd	1H	H-1	^{3}J=4Hz, ^{3}J=2Hz
2 6	ddd	1H	H-8'	^{2}J=13Hz, ^{3}J=10 7Hz, ^{3}J=4Hz
2 5	ddd	1H	H-8	^{2}J=13Hz, ^{3}J=10 3Hz, ^{3}J=4Hz
2 4	dddd	1H	H-7	^{2}J=13Hz, ^{3}J=10 3Hz, ^{3}J=4Hz, ^{3}J=4Hz
2 2	dddd	1H	H-7'	^{2}J=13Hz, ^{3}J=10 7Hz, ^{3}J=4Hz, ^{3}J=2Hz

The bicyclic system **3** shows synthetic potential for bridged analogues of piperazine drugs and piperazine-2,5-diones, i e bioactive cyclic dipeptides [14] The versatility achieved for the substitution pattern of **3** was used to mimic the structure of gliotoxin **6** This compound exhibits fungicidal and antiviral properties [15] Alkylation of **3m** using a phase transfer catalyst afforded the N-methyl compound **7** The target molecule **8** was obtained in good yield by displacing cyanide with the thiophenolate anion [16] However, compound **8** was devoid of any fungicidal or antiviral properties

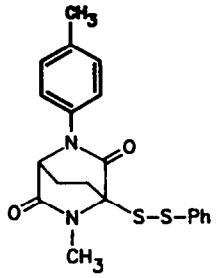


6

3m ⟶



7 ⟶



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CONCLUSION

In conclusion, a new and versatile route to 2,5-diazabicyclo[2 2 2]octane-3,6-diones has been developed proceeding through cycloaddition of ethene to 2(1*H*)-pyrazinones These compounds offer opportunities for conversion into bridged analogues of bioactive cyclic dipeptides Their ring opening reactions are under current investigation

EXPERIMENTAL SECTION

All melting points are uncorrected Infrared spectra were recorded on a Perkin Elmer 257 spectrophotometer Mass spectra were run on a Kratos MS-50 (ionization energy 70 eV) apparatus For the NMR spectra (δ, ppm) a Varian EM-390 and a Bruker WM-250 spectrometer were used Analytical and preparative thin layer chromatography was performed using Merck silica gel 60 PF-224 Column chromatography was carried out using 70-230 mesh silica gel 60 (E M Merck)

I SYNTHESIS OF 2(1*H*)-PYRAZINONES

1 The 3,5-dichloro-2(1*H*)-pyrazinones **1a-g**

The pyrazinones **1a,b** were prepared as reported previously [1] Pyrazinones **1c-g** were synthesized according to the same procedure and were recrystallized from EtOH

3,5-dichloro-1-phenethyl-2(1*H*)-pyrazinone 1c
Yield 83%, m p 192-193°C, IR (KBr) cm^{-1} 1680 (CO), 1590 (C=N), ^{1}H-NMR ($CDCl_3$) 7 3 (m, 5H, Ar-H), 6 8 (s, 1H, H_6), 4 2 (t, 2H, CH_2N), 3 1 (t, 2H, CH_2Ar), m/z 268 (M^+, 37), 91 (100), exact mass for $C_{12}H_{10}Cl_2N_2O$ 268 0168, found 268 0166

3,5-dichloro-1,6-diphenyl-2(1*H*)-pyrazinone 1d
Yield : 56%, m.p : 218-220°C, IR (KBr) cm^{-1} 1680 (CO), 1565 (C=N); ^{1}H-NMR ($CDCl_3$) 7 3-6 9 (m, Ar-H); m/z 316 (M^+, 100), 288 (M^+-CO, 43), 253 (288-Cl, 12), exact mass for $C_{16}H_{10}Cl_2N_2O$ 316 0168, found: 316 0169

3,5-dichloro-1-ethyl-6-phenyl-2(1*H*)-pyrazinone 1e
Yield 72%, m p 157°C, IR (KBr) cm^{-1} 1670 (CO), 1540 (C=N), ^{1}H-NMR ($CDCl_3$) 7 8-7 2 (m, 5H, Ar-H), 3 8 (q, 2H, CH_2), 1 2 (t, 3H, CH_3), m/z 268 (M^+, 96), 240 (M^+-CO, 100), exact mass for $C_{12}H_{10}Cl_2N_2O$) 268 0168, found 268 0176

1-benzyl-3,5-dichloro-6-phenyl-2(1*H*)-pyrazinone 1f
Yield 68%, m p 149-150°C, IR (KBr) cm^{-1} . 1665 (CO), 1560 (C=N), ^{1}H-NMR ($CDCl_3$) 7 7-6 8 (m, 10H, Ar-H), 5 0 (s, 2H, CH_2), m/z : 330 (M^+, 16), 239 (M^+-$PhCH_2$, 100), exact mass for $C_{17}H_{12}Cl_2N_2O$ 330 0325, found· 330 0331

1-benzyl-3,5-dichloro-6-ethyl-2(1*H*)-pyrazinone 1g
Yield 74%, m p 80°C, IR (KBr) cm^{-1} 1670 (CO), 1570 (C=N), ^{1}H-NMR ($CDCl_3$) 7 3 (m, 5H, Ar-H), 5 2 (s, 2H, CH_2-Ar), 2 9 (q, 2H, $\underline{CH_2}$-CH_3), 1 2 (t, 3H, CH_3), m/z 282 (M^+, 6), 91 (100), exact mass for $C_{13}H_{12}Cl_2N_2O$ 282 0325, found 282 0328

2 The 3-substituted 2(1*H*)-pyrazinones **1h-m**

The introduction of cyano and methoxy groups to yield compounds **1h,j** was performed as described in previous work [3]

5-chloro-3-methyl-1-phenethyl-2(1*H*)-pyrazinone 1i
To a suspension of 3 3 g (9.2 mmol) methyltriphenylphosphonium bromide in 50 ml of dry THF, stirred under nitrogen atmosphere at -30°C, was added 3 7 ml of a 2 5N n-BuLi solution in hexane After stirring for 15 minutes at this temperature, the pyrazinone **1c** (1 1 g, 4 2 mmol) dissolved in 15 ml dry THF was added The mixture was allowed to react for six hours at room temperature To the solution of the formed phosphonium ylide, 10 ml of a 1N solution of Na_2CO_3 in water was added and the reaction mixture was refluxed for another six hours After cooling to room temperature and adjusting the solution to pH=3, by slowly adding 3N HCl solution, the solvent was removed under reduced pressure The residue was dissolved in 50 ml water and then extracted with 4 x 25 ml of chloroform The combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure The product was subjected to column chromatography on silica gel using chloroform-ethyl acetate mixtures (0 to 10% EtOAc) as eluent

Yield 0 85 g, 82%, m p (EtOH) 106°C, IR (KBr) cm^{-1} 1650 (CO), 1595 (C=N), ^{1}H-NMR ($CDCl_3$) 7 4-7 0 (m_1 5H, Ar-H), 6 8 (s, 1H, H_6), 4 1 (t, 2H, CH_2N), 3 0 (t, 2H, CH_2Ar), 2 5 (s, 3H, CH_3), m/z 248 (M^+, 4), 104 (100), 91 (7), exact mass for $C_{13}H_{13}ClN_2O$ 248 0716, found 248 0723

1-benzyl-5-chloro-3-phenyl-2(1*H*)-pyrazinone 1k
To a solution of pyrazinone **1b** (2 5 g, 10 mmol) in 150 ml of dry THF at -30°C, was added 3 7 ml of a 3M solution of PhMgBr in diethyl ether After ten minutes some water was added and the mixture was brought to room temperature After separation of the organic phase the aqueous layer was extracted with chloroform The combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure Chromatographic separation of the residue on a silica gel column eluting with a chloroform-ethyl acetate mixture (1 to 6% EtOAc) gave the title compound **1k**

Yield 2 6 g, 90%, m p (EtOH) 86°C, IR (KBr) cm^{-1} 1650 (CO), 1580 (C=N), ^{1}H-NMR ($CDCl_3$) 8 4 (m, 2H, Ar-H), 7 4 (m, 8H, Ar-H), 7 2 (s, 1H, H_6), 5 1 (s, 2H, CH_2), m/z 296 (M^+, 24), 91 (100), exact mass for $C_{17}H_{13}ClN_2O$ 296 0715, found 296 0724, anal calcd C 68 81, H 4 42, N 9 44, found C 68 82, H 4 41, N 9 42

1-benzyl-3-*t*-butyl-5-chloro-2(1*H*)-pyrazinone 1l
The same procedure as for compound **1k** was applied using 5 5 ml of a 2M solution of *t*-BuMgBr in diethyl ether

Yield 0 97 g, 35%, m p. (EtOH) 133°C, IR (KBr) cm^{-1} 1665 (CO), 1590 (C=N), ^{1}H-NMR ($CDCl_3$) 7.3 (s, 5H, Ar-H), 7 05 (s, 1H, H_6), 5 05 (s, 2H, CH_2), 1 4 (s, 9H, CH_3), m/z . 276 (M^+, 11), 185 (M^+-$PhCH_2$, 47), 91 (100), exact mass for $C_{15}H_{17}ClN_2O$ · 276 1028, found. 276 1039

5-chloro-2-oxo-1-tolyl-pyrazin-3-yl thiocyanate 1m
The 3,5-dichloro-1-tolyl-2(1*H*)-pyrazinone (2 5 g, 10 mmol) (prepared according to the method mentioned above) in 100 ml acetone was refluxed in the presence of 3 eq. of KSCN for four hours After reaction, the solvent was evaporated under reduced pressure The residue was dissolved in chloroform and filtered The filtrate was washed with water and dried over magnesium sulphate Chloroform was then removed and the remaining solid was purified on a silica gel column (eluent 0 to 10% $CHCl_3$-EtOAc)

3,5-dichloro-1-tolyl-2(1*H*)-pyrazinone Yield 73%, m p 169-170°C, IR (KBr) cm^{-1} 1670 (CO), 1560 (C=N); ^{1}H-NMR ($CDCl_3$) · 7 4-7 1 (m, 5H, Ar-H + H_6), 2 35 (s, 3H, CH_3), m/z 254 (M^+, 79), 226 (M^+-CO, 26), 91 (100); exact mass for $C_{11}H_8Cl_2N_2O$ 254 0014, found 254 0016

5-chloro-2-oxo-1-tolyl-pyrazin-3-yl thiocyanate **1m** Yield 2 5 g 92%, m p ($CHCl_3$-hexane) 147°C, IR (KBr) cm^{-1} 2170 (SCN), 1660 (CO), 1610 (C=N), ^{1}H-NMR ($CDCl_3$) 7 4 (m, 4H, Ar-H), 7 35 (s, 1H, H_6), 2.4 (s, 3H, CH_3); m/z 277 (M^+, 100), 249 (M^+-CO, 19), 214 (249-Cl, 14), exact mass for $C_{12}H_8ClN_3OS$ 277 0076, found 277 0076

3 2(1*H*)-pyrazinones dehalogenated in position 5

Compound **1n** has been described[3] and the same method has been applied for **1o**

3-methyl-1-phenyl-2(1*H*)-pyrazinone 1o
Yield 89%, m p (EtOH) · 110-111°C, IR (KBr) cm^{-1} 1652 (CO), 1584 (C=N), ^{1}H-NMR ($CDCl_3$) 7 55-7 35 (m, 5H, Ar-H), 7 25 (d, J= 4.5 Hz, 1H, H_5), 7 1 (dq, J= 4 5, O 7 Hz, 1H, H_6)[17], 2 5 (d, J = 0 7Hz, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) 159 6 (CO), 155 6 (C_3), 139 4-125 8 (Ar-C), 126 9 (C_6), 122 2 (C_5), 20 9 (CH_3); m/z 186 (M^+, 100), 158 (M^+-CO, 45), 77 (69), exact mass for $C_{11}H_{10}N_2O$ 186 0793, found 186 0795

II SYNTHESIS OF 2,5-DIAZABICYCLO[2.2.2]OCTANE-3,6-DIONES 3

1. 2,5-diazabicyclo[2.2.2]oct-5-en-3-ones 2

The 2(1*H*)-pyrazinone (1 mmol) was dissolved in 30 to 40 ml of toluene and the solution transferred to a steel bomb under 25 atm ethylene The bomb was heated at 110°C for several hours (see table 1) After careful removal of the gas, the solvent was evaporated under reduced pressure. The unstable residue was used as such for hydrolysis Adducts **2a**, **2e**, **2h** and **2m** were spectroscopically identified using the crude reaction mixtures

4,6-dichloro-2-phenyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one 2a
IR (KBr) cm^{-1} 1692 (CO), ^{1}H-NMR ($CDCl_3$) 7 5-7 15 (m, 5H, Ar-H), 4 9 (m, 1H, H_1), 2 5-1 9 (m, 4H, H_7 + H_8), ^{13}C-NMR ($CDCl_3$) 163 6, 161 0 (CO and C_6), 138 1-123 5 (Ar-C), 88 1 (C_4), 63 4 (C_1), 32 3 (C_8), 25 9 (C_7), m/z 268 (M^+, 5), 149 (M^+-PhNCO, 87), 119 ($PhNCO^+$, 100)

4,6-dichloro-2-ethyl-1-phenyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one 2e
IR (KBr) cm^{-1} · 1675 (CO); ^{1}H-NMR ($CDCl_3$) · 7 5 (m, 5H, Ar-H), 3 5 (qd, 1H, $\underline{CH_2}CH_3$), 3 0 (qd, 1H, $\underline{CH_2}CH_3$), 2.6-2 2 (m, 4H, H_7+H_8), 0 85 (t, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) : 165 5 (CO), 162 6 (C_6), 131.9-128 2 (Ar-C), 87.1 (C_4), 70 0 (C_1), 39 3 (CH_2N), 34 2, 30 2 (C_8 and C_7), 13 2 (CH_3), m/z 297 ($M+H^+$, 0.3), 296 (M^+, 0 1), 225 (M^+-EtNCO, 100), 190 (225-Cl, 50)

3-chloro-6-oxo-5-phenyl-2,5-diazabicyclo[2.2.2]oct-2-ene-1-carbonitrile 2h
IR (KBr) cm^{-1} 2229 (CN), 1705 (CO); ^{1}H-NMR ($CDCl_3$) 7 5-7 2 (m, 5H, Ar-H), 4 9 (dd, 1H, H_4), 2 7-2.0 (m, 4H, H_7+H_8); ^{13}C-NMR ($CDCl_3$) 164 1 (CO), 162 0 (C_3), 137 5-123.5 (Ar-C), 115 6 (CN), 67 3 (C_1), 63 4 (C_4), 27 6 (C_7), 24.9 (C_8); m/z 259 (M^+, 3), 119 ($PhNCO^+$, 100), exact mass calcd for $C_{13}H_{10}ClN_3O$ · 259 0510; found 259 0513

3-chloro-6-oxo-5-tolyl-2,5-diazabicyclo[2.2.2]oct-2-enyl thiocyanate 2m
IR (NaCl) cm^{-1} 2241 (SCN), 1693 (CO), ^{1}H-NMR ($CDCl_3$) 7 3-7 1 (m, 4H, Ar-H), 4 85 (m, 1H, H_4), 2 5-2 0 (m, 4H, H_7 + H_8), 2 35 (s, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) 163 9, 162 6 (CO and C_3), 137 5-123 2 (Ar-C), 110.3 (SCN), 83 1 (C_1), 63 9 (C_4), 30 1 (C_7), 26 0 (C_8), 20 8 (CH_3); m/z 305 (M^+, 4), 133 (*p*-$MeC_6H_4NCO^+$, 100), exact mass calcd for $C_{14}H_{12}ClN_3OS$ 305 0388, found· 305 0389

2. 2,5-diazabicyclo[2.2.2]octane-3,6-diones **3**

Method 1 (if X ≠ Cl or (S)CN) The residue of the cycloaddition reaction containing the 2,5-diazabicyclo[2 2 2]oct-5-en-3-ones **2** was exposed to air for one hour, to allow for rapid and complete hydrolysis of these compounds Purification was achieved by crystallization from a chloroform-hexane mixture

Method 2 (if X = Cl or (S)CN) A mixture of 25 ml 1N NaOH and 50 ml dioxane was added to the residue with the 2,5-diazabicyclo[2 2 2]oct-5-en-3-ones **2** After stirring for one hour at room temperature, the solvent was removed under reduced pressure The residue was dissolved in 50 ml of water and extracted with 4 x 25 ml of chloroform After evaporation of the solvent the product was purified on silica gel plates (eluent = 100% EtOAc) and crystallized from a chloroform-hexane mixture

4-chloro-2-phenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3a
Yield 86% (before crystallization), m p 204°C, IR (KBr) cm^{-1} 1700 (strong, CO), 1H-NMR (DMSO d_6) see table 2; ^{13}C-NMR (DMSO-d_6) 169 0, 164 4 (C_3 and C_6), 139 0-123 8 (Ar-C), 76 9 (C_4), 61 9 (C_1), 35 2 (C_8), 24 3 (C_7), m/z 250 (M^+, 14), 222 (M^+-CO, 43), 131 (M^+-PhNCO, 25), 129 (131-2H, 100), exact mass for $C_{12}H_{11}ClN_2O_2$ 250 0510, found 250 0503

2-benzyl-4-chloro-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3b
Yield 77%, m p 159°C, IR (KBr) cm^{-1} 1700 (strong, CO), ^{1}H-NMR ($CDCl_3$) 8 35 (broad s, 1H, NH), 7 35 (m, 5H, Ar-H), 4 8 (d, J= 14 Hz, 1H, CH_2Ar), 4 4 (d, J= 14 Hz, 1H, CH_2Ar), 4 0 (dd, J= 3 5, 2Hz, 1H, H_1), 2 4 (ddd, J= 13, 10, 5Hz, 1H, H_8), 2 3 (ddd, J= 13, 10, 4 5Hz, 1H, H_8), 2 0-1 7 (m, 2H, H_7), ^{13}C-NMR ($CDCl_3$) 170 0, 165 7 (C_3 and C_6), 135 3-128 1 (Ar-C), 75 8 (C_4), 58 7 (C_1), 49 3 (CH_2Ar), 35 6 (C_8), 24 6 (C_7), m/z : 264 (M^+, 22), 173 (M^+-$PhCH_2$, 26), 91 (100), exact mass for $C_{13}H_{13}ClN_2O_2$ 264 0664, found. 264 0667

4-chloro-2-phenethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3c
Yield 76%, m p 137°C, IR (KBr) cm^{-1} 1700 (strong, CO), ^{1}H-NMR ($CDCl_3$) 7 6 (broad s, 1H, NH), 7 25 (m, 5H, Ar-H), 3 8 (m, 1H, H_1), 3 75 (m, 2H, CH_2N), 2 9 (m, 2H, CH_2Ar), 2 4 (ddd, J= 13, 10 2, 4 5Hz, 1H, H_8), 2 2 (ddd, J= 13, 10 5, 4 5Hz, 1H, H_8), 1 9 (dddd, J= 13 5, 10 5, 4 5, 2Hz, 1H, H_7), 1.72 (dddd, J= 13 5, 10 2, 4 5, 4Hz, 1H, H_7), ^{13}C-NMR ($CDCl_3$) 169 9, 165 6 (C_3 and C_6), 137 7-126 9 (Ar-C), 75 8 (C_4), 60 4 (C_1), 48 2 (CH_2N), 35 3 (CH_2Ar), 34 4 (C_8), 24 5 (C_7), m/z 278 (M^+, 22), 187 (M^+-$PhCH_2$, 4), 131 (M^+-$PhCH_2CH_2NCO$, 17), 104 (100), exact mass for $C_{14}H_{15}ClN_2O_2$ 278 0820, found 278 0825

4-chloro-1,2-diphenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3d
Yield : 64%; m p 235°C; IR (KBr) cm^{-1} · 1700 (strong, CO); ^{1}H-NMR ($CDCl_3$) · 7 2 (m, 10H, Ar-H), 6 8 (broad s, 1H, NH), 3 1-2 5 (m, 4H, H_7+H_8); ^{13}C-NMR ($CDCl_3$) 169 3, 166.1 (C_3 and C_6), 137 0-127.5 (Ar-C), 75 8 (C_4), 69.8 (C_1), 36.1 (C_8), 30.2 (C_7); m/z · 326 (M^+, 10), 291 (M^+-Cl, 53), 283 (M^+-HNCO, 38), 263 (291-CO, 56), 255 (283-CO, 83), 77 (100), exact mass for $C_{18}H_{15}ClN_2O_2$ · 326 0820, found: 326.0820

4-chloro-2-ethyl-1-phenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3e
Yield 80%; m p . 202°C, IR (KBr) cm^{-1} · 1700 (strong, CO), ^{1}H-NMR ($CDCl_3$) . 7.55 (broad s, 1H, NH), 7 50 (m, 5H, Ar-H), 3.35 (dq, J= 14, 7Hz, 1H, $\underline{CH_2}$-CH_3), 2.95 (dq, J= 14, 7Hz, 1H, $\underline{CH_2}$-CH_3), 2 8-2 3 (m, 4H, H_7+H_8), 0 8 (t, J= 7Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) : 169 3, 166.5 (C_3 and C_6), 131 4-128 2 (Ar-C), 75 5 (C_4), 67 8 (C_1), 39.1 ($\underline{CH_2}CH_3$), 36 3 (C_8), 29.9 (C_7), 13.6 (CH_3), m/z . 278 (M^+, 11), 243 (M^+-Cl, 100), 235 (M^+-HNCO, 94), 207 (M^+-EtNCO, 51); exact mass for $C_{14}H_{15}ClN_2O_2$ 278 0820, found· 278.0825

2-benzyl-4-chloro-1-phenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3f
Yield 72%; m.p 207-208°C, IR (KBr) cm^{-1} 1705 (CO); ^{1}H-NMR ($CDCl_3$) 7.5-7 0 (m, 9H, Ar-H + NH), 6 6 (m, 2H, Ar-H), 4 9 (d, J= 15Hz, 1H, CH_2Ar), 4 0 (d, J= 15Hz, 1H, CH_2Ar), 2 7-2 1 (m, 4H, H_7 + H_8), ^{13}C-NMR ($CDCl_3$) 169.2 (C_3), 167.4 (C_6), 136 8-127 5 (Ar-C), 75 6 (C_4), 68 0 (C_1), 46 9 (CH_2Ar), 36 1 (C_8), 29 3 (C_7), m/z 340 (M^+, 2), 305 (M^+-Cl, 27), 304 (M^+-HCl, 47), 297 (M^+-HNCO, 25), 277 (304-CO, 26), 91 (100), exact mass for $C_{19}H_{17}ClN_2O_2$ 340 0977, found 340 0971

2-benzyl-4-chloro-1-ethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3g
Yield 68%, m p . 212°C, IR (KBr) cm^{-1} 1695 (strong, CO), ^{1}H-NMR (DMSO-d_6) 9 7 (s, 1H, NH), 7 4-7 1 (m, 5H, Ar-H), 4.75 (d, J= 15Hz, 1H, CH_2Ar), 4 6 (d, J= 15Hz, 1H, CH_2Ar), 2.35 (m, 2H) and 1 95 (m, 2H, H_7+H_8), 1.95 (dq, 1H, $\underline{CH_2}$-CH_3), 1 7 (dq, 1H, $\underline{CH_2}$-CH_3), 0.95 (t, J= 7Hz, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) 170 4, 167 4 (C_3 and C_6), 138 3-126 0 (Ar-C), 76 1 (C_4), 63 7 (C_1), 44 3 (CH_2Ar), 34 8 (C_8), 27.8 (C_7), 22.0 ($\underline{CH_2}$-CH_3), 8.7 (CH_3), m/z · 292 (M^+, 12), 256 (M^+-HCl, 31), 229 (M^+-CO,Cl, 22), 91 (100), exact mass for $C_{15}H_{17}ClN_2O_2$ 292 0977, found 292 0976, anal calcd C 61 54, H 5 85, N 9 57, found C 61.15, H 5 74, N 9 36

3,6-dioxo-5-phenyl-2,5-diazabicyclo[2.2.2]octane-1-carbonitrile 3h
Yield · 82%, m p · 174°C; IR (KBr) cm-1 2225 (CN), 1695 (strong, CO), ^{1}H-NMR (DMSO-d_6) . 10 05 (broad s, 1H, NH), 7 5-7 3 (m, 5H, Ar-H), 4 5 (m, 1H, H_4), 2 65-2 0 (m, 4H, H_7+H_8), ^{13}C-NMR (DMSO-d_6) · 169 0, 163 1 (C_3 and C_6), 138 3-123 9 (Ar-C), 114 3 (CN), 61 8 (C_4), 56 6 (C_1), 30 4 (C_7), 23.7 (C_8), m/z 241 (M^+, 43), 122 (M^+-PhNCO, 34), 94 (122-CO, 100), exact mass for $C_{13}H_{11}N_3O_2$ 241 0851, found 241 0850

4-methyl-2-phenethyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3i
Yield . 73%, m p sublimation at 293-297°C, IR (KBr) cm^{-1} 1695 (strong, CO), ^{1}H-NMR ($CDCl_3$) 7 90 (broad s, 1H, NH), 7 25 (m, 5H, Ar-H), 3.85 (m, 1H, H_1), 3 7 (t, 2H, CH_2N), 2 9 (t, 2H, CH_2Ar), 2 0-1 6 (m, 4H, H_7-H_8), 1 45 (s, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) 172 7, 171 2 (C_3 and C_6), 138 6-126 5 (Ar-C), 60.3 (C_1), 57 7 (C_4), 46 9 (CH_2N), 34.5 (CH_2Ar), 31 9 (C_8), 24.4 (C_7), 17 7 (CH_3), m/z . 258 (M^+, 89), 167 (M^+-$PhCH_2$, 63), 139 (167-CO, 26), 111 (89), 104 (100), exact mass for $C_{15}H_{19}N_2O_2$ 258 1367, found 258 1372

4-methoxy-2-phenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3j
yield 58%; m p 170°C, IR (KBr) cm^{-1} 1700 (strong, CO); ^{1}H-NMR ($CDCl_3$) 8 6 (broad s, 1H, NH), 7 5-7 3 (m, 5H, Ar-H), 4 42 (m, 1H, H_1), 3 77 (s, 3H, OMe), 2 5-1 9 (m, 4H, H_7+H_8), ^{13}C-NMR ($CDCl_3$) 170 9, 167 3 (C_3 and C_6), 138 6-123 7 (Ar-C), 86 6 (C_4), 62 0 (C_1), 29 9 (C_8), 23 8 (C_7); m/z 246 (M^+,4), 218(M^+-CO,10), 127 (M^+-PhNCO,26), 125(127-2H, 80), 86(100), exact mass for $C_{13}H_{14}N_2O_3$ 246 1004, found 246 1007

2-benzyl-4-phenyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3k
Yield . 83%; m.p. : 168°C, IR (KBr) cm^{-1} 1685 (strong, CO), ^{1}H-NMR ($CDCl_3$) 7 5-7.0 (m, 11H, NH+Ar-H), 4 80 (d, J= 15Hz, 1H, CH_2Ar), 4.37 (d, J = 15Hz, 1H, CH_2Ar), 3 97, (dd, J= 4, 2Hz, 1H, H_1), 2.40-2.25 (m, 2H, H_8), 2 00-1 75 (m, 2H, H_7), ^{13}-NMR ($CDCl_3$) . 171 6, 170 3 (C_3 and C_6), 136.2-127.2 (Ar-C), 64.0 (C_4), 59 2 (C_1), 48.8 (CH_2Ar), 29 8 (C_8), 24 7 (C_7), m/z 306 (M^+, 76), 215 (M^+-$PhCH_2$, 41), 173 (M^+-$PhCH_2NCO$, 47), 171 (173-2H, 73), 145 (173-CO, 100), 91 (89); exact mass for $C_{19}H_{18}N_2O_2$ · 306.1367; found 306 1374, anal calcd for C 74.49, H 5 92, N 9.14, found C 74 27, H 5.76, N 8.91

2-benzyl-4-*t*-butyl-2,5-diazabicyclo[2.2.2]octane-3,6-dione 3l
yield 62%; m.p. · 188°C; IR (KBr) cm^{-1} . 1695 (strong, CO), ^{1}H-NMR ($CDCl_3$) 8 0 (broad s, 1H, NH), 7.3 (m, 5H, Ar-H), 4.75 (d, 1H, CH_2Ar), 4.40 (d, 1H, CH_2Ar), 3.9 (m, 1H, H_1), 2 1-1 7 (m, 4H, H_7+H_8), 1.30 (s, 9H, CH_3), ^{13}C-NMR ($CDCl_3$) 172 9, 170.2 (C_3 and C_6), 136 5-127 7 (Ar-C), 65 6 (C_4), 58 5 (broad, C_1), 48 0 (CH_2Ar), 33 9 ($\underline{C}(CH_3)_3$), 25 8 (C_8), 25 5 (CH_3), 24 3 (C_7), m/z 286 (M^+, 20), 195 (M^+-$PhCH_2$, 5), 153 (M^+-$PhCH_2NCO$, 35), 151 (153-2H, 100), 91 (81), exact mass for $C_{17}H_{22}N_2O_2$ 286 1680; found 286 1682

3,6-dioxo-5-tolyl-2,5-diazabicyclo[2.2.2]octan-1-yl thiocyanate 3m
Yield . 82%, m p 125°C, IR (KBr) cm^{-1} . 2160 (SCN), 1700 (CO), ^{1}H-NMR (DMSO-d_6) 9 1 (broad s, 1H, NH), 7 2 (s, 4H, Ar-H), 4 45 (m, 1H, H_1), 2 6-2 1 (m, 4H, CH_2-CH_2), 2 4 (s, 3H, CH_3), m/z 287 (M^+, 92), 154 (M^+-*p*-MeC_6H_4NCO, 30), 126 (100), exact mass for $C_{14}H_{13}N_3O_2S$ 287 0728, found 287 0730

2-methyl-3,6-dioxo-5-tolyl-2,5-diazabicyclo[2.2.2]octan-1-yl thiocyanate 7
Compound **3m** (1 0 g, 3 7 mmol) dissolved in 50 ml CH_2Cl_2 was mixed with Bu_4NHSO_4 (0 7 mmol), NaOH (1 11 mmol) and dimethyl sulphate (30 mmol) in 50 ml water. This mixture was vigorously stirred at room temperature for 30 minutes After filtration and separation of the organic layer, the water phase was extracted with CH_2Cl_2 and the combined organic layers were dried over magnesium sulphate Filtration and evaporation of the solvent, gave the crude product **7** It was purified by column chromatography on silica gel (eluent 10% EtOAc/$CHCl_3$)

Yield · 1 0 g, 94%, m p · 162°C, IR (KBr) cm^{-1} 2160 (SCN), 1700 (CO), ^{1}H-NMR ($CDCl_3/C_6D_6$, 3/1) 7 0-6 9 (m, 4H, Ar-H), 4 12 (dd, J= 4 2 Hz, 1H, H_4), 2 95 (s, 3H, CH_3N), 2 3 (ddd, J= 14, 10 5, 6 5Hz, 1H, H_7), 2 1 (s, 3H, CH_3Ar), 1.75 (ddd, J= 14, 10 5, 6 5Hz, 1H, H_7), 1 5 (dddd, J= 14, 10 5, 6 5, 2Hz, 1H, H_8), 1 32 (dddd, J= 14, 10 5, 6 5, 4Hz, 1H, H_8), ^{13}C-NMR ($CDCl_3$) 167 2, 163 9 (C_3 and C_6), 137 3-123 4 (Ar-C), 109 6 (SCN), 77 0 (C_1), 62 0 (C_4), 32 7 (C_8), 29 1 (CH_3N), 24 3 (C_7), 20 8 (CH_3Ar), m/z · 301 (M^+, 85), 168 (M^+-*p*-MeC_6H_4NCO, 21), 140 (168-CO, 100), 91 (31), anal calcd for $C_{15}H_{15}N_3O_2S$ C 59 78, H 5 02, N 13 94, S 10 64, found C 59 57, H 4 86, N 13 93, S 10 79

5-methyl-4-phenyldithio-2-tolyl-2,5-diazabicyclo[2-2-2]octane-3,6-dione 8
To a solution of compound **7** (0 93g, 3 08 mmol) in 10 ml DMF was added 1 5 eq NEt_3 (0 46g) and 1 eq of thiophenol (0 34g) The reaction mixture was stirred at 70°C during 24h After removal of the solvent under reduced pressure, the residue was purified by column chromatography (eluent 10% EtOAc/$CHCl_3$)

Yield 0 88 g, 74%, m p (CH_2Cl_2/hexane) 143°C, IR (KBr) cm^{-1} 1680-1690 (CO), ^{1}H-NMR (C_6D_6) 7 4 (m, 2H, H_o on Ph), 7 1 (m, 2H, H_m on *p*-MeC_6H_4), 6 95 (m, 3H, H_m and H_p on Ph), 6 8 (m, 2H, H_o on *p*-MeC_6H_4), 4 2 (dd, J= 4, 2Hz, 1H, H_4), 3 0 (s, 3H, CH_3N), 2 3 (ddd, J= 14 5, 10, 5Hz, 1H, H_7), 2 0 (s, 3H, CH_3Ar), 1 55 (ddd, J= 14 5, 10, 5Hz, 1H, H_7), 1 3 (m, 2H, H_8), ^{13}C-NMR (C_6D_6) 169 4, 166.4 (C_3 and C_6), 136 8-123.7 (Ar-C), 77 4 (C_1), 62 1 (C_4), 30 9 (C_8), 29 8 (CH_3N), 24 7 (C_7), 20 9 (CH_3Ar), m/z 384 (M^+, 100), 275 (M^+-SPh, 75), 242 (M^+-SSPh, 34), anal calcd for $C_{20}H_{20}N_2O_2S_2$. C 62 47, H 5 24, N 7 29, S 16 68, found C 62 39, H 5 04, N 7 23, S 16 49

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