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Cycloadducts of Ethene with 2(1*H*)-Pyrazinones Functionalisation and Reduction to 2,5-Diazabicyclo[2.2.2]octan-3-ones.

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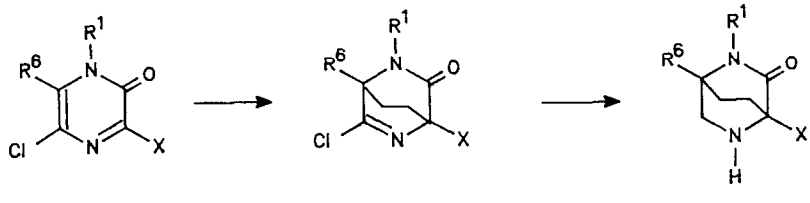
Abstract The title compounds **4** were prepared via Diels-Alder reaction of 3,5-dichloro-2(1*H*)-pyrazinones **1** with ethene, followed by catalytic reduction of the iminochloride group generated in the cycloadducts **2** Substitution of the iminochloride group with various nucleophiles afforded the 6-functionalised analogues of **2** Their reduction can lead to 6-substituted derivatives of compounds **4** One example is given

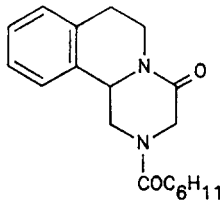
In contrast to the cycloaddition-elimination reactions observed[1,2] for most 2(1*H*)-pyrazinones[2,3] **1** and acetylenic compounds, reaction of **1** and ethene always afforded bicyclic adducts **2**, these adducts were hydrolysed readily to form the 2,5-diazabicyclo[2 2 2]octane-3,6-diones **3** [4] Here we report substitution and reduction of the iminochloride group of the cycloadducts **2**, yielding novel 2,5-diazabicyclo[2 2 2]octan-3-ones **4**



1 2 4

Scheme 1

Whereas bridged compounds of type **4** are unknown, the unbridged piperazinone structure appears in many biologically active compounds, for instance when incorporated in a polycyclic system such as the anthelmintic praziquantel **5** [5] Further reduction of the carbonyl function of **4** could provide access to the 2,5-diazabicyclo[2 2 2]octanes **6**, bridged analogues of piperazine drugs [6]



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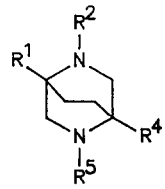


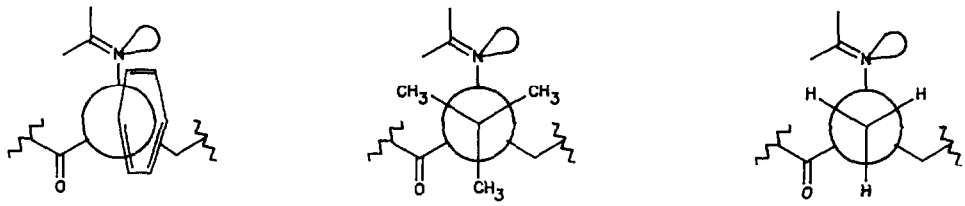
6

In the preceding paper,[4] cycloaddition of ethene to 2(1*H*)-pyrazinones was shown to be general, provided a 5-chloro substituent is present as indicated in Scheme 1 Hydrogenation of the crude compounds **1a-g** in THF, using Pd/C as a catalyst and DABCO as a scavenger of HCl, afforded compounds **4** in good overall yield from **1** (table 1) However when starting from pyrazinones **1h-j** (X = Me, Ph and *t*-Bu), this reaction sequence was inefficient Mainly the hydrolysed bislactam products **3h-j** were isolated on workup of the hydrogenated mixture Scrupulous drying of the solvents, or using the same solvent (toluene) for both Diels-Alder reaction and hydrogenation, did not improve much on this result

Table 1. Yields of compounds 4 obtained after catalytic reduction of adducts 2 from 2(1*H*)-pyrazinones and ethene (25 atm.) in toluene at 110°C.

	R^1	R^6	X	yield 4 %
1a	Ph	H	Cl	67
1b	$PhCH_2$	H	Cl	71
1c	$PhCH_2CH_2$	H	Cl	64
1d	Ph	Ph	Cl	58
1e	Et	Ph	Cl	58
1f	$PhCH_2$	Ph	Cl	64
1g	$PhCH_2$	Et	Cl	60
1h	$PhCH_2CH_2$	H	Me	10
1i	$PhCH_2$	H	*t*-Bu	5
1j	$PhCH_2$	H	Ph	0

The way in which the nature of the angular substituent of adducts **2** (X = Cl, Me, *t*-Bu or Ph) affects the rate of hydrolysis poses an intriguing problem Possibly, steric or electronic interaction with the imino nitrogen is relieved in going from sp^2 to sp^3 nitrogen during formation of a tetrahedral water addition intermediate Inspection of molecular models indicates that the different orientation of electronic orbitals for sp^2 and sp^3 nitrogen probably is the decisive factor Indeed, in the very rigid tetrahedral intermediate, the sp^3 nitrogen cannot leave the original median sp^2 plane Relief of electronic interaction should be especially effective for the phenyl substituted adduct **2j**, which shows a prefered conformation having one ortho position eclipsed with the imino nitrogen By contrast, a less effective relief in structures **2h,i** for the methyl and *t*-butyl compounds accounts for decreased hydrolysis (10 and 5% yield of reduced compounds **4h,i**, compared to 0% for **4j**)

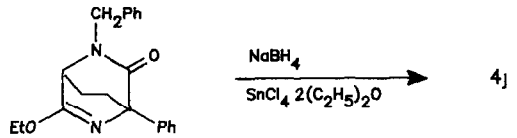


2j 2i 2h

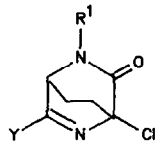
Fig 1

A way around the difficulty of preparing the 4-phenyl substituted compound **4j** was sought by carrying out the cycloaddition of **1j** and ethene in ethanol with an excess of sodium ethoxide. Ethanolysis of the intermediate adduct **2j** afforded the stable iminoether **7j** in 71% yield Subsequent reduction of **7j** to **4j** with $NaBH_4$ required activation of the iminoether group with $SnCl_4$[7] (yield 30%)

In the same context, functionalisation of the 2,5-diazabicyclo[2 2 2]oct-5-en-3-one system was investigated Substitution of the iminochloride group of adduct **2** with the appropriate nucleophiles yielded the amidino compounds **8** and **9**, the 6-ethoxy compound **7b** and the cyano derivative **10** Reaction with arylmagnesium halides failed However, activation of the iminochloride group with $AlCl_3$ allowed the electrophilic substitution of anisole, affording the 6-(p-methoxyphenyl) substituted compound **11** in 60% yield



7j



7b Y = OEt , R^1 = CH_2Ph

8 Y = N—CH_2Ph R^1 = Ph

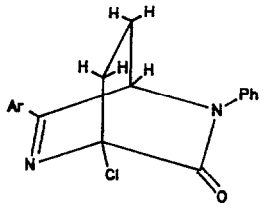
9 Y = N—CH_2Ph , R^1 = Ph

10 Y = CN , R^1 = CH_2CH_2Ph

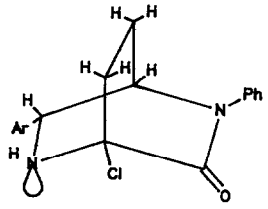
11 Y = —OCH_3 , R^1 = Ph

Further catalytic reduction of **11** gave the dihydro compound **12**, a 6-substituted analogue of **4**, as a single diastereoisomer Model inspection shows that approach of the catalyst surface to the imino group from the lactam side (bottom side of **11**) is impeded by the N-phenyl substituent

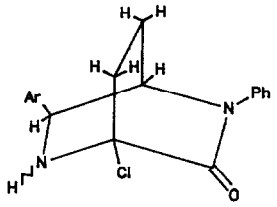
Structure **12a** was differentiated from the diastereoisomers **12c,d** by the absence of a ^4J long range coupling between H-6' and H-7 (^{1}H-NMR in C_6D_6 doublet at δ 1 25 for H-6' and a dddd for proton H-7 at δ 1 35) The cis-relationship of the NH proton with H-6' was demonstrated by the coupling constant $^3J_{5,6'}$ = 8Hz in DMSO-d_6 (compare with **12b**)



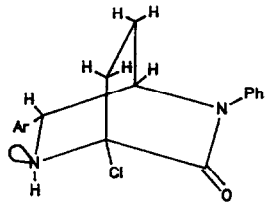
11



12a



12c,d



12b

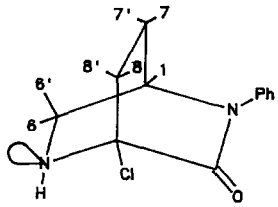
Interestingly, for the 6-unsubstituted compound **4a** this NH proton has the opposite orientation, as shown by the long range coupling with proton H-8 in DMSO-d_6 (ddd at δ 3 95 for NH and a dddd for proton H-8 at δ 2 20) and by the cis [trans] relation between the NH proton and the proton H-6 [H-6'] ($^3J_{5,6}$ = 10 2Hz, $^3J_{5,6'}$ = 5Hz)

This result can be explained as follows In structure **12a** the NH proton avoids the eclipsing interaction with the anisole group observed for **12b** In structure **4a**, the NH proton interferes less with the lactam carbonyl group than with proton H-8' in the isomeric structure **4a'**

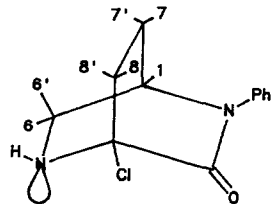
The characteristic W-coupling pattern observed for protons H-6 and H-7 in the ^{1}H-NMR spectra of compound **4** (e g **4a**, table 2) supports the stuctural assignment made above for **12a** Elaboration of the coupling patterns using proton decoupling experiments allowed complete assignment of all protons Further

evidence for the structure of compounds **4** was obtained from the carbonyl carbon absorptions in the ^{13}C-NMR spectrum (δ ca 169) and from the IR carbonyl and NH absorptions around 1670 and 3300 cm^{-1}

Table 2. Proton-NMR spectra of compound 4a in $CDCl_3$ and DMSO-d_6.



4a



4a'

DMSO-d_6	$CDCl_3$	m	#					
7 4-7 2	7 4-7 2	m	5H	Ar-H				
4 2	4 2	dddd	1H	H-1	^3J=3Hz,	^3J=3Hz,	^3J=2Hz,	^3J=1Hz
3 15	3 35	ddd[*d*](1)	1H	H-6	^2J=10 5Hz,	[^3J=*10.2Hz*]	^3J=3Hz,	^4J=3Hz,
3 0	2 25	dd[*d*]	1H	H-6'	^2J=10 5Hz,	[^3J=*5Hz*]	^3J=1Hz	
2 42	2 6	ddd	1H	H-8'	^2J=13Hz,	^3J=10 5Hz,	^3J=5Hz	
3 95	2 5	br s[*ddd*]	1H	NH	[^3J=*10 2Hz*]	[^3J=*5Hz*]	[^4J=*3Hz*]	
2 20	2 37	ddd[*d*]	1H	H-8	^2J=13Hz,	^3J=11 5Hz,	^3J=4Hz	[^4J=*3Hz*]
2 03	2 12	ddddd	1H	H-7	^2J=13Hz, ^4J=3Hz	^3J=11 5Hz,	^3J=5Hz,	^3J=3Hz,
1 90	2 0	dddd	1H	H-7'	^2J=13Hz,	^3J=10 5Hz,	^3J=4Hz,	^3J=2Hz

(1) The additional NMR data obtained in DMSO-d_6 are typed italic

CONCLUSION

A new synthetic route to 2,5-diazabicyclo[2 2 2]octan-3-ones has been developed using substitution and (or) reduction of the cycloaddition products **2** from 2(1*H*)-pyrazinones and ethene Limitations are due to the easy hydrolysis of adducts from 3-alkyl or 3-aryl substituted pyrazinones Probably these can be alleviated by regeneration of the iminochloride function from the secondary lactams, or by Lewis acid activation of the iminoether compounds (e g **7**)

EXPERIMENTAL

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 and column chromatography was done using 70-230 mesh silica gel 60 (E M Merck) as the stationary phase

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

The synthesis of the pyrazinones **1a,b**[3] and **1c-j**[4] was performed as described previously

II SYNTHESIS OF 2,5-DIAZABICYCLO[2 2 2]OCTAN-3-ONES 4

Method a The residue obtained after Diels-Alder reaction was transferred to a Parr hydrogenation apparatus and mixed with 30% w/w of Pd/C 10% and 1 mmol of the base DABCO, dissolved in dry THF The mixture was shaken for four hours at room temperature under 4 atm of hydrogen pressure After filtration of the catalyst, the filtrate was evaporated in vacuo The residue was purified on preparative plate (eluent 100% EtOAc) and crystallized from CCl_4 The yields are shown in table 1

Method b The solvent used for the Diels-Alder reaction was not removed, but the mixture was placed into a hydrogenation bottle together with 50% w/w of Pd/C 10% and 1 mmol DABCO The mixture was stirred instead of shaken for four hours Further isolation of compounds **4** was performed as detailed in Method a

4-Chloro-2-phenyl-2,5-diazabicyclo[2.2.2]octan-3-one (4a)
m p 186°C, IR (KBr) cm^{-1} 3305 (NH), 1685 (CO), ^{1}H-NMR ($CDCl_3$, 45°C) see table 2, ^{13}NMR ($CDCl_3$) 167 4 (CO), 139 9-123 7 (Ar-C), 80 8 (C_4), 55 3 (C_1), 48 9 (C_6), 35 2 (C_8), 27.4 (C_7), m/z 236 (M^+, 3), 208 (M^+-CO, 3), 119 ($PhNCO^+$, 100), 117 (M^+-PhNCO, 45), 115 (117-2H, 77), exact mass for $C_{12}H_{13}ClN_2O$ 236 0716, found 236 0720

2-Benzyl-4-chloro-2,5-diazabicyclo[2.2.2]octan-3-one (4b)
m p 89°C, IR (KBr) cm^{-1} 3300 (NH), 1685 (CO), ^{1}H-NMR ($CDCl_3$) 7 3 (s, 5H, Ar-H), 4 7 (d, J= 15Hz, 1H, CH_2Ar), 4 6 (d, J= 15Hz, 1H, CH_2Ar), 3 6 (m, 1H, H_1), 3 05 (dd, 1H, H_6), 2 9 (ddd, 1H, H_6), 2 6-2 4 (m, 2H, NH+H_8), 2 25 (m, 1H, H_8), 1 90-1 60 (m, 2H, H_7), ^{13}C-NMR ($CDCl_3$) 168 9 (CO), 136 7-128 0 (Ar-C), 80 6 (C_4), 51 7 (C_1), 49 2 (CH_2Ar), 48 8 (C_6), 35 7 (C_8), 27 4 (C_7), m/z 250 (M^+, 9), 159 (M^+-$PhCH_2$, 19), 115 (M^+-PhNCO,-2H, 100), 91 (84), exact mass for $C_{13}H_{15}ClN_2O$ 250 0873, found 250 0874

4-Chloro-2-phenethyl-2,5-diazabicyclo[2.2.2]octan-3-one (4c)
m p 97°C, IR (KBr) cm^{-1} 3290 (NH), 1675 (CO), ^{1}H-NMR ($CDCl_3$) 7 3 (m, 5H, Ar-H), 3 75 (t, J= 7Hz, 2H, CH_2N), 3 4 (m, 1H, H_1), 2 95 (m, 3H, CH_2Ar+H_6), 2 75 (dt, J= 10 3, 3Hz, 1H, H_6), 2 4 (ddd, J= 13, 10 5, 6Hz, 1H, H_8), 2 25 (broad s, 1H, NH), 2 1 (ddd, J= 13, 12, 4Hz, 1H, H_8), 1 80 (m, 2H, H_7), ^{13}C-NMR ($CDCl_3$) 168 7 (CO), 138 4-126 6 (Ar-C), 80 4 (C_4), 53 4 (C_1), 48 8 (C_6), 47 7 (CH_2N), 35 2 (C_8), 34 5 (CH_2Ar), 27 2 (C_7), m/z 264 (M^+, 20), 115 (M^+-$PhCH_2CH_2NCO$,-2H, 100), exact mass for $C_{14}H_{17}ClN_2O$ 264 1028, found 264 1031, anal calcd C 63 51, H 6 47, N 10 58, found C 63 27, H 6 46, N 10 54

4-Chloro-1,2-diphenyl-2,5-diazabicyclo[2.2.2]octan-3-one (4d)
m p 158°C, IR (KBr) cm^{-1} 3290 (NH), 1690 (CO), ^{1}H-NMR ($CDCl_3$) 7 2-6 8 (m, 10H, Ar-H), 3 8 (dd, J= 11, 3 2Hz, 1H, H_6), 3 45 (d, J= 11hz, 1H, H_6), 2 8-2 4 (m, 5H, NH+H_7+H_8), ^{13}C-NMR ($CDCl_3$) 169 0 (CO), 138 5-126 8 (Ar-C), 80 7 (C_4), 63 4 (C_1), 52 3 (C_6), 34 7, 33 9 (C_7+C_8), m/z 312 (M^+, 49), 276 (M^+-HCl, 100), 248 (276-CO, 42), 194 (49), exact mass for $C_{18}H_{17}ClN_2O$ 312 1028, found 312 1032

4-Chloro-2-ethyl-1-phenyl-2,5-diazabicyclo[2.2.2]octan-3-one (4e)
m p. 142°C, IR (KBr) cm^{-1} . 3295 (NH), 1670 (CO), ^{1}H-NMR ($CDCl_3$) 7 45 (s, 5H, Ar-H), 3.6 (dd, J= 11, 3Hz, 1H, H_6), 3 3 (d, J= 11Hz, 1H, H_6), 3 35 (dq, J= 14, 7Hz, 1H, $\underline{CH_2}$-CH_3), 3 15 (dq, J= 14, 7Hz, 1H, $\underline{CH_2}$-CH_3), 2.8 (broad s, 1H, NH), 2.7-2.1 (m, 4H, H_7+H_8), 0.85 (t, J= 7Hz, CH_3); ^{13}C-NMR ($CDCl_3$) : 169 4 (CO), 135 9-127.3 (Ar-C), 80.7 (C_4), 60.8 (C_1), 54 7 (C_6), 38.6 ($\underline{CH_2}$-CH_3), 34.6, 33 6 (C_7+C_8), 14 0 (CH_3), m/z · 264 (M^+, 41), 228 (M^+-HCl, 100), 158 (33); exact mass for $C_{14}H_{17}ClN_2O$ 264.1028; found 264 1031

2-Benzyl-4-chloro-1-phenyl-2,5-diazabicyclo[2.2.2]octan-3-one (4f)
m p ($CHCl_3$-hexane) : 180°C, IR (KBr) cm^{-1} : 3295 (NH), 1660 (CO), ^{1}H-NMR ($CDCl_3$) 7 5-7 0 (m, 8H, Ar-H), 6 6 (m, 2H, Ar-H), 4 65 (d, J= 15Hz, 1H, CH_2Ar), 4 35 (d, J= 15Hz, 1H, CH_2Ar), 3 5 (dd, J= 11, 3Hz, 1H, H_6), 3.2 (d, J= 11Hz, 1H, H_6), 2 67 (broad s, 1H, NH), 2.65 (ddd, J= 13, 11, 5Hz, 1H, H_8), 2 40-2 10 (m, 3H, H_8+H_7), ^{13}C-NMR ($CDCl_3$) : 170 6 (CO), 137 9-127 2 (Ar-C), 80.8 (C_4), 61 3 (C_1), 54 8 (C_6), 46 8 (CH_2Ar), 34 7, 33 5 (C_7+C_8), m/z 326 (M^+, 7), 290 (M^+-HCl, 23), 199 (290-$PhCH_2$, 51), 91 (100); exact mass for $C_{19}H_{19}ClN_2O$ 326 1184, found 326 1180

2-Benzyl-4-chloro-1-ethyl-2,5-diazabicyclo[2.2.2]octan-3-one (4g)
m p. : 128°C, IR (KBr) cm^{-1} . 3295 (NH), 1680 (CO), ^{1}H-NMR ($CDCl_3$) 7 35 (m, 5H, Ar-H), 4 87 (d, J= 15Hz, 1H, CH_2Ar), 4.7 (d, J= 15Hz, 1H, CH_2Ar), 3 15 (d, J= 10 5Hz, 1H, H_6), 2.78 (dd, J= 10 5, 3Hz, 1H, H_6), 2 7 (broad s, 1H, NH), 2.5 (ddd, J= 13 5, 10 5, 5Hz, 1H, H_8), 2 28 (ddd, J= 13.5, 12, 4Hz, 1H, H_8), 1 97 (ddd, J= 13, 10 5, 4Hz, 1H, H_7), 1 75 (q, J= 7 5Hz, 2H, $\underline{CH_2}$-CH_3), 1 6 (dddd, J= 13, 12, 5, 3Hz, 1H, H_7), 0 9 (t, J= 7 5Hz, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) · 169 9 (CO), 138 7-126 6 (Ar-C), 80 8 (C_4), 59 6 (C_1), 52 8 (C_6), 44 3 (CH_2Ar), 34 5, 31 3, 26 2 ($\underline{CH_2}$-CH_3+C_8+C_7), 8.7 (CH_3), m/z 278 (M^+, 68), 242 (M^+-HCl, 72), 187 (M^+-$PhCH_2$, 31), 91 (100), exact mass for $C_{15}H_{19}ClN_2O$ 278 1184, found 278 1183

4-Methyl-2-phenethyl-2,5-diazabicyclo[2.2.2]octan-3-one (4h)
m p 114°C, IR (KBr) cm^{-1} 3300 (NH), 1650 (CO), ^{1}H-NMR ($CDCl_3$) 7 25 (m, 5H, Ar-H), 3 7 (br t, 2H, CH_2N), 3 45 (m, 1H, H_1), 2 9 (br t+dd, 3H, CH_2Ar + H_6), 2 75 (dt, 1H, H_6), 2 2 broad s, 1H, NH), 1 9 (m, 1H, H_8), 1 6 (m, 3H, H_7+H_8), 1 25 (s, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) 174 9 (CO), 139 0-126 6 (Ar-C), 54 2 (C_4), 53 6 (C_1), 47 9 (C_6), 46 7 (CH_2-N), 35 0 (CH_2Ar), 32 1 (C_8), 26 0 (C_7), 20 8 (CH_3), m/z 244 (M^+, 8), 125 (24), 95 (100), exact mass for $C_{15}H_{20}N_2O$ 244 1575, found 244 1575

2-Benzyl-4-*t*-butyl-2,5-diazabicyclo[2.2.2]octan-3-one (4i)
m p 163°C, IR (KBr) cm^{-1} 1655 (CO), ^{1}H-NMR ($CDCl_3$) 7 3 (m, 5H, arom-H), 4 6 (s, 2H, CH_2Ar), 3 5 (m, 1H, H_1), 2 9 (m, 2H, H_6), 2 1-1 5 (m, 4H, H_7 + H_8), 1 2 (s, 9H, Me), ^{13}C-NMR ($CDCl_3$) 160 (CO, not resolved), 137 9, 128 7, 128 4 and 127 6 (arom-C), 62 1 (C_4), 51 3 (C_1), 47 7, 47 6 (C_6 + CH_2Ar), 34 8 ($\underline{C}(CH_3)_3$), 29 6, 25.5 (C_7 + C_8), 26 (Me), m/z 272 (M^+, 12), 181 (M^+-CH_2Ar, 39), 137 (M^+-$PhCH_2NCO$, 2H, 100), 91 (40), exact mass for $C_{17}H_{24}N_2O$ 272 1887, found 272 1881

2-Benzyl-6-ethoxy-4-phenyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (7j)·
To a solution of 0 26 g (1 mmol) of compound **1j** in 40 ml EtOH, was added 2 3 ml sodium ethoxide 1N in EtOH (2 3 mmol) The mixture was heated in a steel bomb for 64h at 80°C under 25 atm ethene pressure After removal of the gas, the solvent was removed under reduced pressure The residue was purified on silica gel preparative plates (eluent 10% EtOAc-chloroform) to yield 0 24 g (71%) of compound **7j**

m p oil, IR (NaCl) cm^{-1} 1680 (CO), 1645 (C=N), ^{1}H-NMR ($CDCl_3$) 7 8 (m, 2H, Ar-H), 7.5-7.2 (m, 8H, Ar-H), 4 6 (d, J= 14 5Hz, 1H, $\underline{CH_2}Ar$), 4 5 (d, J= 14 5Hz, 1H, $\underline{CH_2}Ar$), 4 3 (dq, J= 10 5, 7Hz, 1H, CH_2O), 4 15 (dq, J= 10 5, 7Hz, 1H, CH_2O), 4 05 (dd, J= 3, 2Hz, 1H, H_1), 2 3 (m, 1H, H_8), 1 9-1 6 (m, 3H, H_7+H_8), 1 25 (t, J= 7Hz, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) 172 9 (C_3), 170 1 (C_6), 139 9-127.0 (Ar-C), 68.0 (C_4), 62 0 (CH_2O), 54 1 (C_1), 48 3 (CH_2Ar), 30 8 (C_8), 26 0 (C_7), 14 0 (CH_3), m/z · 334 (M^+, 0.3), 201 (M^+-$PhCH_2NCO$, 100), 91(22)

2-Benzyl-4-phenyl-2,5-diazabicyclo[2.2.2]-octan-3-one (4j)

Compound **7j** (0.11 g, 0 34 mmol) in 10 ml 1,2-dimethoxyethane was mixed with 0.56 g (4mmol) $SnCl_4$ $2(C_2H_5)_2O$ and 0 26 g (20 mmol) $NaBH_4$ and stirred at room temperature for 5 days. Excess reagent was decomposed with cold 5% $CaCO_3$. After extraction with CH_2Cl_2, the organic layers were dried over magnesium sulphate, filtered and evaporated under reduced pressure Purification on silica gel preparative plates yielded 0 03 g (30%) of compound **4j**

m p (CCl_4) 122-123°C, IR (NaCl) cm^{-1} 3300 (NH), 1657 (CO), ^{1}H-NMR ($CDCl_3$) 7 6-7 2 (m, 10H, Ar-H), 4 75 (d, J= 15Hz, 1H, CH_2Ar), 4 6 (d, J= 15Hz, 1H, CH_2Ar), 3 7 (m, 1H, H_1), 3 08 (dd, 1H, H_6), 2 92 (dt, 1H, H_6), 2 15 (m, 2H, H_8), 1 9 (broad s, 1H, NH), 1 75 (m, 2H, H_7), ^{13}C-NMR ($CDCl_3$) 173 4 (CO), 139 8-126 9 (Ar-C), 60 1 (C_4), 52 2 (C_1), 48 2 and 48 0 (C_6 and CH_2Ar), 34 2 (C_8), 26 7 (C_7), m/z · 292 (M^+, 3), 201 (M^+-$PhCH_2$, 23), 157 (M^+-$PhCH_2NCO$,-2H, 100), 91(37), exact mass calcd for $C_{19}H_{20}N_2O$ 292 1575, found 292 1566

III SYNTHESIS OF 6-SUBSTITUTED 2,5-DIAZABICYCLO[2 2 2]OCT-5-EN-3-ONES

All the reactions were performed on the crude adducts **2** which were obtained via a previously described[4] cycloaddition reaction

2-Benzyl-4-chloro-6-ethoxy-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (7b)
To 1mmol of compound **2b** in 40 ml dry ethanol was added 2 3 ml sodium ethoxide 1N in EtOH (2 3 mmol) The reaction mixture was stirred at room temperature for 12h After evaporation of the solvent, the residue was purified on silica gel preparative plates (eluent 5% EtOAc-chloroform) to yield 0 26 g (87%) of compound **7b**

m p oil, IR (NaCl) cm^{-1} 1700 (CO), 1632 (C=N), ^{1}H-NMR ($CDCl_3$) 7 4-7 15 (m, 5H, Ar-H), 4 6 (s, 2H, CH_2Ar), 4 17 (m, 2H, CH_2O), 4 0 (m, 1H, H_1), 2 35-2 15 (m, 2H, H_8), 1 8-1 6 (m, 2H, H_7), 1 22 (t, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) 168 6, 168 1 (C_3 and C_6), 135 9-128 2 (Ar-C), 85 8 (C_4), 63 7 (CH_2O), 54 4 (C_1), 49 0 (CH_2Ar), 34 3 (C_8), 25 7 (C_7), 13 8 (CH_3), m/z 292 (M^+, 1), 159 (M^+-$PhCH_2NCO$, 100), 91 (34), exact mass for $C_{15}H_{17}ClN_2O_2$ 292 0977, found 292 0977

6-(4-Benzylpiperazin-1-yl)-4-chloro-2-phenyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (8)
The adduct **2a** (1 mmol) was stirred for 6h in 20 ml dry THF in the presence of 0 7 g 1-benzylpiperazine (4 mmol) After filtration, the filtrate was stirred in a 1N $NaHCO_3$ solution for 30 minutes After extraction with chloroform, the organic layers were combined, dried over magnesium sulphate, filtered and evaporated under reduced pressure Purification of the residue on silica gel preparative plates (eluent = 100% EtOAc) yielded 0 3 g of compound **8** (72%)

m p ($CHCl_3$-hexane) 165°C, IR (KBr) cm^{-1} 1710 (CO), 1590 (C=N), ^{1}H-NMR ($CDCl_3$) 7 4-7 1 (m, 10H, Ar-H), 5.0 (dd, J = 3, 2Hz, H_1), 3.52 (s, 2H, CH_2Ar), 3 49 (t, J = 5Hz, 4H, $H_{2'}+H_{6'}$), 2 45 (t, J = 5Hz, 4H, $H_{3'}+H_{5'}$), 2.45-2.10 (m, 3H, H_7+H_8), 1 9-1 7 (m, 1H, H_7), ^{13}C-NMR ($CDCl_3$) 167 4, 163 1 (C_3 and C_6), 139 2-123 4 (Ar-C), 87 3 (C_4), 62 5 (CH_2Ar), 54 4 (C_1), 52 3 ($C_{3'}+C_{5'}$), 45 0 ($C_2+C_{6'}$), 34 3 (C_8), 26 2 (C_7), m/z 408 (M^+, 22), 159 (100), 146 (95), 91 (95), anal calcd for $C_{23}H_{25}ClN_4O$ C 67 56, H 6 16, N 13 70, found C 67 50, H 6 08, N 13 50

6-(4-Benzylpiperidin-1-yl)-4-chloro-2-phenyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (9)
The adduct **2a** (1mmol) was stirred for 48h in 20 ml dry toluene in the presence of 0 7 g 4-benzylpiperidine (4 mmol) The obtained mixture was evaporated and separated on silica gel preparative plates (eluent = 15% EtOAc-chloroform) to yield 0 34 g (84%) of compound **9**

m p ($CHCl_3$-hexane) 146°C, IR (KBr) cm^{-1} 1700 (CO), 1585 (C=N), ^{1}H-NMR ($CDCl_3$) 7 4-7 05 (m, 10H, Ar-H), 5 0 (m, 1H, H_1), 4 0 (m, 2H, CH_2N), 2 8 (m, 2H, CH_2N), 2 6 (d, 2H, CH_2Ar), 2 5-2 1 (m, 4H, H_7+H_8), 1 7 (m, 4H, H_3+H_5), 1 25 (m, 1H, $H_{4'}$), ^{13}C-NMR ($CDCl_3$) 167 7, 163 1 (C_3 and C_6), 139 7-123 6 (Ar-C), 87 4 (C_4), 54 7 (C_1), 45 6 ($C_{2'}+C_6$), 42 9 (CH_2Ar), 38 0 ($C_{4'}$), 34 5 (C_8), 31 8 ($C_3+C_{5'}$), 26 5 (C_7), m/z 407 (M^+, 8), 288 (M^+-PhNCO, 100), 91 (59), exact mass for $C_{24}H_{26}ClN_3O$ 407 1764; found 407 1768

1-Chloro-6-oxo-5-phenethyl-2,5-diazabicyclo[2.2.2]oct-2-ene-3-carbonitrile (10)
A solution of 1 mmol of compound **2c** in 30 ml CH_3CN was stirred for 48h in the presence of 0 08 g KCN and a catalytical amount 18-crown-6 at 50°C The reaction mixture was then evaporated, dissolved in chloroform and washed with 2 x 20 ml water The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure The residue was purified on silica gel preparative plates (eluent 10% EtOAc-chloroform) to yield 0 22 g (75%) of compound **10**

m p decomposition, IR (KBr) cm^{-1} 1700 (CO), no CN-absorption observed, ^{1}H-NMR (CD_3COCD_3) 7 45-7 1 (m, 5H, Ar-H), 4 9 (m, 1H, H_4), 3 9-3 6 (m, 2H, CH_2N) 2 95 (br t, 2H, CH_2Ar), 2 3-1 8 (m, 4H, H_8+H_7), ^{13}C-NMR (CD_3COCD_3) 164 4 (C_6), 153 0 (C_3), 139 3-127 5 (Ar-C), 113 3 (CN), 90 4 (C_1), 58 4 (C_4), 48 2 (CH_2N), 34 6 (CH_2Ar), 33 0 (C_7), 26 0 (C_8), m/z 287 (M^+, 6), 104 (96), 91 (100), exact mass for $C_{15}H_{14}ClN_3O$ 287 0820, found 287 0820

4-Chloro-6-(4-methoxyphenyl)-2-phenyl-2,5-diazabicyclo[2.2.2]oct-5-en-3-one (11)
A mixture of 1mmol **2a** and 0 28 g (2 1 mmol) $AlCl_3$ in dry CH_2Cl_2 was stirred for 15 minutes After adding 0 25 g (2 1 mmol) anisole the reaction mixture was stirred for 3 days The mixture was poured in ice water and extracted with $CHCl_3$ The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure The residue was purified on silica gel preparative plates (eluent = 10% EtOAc-chloroform) yielding 0 22 g (60%) of compound **11**

m p 159-160°C, IR (KBr) cm^{-1} 1700 (CO), ^{1}H-NMR ($CDCl_3$) 7 9 (d, 2H, Ar-H), 7 4-7 2 (m, 5H, Ar-H), 6 95 (d, 2H, Ar-H), 5 45 (dd, 1H, H_1), 3 85 (s, 3H, CH_3), 2 6-2 3 (m, 3H, H_7 + H_8), 1 8 (m, 1H, H_7), ^{13}C-NMR ($CDCl_3$) 170 4 (C_6), 165 6 (C_3), 163 3 (Ar-C), 139 3-114 6 (Ar-C), 88 7 (C_4), 56 6 (C_1), 55 5 (CH_3), 33 2 (C_8), 25 9 (C_7), m/z 340 (M^+,1), 221 (M^+-PhNCO, 100), 186 (25), exact mass for $C_{19}H_{17}ClN_2O_2$ 340 0977, found 340 0975

4-Chloro-6-(4-methoxyphenyl)-2-phenyl-2,5-diazabicyclo[2.2.2]octan-3-one (12a)
A mixture of 0 1 g **11** and 0 04 g Pd/C 10% in dry THF was shaken under a pressure of 4 atm of hydrogen After 12h, the catalyst was filtered off and the filtrate was evaporated The residue was separated on preparative plate (eluent = 15% EtOAc-chloroform) affording 0 05 g (49%) of the reduced compound **12a.**

m p 124°C, IR (KBr) cm^{-1} 3305 (NH), 1695 (CO), ^{1}H-NMR (C_6D_6) 7 03 (d, 2H, Ar-H), 7 0-6 8 (m, 5H, Ar-H), 6 65 (d, 2H, Ar-H), 3 90 (broad s, 1H, H_6), 3 50 (ddd, J = 4, 2, 2Hz, 1H,H_1), 3 3 (s, 3H, CH_3), 2 40 (ddd, J = 13, 10 5, 5 5Hz, 1H, H_8), 2 2 (ddd, J = 13, 11 5, 4 2Hz, 1H, $H_{8'}$), 1 50 (dddd, J = 13 5, 11 5, 5 5, 4Hz, 1H, H_7), 1 40 (broad s, 1H, NH), 1 35 (dddd, J = 13 5, 10 5, 4 2, 2Hz, 1H, $H_{7'}$), ^{1}H-NMR (DMSO-d_6) 7 4-6 7 (m, 9H, Ar-H), 4 42 (broad d, J = 8Hz, 1H, H_6), 4 17 (d, J = 8Hz, NH), 4 10 (m, 1H, H_1), 3 7 (s, 3H, CH_3), 2 6-2 1 (m, 4H, H_7 + H_8), ^{13}C-NMR ($CDCl_3$) : 167 3 (C_3), 159 5 (Ar-C), 140 0-114 4 (Ar-C), 80 7 (C_4), 61 9, 61 8 (C_1 and C_6), 55 3 (CH_3), 35 4 (C_8), 27 7 (C_7), m/z 342 (M^+, 30), 306 (M^+-HCl, 100), 278 (306-CO, 40), 171 (61), exact mass for $C_{19}H_{19}ClN_2O_2$ 342 1133, found 342 1134

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