1,3-DIPOLAR CYCLOADDITIONS TO OXIDOPYRAZINIUMS

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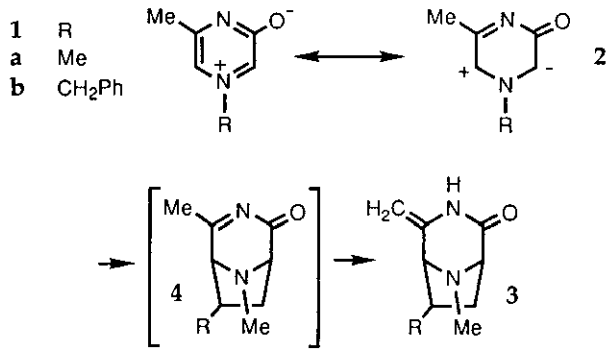
Abstract - The dipolar cycloadditions of a range of dipolarophiles to 1,5-dimethyl- and 1-arylmethyl-5-methyl-3-oxidopyraziniums are described.

This paper is dedicated to Professor Rolf Huisgen, in acknowledgement of his major contributions to the recognition and development of dipolar cycloaddition processes.

We have previously reported[1] some dipolar cycloaddition reactions of 1,5-dimethyl-3-oxidopyrazinium (**1a**), prepared by the *N*-4-quaternisation of 6-methylpyrazin-2-one[2] with iodomethane followed by *N*-deprotonation using triethylamine. The oxidopyrazinium was shown to react in the regiochemical sense implied by a resonance contributor (**2**), for example with methyl acrylate and acrylonitrile – only the regioisomers (**3**, R=MeO_2C, NC) were detected. Products from reactions with other electron-poor dipolarophiles, diethyl maleate, methyl propiolate, dimethyl acetylenedicarboxylate (DMAD) and maleimide, were also described.[1] In all of the examples studied the (presumed) initial adducts (**4**) were not isolated – tautomers (**3**) (Scheme 1) having an exocyclic methylene and therefore a complete (cyclic) secondary amide



Scheme 1

unit, were the only products, mesomeric interactions in, and the hydrogen-bonding opportunities available to, the amide tautomers, presumably being the factors governing the position of tautomeric equilibrium.

BACKGROUND

Cycloadditions of 3-oxidopyridiniums are the subject of an extensive series of benchmark papers by Katritzky and co-workers, which have been reviewed[3] – the predominant mode of addition is across the 2,6-positions. Following these pioneering studies, further work established a relationship between the size of the *N*-substitutent and the number of regio/stereoisomers produced on reaction with electron-poor alkenes.[4] In other recent developments, homochiral aryl vinyl sulfones were shown to react, with low *exo/endo* selectivity but high diastereoselectivity,[5] and extrapolation to cycloadditions using 1-amino-5-methoxy-3-oxidopyridinium were described.[6]

The most obvious route to 3-oxidopyridiniums, and the one by which they have most often been prepared, is the quaternisation of a 3-hydroxypyridine, followed by *O*-deprotonation using mild base. Peracid oxidation of 1-alkyl-1,2,3,6-tetrahydro-5-alkoxy-3-oxopiperidines has also been utilised.[7]

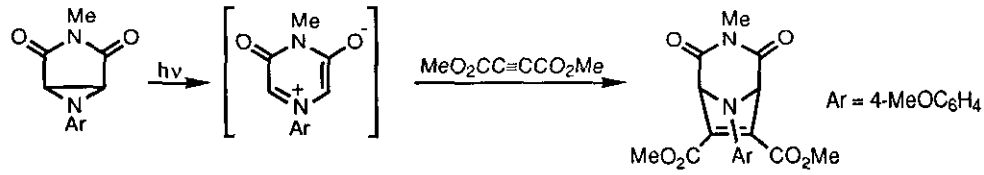
The potential, inherent in the products from oxidopyridinium cycloadditions, for further elaboration – for example into tropolones – has been demonstrated.[7,8] Varying the *N*-substituent has considerable effect on reactivity: electron-withdrawing substituents increase the reactivity of the 3-oxidopyridinium to which they are attached.[9] Inclusion of 5-aryl- or 5-alkoxy groups also increases reactivity, now allowing cycloadditions with styrene, indene, phenylacetylene, cyclopentadiene (as an alkene), and diethyl azodicarboxylate to take place, though a practical disadvantage is that these more reactive oxidopyridiniums tend to dimerise.[10] 1-Methyl-3-oxidopyridinium does not react with simple double bonds nor double bonds of the styrene type, however intramolecular cycloadditions have been demonstrated with simple (*i.e.* neither electron-rich nor electron-poor) alkenes.[11] The extension of this work to include 4-oxido-isoquinoliniums led to the synthesis of benzanellated tropolones,[12] and adducts of berberine alkaloid-type structures.[13]

Comparable cycloadditions to 3-oxidopyryliums[14] have also been shown to have considerable potential for the construction of complex molecules: intramolecular additions with simple alkenes,[15] and additions to 4-oxidobenzo[*c*]pyryliums,[16] including electron-rich, electron-poor, and simple alkenes have also been described. As in the pyridine series, the inclusion of extra alkoxyl substituents on the six-membered oxidopyrylium increases its reactivity; for example 4-methoxy-6-methyl-3-oxidopyrylium reacts with norbornene and styrene, as well as with typical electron-deficient dipolarophiles like DMAD, but once again the more reactive zwitterions have a tendency to dimerise.[17,18]

3-Oxidopyrylium has been prepared by elimination of ethanol from 2,6-dihydro-6-ethoxy-3*H*-pyran; 4-oxidobenzo[*c*]pyryliums have been generated by comparable ethanol eliminations or by photochemical ring opening of 2,3-epoxyindanones.[18]

When we began our studies, little was known of the possibility of extrapolating such cycloadditions to simply substituted oxido-diaziniums or related substances: isolated relevant reports included the reaction between maleic anhydride and 3-oxido-1,4-diphenyl-2,6-diphenylthiopyrazin-5-onium,[19] cycloadditions involving the dipolar tautomeric form of 2,6-dihydroxy-3,5-diphenylpyrazine,[20] and Huisgen's report that 1-aryl-4-methyl-3-oxidopyrazin-5-onium adds DMAD and norbornene.[21] Katritzky had shown that 1-methyl-3-oxidopyridazinium does not react with any of the common dipolarophiles, however limited success, using reactive dipolarophiles, was achieved with phthalazin-1-(2*H*)-one, presumably reacting in its betaine, tautomeric form, and 2-methyl-4-oxidophthalazinium, produced from phthalazin-1-(2*H*)-one by *N*-2-methylation then treatment with base, did add diphenylacetylene, but did not react with phenylacetylene or acrylonitrile;[22] also demonstrated have been the cycloadditions of benzyne[22] and DMAD[22,23] to 4-oxido-cinnoliniums.

The *in situ* generation of 3-oxidopyraziniums and their subsequent cycloaddition/trapping, described separately by Huisgen, and Oida and Ohki and was implicit in the conversion of 3,4-aziridinylpyrrolidine-2,5-diones with dimethyl acetylenedicarboxylate in the presence of light,[21,24] and this elegant method was later developed by Garner[25] into a key step in his total synthesis of (-)-quinocarcin;[26] the method is illustrated (Scheme 2) using an example described by Huisgen.



Scheme 2

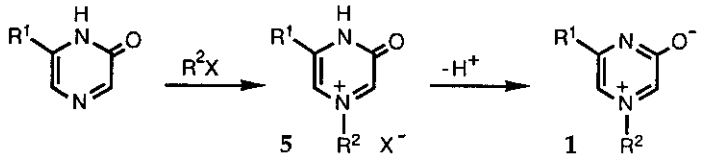
For the sake of completeness, but not directly relevant to the work described here, we note cycloadditions taking place 1,4-across various six-membered zwitterionic systems: 4-oxido-6-oxo-1,3-thiaziniums,[27] 4-oxido-6-oxo-1,3-oxaziniums,[27b] and 4-oxido-6-oxopyrimidiniums.[28]

RESULTS

Preparation of oxidopyraziniums

The efficiency and simplicity of preparation of the 3-oxidopyraziniums used in this work was improved by passing solutions of the precursor salts (**5a-c**) down columns of anion exchange resin (HO^- form) followed by simple evaporation of the eluate. The oxidopyraziniums (**1a** was

obtained as a monohydrate, and used as such) were stable and could be kept for extended periods without deterioration; this contrasts with the relative instability of 3-oxidopyridiniums. It was important to effect the pyrazinone quaternisations in dry ethanol – inferior, darker products were obtained in 95% ethanol. The pyrazinonium salts (5) were hygroscopic and sensitive to hot water.

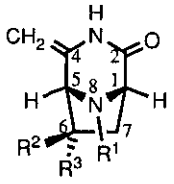


	R^1	R^2	X
a	Me	Me	I
b	Me	CH_2Ph	Br
c	3-MeO-$C_6H_4CH_2$	Me	I

Dipolar cycloadditions of oxidopyraziniums

The *N*-benzyloxidopyrazinium (**1b**) was much more soluble than **1a** and as a consequence, reactions could be carried out using molar equivalents of dipolarophile, rather than the excesses used in our earlier work,[1] and reaction times were considerably shorter.

The structures of the adducts followed from their spectroscopic properties, in particular, each showed signals for an *N*-hydrogen, and two, exocyclic alkene protons; the relative stereochemistry of the substituents was determined by an examination of the coupling constants for the bridgehead hydrogens: Table 1 lists the key ^1H nmr shifts and coupling constants upon which the structural assignments, in particular the stereochemistry (*exo* or *endo* substituent) are based. The ^1H nmr spectra of *exo* adducts had a singlet (or broadened singlet) for the bridgehead proton adjacent to the adjacent (substituent-bearing) carbon (C-6 or C-7): the dihedral angle between a bridgehead hydrogen and an *endo* hydrogen on the adjacent carbon in this bicyclic system, being about 90°.



3	R^1	R^2	R^3		R^1	R^2	R^3
a	Me	MeO_2C	H	**g**	CH_2Ph	Cl	NC
b	Me	H	MeO_2C	**h**	CH_2Ph	NC	H
c	Me	PhO_2S	H	**i**	CH_2Ph	H	NC
d	CH_2Ph	MeO_2C	H	**j**	CH_2Ph	H	4-pyridyl
e	CH_2Ph	PhO_2S	H	**k**	CH_2Ph	H	2-pyridyl
f	CH_2Ph	NC	Cl	**l**	CH_2Ph	H	Ph

In order to provide a firm reference point for these spectroscopic analyses, an X-ray crystallographic determination of the major acrylate adduct, the *exo*-isomer (**3a**), was carried out; a Chem3D™ drawing of the structure is shown in Figure 1. The measured angle between the 5- and 6-hydrogens in the crystalline form of **3a** is 101°.

Since the *exo*-isomer (**3a**) was the major product, and could in principle have been the thermodynamic product produced *via* cycloreversion, we carried out the cycloaddition at room

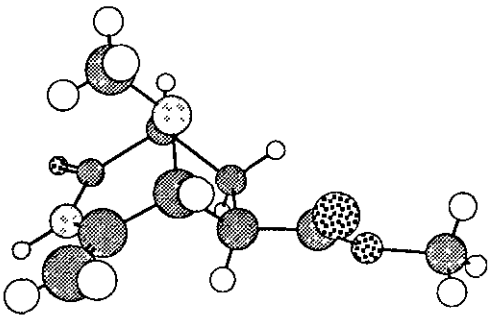
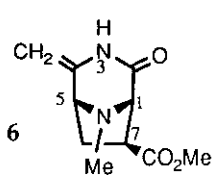
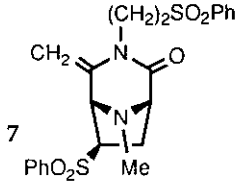


Figure 1 Chem3D™ drawing of the X-ray-determined structure of methyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylate (**3a**)

temperature, in both acetonitrile and THF solution: in both cases the same ratio (*ca.* 4:1) of *exo*- and *endo*-isomers (**3a** and **3b**) was obtained as from reactions conducted in hot solution, from which we conclude that the observed ratio probably reflects the relative rates of formation. Also, it seems likely that cycloreversion is prevented by a rapid isomerisation of initial adducts to the isolated enamide tautomers. The use of acetonitrile, as solvent, allowed reaction with methyl acrylate to proceed smoothly, in a shorter reaction time, using only one mol equivalent of the acrylate, and indeed in considerably higher yield than the partially non-homogenous reaction in THF. A closer examination of the reaction between **1a** and methyl acrylate revealed the presence of a minor amount of the regioisomer (**6**) (*exo*) not detected in our earlier work.





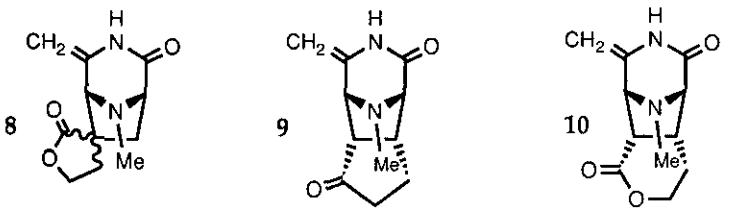
Reaction of **1a** with excess phenyl vinyl sulfone produced cycloadduct (**7**) into which an additional sulfone moiety had been incorporated, as a Michael acceptor, onto the enamide nitrogen; reaction with one mol equivalent for a short time produced the anticipated, simple adduct (**3c**). Further treatment of **3c** with a large excess of the sulfone brought no change and we conclude therefore that the second mol of sulfone is probably incorporated *via* trapping by attack of the imine nitrogen of the immediate cycloadduct (**4** in Scheme 1), followed by the usual loss of side-chain methyl proton.

Other electron-poor alkenes which were found to react with **1b**, some in less good yields, were 2-chloroacrylonitrile producing a mixture of isomers (**3f** and **3g**) in a ratio of about 3:1, but these could not be separated nor a relative stereochemical assignment made to the isomers,

acrylonitrile, giving *exo* and *endo* isomers (**3h** and **3i**), α-methylene-γ-butyrolactone, giving a mixture of the stereoisomers of **8**, to which, although separable, we were not able to assign stereochemistry, cyclopentenone which gave the *endo* adduct (**9**), and 5,6-dihydro-2*H*-pyran-2-one, which afforded the *endo* adduct (**10**).

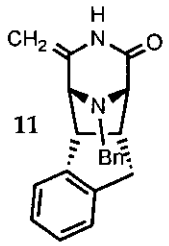
compound	δ H-1 (J)	δ H-3	δ H-5 (J)	δ H-6 (J)	δ C=CH_A (J)	δ C=CH_B (J)	other signals
3a	3.57 (d, 7)	7.85 (bs)	4.02 (s)	3.01 (dd, 6, 10)	4.30 (s)	4.28 (s)	
3b	3.48 (m)	7.70 (bs)	3.88 (d, 7)	3.48 (m)	4.32 (d, 1)	4.10 (s)	
6	3.85 (s)	8.35 (bs)	3.66 (d, 7)				H-7, 3.13 (dd, 5, 10)
3c	3.58 (d, 7)	~7.9	4.07 (s)	3.65 (dd, 6, 9)	4.25 (d, 1.5)	4.12 (d, 1.5)	
7	3.63 (d, 7.5)	-	4.15 (s)	3.67 (dd, 6.5, 9.5)	4.32 (d, 2)	4.23 (d, 2)	
3d	3.62 (d, 7)	8.06 (bs)	4.01 (s)	3.02 (dd, 5, 10)	4.30 (d, 1.5)	4.18 (s)	
3e	3.57 (d, 7)		4.02 (s)	3.67 (dd, 7, 10)	4.30 (s)	4.03 (s)	
3f/3g	3.67 (d, 7.5)	~8.1	~3.9	-	~4.4	4.72 (d, 1.5)	
3h	3.69 (d, 7)	7.79 (bs)	3.94 (s)	3.07 (5, 9)	4.38 (d, 1.5)	4.23 (d, 1.5)	
3i	3.61 (d, 7)	7.65 (bs)	3.85(d, 6.5)	3.40 (ddd, 6.5, 7, 12)	4.35 (d, 1.5)	4.59 (d, 1.5)	
3j	3.79 (d, 6.5)	7.42 (bs)	~3.73 (d, 6.5)	~3.80	4.10 (d, 1)	3.60 (s)	
3k		7.23 (bs)			3.96 (d, 1)	3.58 (s)	
3l	3.17 (d, 6)	~7.3	3.70 (d, 6)	3.87 (6, 6)	4.07 (d, 1.5)	~3.2	
8a or b	3.81 (d, 7.5)	~7.3	3.61 (s)	-	4.18 (d, 2)	4.30 (d, 2)	
8b or a	3.74 (d, 6.5)	7.51 (bs)	3.70 (s)	-	4.12 (d, 1)	4.48 (d, 1.5)	
9	3.92 (d, 7.5)	7.05 (bs)	3.65 (d, 7.5)	-	4.20 (s)	4.41 (s)	
10	4.05 (d, 7)	7.46 (bs)	3.69 (d, 7)	-	4.38 (s)	4.50 (s)	
11	3.96 (d, 7.5)	6,66 (bs)	3.68 (d, 7.5)	4.22 (t, 9)	4.01 (s)	4.06 (d, 2)	
12	~3.75	7.18 (bs)	3.55 (d, 7.5)	3.65 (m)	4.02 (s)	4.22 (s)	HC=CH, 5.69, 5.49
14a	4.05 (m)	7.15 (bs)	4.32 (d, 1)	-	4.36 (d, 1)	4.39 (d, 1)	H-7, 7.13 (d, 2)
14b oc	4.34 (s)	7.45 (bs)	4,25 (s)	-	4.38 (s)	4.52 (s)	
14c or b	4.35 (d, 1)	7.58 (bs)	4,17 (d, 1)	-	4.32 (d, 2)	4.36 (d, 2)	

Table 1 Key ^1H chemical shifts and coupling constants for adducts



No reaction took place between **1b** and simple alkenes, such as cyclohexene or cyclopentene, nor indeed with the more strained alkene, norbornene, however **1b** did react with 4- and 2-

vinylpyridines, and even styrene, indene and cyclopentadiene, producing adducts (**3j**), (**3k**), (**3l**), (**11**), and (**12**) respectively, in poor to moderate yields. The regio- and stereochmistry of **3l**, and by implication **3j** and **3k**, was established by the observation that the signal for one of the exocyclic alkene protons was shifted upfield by 1 ppm. Hydrogenation of **3l** from the top face gave **13**, in which the methyl resonates at δ 0.4 under the influence of the close phenyl ring.



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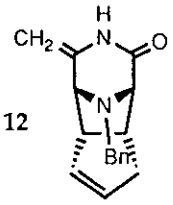

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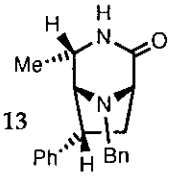

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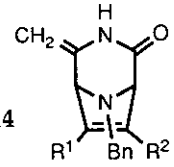
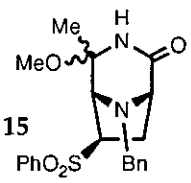
Two alkyne dipolarophiles were also examined: **1b** reacted with methylpropiolate giving **14a**, with methyl phenylpropiolate giving **14b** and **14c**, though these two could not be distinguished.



14

	R^1	R^2
a	MeO_2C	H
b	MeO_2C	Ph
c	Ph	MeO_2C

Cleavage of the six-membered rings in these cycloadducts would produce substituted pyrrolidines. A brief examination of the viability of such processes was carried out, thus phenyl vinyl sulfone and propiolate adducts (**3e** and **14a**) were treated with methanolic hydrogen chloride in the hope of effecting methanolysis of the enamide, however only addition products (**15** and **16** respectively), still having bicyclic structures, were obtained. As an alternative approach to the desired cleavage, the acrylate and sulfone adducts (**3d** and **3e**) were converted into the imides (**17a** and **17b**) respectively, it being the hope that hydride reduction of the imide unit would take place selectively at the ring carbonyl,[29] however only loss of the substituent *t*-butoxycarbonyl group was observed.



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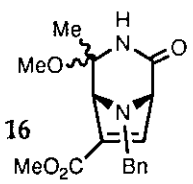

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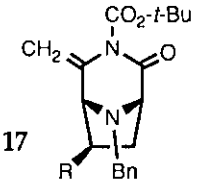
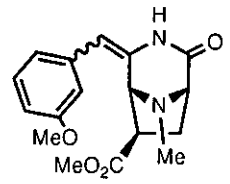


17

Our interest[30] in the synthesis of quinocarcin led us to prepare and examine the more complex oxidopyrazinium (**1c**); it reacted with methyl acrylate to give *exo* adduct (**18**), in which both the

regiochemistry of addition and the relative stereochemistry of the ester were those desired for elaboration into quinocarcin.



18

EXPERIMENTAL

General.- Thin layer chromatography (tlc) was carried out on Merck silica gel F_{254} 0.255mm plates, and spots were visualised, where appropriate, by spraying with potassium permanganate solution or acidified cerium sulphate solution. Column chromatography was performed using Merck Kieselgel (60) (230-400 mesh) silica gel. Organic solutions were dried over anhydrous magnesium sulphate. Tetrahydrofuran was dried by distillation from sodium/benzophenone; toluene and triethylamine were dried by distillation from calcium hydride; dimethylformamide was dried over 4Å molecular sieves; dichloromethane was dried by distillation from calcium hydride. Ultraviolet spectra were recorded in 95% ethanolic solution on a Shimadzu UV260 recording spectrophotometer at fast scan speed, path length 1 cm and are given in nm with absorbance as (log ε). Infrared spectra were recorded on a Perkin-Elmer 1710 Infra Red Fourier transform spectrophotometer and are quoted in cm^{-1}. ^1H Nuclear magnetic resonance spectra were recorded (in $CDCl_3$ unless otherwise stated) on a Varian AC 300E nmr spectrometer at 300 MHz or a Varian Gemini 200 spectrometer operating at 200 MHz. Peak multiplicities are denoted by s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or by a combination of these *e.g.* dd (double doublet) and coupling constants given in Hz ^{13}C Nuclear magnetic resonance spectra were recorded on a Varian AC 300E nmr spectrometer at 75 MHz. Mass spectra were recorded on a Kratos MS 25 for the electron impact (EI) and chemical ionisations (+ve CI) (NH_3) and are recorded with % intensity relative to the base peak in parantheses. Accurate mass measurements were obtained using a Kratos Concept. Reactions were carried out under a dry atmosphere of argon or nitrogen. 6-Methylpyrazin-2-one was prepared in about 30% yield from pyruvic aldehyde and glycinamide hydrochloride following the method of Lutz *et al.*[2]

1,5-Dimethylpyrazin-3-onium iodide (5a).- 6-Methylpyrazin-2-one (3.00 g, 0.027 mol) and iodomethane (5 ml, 0.081 mol) were refluxed in dry absolute ethanol (300 ml) under N_2 for 24 h. The solution was concentrated *in vacuo* to 100 ml, and on cooling the crude salt precipitated, was collected by filtration, and recrystallised from 95% ethanol to give 1,5-dimethylpyrazin-3-onium iodide (**5a**) as purple needles (5.40 g, 80%), mp 254-256 °C; δ (CD_3OD, 80 MHz) 8.5 (1H, s), 7.95 (1H, s), 4.5 (3H, s), 1.75 (3H, s); ν_{max} 3430, 3108, 2985, 1691 (Anal. calcd for $C_6H_9N_2OI$: C, 28.6; H, 3.2; N, 11.1; I, 50.4. Found: C, 28.9; H, 3.6; N, 11.1; I, 50.8).

1-Benzyl-5-methylpyrazin-3-onium bromide (5b).- 6-Methylpyrazin-2-one (3.00 g, 0.027 mol) and benzyl bromide (9.6 ml, 0.081 mol) were refluxed in dry absolute ethanol (300 ml) under N_2 for 24 h. The solution was concentrated *in vacuo* to 100 ml, and on cooling the crude salt was precipitated, filtered off, and recrystallised from absolute ethanol to give 1-benzyl-5-methylpyrazin-3-onium bromide (**5b**) as pale tan needles (6.04 g, 80%), mp 222-3 °C; δ (CD_3OD, 80 MHz) 8.65 (1H, s), 8.0 (1H, s), 7.7, (5H, m), 5.85 (2H, s), 2.7 (3H, s); ν_{max} 3094, 2920, 1685 (Anal. calcd for $C_{12}H_{13}N_2O_3Br$: C, 51.2; H, 4.7; N, 9.9; Br, 28.4. Found: C, 50.6; H, 4.6, N, 9.5, Br, 28.1).

5-(3-Methoxyphenylmethyl)-1-methylpyrazin-3-onium iodide (5c).- A solution of 6-(3-methoxyphenylmethyl)pyrazin-2-one[29,30] (15 mg, 0.070 mmol) and iodomethane (44 µl, 0.706 mmol) in absolute ethanol (0.5 ml) was refluxed for 15 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (chloroform-methanol 9:1 as eluent) to give the iodide (**5c**) as a reddish-purple oil (10.0 mg, 40%), λ_{max} 225 (2.89), 243 (sh, 1.16), 274 (0.35), 280 (0.35), 353 (0.85); ν_{max} (film) 2924, 2853, 1621, 1515; δ (CD_3OD) 7.65 (2H, s), 7.35 (1H, d, J 8), 7.0 (3H, m), 4.3 (3H, s), 4.2 (2H, s), 4.0 (3H, s).

1,5-Dimethyl-3-oxidopyrazinium (1a).- A solution of 1,5-dimethylpyrazin-3-onium iodide (3.00 g, 0.012 mol) in water (25 ml) and methanol (25 ml) was passed down a basic anion exchange column (Amberlite IRA 400, OH^- form); the column was then further eluted with a mixture of water (25 ml) and methanol (25 ml). Evaporation of the eluates *in vacuo* gave 1,5-dimethyl-3-oxidopyrazinium.H_2O (**1a**) as a pale orange solid (1.64 g, 96%), mp 133-5 °C, δ (CD_3OD, 80 MHz) 8.4 (1H, s), 7.7 (1H, s), 4.2 (3H, s), 1.6 (3H, s) (Anal. calcd for $C_6H_8N_2O.H_2O$: C, 50.8; H, 7.0; N, 19.7. Found: C, 51.0; H, 7.0; N, 19.7).

1-Benzyl-5-methyl-3-oxidopyrazinium (1b).- A solution of 1-benzyl-5-methylpyrazin-3-onium bromide (3 g, 0.011 mol) in water (25 ml) and methanol (25 ml) was passed down a basic anion exchange column (Amberlite IRA 400, OH^-). The column was further eluted with a mixture of water (25 ml) and methanol (25 ml). Evaporation of the eluates *in vacuo* gave 1-benzyl-5-methyl-3-oxidopyrazinium (**1b**) as a pale orange solid (2.13 g, 97%), mp 120 °C, δ (80 MHz) 7.2 (7H, m), 5.2 (2H, s), 2.3 (3H, s); *m/z* EI 202 (11), 201 (15), 200 (13), 199 (10), 111 (9), 91 (100); CI 203 (37), 201 (12) 111 (100) ($C_{12}H_{12}N_2O$ requires: M, 200.0950. Found: M^+, 200.0934).

1-Methyl-5-(3-methoxyphenylmethyl)-3-oxidopyrazinium (1c).- A column of Amberlite IRA-400 resin (0.10 g) was eluted with 10% sodium hydroxide (5 ml), then water until the eluate was neutral, and finally methanol (5 ml). A solution of 5-(3-methoxyphenylmethyl)-1-methylpyrazin-3-onium iodide (**1c**) (10.0 mg, 0.028 mmol) in methanol (100 µl) was then introduced onto the column and the product eluted with methanol; fractions containing the oxidopyrazinium were concentrated *in vacuo* to give an oil (6.0 mg, 93%), not purified further but used immediately for reaction with methyl acrylate.

General procedure for the cycloadditions.- The oxidopyrazinium and dipolarophile (1.1-2 mol. eq.) were heated in solution under an inert atmosphere. The reactions were monitored by the disappearance of the oxidodiazinium (t.l.c. system EtOAc:*i*-PrOH:H_2O:NH_3, 25:15:8:2, R_f oxidopyraziniums, *ca.* 0.5). Purification was effected by evaporation of solvent then column chromatography over silica gel.

Methyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylate (3a), methyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*endo*-6-carboxylate (3b), and methyl 8-methyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-7-exo-7-carboxylate (6).- A solution of the oxidodiazinium (**1a**) (3.14 g, 25.3 mmol) and methyl acrylate (11.2 g, 131.0 mmol, 11.8 ml) were refluxed in MeCN (40 ml) for 2 h. Column chromatography (EtOAc eluent) gave first a mixture of *exo* adducts (**3a**) and (**6**), followed by *endo* adduct (**3b**), as colourless prisms (666 mg, 13%), mp 168-170 °C (from EtOAc), δ_H 7.7 (1H, bs), 4.32 (1H, d, J 1.1), 4.1 (1H, s), 3.9 (1H, d, J 1.1), (3H, s), 3.5 (2H, m), 2.5 (1H, m), 2.46 (3H, s), 2.45 (1H, m); *m/z* EI 210 (14, M^+), 185 (16), 124 (58), 96 (54), 84 (55), 49 (100); ν_{max} 3438, 2954, 1736, 1685. The mixture of *exo* adducts was recrystallised to give the 6-*exo*-adduct (**3a**) as a white solid (2.10 g, 40%), mp 106-108 °C, δ_H 7.9 (1H, bs), 4.3 (1H, s), 4.3 (1H, s), 4.02 (1H, s), 3.75 (3H, s), 3.6 (1H, d, J 7.2), 3.0 (1H, dd, J 5.7, 9.9), 2.65 (1H, m), 2.5 (3H, s), 2.3 (1H, dd, J 9.9, 13.5); *m/z* CI 211 (100, MH^+), 52 (15); ν_{max} 3206, 2953, 1738, 1684 (Anal. calcd for $C_{10}H_{14}N_2O_3$: C 57.1; H, 6.7; N, 13.3. Found: C, 57.0; H, 6.8; N, 13.3). The residual solution was concentrated and the residue again passed down a column of silica gel (EtOAc eluent) to give as well as more (**3a**) (84 mg, 2%), the 7-exo-isomer (**6**) a white solid (48 mg, 1%), mp 135-137 °C, δ_H 8.35 (1H, bs), 4.3 (1H, s), 4.2 (1H, s), 3.85 (1H, s), 3.7 (3H, s), 3.65 (1H, d, J 7.2), 3.1 (1H, dd, J 4.6, 9.9), 2.7 (1H, m), 2.45 (3H, s), 2.1 (1H, dd, J 9.8, 13.3); *m/z* CI 211 (100, MH^+), 182 (16); ν_{max} 3204, 2953, 1738, 1685 (Anal. calcd for $C_{10}H_{14}N_2O_3$: C, 57.1; H, 6.7; N, 13.3. Found C, 57.1; H, 6.7; N,13.1).

Crystal data for **3a**: (colourless) crystal dimensions 0.05x0.10x0.55 mm, monoclinic, a = 11.322(4), b = 10.522(2), c = 17.891(4) Å, β = 96.57(2)°, U = 2117(1) Å^3, space group $P2_1/c$ (No. 14), Z = 8, $F(000)$ = 896, $\omega/2\theta$ scans of (1.21 + 0.30tanθ) were made at a speed of 8.0° min^{-1} at 295 K: 3544 reflections were collected with 5°<2θ<125°; of these, 3357 were unique and had $F>6\sigma(F)$ were used in the analysis. The data were collected on a Rigaku AFC5R diffractometer using graphite monchromated Cu-Kα radiation. Lorentz-polarisation, absorption (trans. factors: 0.95-1.03) and decay (-6.40% decline) corrections were applied. The structure was solved by direct methods. The refinement converged with R = 0.049, R_w = 0.065. All calculations were performed with SHELXS-86 software. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

8-Methyl-4-methylene-2-oxo-6-*exo*-6-phenylsulfonyl-3,8-diazabicyclo[3.2.1]octane (3c).- A solution of **1a** hydrate (1.00 g, 7.04 mmol) and phenyl vinyl sulfone (1.30 g, 7.74 mmol) in refluxing THF (20 ml) for 0.3 h gave adduct (**3c**) as a white foam (0.62 g, 30%), δ_H (250 MHz) 7.93

(2H, bd, J 8), 7.92 (1H, N-H), 7.69 (1H, tt, J 1.5, 8), 7.59 (2H, td, J 1.5, 8), 4.25 (1H, d, J 1.5), 4.12 (1H, d, J 1.5), 4.07 (1H, s), 3.65 (1H, dd, J 6, 9 Hz), 3.58 (1H, d, J 7), 2.66 (1H, ddd, J 6, 7, 14), 2.45 (3H, s), 2.27 (1H, dd, J 9, 14); ν_{max} 3374, 2923, 1686, 1632, 1306, 1149; *m/z* EI 264 (6), 124 (43), 123 (36), 82 (100); CI 293 (32, MH^+), 186 (72), 153 (33), 149 (40), 127 (54) (Anal. calcd for $C_{14}H_{16}N_2O_3S$: C, 57.5; H, 5.52; N, 9.58; S, 11.0. $C_{14}H_{17}N_2O_3S$ requires: 293.0960. Found: C, 57.7; H, 5.6; N, 9.3; S, 10.7, MH^+, 293.0964).

***8-Methyl-4-methylene-2-oxo-6-exo-6-phenylsulfonyl-3-(2-phenylsulfonylethyl)-3,8-diazabicyclo[3.2.1]octane* (7).**- A suspension of **1a** hydrate (1.00 g, 7.04 mmol) and phenyl vinyl sulfone (2.60 g, 0.015 mol) refluxed in THF (20 ml) for 3 h gave adduct (7) as a white foam (1.04 g, 32%), δ_H (400 MHz), 7.93 (4H, d, J 8), 7.69 (2H, td, J 1.5, 8), 7.59 (4H, t, J 8), 4.32 (1H, d, J 2), 4.23 (1H, d, J 2), 4.15 (1H, s), 4.01 (1H, m), 3.91 (1H, m), 3.67 (1H, dd, J 9.5, 6.5), 3.63 (1H, d, 7.5), 3.30 (2H, m), 2.60 (1H, ddd, 6.5, 7.5, 14), 2.39 (3H, s), 2.21 (1H, dd, J 9.5, 14); ν_{max} 2932, 1689, 1633, 1581, 1447, 1372, 1305; *m/z* FAB, 461 (100, MH^+), 235 (38), 157 (72) (Anal. calcd for $C_{22}H_{24}N_2O_5S_2$: C, 57.4; H, 5.25; N, 6.08; S, 13.9. $C_{22}H_{25}N_2O_5S_2$ requires: 461.1205. Found: C, 57.0; H, 5.32; N, 5.67; S, 13.5, MH^+, 461.1218).

Methyl 8-benzyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylate (3d).- A solution of the oxidodiazinium (**1b**) (2.00 g, 9.57 mmol) and methyl acrylate (0.88 ml, 10.5 mmol) in dry THF (50 ml) refluxed for 1.5 h gave adduct (**3d**), recrystallisation from EtOAc/hexane producing a pale yellow solid, mp 161-163 °C (2.33 g, 85%), δ_H (250 MHz), 8.06 (1H, bs), 7.31 (5H, m), 4.30 (1H, d, J 1.5), 4.18 (1H, s), 4.01 (1H, s), 3.82 (1H, d, J 13), 3.71 (1H, d, J 13), 3.74 (3H, s), 3.62 (1H, d, J 7), 3.02 (1H, dd, J 5, 10), 2.66 (1H, ddd, J 5, 7, 14), 2.34 (1H, dd, J 10, 14) (some peak doubling was evident, probably due to traces of the *endo* isomer (*ca.* 10:1)); δ_C (100 MHz) 173.36, 171.34, 141.11, 137.66, 128.45, 128.41, 128.30, 127.28, 91.32, 62.99, 62.24, 52.30, 52.26, 48.13, 33.22; ν_{max} 3191, 2953, 1738, 1674, 1658; *m/z* FAB 287 (100, MH^+), 201 (24), 91 (58) (Anal. calcd for $C_{16}H_{18}N_2O_3$: C, 67.1; H, 6.34; N, 9.78. Found: C, 67.0; H, 6.38; N, 9.50).

Methyl 8-benzyl-4-methylene-2-oxo-6-*exo*-6-phenylsulfonyl-3,8-diazabicyclo[3.2.1]octane (3e).- A solution of **1b** (2.00 g, 9.57 mmol) and phenyl vinyl sulfone (1.76 g, 10.5 mmol) in dry THF (50 ml) refluxed for 0.3 h gave adduct (**3e**) as a white foam (2.75 g, 80%), δ_H (400 MHz) 7.82 (2H, d, J 8), 7.63 (1H, t, J 8), 7.47 (2H, t J 8H), 7.23 (3H, m), 7.17 (2H, m), 4.30 (1H, s), 4.03 (1H, s), 4.02 (1H, s), 3.73 (1H, d, J 12), 3.62 (1H, d, J 12), 3.67 (1H, dd, J 7, 10), 3.57 (1H, d, J 7), 2.66 (1H, ddd, J 7, 10, 15), 2.38 (1H, dd, J 10, 15); δ_C (100 MHz) 170.00, 139.41, 137.61, 136.79, 133.92, 129.36, 128.86, 128.56, 128.37, 127.50, 91.96, 68.03, 62.92, 60.60, 52.01, 31.82; ν_{max} 3373, 2957, 1688, 1655, 1446; *m/z* (thermospray) 369 (MH^+) (no significant fragmentation) (Anal. calcd for $C_{20}H_{20}N_2O_3S$: C, 65.2; H, 5.47, N, 7.6; S, 8.7. Found: C, 64.6; H, 5.4; N, 7.4; S, 8.0).

8-Benzyl-6-chloro-6-cyano-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octanes (3f and 3g).- A solution of **1b** (0.150 g, 0.716 mmol) and chloroacrylonitrile (0.057 ml, 0.79 mmol) in dry THF (15

ml) refluxed for 2 h gave two adducts (**3f** and **3g**) as an inseparable mixture of stereoisomers (0.154 g, 70%) (*ca.* 3:1), δ_H (300 MHz), 8.18 (0.25H, bs), 8.12 (0.75H, bs), 7.35 (5H, m), 4.72 (1H, d, J 1.5), 4.44 (0.25H, d, J 1.5), 4.36 (0.75H, d, J 1.5), 4.05 (0.75H, s), 4.0-3.75 (2.5H, m), 3.67 (0.75H, d, J 7.5), 4.05-3.65 (4H), 3.38 (0.75H, dd, J 7.5, 15), 3.04 (0.5H, m), 2.51 (0.75H, d, J 15); *m/z* 287 (27, M^+), 200 (20), 91 (100); ν_{max} ($CHBr_3$) 3373, 2846, 2248, 1696, 1655 (Anal. calcd for $C_{15}H_{14}N_3OCl.0.25H_2O$: C, 61.5; H, 5.0; N, 14.4; Cl, 12.1. Found: C, 61.3; H, 4.84; N, 14.4; Cl, 13.1).

8-Benzyl-6-*exo*-6-cyano-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane (3h) and 8-benzyl-6-*endo*-6-cyano-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane (3i).- A solution of **1b** (0.266 g, 1.27 mmol) and acrylonitrile (0.1 ml, 1.5 mmol) in dry THF (15 ml) refluxed for 2 h gave an *endo* adduct (**3i**) (eluted first) and an *exo* adduct (**3h**) (eluted second) as yellow oils which crystallised: the *exo* adduct (0.79 g, 25 %) had mp 175-178 °C, δ_H (300 MHz) 7.79 (1H, bs), 7.30 (5H, m), 4.38 (1H, d, J 1.5), 4.23 (1H, d, J 1.5), 3.94 (1H, s), 3.88 (1H, d, J 15), 3.75 (1H, d, J 15), 3.69 (1H, d, J 7), 3.07 (1H, dd, J 5, 9), 2.60 (1H, ddd, J 5, 7, 13), 2.50 (1H, dd, J 9, 13); ν_{max} (KBr) 3178, 2243, 1691, 1657; *m/z* EI 253 (M^+, 11), 201 (12), 200 (58), 172 (23), 162 (20), 91 (100); CI 254 (MH^+, 100), 111 (45), 106 (35), 95 (29) (Anal. calcd for $C_{15}H_{15}N_3O.0.25H_2O$: C, 69.3; H, 6.06; N, 16.2. Found: C, 69.3; H, 6.0; N, 16.2); the *endo* adduct (0.094 g, 29 %) had mp 164-166 °C, δ_H (300 MHz) 7.65 (1H, bs), 7.3 (5H, m), 4.59 (1H, d, J 1.5), 4.35 (1H, d, J 1.5), 3.85 (1H, d, J 6.5), 3.83 (1H, d, J 13), 3.72 (1H, d, J 13), 3.61 (1H, d, J 7), 3.40 (1H, ddd, J 6.5, 7, 12), 2.73 (1H, ddd, J 7, 12, 13.5), 2.28 (1H, dd, J 5.5, 13.5); ν_{max} (KBr disc) 3201, 2244, 1689, 1650; *m/z* EI 253 (M^+, 17), 201 (16), 200 (60), 162 (37), 158 (29), 91 (100); CI 254 (MH^+, 100), 111 (45), 106 (35), 95 (29) (Anal. calcd for $C_{15}H_{15}N_3O$: C, 71.1; H, 5.97; N, 16.6. Found: C, 71.0; H, 6.2; N, 16.9).

8-Benzyl-6-(2-hydroxyethyl)-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylic acid lactone (8a) and 8-benzyl-6-(2-hydroxyethyl)-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*endo*-6-carboxylic acid lactone (8b).- A solution of **1b** (0.621 g, 2.97 mmol) and α-methylene-γ-butyrolactone (0.34 g, 3.4 mmol) in dry THF (25 ml) refluxed for 2 h gave an oil from which two cycloadducts (**8a** and **8b**) were obtained as white foams (0.37 g, 42%) and (0.35 g, 40%). The less polar adduct had δ_H ($CDCl_3$, 300 MHz) 7.4-7.2 (6H, m), 4.30 (1H, d, J 2), 4.25 (2H, m), 4.18 (1H, J 2), 3.85 (1H, d, J 13.5), 3.76 (1H, J 13.5), 3.81 (1H, d, J 7.5), 3.61 (1H, s), 2.89 (1H, dd, J 7.5, 13.5), 2.37 (1H, m), 2.25 (1H, m), 1.80 (1H, J 13.5); δ_C (50 MHz) 179.64, 172.11, 138.12, 137.72, 128.98, 128.92, 127.93, 95.24, 66.01, 65.74, 63.65, 53.01, 49.50, 39.86, 33.94; ν_{max} (film) 3199, 2924, 1722, 1686; *m/z* EI 298 (M^+, 13), 200 (37), 172 (18), 91 (100); CI 300 (54), 299 (100, MH^+) ($C_{17}H_{18}N_2O_3$, requires: M, 298.1317. Found:, M^+ 298.1310); the more polar adduct had δ_H (300 MHz) 7.51 (1H, bs), 7.4-7.2 (1H, m), 4.48 (1H, d, J 1.5), 4.25 (1H, m), 4.12 (1H, d, J 1), 4.10 (1H, m), 3.97 (1H, d, J 13.5), 3.74 (1H, d, J 13.5), 3.74 (1H, d, J 6.5), 3.70 (1H, s), 2.88 (1H, dd, J 7.5, 13), 2.42 (1H, m), 2.28 (1H, m), 1.98 (1H, d, J 13.5); δ_H (50 MHz) 181.00, 173.44, 139.67, 139.21, 130.47, 130.42, 129.43, 96.64, 67.55, 67.35, 65.24, 54, 60, 51.08, 41.48, 35.36; ν_{max} 2918, 2850, 1769, 1682; *m/z* EI 298 (M^+, 5), 200 (100), 173 (20), 91 (33); CI 300 (19), 299 (100), 200 (13), 116 (21), 111 (25) ($C_{17}H_{18}N_2O_3$ requires: M, 298.1317. Found: M^+, 298.1314).

8-Benzyl-4-methylene-2-oxo-6-*endo*-6-pyridin-4-yl-3,8-diazabicyclo[3.2.1]octane (3j).- A solution of **1b** (0.366 g, 1.83 mmol) and 4-vinylpyridine (0.20 ml, 1.9 mmol) in dry THF (20 ml) refluxed for 5 h gave adduct (**3j**) as a pale yellow foam (0.15 g, 26%), δ_H (300 MHz) 8.48 (2H, d, J 6), 7.42 (1H, bs), 7.35-7.28 (5H, m), 7.09 (2H, d, J 6), 4.10 (1H, d, J 1), 3.84 (1H, d, J 13), 3.74 (1H, d, J 13), 3.79 (1H, d, J 6.5), 3.73 (1H, d, J 6.5), 3.70 (1H, m), 3.60 (1H, s), 2.74 (1H, m), 2.21 (1H, dd, J 6, 14); ν_{max} 1685, 1640; *m/z* EI 200 (45), 105 (51), 91 (100); CI 306 (3, MH^+), 111 (53), 106 (100), 91 (28) ($C_{19}H_{19}N_3O$ requires: M, 305.1528. Found: M^+, 305.1535).

8-Benzyl-4-methylene-2-oxo-6-*endo*-6-pyridin-2-yl-3,8-diazabicyclo[3.2.1]octane (3k).- A solution of **1b** (0.641 g, 3.06 mmol) and 2-vinylpyridine (0.38 ml, 3.4 mmol) in dry THF (40 ml) refluxed for 2 h gave adduct (**3k**) as a pale yellow foam (0.287 g, 31 %), δ_H (300 MHz) 8.50 (1H, dd, J 0.5, 5), 7.58 (1H, td, J 1.5, 7.5), 7.4-7.25 (5H, m), 7.23 (1H, bs), 7.18 (1H, d, J 7.5), 7.09 (1H, dd, J 5, 7.5), 4.03 (1H, m), 3.96 (1H, d, J 1), 3.91 (1H, d, J 6.5), 3.87 (1H, d, J 12.5), 3.76 (1H, d, J 12.5), 3.71 (1H, d, J 6), 3.58 (1H, s), 2.71-2.65 (2H, m); δ_C (50 MHz) 172.38, 158.99, 149.47, 138.93, 138.45, 136.57, 129.51, 128.91, 127.87, 123.13, 122.13, 93.96, 65.99, 64.29, 53.47, 49.98, 33.09; ν_{max} (KBr) 2964, 1685; *m/z* EI 305 (5, M^+), 200 (100), 91 (59); CI 307 (22) 306 (100, MH^+), 200 (16), 111 (19), 106 (48), 91 (17) ($C_{19}H_{19}N_3O$ requires: M, 305.1528. Found: M^+, 305.1523).

Cyclopent-2-en-1-one adduct (9).- A solution of **1b** (93.5 mg, 0.47 mmol) and 2-cyclopenten-1-one (0.43 ml, 0.51 mmol) in dry THF (10 ml) refluxed for 2.5 h gave adduct (**9**) as a colourless oil (39 mg, 28%), δ_H (300 MHz) 7.30 (5H, s), 7.05 (1H, bs), 4.41 (1H, s), 4.20 (1H, s), 3.92 (1H, d, J 7.5), 3.74 (2H, s), 3.65 (1H, d, J 7.5), 3.42 (1H, m), 3.29 (1H, m), 2.5-2.25 (2H, m), 2.18-1.92 (2H, m); ν_{max} 3212, 2959, 1734, 1682; *m/z* EI 282 (8, M^+), 200 (41), 91 (100); CI 284 (37), 283 (100, MH^+), 200, (20), 111 (26), 91 (27).

5,6-Dihydropyranone adduct (10).- A solution of **1b** (111 mg, 0.55 mmol) and 5,6-dihydro-2*H*-pyran-2-one (47 ml, 0.61 mmol) in dry THF (10 ml) refluxed for 3 h gave adduct (**10**) as colourless oil (25 mg, 15%), δ_H (300 MHz) 7.46 (1H, bs), 7.4-7.2 (5H, m), 4.5 (1H, s), 4.38 (1H, s), 4.40 (1H, m), 4.38 (1H, s), 4.19 (1H, td, J 1.5, 12), 4.05 (1H, d, J 7), 3.78 (2H, s), 3.69 (1H, d, J 7), 3.53 (1H, dd, J 7, 12), 3.03 (1H, m), 1.55 (2H, m); *m/z* EI 298 (22, M^+), 207 (39), 200 (100), 172 (24), 91 (82); CI 300 (49), 299 (96, MH^+), 203 (59), 116 (100), 91 (23); ν_{max} (film) 3230, 2924, 1731, 1682.

Methyl 8-benzyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]oct-6-ene-6-carboxylate (14a).- A solution of **1b** (1.5 g, 7.5 mmol) and methyl propiolate (0.73 ml, 8.25 mmol) in dry THF (25 ml) refluxed for 1.5 h gave adduct (**14a**) as a colourless oil (1.60 g, 75%), δ_H (400 MHz) 7.30 (5H, m), 7.15 (1H, s), 7.13 (1H, d, J 2), 4.39 (1H, s), 4.36 (1H, d, J 1), 4.32 (1H, d, J 1), 4.05 (1H, m), 3.79 (1H, d, J 6.5), 3.73 (1H, d, J 6.5), 3.77 (3H, s); δ_C (100 MHz) 164.9, 162.8, 141.3, 138.9, 137.2, 136.7, 129.0, 128.5, 127.7, 93.4, 69.09, 64.14, 60.45, 53.71, 51.93; ν_{max} ($CHBr_3$) 3377, 2949, 1718, 1687; *m/z* FAB 285 (80,

MH^+), 216 (23), 201 (30), 91 (44) (Anal. calcd for $C_{16}H_{16}N_2O_3.0.25H_2O$: C, 66.6; H, 5.6; N, 9.7. Found: C, 66.6; H, 5.8; N, 9.1).

Methyl 8-benzyl-4-methylene-2-oxo-7-phenyl-3,8-diazabicyclo[3.2.1]octane-6-carboxylate (14b) and methyl 8-benzyl-4-methylene-2-oxo-6-phenyl-3,8-diazabicyclo[3.2.1]octane-7-carboxylate (14c).- A solution of **1b** (1.25 g, 6.25 mmol) and methyl 3-phenylpropiolate (1.1 g, 6.87 mmol) in dry THF (25 ml) refluxed for 5 h gave an oil from which the two regioisomeric esters (**14b** and **14c**) were obtained as pale brown oils (0.14 g, 6 %) and (0.14 g, 6 %); the least polar had δ_H (250 MHz) 7.69 (2H, m), 7.45 (1H, bs), 7.35 (8H, m), 4.52 (1H, s), 4.38 (1H, s), 4.34 (1H, s), 4.25 (1H, s), 3.85 (1H, d, J 15), 3.76 (1H, d, J 15), 3.71 (3H, s); ν_{max} ($CHBr_3$) 3376, 2948, 2843, 1687, 1651; *m/z* EI 360 (10, M^+), 91 (100); CI 363 (14), 362 (24), 361 (100, MH^+), 228 (14), 108 (48), 106 (53) ($C_{22}H_{20}N_2O_3$, requires: M, 360.1474. Found:, M^+, 360.1464); the more polar had δ_H (250 MHz) 7.58 (1H, bs), 7.50 (2H, m), 7.35 (8H, m), 4.36 (1H, d, J 2) 4.35 (1H, d, J 1), 4.32 (1H, d, J 2) 4.17 (1H, d, J 1), 3.83 (2H, m), 3.72 (3H, s); ν_{max} ($CHBr_3$) 3378, 2949, 2842, 1692, 1649; *m/z* EI 360 (5, M^+), 291 (15), 91 (100); CI 363 (17), 362 (27), 361 (100, MH^+), 271 (23), 108 (72), 106 (63) ($C_{22}H_{20}N_2O_3$ requires: M, 360.1474. Found: M^+ 360.1474).

8-Benzyl-4-methylene-2-oxo-6-*endo*-6-phenyl-3,8-diazabicyclo[3.2.1]octane (3l).- A solution of **1b** (0.390 g, 1.87 mmol) and styrene (0.24 ml, 2.1 mmol) in dry THF (20 ml) refluxed for 3 h gave adduct (**3l**) as a pale yellow oil (0.34 g, 60%), δ_H (300 MHz) 7.4-7.1 (11H, m), 4.07 (1H, d, J 1.5), 3.87 (1H, q, J 6), 3.85 (1H, d, J 12.5), 3.78 (1H, d, J 12.5), 3.71 (1H, d, J 6) 3.70 (1H, J 6), 2.76 (1H, m), 2.26 (1H, dd, J 6, 14); ν_{max} (KBr) 3591, 2862, 1673; *m/z* EI 200 (50), 91 (100); CI 306 (49.7) , 305 (100, MH^+), 200 (32.9), 111 (24.9).

4-*endo*-4-Methyl-2-oxo-6-*endo*-6-phenyl-3,8-diazabicyclo[3.2.1]octane (13).- A solution of 8-benzyl-4-methylene-2-oxo-6-*endo*-6-phenyl-3,8-diazabicyclo[3.2.1]octane (269 mg, 0.89 mmol) in ethanol (25 ml) and formic acid (3 ml) was hydrogenated at atmospheric pressure over 10% Pd-C (50 mg) for 2 h. The solution was neutralised with triethylamine, filtered through a pad of celite to remove the catalyst and the filtrate evaporated *in vacuo* to give an oil which was purified by flash column chromatography over silica gel to give the dihydro-derivative (**13**) as a colourless oil (175 mg, 87%), δ_H (CD_3OD, 200 MHz) 7.4-7.2 (5H, m), 4.0-3.7 (4H, m), 2.8-2.6 (2H, m), 0.4 (3H, d, J 8); ν_{max} (film) 3252, 3057, 1662; *m/z* EI 216 (25, M^+), 112 (37); CI 217 (100), 215 (28), 111 (40).

Indene adduct (11).- A solution of **1b** (0.25 g, 1.25 mmol) and indene (0.16 g, 1.38 mmol) in dry THF (5 ml) refluxed for 4.5 h gave adduct (**11**) as a white crystalline solid (0.16 g, 40%), mp 191-194 °C (EtOAc/hexane), δ_H (300 MHz) 7.4-7.1 (9H, m), 6.66 (1H, s), 4.22 (1H, t, J 9), 4.06 (1H, d, J 1), 4.01 (1H, s), 3.96 (1H, d, J 7.7), 3.83 (1H, d, J 12.5), 3.75 (1H, d, J 12.5), 3.68 (1H, d, J 7.5), 3.50 (1H, m), 3.08 (1H, dd, J 10, 18) and 2.92 (1H, dd, J 3, 18); *m/z* EI 200 (46), 91 (100); CI 318 (23), 317 (100, MH^+), 200 (16), 111 (39), 106 (36), 91 (18); ν_{max} (film) 3175, 3027, 2918, 1683 (Anal. calcd for $C_{21}H_{20}N_2O$: C, 79.9; H, 6.3; N, 8.9. Found: C, 79.6; H, 6.4; N, 8.9).

Cyclopentadiene adduct (12).- A solution of **1b** (0.184 g, 0.92 mmol) and cyclopentadiene (0.12 g, 1.84 mmol) in dry THF (1 ml) refluxed for 3 h gave adduct (**12**) as a colourless oil (0.11 g, 47%), δ_H (300 MHz) 7.33 (5H, m), 7.18 (1H, bs), 5.69 (1H, m), 5.49 (1H, m), 4.22 (1H, s), 4.02 (1H, s), 3.75 (3H, m), 3.65 (1H, m), 3.55 (1H, d, J 7.5), 3.25 (1H, m), 2.44 (m, 1H), 2.30 (1H, m), ν_{max} 3201, 3059, 2923, 1681, 1646; *m/z* EI 200 (30), 92 (9), 91 (100), 66 (24); CI 268 (20), 267 (100, MH^+), 200 (15) ($C_{17}H_{19}N_20$ requires: M, 267.1497. Found: M^+, 267.1485).

Methyl 8-benzyl-4-methoxy-4-methyl-2-oxo-3,8-diazabicyclo[3.2.1]oct-6-ene-6-carboxylate (16).- Methyl 8-benzyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]oct-6-ene-6-carboxylate (**14a**) (166 mg, 0.58 mmol) was refluxed in methanolic HCl (20 ml, 0.5 M) under N_2 for 3 h. The solvent was removed *in vacuo* to give an oil to which aq. $NaHCO_3$ (2M, 20 ml) was added then the organic material extracted with $CHCl_3$ (3 x 30 ml). The $CHCl_3$ extracts were combined, dried with anhydrous Na_2SO_4 and evaporated *in vacuo* to give an oil which was purified by flash column chromatography (eluant EtOAc:hexane 1:1) to give the ether (**16**) (73 mg, 39%), δ_H (300 MHz) 7.3-7.2 (6H, m), 5.45 (1H, bs), 4.05 (1H, s), 3.90 (1H, s), 3.70 (3H, s), 3.65 (1H, d, J 14), 3.58 (1H, d, J 14), 3.40 (3H, s), 1.22 (3H, s); ν_{max} (KBr disc) 2935, 1722, 1679; *m/z* EI 284 (1.5), 216 (16), 215 (10), 91 (100); CI 317 (8), 287 (10), 286 (18), 285 (100), 216 (25), 152 (38) ($C_{17}H_{21}N_2O_4$ requires: 317.1263. Found: MH^+, 317.1270).

8-Benzyl-4-methoxy-4-methyl-2-oxo-7-*exo*-7-phenylsulfonyl-3,8-diazabicyclo[3.2.1]octane (15).- 8-Benzyl-4-methylene-2-oxo-6-*exo*-6-phenylsulfonyl-3,8-diazabicyclo[3.2.1]octane (**3e**) (150 mg, 0.42 mmol) was refluxed in methanolic HCl (20 ml, 0.5 M) under N_2 for 3 h. The solvent was removed *in vacuo* to give an oil. Aqueous $NaHCO_3$ (2M, 20 ml) was added and the oil extracted with $CHCl_3$ (3 x 30 ml), the extracts combined, dried with Na_2SO_4 and evaporated *in vacuo* to give an oil which was purified by flash column chromatography to give the ether (**15**) as a white solid (67 mg, 40%), δ_H (250 MHz) 7.95 (2H, dd, J 1.5, 8), 7.70 (1H, td, J 1.5, 8), 7.60 (2H, tt, J 1.5, 8), 7.30 (5H, m), 6.35 (1H, bs), 3.96 (1H, d, J 16), 3.89 (1H, d, J 16), 3.88 (2H, bs), 3.66 (1H, t, J 8), 3.16 (3H, s), 2.60 (1H, m), 2.13 (1H, dd, J 8, 14), 1.22 (3H, s); δ_C (100 MHz) 172.03, 138.55, 137.89, 134.06, 129.59, 128.93, 128.48, 128.28, 127.30, 86.09, 65.61, 65.41, 64 10, 54.76, 50.19, 30.99, 21.48; ν_{max} ($CHBr_3$) 3377, 2953, 2938, 1682, 1446; *m/z* CI 401 (17, MH^+), 387 (10), 369 (100) (Anal. calcd for $C_{21}H_{24}N_2O_4S.0.5H_2O$: C, 61.6; H, 6.1; N, 6.8. Found: C, 61.0; H, 6.0; N, 6.6).

Methyl 8-methyl-4-(3-methoxyphenylmethylene)-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo*-6-carboxylate (18).- Oxidodiazinium (**1c**) (6.0 mg, 0.026 mmol) and methyl acrylate (24 µl, 0.27 mmol) heated for 2 h in refluxing, dry THF (0.5 ml) and elution from the column with ethyl acetate gave adduct (**18**) as a yellowish oil (3.9 mg, 50%), λ_{max} 215 (2.13), 279 (1.49); ν_{max} (film) 2960, 2926, 2854, 1738, 1690, 1599, 1451; δ ($CDCl_3$) 7.57 (1H, bs), 6.81 (3H, m), 6.73 (1H, m), 5.66 (1H, s), 4.07 (1H, s), 3.81 (3H, s), 3.78 (3H, s), 3.63 (1H, d, J 6.5), 3.13 (1H, dd, J 6.5, 10), 2.69 (1H, dt, J 6.5, 13), 2.53 (3H, s), 2.38 (1H, dd, J 10, 13); *m/z* EI 316 (M^+, 8%), 230 (100) ($C_{17}H_{20}N_2O_4$ requires: M, 316.1423. Found: M^+, 316.1427).

Methyl 8-benzyl-3-*t*-butoxycarbonyl-4-methylene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*exo* 6-carboxylate (17a).- To a stirred solution of **3d** (276 mg, 9.65 mmol), triethylamine (0.29 ml, 2.06 mmol) and DMAP (0.25 g, 2.06 mmol) in dichloromethane (10 ml) at 0 °C was added dropwise di-*t*-butyl dicarbonate (0.90 g, 4.12 mmol) over 10 min. The solution was stirred at 0 °C for 1 h then solvent was evaporated *in vacuo* to give an oil which was purified by flash column chromatography (eluant: EtOAc: hexane 1:4) to give the carbamate (**17a**) as a colourless oil (324 mg, 87%), δ_H (300 MHz) 7.28 (5H, m), 4.41 (1H, d, J 1.5), 4.32 (1H, d, J 1.5), 4.06 (1H, s), 3.84 (1H, d, J 13.5), 3.77 (1H, d, J 13.5), 3.72 (3H, s), 3.65 (1H, d, J 7), 3.07 (1H, dd, J 6, 10), 2.63 (1H, dd, J 7, 13), 2.35 (1H, dd, J 10, 13), 1.58 (9H, s); ν_{max} 2982, 1766, 1741, 1702, 1637, 1250, 1149; *m/z* EI 358 (5), 216 (12), 91 (82), 84 (59), 49 (100); CI 388 (39), 387 (100, MH^+), 287 (789) ($C_{21}H_{26}N_2O_5$ requires M, 386.4164. Found M^+, 386.4159).

8-Benzyl-3-*t*-butoxycarbonyl-4-methylene-2-oxo-6-*exo*-6-phenylsulfonyl-3,8-diazabicyclo[3.2.1]-octane (17b).- To a stirred solution of **3e** (136 mg, 0.369 mmol), triethylamine (0.10 ml, 0.74 mmol) and DMAP (90 mg, 0.74 mmol) in dichloromethane (5 ml) at 0 °C was added dropwise di-*t*-butyl dicarbonate (0.32 g, 1.48 mmol) over 10 min. After a further 10 min at 0 °C the solvent was evaporated *in vacuo* to give an oil, purified by flash column chromatography (eluant: ethyl acetate: hexane) to give the carbamate (**17b**) as an oil (136 mg, 81%), δ_H (300 MHz) 7.69 (2H, bd, J 8), 7.69 (1H, t, J 8), 7.56 (2H, t, J 8), 7.33-7.15 (5H, m), 4.39 (1H, d, J 2.5), 4.18 (1H, d, J 2.5), 4.10 (1H, s), 3.80 (1H, d, J 13), 3.68 (1H, d, J 13), 3.73 (1H, dd, J 6, 9), 3.65 (1H, d, J 6), 2.65 (1H, ddd, J 6, 9, 14), 2.38 (1H, dd, J 9, 14); ν_{max} 2982, 1766, 1701, 1639, 1250, 1150; *m/z* EI 369 (18, MH^+), 368 (8), 200 (51), 199 (44), 158 (39), 91 (100); CI 471 (12), 470 (36, MH^+), 469 (91), 370 (32), 369 (100), 329 (38), 229 (96), 137 (80) ($C_{25}H_{29}N_2O_5S$ requires M, 469.1797. Found M^+, 469.1797).

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