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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 21[1] ACTIVATION OF THE ZH PROTON IN IMINES.[2]

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Abstract. Imines, RCH=N-ZH, possessing a range of ZH groups (Z=CHCOPh, CHCOSR, CHCONHR, CHP(O)(OEt)$_2$, 2-CH-pyridyl, 2-CH-thiazolyl, and 9-fluorenyl) undergo thermal 1,2-prototropy generating azomethine ylides stereospecifically. The intermediate azomethine ylides undergo cycloaddition reactions with dipolarophiles either via an endo-transition state or via both endo- and exo-transition states to give polyfunctional pyrrolidines in good yield. In certain instances involving imines in which the amide activating group is present, the imine catalyses cis $\rightleftharpoons$ trans isomerisation of the dipolarophile. X-Ray crystal structures of two of the cycloadducts are reported.

Our recognition of a new type of prototropy, 1,2-prototropy[3], in X=Y-ZH systems, led to a facile entry into a range of novel, and synthetically useful, 1,3-dipoles, $X=\overset{+}{Y}(H)-\overset{-}{Z}$. In the case of imines (X=Z=C, Y=N) we showed that the ease of dipole formation is influenced by the basicity of the central Y atom (nitrogen) and the pK_a of the ZH(CH) proton[4]. Imines of α-amino acid esters and α-amino acids, in which ester[4,5] and carboxylic acid moieties activate the ZH proton, are particularly valuable precursors of azomethine ylides. French workers subsequently introduced the cyano group as a ZH activating group[7] and this was taken up and its usefulness extended by Tsuge.[8] In a number of important respects the acid/base chemistry of imines parallels that of carbonyl compounds[9] and this analogy is useful in suggesting suitable reagents/activating groups for generating either the 1,2-prototropy product (azomethine ylide) or the related 4 -azaallyl anion. Thus both

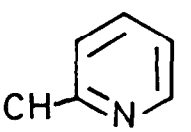
Bronsted and Lewis acids catalyse the formation of azomethine ylides from imines[9] and a combination of metal salt (silver, lithium or zinc) and triethylamine in a polar solvent (MeCN, DMSO, N-methylacetamide) permits rapid (0.1-3.5h) cycloaddition of imines of -amino acid esters to dipolarophiles at room temperature.[10] Analogous, but much slower cycloadditions, were subsequently reported to be effected by lithium bromide in THF.[11]

We now report full details of a range of other activating groups for the ZH proton in imines (1) which permit facile generation of the corresponding azomethine ylide (2).

(1) (2)

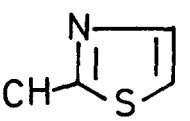
Table 1. Activating groups for the ZH proton in imines (1).[a]

$CHCO_2R$ (30.5)[b]



(-)

$CHCO_2H$ (~31)[c]



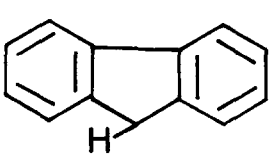
(-)

CHCN (31)[b]

$CHCOPh$ (25)[b]

$CHP(O)(OEt)_2$ (35)[b]

$CHCOSR$ (~28.5)[c,d]



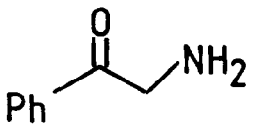
(23)[b]

$CHCONR_2$ (34.5)[b,d]

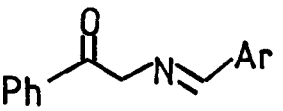
a. Figures in brackets are approximate pK_a values for the analogous methyl substituent; b. Ref.12; c. Estimated values; d. Our examples are lactams and a thiolactone.

It can be seen from Table 1 that the currently successful activating groups have pK_a's ranging from ca.25 to 35 for the corresponding MeX compounds where X = activating group. The presence of the aryl imine functionality will, of course, lower all these values, but the presence of the imine nitrogen atom and its potential for hydrogen bonding (see below) will exert a greater stabilising effect (lower pK_a) on some azomethine ylides, e.g. Z=$CHCO_2R$ compared with Z=CHCN (intramolecular hydrogen bonding not possible), and Z=CHCOPh compared to Z=9-fluorenyl. The various activating groups are now considered in turn.

a. Benzoyl. Attempts to isolate the imines of (3) with aryl aldehydes were unsuccessful due to the high lability of the methylene protons in (4). However, generation of (4) in situ from (3) and benzaldehyde in the presence of (NPM)(acetonitrile, 80°C,8h) gave the desired product as a 1.8:1 mixture of epimeric cycloadducts (5) and (6) in good yield.



(3)



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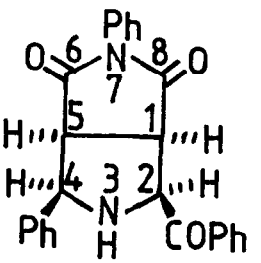
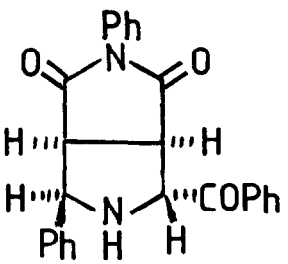


(5)



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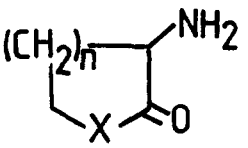


(7) a. X=S, n=1
b. X=NH, n=2
c. X=NH, n=3

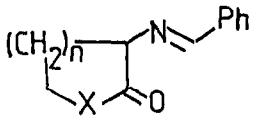
The stereochemistry of (5) and (6) was established by n.O.e. experiments (see experimental section).

b. Thiolactone and Lactams. Condensation of the thiolactone (7a) with benzaldehyde at room temperature yielded a mixture of imine (8a) and the spiro-imidazolidine (9). On keeping the mixture at room temperature complete conversion to (9) occurred. Formation of imidazolidines by

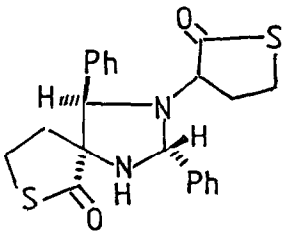
regio-specific dimerisation of imines has been previously observed by us in the reactions of diethyl aminomalonate with aromatic aldehydes.[13] Formation of (9) could involve either an anionic $4\pi + 2\pi$ cycloaddition[14] or a 1,3-dipolar cycloaddition via 1,2-prototropic generation[3] of the dipole (10a) from (8a). The dimerisation reaction is both regio- and stereo-specific. The stereochemistry of (9) is based on the absence of an n.O.e. effect between the 2-H and 4-H imidazolidine ring protons and previous observations of kinetic control of dipole stereochemistry.[5,6]

The propensity for suitably substituted imidazolidines to undergo thermal cycloreversion to a 1,3-dipole and an imine is well established.[13,15] However, in the case of (9) the imine arising from such a cycloreversion is expected to generate a further 1,3-dipole by 1,2-prototropy.[13] Thus, as expected, heating imidazolidine (9) with two equivalents of NPM in xylene at 130°C for 6h. afforded (84%) a ca. 6:1 mixture of (11a) and (12a). The stereochemistry of (11a) and (12a) is assigned on the basis of n.O.e. studies (see experimental section). In an analogous manner heating (9) with two equivalents of acenaphthylene (toluene-d_8, 135°C, 5d) gave (75%) a 2:1 mixture of endo(13)- and exo(13)-cycloadducts, together with a small amount (ca.10%) of the oxidation product (14) arising from (13). Heating endo(13) (xylene-d_{10},140°C,8d) gave a 1.84:1 mixture of endo(13) and (14) confirming oxidation of (13), presumably involving trace amounts of oxygen in the system, occurs under the cycloaddition reaction conditions. Assignment of stereochemistry to (13) and (14) is based on the stereochemistry of (11a) and (12a). One of the aromatic proton signals in endo(13)(δ 5.92) and exo(13)(δ 5.86) occurs at unusually high field. This signal is absent in (14). The azomethine ylide (10a) reacts predominantly via an endo-transition state whilst the related imines of α-amino esters react stereospecifically via an endo-transition state.[6] However, these latter imines do not undergo intermolecular reactions with unactivated dipolarophiles, whereas (10a) does react, albeit slowly, with acenaphthylene. Imines of α-amino acid esters do react in intramolecular cycloadditions with unactivated dipolarophiles.[16]

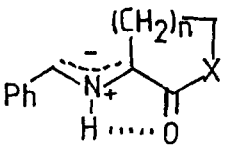
The lactam imines (8b) and (8c) undergo cycloaddition with a range of dipolarophiles. Thus both react with NPM in xylene at 130°C over 3h. to give ca. 1.4:1 mixtures of endo (11b,c)- and exo(12b,c)-adducts in 75-78% yield. These cycloadducts arise from dipoles (10b) and (10c) via endo- and exo-transition states. Thus (8a-c) generate the corresponding 1,3-dipoles (10a-c) stereospecifically and the dipole configuration is analogous to that obtained from imines of α-amino acids and their



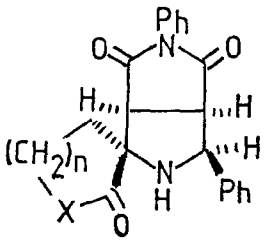
(8) a. X=S, n=1
b. X=NH,n=2
c. X=NH,n=3



(9)



(10) a. X=S, n=1
b. X=NH,n=2
c. X=NH,n=3



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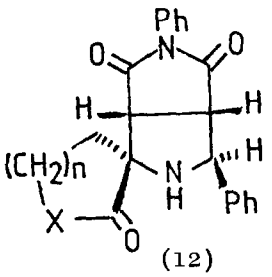
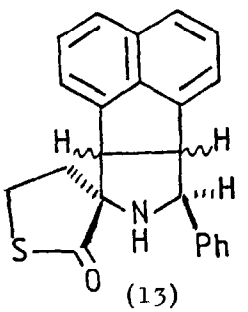
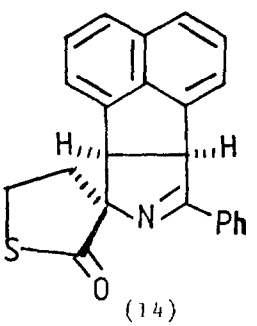


(12)

a. X=S, n=1
b. X=NH, n=2
c. X=NH, n=3



(13)

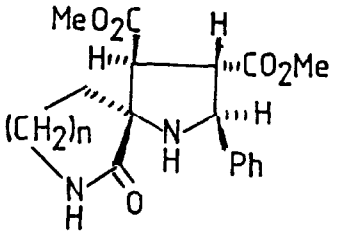


(14)

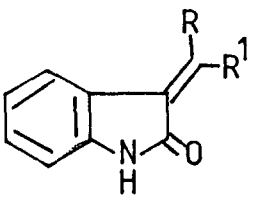
esters.[5,6] In the latter cases the dipoles are formed under kinetic control and hydrogen-bonding of the type depicted in (10) is believed to be responsible for this kinetic preference.≠

≠ The hydrogen bonding may involve a bridging water molecule.

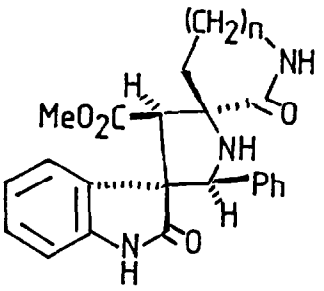
Imines (8b) and (8c) react with dimethyl fumarate (toluene, 110°C) to give (15a) and (15b) respectively in good yield together, in the latter case, with a trace amount of a second isomer. Imines (8b) and products, (15a) and (15b), with dimethyl maleate on heating in toluene (110°C) and in both these cases a trace amount of a second isomer was detected. Careful ^{1}H n.m.r. monitoring of the reaction of (8b) and dimethyl maleate demonstrated that isomerisation of dimethyl maleate to dimethyl fumarate preceded the cycloaddition, i.e. signals for the



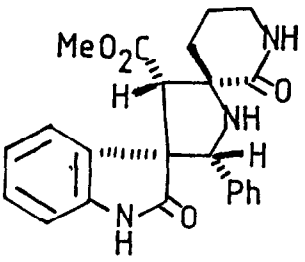
(15) a. n=2
b. n=3



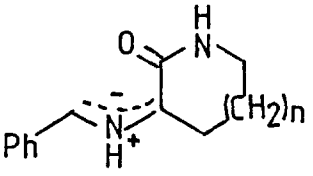
(16) a. R=CO_2Me, R^1=H
b. R=H, R^1=CO_2Me



(17) a. n=2
b. n=3



(18)



(19) n = 1 or 2

olefinic proton of dimethyl fumarate were observed at δ 6.78. Base catalysed isomerisation of maleate to fumarate is well known.[5,17] However, this base catalysed stereomutation is not normally observed to a significant extent[5] in the presence of imines of α-amino acid esters suggesting the lactams (8b) and (8c) are significantly more basic than imines of α-amino acid esters. The substantially greater reactivity of fumarate esters compared to maleate esters, in 1,3-dipolar cycloaddition reactions[18], accounts for the lack of maleate cycloadducts and

indicates that the maleate to fumarate isomerisation is fast compared to the rate of cycloaddition.

The stereochemistry of (15a) and (15b) accords with that found for the major isomer from the cycloaddition of imines of α-amino acid esters to fumarate esters.[5] Assignment of the stereochemistry of (15a) and (15b) is based on their ^{1}H n.m.r. spectra, a key feature being the absence of shielding of the methyl group of the methyl ester that occurs when there is a cis, vicinal, phenyl substituent. Spectral comparisons with the fumarate ester cycloadducts of imines of α-amino acid esters[5] confirm the assignments.

Imine (8b) reacts with the isatin derivative (16a) (xylene, 130°C, 1.5d) to give (84%) a ca. 1.2:1 mixture of pyrrolidines (17a) and (18) whilst imine (8c) reacts with (16a) under analogous conditions to give a single cycloadduct (17b)(79%). Both (17) and (18a) proved stable when recycled under the reaction conditions. The unusual stereochemistry of (17a) and (17b) was partly indicated by n.O.e. studies (see experimental section) which indicated the cis-relationship of the two pyrrolidine ring protons. However, it required an X-ray structure determination (below) to uncover the unexpected involvement of both a stereomutated dipolarophile (16b) and dipole (19) in the cycloaddition leading to (17). The formation of (17) thus requires either (i) a non-concerted cycloaddition or (ii) a base catalysed preequilibration of (16a) with its stereoisomer (16b) together with equilibration of the kinetic dipoles (10b) and (10c) with (19). When (16a) was heated in pyridine-d_5 at 105-110°C monitoring the ^{1}H n.m.r., the slow isomerisation of (16a) to (16b) was clearly visible with an observed ratio of (16a):(16b) of 10.8:1 after 44h, 3:1 after 91h, and 1.7:1 after 117h. This slow isomerisation rate suggests that if the cycloaddition is concerted then (16b) undergoes cycloaddition to (19) at a somewhat faster rate than (10b) and (10c) react with (16a), i.e. a related situation to that observed previously for the cycloaddition of dimethyl maleate and dimethyl fumarate to (8b) and (8c) (above). Dipole stereomutation of the type (10b,c) $\rightleftharpoons$ (19) is unusual even with less reactive dipolarophiles[6,16] and normally requires aryl substituents (i.e. extended conjugation) at both termini of the azomethine ylide. It may be that the slow rate of reaction, coupled with extended conjugation arising from the greater resonance interaction in an amide bond compared to an ester, results in dipole stereomutation. Our preference is for this latter explanation rather than a non-concerted cycloaddition.

Crystal Data for (17a): $C_{23}H_{23}N_3O_4$. M = 405.4, triclinic, space group $P\bar{1}$, a = 10.440(8), b = 11.987(10), c = 8.726(7)Å, α = 83.42(6), β = 109.17(6), γ = 98.95(6)°. U = 1016.5Å^3, Z = 2, D_x = 1.32g cm^{-3}, F(000) = 428, $\lambda(Mo\text{-}K_\alpha)$ = 0.7107Å. Rectangular prisms, dimensions 0.5 x 0.3 x 0.3mm. $\mu(Mo\text{-}K_\alpha)$ = 0.54 cm^{-1}. Data were recorded on a Stoe STADI-2 two-circle diffractometer using the background-ω-scan-background technique, scan width 2.0°, scan speed 0.6 deg min^{-1}, $3 \leq \theta \leq 25°$. 1052 unique data were corrected for Lorentz and polarisation effects; the structure was determined using the direct phasing routines of MULTAN and refined, using SHELX[19], with allowance for anisotropic vibrations for all non-hydrogen atoms. All hydrogens were located in a difference Fourier synthesis but were included in the refinement at positions calculated from the geometry of the molecule. In the final cycles the 1023 data with $I > 2\sigma(I)$ yielded a final conventional R of 0.067, R_w = 0.071. The weighting scheme used was $w = 2.85/[\sigma^2(F) + 0.0008F^2]$. A projection of the molecule is shown in Figure 1.≠

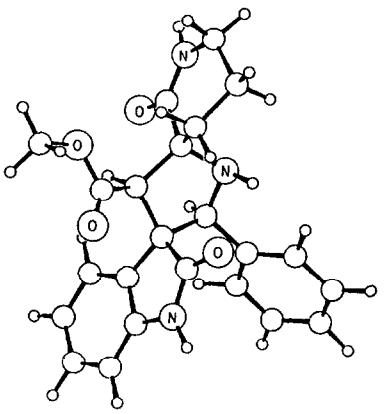


Figure 1

2-Pyridyl and 2-Thiazolyl. A series of imines of 2-aminomethylpyridine (20a-f) and the benzaldehyde imine of 2-aminomethyl-4-methylthiazole (21) have been prepared and their cycloaddition reactions with NPM studied. These imines could not be purified. They decompose on attempted distillation and tend to dimerise to imidazolidines, in an analogous manner to the thiolactone imine (8a), on keeping at room temperature. Thus the imine from pyridine-3-carbaldehyde and 2-aminomethylpyridine on

≠ All crystallographic results have been deposited with the Director, Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, U.K.

keeping at room temperature for 2 dy. afforded the imidazolidine (22)(60%) as a 1.3:1 mixture of trans- and cis-isomers. The crude imines (20a-f) and (21) react with NPM (toluene, 110°C) to give mixtures of endo- and exo-cycloadducts (23) and (24)(Table 2) derived solely from the syn-dipoles (25) and (26)≠, analogous to those found for imines of α-amino acid esters.[5,6] Appropriate blank experiments on separated pairs of isomers (23) and (24) show they are not inter-converted under the reaction conditions.

Stereochemistry of the cycloadducts (23) and (24) was established by n.O.e. difference spectroscopy and by an X-ray crystal structure of

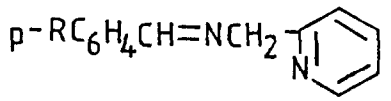
Table 2. Endo-exo cycloadduct ratios from the cycloaddition of imines (20a-f) and (21) with NPM.[a]

	R	R^1	Reaction Time(h)	Yield(%)[b]	Ratio (23):(24)[c]
a.	p-$Me_2NC_6H_4$	2-pyridyl	5	70	0.9:1
b.	p-$MeOC_6H_4$	2-pyridyl	7	72	1.2:1
c.	Ph	2-pyridyl	7	82	1.1:1
d.	p-$F_3CC_6H_4$	2-pyridyl	8	66	1.9:1
e.	p-NCC_6H_4	2-pyridyl	8	80	2:1
f.	p-$O_2NC_6H_4$	2-pyridyl	12	60	2.5:1
g.	Ph	2-(4-methyl thiazoyl	7	60	1:1

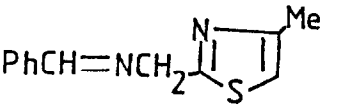
a. Reactions carried out in boiling toluene; b. Isolated yield; c. Ratio determined by integration of the 250MHz ^1H n.m.r. spectra of the crude products.

(23b)(below). A typical set of n.O.e. values is provided by (23g) and (24g). Thus for (23g) irradiation of H_B causes enhancement of the signals for H_A (8.8%) and H_C(7.4%), whilst irradiation of H_C causes enhancement of H_B(9.2%) and H_D(7%) Similarly for (24g) irradiation of H_B results in enhancement of H_C(11%) and H_A(2.7%), whilst irradiation of H_C effects enhancement of H_B(14%) and H_D(1.9%).

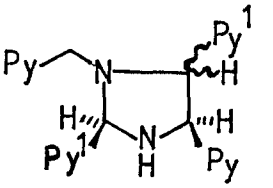
≠ See footnote on page 4.



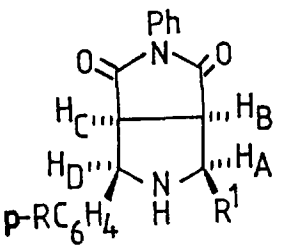
(20) a. R=NMe_2
b. R=MeO
c. R=H
d. R=CF_3
e. R=CN
f. R=NO_2



(21)



(22) Py=2-pyridyl, Py^1=3-pyridyl



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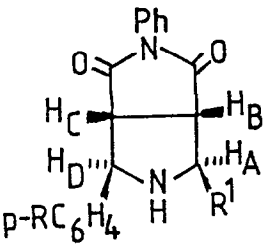

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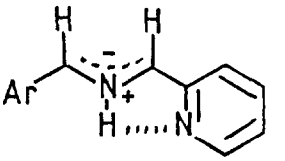
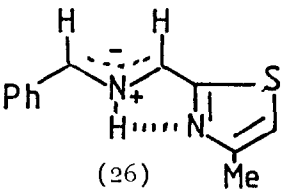


(25)

a. R=NMe_2, R^1=2-pyridyl
b. R=MeO, R^1=2-pyridyl
c. R=H, R^1=2-pyridyl
d. R=CF_3, R^1=2-pyridyl
e. R=CN, R^1=2-pyridyl
f. R=NO_2, R^1=2-pyridyl
g. R=Ph, R^1=2-(4-methyl)thiazolyl



(26)

Crystal Data for (23b): $C_{24}H_{21}N_3O_3$. M = 399.4, monoclinic, space group $P2_1/a$, a = 17.853(15), b = 8.326(7), c = 13.983(10)Å, β = 98.93(7)°. U=2053.3Å^3, Z=4, D_x= 1.29g cm^{-3}, F(000) = 840, λ(Mo-K_α) = 0.7107Å. Colourless rectangular blocks, dimensions 0.5 x 0.4 x 0.3mm, μ(Mo-K)=0.5cm^{-1}. Data were recorded on a Stoe STADI-2 two-circle diffractometer using the background-ω-scan-background technique

scan width 2.0°, scan speed 1.0 deg. min^{-1}, $2.8 \leqslant \theta \leqslant 25°$. The structure was solved using the direct phasing routines of MULTAN and refined by SHELX[19] with allowance for anisotropic vibrations for all non-hydrogen atoms. The hydrogens were located in a difference Fourier synthesis but were included in the refinement at calculated positions. In the final cycles the 748 data with $I > 3\sigma(I)$ gave a final R of 0.044, R_w = 0.046. The weighting scheme used was $w = 1.65/[\sigma^2(F) + .00047\ F^2]$. A projection of the molecule is shown in Figure 2.

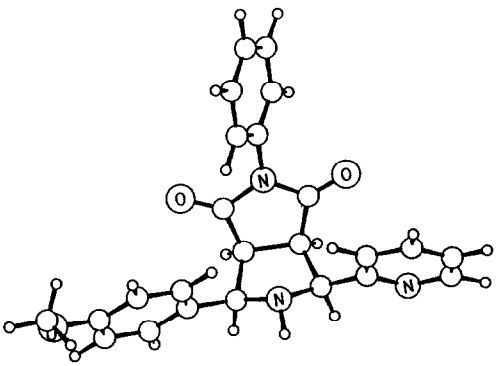
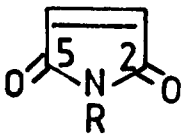


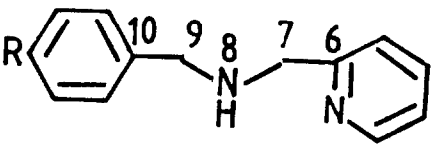
Figure 2

The endo-exo ratios in Table 2 indicate little preference for one transition state over the other, unless an electron withdrawing substituent is present in the R group of (20), i.e. (20d-f). Preference for an endo-transition state is usually ascribed to attractive secondary orbital interactions whilst steric effects, dipole-dipole interactions, and Van der Waals - London interactions can partially or fully reverse attractive secondary orbital interactions[20] and lead to an exo-transition state. Models of the endo- and exo-transition states (Figure 3) show that secondary orbital interactions, if present, would involve C(2) and C(5) of the maleimide (27) and C(6) and C(10) of the dipole (28). Huckel M.O. calculations[21,22] give values for the LUMO coefficients at C(2) and C(5) of (27) of -0.287 and +0.287 respectively. The HOMO coefficients for the central portion of the dipole (28) are given in Table 3. These two sets of coefficients indicate weak attractive secondary orbital interactions for (28, R=CN or NO_2) and weak repulsive

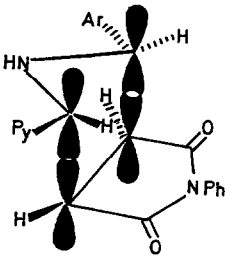
interactions for (28, R=H, OMe or NMe_2) in accord with the endo-exo ratios in Table 2.



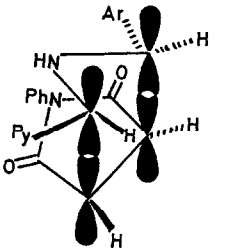
(27)



(28)



EXO



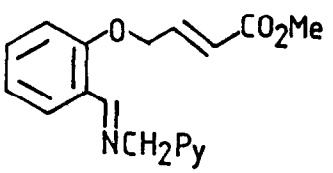
ENDO

Figure 3

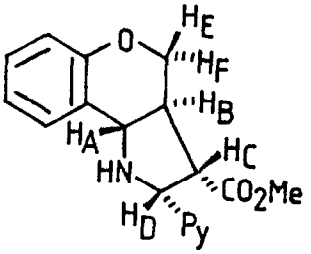
One intramolecular example of activation of the ZH proton by the 2-pyridyl group has been studied. Thus heating (29) in boiling xylene fo 2h afforded a 1.2:1 mixture of (30) and (31) in 60% combined yield. The stereochemistry of (30) and (31) are assigned on the basis of their ^1H n.m.r. spectra and by comparisons with the spectra of analogous adducts from the corresponding imines of α-amino acid esters.[16] The expected shielding of the ester methyl signal in (30)(3.23) compared to (31)(3.73) was observed. Recently we have shown that cycloadditions of imines of α-amino acid esters can be carried out rapidly at room temperature in a polar solvent in the presence of silver, or lithium, salts and triethylamine.[10] Imine (29) reacts rapidly and stereo-specifically under these conditions [AgOAc (1mol), NEt_3 (1.5mol), DMSO, 25°C, 10min.] to give (30) in 70% isolated yield (quantitative yield by ^1H n.m.r.).

Table 3. HOMO coefficients for the 1,3-dipole (28).

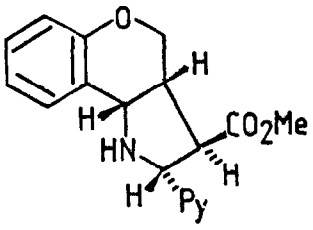
R	C(6)	C(7)	N(8)	C(9)	C(10)
NO_2	-0.014	-0.478	-0.030	0.517	0.076
CN	-0.030	-0.527	0.001	0.525	0.027
H	0.041	0.549	-0.025	-0.515	0.010
OMe	0.055	0.562	-0.055	-0.484	0.056
NMe_2	0.063	0.563	-0.073	-0.459	0.082



(29) Py = 2-pyridyl

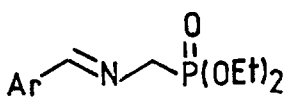


(30)

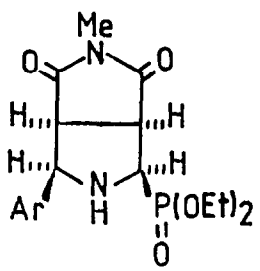


(31)

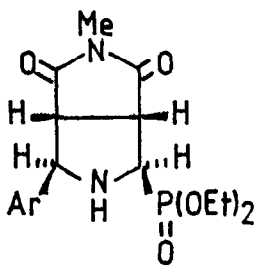
d. Phosphonate. Only one example of this type of activating group has been studied. The imine (32) reacts with N-methylmaleimide (NMM) in



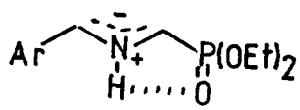
(32) Ar=O-$MeOC_6H_4$



(33) Ar=O-$MeOC_6H_4$



(34) Ar=O-$MeOC_6H_4$

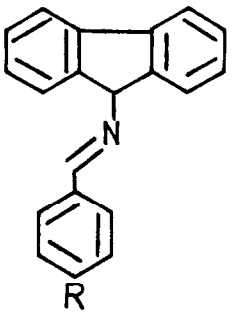


(35) Ar=O-$MeOC_6H_4$

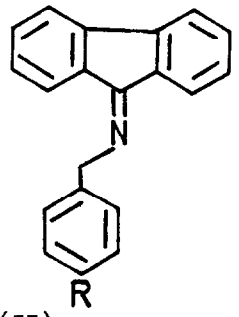
boiling xylene over 17h. to give (80%) a 1:1.5 mixture of endo(33)- and exo(34)-isomers. Once again both adducts arise from the syn-dipole (35) and again hydrogen bonding is thought to be responsible for the kinetically controlled stereospecific formation of (35) as discussed

above for other ZH activating groups. The slight preference for the exo-adduct (34) demonstrates that the phosphonate group is not a strong endo-directing substituent.

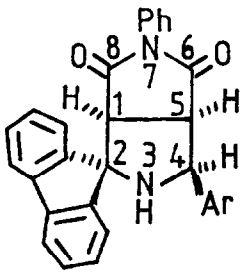
e. Fluorenyl. A series of arylidene imines of 9-aminofluorene (36a-e) were prepared and reacted with NPM (toluene, 110°C). Cycloaddition of (36a-c,e) occurred stereospecifically to give a single cycloadduct, the endo-isomer (38) in each case (Table 4).



(36) a. R=NMe_2
b. R=OMe
c. R=H
d. R=Br
e. R=CF_3



(37)



(38)

Table 4. Cycloaddition of (36a-c,e) with NPM in toluene at 110°C.

Imine	Reaction Time (h)	Product	Yield (%)[a]
35a	12	38a	54
35b	20	38b	64
35c	18	38c	60
35e	24	38e	68

a. Isolated Yield

The cycloadditions of the fluorenyl imines with NPM were complicated by a competing prototropic equilibration (36) (37). The equilibrium constants for this process were determined by ^1H n.m.r. spectroscopy in toluene at 105°C and were found, as might be expected, to be dependent on the substituent on the aromatic ring. The following order was obtained (Keq in brackets): $Me_2N(0.10) < MeO(0.33) < H(1.61) < Br(2.51) < CF_3(3.65)$. Thus electronegative substituents favour (37).

The base catalysed isomerisation of fluorenyl imines has been studied by More O'Ferrall.[23] In our case the imine functions as the basic catalyst.

We have previously reported the acid (6% acetic acid in acetic anhydride) catalysed cycloaddition of (36b) to NPM at room temperature to give (38b)(76%).[9] This result, together with the observed room temperature cycloaddition reactions of metal complexes (Cu,Zn,Cd) of imines of α-amino acids[24], and of (29) → (30) using silver acetate/triethylamine (above) indicates that imines possessing any of the ZH activating groups in Table 1 should undergo Bronsted or Lewis acid catalysed cycloaddition reactions at room temperature.

Experimental. General experimental details are as previously noted.[4] Petroleum ether refers to the fraction with b.p. 40-60°C.

Imines

3-Benzylideneamino-piperidin-2-one (8b). Ornithine methyl ester hydrochloride (8.68g, 4mmol) was added to methanolic sodium methoxide [from sodium (4g) and dry methanol (500ml)]. The mixture was stirred for 10 min., benzaldehyde (5g, 4.7mmol) added and stirring continued for a further 16h at room temperature. The methanol was then removed under reduced pressure and the residue dissolved in chloroform (200ml). The chloroform solution was washed with water, dried (Na_2SO_4), and the chloroform evaporated to leave the crude imine (6.3g, 78%), which crystallised from benzene as colourless needles (4.1g), m.p. 142-144°C (lit.[25] 143-145°C).

3-(N-Benzylideneamino)caprolactam (8c). A solution of 3-amino caprolactam (12g, 9.4mmol) and benzaldehyde (10.6g, 10mmol) in chloroform (300ml) containing anhydrous sodium sulphate (40g) was stirred at room temperature for 16h. The mixture was then filtered to remove the inorganic salts and the filtrate evaporated to leave the crude imine (12g, 58%) as a viscous oil which solidified on trituration with ether. Crystallisation from benzene afforded (8c) as colourless needles, m.p. 125-126°C (Found: C, 72.10; H, 7.50; N, 12.85. $C_{13}H_{16}N_2O$ requires C, 72.20; H, 7.45; N, 12.95%); δ 8.3 (s,1H,CH=N), 8.0-7.3 (m,5H,ArH), 4.2 (br t,1H,CH-N), and 1.9-1.2 [m,8H,$(CH_2)_4$]; $\nu_{max.}$ 3200, 1670 and 1580 cm^{-1}.

Imines (20a-f) and (21). These were prepared from the appropriate amine and aldehyde according to method B.[4] They could not be purified and were used directly for cycloaddition reactions. Their ^1H n.m.r. data are summarised below (Table 5).

Table 5. ^1H N.m.r. data (δ,$CDCl_3$) for imines (20a-f) and (21)

Imine	CH=N	NCH_2	ArH	Other
20a	8.25	4.9	8.5-6.5	2.90 (NMe_2)
20b	8.25	4.8	8.5-6.7	3.6 (OMe)
20c	8.3	4.9	7.8-7.0	
20d	8.5	5.0	8.6-7.3	
20e	8.5	5.0	8.6-7.3	
20f	8.6	5.0	8.8-7.0	
21	8.3	5.0	7.8-6.8	2.4 (Me)

2-[(3-Carbomethoxy-2-propenyl)oxy]-benzylidene-2-aminomethylpyridine (29).
2-[(3-Carbomethoxy-2-propenyl)oxy]-benzaldehyde (3.1g, 1mmol), and 2-aminomethylpyridine (1.08g, 1mmol) were dissolved in anhydrous methylene chloride (80ml) and anhydrous sodium sulphate (10g) added. The mixture was stirred for 4h, filtered to remove the sodium sulphate, and the filtrate concentrated to give the crude imine (29) as a thick yellow oil (1.5g, 50%), which decomposed on attempted distillation. The ^{1}H n.m.r. spectrum of the oil showed it to be essentially pure and it was therefore used immediately in cycloaddition reactions. δ 8.9 (s,1H,CH=N), 8.6-6.8 (m,9H,ArH + $CH{=}CHCO_2Me$), 6.2 (d,1H,$CH{=}CHCO_2Me$), 5.0 (s,2H,CH_2N), 4.7 (dd,2H,CH_2O) and 3.7 (s,3H,Me); $\nu_{max.}$ (film) 1735 and 1630 cm^{-1}.

Diethyl N-(o-Methoxybenzylidene)aminomethylphosphonate (32). Prepared from o-methoxybenzaldehyde and diethyl aminomethylphosphonate in an analogous manner to that described aove but with a reaction time of 16h. The product (77%) was a pale yellow oil, b.p. 160°C/1mmHg (Found: C, 50.55; H, 6.95; N, 4.90. $C_{13}H_{20}NO_4P.1.5H_2O$ requires C, 50.10; H, 6.75; N, 4.50%); δ 8.66 (d,1H,CH=N), 7.88-6.8 (m,4H,ArH), 4.13 (m,4H,CH_2Me), 3.7 (s,2H,CH_2P), and 1.25 (t,6H,CH_2Me) ν_{max} (film) 3000,1640,1600,1500 and 1260 cm^{-1}; m/z(%) 285 (M^+,5), 204(21), 203(23), 165(18), 164(12) and 152(100).

N-(p-Dimethylaminobenzylidene)-9-aminofluorene (36a). Prepared from 9-aminofluorene hydrochloride and p-dimethylaminobenzaldehyde according to method B.[4] The product (76%) crystallised from methanol as pale yellow prisms, m.p. 168-170°C (Found: C, 84.95; H, 6.45; N, 8.90. $C_{22}H_{20}N_2$ requires C, 84.60; H, 6.45; N, 8.95%); δ 8.66 (s,1H,CH=N), 7.76-6.68 (m,12H,ArH), 5.33 (s,1H,ArCH), and 3.01 (s,6H,NMe); ν_{max} 1620, 1520, 1365, 1225,800,770,740 and 730 cm^{-1}; m/z(%) 312 (M^+,93), 311(34), 297(3), 166(21), 165(100), 164(9), 156(12), 134(18) and 122(35).

N-(p-Methoxybenzylidene)-9-aminofluorene (36b). Prepared in an analogous manner to that described above from 9-aminofluorene hydrochloride and p-methoxybenzaldehyde. The product (91%) crystallised from methanol as colourless needles, m.p. 134-135°C (Found: C, 84.40; H, 5.75; N, 4.65. $C_{21}H_{17}NO$ requires C, 84.25; H, 5.70; N, 4.70%); δ 8.71 (s,1H,CH=N), 7.78-7.90 (m,12H,ArH), 5.37 (s,1H,ArCH) and 3.82 (s,3H,OMe); $\nu_{max.}$ 1625, 1600 and 1510 cm^{-1}; m/z(%) 299 (M^+,56), 191(4), 166(17), 165(100) and 164(6).

N-Benzylidene-9-aminofluorene (36c). Prepared from 9-aminofluorene hydrochloride and benzaldehyde in an analogous manner to that described above. The product (82%) crystallised from benzene as colourless prisms, m.p. 139°C (Found: C, 89.05; H, 5.50; N, 5.05. $C_{20}H_{15}N$ requires C, 89.20; H, 5.60; N, 5.20%); δ 8.80 (s,1H,CH=N), 7.85-7.25 (m,13H,ArH), and 5.43 (s,1H,ArCH); $\nu_{max.}$ 1625 and 1570 cm^{-1}; m/z(%) 269 (M^+,48), 268(13), 181(11), 180(69), 166(19), 1165(100), 164(8) and 152(18).

N-(p-Bromobenzylidene)-9-aminofluorene (36d). 9-Aminofluorene hydrochloride and p-bromobenzene were reacted in an analogous manner to that described above. The product (85%) crystallised from methanol as colourless prisms, m.p. 172-174°C (Found: C, 68.45; H, 4.05; N, 4.15. $C_{20}H_{14}BrN$ requires C, 68.90; H, 4.00; N, 4.00%); δ 8.74 (s,1H,CH=N), 7.79-7.30 (m,12H,ArH), and 5.43 (s,1H,ArCH); $\nu_{max.}$ 1630 cm^{-1}; m/z(%) 349,347 (M^+,18 and 19), 166(16) and 165(100).

N-(p-Trifluoromethylbenzylidene)-9-aminofluorene (36e). Prepared from 9-aminofluorene hydrochloride and p-trifluoromethylbenzaldehyde in an analogous manner to that described above. The product (80%) crystallised from methanol as colourless needles, m.p. 171°C (Found: C, 74.75; H, 4.20; N, 4.10. $C_{21}H_{14}F_3N$ requires C, 74.80; H, 4.15; N, 4.15%); δ 8.82 (s,1H,CH=N), 7.95-7.28 (m,12H,ArH), and 5.48 (s,1H,ArCH);

$\nu_{max.}$ 1635 cm^{-1}; m/z(%) 337 (M^+,46), 336(14), 166(19), 165(100) and 164(9).

Imidazolidines

2,4-Diphenyl-3-(3'-tetrahydro-2-oxo-thienyl)-5,5-spiro-(3',3'-tetrahydro thiophen-2-one) (9). Homocysteine thiolactone (1.2g), (freshly liberated from the corresponding hydrochloride) and benzaldehyde (1.06g) were dissolved in chloroform (20ml) and anhydrous sodium sulphate (5g) added. The mixture was stirred at room temperature overnight, filtered to remove the sodium sulphate, and the chloroform evaporated to leave pale yellow oil which comprised a ca.3:2 mixture of imine (8a) and imidazolidine (9). The mixture was kept for 2d. at room temperature and then triturated with benzene-petroleum ether to afford a colourless solid. Crystallisation from benzene afforded the product (9) (1.6g,76%) as colourless needles, m.p. 159-160°C (Found: C, 64.75; H, 5.15; N, 6.65. $C_{22}H_{22}N_2O_2S_2$ requires C, 64.40; H, 5.40; N, 6.85%); δ 7.68-7.26 (m,10H,ArH), 5.46 and 4.59 (2xs, 2x1H, 2-H and 4-H), 3.63 (dd,1H,CHCOS), and 3.05-1.63 (m,8H,CH_2); $\nu_{max.}$ 3270 and 1670 cm^{-1}; m/z(%) 382 ($M-C_2H_4$,1), 206(15) and 177(100).

2,4-Di(3-pyridyl)-3-(2-pyridylmethyl)-5-(2-pyridyl)imidazolidine (22). Freshly prepared N-(3-pyridylidene)-2-aminomethylpyridine was kept for 2d. at room temperature to afford the dimer (60%) as a semisolid whose p.m.r. spectrum showed it to comprise a 1.3:1 mixture of trans- and cis-isomers of (22). [Found (mixed isomers): C, 72.70; H, 5.50; N, 21.30. $C_{24}H_{22}N_6$ requires C, 73.00; H, 5.60; N, 21.30%].

Trans (22). Obtained as a colourless gum admixed with a little of the cis-isomer. δ ($CDCl_3$ + 1 drop D_2O) 8.82-6.75 (m,16H,ArH), 5.25 (s,1H,2-H), 4.37 (d, 1H, J 7.9Hz, 5-H), 4.09 (d,1H,4-H) and 3.89 (dd,2H,NCH_2).

Cis (22). Colourless prisms from methanol-petroleum ether, m.p. 140-142°C. δ ($CDCl_3$ + 1 drop D_2O) 9.02-6.75 (m,16H,ArH), 4.97 (s,1H,2-H), 4.90 (d, 1H, J 9.1Hz, 5-H), 4.52 (d,1H,4-H) and 3.88 (dd,2H,NCH_2).

Cycloadducts

2-Benzoyl-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-2-carboxylate (5) and (6). A mixture of benzaldehyde (530mg), aminomethylacetophenone hydrochloride (800mg), N-phenylmaleimide (860mg) and sodium acetate (410mg) in acetonitrile (30ml) was boiled under reflux for 8h. The solvent was then removed, the residue dissolved in chloroform, washed with water, the chloroform layer dried (Na_2SO_4), and evaporated to leave crude cycloadduct (1.38g,70%). The ^1H n.m.r. spectrum of the crude product showed it to comprise a 1.8:1 mixture of (5) and (6). The crude product mixture was separated by preparative t.l.c. (silica) eluting with 95:5 v/v chloroform-methanol. [Found (mixed isomers): C, 75.15; H, 6.00; N, 7.15. $C_{25}H_{19}N_2O_3$ requires C, 75.20; H, 6.10; N, 7.65%].

(5). Colourless prisms from chloroform-ether, m.p. 202-203°C. δ 8.06-7.0 (m,15H,ArH), 4.95 (d,1H,J 6.8Hz, 2-H), 4.68 (d,1H, J 8.6Hz, 4-H), 3.88 (t,1H,1-H), 3.63 (t,1H,5-H), and 2.19 (br s,1H,NH); ^1H NOEDSY(%): irradiation of the signal for 2-H caused enhancement of the signals of 1-H(7) and 4-H(2.3); m/z(%) 396 (M^+,4) 395(1), 292(35), 291(100), 144(68), 105(41), 91(12) and 77(31).

(6). Colourless prisms from chloroform-ether, m.p. 168-170°C. δ 8.18-7.09 (m,15H,ArH), 5.34 (d, J 0.8Hz, 2-H), 4.81 (d,1H, J 8.95Hz,4-H), 3.8 (dd, 1H, J 1.2 and 8.1Hz,1-H), and 3.46 (dd,1H, J 8.5 and 5.9Hz,5-H); ^1H NOEDSY(%): irradiation of the signal for 4-H caused enhancement of 5-H(10); irradiation of 2-H caused enhancement of the signal for 1-H(1); m/z(%) 396 (M^+,6), 291(100), 144(39), 105(49) and 77(29).

2,2-Spiro-(3',3'-tetrahydro-2-oxo-thienyl)-4,7-diphenyl-6,8-dioxo-3,7-diaza bicyclo[3.3.0]octane (11a) and (12a). A solution of imidazolidine (9)(205mg) and N-phenylmaleimide (1.73g) in dry xylene (10ml) was heated in a sealed tube at 130°C for 6h. during which time a colourless crystalline solid separated out. The mixture was cooled and filtered to afford the product (11a)(280mg) as colourless needles,m.p. 248-250°C. The mother liquor, on keeping at room temperature for ca.1 week, deposited colourless needles of (12a)(50mg), m.p. 162-165°C(decomp.) to give a combined yield of 84%. Examination of a sample of the total crude material by p.m.r. spectroscopy indicated a 6.1:1 ratio of (11a) to (12a). [Found (mixed isomers): C, 66.60; H, 4.85; N, 7.40. $C_{21}H_{18}N_2O_3S$ requires C, 66.65; H, 4.80; N, 7.40%).
(11a). δ (pyridine-d_5) 7.75-7.21 (m,10H,ArH), 5.05 (d,1H,J 8.1Hz, 4-H), 4.16 (t,1H,5-H), 3.99 (d,1H,J 7.7Hz, 1-H), 3.59 and 3.35 (2xm 2x1H,CH_2S), and 2.94 and 2.36 (2xm, 2x1H,CH_2); ^{1}H NOEDSY(%): irradiation of 4-H causes enhancement of 5-H (19.6); irradiation of 5-H results in enhancement of 4-H (14.8) and 1-H(9.7); $\nu_{max.}$ 3310,1710 and 1685 cm^{-1}; m/z(%) 350 (M-28,68), 317(100) and 173(14).
(12a) δ (pyridine-d_5 + 1 drop D_2O) 7.86-7.35 (m,10H, ArH), 5.25 (d, 1H, J 5.0Hz,4-H), 4.33 (d,1H,J 8.9Hz,1-H), 4.22 (dd,1H,5-H), 3.97 and 3.5 (2xm, 2x1H, CH_2S), and 2.8 (m,2H,CH_2); ^{1}H NOEDSY (%): irradiation of 4-H does not enhance 5-H; irradiation of 5-H results in enhancement of 1-H (11.4)but no enhancement of 4-H; $\nu_{max.}$ 3335 and 1695 cm^{-1}; m/z(%) 350 (M-28,74), and 317(100).
2,2-Spiro (3,3-piperidin-2-one)-4,7-diphenyl-6,8-dioxo-diazabicyclo[3.3.0] octane (11b) and (12b). A solution of equimolar amounts (10mmol) of imine (8b) and NPM in dry xylene was heated at 130°C for 3h. during which time a solid separated out from the reaction mixture. The solid was removed by filtration to give one, almost pure, isomer. The second isomer was obtained from the filtrate, giving a combined yield of 75%. Examination of a sample of the total crude product by p.m.r. spectroscopy indicated a 1.37:1 ratio of (12b) and (13b).
(11b). Colourless needles from methanol, m.p. 288°C(decomp.) (Found: C, 70.10; H, 5.70; N, 11.25. $C_{22}H_{21}N_3O_3$ requires C, 70.40; H, 5.65; N, 11.20%);δ (pyridine-d_5) 8.2 (br s,1H,NH), 7.67-7.23 (m,10H,ArH), 5.00 (d,1H,J 7.0Hz, 4-H), 4.22 (t,1H,5-H), 3.74 (d,1H, J 7.7Hz, 1-H), 3.4 (m,2H,CH_2N) and 1.99 (m,4H,2xCH_2); $\nu_{max.}$ 3320, 3240,1705 and 1665 cm^{-1}; m/z(%) 375 (M^+,100), 202(41) and 173(20).
(12b). Colourless rods from xylene, m.p. 233-236°C(decomp) (Found: C, 71.40; H, 5.85; N, 11.05. $C_{22}H_{21}N_3O_3.0.25$ xylene requires C, 71.70; H, 5.90; N, 10.45%);δ (pyridine-d_5 + 1 drop D_2O) 7.88-7.29 (m,10H,ArH), 4.07 (d, 2H, J 7.2Hz, 4-H and 1-H), 4.05 (t,1H,5-H), 3.35 (m,2H,CH_2N), and 2.34-1.2 (m,6H,3xCH_2); $\nu_{max.}$ 3320,3305,1695 and 1675; m/z(%) 375 (M^+,76), 317(100), 202(15) and 173(10).
2,2-Spiro(3,3-hexahydro-2-oxo-azepinyl)-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (11c) and (12c). Prepared in an analogous manner to that described above from imine (8c) and NPM. The product (78%) comprised a 1.38:1 mixture of (11c) and (12c) which were separated by fractional crystallisation.
(11c). Colourless needles from methanol, m.p. 303-304°C(decomp.) (Found: C, 71.15; H, 6.00; N, 10.95. $C_{23}H_{23}N_3O_3$ requires C, 70.95; H, 5.95; N, 10.80%);δ ($CDCl_3$ + 1 drop TFA-d) 7.49-7.67 (m,10H,ArH), 5.97 (d,1H, J 9.8Hz, 4-H), 4.42 (dd,1H,5-H), 4.30 (d,1H, J 8.85Hz, 1-H), 3.5 (m,2H,CH_2N), and 2.5-1.5 (m,6H,3xCH_2).
(12c). Pale yellow prisms from ether, m.p. 198-200°C(decomp.) (Found: C, 67.80; H, 6.60; N, 10.30. $C_{23}H_{23}N_3O_3.H_2O$ requires C, 67.80; H, 6.20; N, 10.30%);δ7.87-7.06 (m,10H,ArH), 6.42 (br s, 1H,4-H), 4.68 (d,1H, J 9.9Hz, 1-H), 3.63 (dd,1H, J 6.1 and 9.9Hz, 5-H),3.25

(m,2H,CH_2N) and 2.7-1.5 (m,6H,3xCH_2); $\nu_{max.}$ 3260,1705 and 1660 cm^{-}.

Cycloaddition of imidazolidine (9) and acenaphthylene. A solution of imidazolidine (9)(204mg, 5mmol) and acenaphthylene (152mg, 10mmol) in dry xylene (10ml) was heated at 135°C in a sealed tube for 5d. The reaction mixture was then cooled and set aside for 1.5d. during which time the endo-isomer of (13)(180mg,50%) crystallised out. The mother liquor was evaporated to dryness and the crude residue purified by preparative t.l.c. to afford the exo-isomer of (13)(90mg,25%). A third isomer was detected in trace amounts and subsequently identified as (14)(below).

endo-(13). Colourless rods from xylene, m.p. 228-230°C (Found: C, 77.15; H, 5.45; N, 3.85. $C_{23}H_{19}NOS$ requires C, 77.30; H, 5.35; N, 3.90%); δ 7.70-6.99 (m,10H,ArH), 5.9 (d,1H, J 7.1Hz,ArH), 4.82 (d,1H, J 7.35Hz, NCH), 4.55 (t, 1H, ArCH), 4.26 (d,1H, J 6.6Hz, ArCH), 3.67 and 3.47 (2xm, 2x1H, CH_2S), and 2.9 and 2.36 (2xm, 2x1H, CH_2); $\nu_{max.}$ 3310,1680, and 1590 cm^{-1}; m/z(%) 329 (M-28,76), 205(100) and 152(17).

exo-(13). Pale yellow prisms from ether, m.p. 120-123°C(decomp.) (Found: C, 75.65; H, 6.45; N, 3.60. $C_{23}H_{19}NOS.Et_2O$ requires C, 75.15; H, 6.75; N, 3.25%); δ 7.67-7.05 (m,10H,ArH), 5.86 (d,1H, J 7Hz,ArH), 5.02 (d,1H, J 7.55Hz, NCH), 4.48 (t,1H,ArCH), 4.36 (d,1H, J 7.2Hz, ArCH), 3.36 (m,2H,CH_2S), and 2.73 and 1.88 (2xm, 2x1H, CH_2); $\nu_{max.}$ 3320 and 1685 cm^{-1}.

2aα,8bα-Dihydro-2-phenyl-spiro[acenaphtho(1,2-c)-8cH-pyrrole-8c,3'-tetrahydrothiophene]-2'-one (14). A solution of endo-(13)(80mg) in dry xylene (3ml) was heated at 140°C in a sealed tube for 8d. to afford a 1.84:1 mixture of endo-(13) and (14). Preparative t.l.c. (silica) eluting with 1:1 ether-petroleum ether afforded the product (22mg), which crystallised from ether as pale yellow prisms, m.p. 198-200°C(decomp.) (Found: C, 75.35; H, 5.25; N, 3.65. $C_{23}H_{17}NOS.0.5\ H_2O$ requires C, 75.75; H, 5.00; N, 3.85%); δ 8.03-6.96 (m,11H,ArH), 5.67 and 4.46 (2xd, 2x1H, J 7.9Hz, 2a -H and 8b -H), and 3.71-1.9 (m,4H,2xCH_2); $\nu_{max.}$ 1685 cm^{-1}.

Dimethyl 2,2-spiro(3,3-piperidin-2-one)-c-5-phenylpyrrolidine-c-3,t-4-dicarboxylate (15a). A solution of 3-benzylideneaminopiperidin-2-one (50mg, 0.25mmol) and dimethyl maleate or fumarate (40mg, 0.28mmol) in toluene-d_8 (0.5ml) was heated at 110°C in a sealed n.m.r. tube for 7.75h(maleate) or 1.25h(fumarate), monitoring the reaction by ^1H n.m.r. spectroscopy. The mixture was then removed from the n.m.r. tube, the solvent evaporated, and the residue crystallised from methanol to afford the product (65-70mg, 80-82%), m.p. 159-161°C (Found: C, 62.25; H, 6.30; N, 8.10. $C_{18}H_{22}N_2O_5$ requires C, 62.50; H, 6.30; N, 8.10%); δ 7.46-7.27 (m,5H,ArH), 5.87 (br s,1H,NH), 4.28 (d,1H, J 10.1Hz,5-H), 3.87 (t,1H,4-H), 3.69 and 3.60 (2xs, 2x3H,OMe), 3.42 (d,1H, J 10Hz,3-H) and 3.39-1.93 (m,6H,3xCH_2); ν_{max} 3375, 2100, 1740, 1725 and 1650 cm^{-1}; m/z(%) 346 (M^+,2.5) and 177(100).

Dimethyl 2,2-spiro(3,3-hexahydro-2-oxo-azepinyl)-c-5-phenylpyrrolidine-c-3,t-4-dicarboxylate (15b). Prepared from 3-(N-benzylideneamino) caprolactam and dimethyl maleate or fumarate in an analogous manner to that described above. The product (67-72%) crystallised from methanol as colourless needles, m.p. 174-176°C (Found: C, 63.10; H, 6.75; N, 7.65. $C_{19}H_{24}N_2O_5$ requires C, 63.30; H, 6.70;N, 7.75%); δ 7.41-7.26 (m,5H,ArH), 5.66 (br s,1H,NH), 4.42 (d,1H,J 8.8Hz,5-H), 3.70 and 3.67 (2xs, 2x3H,OMe), 3.52 (t,1H,4-H), 3.36 (d,1H,J 9.2Hz,3-H), 3.0 and 2.3 (2xm, 2x1H,CH_2N), and 1.59-1.27 (m,4H,2xCH_2); ν_{max} 3340,3300,1725, 1710 and 1645; m/z(%) 360 (M^+,100), 301(9), and 144(9).

Cycloaddition of 3-benzylideneaminopiperidin-2-one (8b) to the isatin derivative (16a). A solution of 3-benzylideneaminopiperidin-2-one (2.02g, 10mmol) and methyl 3-isatylidene acetic acid (2.03g, 10mmol) in dry xylene (50ml) was boiled under reflux under an argon atmosphere for 1.5d. Removal of the solvent and trituration with ether afforded a colourless solid (3.4g, 84%) which proved to be a 1.16:1 mixture of pyrrolidines (17a) and (18). Fractional crystallisation from methanol afforded the pure stereoisomers.

(17a) Colourless needles from methanol, m.p. 274-276°C(decomp.)(Found: C, 67.85; H, 5.55; N, 10.20. $C_{23}H_{23}N_3O_4$ requires C, 68.15; H, 5.70; N, 10.35%); δ ($CDCl_3$ + 1 drop TFA-d) 7.5-6.91 (m,9H,ArH), 5.58 (s,1H,5-H), 4.93 (s,1H,3-H), 3.72 (s,3H,OMe), 3.6 (br t,2H,CH_2N), and 3.3-1.9 (m,4H,2xCH_2); ^{1}H NOEDSY(%): irradiation of the signal for 5-H caused enhancement of the signal for 3-H(12); irradiation of the signal for 3-H caused enhancement of the signal for 5-H (7.6). ν_{max} 1730,1680, and 1640 cm^{-1}; m/z(%) 405 (M$^+$,1) 203(68), 202(85), 99(100) and 98(26).

(18) Colourless rods from methanol, m.p. 252-254°C(decomp.) (Found: C, 68.25; H, 5.50; , 10.4%); δ ($CDCl_3$ + 1 drop TFA-d) 8.03-6.77 (m,9H,ArH), 5.40 (s,1H,5-H), 4.17 (s,1H,3-H), 3.24 (s,3H,OMe), 3.6 (br t,2H,CH_2N), and 2.75-1.8 (m,4H,2xCH_2); ^{1}H NOEDSY(%): irradiation of the signal for 5-H caused enhancement of 3-H(5); irradiation of 3-H caused enhancement of 5-H(5); ν_{max} 3335,1730,1710 and 1660 cm^{-1}; m/z(%) 405 (M$^+$,1), 203(57), 202(41), 99(100) and 98(29).

Cycloaddition of 3-(N-benzylideneamino)caprolactam (8c) to the isatin derivative (16a). Prepared from 3-(N-benzylideneamino)caprolactam and methyl 3-isatylidene acetic acid in a manner analogous to that described above, but with a reaction time of 2d. The product (17b)(79%) crystallised from methanol as colourless needles, m.p. 273-275°C(decomp) (Found: C, 86.75; H, 6.05; N, 10.00. $C_{24}H_{25}N_3O_4$ requires C, 86.70; H, 6.00; N, 10.00%); δ ($CDCl_3$ + 1 drop TFA-d) 8.92-6.83 (m,9H,ArH), 5.45 (s,1H,5-H), 4.92 (s,1H,3-H), 3.72 (s,3H,OMe), 3.5 (m,2H,CH_2N), 2.9 and 2.4 (2xm, 2x1H, CH_2), and 2.0-1.8 (m,4H, 2xCH_2); ν_{max} 1725,1680 and 1640 cm^{-1}; m/z(%) 419 (M$^+$,4) and 216(100).

General procedure for the cycloaddition of aryl imines of 2-aminomethylpyridine (20a-f) and 2-aminomethyl-4-methylthiazole (21) to NPM. A solution of the imine (10mmol) and NPM (10mmol) in dry toluene (80ml) was boiled under reflux for 2-10h. The solvent was then removed under reduced pressure and the residue purified by preparative t.l.c. (silica) eluting with 95:5 v/v chloroform-methanol. Reaction times, isomer ratios, and yields are given in Table 2.

4-(4'-N,N-Dimethylaminophenyl)-7-phenyl-2(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (23a) and (24a).

Endo isomer (23a). Colourless plates from chloroform-petroleum ether, m.p. 127-129°C [Found (mixed isomers): C, 72.90; H, 5.70; N, 12.95. $C_{25}H_{24}N_4O_2$ requires C, 72.80; H, 5.85; N, 13.60%]; δ 8.63-6.73 (m,13H,ArH), 4.79 (d,1H,J 7.7Hz, 2-H), 4.71 (d,1H, J 8.1Hz, 4-H), 3.80 (t,1H,1-H), 3.60 (t,1H,5-H), 2.56 (s,6H,NMe) and 1.38 (br s,1H,NH); m/z(%) 412 (M$^+$,7), 240(23), 239(100), 238(11), 223(34), 134(34) and 120(9).

Exo isomer (24a). Cream prisms from ether-petroleum ether, m.p. 96-99°C. δ ($CDCl_3$ + 1 drop D_2O) 7.7-6.75 (m,13H,ArH), 4.56 (d,1H, J 6.6Hz, 2-H), 4.48 (d,1H,4-H), 3.7 (dd,1H,1-H), 3.6 (dd,1H,5-H), and 2.96 (s,6H,NMe); m/z(%) 412 (M$^+$,32), 239(100), 238(23), 223(35) and 139(53).

4-(4'-Methoxyphenyl)-7-phenyl-2-(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo [3.3.0]octane(23b) and (24b).

Endo isomer (23b). Colourless needles from methanol, m.p. 200-202°C [Found (mixed isomers): C, 72.30; H, 5.25; N, 10.45. $C_{24}H_{21}N_3O_3$ requires C, 72.15; H, 5.30; N, 10.50%]; δ 8.65-6.92 (m,13H,ArH), 4.81 (d,1H, J 8/8Hz,2-H) 4.75 (d,1H, J 8.1Hz,4-H), 3.82 (s,3H,OMe), 3.81 (t,1H,1-H), 3.64 (t,1H,5-H) and 2.4 (br s, 1H,NH); ν_{max} 3300,1700,1605, 1500 and 1380 cm^{-1}; m/z(%) 399 (M^+,0.5), 264(9), 227(16), 226(100), 225(11) and 211(9).

Exo isomer (24b). Colourless prisms from ether-petroleum ether, m.p. 58-60°C. δ 8.63-6.92 (m,13H,ArH), 4.57 (d,1H, J 7Hz,2-H), 4.52 (d,1H, J 7.7Hz,4-H), 3.82 (s,3H,OMe), 3.82 (dd,1H, J 7Hz and 9.9Hz,1-H), 3.64 (dd,1H, J 7.7 and 9.9Hz,5-H), and 1.69 (br s, 1H,NH); ν_{max} 3300,1710, 1510 and 1370 cm^{-1} m/z(%) 399 (M^+,6), 264(100), 226(100), 93(24) and 41(60).

4,7-Diphenyl-2-(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (23c) and (24c).

Endo isomer (23c). Colourless needles from methanol, m.p. 195-196°C. [Found (mixed isomers): C, 74.00; H, 5.35; N, 11.25. $C_{23}H_{19}N_3O_2$ requires C, 74.20; H, 5.20; N, 11.4%]; δ 8.64-7.08 (m,14H,ArH), 4.87 (d,1H, J 7.7Hz,2-H), 4.80 (d,1H, J 8.1Hz,4-H), 3.87 (t,1H,1-H), 3.69 (t,1H,5-H) and 2.05 (br s,1H,NH); ν_{max} 3220,1700,1590,1500 and 1380 cm^{-1}; m/z(%) 369 (M^+,1), 196(100), 180(42), 119(21), 93(22), 59(18) and 31(30).

Exo isomer (24c). Colourless rods from methanol, m.p. 155-156°C. δ 8.62-7.24 (m,14H,ArH), 4.60 (d,2H,2-H and 4-H), 3.84 (dd,1H, J 7Hz and 9.9Hz,1-H), 3.69 (dd,1H, J 7.3Hz and 9.9Hz,5-H), and 1.80 (br s,1H,NH); ν_{max} 3300,1705,1590 and 1380 cm^{-1}; m/z(%) 369 (M^+,3), 196(100), 180(30) and 119(20).

4-(4'-Trifluoromethyl)-7-phenyl-2-(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo[3 .3.0]octane (23d) and (24d).

Endo isomer (23d). Colourless needles from chloroform-petroleum ether, m.p. 210-211°C [Found (mixed isomers): C, 65.60; H, 3.90; N, 9.40. $C_{24}H_{18}F_3N_3O_2$ requires C, 65.90; H, 4.10; N, 9.6%]; δ 8.65-7.06 (m,13H,ArH), 4.85 (m,2H,2-H and 4-H), 3.81 (t,1H,1-H), 3.74 (t,1H,5-H) and 1.66 (br s,1H,NH); m/z(%) 437 (M^+,1), 265(17), 264(100), 248(34), 119(29), 85(22) and 83(34).

Exo isomer (24d). Colourless plates from ether-petroleum ether, m.p. 65-68°C. δ 8.60-7.26 (m,13H,ArH), 4.63 (m,2H,2-H and 4-H), 3.86 (dd,1H, J 7 and 9.6Hz, 1-H), 3.66 (dd,1H, J 7.3 and 9.6Hz, 5-H), and 1.63 (br s, 1H,NH); m/z(%) 437 (M^+,10), 436(6), 264(100), 188(37), 119(37) and 93(49).

4-(4'-Cyanophenyl)-7-phenyl-2-(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo [3.3.0]octane(23e) and (24e).

Endo isomer (23e). Colourless plates from chloroform-petroleum ether, m.p. 215-217°C [Found (mixed isomers): C, 73.05; H, 4.60; N, 14.25. $C_{24}H_{18}N_4O_2$ requires C, 73.10; H, 4.60; N, 14.20%]; δ 8.65-7.05 (m,13H,ArH), 4.84 (m,2H,2-H and 4-H), 3.85 (t,1H,1-H), 3.74 (t,1H,5-H) and 2.8 (br s, 1H,NH); ν_{max} 3320,2220,1700,1590 and 1370 cm^{-1}; m/z(%) 394 (M^+,1), 222(16), 221(100), 205(44), 119(35), 93(12) and 92(23).

Exo isomer (24e). Colourless prisms from ether-petroleum ether, m.p. 87-89°C. δ 8.62-7.26 (m,13H,ArH), 4.64 (m,2H,2-H and 4-H), 3.83 (dd,1H, J 7 and 9.6Hz,1-H), 3.63 (dd,1H, J 7.3 and 9.6Hz,5-H), and 1.61 (br s, 1H,NH); ν_{max} 3300,2220,1710,1600 and 1380 cm^{-1}; m/z(%) 394 (M^+,5), 222(16), 221(100), 205(22) and 119(20).

4-(4'-Nitrophenyl)-7-phenyl-2-(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo [3.3.0]octane (23f) and (24f).

Endo isomer (23f). Pale yellow prisms from methanol, m.p. 222-225°C [Found (mixed isomers): C, 66.80; H, 4.45; N, 13.45. $C_{23}H_{18}N_4O_4$

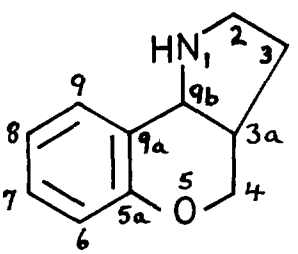
requires C, 66.60; H, 4.40; N, 13.50%); δ 8.66-7.7 (m,13H,ArH), 4.89 (d,2H,2-H and 5-H), 3.87 (t,1H,1-H), 3.77 (t,1H,5-H) and 2.85 (br s, 1H,NH); ν_{max} 3320, 1700, 1580,1510 and 1370 cm^{-1}; m/z(%) 414 (M^+,1), 242(15), 241(100), 225(25), 197(19), 119(31) and 83(14).

Exo isomer (24f). Pale yellow plates from ether-petroleum ether, m.p. 67-70°C. δ 8.62-7.28 (m,13H,ArH), 4.67 (m,2H,2-H and 4-H), 3.90 (dd,1H, J 6.9 and 9.9Hz,1-H), 3.65 (dd,1H, J 7.4 and 9.9Hz,5-H) and 2.17 (br s, 1H,NH); ν_{max} 3320,1710,1590 and 1370 cm^{-1}; m/z(%) 414 (M^+,5), 214(100), 225(25), 119(38), 93(36) and 78(19).

7-Phenyl-4-[2'-(4'-methylthiazolyl)]-2-(2'-pyridyl)-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (23g) and (24g).

Endo isomer (23g). Colourless plates from methanol, m.p. 215-217°C [Found (mixed isomers): C, 67.50; H, 4.80; N, 10.60. $C_{21}H_{18}N_4O_2$ requires C, 67.85; H, 4.90; N, 10.80%]; δ 7.54-7.09 (m,10H,ArH), 6.88 (s,1H,thiazole-H), 5.08 (d,1H, J 8Hz,2-H), 4.79 (d,1H, J 8.2Hz,4-H), 3.82 (t,1H,1-H), 3.64 (t,1H,5-H), 2.49 (s,3H,Me) and 1.74 (br s,1H,NH); ν_{max} 3320,1700,1590,1500 and 1380 cm^{-1}; m/z(%) 389 (M^+,6), 216(100), 200(15), 183(17), 117(18) and 100(13).

Exo isomer (24g). Colourless prisms from chloroform-petroleum ether, m.p. 195-196°C. 7.64-7.32 (m,10H,ArH), 6.89 (s,1H,thiazole-H), 4.91 (d,1H, J 6.2Hz,2-H), 4.60 (d,1H, J 7.2Hz,4-H), 3.84 (dd,1H, J 6.2 and 9.4Hz,1-H), 3.59 (dd,1H, J.7.2 and 9.4Hz,5-H), 2.46 (s,3H,Me) and 1.67 (br s, 1H,NH); ν_{max} 3300,1710,1500 and 1390 cm^{-1}; m/z(%) 389 (M^+,2), 217(15), 216(100), 173(14), and 59(14).



2,3,3a,9b-tetrahydro-4H-chromeno[4,3-b]pyrrole

2β,3β,3aα,9bβ-and 2β,3α,3aβ,9bβ-Tetrahydro-3-carbomethoxy-2-(2'-pyridyl)-4H-chromeno[4,3-b]pyrrole (30) and (31). a. A solution of 2-[3-carbomethoxy-2-propenyl)oxy]-benzylidene-2-aminomethylpyridine (1.4g) in xylene (80ml) was boiled under reflux for 2h. The solvent was removed under reduced pressure to leave a thick oil which comprised a 1.2:1 mixture of (30) and (31) which was separated by preparative t.l.c.

(30) Colourless plates (490mg,33%) from methanol, m.p. 115-116°C (Found: C, 69.65; H, 5.85; N, 9.05. $C_{18}H_{18}N_2O_3$ requires C, 69.55; H, 5.80; N, 8.95%); δ 8.5-6.85 (m,9H,ArH), 5.02 (d,1H, J 10.2Hz,2β-H), 4.60 (dd,1H, J 4.3 and 10Hz, 4β-H), 4.18 (dd,1H, J 10 and 11.7Hz, 4α-H), 3.93 (d,1H, J 11.2Hz, 9bβ-H), 3.18 (dd,1H, J 10.3 and 11.8Hz, 3β-H), 3.23 (s,3H,OMe) and 2.70 (m,1H, 3aα-H); ^{1}H NOEDSY(%): irradiation of 2β-H resulted in enhancement of 3β-H(13) and 9bβ-H(3.5); irradiation of 9bβ-H caused enhancement of 2β-H(4); irradiation of 3aα-H resulted in enhancement of 3-H(5) and 9bβ-H(3); m/z(%) 310 (M^+,100), 309(60), 211(88), 131(48), 92(65) and 91(43).

(31). Obtained as a thick pale yellow oil (27%). δ 8.49-6.91 (m,9H,ArH), 4.59 (d,1H J 7.7Hz,2β-H), 4.34 (d,1H, J 6.6Hz,9bβ-H), 4.23 (dd,1H, J 5.1 and 11Hz, 4β-H), 3.85 (t,1H, J 11.1Hz,4α-H), 3.73 (s,3H,OMe), 2.89 (m,1H,3aβ-H), and 2.74 (dd,1H, J 4.3 and 7.7Hz, 3α-H).

b. A mixture of 2-[(3-carbomethoxy-2-propenyl)oxy]-benzylidene-2-amino methylpyridine (750mg), silver acetate (600mg) and triethylamine (260mg) in DMSO (5ml) was stirred at room temperature for 10 min. The reaction

mixture was then poured into saturated aqueous ammonium chloride solution and extracted with ether. Evaporation of the dried ether extract and crystallisation of the residue from methanol afforded the product (30) (520mg, 70%), m.p. 115-116°C, identical to that described above.

General procedure for the cycloaddition of aryl imines of 9-aminofluorene (36a-e) and NPM. A solution of the imine (0.2mmol) and NPM (0.22mmol) in toluene-d_8 (0.5ml) was heated at 110°C in a sealed n.m.r. tube, preflushed with argon, for the time noted in Table 4. The adduct usually crystallised on cooling the hot reaction mixture. Yields are given in Table 4.

2,2-Spiro(9',9'-fluorenyl)-4-(4'-dimethylaminophenyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (38a). Yellow prisms from toluene, m.p. 241-243°C (Found: C, 77.15; H, 5.60; N, 8.45. $C_{32}H_{27}N_3O_2$ requires C, 79.15; H, 5.60; N, 8.65%); δ7.76-6.72 (m,17H,ArH), 5.48 (d,1H, J 8.6Hz,4-H), 3.99 (t,1H,5-H), 3.60 (d,1H, J 8.1Hz,1-H), 2.95 (s,6H,NMe) and 2.18 (br s,1H,NH); ν_{max} 3340,1775,1715,1710 and 1610 cm^{-1}; m/z(%) 485 (M^+,2), 312(32), 311(19), 165(6), 92(67), 91(100) and 65(10).

2,2-Spiro(9',9'-fluorenyl)-4-(4'-methoxyphenyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3..o]octane (38b). Colourless prisms from toluene, m.p. 290°C (Found: C, 78.40; H, 5.25; N, 5.70. $C_{31}H_{24}N_2O_3$ requires C, 78.80; H, 5.10; N, 5.95%); δ7.76-6.90 (m,17H,ArH), 5.51 (d,1H, J 8.6Hz,4-H), 4.02 (t,1H,5-H), 3.81 (s,3H,OMe), and 3.63 (d,1H, J 8.1Hz, 1-H); ν_{max} 3460,1780,1720 and 1655 cm^{-1}; m/z(%) 472 (M^+,38), 471(21), 455(14), 307(20), 299(14), 205(18), 176(38), 165(10) and 134(8).

4,7-Diphenyl-2,2-(Spiro-9',9'-fluorenyl)-6,8-dioxo-3,7-diazabicyclo[3.3.0] octane (38c). Colourless prisms from toluene, m.p. 280°C (Found: C, 81.20; H, 5.05; N, 6.20. $C_{30}H_{22}N_2O_2$ requires C, 81.45; H, 5.00; N, 6.35%); δ7.78-6.98 (m,18H,ArH), 5.43 (d,1H, J 5.9Hz,4-H), 4.10 (d,1H, J 10.3Hz,1-H), 3.81 (dd,1H,5-H), and 2.30 (br s, 1H,NH); ν_{max} 3460,1770,1710,1680 and 1600 cm^{-1}; m/z(%) 442 (M^+,10), 269(100), 165(18), 100(21), 98(22) and 77(5).

2,2-Spiro(9',9'-fluorenyl)-4-(4'-trifluoromethylphenyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (38e). Colourless prisms from methanol-ether, m.p. 212-214°C (Found: C, 73.05; H, 4.05; N, 5.50. $C_{31}H_{21}F_3N_2O_2$ requires C, 72.95; H, 4.10; N, 5.50%); δ7.94-6.99 (m,17H,ArH), 5.49 (br t,1H,4-H), 4.12 (d,1H, J 10.1Hz,1-H), 3.77 (dd,1H, J 6.2 and 10.1Hz,5-H) and 2.41 (br s,1H,NH); ν_{max} 3320,1770,1710 and 1610 cm^{-1}; m/z(%) 510 (M^+,12), 337(100) and 165(15).

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