X=Y–ZH Systems as Potential 1,3-Dipoles. Part 1. Background and Scope

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X=Y–ZH Systems are considered in general terms and divided into four classes according to the number of constituent atoms that possess lone-pair electrons. Those systems in which the central Y atom possesses a lone pair are shown to be capable of participating in formal 1,2-H shifts generating 1,3-dipolar species. The scope of the reaction, including its possible relevance to the biochemistry of pyridoxal enzymes is discussed and the influence of structure on reactivity is demonstrated with rate data for the cycloaddition of a series of aryl imines of phenylglycine and alanine methyl esters to *N*-phenylmaleimide.

Proton transfer processes are important in synthetic and mechanistic chemistry, and in biological systems, and have consequently been the object of many detailed studies.[1] Formal intramolecular proton transfers can be divided into two broad classes. Firstly unassisted or concerted hydrogen migrations where the migrating hydrogen moves over a π-electron framework under thermal or photochemical activation. The electronic requirements for this type of migration, sigmatropic reactions,[2] were delineated by Woodward and Hoffmann in their classic series of papers on orbital symmetry controlled reactions and have been confirmed by many subsequent studies.[3] The second type of formal intramolecular proton transfer requires the presence of an acid, base, transition metal, or transition-metal complex. This latter class encompasses the important four atom X=Y–ZH systems, which are the subject of this series of papers.

X=Y–ZH Systems can be divided into four classes (Scheme 1) depending on the number of constituent atoms that possess lone pairs of electrons (note that more than one lone pair may be located on each atom).

Formal 1,3-H shifts from Z to X (1 ⇌ 2) in X=Y–ZH systems have been the focus of numerous kinetic studies dating from Lapworths remarkable paper on the bromination of acetone, a type II System, in acid solution.[4] Concerted 1,3-hydrogen transfers are predicted to occur in a suprafacial manner under photochemical activation with ψ_3 the dominant molecular orbital (Figure) whilst a thermal 1,3-H shift

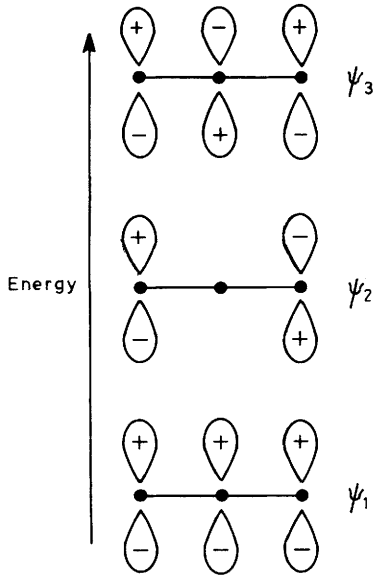


Figure. Molecular orbitals of the allyl system (X, Y, and Z = C)

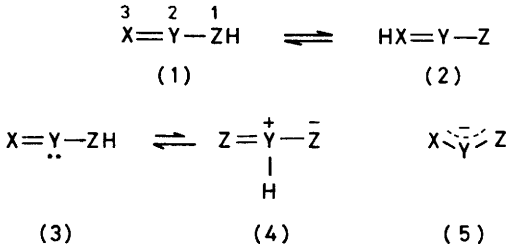
Type				Examples
I	X=Y–ZH			Alkenes
II	$\ddot{X}$=Y–ZH	X=$\ddot{Y}$–ZH	Z=Y–$\ddot{Z}$H	Imines, aldehydes, ketones, nitroalkanes
III	$\ddot{X}$=$\ddot{Y}$–ZH	X=$\ddot{Y}$–$\ddot{Z}$H	$\ddot{X}$=Y–$\ddot{Z}$H	Azo compounds, hydrazones, oximes, amidines
IV	$\ddot{X}$=$\ddot{Y}$–$\ddot{Z}$H			Triazenes

Scheme 1.

would involve ψ_2 and require an antarafacial migration.[2] The geometrical constraints imposed by the three-atom framework and the availability of only an s orbital on the migrating H-atom conspire to make the thermal antarafacial process unrealisable. Thus 1,3-hydrogen shifts in X=Y–ZH systems are normally achieved by the intervention of a suitable catalyst and include the synthetically important keto-enol, imine-enamine, nitroalkyl-*aci*-nitro and oxime-nitroso systems, and alkene isomerisations. Despite the necessity for a catalyst, labelling studies show that these tautomeric equilibria often involve a substantial intramolecular component. Thus in base catalysed alkene isomerisations, a type I system, greater than 90% intramolecularity has been observed [5] whilst in imines a type II system up to *ca.* 50% intramolecularity has been reported.[6] The stereoselectivity and intramolecularity of the latter type of isomerisations have attracted attention [7] because of their relationship to the biochemical transformations of α-amino acids catalysed by pyridoxal enzymes. The enzymic isomerisations involve a suprafacial 1,3-proton transfer process in imines.[8] The precise mode of association between the protonated base and the allyl or aza-allyl-anion leading to intramolecular 1,3-proton transfer is still unclear. The X=Y–ZH system may act as its own catalyst for a formal 1,3-H shift. Thus triazene isomerisations ($R^1N{=}N{-}NHR^2$ $R^1NH{-}N{=}NR^3$) are usually bimolecular although a radical mechanism may be dominant in some cases.[8]

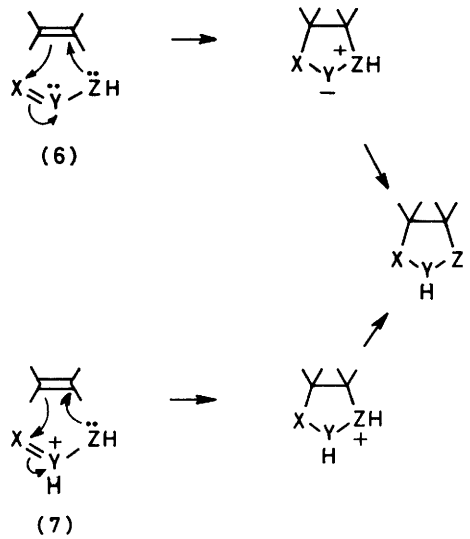
When the central Y atom in an X=Y–ZH system possesses a lone pair of electrons (Types II–IV) a formal 1,2-H shift (3 ⇌ 4) becomes possible. A concerted 1,2-H shift involving the electrons of the XY double bond and a 1,3-charge separation involves unfavourable orbital interactions and prohibitively high energies,[10] *e.g.* reference to the Figure shows a node at Y in the dominant orbital (ψ_2) in such processes, although when Y ≠ C there is a small coefficient at Y.[11] The lone pair on Y is orthogonal to the XY π-system and proton transfer from Z to this orthogonal lone pair on Y would produce a 1,3-dipole. These considerations led us to suggest that such formal 1,2-proton shifts (3 ⇌ 4) should occur and would be a general method for generating certain 1,3-dipolar

species.[12] These protons shifts are expected to be intermolecular unless the substrate also contains an internal acidic or basic group correctly positioned to achieve the transfer.[13]



(1) (2) (3) (4) (5)

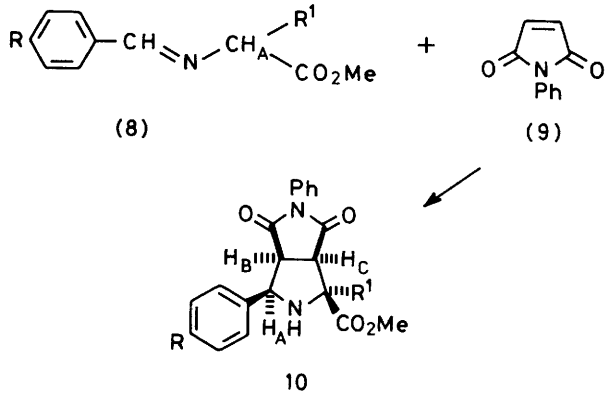
1,3-Dipolar cycloaddition reactions provide the most versatile synthesis of 5-membered heterocycles.[14] The catholic nature of the reaction is due to Huisgen's recognition [15] of the generality of the 1,3-dipolar concept. A substantial body of results attests to the stereospecificity of 1,3-dipolar cycloaddition reactions [16] and species such as (4) would be expected to conform with these results. X=Y–ZH Systems (3) give rise to 4π-anions (5) in the presence of appropriate bases, and Kauffmann [17] has made extensive studies of the chemistry of the aza-allyl anions (3; X=Z=C, Y=N). Aza-allyl anions generated with lithium counterions undergo cycloadditions to olefins, but the choice of 2π-component is restricted by the nucleophilicity of the anion (5). Thus 4π + 2π cycloadditions involving (3) would be expected to be both acid [*via* (4)] and base [*via* (5)] catalysed. Further possibilities arise with Type III systems [(6) *e.g.* hydrazones, oximes] which could undergo cycloaddition in the neutral (6) or monoprotonated (7) state (Scheme 2).



(6) (7)

Scheme 2.

We have observed cycloadditions of hydrazones under neutral conditions [11] which we interpret as involving the 1,3-dipole (4; X=C, Y=Z=N) whilst others have studied Bronsted and Lewis acid catalysed cycloadditions of hydrazones and interpreted these reactions in terms of (7; X=C, Y=Z=N).[18] Oximes are a more complicated case and are dealt with both in the following paper and a future one.[19] Imines are Type II systems and do not suffer from the uncertainties presented by Scheme 2. Formation of 1,3-dipoles by thermal tautomeric equilibration, (3) ⇌ (4), would be expected to be sensitive to the basicity of Y and the pK_a of the ZH proton. Such a dependance, albeit a modest one, is observed when the imines (8) are heated (105 °C) with *N*-phenylmaleimide (9) in toluene (Table). Cycloadducts (10) are obtained in good yield as single isomers.



(8) (9) 10

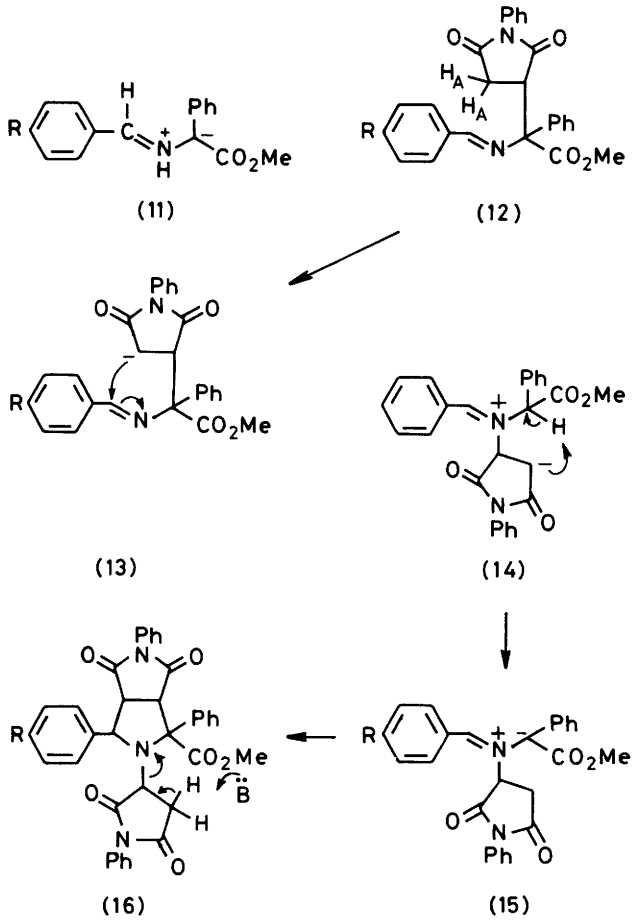
Table. First-order rate constants (k_1) for the cycloaddition of (8) and (9) ([$^2H_8$]toluene, 105 °C) *

R	R^1	k_1/s^{-1}	Yield of (10) (%)
NMe_2	Ph	53.80	78
OMe	Ph	16.70	84
H	Ph	9.60	86
CF_3	Ph	1.80	87
CN	Ph	1.98	90
NO_2	Ph	1.73	73
NMe_2	Me	21.4	80
OMe	Me	9.04	92
H	Me	5.57	89
CF_3	Me	2.07	72

* Kinetic runs were performed on 0.2M-solutions of imine and *N*-phenylmaleimide in the probe of a Bruker WH 90 n.m.r. spectrometer: spectral width 1 000 Hz, 4 K data points, temperature accurate to ±0.5 °C

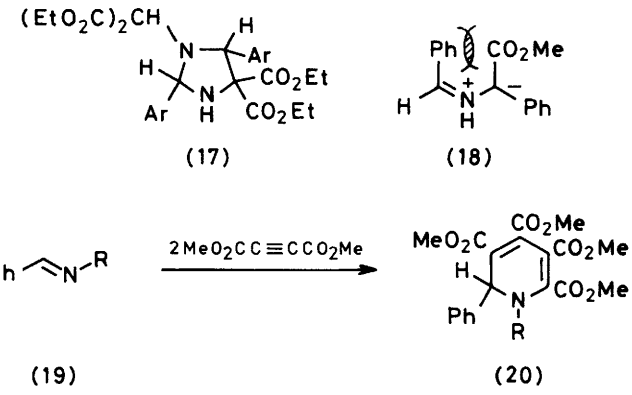
The isolation of stereospecifically formed pyrrolidines (10) is in itself a strong indication that a concerted cycloaddition is involved. Apart from the intervention of the 1,3-dipole (11) other alternative pathways that could lead to (10) include (i) a Michael addition (8) + (9) ⟶ (12), followed by a 5-*endo-trig* cyclisation (12) ⟶ (13) ⟶ (10); (ii) an ene reaction (8) + (9) ⟶ (12), followed by a 5-*endo-trig* cyclisation (12) ⟶ (13) ⟶ (10); (iii) Michael addition *via* the nitrogen atom (8) + (9) ⟶ (14) and proton transfer to generate a conventional 1,3-dipole (15), followed by cycloaddition to a further mole of *N*-phenylmaleimide (9) to give the 2 : 1 adduct (16). Elimination of *N*-phenylmaleimide (16; arrows) would then be necessary to generate the observed product (10).

Michael addition reactions involving the central Y atom in (3) or the Z atom in Types III and IV X=Y–ZH systems are always likely to compete with dipole generation (3) ⇌ (4). Indeed oximes react preferentially *via* the central nitrogen atom to give 2 : 1 adducts [path (iii)] [19] although suitable structural modification allows 1,3-dipolar cycloaddition *via* (4) to occur.[19] Similarly, we have observed both Michael addition and 1,3-dipolar cycloaddition with hydrazones.[12,20] However, the Michael addition [pathway (i)] or ene reaction

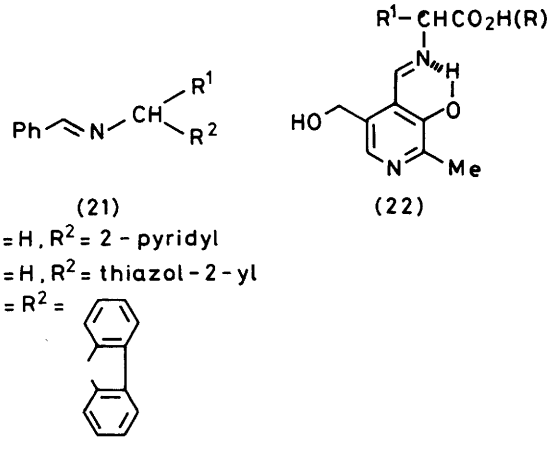


[pathway (ii)] are not thought to give rise to (10) for the following reasons. Firstly no uncyclised product (12) can be detected, secondly the pK_a of protons H_A in (12) are too high (*ca.* 24) to be abstracted by the imine (pK_a *ca.* 5—7) [21] which is the only base present, and thirdly cyclisations of the type (12) ⟶ (13) are disfavoured *5-endo-trig* processes. Ene reactions of benzylidenebenzylamine with diethyl azodicarboxylate have been reported [22] but our own work with imines of this type leads us to question this report.[23] Ene reactions in which the imine group acts as the enophile are also known [24] although the imine requires activation by an electron-withdrawing group. Two-step Michael addition-cyclisation processes equivalent to (8) + (9) ⟶ (12) ⟶ (10) have been studied by us and shown to occur in the presence of strong base and to give rise to mixtures of stereoisomeric products.[25] Thus the *5-endo-trig* cyclisation step is not, in itself, an insuperable barrier.

The rate data in the Table illustrate the effect of the fall in basicity of the imine nitrogen from (8; R = NMe_2), the most basic imine, to (8; R = NO_2) the least basic imine.[21] Similarly the rate difference between pairs of imines (8; R^1 = Ph) and (8; R^1 = Me) illustrates the effect of R^1 on the pK_a of the CH_A proton. Moreover imines (8; R^1 = CO_2Me) are difficult to isolate since they readily dimerise to (17) at room temperature.[26] The stereochemistry of the cycloadducts (10) is based on a single crystal *X*-ray structure [27] and on n.m.r. correlations and provides evidence on the configuration of the dipole. Thus (10) must arise from a dipole with configuration (11) and the cycloaddition involves an *endo* transition state. The alternative dipole configuration (18) which could also give rise to (10) is rejected on steric grounds. The configuration of the thermally generated dipole will be discussed more fully in a future paper.[28] The problem of dipole configuration does not arise with oximes and hydrazones. As expected, the cycloadditions (8) + (9) ⟶ (10) show substantial rate enhancements * in the presence of Lewis and Bronsted acids [29] and the free α-amino acid imines undergo the cycloaddition reactions in good yield.[30]



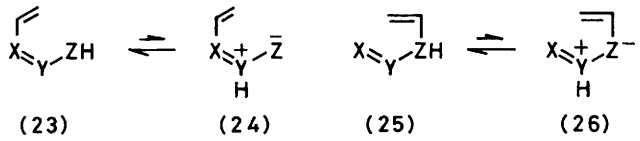
In the cycloaddition of (8) with (9) or (8) with dimethyl acetylenedicarboxylate [23] no six-membered ring products of the type reported by Huisgen [31] [*e.g.* (19) ⟶ (20)], Acheson [32] and others [33] were observed. Furthermore no isomerisation of the imine (8) could be detected when the reactions were monitored by n.m.r. spectroscopy. The effect of substitution at both ends of the imine system ($RR^1C{=}NCHR^2R^3$) has been studied in detail and will be reported in later papers in this series. It is not necessary to have an ester group present to activate the ZH proton. Thus (21a—c) undergo similar cycloadditions.[34] An important biochemical example of the generation of a 1,3-dipole from an X=Y–ZH system is provided by pyridoxal enzymes. These enzymes play a central role in connecting carbon and nitrogen metabolism including the formation of biogenic amines. Indeed, pyridoxal phosphate is one of the most versatile of biochemical catalysts.[35] Despite extensive mechanistic work, and speculation, over many years no one had considered pyridoxal imines (22) as potential 1,3-dipoles until our work.[36] We were able to show that they behave as typical 1,3-dipoles and undergo cycloaddition to *N*-phenylmaleimide [36] and other dipolarophiles.[37] 1,3-Dipole formation from imines of α-amino acid ester has also led to a new synthesis of dehydroamino acid esters.[38]



a; R^1 = H, R^2 = 2-pyridyl
b; R^1 = H, R^2 = thiazol-2-yl
c; R^1 = R^2 =

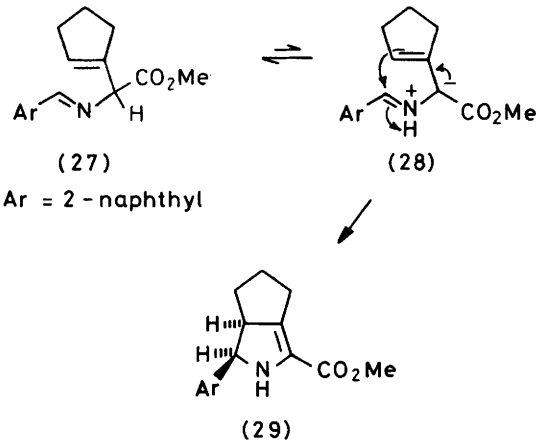
* Dipole formation is rate determining when reactive dipolarophiles such as *N*-phenylmaleimide are used. Results of a detailed kinetic study are in preparation for publication.

When the concept of a 1,2-shift in X=Y–ZH systems is considered in more general terms it becomes clear that such processes have considerable scope. For example the vinylic analogues (23) and (25) are potential precursors of 1,5-dipolar species (24) and (26).

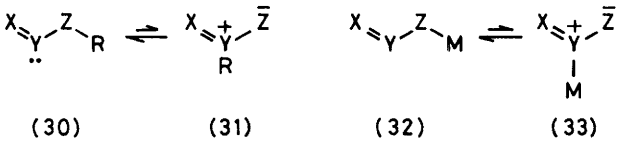


(23) (24) (25) (26)

We have recently reported an example analogous to (25) ⇌ (26) [39]. Thus the naphthyl imine (27) undergoes a 1,5-electrocyclisation *via* (28) to the dihydropyrrole (29).



(27) Ar = 2-naphthyl (28) (29)



(30) (31) (32) (33)

The concept of a formal 1,2-shift is not limited to proton transfers. Transfers of other groups (30) ⇌ (21) or metal ions (32) ⇌ (33) should be possible provided a low-energy inter- or intra-molecular pathway exists. Thus, in summary, the new general concept of formal 1,2-shifts in Types II–IV X=Y–ZH systems is of broad synthetic and mechanistic importance and many more applications can be confidentially expected.

Experimental

N.m.r. spectra were recorded on Jeol PMX60, Bruker WH90 or Bruker WP250 instruments and refer to deuteriochloroform solutions, with tetramethylsilane as internal standard, unless otherwise stated. I.r. spectra were measured for KBr discs on Perkin-Elmer 157G or 598 instruments. Mass spectra were determined on an MS902 operating at 70 eV. M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer PE240 automatic analyser. *N*-Phenylmaleimide was recrystallised three times from cyclohexane before use in the kinetic experiments. The imines (8) were also recrystallised three times from the appropriate solvent. Note that *N*-phenylmaleimide as supplied (Aldrich) apparently contains traces of acid (*N*-phenylmaleamic acid?) and gives anomalously high rates of cycloaddition. Light petroleum refers to the fraction b.p. 40—60 °C.

Preparation of Imines (8).—*Method A*. The amino-acid ester hydrochloride (*ca.* 0.074 mol) and sodium carbonate (0.074 mol) were dissolved in water (200—250 ml) and the appropriate *p*-substituted benzaldehyde (0.074 mol) was added. The mixture was stirred at 40 °C for 45 min and then at room temperature for a further 16 h. The mixture was then extracted with chloroform (3 × 100 ml) and the combined chloroform layers washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude imine.

Method B. Sodium metal (0.107 g-atom) was dissolved in dry methanol (150 ml) and the amino acid hydrochloride (0.107 mol) added. The resulting mixture was stirred at room temperature until the amino acid hydrochloride dissolved. The appropriate *p*-substituted benzaldehyde (0.107 mol) was then added and the mixture stirred at room temperature for *ca.* 12 h. The solvent was then evaporated under reduced pressure and the residue dissolved in chloroform; the solution was then washed with water, dried ($MgSO_4$), and the chloroform evaporated under reduced pressure to give the crude imine (8).

Methyl N-p-*dimethylaminobenzylidenephenylglycinate*. Prepared (72%) by method A, the imine crystallised from methanol as pale yellow needles, m.p. 91—92 °C (Found: C, 72.95; H, 6.8; N, 9.45. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45%); *m/z* (%) 296 (M^+, 24), 238 (19), 237 (100), 193 (11), 91 (3), and 77(2); $\nu_{max.}$ 3 100, 2 980, 1 733, 1 627, and 1 600 cm^{-1}; δ 8.20 (s, 1 H, CH=N), 7.73—6.65 (m, 9 H, ArH), 5.15 (s, 1 H, CH), 3.73 (s, 3 H, CO_2Me), and 3.00 (s, 6 H, NMe_2).

Methyl N-p-*methoxybenzylidenephenylglycinate*. Prepared (85%) by method A, the imine crystallised from light petroleum as colourless plates, m.p. 108 °C (lit.,[40] m.p. 107—108 °C); $\nu_{max.}$ 3 020, 2 920, 1 720, 1 630, and 1 600 cm^{-1}; δ 8.27 (s, 1 H, CH=N), 7.79—6.90 (m, 9 H, ArH), 5.17 (s, 1 H, CH), 3.84 (s, 3 H, OMe), and 3.74 (s, 3H, CO_2Me).

Methyl N-*benzylidenephenylglycinate*. The imine, prepared (85%) by method A, crystallised from light petroleum as colourless prisms, m.p. 64 °C (lit.,[40] m.p. 62—64 °C).

Methyl N-p-*trifluoromethylbenzylidenephenylglycinate*. Prepared (72%) by method B, the imine crystallised from methanol as colourless needles, m.p. 81 °C (Found: C, 63.45; H, 4.4; N, 4.3. $C_{17}H_{14}F_3NO_2$ requires C, 63.55; H, 4.35; N, 4.35%); *m/z* (%) 321 (M^+, 0.14), 264 (17), and 262 (100); $\nu_{max.}$ 3 020, 2 945, 1 730, and 1 635 cm^{-1}; δ 8.38 (s, 1 H, CH=N), 7.95—7.25 (m, 9 H, ArH), 5.25 (s, 1 H, CH), and 3.75 (s, 3 H, CO_2Me).

Methyl N-p-*cyanobenzylidenephenylglycinate*. The imine, prepared (85%) by method B, crystallised from ethanol as colourless rods, m.p. 122 °C (Found: C, 73.6; H, 5.25; N, 10.0. $C_{17}H_{14}N_2O_2$ requires C, 73.35; H, 5.05; N, 10.05%); *m/z* (%) 278 (M^+, 1), 219 (100), 116 (10), and 89 (6); $\nu_{max.}$ 3 040, 3 020, 2 940, 2 220, 1 720, and 1 640 cm^{-1}; δ 8.37 (s, 1 H, CH=N), 7.95—7.26 (m, 9 H, ArH), 5.25 (s, 1 H, CH), and 3.75 (s, 3 H, CO_2Me).

Methyl N-p-*nitrobenzylidenephenylglycinate*. Prepared (90%) by method A, the imine crystallised as yellow prisms from chloroform–light petroleum, m.p. 139—140 °C (lit.,[40] m.p. 137—139 °C).

Methyl N-p-*dimethylaminobenzylidenealaninate*. The imine, prepared (69%) by method B, crystallised from pentane as yellow plates, m.p. 37—38 °C (Found: C, 66.6; H, 7.9, N, 11.95. $C_{13}H_{18}N_2O_2$ requires C, 66.65; H, 7.75; N, 11.95%);

m/z (%) 234 (M^+, 23), 176 (23), 175 (100), 174 (16), 160 (20), and 148 (26); $\nu_{max.}$ (film) 2 980, 2 840, 1 735, 1 630, and 1 600 cm^{-1}; δ 8.16 (s, 1 H, CH=N), 7.70—6.63 (m, 4 H, ArH), 4.13 (q, 1 H, CHMe), 3.73 (s, 3 H, CO_2Me), 3.02 (s, 6 H, NMe_2), and 1.51 (d, 3 H, CH*Me*).

Methyl N-p-*methoxybenzylidenealaninate*. Prepared (76%) by method B (reaction time 48 h), the imine was a colourless oil, b.p. 99—105 °C/0.05 mmHg (Found: C, 64.95; H, 6.95; N, 6.15. $C_{12}H_{15}NO_3$ requires C, 65.15; H, 6.85; N, 6.35%); *m/z* (%) 221 (M^+, 57), 163 (18), 162 (100), and 136 (12); $\nu_{max.}$ 2 940, 1 735, 1 635, and 1 600 cm^{-1}; δ 8.21 (s, 1 H, CH=N), 7.45—6.85 (m, 4 H, ArH), 4.10 (q, 1 H, CH), 3.81 (s, 3 H, CO_2Me), 3.71 (s, 3 H, OMe), and 1.51 (d, 3 H, CH*Me*).

Methyl N-*benzylidenealaninate*. Prepared (71%) by method B, this was a colourless oil, b.p. 109—118 °C/0.02 mmHg (lit.,[41] 105—107 °C/2 mmHg).

Methyl N-p-*trifluoromethylbenzylidenealaninate*. Method B gave the imine as a colourless oil (73%), b.p. 90—93 °C/0.05 mmHg (Found: C, 55.6; H, 4.7; N, 5.3. $C_{12}H_{13}F_3NO_2$ requires C, 55.60; H, 4.65; N, 5.40%); *m/z* (%) 259 (M^+, 0.4), 244 (9), 200(10), and 173 (11); $\nu_{max.}$ (film) 2 980, 2 950, 2 870, 1 735, 1 645, and 1 615 cm^{-1}; δ 8.36 (s, 1 H, CH=N), 7.95—7.49 (m, 4 H, ArH), 4.20 (q, 1 H, C*H*Me), 3.75 (s, 3 H, CO_2-Me), and 1.55 (d, 3 H, CH*Me*).

Preparation of Cycloadducts (10).—*Methyl* c-4-(4-*dimethylaminophenyl*)-2,7-*diphenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]-*octane*-r-2-*carboxylate* (10; R = NMe_2, R^1 = Ph). Methyl *N-p*-dimethylaminobenzylidenephenylglycinate (59 mg, 0.2 mmol) and *N*-phenylmaleimide (36 mg, 0.21 mmol) were dissolved in dry toluene (0.5 ml), and the solution flushed with argon and heated in a sealed tube at 110 °C for 1 h. Some product crystallised on cooling and was removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residue crystallised from methanol as colourless prisms; it was combined with the material from toluene (73 mg, 78%), m.p. 214—215 °C (Found: C, 71.45; H, 5.75; N, 8.9. $C_{28}H_{27}N_3O_4$ requires C, 71.65; H, 5.75; N, 8.95%); *m/z* (%) 469 (M^+, 10), 410 (7), 296 (81), 236 (100), 205 (13), and 133 (17); $\nu_{max.}$ 3 320, 2 940, 1 775, 1 735, 1 710, and 1 610 cm^{-1}; δ 7.77—7.14 (m, 14 H, ArH), 4.34 (d, 1 H, J_{AB} 9.25 Hz, H_A), 4.24 (d, 1 H, J_{BC} 7.34 Hz, H_C), 3.79 (s, 3 H, CO_2Me), 3.46 (dd, 1 H, H_B), and 2.96 (s, 6 H, NMe_2).

Methyl c-4-(4-*methoxyphenyl*)-2,7-*diphenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = MeO, R^1 = Ph). Methyl N-*p*-methoxybenzylidenephenylglycinate (1×10^{-2} mol) and *N*-phenylmaleimide (1×10^{-2} mol) were heated in boiling toluene (50 ml) under reflux for 5 h. Removal of the solvent and crystallisation of the crude product from dichloromethane–light petroleum afford the *product* as colourless needles (3.8 g, 84%), m.p. 184—186 °C (Found: C, 70.85; H, 5.5; N, 5.85. $C_{27}H_{24}N_2O_5$ requires C, 71.05; H, 5.30; N, 6.15%); $\nu_{max.}$ (Nujol) 3 340, 1 735, and 1 700 cm^{-1}; δ 7.62—6.82 (m, 14 H, ArH), 4.36 (d, 1 H, J_{AB} 9.03 Hz, H_A), 4.24 (d, 1 H, J_{BC} 7.32 Hz, H_C), 3.79 (s, 6 H, OMe, CO_2Me), and 3.46 (dd, 1 H, H_B).

Methyl 2, c-4,7-*triphenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]-*octane*-r-2-*carboxylate* (10; R = H, R^1 = Ph). Prepared as above by boiling in toluene for 48 h, the product (3.7 g, 86%) crystallised from dichloromethane–light petroleum as colourless prisms, m.p. 238—240 °C (Found: C, 72.95; H, 5.25; N, 6.3. $C_{26}H_{22}N_2O_4$ requires C, 73.20; H, 5.20; N, 6.55%); *m/z* (%) 426 (M^+, 0.5), 367 (M − CO_2Me, 100), and 253 (M − phenylmaleimide, 28); $\nu_{max.}$ 3 340, 1 785sh, 1 750, and 1 730 cm^{-1}; δ 7.9—6.7 (m, 15 H, ArH), 4.45 (d, 1 H, H_A), 4.15 (d, 1 H, H_C), 3.7 (s, 3 H, CO_2Me), and 4.4 (dd, 1 H, H_B).

Methyl c-4-(4-*trifluoromethylphenyl*)-2,7-*diphenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = CF_3, R^1 = Ph). Prepared by heating methyl *N-p*-trifluorobenzylidenephenylglycinate (64 mg, 0.2 mmol) and *N*-phenylmaleimide (37 mg, 0.22 mmol) in dry toluene, under argon in a sealed tube, at 110 °C for 48 h. The product (86 mg, 87%) crystallised from toluene as colourless prisms, m.p. 215—216 °C (Found: C, 65.3; H, 4.2; N, 5.55. $C_{27}H_{21}F_3N_2O_4$ requires C, 65.60; H, 4.25; N, 5.65%); *m/z* (%) 494 (M^+, 0.3), 435 (100), 321 (9), 288 (25), and 261 (32); $\nu_{max.}$ 3 420, 1 785, 1 755, and 1 715 cm^{-1}; δ 7.68—7.07 (m, 14 H, ArH), 4.43 (d, 1 H, J_{AB} 9.27 Hz, H_A), 4.26 (d, 1 H, J_{BC} 7.38 Hz, H_C), 3.80 (s, 3 H, CO_2Me), and 3.59 (dd, 1 H, H_B).

Methyl c-4-(4-*cyanophenyl*)-2,7-*diphenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = CN, R^1 = Ph). Prepared (110 °C, 48 h) from methyl *p*- cyanobenzylidenephenylglycinate (55 mg, 0.198 mmol) and *N*-phenylmaleimide (37 mg, 0.22 mmol) in a sealed tube under argon as described above, the product (81 mg, 90%) crystallised from toluene as colourless prisms, m.p. 270—272 °C (Found: C, 70.8; H, 4.75; N, 9.2. $C_{27}H_{21}N_3O_4$ requires C, 71.85; H, 4.70; N, 9.30%); *m/z* (%) 451 (M^+, 0.2), 393 (40), 392 (100), 278 (7), 245 (22), 219 (6), and 218 (21); $\nu_{max.}$ 3 310, 3 025, 2 220, 1 775, 1 745, 1 710, and 1 605 cm^{-1}; δ 7.85—6.87 (m, 14 H, ArH), 4,41 (dd, 1 H, J_{AB} 9.0 Hz, $J_{H_AH_N}$ 4.63 Hz, H_A), 4.26 (d, 1 H, J_{BC} 7.33 Hz, H_C), 3.80 (s, 3 H, CO_2Me), 3.59 (dd, 1 H, H_B), and 3.19 (br d, 1 H, NH).

Methyl c-4-(4-*nitrophenyl*)-2,7-*diphenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = NO_2, R^1 = Ph). Methyl *N-p*-nitrobenzylidenephenylglycinate (59 mg, 0.2 mmol) and *N*-phenylmaleimide (37 mg, 0.22 mmol) were allowed to react in toluene (0.5 ml) in a sealed tube at 110 °C for 60 h as described above. The product (68 mg, 73%) crystallised from toluene as colourless prisms, m.p. 252—253 °C (Found: C, 66.05; H, 4.65; N, 8.70. $C_{26}H_{21}N_3O_6$ requires C, 66.25; H, 4.50; N, 8.90%); $\nu_{max.}$ (Nujol) 3 350, 1 785sh, 1 750, and 1 715 cm^{-1}; δ 8.25—6.99 (m, 14 H, ArH), 4.45 (d, 1 H, J_{AB} 9.28 Hz, H_A), 4.27 (d, 1 H, J_{BC} 7.32 Hz, H_C), 3.80 (s, 3 H, CO_2Me), and 3.60 (dd, 1 H, H_B).

Methyl c-4-(4-*dimethylaminophenyl*)-2-*methyl*-7-*phenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = NMe_2, R^1 = Me). Methyl *N-p*-dimethylaminobenzylidenealaninate (47 mg, 0.2 mmol) and *N*-phenylmaleimide (37 mg, 0.22 mmol) were allowed to react in toluene in a sealed tube at 110 °C for 5 h as above. The product (65 mg, 80%) crystallised from toluene as pale yellow rods, m.p. 230—232 °C (Found: C, 67.6; H, 6.3; N, 10.3. $C_{23}H_{25}N_3O_4$ requires C, 67.80; H, 6.20; N, 10.30%); *m/z* (%) 407 (M^+, 14), 348 (7), 234 (75), 174 (100), and 133 (20); $\nu_{max.}$ 3 325, 2 800, 1 770, 1 740, 1 705, and 1 610 cm^{-1}; δ 7.42—6.71 (m, 9 H, ArH), 4.83 (d, 1 H, J_{AB} 9.11 Hz, H_A), and 3.88 (s, 3 H, CO_2Me).

Methyl c-4-(4-*methoxyphenyl*)-2-*methyl*-7-*phenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = MeO, R_1 = Me). Prepared in a sealed tube in toluene at 110 °C for 18 h from methyl *N-p*-methoxybenzylidenealaninate (45 mg, 0.2 mmol) and *N*-phenylmaleimide (38 mg, 0.22 mmol), the product (73 mg, 92%) crystallised from toluene as colourless needles, m.p. 255—257 °C (Found: C, 66.9; H, 5.55; N, 7.05. $C_{22}H_{22}N_2O_5$ requires C, 67.00; H, 5.60; N, 7.10%); *m/z* (%) 394 (M^+, 4), 335 (19), 333 (9), 222 (15), 221 (100), 180 (9), and 161 (70); $\nu_{max.}$ 3 320, 2 980, 1 770, 1 740, 1 705, and 1 600 cm^{-1}; δ 7.42—6.87 (m, 9 H, ArH), 4.87 (d, 1 H, J_{AB} 9.15 Hz, H_A), 3.88 (s, 3 H, CO_2Me), 3.79 (s, 3 H, OMe), 3.66 (dd, 1 H, H_B), 3.46 (d, 1 H, J_{BC} 7.68 Hz, H_C), and 1.67 (s, 3 H, Me).

Methyl c-4,7-*diphenyl*-2-*methyl*-6,8-*dioxo*-3,7-*diazabicyclo*-[3.3.0]*octane*-r-2-*carboxylate* (10; R = H, R^1 = Me). Prepared as above (110 °C, 48 h) from methyl *N*-benzylidenealaninate (1×10^{-2} mol) and *N*-phenylmaleimide (1×10^{-2}

mol) in toluene (50 ml). The product crystallised from dichloromethane–ether as colourless needles (3.1 g, 85%), m.p. 219—221 °C (Found: C, 67.3; H, 5.4; N, 7.3. $C_{21}H_{20}N_2O_4$ requires C, 69.20; H, 5.55; N, 7.70%); *m/z* (%) 364 (M^+, 2.5), 305 (M − CO_2Me, 56), and 191 (M − phenylmaleimide, 100); $\nu_{max.}$ 3 250, 1 710, and 1 590 cm^{-1}; δ 7.5—7.0 (m, 10 H, ArH), 4.9 (t, 1 H, H_A), 6.1 (s, 3 H, CO_2Me), 6.35 (dd, 1 H, H_B), 6.55 (d, 1 H, H_C), 7.35 (d, 1 H, NH), and 8.35 (s, 3 H, Me).

Methyl c-4-(4-*trifluoromethylphenyl*)-2-*methyl*-7-*phenyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-r-2-*carboxylate* (10; R = CF_3, R^1 = Me). Methyl N-*p*-trifluoromethylbenzylidenealaninate (52 mg, 0.2 mmol) and *N*-phenylmaleimide (38 mg, 0.22 mmol) were allowed to react in toluene (110 °C, 48 h) in a sealed tube as described above. The product crystallised from methanol as colourless needles (62 mg, 72%), m.p. 207—209 °C (Found: C, 61.3; H, 4.55; N, 6.4. $C_{22}H_{19}F_3N_2O_4$ requires C, 61.15; H, 4.40; N, 6.50%); *m/z* (%) 432 (M^+, 2), 374 (24), 373 (100), 259 (67), 226 (46), 199 (63), and 158 (12); $\nu_{max.}$ 3 330, 2 950, 1 775, 1 740, 1 710, and 1 615 cm^{-1}; δ 7.58—6.97 (m, 9 H, Ar*H*), 4.92 (d, 1 H, J_{AB} 8.55 Hz, H_A), 3.88 (s, 3 H, CO_2Me), 3.73 (dd, 1 H, H_B), 3.44 (d, 1 H, J_{BC} 7.57 Hz, H_C), and 1.67 (s, 3 H, Me).

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