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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 16. CYCLOPROPYL SUBSTITUTED AZOMETHINE YLIDES AS MECHANISTIC PROBES IN 1,3-DIPOLAR CYCLOADDITION REACTIONS

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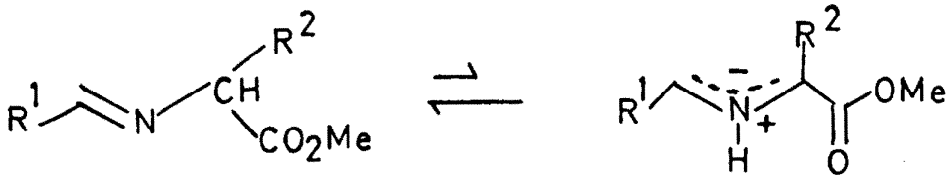
Abstract Cycloadditions involving the 1,2-prototropic route and the decarboxylative route to azomethine ylides were studied with cyclopropyl substituents located on one or both carbon atoms of the azomethine ylides and in several instances in the dipolarophile. Cycloadducts were obtained in good yield with no evidence of biradical intermediates, i.e. no products arising from cyclopropyl radical ⇌ but-3-enyl radical rearrangements were detected.

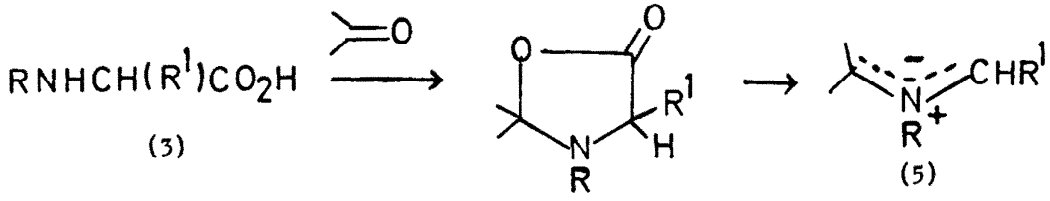
The mechanism of 1,3-dipolar cycloaddition reactions has been the subject of lively debate since Huisgen's perceptive and monumental paper unifying this area of chemistry.[1] Huisgen's original suggestion that these processes were concerted received support, and a molecular orbital explanation, from Woodward and Hoffmann[2] and has withstood the onslaughts of both time and Firestone.[3] The espousal of the stepwise diradical mechanism by Firestone stimulated both calculation and experimentation but apparent support for a biradical mechanism from calculations was later shown to be an artifact of the methodology.[4] Recently careful studies of the 1,3-dipolar cycloaddition of p-nitrobenzonitrile oxide to cis- and trans-dideuterioalkylene have shown these cycloadditions to occur with ⩾ 98% retention of stereochemistry supporting Husigen's original proposal that these reactions are concerted.[5] Firestone has recently challenged this conclusion[6] and has suggested that rotational barriers in diradicals may be higher than expected. This factor combined with the well known rapid rate of cyclisations forming 5-membered rings are proposed to account for the high stereospecificity. Nevertheless, the presence of suitable substituents on the 1,3-dipole and dipolarophile might be expected to lead to detectable stepwise cycloaddition via either a biradical or zwitterionic intermediate in favourable cases. Careful studies on the Diels-Alder reaction revealed instances of two-step biradical processes[7], and Sustmann has identified, in terms of PMO theory, two cases for 1,3-dipolar cycloadditions in which a stepwise mechanism might compete with the concerted process.[8] Thus two similar HOMO-LUMO interaction energies between the 1,3-dipole and the dipolarophile are predicted to result in a minimum cycloaddition rate and, in such cases, the presence of suitable stabilising substituents should lead to a biradical pathway. The other limiting case arises when the HOMO(1,3-dipole)-LUMO(dipolarophile) interaction is dominant with little contribution from the alternative LUMO(1,3-dipole)-HOMO(dipolarophile) interaction in the transition state. In this

situation a reactant pair with a large difference in energy between their frontier orbitals should lead to a cycloaddition via a zwitterionic intermediate. Huisgen has recently reported the first examples of this latter type involving thiocarbonyl ylides.[9]



(1) a. R^1=Ph, R^2=c-C_3H_5
b. R^1=c-C_3H_5, R^2=Ph
c. R^1=R^2=c-C_3H_5

(2)



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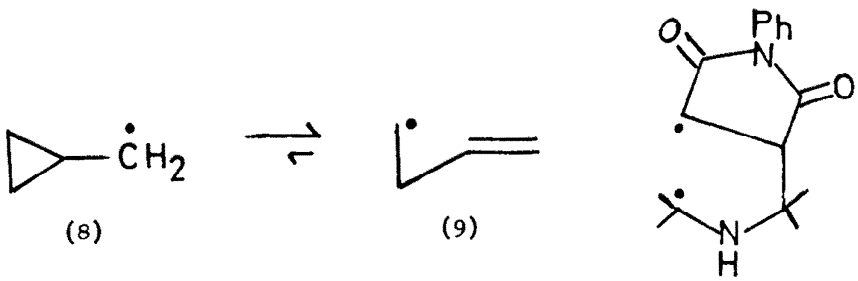

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(10)

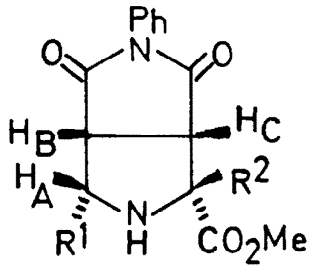
We have developed three new routes to azomethine ylides involving either (i) a formal 1,2-prototropic shift (1⇄2)[10], (ii) the reaction of carbonyl compounds with α-amino acids with concomitant decarboxylation (3)→(4)→(5)[11] or (iii) the reaction of primary- and secondary-amines with carbonyl compounds containing the moiety O=C-C=X (6)→(7).[12] We now describe examples of cycloadditions involving routes (i) and (ii) in which the azomethine ylides bear one or more cyclopropyl substituents. The cyclopropyl group was chosen as a mechanistic probe for biradical intermediates in the cycloaddition processes because of the facile nature of the cyclopropylmethyl radical (8) to 3-butenyl radical (9)

rearrangement[13]. This rearrangement has been widely used as a mechanistic probe for radical processes[14] because the rearrangement (8)⟶(9) is so rapid (ca. $10^{-8}sec^{-1}$)[15] and the equilibrium constant (3.8×10^{-5} at 25°C) overwhelmingly favours the butenyl radical.[15] Recently cyclopropyl probes have been used to study hydrogenase enzymes in vivo[16], and in model systems[17], and in ethylene biosynthesis from ∝-amino acid precursors.[18]

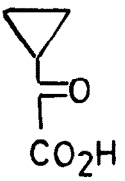
There do not appear to be any reports in the literature where cyclopropyl substituents have been deliberately used as mechanistic probes in 1,3-dipolar cycloaddition reactions. However, cycloadditions of cyclopropyl nitrones[19], and of nitrones[20] and nitrile oxides[21] to cyclopropyl substituted dipolarophiles have been reported without comment regarding possible radical rearrangement products.

Cyclopropyl substituted azomethine ylides via formal 1,2-prototropy. The three imines (1a-c) were prepared from the appropriate aldehydes and ∝-amino acid esters. Cycloaddition of the azomethine ylides (2) derived from these imines to N-phenylmaleimide (NPM) would, if proceeding via a biradical pathway, involve intermediates such as (10). When (1a-c) were heated (xylene, 140°C, 3h) with NPM the cycloadducts (11a-c) were formed stereospecifically and in good yield (⩾ 57% isolated yield). Inspection of the p.m.r. spectra of the crude products showed them to comprise ⩾ 95% (11a-c) and no products derived from rupture of the cyclopropane ring were observed. The stereochemistry of (11a-c) is based on n.O.e. experiments (Table) and accords with our previous observations that imine (1) and NPM react to give the adduct of the kinetic dipole (2).[10,22] The reactions were repeated (n.m.r. tube experiments) (toluene, 110°C, 1-1.5h) in the presence of bromotrichloromethane (1mol), a radical trap, to act as terminator for the cyclopropyl to 3-butenyl radical rearrangement, but no rearrangement products were observed. When the imines (1a-c) were heated in neat bromotrichloromethane in the presence of NPM black tars quickly formed (20 mins) and the p.m.r. spectra of these decomposition products became broad and uninterpretable. We have shown that a range of other activating groups, including 2-pyridyl, can replace the ester group in (1).[23] It was of interest therefore to study an example of cyclopropyl substitution in one of these cases. When cyclopropylglyoxylic acid (12), and (13), were heated with NPM (CH_2Cl_2, 40°C, 24h), the cycloadduct (14) was obtained in 90% yield. Once again no radical rearrangement products were observed. Stereochemical assignments are based on n.O.e. results (Table).

Two examples of intramolecular cycloadditions of imines[24] to dipolarophiles incorporating cyclopropyl substituents as radical probes were also studied. 2-Hydroxy-1-naphthaldehyde and the cyclopropylpropenoic acids (15a) and (15b) are readily coupled by dicyclohexylcarbodiimide in pyridine at room temperature to give (16a) and (16b) in ca. 90% yield and the derived imines (17a) and (17b) were prepared from these by standard methodology in 82 and 95% yield respectively. On heating (17a) in xylene (140°C, 24h) the expected cycloadduct (18a) was only obtained in 38% yield together with a mixture of the degradative by-products (16a), (19) and (20). However, no radical fragmentation products were detected. Imine (17b) under identical conditions gave a 62:38 mixture of (18b) and (18c) together with traces of degradative by-products (16b), (19) and the analogue of (20), but no radical fragmentation products. The stereochemistry of (18a-c) was assigned from n.O.e. studies (Table). Thus these intramolecular cycloadditions proceed, as expected, via endo-transition states[24] and incorporation of the cyclopropyl substituent in (17b) slows the cycloaddition sufficiently to permit dipole equilibration.[24]. In this latter case, the expected kinetic dipole (21a) gives rise to the minor isomer (18c) whilst the stereomutated dipole (21b) furnishes the major product. This is the first case where we have observed dipole stereomutation



(11) a. R^1=Ph, R^2=c-C_3H_5
b. R^1=c-C_3H_5, R^2=Ph
c. R^1=R^2=c-C_3H_5



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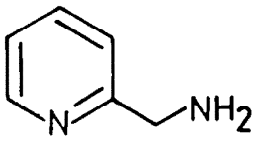

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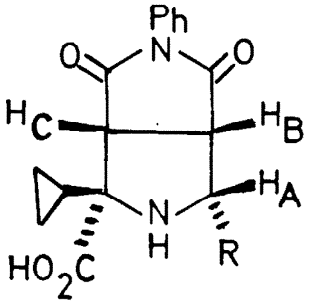
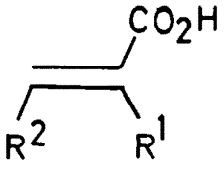
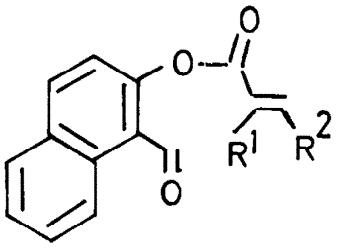


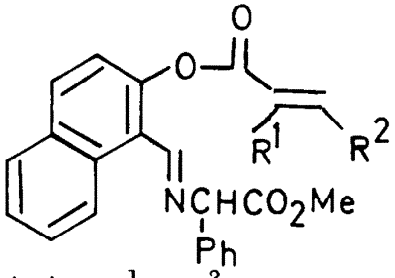
(14) R = 2-pyridyl



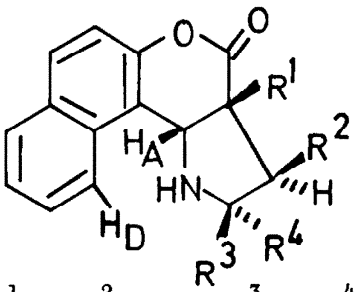
(15) a. R^1=H, R^2=c-C_3H_5
b. R^1= c-C_3H_5, R^2= H



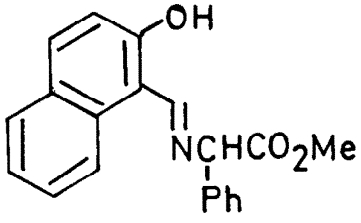
(16) a. R^1=H, R^2=c-C_3H_5
b. R^1= c-C_3H_5, R^2=H



(17) a. R^1=H, R^2=c-C_3H_5
b. R^1=c-C_3H_5, R^2=H



(18) a. R^1=H_B, R^2=c-C_3H_5, R^3=Ph, R^4=CO_2Me
b. R^1=c-C_3H_5, R^2=H_c, R^3=CO_2Me, R^4=Ph
c. R^1=c-C_3H_5, R^2=H_c, R^3=Ph, R^4=CO_2Me



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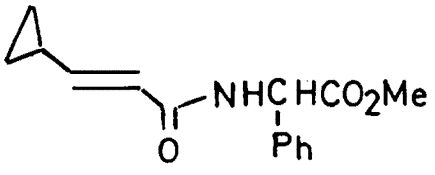
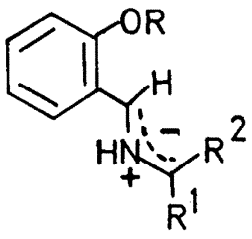


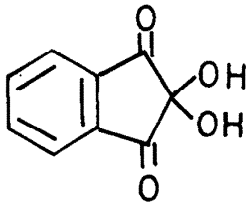
(20)

to proceed substantially beyond the 50:50 ratio.[24,25]

Cyclopropyl substituted azomethine ylides generated by the decarboxylative route. Primary and secondary α-amino acids react with aldehydes and ketones, with concomitant decarboxylation, to give azomethine ylides, via an intermediate oxazolidin-5-one (4). The stereochemistry of the oxazolidin-5-one (4), which undergoes a stereospecific 1,3-cycloreversion reaction, controls the stereochemistry of the azomethine ylide.[11,26] Thus in this instance the cyclopropyl probes monitor both the 1,3-cycloreversion (4)⟶(5) and the cycloaddition of the azomethine ylide (5).



(21) a. R^1=CO_2Me, R^2=Ph
b. R^1=Ph, R^2=CO_2Me



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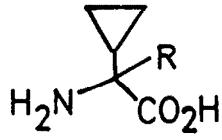
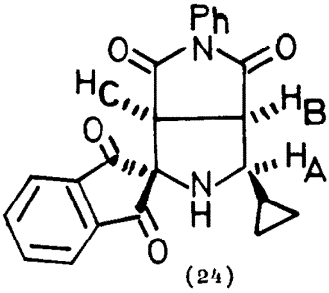


(23) a. R=H
b. R=c-C_3H_5
c. R=Ph
d. R=Me



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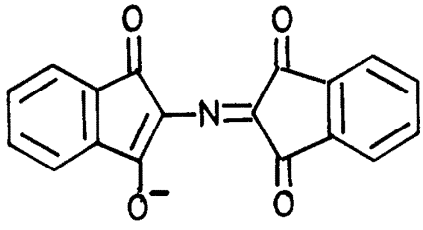

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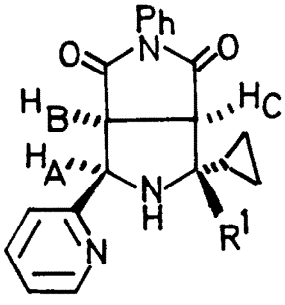
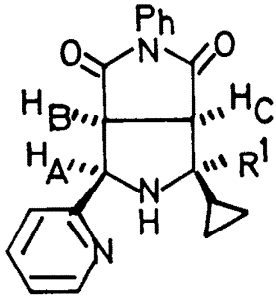
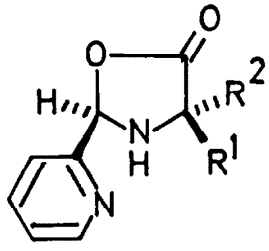


(26) a. R^1=H_D
b. R^1=c-C_3H_5
c. R^1=Ph
d. R^1=Me



(27) a. R^1=H_D
b. R^1=c-C_3H_5
c. R^1=Ph
d. R^1=Me



(28) a. R^1=Me, R^2=c-C_3H_5
b. R^1=c-C_3H_5, R^2=Me

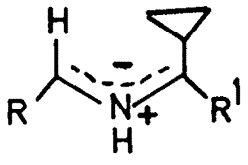
Ninhydrin (22), (23a) and NPM react (MeOH, 65°C, 1.5h) to give a single cycloadduct (24, 62%), whose stereochemistry is assigned on the basis of n.O.e. experiments (Table). The p.m.r. spectrum of the reaction mixture revealed no sign

Table. n.O.e. enhancements ($CDCl_3$) observed for cycloadducts (10a-c)

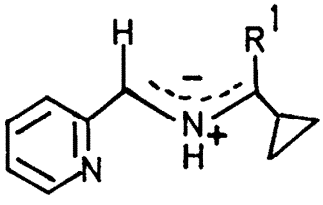
Cycloadduct	Proton Irradiated	n.O.e. (%) H_A	H_B	H_C	R^1	R^2
	H_A		12		9	
10a	H_B	8		9		
	R^2	2		12		
	H_A		21	-3	14	8
10b	H_B	15		12		
	H_C		14		30	
	H_A		15		2	2
10c	R^1	2				
	R^2	1	1	8		
	H_A		15			
13	H_B	9		9		
	H_C		11			
	H_A		14			7
18a	H_B					3
	R^2	4	4			
	H_A			2	8	
18b[a]	H_C	3			4	
	R^1	3		1		
	H_A			2	9	
18c[b]	H_C	3			4	
	R^1	3		2		
	H_A		18			
24	H_B	12		7		
	H_C		20			
	H_A		12	2		
26a	H_B	6		8		
	H_C		5			4[c]
	H_A		18			8[c]
26b	H_B	10		10		
	H_C		13			6[c]
	H_A		18			4[c]
26c	H_B	11		10		2[c]
	H_C		14			7[c]
	H_A		10			2[c]
26d	H_B	5		9		
	H_C		7			3[c]
	H_A		10		6	
27d	H_B	6		10		
	H_A		8			
31	H_B	4		4		
	H_C		9			
	H_A					7[c]
32	H_B			12		3[c]
	H_C		12			

a. Irradiation of H_A effects enhancement of H_D (22%)
b. Irradiation of H_A effects enhancement of H_D (23%)
c. R^2 = c-C_3H_5

of cyclopropyl ring opening products. Analogous reactions with the amino acids (23b-d) did not give cycloadducts but instead gave Ruhemann's purple (25).[27] In the case of (23b-d) the derived azomethine ylide is tetrasubstituted and the steric hindrance accruing from this substitution severely retards cycloaddition leading to ylide decomposition forming Ruhemann's purple. The amino acids (23a-c) react with pyridine-2-carboxaldehyde and NPM (MeCN, 80°C, 1h) to give ca. 9:1 mixtures of cycloadducts (26a-c) and (27a-c), whilst (23d), pyridine-2-carboxaldehyde and NPM under the same conditions give a 1.2:1 mixture of (26d) and (27d) together with traces of two other stereoisomers. The increased amount of (27d) compared to (27a-c) reflects the close correspondence of steric effects of the methyl and cyclopropyl substituents on the cyclisation of the intermediate imine to the oxazolidin-5-ones and their cycloreversion[11,28] to azomethine ylides with (28a) the precursor of (26), and (28b) the precursor of (27). The major isomers (26a-d) and (27d) were isolated by fractional crystallisation or preparative t.l.c. and their stereochemistry is assigned on the basis of n.O.e. experiments (Table). There are two possible azomethine ylide precursors for each of (26) and (27) but steric considerations suggest (29a) and (30) as the most probable precursors of (26) and (27) respectively. These cycloadducts would then be derived via endo-transition states.



(29) a. R=2-pyridyl
b. R=c-C_3H_5, R^1=Ph



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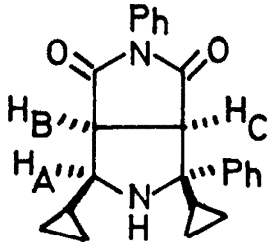

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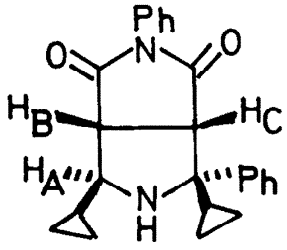

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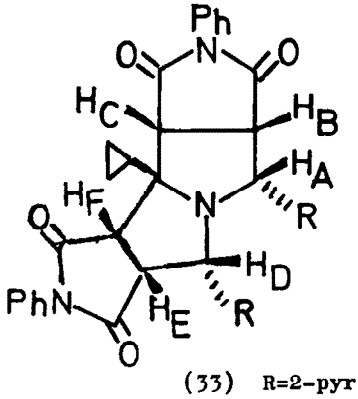

(33) R=2-pyridyl

Cyclopropane carboxaldehyde reacts with (23c) and NPM (MeCN, 80°C, 2h) to give a 1.27:1 mixture of (31) and (32) in quantitative yield. These products are the endo- and exo-cycloadducts of dipole (29b) and their stereochemistry was assigned by n.O.e. studies (Table). Finally, when (14) was heated (DMF, 120°C, 2h) with pyridine-2-carboxaldehyde and NPM it afforded (33) as the major product (61%)(see experimental section for n.O.e. studies). In this latter case the crude product was dark coloured and tarry and fragmentation products of the cyclopropane substituents cannot be ruled out. However, we found no positive evidence for

radical intermediates in our two new routes to azomethine ylides.

Experimental. General experimental details were as previously noted.[10] Petroleum ether refers to the fraction with b.p. 40-60°C.

Methyl 2-cyclopropylpropenoate. A 1.5M solution of n-butyl lithium in hexane (40mls, 60mmol) was added to a suspension of methyltriphenylphosphonium bromide (21.5g, 60mmol) in dry ether (400ml). After stirring for 4h at room temperature, a solution of methyl cyclopropylglyoxylate (6.92g, 60mmol) in dry ether (80ml) was added dropwise over 5 min. and the resulting thick white suspension was stirred at room temperature for 15h when water (200ml) was added and the phases separated. The aqueous layer was extracted with ether (2 x 100ml) and the combined ether layers were dried (anhyd. Na_2SO_4), chromatographed (silica, Et_2O) and then vacuum distilled to afford the product as a colourless oil (3.65, 52%), b.p. 44-48°C/10mmHg (Found: C, 66.64; H, 8.17. $C_7H_{10}O_2$ requires C, 66.64; H, 7.99); ν_{max} 3080, 1720, 435, 936 and 812 cm^{-1}; m/z(%) 126 (M^+, 31), 111(41), 69(20), 67(100), 66(40), 41(76) and 39(53); 6.03 (d, 1H, =CH, J 1.0Hz), 5.31 (d, 1H, =CH), 3.78 (s, 3H, OMe), 1.75 (m, 1H, cyclopropyl H), and 0.78 and 0.51 (2 x m, 2 x 2H, cyclopropyl H).

2-Cyclopropylpropenoic acid. Methyl 2-cyclopropylpropenoate (1.8g, 17mmol) was boiled under reflux for 3h in 0.5M 30% aqueous ethanolic sodium hydroxide (35mls, 17mmol). The ethanol was removed in vacuo and the aqueous solution acidified with dilute hydrochloric acid. The oil which separated was extracted with chloroform (3 x 50ml), dried (anhyd. $MgSO_4$) and evaporated to leave a pale yellow oil which on distillation afforded the product (1.1g, 69%) as a colourless oil, b.p. 48-54°C/15mmHg. (Found: C, 64.29; H, 7.56. $C_6H_8O_2$ requires C, 64.27; H, 7.19); ν_{max} 3300-2500, 1715-1680, 1430, 1200, 940 and 755 cm^{-1}; m/z(%) 112 (M^+, 58), 111(27), 67(100), 55(11), 45(13) and 41(59); 11.30 (br s, 1H, OH), 6.20 (d, 1H, =CH, J 0.8Hz), 5.44 (s, 1H, =CH), 1.76 (m, 1H, cyclopropyl H), and 0.82 and 0.55 (2 x m, 2 x 2H, cyclopropyl H).

Aldehydes (16a) and (16b). Dicyclohexylcarbodiimide (11mmol) was added to a solution of the cyclopropyl propenoic acid (10mmol), 2-hydroxy-1-naphthaldehyde (11mmol) and p-toluenesulphonic acid (90mg) in dry pyridine (9ml) and the mixture stirred for 24h at ambient temperature. Glacial acetic acid (1ml) was then added, the mixture stirred for 2h and then kept at 0°C overnight. The mixture was then filtered, the precipitate washed with cold pyridine (5ml) and the filtrate partitioned between chloroform (15ml) and ice water. The $CHCl_3$ layer was separated, washed with water (20ml), saturated sodium bicarbonate solution (20ml), dried (anhyd. Na_2SO_4) and the solvent removed in vacuo to leave the crude product which was crystallised from ether-petroleum ether.

(16a) Obtained (91%) as colourless needles, m.p. 75°C (Found: C, 76.80; H, 5.50. $C_{17}H_{14}O_3$ requires C, 76.65; H, 5.30%); ν_{max} 1730, 1672, 1502, 1113, 939 and 823 cm^{-1}; m/z(%) 266 (M^+, 8), 171(13), 115(11), 95(100), 67(35) and 41(16); 10.67 (s, 1H, CHO), 9.24-7.26 (m, 6H, ArH), 6.73 (dd, 1H, =CHCO), 6.20 (d, 1H, =CH), 1.73 (m, 1H, cyclopropyl H), and 0.94 (m, 4H, cyclopropyl H).

(16b) Obtained as colourless plates, m.p. 57°C (Found: C, 76.65; H, 5.45. $C_{17}H_{14}O_3$ requires C, 76.65; H, 5.30%); ν_{max} 1740, 1680, 1500, 1200, 1075 and 795 cm^{-1}; m/z(%) 266 (M^+, 11), 171(43), 144(12), 115(24), 95(92), 67(100) and 41(27); 10.72 (s, 1H, CHO), 9.23 (d, 1H, ArH), 8.14-7.32 (m, 5H, ArH), 6.40 and 5.63 (2 x s, 2 x 1H, CH=CH), 1.90 (m, 1H, cyclopropyl H) and 0.93-0.64 (m, 4H, cyclopropyl H).

Imines

General Procedure. A mixture of the amino acid ester hydrochloride (11mmol), anhydrous magnesium sulphate (1g) and triethylamine (1.1g, 11mmol) in dry methylene chloride (30ml) was stirred for 10 min. after which a solution of the aldehyde (10mmol) in dry methylene chloride (10ml) was added. The resulting mixture was stirred at room temperature for 16h and then filtered. The filtrate was washed with water (3 x 40ml), dried ($MgSO_4$), and evaporated to dryness. The crude imine was distilled or crystallised as appropriate.

Methyl N-benzylidene cyclopropyl glycine (1a). Obtained as a colourless oil (1.8g, 85%C) b.p. 140-153°C/0.01mmHg (Found: C, 71.63; H, 7.01; N, 6.38. $C_{13}H_{15}NO_2$ requires C, 71.86; H, 6.96; N, 6.45%); ν_{max} 3000, 1732, 1637, 1508, 1380, 1201, 1023, 825 and 700 cm^{-1}; m/z(%) 217 (M^+, 1), 158(100), 131(18), 121(11), 105(20), 104(11), 91(16), and 77(21); 8.27 (s, 1H, CH=N), 7.78 (m, 2H, ArH), 7.42 (m, 3H, ArH), 3.78 (s, 3H, OMe), 3.35 (d, 1H, $CHCO_2Me$), 1.51 (m, 1H, cyclopropyl H), and 0.61-0.31 (m, 4H, cyclopropyl H).

Methyl N-cyclopropylidene phenylglycine (1b). Obtained as a pale yellow oil (1.26g, 58%) b.p. 74-78°C/0.01mmHg (Found: C, 71.74; H, 6.96; N, 6.55. $C_{13}H_{15}NO_2$ requires C, 71.86; H, 6.96; N, 6.45%); ν_{max} 3000, 1735, 1650, 1490, 1155, 1028, 700 and 717 cm^{-1}; m/z(%) 217 (M^+, 1), 158(100), 131(19), 106(11), 104(8), 91(16), and 77(7); 7.35 (m, 5H, ArH), 7.01 (d, 1H, CH=N) 4.91 (s, 1H, $CHCO_2Me$), 3.72 (s, 3H, OMe), 1.85 (m, 1H, cyclopropyl H), and 0.94 and 0.72 (2 x m, 4H, cyclopropyl H).

Methyl N-cyclopropylidene cyclopropylglycine (1c). Obtained as a colourless oil (1.21g, 67%) b.p. 120-130°C/2mmHg (Found: C, 66.38; H, 8.30; N, 7.76. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 8.34; N, 7.73%); ν_{max} 3000, 1735, 1651, 1430, 1265, 1022, 948 and 823 cm^{-1}; m/z(%) 181 (M^+, 2), 180(11), 150(12), 122(100), 120(30), 113(22), 95(12) and 69(30); 6.89 (d, 1H, CH=N), 3.74 (s, 3H, OMe), 3.02 (d, 1H, $CHCO_2Me$), 1.79 and 1.36 (2 x m, 2 x 1H, cyclopropyl H), and 0.90-0.21 (m, 8H, cyclopropyl H).

Imines (17a) and (17b). A mixture of the aldehyde (16a) or (16b) (6.3mmol), phenyl glycine methyl ester (6.5mmol) and anhydrous sodium sulphate (2g) was boiled under reflux in dry methylene chloride (25ml) for 1h and then stirred at room temperature for 10h. The mixture was then filtered and the filtrate evaporated to dryness. The residue was used for the next stage without purification.
(17a) Obtained (82%) as a colourless gum. $\nu_{max.}$ 1725, 1642, 1628, 1233, 1057, 820 and 771 cm^{-1}; m/z(%) 413 (M^+, 17), 354(4), 319(22), 260(30) and 95(100); δ 9.22 (d, 1H, ArH), 8.85 (d, 1H, CH=N, J 0.5Hz), 7.92-7.20 (m, 10H, ArH), 6.62 (dd, 1H, C=CH), 6.08 (d, 1H, =CHCO), 5.27 (s, 1H, PhCH), 3.77 (s, 3H, OMe), 1.69 (m, 1H, cyclopropyl H), and 1.06 and 0.75 (2 x m, 2 x 2H, cyclopropyl H).
(17b) Obtained (95%) as a colourless semi-solid. $\nu_{max.}$ 1735, 1638, 1430, 1245, 1088 and 751 cm^{-1}; m/z(%) 413 (M^+, 5), 354(10), 260(24), 200(19), 171(32), 115(24) and 67(100); δ 9.21 (d, 1H, ArH), 8.87 (d, 1H, CH=N, J 0.5Hz), 7.95-7.25 (m, 10H, ArH), 6.26 and 5.51 (2 x s, 2 x 1H, CH=CH), 5.26 (s, 1H, PhCH), 3.77 (s, 3H, OMe), 1.81 (m, 1H, cyclopropyl H), and 0.85 and 0.59 (m, 4H, cyclopropyl H).
Methyl c-2-cyclopropyl-4,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (11a). Methyl N-benzylidene cyclopropylglycine (270mg, 1mmol) and NPM (170mg, 1mmol) were boiled under reflux in xylene (20ml) for 3h. The xylene was removed and the residue triturated with ether-petroleum ether to give the solid cycloadduct which crystallised as colourless prisms (65%) from methanol-petroleum ether, m.p. 138-140°C. (Found: C, 70.85; H, 5.60; N, 6.98. $C_{23}H_{22}N_2O_4$ requires C, 70.75; H, 5.68; N, 7.18%); $\nu_{max.}$ 3450, 3080, 1721, 1702, 1495, 1378, 1022, 822 and 750 cm^{-1}; m/z(%) 332(23), 331(100), 217(34), 216(28), 156(71), 128(16), 115(33), and 89(26); δ 7.35 (m, 8H, ArH), 6.83 (m, 2H, ArH), 4.92 (d, 1H, H_A, J 9.7Hz), 3.92 (s, 3H, OMe), 3.83, (dd, 1H, H_B) 3.61 (d, 1H, H_C, J 7.8Hz), 2.52 (br s, 1H, NH), 1.40 (m, 1H, cyclopropyl H), and 0.55 (m, 4H, cyclopropyl H).
Methyl c-4-cyclopropyl-2,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (11b). Prepared in an analogous manner from methyl N-cyclopropylidene phenylglycine. The product (0.22g, 57%) crystallised from MeOH as colourless prisms m.p. 150°C (Found: C, 70.81 H, 5.76; N, 7.10. $C_{23}H_{22}N_2O_4$ requires C, 70.75; H, 5.68; N, 7.18%); $\nu_{max.}$ 3450, 3080, 1730, 1710, 1590, 1488, 1373, 1273 and 811 cm^{-1}; m/z(%) 391 (M^+, 1), 332(24), 331(100), 184(12) and 158(14); δ 7.61 (m, 2H, ArH), 7.38 (m, 8H, ArH), 4.15 (d, 1H, H_C, J_{BC} 7.5Hz), 3.74 (s, 3H, OMe), 3.30 (dd, 1H, H_B, J_{AB} 8.8Hz), 2.56 (t, 1H, H_A), 2.41 (br s 1H, NH), 0.86 (m, 1H, cyclopropyl H), and 0.66 and 0.31 (2 x m, 4H, cyclopropyl H).
Methyl c-2,4-cyclopropyl-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylate (11c). Prepared in analogous manner from methyl N-cyclopropylidene cyclopropylglycine. The product (250mg, 72%) crystallised from methanol-petroleum ether as colourless prisms m.p. 113-115°C (Found: C, 67.95; H, 6.16; N, 7.95. $C_{20}H_{22}N_2O_4$ requires C, 67.78; H, 6.26; N, 7.91%); $\nu_{max.}$ 3300, 1730, 1705, 1490, 1381, 1269, 1190, 952, 691 and 624 cm^{-1}; m/z(%) 355 (M^+ + 1,1), 296(60), 295(100), 181(5), 166(3), 148(24) 120(15) and 106(18); δ 7.41 (m, 3H, ArH), 7.24 (m, 2H, ArH), 3.84 (s, 3H, OMe), 3.54 (d, 1H, H_A, J 7.9Hz), 3.44 (d, 1H, H_C, J_{BC} 7.9Hz), 2.92 (t, 1H, H_B), 1.26 and 0.82 (2 x m, 2 x 1H, cyclopropyl H), and 0.68-0.33 (m, 8H, cyclopropyl H).
4-Cyclopropyl-2-(2-pyridyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-r-2-carboxylic acid (14). A mixture of cyclopropylglyoxylic acid (760mg, 6.6mmol)[29], 2-aminomethylpyridine (720mg, 6.6mmol) and NPM (1.15g, 6.6mmol) was boiled under reflux in CH_2Cl_2 (40ml) for 24h. The solvent was removed to leave a pale yellow solid (2.51g, 100%) which comprised (14) (90%) together with trace amounts of minor isomers. The crude solid was triturated with chloroform-ether to yield the pure major isomer (1.56g, 63%), which crystallised as colourless rods from aqueous acetone, m.p. 212-215°C (Found: C, 66.99; H, 4.87; N, 10.98. $C_{21}H_{19}N_3O_4$ requires C, 66.83; H, 5.07; N, 11.14%); $\nu_{max.}$ 3260, 1720, 1605, 1495, 1387, 1191, 946, 831, 751, 732 and 690 cm^{-1}; m/z(%) 377 (M^+, 3), 333(27), 332(100), 318(8), 305(9), 185(22), 158(24), 144(20), 117(41), 93(52), 83(83); δ (pyridine d_5), 8.54 (d, 1H, ArH), 7.65-7.01 (m, 8H, ArH), 5.16 (d, 1H, H_A, J_{AB} 9.3Hz), 4.15 (dd, H_C, J_{BC} 7.8Hz), 3.95 (d, 1H, H_B), 1.81 (m, 1H, cyclopropyl H), and 0.81 and 0.66 (2 x m, 4H, cyclopropyl H).
3-Cyclopropyl-2-methoxycarbonyl-4-oxo-2-phenyl-4H-2,3,3a,11c-tetrahydropyrro[2,3-d]naphtho[2,1-b]pyran (18a). A solution of the imine (17a) (5mmol) in dry xylene (50ml) was boiled under reflux under an argon atmosphere for 48h. The xylene was removed under reduced pressure and the residual oil analysed by p.m.r. spectroscopy and found to comprise a 7.6:5.6:3.8:2:1 mixture of (18a), (20), (19), 2-hydroxy-1-naphthaldehyde and (16a). Preparative t.l.c. (silica) eluting with 3:2 v/v petroleum ether-ether yielded the product (50mg, 22%, i.e. 57% recovery) which crystallised from ether-petroleum ether as hexagonal prisms, m.p. 154-155°C. (Found: C, 75.25; H, 5.50; N, 3.44. $C_{26}H_{23}NO_4$ requires C, 75.53; H, 5.61; N, 3.39); $\nu_{max.}$ 3310, 1740, 140, 1712, 1260, 951, 825, 743 and 700 cm^{-1}; m/z(%) 413 (M^+, 2) 355(30), 354(100), 250(13), 209(8), 168(7) and 104(17); δ 8.23-7.10 (m, 11H, ArH), 5.46 (d, 1H, H_A, J_{AB} 7.2Hz), 3.80 (s, 3H, OMe), 3.24 (dd, 1H, H_B), 2.93 (dd, 1H, CHC_3H_5) 1.64 (br s, 1H, NH), 1.10 (m, 1H, cyclopropyl H), and 0.82-0.48 (m, 4H, cyclopropyl H).
3a-Cyclopropyl-2-methoxycarbonyl-4-oxo-2-phenyl-4H-2,3,3a,11c-tetrahydropyrro[1,3-d]naphtho[2,1,-b]pyran (18b) and (18c). Prepared from imine (17b) as above but with a reaction time of 24h. The crude brown oil obtained comprised a 1.6:1 mixture of (18b) and (18c) in 85% yield, together with minor hydrolysis products. The crude oil (200mg) was subjected to preparative tlc (silica) eluting with 1:1 ether-

petroleum-ether to afford the pure major isomer (18b) (70mg, 35% recovery), and (18c) (40mg, 20% recovery) contaminated with ca.10% (18b). The minor isomer was not purified further.

(18b) Colourless prisms from ether, m.p. 166°C (Found: C, 75.53; H, 5.63; N, 3.28 $C_{26}H_{23}NO_4$ requires C, 75.53; H, 5.61; N, 3.39%); ν_{max} 3315, 1760, 1713, 1442, 1224, 1136, 821 and 747 cm^{-1}; m/z(%) 355(24), 354(100), 352(2), 296(3), 177(3), 105(3), 104(5) and 28(11); δ 8.06-7.19 (m, 11H, ArH), 4.62 (s, 1H, H_A), 3.90 (s, 3H, OMe), 3.40 (br s, 1H, NH), 3.15 (d, 1H, 2.85 (d, 1H, H_C), 1.00 (m, 1H, cyclopropyl H), and 0.42 (m, 4H, cyclopropyl H).

(18c) δ 8.17-7.26 (m, 11H, ArH), 4.65 (s, 1H, H_A), 3.79 (d, 1H), 3.66 (s, 3H, OMe), 3.50 (br s, 1H, NH), 2.41 (d, 1H, H_C), 0.95 (m, 1H, cyclopropyl H), and 0.39 (m, 4H, cyclopropyl H).

2-Cyclopropyl-4-(2,2-spiroindan-1,3-dione)-7-phenyl-6,8-dioxo-3,7-diazabicyclo [3.3.0] octane (24). A mixture of cyclopropylglycine (150mg, 1.3mmol), ninhydrin (230mg, 1.3mmol) and NPM (230mg, 1.3mmol) was boiled under reflux in methanol (25ml) for 1h. On concentrating the solution the product (310mg, 61%) crystallised as yellow needles, m.p. 179-180°C. (Found: C, 71.55; H, 4.85; N, 7.20. $C_{23}H_{18}N_2O_4$ requires C, 71.49; H, 4.70; N, 7.25%); ν_{max} 3290, 1710, 1585, 1495, 1370, 1190, 1178, 1029 and 614 cm^{-1}; m/z(%) 386 (M^+, 100), 210(9), 198(50), 173(13), 105(27), 77(26); δ (C_6D_6) 7.95-7.15 (m, 9H, ArH), 3.58 (dd, 1H, H_A, J 7.5 and 9.4Hz), 3.34 (d, 1H, H_C, J_{BC} 7.5Hz), 3.18 (t, 1H, H_B), 2.54 (br d, 1H, NH), 1.26 (m, 1H, cyclopropyl H), 0.91-0.47 (m, 4H, cyclopropyl H).

2-Cyclopropyl-4-(2-pyridyl)-7-phenyl-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane (26a). A mixture of cyclopropylglycine (150mg, 1.3mmol), 2-pyridine carboxaldehyde (140mg, 1.5mmol) and NPM (230mg, 1.3mmol) was boiled under reflux in acetonitrile (20ml) for 1h. Removal of the acetonitrile left a yellow gum whose p.m.r. spectrum showed it to comprise a 10:1 mixture (100%) of (26a) and (27a). Preparative t.l.c. (silica) eluting with 9:1 v/v chloroform-methanol, yielded the major isomer (26a) (150mg, 39% recovery) as colourless prisms from ether-methanol, m.p. 115-117°C (Found: C, 71.60; H, 5.46; N, 12.51. $C_{20}H_{19}N_3$ requires C, 72.05; H, 5.74; N, 12.61%); ν_{max} 3295, 1705, 1591, 1496, 1373, 1178, 758 and 691 cm^{-1}; m/z(%), 333 (M^+, 78), 318(100), 290(11), 160(16), 145(25), 143(30), 117(18) and 93(47); δ 8.53 and 7.53 (2 x m, 2H, pyr H), 7.33 (m, 7H, ArH), 4.99 (d, 1H, H_A, J_{AB} 8.9Hz), 3.81 (t, 1H, H_B), 3.52 (dd, 1H, H_C), 3.37 (dd, 1H, H_D), 2.62 (br s, 1H, NH), 1.16 (m, 1H, cyclopropyl H), and 0.66 and 0.48 (2 x m, 4H, cyclopropyl H).

2,2-Dicyclopropyl-4-(2-pyridyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (26b). Prepared in an analogous manner to the above from dicyclopropylglycine[30], 2-pyridine carboxaldehyde and NPM. The crude product was a pale yellow gum (100%) whose p.m.r. spectrum showed it to comprise an 85:15 mixture of (26b) and (27b). Trituration with ether-petroleum ether yielded the pure (26b) (360mg, 72%) which crystallised as colourless prisms from methanol, m.p. 181-183°C (Found: C, 73.95; H, 6.15; N, 11.20. $C_{23}H_{23}N_3O_2$ requires C, 73.97; H, 6.21; N, 11.25%); ν_{max} 3315, 1702, 1587, 1497, 1370, 1186, 861, 756, 640 and 622 cm^{-1}; m/z(%) 373 (M^+, 3), 333(37), 332(100), 200(24), 159(12), 117(10), 93(10); δ 8.55 and 7.64 (2 x m, 2 x 1H, pyr H), 7.33 (m, 7H, ArH), 5.05 (d, 1H_A, J_{AB} 7.8Hz), 3.74 (t, 1H, H_B), 3.15 (d, 1H H_C), 2.07 (br s, 1H, NH), 1.27 (m, 2H, cyclopropyl H), and 0.54 (m, 8H, cyclopropyl H).

2-Cyclopropyl-4-(2-pyridyl)-2,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (26c). Prepared in an analogous manner to the above from cyclopropyl phenylglycine, 2-pyridine carboxaldehyde and NPM. The crude product was a pale yellow gum (100%) whose p.m.r. spectrum showed it to comprise a 92:8 mixture of (26c) and (27c). Trituration with ether-petroleum ether yielded pure (26c) (410mg, 78%) which crystallised as colourless prisms from ethanol, m.p. 203-204°C (Found: C, 76.02: H, 5.87; N, 10.51. $C_{26}H_{23}N_3O_2$ requires C, 76.26; H, 5.66; N, 10.26%); ν_{max} 3285, 1715, 1489, 1375, 1268, 1100, 857, 738 and 690 cm^{-1}; m/z(%) 409 (M^+, 3), 369(26), 368(100), 236(32), 235(22), 221(17), 195(18), 117(24); δ 8.59-6.88 (m, 14H, ArH), 5.23 (d, 1H, H_A, J_{AB} 7.9Hz), 3.87 (t, 1H, H_B), 3.44 (d. 1H. H_C). 3.30 (br s, 1H, NH), 1.43 (m, 1H, cyclopropyl H) and 0.72 and 0.55 (2 x m, 4H, cyclopropyl H).

2-Cyclopropyl-2-methyl-4-(2-pyridyl)-7-phenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0] octane (26d) and (27d). Prepared in an analogous manner to the above from cyclopropylalanine, 2-pyridine carboxaldehyde and NPM. The crude product was a pale yellow gum whose p.m.r. spectrum showed it to comprise a 1.2:1 mixture of (26d) and (27d) together with minor amounts of two other isomers. Preparative t.l.c. (silica) eluting with 9:1 v/v chloroform-methanol yielded pure samples of the major isomers (26d, 150mg, 33% recovery)) and (27d, 110mg, 24% recovery).

(26d) Colourless prisms from chloroform, m.p. 146°C (Found: C, 72.42; H, 6.09; N, 12.00. $C_{21}H_{21}N_3O_2$ requires C, 72.60; H, 6.09; N, 12.10%); ν_{max} 3290, 1705, 1591, 1379, 1168, 817, 769 and 595 cm^{-1}; m/z(%) 347 (M^+, 8), 332(44), 306(96), 174(100), 139(44), 133(43), 117(34), 93(23) and 80(21); δ 8.54 and 7.68 (2 x m, 2H, pyr H), 7.30 (m, 7H, ArH), 4.99 (d, 1H, H_A, J_{AB} 8.4Hz), 3.74 (t, 1H, H_B), 3.07 (d, 1H, H_C), 2.29 (br s, 1H, NH), 1.46 (s, 3H, Me), 1.18 (m, 1H, cyclopropyl H), and 0.59 and 0.45 (2 x m, 4H, cyclopropyl H).

(27d) Colourless prisms from chloroform, m.p. 179-180°C; δ 8.54 and 7.70 (2 x m, 2H, pyr H), 7.31 (m, 7H, ArH), 4.98 (d, 1H, H_A, J_{AB} 8.0Hz), 3.85 (t, 1H, H_B), 3.29 (d, 1H, H_C), 2.33 (br s, 1H, NH), 1.47 (s, 3H, Me), 1.44 (m,1H,cyclopropyl H) and 0.58 (m, 4H, cyclopropyl H).

2,4-Dicyclopropyl-2,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane (31) and (32) A solution of cyclopropylphenylglycine (250mg, 1.28mmol), cyclopropane carboxaldehyde (180mg, 2.56mmol) and NPM (220mg, 1.28mmol) was boiled under reflux in acetonitrile (20ml) for 2h. Removal of the solvent left a pale yellow gum whose p.m.r. spectrum showed it to comprise a 1.27:1 mixture (100%) of (31) and (32). Trituration with ether-petroleum ether and cooling overnight produced colourless prisms of (31) (210mg, 45%). The mother liquor was evaporated and the resulting gum extracted with ether to yield a semi-solid (0.12g, 25%) which comprised 90% (32) contaminated with (31) and was not purified further.(31) m.p. 146-148°C (Found: C, 77.60; H, 6.64; N, 7.37. $C_{24}H_{24}N_2O_2$ requires C, 77.39; H, 6.50; N, 7.52%); $\nu_{max.}$3315, 1710, 1494, 1383, 1200, 1020, 860, 752, 690 and 624 cm^{-1}; m/z(%), 372 (M^+, 2), 331(100), 199(10), 184(10), 74(12), 59(19); δ (C_6D_6) 8.22 (m, 2H, ArH), 7.72-7.34 (m, 8H, ArH), 3.21 (dd, H_A, J 7.1 and 8.5Hz), 3.05 (t, 1H, H_B), 2.86 (d, 1H, H_C, J_{BC} 7.8Hz), 1.82 (m, 1H), 1.78 (br s, 1H, NH), and 1.25-0.35 (m, 9H, cyclopropyl H).
(32) δ (C_6D_6) 8.19 (m, 2H, ArH), 7.95 (m, 2H, ArH), 7.70-7.44 (m, 6H, ArH), 3.85 (d, 1H, H_C, J_{CB} 9.8Hz), 3.47 (dd, 1H, H_A, J 4.7 and 9.8Hz), 3.08 (dd, 1H, H_B), 1.67 (br s, 1H, NH), 1.57 (m, 1H) and 1.28-0.43 (m, 9H, cyclopropyl H).
Cycloadduct (33) A mixture of 4-cyclopropyl-2-(2-pyridyl)-7-phenyl-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-r-2-carboxylic acid (250mg, 0.66mmol), 2-pyridine carboxaldehyde (70mg, 0.66mmol) and NPM (120mg, 0.66mmol) was heated in DMF (15ml) at 120°C for 2h. The resulting dark brown solution was poured onto crushed ice (20ml) and stirred for 1h. The dark brown precipitate was filtered and dried and showed by p.m.r. to comprise mainly the cycloadduct (33) (240mg, 61%). The mother liquor was evaporated to give a black tar whose p.m.r. spectrum showed it to comprise mainly the cycloadduct (33), together with some uncharacterised degradation by-products. The crude precipitate crystallised from chloroform-ether as colourless prisms, m.p. 251-254°C (Found: C, 72.20; H, 4.89; N, 11.74. $C_{36}H_{29}N_5O_4$ requires C, 72.59; H, 4.91; H, 11.76%); $\nu_{max.}$1705, 1583, 1491, 1380, 1194, 1177, 835, 747, 732, 689 and 622 cm^{-1}; m/z(%) 595 (M^+, 100), 554(11), 344(43), 331(62), 264(61), 211(29), 173(47), 157(20), 132(38), 117(63); δ (pyridine-d_5) 8.06 (m, 2H, ArH), 7.49 (m, 2H, ArH), 7.21-6.84 (m, 12H, ArH), 6.46 (m, 2H, ArH), 5.49 (d, 1H, H_E, J_{EG} 9.4Hz), 5.09 (d, 1H, H_A, J_{AC} 9.7Hz), 5.03 (d, 1H, H_F, J_{FG} 8.9Hz), 3.89 (t, 1H, H_G, J 9.1Hz), 3.78 (dd, 1H, H_C, J_{CB} 8.3Hz), 3.01 (d, 1H, H_B), 1.24 (m, 1H, cyclopropyl H), and 0.66-0.34 (m, 4H, cyclopropyl H). NOEDS(%) ($CDCl_3$) irradiation of H_A effects enhancement of the signals for H_B (12) and the cyclopropyl group (5); irradiation of H_C enhances H_B (9) and the cyclopropyl group (5); NOEDS(%) [$^2H_5$]-pyridine irradiation of H_D enhances the signal for H_E (18) and irradiation of H_F enhances H_E (12).

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