X=Y–ZH Systems as Potential 1,3-Dipoles. Part 7.† Stereochemistry of the Cycloaddition of Imines of α-Amino Acid Esters to Fumarate and Maleate Esters

Ronald Grigg,* James Kemp, and William J. Warnock
Department of Chemistry, Queen's University, Belfast BT9 5AG, Northern Ireland

Aryl imines of α-amino acid esters undergo 1,3-dipolar cycloadditions with maleate and fumarate esters in quantitative yield when heated in boiling toluene to give mixtures of mainly two pyrrolidines. The major isomer in each case arises from cycloaddition *via* an *endo*-transition state to the same kinetically formed dipole. In aryl imines of methyl phenylglycinate the kinetic dipole undergoes partial stereomutation giving *ca.* 3:1 mixtures of cycloadducts derived from the kinetic dipole and the stereomutated dipole. Structural assignments are based on ^{1}H n.m.r. data including n.O.e. difference spectroscopy.

X=Y–ZH Systems may be divided into four classes (Scheme) 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).[2] We have proposed that a formal 1,2-H shift (**1**) ⇌ (**2**) in X=Y–ZH systems in which the central Y atom possesses a lone pair (types II—IV) should provide a new general method for generating 1,3-dipolar species. The importance of the concept of a formal 1,2-H shift (**1**) ⇌ (**2**) and its synthetic realisation is two-fold. Firstly, it introduces a new and mechanistically important general prototropic process and secondly the trapping of the 1,3-dipoles (**2**) with dipolarophiles provides a facile entry into a wide range of heterocycles including bridged-, fused-, and spiro-ring systems.[2–5] To date we have provided examples of cycloadditions involving imines (type II),[2–5] hydrazones (type III),[6] and oximes (type III),[7] and have emphasised the possible importance of such prototropic processes in biochemical processes mediated by pyridoxal enzymes,[8] and in the racemisation of α-amino acids in the presence of catalytic amounts of aldehydes.[9]

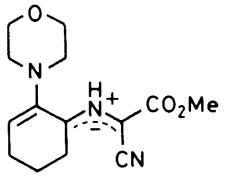
Type				No. of atoms with one pairs
I	X=Y–ZH			0
II	Ẍ=Y–ZH	X=Ÿ–ZH	X=Y–Z̈H	1
III	Ẍ=Ÿ–ZH	X=Ÿ–Z̈H	Ẍ=Y–Z̈H	2
IV	Ẍ=Ÿ–Z̈H			3

Scheme.

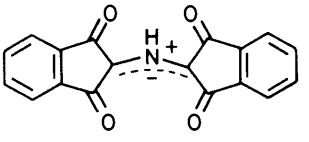
X=Ÿ–ZH ⇌ X=Y̊⁺–Z̄ (H)

(**1**) (**2**)

Prior to our own work dipoles (**2**) bearing a proton on the central Y atom were rare. Such species have been generated in 1,3-dipolar cycloreversions[10] involving 2-oxa-7-azabicyclo-[2.2.1]heptan-3-ones,[11] pyrrolidines,[12] pyrazolidines,[13] and imidazolidines.[14] One well characterised example (**3**)[15] of the dipole (**2**), generated by a formal 1,2-proton shift has recently come to our attention. However, the general nature of the process (**1**) ⇌ (**2**) was not perceived by these earlier workers. Recently we have characterised a second stable nitrogen-protonated azomethine ylide (**4**) and discussed its relevance to the mechanism of the ninhydrin reaction.[16] Analogues of (**2**), in which the proton is replaced by a metal ion, give rise to a family of metallo-1,3-dipoles.[17,18]

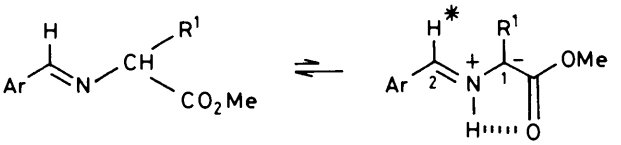


(**3**)



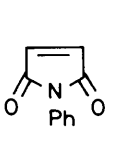
(**4**)

The characteristics of 1,3-dipolar cycloaddition reactions include their concerted nature, stereospecificity with respect to both 1,3-dipole and dipolarophile, and relative insensitivity to solvent polarity as measured by the polarity parameter E_T.[19] Firestone after several decades of arguing for a biradical mechanism for 1,3-dipolar cycloadditions has now conceded[20] the correctness of Huisgen's concerted mechanism.[21] This paper is concerned with our studies of the stereochemistry of cycloadditions involving *N*-protonated azomethine ylides generated by a formal 1,2-prototropic shift from aryl imines of α-amino acid esters (**5**) to maleate and fumarate esters. In cycloadditions of (**5**) with dipolarophiles we need to consider the stereochemistry of the process with respect to both the 1,3-dipole and the dipolarophile. Extensive studies of both inter-[2] and intra-[5] molecular cycloadditions of azomethine ylides generated from imines of type (**5**) have shown that (**6**) is the kinetically formed dipole rather than (**7**). When *N*-phenylmaleimide (**8**) is used as the dipolarophile kinetic studies show that dipole formation is

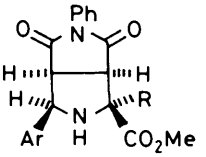


(**5**) a; R^1 = Me
b; R^1 = CH_2Ph
c; R^1 = Ph
d; R^1 = Pr^i
e; R^1 = Bu^t

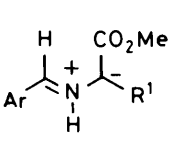
(**6**)



(**8**)



(**9**)



(**7**)

† Part 6, see ref. 18.

Table 1. Pyrrolidines (**10**) and (**11**) or (**12**) derived from cycloaddition of the imines (**5**) and maleate esters in toluene at 110 °C for 48 h

					N.m.r. chemical-shift data (δ, $CDCl_3$ + 1 drop D_2O)								
Ar	R	R^1	Isomer ratio[a] (**10**):(**11**) or (**12**)	Isomer	5-H	4-H	3-H	$J_{5,4}$ (Hz)	$J_{4,3}$ (Hz)	OMe			
2-Furyl	Ph	Me	3:1	(**10**)	4.6	3.35	3.85	9.0	7.8	3.8	3.7	3.4	
				(**12**)	4.85	3.75	4.30	10.0	7.6	3.74	3.42	3.36	
p-$MeOC_6H_4$	Ph	Me	2.7:1	(**10**)	4.45	3.42	3.9	8.8	8.0	3.85	3.8	3.7	3.17
				(**12**)	4.66	*	4.35	11.0	8.5	3.8	3.75	3.43	3.15
p-$NO_2C_6H_4$	Ph	Me	3:1	(**10**)	4.57	3.55	3.97	8.8	8.2	3.85	3.7	3.2	
				(**12**)	4.83	3.6	4.33	10.7	8.3	3.8	3.3	3.2	
Ph	Ph	Me	2.9 1	(**10**)	4.5	3.5	3.95	8.6	7.1	3.83	3.7	3.14	
				(**12**)	4.7	3.7	4.35	11.0	8.5	3.75	3.4	3.1	
Ph	Ph	Ph	3.4:1[b]	(**10**)	4.6	3.85	4.41	9.2	8.5	3.74			
				(**12**)	4.89	4.26	4.69	10.9	8.2	3.83			
Ph	CH_2Ph	Me	2.4:1	(**10**)	4.05	3.21	3.21	5.2	*	3.85	3.75	3.3	
				(**11**)	5.1	3.45	4.05	*	*	3.85	3.75	3.61	
Ph	Me	Me	4:1	(**10**)	4.6	3.44	3.3	5.9	7.1	3.8	3.75	3.25	
				(**11**)	4.96	3.29	3.87	9.7	7.9	3.8	3.72	3.62	
Ph	Me	Ph	2.8:1[c]	(**10**)	4.87	3.85	3.66	6.6	6.9	3.76			
				(**11**)	5.19	3.72	4.32	9.4	7.5	3.84			
p-$Me_2NC_6H_4$	CH_2Ph	Me	8:1	(**10**)	3.96	3.2	3.2	5.4	*	3.83	3.75	3.35	
				(**11**)	5.08	3.24	4.08	10.2	7.9	3.82	3.67	3.58	

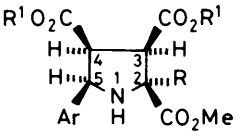
* Signals or coupling constants obscured by overlapping signals.
[a] Estimated from the n.m.r. spectra of the crude cycloaddition product. [b] Isomer (**10**) comprised the major product and no (**11**) was detected. As well as (**10**) and (**12**) there were three isomers derived from diphenyl fumarate (see text). [c] Four major isomers were formed, two of which were derived from diphenyl fumarate (see text). Trace amounts of two other isomers were detected.

rate determing,[22] *i.e.* the stereochemistry of the cycloadducts reflect the stereochemistry of the kinetically formed dipole. Thus (**5**) reacts with (**8**) *via* the dipole (**6**) in toluene at 110 °C to give (**9**) as the sole product *via* an *endo*-transition state.[2,3]

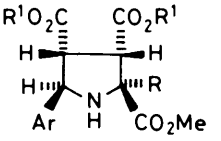
The imines (**5**) when heated with dimethyl maleate in boiling toluene for 48 h gave an essentially quantitative yield of a mixture of two major pyrrolidines (Table 1) which proved difficult to separate by preparative t.l.c. on silica. Similarly (**5**) and dimethyl fumarate gave two major pyrrolidine isomers (Table 2), again in essentially quantitative yield, which proved to be different from those derived from the reaction of (**5**) and dimethyl maleate. These cycloadditions, assuming the stereochemical integrity of the dipolarophile is maintained, could conceivably each give rise to a mixture of four diastereoisomers (**10**)—(**13**) from dimethyl maleate and (**14**)—(**17**) from dimethyl fumarate.

However, cycloadditions of (**5a**) and (**5b**) were found to give rise to adducts derived solely from the kinetic dipoles (**6a**) and (**6b**) whilst (**5c**) gave rise to adducts derived from both (**6c**) and (**7c**) with a predominance of adducts derived from (**6c**). The major part of the studies reported herein was completed prior to 1980 using a Bruker 90 MHz n.m.r. spectrometer, and structural assignments for this phase of the work are based on (i) chemical-shift arguments and (ii) on chemically relating maleate adducts to maleic anhydride adducts.[23,24] A number of cycloadditions using diphenyl maleate, diphenyl fumarate, and fumaronitrile were carried out recently and in these cases structural assignments are based on n.O.e. difference spectra obtained using Bruker 250 and 400 MHz spectrometers. The cycloadducts are configurationally stable under the reaction conditions as shown by the appropriate blank experiments and by an n.m.r. study of the reaction of (**5c**; Ar = Ph) with diphenyl fumarate which showed that the stereoisomeric pyrrolidines are formed concurrently and that their ratio remains unchanged throughout the reaction.

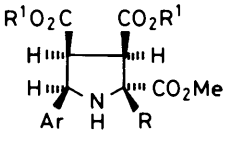
Structural Assignments for Maleate Cycloadducts.—The major isomers are assigned configuration (**10**) on the basis of their ^1H n.m.r. spectra. One methoxycarbonyl methyl resonance occurs at highfield, the extent of shielding being dependent on the nature of the Ar group at C5, *e.g.* (CO_2Me) *ca.* 3.1—3.2 when Ar = Ph and *ca.* 3.4 when Ar = 2-furyl (Table 1).



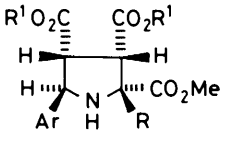
(**10**)



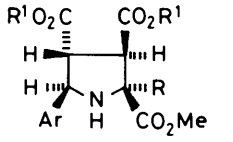
(**11**)



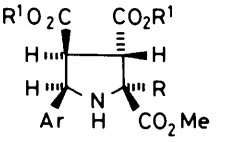
(**12**)



(**13**)



(**14**)



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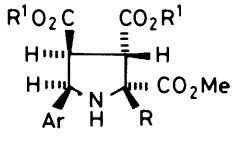
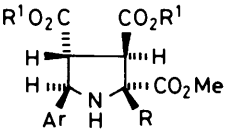
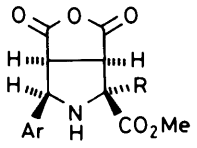


(**16**)



(**17**)

Assuming that the shielding of the ester methyl group by a *cis*-5-aryl substituent is in the order 4-CO_2Me > 3-CO_2Me, the OMe signal at lowest δ is assigned to the 4-ester group. Treatment of the maleic anhydride adducts (**18a—e**), prepared from imines (**5**) and maleic anhydride[23] in toluene at 110 °C, with methanolic hydrogen chloride followed by basic work-up gave (**10a—e**) as single diastereoisomers. These pyrrolidines



(**18**) a; Ar = Ph, R = Me
b; Ar = Ph, R = CH_2Ph
c; Ar = R = Ph
d; Ar = 2-furyl, R = Me
e; Ar = 2-furyl, R = Ph

were identical in all respects with the major isomers obtained from the reaction of (**5**) with dimethyl maleate. The stereochemistry of (**18a—e**) is assigned by analogy with the corresponding *N*-phenylmaleimide adducts[2,23] which, in turn, is based on an *X*-ray structure determination.[24] The stereochemistry of the major isomers from the reactions of (**5a**) and (**5c**) with diphenyl maleate was assigned by n.O.e. difference spectroscopy. Thus for (**10**; R = R^1 = Ph) irradiation ($CDCl_3$) of the signal for 3-H resulted in a 7% enhancement of the signal for 4-H, whilst irradiation of 4-H caused an enhancement in the signals of 3-H (8%) and 5-H (4%). Irradiation of the signal for 5-H effected an enhancement in the signals for 3-H (1%) and 4-H (10%). Analogously for (**10**; R = Me, R^1 = Ph), irradiation ($CDCl_3$) of the signal for 3-H effected enhancements in the signals for 4-H (8%), 5-H (9%), and 2-Me (4%) whilst irradiation of 4-H resulted in enhancement of 3-H (11%) and 5-H (7%). Similar enhancements were observed on irradiation of 5-H (3-H 6%, 4-H 14%, 2-Me 2%). and 2-Me (3-H 5%, 5-H 1%). Thus the major isomer arises from an *endo*-transition state as expected.

The minor isomers obtained from (**5c**) and maleate esters are assigned structure (**12**) based on their ^1H n.m.r. spectra. Two ester methyl signals occur at highfield, indicating that 2-Ph is *cis* to 3-CO_2Me and 5-aryl is *cis* to 4-CO_2Me. The 4-ester methyl is shielded to a greater extent than 3-CO_2Me as shown by a change in the 5-substituent from 2-furyl to phenyl (Table 1). Assignment of the minor maleate isomer (**12**; R = R^1 = Ph) arising from the reaction of (**5c**) with diphenyl maleate was made by n.O.e. difference spectroscopy. Thus irradiation ($CDCl_3$) of the signal for 3-H effected an enhancement in the signal for 4-H (11%) whilst irradiation of 4-H resulted in an enhancement of 3-H (13%) and 5-H (9%). When 5-H was irradiated the signal for 4-H was enhanced (17%). Thus the minor isomer from (**5c**) and maleate esters arises not from the kinetic dipole (**6c**) but from (**7c**). Dipole stereomutation (**6c**) ⇌ (**7c**) is a consequence of both the lower reactivity of maleate compared to *N*-substituted maleimides [which give adducts derived from (**6c**)] and the presence of two aryl substituents at the terminii of the azomethine ylide. The reduced dipolarophile reactivity results in a change of the rate determining step from dipole formation to the cycloaddition step,[5] whilst the two terminal aryl substituents lower the barrier to stereomutation in two ways: (i) by partial delocalisation of charge over the aryl rings with concomitant reduction of the C–N–C bond order in (**6**) and (ii) by steric interaction of the R^1(Ph) group with the imine hydrogen atom H*.

The minor isomers obtained from (**5a**) and (**5b**) and maleate esters are assigned structure (**11**) and arise from the kinetically formed dipole (**6**) *via* an *exo*-transition state. The structures of the dimethyl maleate adducts are assigned from their ^1H n.m.r. spectra which do not exhibit highfield OMe signals indicating that the *cis*-3/4 ester groups bear a *trans* relationship to the 5-phenyl group. Both (**11**) and (**13**) satisfy this condition but 3-H is deshielded relative to the chemical shift of the equivalent proton of (**10**) from which it is deduced that the 2-ester and 3-H bear a *cis*-relationship. The structure of the maleate isomer (**11**; Ar = R^1 = Ph, R = Me) from (**5a**) and diphenyl maleate was assigned by n.O.e. difference spectroscopy. Thus irradiation ($CDCl_3$) of 3-H effected a 15% enhancement in the signal for 4-H, whilst irradiation of 4-H resulted in enhancements of 3-H (16%) and 5-H (4%). Irradiation of the signal for 5-H caused very small enhancements of 3-H (1%) and 4-H (2%) whilst irradiation of 2-Me resulted in small enhancements of the signals for 3-H (2%) and 5-H (1%).

The reactions of (**5a**; Ar = Ph) and (**5c**; Ar = Ph) with diphenyl maleate were analysed with the aid of 250 and 400 Mz ^1H n.m.r. spectra. The increased sensitivity of the n.m.r. analyses revealed the presence of adducts of diphenyl fumarate. Thus (**5a**; Ar = Ph) gave a 5:2.4:1.8:1 mixture of (**10**), (**14**), (**11**), and (**15**) (R = Me, R^1 = Ph) together with traces (1—2%) of two other isomers, whilst (**5c**) gave a 19:5.7:5:2.3:1 mixture of (**10**), (**12**), (**14**), (**17**), and (**16**) (R = R^1 = Ph). It seems likely, therefore, that all the reactions summarised in Table 1 also give rise to some fumarate adducts. The assignment of stereochemistry to the fumarate adducts is discussed below. The occurrence of fumarate cycloadducts from cycloadditions involving maleate esters could be construed as evidence for a non-concerted (two step) mechanism for the cycloaddition. However, the facile base-catalysed conversion of maleate esters into fumarate esters is a well known process[25] and is undoubtedly responsible for the formation of fumarate adducts in the cases discussed above.

Structural Assignments for Fumarate Cycloadducts.—The major isomers from (**5a—c**) and fumarate esters are assigned structure (**14**) on the basis of their ^1H n.m.r. spectra. In particular, no highfield ester methyl resonances are observed indicating that the 4-CO_2Me and 5-aryl substituents are mutually *trans*. The pyrrolidine (**10**; Ar = *p*-$MeOC_6H_4$, R = Ph, R^1 = Me) is epimerised to (**14**; Ar = *p*-$MeOC_6H_4$, R = Ph, R^1 = Me) by 1 equiv. of benzyltrimethylammonium methoxide at room temperature. Under these conditions only epimerisation of the 4-CO_2Me group was observed. This establishes that (**10**) and (**14**) have the same relative configuration of the 2- and 5-substituents. The 3-H signal (Table 2) for the major fumarate adduct derived from (**5a**) and (**5b**) is not deshielded, indicating that it bears a *cis*-relationship to the 2-methyl or -benzyl substituent respectively. Finally, the structure of the major adduct from (**5a**; Ar = Ph) and (**5c**; Ar = Ph) and diphenyl fumarate was established as (**14**; Ar = R^1 = Ph, R = Ph or Me) by n.O.e. difference spectroscopy. Thus for (**14**; Ar = R = R^1 = Ph) irradiation ($CDCl_3$) of the signal for 3-H resulted in enhancement of 4-H (6%) and 5-H (2%), whilst irradiation of 4-H effected enhancement of 3-H (3%) and 5-H (7%). When 5-H was irradiated there was a 6% enhancement of the signal of 4-H but no enhancement of the signal for 3-H. This isomer was identical with the major fumarate isomer obtained from (**5c**; Ar = Ph). A similar n.O.e. study was carried out on (**14**; Ar = R^1 = Ph, R = Me) but in this case the 2-Me substituent provides an additional useful stereochemical probe. Irradiation (C_6D_6) of 3-H effects enhancement of 4-H (4%), 5-H (6%), and 2-Me (4%) whilst irradiation of 4-H results in 3 and 2% enhancements of 3-H and 5-H respectively. Irradiation of 5-H results in enhancement of the signals for 3-H (8%) and 4-H (2%) whilst irradiation of the 2-Me group effects enhancement of 3-H (5%). This stereoisomer

Table 2. Pyrrolidines (**14**) and (**15**) or (**16**) derived from cycloaddition of the imines (**5**) and fumarate esters in toluene at 110 °C for 48 h

					N.m.r. chemical-shift data (δ, $CDCl_3$ + 1 drop D_2O)							
Ar	R	R^1	Isomer ratio[a] (**14**):(**15**) or (**16**)	Isomer	5-H	4-H	3-H	$J_{5,4}$ (Hz)	$J_{4,3}$ (Hz)	OMe		
2-Furyl	Ph	Me	3.1:1	(**14**)	4.55	3.7	4	*	*	3.75	3.6	3.55
				(**16**)	4.85	3.95	3.85	10.2	8.3	3.7	3.65	3.4
p-$MeOC_6H_4$	Ph	Me	3:1	(**14**)	4.25	3.35	4.1	9.3	8.5	3.75 (6 H),	3.6	3.5
				(**16**)	4.4	3.5	4.4	8.5	6.0	3.8 (6 H)	3.65	3.1
p-$NO_2C_6H_4$	Ph	Me	4:1	(**14**)	4.45	3.4	4.15	9.0	8.3	3.8	3.65	3.55
				(**16**)	4.6	3.6	4.4	*	*	3.85	3.7	3.15
Ph	Ph	Me	3:1	(**14**)	4.3	3.45	4.1	9.3	8.3	3.8	3.65	3.53
				(**16**)	4.4	3.55	3.35	9.0	5.9	3.83	3.64	3.12
Ph	Ph	Ph	9:2[b]	(**14**)	4.6	3.85	4.41	9.2	8.5	3.74		
				(**16**)	4.9	4.31	4.17	10.2	9.1	3.89		
Ph	CH_2Ph	Me	6:1	(**14**)	4.1	3.36	3.6	9.5	10.7	3.75	3.7	3.55
				(**15**)	4.9	*	*	10.2	*	3.8	3.53	3.17
Ph	Me	Me	2.3:1	(**14**)	4.5	3.5	3.45	6.8	*	3.7 (6 H)	3.6	
				(**15**)	4.85	3.8	4.0	8.5	9.3	3.85	3.7	3.15
Ph	Me	Ph	2.4:1	(**14**)	4.65	3.89	3.78	9.5	*	3.81		
				(**15**)	5.02	4.25	4.32	8.5	9.4	3.90		

[a] Estimated from the n.m.r. spectra of the crude cycloaddition product. [b] Mixture of four isomers in the ratio 9:2:2:1 was obtained, two of which are derived from dipole (**7b**). * Signals or coupling constants obscured by overlapping signals.

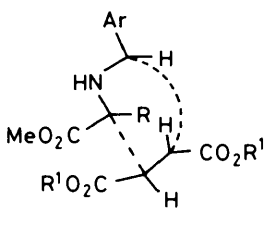
proved identical with the second most abundant pyrrolidine obtained from (**5a**; Ar = Ph) and diphenyl maleate.

A study of the ^1H n.m.r. spectra of the minor isomers obtained from (**5c**) and fumarate esters leads to the assignment of structure (**16**). One ester methyl resonance occurs at highfield (Table 2), thus excluding structures (**14**) and (**15**). It follows that the 5-aryl and 2-phenyl substituents are mutually *cis*. The similarity of chemical shifts for the 3-H's of (**12**) and the minor isomers derived from (**5c**) and fumarate esters suggest they have the same relative configuration of 2- and 3-substituents. However, the chemical shift (Table 2) for the shielded ester methyl resonance of (**16**; Ar = *p*-$MeOC_6H_4$, R = R^1 = Ph) (δ 3.1) indicates that the 4-ester and 5-aryl substituents are *cis*. Assignment of stereochemistry to cycloadduct (**16**; Ar = R = R^1 = Ph) is based on n.O.e. difference spectroscopy. Thus irradiation ($CDCl_3$) of 3-H effected very small enhancements in the signals for 4-H (1%) and 5-H (1%), whilst irradiation of 4-H resulted in enhancement of the signals for 3-H (2%) and 5-H (10%). When the signal for 5-H was irradiated the signals for 3-H (2%) and 4-H (20%) were enhanced. This isomer proved to be identical with the major fumarate isomer obtained from (**5c**) and diphenyl maleate.

Two further isomers were also formed in the reaction of (**5c**; Ar = Ph) with diphenyl fumarate and these are assigned structures (**17**) and (**15**) based on n.O.e. difference spectroscopy. Analogous isomers are probably also formed from (**5c**; Ar = 2-furyl, *p*-C_6H_4) but were undetected by the less sensitive 90 MHz n.m.r. analysis used in the early phase of this work. The ^1H n.m.r. spectrum of the crude reaction mixture from (**5c**; Ar = Ph) and diphenyl fumarate showed it to comprise a 9:2:2:1 mixture of (**14**), (**16**), (**17**), and (**15**). Further n.m.r. studies established that (**17**) and (**15**) were identical with the second most abundant and minor fumarate isomers respectively obtained from (**5c**; Ar = Ph) and diphenyl maleate. Thus n.O.e. difference spectra ($CDCl_3$) of (**17**; Ar = R = R^1 = Ph) showed that irradiation of 3-H effected enhancement of the signal for 4-H (3%) but not 5-H, whilst irradiation of the signal of 4-H resulted in enhancement of 3-H (6%) and 5-H (3%). Irradiation of 5-H effected enhancements in the signals for 3-H (7%) and 4-H (4%). Assignment of stereochemistry to (**15**; Ar = R = R^1 = Ph) was made in a similar fashion. Thus irradiation of 3-H effected a 5% enhancement in the signal for 4-H whilst irradiation of 4-H resulted in enhancement of the signals of 3-H (7%) and 5-H (12%). Irradiation of the signal for 5-H gave a strong enhancement (19%) of the signal for 4-H but had no effect on 3-H.

The minor isomers obtained from (**5a**) and (**5b**) and fumarate esters are assigned structure (**15**). Inspection of the ^1H n.m.r. spectra (Table 2) of the minor adducts from dimethyl fumarate reveals that one ester methyl resonance occurs at highfield suggesting that the 4-CO_2Me group and 5-aryl substituent are *cis*. 3-H Is deshielded relative to the chemical shift of the equivalent proton in (**10**; Ar = R^1 = Ph, R = Me) from which it is deduced that the 2-CO_2Me group and 3-H bear a *cis*-relationship. The structure of the minor isomer (**15**; Ar = R^1 = Ph, R = Me) from (**5a**) and diphenyl fumarate is assigned on the basis of n.O.e. difference spectroscopy. Irradiation (C_5D_5N) of 3-H produced a minor enhancement of 4-H (2%) but had no effect on 5-H and 2-Me. Irradiation of 4-H effected enhancement of the signals of 3-H (3%), 5-H (12%) and 2-Me (4%), whilst irradiation of 5-H effected a 16% enhancement of the signal for 4-H and a 2% enhancement of the 2-Me signal. This isomer proved identical with the minor isomer obtained from the reaction of (**5a**; Ar = Ph) and diphenyl maleate.

Stereoselectivity of the Cycloadditions.—The major cycloadducts (**14**) from the cycloaddition of imines (**5a**—**c**) and fumarate esters involves the kinetic dipole (**6**) and a transition state (**19**) involving an *endo* relationship between the dipole methoxycarbonyl group and one of the fumarate ester groups and *exo*-relationship between the dipole aryl group and the other fumarate ester group. The minor cycloadduct from dipoles (**6a**) and (**6b**) and fumarate esters arises *via* transition state (**20**) involving the reverse stereochemical relationships between dipole and dipolarophile substituents, *i.e.* ester/ester secondary orbital interactions are more stabilising and/or steric effects less than for ester/aryl interactions. Similar, but enhanced, preference is displayed in the cycloaddition (toluene, 110 °C, 48 h) of (**5a**) with fumaronitrile which affords a 6.9:1



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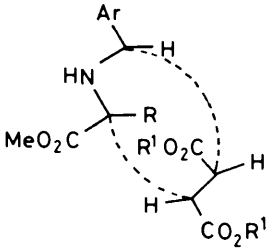
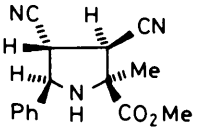
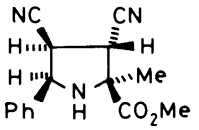


(20)

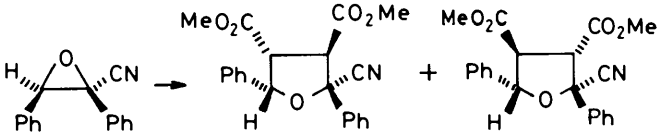
mixture of (**21**) and (**22**). This suggests nitrile/ester interactions are more favourable than nitrile/phenyl interactions. Stereochemical assignments for (**21**) and (**22**) are based on n.O.e. studies (see Experimental section). Huisgen[26] has reported the cycloaddition of the stilbene oxide (**23**) and dimethyl fumarate to give two adducts (**24**) and (**25**) in which the predominant



(21)

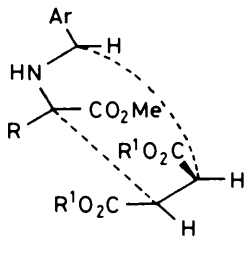


(22)

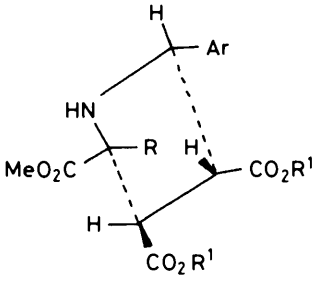


(23) (24) (25)

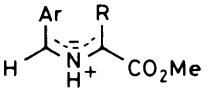
isomer (**25**) has *cis*-ester and -nitrile groups. Pyrrolidines derived from (**5a**) and (**5b**) and maleate esters arise *via* both *endo* (major)- and *exo* (minor)-transition states in contrast to cycloaddition of (**5a**) and (**5b**) to cyclic dipolarophiles (maleimides, maleic anhydride *etc.*) which give rise to single pyrrolidines *via* an *endo*-transition state.[23] The minor adduct (**12**) arising from (**5c**) and maleate esters is believed to involve the transition state (**26**) rather than (**27**) based on the usual tendency for *endo* selectivity and the steric preferences in the transition state for fumarate cycloadditions discussed above. This stereochemical result is good evidence for regiospecific



(26)



(27)

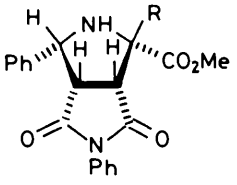


(28)

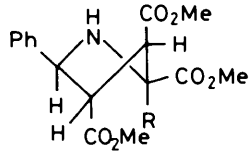
rotation about the C(1)–N bond in (**6c**) in dipole stereomutation rather than either rotation about the C(2)–N bond or competition between the two, *i.e.* (**28**) is not produced by dipole stereomutation.

Two further cycloadditions were investigated in attempts to probe the influence of steric effects on dipole stereomutation. The imine (**5d**; Ar = Ph) was heated in boiling toluene with diphenyl fumarate for 48 h and gave a 32:4:1 mixture of (**14**), (**15**), and the minor isomer (**16**) or (**17**) (Ar = R^1 = Ph, R = Pr^i). Structures of the two major isomers were assigned on the basis of n.O.e. difference spectroscopy but the data for the minor isomer is unreliable because of its low concentration. Thus the presence of the bulky isopropyl group in (**6d**) results in a few percent of stereomutated dipole (**7d**). The minor product arising from (**7d**) would have been expected to have structure (**16**), rather than (**17**), by analogy with the results from imine (**5c**) and is thus tentatively assigned structure (**16**). Attempts to effect the cycloaddition of (**5e**; Ar = Ph) and diphenyl maleate (toluene, 110 °C, 48 h) were unsuccessful. Hydrolysis and decomposition of the imine occurred but no cycloadduct was detected.

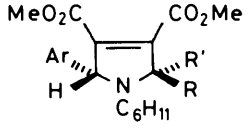
Trends in ^{1}H *N.m.r. Chemical Shifts of Maleate and Fumarate Cycloadducts.*—The n.m.r. spectra of the cycloadducts (**29**) of imines of α-amino acid esters and *N*-phenylmaleimide show apparent shielding of 5-H and deshielding of 3-H when R is changed from alkyl to phenyl.[23] Inspection of the chemical shifts of protons for the pyrrolidines in Tables 1 and 2 indicates that the former trend does not apply to the dimethyl maleate and fumarate adducts. This difference between the two series is probably due to conformational differences. Thus pyrrolidines bearing ester substituents at C-3 and C-4 are likely to adopt the 'half chair' conformation, *e.g.* (**30**) in solution[27] with maximum puckering occurring at C-3 and C-4. In (**29**) the envelope conformation should be favoured due to the conformational restrictions imposed by the additional fused five-membered ring. This leads to compression of the pseudo axial 2-Ph group and 5-H in (**29**), compared with the situation in (**30**), leading to shielding of 5-H in (**29**).



(29)



(30)



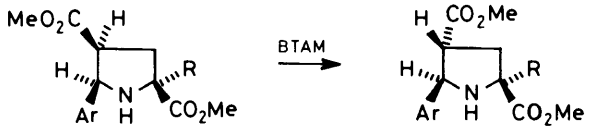
(31) a; R = H, R^1 = CO_2Me
b; R = CO_2Me, R^1 = H

The data presented in Tables 1 and 2 allow certain trends to be discerned. When the 3-H or 4-H is *trans* to an adjacent phenyl substituent located at C-2 or C-5 respectively it is deshielded relative to the case where the proton and phenyl group are *cis*. Husigen has made a similar observation on pyrrolidines derived from cycloadditions to aziridines.[28] 4-H and 5-H Are deshielded when *cis* to a pseudoaxial 2-ester [compare 4-H and 5-H in (**10**; Ar = 2-furyl, R = Ph, R^1 = Me) with (**12**; Ar = 2-furyl, R = Ph, R^1 = Me), Table 1], and shielded by a pseudoaxial 2-benzyl substituent [compare 4-H

and 5-H in (**10**; Ar = R = Ph, R^1 = Me) and (**10**; Ar = Ph, R = CH_2Ph, R^1 = Me)].

The deshielding of 5-H by a *cis*-2-ester is also apparent in pyrrolidines derived from cycloaddition of aziridines to dimethyl acetylenedicarboxylate, *e.g.* [(**31a**), 5-H δ 4.81 and (**31b**), 5-H δ 5.17].[29] The *cis*-vicinal relationship of the 3- or 4-ester substituents and 4-H or 3-H respectively may lead to a small deshielding of these protons [compare 4-H and 3-H in (**10**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me) (Table 1) with (**16**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me) (Table 2)].

In order to highlight potential pitfalls in stereochemical assignments based primarily on chemical-shift data, the stereochemical assignments of some of the pyrrolidines in Tables 1 and 2 are briefly discussed in the light of the above general trends. In the maleate adducts (**10**; R = Ph, R^1 = Me, Ar = 2-furyl, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$ or Ph) compared with (**12**; R = Ph, R^1 = Me, Ar = 2-furyl, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$ or Ph) 3-H occurs at lower field in (**12**) than in (**10**) (Table 1). In (**12**) the deshielding [*ca.* 1 p.p.m. for (**12**; Ar = R = Ph, R^1 = Me) relative to (**10**; Ar = Ph, R = R^1 = Me)] of 3-H is attributed to both the *cis*-2-ester and the *trans*-2-phenyl whereas deshielding of 3-H (*ca.* 0.65 p.p.m.) for (**10**; Ar = R = Ph, R^1 = Me) relative to (**10**; Ar = Ph, R = R^1 = Me) is attributed to the *cis*-2-phenyl substituent only. Comparison of the maleate adducts (**10**; R = Ph, R^1 = Me, Ar = 2-furyl, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$ or Ph) (Table 2) and analogous adducts lacking the 3-ester substituent[30] allows effects due to the 5-phenyl substituent to be identified. Thus in the pyrrolidines (**32**) and (**33**) which can be equilibrated by benzyltrimethylammonium methoxide (BTAM) the chemical shift of 4-H is *ca.* δ 3.3 in (**32**) and *ca.* δ 3.0 in (**33**). The chemical shift of 4-H in (**10**) (*ca.* δ 3.5) is consistent with this whereas the chemical shift 4-H in (**16**) (*ca.* δ 3.4) which is *trans* to the 5-phenyl group indicates deshielding of 4-H by the 2- and/or 4-ester substituents.



(**32**) (**33**)

Inspection of the chemical shifts for 3-H to 5-H for the minor fumarate adducts [(**16**) Table 2] derived from (**5c**) indicates that the assignment for (**16**; Ar = 2-furyl) appear anomalous. A similar situation exists for (**32**; Ar = 2-furyl). These anomalies presumably reflect the different steric requirements of the phenyl and furyl substituents and their effects on the conformational preferences of the pyrrolidines. The structure of the pyrrolidine (**16**; R = Ph, R^1 = Me, Ar = 2-furyl) (Table 2) was assigned by comparison of its ^{1}H n.m.r. with those of (**10**; Ar = 2-furyl, R = Ph, R^1 = Me) and (**12**; Ar = 2-furyl, R = Ph, R^1 = Me) (Table 1). The chemical shifts of 3-H in (**10**) and (**16**) (Ar = 2-furyl) are similar suggesting the relative configuration of the 2- and 3-substituents in the two isomers are the same, *i.e.* the 2- and 3-ester substituents are *cis*. The chemical shift of 5-H in (**12**) and (**16**) (Ar = 2-furyl) is the same suggesting that the 2-ester and 5-H are *cis*. 4-H In (**16**; Ar = 2-furyl) is deshielded with respect to the resonances of the equivalent protons in (**10**) and (**12**) (Ar = 2-furyl), indicating that 4-*H* in (*16*; Ar = 2-furyl) is deshielded by both the 2- and 3-ester substituents.

Experimental

General spectroscopic details were as previously noted.[2] 400 MHz N.m.r. spectra were obtained from the S.E.R.C. service at Warwick University. I.r. spectra were determined as Nujol mulls unless otherwise stated. Dimethyl fumarate was recrystallised from dichloromethane–light petroleum (b.p. 40—60 °C) prior to use. Diphenyl maleate and fumarate were prepared by literature methods.[31] Most imines were prepared by methods A and B as described previously.[2] Light petroleum refers to the fraction b.p. 40—60 °C.

Methyl N-2-*Furfurylidene(phenyl)glycinate*.—Prepared (87%) by method A,[2] the imine crystallised from ether–hexane as colourless prisms, m.p. 87—90 °C (Found: C, 69.3; H, 5.35; N, 5.8. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.7%); *m/z*(%) 243 (M^+, 1) and 184 (M − CO_2Me, 100); $\nu_{max.}$(KBr) 1 730 and 1 640 cm^{-1}; δ 8.2 (s, 1 H, CH=N), 7.5 (m, 6 H, ArH and furyl 5-H), 6.9 (d, 1 H, furyl 3-H), 6.5 (dd, 1 H, furyl 4-H), 4.75 (s, 1 H, CHPh), and 6.2 (s, 3 H, OMe).

Cycloaddition of Imines with Maleate Esters: General Procedure.—A solution of the imine (5 mmol) and maleate ester (5 mmol) in toluene (25 ml) was boiled and stirred under reflux for 48 h. Removal of the solvent afforded the crude product whose n.m.r. spectrum ($CDCl_3$) was used to estimate the isomer ratio. Yields were essentially quantitative as judged by n.m.r. Preparative t.l.c. or crystallisation followed by preparative t.l.c. was used to obtain pure samples of the stereoisomeric cycloadducts.

Trimethyl c-5-(2-*furyl*)-2-*phenylpyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = 2-furyl, R = Ph, R^1 = Me). This was the major isomer and was obtained by preparative t.l.c. [silica, 3:7 (v/v) ether–light petroleum] as colourless prisms (62%), m.p. 102—104 °C, from dichloromethane–light petroleum (Found: C, 61.45; H, 5.6; N, 3.9. $C_{20}H_{21}NO_7$ requires C, 62.0; H, 5.45; N, 3.6%); *m/z*(%) 387 (M^+, 0.5) and 328 (M − CO_2Me, 100); $\nu_{max.}$ 3 330 and 1 720 cm^{-1}; δ (see Table 1) 7.85 (m, 2 H, ArH), 7.4 (m, 4 H, ArH and furyl 5-H), and 6.35 (m, 2 H, furyl-H).

Trimethyl t-5-(2-*furyl*)-2-*phenylpyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**12**; Ar = 2-furyl, R = Ph, R^1 = Me). This was the minor isomer and formed colourless plates (20%), m.p. 91—93 °C, from ether–light petroleum at −20 °C (Found: C, 61.8; H, 5.75; N, 3.7. $C_{20}H_{21}NO_7$ requires C, 62.0; H, 5.45; N, 3.6%); $\nu_{max.}$(KBr) 3 385, 1 735, and 1 710 cm^{-1} δ (see Table 1) 7.2—7.7 (m, 6 H, ArH and furyl 5-H) and 6.6 (d, 1 H, furyl 3-H).

Trimethyl c-5-(4-*methoxyphenyl*)-2-*phenylpyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = *p*-$MeOC_6H_4$, R = Ph, R^1 = Me). This comprised the major product and was isolated as a pale yellow oil by preparative t.l.c. It crystallised from ether–light petroleum at −20 °C as off-white prisms (54%), m.p. 118—120 °C (Found: C, 65.1; H, 6.0; N, 2.95. $C_{23}H_{25}NO_7$ requires C, 64.6; H, 5.9; N, 3.25%); $\nu_{max.}$ 3 390, 1 730, and 1 710 cm^{-1}; δ (see Table 1) 7.9 (m, 2 H, ArH), 7.35 (m, 5 H, ArH), and 6.85 (d, 2 H, ArH).

Trimethyl t-5-(4-*methoxyphenyl*)-2-*phenylpyrrolidine*-r-2,t-3-,t-4-*tricarboxylate* (**12**; Ar = *p*-$MeOC_6H_4$, R^1 = Me). This minor isomer was obtained as colourless prisms (11%), m.p. 99—101 °C, from light petroleum at −20 °C; *m/z*(%) 427 (*M*, 0.5), 368 (M − CO_2Me, 32), and 223(100); $\nu_{max.}$ 3 400, 1 730, and 1 700 cm^{-1}; δ (see Table 1) 7.23—7.67 (m, 7 H, ArH) and 6.85 (d, 2 H, ArH).

Trimethyl c-5-(4-*nitrophenyl*)-2-*phenylpyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me). Preparative t.l.c. [silica, 1:1 (v/v) ether–light petroleum] followed by crystallisation from ether–light petroleum afforded this major isomer (50%) as pale yellow prisms, m.p. 110—112 °C (Found: C, 60.1; H, 5.35; N, 6.2. $C_{22}H_{22}N_2O_8$ requires C, 59.7; H, 5.0; N, 6.35%); $\nu_{max.}$ 3 360, 1 760, and 1 715 cm^{-1}; δ (see Table 1) 8.2 (d, 2 H, ArH), 7.85 (m, 2 H, ArH), 7.65 (d, 2 H, ArH), and 7.4 (m, 3 H, ArH).

Trimethyl t-5-(4-*nitrophenyl*)-2-*phenylpyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**12**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me). This minor isomer was obtained as pale yellow prisms (22%), m.p. 120—122 °C, from dichloromethane–light petroleum (Found: C, 60.35; H, 5.3; N, 6.1. $C_{22}H_{22}N_2O_8$ requires C, 59.7; H, 5.0; N, 6.35%); $\nu_{max.}$ 3 350 and 1 720 cm^{-1}; δ (see Table 1) 8.2 and 7.9 (2 × d, 2 × 2 H, ArH), and 7.7—7.2 (m, 5 H, ArH).

Trimethyl 2,c-5-*diphenylpyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = R = Ph, R^1 = Me). The crude cycloaddition product was a colourless oil which was subjected to preparative t.l.c. on silica eluting with 3:7 (v/v) ether–light petroleum. The major isomer was obtained as a colourless oil which crystallised from light petroleum at −20 °C as colourless prisms (60%), m.p. 100—102 °C (Found: C, 66.55; H, 5.8; N, 3.6. $C_{22}H_{23}NO_6$ requires 66.5; H, 5.85; N, 3.5%); *m*/*z*(%) 397 (M^+, 0.5) and 338 ($M - CO_2Me$, 100); $\nu_{max.}$ 3 360, 1 750, 1 720, and 1 700 cm^{-1}; δ (see Table 1) 7.9 (m, 2 H, ArH) and 7.3 (m, 8 H, ArH).

Trimethyl 2,t-5-*diphenylpyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**12**; Ar = R = Ph, R^1 = Me). This minor isomer was not isolated in pure form. Structural assignments are based on the ^1H n.m.r. spectrum of a sample contaminated with the major isomer (above); δ (see Table 1) 7.8 (m, 2 H, ArH) and 7.3 (m, 8 H, ArH).

Diphenyl r-2-*methoxycarbonyl*-2,c-5-*diphenylpyrrolidine*-c-3,c-4-*dicarboxylate* (**10**; Ar = R = R^1 = Ph). This major isomer (58%) crystallised on cooling the reaction mixture and was recrystallised from benzene to afford colourless prisms, m.p. 239—241 °C [Found (mixed isomers): C, 73.5; H, 5.35; N, 2.6. $C_{32}H_{27}NO_6$ requires C, 73.7; H, 5.2; N, 2.7%]; *m*/*z*(%) 463(35) and 462 ($M - CO_2Me$, 100); δ (see Table 1) 8.0—6.2 (m, 20 H, ArH).

Diphenyl r-2-*methoxycarbonyl* 2,t-5-*diphenylpyrrolidine*-t-3,t-4-*tricarboxylate* (**12**; Ar = R = R^1 = Ph). The mother liquor remaining from crystallisation of the major isomer (above) was evaporated to afford a yellow gum (42%) whose n.m.r. indicated it comprised a mixture of four additional pyrrolidines. This mixture was separated by preparative t.l.c. (silica, dichloromethane). Crystallisation from light petroleum afforded the *product* as colourless needles, m.p. 148—150 °C; *m*/*z*(%) 463(34) and 462 ($M - CO_2Me$, 100); δ (see Table 1) 7.77—6.2 (m, 20 H, ArH).

As well as the two maleate isomers (above), three fumarate isomers were also isolated by preparative t.l.c. N.m.r. analysis of total crude reaction product showed it to comprise 19:5.7:5:2.3:1 mixture of (**10**), (**12**), (**14**), (**17**), and (**16**) (R = R^1 = Ph).

Trimethyl 2-*benzyl*-c-5-*phenylpyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = Ph, R = CH_2Ph, R^1 = Me). Addition of ether to the gummy crude reaction product precipitated the minor isomer (below). Preparative t.l.c. (silica, ether–light petroleum) of the soluble fraction afforded the major isomer (68%) which crystallised from dichloromethane–light petroleum as colourless prisms, m.p. *ca.* 30 °C (hygroscopic) [Found (on mixed isomers): C, 67.25; H, 6.2; N, 3.25. $C_{23}H_{25}NO_6$ requires C, 67.15; H, 6.1; N, 3.4%]; *m*/*z*(%) 411 (M^+, 0.5), 352 ($M - CO_2Me$, 19) and 320 ($M - CH_2Ph$, 100); $\nu_{max.}$ 3 350, 1 750, 1 735, and 1 710 cm^{-1}; δ (see Table 1) 7.4 (m, 5 H, ArH), 7.3 (s, 5 H, ArH), and 3.2 [m, 4 H, CH_2Ph overlapping with 3-H and 4-H].

Trimethyl 2-*benzyl*-c-5-*phenylpyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**11**; Ar = Ph, R = CH_2Ph, R^1 = Me). This minor isomer crystallised from dichloromethane–light petroleum as colourless prisms (22%), m.p. 87—88 °C; $\nu_{max.}$ 3 390, 1 735, and 1 720 cm^{-1}; δ (see Table 1) 7.6—7.2 (m, 10 H, ArH) and 6.85 (dd, 2 H, CH_2Ph).

Trimethyl 2-*methyl*-c-5-*phenylpyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**10**; Ar = Ph, R = R^1 = Me). The crude product which comprised two compounds in the ratio 4:1 was a colourless oil (93%), b.p. 172 °C/0.2 mmHg. Separation of the two isomers by preparative t.l.c. proved difficult and resulted in low recoveries from the t.l.c. plates. The major isomer (35%) was a colourless oil (Found: C, 60.75; H, 6.45; N, 4.4. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2%); *m*/*z*(%) 335 (M^+, 0.2) and 276 ($M - CO_2Me$, 100); $\nu_{max.}$(film) 3 360, 1 750, and 1 730 cm^{-1}; δ (see Table 1) 7.3 (m, 5 H, ArH).

Trimethyl 2-*methyl*-c-5-*phenylpyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**11**; Ar = Ph, R = R^1 = Me). This minor isomer was obtained (6%) as a colourless oil by preparative t.l.c.; δ (see Table 1) 7.3 (m, 5 H, ArH).

Diphenyl 2-*methyl*-c-5-*phenyl*-r-2-*methoxycarbonylpyrrolidine*-c-3,c-4-*dicarboxylate* (**10**; Ar = R^1 = Ph, R = Me). The crude reaction product was a colourless semisolid (94%) whose n.m.r. spectrum indicated it comprised a 5:2.4:1.8:1:0.2:0.1 mixture of six pyrrolidines. Trituration with ether afforded a colourless solid which proved to be a mixture of the two major pyrrolidines. These were separated by fractional crystallisation from ethanol. The major isomer crystallised as colourless needles, m.p. 166—168 °C [Found (mixed isomers): C, 70.35; H, 5.35; N, 3.0. $C_{27}H_{25}NO_6$ requires C, 70.6; H, 5.5; N, 3.05%]; *m*/*z*(%) 459 (M^+, 0.5) and 400 ($M - CO_2Me$, 100); δ (see Table 1) 7.52—6.36 (m, 15 H, ArH) and 1.84 (s, 3 H, Me). The next most abundant pyrrolidine is the fumarate adduct (**14**; Ar = R^1 = Ph, R = Me) and this is discussed later.

Diphenyl, r-2-*methoxycarbonyl*-2-*methyl*-c-5-*phenylpyrrolidine*-t-3,t-4-*dicarboxylate* (**11**; Ar = R^1 = Ph, R = Me). The filtrate from the ether trituration (above) was evaporated to dryness and crystallised from ethanol to afford the *fumarate* adduct (**15**; Ar = R^1 = Ph, R = Me). Evaporation of the filtrate gave a brown gum which mainly comprised the *product* but could not be further purified; δ (see Table 1) 7.6—6.95 (m, 15 H, ArH) and 1.71 (s, 3 H, Me).

Trimethyl 2-*benzyl*-c-5-(4-N,N-*dimethylaminophenyl*)*pyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = *p*-$NMe_2C_6H_4$, R = CH_2Ph, R^1 = Me). Preparative t.l.c. afforded this major isomer (79%) as pale yellow prisms, m.p. 106—108 °C, from dichloromethane–light petroleum at −20 °C (Found: C, 66.45; H, 6.8; N, 6.25. $C_{25}H_{30}N_2O_6$ requires C, 66.05; H, 6.6; N, 6.2%); $\nu_{max.}$ 3 320, 1 740, and 1 725 cm^{-1}; δ (see Table 1) 7.74—7.4 (m, 5 H, ArH), 7.3 and 6.81 (2 × d, 2 × 2 H, ArH), 3.2 (m, 4 H, CH_2Ph overlapping with 3-H and 4-H), and 2.9 (s, 6 H, NMe_2).

Trimethyl 2-*benzyl*-c-5-(4-N,N-*dimethylaminophenyl*)*pyrrolidine*-r-2,t-3,t-4-*tricarboxylate* (**11**; Ar = *p*-$NMe_2C_6H_4$, R = CH_2Ph, R^1 = Me). This minor isomer was obtained as colourless prisms (9%), m.p. 133—136 °C, from ether–light petroleum at −20 °C (Found: C, 64.3; H, 6.5; N, 6.65. $C_{25}H_{30}N_2O_6$ requires C, 64.05; H, 6.6; N, 6.2%); $\nu_{max.}$ 3 410, 1 720, and 1 710 cm^{-1}; δ (see Table 1) 7.48 (m, 2 H, ArH), 7.35 (s, 5 H, ArH), 6.8 (m, 2 H, ArH), and 2.91 (s, 6 H, NMe_2).

Conversion of Maleic Anhydride Cycloadducts (**18**) *into Dimethyl Maleate Cycloadducts* (**10**) *General Procedure.*—Dry hydrogen chloride gas was passed into a solution of the maleic anhydride cycloadducts (**18a—e**) (500 mg)[23] in dry methanol (25 ml) with external cooling (ice-bath), until saturation occurred. The ice-bath was then removed and solution kept at room temperature for 12 h. Removal of the solvent under reduced pressure gave the pyrrolidine hydrochloride as a white solid, which was suspended in ether, treated with triethylamine (1 ml), and partitioned between water and ether. The ether extract was dried ($MgSO_4$) and the solvent removed to leave the dimethyl maleate adduct (**10**), identical with those described above. In this way the following was prepared: (**10**; Ar = Ph, R = R^1 = Me), 72%; (**10**; Ar = Ph, R = CH_2Ph, R^1 = Me), 87%; (**10**; Ar = R = Ph, R^1 = Me), 70%; (**10**; Ar = 2-furyl, R = Ph, R^1 = Me), 82%; (**10**; Ar = *p*-$MeOC_6H_4$, R = Ph,

R^1 = Me), 85%; (**10**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me), 88%.

Trimethyl c-5-(2-*furyl*)-2-*methylpyrrolidine*-r-2,c-3,c-4-*tricarboxylate* (**10**; Ar = 2-furyl, R = R^1 = Me). Prepared as described above from (**18d**), the product (400 mg, 69%) was obtained as a colourless oil, b.p. 138—142 °C/0.1 mmHg (Found: C, 55.55; H, 5.9; N, 4.3. $C_{15}H_{19}NO_7$ requires C, 55.4; H, 5.9; N, 4.3%); *m*/*z*(%) 325 (M^+, 0.7) and 266 (M − CO_2Me, 100); $\nu_{max.}$ 3 340, 1 750, and 1 720 cm^{-1}; δ ($CDCl_3$ + 1 drop D_2O) 7.35 (m, 1 H, furyl-H), 6.3 (m, 2 H, furyl-H) 4.6 (d, 1 H, 5-H, $J_{4,5}$ 6 Hz), 3.8, 3.75, and 3.5 (3 × s, 3 × OMe), 3.4 (dd, 1 H, 4-H), 3.2 (d, 1 H, 3-H, $J_{3,4}$ 6.3 Hz), and 2.65 (s, 3 H, Me).

Cycloaddition of Imines with Fumarate Esters.—The general procedure was as described for cycloadditions to maleate esters. Yields are essentially quantitative as judged by n.m.r. analysis of the crude product.

Trimethyl c-5-(2-*furyl*)-2-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**14**; Ar = 2-furyl, R = Ph, R^1 = Me). This major isomer was separated by preparative t.l.c. and obtained (62%) as colourless prisms, m.p. 97—100 °C, from ether at −20 °C (Found: C, 61.65; H, 5.7; N, 4.95. $C_{20}H_{21}NO_7$ requires C, 62.0; H, 5.45; N, 4.6%); *m*/*z*(%) 387 (M^+, 9) and 328 (M − CO_2Me, 100); $\nu_{max.}$ 3 290, 1 720, and 1 700 cm^{-1}; δ (see Table 2) 7.7 (m, 2 H, ArH), 7.3 (m, 4 H, ArH and furyl 5-H), and 6.35 (dd, 2 H, furyl H).

Trimethyl t-5-(2-*furyl*)-2-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**16**; Ar = 2-furyl, R = Ph, R^1 = Me). This minor isomer was separated by preparative t.l.c. and on crystallisation afforded (21%) colourless plates, m.p. 105—107 °C, from ether–light petroleum at −20 °C (Found: C, 62.25; H, 5.65; N, 4.35%); *m*/*z*(%) 387 (M^+, 5) and 328 (M − CO_2Me, 100); $\nu_{max.}$ 3 360 and 1 720 cm^{-1}; δ (Table 2) 7.7 (m, 2 H, ArH), 7.35 (m, 4 H, ArH and furyl 5-H), and 6.25 (dd, 2 H, furyl H).

Trimethyl c-5-(4-*methoxyphenyl*)-2-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**14**; Ar = *p*-$MeOC_6H_4$, R = Ph, R^1 = Me). This major isomer was separated by preparative t.l.c. and it crystallised as colourless prisms (58%) from ether–light petroleum, m.p. 60—62 °C (Found: C, 64.24; H, 6.1; N, 2.9. $C_{23}H_{25}NO_7$ requires C, 64.6; H, 5.9; N, 3.3%); $\nu_{max.}$ 3 290, 1 720, and 1 700 cm^{-1}; δ (see Table 2) 7.8 (m, 2 H, ArH), 7.4 (m, 3 H, ArH), and 3.1 (d, 2 H, ArH).

Trimethyl t-5-(4-*methoxyphenyl*)-2-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**16**; Ar = *p*-$MeOC_6H_4$, R = Ph, R^1 = Me). After separation by preparative t.l.c. and crystallisation from ether–light petroleum, the *product* (24%) was obtained as colourless prisms, m.p. 103—105 °C (Found: C, 64.55; H, 6.0; N, 3.2%); *m*/*z*(%) 368 (*M*-CO_2Me, 100); $\nu_{max.}$ 3 360, 1 735, 1 720, and 1 710 cm^{-1}; δ (see Table 2) 7.45 (m, 7 H, ArH) and 6.9 (d, 2 H, ArH).

Trimethyl c-5-(4-*nitrophenyl*)-2-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**14**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me). After separation by preparative t.l.c.; and crystallisation from dichloromethane–light petroleum at −20 °C, this major isomer was obtained as colourless prisms, m.p. 92—94 °C (Found: C, 59.8; H, 5.2; N, 5.75. $C_{22}H_{22}N_2O_8$ requires C, 59.7; H, 5.0; N, 6.35%); $\nu_{max.}$ 3 370, 1 710, and 1 700 cm^{-1}; δ (see Table 2) 8.2 (d, 2 H, ArH), 7.7 (m, 4 H, ArH), and 7.4 (m, 3 H, ArH).

Trimethyl t-5-(4-*nitrophenyl*)-2-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**16**; Ar = *p*-$NO_2C_6H_4$, R = Ph, R^1 = Me). This minor isomer was obtained (16%) as pale yellow prisms, m.p. 140—142 °C, from dichloromethane–light petroleum (Found: C, 59.5; H, 5.6; N, 6.45%); *m*/*z*(%) 442 (M^+, 0.5) and 383 (M − CO_2Me, 100); δ (see Table 2) 8.15 (dd, 4 H, ArH) and 7.5 (m, 5 H, ArH).

Trimethyl 2,c-5-*diphenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**14**; Ar = R = Ph, R^1 = Me). Preparative t.l.c. (silica, ether–light petroleum) separated the two isomers. This major isomer was obtained as colourless prisms (64%), m.p. 74—76 °C, from dichloromethane–light petroleum at −20 °C (Found: C, 66.45; H, 6.1; N, 3.75. $C_{22}H_{23}NO_6$ requires C, 66.5; H, 5.85; N, 3.5%); *m*/*z*(%) 338 (M − CO_2Me, 100); $\nu_{max.}$ 3 360 and 1 720 cm^{-1}; δ (see Table 2) 7.85 (m, 2 H, ArH) and 7.4 (m, 8 H, ArH).

Trimethyl 2,t-5-*diphenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**16**; Ar = R = Ph, R^1 = Me). This minor isomer was obtained as colourless prisms (19%) from light petroleum at −20 °C, m.p. 104—105 °C (Found: C, 66.65; H, 5.95; N, 3.25%); *m*/*z*(%) 338 (M − CO_2Me, 100); $\nu_{max.}$ 3 340, 1 720, and 1 700 cm^{-1}; δ (see Table 2) 7.5 (m, 10 H, ArH).

Diphenyl r-2-*methoxycarbonyl*-2,c-5-*diphenylpyrrolidine*-c-3,t-4-*dicarboxylate* (**14**; Ar = R = R^1 = Ph). The reaction product was a pale yellow gum (100%) whose n.m.r. spectrum showed it to comprise a 9:2:2:1 mixture of pyrrolidines (**14**), (**16**), (**17**), and (**15**) (Ar = R = R^1 = Ph). The bulk of this major isomer crystallised from ether as colourless prisms, m.p. 122—123 °C [Found (mixed isomers): C, 73.55; H, 5.15; N, 2.7. $C_{32}H_{27}NO_6$ requires C, 73.7; H, 5.2; N, 2.7%); *m*/*z*(%) 521 (M^+, 0.5) and 462 (M − CO_2Me, 100); δ (see Table 2) 7.91—6.82 (m, 20 H, ArH).

Diphenyl r-2-*methoxycarbonyl*-2,t-5-*diphenylpyrrolidine*-c-3,t-4-*dicarboxylate* (**16**; Ar = R = R^1 = Ph). The ether filtrate from the crystallisation of the major isomer (above) comprised a *ca.* 1:1:1:1 mixture of the four pyrrolidines (above) and was separated by h.p.l.c. (Partisil 10M9, mobile phase 6:4 dichloromethane–hexane, flow rate 6 ml/min). This minor isomer crystallised from dichloromethane–hexane as colourless rods, m.p. 153—155 °C; *m*/*z*(%) 521 (M^+, 0.5) and 462 (M − CO_2Me, 100); δ (see Table 2) 7.85—6.19 (m, 20 H, ArH).

Isomer (**17**; Ar = R = R^1 = Ph) crystallised from dichloromethane–hexane as colourless rods, m.p. 148—150 °C; *m*/*z*(%) 462 (M − CO_2Me, 100); δ 7.8—6.22 (m, 20 H, ArH), 4.82 [d, 1 H, 3-H, $J_{3,4}$ 5.2 Hz], 4.61 (d, 1 H, 5-H, $J_{4,5}$ 8.3 Hz), 3.9 (t, 1 H, 4-H), and 3.87 (s, 3 H, OMe).

Isomer (**15**; Ar = R = R^1 = Ph) could not be obtained pure despite further h.p.l.c., spectral data were thus obtained on a slightly impure sample; δ 7.76—7.38 (m, 20 H, ArH), 5.38 (d, 1 H, 5-H, $J_{4,5}$ 7.9 Hz), 4.9 (d, 1 H, 3-H, $J_{3,4}$ 6.7 Hz), 4.13 (t, 1 H, 4-H), and 3.81 (s, 3 H, OMe).

Trimethyl 2-*benzyl*-c-5-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**14**; Ar = Ph, R = CH_2Ph, R^1 = Me). The crude product (100%) was a colourless oil which on trituration with ether–light petroleum afforded the major isomer. Crystallisation from ether–light petroleum gave the *product* as fine colourless needles, m.p. 72—74 °C (Found: C, 66.65; H, 6.1; N, 3.05. $C_{23}H_{25}NO_6$ requires C, 67.15; H, 6.1; N, 3.4%); *m*/*z*(%) 411 (M^+, 1), 352 (M − CO_2Me, 15), and 320 (M − CH_2Ph, 100); $\nu_{max.}$(KBr) 3 340, 1 740, and 1 720 cm^{-1}; δ (see Table 2) 7.3 (s + m, 10 H, ArH) and 3.36 and 3.29 (2 × dd, 2 H, CH_2Ph).

Trimethyl 2-*methyl*-c-5-*phenylpyrrolidine*-r-2,c-3,t-4-*tricarboxylate* (**14**; Ar = Ph, R = R^1 = Me). A quantitative yield of a 2.3:1 mixture of two adducts was obtained. Preparative t.l.c. afforded the major isomer which crystallised from ether–light petroleum as colourless prisms, m.p. 78—81 °C [Found (mixed isomers): C, 60.95; H, 6.15; N, 4.1. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2%]; $\nu_{max.}$ 3 360, 1 735, 1 720, and 1 710 cm^{-1}; δ (see Table 2) 7.35 (m, 5 H, ArH) and 1.5 (s, 3 H, Me).

Trimethyl 2-*methyl*-c-5-*phenylpyrrolidine*-r-2,t-3,c-4-*tricarboxylate* (**15**; Ar = Ph, R = R^1 = Me). The minor isomer was not isolated in pure form and its structure was assigned on the basis of its ^1H n.m.r. admixed with some of the major isomer (above); δ (see Table 2) 7.4 (m, 5 H, ArH) and 1.4 (s, 3 H, Me).

Diphenyl r-2-*methoxycarbonyl*-2-*methyl*-c-5-*phenylpyrrolidine*-c-3,t-4-*dicarboxylate* (**14**; Ar = R^1 = Ph, R = Me). The crude product was a colourless solid (100%) whose n.m.r. indicated it comprised a 2.4:1 mixture of two cycloadducts,

which were separated by fractional crystallisation from ethanol. The major isomer crystallised as colourless plates, m.p. 139—141 °C [Found (mixed isomers): C, 70.6; H, 5.5; N, 3.05%]; *m/z*(%) 459 (*M*, 4) and 400 (*M* − CO_2Me, 100); δ (see Table 2) 7.53—6.87 (m, 15 H, ArH) and 1.85 (s, 3 H, Me).

Diphenyl r-2-*methoxycarbonyl*-2-*methyl*-c-5-*phenylpyrrolidine*-t-3,c-4-*dicarboxylate* (**15**; Ar = R^1 = Ph, R = Me). Obtained as colourless rods, m.p. 123—124 °C, from ethanol; *m/z*(%) 459 (M^+, 8), 400 (*M* − CO_2Me, 69), and 146 (100); δ (see Table 2) 7.51—6.25 (m, 15 H, ArH), 1.9 (br s, 1 H, NH), and 1.61 (s, 3 H, Me).

Diphenyl 2-*isopropyl*-r-2-*methoxycarbonyl*-c-5-*phenylpyrrolidine*-c-3,t-4-*dicarboxylate* (**14**; Ar = R^1 = Ph, R = Pr^i). The crude product (100%) was a thick brown oil whose n.m.r. spectrum indicated it comprised 32:4:1 mixture of three isomeric pyrrolidines. The mixture was separated by repeated (three times) preparative t.l.c. (silica, 7% ether in light petroleum). The major isomer (**14**; Ar = R^1 = Ph, R = Pr^i) was a colourless oil [Found (mixed isomers): C, 71.35; H, 5.8; N, 3.15. $C_{29}H_{29}NO_6$ requires C, 71.45; H, 6.0; N, 2.85%); *m/z*(%) (mixed isomers) 487 (M^+, 3), 444 (*M* − Pr^i, 100), and 428 (*M* − CO_2Me, 63); δ 7.55—6.75 (m, 15 H, ArH), 4.28 (d, 1 H, 5-H, $J_{4,5}$ 10.6 Hz), 3.97 (d, 1 H, 3-H, $J_{3,4}$ 11.8 Hz), 3.71 (s, 3 H, OMe), 3.57 (dd, 1 H, 4-H), 2.98 (br s, 1 H, NH), 2.55 (m, 1 H, C*H*Me_2), 1.17 (d, 3 H, CH*Me*), and 0.86 (d, 3 H, C*H*Me). Stereochemistry was assigned by n.O.e. difference spectroscopy ($CDCl_3$, 250 MHz). Thus irradiation of 3-H effected enhancements in the signals for 4-H (3%), 5-H (10%), C*H*Me_2 (5%), and CH*Me* (6%). Irradiation of 4-H enhanced the signals for 3-H (1%) and 5-H (2%). Irradiation of 5-H enhanced the signals for 3-H (7%) and 4-H (3%).

Diphenyl 2-*isopropyl*-r-2-*methoxycarbonyl*-c-5-*phenylpyrrolidine*-t-3,c-4-*dicarboxylate* (**15**; Ar = R^1 = Ph, R = Pr^i). This minor isomer could not be obtained pure and was characterised from a 4:1 mixture (pale brown gum) with the third trace isomer (below); δ 7.46—6.11 (m, 15 H, ArH), 4.97 (d, 1 H, 5-H), $J_{4,5}$ 10.4 Hz), 4.05 (d, 1 H, 3-H, $J_{3,4}$ 8.7 Hz), 3.96 (t, 1 H, 4-H), 3.74 (s, 3 H, OMe), 2.73 (m, 1 H, C*H*Me_2), 2.5 (br s, 1 H, NH), 1.33 (d, 3 H, CH*Me*), and 0.88 (d, 3 H, CH*Me*). Stereochemistry was assigned by n.O.e. difference spectroscopy (C_6D_6, 400 MHz). Irradiation of 3-H effected enhancements in the signals for 5-H (2%), C*H*Me_2 (2%) and CH*Me* (7%) whilst irradiation of 4-H resulted in enhancement of 3-H (1%), 5-H (9%) and CH*Me* (1%). Irradiation of 5-H caused enhancements in 3-H (1%) and 4-H (11%).

Isomer (**16**; Ar = R^1 = Ph, R = Pr^i). The ^1H n.m.r. spectrum of this isomer was deduced from the n.m.r. spectrum of its mixture with (**15**; Ar = R^1 = Ph, R = Pr^i) (above); δ (C_6D_6, 400 MHz) 7.72—6.78 (m, 15 H, ArH), 4.74 (d, 1 H, 5-H, $J_{4,5}$ 9.4 Hz), 4.58 (d, 1 H, 3-H, $J_{3,4}$ 8.7 Hz), 3.99 (dd, 1 H, 4-H), 3.38 (s, 3 H, OMe), 2.83 (m, 1 H, C*H*Me), 1.17 (d, 3 H, CH*Me*) and 0.98 (d, 3 H, CH*Me*). Note that this spectrum is also consistent with structure (**17**; Ar = R^1 = Ph, R = Pr^i).

Reaction of methyl N-*benzylidenealaninate with fumaronitrile.* The reaction was carried out in boiling toluene as described in the general procedure (above). The crude product was a colourless solid whose ^1H n.m.r. spectra indicated it comprised a 6.9:1 mixture of two pyrrolidines. Crystallisation from ethanol afforded the *major isomer* (**21**) as colourless needles, m.p. 143—144 °C (Found: C, 66.7; H, 5.55; N, 15.65. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.6; N, 15.6%); *m/z*(%) 269 (*M*, 0.2) and 210 (*M* − CO_2Me, 100); δ 7.49—7.35 (m, 5 H, ArH), 4.57 (d, 1 H, 5-H, $J_{4,5}$ 9.4 Hz), 3.89 (s, 3 H, OMe), 3.44 (dd, 1 H, 4-H), 3.3 (d, 1 H, 3-H, $J_{3,4}$ 10.3 Hz), 2.7 (br s, 1 H, NH), and 1.69 (s, 3 H, Me). Stereochemistry was assigned by n.O.e. difference spectroscopy (C_6D_6). Irradiation of the signal for 3-H effected enhancements in 4-H (5%), 5-H (6%), and the 2-Me group (4%), whilst irradiation of 4-H caused 2% enhancements in both 3-H and 5-H. Irradiation of 5-H resulted in enhancements in 3-H(5%) and 4-H (3%), and irradiation of the 2-Me group caused enhancement of 3-H (5%) and 5-H (1%).

Minor isomer (**22**). This isomer was not obtained pure but only as an enriched mixture containing isomer (**21**); δ 7.47—7.34 (m, 5 H, ArH), 4.82 (d, 1 H, 5-H, $J_{4,5}$ 6.7 Hz), 4.02 (d, 1 H, 3-H, $J_{3,4}$ 5.2 Hz), 3.89 (s, 3 H, OMe), 3.63 (dd, 1 H, 4-H), 2.5 (br s, 1 H, NH), and 1.71 (s, 3 H, Me). Stereochemistry was assigned based on n.O.e. difference spectroscopy ($CDCl_3$). Thus irradiation of 3-H effected enhancements in 4-H (3%), 5-H (2%), and 2-Me (1%), whilst irradiation of 4-H resulted in enhancements of 3-H (7%), 5-H (11%), and the 2-Me (1%). Irradiation of 5-H caused enhancement of 3-H (2%) and 4-H (16%), whilst irradiation of the 2-Me group resulted in enhancements of 3-H (2%), 4-H (1%), and 5-H (1%).

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