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Non-Decarboxylative 1,3-Dipolar Cycloadditions of Imines of α-Amino Acids as a Route to Proline Derivatives.

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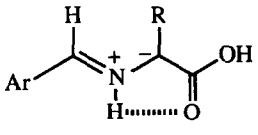
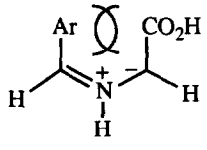
Abstract. *α–Amino acids react with aryl aldehydes in the presence of N-substituted maleimides to yield stereospecific cycloadducts (**3a,b**) and with dimethyl fumarate to give isomeric mixtures of (**4a-i**) and (**5a-i**). The relatively low yield in the case of dimethyl fumarate is presumably due to the steric interaction between the dipolarophile and the substituents at both ends of the dipole.*

Yamada et al[1] reported that heating α- amino acids with aryl aldehydes in acetic acid in sealed tubes leads to racemisation of α-amino acids via the 1, 3- dipole intermediate (**1**). Others have shown that such 1,3- dipoles may decarboxylate via a retro 1,3- dipolar cycloaddition process (Scheme)[2-5].



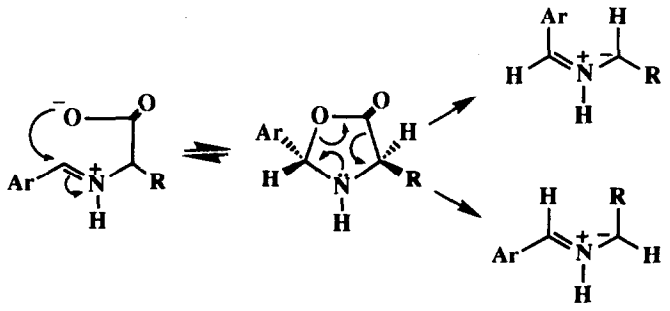
(1)



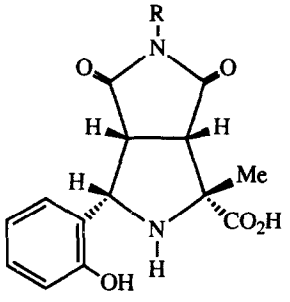
(2)

However, prior to that work, Grigg and his co-workers[6] in their extensive studies trapped the azomethine ylide (**1**) by heating a mixture of alanine, salicylaldehyde and N- phenylmaleimide in glacial acetic acid (110°C, 0.5 h) to give the corresponding cycloadduct (**3b**) in 88% yield. They noted that the acetic solvent suppresses the decarboxylation of the intermediate (**1**).

Aly et al[7,8] , showed that heating an equimolar mixture of alanine, salicylaldehyde and dimethyl fumarate in glacial acetic acid gave only 38% of the cycloadduct (**4a**) together with decomposition products. We now report that acidified methanol serves as a good solvent for such non-decarboxylative 1, 3- dipolar cycloaddition reactions. Thus, boiling a mixture of alanine, salicylaldehyde and N- substituted maleimides in methanol containing a few drops of glacial acetic acid for 2 hours gave stereospecific cycloadducts (**3a, b**) in 92 and 90% yield respectively. The stereochemistry of (**3a, b**) has been established on the basis of spectral data and by comparison with similar systems[6,7]. Interestingly, salicylaldehyde reacts with alanine in the presence of dimethyl fumarate (less reactive dipolarophile) to give a 1.4 : 1 mixture of two isomers (**4a**) and (**5a**) respectively in 66% combined yield.



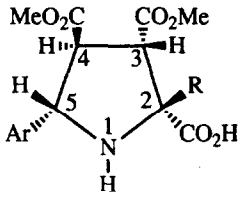
Scheme



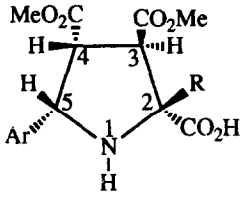
(3) a, R = CH_3
b, R = C_6H_5

The stereochemistry of the major isomer (**4a**) is established on the basis of n.O.e. data. Thus irradiating (C5D5N) 5-H results in enhancement of 4-H (4%) and a cross-ring enhancement of 3-H (9%), whilst irradiation of 4-H causes only 2% enhancement of 5-H. On the other hand irradiation of 3-H gives rise to only 3% enhancement of 4-H whereas it causes a cross- ring enhancement of 5-H (7%) together with an enhancement of 2-Me (4%). Finally, irradiation of 2-Me results in enhancement of 3-H (7%). The structure of the minor isomer is assigned in an analogous fashion based on n.O.e. experiments; thus irradiation (C_5D_5N) of 5-H causes enhancement of 4-H (16%) and gives a cross- ring enhancement of the 2- Me (4%). Irradiation of 4-H results in enhancement of 5-H (11%), 3-H (5%) and the 2-Me (2%). Irradiation of 3-H gives rise to a weak enhancement of 4-H (3%) and only 1% enhancement of the 2-Me. Finally irradiation of the 2-Me causes a cross- ring enhancement of 4-H (3%) and 5-H (2%), but only a 1% enhancement of 3-H. There is further supporting evidence based on chemical shift data. It is well documented that a pyrrolidine ring proton is shielded by a *cis* - vic- phenyl group but deshielded by a *trans* - vic- phenyl group[9]. Thus the 4-H signal in isomer (**5a**) (C_5D_5N, 4.47 ppm) is deshielded relative to the corresponding signal in the other isomer (**4a**) (C_5D_5N, 4.35 ppm); suggesting that 4-H and C(5) o- hydroxyphenyl group bear a *trans* - vic relationship in (**5a**). Moreover, the 3-H signal in (**5a**) (C_5D_5N, 4.93 ppm) is deshielded relative to the corresponding signal in (**4a**) (C_5D_5N, 3.95

ppm), suggesting that 3-H and the C(2)- carboxyl group bear a *cis* - vic relationship in (**5a**)[10,11]. A wide variety of α- amino acids (glycine, leucine, methionine, phenylalanine and tryptophan) react with salicylaldehyde and dimethyl fumarate to give analogous isomeric mixtures of cycloadducts (**4b-i**) and (**5b-i**) in 50- 70% combined yield. Alanine reacts in the same manner with other aryl aldehydes (benzaldehyde, 2-methoxybenzaldehyde and 2,4- dimethoxybenzaldehyde) in the presence of dimethyl fumarate to give the corresponding adducts.

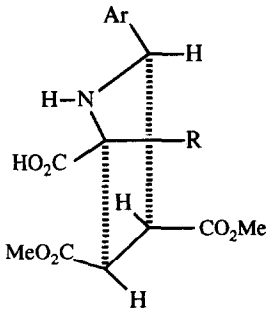


(4a-i)

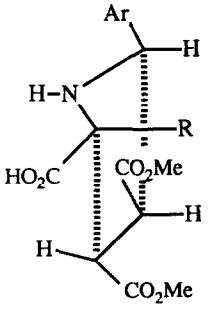


(5a-i)

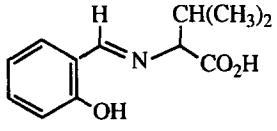
a. Ar = 2-OHC_6H_4, R = CH_3
b. Ar = 2-OHC_6H_4, R = H
c. Ar = 2-OHC_6H_4, R = $CH_2CH(CH_3)_2$
d. Ar = 2-OHC_6H_4, R = $(CH_2)_2SCH_3$
e. Ar = 2-OHC_6H_4, R = $CH_2C_6H_5$
f. Ar = 2-OHC_6H_4, R = CH_2-(3-indolyl)
g. Ar = C_6H_5, R = CH_3
h. Ar = 2-$OMeC_6H_4$, R = CH_3
i. Ar = 2,4-$(OMe)_2C_6H_3$, R = CH_3



(6)



(7)



(8)

Table. Cycloadducts from the reaction of α- amino acids with aromatic aldehydes and dimethyl fumarate[a].

Aldehyde	Amino Acid	Time(h)	Cycloadducts	Ratio (4):(5)[b]	Yield%[c]
Salicaldehyde	Alanine	2	**(4a)+(5a)**	1.40 : 1	66
Salicaldehyde	Glycine	3	**(4b)+(5b)**[d]	1 : 1.14	67
Salicaldehyde	Leucine	4	**(4c)+(5c)**	1.31 : 1	61
Salicaldehyde	Methionine	4	**(4d)+(5d)**	1.35 : 1	65
Salicaldehyde	Phenylalanine	4	**(4e)+(5e)**[d]	1.33 : 1	70
Salicaldehyde	Tryptophan	4	**(4f)+(5f)**[d]	1.20 : 1	66
Benzaldehyde	Alanine	20	**(4g)+(5g)**	1.21 : 1	50
2-MeO-Benzaldehyde	Alanine	20	**(4h)+(5h)**	1.31 : 1	66
2,4(MeO)2-Benzaldehyde	Alanine	20	**(4i)+(5i)**	1.27 : 1	68

a. All reactions are carried out in boiling acidified MeOH using a 1: 1: 1 molar ratio of amino acid, aromatic aldehyde and dimethyl fumarate.

b. The ratio of isolated isomers.

c. Isolated combined yield.

d. Calculated from the pmr spectrum of the reaction mixture.

The cycloadducts **(3a, b)** are obtained from the kinetically formed dipole **(1)** via an endo- transition state, whereas **(4a-i)** and **(5a-i)** arise from the same dipole via transition states **(6)** and **(7)** respectively. In the case of glycine the isomeric ratio is reversed. However, it is clear from the isomer ratios (Table) that the two transition states differ little in energy. The polarity of the solvent may, in part, affect the isomeric ratio, since similar reactions carried out in toluene gave a 6 : 1 mixture of cycloadducts analogous to **(4e)** and **(5e)** respectively[12]. Stereomutation of the kinetically formed dipole **(1)** to give the alternative dipole **(2)** is ruled out on both steric and electronic grounds[13]. When valine was used as the α-amino acid component, the cycloaddition did not take place but instead the Schiff's base **(8)** was obtained in 40% yield and unreacted valine was recovered. Steric hindrance by the iso- propyl group prevents cycloaddition under these conditions.

Experimental.

General Data. All the spectroscopic and elemental data were obtained at the University of Leeds. Proton nmr spectra were recorded at: (a) 300 MHz using a GE QE 300 instrument and (b) 400 MHz using a Bruker WP 400 instrument and deuteropyridine was used a solvent in all cases, the δ value is referenced to one of the deuteriopyridine signals (δ 8.71 ppm, br). Chemical shifts are given in ppm(δ); peaks are indicated by s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet), or br. (broad). Mass spectra were recorded at 70 eV using a VG-Autospec mass spectrometer. Accurate molecular weights were determined using perfluorokerosene as internal standard. Elemental analysis were performed using a Carlo Erba Elemental Analyser MOD 1106. Melting points (m.p.) were determined on a Kofler hot-stage apparatus and are uncorrected. The starting materials were commercially avaliable from either Aldrich or Lancaster Chemical Companies.

General procedure for preparing cycloadducts.

A mixture of aromatic aldehyde (10mmol), amino acid (10mmol) and dipolarophile (10mmol) in methanol (70ml) containing a few drops of acetic acid was heated under reflux for 2- 20 h.The amino acid went into solution and the major isomer (or the stereospecific adduct in the case of N- substituted maleimides derived products) came out of the hot solution as a colourless crystalline precipitate. The filtrate was evaporated under reduced pressure and the residue triturated with chloroform (50ml) to afford the minor isomer. The yields and the isomeric ratio are given in the Table. All the cycloadducts were crystallised from methanol except where otherwise noted.

4 (2/-Hydroxyphenyl)-2,7- dimethyl-6,8- dioxo-3,7- diazabicyclo(3.3.0) octane-2- carboxylic acid (3a) and 4- (2/-hydroxyphenyl)-2-methyl-6,8-dioxo-7-phenyl-3,7-diazabicyclo(3.3.0) octane-2-carboxylic acid (3b). Salicylaldehyde (1.22g, 10mmol), alanine (0.89g, 10mmol) and N-substituted maleimide (10mmol) were boiled in methanol (70ml) containing a few drops of acetic acid for 2h followed by work up as described above.

(3a) Crystallised from methanol as colourless cubes m.p. 252-254°C decomp. (Found: C, 57.05; H, 5.9; N, 8.35. $C_{15}H_{16}N_2O_5.CH_3OH$ requires C, 57.13; H, 5.99; N, 8.33%); Accurate mass(found: 304.106267. $C_{15}H_{16}N_2O_5$ requires 304.105922); m/z (%) 304 (15), 259 (33), 201 (100), 193 (62), 147 (72) and 106 (16); δ (C_5D_5N) 7.48- 6.9 (m, 4H, Ar-H),5.22 (d, 1H, J 9 Hz, 4-H), 3.98 (t, 1H, 5-H), 3.66 (d, 1H, J 7.7 Hz, 3-H), 3.59 (s, 3H, MeOH solvent of crystallisation), 2.85 (s, 3H, NMe) and1.88 (s, 3H, C-Me).

(3b) Crystallised from aqueous acetone as colourless prisms m.p. 250-252°C decomp. (Lit.[2,7] 250- 252°C decomp.); m/z(%) 366 (M+, 10), 321 (31), 193 (99), 173 (65), 147 (100), 131 (23), 106 (23), 93 (17), 77 (40) and 44 (12); δ (C_5D_5N) 7.59- 6.91 (m, 9H, Ar-H), 5.33 (d, 1H, J 8.9 Hz, 4-H), 4.19 (t, 1H, 5-H), 3.87 (d, 1H, J 7.9 Hz, 3-H) and 1.95 (s, 3H, C-Me).

Dimethyl 2-methyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid(4a) and dimethyl 2-methyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5a). Salicylaldehyde (1.22g, 10mmol), alanine (0.89g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) were refluxed in acidified methanol for 2h. The major isomer **(4a)** (1.3g, 38.6%) precipitated from the hot reaction mixture. The filtrate was evaporated under reduced pressure and then triturated with chloroform to give the minor isomer **(5a)** (0.93g, 27.6%).

(4a) Crystallised from methanol as colourless needles m.p. 255-257°C subl. (Lit.[7,8] 249-251°C, subl.). (Found: C, 56.75: H, 5.80; N, 4.00. $C_{16}H_{19}NO_7$ requires C, 56.97; H, 5.68; N, 4.15%); m/z(%) 337 (M+, 13), 306 (6), 292 (27), 260 (44), 232 (58), 200 (100), 193 (69), 147 (55), 131 (27), 106 (12) and 77 (23); δ (C_5D_5N) 7.47-6.84 (m, 4H, Ar-H), 5.18 (d, 1H, J 10.4 Hz, 5-H), 4.35 (t, 1H, 4-H), 3.95 (d,1H, J 11.1 Hz, 3-H) 3.65 and 3.56 (2s, 6H, 2xCO_2Me) and 2.07 (s, 3H, C-Me). The n.O.e. data for **(4a)** is given below:

Protons		Enhancement (%)			
irradiated	3	4	5	C-Me	Ar-H
3		4	7	4	
4			2		6
5	9	4			14
C-Me	7				

(5a) Crystallised from methanol as colourless needles m.p. 193-195°C, decomp. (Found: C, 57.2; H, 5.7; N, 4.2. C16H19NO7 requires C, 56.97; H, 5.68; N, 4.15%); m/z (%) 337 (M+,10), 292 (18) 200 (75) 193 (100)

and 147 (66); δ (C_5D_5N) 7.53- 6.92 (m, 4H, Ar-H), 5.58 (d, 1H, J 10.2 Hz, 5-H) 4.93 (d, 1H,J 8.9 Hz, 3-H) 4.47 (t, 1H, 4-H),3.7 and 3.32 (2s, 6H, 2xCO_2Me) and 1.9 (s, 3H, C-Me). The n.O.e.data is given below:

Protons		Enhancement (%)			
irradiated	3	4	5	C-Me	Ar-H
3		3		1	2
4	5		11	2	
5		16		4	10
C-Me	1	3	2		

Dimethyl c-5-(2/-hydroxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4b) and dimethyl c-5-(2/-hydroxyphenyl)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxlic acid (5b). A mixture of salicylaldehyde (1.22g, 10mmol), glycine (0.75g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) was boiled in methanol with a few drops of acetic acid over 2h. A colourless precipitate came out of the hot solution (2.16g,67%) whose pmr spectrum showed it to comprise a 1 : 1.14 mixture of **(4b)** and **(5b)** respectively. Fractional crystallisation from methanol afforded only isomer **(4b)** (0.58g, 18%) in a pure state.

(4b) Crystallised from methanol as colourless needles m.p. 237-239°C decomp. (Found: C, 55.5; H, 5.2; N, 4.6 $C_{15}H_{17}NO_7$ requires C, 55.72; H, 5.3; N, 4.33%); m/z(%) 323 (M+,20), 277 (10), 218 (55), 186 (96), 179 (71), 133 (100) and 44 (27); δ (C_5D_5N; 400 MHz) 9.4 (br, 1H, CO2H), 7.58- 6.93 (m, 4H, Ar-H), 5.11 (d, 1H, J 9.8 Hz, 5-H), 4.88 (d, 1H, J 9.3 Hz, 2-H),4.38 (t, 1H, 3-H), 4.24 (t, 1H, 4-H), 3.73 and 3.63 (2s, 6H, 2xCO_2Me). The n.O.e. data is given below:

Protons		Enhancement(%)			
irradiated	2	3	4	5	Ar-H
2		17		3	
3	14			6	
4				3	4
5	3	7	3		14

(5b) Obtained as a mixture with **(4b)**. The pmr data is extracted from the spectrum of the reaction mixture. δ (C_5D_5N, 400 MHz) 7.61- 6.93 (m, 4H, Ar-H), 5.51 (d, 1H, J 8.27 Hz, 5-H), 4.91 (d, 1H, J 7.69 Hz, 2-H), 4.54 (dd, 1H, J 5.10 and 7.61 Hz, 3-H), 4.31 (dd, 1H, J 5.10 and 8.27 Hz, 4-H), 3.71 and 3.34 (2s, 6H, 2xCO_2Me). The n.O.e. data is given below:

Protons		Enhancement(%)			
irradiated	2	3	4	5	Ar-H
4		5		12	
5	5		16		11

Dimethyl 2-isobutyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4c) and dimethyl 2-isobutyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-caboxylic acid (5c). Salicylaldehyde (1.22g, 10mmol), leucine (1.31g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) were boiled under reflux in acidified methanol (70ml) over 4h. In this case the minor isomer **(5c)** (1g, 26.4%) precipitated out of the hot solution and work up of the mother liquor gave the major isomer **(4c)** (1.31g, 34.6%).

(4c) Crystallised from methanol as colourless fine needles m.p. 204-206°C decomp. (Found: C, 60.1; H, 6.6; N, 3.95. $C_{19}H_{25}NO_7$ requires C, 60.14; H, 6.64; N, 3.69%); m/z(%) 379 (M+,16), 334 (81), 302 (68), 274

(100), 242 (96), 216 (76), 193 (74), 192 (71), 86 (52), 57 (15) and 44 (24); δ (C_5D_5N) 7.61-6.87 (m, 4H, Ar-H), 5.16 (d, 1H, J 10.3 Hz, 5-H), 4.15 (t, 1H, 4-H), 3.96 (d, 1H, J 10.8 Hz, 3-H), 3.71 and 3.51 (2s, 6H, 2xCO_2Me), 2.67- 2.07 (m, 3H, CH_2CH), 1.09 and 1.04 (2d, 6H, J 6.4 Hz, 2Me).

(5c) Crystallised from methanol as colourless fine needles m. p. 217-219°C sublimed. (Found: C, 59.9; H, 6.45; N, 3.75. $C_{19}H_{25}NO_7$ requires C, 60.14; H, 6.64; N, 3.69%); m/z(%) 379 (M+, 4), 334 (13), 302 (23), 274 (25), 242 (22), 193 (29), 192 (39), 86 (95), 57 (22) and (100); δ (C_5D_5N) 7.59-6.84 (m, 4H, Ar-H), 5.56 (d, 1H, J 8.8 Hz, 5-H), 4.54 (t, 1H, 4-H), 4.46 (d, 1H, J 7.3 Hz, 3-H), 3.7 and 3.21 (2s, 6H, 2xCO_2Me) 2.33-2.08 (m, 3H, CH_2CH) and 1.05 (t, 6H, 2Me).

Dimethyl 2-methylthioethyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4d) and dimethyl 2-methylthioethyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5d). Salicylaldehyde (1.22g, 10mmol), methionine (1.49g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) after 4h gave **(4d)** (1.49g, 37.5%) and the usual work up of the mother liquor gave isomer **(5d)** (1.1g, 27.7%).

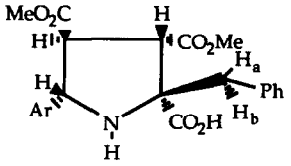
(4d) Crystallised from methanol as colourless needles m.p. 191- 193°C decomp. (Found C, 54.1; H, 5.8; N, 3.5; S, 8.1. $C_{18}H_{23}NO_7S$ requires C, 54.39; H, 5.83; N, 3.52; S,8.07 %); m/z(%) 397 (M+,5), 352 (40), 320 (34), 260 (67), 193 (100), 172 (21), 75 (26), 61 (47) and 44 (15); δ (C_5D_5N) 7.61- 6.87 (m, 4H, Ar-H), 5.17 (d, 1H, J 10.3 Hz, 5-H), 4.25 (t, 1H, 4-H), 4.06 (d, 1H, J 11 Hz, 3-H), 3.68 and 3.5 (2s, 6H, 2xCO_2Me), 3.12- 2.62 (m, 4H, $2CH_2$) and 2.04 (s, 3H, SMe).

(5d) Crystallised from methanol as colourless needles m.p. 202- 204°C decomp. (Found C, 54.2; H, 5.75; N, 3.7; S, 7.9. $C_{18}H_{23}NO_7S$ requires C, 54.39; H, 5.83; N, 3.52; S, 8.07 %); m/z(%) 397 (M+,14), 352 (26), 320 (35), 260 (55), 193 (100), 172 (20), 75 (36), 61 (74) and 44 (13); δ (C_5D_5N) 7.52- 6.84 (m, 4H, Ar-H), 6.76 (br, 2H, OH and CO_2H) 5.58 (d, 1H, J 8.7 Hz, 5-H), 4.57 (d, 1H, J 7.3 Hz, 3-H), 4.5 (t, 1H, 4-H), 3.66 and 3.21 (2s, 6H, 2xCO_2Me), 3.21-2.45 (m, 4H, $2CH_2$) and 2.04 (s, 3H, SMe).

Dimethyl 2-benzyl-c-5-(2/-hydroxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4e) and dimethyl 2-benzyl-c-5-(2/-hydroxyphenyl)- pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5e). Salicylaldehyde (1.22g, 10mmol), phenylalanine (1.65g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) over 4h gave a colourless crystalline precipitate (2.89g, 70%) whose pmr showed to comprise a 1.33 : 1 mixture of two isomers. The isomeric mixture was partially soluble in pyridine at room temperature and filtration afforded **(4e)** (0.91g, 22%). The filtrate was evaporated under reduced pressure to give a mixture of the two adducts (1.98g, 48%).

(4e) Crystallised from methanol as colourless needles m.p. 231- 233°C decomp. (Found: C, 63.7; H, 5.5; N, 3.25. $C_{22}H_{23}NO_7$ requires C, 63.91; H, 5.61; N, 3.39 %); m/z(%) 413 (M+,6), 368 (36), 322 (54), 290 (60), 230 (52) and 91 (100); δ (C_5D_5N, 400 MHz) 7.86- 6.93 (m, 9H, Ar-H), 5.05 (d, 1H, J 10 Mz, 5-H), 4.3 (t, 1H, 4-H), 4.23 (d, 1H, J 11.1 Hz, 3-H), 3.98 and 3.75 (2d, 2H, J 13.6 Hz, Ha and Hb), 3.84 and 3.55 (2s, 6H, 2xCO_2Me). The n.O.e. data is given below:

Protons	Enhancement (%)						
irradiated	3	4	5	a	b	Ar-H	Ph-H
5	4	4				9	
a					19		7
b	10		4	21			6



(4e) Ar = 2- HOC_6H_4

(5e) Obtained as a mixture with **(4e)**. The pmr data is extracted from the spectrum of the reaction mixture. δ (C_5D_5N, 400 MHz) 7.73- 6.88 (m, 9H, Ar-H), 5.62 (d, 1H, J 9.5 Hz, 5-H), 4.58 (d, 1H, J 8.3 Hz, 3-H), 4.49 (t, 1H, 4-H),3.83 and3.29 (2s, 6H, 2xCO_2Me), 3.73 and 3.33 (AB dd, 2H, J 13.5 Hz, CH_2Ph).

Dimethyl 2-(3/-indolylmethyl)-c-5-(2/-hydroxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4f) and dimethyl 2-(3/-indolylmethyl)-c-5-(2/-hydroxyphenyl)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5f). Salicylaldehyde (1.22g, 10mmol), tryptophan (2.04g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) were refluxed over 4h. A colourless precipitate came out of the hot solution whose pmr showed a 1.2 : 1 mixture of adducts **(4f)** and **(5f)** respectively. The isomeric mixture was partially soluble in pyridine at room temprature and filtration gave cycloadduct **(4f)** (1.08g, 24%). Work up of the filtrate afforded a mixture of **(4f)** and **(5f)** (1.9g, 42%) which by successive fractional crystallisations from methanol gave **(5f)** (0.54g, 12%).

(4f) Crystallised from methanol as colourless needles m.p. 235- 237°C decomp. (Found: C, 63.55; H, 5.3; N, 5.9. $C_{24}H_{24}N_2O_7$ requires C, 63.71; H, 5.35; N, 6.19%); m/z(%) 452 (M+, 1), 406 (4), 322 (11), 290 (38), 130 (100) and 44 (6); δ (C_5D_5N) 12.11 (s, 1H,CO_2H), 9.51 (br, 3H, OH, 2NH), 8.23- 6.79 (m, 9H, Ar-H), 5.05 (d, 1H, J 9.7 Hz, 5-H), 4.38- 4.04 (m, 4H, 3-H, 4-H and CH_2Ar), 3.78 and 3.44 (2s, 6H, 2xCO_2Me).

(5f) Crystallised from methanol as colourless needles m.p. 215-217°C decomp. (Found: C,63.4; H, 5.1; N, 6.1. $C_{24}H_{24}N_2O_7$ requires C, 63.71; H, 5.35; N, 6.19%); m/z(%) 334 (44), 290 18), 270 (88), 192 (100), 130 (19), 115 (42) and 44 (5); δ (C_5D_5N) 12.02 (s, 1H, CO_2H), 8.28- 6.75 (m, 12H, OH, 2NH, Ar-H), 5.78 (d, 1H, J 9.4 Hz, 5-H), 4.8 (d, 1H, J 8.4 Hz, 3-H), 4.72 (t, 1H, 4-H), 4.1 and 3.69 (AB dd, 2H, J 14.5 Hz, CH_2 indole), 3.75 and 3.24 (2s, 6H, 2xCO_2Me).

Dimethyl 2-methyl-c-5-phenyl-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4g) and dimethyl 2-methyl-c-5-phenyl-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5g). Benzaldehyde (1.06g, 10mmol), alanine (0.89g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) were refluxed over 20h. The major isomer **(4g)** (0.88g, 27.4%) came out of the hot solution and work up of the mother liquor gave **(5g)** (0.73g, 22.7%).

(4g) Crystallised from methanol as colourless needles m.p. 241- 243°C decomp. (Found: C, 59.5; H, 5.75; N, 4.5. $C_{16}H_{19}NO_6$ requires C, 59.8; H, 5.96; N, 4.36%); m/z(%) 321 (M+, 2), 276 (52), 244 (74), 216 (91), 177 (100), 115 (61) and 77 (14); δ (C_5D_5N) 7.75- 7.15 (m, 5H, Ar-H), 4.8 (d, 1H, J 9.9 Hz, 5-H), 4.12 (t, 1H, 4-H), 3.91 (d, 1H, J 10.9 Hz, 3-H), 3.66 and 3.54 (2s, 6H, 2xCO_2Me) and 2.02 (s, 3H, C-Me).

(5g) Crystallised from methanol as colourless prisms m.p. 206- 208°C decomp. (Found: C, 59.8; H, 5.85; N, 4.4. $C_{16}H_{19}NO_6$ requires C, 59.8; H, 5.96; N, 4.36%); m/z (%) 321 (M+, 2), 276 (28), 244 (34), 216 (74), 177 (100), 115 (49) and 77 (12); δ (C_5D_5N) 7.7- 7.21 (m, 5H, Ar-H), 5.13 (d, 1H, J 9.7 Hz, 5-H), 4.78 (d, 1H, J 10.1 Hz, 3-H), 4.33 (t, 1H, 4-H), 3.63 and 3.17 (2s, 6H, 2xCO_2Me) and 1.78 (s, 3H, C-Me).

Dimethyl 2-methyl -c-5-(2/-methoxyphenyl)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4h) and dimethyl 2-methyl-c-5-(2/-methoxyphenyl)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5h). 2-Methoxybenzaldehyde (1.36g, 10mmol), alanine (0.89g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) were boiled under reflux for 20h. The major isomer **(4h)** (1.31g, 37.3%) came out of the hot solution and the usual work up of the filtrate afforded **(5h)** (1g, 28.5%).

(4h) Crystallised from methanol as colourless needles m.p.230- 232°C decomp. (Found: C,57.8; H, 5.95; N, 4.15. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.03; N, 3.99%); m/z(%) 351 (M+, 1), 306 (52), 274 (34), 246 (23), 214 (100), 207 (81), 161 (48) and 115 (43); δ (C_5D_5N) 8.04- 6.85 (m, 4H, Ar-H), 5.3 (d, 1H, J 9.9 Hz, 5-H), 4.1 (t,1H, 4-H), 3.93 (d, 1H, J 10.9 Hz, 3-H), 3.64 and 3.57 (2s, 6H, 2xCO_2Me), 3.64 (s, 3H, OMe) and 2.04 (s, 3H, C-Me).

(5h) Crystallised from methanol as colourless plates m.p. 220- 222°C decomp. (Found: C, 58.25; H, 6.1; N, 4.05. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.03; N, 3.99%); m/z(%) 351 (M+, 1), 306 (22), 274 (15), 246 (32), 214 (80), 207 (100), 161 (62) and 115 (17); δ (C_5D_5N) 7.76- 6.87 (m, 4H, Ar-H), 5.5 (d, 1H, J 9.2 Hz, 5-H), 4.69 (d, 1H, J 8.2 Hz, 3-H), 4.38 (t, 1h,4-H), 3.72 and 3.14 (2s, 6H, 2xCO_2Me), 3.63 (s, 3H, OMe) and 1.78 (s, 3H, C-Me).

Dimethyl 2-methyl-c-5-(2/,4/-dimethoxybenzaldehyde)-pyrrolidine-c-3-,t-4-dicarboxylate-r-2-carboxylic acid (4i) and dimethyl 2-methyl-c-5-(2/,4/-dimethoxybenzaldehyde)-pyrrolidine-t-3-,c-4-dicarboxylate-r-2-carboxylic acid (5i). 2,4-Dimethoxybenzaldehyde (1.66g, 10mmol), alanine (0.89g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) were boiled under reflux for 20h. Isomer **(4i)** (1.45g, 38%) came out of the hot solution and **(5i)** (1.14g, 30%) was obtained by the usual work up of the filtrate.

(4i) Crystallised from methanol as colourless needles m.p. 188- 190°C decomp. (Found: C,56.55; H, 5.95; N, 3.8. $C_{18}H_{23}NO_8$ requires C, 56.69; H, 6.08; N, 3.67%); m/z(%) 382 (M+1, 1), 336 (26), 276 (20), 244 (54), 237 (100), 218 (40), 191 (77) and 164 (39); δ (C_5D_5N) 7.91- 6.54 (m, 3H, Ar-H), 5.23 (d, 1H, J 9.9 Hz, 5-H), 4.13 (t, 1H, 4-H), 3.94 (d, 1H, J 11 Hz, 3-H), 3.68 and 3.6 (2s, 6H, 2xCO_2Me), 3.66 and 3.62 (2s, 6H, 2OMe) and 2.06 (s, 3H, C-Me).

(5i) Crystallised from methanol as colourless needles m.p. 202- 204°C decomp. (Found: C, 56.45; H, 5.9; N, 3.6. $C_{18}H_{23}NO_8$ requires C, 56.69; H, 6.08; N, 3.67%); m/z(%) 382 (M+1, 0.4), 336 (12), 276 (10), 244 (33), 237 (95), 218 (100), 191 (85) and 164 (59); δ (C_5D_5N) 7.7- 6.55 (m, 3H, Ar-H), 5.48 (d, 1H, J 9.3 Hz, 5-H), 4.71 (d, 1H, J 8.4 Hz, 3-H), 4.38 (t, 1H, 4-H), 3.74 and 3.23 (2s, 6H, 2xCO_2Me), 3.66 (s, 6H, 2OMe) and 1.79 (s, 3H, C-Me).

(8) N- Salicylidenevaline. An equimolar mixture of salicylaldehyde (1.22g, 10mmol), valine (1.17g, 10mmol) and dimethyl fumarate (1.44g, 10mmol) was refluxed in methanol (70ml) for 2h. The unreacted valine (0.7g, 60%) was recovered by filtration. The filtrate was concentrated to 1/3 and addition of chloroform (50ml) gave **(8)** (0.88g, 40%) as a yellow precipitate; and the solvent was removed from the filtrate under reduced pressure to give the unreacted dimethyl fumarate.

(8) Crystallised from methanol as pale yellow prisms m.p. 155-157°C decomp. (Lit.[14] 160- 162°C. Accurate mass (found: 221.105443. $C_{12}H_{15}NO_3$ requires 221.105194); m/z(%) 221 (M+, 54), 176 (48), 132 (100), 120 (19), 113 (68), 107 (64) and 77 (40); δ (C_5D_5N) 14.04 (br, 1H, CO_2H), 8.58 (s, 1H, CH=N), 7.44- 6.89 (m,4H, Ar-H), 4.06 (d, 1H, J 5.3 Hz,NCH), 2.6 (m, 1H, CHMe2) and 1.11 and 1.04 (2d, 6H, J 6.7Hz, 2Me).

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