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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 17. SEQUENTIAL MICHAEL ADDITION-5-ENDO-TRIG CYCLISATION OF ARYLIDENE IMINES OF α-AMINO ACID ESTERS.[1,2]

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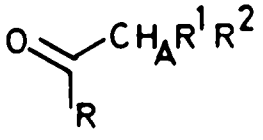
Abstract. Imines of α-amino acid esters undergo regiospecific Michael addition to methyl acrylate or acrylonitrile in good yield in benzene at 25°C catalysed by benzyltrimethylammonium methoxide (BTAM). The Michael adducts cyclise to a mixture of two stereoisomeric polysubstituted proline ester derivatives in the presence of 1 mol. of BTAM. Mechanistic studies, involving chiral intermediates, show this cyclisation to be an example of a disfavoured 5-(enolexo)-endo-trig process.

There is a close analogy between the acid and base catalysed reactions of carbonyl compounds (1) and imines (2) involving activation of the proton H_A in each case and subsequent reaction of the enol/enolate or 2-azaallyl anion with electrophiles.[3,4] Ingold first studied imines as precursors of 2-azaallyl anions[5] and Stork[6], and later others, showed that the 2-azaallyl anions derived from α-amino acid imines (3) by the action of lithium diisopropylamide could be regiospecifically alkylated α to the ester group. Regiospecific Michael addition[1,6] and aldol-type condensations[7] also occur α to the ester group. This work, however, was predated by analogous reactions developed for the synthesis of various 6-substituted penicillins and cephalosporins[8]. The alkylation[9] and, recently, Michael addition[10] reactions have been achieved under phase transfer conditions. Formamidine derivatives of α-amino acid esters undergo analogous alkylation and Michael addition reactions via the intermediate (4a).[11] A simple and ingenious asymmetric synthesis of α-amino acids involving the chiral lithiated imine (5) ⟶ (6) has been reported.[12]



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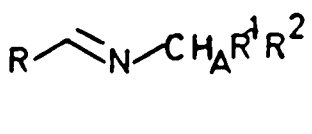

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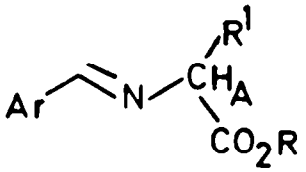

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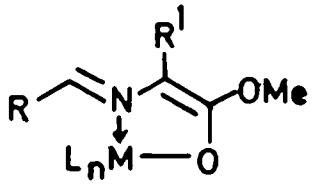
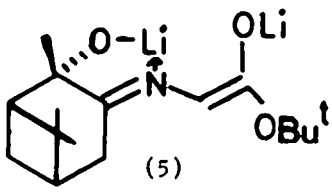


(4) a. R=NMe_2, R^1=H, M=Li

b. R=Ar, R^1= H, Me or Ph



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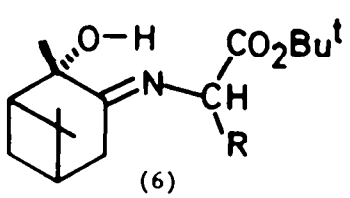
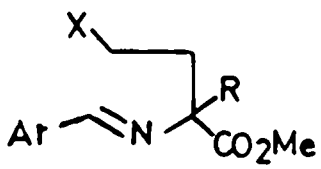


(6)

Our own work in this area concerns the sequential Michael addition of (3) to methyl acrylate, or acrylonitrile, to give (7) followed by 5-endo-trig cyclisation to (8) and (9). In this sequence the cyclisation step (7)⟶(8)/(9) is predicted to be disfavoured.[13]



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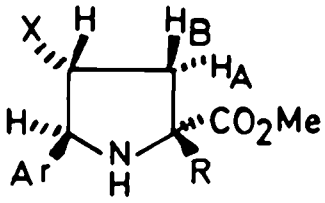

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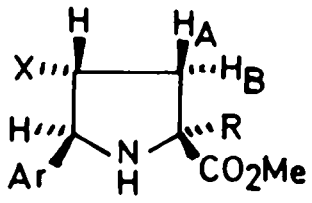

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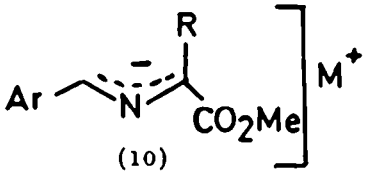

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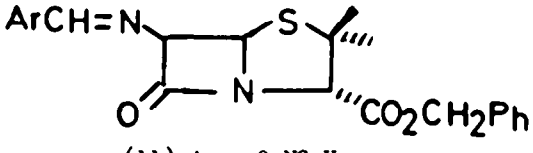
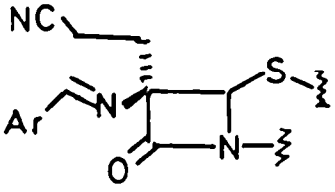


(11) Ar=p-$O_2NC_6H_4$



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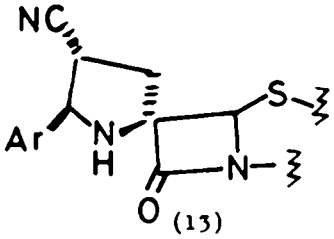

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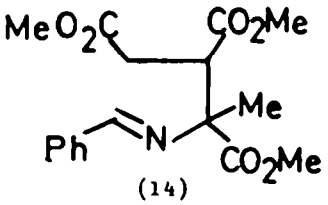

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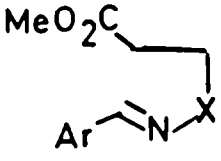
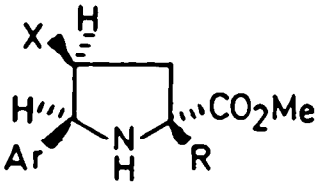


(15) a. Ar=Ph, X=CHPh
b. Ar=2-thienyl, X=CHPh
c. Ar=3-pyridyl, X=CHPh
d. Ar=Ph, X=NPh
e. Ar=Ph, X=CPh_2
f. Ar=Ph, X=CH_2



(16)

Kauffmann was the first to perceive the potential of 2-azaallyl anions as 4π-components in 4π + 2π anionic cycloadditions.[14] His studies involved simple aryl substituted imines but others[15,16] subsequently extended Kauffmann's conditions (LDA, THF, -80 to +20°C) to imines of α-amino acid esters. We suggested that Kauffmann's anionic cycloadditions might be examples of metallo-1,3-dipoles in which the lithium ion was located on the nitrogen atom[17], i.e. a metallo-1,3-dipole, and subsequently provided examples of a range of such species.[3,4,18,19] Tsuge has recently used these ideas in a novel synthesis of 1-pyrrolines[20] and we have shown that metallo-1,3-dipoles (4b, M=Zn, Ag or Li) are readily produced from (3), triethylamine, and zinc, silver or lithium salts at room temperature in a range of solvents.[3] These metallo-1,3-dipoles undergo rapid (0.1-3.5h) regio- and stereo-specific or highly stereoselective inter- and intra-molecular cycloaddition to a range of dipolarophiles at room temperature.[3] However, when BTAM is used as the base metallo-1,3-dipole formation is precluded and the reactive species is (10, M=$PhCH_2NMe_3$) or some related aggregated and/or hydrogen bonded species. The existence of a possible dichotomy in the reaction of 2-azaallyl anions with electronegative olefins was first indicated in studies of the reaction of penicillin imines (11) with triethylamine and acrylonitrile[21]

which gave a mixture of the Michael adduct (12) and the pyrrolidine (13) (partial formulae). We have recently shown that imines of α-amino acid esters can be deprotonated by tertiary amines[3,22] and the resultant 2-azaallyl anions trapped in cycloaddition reactions.

Pyrrolidines from sequential Michael addition-5-endo-trig cyclisation. Michael Addition. It appeared to us that regiospecific formation of pyrrolidines (8) and (9) from (3) and suitable electronegative olefins should be possible by a two-step Michael addition-cyclisation sequence via (7). This approach inevitably led to a consideration of the factors determining (a) whether 2-azaallyl anions undergo Michael addition or $4\pi + 2\pi$ anionic cycloaddition to electronegative olefins and (b) the nature of the 2-azaallyl anions produced by the action of various bases on imines of α-amino acid esters.

Benzyltrimethylammonium methoxide (BTAM) was selected as a suitable base for achieving the two-step Michael addition-cyclisation sequence since it precluded metallo-dipole formation. Typically the Michael addition of α-amino acid ester imines (3) and methyl acrylate or acrylonitrile occurs over 1-24h in benzene solution in the presence of 10 mol% of BTAM (40% solution in methanol). The Michael additions are regiospecific and yields of imines of α,α-disubstituted α-amino acid esters (7) are usually excellent (Table 1).

Table 1. BTAM mediated Michael addition of imines (3, R=Me) to electronegative olefins[a]

Imine (3)		Olefin[b]	Product (7)			Yield (%)[c]
Ar	R^1		Ar	R	X	
Ph	H		Ph	H	CO_2Me	53
Ph	Me	ME	Ph	Me	CO_2Me	92
p-$MeOC_6H_4$	Me	ME	p-$MeOC_6H_4$	Me	CO_2Me	85
p-$MeOC_6H_4$	Me	AN	p-$MeOC_6H_4$	Me	CN	90[d]
Ph	Ph	ME	Ph	Ph	CO_2Me	84
p-$MeOC_6H_4$	Ph	ME	p-$MeOC_6H_4$	Ph	CO_2Me	87
Ph	Ph	AN	Ph	Ph	CN	78
p$MeOC_6H_4$	Ph	AN	p-$MeOC_6H_4$	Ph	CN	71
Ph	p-$MeOC_6H_4$	ME	Ph	p-$MeOC_6H_4$	CO_2Me	93
p-$MeOC_6H_4$	p-$MeOC_6H_4$	ME	p-$MeOC_6H_4$	p-$MeOC_6H_4$	CO_2Me	74
Ph	CH_2CO_2Me	ME	Ph	CH_2CO_2Me	CO_2Me	67
Ph	Pr^i	ME	Ph	Pr^i	CO_2Me	85[e]
p-$MeOC_6H_4$	Pr^i	ME	p-$MeOC_6H_4$	Pr^i	CO_2Me	75[e]
Ph	Pr^i	AN	Ph	Pr^i	CN	82[f]
p$MeOC_6H_4$	Pr^i	AN	p-$MeOC_6H_4$	Pr^i	CN	80[f]

a. reactions carried out in benzene using 10 mol% of BTAM, for 1-24h at 25°C. b. ME = methyl acrylate, AN = acrylonitrile; c. isolated yield d. estimated from the p.m.r. spectrum of the crude product; e. reaction carried out at 80°C for 24h f. reaction carried out at 80°C for 7 dy.

Similar reactions can be carried out with dimethyl fumarate and imines (3). Thus (3, Ar=Ph, $R=R^1$=Me) and dimethyl fumarate give (14, 93%). A further series of Michael adducts (15a-f) were prepared in an analogous manner for mechanistic studies (below). The Michael addition of valine imines (3, $R^1=Pr^i$, R=Me) to electronegative olefins required more forcing conditions and a much longer reaction time (table 1), reflecting the steric and inductive retardation arising from the bulky isopropyl group. The rate depressing effect of isopropyl groups has been

noted in other Michael addition reactions.[23] Although it is known that the presence of bulky substituents α to the ester functionality in imines (3) can alter the regioselectivity of alkylation of the corresponding 2-azaallyl anion[24] we observed only formation of the "normal" Michael adducts (7, R=Pr^i) with valine imines.

5-Endo-Trig Cyclisation. The Michael adducts (7) always contain a small amount of the corresponding pyrrolidine (8) and/or (9) which approximately corresponds to the catalytic amount of BTAM employed. This implies that the pyrrolidine anion is only weakly active as a base for the cyclisation of (7) and that the pyrrolidines (8) and (9) are more acidic than methanol under the reaction conditions i.e. in benzene containing a trace amount of methanol. When the Michael addition of (3, Ar=R^1=Ph, R=Me) with methyl acrylate was carried out with 10 mol% BTAM over 5 days complete conversion to a mixture of (8, Ar=R=Ph, X=CO_2Me) and (9, Ar=R=Ph, X=CO_2Me) occurred. However, the cyclisation of (7) is, in general, more efficiently carried out in benzene at room temperature over 24h by using 1 mol of BTAM. Imines (7, Ar=p-$MeOC_6H_4$) and (7, R=Pr^i) require more forcing conditions for cyclisation and are best cyclised by heating in boiling benzene for 5h and 2-7dy respectively. Under these conditions the imines (7) (table 1) gave a mixture of the corresponding stereoisomeric pyrrolidines (8) and (9) together in the case of (7, X=CN) with a third isomer (16) (table 2). The mixtures of stereoisomeric pyrrolidines were separated by preparative t.l.c.

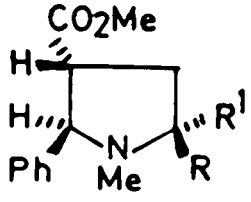
Table 2. Isomeric pyrrolidines from the action of BTAM (1 mol) on the Michael adducts (7) in benzene at 25°C.[a]

Ar	R	X	Yield (%)[b]	Ratio[c] (8)	(9)	(16)
Ph	H	CO_2Me	78[d]	1.4	1	-
Ph	Me	CO_2Me	74	7	1	-
p-$MeOC_6H_4$	Me	CN	72[e]	4	1	1.2
Ph	Ph	CO_2Me	81	3.7	1	-
p-$MeOC_6H_4$	Ph	CO_2Me	78[e]	3.4	1	-
Ph	Ph	CN	70	4.5	1.5	1
p-$MeOC_6H_4$	Ph	CN	77[e]	5	1	-
Ph	p-$MeOC_6H_4$	CO_2Me	88	3	1	-
Ph	Pr^i	CO_2Me	80[f]	3	1	-
p-$MeOC_6H_4$	Pr^i	CO_2Me	80[g]	3	1	-
Ph	Pr^i	CN	78[f]	7.5	1	1.5
p-$MeOC_6H_4$	Pr^i	CN	76[g]	6.7	1.7	1[h]

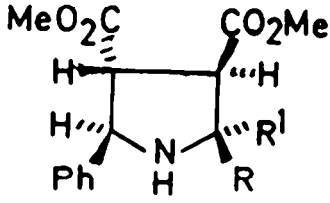
a. reaction time 24h; b. combined isolated yield of all isomers; c. ratios estimated by integration of the p.m.r. spectra of the crude products; d. KOBu (1mol) used as base. Reaction time 24h; e. reaction carried out at 80°C for 5h; f. reaction carried out at 80°C for 2dy; g. reaction carried out at 80°C for 7dy; h. trace amount of a fourth isomer detected.

The cyclisation of (7, Ar=Ph, R=H, X=CO_2Me) (table 2) was carried out using potassium tert-butoxide as base and on quenching with methyl iodide a 1.2:1 mixture of the N-methyl pyrrolidines (17a) and (17b) was obtained. Cyclisation of (14) using BTAM (1mol) in benzene gave a 4:4:1 mixture of (18a), (18b) and (19) but attempts to cyclise the imines (15a-f) with BTAM (1mol) under the standard conditions (benzene, 25°C, 24h) failed to yield any cyclisation products. Pyrrolidine (18a) is identical to the major cycloadduct obtained from the thermal cycloaddition of (3, Ar=Ph, R=R^1=Me) and dimethyl fumarate.[26] The Michael

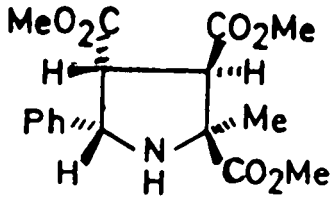
addition-cyclisation sequence can be carried out in tandem to give pyrrolidines directly from imines (3), without isolation of (7), if required.



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



(18) a. R=CO_2Me, R^1-Me
b. R=Me, R^1=CO_2Me



(19)

Stereochemistry of the pyrrolidines derived by the action of BTAM on imines (7)

The assignment of stereochemistry to the stereoisomeric pyrrolidines (8), (9) and (16) is based on p.m.r. spectral data together with an X-ray crystal structure (below). Coupling constants are often an unreliable guide to stereochemistry in pyrrolidines unless supported by chemical shift data arising from shielding/ /deshielding effects of aryl and ester substituents. Thus it is well documented that a pyrrolidine ring proton or the methyl resonance of a CO_2Me group is shielded by a cis-vicinal aryl group whilst a cis-vicinal ester substituent results in deshielding of a pyrrolidine ring proton.[25,26] Proton decoupling experiments established that the ester- and cyano-substituents in (8), (9) and (16) are located a C(4), whilst the chemical shift of the C(4) proton (ca. δ 2.7-3.0) indicates a trans-relationship between the C(5)-aryl and C(4)-X substituents for (8) and (9). This trans-arrangement is supported by the absence of a high field ester OMe resonance in both (8, X=CO_2Me) and (9, X=CO_2Me). The p.m.r. data on the pyrrolidines (8), (9) and (16) are collected in table 3. The similarity in chemical shift and coupling constants of the pairs of pyrrolidines epimeric at C(2) precluded assignment of the relative stereochemistry at C(2) solely on the basis of p.m.r. data. The relative stereochemistry of the major isomers at C(2) was unambiguously established by a single crystal X-ray structure of the major isomer (8, Ar=Ph, R=p-$MeOC_6H_4$, X=CO_2Me) arising from cyclisation of imine (7, Ar=Ph, R=p-$MeOC_6H_4$, X=CO_2Me) (below).

The formation of three isomers in most cycloadditions involving acrylonitrile introduced a further complication in structural assignment. This was resolved by a comparison of the products from the BTAM induced cyclisation with those from the thermal cycloaddition in the absence of base.[29] Thus the thermal cycloaddition of (3, Ar=p-$MeOC_6H_4$, R=R^1=Me) and acrylonitrile gives a 1.2:1 mixture (88%) of (20, R^1=p-$MeOC_6H_4$, R^2Me) and (9, Ar=p-$MeOC_6H_4$, R=Me, X=CN) derived from the dipole (21a), formed under kinetic control, by way of endo- and exo-transition states.[26,31]. The minor isomer from the thermal cycloaddition proved identical to one of the minor cycloadducts from the BTAM induced cyclisation whilst the major isomer from the thermal process was absent from the product mixture of the BTAM induced cyclisation. There are four possible stereoisomeric pyrrolidines with the nitrile substituent at C(4) and it therefore follows that (8) and (16) (Ar=p-$MeOC_6H_4$, R=Me, X=CN) have a cis-arrangement of the C(2)-methyl and C(5)-aryl substituents. The chemical shift of the 4-H in (8) and (16) (Ar=p-$MeOC_6H_4$, R=Me, X=CN) is δ 2.81 and 3.18 respectively indicating a trans- and cis-relationship respectively of C(5)-aryl and C(4)-nitrile substituents. Similar arguments were developed for the other cases where three stereoisomers were produced. The observation of a third isomer (16) in the cyclisation of many of the

Table 3. P.m.r. data ($CDCl_3$) for pyrrolidines (8), (9) and (16)

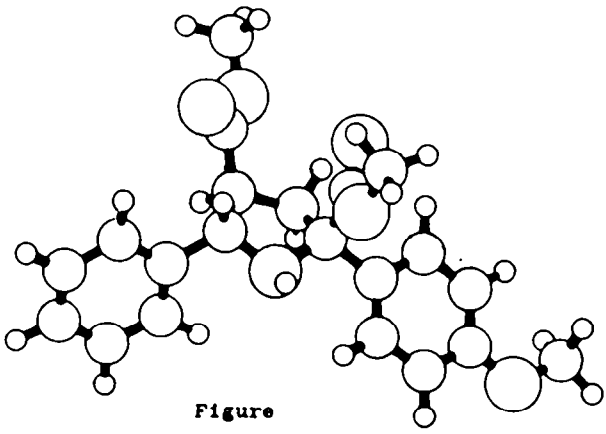
Pyrrolidine			Chemical Shift (δ)					Coupling constants (Hz)		
Ar	R	X	5-H	4-H	3-H_A	3-H_B	OMe	$J_{4,5}$	$J_{3A,4}$	$J_{3B,4}$
8, Ph	R	CO_2Me	4.56	2.87	2.6	2.35	3,78,3.63	7.7	8.3	8.3
9, Ph	H	CO_2Me	4.41	2.87	2.5	2.35	3.78,3,64	8.3	8.3	8.3
8, Ph	H	CO_2Me	4.46	2.91	2.65	2.15	3.73,3.60	8.2	9.3	7.1
9, Ph	Me	CO_2Me	4.47	2.96	2.68	2.07	3.72,3.55	9.0	10.6	7.4
8, p-$MeOC_6H_4$	Me	CN	4.30	2.81	2.65	2.26	3.80(6H)	8.4	-	-
9, p-$MeOC_6H_4$	Me	CN	4.42	2.78	2.85	2.13	3.78(6H)	9.3	14.0	7.1
16, p-$MeOC_6H_4$	Me	CN	4.36	3.18	2.80	2.20	3.80,3.75	6.6	4.30	8.3
8, Ph	Ph	CO_2Me	4.60	2.91	3.17	2.51	3.72,3.64	9.0	6.3	8.5
9, Ph	Ph	CO_2Me	4.50	3.00	3.30	2.55	3.71,3.57	9.6	-	-
8, p-$MeOC_6H_4$	Ph	CO_2Me	4.52	2.85	3.16	2.50	3.79,3.74,3.64	8.3	6.7	9.0
9, p-$MeOC_6H_4$	Ph	CO_2Me	4.47	2.98	3.28	2.56	3.80,3.73,3.58	9.7	6.6	10.2
8, Ph	Ph	CN	4.44	2.77	3.28	2.56	3.77	9.7	-	-
9, Ph	Ph	CN	4.49	2.98	3.36	3.38	3.73	8.7	-	-
16, Ph	Ph	CN	4.37	3.24	2.94	2.56	3.71	5.8	-	-
8, p-$MeOC_6H_4$	Ph	CN	4.39	2.78	3.25	2.61	3.81,3.79	8.8	7.5	9.7
9, p-$MeOC_6H_4$	Ph	CN	4.41	2.86	3.40	2.56	3.82,3.75	9.7	7.1	11.4
8, Ph p-$MeOC_6H_4$		CO_2Me	4.58	2.91	3.13	2.49	3.81,3.74,3.65	7.8	6.3	8.0
9, Ph p-$MeOC_6H_4$		CO_2Me	4.51	3.00	3.27	2.56	3.82,3.74,3.60	8.7	6.1	11.0
8, Ph	Pr^i	CO_2Me	4.38	2.76	2.48	2.29	3.76,3.59	9.2	8.9	9.4
9, Ph	Pr^i	CO_2Me	4.34	2.83	2.65	2.31	3.80,3.58	10.0	6.7	12.6
8, p-$MeOC_6H_4$	Pr^i	CO_2Me	4.31	2.73	2.46	2.28	3.79,3.76,3.59	9.3	9.1	9.4
9, p-$MeOC_6H_4$	Pr^i	CO_2Me	4.28	2.77	2.62	2.30	3.79,3.78,3.57	10.0	6.6	12.6
8, Ph	Pr^i	CN	4.28	2.68	2.52	2.40	3.79	9.3	9.1	9.4
9, Ph	Pr^i	CN	4.30	2.74	2.51	2.24	3.70	9.6	-	-
16, Ph	Pr^i	CN	4.31	3.19	2.72	2.31	3.76	6.4	8.9	3.9
8, p-$MeOC_6H_4$	Pr^i	CN	4.23	2.62	2.52	2.40	3.81,3.80	9.2	9.0	9.3
9, p-$MeOC_6H_4$	Pr^i	CN	4.24	2.64	2.76	2.29	3.85,3.81	9.8	6.6	11.8
16, p-$MeOC_6H_4$	Pr^i	CN	4.25	3.14	2.72	2.30	3.81,3.76	6.4	9.0	3.8

acrylonitrile Michael adducts reflects the small steric demand of the nitrile substituent.

The stereochemistry of the three isomeric pyrrolidines (18a), (18b) and (19) derived from cyclisation of (14) was also assigned by comparisons with the products derived from the thermal cycloadditions of (3, Ar=Ph, R=R^1=Me) and dimethyl fumarate. Thus (18a) is identical to the major thermal cycloadduct[26] whilst no OMe resonance occurs at high field in the p.m.r. spectrum of (18b) supporting a trans-arrangement of the C(4)-ester and C(5)-phenyl groups. The p.m.r. signal for the 3-H in (18b) is deshielded relative to the 3-H signal in (18a) and (19) indicating a cis-relationship between the C(2)-methyl and C(3)-ester groups in (18b). The p.m.r. spectrum of (19) has one ester methyl signal at high field indicating a cis-relationship between the C(4)-ester and C(5)-phenyl groups, whilst the 3-H and C(2)-methyl signals occur at the normal positions indicating the C(2)-methyl and C(3)-ester groups are trans-orientated.

Crystal data for (8, Ar=Ph, R=p-$MeOC_6H_4$. X=CO_2Me). $C_{21}H_{23}NO_5$. M = 369.4. Monoclinic, space group $P2_1/c$. a = 13.103(13), b = 14.913(15), c = 10.436(10)Å, β = 106.6(1)°, U = 1954.3Å^3. Z = 4. D_x = 1.26g cm^{-3}. F(000) = 784. λ(Cu-K_α) = 1.5418Å. Diamond-shaped thick blocks, dimensions 0.7 x 0.5 x 0.4mm, μ(Cu-K_α) = 6.5 cm^{-1}.

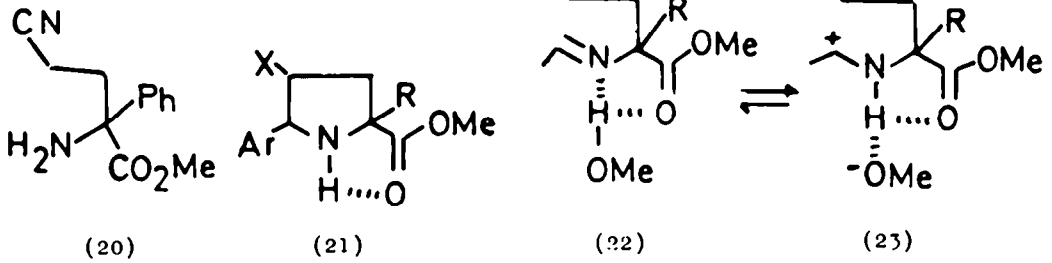
Data were recorded on an Enraf-Nonius CAD3 automatic diffractometer (using the $\theta/2\theta$ scan mode with scan width 1.2°; $2.5 \leq \theta \geq 67.5°$) and were corrected for Lorentz and polarization effects. After merging equivalent reflections the 1799 unique data with I 3 (I) were used in the subsequent analysis. The structure was solved by the direct phasing procedures of MULTAN[27] and refined by least squares, allowing anisotropic vibrations for non-hydrogen atoms, using SHELX[28]. The 22 hydrogens attached to carbon atoms were included in the refinement in positions calculated from the geometry of the molecule (C-H = 1.08Å). Common isotropic temperature factors were applied to tertiary CH, methylene, methyl and phenyl-type hydrogen atoms and these refined to final values of U = 0.08(2), 0.07(1), 0.16(1) and 0.10(1)Å^2 respectively. As there was more than one possible position for the hydrogen atom on the nitrogen (which is pyramidal) this atom was located in a difference Fourier and was allowed to refine independently. Uiso refined to 0.08(2)Å^2. In the final cycles the 1661 data with $I > 6\sigma(I)$ yielded a final R of 0.086. A projection of the molecule is shown in the Figure.≠



Figure

≠ Tables of atomic coordinates, temperature factors, derived results and supporting data have been deposited with the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

Mechanism of Pyrrolidine Formation from Michael Adducts (7). The cyclisation of the imines of α,α-disubstituted α-amino acid esters (7) to the isomeric pyrrolidines (8), (9) and (16) constitutes an example of a disfavoured 5-(enolexo)-endo-trig process.[13,32] Although there are many examples of disfavoured 5-endo-trig cyclisations[33] we felt it prudent to explore the possibility that (8), (9) and (16) might arise from (7) via a retro-Michael reaction regenerating the 4π-anion (10, M^+ = $PhCH_2NMe_3$) followed by a slow (compared to Michael addition) 4π + 2π anionic cycloaddition. However, crossed products were not observed when the cyclisation of (7, Ar=p-$MeOC_6H_4$, R=Ph, X=CN) was carried out in the presence of a 40 mole excess of methyl acrylate or when (7, Ar=p-$MeOC_6H_4$, R=Ph, X=CO_2Me) was cyclised in the presence of a 40 mole excess of acrylonitrile. The absence of crossed products supports a direct 5-endo-trig cyclisation. Further evidence for a direct 5-endo-trig cyclisation was provided by studying the cyclisation of a chiral imine. The racemic imine (7, Ar=p-$MeOC_6H_4$, R=Ph, X=CN) was hydrolysed and the resultant α,α-disubstituted α-amino acid ester (20) resolved as its salt with (+)-tartaric acid. The pure chiral amine (20) was a colourless liquid with $[\alpha]_D$ + 9.2 and its optical purity was confirmed by p.m.r. spectroscopy in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Condensation of chiral amine (20) with benzaldehyde afforded the chiral imine (7, Ar=R=Ph,X=CN), $[\alpha]_D$ -42.7, which was cyclised by boiling in dry benzene for 5h in the presence of BTAM (1mol) to give a mixture of three pyrrolidines (8), (9) and (16) (Ar=R=Ph,X=CN). Two of the pyrrolidines, (8) and (16) (Ar=R=Ph, X=CN), were isolated by preparative t.l.c. and both proved to be optically active with $[\alpha]_D$ + 17.4 and -45.3 respectively. Loss of optical activity would be expected if the cyclisation of (7) involved an initial retro-Michael reaction to (10). However, the failure of imines (15a-f) to cyclise under the same conditions as (7) indicates that the ester group to the imine nitrogen atom plays an important role in the cyclisation. The failure of (15e) to cyclise militates against this role being due to a simple acceleration of rate of cyclisation by gem-disubstitution (Thorpe-Ingold effect)[34] as does the slow cyclisation of (7, Ar=Ph, R=Pr^i, X=CN or CO_2Me). It seems probable that the role of the ester group is to stabilise the pyrrolidine products with respect to the imine (7) by hydrogen bonding (21), and that this free energy difference is reflected in the cyclisation transition state. Thus it is suggested that the species undergoing cyclisation is the hydrogen-bonded imine (22)* and that this hydrogen bonding reduces the C=N torsional energy barrier, (22) ⇌ (23), giving a product like transition state.



(20) (21) (22) (23)

The trans-4,5-stereochemistry in (8) and (9) is expected on steric grounds but might also arise by equilibration of the corresponding cis-4,5-isomers. However, epimerisation studies on (24)[1] indicate that the rate of cyclisation of (7, R ≠ Pr^i) >> rate of epimerisation of cis-4,5-isomers.

* More than one mole of methanol may be involved in the hydrogen bonding.

Experimental. General experimental details were as previously noted[30] and imines were prepared as previously described[30,31] except as noted below. Petroleum ether refers to the fraction with b.p. 60-80°C. Infrared spectra were determined for thin films unless otherwise stated.

Chiral methyl 2-(2'-cyanoethyl)phenylglycinate (23). The method used is adapted from the literature.[35] DL-Methyl p-methoxybenzylidene-2-(2'-cyanoethyl)phenyl glycinate (3.36g, 10mmol) was dissolved in ethanol (20ml) and (+)-tartaric acid (1.53g, 10.2mmol) and water (0.17ml) added. The mixture was stirred at room temperature for 16h and the precipitated tartrate salt of methyl 2-(2'-cyanoethyl) phenylglycinate (1.2g, 33%), m.p. 144-146°C, removed by filtration. The initial specific rotation of -2.7 was raised to -9.2 after several further crystallisations from ethanol-water. The chiral salt (2g, $[\alpha]_D$ -9.2) was dissolved in water and the pH adjusted to 7 by the addition of 20% aqueous sodium hydroxide. The turbid solution was then extracted with chloroform (3 x) and the combined chloroform extracts washed with water, dried (Na_2SO_4) and evaporated to leave a yellow oil. Distillation afforded the product as a colourless oil (0.6g, 51%), b.p. 132°C/0.1mmHg, $[\alpha]_D$ + 9.2 (Found: C, 66.15; H, 6.70; N, 12.60. $C_{12}H_{14}N_2O_2$ requires C, 66.05; H, 6.45; N, 12.85%); δ 7.39 (m, 5H, ArH), 3.73 (s, 3H, OMe) and 2.35 (m, 4H, CH_2CH_2).

Imines

Methyl N-benzylidenevalinate (3, Ar=Ph, R=Me, R^1=Pr^i). Prepared by method B as described previously.[28] The product (87%) distilled as a colourless oil, b.p. 100-102°C/0.05mmHg (Found: C, 70.95; H, 7.55; N, 6.25. $C_{13}H_{17}NO_2$ requires C, 71.20; H, 7.80; N, 6.40%); δ 8.26 (s, 1H, CH=N), 7.4 and 7.8 (m, 5H, ArH), 3.7 (d, 1H, CHN), 3.78 (s, 3H, OMe), 2.4 (m, 1H, C<u>H</u>Me_2) and 1.1 (d, 6H, 2 x Me); ν_{max} 1745 and 1640 cm^{-1}.

Methyl N-p-methoxybenzylidenevalinate (3, Ar=p-$MeOC_6H_4$, R=Me, R^1=Pr^i). Prepared (81%) as a colourless oil, b.p. 140-142°C/0.05mm, by method B as described previously.[28] (Found: C, 67.50; H, 7.40; N, 5.35. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.70; N, 5.60%); δ 8.15 (s, 1H, CH=N), 7.78, 7.7 and 6.92 (m and d, 9H, ArH), 3.8 and 3.77 (2 x s, 2 x 3H, OMe), 3.68 (d, 1H, CHN), 2.4 (m, 1H, C<u>H</u>Me_2) and 0.94 (d, 6H, 2 x Me); ν_{max} 1750 and 1650 cm^{-1}.

Methyl N-p-chlorobenzylidene(phenyl)glycinate (3, Ar=p-ClC_6H_4, R=Me, R^1=Ph). Obtained (70%) as colourless needles, m.p. 75-76°C, from ether-petroleum ether using method A.[28] (Found: C, 67.10; H, 5.10; N, 4.75. $C_{16}H_{14}ClNO_2$ requires C, 66.80; H, 4.85; N, 4.85%); δ 8.3 (s, 1H, CH=N), 7.8 (d, 2H, ArH), 7.45 (m, 7H, ArH), 5.2 (s, 1H, CHN) and 3.75 (s, 3H, OMe).

Methyl N-benzylidene (p-methoxyphenyl)glycinate (3, Ar=Ph, R=Me, R^1=p-$MeOC_6H_4$). Obtained (72%) as colourless needles, m.p. 63-64°C, from ether-hexane using method A.[28] (Found: C, 71.55; H, 6.00; N, 4.80. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.95%); δ 8.3 (s, 1H, CH=N), 7.8 (m,2H,ArH), 7.45 (m, 5H, ArH), 6.9 (d, 2H, ArH), 5.2 (s, 1H, CHN), and 3.8 and 3.75 (2 x s, 2 x 3H, OMe); ν_{max}(nujol) 1730 and 1625 cm^{-1}.

Methyl N-p-methoxybenzylidene(p-methoxyphenyl)glycinate (3, Ar=R^1=p-$MeOC_6H_4$, R=Me). Prepared using method A[28] as previously described. The product (65%) crystallised as colourless prisms from ether-petroleum ether, m.p. 68-69°C (Found: C, 68.60; H, 6.20; N, 4.70. $C_{18}H_{19}NO_4$ requires C, 69.00; H, 6.10; N, 4.45%); δ 8.25 (s, 1H, CH=N), 7.75 (d, 2H, ArH), 7.45 (d, 2H, ArH), 6.85 (d, 4H, ArH), 5.1 (s, 1H, CHN), and 3.8, 3.75 and 3.7 (3 x s, 3 x 3H, OMe); ν_{max}(nujol) 1720 and 1615 cm^{-1}.

Michael Adducts of Imines

General Procedure. Benzyltrimethylammonium methoxide (BTAM) (40% solution in methanol, 3.4g, 5.3mmol) in dry benzene (50ml) was added dropwise to a stirred solution of imine (3) (53mmol) in dry benzene (100ml) under an atmosphere of argon over 20 mins, followed by dropwise addition of methyl acrylate (4.6g, 53mmol) or acrylonitrile (2.9g, 53mmol) over 20 min. The resulting mixture was stirred at room temperature for a further 24h, or boiled in benzene under reflux for 7dy in the case of the valine imines. The mixture was worked up by washing with 10% cold aqueous ammonium chloride (100ml) and extracting the aqueous layer with ether (3 x 150ml). The combined organic extracts were washed with water (3 x 200ml), dried (Mg_2SO_4), evaporated and the crude Michael adduct purified by distillation under reduced pressure. Yields are recorded in table 1.

Dimethyl N-benzylideneglutamate (7, Ar=Ph, R=H, X=CO_2Me). Obtained as a colourless oil, b.p. 134-138°C/0.01mmHg (Found: C, 63.65; H, 6.60; N, 5.20. $C_{14}H_{17}NO_4$ requires C, 63.90; H, 6.45; N, 5.30%); δ 8.2 (s, 1H, CH=N), 7.4 (m, 5H, ArH), 4.0 (t, 1H, CHN), 3.7 and 3.6 (2 x s, 2 x 3H, OMe), and 2.35 (m, 4H, CH_2CH_2); ν_{max} 1735 and 1640 cm^{-1}; m/z(%) 263 (M^+, 42), 232(22), 204(77), 144(53), 118(77), 105(72) and 91(100).

Dimethyl N-benzylidene-2-methylglutamate (7, Ar=Ph, R=Me, X=CO_2Me). Obtained as a colourless oil, b.p. 155-157°C/1.5mmHg (Found: C, 65.15; H, 7.15; N, 5.65. $C_{15}H_{19}NO_4$ requires C, 64.95; H, 6.90; N, 5.05%); δ 8.3 (s, 1H, CH=N), 7.8 (m, 2H, ArH), 7.45 (m, 3H, ArH), 3.75 and 3.7 (2 x s, 2 x 3H, OMe), 2.45 (m, 4H, CH_2CH_2) and 1.5 (s, 3H, Me); m/z(%) 277 (M^+, 0.5), 262(2), 246(6) and 218(100)

Dimethyl N-p-methoxybenzylidene-2-methylglutamate (7, Ar=p-$MeOC_6H_4$, R=Me, X=CO_2Me). Obtained as a pale yellow oil and used without further purification. δ 8.15 (s, 1H, CH=N), 7.7 and 6.9 (2 x d, 2 x 2H, ArH), 3.8, 3.7 and 3.6 (3 x s, 3 x 3H, OMe), 2.4 (m, 4H, CH_2CH_2) and 1.5 (s, 3H, Me); ν_{max} 1730 and 1645 cm^{-1}

Methyl N-p-methoxybenzylidene-2-(2'-cyanoethyl)alaninate (7, Ar=p-$MeOC_6H_4$, R=Me, X=CN). Obtained as a pale yellow oil and used without further purification. δ 8.2 (s, 1H, CH=N), 7.7 and 7.0 (2 x d, 2 x 2H, ArH), 3.85 and 3.75 (2 x s, 2 x 3H, OMe), 2.4 (m, 4H, CH_2CH_2) and 1.5 (s, 3H, Me); ν_{max} 2240, 1725 and 1635 cm^{-1}

Dimethyl N-benzylidene-2-phenylglutamate (7, Ar=R=Ph, X=CO_2Me). Obtained as a colourless oil, b.p. 202-205°C/1.5mmHg (Found: C, 70.80; H, 6.25;; N, 4.15. $C_{20}H_{21}NO_4$ requires C, 70.75; H, 6.30; N, 4.10%); δ 8.18 (s, 1H, CH=N), 7.75 and 7.34 (m, 10H, ArH), 3.62 and 3.45 (2 x s, 2 x 3H, OMe), and 2.58 and 2.4 (2 x m, 2 x 2H, CH_2CH_2); ν_{max} 1730 and 1643 cm^{-1}; m/z(%) 339 (M^+, 0.5), 308(3), 280(100), 220(16) and 193(10).

Dimethyl N-p-methoxybenzylidene-2-phenylglutamate (7, Ar=p-$MeOC_6H_4$, R=Ph, X=CO_2Me). Obtained as a colourless oil, b.p. 184-188°C/0.05mmHg (Found: C, 68.20; H, 6.50; N, 4.00. $C_{21}H_{23}NO_5$ requires C, 68.30; H, 6.30; N, 3.80%); δ 8.2 (s, 1H, CH=N), 7.8 and 6.95 (2 x d, 2 x 2H, ArH), 7.4 (m, 5H, ArH), 3.8, 3.7 and 3.55 (3 x s, 3 x 3H, OMe) and 2.5 (m, 4H, CH_2CH_2); ν_{max} 1725 and 1655 cm^{-1}; m/z(%) 369 (M^+, 0.5), 338(4) and 310(100).

Methyl N-benzylidene-2-(2'-cyanoethyl)phenylglycinate (7, Ar=R=Ph, X=CN). Obtained as a colourless oil, b.p. 200-202°C/0.01mmHg (Found: C, 74.45; H, 6.00; N, 9.30. $C_{19}H_{18}N_2O_2$ requires C, 74.50; H, 5.90; N, 9.15%); δ 8.18 (s, 1H, CH=N), 7.8 and 7.34 (2 x m, 10H, ArH), 3.65 (s, 3H, OMe), and 2.51 and 2.36 (2 x m, 4H, CH_2CH_2); ν_{max} 2240, 1730 and 1640 cm^{-1}; m/z(%) 306 (M^+, 1), 247(100), 206(5) and 193(11).

Chiral methyl N-benzylidene-2-(2'-cyanoethyl)phenylglycinate (7, Ar=R=Ph, X=CN). Methyl 2-(2'-cyanoethyl)phenylglycinate (1.0g, 4.58mmol) (α]$_D$ + 9.2) and benzaldehyde (480mg, 4.58mmol) were reacted in dry dichloromethane containing a little anhydrous magnesium sulphate for 2dy at room temperature. Work up followed by column chromatography on silica eluting with 1:3 v/v ether-petroleum ether, afforded, the chiral product (650mg, 46%) (α]$_D$ -42.7°), whose spectral data was identical to the DL-isomer described above.

Methyl N-p-methoxybenzylidene-2-(2'-cyanoethyl)phenylglycinate (7, Ar=p-$MeOC_6H_4$, R=Ph, X=CN). Obtained as a colourless oil, b.p. 251-253°C/1 x 10^{-4}mmHg (Found: C, 71.65; H, 6.05; N, 8.20. $C_{20}H_{20}N_2O_3$ requires C, 71.40; H, 6.00; N, 8.35%); δ 8.2 (s, 1H, CH=N), 7.8 and 7.0 (2 x d, 2 x 2H, ArH), 7.4 (broad s, 5H, ArH), 3.85 and 3.75 (2 x s, 2 x 3H, OMe), and 2.5 (m, 4H, CH_2CH_2); ν_{max} 2235, 1730 and 1645 cm^{-1}.

Dimethyl N-benzylidene-2-p-methoxyphenylglutamate (7, Ar=Ph, R=p-$MeOC_6H_4$, X=CO_2Me). Obtained as a pale yellow oil, b.p. 194°C/0.1mmHg (Found: C, 71.40; H, 6.70; N, 4.50. $C_{21}H_{23}NO_5$ requires C, 71.35; H, 6.55; N, 4.00%); δ 8.2 (s, 1H, CH=N), 7.8 (m, 2H, ArH), 7.4 (m, 5H, ArH), 6.9 (d, 2H, ArH), 3.8, 3.75 and 3.55 (3 x s, 3 x 3H, OMe) and 2.5 (m, 4H, CH_2CH_2); ν_{max} 1725 and 1660 cm^{-1}.

Dimethyl N-p-methoxybenzylidene-2-p-methoxyphenylglutamate (7, Ar=R=p-$MeOC_6H_4$, X=CO_2Me). Obtained as a pale yellow oil, b.p. 210-212°C/0.1mmHg (Found: C, 65.95; H, 6.40; N, 3.75. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.30; N, 3.50%); δ 8.1 (s, 1H, CH=N), 7.8 and 7.4 (2 x d, 2 x 2H, ArH), 7.0 (m, 4H, ArH), 3.85, 3.80, 3.75 and 3.65 (4 x s, 4 x 3H, OMe) and 2.5 (m, 4H, CH_2CH_2); ν_{max} 1720 and 1650 cm^{-1}.

Dimethyl N-benzylidene-2-methoxycarbonylmethylglutamate (7, Ar=Ph, R=CH_2CO_2Me, X=CO_2Me). Obtained as a colourless oil, b.p. 174-180°C/0.2mmHg (Found: C, 61.00; H, 6.35; N, 4.30. $C_{17}H_{21}NO_6$ requires C, 60.90; H, 6.30; N, 4.20%); δ 8.4 (s, 1H, CH=N), 7.9-7.25 (m, 5H, ArH), 3.8 (s, 3H, OMe), 3.7 (s, 6H, 2 x OMe), 3.05 (s, 2H, $C\underline{H}_2CO_2Me$) and 2.45 (s, 4H, CH_2CH_2); ν_{max} 1750, 1730 and 1640 cm^{-1}.

Dimethyl N-benzylidene-2-isopropylglutamate (7, Ar=Ph, R=Pr^i, X=CO_2Me). Obtained as a colourless oil, b.p. 150-152°C/0.005mmHg (Found: C, 66.80; H, 7.60; N, 4.60. $C_{17}H_{23}NO_4$ requires C, 66.90; H, 7.55; N, 4.60%); δ 8.36 (s, 1H, CH=N), 7.9 and 7.29 (2 x m, 5H, ArH), 3.74 and 3.6 (2 x s, 2 x 3H, OMe), 2.31 (m, 4H, CH_2CH_2), 2.27 (m, 1H, $CHMe_2$), and 1.0 and 0.93 (2 x d, 2 x 3H, Me); ν max 1740 and 1650 cm^{-1}; m/z(%) 262(41), 246(100) and 174(15).

Dimethyl N-p-methoxybenzylidene-2-isopropylglutamate (7, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CO_2Me). Obtained as a colourless oil, b.p. 164-166°C/0.05mmHg (Found: C, 64.50; H, 7.60; N, 4.00. $C_{18}H_{25}NO_5$ requires C, 64.50; H, 7.65; N, 4.20%); δ 8.27 (s, 1H, CH=N), 7.71 and 6.9 (2 x d, 2 x 2H, ArH), 3.82, 3.74, and 3.6 (3 x s, 3 x 3H, OMe), 2.29 (m, 4H, CH_2CH_2), 2.2 (m, 1H, $C\underline{H}Me_2$) and 1.0 and 0.92 (2 x d, 2 x 3H, Me); ν_{max} 1740, and 1650 cm^{-1}; m/z(%) 336 (M + 1,2), 276(14), 190(72) and 142(100).

Methyl N-benzylidene-2-(2'-cyanoethyl)valinate (7, Ar=Ph, R=Pr^i, X=CN). Obtained as a colourless oil, b.p. 158-160°C/0.005mmHg (Found: C, 70.15; H, 7.20; N, 10.75. $C_{16}H_{20}N_2O_2$ requires C, 70.15; H, 7.35; N, 10.50%); δ 8.40 (s, 1H, CH=N), 7.72 and 7.39 (m, 5H, ArH), 3.73 (s, 3H, OMe), 2.41 and 2.33 (2 x m, 2 x 2H, CH_2CH_2), 2.18 (m, 1H, $CHMe_2$) and 0.97 and 0.89 (2 x d, 2 x 3H, Me); ν_{max} 2228, 1740 and 1652 cm^{-1}; m/z(%) 272 (M^+, 5), 229(24), 213(100) and 130(12).

Methyl N-p-methoxybenzylidene-2-(2'-cyanoethyl)valinate (7, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CN). Obtained as a colourless oil, b.p. 180-182°C/0.05mmHg (Found: C, 67.60; H, 7.35; N, 9.40. $C_{17}H_{22}N_2O_3$ requires C, 67.55; H, 7.30; N, 9.25%); δ 8.32 (s, 1H, CH=N), 7.72 and 6.92 (2 x d, 2 x 2H, ArH), 3.82 and 3.75 (2 x s, 2 x 3H, OMe), 2.43 and 2.4 (2 x m, 2 x 2H, CH_2CH_2), 2.24 (m, 1H, $CHMe_2$) and 0.98 and 0.9 (2 x d, 2 x 3H, Me); ν_{max} 2228, 1738 and 1650 cm^{-1}; m/z(%) 302 (M^+,9), 259(66), 243(100) and 190(24).

Dimethyl N-benzylidene-3-methoxycarbonyl-2-methylglutamate (14). Obtained (93%) as a colourless viscous oil, b.p. 178°C/1mmHg (Found: C, 60.60; H, 6.55; N, 4.30.

$C_{17}H_{21}NO_6$ requires C, 60.90; H, 6.30; N, 4.20%); δ 8.2 (s, 1H, CH=N), 7.75 (m, 2H, ArH), 7.35 (m, 3H, ArH), 3.75 (s, 3H, OMe), 3.65 (s, 6H, 2 x OMe), 3.3 (m, 1H, $CHCO_2Me$), 2.9 (dd, 2H, CH_2CO_2Me) and 1.45 (s, 3H, Me); ν_{max} 1730, 1700 and 1650 cm^{-1}; m/z(%) 320(5) and 276(100).

Methyl N-benzylidene-4-amino-4-phenylbutyrate (15a). Obtained (85%) as a yellow oil, b.p. 164-168°C/0.05mmHg (Found: C, 77.05; H, 7.05; N, 5.10. $C_{18}H_{19}NO_2$ requires C, 76.85; H, 6.80; N, 5.00%); δ 8.35 (s, 1H, CH=N), 7.8 (m, 2H, ArH), 7.4 (m, 8H, ArH), 4.4 (m, 1H, PhCH), 3.8 (s, 3H, OMe) and 3.3 (m, 4H, CH_2CH_2); ν_{max} 1735 and 1640 cm^{-1}; m/z(%) 281 (M^+,5) 195(78) and 194(100).

Methyl N-2'-thienylmethylene-4-amino-4-phenylbutyrate (15b). Obtained (68%) as a yellow oil, b.p. 173-178°C/0.2mmHg (Found: C, 66.50; H, 5.75; N, 4.65. $C_{16}H_{17}NO_2S$ requires C, 66.85; H, 5.95; N, 4.85%); δ 8.45 (s, 1H, CH=N), 7.4 (m, 6H, ArH and thienyl 5-H), 7.0 (m, 2H, thienyl H), 4.3 (m, 1H, PhCH), 3.65 (s, 3H, OMe) and 2.4 (m, 4H, CH_2CH_2).

Methyl N-3'-pyridylmethylene-4-amino-4-phenylbutyrate (15c). Obtained (75%) as a yellow oil, b.p. 197-202°C/0.2mmHg (Found: C, 72.15; H, 6.40; N, 9.60. $C_{17}H_{18}N_2O_2$ requires C, 72.30; H, 6.45; N, 9.90%); δ 8.4 (m + S, 3H, CH=N and PyH), 7.85 (m, 2H, PyH), 7.4 (m, 5H, ArH), 4.4 (t, 1H, PhCH), 3.6 (s, 3H, OMe) and 3.3 (m, 4H, CH_2CH_2).

Cyclisation of Michael Adducts

General Procedure

BTAM (40% solution in methanol, 20.7g, 4.56 mmol) in dry benzene (50ml) was added dropwise to a stirred solution of Michael adduct (7) or (14) (4.56 mmol) in dry benzene (200ml) over 20 mins. The reaction mixture was then stirred for 24h at room temperature or heated in boiling benzene for 5h (7, Ar=p-$MeOC_6H_4$) or for 2-7dy (7, R=Pr^i). The reaction mixture was then poured into cold 10% aqueous ammonium chloride (250ml). The aqueous layer was extracted with ether (3 x 200ml) and the combined organic extracts washed with water (3 x 250ml), dried (Mg_2SO_4) and evaporated to afford the crude pyrrolidines as stereoisomeric mixtures which were separated by preparative t.l.c. (SiO_2) eluting with ether-petroleum ether or ether-pentane. Most of the p.m.r. data of the pyrrolidines is collected in table 3.

Cyclisation of dimethyl N-benzylideneglutamate (7, Ar=Ph, R=H, X = CO_2Me).

a. The crude product comprised a 1.4:1 mixture of two pyrrolidines which were separated by preparative t.l.c. eluting with 3:7 v/v ether-petroleum ether. The major product, dimethyl t-5-phenyl-r-2,c-4-pyrrolidinedicarboxylate (8, Ar=Ph, R=H, X=CO_2Me) (54%), was obtained as a colourless oil (Found: C, 63.55; H, 6.20; N, 5.15. $C_{14}H_{17}NO_4$ requires C, 63.85; H, 6.50; N, 5.30%); δ ($CDCl_3$ + 1 drop D_2O) 7.35 (m, 5H, ArH).

The minor isomer, dimethyl c-5-phenyl-r-2,t-4-pyrrolidinedicarboxylate (9, Ar=Ph, R=H, X=CO_2Me)(24%), was a colourless oil (Found: C, 63.45; H, 6.35; N, 5.05. $C_{14}H_{17}NO_4$ requires C, 63.85; H, 6.50; N, 5.30%); δ ($CDCl_3$ + 1 drop D_2O) 7.34 (m, 5H, ArH).

b. Quenching the cyclisation with excess methyl iodide (2.5mol) and stirring at 25°C for 48h, followed by the usual work up, afforded a ca. 1.2:1 mixture of the corresponding N-methylpyrrolidines which were separated by preparative t.l.c. [Found (mixed isomers): C, 64.80; H, 6.75; N, 5.25. $C_{15}H_{19}NO_4$ requires C, 64.95; H, 6.90; N, 5.05%].

The major isomer, tentatively assigned as dimethyl 1-methyl-t-5-phenyl-r-2,c-4-pyrrolidinedicarboxylate (17a), (40%), was a colourless oil; δ 7.33 (m, 5H, ArH), 3.77 and 3.62 (2 x s, 2 x 3H, OMe), 3.67 (dd, 1H, 5-H), 3.36 (dd, 1H, 2-H), 2.39 (dd, 1H, 2 x 3-H), and 2.22 (s, 3H, NMe).

The minor isomer, tentatively assigned as dimethyl 1-methyl-c-5-phenyl-r-2,t-4-pyrrolidinedicarboxylate (17b) (30%); δ 7.43 (broad s, 5H, ArH), 3.69 and 3.39 (2 x s, 2 x 3H, OMe), 3.04 (d, 1H, 5-H), 2.72 (s, 3H, NMe) and 2.72-2.2 (m, 4H, 2-H, 4-H and 2 x 3-H).

Cyclisation of dimethyl N-benzylidene-2-methylglutamate (7, Ar=Ph, R=Me, X=CO_2Me). The crude product comprised a 7:1 mixture of two pyrrolidines which distilled unchanged to afford a colourless oil, b.p. 140-142°C/0.5mmHg [Found (mixed isomers): C, 64.90; H, 6.95; N, 5.20. $C_{15}H_{19}NO_4$ requires C, 64.95; H, 6.90; N, 5.05%]. Preparative t.l.c. eluting with 1:1 v/v ether-petroleum ether afforded the pure isomers.

The major isomer, dimethyl 2-methyl-t-5-phenyl-r-2,c-4-pyrrolidinedicarboxylate (8, Ar=Ph, R=Me, X=CO_2Me) (65%), was a colourless oil. δ ($CDCl_3$ + 1 drop D_2O) 7.34 (m, 5H, ArH), and 1.5 (s, 3H, Me).

The minor isomer, dimethyl 2-methyl-c-5-phenyl-r-2,t-4-pyrrolidinedicarboxylate (9, Ar=Ph, R=Me, X=CO_2Me) (8.5%), was a colourless oil. δ ($CDCl_3$ + 1 drop D_2O) 7.35 (m, 5H, ArH), and 1.55 (s, 3H, Me).

Cyclisation of methyl N-p-methoxybenzylidene-2-(2'-cyanoethyl)alaninate (7, Ar=p-$MeOC_6H_4$, R=Me, X=CN). The crude product was a yellow oil which comprised a 4:1:1.2 mixture of three pyrrolidines. Preparative t.l.c. eluting with 3:7 v/v ether-petroleum ether afforded the pure isomers. [Found (mixed isomers) C, 65.45; H, 6.40; N, 10.35. $C_{15}H_{18}N_2O_3$ requires C, 65.65; H, 6.60; N, 10.20%].

The major isomer methyl c-4-cyano-t-5-(p-methoxyphenyl)-2-methyl-r-2-pyrrolidine carboxylate (8, Ar=p-$MeOC_6H_4$, R=Me, X=CN) (51%) was a pale yellow oil. δ 7.41 and 6.89 (2 x d, 2 x 2H, ArH) and 1.49 (s, 3H, Me).

The minor isomer, methyl t-4-cyano-c-5-(p-methoxyphenyl)-2-methyl-r-2-pyrrolidine carboxylate (9, Ar=p-$MeOC_6H_4$, R=Me, X=CN) (9%), was obtained as a pale yellow oil. δ 7.4 and 6.9 (2 x d, 2 x 2H, ArH) and 1.55 (s, 3H, Me).

A third isomer, methyl t-4-cyano-t-5-(p-methoxyphenyl)-2-methyl-r-2-pyrrolidine carboxylate (16, Ar=p-$MeOC_6H_4$, R=Me, X=CN) (12%), was obtained as a pale yellow oil. δ 7.4 and 6.9 (2 x d, 2 x 2H, ArH) and 1.6 (s, 3H, Me).

Cyclisation of dimethyl N-benzylidene-2-phenylglutamate (7, Ar=R=Ph, X=CO_2Me). The crude product was a colourless oil which comprised a 3.7:1 mixture of two pyrrolidines. Distillation gave a colourless oil (82%), b.p. 204-206°C/1mmHg in which the isomer ratio was unchanged (Found: C, 70.90; H, 6.25; N, 4.20. $C_{20}H_{21}NO_4$ requires C, 70.80; H, 6.25; N, 4.15%). Preparative t.l.c. eluting with 1:1 v/v ether-petroleum ether afforded the pure isomers.

The major isomer, dimethyl 2,t-5-diphenyl-r-2,c-4-pyrrolidinedicarboxylate (8, Ar=R,Ph, X=CO_2Me) (65%), was obtained as a colourless oil. δ 7.73-7.23 (m, 10H, ArH); m/z(%) 308 (M-OMe, 3), 280(100), 248(3), 220(15) and 193(19).

The minor isomer, dimethyl 2,c-5-diphenyl-r-2, t-4-pyrrolidinedicarboxylate (9, Ar=R=Ph, X=CO_2Me) (16%), was obtained as a colourless oil. δ 7.5 (m, 10H, ArH).

Cyclisation of dimethyl N-p-methoxybenzylidene-2-phenylglutamate (7, Ar=p-$MeOC_6H_4$,R=Ph, X=CO_2Me). The crude product was a colourless oil which comprised a 3.4:1 mixture of two pyrrolidines which could be separated by preparative t.l.c. eluting with 3:7 v/v ether-petroleum ether [Found (mixed isomers) C, 68.10; H, 6.35; N, 3.60. $C_{21}H_{23}NO_5$ requires C, 68.30; H, 6.25; N, 3.80%].

The major product, dimethyl t-5-p-methoxyphenyl-2-phenyl-r-2-,c-4-pyrrolidinedicarboxylate (8, Ar=p-$MeOC_6H_4$, R=Ph, X=CO_2Me)(59%), was obtained as a pale yellow oil. δ 7.73-7.24 (m, 7H, ArH) and 6.9 (d, 2H, ArH).

The minor isomer, dimethyl c-5-p-methoxyphenyl-2-phenyl-r-2,t-4-pyrrolidine dicarboxylate (9, Ar=p-$MeOC_6H_4$, R=Ph, X=CO_2Me)(19%), crystallised from ether-petroleum ether at colourless needles, m.p. 92-92°C. δ 7.63-7.20 (m, 7H, ArH) and 6.89 (d,2H,ArH); ν_{max}(nujol) 3360, 1710 and 1690 cm^{-1}; m/z(%) 369 (M^+,2).

Cyclisation of methyl N-benzylidene-2-(2'-cyanoethyl)phenylglycinate (7, Ar=R=Ph, X=CN). The crude product was a colourless oil which comprised a 4.5:1.5:1 mixture of three isomeric pyrrolidines which could be separated by preparative t.l.c. eluting with 2:3 v/v ether-petroleum ether [Found (mixed isomers) C, 74.25; H, 6.15; N, 9.05. $C_{19}H_{18}N_2O_2$ requires C, 74.30; H, 5.90; N, 9.15%]; ν_{max} (mixed isomers) 3330, 2220, 2180, and 1725 cm^{-1}; m/z(%) (mixed isomers) 248(14), 247(44), 144(10) and 91(100).

The major isomer, methyl c-4-cyano-t-5,2-diphenyl-r-2-pyrrolidinecarboxylate (8, Ar=R=Ph, X=CN) (45%), was obtained as colourless plates, m.p. 75-77°C. δ 7.56 and 7.34 (2 x m, 2 x 5H, ArH).

A second isomer, methyl t-4-cyano-c-5,2-diphenyl-r-2-pyrrolidinecarboxylate (9, Ar=R=Ph, X=CN) (15%), was obtained as a colourless viscous oil. δ 7.52-7.36 (m, 10H, ArH).

The minor isomer, methyl t-4-cyano-t-5,2-diphenyl-r-2-pyrrolidinecarboxylate (16, Ar=R=Ph, X=CN) (10%), was obtained as a colourless viscous oil. δ 7.6-7.37 (m, 10H, ArH). When the reaction was repeated with chiral methyl N-benzylidene-2-(2'-cyanoethyl)phenylglycinate ($[\alpha]_D$ -42.7) work up as before afforded the chiral major isomer (8, Ar=R=Ph, X=CN), ($[\alpha]_D$ + 17.4), and the chiral minor isomer (16, Ar=R=Ph, X=CN), ($[\alpha]_D$ -45.3).

Cyclisation of methyl N-p-methoxybenzylidene-2-(2'-cyanoethyl)phenylglycinate (7, Ar=p-$MeOC_6H_4$, R=Ph, X=CN). The crude product was a pale yellow oil which comprised a 5:1 mixture of two pyrrolidines. The mixture was separated by preparative t.l.c. eluting with 1:1 v/v ether-petroleum ether.

The major isomer, methyl c-4-cyano-t-5-p-methoxyphenyl-2-phenyl-r-2-pyrrolidinecarboxylate (8, Ar=p-$MeOC_6H_4$, R=Ph, X=CN) (64%), was obtained as colourless prisms, m.p. 138-140°C, from dichloromethane-petroleum ether (Found: C, 71.70; H, 6.15; N, 8.10. $C_{20}H_{20}N_2O_3$ requires C, 71.40; H, 6.00; N, 8.35%); δ 7.6-7.26 (m, 7H, ArH) and 6.88 (d, 2H, ArH); ν_{max} 3340, 2230 and 1730 cm^{-1}; m/z(%) 277 (M-CO_2Me, 100) and 223(10).

The minor isomer, methyl t-4-cyano-c-5-p-methoxyphenyl-2-phenyl-r-2-pyrrolidinecarboxylate (9, Ar=p-$MeOC_6H_4$, R=Ph, X=CN) (13%), was obtained as colourless plates from dichloromethane-petroleum ether, m.p. 160-162°C (Found: N, 8.25. $C_{20}H_{20}N_2O_3$ requires N, 8.35%); δ 7.6-7.3 (m, 7H, ArH) and 6.94 (d, 2H, ArH); ν_{max} 3350, 2240 and 1730 cm^{-1}.

Cyclisation of dimethyl N-benzylidene-2-p-methoxyphenylglutamate (7, Ar=Ph, R=p-$MeOC_6H_4$, X=CO_2Me). The crude product was a colourless oil comprising a 3:1 mixture of two pyrrolidines which were separated by preparative t.l.c. eluting with 3:7 v/v ether-petroleum ether. The major isomer, dimethyl 2-p-methoxyphenyl-t-5-phenyl-r-2-c-4-pyrrolidinedicarboxylate (8, Ar=Ph, R=p-$MeOC_6H_4$, X=CO_2Me) (65%), was obtained as colourless plates from chloroform-petroleum ether, m.p. 79-81°C (Found: C, 68.00; H, 6.40; N, 3.85. $C_{21}H_{23}NO_5$ requires C, 68.30; H, 6.25; N, 3.80%); δ 7.56 (d, 2H, ArH), 7.39 (m, 5H, ArH) and 6.89 (d, 2H, ArH); ν_{max}(nujol) 3360, 1730 and 1715 cm^{-1}; m/z(%) 310 (M-CO_2Me,100), and 250(20).

The minor isomer, dimethyl 2-p-methoxyphenyl-c-5-phenyl-r-2,t-4-pyrrolidinedicarboxylate (9, Ar=Ph, R=p-$MeOC_6H_4$, X=CO_2Me) (23%), crystallised as colourless plates from ether-petroleum ether, m.p. 41-43°C (Found: C, 68.10; H, 6.40; N, 3.60. $C_{21}H_{23}NO_5$ requires C, 68.30; H, 6.25; N, 3.8%); δ 7.46 (d, 2H, ArH), 7.35 (broad s, 5H, ArH) and 6.86 (d, 2H, ArH); ν_{max}(nujol) 3330 and 1720 cm^{-1}.

Cyclisation of dimethyl N-benzylidene-2-isopropylglutamate (7, Ar=Ph, R=Pr^i, X=CO_2Me). The crude product was a colourless oil comprising a 3:1 mixture of two pyrrolidines which were separated by preparative t.l.c. eluting with 1:3 v/v ether-petroleum ether. [Found (mixed isomers): C, 66.30; H, 7.70; N, 4.60.

$C_{17}H_{23}NO_4$ requires C, 66.50; H, 7.55; N, 4.60%]; m/z(%) (mixed isomers) 246(13), 142(34) and 126(100).

The major isomer, dimethyl 2-isopropyl-t-5-phenyl-r-2,c-4-pyrrolidinedicarboxylate (8, Ar=Ph, R=Pr^i, X=CO_2Me)(60%), was a colourless oil. δ 7.50-7.28 (m, 5H, ArH), 2.08 (m, 1H, C<u>H</u>Me_2), and 1.02 and 0.87 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

The minor isomer, dimethyl 2-isopropyl-c-5-phenyl-r-2,t-4-pyrrolidinedicarboxylate (8, Ar=Ph, R=Pr^i, X=CO_2Me)(20%), was a colourless oil. δ 7.40-7.24 (m, 5H, ArH), 2.09 (m, 1H, C<u>H</u>Me_2), and 0.98 and 0.92 (d, 6H, CH<u>Me</u>$_2$).

Cyclisation of dimethyl N-p-methoxybenzylidene-2-isopropylglutamate (7, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CO_2Me). The crude product was a colourless liquid comprising a 3:1 mixture of two pyrrolidines which were separated by preparative t.l.c. eluting with 1:10 v/v ether-petroleum ether. [Pound (mixed isomers): C, 64.60 H, 7.55; N, 4.05. $C_{18}H_{25}NO_5$ requires C, 64.50; H, 7.45; N, 4.20%]; m/z(%) (mixed isomers) 335 (M^+,6), 292(57), 276(100), 260(12), 232(12) and 174(12).

The major isomer, dimethyl 2-isopropyl-t-5-p-methoxyphenyl-r-2,c-4-pyrrolidinedicarboxylate (8, Ar= p-$MeOC_6H_4$, R=Pr^i, X=CO_2Me)(60%), was a colourless oil. δ 7.44 and 6.9 (2 x d, 2 x 2H, ArH), 2.08 (m, 1H, C<u>H</u>Me_2), and 0.99 and 0.86 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

The minor isomer, dimethyl 2-isopropyl-c-5-p-methoxyphenyl-r-2,t-4-pyrrolidinedicarboxylate (9, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CO_2Me)(20%) was a colourless oil. δ 7.38 and 6.94 (2 x d, 2 x 2H, ArH), 2.10 (m, 1H, C<u>H</u>Me_2) and 0.98 and 0.92 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

Cyclisation of methyl N-benzylidene-2-(2'-cyanoethyl)valinate (7, Ar=Ph, R=Pr^i, X=CN). The crude product was a pale yellow oil comprising a 7.5:1:1.5 mixture of three pyrrolidines which could be separated by preparative t.l.c. eluting with 1:3 v/v ether-petroleum ether [Pound (mixed isomers): C, 70.70; H, 7.70; N, 10.55. $C_{16}H_{20}N_2O_2$ requires C, 70.55; H, 7.40; N, 10.30%]; m/z(%) (mixed isomers) 273 (M+1,1), 229(43) and 213(100). The major isomer, methyl 2-isopropyl-c-4-cyano-t-5-phenyl-r-2-pyrrolidine carboxylate (8, Ar=Ph, R=Pr^i, X=CN) (58%), was obtained as a colourless oil. δ 7.56-7.32 (m, 5H, ArH), 2.09 (m, 1H, C<u>H</u>Me_2), and 0.99 and 0.87 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

The minor isomer, methyl 2-isopropyl-t-4-cyano-c-5-phenyl-r-2-pyrrolidinecarboxylate (9, Ar=Ph, R=Pr^i, X=CN) (8%), was obtained as a colourless oil. δ 7.38 and 6.94 (2 x d, 2 x 2H, ArH), 2.10 (m, 1H, C<u>H</u>Me_2) and 0.98 and 0.92 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

A third isomer, methyl 2-isopropyl-t-4-cyano-t-5-phenyl-r-2-pyrrolidinecarboxylate (16, Ar=Ph, R=Pr^i, X=CN) (12%), was obtained as a colourless oil. δ 7.44 and 6.92 (2 x d, 2 x 2H, ArH), 2.15 (m, 1H, C<u>H</u>Me_2) and 1.06 and 0.98 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

Cyclisation of methyl N-p-methoxybenzylidene-2-(2'-cyanomethyl)valinate (7, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CN). The crude product was a colourless oil comprising a 6.7:1.7:1 mixture of three pyrrolidines together with a trace amount of a fourth isomer. Preparative t.l.c. of the mixture eluting with 1:3 v/v ether-petroleum ether afforded the pure isomers which were all colourless oil. [Found (mixed isomers): C, 67.45; H, 7.65; N, 9.20. $C_{17}H_{22}O_3N_2$ requires C, 67.50; H, 7.35; N, 9.35%]; m/z(%) (mixed isomers) 302 (M^+,10), 276(59), 259(41), 243(100), 200(10) and 189(36).

Major isomer, methyl 2-isopropyl-c-4-cyano-t-5-p-methoxyphenyl-r-2-pyrrolidinecarboxylate (8, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CN)(54%); δ 7.36 and 6.84 (2 x d, 2 x 2H, ArH), 2.1 (m, 1H, C<u>H</u>Me_2) and 0.99 and 0.86 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

The second most abundant isomer proved to be methyl 2-isopropyl-t-4-cyano-c-5-p-methoxyphenyl-r-2-pyrrolidinecarboxylate (9, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CN)(14%); δ 7.33 and 6.89 (2 x d, 2 x 2H, ArH), 2.13 (m, 1H, C<u>H</u>Me_2) and 0.98 and 0.92 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

Minor isomer, methyl 2-isopropyl-t-4--cyano-t-5-p-methoxyphenyl-r-2-pyrrolidinecarboxylate (16, Ar=p-$MeOC_6H_4$, R=Pr^i, X=CN)(8%); δ 7.32 and 6.84 (2 x d, 2 x 2H, ArH), 2.05 (m, 1H, C<u>H</u>Me_2) and 1.06 and 0.98 (2 x d, 2 x 3H, CH<u>Me</u>$_2$).

Cyclisation of dimethyl N-benzylidene-3-methoxycarbonyl-2-methylglutamate (14). The crude product was a colourless oil comprising a 4:4:1 mixture of three pyrrolidines which were separated by preparative t.l.c. eluting with 1:1 ether-petroleum ether.

Trimethyl 2-methyl-c-5-phenyl-r-2,c-3,t-4-pyrrolidinetricarboxylate (18a)(39%) crystallised as colourless prisms from ether-petroleum ether, m.p. 78-81°C, (lit.[26] 78-81°C).

The other major isomer, trimethyl 2-methyl-t-5-phenyl-r-2,t-3,c-4-pyrrolidinetricarboxylate (18b)(31%), crystallised as colourless prisms from ether-petroleum ether, m.p. 50-52°C (Found: C, 60.80; H, 6.20; N, 4.30. $C_{17}H_{21}NO_6$ requires C, 60.90; H, 6.30; N, 4.20%); δ($CDCl_3$ + 1 drop D_2O) 7.41 (m, 5H, ArH), 4.33 (d, 1H, 5-H), 3.87 (d, 1H, 3-H), 3.83, 3.81 and 3.78 (3 x s, 3 x 3H, OMe), 3.48 (dd, 1H, 4-H) and 1.39 (s, 3H, Me); ν_{max}(nujol) 3330, 1730, 1720 and 1710 cm^{-1}.

The minor isomer, trimethyl 2-methyl-t-5-phenyl-r-c-3,t-2-methyl-t-5-phenyl-r-2,2-t-4-pyrrolidinetricarboxylate (19)(9%), was obtained as colourless prisms, m.p. 87-90°C, from ether-petroleum ether (Pound: C, 61.00; H, 6.50; N, 4.20. $C_{17}H_{21}NO_6$ requires C, 60.90; H, 6.30; N, 4.20%); δ 7.27 (broad s, 5H, ArH), 4.74 (d, 1H, 5-H), 3.78 (dd, 1H, 4-H), 3.51 (d, 1H, 3-H), 3.82, 3.74 and 3.10 (3 x s, 3 x 3H, OMe), and 1.8 (s, 3H, Me); ν_{max}(nujol) 3360, 1725 and 1710 cm^{-1}.

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