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A NEW SYNTHESIS OF α-AMINO ACIDS—III[1]

AMIDOALKYLATION OF ACTIVE METHYLENE COMPOUNDS WITH GLYOXYLIC ACID DERIVATIVES[2]

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Abstract—The synthesis of N-acyl derivatives of γ - keto - α - amino acids (3, 4, 5) by the amidoalkylation of 1,3-dicarbonyl compounds with glyoxylic acid-amide adducts (1, 2) is described. The γ - keto - α - amino acid derivatives (4, 5) were further converted to the corresponding butenolides (6, 7) and to pyrazolylglycine (12).

γ - Keto - α - amino acids and γ - hydroxy - α - amino acids are natural occuring amino acids.[3-5] Thus Kynurenine and its N-formyl derivatives are important intermediates in the metabolism of tryptophan.[6] Recently furoylalanine was isolated and characterized from buckwheat seeds.[7] The γ-ketoacids can be converted to γ - hydroxy - α - amino acids, which are more stable in a γ-lactone form, [4,5] to α,γ-diamino acids on reductive amination and to heterocyclic α-amino acids on treatment with hydrazine. We now report a new and direct synthesis of N-acyl derivatives of γ - keto - α - amino acids using 1,3-diketones and β-ketoesters and glyoxylic acid-amide adducts as starting materials.

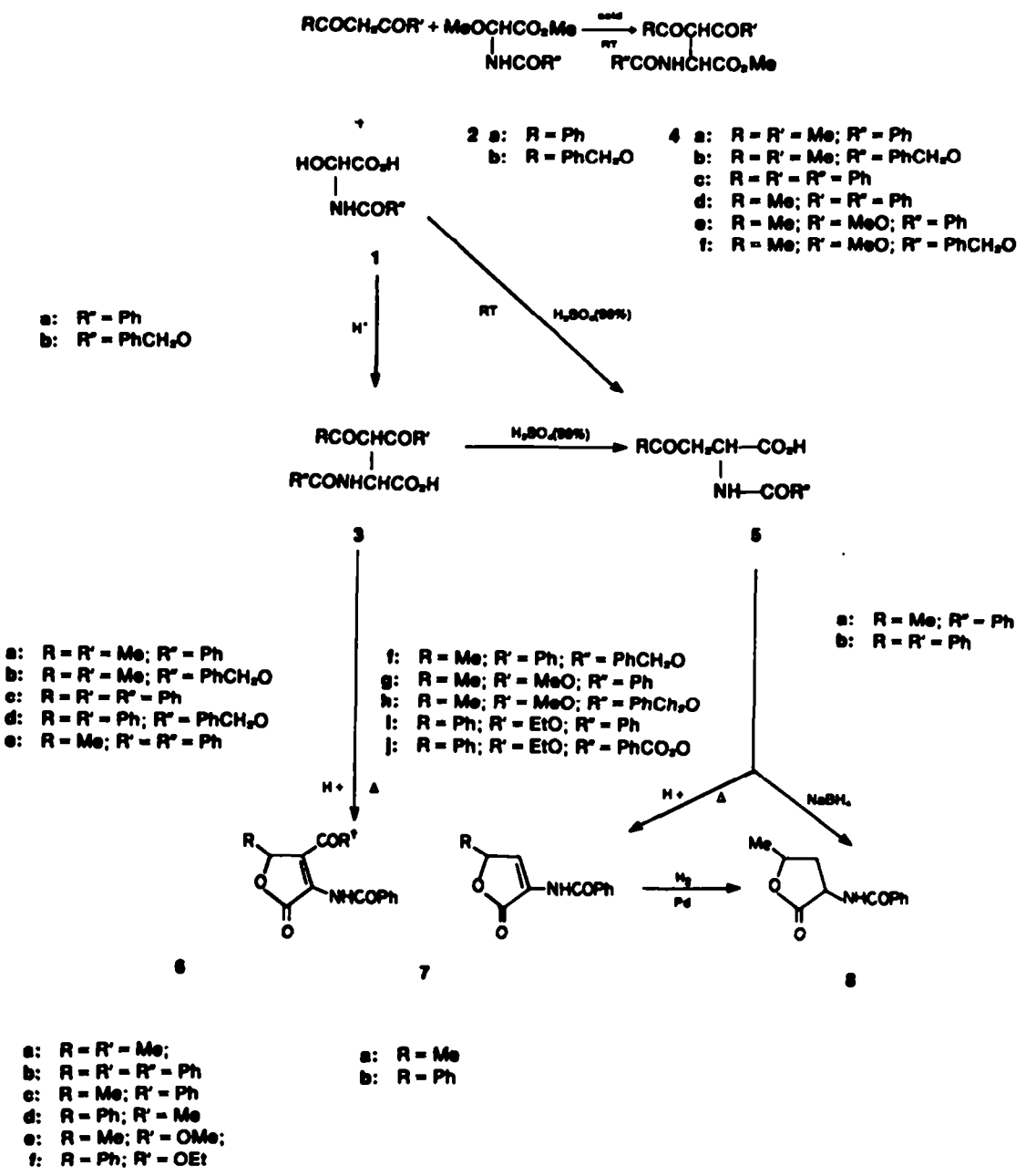
Sulfuric acid is the most commonly used acid catalyst and reaction medium in amidoalkylations. Its use is limited however to those nucleophiles which are stable in the concentrated acid and do not undergo self condensation, sulfonation or extensive decomposition. Amidoalkylation of β-diketones or β-ketoesters with α-hydroxyhippuric acid in concentrated sulfuric acid is generally accompanied by deacylation or decarboalkoxylation of the primary formed product 3 giving the α - benzamido - γ - ketoacid 5. Thus reacting α-hydroxyhippuric acid with benzoylacetone, dibenzoylmethane and ethyl benzoylacetate in concentrated sulfuric acid gave the same product, the N - benzoyl - β - benzoylalanine (5b). Methyl acetoacetate reacted with α-hydroxyhippuric acid under the same conditions to give α-benzamidolevulinic acid (5a). Only acetylacetone afforded in concentrated sulfuric acid the primary product the N-benzoyl-β,β-diacetylalanine (3a).

A milder reaction medium which has most of the advantage of sulfuric acid (strong acid, powerful solvent) and is less destructive is methanesulfonic acid.[8] Reacting dibenzoylmethane and ethyl benzoylacetate with α-hydroxyhippuric acid in methanesulfonic acid at room temperature afforded the expected primary products 3c and 3f in 75 and 72% yield. Trifluoroacetic acid which is even a weaker acid than methanesulfonic acid was also used successfully in the amidoalkylations of acetylacetone, benzoylacetone and dibenzoylmethane with α-hydroxyhippuric acid and methyl α-methoxyhippurate (1a, 2a). Very little hydrolyses of the ester group were observed in the last cases (4a, 4c, 4d).

A mixture of 10% sulfuric-acetic acid (v/v) was also found to be useful in the amidoalkylations of active methylene compounds. In this reaction medium the adducts of benzyl carbamate and glyoxylic acid (1b) can be used to amidoalkylate the 1,3-diketones with little decomposition of the acid labile N-benzyloxycarbonyl group. Thus reacting acetylacetone, benzoylacetone and ethyl benzoylacetate with α - hydroxy - N - benzyloxycarbonylglycine in sulfuric-acetic acid mixture afforded N - benzyloxycarbonyl - β,β - diacetyl alanine (3b), N - benzyloxycarbonyl - β - benzoyl - β - acetylalanine (3f) and N - benzyloxycarbonyl - β - benzoylaspartic acid β-monomethyl ester (3f) in 44, 56 and 54% yield. In the last two cases (3f, 3j) a mixture of two isomers were obtained. Trituration with ether afforded in each case one of the isomers in pure form.

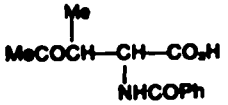
The amidoalkylation of methyl acetoacetate and ethyl α-methylacetoacetate with methyl α-methoxyhippurate (2a) and methyl α - methoxy - N - benzyloxycarbonylglycinate (2b) to give 4e, 4f and 11 were best carried out in methylene chloride and carbon tetrachloride and in the presence of $BF_3{\cdot}OEt_2$. The use of anhydrous solvents minimized the hydrolyses of the ester groups and the formation of undesired bisadducts. Carbon tetrachloride was found to be very effective solvent in the amidoalkylation of the acetoacetates probably because the less polar the solvent, the more enolic is the β-ketoester. The enolic form is the reactive entity in the acid catalyzed reactions. The products obtained in the amidoalkylation of the acetoacetates were according to the NMR a mixture of two isomers. The NMR showed two acetyl groups. On trituration with ether the stereomers 4a was slowly converted to one isomer.

The primary products 3 and 4 obtained from benzoylacetone (3e, 3f and 4d), methyl acetoacetate (3g, 3h, 4e and 4f) and ethyl benzoylacetate (3i, 3j) have two chiral centers and can therefore be obtained as mixtures of two stereomers. One of the two chiral centers is an active methine group (β-carbon) and will therefore equilibrate easily. Furthermore, being derivatives of β-diketones and β-ketoesters these products (3 and 4) can also exist as keto-enol tautomers. According to the NMR spectra there is little if any enol forms in 3 and 4. There is no absorptions below 10 ppm and the integration of the β-methine hydrogen is approximately the same as that of the α-hydrogen. The first showed a doublet and the second a quartet or triplet in the NMR. In order to prove that the primary products 3 can be the intermediate in



the formation of 5 when the reactions were carried out in concentrated sulfuric acid, 3e and 3g were dissolved in concentrated sulfuric acid. After 48 hr at room temperature they were converted in high yields to 5a and 5b.

Ethyl α-methylacetoacetate was found to react with α-hydroxyhippuric acid in concentrated sulfuric acid to give a mixture of the acid 9 and the butenolide 10. In carbon tetrachloride and in the presence of BF_3·OEt_2 2a and 2b reacted with ethyl α-methylacetoacetate to give 11a and 11b as mixtures of isomers. The isomers of 11a were separated by fractional crystallization.



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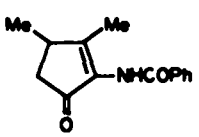
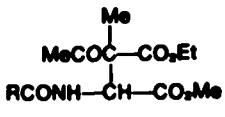


10

The β,β-diacylalanine derivatives 3 and the N - acyl - β - acylalanines (5) were found to cyclize smoothly in boiling 1,2 - dichloroethane solutions and in the presence of β-naphthalenesulfonic acid catalyst to the butenolides 6 and 7. The butenolides have only one chiral center and therefore stereomers are not possible. However, in the case of the non symmetrical N - benzoyl - β - benzoyl - β - acetylalanine (3e) cyclization to the butenolide 6 afforded a mixture of two isomers 6c and 6d in the ratio of 1:3 (according to the NMR). Trituration with ether or crystallization afforded pure 6d while chromatography of the mother liquor gave pure 6c. The butenolide 7a was further catalytically hydrogenated to the corresponding α - benzamido - 5 - methyl butyrolactone 8. Only the *cis*



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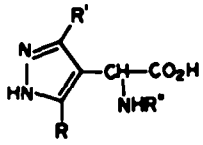
a: R = Ph
b: R = $PhCH_2O$



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a: R = R' = Me; R'' = H
b: R = R' = Me; R'' = PhCO
c: R = R' = Me; R'' = $PhCH_2O$
d: R = R' = Ph; R'' = H
e: R = R' = Ph; R'' = PhCO
f: R = Me; R' = Ph; R'' = H
g: R = Me; R' = Ph; R'' = PhCO
h: R = Me; R' = Ph; R'' = $PhCH_2O$

lactone was obtained in the catalytic hydrogenation while treatment of the γ-ketoacid 5a with sodium borohydride afforded a mixture of the *cis–trans* lactones 8.[12]

The diketoamino acids 3 were further reacted with hydrazine in methanolic solution to give the (pyrazolyl-4) glycine derivatives (12b, 12c, 12e, 12g and 12h) in 50–80% yield. The benzoyl groups in 12b, 12e and 12g were removed by acid hydrolyses to give the amino acid hydrochlorides which were converted to the free amino acids 12a, 12d and 12f. Acid hydrolyses of the N-benzoylamino acids 3, 4 or 5 in 6 N HCl afforded the hydrochlorides of the γ - keto - α - amino acids β-acetylalanine (13a) and β-benzoylalanine (13b). The hydrolyses of 3 and 4 were accompanied by deacylation to give the monoketo - α - amino acids.

13

a, R = Me
b, R = Ph

14

a, R = Me
b, R = Ph

Treatment of the N-benzyloxycarbonyl derivatives 3b and 3d with hydrogen bromide in acetic acid at room temperature afforded the corresponding β,β - diacyl - α - amino acid hydrobromides 14a and 14b. No deacylation on carbon was obtained under the conditions of hydrogen bromide in acetic acid.

EXPERIMENTAL

General. M.ps are uncorrected. The IR spectra were recorded on a Perkin–Elmer 237 spectrophotometer; NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts are reported in ppm downfield from TMS.

Amidoalkylations of 1,3-diketones and β-ketoesters

Procedure A—Concentrated strong acids (sulfuric, methanesulfonic and trifluoroacetic). To a cooled soln (ice-water) of 1a (1.95 g; 0.01 mole) in conc H_2SO_4 (10 ml Merck 96%) there was added the active methylene component (0.01–0.02 mole). After stirring at room temp. for 48 hr the soln was poured into crushed ice and extracted with EtOAc (2 × 75 ml). The organic soln was washed with water (2 × 50 ml) and extracted with $NaHCO_3$ aq (2 × 25 ml of 1 molar soln). The $NaHCO_3$ soln was cooled, acidified with conc. HCl and re-extracted with EtOAc (2 × 75 ml). It was dried over $MgSO_4$ and evaporated.

The same procedure was used with methanesulfonic acid (10 ml Fluka puriss) and trifluoroacetic acid (10 ml).

Procedure B—sulfuric-acetic acid mixture (10% v/v). To a cooled soln of 1b (2.25 g; 0.01 mole) in H_2SO_4–AcOH mixture (10 ml of a 10% soln v/v) there was added the active methylene component (0.01–0.02 mole). The mixture was treated as described above in procedure A.

Procedure C—BF_3·OEt_2 in an inert solvent. To a cooled mixture of 2a (2.24 g, 0.01 mole) or 2b (2.53 g, 0.01 mole) in an inert solvent (50 ml, CCl_4) there was added the acetoacetate component (0.01–0.02 mole) followed by freshly distilled BF_3·OEt_2 (2 ml). After stirring overnight, at room temp., the soln was poured into crushed ice and extracted with EtOAc (2 × 75 ml). The organic layer was washed with water, $NaHCO_3$ aq (2 × 25 ml of a 5% soln), dried over $MgSO_4$ and evaporated.

N - *Benzoyl* - *β,β* - *diacetylalanine* (3a) was prepared from 1b (1.95 g; 0.01 mole) and acetylacetone (2.0 g; 0.02 mole) in conc. H_2SO_4 (10 ml) according to procedure A. The crude product was triturated with dry ether filtered and crystallized from EtOAc–petroleum ether m.p. 155° (62.5%). IR (KBr): 3260, 1750, 1710, 1640 and 1550 cm^{-1}; NMR (DMSO-d_6): 8.13–7.50 (m, 6H, Ph + NH), 5.40–5.05 (g, 1H, CH), 2.3 (g, 6H, CH_3). (Found: C, 60.61; H, 5.47; N, 5.27. $C_{14}H_{15}NO_5$ requires: C, 60.64; H, 5.45; N, 5.07%).

The same compound was also obtained in 39% yield when 1a was reacted with acetylacetone in trifluoroacetic acid (10 ml).

N - *Benzyloxycarbonyl* - *β,β* - *diacetylalanine* (3b) was prepared from α - hydroxy - N - benzyloxycarbonylglycine (2.25 g; 0.01 mole) and acetylacetone (2.0 g; 0.02 mole) in H_2SO_4–AcOH mixture (10 ml, 10% solution) according to procedure B. The crude product was triturated in ether-petroleum ether, filtered and crystallized from EtOAc–hexane; m.p. 124–125° (44%). IR ($CHCl_3$): 3410, 1730–1710 and 1520 cm^{-1}; NMR ($CDCl_3$): δ 7.90–7.65 (m, 1H); 7.34 (s, 5H, Ph), 6.01 (d, 1H, J = 8 c/s), 5.12 (s, 2H, CH_2), 5.10–4.95 (m, 1H, 4.45 (d, 1H, J = 5 c/s), 2.30 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). (Found: C, 58.35; H, 5.74; N, 4.64. $C_{15}H_{17}NO_6$ requires: C, 58.63; H, 5.58; N, 4.56%).

N - *Benzoyl* - *β,β* - *dibenzoylalanine* (3c) was prepared from α-hydroxyhippuric acid (9.75 g; 0.05 mole) and dibenzoylmethane (12.3 g; 0.07 mole) in methanesulfonic acid (50 ml). After stirring at room temp. for 24 hr the soln was treated as described in procedure A. The crude product was triturated with dry ether to give 15.3 g (75.5%) of product; m.p. 203–204 (EtOAc); IR (KBr): 3360, 1730, 1680 and 1550 cm^{-1}; NMR (DMSO-d_6): δ 8.71 (d, 1H, J = 8 c/s), 8.23–7.16 (m, 16H), 6.66 (D, 1H, J = 10 c/s), 5.54–5.33 (t, 1H). (Found: C, 71.82; H, 4.88; N, 3.45. $C_{34}H_{19}NO_5$ requires: C, 71.81; H, 4.77; N, 3.49%).

N - *Benzyloxycarbonyl* - *β,β* - *dibenzoylalanine* (3d) was prepared from 1b (2.25 g; 0.01 mole) and dibenzoylmethane (2.42 g; 0.011 mole) in dry ether (50 ml) and BF_3OEt_2 (2 ml) in 47% yield by procedure C. The EtOAc soln was filtered from insoluble material, dried and evaporated. The crude product was triturated with ether, filtered and crystallized from EtOAc–

hexane, m.p. 164–165°; IR (KBr): 3300, 1710, 1600, 1550 cm^{-1}; NMR (DMSO-d_6): δ 8.20–7.06 (m, 15H), 6.38 (d, 1H, J = 9 c/s), 5.26–4.83 (m, 2H). (Found: C, 69.58; H, 5.02; N, 3.30. $C_{25}H_{21}NO_6$ requires: C, 69.59; H, 4.91; N, 3.25%).

N - *Benzoyl* - *β* - *benzoyl* - *β* - *acetylalanine* (3e) was obtained in 89% yield by reacting *α*-hydroxyhippuric acid (9.75 g; 0.05 mole) and benzoylacetone (16.2 g; 0.1 mole) in H_2SO_4–AcOH mixture (50 ml, 10%) according to procedure B. Most of the product precipitated from the mixture and was filtered and triturated with dry ether (12.38 g). The filtrate was treated according to procedure B to give an additional crop of 2.64 g (total yield 15.02 g; 89%). It was crystallized from EtOAc–hexane m.p. 186–188; IR (KBr): 3420, 3300, 1750, 1700, 1640 and 1550 cm^{-1}; NMR (DMSO-d_6): δ 9.1 (d, 1H, J = 7 c/s), 8.76 (d, 1H, J = 7 c/s), 8.26–7.35 (m, 11H, Ph + NH), 5.94–5.20 (m, 2H), 2.36 (s, CH_3CO), 2.20 (s, CH_3CO). (Found: C, 67.09; H, 5.22; N, 4.32. $C_{19}H_{17}NO_5$ requires: C, 67.25; H, 5.05; N, 4.13%).

N - *Benzoyloxycarbonyl* - *β* - *phenyl* - *β* - *acetylalanine* (3f) was prepared from *α* - hydroxy - N - benzyloxycarbonylglycine (2.25 g; 0.01 mole) and benzoylacetone (3.24 g; 0.02 mole) in a mixture of H_2SO_4–AcOH (10 ml) according to procedure B. The crude product 2.03 g (56%) is a mixture of two stereoisomers. Trituration with dry ether gave a white solid (0.92 g; 25%) which according to the NMR is one of the two isomers; m.p. 150–152; IR (KBr) 3300, 1720, 1660 and 1550 cm^{-1}; NMR (DMSO-d_6): δ 8.23–7.26 (m, 1H), 5.50–4.47 (m + s, 4H), 2.16 (s, 3H). (Found: C, 64.82; H, 5.23; N, 3.75. $C_{28}H_{19}NO_6$ requires: C, 65.03; H, 5.19; N, 3.79%).

β - *Methyl* N - *benzoyl* - *β* - *acetylaspartate* (3g) was obtained as a mixture of two isomers from *α*-hydroxyhippuric acid (1.95 g; 0.01 mole), methyl acetoacetate (1.3 ml; 0.012 mole) and $BF_3{\cdot}OEt_2$ (2 ml) in CH_2Cl_2 (50 ml) according to procedure C. The crude acidic product (3 g) was triturated with dry ether to give 0.88 g (30%) of pure acid; m.p. 166–168° (EtOAc–hexane); IR (KBr): 3290, 1740 (sh), 1700, 1640 and 1540 cm^{-1}; NMR (DMSO-d_6) δ: 9.06 (d, 1H, NH), 8.81 (d, 1H, J = 10 c/s, NH), 8.14–7.50 (m, 5H, Ph), 5.15 (d of t, 1H, CH), 4.37 (d, 1H, J = 10 c/s, CH), 3.73, 3.70 (s, s, 3H, OMe), 2.25 (s, 3H, MeCO). (Found: C, 57.22; H, 5.29; N, 4.82. $C_{13}H_{13}NO_6$ requires: C, 57.33; H, 5.16; N, 4.78%).

β - *Methyl* - N - *benzyloxycarbonyl* - *β* - *acetylaspartate* (3h) was obtained as a mixture of two isomers by reacting *α* - hydroxy - N - benzyloxycarbonylglycine (2.25 g; 0.01 mole) with methyl acetoacetate (1.3 ml, 0.012 mole) in CH_2Cl_2 and in the presence of $BF_3{\cdot}OEt_2$ (2 ml) according to procedure C. The crude product 1.24 g (55.1%) was purified on a silica column using $CHCl_3$ as eluent (the isomers did not separate). IR ($CHCl_3$): 3400, 1750 (wide) 1600 and 1490 cm^{-1}. NMR ($CDCl_3$) δ: 7.36 (s, 5H, Ph), 6.08 (d, 1H, J = 8 c/s, NH), 5.14 (s, 2H, CH_2O), 5.11–4.85 (m, 1H, CH), 4.23 (m, 1H, CH), 3.70, 3.73 (s, s, 3H, OMe), 2.25 (s, 3H, MeCO), 2.18 (s, 3H, MeCO). (Found: C, 55.42; H, 5.74; N, 3.99. $C_{14}H_{11}NO_3$ requires: C, 55.72; H, 5.30; N, 4.33%).

β - *Ethyl* N - *benzoyl* - *β* - *benzoylaspartate* (3i) was obtained as a mixture of two diastereomers by reacting *α*-hydroxyhippuric acid (5.85 g; 0.03 mole) and ethyl benzoylacetate (6.33 g; 0.03 mole) in methanesulfonic acid according to procedure A. The crude product was triturated with dry ether to give 8 g (72.5%) of a white solid; m.p. 171–173; IR (KBr): 3400, 1730, 1670–1650 and 1540 cm^{-1}. NMR (DMSO-d_6): δ: 9.45–9.21 (m, 10H, 2 PhCO), 5.56–5.00 (m + s, 2H), 4.34–3.8 (q, 2H), 1.30–0.83 (m, 3H). (Found: C, 64.96; H, 5.07; N, 3.93. $C_{28}H_{19}NO_6$ requires: C, 65.03; H, 5.19; N, 3.79%).

β - *Ethyl* N - *benzyloxycarbonyl* - *β* - *benzoylaspartate* (3j) was prepared from 1b and ethyl benzoylacetate (3.84 g; 0.02 mole) in a mixture of H_2SO_4–AcOH according to procedure B. The crude product was triturated with $CHCl_3$ to remove a small quantity of an insoluble material (bisadduct of benzyl carbamate and glyoxylic acid). The residue obtained after the removal of the $CHCl_3$ 4.46 g (56%) was triturated with dry ether to give 1.1 g (14%) of a white solid m.p. 128–129 which is according to the NMR one of the two stereomers. IR ($CHCl_3$): 3400, 1750–1670 and 1510 cm^{-1}. NMR ($CDCl_3$) δ: 9.80 (s, 1H), 8.16–7.33 (m, 10H), 6.30 (d, 1H, 8 c/s), 5.40–5.06 (s + m, 3H), 4.37–3.90 (q, 2H); 1.30–0.86 (t, 3H). (Found: C, 63.18; H, 5.39; N, 3.69. $C_{21}H_{21}NO_7$ requires: C, 63.15; H, 5.30; N, 3.51%).

Methyl N - *benzoyl* - *β,β* - *diacetylalaninate* (4a) was prepared by reacting methyl *α*-methoxyhippurate (2.23 g; 0.01 mole) with acetylacetone (1.5 g; 0.015 mole) in TFA (10 ml) according to procedure A. The neutral crude product was triturated with dry ether to give 1.31 g (45%) of a white solid, m.p. 118–119°. IR (KBr): 3370, 1746, 1725, 1640 and 1525 cm^{-1}; NMR ($CDCl_3$) δ: 8.12–7.33 (m, 6H, Ph + NH); 5.58 (q, 1H), 4.66 (d, 1H, J = 4 c/s), 3.73 (s, 3H, OMe), 2.37 (s, 3H, MeCO), 2.28 (s, 3H, MeCO). (Found: C, 61.69; H, 6.03; N, 4.96. $C_{15}H_{17}NO_5$ requires: C, 61.85; H, 5.88; N, 4.81%).

Methyl N - *benzyloxycarbonyl* - *β,β* - *diacetylalaninate* (4b) was obtained by reacting methyl *α* - methoxy - N - benzyloxycarbonylglycinate (2.53 g; 0.01 mole) with acetylacetone (1.2 g; 0.012 mole) in dry ether (50 ml) for 48 hr according to procedure C. The crude oil was purified on a florisil column (100 g) and eluted with $CHCl_3$. Trituration with ether gave 1.23 g (40%) of a white solid m.p. 78–80°. IR ($CHCl_3$): 3410, 1715 (wide) and 1475 cm^{-1}; NMR ($CDCl_3$) δ: 7.37 (s, 5H, Ph), 6.0 (d, 1H, J = 8 c/s), 5.30–4.92 (m, 1H), 5.14 (s, 2H, CH_2O), 4.46 (d, 1H, J = 9.5 c/s), 3.70 (s, 3H, OMe), 2.30 (s, 3H, MeCO), 2.22 (s, 3H, MeCO); M.S (HR): *m/e* 321.1278 $C_{16}H_{19}NO_6$ calcd. 321.1211. (Found: C, 60.11; H, 5.98; N, 4.36. $C_{16}H_{19}NO_6$ requires: C, 59.80; H, 5.96; N, 4.36%).

The same ester was also obtained by the esterification of the acid 3b with methanol and sulfuric acid.

Methyl N - *benzoyl* - *β,β* - *dibenzoylalaninate* (4c) was prepared from methyl *α*-methoxyhippurate (2.23 g; 0.01 mole) and dibenzoylmethane (2.35 g; 0.012 mole) in TFA (10 ml) according to procedure A. The crude neutral fraction was triturated with dry ether to give 3.43 g (83%) of a white crystalline material; m.p. 155° (EtOAc–hexane); IR ($CHCl_3$): 3420, 1735, 1660 and 1580 cm^{-1}; NMR ($CDCl_3$) δ: 8.25–7.25 (m, 16H, 3Ph + NH), 6.40 (d, 1H, J = 4.5 c/s), 5.66 (q, 1H), 3.75 (s, 3H, OMe). (Found: C, 72.26; H, 5.33; N, 3.32. $C_{25}H_{21}NO_5$ requires: C, 72.28; H, 5.10; N, 3.37%).

Addition of H_2O + TFA to the NMR tube changed the quartet at 5.66 into a triplet and after 24 hr the quartet changed to a doublet and the doublet at 6.40 disappeared.

The same methyl ester was also obtained by the esterification of the acid 3c in MeOH–H_2SO_4.

Methyl N - *benzoyl* - *β* - *benzoyl* - *β* - *acetylalaninate* (4d) was prepared by reacting methyl *α*-methoxyhippurate (2.23 g; 0.01 mole) with benzoylacetone (1.70 g, 0.0105 mole) in TFA (10 ml) according to procedure A (24 hr). Trituration of the crude neutral fraction gave 2.36 g (67%) of a white solid which is according to the NMR a mixture of two isomers (m.p. 101–113°). IR ($CHCl_3$): 3420, 1720, 1665, 1660 and 1585 cm^{-1}. (KBr): 3410, 1725, 1710, 1670, 1650, 1600, 1580 and 1520 cm^{-1}; NMR ($CDCl_3$) δ: 8.30–7.29 (m, 11H, 2Ph + NH), 5.76–5.39 (m, 2H, 2CH), 3.73, 3.68 (s, s, 3H, OMe), 2.39, 2.27 (s, s, 3H, MeCO). In DMSO-d_6 two distinct NH peaks at 9.13 (d, J = 6 c/s) and 8.86 (d, J = 8 c/s) were observed (1:1 ratio) supporting the presence of two isomers. (Found: C, 67.63; H, 5.43; N, 4.22. $C_{28}H_{19}NO_5$ requires: C, 67.93; H, 5.42; N, 3.96%).

The same product was also obtained in only 13% yield when the reaction was carried out in CCl_4 or Et_2O and in the presence of $BF_3{\cdot}OEt_2$. The low yield is probably due to the competing formation of the stable and unreactive benzoylacetone BF_3 complex.[9] The latter was indeed isolat in 42–56% yield.

Dimethyl N - *benzoyl* - *β* - *acetylaspartate* (4e). A well grounded suspension of methyl *α*-methoxyhippurate (2.23 g; 0.01 mole) and methyl acetoacetate (1.74 g; 0.015 mole) in CCl_4 (50 ml) was treated with $BF_3{\cdot}OEt_2$ (2.5 ml) as described above for procedure C. The crude neutral fraction which was obtained in almost quantitative yield was according to the NMR, a mixture of two isomers. On trituration with dry ether the mixture was slowly converted to one isomer which precipitated. Repeated trituration of the mother liquors gave 61% of a crystalline product, m.p. 110–112°; IR ($CHCl_3$): 3420, 1725 (wide), 1655, 1600 and 1580 cm^{-1}; NMR ($CDCl_3$): 8.03–7.40 (m, 6H, Ph + NH), 5.59 (d of d, 1H, J = 4.5 and J = 9 c/s), 4.5 (d, 1H, J = 4.5), 3.83, 3.80 (s, s, 3H, OMe), 2.37 (s, 3H, MeCO). MS (HR): *m/e* 307.1036 (M^+), $C_{15}H_{17}NO_6$ calcd 307.1054. (Found: C, 58.61; H, 5.47; N, 4.50. $C_{13}H_{17}NO_6$ requires: C, 58.63; H, 5.58; N, 4.56%).

If 3 ml of $BF_3{\cdot}OEt_2$ was used in reaction, an appreciable

quantity of a third component was isolated on trituration with ether (m.p. 101°). The NMR of the latter agrees best with the enolic form of 4e. IR (KBr): 3410, 3310, 1725, 1640 and 1525 cm^{-1}; NMR ($CDCl_3$) δ: 12.7 (s, 1H, (C–C–OH), 7.95–7.03 (m, 6H, Ph + NH), 5.72 (d, 1H, J = 8), 3.82 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.41, 2.38 (s, s, 3H). The enol form slowly changes in solution to the keto form 4e (NMR). (Found: C, 58.58; H, 5.59; N, 4.63. $C_{15}H_{17}NO_6$ requires: C, 58.63; H, 5.47; N, 4.50%).

N - *Benzoyl* - β - *acetylalanine* (5a) was prepared from 1a (5.85 g; 0.03 mole) and methyl acetoacetate (6.96 g; 0.06 mole) in conc. H_2SO_4 (30 ml) according to procedure A. The yield was 3.05 g (43.5%); m.p. 125° (from benzene). lit.[10] 138–139°. IR ($CHCl_3$): 3420, 1725, 1665, 1600, 1530 and 1510 cm^{-1}. NMR ($CDCl_3$) δ: 10.3 (vb, 1, CO_2H); 7.20–8.0 (m, 6, Ph + NH) 5.04 (q, 1, CH, J = 4 c/s); 3.22 (t, 2, CH_2, J = 4 c/s); 2.17 (s, 3, CH_3). (Found: C, 61.05; H, 5.42; N, 6.03. $C_{12}H_{13}NO_4$ requires: C, 61.27; H, 5.57; N, 5.96%).

From the neutral fraction, methyl N - benzoyl - β - acetylalaninate was isolated (2.19 g; 29%) m.p. 88° (from EtOAc and hexane). IR ($CHCl_3$): 3430, 1750 and 1670 cm^{-1}. NMR ($CDCl_3$) δ: 7.3–8.0 (m, 6, Ph + NH), 5.05 (q, 1, CH, J = 4 c/s); 3.8 (s, 3, CH_3); 3.25 (t, 2, CH_2, J = 4 c/s); 2.2 (s, 3, CH_3). (Found: C, 62.46; H, 6.04; N, 5.77. $C_{13}H_{15}NO_4$ requires: C, 62.64; H, 6.07; N, 5.62%).

N - *benzoyl* - β - *benzoylalanine* (5b) was prepared from α-hydroxyhippuric acid (5.85 g; 0.03 mole) and ethyl benzoylacetate (11.53 g; 0.06 mole) in conc. H_2SO_4 (30 ml) according to procedure A. The crude product was triturated with dry ether to give a white solid (7.26 g; 81.5%) which was contaminated, according to the NMR, with 4f. Trituration with $CHCl_3$ gave 5.0 g (56%) of the pure product; m.p. 181–182°: lit.[5,11] 182°; IR (KBr): 3300, 3280–2900, 1740, 1730, 1680 and 1540 cm^{-1}; NMR (DMSO-d_6) δ: 8.71 (d, 1H, 8 c/s), 8.17–7.15 (m, 10H, 2 PhCO), 5.30–4.83 (q, 1H), 3.63 (d, 2H, J = 6 c/s). (Found: C, 68.23, H, 5.33; N, 9.71%).

The same product was also obtained by reacting benzoylacetone or dibenzoylmethane with α-hydroxyhippuric acid in H_2SO_4 according to procedure A. Treatment of 3c with conc. H_2SO_4 for 48 hr at room temp. afforded 5b in 74% yield.

α - *Benzamido* - β - *acetyl* - γ - *methyl* - $\Delta^{\alpha\beta}$ - *butenolide* (6a). A mixutre of 3a (2 g) and β-naphtalenesulfonic acid (0.2 g) in 1,2 - dichloroethane (50 ml) was refluxed overnight. The water formed was removed by azeotropic distillation and trapped by silica gel. The soln was washed with water, $NaHCO_3$ aq (5%, 25 ml) dried over $MgSO_4$ and evaporated. The residue was triturated with ether and crystallized from EtOAc–hexane; m.p. 148–150° (71%) IR: 3300 (NH); 1770, 1715, 1655 (CO) cm^{-1}. NMR ($CDCl_3$): δ: 8.42 (bs, 1, NH); 7.4–8.12 (m, 5H, Ar) 5.55 (q, 1H, CH, J = 7 c/s), 2.35 (s, 3H, Me) 1.52 (d, 3H, Me, J = 7 c/s). (Found: C, 64.52; H, 4.99; N, 5.37. $C_{14}H_{13}NO_4$ requires: C, 64.86; H, 5.05; N, 5.40%).

α - *Benzamido* - β - *benzoyl* - γ - *phenyl* - $\Delta^{\alpha\beta}$ - *butenolide* (6b). Compound 3c (2.5 g) was subjected to the conditions as described for 6a; 1.73 g (72%) was obtained, m.p. 211° (from EtOAc–hexane). IR (KBr): 3340, 1765, 1685 sh, 1655 cm^{-1}. NMR ($CDCl_3$) δ: 8.32 (s, 1, NH); 7.3–7.8 (m, 10, Ph); 7.8 (s, 5, Ar); 6.47 (s, 1, CH). (Found: C, 75.05; H, 4.40; N, 3.82. $C_{24}H_{17}NO_4$ requires: C, 75.18; H, 4.47; N, 3.65%).

Dimethyl N - *benzyloxycarbonyl* - β - *acetylaspartate* (4f) was obtained in 72% yield as a mixture of two isomers (oil) by reacting 2b with methyl acetoacetate in CCl_4 and in the presence of $BF_3{\cdot}OEt_2$ as described in procedures C. NMR ($CDCl_3$) δ: 7.4 (s, 5H); 5.94 (d, J = 10, 1H); 5.15 (s, 2H), 5.3–4.91 (m, 1H), 4.28 (d of d, J_{12} = 4, J_{23} = 0.5, 1H); 3.75, 3.73 (s, s, 3H); 2.32, 2.28 (s, s, 3H); IR ($CHCl_3$): 3410, 3040 (sh), 2950, 1720, 1600, 1510 (sh) cm^{-1}; MS (HR) *m/e* 337.1191. Calcd. for $C_{16}H_{19}NO_7$ 337.1161. For analysis the product was purified on a fluorisil column and eluted with $CHCl_3$. (Found: C, 56.87; H, 6.14; N, 4.09. $C_{16}H_{19}NO_7$ requires: C, 56.97; H, 5.68; N, 4.15%).

α - *Benzamido* - β - *benzoyl* - γ - *methyl* $\Delta^{\alpha\beta}$ - *butenolide* (6e) *and* α - *benzamido* - β - *acetyl* - γ - *phenyl* $\Delta^{\alpha\beta}$ - *butenolide* (6d). The diastereoisomeric mixture of 3e (4.5 g; 0.011 mole) was added to the boiling soln of NSA (400 mg) in 1,2-dichloroethane (90 ml) and refluxed overnight with azeotropic removal of water. The soln was washed with water, 5% $NaHCO_3$ aq dried over $MgSO_4$ and evaporated. NMR spectrum of the crude mixture (4.4 g) indicated the presence of two isomeric butenolides (6e and 6d) in the ratio 1:3. After trituration with ether and recrystallization from EtOAc pure 6d was obtained (2.044 g, 48%) m.p. 179–180°. IR (KBr) 3340, 1760, 1685 cm^{-1}. NMR ($CDCl_3$) δ: 8.54 (s, 1H, NH); 7.25–8.05 (m superimposed at 7.4 by s, 10H, Ph) 6.20 (s, 1H, CH); 2.10 (s, 3H, CH_3). (Found: C, 71.10; H, 4.82; N, 4.35. $C_{19}H_{15}NO_4$ requires: C, 71.02; H, 4.71; N, 4.36%).

The solns from trituration and crystallization were concentrated and the residue was chromatographed on florisil column (30 g) using benzene as eluent. In the first 10 fractions at 100 ml, pure 6e was obtained (278 mg, 6.5%) m.p. 154° (from EtOAc hexane). IR (KBr): 3360, 1785, 1720 sh, 1680 cm^{-1}. NMR ($CDCl_3$) δ: 8.32 (s, 1H, NH); 7.2–8.1 (m, 10H, Ph); 5.55 (q, 1H, CH, J = 7 c/s); 1.55 (d, 3H, CH_3, J = 7 c/s). (Found: C, 71.06; H, 4.69; N, 4.43. $C_{19}H_{15}NO_4$ requires: C, 71.02; H, 4.71; N, 4.36%).

α - *Benzamido* - β - *carbomethoxy* - γ - *methyl* $\Delta^{\alpha\beta}$ - *butenolide* (6e). 3g (1 g) was treated with NSA (200 mg) in boiling 1,2-dichloromethane (50 ml) as described for 6a yielding α - benzamido - β - carbomethoxy - γ - methyl $\Delta^{\alpha\beta}$-butenolide 470 mg, 56%, m.p. 123° (from EtOAc–hexane). IR (KBr) 3300, 1760, 1720, 1655 cm^{-1}; NMR ($CDCl_3$) δ: 8.4 (s, 1H, NH); 7.3–8.1 (m, 5H, Ph). 5 40 (q, 1H, CH, J = 7 c/s). (Found: C, 61.03; H, 5.04; N, 5.15. $C_{14}H_{13}NO_5$ requires: C, 61.09; H, 4.76; N, 5.09%).

α - *Benzamido* - β - *carbethoxy* - γ - *phenyl* $\Delta^{\alpha\beta}$ *butenolide* (6f). 3f (2.5 g) was treated with NSA (400 mg) in boiling 1,2-dichloroethane (80 ml) as described for 6a, yielding 6f (1.99 g, 83%), m.p. 135° (from EtOAc–hexane). IR (KBr) 3300, 1765, 1650 cm^{-1}; NMR ($CDCl_3$) δ: 8.6 (s, 1, NH); 7.3–8.1 (m superimposed at 7.35 by s, 10H, Ph); 1.10 (t, 3H, CH_3, J = 7 c/s). (Found: C, 68.30; H, 5.12; H, 4.08. $C_{20}H_{17}NO_5$ requires: C, 68.31; H, 4.88; N, 3.99%).

α - *Benzamido* - γ - *methyl* - $\Delta^{\alpha\beta}$ - *butenolide* (7a). A mixture of 5a (5 g) and β-naphtalenesulfonic acid (0.5 g) in 1,1,2-trichloroethane (110 ml) was refluxed overnight. The water formed was removed by azeotropic distillation and trapped by silica gel. The soln was concentrated and the residue was chromatographed on florisil column (170 g) using methylene chloride as eluent. The fractions 6 to 11 contained pure 7a 3.318 g (72%); m.p. 73–74°. IR (KBr) 3320, 1750, 1680, 1650 cm^{-1}. NMR ($CDCl_3$) δ: 8.3 (s, 1, NH); 7.3–7.1 (m, 6H, Ph + CH); 5.2 (octet, 1H, CH, J = 7 c/s and 2 c/s), 1.5 s (d, 3H, CH_3, J = 7 c/s). (Found: C, 65.90; H, 5.38; N, 6.31. $C_{12}H_{11}NO_3$ requires: C, 66.35; H, 5.10; N, 6.45%).

α - *Benzamido* - γ - *phenyl* - $\Delta^{\alpha\beta}$ - *butenolide* (7b). A mixture of 5b (1 g) and β-naphtalenesulfonic acid (0.1 g) in 1,2-dichloroethane was treated as described above. The crude product was crystallized from EtOAc; m.p. 138° (48%). IR ($CHCl_3$): 3380, 1770, 1690 and 1410 cm^{-1}; NMR ($CDCl_3$): 8.40 (s, 1H, NH); 8.0–7.35 (m, 11H, Ar + CH); 6.14 (d, 1H, CH, J = 2 c/s). (Found: C, 72.89; H, 4.55; N, 5.04. $C_{17}H_{13}NO_3$ requires: C, 73.11; H, 4.69; N, 5.02%).

α - *Benzamido* - γ - *valerolactone* (8a).[12] Compound 7a (550 mg) was hydrogenated in MeOH soln (50 ml) over 10% Pd–C catalyst (60 mg) in a Parr Apparatus. After filtration and concentration, the residue was crystallized from EtOAc–hexane yielding pure *cis* isomer 448 mg (81.5%) m.p. 137–139°. IR (KBr) 3320, 1760, 1655 cm^{-1}. NMR ($CDCl_3$) δ: 7.0–8.0 (m, 6H, Ph + NH); 4.4–5.2 (m, 2H, CH); 1.6–3.2 (m, 2H, CH_2); 1.48 (d, 3H, CH_3). (Found: C, 66.08; H, 5.85; N, 6.41. $C_{12}H_{13}NO_3$ requires: C, 65.74; H, 5.98; N, 6.39%). The mother liquid was concentrated. The spectral data run on the residue (60 mg) indicated the presence of the same compound.

When 5a (4.1 g) was subjected to the reduction with $NaBH_4$ (3.5 g) in MeOH (60 ml) a mixture of two isomeric lactones (3.44 g, 90%) was obtained. The NMR spectrum in DMSO-d_6 showed two Me groups in a 1:3 ratio.

After the first recrystallization from EtOAc, the crystalline product obtained had a ratio of 1:1 of the two isomers whereas in the mother liquid, the ratio was 1:9. Four successive recrystallizations of the first crop of crystals gave the more polar isomer in a pure form (55 mg) which is assumed to be *trans* isomer. m.p. 138°.[12] IR (KBr) 3280, 1775, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 7.3–8.0 (m, 5H, Ph), 7.05 (vb, 1H, NH), 4.7–5.2 (m, 2H, CH); 2.1–2.7 (m, 2H, CH_2); 1.48 (d, 3H, CH_3). (Found: C,

65.69; H, 5.93; N, 6.49. $C_{12}H_{13}NO_3$ requires: C, 65.74; H, 5.98; N, 6.39%).

The residue from the mother liquid from the first crystallization was crystallized several times from EtOAc–hexane yielding pure *cis*-isomer, identical in all respects to that obtained by catalytical hydrogenation of 7a.

2 - *Benzamido* - 3 - *methyllevulinic acid* (9) *and* α - *benzamido* - β,γ - *dimethyl* - $\Delta^{\alpha\beta}$ - *butenolide* (10). Reacting α-hydroxyhippuric acid (1.95 g; 0.01 mole) with ethyl 2-methylacetoacetate (0.02 mole) in conc. H_2SO_4 for 72 hr according to procedure A gave an acid and neutral fractions. The acid fraction (1.1 g) afforded on trituration with dry ether, a crystalline product (9, 13%) m.p. 164–165° (EtOAc–hexane); IR: 3380–3200, 1740, 1650 and 1510 cm^{-1}; NMR ($CDCl_3$ + TFA) δ: 7.90–7.42 (m, 6H, Ph + NH), 5.22–4.59 (q, 1H, CH), 3.56–3.33 (m, 1H, CH), 2.38 (s, 3H, Me), 1.50 (d, 3H, Me, J = 7 c/s). (Found: C, 62.59; H, 6.04; N, 5.59. $C_{13}H_{15}NO_4$: requires: C, 62.64; H, 6.07; N, 5.62%).

The neutral fraction afforded 10 on trituration with dry ether (28%); IR ($CHCl_3$): 3390, 1750, 1675 and 1510 cm^{-1}; NMR ($CDCl_3$) δ: 8.14–7.47 (m, 6H, Ph + NH), 4.85–5.12 (q, 1H, CH), 2.18 (s, 3H, Me), 1.52 (d, 3H, Me, J = 6 c/s). (Found: C, 67.28; H, 5.74; N, 6.02. $C_{13}H_{13}NO_3$ requires: C, 67.52; H, 5.67; N, 6.06%).

The mother liquor of the acid and neutral fraction contained an additional acidic and neutral products of type 11 (NMR).

Methyl α - *benzamido* - β - *methyl* - β - *carboethoxylevulinate* (11a) was obtained by reacting methyl α-methoxyhippurate (2.23 g; 0.01 mole), ethyl α-methylacetoacetate (2.2 ml; 0.015 mole) and BF_3OEt_2 (2.5 ml) in CCl_4 as described above in procedure C. The neutral crude oil (94%) was triturated with dry ether to give 1.3 g (42%) of a crystalline product m.p. 80–105° (mixture of two isomers in a 1:1 ratio). Further trituration of the solid in dry ether (50 ml) gave one pure isomer, 0.37 g (12%) m.p. 119–121°; IR (KBr) 3380, 3200 (sh), 1740 (sh), 1690, 1665 and 1520 cm^{-1}; NMR ($CDCl_3$) δ: 8.03–7.35 (m, 5H, Ph), 7.08 (d, 1H, J = 10 c/s), 5.57 (d, 1H, J = 10 c/s), 4.27 (q, 2H), 3.75 (s, 3H, OMe), 2.38 (s, 3H, MeCO), 1.63 (s, 3H, Me), 1.27 (t, 3H, Me). (Found: C, 60.91; H, 6.24; N, 4.23. $C_{17}H_{21}NO_6$ requires: C, 60.88; H, 6.31; N, 4.18%).

A pure sample of the second isomer (0.26 g, 8.5%, m.p. 68–70°) was obtained from the mother liquor on precipitation with petether and crystallization of the oil from hexane. IR (KBr): 3360, 1720, 1705, 1665 and 1530 cm^{-1}. NMR ($CDCl_3$) δ: 7.97–7.40 (m, 5H, Ph), 7.22 (d, 1H, J = 10 c/s), 5.53 (d, 1H, J = 10 c/s), 4.32 (d, 2H, CH_2), 3.75 (s, 3H, OMe), 2.33 (s, 3H, MeCO), 1.65 (s, 3H, Me), 1.33 (t, 3H, Me). (Found: C, 61.01; H, 6.30; N, 4.24. $C_{17}H_{21}NO_6$ requires: C, 60.88; H, 6.31; N, 4.18%).

Methyl α - *benzyloxycarbonylamino* - β - *methyl* - β - *carbethoxylevulinate* (11b) was prepared from methyl α - methoxy - N - benzyloxycarbonylglycinate (2.53 g; 0.01 mole), and ethyl α-methylacetoacetate (2.2 ml; 0.015 mole) in CCl_4 and in the presence of BF_3OEt_2 (2.5 ml), according to procedure C. The crude oil (69%) was according to the NMR, a mixture of two isomers in a 1:1 ratio. IR ($CHCl_3$) 3420, 1710 and 1500 cm^{-1}. NMR ($CDCl_3$) δ: 7.37 (s, 5H, Ph), 5.67, 5.62 (2d, 1H, J = 10 c/s), 5.17 (s, 2H, CH_2), 5.03, 4.97 (2d, 1H, J = 3 c/s), 4.27, 4.22 (2q, 2H), 3.68 (s, 3H, OMe), 2.30, 2.27 (2s, 3H, MeCO) 1.57, 1.53 (2s, 3H, Me) 1.28, 1.25 (2t, 3H, Me). Chromatography on a florisil column afforded one of the isomers in pure form (low yield); m.p. 60–61°; IR ($CHCl_3$) 3420, 1700 (wide) and 1550 cm^{-1}; NMR ($CDCl_3$) δ: 7.38 (s, 5H, Ph), 5.57 (d, 1H, J = 10 c/s), 5.18 (s, 2H, CH) 5.03 (d, 1H, J = 10 c/s), 4.23 (q, 2H), 3.72 (s, 3H, OMe), 2.32 (s, 3H, MeCO), 1.53 (s, 3H, Me), 1.27 (t, 3H, Me). (Found: C, 59.40; H, 6.61; N, 4.04. $C_{18}H_{23}NO_7$ requires: C, 59.18; H, 6.33; N, 3.83%).

N - *Benzoyl* - (3,5 - *dimethylpyrazolyl* - 4)*glycine* (12b). A soln of N - benzoyl - β,β - diacetylalanine (2.77 g; 0.01 mole) and hydrazine hydrate (1.0 g; 0.02 mole) in MeOH (50 ml) was refluxed for 24 hr. The MeOH was evaporated and the residue was triturated with chloroform (40 ml). The solid salt was filtered, dissolved in water (15 ml) and acidified. The product was extracted into EtOAc, dried over Na_2SO_4 and evaporated. It was crystallized from EtOAc–hexane; m.p. 237–238° (78%). IR (KBr): 3320, 1730, 1650 and 1510 cm^{-1}; NMR (DMSO-d_6) δ: 8.80–8.62 (d, 1H, NH, J = 6 c/s), 8.15–7.50 (m, 6H, Ar + NH), 5.53 (d, 1H, J = 6 c/s), 2.22 (s, 6H, 2Me). (Found: C, 61.75; H, 5.50; N, 15.39. $C_{14}H_{15}N_3O_3$ requires: C, 61.53; H, 5.53; N, 15.38%).

(3,5 - *Dimethylpyrazolyl* - 4) - *glycine* (12a). N - Benzoyl - (3,5 - dimethylpyrazolyl - 4)glycine (1 g) was refluxed overnight in 10% HCl (30 ml). The cold mixture was filtered from benzoic acid, lyophilised triturated with ether, dissolved in MeOH, filtered and precipitated with ether as dihydrochloride 732 mg, (83%) m.p. 232° (decomp). IR (KBr) 1740, 1720 sh, 1700 sh, 1670 sh, 1580, 1500 cm^{-1}. NMR (D_2O) δ: 5.20 (s, 1, CH); 2.25 (s, 6, CH_3); R_f = 0.09 (nBuOH : H_2O : AcOH; 10:1:3); R_f = 0.62 and 0.71 (MeOH : H_2O : Py, 40:20:2). (Found: C, 34.73; H, 5.32; N, 17.31; Cl, 23.38. $C_7H_{11}N_3O_2Cl_2$ requires: C, 34.69; H, 5.41; N, 17.35; Cl, 29.27%). The zwitterion had m.p. 254° (dec). IR (KBr): 1625, 1580, 1520, 1380 and 1345 cm^{-1}. (Found: C, 49.36; H, 6.52; N, 24.51. $C_7H_{11}N_3O_2$ requires: C, 49.69; H, 6.55; N, 24.84%).

N - *Benzyloxycarbonyl* - (3,5 - *dimethylpyrazolyl* - 4)*glycine* (12c) was prepared in 82% yield from 3b and hydrazine as described above for the benzoyl derivative; m.p. 207–208° (EtOAc–hexane); IR (KBr): 3320–3210, 1720 and 1530 cm^{-1}; NMR (DMSO-d_6): 7.60 (d, 1H, NH, J = 6 c/s), 7.37 (s, 6H, Ph), 5.05 (s + d, 3H) 2.10 (s, 6H, 2Me). (Found: C, 59.46; H, 6.13; N, 13.64. $C_{15}H_{17}N_3O_4$ requires: C, 59.39; H, 5.65; N, 13.86%).

N - *Benzyloxycarbonyl*(3 - *methyl* - 5 - *phenylpyrazolyl* - 4) - *glycine* (12h) was prepared from 3f and hydrazine in refluxing MeOH as described above for 12b. The crude product was triturated with dry ether filtered to give 1.93 g (53%) of a white solid; m.p. 200–202° (EtOAc); IR (KBr): 3320, 3200, 1720–1680 and 1550 cm^{-1}; NMR (DMSO-d_6) 7.96–7.33 (m, 11H, Ar + NH), 5.30–5.06 (s + d, 3H, CH_2 + CH), 2.20 (s, 3H, Me). (Found: C, 65.74; H, 5.27; N, 11.50. $C_{20}H_{19}N_3O_4$ requires: C, 65.99; H, 5.30; N, 11.48%).

N - *Benzoyl*(3,5 - *diphenylpyrazolyl* - 4) - *glycine* (12e) was prepared from 3e and hydrazine as described above. The crude product was triturated with dry ether to give 3.65 g (79%) of a white crystalline material; m.p. 232° (dec, from EtOAc–hexane). IR (KBr): 3410, 1710, 1640 and 1550 cm^{-1}. NMR (DMSO) δ: 8.8 (d, 1, NH, J = 6 c/s) 6.9–8.1 (m, 17, Ar + NH + CO_2H); 5.6 (d, 1, CH, J = 6 c/s). (Found: C, 71.90; H, 5.00; N, 10.26. $C_{26}H_{19}N_3O_3$ requires: C, 72.53; H, 4.82; N, 10.57%).

(3,5 - *Diphenylpyrazolyl* - 4) - *glycine* (12d). A suspension of N - benzoyl(3,5 - diphenylpyrazolyl - 4) - glycine (1 g) in 30 ml of 10% HCl was refluxed for 48 hr. Lyophilization and trituration with dry ether afforded the hydrochloride (780 mg); m.p. 209–211° (dec.); IR (KBr) 1740 cm^{-1}; NMR (D_2O + TFA) δ: 7.75 (s, 10H, Ar), 5.50 (s, 1H, CH); R_f = 0.64 (n-BuOH : H_2O : AcOH 10:1:3). The free amino acid was obtained by the addition of Et_3N to a water suspension of the hydrochloride. The solid was tritrated with MeOH; m.p. 283° (dec). (Found: C, 69.44; H, 5.18; N, 13.97. $C_{17}H_{15}N_3O_2$ requires: C, 69.61; H, 5.15; N, 14.33%).

N - *Benzoyl*(3 - *methyl* - 5 - *phenylpyrazolyl* - 4) - *glycine* (12g) was prepared from 3e and hydrazine as described above for 12b. The crude product was triturated with dry ether to give 3.46 g of a white crystalline product; m.p. 163–165°; IR (KBr): 3400, 1640 and 1550 cm^{-1}; NMR (DMSO-d_6) δ: 8.70 (d, 1H, J = 6 c/s), 8.16–7.35 (m, 10H, Ar), 5.53 (d, 1H, J = 6 c/s, CH), 2.34 (s, 3H, Me). (Found: C, 67.79; H, 5.07; N, 12.36. $C_{19}H_{17}N_3O_3$ requires: C, 68.05; H, 5.11; N, 12.53%).

(3 - *Methyl* - 5 - *phenylpyrazolyl* - 4) - *glycine* (12f). N - Benzoyl(3 - methyl - 5 - phenylpyrazolyl - 4) - glycine (4.7 g) was refluxed overnight in a mixture of AcOH (45 ml), conc. HCl (45 ml) and water (45 ml), lyophilized and triturated with ether. The hygroscopic hydrochloride was dissolved in MeOH, filtered and treated with Et_3N. The precipitated free amino acid (2.95 g, 88%) had m.p. 242° (dec). IR (KBr) 1640 sh, 1605, 1450, 1490 cm^{-1}. NMR (D_2O and TFA) δ: 7.55 (s, 5H, Ar), 5.2 (s, 1H, CH); 2.3 (s, 3H, CH_3). R_f = 0.26 (nBuOH : H_2O : AcOH). R_f = 0.72 (MeOH : H_2O : Py, 40:20:2). (Found: C, 61.76; H, 5.59; N, 18.12. $C_{12}H_{13}N_3O_2$ requires: C, 62.32; H, 5.67; N, 18.17%).

α - *Aminolevulinic acid* (β - *acetylalanine*) *hydrochloride* (13a).[5] Compound 5a (602 mg) was refluxed overnight in 10% HCl (15 ml), filtered from benzoic acid, lyophilized and triturated with ether. The hydrochloride (407 mg, 99%); m.p. 162°, lit.[5] 158–160°. IR (KBr): 1740, 1705 cm^{-1}. NMR (D_2O) δ: 4.32 (t, 1H, CH, J = 5 c/s); 3.38 (d, 2H, CH_2, J = 5 c/s); 2.22 (s, 3H, CH_3). R_f = 0.16 (nBuOH : H_2O : AcOH, 10:1:3).

N - *Benzyloxycarbonyl* - β - *acetylalanine* was obtained by Schotten–Baumann reaction in the presence of $NaHCO_3$ as base

in 78% yield; m.p. 122° (from EtOAc–hexane); IR (KBr): 3320, 1755, 1720, 1670 cm^{-1}. NMR ($CDCl_3$) δ: 9.48 (s, 1, H); 7.35 (s, 5, Ar); 5.9 (d, 1, NH, J = 8 c/s); 5.14 (s, 2, CH_2 benzylic); 4.60 (m, 1, CH); 3.08 (t, 2, CH_2); 2.14 (s, 3, CH_3). (Found: C, 58.85; H, 5.75; N, 5.30. $C_{13}H_{15}NO_4$ requires: C, 58.86; H, 5.70; N, 5.28%).

β-Benzoylalanine hydrochloride (13b). Compound 5b (900 mg) was refluxed in 10% HCl (40 ml) for 48 hrs, lyophilized and triturated with ether, gave the hydrochloride (634 mg, 99%); m.p. 208–210°, lit.[11] 202. IR (KBr): 1740, 1720 sh, 1660 cm^{-1}. NMR (D_2O) δ: 7.4–8.2 (m, 5, Ar); 4.5 (t, 1, CH, J = 5 c/s); 3.8 (d, 2, CH_2, J = 5 c/s). R_f = 0.37 (nBuOH : H_2O : AcOH, 10 : 1 : 3).

N - *Benzyloxycarbonyl - β - benzoylalanine* was prepared by Schotten–Baumann reaction conditions using $NaHCO_3$ as base, m.p. 124° (from EtOAc–hexane). IR (KBr): 3415, 1750, 1720, 1670 and 1540 cm^{-1}. NMR ($CDCl_3$) δ: 10.28 (s, 1H, H); 7.25–8.1 (m, 10H, Ar); 6.05 (d, 1H, NH); 5.15 (s, 2H, CH_2); 4.1 (m, 1H, CH); 3.7 (t, 2H, CH_2). (Found: C, 66.25; H, 5.39; N, 5.25. $C_{18}H_{17}NO_5$ requires: C, 66.05; H, 5.24; N, 4.28%).

β,β - Diacetylalanine hydrobromide (14c). Compound 3b (1 g) was treated with freshly prepared saturated soln of HBr in AcOH (30%, 4 ml) for 20 min, precipitated with ether and several triturations with ether, gave 694 mg (84%), m.p. 134–136° (dec). IR (KBr): 1740, 1705, 1580, 1555 and 1505 cm^{-1}. NMR (D_2O) δ: 4.75 (s, 1H, CH); 2.44 (s, 6H, CH_3). R_f = 0.21 (nBuOH : H_2O : AcOH; 10 : 1 : 3). (Found: C, 32.96; H, 4.86; N, 5.49; Br, 31.76. $C_7H_{12}NO_4Br$ requires: C, 33.09; H, 4.76; N, 5.51; Br, 31.48%).

β,β-Dibenzoylalanine (14b). N - Benzyloxycarbonyl - β,β - dibenzoylalanine (1 g) was treated with freshly saturated soln of HBr in AcOH (2.5 ml) for 40 min. The hydrobromide was precipitated with ether, the solvent was decanted and the solid was triturated several times with ether. It crystallized with one molecule of ether (0.814 g, 77%), m.p. 128–130° (dec). IR (KBr): 1770 sh, 1670, 1595, 1580, 1500, 1270, 1210 cm^{-1}. NMR ($CDCl_3$) δ: 9.4–8.1 (m, 4H, $NH_3^+ + H^+$); 7.1–8.0 (m, 10, Ar); 6.85 (bs, 1, CH); 5.2 (s, 1H, CH); 3.5 (q, 4H, CH_2); 1.2 (t, 6H, CH_3). R_f = 0.53 with tailing (nBuOH : H_2O : AcOH; 10 : 1 : 3). (Found: C, 55.81; H, 5.64; N, 3.09; Br, 17.81. $C_{17}H_{15}NO_4 \cdot HBr \cdot Et_2O$. $C_{21}H_{26}NO_5Br$ requires: C, 55.77; H, 5.79; N, 3.07; Br, 17.67%). The zwitterion was prepared by adding Et_3N to a methanolic solution of the hydrobromide. m.p. 149–150° (dec). IR (KBr) 1670, 1600 cm^{-1}. (Found: C, 68.49; H, 5.06; N, 4.66. $C_{17}H_{15}NO_4$ requires: C, 68.67; H, 5.08; N, 4.71%).

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