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# A NEW SYNTHESIS OF AMINO ACIDS—II[1]

## AMIDOALKYLATION OF OLEFINS WITH GLYOXYLIC ACID DERIVATIVES[2]

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**Abstract**—A new synthesis of leucine, aspartic acid, aspartic acid semialdehyde and unsaturated *N*-acyl-$\alpha$-amino acid from olefins and glyoxylic acid-primary amide adducts is described. The chemistry and stereochemistry of the intermediate oxazines **7** and $\alpha$-amidobutyrolactones **8** is also discussed.

Synthetic amino acids have found applications as food additives (e.g. methionine, lysine),[3] in the synthesis of semisynthetic penicillins and cephalosporins,[4] as sweetening agents (aspartam)[5] or as chelating agents (e.g. EDTA). The predominant methods used in recent years for the synthesis of $\alpha$-amino acids were the acetamidomalonate, hydantoin and the Strecker synthesis.[3]

In the course of a study on the chemistry of cyclic acylimines and 2-alkoxylactams it was found that 5-methoxyhydantoins **1** will amidoalkylate olefins, in the presence of an acid catalyst, to give 5-substituted hydantoins with an unsaturated side chain[6] **2**. 5-Substituted hydantoins are known as synthetic precursors or derivatives of $\alpha$-amino acids.

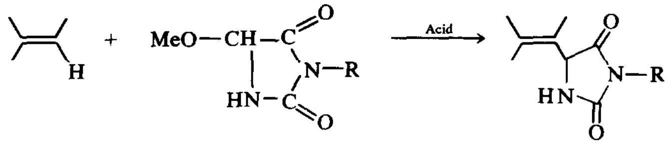
In the attempt to extend the above observation and develop a new and general synthesis of $\alpha$-amino acids we studied the reactions of olefins with the open chain adducts of glyoxylic acid and primary amides, primary carbamates and ureas. These adducts resemble the 5-alkoxyhydantoins in having a carbinolamide group attached to a potential carboxy function are easily prepared from glyoxylic acid monohydrate and primary amides or primary carbamates.[7] These adducts **3** and **4** were indeed found to amidoalkylate olefins under acidic conditions to give three types of products: *N*-acyl derivatives of unsaturated $\alpha$-amino acids **5**, **6**, **9** and **10**), 4-carbomethoxy 1,3-oxazines **7** and 2-amidobutyrolactones, **8**. The type of product obtained depends on the structure of the adduct used (acid or ester), the reaction conditions and to a lesser extent on the nature of the olefin. Amidoalkylation of olefins was first described only in 1962[8] and the stereochemistry of the reaction was reported later.[9]

Thus reacting 1,1-diphenylethylene, $\alpha$-methylstyrene, styrene, tetramethyl ethylene and 2,5 - dimethyl - 2,4 - hexadiene with methyl $\alpha$-methoxyhippurate (**4**, $R'' = Ph$) in boiling benzene and in the presence of NSA afforded the corresponding methyl esters of the $\alpha$-benzamido $\beta,\gamma$-unsaturated acids **5**. In the case of $\alpha$-methyl styrene the crude product was a mixture of the $\beta,\gamma$ and $\gamma,\delta$-unsaturated esters. Under similar experimental conditions, diphenylethylene and tetramethylethylene reacted also with methyl $\alpha$ - methoxy - *N* - benzyloxycarbonylglycinate (**3**, $R'' = PhCH_2O$) to give the corresponding carbobenzyloxy derivatives **5d**.

The $\beta,\gamma$-unsaturated esters were saponified to the free acids **6** which cyclized in refluxing methylene chloride in the presence of $\beta$-naphthalenesulfonic acids to the corresponding butyrolactones **8**. Tetramethylethylene and 2,5-dimethyl-2,4-hexadiene on reacting with methyl $\alpha$-methoxyhippurate in boiling benzene and in the presence of acid catalyst afforded the esters which were saponified to the acids 2 - benzamido - 3,3,4 - trimethyl - 4 - pentenoic acid **9** and 2 - benzamido - 3,3,6 - trimethyl - 4,6 - haptadienoic acid **10**.

Reacting methyl $\alpha$-methoxyhippurate with isobutylene, styrene and vinyl acetate in ether or benzene solution and in the presence of borontrifluoride etherate at room temperature afforded 1,3-oxazine derivatives **7**. The oxazine derived from styrene was obtained in high yield (82%) as a crystalline borontrifluoride complex which precipitated from the reaction mixture (ether). It showed two methoxy singlets in the NMR in a 3:1 ratio indicating a mixture of two stereomers. The complex was converted to the free oxazines **7b**. Upon trituration with hexane the more polar *cis* isomer was precipitated as white crystals (m.p. 74–75°) whereas upon chromatography of the mother liquid from trituration, on florisil column, the less polar pure *trans* isomer was isolated. The *cis* isomer tended to hydrolyze on the column.

No isomerization was observed when pure *cis* or pure *trans* isomer were dissolved in ether and subjected to $BF_3$–$Et_2O$ treatment. Catalytic hydrogenolysis of the crude mixture over Pd–C afforded methyl $\alpha$-benzamido-



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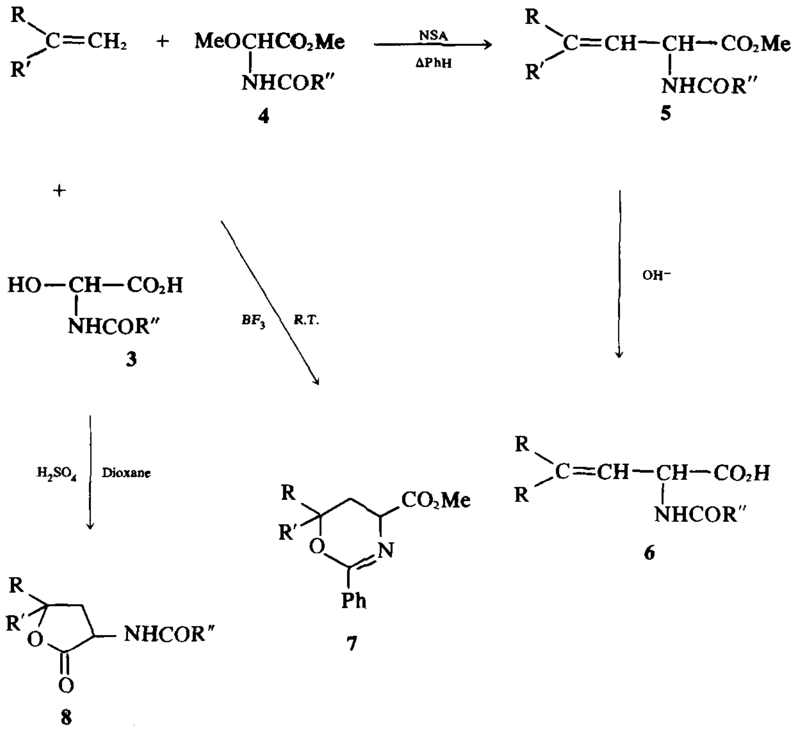
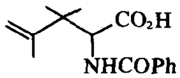
Scheme 1.



a: R = R' = Me; R'' = Ph
b: R = R' = Ph; R'' = Ph
c: R = Ph; R' = Me; R'' = Ph
d: R = Ph; R' = H; R'' = Ph
e: R = OMe; R' = H; R'' = Ph
f: R = R' = Me; R'' = PhCH$_2$O
g: R = R' = Ph; R'' = PhCH$_2$O
h: R = Ph; R' = H; R'' = PhCH$_2$O

a: R = R' = Me
b: R = Ph; R' = H
c: R = AcO; R' = H

a: R = R' = Ph; R'' = Ph
b: R = Ph; R' = Me; R'' = Ph
c: R = Ph; R' = H; R'' = Ph
d: R = R' = Ph; R'' = PhCH$_2$O



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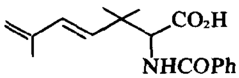

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Scheme 2.

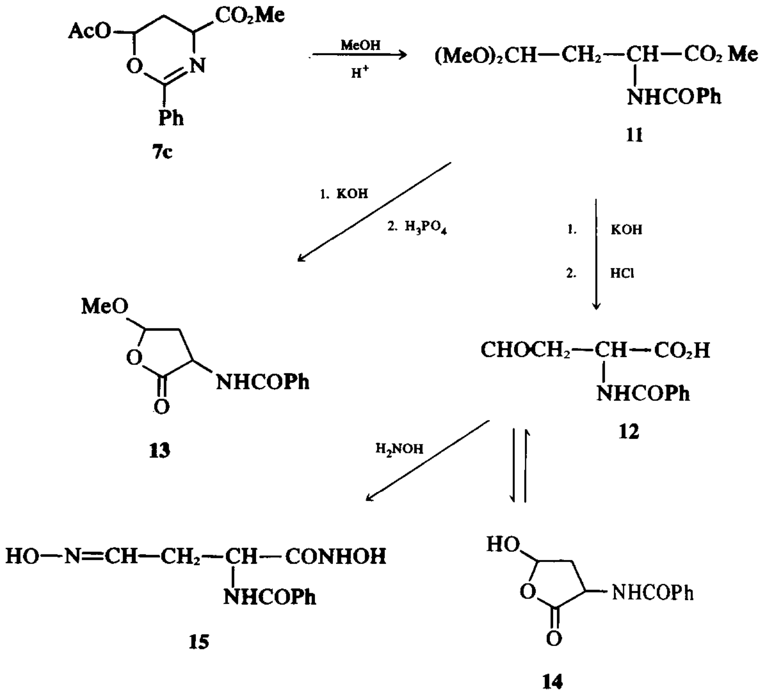
δ-phenyl butyrate, in 96% yield. The saturated ester was further hydrolysed in 6N hydrochloric acid to the free γ-phenyl-α-aminobutyric acid.

The oxazine obtained from isobutylene and methyl α-methoxyhippurate in 53% yield was purified on an alumina column. The crude product is accompanied by the unsaturated methyl esters described above (13–20%) and the butyrolactone derivative **8a** (3–7%). The oxazine was found to rearrange in boiling toluene and in the presence of β-naphthalene sulfonic acid to a mixture of unsaturated open chain esters (**16** and **17** type).

The oxazine obtained from the reaction of vinyl acetate and methyl α-methoxyhippurate **7c** was also obtained as a mixture of two isomers which were separated on a florisil column. The two oxazines were obtained in only 30% (70%) yield. The less polar isomer was obtained as an oil while the more polar isomer was isolated as a solid (m.p. 64°C). The less polar isomer isomerized to the more polar one when subjected to the action of boron-trifluoride probably because of the acetal nature of C-6. Both oxazines were unstable on storage. In methanol solution and in the presence of an acid catalyst they underwent methanolysis to give the more stable open chain dimethylacetal **11**, a derivative of aspartic acid semialdehyde. When the methanolysis was applied to the crude reaction mixture of the oxazine salt, the same diacetal was isolated in 50% yield.

The acetal **11** was hydrolyzed under mild acidic conditions to the methyl ester of *N*-benzoylaspartic acid-β-semialdehyde (methyl ester of **12**).[11] Both the aldehyde and acetal gave the same DNP derivative. If the acetal **11** was first saponified with KOH in methanol and then acidified with hydrochloric acid, *N*-benzoylaspartic acid-β-semialdehyde **12** was obtained. The aldehydoacid gave a normal DNP derivative but with hydroxylamine it yielded a compound **15** containing an hydroxamic acid function in addition to the oxime group. Such a behaviour with hydroxylamine might be attributed to the hydroxylactone form **14**. There is additional spectroscopic evidence (IR and NMR spectra) that the aldehydoacid is in tautomeric equilibrium with the 4-hydroxylactone **14**. If the saponified acetal ester **11** mixture was carefully acidified with cold diluted phosphoric acid a mixture of two isomeric 4-methoxy-2-benzamidobutyrolactones **13** was obtained. The *cis* and *trans* isomers were separated by fractional crystallization.

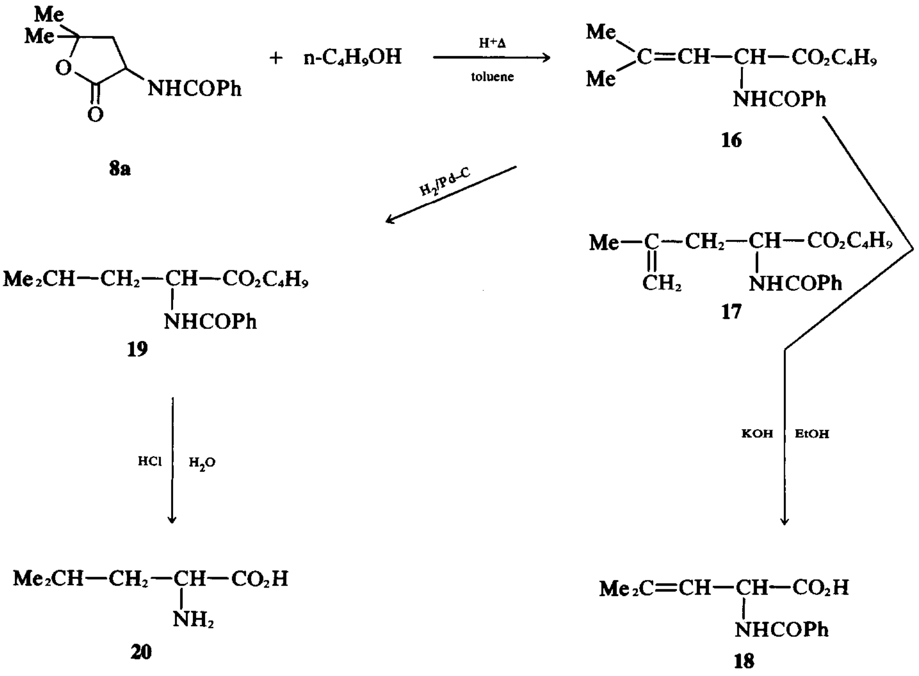
Catalytic hydrogenation of the dimethyl acetal over



Scheme 3.

Adams catalyst followed by acid hydrolysis afforded $\alpha$-aminobutyrolactone hydrochloride in 50% yield. The lactone was identical with the commercially available product. Catalytic hydrogenation of the ester oxime of **12** over Adams catalyst and subsequent hydrolysis afforded *d,l*-2,4-diaminobutyric acid dihydrochloride which was also characterized as its dibenzoyl derivative.[19]

Reacting the olefins isobutylene, diphenylethylene and styrene with $\alpha$-hydroxyhippuric acid or $\alpha$-hydroxy *N*-benzyloxycarbonylglycine in dioxane-sulfuric acid afforded the corresponding butyrolactones **8** which were obtained as stable high melting crystalline solids. The 4,4-dimethyl-2-amidobutyrolactones **8a** and **8f** were found to be rather stable to ring opening reactions. The $\gamma$-hydroxy benzylamides obtained on refluxing a toluene solution of the lactone with benzylamine were reconverted to the lactones on crystallization or treatment with an acid catalyst. We did however succeed in converting the lactones **8a** to a mixture of unsaturated butyl esters **16** and **17** on treatment with butanol in refluxing toluene

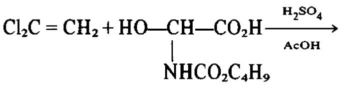


Scheme 4.

solution and in the presence of β-naphtalenesulfonic acid as catalyst. The ratio of the two esters **16**:**17** was according to the NMR 2:1. No opening of the lactone **8a** was observed on prolonged reflux in 48% hydrobromic acid or 55% hydroiodic acid and phosphor. The 4 unsubstituted analog of **8a** is known to undergo ring opening in acid solutions. The butyl ester mixture was hydrogenated over Pd–C and acid hydrolyzed to give *d,l*-leucine in 70% yield. The product was identical with an authentic sample of leucine (IR, NMR and $R_f$ on paper chromatography). The pure butyl ester **16** was isolated in about 50% yield on crystallization of the reaction mixture, it was found to equilibrate with the isomeric butyl ester **17** in refluxing toluene in the presence of β-naphthalenesulfonic acid (ratio of mixture 2:1). Saponification of the pure ester **16** in ethanolic KOH afforded the free acid **18**. Catalytic hydrogenation of the unsaturated butyl ester **16** afforded the butyl ester of *N*-benzoyl-*d,l*-leucine **19** identical with an authentic sample prepared from benzoyl-*d,l*-leucine and butanol. A pure sample of N-benzoyl-γ-δ, -dehydroleucine was obtained from the filtrate after the crystallization of the ester **16**, chromatography over a silica column and saponification of the fraction enriched in **17**.

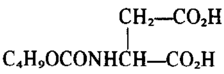
The γ-phenyl-α-amidolactones **8d** and **8h** were obtained by reacting styrene and α-hydroxyhippuric acid **3a** and α-hydroxy *N*-benzyloxycarbonylglycine **3b** in 23 and 48% yield. The lactones which were obtained as *cis-trans* isomers were separated on a florisil column. Catalytic hydrogenolysis over Pd–C afforded derivatives of α-amino-γ-phenylbutyric acid which were also obtained by the hydrogenolysis of the 6-phenyloxazine described above **7b**. In the case of the *N*-carbobenzoxylactone **8h** hydrogenolysis afforded the free amino acid.

α-Hydroxy-*N*-butoxycarbonylglycine **21** which was prepared from glyoxylic acid and butyl carbamate was found to react in sulfuric-acetic acid mixture with 1,1-dichloroethylene to give in one step *N*-butoxycarbonylaspartic acid **22** in 47% yield. The product was identical with an authentic sample prepared from *d,l*-aspartic acid and *m*-butyl chloroformate:



$$Cl_2C=CH_2+HO{-}\underset{\displaystyle NHCO_2C_4H_9}{\underset{|}{CH}}{-}CO_2H \xrightarrow[AcOH]{H_2SO_4}$$

**21**



$$C_4H_9OCONH\overset{\displaystyle CH_2{-}CO_2H}{\overset{|}{C}}H{-}CO_2H$$

**22**

The stereochemical assignment to the 1,3-disubstituted oxazines **7** and butyrolactones **8** is based on the analogy with other known oxazines[9] and butyrolactones.[10] A more detailed discussion of the stereochemistry of these compounds based on their NMR and $^{13}C$ spectra will be published separately.

## EXPERIMENTAL

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

### *Methyl 2 - benzamido - 4,4 - diphenyl - 3 - butenoate* **5a**

A mixture of methyl α-methoxyhippurate (6.70 g, 0.03 mole), 1,1-diphenylethylene (5.40 g, 0.03 mole) and β-naphtanenesulfonic acid (0.30 g) in benzene (100 ml) was refluxed for 24 h. The benzene solution was filtered and evaporated to dryness. The solid residue was dissolved in ethyl acetate (200 ml) and the solution was washed with water, dried and evaporated. Crystallization from benzene–petroleum ether afforded 5.29 g (52%) of product, m.p. 162–163°; IR ($CHCl_3$): 3450, 1740, 1680 and 1510 $cm^{-1}$. NMR ($CDCl_3$) δ 8.0–7.2 (m, 15H aro) 6.97–6.90 (m, 1H), 6.20 (d, 1H J 9 cps–CH–), 5.50–5.20 (q, 1H, N–CH–CO), 3.88 (s, 3H, OMe). MS: *m/e* 371 (M+). (Found: C, 77.58; H, 5.56; N, 3.83. $C_{24}H_{21}NO_3$ requires: C, 77.60; H, 5.70: N, 3.77%).

### 2 - *Benzamido - 4,4 - diphenyl - 3 - butenoic acid* **6a**

The methyl ester described above (4.02 g, 0.018 mole) was hydrolyzed in aqueous methanolic KOH solution (2.0 g. KOH + 45 ml methanol + 5 ml water). After 24 h at room temp. the methanol was evaporated and water (50 ml) added. The aqueous layer was extracted twice with ether acidified and the acid extracted twice with ethyl acetate to give 2.93 g. (76%), m.p. 205–206 (ethyl acetate-pet. ether) IR (KBr): 3300, 1730, 1620, 1580, 1560 $cm^{-1}$, NMR (DMSO $d_6$): 9.05–8.70 (d, 1H), 8.1–7.2 (m, 15H) 6.4–6.2 (d, 1H, J 9 cps), 5.2–4.8 (q, 1H) (Found: C, 76.96; H, 5.59; N, 4.09. $C_{23}H_{19}NO_3$ requires: C, 77.29; H, 5.36; N, 3.92%).

### 2 - *Benzyloxycarbonylamino - 4,4 - diphenyl - 3 - butenoic acid* **6d**

A mixture of methyl α - methoxy - *N* - benzyloxycarbonylglycinate (7.58g, 0.030 mole), 1,1-diphenylethylene (5.4g, 0.03 mole) and β-naphtalenesulfonic acid (0.50 g) in benzene (100 ml) was refluxed for 48 h. The solution was filtered and evaporated. The oily ester was hydrolysed with potassium hydroxide in aqueous methanol (3.0 g KOH + 90 ml methanol + 10 ml water). After 24 h at room temperature the methanol was evaporated and water (75 ml) added. The aqueous layer was extracted twice with ether, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated and the residue was chromatographed over silica (Woelm activity grade III). The acid was eluted with ethyl acetate to give 3.38 g (33%) of product; m.p. 130°. IR ($CHCl_3$): 3440, 1750–1730, 1510 $cm^{-1}$. NMR ($CDCl_3$): δ 7.30 (s, broad 15 H), 6.8–5.8 (d, 1H: J 9 cps), 5.10–4.80 (s + m 3H). MS: *m/e* 342 (*M*+). (Found: C, 74.29; H, 5.49; N, 3.65, $C_{24}H_{21}NO_4$ requires: C, 74.40: H, 5.46; N, 3.62%).

### 2-*Benzamido-4-phenyl-3-pentenoic acid and* 2-*benzamido*-4-*phenyl*-4-*pentenoic acid* **6b**

A mixture of 6.70 g (0.03 mole) methyl α-methoxyhippurate, 7.5 g (0.06 mole), of α-methylstyrene and β-naphtalenesulfonic acid (0.45 g) in benzene (100 ml) was refluxed for 24 h. The benzene was removed *in vacuo* and the residue was taken up in ethyl acetate (200 ml) washed with water, dried over $MgSO_4$ and evaporated. The oily residue (6.8 g) was hydrolysed with methanolic potassium hydroxide (3.0 g KOH + 90 ml methanol + 10 ml water) as described above. The oily residue obtained after the removal of the ethyl acetate was triturated with petroleum ether to give a solid (5.75 g 65%) which was according to the NMR a mixture of two isomers. Trituration of the mixture with ether (30 ml) afforded the 2 - benzamido - 4 - phenyl - 3 - pentenoic acid (2.28 g, 25%): m.p. 192–193. IR (KBr): 3380, 1730, 1630, 1550 $cm^{-1}$. NMR (DMSO-$d_6$): 8.1–7.2 (m, 10H), 6.2–5.9 (d, 1H, J 10 cps), 5.5–5.2 (m, 1H), 2.18 (s, 3H). MS: *m/e* = 295 (M+). (Found: C, 72.92; H, 5.97; N, 5.00. $C_{18}H_{17}NO_3$ requires: C, 73.20; H, 5.80; N, 4.74%). The ether solution, left after the filtration of the 2 - benzamido - 4 - phenyl - 3 - pentenoic acid, was evaporated and the residue was chromatographed over silica (100 g + 15 ml $H_2O$). The pure *N* - benzamido - 4 - phenyl - 4 - pentenoic acid was eluted with chloroform to give 0.48 g. (5%) of a crystalline material, m.p. 132° (benzene-petroleum ether). IR (KBr) 3340, 1735, 1620 and 1550 $cm^{-1}$; NMR ($CDCl_3$): δ 8.63 (s, 1H), 8.0–7.1 (m, 10H aromatics), 6.5 (d, 1H broad), 5.24 (d, 2H) 3.1 (m, 2H). (Found: C, 72.47; H, 5.86; N, 4.96).

*α - Benzamido - γ - phenyl - γ - methylbutyrolactone* **8c**

A solution of 2 - benzamido - 4 - phenyl - 3 - pentenoic acid (0.63 g) in methylene chloride (40 ml) containing β-naphtalenesulfonic acid (0.2 g) was refluxed for 24 h. The solution was evaporated and the residue chromatographed over deactivated neutral alumina (50 g + 5 ml methanol). Chloroform eluted 0.29 g of lactone (46%), m.p. 181–182 (Chloroform pet. ether). IR ($CHCl_3$): 3440, 1790, 1680, 1510 $cm^{-1}$. NMR ($CDCl_3$): δ 8.0–7.0 (m, 10 H), 5.5–4.9 (m, 1H), 3.4–2.9 (q, 1H), 2.7–2.2 (t, 1H), 1.78 (s, 3H). (Found: C, 72.86, H, 6.02, N, 4.81. $C_{18}H_{17}NO_3$ requires: C, 73.20; H, 5.80, N, 4.74%).

2 - *Benzamido - 4 - phenyl - 3 - butenoic acid* **6c**

A mixture of 6.7 g (0.03 mole) of methyl α-methoxyhippurate, styrene (6.4 g, 0.06 mole) and β-naphtalene sulfonic acid (0.5 g) in toluene (100 ml) was refluxed for 6 h. The solvent was removed and the residue chromatographed over deactivated neutral alumina (150 g + 15 ml methanol). The ester which was eluted with benzene-pet. ether (5.5 g 62%) was hydrolyzed with methanolic KOH as described above. The 2 - benzamido - 4 - phenyl - 3 - butenoic acid was triturated with ether filtered and crystallized from ethyl acetate-pet. ether; m.p. 210–212 yield 2.90 g (42%). IR (KBr): 3280, 1735, 1635, 1590, 1545. NMR (DMSO) δ: 9.0–8.6 (d, 1H), 8.1–7.1 (m, 10H), 6.8–6.2 (q, 2H), 5.3–5.1 (m, 1H). (Found: C, 72.22; H, 5.29; N, 5.41. $C_{17}H_{15}NO_4$ requires: C, 72.58; H, 5.37; N, 4.98%).

2 - *Benzamido - 3,3,4 - trimethyl - 4 - pentenoic acid* **9**

A mixture of methyl 2-methoxyhippurate (2.23 g 0.01 mole), tetramethylene (2.52 g 0.03 mole) and β-naphtalenesulfonic acid (0.20 g) in 1,2-dichloroethane (25 ml) was refluxed for 48 h. The solvent was removed and the residue was filtered over deactivated alumina (100 g + 10 ml methanol) and eluted with benzene-pet. ether (1:9). The ester obtained (0.69 g) was hydrolyzed with methanolic KOH as described above. The 2 - benzamido - 3,3,4 - trimethyl - 4 - pentenoic acid melted at 146° (benzene); yield 27%. IR ($CHCl_3$): 3440, 1720, 1665, 1510. NMR ($CDCl_3$): δ 8.0 (s, 1H), 7.9–7.3 (m, 5H), 6.58 (d, 1H, J 7 cps), 4.9 (s, 2H), 1.9 (s, 3H), 1.3 (s, 3H). (Found: C, 68.78; H, 7.10; N, 5.51. $C_{15}H_{19}NO_3$ requires: C, 68.94; H, 7.33; N, 5.36%).

2 - *Benzyloxycarbonylamino - 3,3,4 - trimethyl - 4 - pentenoic acid*

This compound was obtained in overall 11% by the procedure described above for the preparation of the benzoyl derivative; m.p. 106–107° (benzene-pet. ether). IR ($CHCl_3$): 3440, 1720, 1510 $cm^{-1}$. NMR ($CDCl_3$): 8.5 (s, 1H), 7.40 (s, 5H), 5.2 (s, 2H), 4.85 (s, 2H), 4.45 (d, 1H, J 7 cps), 1.8 (s, 3H), 1.2 (s, 6H). (Found: C, 65.80; H, 7.29; N, 4.99. $C_{16}H_{21}NO_4$ requires: C, 65.95; H, 7.27; N, 4.81%).

2 - *Benzamido - 3,3,6 - trimethyl - 4,6 - heptadienoic acid* **10**

A mixture of methyl α-methoxyhippurate (5.57 g 0.025 mole), 2,5-dimethyl-2,4-hexadiene (10.0 g 0.09 mole) and β-naphtalenesulfonic acid (0.50 g) in 1,2-dichloroethane (80 ml) was refluxed for 48 h. The solvent was evaporated and the residue chromatographed over florisil (100 g 100 mesh). The ester was eluted with benzene (4.45 g 61%) and hydrolyzed to the acid with methanolic KOH as described above; m.p. 96–97 (ethyl acetate-pet. ether), yield 2.94 g (45%). IR ($CHCl_3$): 3420, 1720, 1675, 1510 $cm^{-1}$. NMR ($CDCl_3$): δ 8.6 (s, 1H), 8.0–7.3 (m, 5H) 6.65 (d, 1H, J 9 cps), 6.0 (q, 2H), 5.0 (s, 2H), 4.72 (d, 1H, J 9 cps), 1.8 (s, 3H), 1.15 (s, 6H). Found: C, 70.81; H, 7.19; N, 4.88. $C_{17}H_{21}NO_3$ requires: C, 71.05: H, 7.37: N, 4.87%).

4 - *Carboxymethyl - 6,6 - dimethyl - 2 - phenyl - 5,6 - dihydro - 4H - 1,3 - oxazine* **7a**

Methyl - α - methoxyhippurate **4** (2.23 g 0.01 mol) was dissolved in cold solution of ether (or benzene) (30 ml) in a pressure bottle containing borontrifluoride etherate (2.4 ml) and 5 ml of condensed isobutylene was added. The mixture was stirred for 72 h at room temp., poured into ice water and extracted twice with ethyl acetate. To the acidic water layer $NaHCO_3$ was added until pH 8. Extraction and concentration yielded crude oxazine **7a** (1.32 g 53%) as an oil. For analysis filtration was done through deactivated neutral alumina using hexane as eluant. IR ($CHCl_3$): 1725, 1635 $cm^{-1}$. NMR ($CDCl_3$) δ: 7.3–8.1 (m, 2, aromatic); 7.2–7.5 (m, 3, aromatic); 4.32 (q, H-4, J 5 and 11.5 cps); 3.80 (s, 3, $OCH_3$); 1.6–2.3 (and 11.5 cps); 3.80 (s, 3, $OCH_3$); 1.6–2.3 (m, 2, $CH_2$): 1.45 (s, 3, $CH_3$); 1.35 (s, 3, $CH_3$). (Found: C, 67.62; H, 7.04; N, 5.74. $C_{14}H_{17}NO_3$ requires: C, 67.99; H, 6.93; N, 5.74%).

Organic layer from the extraction of acidic solution, contained, according to NMR, lactone **8a**, unsaturated esters and some starting material.

Oxazine **7a** (864 mg), upon reflux in 10% HCl (10 ml) during 3 h and extraction with ethyl acetate, yielded from the water layer, after lyophilisation, 2 - amino - 4,4 - dimethylbutyrolactone hydrochloride (349 mg, 61%) m.p. 199–201°. From the concentration of ethyl acetate and trituration with ether 2 - benzamido - 4,4 - dimethylbutyrolactone **8a** was isolated (80 mg 10%) m.p. 176° and benzoic acid (322 mg, 75%). The amino lactone hydrochloride was also obtained by the catalytic hydrogenolysis of the lactone **8f** (see below).

When oxazine **7a** was refluxed in toluene in the presence of NSA, with azeotropic removal of water, two unsaturated isomeric esters were formed in 45% yield and lactone **8a** in 25% yield.

N - *Benzoyl - γ - hydroxy -* DL *- leucine lactone* **8a** (2 - *Benzamido - 4,4 - dimethylbutyrolactone*)

A solution of dioxane (50 ml) and conc. sulfuric acid (3.7 ml Merck 96%) was cooled in a 200 ml-pressure bottle to 0°C. α-Hydroxyhippuric acid (5.85 g 0.03 mol) and condensed *iso*-butylene (30 ml) were added. The bottle was closed and the content was stirred. After 3 h all starting acid went into solution and a two-liquid layer appeared. The stirring was continued overnight, the bottle was cooled prior to opening, the content was poured into ice water (300 ml) and extracted three times with ethyl acetate (200 ml portions). The organic layer was washed until neutral, dried over $MgSO_4$ and evaporated. The residue was triturated with ether, and crystallized from ethyl acetate yielding 4.75 g 68% of white crystals. m.p. 176°, lit[12] 176°. IR($CHCl_3$): 3420; 1770, 1670 $cm^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) δ: 7.2–8 (m, 5, aromatic): 5.10 (q, H-2, J 9 and 12 cps); 1.9–2.9 (m, 2, $CH_2$); 1.54, 1.51 (s and s, 6, $CH_3$) ($CDCl_3$) δ: 7.3–8.0 (m, 6, NH and aromatic): 5.08 (m, H-2, J 6, 8 and 12 cps); 1.9–2.9 (m, 2, $CH_2$) 1.50 and 1.52 (s and s, 6, $CH_3$) (Found: C, 66.69; H, 6.48; N, 6.01. $C_{13}N_{15}NO_3$ requires: C, 66.93, H, 6.53; N, 6.01%).

The mother liquid from trituration contained a mixture of *t*-butyl esters of *N*-benzoyl-γ-hydroxy-*DL*-leucine and some unsaturated esters. These crude esters, after heating with NSA (200 mg) in toluene (50 ml), yielded another crop of lactone bringing the overall yield to 80%.

N - *Benzyloxycarbonyl - γ - hydroxy -* DL *- leucine lactone* **8f** (2 - *Benzyloxycarbonylamino - 5,5 - dimethylbutyrolactone*)

Lactone **8f** was prepared according to the previous procedure starting from α - hydroxy - *N* - benzyloxycarbonylglycine **3b** (6.73 g 0.03 mol); 5.5 g (70%) was obtained, m.p. 94° (from ethyl acetate-hexane) lit.[13] 92°–93°. IR ($CHCl_3$): 3420, 1770, 1665 $cm^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) δ: 7.22 (bs, 5, aromatic); 5.18 (s, 2, $CH_2Ph$); 4.64 (bt, H-2, J 10 and 12 cps): 1.8–2.8 (m, 2, $CH_2$); 1.45 and 1.50 (two singlets, 6, $CH_3$). ($CDCl_3$) δ: 7.38 (s, 5, aromatic); 5.55 (bd, 1, NH, J 7 cps); 5.10 (s, 2, $CH_2$ Ph): 4.58 (m, H-2, J 7, 10 and 12 cps); 1.80–2.80 (m, 2, $CH_2$); 1.50 (s, 3, $CH_3$); 1.44 (s, 3, $CH_3$). (Found: C, 63.84; H, 6.58; N, 5.36. $C_{14}H_{17}NO_4$ requires: C, 63.86; H, 6.51; N, 5.32%).

*α - Benzamido - γ - hydroxy -* DL *- leucinamide*

Lactone **8a** (500 mg) was dissolved in methanol saturated with dry ammonia and was left to stand at room temperature during 1 week. The solvent was removed and the product was recrystallized from ethyl acetate. (435 mg 81%), m.p. 161–162° (decomp). IR(KBr): 3460, 3430, 3270, 1680, 1635 $cm^{-1}$. NMR (DMSO $d_6$) δ: 8.45 (d, 1, NH): 7.40–8.00 (m, 5, aromatic); 7.30 (bs, 2, $NH_2$); 6.95 (bs, 1, OH), 4.35–4.72 (m, 1, CH); 1.94 (d, 2, $CH_2$); 1.19 (s, 6, $CH_3$). (Found: C, 62.34; H, 7.04; N, 11.19. $C_{13}H_{18}N_2O_3$ requires: C, 62.38; H, 7.25; N, 11.19%). Upon prolong boiling the amide tended to cyclize back to lactone **8a** with evolution of ammonia.

### *α Benzamido - γ - hydroxy* - DL - *leucine benzylamide*

Lactone **8a** (582 mg) and benzylamine (1.35 g) were refluxed in toluene (15 ml) for 72 h, then concentrated, diluted with ethyl acetate, washed with 10% HCl, water and 10% $NAHCO_3$. The amide (560 mg 66%) melted at 84°, than solidified and melted again at 126–128° (from benzene-petroleum ether). IR ($CHCl_3$): 3400, 3580, 1660 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 7.2–8.2 (m, 5, aromatic); 7.2 (s, 5, aromatic); 4.92 (q, 1, CH); 4.35 (d, 2, $CH_2Ph$); 3.15 (s, 1, OH); 2.0 (d, 2, $CH_2$); 1.13; 1.19 (s,s, 6, $CH_3$). (Found: C, 70.40; H, 7.23; N, 7.98. $C_{20}H_{24}N_2O_3$ requires: C, 70.56; H, 7.11; N, 8.23%).

The amide cyclized back to lactone **8a** with elimination of benzylamine upon reflux in methanol containing anhydrous HCl.

### 2 - *Formamido - γ - hydroxy* - DL - *leucine lactone* (2 - *Formamido* - 4,4 - *dimethylbutyrolactone*)

Lactone **8f** (500 mg) was heated for 12 h in 99% formic acid (10 ml) at 100°. The acid was evaporated and the residue was triturated with a mixture ether-petrol ether 1 : 1. (256 mg, 86%) m.p. 123–126° (from ethyl acetate-petrol ether) IR ($CHCl_3$): 3400, 1765, 1675 $cm^{-1}$. NMR (acetone-$d_6$) $\delta$: 8.24 (s, 1, CHO); 4.97 (q, H-2, J 9 and 12 cps); 1.90–2.90 (m, 2, $CH_2$); 1.48 and 1.46 (2s, 6, $CH_3$). (Found: C, 53.34; H, 6.86; N, 8.84. $C_7H_{11}NO_3$ requires: C, 53.49; H, 7.05; N, 8.91%).

### 2 - *Amino - γ - hydroxy* - DL - *leucine lactone hydrochloride* (2 - *Amino* - 4,4 - *dimethylbutyrolactone*)

Lactone **8f** (500 mg) was hydrogenolyzed in a Parr apparatus in methanol (25 ml) saturated with dry HCl, using 10%Pd|C (80 mg) during 12 h the solution was filtered and concentrated to a small volume. Hydrochloride was triturated with ether, (268 mg 86%), m.p. 205–207°, lit. 2.8–209°[14]; 210–211°.[12] IR (KBr): 1770 $cm^{-1}$. NMR ($CD_3OD$) $\delta$: 4.56 (9, H-2, J 9 and 12 cps); 2.0–3.0 (m, 2, $CH_2$) 1.55 (s, 3, $CH_3$); 1.51 (s, 3, $CH_3$). (Found: N, 8.16; Cl, 21.47. $C_6H_{12}NO_2Cl$ requires: N, 8.47; Cl, 21.41%).

### DL-*Leucine* **20**

Lactone **8a** (1.293 g 5.5 mmol), NSA (250 mg), toluene (40 ml) and *n*-butanol (1.2 ml) were refluxed for 48 h with azeotropic removal of water. The solution was concentrated into a small volume, diluted with ethyl acetate, washed with water and 10% $NaHCO_3$ to remove NSA, dried over $MgSO_4$ and evaporated. The residue, containing mainly the esters **16** and **17** in the ratio 2 : 1, was dissolved in hot hexane (100 ml) and filtered when hot to remove some traces of unreacted lactone, then concentrated and submitted to hydrogenation in a Parr apparatus using methanol (50 ml) as solvent and 10% Pd/C (50 mg) as catalyst yielding *N*-benzoyl-DL-leucine-*n*-butyl ester **19** 1.583 g. The crude ester was submitted to hydrolysis with 6N HCl (25 ml) under reflux overnight. After cooling, the solution was extracted with ether to remove benzoic acid and evaporated. The residue was dissolved in water and treated with diluted ammonium hydroxide solution. The precipitated leucine was filtered and crystallized from ethanol yielding 511 mg, 70.5% (based on lactone **8a**).

The melting point, $R_f$-value on paper chromatography and all spectroscopic data were identical with those of authentic sample of DL-leucine (Fluka).

DL-Leucine was also prepared from *N*-benzyloxycarbonyl-γ-hydroxy-leucine lactone **8f** (1.129 g. 4.3 mmol) by a similar sequence of reactions. Catalytical reduction in this case was performed in methanol (60 ml) containing anhydrous HCl (700 mg). The hydrolysis of ester was done with 10% hydrochloric acid. The yield in this case was 234 mg 47% (based on lactone **8f**).

### *Butyl* N - *benzoyl - β,γ - dehydro* - D,L - *leucinate* **16** (*Butyl* 2 - *benzamido* - 4 - *methyl* - 3 - *pentenoate*)

When lactone **8a** 1.293 g was treated with NSA (250 mg) and *n*-BuOH (1.2 ml) in boiling toluene (40 ml) as described above and the crude reaction mixture workup was triturated with hexane at room temp. the β-γ unsaturated butyl ester precipitated (790 mg 50%) m.p. 87–89° (from hexane) IR ($CHCl_3$): 3420, 1725, 1655 $cm^{-1}$; NMR ($CCl_4$)$\delta$: 7.14–8.00 (m, 5, aromatic); 7.10 (d, 1, NH); 4.98–5.50 (m, 2, olefinic and CHN); 4.18 (t, 2, $OCH_2$); 1.82 (s, 3, $CH_3$); 1.70 (s, 3, $CH_3$); 0.6–1.6 (m, 7 $(CH_2)_2CH_3$); (Found: C, 70.36; H, 7.75; N, 5.02. $C_{17}H_{23}NO_3$ requires: C, 70.56, H, 8.01; N, 4.84%).

### N - *Benzoyl - β,γ - dehydro* - D,L - *leucine* **18** (2 - *Benzamido* - 4 - *methyl* - 3 - *pentenoic acid*)

The ester **16** (265 mg) was saponified in ethanol (7 ml) containing KOH (110 mg) at room temp. during 48 h. The solvent was removed, the product was acidified with cold formic acid (192 mg 90%) m.p. 132–133°. IR ($CHCl_3$): 3420, 1715, 1650 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 9.30 (bs, 1, $CO_2H$): 7.3–8.0 (m, 5, aromatic): 6.80 (d, 1, NH): 5.10–5.60 (m, 2, olefinic and CHN); 1.97 (s, 3, $CH_3$); 1.80 (s, 3, $CH_3$). (Found: C, 66.78: H, 6.47; N, 6.05. $C_{13}H_{15}NO_3$ requires: C, 66.93; H, 6.48; N, 6.01%).

### *Methyl* N - *benzoyl - β,γ - dehydro* - DL - *leucinate*

The ester was prepared in quantitative yield by methylation with diazomethane, m.p. 95–6° (from hexane). IR ($CHCl_3$): 3420, 1730, 1650 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 7.3–7.9 (m, 5, aromatic); 6.95 (d, 1, NH): 4.95–5.60 (m, 2, CH olefinic and CHN); 3.74 (s, 3, $OCH_3$); 1.86 (s, 3, $CH_3$); 1.75 (s, 3, $CH_3$); (Found: C, 67.85; H, 6.88; N, 5.76. $C_{14}H_{17}NO_3$ requires: C, 67.99; H, 6.93; N, 5.66%).

### N - *Benzoyl - γ,δ - dehydro* - DL - *leucine* (2 - *Benzamido* - 4 - *methyl* - 4 - *pentenoic acid*)

The mixture of butyl esters **16** and **17** (4.02 g) was saponified as described for pure ester **16**. After workup the residue (3.59) was triturated with ether-hexane 1 : 1 (40 ml). Crystalline product (630 mg) was enriched in the acid with the terminal double bond. Three recrystallization gave pure *N* - benzoyl - γ,δ - dehydro - DL - leucine (370 mg). m.p. 134°. IR ($CHCl_3$): 1725, 1660 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 7.3–8.0 (m, 5, aromatic): 6.98 (d, 1, NH): 4.76–5.20 (m, 3, $CH_2$ olefinic and CHN); 2.56–2.82 (m, 2, $CH_2$ allylic) 1.80 (s, 3, $CH_3$). (Found: C, 66.96; H, 6.54; N, 6.03. $C_{13}H_{15}NO_3$ requires: C, 66.93; H, 6.48; N, 6.01%).

### *Methyl* N - *benzoyl - γ,δ - dehydro* - DL - *leucinate*

This was prepared by methylation of the acid with diazomethane. It was on oil. IR ($CHCl_3$): 3420, 1735, 1655 $cm^{-1}$. NMR ($CDCl_3$) $\delta$: 7.38–8.00 (m, 5, aromatic); 6.8 (bd, 1, NH): 4.78–5.16 (m, 3, $CH_2$ olefinic and CHN); 3.80 (s, 3, $OCH_3$); 2.5–2.8 (m, 2, $CH_2$ allylic); 1.78 (s, 3, $CH_3$). (Found: C, 67.49; H, 6.83; N, 6.00. $C_{14}H_{17}NO_3$ requires: C, 67.99; H, 6.93; N, 5.66%).

### *Butyl* N - *benzoyl* - D,L - *leucinate* **19**

Catalytic hydrogenation of pure *N* - benzoyl - β,γ - dehydro - DL - leucine *n*-butyl ester **16** as well as the hydrogenation of the mixture **16** and **17** over 10% Pd–C in methanol solution gave in quantitative yield *N* - benzoyl - *DL* - leucine *n*-butyl ester, m.p. 59–60° (from hexane). IR ($CHCl_3$): 3420, 1725, 1660 $cm^{-1}$. NMR ($CCl_4$) $\delta$: 7.22–8.00 (m, 5, aromatic); 7.04 (d, 1, NH); 4.5–5.0 (m, 1, CH); 4.15 (t, 2, $CH_2O$); 1.2–1.95 (m, 7, $CH_2CH$), 0.7–1.2 (m, 9, $CH_3$). (Found: C, 70.28; H, 8.69; N, 4.86. $C_{17}H_{25}NO_3$ requires: C, 70.07; H, 8.65; N, 4.81%). The ester was identical in all respects with the sample prepared by benzoylation and esterification of commercial available DL-leucine. N - benzoyl - DL - leucine, m.p. 139–140°, no depression in mixed melting point with authentic sample, lit: 138–141.[15]

### *Diastereomeric* 4 - *carboxymethyl* - 2,6 - *diphenyl* - 5,6 - *dihydro* - 4*H* - 1,3 *oxazine* **7b**

Methyl-α-methoxyhippurate (8.92 g 0.04 mol), styrene (10 ml) and borontrifluoride etherate (11.2 g 0.08 mol) were stirred in absolute ether (120 ml) for 72 h. During this time oxazine borontrifluoride complex was formed as white crystals. The complex was filtered, triturated with a new portion of ether and filtered again: 11.82 g 82% m.p. 170° (with decomp.) IR (KBr) 1750, 1645 $cm^{-1}$. NMR (DMSO $d_6$) $\delta$: 7.2–8.2 (m, 10, aromatic), 6.0 (q, 1, CH); 4.8–5.2 (m, 1, CH); 3.85 and 3.78 (two singlets, 3, $OCH_3$, approximative ratio 3 : 7); 2.3–2.9 (m, $CH_2$ with superposition of DMSO). The complex (2.1 g) was suspended in 10% $NaHCO_3$

solution (35 ml), extracted with ether (100 ml) and concentrated. The mixture of crude diastereoisomeric oxazines **7b** was obtained as an oil (1.65 g, 98%). Trituration with hexane gave white crystals of pure *cis* isomer (920 mg, 55%) m.p. 74–75% (from benzene-hexane). IR ($CHCl_3$) 1740, 1650 cm$^{-1}$. NMR ($CDCl_3$) $\delta$: 8.0–8.15 (m, 2, aromatic); 7.42 (m and s, 8 aromatic), 5.27 (q, H-6. J 3 and 11 cps); 4.46 (q, H-4, J 4 and 6 cps); 3.82 (s, 3, $OCH_3$); 1.8–2.8 (m, 2, $CH_2$); (Found: C, 72.76; H, 5.95; N, 4.75. $C_{18}H_{17}NO_3$ requires: C, 73.20; H, 5.80; N, 4.74%).

The mother liquid from the trituration was concentrated and chromatographed on the column of florisil (40 g). The elution with benzene gave in the first six fractions of 75 ml the pure *trans* isomer as an oil (265 mg, 15.5%); IR ($CHCl_3$) 1740, 1650 cm$^{-1}$, NMR ($CDCl_3$) $\delta$: 8.0–8.15 (m, 2, aromatic), 7.40 (m and s, 8, aromatic); 5.52 (q, H-6, J 4 and 9 cps); 4.46 (q, H-4, J 4 and 6 cps); 3.82 (s, 3, $OCH_3$); 1.9–2.7 (m, 2, $CH_2$). (Found: C, 73.16; H, 5.99; N, 4.61. $C_{18}H_{17}NO_3$ requires: C, 73.20; H, 5.80; N, 4.74%).

### *Methyl α-benzamido-δ-phenylbutyrate*

Crude oxazine **7** (750 mg) was hydrogenated in methanol (70 ml) in the presence of 10% Pd–C (70 mg) in a Parr apparatus for 18 h. The solution was filtered and evaporated yielding 728 mg 96% of ester m.p. 116–118° (from ethyl acetate-hexane) IR ($CHCl_3$), 3400, 1735, 1660 cm$^{-1}$. NMR ($CDCl_3$) $\delta$: 7.2–7.9 (m, 5, aromatic): 7.25 (s, 5, aromatic); 6.85 (d, 1, NH): 4.90 (q, 1, CH); 3.76 (s, 3, $OCH_3$); 2.5-2.9 (m, 2, $CH_2$); 1.9–2.4 (m, 2, $CH_2$). (Found: C, 72.87; H, 6.33; N, 4.80. $C_{18}H_{19}NO_3$ requires: C, 72.70; H, 6.44; N, 4.71%).

### *2 - Amino - δ - phenylbutyric acid hydrochloride*

The ester described above (342 mg) was refluxed in 6N HCl (10 ml) for 12 h. After cooling the mixture was shaken with ether to remove benzoic acid. The aqueous layer was liophylised, the residue was triturated with absolute ether, dissolved in absolute ethanol and precipitated with ether as a monohydrate (232 mg 94%), m.p. 268–270°. IR (KBr) 1725, 1600, 1570, 1515 cm$^{-1}$. NMR ($D_2O$, TMS as external standard) $\delta$: 7.57 (s, 5, aromatic); 4.10–4.28 (t, 1, CH, J 6 cps); 2.76–3.15 (m, 2, $CH_2$); 2.14–2.54 (m, 2, $CH_2$). (Found: C, 51.68; H, 6.88; N, 6.09; Cl, 15.27. $C_{10}H_{14}NO_2Cl{\cdot}H_2O$ requires: C, 51.50; H, 6.88; N, 6.00; Cl, 15.25%).

### *2 - Benzamido - 4 - phenylbutyrolactone* **8d**

*α*-Hydroxyhippuric acid **3a** (8g 0.04 mol) and styrene (40 ml) were dissolved in the cold solution of dioxane (120 ml) containing conc. sulfuric acid (9 ml). The mixture was stirred for 48 h at room temp., poured into ice and extracted with ethyl acetate. The organic layer was washed with 10% $NaHCO_3$ solution to remove acidic byproducts, drier over $MgSO_4$ and concentrated at high vacuum to remove excess of styrene. The residue was triturated with petrol.ether, giving a crude mixture of *trans* and *cis* lactones (7.6 g) in an approximative ratio 1:4, then chromatographed on florisil column (220 g). Traces of styrene and carbinolic byproducts were eluted with benzene-methylene chloride 1:1 in the first 10 fractions of 75 ml. Elution with benzene–methylene chloride 1:4, in the next 10 fractions gave *trans* lactone still contaminated by carbinolic compound. Concentration of those fractions and trituration with ether gave pure *trans* isomer (271 mg 2%) m.p. 165–166° (from ethyl acetate-hexane). IR (KBr): 3290, 1780, 1645 cm$^{-1}$. ($CHCl_3$): 3420, 1775, 1660 cm$^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) $\delta$: 7.0–8.0 (m, 10, aromatic); 5.77 (t, H-4, J 7 and 6 cps); 4.82 (t, H-2, J 9.5 cps); 2.6–3.0 (m, 2, $CH_2$); ($CDCl_3$) $\delta$: 7.1–8.0 (m, 11, NH and aromatic); 5.77 (q, $H_4$, J 7 and 5 cps); 4.82 (m, H-2, J 6 and 9.5 cps); 2.7–3.0 (m, 2, $CH_2$). (Found: C, 72.43; H, 5.46; N, 5.06. $C_{17}H_{15}NO_3$ requires: C, 72.58; H, 5.37; N, 4.98%).

Eluting with methylene chloride in the next 15 fractions, a mixture at *cis* and *trans* lactones was obtained (566 mg, 5%). Further elution yielded pure *cis* isomer, (2.018 g, 17.6%) m.p. 173–174° (from ethanol). Upon deactivation of column more *cis* isomer was obtained, contaminated by benzamide. (The total yield of lactone **8d** was 25%). IR (KBr): 3360, 1760, 1655 cm$^{-1}$; ($CHCl_3$): 3420, 1775, 1650 cm$^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) $\delta$: 7.3–7.9 (m, 10, aromatic); 5.54 (q, H-4, J 5 and 11 cps); 5.12 (q, H-2, J 8 and 12.5 cps); 2.0–3.4 (m, 2, $CH_2$). ($CDCl_3$): 7.3–8.1 (m, 11, NH and aromatic); 5.55 (q, H-4, J 5 and 11 cps); 5.08 (m, H-2, J 6.5; 8 and 12.5 cps); 2.0–3.4 (m, 2, $CH_2$). (Found: C, 72.20; H, 5.32; N, 5.03. $C_{17}H_{15}NO_3$ requires: C, 72.58; H, 5.37; N, 4.98%).

### *2 - Benzyloxycarbonyl - amino - 4 - phenylbutyrolactone* **8h**

*α* - Hydroxy - *N* - benzyloxyglycine (11.25 g 0.05 mol) and styrene (30 ml) were dissolved in the cold solution of dioxane (120 ml) containing conc. sulfuric acid (9 ml). The mixture was stirred at room temp. for 24 h, then workup was done as described for **8d**. A crude mixture of *trans* and *cis* isomer was obtained in an approximative ratio 1:3. Upon chromatography on florisil column (260 g) traces of styrene and carbinolic by products were eluted with benzene in the first 10 fractions of 75 ml. Pure, less polar *trans* lactone was eluted in the fractions 11–20. 1.04 g, 6.7%, m.p. 104–105° (from ethyl acetate–hexane). IR ($CHCl_3$): 3420, 1780, 1720 cm$^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) $\delta$: 7.35 (s, 10, aromatic); 5.73 (t, H-4, J 5.5 and 6 cps); 5.16 (s, 2, $CH_2$ benzylic); 4.48 (t, H-2, J 9.5 and 10 cps); 2.50–2.90 (m, 2, $CH_2$). ($CDCl_3$) $\delta$: 7.30 (s, 10, aromatic); 5.93 (d, 1, NH, J 7 cps); 5.70 (t, H-4, J 5.5 and 6); 5.12 (s, 2, $CH_2$ benzylic); 4.46 (m, H-2, $J_{NH}$ 7, $J_{CH}$ 9.5 and 10); 2.47–2.82 (m, 2, $CH_2$). (Found: C, 69.33. H, 5.51; N, 4.59. $C_{18}H_{17}NO_4$ requires: C, 69.44; H, 5.50; N, 4.50%).

Further elution with a mixture of methylene chloride-benzene (1:4), gave in the next six fractions a mixture of two isomeric lactones (1.89 g 12.2%). Succeeding fractions, gradually enriched in methylene chloride, contained pure *cis* isomer (4.59 g 29.5%). (The total yield of lactone *8h* was 48%). m.p. 101° (from ethyl acetate-hexane); IR (3420, 1780, 1720 cm$^{-1}$); NMR ($CDCl_3$, $(C_2H_5)_3N$ and $D_2O$) $\delta$: 7.32 (s, 10, aromatic); 5.42 (q, H-4, J 5 and 11 cps); 5.15 (s, 2, $CH_2$ benzylic); 4.67 (q, H-2, J 8 and 12.5 cps); ($CDCl_3$) $\delta$: 7.35 (s, 10, aromatic); 5.75 (d, 1, NH, J 6 cps); 5.35 (q, H-4, J 5 and 11 cps); 5.15 (s, 2, $CH_2$ benzylic); 4.60 (m, H-2, J 6, 8 and 12.5 cps), 1.9-3.3 (m, 2, $CH_2$). (Found: C, 69.62; H, 5.54; N, 4.55. $C_{18}H_{17}NO_4$ requires: C, 69.44, H, 5.50; N, 4.50%).

### *Methyl α - amino - δ - phenylbutyrate hydrochloride*

A mixture of lactone **8h** (445 mg) was hydrogenated in Parr apparatus in 0.5N HCl–methanolic solution (50 ml) using 10% Pd–C (50 mg) as a catalyst. The solution was filtered, concentrated to a small volume and the hydrochloride was precipitated with absolute ether (296 mg 88%) m.p. 150–152° (with decomp.). IR (KBr) 1747 cm$^{-1}$. NMR ($D_2O$, TMS external standard): 7.50 (s, 5, aromatic) 4.28 (t, 1, CH, J 6 cps); 3.94 (s, 3, $OCH_3$); 2.7–3.1 (m, 2, $CH_2$); 2.1-2.5 (m, 2, $CH_2$).(Found: C, 56.94; H, 6.91; N, 6.01; Cl, 15.47. $C_{11}H_{16}NO_2Cl$ requires: C, 57.50; H, 7.01; N, 6.09; Cl, 15.80%).

### DL - *α - amino - δ - phenylbutyric acid*

The mixture of lactones **8h** (920 mg) was hydrogenated as above. The crude methyl ester hydrochloride was refluxed in water (10 ml) for 1 h. Upon cooling and neutralization with triethylamine the acid was precipitated (462 mg 87%)[16] m.p. 291–294° (decomp) (from water). It had $R_f = 0.660$ upon paper chromatography using *n*BuOH:$H_2O$:AcOH as eluant. Phenylalanine had $R_f = 0.575$. IR (KBr) 1660 sh, 1620 sh, 1580 cm$^{-1}$. NMR ($D_2O$ and TFA) was identical to that of hydrochloride described above. (Found: C, 67.14; H, 7.34; N, 8.00. $C_{10}H_{13}NO_2$ requires: C, 67.02: H, 7.31: N, 7.82%).

### DL - *α - benzamido - δ - phenylbutyric acid*

*α*-aminophenylbutyric acid (173 mg, 1 mmol) was benzoylated under Shotten–Baumen conditions with benzoyl chloride (240 mg) in the presence of 0.1N KOH solution (20 ml). Acidification with conc. HCl, extraction with ethyl acetate and concentration yielded, after recrystallization, DL - *α* - benzamido - *δ* - phenylbutyric acid[17] (189 mg, 62%) m.p. 162–163° (from ethyl-acetate-hexane). IR (KBr): 3295, 1730, 1640, 1520 cm$^{-1}$. NMR ($CD_3OD$) $\delta$: 7.45–8.05 (m, 5, aromatic); 7.30 (s, 5, aromatic); 4.54 (m, 1, CH); 2.5–2.9 (m, 2, $CH_2$); 2.0–2.4 (m, 2, $CH_2$); (Found: C, 63.04; H, 5.62; N, 8.25. $C_{18}H_{18}N_2O_5$ requires: C, 63.15; N, 5.30; N, 8.18%).

The same acid was obtained in 92% yield when a mixture of two isomeric lactones **8d** was hydrogenated in Parr Apparatus using 10% Pd–C as catalyst and methanol as solvent.

### 2 - *Benzamido* - 4,4 - *diphenylbutyrolactone* **8b**

α-Hydroxyhippuric acid **3a** (1.95 g, 0.01 mol) and 1,1-diphenylethylene (2 g, 1.1 mol) were dissolved in cold solution of dioxane (15 ml) containing conc. sulfuric acid (1.5 ml). the mixture was stirred at room temp. for 48 h, poured into $NaHCO_3$ and ice, extracted with ethyl acetate, concentrated and triturated with ether. 2 - Benzamido - 4,4 - diphenylbutyrolactone **8b** was formed as white solid (1.558 g, 44%) m.p. 195–196° (from ethyl acetate hexane). When the reaction was done in the presence of 2.5 equivalent of 1,1-diphenylethylene the lactone **8b** was isolated in 57% yield. IR(CHCl)$_3$: 3410, 1780, 1670 cm$^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) δ: 7.2–7.9 (m, 15, aromatic); 4.85 (q, H-2, J 8 and 12 cps); 3.76 (q, H-3β, J 8 and 12.5 cps); 2.84 (t, H-3α, J 12 and 12.5 cps); NMR ($CDCl_3$) δ: 7.2–7.9 (m, 15, aromatic): 7.08 (d, NH, J 6 cps); 4.82 (m, H-2, J 6, 8 and 12 cps); 3.64 (q, H-3β, J 8 and 12.5 cps); 2.80 (t, H-3α, J 12 and 12.5 cps); (Found: C, 77.26; H, 5.56; N, 3.97. $C_{23}H_{19}NO_3$ requires: C, 77.29; H, 5.36; N, 3.92%).

The same lactone was obtained by refluxing a methylene chloride solution (50 ml) of 2 benzamido - 4,4 - diphenyl - 3 - butenoic acid (0.5 g) and β-naphtalenesulfonic acid (0.2 g) for 24 h. The solution was evaporated to dryness and the residue was chromatographed over methanol deactivated alumina (25 g alumina + 1.5 ml MeOH). The lactone was eluted with chloroform; yield 34%.

### 2 - *Benzyloxycarbonylamino* - 4,4 - *diphenylbutyrolactone* **8g**

α - Hydroxy - *N* - benzyloxycarbonylglycine (2.25 g, 0.01 mol) and 1,1 - diphenylethylene (2g, 0.011 mol) were dissolved in cold solution of dioxane (15 ml) containing conc. sulfuric acid (1.5 ml). The reaction mixture was stirred for 48 h, poured into ice with $NaHCO_3$, extracted with ethyl acetate and concentrated. The residue was triturated with ether yielding white solid of lactone **8g** (1.558 g, 40%), m.p. 125–126° (from ethylacetate-hexane). The mother liquid from the trituration was concentrated to a small volume and chromatographed on florisil column (40 g) using benzene as eluant. In the first three fractions of 75 ml unreacted 1,1-diphenylethylene was recovered. In the next fractions lactone **8g** was collected (1.086 g, 28%) bringing the total yield of reaction to 68%, m.p. 125.6°. IR($CHCl_3$): 3410, 1780, 1720 cm$^{-1}$. NMR ($CDCl_3$, TFA and $D_2O$) δ: 7.18 s, 5, aromatic); 7.12 (s, 10, aromatic); 5.10 (s, 2, $CH_2Ph$); 4.43 (q, H-2, J 8 and 12 cps); 3.50 (q, H-3β, J 8, 12 and 12.5 cps); 2.72 (t, H-3α, J 12 and 12.5 cps); NMR ($CDCl_3$) δ: 7.2–7.6 (m, 15, aromatic); 5.56 (d, NH, J 6 cps); 5.12 (s, 2, $CH_2Ph$); 4.41 (m, H-2, J 6, 8 and 12 cps); 3.53 (q, H-3β, J 8 and 12.5 cps); 2.68 (t, H-3α, J 12 and 12.5 cps). (Found: C, 74.16; H, 5.36; N, 3.60. $C_{24}H_{21}NO_4$ requires: C, 74.40; H, 5.46; N, 3.62%).

### 6 - *Acetoxy* - 4 - *carboxymethyl* - 2 - *phenyl* - 5,6 - *dihydro* - 4H - 1,3 - *oxazine* **7c**

Methyl - α - methoxyhippurate **4** (2.24 g, 0.01 mol) was dissolved in a solution of dry benzene (30 ml) containing distilled boron trifluoride etherate (2.4 ml) and vinyl acetate (5 ml) was added. The reaction mixture was stirred for 48 h. The formed oxazines were precipitated as black boron trifluoride salts. Benzene was decanted, the salts were washed with benzene (20 ml), then decomposed by sodium bicarbonate and ice, extracted with ethyl acetate (200 ml), filtered from some tar materials formed by polymerisation of vinylacetate, washed with water, dried over $Na_2SO_4$ and evaporated. The NMR spectrum of the crude product indicated the presence of two isomeric oxazines in an approximative ration 1:2, according to the intensities of $CH_3CO$ absorption peaks at 2.01 and 2.07 ppm. The crude mixture was dissolved in a small volume of benzene and put on a florisil column (60 g). The elution was started with methylene-chloride-benzene 1:1 and fractions were collected in 50 ml portions. TLC on neutral alumina plates using methylene chloride as eluant permitted to follow the composition of fractions. The first two fractions contained impurities; the fractions 3–7 contained the less polar pure *trans* isomer (302 mg) which was an oil. IR ($CHCl_3$): 1735, 1655 cm$^{-1}$. NMR ($CCl_4$) δ: 7.8–8.1 (m, 2, aromatic); 7.15–7.45 (m, 3, aromatic): 6.53 (t, H-6, J 2 and 2.5 cps); 4.35 (t, H-4, J 8.5 and 9 cps); 3.76 (s, 3, $OCH_3$); 2.16 (m, 2, $CH_2$); 2.07 (s, 3, $CH_3CO$). (Found: C, 60.78; H, 5.57; N, 4.75. $C_{14}H_{15}NO_5$ requires: C, 60.64; H, 5.45; N, 5.05%).

The fractions 8–11 contained a mixture of two isomers (285 mg). The more polar pure *cis* isomer was eluted with methylene chloride in the fractions 12–16 (117 mg) m.p. 64° (from hexane). The overall yield was 30%. IR ($CHCl_3$): 1735 1655 cm$^{-1}$. NMR ($CCl_4$) δ: 7.8–8.1 (m, 2, aromatic); 7.2–7.4 (m, 3, aromatic); 6.46 (t, H-6, J 4.5 cps); 4.35 (t, H-4, J 6 and 7 cps); 3.70 (s, 3, $OCH_3$); 2.32 (m, 2, $CH_2$); 2.01 (s, 3, $CH_3CO$). (Found: C, 60.45; H, 5.30; N, 5.43. $C_{14}H_{15}NO_5$ requires: C, 60.64; H, 5.54; N, 5.05%). Both oxazines tended to decompose with a few days of storage.

Fast purification of crude oxazines through florisil column using methylene chloride-methanol (9:1) solution as eluant gave a mixture of both oxazines as an oil (1.95 g, 70%). For further use the isolation of free oxazines was not required.

### N - *Benzoyl* - β - *dimethoxyacetal* - DL - *aspartic semialdehyde methylester* **11** (*Methyl* 2 - *benzamido* - 4,4 - *dimethoxybutyrate*)

Methyl α-methoxyhippurate **4** (11.2 g 0.05 mol) was dissolved in a solution of dry benzene (140 ml) containing distilled boron trifluoride etherate (15 ml) and vinylacetate (25 ml). The reaction mixture was stirred for 48 h, benzene was decanted, the crude boron fluoride salts were washed with benzene (50 ml), then dissolved in dry methanol (200 ml) and left for 48 h. Methanol solution was filtered from some tar materials, concentrated to third of its volume, diluted with ethyl acetate (250 ml), washed first with 10% $NaHCO_3$, when with water, dried over $Na_2SO_4$ and evaporated. The residue was filtered through the florisil column (240 g) using chloroform as eluant. Pure *N* - benzoyl - β - dimethoxyacetal aspartic semialdehyde methylester **11** was obtained as an oil (7.15 g 51%). It was found to be stable on prolonged storage. IR ($CHCl_3$): 3410, 1740, 1655 cm$^{-1}$. NMR ($CDCl_3$) δ: 7.1–7.9 (m, 6, aromatic and NH); 4.85 (q, 1, CHO, J 5.5 cps); 4.52 (t, 1, CHN, J 5.5 cps); 3.76 (s, 3, $CO_2CH_3$); 3.38 (s, 3, $OCH_3$); 3.36 (s, 3, $OCH_3$); 2.25 (t, 2, $CH_2$, J 5.5 cps); (Found: C, 59.58; H, 6.79; N, 4.94. $C_{14}H_{19}NO_5$ requires: C, 59.77; H, 6.81; N, 4.98%).

*DNP*. The DNP derivative was prepared from water–methanol-sulfuric acid dilute solution of reagent, m.p. 161°. (Found: C, 52.13; H, 4.14; N, 16.76. $C_{18}H_{17}N_5O_7$ requires: C, 52.05; H, 4.13; N, 16.80%).

*Oxime*. The oxime was prepared by allowing the acetal **11** (3.44 g) to stand overnight in methanol–water 1:1 solution (60 ml) of hydroxylamine hydrochloride at pH 1, followed by the addition of sodium acetate to pH 6. After 48 h ethyl acetate (100 ml) and water (20 ml) were added and the layers separated. The oxime was isolated from the organic layer (1.87 g 61%) m.p. 117–118°. (Found: C, 57.28; H, 5.86; N, 11.29. $C_{12}H_{14}N_2O_4$ requires: C, 57.59; H, 5.64; N, 11.20%).

### N - *Benzoyl* - DL - *aspartic* - β - *semialdehyde methyl ester*

Acetal **11** (1.2 g) was dissolved in a mixture of acetone (5 ml), water (7 ml) and 10% HCl (0.5 ml), and left overnight at room temp. The solution was lyophilized and extracted with benzene. After the removal of solvent the aldehyde was obtained as an oil (693 mg, 69%). For analysis it was filtered through a silica column using chloroform as eluant which was previously purified from alcohol by filtration through basic alumina (584 mg, 58%). IR ($CHCl_3$): 1730, 1660 cm$^{-1}$. NMR ($CDCl_3$) δ: 9.75 (s, 1, CHO); 7.3–8.1 (m, 6, aromatic and NH); 4.9–5.3 (m, 1, CHN); 3.74 (s, 3, $OCH_3$); 3.16 (d, 2, $CH_2$. J 5.5 cps); (TFA) δ: 7.5–8.2 (m, 5, aromatic), 5.1 (m, 1, CHN); 4.03 (s, 3, $OCH_3$); 3.02 (q, 2, CH, J 2 and 5.5 cps). (Found: C, 60.65, H, 5.83; N, 5.45. $M^+$ 235; $C_{12}H_{13}NO_4$ requires: C, 61.27; H, 5.57; N, 5.96% MW 235.23). DNP had m.p. 161° and showed no depression in mixed melting point with the DNP prepared from acetal **11**.

### N - *Benzoyl* - DL - *aspartic acid* β - *semialdehyde* **12** *and* **14**

Acetal **11** (610 mg) was dissolved in methanol (12 ml) containing potassium hydroxide (400 mg). The solution was left to stand at room temp. for 48 h. Methanol was removed and residue acidified with 10% HCl. Upon standing the product began to crystallize. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated. The residue was triturated with ether (307 mg 64%), m.p. 120–130° (from water). IR ($CHCl_3$): 1780 (CO of lactone **14**); 1720 (CO of acid form **12**); 1655 (CO of amide ) $Cm^{-1}$. (KBr) 1760, 1640 $cm^{-1}$. NMR (TFA) $\delta$: 8.5–8.0 (m, s, aromatic); 5.2 (m, 1, CH); 3.13 (q, 2, $CH_2$, J 2 and 5.5 cps). This pattern is very similar to that of the corresponding ester. ($D_2O$ with external TMS) $\delta$: 7.4–8.0 (m, 5, aromatic), 4.6–5.6 (m, CH superposition with $H_2O$); 2.1–2.9 (m, 2, $CH_2$). When to the $D_2O$ solution of acid in the NMR tube few crystals of $K_2CO_3$ were added, the absorption peak of $CH_2$ hydrogens disappeared, due to decomposition of the product.[18] *DNP*, m.p. 155–158°, (Found: C, 50.87; H, 4.12; N, 17.34. $C_{17}H_{15}N_5O_7$ requires: C, 50.41; H, 3.77; N, 17.45%).

*Oxime* **15**. Under standard conditions a product is obtained containing an oxime as well as hydroxamic acid function (positive test with $FeCl_3$). M.P. 182–183°; (Found: C, 52.71; H, 5.20; N, 16.46. $C_{11}H_{13}N_3O_4$ requires: C, 52.58; H, 5.22; N, 16.73%).

### 2-*Benzamido*-4-*methoxybutyrolactone* 13

Acetal **11** (530 mg) was dissolved in methanol (15 ml) containing potassium hydroxide (200 mg). After 48 h the solvent was evaporated, water was added and the mixture acidified with cold dilute phosphoric acid, extracted with ethyl acetate, washed with water and with $NaHCO_3$ solution, dried and evaporated.

The residue contained a mixture of *trans* and *cis* isomeric lactones **13** (304 mg 69%), in an approximative ratio 1:2. Upon crystallization from ethyl acetate the more polar pure *cis* isomer was obtained: m.p. 183°. IR (KBr) 3300, 1760, 1655 $cm^{-1}$; ($CHCl_3$): 1780, 1665 $cm^{-1}$. NMR (acetone $d_6$) $\delta$: 7.4–8.1 (m, 5, aromatic) 5.45 (q, H-4, J 4.5 and 6 cps); 4.95 (q, H-2, J 8 and 9 cps); 3.62 (s, 3, $OCH_3$); 2.1–3.1 (m, 2, $CH_2$). ($CD_3CN$) $\delta$: 7.4–8.0 (m, 5, aromatic); 5.45 (q, H-4, J 4.5 and 6 cps); 4.95 (m, H-2, J 6, 8 and 9 cps); 3.52 (s, 3, $OCH_3$); 2.2–3.1 (m, 2, $CH_2$). (Found: C, 61.28; H, 5.69; N, 6.04. $C_{12}H_{13}NO_4$ requires: C, 61.27; H, 5.57; N, 5.96%).

Hexane was added to the mother liquid and the precipitated *trans* isomer was several times recrystallized from ethyl acetate–hexane, m.p. 147°. IR (KBr): 3280, 1785, 1635 $cm^{-1}$. ($CHCl_3$): 3420, 1780, 1665 $cm^{-1}$. NMR ($CD_3OD$ and $CH_3CO_2H$) $\delta$: 7.4–8.1 (m, 5, aromatic); 5.65 (q, H–4, J 2 and 5 cps); 4.82 (t, H-2, J 9 and 9.5 cps); 3.50 (s, 3, $OCH_3$); 2.3–2.7 (m, 2, $CH_2$); ($CD_3CN$) $\delta$: 7.8–8.0 (m, 6, aromatic and NH); 5.64 (q, H-4, J 2 and 5 cps); 4.68 (m, H-2, J 5, 9 and 9.5 cps); 3.50 (s, 3, $OCH_3$); 2.4–2.7 (m, 2, $CH_2$). (Found: C, 61.51; H, 5.69; N, 5.97. $C_{12}H_{13}NO_4$ requires: C, 61.27; H, 5.57; N, 5.96%).

### DL-2-*Aminobutyrolactone hydrochloride* (*homoserine lactone hydrochloride*)

Acetal **11** (1.3 g) was dissolved in the mixture of methanol (5 ml), 5N HCl (15 ml) and water (20 ml). Adam's catalyst (75 mg) was added and the mixture was hydrogenated in Parr Apparatus during 15 h. After filtration conc. hydrochloric acid (2 ml) was added; the content was hydrolized upon reflux during 12 h, lyophilized and triturated with a mixture ether-ethanol. The crude material (639 mg) was recrystallized from ethanol (319 mg, 50%) m.p. 196–197, lit. 198–199.5°.[12] No depression in the mixed melting point with the authentic sample of lactone hydrochloride prepared from DL-homoserine supplied by NBC (Nutritional Biochemical Corporation). IR (KBr): 1775 $cm^{-1}$. NMR ($CD_3OD$) $\delta$: 4.2–4.7 (m, 3, $CH_2O$ and CHN); 2.1–2.9 (m, 2, $CH_2$).

### DL-2,4-*Diaminobutyric acid dihydrochloride*

Oxime (prepared from diacetal **11**) (612 mg) was dissolved in methanol (30 ml) containing dry HCl(365 mg) and hydrogenated in Parr Apparatus using $PtO_2$ (60 mg) as catalyst. After filtration and concentration the residue was triturated with ethyl acetate and hydrolized in boiling 6N HCl (10 ml). After lyophilisation and trituration with ether 300 mg of crude acid was obtained. Upon paper chromatography, using a mixture of *n* - BuOH - 2 - butanone - 17N $NH_4OH$-$H_2O$ (5:3:1:1) as eluant it had a $R_f$ = 0.071. Lysine, under the same conditions had $R_f$ = 0.067. NMR ($D_2O$, external TMS) $\delta$: 4.40 (t, CH, J 6 cps); 3.2–3.6 (m, 2, $CH_2N$); 2.2–2.8 (m, 2, $CH_2$). The acid was characterized as its dibenzoyl derivative, m.p. 197–198° (decomp); lit. 200–201°.[19] IR (KBr): 3370, 1730 sh, 1710, 1655, 1600 $cm^{-1}$. NMR (TFA) $\delta$: 5.4 (m, 1, CH); 4.1 (m, 2, $CH_2N$); 2.6 (m, 2, $CH_2$). (Found: C, 65.80; H, 5.60; N, 8.57. $C_{18}H_{18}N_2O_4$ requires: C, 66.24; H, 5.56; N, 5.58%).

### $\alpha$-*Hydroxy*-N-*butoxycarbonylglycine* 21

A mixture of 5.85 g (0.05 mole) of *n*-butyl carbamate and 4.65 (0.05 mole) of glyoxylic acid monohydrate in dry ether (50 ml) was stirred at room temperature until a clear solution was obtained (48 h). The solvent was evaporated and the residue triturated with petroleum ether. The solid product was filtered (6.5 g 62%); m.p. 75–76°. IR ($CHCl_3$): 3420, 1730 and 1510 $cm^{-1}$; NMR ($CDCl_3$): $\delta$: 6.60 (1H NH broad), 5.5 (q, 1H, CH), 4.20 (t, 2H, $OCH_2$), 1.6–0.8 (m, 7H, $C_3H_7$). (Found: C, 44.13; H, 7.10; N, 7.46. $C_7H_{13}NO_5$ requires: C, 43.97; H, 6.85; N, 7.33%).

### N-*Butoxycarbonyl*-DL-*aspartic acid* 22

$\alpha$-Hydroxy-*N*-carbobutoxyglycine **21** (1.91, 0.01 mol) and dichloroethylene (10 ml) were added at 0°C to the cold mixture of conc. sulfuric acid (5 ml) and glacial acetic acid (5 ml). The reaction mixture was stirred for 48 h, poured into ice (50 g) and extracted with ethyl acetate (200 ml). The ethyl acetate solution was filtered from a small amount of side product, washed once with water, dried over $MgSO_4$ and concentrated. The NMR data indicated that 60% of product was present in the crude oily residue. Trituration with chloroform and crystallisation from ethyl acetate–hexane yielded pure **22** (1.085 g, 47%) m.p. 114°C. IR ($CHCl_3$), 1720 $cm^{-1}$; NMR (TFA) $\delta$: 5.05 (m, 1, CH); 4.38 (t, 2, $OCH_2$, J 7 cps); 3.35 (d, 2, $CH_2$, J 5 cps); 0.8–2.0 (m, 7, $C_3H_7$). Melting point and spectroscopic data were identical in all respects with an authentic sample of *N*-carbobutoxy-DL-aspartic acid prepared by Shothen–Baumen reaction of DL-aspartic acid with *n*-butyl chloroformate.

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