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INTRA VS INTERMOLECULAR AMIDOALKYLATION OF AROMATICS[1]

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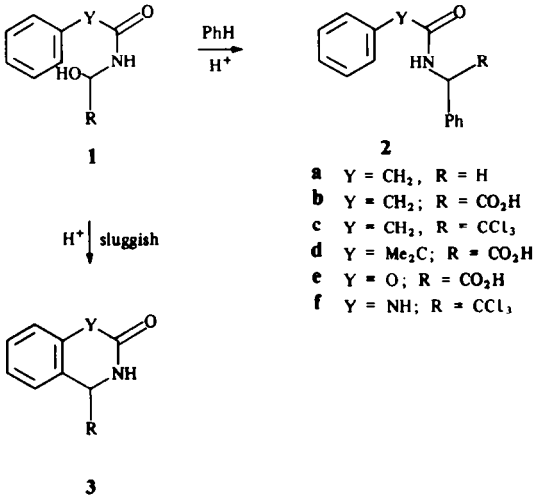
Abstract—Three types of intramolecular amidoalkylation reactions of aromatics, two endotrigonal and one exotrigonal (I, II, III), leading to indolone, N-acylisoquinolines, isoquinolone and benzazepinone derivatives were studied. In the presence of external aromatic nucleophiles competing intermolecular amidoalkylations were observed (**1** → **2**, **13** → **14**). The mechanism and the synthetic limitations of the three types of cyclization is discussed.

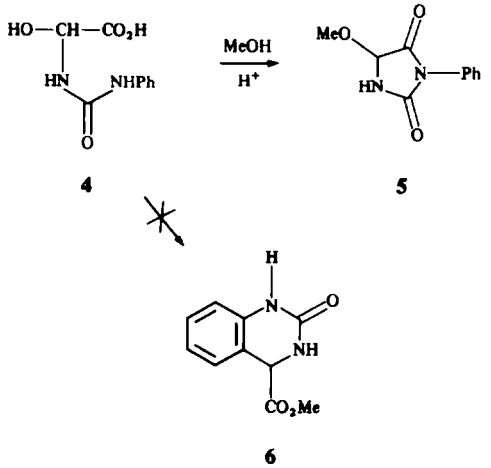
INTRODUCTION

Recently we have described a new synthesis of α-aminoacids based on the amidoalkylation of aromatics, olefins and active methylene compounds with the adducts of glyoxylic acid-primary amides.[2] The reaction with the aromatics is an electrophile substitution of the Friedel–Crafts type and is strongly catalyzed by acids.[2] During this investigation we were puzzled by the observation that the adduct of phenylacetamide and glyoxylic acid (**1b**) reacted smoothly in an intermolecular fashion with benzene in methanesulfonic acid to give in 92% yield the N-phenylacetylphenylglycine (**2b**). We did not observe formation of any isoquinolone (**3b**) derivative which could have resulted from an intramolecular amidoalkylation. Furthermore, omitting the benzene as the external aromatic nucleophile from the reaction mixture led to an intractable mixture of polar products.



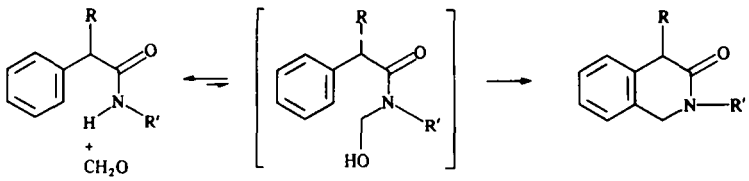
This observation was puzzling in view of the fact that intramolecular alkylations of the Picket–Spengler type are useful in the synthesis of isoquinoline derivatives.[3] Intramolecular amidoalkylation of an aromatic system was first reported by Krafts in 1948 when he reacted α-methylcinnamaldehyde with ethyl carbamate in the presence of an acid and obtained an aminoindene derivative.[4] This type of reaction was later used by Belleau,[5] Mondon and Hassenmeyer,[6] Boekelheide *et al.*,[7] and more recently by Maryanoff *et al.*[8] and others[9] in the synthesis of alkloids. Intramolecular amidoalkylation was recently received by Speckamp and Heimstra.[10]

The preferred intermolecular reaction in our case was found to be rather general, formaldehyde and chloral adducts of phenylacetamide **1a** and c also afforded N-benzylphenylacetamide (**2a**) and N-(β,β,β-trichloro-α-phenylethyl)phenylacetamide (**2c**) in 73 and 82% yield, respectively. The adduct of α,α-dimethylphenylacetamide and glyoxylic acid (**1d**) behaved similarly to give the intermolecular product (**2d**) when reacted with benzene in concentrated sulfuric acid at room temperature. The gem-dimethyls did, however, improve the yield of the isoquinolone formation when the reaction was carried out in the absence of benzene (38%). Substituting the methylene group of the phenylacetamide moiety for heteroatoms like O and N did not improve the yield of the intramolecular reactions. Thus the adduct of phenylcarbamate and glyoxylic acid (**1e**) afforded N-phenoxycarbonyl-*d,l*-phenylglycine (**2e**) in 61% yield. The same starting material (**1e**) reacted sluggishly in methanesulfonic acid, in the absence of benzene, to give an intractable mixture of polar products. The adduct of phenylurea and glyoxylic acid **4** afforded, in methanolic HCl, 5-methoxy-2-phenylhydantoin (**5**) and no **6**. The adduct of phenylurea and chloral (**1f**),



which cannot cyclize to a hydantoin, reacted with benzene in concentrated sulfuric acid to give **2f** in 87% yield. Activating the aromatic ring of the phenylacetamide adduct by introducing a methoxy group into the 3-position did not improve the yield of the intramolecular reaction. N-Hydroxymethyl-3-methyoxy acetamide afforded a polymeric mixture when allowed to react in methanesulfuric acid or trifluoroacetic acid at room temperature.

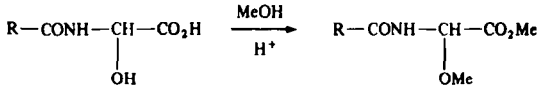
We have tried also to react N-methylamides with formaldehyde and glyoxylic acid. Substitution on nitrogen should affect the conformation of the amide bond and shift the equilibrium toward the *s-cis* conformer and thus facilitate intramolecular cyclization. The main problem with secondary amides is that it is not easy to prepare their carbinolamides. The reaction is probably slow and the equilibrium of their reaction with aldehydes favours starting materials (**7** → **8**). Generally a one-pot reaction can be carried out without the first isolation of the carbinolamide (**7** → **9**).



7 **8** **9**

N-Methyl-*p*-tolylacetamide and N-methyl-α-naphthylacetamide gave mixtures of polar products when treated with paraformaldehyde in methanesulfonic acid solution at room temperature. Only N-methyldiphenylacetamide (**7**, R = Ph, R′ = Me) reacted smoothly with paraformaldehyde in MSA to give 2-methyl-4-phenylisoquinoline-3-one (**9**, R = Ph, R′ = Me) in 81% yield.

The adducts of phenylacetamide, α,α-dimethylphenylacetamide, phenylcarbamate, diphenylacetamide, 1-naphthylacetamide and *p*-tolylacetamide with glyoxylic acid were further converted to the less polar methyl α-methoxy-N-acylglycinates **10** by treatment with MeOH–HCl.



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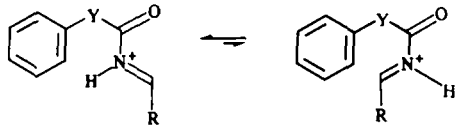
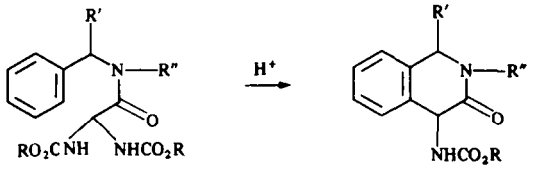
The methoxy esters **10** were also found to react smoothly in the intermolecular alkylation of toluene in methanesulfonic acid at room temperature to give the *p*-tolylglycine derivatives of type **2** in 65–85% yield. In all these cases the reactions, carried out in the absence of toluene as an external nucleophile, led to mixtures of polar products.

The preferred intermolecular amidoalkylation of aromatics in the "phenylacetamide" series and the sluggishness of the intramolecular cyclization might be attributed to three effects that operate in the same direction. The deactivation of the phenyl ring in the intermediate acylimmonium ion formed in the strong acid medium (**11**, **12**), the preferred *s-trans* conformation of the amide bond in the reactive intermediate† (**11**) and a stereoelectronic effect which for a smooth intramolecular reaction requires a proper alignment (overlap) between the aromatic π system (HOMO) and the immonium double bond (LUMO) in **12**.



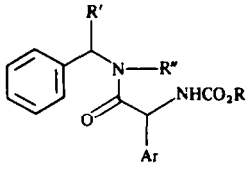
11 **12**

In order to obtain further information concerning the role of the various effects on the inter vs intramolecular amidoalkylations we have synthesized another series of compounds, the benzylamides of biscarbalkoxycarbonylaminoacetic acid **13**.



13 **15**

a R = Me; R′ = R″ = H
b R = R′ = Me, R″ = H
c R = R″ = Me; R′ = H
d R = Bu; R′ = Me; R″ = H
e R = Me; R′ = H, R″ = $PhCH_2$
f R = Bu, R′ = CO_2Me; R″ = H



14

Ar = Ph or C_6H_4Me

Reacting the benzylamide of bismethoxycarbonylaminoacetic acid (**13a**) with toluene in MSA at room temperature afforded the 4-N-methoxycarbonyl-*p*-methylphenylglycine (**14a**) in 75% yield. If toluene, the external aromatic nucleophile, was omitted from the reaction mixture a smooth intramolecular cyclization occurred affording the 4-methoxycarbonylamino-3-isoquinolone (**15a**) in 85% yield. Even in the presence of benzene, as the external

† If one considers the acylimine as a heterodiene then **11** is the N-protonated *s-cis* conformer. In the case of methyleneformamide the protonated *s-cis* conformer was calculated to be 2.2 kcal mol^{-1} more stable than the *s-trans* conformer.[11]

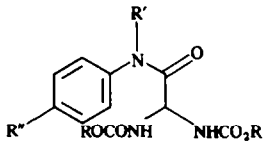
aromatic nucleophile, the main product in the reaction was the cyclic isoquinolone derivative (**15a**) (9:1). Smooth cyclizations were observed with a number of benzylamide derivatives (**13a–f**) leading to 1-alkoxycarbonylamino-3-isoquinolones (**15a–f**). The dibenzylamide (**13e**) afforded the cyclic N-benzyl-3-isoquinolone derivative (**15e**) in 90% yield. The reactive intermediate, in this case, was trapped only on adding the more reactive anisole as the external aromatic nucleophile. The ratio on the inter (**14**) to the intramolecular (**15**) reaction products, in this case, was 4:1 favouring the intermolecular alkylation.

The improved cyclizations in the tertiary amide cases **15c** and **e** are attributed to the shift in the equilibrium between the two amidic conformers (rotamers) towards the *s-cis* conformer. In the case of **15b, d** and **f**, two isomers were observed in the crude mixture (1,4-*cis* and 1,4-*trans*). The major isomer was obtained pure on trituration or chromatography.

The cyclization of bisalkoxycarbonyl acetamide **13** was further extended to acetanilides **16** and β-phenylethylamide derivatives **18** leading to the synthesis of both 5- (indolones) and 7-membered (benzazepinones) lactams **17** and **19**.

The *p*-methylanilide (**16d**) afforded 5-methyl-3-methoxycarbonylamino-2-indolone (**17d**) in better than 90% yield. The *p*-substituent probably decreases the rate of the competing intermolecular reaction. 3-Amino-2-indolone and 3-benzamido-2-indolones were described in the literature. They were prepared from *o*-nitrophenylglycine by reduction, cyclization and benzoylation.[9] The β-phenylethylamide of bismethoxycarbonylaminoacetic acid (**18a**) afforded 1-methoxycarbonylamino-3-benzazepine-2-one (**19a**) in 67% yield when cyclized in MSA. In the presence of toluene both the anilide **16a** and the phenylethylamide **18a** of the bismethoxycarbonylaminoacetic acid gave in MSA the anilide and the phenylethylamide of N-methoxycarbonyl-*d,l-p*-tolylglycine in 59 and 76% yield, respectively (intermolecular reaction product). In addition to the three azepinones mentioned above we also obtained, by the above general procedure, 7,8-dimethoxy-3-benzazepine-2-one (**20**) and the 3,4-dimethylbenzazepinone derivative (**21**) in 65 and 70% yield, respectively.

Compound **21** was obtained as a mixture of two isomers. Compound **19d** was prepared from N-(α - butoxycarbonylamino - α - methoxy)acetyltyramine



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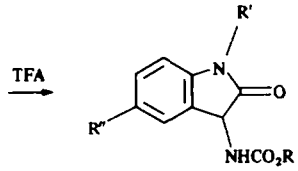
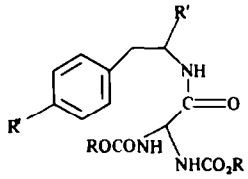


17

a R = Me, R′ = R″ = H
b R = R′ = Me; R″ = H
c R = R″ = Me; R′ = H
d R = Bu; R′ = H; R″ = Me
e R = Me; R′ = $PhCH_2$; R″ = H
f R = Me; R′ = H; R″ = Cl



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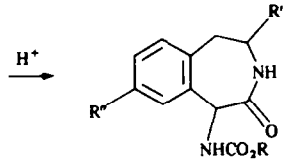
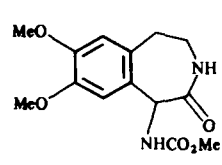


19

a R = Me; R′ = R″ = H
b R = Me; R′ = CO_2Me; R″ = H
c R = Me; R′ = H; R″ = OH
d R = Bu; R′ = H; R″ = OH

Reacting the anilide of bismethoxycarbonylaminoacetic acid in TFA afforded two products. The less polar 3-methoxycarbonylamino-2-indolene (**17a**) was obtained pure by chromatographic separation on a florisil column. The more polar component is probably the product of intermolecular reaction (dimer). The ratio of the two products is concentration dependent. In a 0.1 M solution in TFA the ratio of the indolone to the more polar product according to the NMR of the crude mixture was about 4.1.

rather than the bisadduct **18d**. The methoxy group is a better leaving group than the carbamate group and



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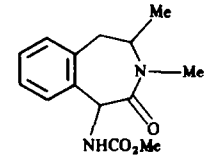


21

the cyclization proceeded in dichloroacetic acid at room temperature.

The amides of bisalkoxycarbonylaminoacetic acid (**24**) were prepared from glyoxylic acid, methyl or butyl carbamate and the corresponding amine.

ylacetamide were found to react smoothly with paraformaldehyde in H_2SO_4–AcOH (25%) to give the N-acylated tetrahydroisoquinoline (**27**) in 75–95% yield. Glyoxylic acid reacted, under the same conditions, only with the N-phenylethylcarbamates.

$$2ROCONH_2 + CHOCO_2H \xrightarrow{H^+} (ROCONH)_2CHCO_2H$$

22

$$(ROCONH)_2CHCONH(CH_2)_nAr \leftarrow Ar(CH_2)_nNH_2 + (ROCONH)_2CHCOX$$

24 **23**

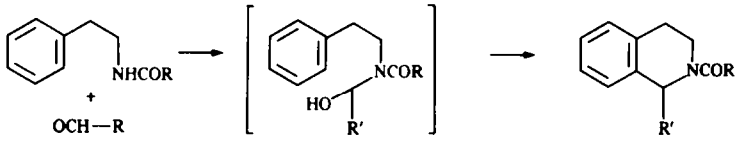
a, R = Me
b, R = n-Bu

Condensing 2 equiv of carbamate with 1 equiv of glyoxylic acid monohydrate in refluxing chloroform and in the presence of β-naphthalenesulfonic acid as the acid catalyst afforded the bisalkoxycarbonylaminoacetic acid (**22**) in over 90% yield. The crystalline acids (**22a, b**) were converted to crystalline acid chlorides (**23**, X = Cl), by treatment with PCl_5 in EtO_2 or CH_2Cl_2, and further coupled with the various amines to give the bisalkoxycarbonylaminoacetamides **24**. The acid chloride method was found to give cleaner reactions than the use of the DCC or mixed anhydride methods to form the amide bond. In the case of the more basic and less hindered amines direct amidation of the methyl ester **23** (X = OMe) with the corresponding amine in refluxing methanol for a few hours gave good yields of pure products.

Simple N-phenylethylamides were also found to react with formaldehyde or glyoxylic acid in a one-pot reaction to give N-acetyltetrahydroisoquinoline.

N-Benzylphenylacetamide did not react with either formaldehyde or glyoxylic acid in H_2SO_4–AcOH (25%) to give either the isoquinolone **29** or the isoindoline **30** derivatives.

We encountered in this work three distinct types of intramolecular amidoalkylations of aromatics. In terms of Baldwin's rules for intramolecular cyclization[12] one can, by looking at the reactive intermediates, **32**, **35** and **38**, classify the three types of cyclizations into endotrigonal (types I and II) and exotrigonal (type III). Types I and III are lactamization reactions leading to the formation of new lactam rings while type II cyclization is an extension of the Pictet–Spengler reaction to less reactive aromatic systems. The amide carbonyl in this last case is not incorporated into the newly formed ring and therefore this reaction is less prone to amide conformation interference. The main synthetic problem with type II cyclization is the preparation of the starting materials. As mentioned above the reaction of secondary amides

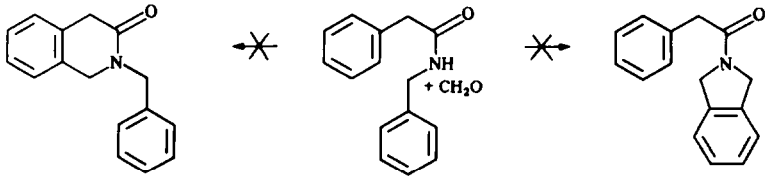


25 **26** **27**

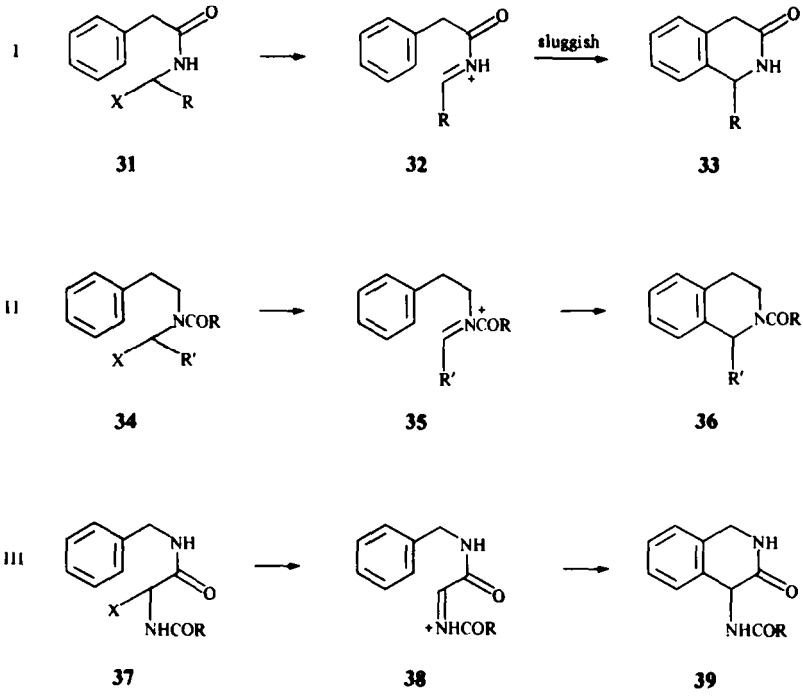
a R = Ph; R' = H
b R = OMe; R' = H
c R = OEt; R' = H
d R = OMe; R' = CO_2H
e R = OEt; R' = CO_2Me

This is a modified Pictet–Spengler cyclization[3] to less reactive aromatics. The N-phenylethyl derivative of benzamide (**25**, R = Ph), methylcarbamate (**25**, R = OMe), ethylcarbamate (**25**, R = OEt) and phenyl-

with aldehydes to form the carbinolamide type intermediates (**34**) is not a favoured reaction. To overcome this difficulty one can try a one-pot reaction of the amide with the carbonyl component. In our cases it



29 **28** **30**



was found that the relative rate of reaction is strongly dependent both on the amide used and the aldehyde component. Carbamates were found to react faster than ordinary amides and formaldehyde reacted faster than glyoxylic acid (steric effect?). Six-membered rings are formed in these cases faster than five-membered rings.

The preferred *s-trans* conformation of the amide bonds in both type I and type III lactamizations explains the observed intermolecular reactions when an external nucleophile is present in the reaction. The main difference between the two is the preferred cyclization of intermediate **38** (type III) compared with intermediate **32** (type I). The exotrigonal cyclization is preferred over the endotrigonal in type I. This means that the alignment of the aromatic π system (HOMO) with the immonium double bond (LUMO) in **38** is much better than in **32**.

Type II cyclizations were used successfully by Mondon and Hassenmeyer,[6] Boekelheide *et al.*,[7] Winterfeldt,[13] Zaugg and Arendsen[14] and more recently by Danishefsky and Berman[15] and others to synthesise isoquinolines and other polyheterocyclic derivatives. Type I cyclizations were used in relatively fewer cases by Belleau[5] in the synthesis of the Erythrina alkloides, by Wittekind and Lazaros[16] in the synthesis of benzazepinones and by Deak *et al.*[17] in the synthesis of isoquinolone. The general nature of this type of cyclization is somewhat controversial.[16,18-20] According to Watanabe *et al*[19] the yields of the intramolecular cyclization are strongly dependent on the reaction conditions. At higher temperature (140–160°) in polyposphoric acid yields were much higher (e.g. 56.7%) than in the reactions carried out at room temperature (unseparable mixture of products).

Type III cyclizations which were discussed above seem to be a promising way of synthesising, indolones, isoquinolinones, benzazepinones and related ring systems and was rarely used in cyclization reactions.

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 and chemical shifts are reported in ppm downfield from TMS. Mass spectra were obtained on a Varian Mat-711 double focusing instrument.

Amides. Most of the amides and carbamates used are commercially available. The secondary amides were prepared by the Schotten–Baumann procedure from the corresponding acid chlorides and the corresponding primary amine.

Adducts of aldehydes with primary amides or carbamates. N-Hydroxymethylphenylacetamide (**1a**) was prepared from phenylacetamide and aqueous formaldehyde[19] and α-hydroxy-N-phenylacetylglycine (**1b**) was prepared from glyoxylic acid and phenylacetamide.[2b]

N-(α-Hydroxy-β,β,β-trichloroethyl)phenylacetamide (**1c**). A mixture of phenylacetamide (1.35 g, 0.01 mol) and chloral hydrate (3.3 g, 0.02 mol) in benzene (50 ml) was refluxed overnight and the water formed was removed by azeotropic distillation. The crystalline product which separated on cooling the soln was filtered and dried; yield 2.0 g (74%); m.p. 141–142°. IR ($CHCl_3$) 3420 (OH), 3380–3100 (NH), and 1700 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) δ 8.80 (d, 1H, J = 9, OH), 8.0–7.7 (1H, NH broad), 7.30 (s, 5H, Ph), 5.86–5.70 (t, 1H, CH), 3.63 (s, 2H, CH_2). (Found: C, 42.53; H, 3.53; N, 5.02; Cl, 37.38. $C_{10}H_{10}NO_2Cl_3$ requires: C, 42.51; H, 3.56; N, 4.96; Cl, 37.64%.)

α-Hydroxy-N-α′,α′-dimethylphenylacetylglycine (**1d**). A mixture of α,α-dimethylphenylacetamide (8.15 g, 0.05 mol) and glyoxylic acid monohydrate (5.5 g, 0.06 mol) in dry acetone (75 ml) was refluxed for 8 h. The solvent was removed *in vacuo* and the oily residue was triturated with dry ether overnight. The white solid was filtered and dried; yield 8.0 g (67.5%); m.p. 107–108°. IR (KBr) 3500–2700 (OH, NH, CO_2H), 1700 and 1690 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6)

δ 8.00–7.60 (1H, NH broad), 7.39 (s, 5H, Ph), 5.44–5.26 (t, 1H, CH), 1.46 (s, 6H, CMe_2). (Found: C, 60.54; H, 6.48; N, 5.83. $C_{12}H_{15}NO_4$ requires: C, 60.75; H, 6.37; N, 5.90%.)

α-Hydroxy-N-phenoxycarbonylglycine (**1e**). A mixture of phenyl carbamate (2.74 g, 0.02 mol) and glyoxylic acid monohydrate (2.0 g, 0.22 mol) were stirred in dry ether (30 ml) at room temp for 12 h. The solid slowly dissolved and after 2 h the product starts to precipitate from the mixture. It was filtered and washed with dry ether to give 1.65 g (61%) of a crystalline material; m.p. 119–121°; IR (KBr) 3500 (OH), 3420 (NH, CO_2H) and 1720 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) δ 5.27–5.46 (m, 1H, CH—NH), 7.05–7.68 (m, 5H, Ph), 8.30–8.66 (b, NH). (Found: C, 51.17; H, 4.18; N, 6.50. $C_9H_9NO_5$ requires: C, 51.19; H, 4.30; N, 6.63%.)

2-Hydroxy-5-phenylhydantoic acid (**1f**). A mixture of phenyurea (1.37 g, 0.01 mol) glyoxylic acid monohydrate (1 g, 0.11 mol) in acetone (10 ml) was stirred for 24 h at room temp. The crystalline ppt was filtered off and washed with dry acetone to give 1.60 g (76%) of a solid, m.p. 159–161°; IR (KBr) 3430–3320 (OH, NH, CO_2H), 1740 and 1660 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) δ 5.27–5.66 (g, 1H, NHCH), 6.54–7.66 (m, 5H, Ph), 8.78 (d, 1H, J = 5.0, NH—CH—OH). MS 192 ($M^+ - H_2O$).

1-Phenyl-3-(α-hydroxy-β,β,β-trichloroethyl)urea. A mixture of phenylurea (1.36 g, 0.01 mol) and chloralhydrate (3.3 g, 0.02 mol) in benzene (35 ml) was refluxed for 5 h while the water formed was removed by azeothropic distillation. The solid ppt on cooling was filtered off and triturated with ether–petroleum ether. The filtered solid melted at 143–145°; yield 2.07 g (73%).

N-Hydroxymethyl-3-methoxyphenylacetamide. A mixture of 3-methoxyphenylacetamide (2.00 g), formaldehyde soln (5 ml, 40%) and $NaHCO_3$ aq (3 ml, 5%) was heated on a steam bath until all the solid dissolved. The soln was left at room temp for 5 h and extracted with EtOAc (3 × 25 ml). The EtOAc soln was dried and evaporated. The residue was triturated with dry ether to give 1.58 g (65%); m.p. 91–93°. ^{1}H-NMR ($CDCl_3$) δ 3.50 (s, 2H, CH_2), 3.76 (s, 3H, OMe), 4.60 (d, 2H, J = 6, N—CH_2—O), 6.70–7.70 (m, 5H, Ph + NH).

3-Phenyl-5-methoxyhydantoin (**5**). A mixture of 5-phenyl-2-hydroxyhadantoic acid (4.0 g) and conc H_2SO_4 (2 ml) in abs MeOH (50 ml) was refluxed overnight (18 h). The soln was filtered, to remove some bisadduct formed, neutralized with solid $NaHCO_3$ and evaporated. The residue was extracted into EtOAc (100 ml) washed with H_2O dried over $MgSO_4$ and evaporated. The oily residue, 3.52 g, was chromatographed over deactivated alumina (10% MeOH) to give 1.60 g (41%) of pure product, m.p. 110–112°. The methoxyhydantoin was identical with an authentic sample.[20]

Methyl α-methoxy-N-acylglycinates

Methyl α-methoxy-N-phenylacetylglycinate (**10**, R = $PhCH_2$). To a cooled soln of α-hydroxy-N-phenylacetylglycine (3.0 g) in MeOH (30 ml) was added conc H_2SO_4 (1 ml) and the soln was left overnight at room temp. The acid was neutralized with solid $NaHCO_3$ and the mixture evaporated and divided between EtOAc and water. The EtOAc soln was washed with water, dried aover $MgSO_4$ and evaporated. Trituration of the oily residue with hexane for 24 h afforded a crystalline product, 1.95 g (57%); m.p. 70–71°. IR ($CHCl_3$) 3450 (NH), 1750, 1680 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.45 (s, 3H, OMe), 3.68 (s, 2H, Ph CH_2), 3.80 (s, 3H, CO_2Me), 5.58 (dl, 1H, J = 9, NHCH), 7.21 (s, 5H, Ph). (Found: C, 60.41; H, 6.46; N, 6.01%. Calc for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%.)

Methyl α-methoxy-N-p-tolylacetylglycinate (**10**, R = *p*-$MeC_6H_4CH_2$). A mixture of *p*-tolylacetamide (0.94 g, 0.0063 mol) and glyoxylic acid monohydrate (0.64 g, 0.007 mol) in acetone (30 ml) was refluxed for 24 h. The acetone was evaporated and the product triturated with dry ether to give 0.8 g (56.6%) of the α-hydroxy-N-*p*-tolylacetylglycine which was further converted to the α-methoxymethyl ester on treatment with abs MeOH (20 ml) and conc H_2SO_4 (0.5 ml) at room temp for 24 h. The MeOH was evaporated and the residue was dissolved in EtOAc and the soln washed with $NaHCO_3$ aq (5%) and H_2O, dried over $MgSO_4$ and evaporated. The product was triturated with ether to give 0.43 g (43%) of a crystalline material; m.p. 104–106°. IR ($CHCl_3$) 3420 (NH), 1755, 1690 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 2.53 (s, 3H, MeAr), 3.57 (s, 3H, OMe), 3.77 (s, 2H, Ar—CH_2—CO), 3.93 (s, 3H, CO_2Me), 5.60 (d, 1H, J = 9, NH—CH—), 6.40–6.60 (b, 1H, NH), 7.23 (s, 3H, Ar).

Methyl α-methoxy-N-1-naphthylacetylglycinate (**10**, R = $C_{10}H_9$). A mixture of 1-naphthylacetamide (8.0 g, 0.043 mol) and glyoxylic acid monohydrate (4.38 g, 0.047 mol) in acetone)50 ml) was refluxed for 24 h. The acetone was evaporated and the residue triturated with ether to give 6.45 g of product (57.6%) which was further converted to the α-methoxy ester on treatment with methanolic H_2SO_4 as described above. The product was triturated with ether to give 4.60 g (65%); m.p. 132–134°. IR ($CHCl_3$) 3410 (NH), 1760, 1690 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.33 (s, 3H, OMe), 3.70 (s, 3H, CO_2Me), 4.13 (s, 2H, —CH_2—), 5.53 (d, 1H, J = 8, NHCH—CO), 6.70–7.00 (b, 1H, NH), 7.40–8.07 (m, 7H, Ar). MS *m/z* 287.1151 (M^+, 12.40%), calc for $C_{16}H_{17}NO_4$ 287.1157. (Found: C, 66.94; H, 5.95; N, 4.77. Calc: C, 66.88; H, 5.96; N, 4.88%.)

Methyl N-diphenylacetyl-α-methoxyglycinate (**10**, R = Ph_2CH). This compound was prepared from diphenylacetamide (5 g, 0.023 mol) and glyoxylic acid monohydrate (2.43 g, 0.025 mol) in practically the same way as the *p*-tolylamide and naphthyl amide derivatives (**10**, R = Me-$C_6H_4CH_2$; **10**, R = $C_{10}H_7$). The methoxymethyl ester was purified by chromatography on a silica column. The product which was eluted with EtOAc–hexane (3:2) to give 2.2 g (61%) crystalline product; m.p. 97–99°. IR ($CHCl_3$) 3420 (NH), 1760, 1690 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.50 (s, 3H, OMe), 3.87 (s, 3H, CO_2Me), 5.07 (s, 1H, Ph_2CH), 5.67 (d, J = 9, 1H, NH—CH—CO), 6.70 (bd, J = 9, NH), 7.37 (s, 10H, Ar). MS *m/z* 313.1327 (M^+, 0.8%), calc for $C_{18}H_{19}NO_4$ *m/z* 313.1314 (M^+). (Found: C, 69.19; H, 6.15; N, 4.42. Calc: C, 68.99; H, 6.11; N, 4.47%.)

Amidoalkylation of aromatics

General procedure. To a stirred and cooled suspension (ice + water) of the α-hydroxy-N-acylglycine (1.0 g) in acid (10 ml) was added benzene or toluene (4–7 equiv). The suspension was stirred at room temp for 24–72 h, poured on crushed ice and extracted 3 times with an organic solvent. The organic soln was dried over $MgSO_4$, evaporated and the product purified by trituration and chromatography.

N-Benzylphenylacetamide (**2a**). A mixture of N-hydroxymethylphenylacetamide (2.72 g, 16.46 mmol), benzene (5 ml) in methanesulfonic acid (15 ml) was treated as described above (general procedure). Trituration with hexane of the crude material gave 3.38 g (91%) of product, m.p. 117–118°, identical with an authentic sample prepared from benzylamine and phenylacetyl chloride.

The same reaction was also carried out in TFA for 72 h and gave 87% of product.

N-Phenylacetyl-α-phenylglycine (**2b**). Reacting α-hydroxy-N-phenyacetylglycine (1.0 g) with benzene (2 ml) in conc H_2SO_4 acid (5 ml) for 24 h as described above (general procedure). The product obtained after the evaporation of the EtOAc was triturated with hexane for 24 h to give 1.2 g (92%) of product, m.p. 122–124°. IR ($CHCl_3$) 3400 (NH), 3100–2700 (CH_2H), 1720, 1660 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR δ 3.57 (s, Ph—CH_2CO), 5.53 (d, 1H, J = 7, CH—NH), 7.30 (s, 10H, 2Ph). (Found: C, 71.16; H, 5.41; N, 5.20. Calc for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20%.) NMR and TLC of the crude product did not show the presence of any additional product.

N-(β,β,β-Trichloro-α-phenyl)phenylacetamide (**2c**). A mixture of N-(α-hydroxy-β,β,β-trichloroethyl)phenylacetamide (1.0 g) and benzene (2 ml) in conc H_2SO_4 (5 ml) was treated for 48 h as described in the general procedure. The crude product obtained after removal of the EtOAc was chro-

matographed over alumina and eluted with CH_2Cl_2 to give 0.975 g (81.5%) product; m.p. 153–155° (from cyclohexane). IR ($CHCl_3$) 3400 (NH), 1700 cm^{-1} (CO). ^{1}H-NMR δ 3.71 (s, 2H, Ph—CH_2), 5.95 (d, 1H, J = 10, CH—NH), 7.31–7.41 (m, 10H, $PhCH_2$, PhCH). (Found: C, 55.97; H, 4.43; N, 3.91. Calc for $C_{16}H_{14}NOCl_3$: C, 56.08; H, 4.12; N, 3.91%.)

N-(α,α-*Dimethylphenylacetyl*)*phenylglycine* (**2d**). A mixture of 2-hydroxy-N-(α,α-dimethylphenylacetyl)glycine (1 g) and benzene (2 ml) in conc H_2SO_4 (5 ml) was stirred for 48 h as described above (general procedure). The crude product obtained after removal of EtOAc was triturated with dry ether for 24 h to give 1.0 g (80%) of product; m.p. 166–168°. IR (KBr) 3400 (NH), 1730, 1640 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 1.46 (s, 6H, Me_2C), 5.26–5.50 (d, 1H, J = 10, NHCH), 7.30 (s, 10H, 2Ph). MS *m/z* 297.01, calc for $C_{18}H_{19}NO_3$ 297.152.

4,4-*Dimethyl*-3-*isoquinolone*-1-*carboxylic acid* (**3d**). N-(α,α-Dimethylphenylacetyl)-α-hydroxyglycine (1 g) was stirred in conc H_2SO_4 for 48 h as described (general procedure). The residue obtained after the removal of the solvent was triturated with ether to give 0.49 g (53%) of product, m.p. 209–212°. IR (KBr) 3260 (b, NH + CO_2H), 1710, 1660 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) δ 1.36 (s, 3H, Me), 1.50 (s, 3H, Me), 5.06 (d, J = 4, 1H, NHCH), 7.26–7.50 (m, 4H, C_6H_4), 8.11 (d, 1H, J = 4, NHCH). (Found: C, 65.42; N, 6.18; N, 6.31. Calc for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.)

N-*Phenoxycarbonylphenylglycine* (**2e**). A mixture of α-hydroxy-N-phenoxycarbonylglycine (0.91 g, 4.31 mmol) and benzene (4 ml) in MSA was treated for 24 h as described above (general procedure). The product was obtained in 61%, m.p. 139–140° (ether–hexane). IR (KBr) 3300 (NH + CO_2H), 1700 (CO), 1515 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 5.45 (d, 1H, J = 7, CH), 7.10–7.50 (m, 10H, 2 Ar). (Found: C, 66.49; H, 4.82; N, 5.26. $C_{15}H_{13}NO_4$ requires: C, 66.41; H, 4.83; N, 5.16%.)

N-*Phenoxycarbonyl*-p-*tolylglycine*. A mixture of the hydroxyacid (1.0 g, 4.73 mmol) and toluene (3.0 ml) in MSA (10 ml) was treated for 24 h as described above (general procedure). The crude product was a mixture of *ortho–para* isomers. The *para* isomer was obtained in 50% yield, m.p. 125–126° (ether–hexane). IR (KBr) 3250 (NH + CO_2H), 1770 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3H, Me), 5.41 (d, 1H, J = 7, CH), 7.00–7.50 (m, 9H, Ar). (Found: C, 67.48; H, 5.19; N, 4.92. $C_{16}H_{15}NO_4$ requires: C, 67.36; H, 5.30; N, 4.91%.) MS *m/z* 285.1 (M^+).

2-*Methyl*-4-*phenyl*-1,2,3,4-*tetrahydroisoquinoline*-3-*one* (**9**, R = Ph). A mixture of N-methyldiphenylacetamide (2.0 g) and paraformaldehyde (0.3 g) in methanesulfonic acid (20 ml) was treated for 24 h as described above (general procedure). The crude product obtained after the evaporation of the $CHCl_3$ was chromatographed over silica and eluted with EtOAc–hexane (2:1) to give 1.75 g (81%) of product; m.p. 104–106° (EtOAc–hexane). IR ($CHCl_3$) 1655 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 3.03 (s, 3H, Me), 4.50–4.33 (2s, 2H, CH_2), 4.83 (s, 1H, CH), 7.07–7.30 (m, 9H, Ar). MS (HR) *m/z* 237.1153 (M^+), calc for $C_{16}H_{15}NO$ 237.1153 (M^+). (Found: C, 80.59; H, 6.31; N, 5.90. Requires: C, 80.98; H, 6.37; N, 5.90%.)

Methyl N-*diphenylacetyl*-p-*tolylglycinate*. A mixture of methyl *N*-diphenylacetyl-α-methoxyglycinate (0.5 g) and toluene (1.2 ml) in methanesulfonic acid (6 ml) was treated for 24 h as described in the general procedure. The crude product obtained after evaporation of $CHCl_3$ was a mixture of *ortho* and *para* tolyl derivatives (1:2). Trituration with dry ether and crystallization from EtOAc–hexane afforded 0.38 g (64%) of the pure *para* derivative; m.p. 158–160°. IR ($CHCl_3$) 3435 (NH), 1680, 1750 (CO), 1505 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, 3H, ArMe), 3.50 (s, 3H, CO_2Me), 4.97 (s, 1H, Ph_2CH), 5.53 (d, J = 3, 1H, HNCHCO), 6.43–6.70 (b, 1H, NH), 7.07 (s, 4H, MeC_6H_4—CH), 7.20 (s, 10H, 2PH). MS (HR) *m/z* 373.1717 (M^+, 18.2%), calc for $C_{24}H_{23}NO_3$ 373.1677. (Found: C, 77.09; H, 6.22; N, 3.79. Calc: C, 77.19; H, 6.21; N, 3.75%.)

Methyl N-1-*naphthyl*-p-*tolylglycinate*. A mixture of methyl N-1-naphthylacetyl-α-methoxyglycinate (0.4 g) and toluene (0.74 ml) in MSA was treated as described above. The $CHCl_3$ soln was evaporated and the crude product chromatographed over silica. EtOAc–hexane (2:1) eluted 0.30 g (62%) of pure product, m.p. 109–111°. IR ($CHCl_3$) 3430 (NH), 1745,. 1675 (CO), 1500 cm^{-1} (NH). ^{1}H-NMR δ 2.23 (s, 3H, ArMe), 3.50 (s, 3H, CO_2Me), 4.00 (s, 2H, CH_2), 5.43 (d, J = 6, 1H, NHCHCO), 6.00–6.40 (b, 1H, NH), 6.67–7.90 (m + s, 11H, ArH). (Found: C, 75.72; H, 6.15; N, 3.95. Calc for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03%.)

Methyl N-*p*-*tolylacetyl*-p-*tolylglycinate*. A mixture of methyl N-*p*-tolylacetyl-α-methoxyglycinate (0.29 g) and toluene (0.5 ml) in 6 ml MSA–CH_2Cl_2 (1:1) was treated for 24 h as described above (general procedure). Trituration with ether afforded 0.17 g (72%) of product, m.p. 126–128°. IR ($CHCl_3$) 3440 (NH), 1745, 1675 (CO), 1505 cm^{-1} (NH). ^{1}H-NMR δ 2.23 (s, 3H, ArMe), 3.43 (s, 2H, $ArCH_2CO$), 3.53 (s, 3H, CO_2Me), 5.30 (d, J = 6, 1H, NCCHCO), 6.07–6.30 (b, 1H, NH), 6.87, 6.90 (2s, 8H, ArH). MS (HR) *m/z* 311.1537 (17.46%, M^+), calc for $C_{19}H_{21}NO_3$ 311.1521 (M^+).

Amides of bisalkoxycarbonylaminoacetic acid

Bismethoxycarbonylaminoacetic acid (**22a**). A mixture of methylcarbamate (75 g, 1 mol), glyoxylic acid (46.0 g, 0.5 mol) and naphthalenesulfonic acid (1.0 g) in EtOH free $CHCl_3$ (500 ml) was refluxed for 6 h. The water formed in the reaction was removed by azeotropic distillation (Dean–Stark receiver). The solid ppt on cooling was filtered off to give a crystalline product; m.p. 149–150° (EtOAc–hexane), yield 96 g (93%). IR (KBr) 3360–3340 (OH + NH), 1740, 1710, and 1660 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) δ 3.59 (s, 6H, OMe), 5.38 (t, 1H, J = 4, CH), 7.71 (brd, 2H, J = 4, NH). (Found: C, 34.33; H, 4.97; N, 13.42. Calc for $C_6H_{10}N_2O_6$: C, 34.59; H, 4.89; N, 13.59%.)

Bisbutoxycarbonylaminoacetic acid (**22b**). A mixture of butylcarbamate (117 g, 1 mol), glyoxylic acid (46.0 g, 0.5 mol) and β-naphthalenesulfonic acid (1.0 g) in 600 ml EtOH free $CHCl_3$ was treated as described above for the methylcarbamate derivative. Hexane (400 ml) was added and the crystalline product filtered off and washed with hexane; m.p. 154–155°; yield 130 g (90%). IR ($CHCl_3$) 3440 (NH), 1730 (CO_2H), 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 1.00–1.80 (m, 14H, C_3H_7), 3.95 (t, 4H, J = 6, OCH_2), 5.15 (t, 1H, J = 8, CH), 7.42 (d, 2H, J = 8, NH). This compound was also characterized as the methyl ester (**23b**, X = Me). (Found: C, 49.84; H, 7.71; N, 9.48. Calc for $C_{12}H_{22}N_2O_6$: C, 49.64; H, 7.64; N, 9.65%.)

Methyl bismethoxycarbonylaminoacetate (**23**, X = OMe). To a suspension of the bismethoxycarbonylaminoacetic acid (20.6 g, 0.1 mol) in abs MeOH (100 ml) was added dropwise with stirring $SOCl_2$ (0.11 mol). The suspension was stirred overnight, the MeOH was evaporated and the residue triturated with dry ether and filtered. Yield 21.0 g (95%), m.p. 158–159° (EtOAc–hexane). IR (KBr) 3310 (NH), 1750, 1690 (CO), and 1520 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.65 (s, 6H, OMe), 3.76 (s, 3H, OMe), 5.38 (t, 1H, J = 7, CH), 6.30 (d, 2H, J = 7, NH). MS (HR) *m/z* 161.0555 ($M^+ - CO_2Me$, 100%). (Found: C, 38.36; H, 5.54; N, 12.75. Calc for $C_7H_{12}N_2O_6$: C, 38.18; H, 5.49; N, 12.72%.)

Methyl N-*butoxycarbonyl*-α-*methoxyglycinate*. A mixture of butyl carbamate (23.4 g, 0.2 mol), glyoxylic acid monohydrate (18.4 g, 0.2 mol) in dry ether (150 ml) was stirred at room temp for 24h. The EtOH soln was dried over $MgSO_4$ and evaporated. The oily residue was dissolved in abs MeOH (150 ml) cooled (ice + water) and conc H_2SO_4 (3 ml) was added. After standing at room temp overnight the acidic soln was neutralized with Cs_2CO_3, the salts were filtered off and the MeOH evaporated. The residue was taken into EtOAc (250 ml) washed with water and dried over $MgSO_4$. The EtOAc was evaporated and the residue was chromatographed on deactivated (10% MeOH) neutral alumina. The product was eluted with CH_2Cl_2–hexane (1:10) to give 22.8 g (52%) of an oil. IR ($CHCl_3$) 3420 (NH), 1750–1700

(b, CO), and 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 0.83–2.00 (m, 7H, C_3H_7), 3.50 (s, 3H, OMe), 3.87 (s, 3H, CO_2Me), 4.20 (t, J = 6, 2H, OCl_2), 5.37 (d, J = 9, 1H, ChNH), 6.20 (d, J = 9, 1H, NH). (Found: C, 49.10; H, 7.85; N, 6.45. $C_9H_{17}NO_5$ requires: C, 49.30; H, 7.82; N, 6.39%.)

Methyl bisbutoxycarbonylaminoacetate (**23b**, X = OMe). To a suspension of bisbutoxycarbonylaminoacetic acid (29.0 g, 0.1 mol) in abs MeOH (150 ml) was added, dropwise with stirring, $SOCl_2$ (10 ml). The bisacid dissolved in the hot soln and after 0.5 h the ester started to precipitate. After 24 h the solid was filtered off and dried *in vacuo* at 60°. The yield was 26.0 g (86%), m.p. 108°. IR ($CHCl_3$) 3460 (NH), 1760, 1730 (CO), and 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 1.00–1.80 (m, 14H, C_3H_7), 3.80 (s, 3H, OMe), 4.10 (t, 4H, J = 6, OCH_2), 5.50 (t, 1H, J = 8, CH), 6.60 (d, 2H, J = 8, NH). MS (HR) *m/z* 245.1502 (100%, $M^+ - CO_2Me$).

Bismethoxycarbonylacetyl chloride (**23a**, X = Cl). To a suspension of bismethoxycarbonylaminoacetic acid (20.6 g, 0.1 mol) in CH_2Cl_2 (200 ml) was added, with stirring and cooling PCl_5 (22.9 g, 0.11 mol). Stirring was continued until all the solid dissolved. The soln was evaporated and the acid chloride triturated with dry hexane and filtered. The solid acid chloride was washed with dry hexane and used directly in coupling reactions with amines to give the amides (see below). The yield was 21.1 g (94%).

Bisbutoxycarbonylaminoacetyl chloride (**22b**, X = Cl). To a suspension of the bisbutoxycarbonylaminoacetic acid (14.5 g, 0.05 mol) in dry ether (200 ml) was added, with stirring and cooling (ice + water) PCl_5 (12.0 g, 0.6 mol). Stirring was continued until all the solid dissolved. The ether was evaporated and the product triturated with dry hexane, filtered and coupled directly with the proper amine (see below).

N-*Benzylbismethoxycarbonylaminoacetamide* (**13a**). A soln of methyl bismethoxycarbonylaminoacetate (22.0 g, 0.1 mol) and benzylamine (15.0 g, 0.15 mol) in MeOH (150 ml) was refluxed for 5 h. The soln was cooled in the refrigerator overnight and the product filtered off and washed with dry ether, m.p. 185–186°. The yield was 18.85 g (64%). IR (KBr) 3280 (NH), 1705, 1640 (CO), 1545, 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 3.56 (s, 6H, $HNCO_2Me$), 4.30 (d, J = 6, 2H, CH_2), 5.46 (t, J = 8, 1H, CH), 7.30 (s, 5H, Ar), 7.54 (d, 2H, 2NH), 8.57 (t, 1H, NH). (Found: C, 52.92; H, 5.72; N, 14.58. $C_{13}H_{17}N_3O_5$ requires: C, 52.87; H, 5.80; N, 14.23%.)

N-(-1-*Phenylethyl*)*bismethoxycarbonylaminoacetamide* (**13b**). This compound was prepared from **23a** (0.10 mol) and *d,l*-α-phenylethylamine (14.52 g, 0.12 mol) in cooled (ice + water) CH_2Cl_2 (200 ml) and in the presence of Et_3N (15.0 g, 0.15 mol). The acid chloride was added slowly to the cooled soln of the amine (20 min). The soln was stirred for 1 h, concentrated and divided between EtOAc and water. The organic layer was washed with HCl (1%), bicarbonate (5%), H_2O, and dried over $MgSO_4$. Evaporation of EtOAc and trituration with hexane gave 18.0 g (62%) of product; m.p. 162–163° (CH_2Cl_2–hexane). IR (KBr) 3300 (NH), 1710, 1660 (CO), 1550 and 1520 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.80 (t, 2H, J = 7, CH_2), 3.50 (q, 2H, CH_2), 3.50 (q, 2H, J = 7, CH_2), 3.65 (s, 6H, OMe), 5.52 (t, 1H, J = 6, CH), 6.35 (d, 2H, J = 6, NH), 6.90 (t, 1H, J = 7, NH), 7.26 (s, 5H, Ph). (Found: C, 54.28; H, 6.32; N, 13.42. Calc for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.58%.)

N-*Benzyl*-N-*methylbismethoxycarbonylaminoacetamide* (**13c**). This compound was prepared from **23a** and N-methylbenzylamine in 70% yield in analogy to the preparation of **13b**, m.p. 95–97°. IR ($CHCl_3$) 3400 (NH), 1720, 1650 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 3.03, 2.90 (2s, 3H, N—Me), 3.67, 3.60 (2s, 6H, $HNCO_2Me$), 4.63, 4.53 (2s, 2H, Ph—CH_2), 6.13 (b, $CH(NHCO_2Me)_2$), 7.20 (s, 5H, Ph). The NMR showed the two amidic conformers. MS (HR) *m/z* 161.0547 (100%), 148.0755 (2%). $C_{14}H_{19}N_3O_5$ requires 309.1324 (161.0562 + 148.0762).

N-(1-*Phenylethyl*)*bisbutoxycarbonylaminoacetamide* (**13d**). This compound was prepared from bisbutoxycarbonylaminoacetic acid (14.5 g, 0.05 mol), 1-phenylethylamine and DCC (11.0 g) in CH_2Cl_2 (200 ml). The mixture was stirred overnight, the urea filtered and the soln washed with $NaHCO_3$ aq (5%), H_3PO_4 (8%) and H_2O. The soln was evaporated after drying over $MgSO_4$. The residue was triturated with dry ether to give 18.2 g (98%) of product; m.p. 132–134° (EtOAc). IR ($CHCl_3$) 3440 (NH), 1740, 1700 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 0.73–2.30 (m + d, 17H, 2, C_3H_7 + 1 CH—CH_3), 4.10 (t, J = 6, 4H, 2 OCH_2), 4.90–5.30 (m, 1H, CH—NH), 5.50 (t, J = 6, HN—CH—NH), 7.27 (s, 5H, Ph). (Found: C, 61.41; H, 7.85; N, 10.44. $C_{20}H_{31}N_3O_5$ requires: C, 61.05; H, 7.94; N, 10.68%.)

N,N-*Dibenzylbismethoxycarbonylaminoacetamide* (**13e**). This compound was prepared from **22a** (6.2 g) and dibenzylamine (6 ml) via the acid chloride procedure (see **13b**). The solid obtained melted at 178–179° (EtOAc), yield 6.3 g (55%). IR ($CHCl_3$) 3400 (NH), 1730, 1650 (CO), 1505 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.67 (s, 6H, $2NHCO_2Me$), 4.63 (s, 4H, CH_2Ph), 6.27 (b, 3H, $CH(NHCO_2Me)_2$), 7.27 (bs, 10H, 2Ph). MS (HR) *m/z* 385.1596 (31.38% M^+), $C_{20}H_{23}N_3O_5$ requires 385.1637. (Found: C, 62.19; H, 5.90; N, 10.91. Requires: C, 62.32; H, 6.02; N, 10.90%.)

Methyl N-*bisbutoxycarbonylaminoacetyl-d,l-phenylglycinate* (**13f**). This compound was prepared from **23b** (0.05 mol) and methyl-*d,l*-phenylglycinate hydrochloride (0.05 mol) in CH_2Cl_2 (150 ml) and in the presence of Et_3N (0.11 mol). The product was obtained in 44% yield; m.p. 134–136° (EtOAc). IR ($CHCl_3$) 3430 (NH), 1740–1670 (CO), 1510–1540 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 0.70–1.86 (m, 14H, $2C_3H_7$), 3.93–4.25 (m, 4H, $2OCH_2$), 5.50 (t, J = 7, 1H, HN—CH—NH), 5.55 (d, J = 8, 1H, Ph—CH), 5.97 (d, J = 7, 2H, 2CH—NHCO), 7.37 (s, 5H, Ph), 7.63 (d, J = 8, 1H, NH). (Found: C, 57.83; H, 7.17; N, 9.49. Calc for $C_{21}H_{31}N_3O_7$: C, 57.65; H, 7.14; N, 9.61%.)

Bismethoxycarbonylaminoacetanilide (**16a**). This compound was prepared from **22a** (0.1 mol) and aniline (0.11 mol) by the acid chloride procedure (see preparation of **13b**). The sparingly soluble material was crystallized from EtOAc; m.p. 201–202°; yield 64%. IR (KBr) 3280 (NH), 1705, 1660 (CO), 1520 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 3.59 (s, 6H, 2Me), 5.58 (t, J = 8, 1H, CH), 7.05–7.85 (m, 7H, ArH + NH). (Found: C, 51.26; H, 5.44; N, 14.89. $C_{12}H_{15}N_3O_5$ requires: C, 51.24; H, 5.38; N, 14.94%.)

N-*Methylbismethoxycarbonylaminoacetanilide* (**16b**). This compound was prepared from **22a** (7.0 g) and N-methylaniline (10 ml) by the acid chloride procedure. The yield was 6.1 g (68.7%). IR ($CHCl_3$) 3440 (NH), 1730, 1670 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.30 (s, 3H, N—Me), 3.56 (s, 6H, $NHCO_2Me$), 5.46–6.40 (m, 3H, $CH(NHCO—)_2$), 7.06–7.66 (m, 5H, N—Ph). (Found: C, 53.02; H, 5.94; N, 14.17. Calc for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23%.)

4-*Methyl*(*bismethoxycarbonylamino*)*acetanilide* (**16c**). This compound was prepared from bismethoxycarbonylaminoacetic acid and 4-methylaniline by the acid chloride procedure. The yield was 87%; m.p. 223–224° (CH_2Cl_2–hexane). IR (KBr) 3280 (NH), 1705, 1658 (CO), and 1525 cm^{-1} $(NH)^+$. ^{1}H-NMR (DMSO-d_6) δ 2.25 (s, 3H, Me), 3.58 (s, 6H, Me), 5.57 (t, 1H, J = 8, CH), 7.02–7.66 (q, 4H, Ar), 7.70 (d, 2H, J = 8, NH). (Found: C, 52.81; H, 6.07; N, 14.23. $C_{13}H_{17}N_3O_5$ requires: C, 52.88; H, 5.80; N, 14.23%.)

Bisbutoxycarbonylamino-p-methylacetanilide (**16d**). This compound was prepared from bisbutoxycarbonylaminoacetic acid (8.9 g) and *p*-toluidine (3.22 g) by the acid chloride method. The product was crystallized from MeOH to give 6.2 g (54.3%); m.p. 192–193°. IR ($CHCl_3$) 3420 (NH), 1735, 1710 (CO), 1510–1580 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 0.70–1.80 (m, 14H, $2C_3H_7$), 2.30 (s, 3H, MeC_6H_4), 4.06 (t, J = 6, 4H, OCH_2), 5.60 (t, J = 7, 1H, COCHNH), 5.93 (d, J = 7, 2H, $CH(NH—)_2$), 7.30, 7.10 (2d, J = 10, 4H, MeC_6H_4—NH), 8.46 (s, 1H, PhNHCO). MS (HR) *m/z* 379.2133, $C_{19}H_{29}N_3O_5$ requires *m/z* 379.2107.

N-*Benzylbismethoxycarbonylaminoacetanilide* (**16c**). This compound was prepared from the acid (11.3 g) and N-benzyl-

aniline by the acid chloride procedure; yield 12.0 g (64%); m.p. 110°. IR ($CHCl_3$) 3410 (NH), 1720, 1660 (CO), 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.60 (s, 6H, $NHCO_2Me$), 4.90 (s, 2H, N—CH_2—Ph), 5.56 (t, J = 7, 1H, CH—NH), 6.06 (d, J = 7, 2H, NH), 6.83–7.43 (m, 5H, Ph—N), 7.20 (s, 5H, CH_2Ph). MS (HR) *m/z* 371.1466, $C_{19}H_{21}N_3O_5$ requires 371.1481 (M^+). (Found: C, 61.13; H, 5.79; N, 11.12. Requires: C, 61.44; H, 5.70; N, 11.32%.)

4-*Chlorobismethoxycarbonylaminoacetanilide* (**16f**). This compound was prepared from **22a** (3.80 g) and *p*-chloroaniline by the acid chloride procedure. Trituration with ether afforded 5.4 g (58%) of product, m.p. 198–200°. IR ($CHCl_3$) 3420 (NH), 1740, 1715 (CO), 1510–1570 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.77 (s, 6H, $NHCO_2Me$), 5.73 (t, J = 7, 1H, CHNH), 6.23 (d, J = 7, 2H, NHCO—), 7.30, 7.57 (2d, J = 8, 4H, —C_6H_4—), 8.80 (s, 1H, ArNH). MS (HR) *m/z* 317.0588 and 315.0660, $C_{12}H_{14}N_3O_5Cl$ requires 317.0592 and 315.0622.

N - 2 - *Phenylethylbismethoxycarbonylaminoacetamide* (**18a**). This compound was obtained in 77% yield by refluxing a soln of **23** (R = X = Me, 22.0 g, 0.1 mol) and β-phenylethylamine (18.0 g, 0.15 mol) in MeOH (150 ml) for 6 h. The MeOH was evaporated and the residue triturated with dry ether; m.p. 162–163° (CH_2Cl_2–hexane). IR (KBr) 3290 (NH), 1705, 1650 (CO), 1550, 1515 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 2.57–2.90 (t, J = 7, 2H, Ph—CH_2), 3.10–3.50 (m, 2H, CH_2NH), 5.39 (t, J = 8, 1H, CH), 7.25 (s, 5H, Ph), 7.45 (d, 2H, 2NH), 8.08 (bs, 1H, NH). (Found: C, 54.52; H, 6.27; N, 13.54. $C_{14}H_{19}N_3O_5$ requires: C, 54.36; H, 6.19; N, 13.58%.)

Methyl N-*bismethoxycarbonylaminoacetyl-d,l-phenylalaninate* (**18b**). This compound was prepared from **22a** (6.2 g) and methyl-d,l-phenylalaninate hydrochloride (6.5 g) by the acid chloride method. The product was triturated with ether and filtered to give 6.9 g (70%); m.p. 171–172°. IR (KBr) 3300 (NH), 1740, 1690 (CO), 1530 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 3.10 (d, J = 8, 2H, CH_2Ph), 3.60 (s, 6H, $HNCO_2Me$), 3.67 (s, 3H, CO_2Me), 4.33–4.70 (m, 1H, CH_2—CH—CO), 5.48 (t, J = 8, 1H, HN—CH—NH), 7.30 (s, 5H, Ph), 7.43 (d, J = 8, 1H, NHCO), 8.37 (d, J = 8, 1H, CHNHCO). (Found: C, 52.13; H, 5.88; N, 11.62. $C_{16}H_{21}N_3O_7$ requires: C, 52.31; H, 5.76; N, 11.44%.)

Bismethoxycarbonylaminoacetyltyramine (**18c**). This compound was obtained by refluxing a MeOH soln (75 ml) of **23** (6.58 g, 0.3 mol) and tyramine (4.67 g, 0.33 mol) for 48 h. The MeOH was evaporated and the residue chromatographed over florisil. Elution with 2% MeOH in $CHCl_3$ and trituration with dry ether gave 5.5 g (56.5%) product. IR ($CHCl_3$) 3600–3120 (OH + NH), 1740, 1700 (CO), 1505 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 2.30–2.60 (m, 2H, $ArCH_2$), 2.73–3.07 (m, 2H, CH_2—NH), 3.30 (s, 6H, $NHCO_2Me$), 5.07 (t, J = 7, 1H, CH—NH), 6.70, 6.37 (2d, J = 7, 4H, Ar), 7.33 (d, J = 7, 2H, —NH—CO), 7.70 (t, J = 6, 1H, CH_2NHCO), 8.85 (s, 1H, OH). (Found: C, 51.81; H, 5.96; N, 12.77. $C_{14}H_{19}N_3O_6$ requires: C, 51.68; H, 5.89; N, 12.92%.)

N - (3,4 - *Dimethoxyphenyl*)*ethylbismethoxycarbonylaminoacetamide*. A mixture of **23** (11.0 g, 0.05 mol) and β-(3,4-dimethoxyphenyl)ethylamine (13.5 g, 0.075 mol) in MeOH (75 ml) was refluxed for 5 h. The crystalline product which separated on cooling was filtered to give 12.0 g of product; m.p. 176–177°. Concentration of the MeOH soln gave an additional 3.0 g of amide, total yield 81%. IR ($CHCl_3$) 3440 (NH), 1740, 1700 (CO), and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO d_6) δ 2.80 (t, 2H, J = 7, CH_2), 3.35 (q, 2H, CH_2), 3.56 (s, 6H, OMe), 3.74 (s, 3H, OMe), 3.76 (s, 3H, OMe), 5.40 (t, 1H, J = 8, CH), 6.83 (br s, 3H, Ar), 7.45 (d, 2H, J = 8, NH), 8.05 (t, 1H, J = 6, NH). (Found: C, 51.95; H, 6.41; N, 11.14. $C_{16}H_{23}N_3O_7$ requires: C, 52.02; H, 6.28; N, 11.38%.)

N - *Methyl* - N - (1 - *phenyl* - 2 - *propyl*)*bismethoxycarbonylaminoacetamide*. This compound was prepared from **22a** (4.30 g) and N-methyl-1-phenyl-2-propylamine by the acid chloride procedure. Trituration with ether gave 6.90 g (69%) of an oily product. IR ($CHCl_3$) 3410 (NH), 1730 and 1650 cm^{-1} (CO). The ^{1}H-NMR spectra showed a mixture of two amidic conformers ($CDCl_3$) δ 1.23, 1.33 (2d, C—Me), 2.70 (d, J = 2), 2.83 (s), 2.90 (s), 2.93 (s), altogether 5H, $PhCH_2$ + N—Me), 3.70 (s, 6H, 2OMe), 4.13–5.13 (m, 1H, CHMe), 5.93–6.53 (m, 3H, Ch—NH), 7.20 (s, 5H, Ph). (Found: C, 60.11; H, 6.93; N, 12.29. $C_{16}H_{23}N_3O_5$ requires: C, 56.96; H, 6.87; N, 12.46%.)

N-(*α-Butoxycarbonylamino-α-methoxy*)*acetyltyramine*. A mixture of methyl α-butoxycarbonylamino-α-methoxyacetate (7.7 g, 0.035 mol) and tyramine (5.1 g, 0.037 mol) in MeOH (50 ml) was refluxed for 72 h. The solvent was removed and the residue chromatographed over florisil. The product was eluted with 3% MeOH in $CHCl_3$. Trituration with dry ether gave 7.0 g (61%) product, m.p. 102–103°. IR ($CHCl_3$) 3580 (OH), 3410 (NH), 1710, 1660 (CO), and 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 0.83–1.90 (m, 7H, C_3H_7), 2.63–3.00 (m, 2H, $ArCH_2$), 3.33–3.77 (m + s, 5H, CH_2N-H + OMe), 4.17 (t, 2H, J = 6, OCH_2), 5.25 (d, 1H, J = 9, CH), 6.00 (d, 1H, J = 9, NH), 6.70–7.30 (m, 6H, OH + N-H + Ar). MS (HR) *m/z* 324.1719 (M^+ 6.2%), calc for $C_{16}H_{24}N_2O_5$ 324.1685 (M^+).

Amidoalkylations in the bisalkoxycarbonylaminoacetamides series

4-*Methoxycarbonylamino*-1,2,3,4-*tetrahydro isoquinoline*-3-one (**15a**). The benzylamide **13a** (1.48 g, 5 mmol) was dissolved in 10 ml of MSA under cooling (ice + water), followed by stirring at room temp for 24 h. The mixture was poured on crushed ice, extracted 5 times with EtOAc, dried over $MgSO_4$ and evaporated. Trituration with dry ether gave 0.93 g (84%) of product, m.p. 164–165°. IR (KBr) 3370, 3280 (NH), 1720, 1655 (CO), 1547 (NH). ^{1}H-NMR (DMSO-d_6) δ 3.65 (s, 3H, Me), 4.38 (m, 2H, CH_2), 5.13 (d, 1H, J = 9, CH), 7.31 (s, 4H, ArH), 7.67 (d, 1H, NH), 8.28 (bs, 1H, NH). MS *m/z* 220.1 (100%), $C_{11}H_{12}N_2O_3$ requires 220.2. (Found: C, 58.89; H, 5.63; N, 12.25. Requires: C, 59.29; H, 5.49; N, 12.52%.)

If the reaction is carried out in the presence of benzene (4 ml) and treated as described above the main product is the isoquinolone which according to the NMR of the crude is accompanied by 5–10% of intermolecular reaction product the benzylamide of **14a** (Ar = Ph). The latter was isolated from the mother liquor after trituration with ether. ^{1}H-NMR ($CDCl_3$) δ 7.05–7.45 (m, 10H, ArH), 5.34 (d, 1H, CH), 4.37 (d, J = 6, 2H, CH_2), 3.54 (s, 3H, Me).

N′-*Benzyl*-N-*methoxycarbonylamino-p-tolylglycine* (**14**, Ar = C_6H_4Me). The benzylamide **13a** (1.00 g, 3.4 mmol), toluene (1.0 g, 11 mol) and MSA (5 ml) were treated as described above. The crude product was a mixture of *ortho*–*para* isomers (1:9). Trituration with dry ether overnight gave 0.77 g (73%) of the *p*-isomer, m.p. 151–152° (CH_2Cl_2–hexane). IR (KBr) 3300 (NH), 1695, 1645 (CO), 1540 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, 3H, Ar—Me), 3.57 (s, 3H, OMe), 5.22 (d, J = 7, 1H, CH), 7.00–7.40 (m, 9H, ArH). (Found: C, 69.11; H, 6.52; N, 8.85. $C_{18}H_{20}N_2O_3$ requires: C, 69.21; H, 6.45; N, 8.97%.)

4 - *Methoxycarbonylamino* - 1 - *methyl* - 1,2,3,4 - *tetrahydroisoquinoline*-3-*one* (**15b**). The bisadduct amide **13b** (1.0 g) was stirred in MSA (7.5 ml) at room temp for 6 h. The acid soln was poured onto crushed ice and extracted with EtOAc (3 × 100 ml). The organic layer was dried over $MgSO_4$ and evaporated to give 0.520 g (65%) of crude product which was according to the NMR (two Me doublet at 1.39 and 1.55) a mixture of two isomers in a 2:1 ratio. Chromatography and three crystallizations from EtOAc–hexane gave the more polar isomer, m.p. 194°. IR ($CHCl_3$) 3410 (NH), 1720, 1680 (CO), and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) 1.39 (d, 3H, J = 7, CH—Me); 3.65 (s, H, OMe), 4.50 (m, 1H, CH), 5.19 (d, 1H, J = 9, CH), 7.33 (s, 4H, Ph), 7.65 (d, 1H, J = 9, NH), 8.25 (d, 1H, J = 6, NH). (Found: C, 61.46; H, 5.98; N, 11.85. Calc for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96%.) MS (HR) *m/z* 234.0997 (86%), requires M^+ 234.1004.

4 - *Methoxycarbonylamino* - 2 - *methyl* - 1,2,3,4 - *tetra* - *hydroisoquinoline* - 3 - *one* (**15c**). This compound was prepared in 98% yield by reacting **13d** (1 g) in MSA (10 ml) as described above (general proceduure); m.p. 148–149° (EtOAc–hexane). IR ($CHCl_3$) 3400 (NH), 1715, 1625 (CO), 1510 (NH). ^{1}H-NMR ($CDCl_3$) δ 3.07 (s, 3H, N—Me), 3.70 (s, 3H, CO_2Me), 4.77–4.00 (2d, +2s, J = 2, 2H, CH_2), 5.20 (d, J = 8, 1H, CH—NH), 5.77–6.10 (b, 1H, NHCO—), 7.27–7.37 (2d, J = 4, 4H, ArH). MS (HR) *m/z* 234.1046 (15.43%), $C_{12}H_{14}N_2O_3$ requires 234.1004 (M^+). (Found: C, 61.55; H, 6.05; N, 12.03. Requires: C, 61.53; H, 6.02; N, 11.96%.)

4 - *Butoxycarbonyamino*-1-*methyl* - 1,2,3,4 - *tetra* - *hydroisoquinoline*-3-*one* (**15d**). The N-1-phenylethylamide **13d** (3.0 g) was reacted in MSA for 24 h as described above. The crude product was purified on a florisil column and eluted with 2% MeOH in $CHCl_3$. The yield was 1.32 g (63%) oil. IR ($CHCl_3$) 3430 (NH), 1730, 1690 (CO), and 1505 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 0.70–2.10 (m+d, 10H, C_3H_7+CH—CH_3), 4.13 (t, J = 6, 2H, OCH_2—CH_2), 4.40–4.80 (m, 1H, CH—CH_3), 5.30 (d, J = 8, 1H, CH—NH), 5.90 (d, J = 8, 1H, NH—CO—), 6.86–7.43 (m, 4H, Ar), 7.60–7.90 (bs, 1H, NH—COCH). MS (HR) *m/z* 276.1488, $C_{15}H_{20}N_2O_3$ requires 276.1473 (M^+).

4 - *Methoxycarbonylamino* - 2 - *benzyl* - 1,2,3,4 - *tetra* - *hydroisoquinoline*-3-*one* (**15e**). This compound was prepared by reacting **13f** (4.0 g) in 40 ml MSA for 24 h as described above. The product 2.2 g (70%) melted at 167–168° (EtOAc). IR ($CHCl_3$) 3400 (NH), 1720, 1660 (CO), and 1500 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 3.80 (s, 3H, CO_2Me), 4.43–4.30 (d+s, J = 2, 2H, CH_2), 4.77 (d, J = 2, 2H, CH_2Ph), 5.30 (d, J = 8, 1H, CH—NHCO—), 6.07 (d, J = 8, 1H, NHCO—), 7.00–7.27 (m+s, 9H, ArH). MS (HR) *m/z* 310.1311 (4.64%), $C_{18}H_{18}N_2O_3$ requires 310.1317 (M^+). (Found: C, 69.51; H, 5.69; N, 8.94. Requires: C, 69.66; H, 5.85; N, 9.03%.)

Methyl - 4 - *butoxycarbonylamino* - 1,2,3,4 - *tetra* - *hydroisoquinoline*-3-*one*-1-*carboxylate* (**15f**). This compound was prepared by treating **13h** (2.16 g) in MSA (20 ml) for 24 h as described above. The crude product which showed two isomers was chromatographed over floril column and the product eluted with 2.5% MeOH in $CHCl_3$; yield 1.0 g (63%) oil. IR ($CHCl_3$) 3420 (NH), 1740–1690 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 0.73–1.87 (m, 7H, C_3H_7), 3.67 (s, 3H, CO_2Me), 4.33 (t, J = 6, 2H, OCH_2—CH_2), 5.15 (d, J = 6, 1H, CH—CO), 5.47 (d, J = 7, 1H, CH—NH), 5.87 (d, J = 7, 1H, NHCO—), 7.30 (s, 4H, C_6H_4), 8.00 (d, J = 6, 1H, CH—NHCO—). MS (HR) *m/z* 320.1368 (11.2%), $C_{16}H_{20}N_2O_5$ requires 320.1372.

The methyl ester was hydrolyzed to the acid with KOH–MeOH (1 equiv) at room temp to give crystalline product (71%); m.p. 205° (dec, EtOAc). IR (KBr) 3440, 3400 (NH), 3600–2200 (b, CO_2H), 1730, 1680, 1640 (CO), and 1550 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 0.70–1.87 (m, 7H, C_3H_7), 4.10 (t, J = 6, 2H, OCH_2), 5.10 (d, J = 4, 1H, CH—CO), 5.30 (d, J = 10, 1H, CH—NH), 7.40 (bs, 4H, C_6H_4), 7.67 (d, J = 10, 1H, NHCO), 8.47 (d, J = 4, 1H, NHCO), 11.0 (bs, 1H, CO_2H). (Found: C, 58.74; H, 6.06; N, 8.80. $C_{15}H_{18}N_2O_5$ requires: C, 58.81; H, 5.92; N, 9.15%.)

3-*Methoxycarbonylamino*-2-*indolinone* (**17a**). The anilide **16a** (1.0 g, 3.55 mmol) in TFA (80 ml) was stirred at room temp for 72 h. The TFA was evaporated and the residue triturated with dry ether to give 0.66 g product which showed two spots on TLC. The less polar was purified on chromatography over florisil yield 71%; m.p. 222–224°. IR (KBr) 3330 (NH), 1730 and 1690 cm^{-1} (CO), 1545 (NH). ^{1}H-NMR (DMSO-d_6) δ 3.56 (s, 3H, Me), 4.88 (d, J = 8, 1H, CH), 6.70–7.40 (m, 4H, ArH), 7.94 (d, 1H, NHCO). MS *m/z* 206.06, $C_{10}H_{10}N_2O_3$ requires 206.2 (M^+). (Found: C, 57.85; H, 5.26; N, 12.78. Requires: C, 58.25; H, 4.89; N, 13.59%.)

N^1 - *Phenyl* - N - *methoxycarbonylamino* - *p* - *tolyl*-*glycinamide*. The anilide **16a** (0.46 g, 1.63 mmol) and toluene (1.8 g, 19.5 mmol) in MSA (10 ml) was treated for 24 h as described above (general procedure). The crude product showed two spots on TLC. The major product was obtained pure on trituration with dry ether and crystallization from CH_2Cl_2–Et_2O; yield 0.29 g (59%), m.p. 189–191°. IR (KBr) 3300 (NH), 1685, 1655 (CO). ^{1}H-NMR (DMSO-d_6) δ 2.28 (s, 3H, PhMe), 3.58 (s, 3H, OMe), 5.42 (d, J = 8, 1H, CH), 7.03–7.96 (m, 11H, NH+2Ph). MS *m/z* 298.1, $C_{17}H_{18}N_2O_3$ requires 298.1 (M^+).

3-*Methoxycarbonylamino*-1-*methyl*-2-*indolinone* (**17b**). This compound was prepared by treating the N-methylanilide **16b** (3.16 g) in MSA for 48 h as described above (general procedure). Trituration with ether and crystallization from EtOAc afforded 1.50 g (63%) of a crystalline product: m.p. 162–164°. IR ($CHCl_3$) 3440 (NH), 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ 3.13 (s, 3H, N—Me), 3.63 (s, 3H, $NHCO_2Me$), 5.00 (d, J = 8, 1H, CH—NH), 5.80 (d, J = 8, 1H, NH), 6.70–7.43 (m, 4H, ArH). MS (HR) *m/z* 220.0839 (58.7%), $C_{11}H_{12}N_2O_3$ requires 220.0847 (M^+). (Found: C, 59.96; H, 5.50; N, 12.64. Requires: C, 59.99; H, 5.49; N, 12.72%.)

3-*Methoxycarbonylamino*-5-*methyl*-2-*indolinone* (**17c**). The *p*-methylanilide **16e** (0.80 g, 2.71 mmol) in TFA (15 ml) was stirred at room temp for 24 h. The residue left after the evaporation of the TFA was triturated with dry ether to give 0.57 g (95%) of a colorless solid; m.p. 231–232° (CH_2Cl_2–hexane). IR (KBr) 3340 (NH), 1720, 1700 (CO), and 1530 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 2.24 (s, 3H, Ar—Me), 3.57 (s, 3H, OMe), 4.84 (d, J = 8, 1H, CH) 6.60–7.15 (m, 3H, ArH), 7.89 (d, 1H, NH). MS *m/z* 220.1, $C_{11}H_{12}N_2O_3$ requires 220.2 (M^+). (Found: C, 59.75; H, 5.46; N, 12.64. Requires: C, 59.99; H, 5.49; N, 12.72%.) (Found: C, 68.14; H, 6.26; N, 9.26. Requires: C, 68.44; H, 6.08; N, 9.39%.)

Compound **17d** was prepared similarly in 61% yield; m.p. 174–175°. IR ($CHCl_3$) 3560, 3450 (NH), 1730 (CO), 1520 (NH). ^{1}H-NMR ($CDCl_3$) δ 0.66–1.10 (m, 7H, C_3H_7), 4.03 (t, J = 6, 2H, OCH_2), 5.46 (d, J = 8, 1H, CH), 5.96 (d, J = 8, 1H, NH), 6.53–7.00 (m, 3H, C_6H_3), 8.50 (s, 1H, NH). MS (HR) *m/e* 262.1298 (75.5%), $C_{14}H_{18}N_2O_3$ requires 262.1317 (M^+). (Found: C, 64.11; H, 7.00; N, 10.47. Requires: C, 64.10; H, 6.92; N, 10.68%.)

1-*Benzyl*-3-*methoxycarbonylamino*-2-*indolinone* (**17e**). This compound was prepared from the N-benzyl-N-phenylbismethoxycarbonylaminoacetamide (10.4 g) in MSA (10 ml) for 24 h as described above (general procedure). The product was triturated with dry ether–hexane to give 8.14 g (98%); m.p. 169–171° (EtOAc). IR ($CHCl_3$) 3430 (NH), 1720 (CO). MS (HR) *m/z* 296.1138 (100%), $C_{17}H_{16}N_2O_3$ requires 296.1160 (M^+). ^{1}H-NMR ($CDCl_3$) δ 3.80 (s, 3H, $NHCO_2Me$), 5.00 (s, 2H, CH_2Ph), 5.16 (d, J = 7, 1H, CH—NH), 5.73 (d, J = 7, 1H, NH), 6.7–7.5 (m+s, 9H, C_6H_4+Ph).

5-*Chloro*-3-*methoxycarbonylamino*-2-*indolinone* (**17f**). This compound was prepared from **16g** (0.39 g) in MSA (6 ml) by the general procedure described above. The yield was 0.28 g (94%); m.p. 236–238° (EtOAc). IR (KBr) 3350 (NH), 1730, 1700 (CO), and 1530 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 3.27 (s, 3H, $NHCO_2Me$), 4.9 (d, 1H, J = 9, CH—NH), 7.30, 7.36 and 6.77 (s+d+d, J = 8, 3H, Ar), 7.70 (d, 1H, J = 9, $NHCO_2Me$), 10.33 (s, 1H, NH). MS (HR) *m/z* 240.0285 (60%) and 242.0281 (20%), calc for $C_{10}H_9N_2O_3Cl$ *m/z* 240.0301 and 242.0272.

1 - *Methoxycarbonylamino* - 1,2,3,4,5 - *pentahydro* - 3 - *benzazepine* - 2 - *one* (**19a**). Compound **16a** (1.54 g, 5 mmol) was treated in MSA (20 ml) for 72 h as described above (general procedure). Trituration with ether gave a colourless solid: 0.78 g (67%), m.p. 223–224° (EtOAc). IR (KBr) 3300, 3220 (NH), 1700, 1670 (CO), 1550 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ 3.05–4.00 (m, 4H, CH_2—CH_2), 3.62 (s, 3H, $NHCO_2Me$), 5.91 (d, J = 8, 1H, CH), 7.23 (s, 4H, C_6H_4). MS *m/z* 234 (100%), $C_{12}H_{14}N_2O_3$ requires 234. (Found: C, 61.83; H, 6.40; N, 11.74. Requires: C, 61.52; H, 6.02; N, 11.96%.)

N^1 - *Phenylethyl* - N - *methoxycarbonylamino* - *p* - *tolyl*-*glycinamide*. A mixture of **18a** (1.04 g, 3.36 mmol) and toluene (1.75 g, 19 mmol), in MSA (10 ml) was treated for 24

h as described above (general procedure). Trituration with ether gave 0.83 g (76%) of a colourless solid showing one spot on TLC different from **19a**; m.p. 127–128° (CH_2Cl_2–hexane). IR (KBr) 3300 (NH), 1705, 1660 (CO), and 1520 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, ArMe), 2.53–2.86 (t, 2H, PhCH$_2$), 3.24–3.70 (m, 2H, CH$_2$—NH), 3.59 (s, 3H, Me), 5.11 (d, J = 7, 1H, CH), 6.87–7.38 (m, 9H, ArH). (Found: C, 69.65; H, 6.91; N, 8.59. $C_{19}H_{22}N_2O_3$ requires: C, 69.92; H, 6.79; N, 8.58%.)

Methyl 1-*methoxycarbonylamino*-1,2,3,4,5-*pentahydro*-3-*benzazepine*-2-*one*-4-*carboxylate* (**19b**). Methyl N-bismethoxycarbonylaminoacetyl-*d,l*-phenylalaninate (4.5 g) in conc H_2SO_4 (65 ml) was treated for 72 h as described above (general procedure). After the evaporation of the chloroform the residue 2.3 g (63%) was triturated with dry ether and crystallized from EtOAc; m.p. 163–165°. IR (KBr) 3350 (NH), 1750, 1710, 1670 (CO). ^{1}H-NMR (DMSO-d$_6$) δ 2.90–3.07 (m, 2H, CH$_2$), 3.63, 3.67 (2s, 6H, CO$_2$Me), 4.50–4.80 (m, 1H, CHCO), 5.90 (d, J = 8, 1H, CHNH), 7.03–7.70 (m, 6H, NH+ArH). MS (HR) *m/z* 292.1070 (100%), $C_{14}H_{16}N_2O_5$ requires 292.1059 (M^+). (Found: C, 57.95; H, 5.10; N, 9.74%. Requires: C, 57.53; H, 5.52; N, 9.59%.)

1 - *Methoxycarbonylamino* - 8 - *hydroxy* - 1,2,3,4,5 - *pentahydro* - 3 - *benzazepine* - 2 - *one* (**19c**). N-bismethoxycarbonylaminoacetyltyramine **18a** (2.0 g) in TFA (50 ml) was stirred for 72 h at room temp. The TFA was evaporated and the residue triturated with acetone to give 0.12 g of the product. The acetone soln was evaporated and chromatographed over florisil. The product was eluted with 5% MeOH in $CHCl_3$ to give an additional 0.80 g of product. Total yield 0.92 g (66%); m.p. >120° (dec.). IR (KBr) 3460 (OH), 3360, 3300 (NH), 1730, 1665 (CO), 1525 (NH). ^{1}H-NMR (DMSO-d$_6$) δ 2.80–3.60 (m, 4H, —CH$_2$CH$_2$—), 3.60 (s, 3H, NHCO$_2$Me), 5.77 (d, 1H, J = 8, CH—NH—), 6.63–7.43 (m, 5H, NH+ArH), 9.43 (s, 1H, OH). MS (HR) *m/z* 250.0901 (2.63%), $C_{12}H_{14}N_2O_4$ requires 250.0935.

1 - *Butoxycarbonylamino* - 8 - *hydroxy* - 1,2,3,4,5 - *pentahydro* - 3 - *benzazepine* - 2 - *one* (**19d**). α - Butoxycarbonylamino-α-methoxyacetyltyramine (4.0 g) in dichloroacetic acid was stirred at room temp for 48 h as described above (general procedure). The crude product obtained after the evaporation of the EtOAc (3.50 g) was chromatographed over florisil. Elution with 3% MeOH in $CHCl_3$ and trituration with dry ether gave 1.0 g (41%); m.p. 220 (dec.). IR ($CHCl_3$) 3400 (OH), 3320, 3270 (NH), 1740, 1680 (CO), 1510 (NH). ^{1}H-NMR (DMSO-d$_6$) δ 0.77–1.83 (m, 7H, C_3H_7), 2.47–3.80 (m, —CH$_2$—CH$_2$—), 4.03 (t, J = 5, 2H, OCH$_2$—), 5.40 (d, J = 8, 1H, —CH—NH), 6.90–7.70 (m, 5H, NH+ArH), 9.57 (s, 1H, OH). MS *m/z* 292.01 (1.24%), $C_{15}H_{20}N_2O_4$ requires 292.1423. (Found: C, 61.07; H, 6.82; N, 9.42. Requires: C, 61.63; H, 6.90; N, 9.58%.)

1 - *Methoxycarbonylamino* - 7,8 - *dimethoxy* - 1,2,3,4,5 - *pentahydro*-3-*benzazepinone*-2-*one* (**20**). The amide N(3,4-dimethoxyphenyl)ethylbismethoxycarbonylaminoacetamide (described above) 6.30 g) in TFA (40 ml) was stirred for 48 h. The TFA was evaporated and the residue triturated with dry ether to give 3.6 g (60%) product; m.p. 229–231°. IR ($CHCl_3$) 3430 (NH), 1720, 1680 (CO), 1510 (NH). ^{1}H-NMR ($CDCl_3$) δ 2.95–3.60 (m, 4H, CH$_2$—CH$_2$), 3.75 (s, 3H, OMe), 3.85 (s, 6H, OMe), 5.95 (d, 1H, J = 7), 6.40 (d, 1H, J = 7, CH), 6.65 (s, 1H, Ar), 6.90 (s, 1H, Ar). (Found: C, 56.43; H, 6.05; N, 9.12. $C_{14}H_{18}N_2O_5$ requires: C, 57.14; H, 6.16; N, 9.52%.)

1 - *Methoxycarbonylamino* - 3,4 - *dimethyl* - 1,2,3,4,5 - *pentahydro* - 3 - *benzazepine* - 2 - *one* (**21**). N - Methyl - N - (1 - phenyl - 2 - propyl)bismethoxycarbonylaminoacetamide (4.8 g) in MSA (100 ml) was treated for 72 h as described above (general procedure). The product obtained after the removal of the $CHCl_3$ (2.60 g, 70%) was a mixture of two isomers (5 : 3). Chromatography over florisil and elution with CH_2Cl_2–hexane (1 : 1) followed by trituration with dry ether gave one of the isomer; m.p. 122°. IR ($CHCl_3$) 3400 (NH), 1720, 1650 (CO), and 1705 (NH). ^{1}H-NMR ($CDCl_3$) δ 1.40 (d, J = 6, 3H, CH—Me), 2.67 (s, 3H, N—Me), 3.10–3.63 (m, 2H, CH$_2$), 3.80 (s, 3H, NHCO$_2$Me), 4.37–4.83 (m, 1H, CH—Me), 6.36 (d, J = 8, CH—NH), 6.50 (d, J = 8, NH), 7.00–7.30 (m, 4H, C_6H_4). MS (HR) *m/z* 262.1268, $C_{14}H_{18}N_2O_3$ requires 262.1317 (M^+). (Found: C, 63.69; H, 6.99; N, 10.54. Requires: C, 64.10; H, 6.92; N, 10.68%.)

The reaction of N-*phenylethylamides with aldehydes*

N-*Benzoyl*-1,2,3,4-*tetrahydroisoquinoline* (**27a**). A mixture of N-phenylethylbenzamide (1.12 g, 5 mmol), paraformaldehyde (0.17 g, 5.7 mmol) in H_2SO_4–AcOH (25%; 1v+3v) was stirred at room temp for 24 h and treated as described above (general procedure). The crude product obtained after the removal of the EtOAc was chromatographed over neutral alumina and eluted with CH_2Cl_2–hexane (1 : 1); yield 1.05 g (88%). IR ($CHCl_3$) 1640 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 2.80–3.18 (t, 2H, PhCH$_2$—CH$_2$), 3.58–4.12 (m, 2H, CH$_2$—CH$_2$—N), 4.85 (bs, Ph—CH$_2$—N), 7.21 (s, 4H, C_6H_4), 7.50 (s, 5H, Ph). This compound was identical with a sample prepared from tetrahydroisoquinoline and benzoyl chloride.

N-*Methoxycarbonyl*-1,2,3,4-*tetrahydroisoquinoline* (**27b**). A mixture of N-(2-phenylethyl)methylcarbamate (0.9 g, 5 mmol), in H_2SO_4–AcOH) (10 ml, 25%) was treated for 24 h as described above to give 0.907 g (93%) of an oil. IR ($CHCl_3$) 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 2.67–3.00 (t, 2H, CH$_2$CH$_2$N), 3.54–3.90 (t, 2H, CH$_2$—CH$_2$—N), 3.70 (s, 3H, CO$_2$Me), 4.63 (s, PhCH$_2$—N), 7.20 (s, 4H, C_6H_4). This compound was identical with a sample prepared from tetrahydroisoquinoline and methyl chloroformate.

N-*Ethoxycarbonyl*-1,2,3,4-*tetrahydroisoquinoline* (**27c**). This compound was obtained in 95% yield by reacting N-(2-phenylethyl)ethylcarbamate with paraformaldehyde as described above for the methoxycarbonyl derivative. IR ($CHCl_3$) 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 1.06–1.43 (t, 3H, CO$_2$CH$_2$—Me), 2.66–3.00 (t, 2H, CH$_2$—CH$_2$—N), 3.56–3.86 (t, 2H, CH$_2$—CH$_2$—N), 3.96–4.43 (q, 2H, CO$_2$CH$_2$—Me), 4.66 (s, 2H, C_6H_4CH$_2$—N), 7.23 (s, 4H, C_6H_4). This compound was identical with a sample prepared from tetrahydroisoquinoline and ethyl chloroformate.

N - *Methoxycarbonyl* - 1,2,3,4 - *tetrahydroisoquinoline* - 1 - *carboxylic acid* (**27d**). N-(2-phenylethyl)methylcarbamate (0.9 g, 5 mmol), glyoxylic acid (0.506 g, 5.5 mmol) in H_2SO_4–AcOH (10 ml, 25%) was treated for 48 h as described above (general procedure) to give 0.950 g (80%) of an oil. IR ($CHCl_3$) 3500–3000 (CO_2H) and 1740–1720 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 2.66–3.02 (t, 2H, CH$_2$—CH$_2$—N), 3.53–3.94 (t+s, 5H, CH$_2$CH$_2$—N, CO$_2$Me), 5.52 (d, 1H, J = 5, CH), 6.97–7.76 (m, 4H, C_6H_4). The dicyclohexyl amine salt melted at 158–159°. (Found: C, 69.38; H, 8.42; N, 6.68. $C_{24}H_{35}N_2O_4$ requires: C, 69.20; H, 8.71; N, 6.73%.)

The acid (0.6 g) was esterified in MeOH and in the presence of conc H_2SO_4 to give the methyl ester which was chromatographed over deactivated neutral alumina (10% MeOH) to give an oil (0.5 g, 78%). IR ($CHCl_3$) 1760 and 1700 cm^{-1} (CO). ^{1}H-NMR δ 2.77–3.10 (t, CH$_2$—CH$_2$—N), 3.73, 3.76, 3.70–4.16 (2s+t, 8H, NCO$_2$Me, CH$_2$—CH$_2$—N), 5.56 (bs, 1H, CH), 7.06–7.70 (m, 4H, C_6H_4). (Found: C, 62.45; H, 6.22; N, 5.48. $C_{13}H_{15}NO_4$ requires: C, 62.64; H, 6.07; N, 5.62%.)

Methyl N - *ethoxycarbonyl* - 1,2,3,4 - *tetrahydro* - *isoquinoline* - 1 - *carboxylate* (**27e**). This compound was prepared from N-(2-phenylethylethyl)carbamate and glyoxylic acid followed by the esterification of the isoquinolinecarbocylic acid as described above for the methoxycarbonyl derivative. The crude product was purified on a silica column to give an oil (84%). IR ($CHCl_3$) 1760 and 1700 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ 1.10–1.46 (t, 3H, CO$_2$CH$_2$Me), 2.76–3.06 (t, 2H, CH$_2$—CH$_2$—N), 3.73 (s, 3H, CO$_2$Me), 3.60–4.00 (t, 2H, CH$_2$—CH$_2$—N), 4.03–4.43 (q, 2H, CO$_2$CH$_2$Me), 5.60 (d, 1H, J = 4, CH), 7.10–7.66 (m, 4H, C_6H_4). (Found: C, 63.98; H, 5.24. $C_{14}H_{17}NO_4$ requires: C, 63.86; H, 6.51; N, 5.32%.)

REFERENCES

[1] For preliminary reports of this work see: D. Ben-Ishai, N. Peled and I. Satati, International Congress of Heterocyclic Chemistry, Tampa, Florida 115 (TI 545B) (1979); *Tetrahedron Lett.* **21**, 569 (1980).

[2a] D. Ben-Ishai, I. Satati and Z. Bernstein, *Tetrahedron* **34**, 467 (1978); [b] *Tetrahedron* **32**, 1571 (1976); [c] H. E. Zaugg, *Synthesis* 93, 187, 195 (1984), and refs cited therein.

[3] W. H. Whaley and T. R. Govindarachari, *Org. Reactions* **6**, 151 (1951).

[4] W. H. Kraft, *J. Am. Chem. Soc.* **70**, 3569 (1948).

[5] B. Belleau, *Can. J. Chem.* **35**, 651 (1967).

[6] A. Mondon and G. Hassenmeyer, *Chem. Ber.* **92**, 2552 (1959); **104**, 2960 (1971).

[7] V. Boekelheide, M. Muller, T. T. Grossmicle and M. Chanon, *J. Am. Chem. Soc.* **81**, 3955 (1959).

[8] B. E. Maryanoff, D. F. McComsey and B. A. Emsmiller, *J. Org. Chem.* **48**, 5062 (1983).

[9a] A. L. Davis, D. R. Smith and T. J. McCord, *J. Med. Chem.* **16**, 1043 (1973); [b] K. T. Potts and J. L. Marshall, *J. Org. Chem.* **41**, 129 (1976).

[10] W. N. Speckamp and H. Heimstra, *Tetrahedron* **41**, 4367 (1985).

[11] D. Ben-Ishai and S. Hirsch, *Tetrahedron Lett.* 958 (1983), Ref. 9.

[12] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* 734 (1976).

[13] E. Winterfeldt, *Chem. Ber.* **97**, 24 (1964).

[14] H. E. Zaugg and D. L. Arendsen, *J. Heterocyclic Chem.* **11**, 803 (1974).

[15] S. Danishefsky and E. Berman, *Tetrahedron Lett.* **21**, 4819 (1980).

[16] R. R. Wittekind and S. Lasaros, *J. Heterocyclic Chem.* **8**, 495 (1971).

[17] G. Deak, K. Gall, L. Harari and L. Sterk, *Synthesis* 393 (1975).

[18] F. W. Hoover, H. B. Stevenson and H. S. Rothrock, *J. Org. Chem.* **28**, 1825 (1963).

[19] Y. Watanabe, Y. Kamochi and T. Miyaraki, *Heterocycles* **16**, 609 (1981).

[20] O. O. Orazi and R. A. Corral, *J. Chem. Soc. Chem. Commun.* 470 (1976).