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INTRAMOLECULAR AMIDOALKYLATION OF AROMATICS II. SYNTHESIS OF CONFORMATIONALLY RESTRICTED BRIDGED PEPTIDES ANALOGUES OF Phg-Gly OR Gly-Phg.

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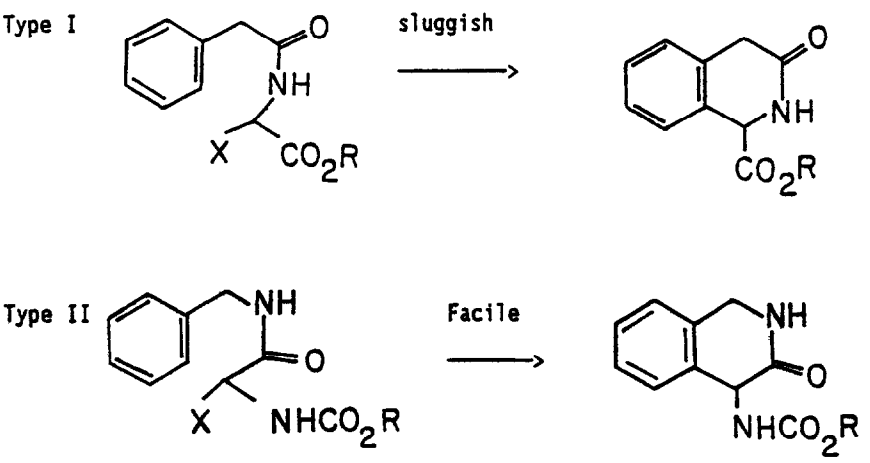
Abstract: Derivatives of Phg-α-MeO-GlyOH(3) and its isomer α-MeO-Gly-Phg(2) were prepared and their inter and intramolecular amidoalkylation reactions were studied. Derivatives of 2 underwent smooth cyclization to give 4-amino-3-isoquinolon-1-carboxylic acid derivatives (4, 8). The isomer 3, which reacted smoothly intermolecularly with toluene to give the open chain peptide 7, reacted sluggishly intramolecularly.

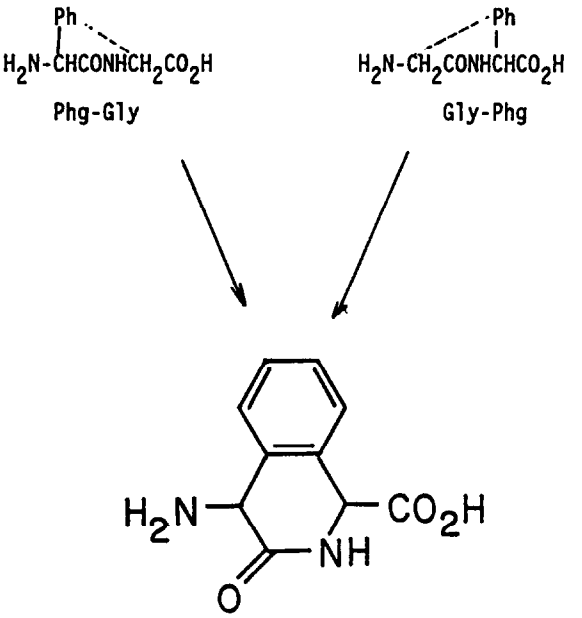
In the course of a study on the intra versus intermolecular amidoalkylation of aromatic compounds we encountered two types of lactamization reactions[1a]:



Type I lactamization which is the better known reaction[1b,2a-e] was found to be, in our case, a sluggish reaction which led to mixtures of polar products.

Type II lactamization which is the least known reaction[1b] was found to be a facile reaction and afforded the isoquinolone derivatives in good yields.[1a]

We have now extended type II cyclization and used it in the synthesis of conformationally restricted bridged peptides containing aromatic amino acids. The first peptide analogues we have synthesized are derivatives of Phg-Gly or Gly-Phg:



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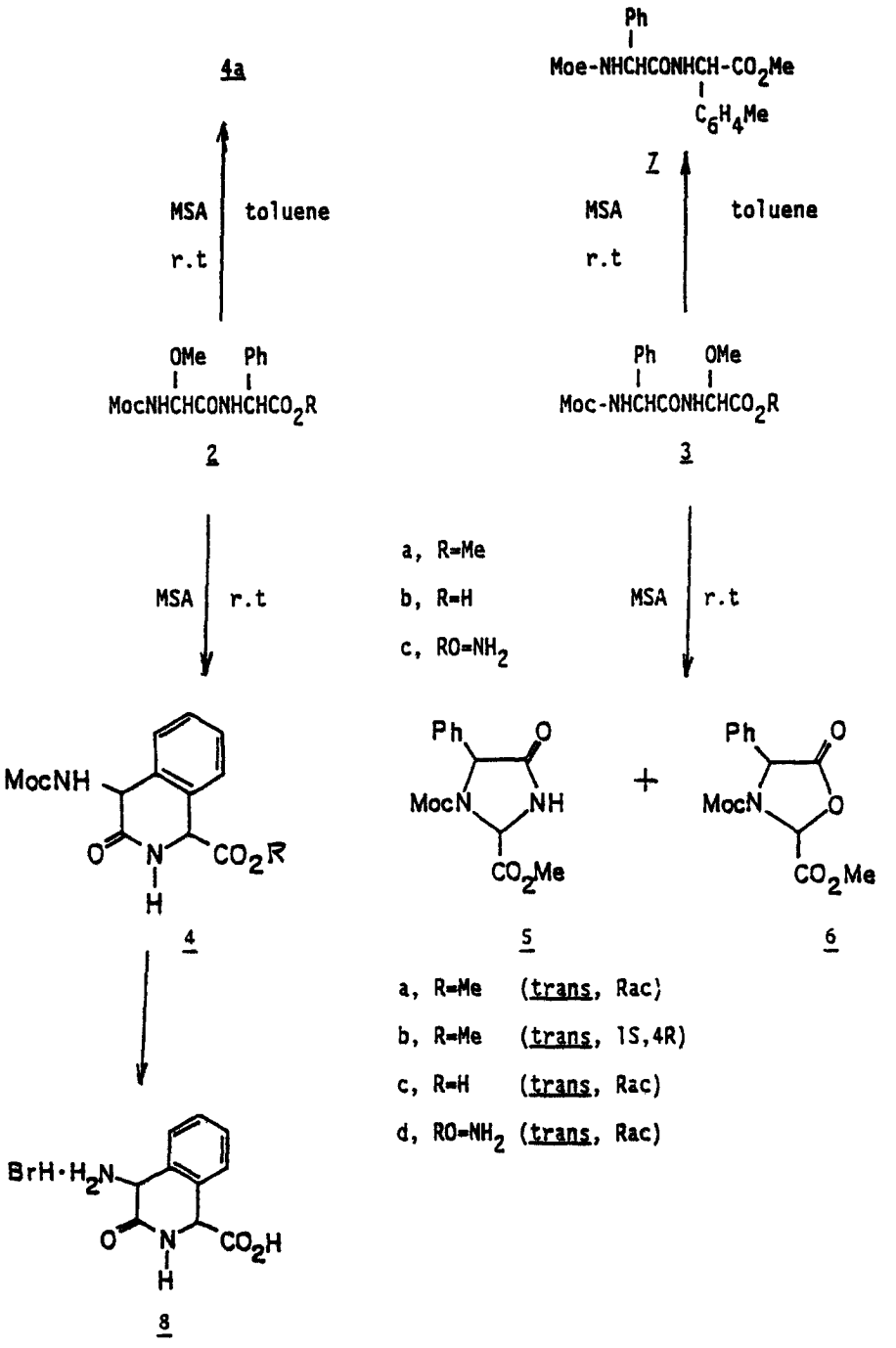
The 4-amino-3-isoquinolone-1-carboxylic acid (AIQC, 1) is a cyclic analogue of either Phg-Gly or Gly-Phg in which the side chain phenyl group of phenyl-glycine is connected to the α-carbon of glycine. It is a side chain bound to the peptide backbone analogue. We have synthesised two possible dipeptide precursors 2 and 3

in which we have substituted GlyOH for the electrophilic α-Meo-Gly-OH. The α-methoxy group is a good enough leaving group in strong acid solutions and enables to carry out intra as well as intermolecular amidoalkylations of an aromatic ring.

The two isomeric dipeptides 2 and 3 were found to behave differently in both the intra and the intermolecular amidoalkylation reaction. Reacting N-Moc-α-MeO-Gly-R,S-Phg-OMe (2a) in methanesulfonic acid, at room temperature overnight, afforded the expected 4-amino-isoquinolone-1-carboxylic acid derivative (AIQC, 4a) in 69% yield. This cyclization is of type II lactamization mentioned above. On the other end, under the same experimental conditions, the N-Moc-R,S-Phg-α-MeO-Gly-OMe (3a) did not afford any AIQC derivative (4a). The dipeptide 3a gave a mixture of products from which we have isolated, after chromatography, an oxazolidinone derivative 5 (13%) and an imidazolidinone derivartive 6 (15%). This results confirms our previous observation[1a] as to the sluggishness of type I lactamization reactions in the formation of six member rings. A more convincing difference in the behaviour of the two isomers 2 and 3 in amidoalkylation reactions was observed when we carried out the reactions in the presence of an external aromatic nucleophile such as toluene. The dipeptide 2 gave in methanesulfonic acid and in the presence of excess toluene only the cyclic AIQC derivative (4a). The dipeptide 3 reacted with the toluene in methanesulfonic acid to give only N-Moc-R.S-Phg-R,S-tolyl•Gly-OMe (7). This dipeptide is the product of an intermolecular alkylation of toluene. It was obtained, according to the NMR spectra of the crude, as a mixture of dipeptide isomers. No peaks of the cyclic AIQC derivative (4a) was observed in the spectra.

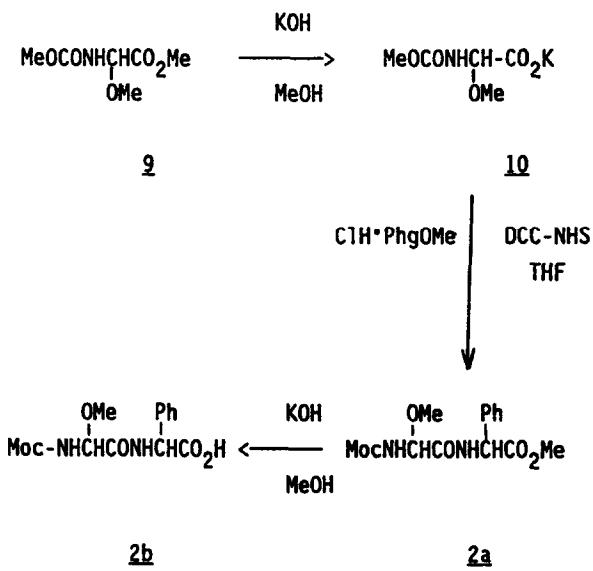
The different behaviour of compounds 2 and 3. In the intra and intramolecular amidoalkylations is most probably due to stereoelectronic effects. The overlap of the π system of the aromatic ring with the electrophilic acyliminum side chain, in the transition state for the intramolecular reaction, is much better for 2 than for 3.[1a] In the case of 3, the actal type of cyclization to give the imidazolidinone 5 and the oxazolidinone 6 is therefore favoured. The sluggishness of the intramolecular cyclization of compound 3 makes the reaction less interesting from the synthetic point of view and was not proceeded.


4a
MSA
toluene
r.t
OMe
Ph
MocNHCHCONHCHCO2R
2
Ph
Moe-NHCHCONHCH-CO2Me
C6H4Me
1
MSA
toluene
r.t
Ph
OMe
Moc-NHCHCONHCHCO2R
3
a, R=Me
b, R=H
c, RO=NH2
MSA
r.t
MSA
r.t
MocNH
CO2R
4
Ph
MocN
NH
CO2Me
5
+
Ph
MocN
O
CO2Me
6
a, R=Me (trans, Rac)
b, R=Me (trans, 1S,4R)
c, R=H (trans, Rac)
d, RO=NH2 (trans, Rac)
BrH·H2N
CO2H
8

Repeating the synthesis of 2 (R=Me) with S-phenylglycine, instead of the racemic acid, and subsequent cyclization in methanesulfonic acid led to the preparation of the optically active cyclic analogue (1S, 4R) of AIQC derivative 4a. An X-ray crystal structure analysis of racemic 4a showed it to be the trans isomer, the carbamate group at the 4 position of the isoquinolone ring is trans to the carbomethoxy group at the 1 position. In the solid state the carbamate group is equatorial while the carbomethoxy group is axial to the isoquinolone ring.

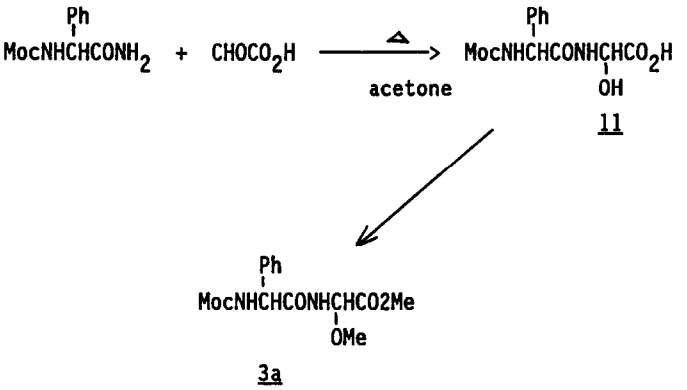
In addition to the synthesis of the methyl ester of the isoquinolone derivative 4a we have also prepared the N-moe-4-amino-3-isoquinolone-1-carboxylic acid (4c). The acid 4c was prepared by either the hydrolysis of the methyl ester 4a with KOH-MeOH at room temperature under nitrogen, or better by the cyclization, in methane-sulfonic acid of N-Moc-α-MeO-Gly-R.S-Phg-OH (2b). The Moc group was then removed with HBr-AcOH (10%) at 60°C for 3h. to give the hydrobromide of 4-amino-3-isoquinolone-1-carboxylic acid (AIQC, 8, 90%). For further identification the AIQC hydrobromide (8) was converted to N-Cbz-4-amino-3-isoquinolone-1-carboxylic acid.

N-Moc-α-Meo-Gly-R.S-Phg-OMe (2a), which is the precursor of the AIQC derivative 4, was prepared by the following procedure:



N-Moc-α-MeO-Gly-OMe[3] was hydrolyzed with one equivalent of KOH-MeOH at room temperature to give the potassium salt 10. The salt was used as such in the proceeding condensation with the hydrochloride of Phg-OMe to give the blocked dipeptide 2a as a mixture of two isomers (2 chiral centers). We used the potassium salt 10 in the condensation reaction because the corresponding free acid is very water soluble and was hard to isolate.

The isomeric N-Moc-R,S-Phg-α-MeO-Gly-OMe (3a) was prepared from N-Moc-R,S-Phg-NH_2 and glyoxylic acid:[4]



The intermediate adduct N-Moc-R,S-Phg-α-HO-Gly-OH (11), which was prepared by refluxing a mixture of the primary amide and glyoxylic acid in acetone overnight, was converted directly to the N-Moc-Phg-α-MeO-Gly-OMe (3a) on treatment with MeOH-HCl. It was obtained as a mixture of two isomers (2-chiral centers). We have not tried to separate the isomers of either 2a or 3a. In the course of the cyclization reactions one of the two chiral centers is anyway lost in the formation of the reactive acyliminium intermediate. A new second chiral center reforms on cyclization.

The structures assigned to the new compounds described above are based on their IR, NMR and high resolution mass spectra. In one case the stereochemistry was obtained by an X-ray crystal structure analysis.

This method of synthesising conformationally restricted cyclic peptides is being extended to the preparation of cyclic analogues of Phe-Gly and Gly-Phe.

Experimental

General. M.p's are uncorrected. The IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. NMR spectra were obtained on a Brucker 200 MHz. Mass spectra were obtained on a Varian Matt-711 double focusing instrument.

Potassium N-moc-α-methoxyglycinate (10). To a solution of Methyl N-moc-α-methoxyglycinate (9) (56.50g. 0.31 mole) in MeOH (100 ml) there was added a solution of KOH (85% 22.13g; 0.335 mole; in MeOH (200 ml). After stirring overnight the potassium salt was precipitated by the addition of anhydrous ether (300 ml). The salt was filtered off, washed twice with ether and dried. The yield of the none hygroscopic potassium salt was 56.08 g. (87.4%). The salt was used as such in the proceeding procedures. IR(KBr) 2600-2900 (OH, NH br) 1700 (CO), 1620 (CO) and 1540 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6):δ 6.99 (d, J=7 1H, NH)) 4.57 (d, J=7 1H, HN-CH), 3.41 (s, 3H, OMe) 3.13 (s, 3H, OMe).

Methyl N-moc-α-methoxyglycyl-R,S-phenylglycinate (2, R=Me). A mixture of R,S-phenyglycine methyl ester hydrochloride (10.9, 0.050 mole) and potassium N-moc-α-methoxyglycinate (11.05g. 0.055 mole) in THF (200 ml) was stirred at room temperature for 30 minutes. The mixture was then cooled to 0°C (ice + water) and N-hydroxysuccinimide (5.75g, 0.050 mole) and DCC (10.83g, 0.0525 mole) were added to the stirred slurry. Stirring was continued at room temperature overnight. Acetic acid (2 ml) was added to quench unreacted DCC, the urea was filtered and the THF evaporated. The residue was dissolved in $CHCl_3$ (150 ml) and the solution washed with aq. HCl (2x30 ml, 2%), aq. $NaHCO_3$ (40 ml, 7.5%) and H_2O (40 ml). It was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to give 14.56g. of crude product (94%). The product was purified by chromatography over silica (Merck 70-200 mesh, 200g.) and eluted with acetone-CH_2Cl_2 (1:20). The yield of the purified material was 10.68g. (69.0%) and it is according to the NMR a mixture of two isomers (2 chiral centers). IR($CHCl_3$): 3420 cm^{-1} (NH), 1740 (CO), 1690 (CO) and 1490 cm^{-1} (NH). NMR($CDCl_3$) δ: 7.54 (d, J=7.0, 1H, NHCO), 7.30 (s, SH ar.), 5.84 (d, J=9.0, $NHCO_2R$), 5.50 (d, J=7.6, CH-OMe, 5.29 (d, J=7.6, PhCH-NH-), 3.68 (s, CO_2Me), 3.62 (s, CO_2Me), 3.38 (s, OMe) 3.36 (s, OMe). MS(HR) m/z 310.1166 (M^+) calcd. for $C_{14}H_{18}N_2O_6$ 310.1167 (M^+).

Methyl N-moc-α-methoxyglycyl-S-phenylglycinate (2) R=Me). This compound was prepared exactly as described above for the preparation of the R,S-phenylglycine derivative. It was obtained, after chromatography, as a mixture of two isomers in 66% yield.

trans-Methyl N-moc-4-aminoisoquinolone-1-carboxylate (4a). Methyl-N-moc-α-methoxyglycyl-R.S-phenylglycinate (2, 6.0g. 0.01935 mole) was dissolved in methanesulfonic acid (90 ml) and the solution was stirred overnight at room temp. The solution was poured onto crushed ice and extracted with $CHCl_3$ (3x70 ml). The combined $CHCl_3$ extracts was washed with aqueous $NaHCO_3$ (20 ml of a 7.5% solution), H_2O and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 4.70g. (87%) of crude product which was crystallized from EtOAc; M.p. 163-165°C (69%). The NMR of the crude product did show the possible presence of a minor isomer in the reaction product. I.R.($CHCl_3$): 3420 (NH), 1740 (CO, ester) 1730 (CO, carbamate), 1690 (CO, amide) and 1510 cm^{-1} (NH). NMR($CHCl_3$):δ, 7.92 (d, J=5.1, NH-CO), 7.1-7.4 (m, ar. 4H), 5.87 (d, J=7.5, $NHCO_2R$), 5.46 (d, J=7.5, 1H, CH-N-CO) 5.10 (d, J=5.1, 1H, -CH-CO), 3.71 (s, 3H, CO_2Me) 3.65 (s, 3H, N-CO_2Me). MS (HR) m/z 278.0911 (M^+) $C_{13}H_{14}N_2O_5$: M^+ requires 278.0919. The base peak is (M^+-CO_2Me).

An X-ray crystal structure analysis showed the compound 4 to have the trans configuration.

The trans (1S, 4R) isomer (4a) was also prepared by the same procedure from 2a. The crude product was purified by chromatography to give the isoquinolone derivative in 77.3% yield, m.p. 78-82°C, $[\alpha]_D$ = +33.57 (2% in MeOH).

Equilibration of the trans isomer in refluxing methanol, in the presence of DBU, overnight did not show any difference.

N-Moc-α-methoxyglycyl-R,S-phenylglycine (2b). A solution of KOH (85%, 0.65g. 9.84 mmole) in MeOH (50 ml) was slowly added to a solution of methyl N-moc-α-methoxyglycyl d.l-phenylglycinate (2.17g. 7.0 mmole) in MeOH (30ml). The solution was stirred overnight at room temp. The MeOH was removed and the residue was dissolved in H_2O (120 ml) and extracted with CH_2Cl_2 (2x20 ml). The aqueous solution was acidified to pH 3 and extracted with EtOAc (3x75 ml). The combined extracts were dried over anhydrous $MgSO_4$, filtered and evaporated. The yield of the solid product was 1.48g. (71.5%). It was according to the NMR a mixture of two isomers (m.p. 181-184° dec) I.R.(KBr) 3600-2900 (OH) 3300 (NH) 1740 (CO),

1700 (CO, carbamate) 1660 (CO amide) 1530 (NH). NMR(DMSO-d_6): δ, 8.53 (d, J=7.0, 1H, NH amide), 7.94 (d, J=9.0, 1H, NH carbamate), 7.34 (s, 5H, ar), 5.33 (d.d, J=7.0, 1H, -CH-N) 5.15 (d,d, J=9.0, 1H, -N-CH-CO_2H), 3.56 (s, 3H, CO_2Me) 3.27+3.24 (s,s, 3H, OMe) M.S.(HR) m/z 220.0835 (M^+-MeOH-CO_2).

Trans-N-Moc-4-amino-1,4-dihydroisoquinolone-1-carboxylic acid (4c), racemate). The racemic acid described above (2b, 3.10g. 1.05 mmole) was dissolved in methanesulfonic acid (60 ml) and glacial acetic acid (7.0 ml). After stirring overnight at room temp. the solution was poured onto crushed ice and extracted with EtOAc (3x100 ml). The combined extract was washed with H_2O dried over anhydrous $MgSO_4$, filtered and evaporation. The residue was triturated with dry ether to give 1.27 (46%) of a white solid (m.p. dec). I.R.(KBr) 3700-2650 (OH, NH), 3390 (NH), 1740 (CO acid), 1720 (CO, carbamate), 1640 (CO amide), 1550 (NH). NMR(DMSO-d_6):δ, 8.52 (d, J=4.0, 1H, NH amide), 7.75 (d, J=9.0, 1H, NH carbamate). 7.50-7.00 (m, 5H, ar.+OH), 5.24 (d, J=9.0, 1H, CH-NHCO-) 5.05 (d, J=4.0, HN-CHCO) 3.62 (s, 3H, $HNCO_2$Me). M.S(HR) m/2 264.0767 (M^+) calcd. for $C_{12}H_{12}N_2O_5$:264.0746.

A sample of the crude acid was treated with CH_2N_2 to give a methyl ester which was identical with the trans methyl ester 4a according to the I.R. and NMR.

The acid 4c was also obtained by the hydrolysis of the methyl ester 4a with KOH in MeOH at room temp. under nitrogen. The yellowish product has the same I.R. and NMR spectra as the acid obtained by the cyclization of the acid 2c.

4-Amino-1,4-dihydroisoquinolone-1-carboxylic acid hydrobromide (8). N-Moc-4-amino-1,4-dihydroisoquino- lone-1-carboxylate (0.50g.) was dissolved in 10% HBr-AcOH (9 ml) and the solution heated to 70% for 3 hrs. The solution was cooled and evaporated under reduced pressure. The residue was triturated with ether and filtered to give 0.4g (90% yield) of a nonhydroscopic solid. I.R(KBr) 3600-2100 (OH, NH), 1730 (CO acid) 1680 (CO amide) and 1510 cm^{-1} (NH). NMR(DMSO-d_6):δ 9.17 (d, J=4.6, 1H, NH amide) 8.85 (s, br, 3H), 7.70-7.30 (m, 4-5H, ar) 5.21 (d, J=4.6, 1H, -CH-) 5.06 (s, br, H_3NCHCO).

The 4-aminoisoquinolone-1-carboxylic acid was further characterized by its conversion to:

N-Z-4-iso-1,4-dihydroquinolone-1-carboxylic acid. The above mentioned hydrobromide (0.38g) was carbobenzoxylated with benzyl chlorocarbonate (0.28g) in aq. $NaHCO_3$. The crude product was triturated with dry ether to give the Z derivative in 54% yield (m.p. 188-190°C dec). I.R(KBr) 3600-3100 (OH), 3220 (NH),

1720 (CO) 1700 (CO) and 1540 cm^{-1} (NH). NMR(DMSO-d_6) δ 8.55 (d, J=3.8, 1H amide) 7.95 (d, J=9.0, 1H, NH-carbamate) 7.70-7.20 m(9H, ar.) 5.27 (d, J=9.0, 1H, CH-NHCO) 5.13 (s, 2H, $PhCH_2$), 5.06 (d, J=3.8, CH-CO_2H) MS(HR) m/z=340.1044 (M^+) calcd. for $C_{18}H_{16}N_2O_5$ 340.1059,

N-Moc-4-amino-1,4-dihydroisoquinolone-1-carboxamide. The methyl ester 4a was stirred for 48 hr in a MeOH-NH_3 solution (15%). Evaporation of the excess ammonia and the methanol gave a solid. It was triturated with CH_2Cl_2 to give the expected product in 74% yield; m.p. 216-219 dec I.R(KBr):341-3200 (NH), 1740, 1690, 1670 (CO) and 1540 cm^{-1} (NH) NMR(DMSO-d_6):δ 8.37 (d, J=4.6, 1H, ring NH), 7.62 (d, J=9.3, 1H, NH carbamate), 7.82+7.40, 2H, NH_2, 7.40-7.20 (m, 4H, ar.), 5.48 (d, J=9.3, -CH-NHCO) 4.90 (d, J=4.6, 1H, -N-CH-CO_2NH_2) and 3.60 ppm (s, 3H, $HNCO_2Me$). MS(HR) m/z=219.0758 (M^+-$CONH_2$). Attempts to synthesis the isoquinolone carboxamide der. by the cyclization of the open chain dipeptide amide (2, OR=NH_2) did not lead to the expected product.

Methy N-moc-R,S-phenylglycine-α-methoxyglycinate (3, R=Me). A mixture of N-moc-phenylglycineamide (3.86. 18.6 mmole) and glyoxylic acid monohydrate (3.41g, 37.1 mmole) in acetone (120 ml) was refluxed for 40 hr. The acetone was evaporated and the residue (11) was dissolved in methanol (120 ml). To the cooled (ice+H_2O) solution there was added dropwise thionyl chloride (2.7 ml). After stirring overnight the solution was neutralized with solid $NaHCO_3$ and the methanol evaporated. Water (75 ml) was added and the product extracted with EtOAc (3x100 ml), washed with water and dried over anhydrous $MgSO_4$. Evaporation of the EtOAc solution gave a crude product which was chromatographed over silica (100g. 70-230 mesh) and eluted with acetone-CH_2Cl_2. The first fraction that came out of the column was methyl moc-phenylglycinate (1.0g. 24%) followed by the desired product as a mixture of two isomers (1.0g. 35%, m.p. 92-101). IR($CHCl_3$): 3420 (NH), 1750 (CO ester), 1730 (CO carbamate) 1700 (CO amide) and 1510 cm^{-1} (NH). NMR($CDCl_3$)δ: 7.50-7.20 (m, 5H, ar) 7.05-6.95 (d.d, 1H, NH amide), 6.02 (d, J=6.0, 1H, NH carbamate), 5.50 (d.d, 1H, CH-OMe), 5.31 (d.d, 1H, CH-$NHCO_2Me$), 3.67+3.63 (s,s, 3H, CO_2Me) 3.59 (s, 3H, $NHCO_2Me$), 3.41+3.18 (s,s, 3H, OMe) MS(LR) 310.2 (M^+).

Methyl N-moc-R,S-phenylglycyl-α-tolylglycinate (7). A mixture of N-moc-R,S-phenylglycyl-α-methoxyglycinate (0.53g. 1.71 mmole), toluene (0.63g. 6.84 mmole) in methane-sulfonic acid, were stirred overnight at room temp. The reaction

mixture was poured onto crushed ice and extracted with EtOAc (3x50 ml). The combined EtOAc extracts were washed with H_2O (3x20 ml) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave methyl N-moc-phenylglycyl-α-tolylglycinate (0.61, 96% yield) as a mixture of isomers. The crude material was chromatographed over silica (12g, 70-130 mash) and eluted with acetone-CH_2Cl_2 to give 0.48g (76%) of an amorphous solid. IR($CHCl_3$): 3400 (NH), 1730 (CO, ester) 1710 (CO, carbamate) 1680 (CO, amide) and 1500 cm^{-1} (NH). NMR($CDCl_3$):δ, 7.50-6.80 (m, 10H, ar. +NH), 6.05 (s, br, NH), 5.67 (d.d, J=4.6, 1H), 5.70-5.30 (m, 1H, NHCH-Ph), 3.63 (s, CO_2Me) 3.60 (s, CO_2Me), 3.56 (s, $HNCO_2$Me), 2.42-2.13 (4s, 3H, CH_3-Ar); M.S(H.R) m/z=370, 1551. Calcd. for $C_{20}H_{22}N_2O_5$ 370.1529.

Cyclization of Methyl-N-moc-R,S-phenylglycyl-α-methoxyglycinate (3, R=Me). Compound 7 (1.0g) was dissolved in methanesulfonic acid (20 ml) and the solution was stirred overnight. The reaction mixture was poured onto crushed ice and extracted with EtOAc (3x75 ml). The combined EtOAc solution was washed with H_2O (3x20 ml) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 0.70g. of crude product which showed a few spots on tlc. The NMR of the crude material did not show the presence of compound 4 in the mixture. Chromatography on silica and elution with acetone-CH_2Cl_2 gave a lactone (5) and a lactam 6.

Methyl N-moc-5-phenyloxazolidinone-5-imidazolidinone-2-carboxylate (5). Compound 5 was eluted with acetone-CH_2Cl_2 (1:20) to give an oily product in 13% yield: I.R($CHCl_3$:δ 1820 (CO lactone) 1760 (CO, ester), 1720 (CO, carbamate). NMR ($CDCl_3$):δ 7.5-7.3 (m, 5H, ar), 6.02 (s, 1H, -HCH-CO), 5.30 (s, 1H-CH-Ph), 3.82 (s-3H, CO_2Me), 3.72 (s, 3H, $HNCO_2$Me) M.S(HR) m/z=279.0726. Calcd. for $C_{13}H_{14}N_2O_5$ 279.0743.

5-Methyl-5-phenyl N-moc-4-imidazolidinone-2-carboxylate acid (6). The lactone was followed on chromatography by a second compound (6, 15%) I.R($CHCl_3$): 3320 (NH), 1760 (CO-ester) and 1720 cm^{-1} (CO, carbamate). NMR($CDCl_3$)δ: 8.00 (brS, 1H, NH), 7.60-7.20 (m, 5H, ar), 5.50 (s, 1H, N-CH-N), 5.10 (s, -CH-Ph), 3.70 (s, 3H, CO_2Me), 3.61 (s,3H,$HNCO_2$Me). MS(HR) m/z=278.0910. Calcd. for $C_{13}H_{14}N_2O_5$: 278.0902.

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