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Amide Bond Replacements : Incorporation of a 2,5,5-Trisubstituted Imidazoline into Dipeptides and into a CCK-4 Derivative.

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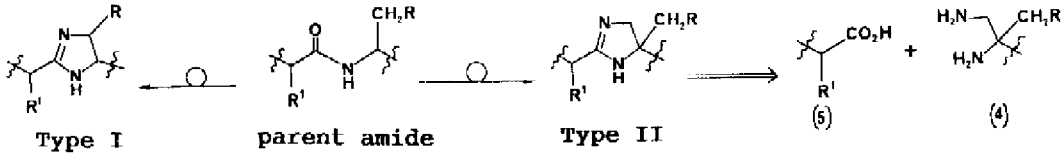
Key words : amide replacements; peptide analogues; cholecystokinin; pentagastrin; imidazoline.

Abstract : *Synthetic methodology for the introduction of a 2,5,5-trisubstituted imidazoline ring as an amide replacement into dipeptide derivatives of Phe, Trp, Lys(N^{ε}-CBZ) and Nle is described. This replacement is also incorporated into the Trp-Nle bond of the tetrapeptide CCK-4 derivative Trp-Nle-Asp-Phe-NH_2 and the pentagastrin derivative Gly-Trp-Nle-Asp-Phe-NH_2.*

Replacing the amide bond (CONH) of biologically active peptides with a variety of groups including NHCO, $CH(OH)CH_2$, CH_2NH, $COCH_2$, HC=CH and COO in an attempt to design agonists/antagonists for peptide receptors or proteolytic enzyme inhibitors has attracted considerable interest.[1] This has led to the synthesis and biological evaluation of peptide derivatives possessing new types of amide replacements.[2]

The first use of an imidazoline ring as an amide alternative was reported by Jones and Ward[3] who incorporated replacements of Type I (Scheme 1) into enkephalin derivatives. In compounds of Type I the orientation of the amino acid side chain is sterically constrained by the 5-membered ring compared to that of the CH_2R side chain of the parent peptide. The purpose of the present study was to prepare compounds of Type II which could mimic the parent peptide more closely.

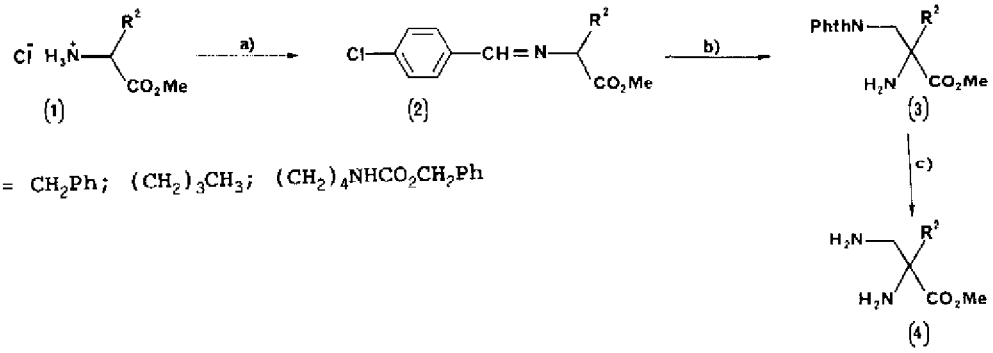


Scheme 1

The synthesis of Type II compounds is achieved by preparing a 1,2-diamine (4) followed by coupling to an activated derivative of the carboxylic acid (5) (Scheme 1). The diamine (4) is prepared from an amino ester (1) by conversion into the Schiff base (2), alkylation[4] with N-

bromomethylphthalimide and deprotection with aqueous acid followed by hydrazine (Scheme 2). The carboxylic acid (5) is activated by conversion into an S-methylthioimidate (Scheme 3) using the method of Jones and Ward[3] prior to coupling with the diamine (4).

The scope of this methodology is illustrated by the preparation of racemic diastereoisomeric derivatives of the protected dipeptides Phe-Phe (7), Trp-Phe (8), Lys(N^{ϵ}-CBZ)-Lys(N^{ϵ}-CBZ) (9) and Trp-Nle (10).[5]

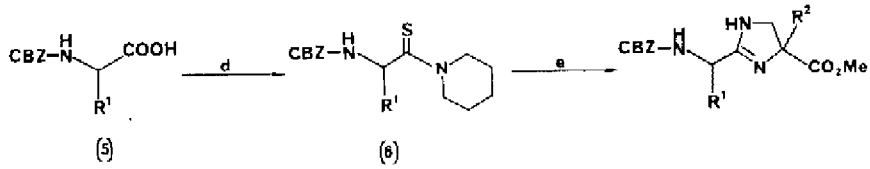


(1) (2) (3) (4)

R^2 = CH_2Ph; $(CH_2)_3CH_3$; $(CH_2)_4NHCO_2CH_2Ph$

Reagents : a) p-chlorobenzaldehyde, $MgSO_4$, Et_3N, CH_2Cl_2; b)i. $LiN(SiMe_3)_2$, THF;ii. N-bromomethylphthalimide; iii. aq-HCl; iv. $NaHCO_3$;
c) $N_2H_4.H_2O$, MeOH.

Scheme 2



(5) (6)

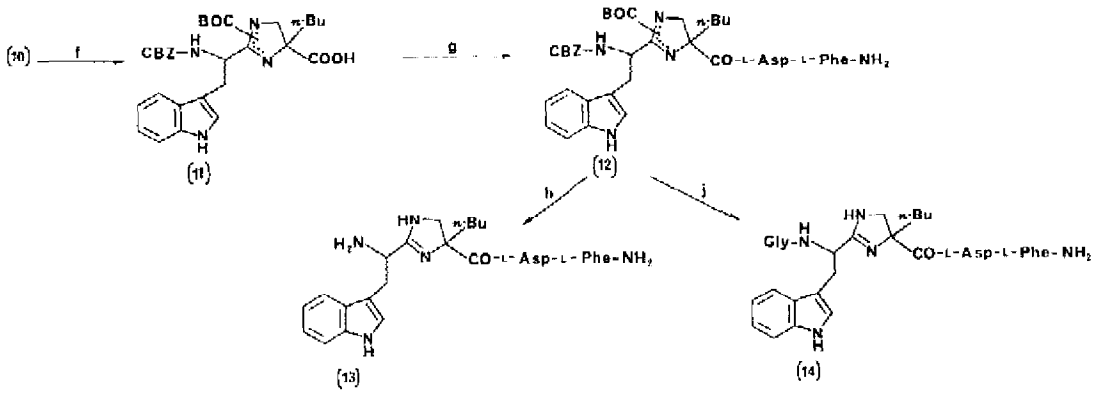
	R^1	R^2	% Yield
(7)	$PhCH_2$	$PhCH_2$	87
(8)	Indole-3-CH_2	$PhCH_2$	77
(9)	CBZ-NH-$(CH_2)_4$	CBZ-NH-$(CH_2)_4$	42
(10)	Indole-3-CH_2	$CH_3(CH_2)_3$	91

Reagents : d) i. pentafluorophenol, N,N-dicyclohexylcarbodiimide, CH_2Cl_2; ii. piperidine; iii. Lawesson's reagent, toluene; e) i. MeI; ii. diamine (4), MeOH.

Scheme 3

In the above examples both the carboxyl and amino termini of the modified dipeptide are protected. In order to develop the synthetic utility it was decided to elaborate one of the dipeptides into larger peptides by deprotection followed by coupling to other amino acids. The C-terminal tetrapeptide derivative of cholecystokinin CCK (30-33), Trp-Nle-Asp-Phe-NH_2,[6] and a pentagastrin derivative, Gly-Trp-Nle-Asp-Phe-NH_2 were selected for this purpose because of the considerable current interest in the biological activity of mimetics of these peptides.[7]

Protection of the imidazoline moiety of (10) with a t-butoxycarbonyl group followed by ester hydrolysis gave the carboxylic acid (11) which was coupled with L-Asp-L-Phe-NH_2 using the active ester method to give the tetrapeptide derivative (12) (Scheme 4). Removal of the protecting groups gave the CCK analogue (13) as a mixture of four diastereoisomers. The amino terminus was coupled to Boc-Gly-OPfp which gave the desired pentagastrin analogue (14).



Reagents : f) i. $(Boc)_2O$, $NaHCO_3$, H_2O-THF; ii. LiOH, H_2O-THF; g) i. pentafluorophenol, EtOAc, dicyclohexylcarbodiimide; ii. L-Asp-L-Phe-NH_2, Et_3N, DMF; h) i. H_2-Pd, MeOH; ii. CF_3COOH, anisole; j) i. H_2,$Pd(OH)_2$-C; ii. $BocHNCH_2CO-OC_6F_5$, Et_3N, EtOAc; iii. CF_3COOH, anisole.

Scheme 4

To our knowledge this is the first example of an amide replacement in a peptide using an imidazoline where the amino acid side chains are retained. The biological activity of these novel CCK analogues is under investigation.

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5. Selected data for key compounds are : compound (**7**) NMR δ (300MHz, CD_3OD) 7.32-7.13 (15H, m, 3xPh), 5.03 (2H, m, $PhC\underline{H}_2O$), 4.54-4.49 (1H, m, NCHC=N), 3.93-3.87 (1H, m, one of CH_2N=C), 3.73-3.59 (4H, m, OCH_3 and one of CH_2N=C), 3.13-2.80 (4H, m, $2xC\underline{H}_2Ph$); MS (m/e)(CI) 472 (M^++1, 5%), 91 (100). Compound (**8**) NMR δ (300 MHz, CD_3OD) 7.65-7.05 (15H, m, Ar-H), 5.10 (2H, m, $PhC\underline{H}_2O$), 4.61 (1H, m, NCHC=N), 3.90 (1H, m, one of CH_2N=C), 3.72 (s) and 3.71 (s) together are (3H, CO_2CH_3), 3.65 (1H, m, one of CH_2N=C), 3.25-2.85 (4H, m, $2xArC\underline{H}_2$); MS (CI) (found M^++H, 511.2345. $C_{30}H_{31}N_4O_4$ Requires M^++H, 511.2345). Compound (**9**) NMR δ (300MHz, CH_3OD) 7.40-7.25 (15H, m, Ar-H), 5.08 (s) and 5.06 (s) together are (6H, $3xC\underline{H}_2Ph$), 4.25 (1H, m, NCHC=N), 3.92 (1H, m, one of CH_2N=C), 3.70 (s) and 3.69 (s) together are (3H, CO_2CH_3), 3.50 (1H, m, one of CH_2N=C), 3.10 (4H, m, 2 x $C\underline{H}_2NHCBZ$), 1.90-1.15 (12H, m, $6xCH_2$); MS (FAB) 702.4 (38%). Compound (**10**) NMR δ (300MHz, d_6-DMSO) 10.86 (1H, br s, ind 1-H), 7.60-7.45 (2H, m, ind 4-H and 7-H), 7.40-7.2 (5H, m, Ph), 7.16 (1H, m, ind 2-H), 7.07 (1H, m, ind 6-H), 6.99 (1H, m, ind 5-H), 4.98 (2H, s, $PhC\underline{H}_2O$), 4.55 (1H, m, CHC=N), 3.89 (1H, m, one of CH_2N=C), 3.69 (s) and 3.66 (s) together are (3H, CO_2CH_3), 3.52 (1H, m, one of CH_2N=C), 3.3-3.0 (2H, m, $C\underline{H}_2$-ind), 1.7-1.45 (2H, m), 1.3-0.95 (4H, m), 0.85 (3H, m); MS (CI) found M^++H, 477.2502. $C_{27}H_{33}N_4O_4$ Requires M^++H, 477.2502).

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