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AMIDE BOND ISOSTERES: IMIDAZOLINES IN PSEUDOPEPTIDE CHEMISTRY

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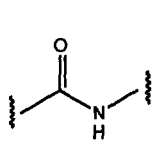
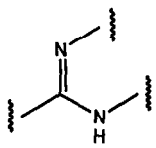
Summary: The 2-imidazoline ring has been incorporated as an amide bond replacement into pseudodipeptides, a pseudotripeptide, and pseudopentapeptide enkephalin analogues.

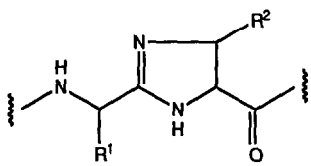
The isosteric replacement of crucial amide bonds in biologically active peptides is a recognised strategy in programmes aimed at either the inhibition of proteolytic enzymes or the development of agonists and antagonists at peptide receptors.[1] Recognising the relationship between the amide (1) and amidine (2) functional groups,[2] and as an extension of our involvement with 2-imidazolines (4,5-dihydroimidazoles),[3] we have developed the 2-imidazoline moiety as an amide bond replacement. In this Letter we report the preparation of 2-(1-aminoalkyl)-4(5)carboxy-2-imidazoline derivatives (3) as pseudodipeptides, and the incorporation of segment (3) into a potential inhibitor of angiotensin converting enzyme (ACE) and into analogues of the opioid pentapeptide, leucine enkephalin (4). We thus replace the amide bond with a basic heterocycle likely to be stable to proteolytic degradation.[4]



(1)



(2)

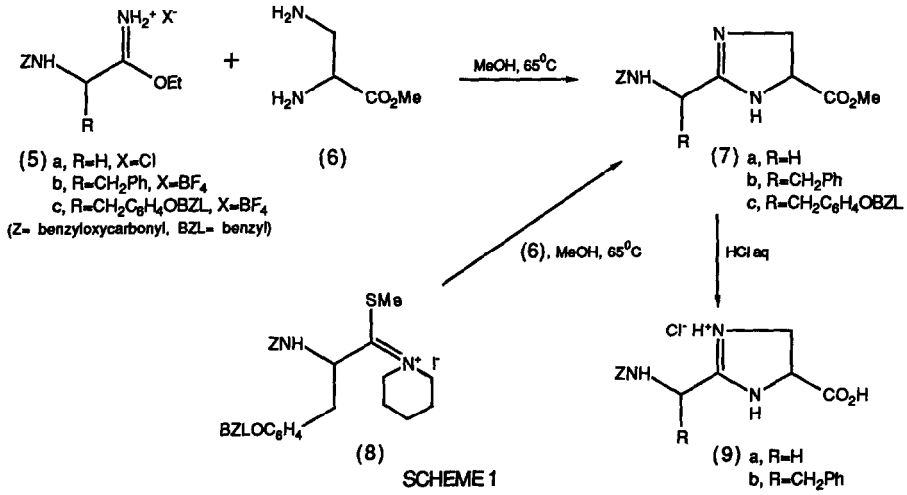


(3)

H-Tyr[1](H)-Gly[2]-Gly[3]-Phe[4]-Leu[5]-OH

(4)

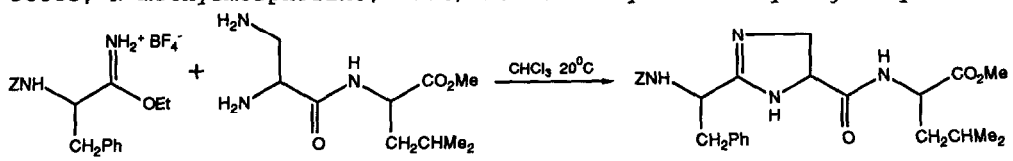
The first strategy was to prepare pseudodipeptides (7) that could be separately coupled at N and/or C termini to appropriate peptides or aminoacids, the heterocycle being assembled from an α,β-diaminoacid derivative and a protected α-aminoimidate (Scheme 1). Thus L-2,3-diaminopropionic acid hydrobromide, prepared from L-asparagine,[5] was converted into the methyl ester (6) (MeOH, HCl; then NH_3-$CHCl_3$; 47%) and treated in MeOH at reflux with the imidate salt (5a) derived from aminoacetonitrile hydrochloride[6] to produce the protected pseudodipeptide imidazoline (7a) (66%).[7] Likewise when the imidate tetrafluoroborate (5b) was prepared from N-benzyloxycarbonyl-L-phenylalanine methyl ester *via* the amide (NH_3-MeOH; 64%) and O-alkylation ($Et_3O^+BF_4^-$; 96%),[8]



SCHEME 1

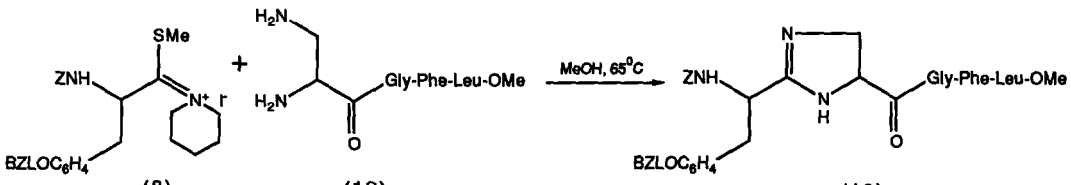
and was condensed under the same conditions with diaminoester (6) the imidazoline (7b) was isolated (67%).[9] The corresponding imidate salt (5c) obtained from O-benzyl-N-benzyloxycarbonyl-L-tyrosine methyl ester was unstable towards the conditions of imidazoline formation; instead, the S-methyl thioimidate salt (8) was prepared from O-benzyl-N-benzyloxycarbonyl-L-tyrosine via the piperidine amide [Lawesson's reagent (LR), piperidine; 80%] and thioamide (LR; 64%) with S-methylation (MeI).[6] Reaction of the salt (8) (without purification) with (6) (MeOH, reflux) afforded the pseudodipeptide (7c) (66%).[9] Imidazolines (7a-c) may be considered as masked Gly-Gly, Phe-Gly, and Tyr-Gly analogues, respectively. With the access to pseudodipeptides now secure, the C-termini were unmasked in two cases (5M HCl aq.) to produce the imidazoline acid hydrochlorides (9a) (87%) and (9b) (90%). We have not to date succeeded in coupling aminoacids or peptides to these acids,[10] so that whilst the unit (3) can be successfully prepared, it cannot yet be incorporated intact into longer pseudopeptides.

In a second strategy we generate the imidazoline moiety as the last stage of the synthesis, from a peptide imidate and a diaminopeptide. As a first simple example of this approach we synthesized the imidazoline (11) as a mimic of known tripeptide inhibitors of ACE,[11] i.e. as a potential antihypertensive agent. The phenylalanine imidate salt (5b) was condensed ($CHCl_3$, 20°C) with a diaminodipeptide (10), prepared by a mixed anhydride coupling of L-2,3-bis(benzyloxycarbylamino)propionic acid [available from L-2,3-diamino-propionic acid ($PhCH_2OCOCl$, NaOH aq.; 52%)] with L-leucine methyl ester (Bu^tOCOCl, N-methylmorpholine; 77%) followed by acidic hydrogenolysis and



basification (H_2-Pd, MeOH, HCl; then NH_3-$CHCl_3$; 73%), to yield (11) as a 1:1 mixture of two diastereoisomers epimeric at the 'phenylalanine' α-carbon.[9]

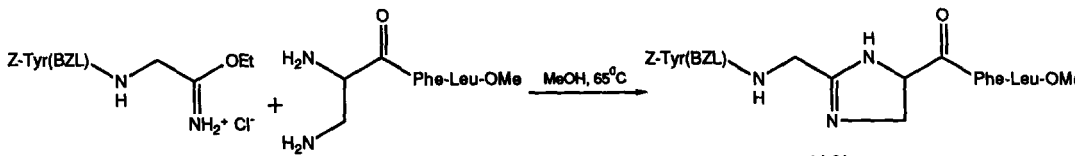
To construct a pseudoenkephalin containing the 2-imidazoline unit as a replacement of the 1,2-amide bond, the site of cleavage by aminopeptidase,[12] the thioimidate salt (8) and the tetrapeptide (12) were required. The latter was assembled by coupling of N-benzyloxycarbonylglycine with L-phenylalanine 4-nitrophenyl ester (DCC) and treatment of the dipeptide with L-leucine methyl ester to form the protected tripeptide Z-Gly-Phe-Leu-OMe (77% overall);[13] acidic hydrogenolysis (86%) and mixed anhydride coupling with L-2,3-bis(benzyloxycarbonylamino)propionic acid (83%) afforded a masked tetrapeptide that was converted into (12) by acidic hydrogenolysis and basification (68%). Condensation of (12) with the thioimidate salt (8) (MeOH, reflux) gave the [1,2]pseudoenkephalin derivative (13) (40%).[9]



(8) (12) (13)

(Z= benzyloxycarbonyl, BZL= benzyl)

Using the same approach, a [2,3]pseudoenkephalin was also prepared. The imidate component (14) was accessed from O-benzyl-N-benzyloxycarbonyl-L-tyrosine 4-nitrophenyl ester by reaction with aminoacetonitrile (66%) and Pinner reaction of the dipeptide nitrile (EtOH, HCl; 90%). The required diaminotripeptide (15) was assembled *via* the coupling of N-benzyloxycarbonyl-L-phenylalanine with L-leucine methyl ester (mixed anhydride; 85%), acidic hydrogenolysis (89%), a further mixed anhydride coupling with L-2,3-bis(benzyloxycarbonylamino)-propionic acid (98%), and liberation of the N-terminus by acidic hydrogenolysis-basification (74%). Tripeptide (15) was condensed with the imidate salt (14) (MeOH, reflux) to generate the [2,3]pseudoenkephalin derivative (16) as a single diastereoisomer (55%).

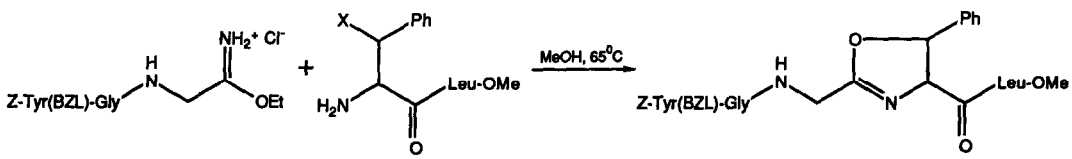


(14) (15) (16)

(Z= benzyloxycarbonyl, BZL= benzyl)

Our remaining target in the enkephalin group contained an imidazoline replacement at the 3,4-amide bond, the site of cleavage by enkephalinase.[12] Thus N-tritylglycine cyanomethyl ester was coupled with aminoacetonitrile (51%) with subsequent detritylation (AcOH aq.; 74%).[14] Reaction with O-benzyl-N-benzyloxycarbonyl-L-tyrosine 4-nitrophenyl ester (77%) and ethanolysis of the nitrile (EtOH, HCl; 30%) led to the required tripeptide imidate salt (17). Unfortunately we have to date been unable to prepare the 2,3-diamino-3-phenylpropionic acid needed to construct the diaminodipeptide

component (18a).[15] Instead we have synthesized an oxazoline [3,4]pseudoenkephalin employing our strategy. The dipeptide representing residues 4 and 5 was now (18b), available as a mixture of diastereoisomers from DL-threo-3-phenylserine after bis(benzyloxycarbonylation) ($PhCH_2OCOCl$, NaOH aq.; 71%), mixed anhydride coupling to L-leucine methyl ester (51%) and acidic hydrogenolysis-basification (89%). Condensation of (18b) with the imidate salt (17) (MeOH, reflux) indeed gave the [3,4]pseudoenkephalin derivative (19) (55%) as a 1:1 mixture, inseparable by column chromatography, of the two diastereoisomers (4S,5R) and (4R,5S) at the 2-oxazoline moiety (i.e. Ph and CO trans).



(17) (Z= benzyloxycarbonyl, BZL= benzyl)

(18) a, X=NH_2 b, X=OH

(19)

The pseudopeptides prepared herein are undergoing biological evaluation.

We thank G.D. Searle and SERC for a CASE studentship (G.J.W.).

References and Notes

1. See for example. A.F Spatola, in 'Chemistry and Biochemistry of Amino acids, Peptides and Proteins', ed. B Weinstein, Marcel Dekker, New York, 1983, Vol.7, p.308.
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3. M.W. Anderson, R C.F. Jones, and J. Saunders, J.Chem.Soc., Perkin Trans 1, 1986, 205, 1995, and refs. therein.
4. Preliminary molecular modelling studies indicate acceptable conformational overlap between fragment (3) and comparable dipeptides
5. By a modification of the method of J. Rudinger, K. Podvuska, and M Zaoral, Collect Czech Chem.Commun., 1960, 25, 2022.
6 K Clausen, M. Thorsen, and S -O Lawesson, J.Chem Soc., Perkin Trans 1, 1984, 785.
7. All new compounds gave spectra (IR,NMR,MS) consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement; purity was also assessed by t.l c examination
8 J S. Fruton and M. Bergmann, J.Biol.Chem., 1942, 145, 253; W. Ried and E Schmidt, Justus Liebigs Ann Chem., 1966, 695, 217.
9. Imidazoline pseudopeptides substituted at the carbon atom attached to C-2 of the heterocycle were obtained as inseparable mixtures of diastereoisomers epimeric at this centre. Proton exchange at this position is precedented in our own work (ref.3), see also K Yonetani, Y Hirotsu, and T. Shiba, Bull.Chem Soc Japan, 1975, 48, 3302.
10. Mixed anhydride, azide, DCC, and 4-nitrophenyl ester procedures were attempted. For a related finding with 2-thiazolines, see K Inami and T Shiba, Tetrahedron Lett., 1984, 25, 2009. The N-terminus of (7a) was selectively deprotected (H_2-Pd, MeOH, HCl, or HBr-HOAc).
11. E W Petrillo and M A Ondetti, Med Res Reviews, 1982, 2, 1
12 T.W. Smith and S Wilkinson, in 'Chemical Regulation of Biological Mechanisms', eds. A.M Creighton and S Turner, Royal Society of Chemistry, London, 1981, p.230
13. Cf. C S Yang, K. Blaha, and J Rudinger, Collect Czech.Chem.Commun , 1964, 29, 2633.
14 K Kawashiro, H Yoshida, and S. Morimoto, Chem Lett , 1974, 1.
15 Attempted substitution of oxygen in 3-phenylserine led either to failure or to β-elimination, neither have we been able to reduce the benzyl enamine prepared from 2-benzyloxycarbonylamino-3-oxo-3-phenylpropionic acid

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