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RETROINVERSO ENDOTHIONOPEPTIDES

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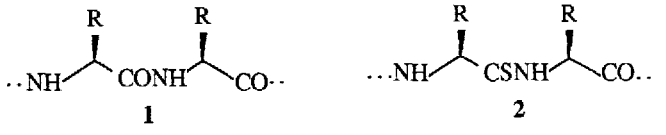
Summary; A new family of peptide surrogates,the retroinverso endothionopeptides, are described. Procedures for synthesis of di- and tripeptide variants have been developed

The search for surrogates for amide bonds in peptides has produced a range of new structural types designed to mimic the natural functional group[1]. We, and others, were earlier concerned with replacing the amide of the natural structural types (1) by endothiono variants (2)[2] designed to be isosteric and isopolar 'peptoids'.

Figure 1

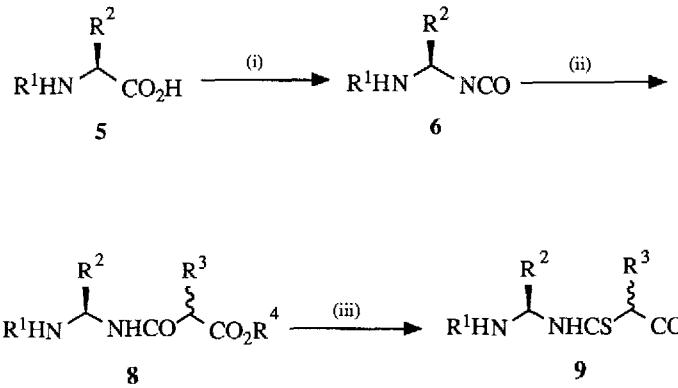


We now wish to report an extension of these studies in which the concept of retro-inverso peptides (3)[3] is taken further, and a new family of peptide surrogates, the retro-inverso endothionopeptides (4) is introduced. The synthetic strategy for preparation of the retro-thioamide peptides involved preparation of a retro-inverso pseudodipeptide, followed by specific endothionation. The resultant pseudodipeptide can then be elaborated from both the amino and carboxyl termini and can thus be incorporated into larger

peptides at a desired site.

Useful retroinverso dipeptide analogues are not readily prepared by acylation of mono-protected geminal diamines (the method of choice for larger retroinverso peptides[4]) as these species,in our experience, are unstable when the protecting group in question is a carbamate. Hence we turned our attention to the reaction of the Curtius isocyanate of N-protected amino acids with malonate monoesters. (Fig 2)[5]. This well known reaction[6] has surprisingly received little attention in the peptide area[7]. A series of lipophilic amino acids with various common N-protecting groups (5) were converted via their acyl azides to the corresponding isocyanates (6). Reaction of the isocyanates with either monoethyl or monophenyl malonate (7, R^3=H) afforded the series of retroamide pseudodipeptides (8) in 60-75% yield. Reaction of isocyanates with alkylated monomalonates (7, $R^3 \neq H$) also resulted in the desired pseudodipeptide,but as a mixture of diastereomers and in poorer yield (20-30%). This drawback with the general method can be overcome as the retroamide pseudodipeptides (8,R^3=H) are readily and specifically alkylated at the active methylene by reaction with KO^tBu and a suitable alkylating agent to give diastereomeric mixtures of (8,$R^3 \neq H$) in good yield.

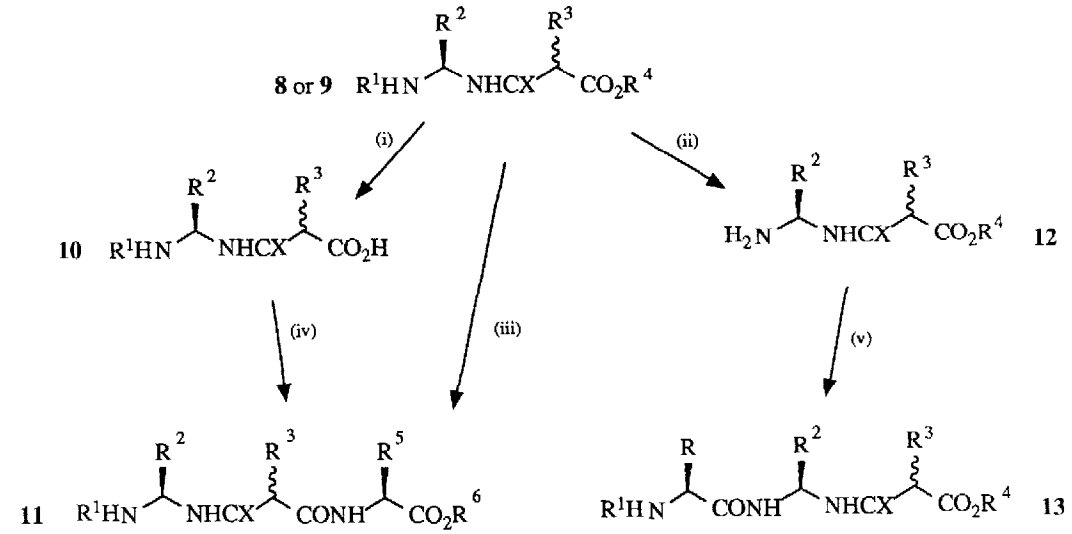
Figure 2



REAGENTS (i) a) Bu_3N, EtCOCl, b) NaN_3 c) Δ (ii) **7** ($HO_2CCH(R^3)CO_2R^4$) (iii) Belleau's Reagent

Protected dipeptides can be specifically endothionated with Lawesson's reagent[2], but the reaction requires elevated temperatures due to the insolubility of the reagent, and consequently results in extensive decomposition of the retro species and thus very poor yields ($\leq$ 10%) of retrothioamide pseudodipeptides. Use of Belleau's reagent[8] and reaction between 0°C and room temperature enabled this new class of peptoids to be isolated in 45-60% yield as stable, colourless solids, or oils.

Figure 3



REAGENTS (i) R^4=Et, NaOH,EtOH (ii) a) X=O; H_2, Pd / C, AcOH b) X=S; Na / liq NH_3 (iii) R^4=Phenyl; $HCl.NH_2CH(R^5)CO_2R^6$,Et_3N, ^iPrOH, reflux (iv) $HCl.NH_2CH(R^5)CO_2R^6$, Et_3N, DCC (v) $R^1NHCH(R)CO_2CO_2Et$

Elongation from the C-terminus of both the retroamide and retrothioamide series of pseudodipeptides is readily achieved (Fig 3). Saponification of the ethyl esters gives the free carboxylic acid which can be further reacted by conventional peptide coupling. Alternatively, the phenyl esters may be reacted directly with an amino acid ester in isopropanol to give the tripeptide analogue directly.

Deprotection at the N-terminus of t-butyl carbamate protected species by conventional acid hydrolysis methods leads to decomposition and hence elaboration of the two peptoid series is only possible from the benzyl carbamates. Reductive removal of this group either by catalytic hydrogenation (for retroamides) or by sodium in liquid ammonia reduction (for retrothioamides) gives the unstable monoacyl gem diamines (12) which if reacted immediately with a suitable activated amino acid give the tripeptide analogues (13) in modest yield (30-35%).

Thus we have presented a convenient method of synthesis of a wide range of retroinverso and retroinverso-endothiono peptoids in the synthetically useful pseudodipeptide form, and have shown that they can be elaborated to enable incorporation of the retroamide and retrothioamide surrogates into specific sites of larger peptides.

Diastereoselective routes into these and related peptoids, are under investigation and will be reported elsewhere, along with full experimental details.

New compounds and diastereomeric pairs, gave satisfactory elemental analyses and spectroscopic data.

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REFERENCES and NOTES

1 A F Spatola in "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins" (B. Weinstein ed.) Marcel Dekker, New York, 1983, Vol 7, p 267-357.

2 a) D W Brown, M M Campbell and C V Walker, *Tetrahedron*, (1983), 39, 1075.

b) K.Clausen, M.Thorsen and S-O.Lawesson, *Tetrahedron*, (1981), 37, 3635.

3 M Goodman and M Chorev, *Acc. Chem. Res.* (1979), 12, 1.

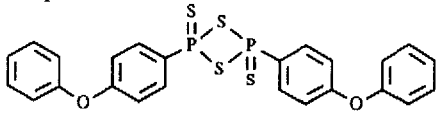
4 P Pallai and M Goodman, *J. Chem. Soc. Chem. Commun.*,(1982), 280.

5 For Figures 2 and 3 : R= ^{i}Pr, Me; R^1= Z, Boc, Ac; R^2= Me, ^{i}Pr, Bz; R^3= H, Me, ^{i}Pr, Bz; R^4= Et, Ph; R^5, R^6= Me.

6 The Chemistry of Amides, J Zabicky ed, Wiley (1970).

7 This reaction is briefly mentioned in: M.Chorev and M Goodman, *Int. J. Pept. Protein Res.* (1983), 21, 258.

8 Belleau's reagent is the dithiaphosphetane disulphide derived from diphenyl ether and phosphorus pentasulphide:



It has greater solubility in ordinairy organic solvents than Lawesson's reagent.

G Lajoie, F Lepine, L Maziak and B Belleau, *Tetrahedron Letts.*, (1983) 3815.

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