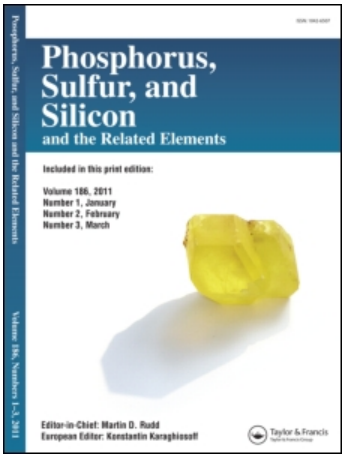

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Search on Enzyme Inhibitors of the Glutathione Metabolism: Synthesis of Phosphonopeptides

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SEARCH ON ENZYME INHIBITORS OF THE GLUTATHIONE METABOLISM : SYNTHESIS OF PHOSPHONOPEPTIDES

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In a program designed to prepare peptide derivatives with altered biological activity, methods for incorporating α-amino phosphonic acids at the "C-terminal" position were investigated.

Replacement of one amino acid residue in a peptide chain with an aminoalkanephosphonic acid, to give a phosphonopeptide offers numerous structural possibilities to study particular biological mechanisms. This replacement leads to P-analogs of peptides possessing substrate activity or inhibitory power against certain enzymes.

We report here simple methods for the synthesis of di and tripeptides related to glutathione and ophthalmic acid.

$$H_2N\text{-}CH(COOH)\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}\mathbf{X}\text{-}NH\text{-}CH_2\text{-}COOH$$

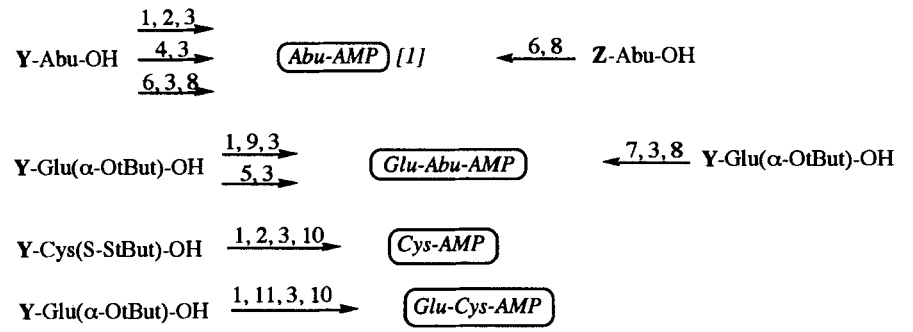
L-γ-glutamyl residue (Glu) — *glycyl residue*

X = -NH-CH(CH_2-CH_3)-CO- = L-α-aminobutyryl residue (Abu) → Ophthalmic acid

X = -NH-CH(CH_2-SH)-CO- = L-cysteinyl residue (Cys) → Glutathione

In these compounds the terminal carboxylic group of the natural compounds (Glycyl residue) is replaced with a terminal phosphonic group (aminomethyl phosphonic residue, AMP).

To realize the preparation of these phosphonic analogs, we have used conventional methods of the peptide chemistry adapted to the particular characteristics of the new products :



Y = $(CH_3)_3C$-O-CO- ; **Z** = C_6H_5-CH_2-O-CO- ; 1 : N-hydroxysuccinimide (SuOH) ; 2 : AMP ; 3 : CF_3COOH ; 4 : iButOCOCl + AMP ; 5 : iButOCOCl + Abu-AMP ; 6 : EDCI + $AMP(OEt)_2$; 7 : EDCI + $Abu\text{-}AMP(OEt)_2$; 8 : HBr + CH_3COOH ; 9 : Abu-AMP ; 10 : PBu_3 ; 11 : Cys(S-StBut)-AMP

All molecules have been characterized by IR and ^{31}P, ^{13}C, ^{1}H NMR spectroscopy.

From these results it is apparent that N-ethyl-N'-(3-dimethylamino-propyl)carbodiimide hydrochloride (EDCI) is an excellent coupling agent between esters of aminomethylphosphonic acid and N-carbobenzoxy or N-*t*butyloxyamino acids.

In the same way we obtained satisfactory results with the mixed carbonic-carboxylic anhydride and N-hydroxysuccinimide active ester methods using free amino-phosphonic acids as substrates.

This work describes a new synthetic entry to a range of phosphonopeptides which may be considered as phosphono analogs of glutathione. The latter is implicated in biologically important processes and the interest of these parent compounds which possess structural relationships arises from their possible interaction with enzymes of the glutathione metabolism. Enzymatic tests which these mimetic compounds are under investigation in this field.

[1] ATHERTON F.R. *et al.* - German Patent N° 2.854.292, 1979.