PRO EXPERIMENTIS

A simple method for the preparation of diastereoisomeric phosphonodipeptides

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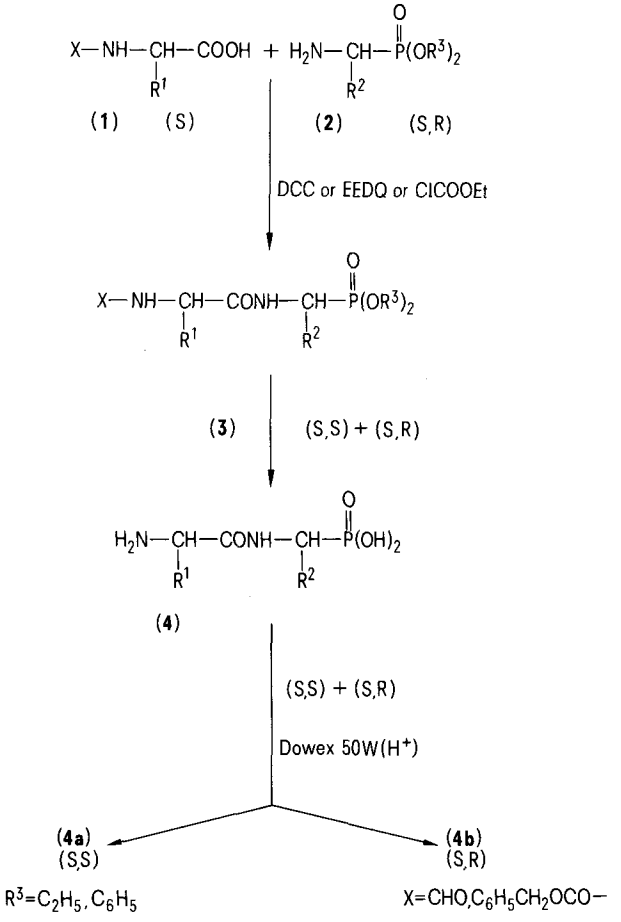
Summary. Diastereoisomeric mixtures of phosphonodipeptides, prepared from racemic dialkyl 1-aminoalkanephosphonates, were separated by ion-exchange column chromatography.

Phosphonodipeptides are now receiving considerable interest because some representatives of this class have been shown to repress bacterial growth[1-3]. There is a need to have their pure diastereoisomers available for further biological and biochemical work. In studying their preparation, we have found that mixtures of the diastereoisomers formed from some L-amino acids and some racemic 1-aminoalkanephosphonates are effectively separable by ion-exchange chromatography. In the past this method has been successfully applied to the analytical separation of diastereoisomeric dipeptides[4,5].

Phosphonodipeptides (**4**) were obtained by condensation of N-acylamino acids (**1**) with corresponding diesters of 1-aminoalkanephosphonic acids (**2**) by standard methods. The blocking groups were removed with hydrogen bromide in glacial acetic acid solution or by hydrogenolysis.

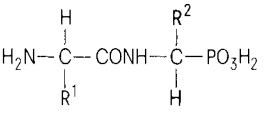


The phosphonodipeptides obtained (**4**) were separated by means of a Dowex 50W (H^+) 100-200 mesh chromatography column. The column was washed with water, and yielded quantitatively the pure diastereoisomers (**4a**) and (**4b**). The use of a 200×20 mm column enabled us to separate from 0.7 to 2.0 g of the mixture of diastereoisomers, applied in 3-5 ml of water, and eluted with 1000-3000 ml of water.

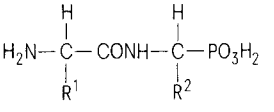
The configurations of those peptides containing 1-aminoethanephosphonic acid and of another one containing 1-aminopropanephosphonic acid are given in the literature[6,7]. For the others the structure is proposed by analogy, based on successive elution from the column as well as on relative mobilities on TLC.

The diastereoisomers obtained were chromatographically pure. Their structure was additionally confirmed by spectroscopic data (IR, NMR) and elemental analyses.

Diastereoisomers of phosphonodipeptides obtained by separation on Dowex 50W X8 (H^+)



S-S Dipeptide (**4a**)



S-R Dipeptide (**4b**)

R^1	R^1	$[\alpha]_{578}^{20}$ (c=1, H_2O)		R_f	
		4a	**4b**	**4a**	**4b**
CH_3	CH_3	+75°	−49°	0.08	0.06
$CH/CH_3/_2$	CH_3	+84°	− 9°	0.15	0.10
$CH_2CH/CH_3/_2$	CH_3	+73°	−13°	0.23	0.17
CH_3	CH_2CH_3	+75°	−53°	0.11	0.09
$CH_2CH/CH_3/_2$**	CH_2CH_3	+83°	−22°	0.26	0.20
$CH/CH_3/_2$**	$CH/CH_3/_2$	+66°	+ 7°	0.38	0.31
$CH_2CH/CH_3/_2$**	$CH/CH_3/_2$	+51°	+ 1°	0.30	0.26
$CH/CH_3/_2$**	$CH_2CH/CH_3/_2$	+87°	−23°	0.30	0.26

* Silica-gel Merck 60F 254, n-butanol-acetic acid-water (12:3:5).
** Configuration proposed by analogy.

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