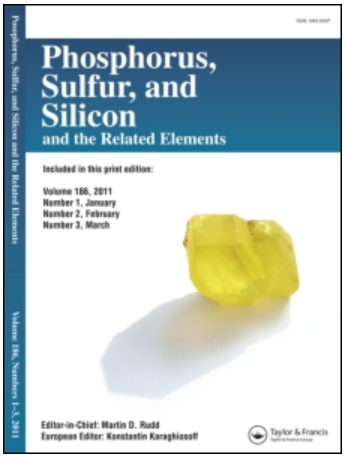

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Ru-Yu Chen[a]; Shi-Cain Dan[a]
[a] Institute of Elemento-organic Chemistry, Nankai University, Tianjin, P. R. China

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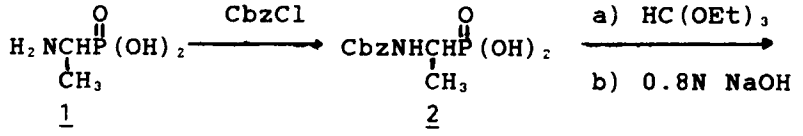
THE SYNTHESIS OF DIPEPTIDES OF AMINOALKYLPHOSPHONIC ACID AND THEIR CYCLIC COMPOUNDS

RU-YU CHEN AND SHI-CAIN DAN
Institute of Elemento-organic Chemistry, Nankai University, Tianjin, P. R. China

Abstract Dipeptides and cyclodipeptides containing aminoalkylphosphonyl group have been synthesized. The diastereomers of some of them are separated and the molecular structures are confirmed by NMR, IR, MS or x-ray diffraction.

It was reported that N-alanyl-aminoethylphosphonic acid (alafosfalin) and its di- to hexa-peptides had strong antibacterial activity[1], but there were very few phosphonopeptides containing P-N bond[2]. Neither had been found any cyclic peptide containing phosphonyl group so far. For the purpose of looking for new biologically active phosphorus-containing dipeptides we synthesized a number of dipeptides containing 1-aminoalkylphosphonyl (or phosphinyl) group 4, and their cyclic compounds 5.

1-Aminoethylphosphonic acid 1 was prepared from triphenylphosphite, aldehyde, and benzamide in a yield of 92%.[3] Compound 3a was prepared by the esterification of 2 with triethyl orthoformate followed by saponification with 0.8 N NaOH in an overall yield of 75%. Compounds 4a and 4b were obtained by the reaction of 3a with $SOCl_2$ followed by coupling with amino acid ester in a good yield, and the reaction was completed in only a few hours (Method A), or by direct condensation of 3a with HCl salt of amino acid ester in the presence of 20% excess of diphenylphosphoryl azide (DPPA) and triethylamine at room temperature for three days (Method B), but Method B gave lower yields (see TABLE I).



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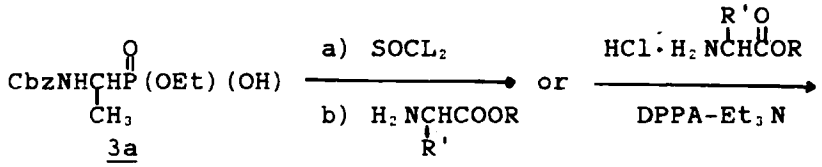
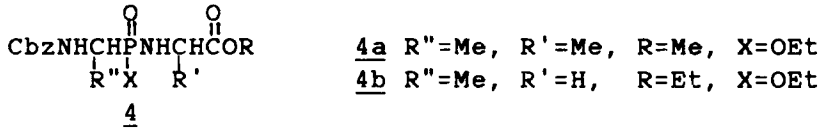
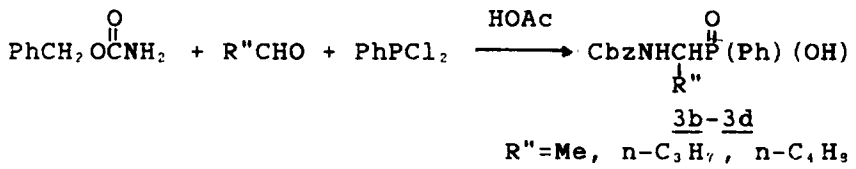
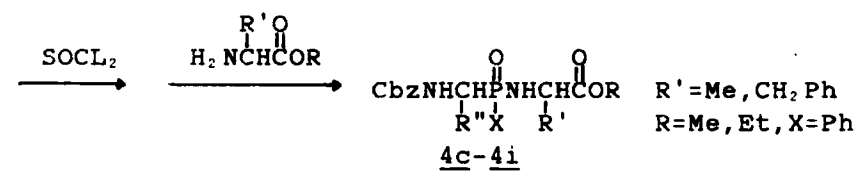




According to the method in literature[4] 1-aminoalkylphenyl phosphinic acids were prepared by the reaction of benzyl carbamate, an aldehyde and phenyldichlorophosphine in glacial acetic acid, followed by reflux with 4N HCl and then the treatment with epoxypropane in the yields of 40-50%. The amino group of these products was protected by carbobenzyloxylation to give 3b, 3c and 3d. By the reaction with the same starting materials in glacial acetic acid and then treating the reacion mixture with a large amount of water at room temperature instead of reflux with 4N HCl,the N-protcted products 3b ,3c and 3d were obtained directly in one step with the yields of 75-90%.





Deprotection of the amino group of compound 4 was done by the hydrogenolysis of 4 with 5% Pd-C as the catalyst giving corresponding dipeptide quantitavely. Most of these dipeptides were converted to 5 by reflux in n-butanol-toluene (3:1) for 30-60 hours without further purification (see TABLE I).

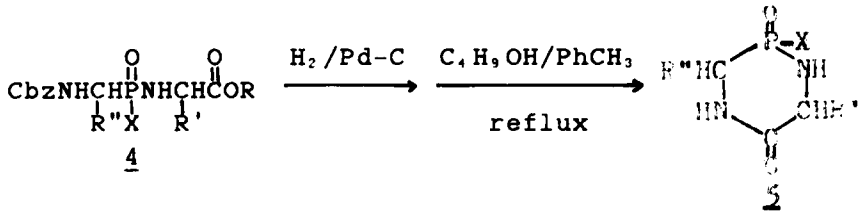


TABLE I Physical data for compounds 4 and 5

NO	R"	R'	R	X	YIELD(%)	MP(°C)
4a	Me	Me	Me	OEt	87(A)	88-90
					31(B)	
4b	Me	H	Et	OEt	73(B)	94-96
4c	Me	H	Et	Ph	71(A)	106-108
					37(B)	
4d	Me	Me	Me	Ph	62(A)	145-150
					27(B)	
4e	Me	$PhCH_2$	Me	Ph	65(A)	124-140
4f	n-C_3H_7	H	Et	Ph	63(A)	134-137
4g	n-C_4H_9	H	Et	Ph	49(A)	137-139
4h	n-C_4H_9	Me	Me	Ph	34(A)	106-108
4i	Me	H	Me	Ph	44(A)	128-130
5a	Me	Me		OEt	37	150-152
5b	Me	H		OEt	32	126-130
5c	Me	H		Ph	61	234,dec.
5d	Me	Me		Ph	70	250,dec
5e	Me	$PhCH_2$		Ph	40	222,dec.
5f	n-C_3H_7	H		Ph	7.6	204,dec.
5g	n-C_4H_9	H		Ph	33	214,dec.
5h	n-C_4H_9	Me		Ph	48	211,dec.

Compounds 3, 4 and 5 were characterized by elemental analysis, and MS, IR, NMR (^1H, ^{31}P) spectra. ^1H NMR spectrum of 4a showed four proton signals for OCH_3 at 3.6-3.7 ppm. ^{31}P NMR of 4a showed four signals at about 29 ppm. These results were probably due to the existence of diastereomers. ^1H NMR spectrum of 4e showed two single peaks for OCH_3 at 3.4 and 3.5 ppm, and these two diastereomers were separated by chromatography on silica gel. They had ^{31}P chemical shifts at 33.65 and 34.32 ppm respectively.

^{31}P NMR spectrum of 5c gave only one signal at 31 ppm, but its IR spectrum showed two C=O absorption peaks at 1640 and 1675 cm^{-1}, and its ^{13}C NMR spectrum also gave two C=O signals. These phenomena might be resulted

by the existence of two isomers. Compound 5e was separated into two components by thin layer chromatography on silica gel. Each of them exhibited a different C=O absorption peak in IR spectrum and a different P signal in ^{31}P NMR spectrum. The structure of one component was confirmed by x-ray diffraction (shown in Figure 1). The structural confirmation of the other is on the way. similarly 5h was separated into two components with R_f values of 0.54 and 0.41, and their structures are being determined.

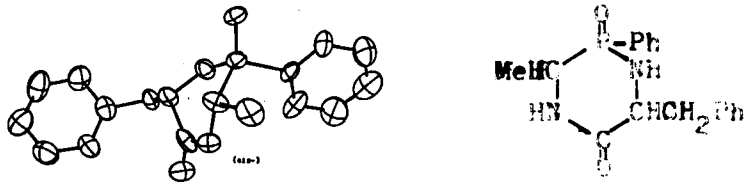


FIGURE 1 Molecular structure of 5e

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