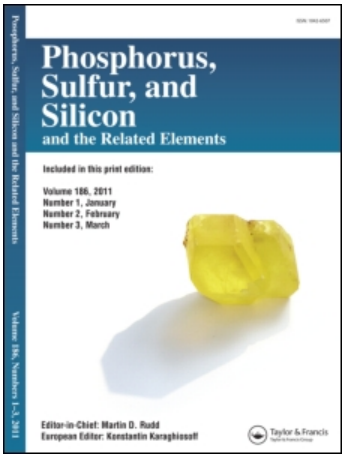

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Synthesis of Novel Phosphonopeptides Derived from Pyridylmethylphosphonate Diphenyl Esters

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SYNTHESIS OF NOVEL PHOSPHONOPEPTIDES DERIVED FROM PYRIDYLMETHYLPHOSPHONATE DIPHENYL ESTERS

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A series of dipeptides derived from 2-pyridyl- and 3-pyridylmethyl-phosphonic diphenyl esters were synthesized. These dipeptides were obtained in the reaction of the diphenyl 2-pyridylmethyl(amino) phosphonate or diphenyl 3-pyridylmethyl-(amino)phosphonate with the corresponding Z-blocked aminoacids (alanine, valine, and proline) by the DCC coupling method.

Keywords: Amino acids; dipeptide pyridylphosphonates; peptide synthesis; pyridylmethyl(amino)phosphonates

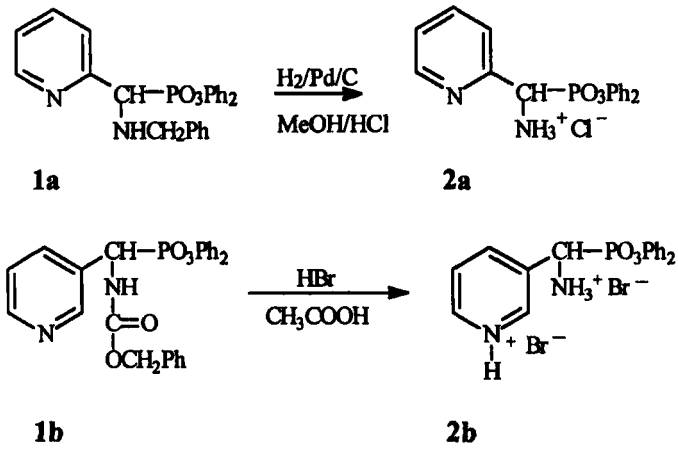
INTRODUCTION

Peptides containing aminophosphonate moieties in peptide chains are interesting compounds, due to their biological activity.[1] Lately, there is a growing interest for evaluation of these compounds; a number of such derivatives were synthesized and proved as enzyme inhibitors[2–7] or as antibacterial agents.[8,9]

Phosphono-peptides composed with a pyridine moiety were not described yet, beyond a short mention.[10] There is an indication, that some phosphono-peptides comprised with heterocyclic moieties should show a biological activity.[10] Therefore, it was decided to obtain a few examples of phosphono-peptides containing pyridines to check their biological activity. The synthetic work focused on the simplest dipeptides available in which the phosphonic group was protected as the diphenyl phosphonate ester. As it was shown, existence of diphenyl phosphonate esters in phosphono-peptides is a substantial condition for occurrence of a specific biological activity in the phosphono-peptides.[7]

RESULTS AND DISCUSSION

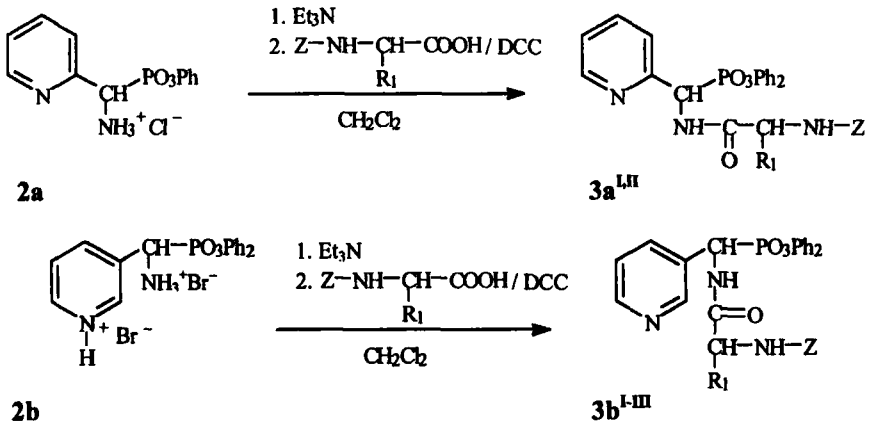
Starting materials for the synthesis of desired phosphono-peptides were diphenyl 2-pyridyl-1-[*N*-benzyl)-amino]-methylphosphonate (**1a**) and diphenyl 3-pyridyl-1-[*N*-(benzyloxycarbonyl)-amino]-methylphosphonate (**1b**). These compounds were obtained according to a literature procedure.[11] In order to have an appropriate compound for peptide synthesis, the *N*-benzyl derivative **1a** was catalytically reduced to the corresponding aminophosphonate **2a**. Similarly, the benzyloxycarbonyl group in the **1b** was removed by action of 30% HBr in acetic acid solution to give the needed aminophosphonate **2b** as hydrobromide salt (Scheme 1). Such prepared aminophosphonates were then used in the peptide synthesis.



SCHEME 1 Pyridylmethyl(amino)phosphonates for peptide synthesis.

Three *Z*-blocked aminoacids (*Z*-alanine, *Z*-valine, and *Z*-proline) with *L* configuration were chosen for the peptide synthesis. Synthesis of the phosphono-peptides **3** were carried out in a classical way, using the DCC (dicyclohexylcarbodiimide) as a coupling agent. Synthesis of these peptide phosphonates (**3a**^{I,II} and **3b**$^{I-III}$) is illustrated in Scheme 2.

In the first stage of the peptide synthesis, the salt of the pyridyl phosphonate (**2a** or **2b**) was treated with triethylamine in order to liberate the amino group. Then the *Z*-protected aminoacid was added, followed by addition of dicyclohexylcarbodiimide (DCC) as a coupling agent. The reaction was carried out in methylene chloride solution. On the final stage of the reaction, the formed dicyclohexylurea (DCU) was removed



$\mathbf{a}^{\mathbf{I}}$ or $\mathbf{b}^{\mathbf{I}}$: R_1 = Me, $\mathbf{a}^{\mathbf{II}}$ or $\mathbf{b}^{\mathbf{II}}$: R_1 = Me_2CH, $\mathbf{b}^{\mathbf{III}}$: R_1 = pyrrolidin-2-yl

Z = $PhCH_2OC(O)$-

SCHEME 2 Synthesis of the peptidyl derivatives of diphenyl pyridylmethylphosphonates.

by filtration and the remaining solution was worked-up to isolate the peptide products.

All of the obtained phosphonopeptides were not enantiomerically pure and were mixtures of R and S diastereomers. However, on the basis of ^{31}P NMR spectra (see Table I) one can notice that there is a preference for one diastereomer in the phosphonopeptide products obtained. Excessive amount of one diastereomer in the products might be caused by a purification process of the crude products (i.e., a repeated crystallization). No further attempts were made to separate these diastereomers.

In conclusion, the method presented here can be useful for further synthesis of phosphonopeptides composed with heterocyclic moieties.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in $CDCl_3$, or in D_2O, using 300.13 MHz for ^1H NMR, and 121.51 MHz for ^{31}P NMR spectra. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200 and were uncorrected. Elemental analyses were done in the Laboratory of Instrumental Analysis, in the Institute. The M.S. analyses were performed on a Finnigan TSQ 700 instrument (electrospray ionization on mode: ESI + Q1MS).

TABLE I Analytical Data of the Peptide Diphenyl Pyridylphosphonates **3**

Compd. no.	Yield %	m.p.°C	^{1}H NMR ($CDCl_3$) δ, ppm	^{31}P NMR ($CDCl_3$) δ, ppm	M.S. ESI + Q1MS
3a^{I}	35	oil	8.64 (m, 1H, py-6), 8.52 (m, 1H, py-4), 7.90 (m, 1H, py-3), 7.67 (m, 1H, py-5), 7.3–6.8 (m, 15H, arom.), 6.04 (dd, 1H, CH-P, J_{CH-P} = 28 Hz, J_{CH-NH} = 8.9 Hz), 5.32 (m, 1H, NH), 5.1 (s, 2H, CH_2O), 3.4 (m, 1H, CH), 1.37 (m, 3H, CH_3)	13.12 (s, 100%) 13.06 (s, 27%)	546.6 (M + 1)(30%) 431.5 (M − 115) (100%)
3a^{II}	28	142–149	8.53 (m, 1H, py-6), 7.90 (m, 1H, py-4), 7.67 (m, 1H, py-3), 7.50 (m, 1H, py-5), 7.3–7.0 (m, 15H, arom.), 6.05 (dd, 1H, CHP, J = 21.5 Hz), 5.36(d, 1H, NH, J = 8.9 Hz), 5.1 (s, 2H, CH_2O), 4.2 (m, 1H, 3.4 (m, 1H, CH), 2.2 (m, 1H, CH), 1.1–0.85 (m, 6H, 2x CH_3)	13.25 (s, 100%) 13.04 (s, 25%)	574.5 (M + 1) (100%)
3b^{I}	67	119–120	8.79 (s, 1H, py-2), 8.56(bs, py-6), 8.44 m, 1H, py-4), 7.83(bs, 1H, py-5), 7.2–6.9 (m, 15H, arom.), 6.0 (dd, 1H, CHP, J = 21.8 Hz), 5.57 (dd, 1H, NH, 5.07 (m, 2H, CH_2O), 4.3 (m, 1H, NH), 2.2 (m, 1H, CH), 1.2 (m, 3H, CH_3)	13.93 (s, 100%) 13.73 (s, 58%)	546.5 (M + 1) (100%)
3b^{II}	76	152–154	8.76 (s, 1H, py-2), 8.53 (m, 1H, py-6), 8.18 (m, 1H, py-4), 7.85 (m, 1H, py-5), 7.2–6.9 (m, 15H, arom.), 6.04 (dd, 1H, CHP, J = 21 Hz), 5.5 (dd, 1H), 5.06 (m, 2H, CH_2O), 4.2 (m, 1H), 2.1–1.1 (m, 3H), 1.1–0.7 (m, 6H, 2 × CH_3)	13.98 (s, 100%) 13.65 (s, 81%)	574.5 (M + 1) (100%)
3b^{III}	75	154–156	8.72 (s, 1H, py-2), 8.56 (m, 2H, py-6, py-4), 7.77 (m, 1H, py-5), 7.34–7.02 (m, 15H, arom.), 5.90 (dd, 1H, CHP, J = 17.5 Hz), 5.20(bs, 2H, CH_2O), 4.39(bs, 1H, NH), 3.46 (m, 2H, pyrrolid.), 2.37–1.06 (m, 6H, pyrrolid.)	14.11 (s, 100%) 13.85 (s, 5%)	572.5 (M + 1) (100%)

All commercially available reagents were used as received from the supplier (Aldrich Company).

The diphenyl pyridylmethyl(amino)phosphonates **1a** and **1b** were prepared as described.[11]

Diphenyl 2-Pyridylmethyl(1-amino)phosphonate Hydrochloride (2a)

A solution of **1a** (2.0 g, 4.6 mmol) in methanol was hydrogenated using 10% Pd/C (1.0 g) as a catalyst in the presence of 1 equiv. of HCl (4.6 mmol), until the consumption of H_2 had ceased. The catalyst was removed by filtration, and the methanolic solution was evaporated to dryness. The resulting product (hygroscopic solid) was dried in vacuo and used in the peptide synthesis without additional purification. Yield: 81%. ^{1}H NMR(D_2O): 8.68(s, 1H, py-6), 8.56(m, 1H, py-4), 7.96(m, 2H, py-3, and 5), 7.4-7.0(m, 10H, Ph's), 4.37(d, 1H, CH-P, J = 23 Hz). ^{31}P NMR(D_2O): 3.83(s).

Diphenyl 3-Pyridylmethyl(1-amino)phosphonate Dihydrobromide (2b)

The diphenyl ester **1b** (2.4 g, 5.0 mmol) was mixed with 30% HBr in acetic acid (10 mL). The mixture was stirred for 1 h under anhydrous conditions. Then 150 mL of dry diethyl ether was added, the mixture was stirred for approximately 15 min, and the supernatant ethereal layer was removed by decantation. This procedure was repeated twice to give a solid. The product was dried in vacuo to give a yellowish solid, somewhat hygroscopic. The product was used directly to the next step without further purification. Yield 91%. mp. 180-181(dec.).^{1}H NMR(D_2O): 8.85(s, 1H, py-2), 8.70(m, 1H, py-6), 8.04(m, 1H, py-4), 7.4-6.9(m, 11H, Ph's, and py-5), 5.05(d, 1H, CH-P, J = 17 Hz). ^{31}P NMR(D_2O): 8.096(s).

General Procedure for Synthesis of the Peptide Phosphonates 3a^{I,II} and 3b^{I-III}

The dipeptide phosphonates **3** were synthesized from the corresponding heterocyclic diphenyl phosphonates **2a** or **2b**, and Z-Ala-OH, Z-Val-OH, and Z-Pro-OH, respectively. The dipeptide product was isolated from the reaction mixture by removing dicyclohexylurea (DCU), then extraction with ethyl acetate, and subsequent washing with 1 M aq. $NaHCO_3$ and water. The protected dipeptide phosphonate esters **3** were isolated by evaporation of the dried ethyl acetate extract and

crystallized twice from a mixture of ether and hexane. A typical procedure follows: to a suspension of *Z*-protected aminoacid (1.0 mmol) in methylene chloride (20 mL) was added a solution of the **2a** (or **2b**) (1.0 mmol) and triethylamine (0.11 g, 1.0 mmol) (or 0.22 g, 2.0 mmol in the case of **2b**) in methylene chloride (20 mL). The mixture was stirred and cooled to 0°C, and then a solution of DCC (0.23 g, 1.1 mmol) in methylene chloride (5 mL) was added. The mixture was stirred for 2 h at 0°C, then overnight at room temperature. The formed DCU was removed by filtration, the filtrate was evaporated to dryness, the residue dissolved in ethyl acetate (50 mL), filtered, and the filtrate washed subsequently with 1 M aq. $NaHCO_3$ (25 mL), water (twice) (2 × 25 mL), dried (anh. Na_2SO_4), filtered, and evaporated in vacuo to give the crude dipeptide product. Pure products **3** were obtained by repeated crystallizations from a mixture of diethyl ether and hexane. All the products were solids with one exception; the **3a**[I] was an oil and it was purified by column chromatography (eluant: ether-hexane 2:1). The physicochemical data of the obtained products are given in Table I.

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REFERENCES

[1] P. Kafarski and P. Mastalerz, *Beiträge zur Wirkstofforschung*, Heft 21, Berlin (1984).
[2] K. D. Collins and G. R. Stark, *J. Biol. Chem.*, **246,** 6599 (1971).
[3] J. Oleksyszyn and J. C. Powers, *Biochem.*, **30,** 485 (1991).
[4] J. Oleksyszyn, B. Boduszek, Ch. M. Kam, and J. C. Powers, *J. Med. Chem.*, **37,** 226 (1994).
[5] B. Boduszek, J. Oleksyszyn, Ch. M. Kam, J. Selzler, R. E. Smith, and J. C. Powers, *J. Med. Chem.*, **37,** 3969 (1994).
[6] B. Boduszek, A. D. Brown, and J. C. Powers, *J. Enzyme Inhibition*, **8,** 147 (1994).
[7] J. C. Powers, B. Boduszek, and J. Oleksyszyn, Pat. USA, No. 5543396 (1996).
[8] F. R. Atherton, M. J. Hall, C. H. Hassal, R. W. Lambert, W. J. Lloyd, and P. S. Rindgrose, *Antimicrob. Agents Chemother.*, **15,** 696 (1979).
[9] E. Bayer, K. H. Gugel, H. Hägele, H. Hagenmaier, S. Jessipow, W. A. König, and H. Zähner, *Helv. Chim. Acta*, **55,** 224 (1972).
[10] B. Boduszek, *Phosphorus, Sulfur and Silicon*, **144–146,** 433 (1999).
[11] B. Boduszek, *Phosphorus, Sulfur and Silicon*, **114,** 209 (1996).