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Synthesis of Phosphinic Acids on the Basis of Hypophosphites: VI.[1] General Method for Synthesis of Pseudo-γ-glutamylpeptides

V. V. Ragulin

Institute of Physiologically Active Compounds, Russian Academy of Sciences, Severnyi pr. 1, Chernogolovka, Moscow oblast, 142432 Russia

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Abstract — A general method for synthesis of 2-substituted pseudo-γ-glutamylpeptides, namely, [2-(hydroxycarbonyl)ethyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acids **I** which are phosphinic acid analogs of γ-glutamylpeptides. Bis(trimethylsilyl) hypophosphite (**IV**) formed from ammonium hypophosphite (**II**) in situ was added to the respective α-substituted acrylate to form bis(trimethylsilyl) [2-R-2-(alkoxycarbonyl)ethyl]-phosphonites **V**. Treatment of compounds **V** in situ with excess dibromoethane followed by alcoholysis gave [2-R-2-(alkoxycarbonyl)ethyl](2-bromoethyl)phosphinic acids **VI** which without isolation were treated with excess triethyl orthoformate. The simultanious esterification and dehydrobromination led to [2-R-2-(alkoxycarbonyl)ethyl](vinyl)phosphinates **III** which were isolated and characterized. The Michael addition of diethyl acetamidomalonate to vinylphosphinates **III** followed by acid hydrolysis of phosphinates **VII** without their isolation resulted in formation of target [2-R-2-(hydroxycarbonyl)ethyl][3-amino-3-(hydroxycarbonyl)]propyl]phosphinic acids–pseudo-γ-glutamylpeptides **I**.
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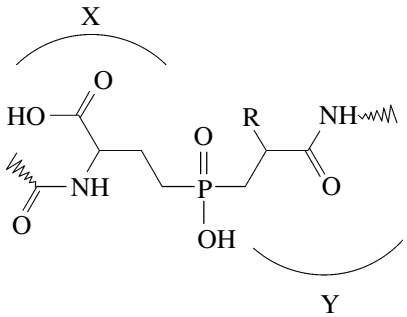
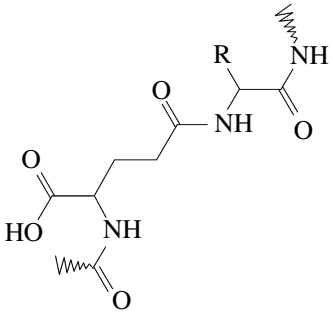
Glutamic acid belongs to excitation mediators of the mammalian and human nervous system and plays a significant role in the development of various normal and pathogenic processes.

Phosphinic acid peptides are peptide analogs (peptide isosters) with one peptide bond substituted by the nonhydrolyzable nonhydrolysable phosphinate moiety –P(O)(OH)–CH_2–. This substitution represents a very convenient mimic of a substrate in the transition state for at least two distinct classes of hydrolytic enzymes, Zn-metalloproteinases and aspartic acid proteinases [2].

The development of general convenient methods for synthesis of pseudo-γ-glutamylpeptides **A** which are phosphinic analogs of peptides **B** is a perspective synthetic approach to physiologically active compounds, specifically inhibitors of corresponding enzymes involved in biosynthesis of various glutamylpeptide derivatives [3–5].



A



B

A known approach to building the molecules of phosphinic analogs **A** of γ-glutamylpeptides **B** consists in the synthesis of an N-protected aminoalkylphosphonic component of the pseudopeptide, viz. phosphonous amino acid analog X, followed by its addition to an appropriate α-substituted acrylate to obtain pseudopeptide fragment Y [6]. In this case, the

[1] For communication V, see [1].

synthesis of the aminoalkylphosphoryl fragment (pseudocarboxyl component of the peptide), resulting in the formation of the first phosphorus–carbon bond, requires protection of both nitrogen and phosphorus atoms and thus involves three- or more stages [7, 8]. The building of pseudopeptide fragment Y to form the second phosphorus–carbon bond is usually performed by adding an aminoalkylphosphonous component in the form of silyl ester to acrylates [8]. However, this general procedure has some restrictions in the construction of complicated aminoalkylphosphonous building blocks. For example, attempted preparation of phosphinic pseudo-Asp-Ala-dipeptide by adding trimethylsilyl esters of the aminophosphonous analog of aspartic acid to ethyl metacrylate failed [9].

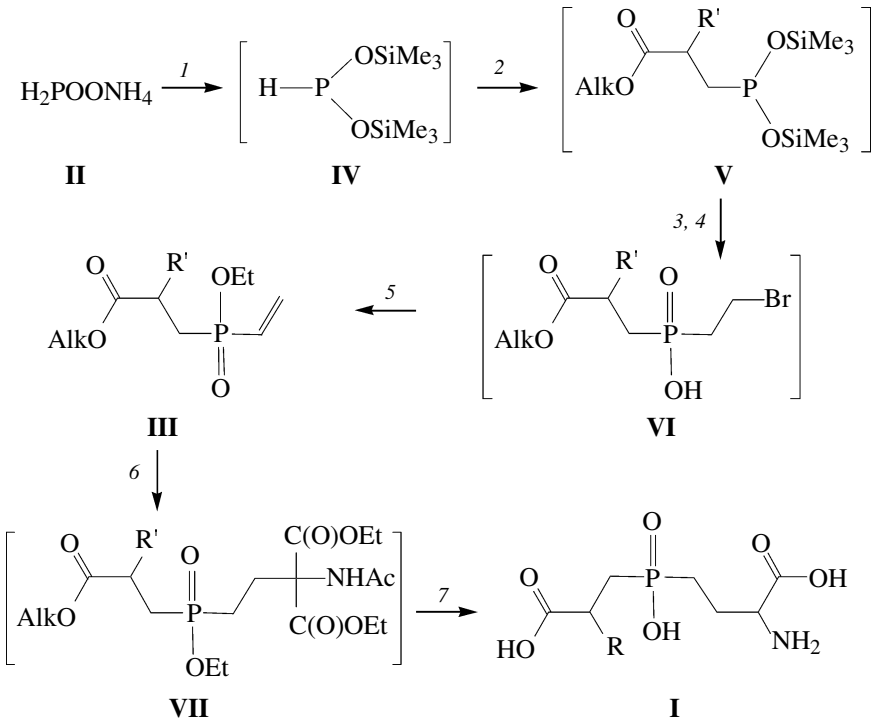
In this connection an actual line of research is developing alternative methods of pseudopeptide design. Earlier we described a new method for synthesis of pseudo-γ-glutamylglycine, in which the target molecule is built in the inverse order, namely, by adding hypophosphite to acrylate (serving as the pseudoamino component of the peptide) to form the first phosphorus–carbon bond, followed by adding the amino acid function to form the second phosphorus–carbon bond of the pseudopeptide [10, 11].

In the present work we offer a general method of synthesis of a number of pseudo-γ-glutamylpeptides **I** (Scheme 1), as further development of the above procedure. In this case, phosphinic acids are easier and more conveniently prepared by a one-pot procedure involving construction of both phosphorus–carbon bonds. We have developed this methodology for preparing various functional substituted phosphinic acids from hypophosphoric acid salts, for example, ammonium hypophosphite (**II**) [12–16].

The construction of pseudo-γ-glutamylpeptides by this procedure is a two-step process (Scheme 1). The first step is the one-pot formation of two phosphorus–carbon bonds to obtain the key intermediates of this synthesis, vinylphosphinates **III**, which contain a β-substituted β-(alkoxycarbonyl)ethyl radical, pseudopeptide fragment Y in target pseudopeptide **A**.

Bis(trimethylsilyl) hypophosphite (**IV**) readily forming from ammonium hypophosphite (**II**) and hexamethyldisilazane [17, 18] is added to α-substituted acrylates, affording bis(trimethylsilyl) [2-R-2-(alkoxycarbonyl)ethyl]phosphonites **V** (Scheme 1). The latter react in situ with excess 1,2-dibromoethane along the Arbuzov reaction scheme to form silyl 2-bromoethylphosphinates whose subsequent

Scheme 1.



(*1*) $(Me_3Si)_2NH$; (*2*) $EtO(O)C–C(R)=CH_2$; (*3*) $BrCH_2CH_2Br$ ($–Me_3SiBr$); (*4*) EtOH; (*5*) $CH(OEt)_3$; (*6*) $AcNHCH(COOEt)_2$; (*7*) HCl, reflux; Dowex 50W(H^+); R': Me (**a**), *i*-Bu (**b**), $CH_2C(O)OMe$ (**c**), $CH_2CH_2C(O)OEt$ (**d**); R: Me (**a**), *i*-Bu (**b**), $CH_2C(O)OH$ (**c**), $CH_2CH_2C(O)OH$ (**d**).

alcoholysis gives 2-substituted [2-(alkoxycarbonyl)-ethyl](2-bromoethyl)phosphinic acids **VI**. Further on we applied the procedure for simultaneous dehydrobromination and esterification of (2-bromoethyl)phosphinic acids **VI** by treatment with excess triethyl orthoformate [10, 11, 14]. Our earlier proposed synthesis of [2-(alkoxycarbonyl)ethyl]- [11] and (2-phenylethyl)phosphinates [15] was extended in the present work to the synthesis of various [2-R-2-(alkoxycarbonyl)ethyl](vinyl)phosphinates **III**, which allows this method to be considered as a convenient general synthetic route to various functionally substituted vinylphosphinates.

[2-Alkyl-2-(alkoxycarbonyl)ethyl](vinyl)phosphinic esters **III** were isolated as individual compounds, characterized, and applied in the second step of the synthesis for introducing the amino acid fragment to form the phosphoryl analog of the glutamine pseudopeptide fragment. The Michael addition of acetamidomalonic ester to vinylphosphinates **III** in THF in the presence of potassium carbonate provides [2-(alkoxycarbonyl)-2-alkylethyl][3-(*N*-acetylamino)-3,3-bis-(ethoxycarbonyl)propyl]phosphinates **VII**. Compounds **VII** were converted into the target pseudopeptides without isolation by acid hydrolysis followed by ion-exchange chromatography on a cationite. [2-(Hydroxycarbonyl)ethyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acids **I** (pseudo-γ-glutamylpeptides) were isolated in 50–71% yields and characterized.

Thus, we proposed a genera two-stepl method for synthesis of pseudo-γ-glutamylpeptides **I**, starting from ammonium hypophosphite (**II**), involving formation of key intermediate products, namely β-substituted [β-(alkoxycarbonyl)ethyl](vinyl)phosphinates **III**, in the first step and addition of the amino acid function in the second step.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on Bruker DPX-200 and Bruker CXP-300 Fourier spectrometers with internal TMS and external H_3PO_4 references. The melting points were measured on a Boetius-PHMK hot stage or in a block in an open capillary. Thin-layer chromatography was performed on Silufol (eluent chloroform–acetone, 4–5 : 1), Alufol (Kavalier) (neutral alumina on aluminum foil), and Merck glass plates with silica gel UV-254 (layer thickness 0.2 mm; eluent isobutanol–acetic acid–water, 5 : 1 : 1). Amino acid spots on the plates were developed by spraying with ninhydrin and heating at 100°C. Vinylphosphinates were isolated by column chromatography on Silpearl and Silica gel L 100/600 μm (Chemapol). Aminophosphinic acids were purified by ion-exchange chromatography on Dowex 50WX8-200 (H^+) (Lancaster) and KUIKhT(H^+) (Russian Institute of Chemical Technology). Ammonium hypophosphite was prepared by treatment of 50% aqueous hypophosphoric acid with excess ammonia, followed by concentration and crystallization of the salt from ethanol. Acetamidomalonic ester, propylene oxide, triethyl orthoformate, dibromoethane, and hexamethyldisilazane were purchased from Acros Organics. All operations with bis(trimethylsilyl) hypophosphite and trimethylsilyl phosphonites in situ were carried out in under dry argon, all solvents were carefully dried. Ethyl α-isobutylacrylate was purchased from Khimeks (St. Petersburg), and ethyl acrylate, ethyl methacrylate, and dimethyl itaconate were supplied by C-Reakor (Lancaster). Diethyl α-methyleneglutarate was prepared from ethyl acrylate by the procedure described in [19].

2-Substituted [2-(alkoxycarbonyl)ethyl]vinylphosphinic acids III *(general procedure).* A mixture of 0.04 mol of ammonium hypophosphite (**II**) and 0.07 mol of hexamethyldisilazane was stirred for 2 h at 120–130°C [17,18]. The reaction mixture was cooled to room temperature, and α-substituted acrylate was then slowly added dropwise at a temperature below 25–30°C, the mixture was stirred for 2 h at 40°C [10,11], and cooled to room temperature. 1,2-Dibromoethane was then added in one portion, and the resulting mixture was stirred under reflux for 4 h. Excess 1,2-dibromoethane and bromotrimethyl were removed in a vacuum, the residue was treated with 30–40 ml of ethanol, and the mixture was heated under reflux for 15–30 min and filtered. The filtrate was concentrated in a vacuum, diluted with a 1 : 1 toluene–ethanol mixture, and evaporated. The oily residue was refluxed with 0.20 mol of triethyl orthoformate with a Dean–Stark trap for 2–3 h to remove the ethanol and ethyl formate formed [14, 15]. Unreacted triethyl orthoformate was removed in a vacuum, and the residue was distilled to obtain target vinylphosphinate **III** as a mixture of diastereoisomers (~1 : 1). Compounds **IIIa**–**IIId** were used for further conversions; analytically pure samples were obtained by repeated distillation in a vacuum. Column chromatography on silica gel allowed to the yield of vinylphosphinates **IIIa** and **IIIb** to be increased to 39% and 37%, respectively (calculated per ammonium hypophosphite), eluent petroleum ether–chloroform (1 : 1), chloroform. R_f 0.4–0.5 (chloroform–acetone, 8 : 1). The synthesized vinylphosphinates are light yellow oily liquids.

Ethyl [2-(ethoxycarbonyl)propyl](vinyl)phosphinate (IIIa). Yield 3.3 g, (35% after four stages,

calculated per ammonium hypophosphite), bp 103–107°C (0.5 mm Hg), oil, n_D^{20} 1.4510. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (3H, CH_3); 1.25 t (3H, CH_3), 1.23 m (3H, CH_3), 1.80 m (1H, CH_2P), 2.30 m (1H, PCH_2), 2.87 m [1H, CHC(O)], 4.00 m (4H, CH_2OC), 4.15 m (2H, CH_2OP), 5.90–6.40 m (3H, $CH{=}CH_2$). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 41.4, 40.8. Found, %: C 51.14, 50.97; H 8.23, 8.11; P 12.93, 13.03. $C_{10}H_{19}O_4P$. Calculated, %: C 51.28, H 8.18, P 13.22.

Ethyl [2-(ethoxycarbonyl)-4-methylpentyl](vinyl)phosphinate (IIIb). Yield 31%, bp 123–127°C (0.8 mm Hg), n_D^{20} 1.4500. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.87–0.92 2t (6H, $2CH_3$); 1.23–1.35 m (6H, $2CH_3$), 1.40 m (1H, CH), 1.58 m (2H, CH_2CH), 1.82 m (1H, CH_2P), 2.30 m (1H, CH_2P), 2.81 m [1H, CHC(O)], 3.98 m (2H, CH_2OP), 4.12 m (2H, CH_2OC), 6.08–6.30 m (3H, $CH{=}CH_2$). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 41.1, 40.7. Found, %: C 56.34, 56.23; H 9.13, 9.17; P 11.11, 11.03. $C_{13}H_{25}O_4P$. Calculated, %: C 56.51, H 9.12, P 11.21.

Ethyl [2,3-bis(methoxycarbonyl)propyl](vinyl)phosphinate (IIIc). Yield 32%, bp 161–165°C (0.7 mm Hg), n_D^{20} 1.4620. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, CH_3); 2.02 m (1H, CH_2P), 2.27 m (1H, CH_2P), 2.83 d [2H, $CH_2C(O)$], 3.18 m [1H, CHC(O)], 3.67 s (3H, CH_3O), 3.72 s (3H, CH_3O), 4.08 m (2H, CH_2O), 6.05–6.45 m (3H, $CH{=}CH_2$). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 40.8, 40.0. Found, %: C 48.03, 47.94; H 7.05, 6.97; P 10.77, 10.73. $C_{11}H_{19}O_6P$. Calculated, %: C 47.48, H 6.88, P 11.13.

Ethyl [2,4-bis(ethoxycarbonyl)butyl](vinyl)phosphinate (IIId). Yield 34%, bp 168–171°C (0.5 mm Hg), n_D^{20} 1.4550. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (3H, CH_3); 1.28 t (3H, CH_3); 1.32 t (3H, CH_3); 1.83 m (1H, CH_2P), 1.98 m (2H, CH_2CH), 2.21 m (1H, CH_2P), 2.33 t [2H, $CH_2C(O)$], 2.40 t [2H, $CH_2C(O)$], 2.82 m [1H, CHC(O)], 3.95 m (2H, CH_2O), 4.10 m (2H, CH_2O), 6.00–6.45 m (3H, $CH{=}CH_2$). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 40.7, 40.1. Found, %: C 52.33, 52.24; H 7.95, 8.07; P 9.51, 9.43. $C_{14}H_{25}O_6P$. Calculated, %: C 52.50, H 7.87, P 9.67.

2-Substituted [2-(hydroxycarbonyl)ethyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acids (pseudo-γ-glutamylpeptides) (I). A mixture of 30 mmol of diethyl acetamidomalonate, 32–33 mmol of vinylphosphinate **IIIa**–**IIId**, and 70 mmol of thoroughly ground potassium carbonate was stirred in 30 ml of absolute THF under reflux in the presence of tetrabutylammonium bromide (0.3–0.5 g) until acetamidomalonic ester was consumed completely (~12–15 h). The reaction progress was monitored by TLC (chloroform–acetone, 4–5 : 1), R_f 0.5–0.6 (Silufol). The reaction mixture was cooled and filtered, and the filtrate was concentrated in a vacuum. The residue was partitioned in 70 ml of chloroform and 30 ml of water. The aqueous phase was neutralized with 6 N HCl and extracted with chloroform (2 × 30 ml). The combined organic extract was concentrated in a vacuum, and the oily residue was adduct **VIIa**–**VIId** (δ_P 53–58 ppm) contaminated (5–10%) with starting vinylphosphinate **IIIa**–**IIId** (δ_P 40–42 ppm). The residue was heated under reflux with 80 ml of 6 N HCl for 15–17 h and then cooled to room temperature and washed with ether or toluene (3 × 30 ml) and concentrated in a vacuum. The residue was purified on a KU IKhT(H^+) column (volume 200 ml), eluent water and 0.5–0.7 N HCl. Fractions showing a positive ninhydrin reaction were evaporated, and the residue was dissolved in 25 ml of aqueous ethanol and treated with excess propylene oxide. Additional recrystallization from aqueous ethanol gave target aminophosphinic acids **Ia**–**Id** as mixtures of two diastereoisomers. The spectral and analytical data show that pseudopeptides **Ia**, **Ic**, and **Id** crystallize as ethanol solvates, and the ethanol content of the solvates is independent of the composition of the ethanol–water mixture used for crysllization. Pseudopeptide **Ib** was isolated in the free state. The yields of pseudopeptides were 31–43% (calculated per acetamidomalonic ester).

[2-(Hydroxycarbonyl)propyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acid (pseudo-γ-glutamylalanine) (Ia). Yield 43%, mp 93–97°C (frothing), 174–178°C (decomp.). ^{1}H NMR spectrum (D_2O, δ, ppm): 0.95 t (3/2H, CH_3), 1.05 d (3H, CH_3, J_{HH} 7.5 Hz), 1.52 m [3H, CH_2P + CH (one of $CHCH_2P$)], 1.90 m [3H, CH_2CHN + CH (one of $CHCH_2P$)], 2.60 m (1H, $CHCH_3$), 3.43 q (2/2H, CH_2O), 3.78 t (1H, CHN). ^{31}P NMR spectrum (D_2O, δ, ppm): 45.1, 43.5 (~5%). ^{13}C NMR spectrum (D_2O), δ, ppm: 17.08 s (CH_3), 18.86 d (J 7.85 Hz, CH_3CH), 23.58 s (CCH_2CH), 25.84 d (J 92.15 Hz, PCH_2CH_2), 32.73 d (J 91.90 Hz, PCH_2CH), 34.48 s ($CHCH_3$), 54.23 d (J 15.59 Hz, CHN), 57.71 s (CH_2O), 172.89 s [C(O)CHN], 180.89 d (J 8.35 Hz, [C(O)$CHCH_3$]. Found, %: C 38.93, 39.07; H 6.97, 7.05; N 4.95, 4.91; P 11.03, 10.87. $C_8H_{16}NO_6P \cdot 0.5C_2H_5OH$. Calculated, %: C 39.13, H 6.93, N 5.07, P 11.21.

[2-(Hydroxycarbonyl)-4-methylpentyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acid (pseudo-γ-glutamylvaline) (Ib). Yield 41%, mp 201–204°C (decomp.). ^{1}H NMR spectrum (D_2O + DCl, δ, ppm): 0.50 d (3H, CH_3, J_{HH} 7.7 Hz), 0.54 d (3H, CH_3, J_{HH} 7.7 Hz), 1.08 m [1H, $CH(CH_3)_2$], 1.23 m [2H, $CH_2CH(CH_3)_2$], 1.48–1.75 m (3H, CH_2CH_2P +

one of CHCH_2P), 1.75–1.98 m (3H, CH_2CH_2P + one of CHCH_2P), 2.42 m [1H, $PCH_2CHC(O)$], 3.83 t (1H, CHN). ^{31}P NMR spectrum (D_2O + DCl, δ, ppm): 53.6, 53.2 (~7%). ^{13}C NMR spectrum (D_2O + DCl), δ, ppm: 21.37 s (CH_3), 22.00 s (CH_3), 22.35 d (*J* 2.82 Hz, PCH_2CH_2), 24.46 d (*J* 91.50 Hz, PCH_2CH_2), 25.37 s [$CH(CH_3)_2$] 30.36 d (*J* 91.50 Hz, PCH_2CH), 37.48 d (*J* 3.92 Hz, PCH_2CH), 42.76 d (*J* 12.27 Hz, PCH_2·$CHCH_2$), 52.76 d (*J* 16.80 Hz, *C*HN), 170.90 s [*C*(O)CHN], 179.60 d (*J* 4.63 Hz, [*C*(O)$CHCH_2$]. Found, %: C 44.49, 44.53; H 7.67, 7.73; N 4.59, 4.67; P 10.37, 10.31. C11H22NO6P. Calculated, %: C 44.75, H 7.51, N 4.74, P 10.49.

[2,3-Bis(hydroxycarbonyl)propyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acid (pseudo-γ-glutamylaspartate) (Ic). Yield 40%, mp 102–105°C (foaming), 167–172°C (decomp.). ^{1}H NMR spectrum (D_2O, δ, ppm): 1.10 t (2/3 × 3H, CH_3), 1.60–1.85 m [3H, CH_2P + CH (one of CH·CH_2P)], 2.00–2.20 m [3H, CH_2CHN + CH (one of CHCH_2P)], 2.73 d [1H, $CH_2C(O)$], 2.77 br. s [1H, $CH_2C(O)$], 3.04 m [1H, $CHC(O)$], 3.57 q (2/3 × 2H, CH_2O), 3.99 t (1H, CHN). ^{31}P NMR spectrum (D_2O), δ, ppm: 44.5, 43.0 (~6%). ^{13}C NMR spectrum (D_2O), δ, ppm: 17.05 s (CH_3), 23.44 s (CH_2CHN), 25.67 d (*J* 91.55 Hz, PCH_2CH_2), 30.54 d (*J* 90.94 Hz, PCH_2CH), 36.13 s [$PCH_2CHC(O)$], 36.88 d [*J* 7.55 Hz, $CH_2C(O)$], 53.93 d (*J* 15.04 Hz, *C*HN), 57.70 s (CH_2O), 172.46 s [*C*(O)CHN], 176.04 s [*C*(O)CH_2], 178.54 d [*J* 9.20 Hz, *C*(O)$CHCH_2$]. Found, %: C 37.62, 37.57; H 6.17, 6.23; N 4.05, 4.09; P 9.23, 9.13. $C_9H_{16}NO_8P \cdot 2/3C_2H_5OH$. Calculated, %: C 37.85, H 6.15, N 4.27, P 9.44.

[2,4-Bis(hydroxycarbonyl)butyl][3-amino-3-(hydroxycarbonyl)propyl]phosphinic acid (pseudo-γ-glutamylglutamate) (Id). Yield 31%, mp 100–104°C (foaming), 181–187°C (decomp.). ^{1}H NMR spectrum (D_2O, δ, ppm): 1.13 t (3H, CH_3), 1.60–1.85 m (3H, CH_2P + one of CHCH_2P), 1.85–1.95 m (2H, CH_2CHN), 1.95–2.15 m [3H, CH_2·$CH_2C(O)$ + one of CHCH_2P], 2.45 t [2H, $CH_2C(O)$], 2.73 m [1H, $CHC(O)$], 3.60 q (2H, CH_2O), 3.95 t (1H, CHN). ^{31}P NMR spectrum (D_2O), δ, ppm : 43.9, 42.4 (~5%). ^{13}C NMR spectrum (D_2O), δ, ppm: 17.09 s (CH_3), 23.60 s (CH_2CHN), 25.76 d (*J* 90.49 Hz, PCH_2CH_2), 28.70 d (*J* 9.86 Hz, CH_2CH_2·C(O)], 31.30 d (89.17 Hz, PCH_2CH), 31.45 s [$CH_2C(O)$], 39.32 s [CHC(O)], 54.12 d (*J* 13.75 Hz, CHN), 57.73 s (CH_2O), 173.54 d [*J* 8.70 Hz, *C*(O)·CH], 177.80 s [*C*(O)CH_2], 179.29 s [*C*(O)CHN]. Found, %: C 40.06, 40.17; H 6.83, 6.78; N 3.85, 3.81; P 8.53, 8.44. $C_{10}H_{18}NO_8P \cdot C_2H_5OH$. Calculated, %: C 40.34, H 6.77, N 3.92, P 8.67.

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