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To the 80th Anniversary of B.I. Ionin

Amidoalkylation of Phosphorous Acid

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Abstract—A convenient approach to prepare *N*-protected α-aminophosphonic acids (phospho-isosteres of natural amino acids) via amidoalkylation of phosphorous acid in a mixture of acetic anhydride and acetyl chloride upon cooling has been developed.

Keywords: amino acids phospho-isostere, *N*-alkyloxycarbonyl-α-aminophosphonic acid, alkyl carbamate, Oleksyszyn reaction

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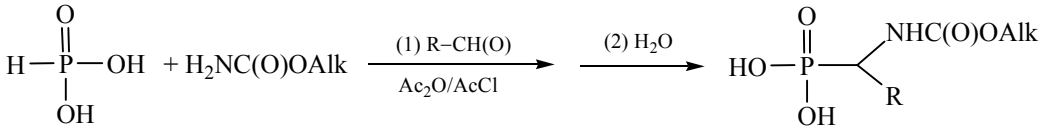
One of the approaches to discover promising physiologically active substances is synthesis of structural analogs of natural compounds of oligopeptide nature [1–5]. *N*-Protected phospho-isosteres of natural amino acids are convenient building blocks for peptide synthesis [4, 5]. Amide version of the Kabachnik–Fields reaction can serve as a convenient method to prepare *N*-protected α-amino-phosphoryl compounds [6–9]. Originally, the reaction was carried out via amidoalkylation of phosphorus(III) chlorides in acetic acid medium (the Oleksyszyn reaction) [10–14]. Further modification with dialkyl phosphites in acetyl chloride or in a mixture of acetic acid and thionyl chloride involving aldehydes, ketones, amides, or carbamates [15–19] was not widely applied, possibly due to pronounced dealkylation of the ester moieties at the phosphorus atom and hydrolysis of other functional acid-sensitive groups [5–7].

Development of convenient methods of amidoalkylation of phosphorous acid, a simple hydrophosphoryl compound containing no ester linkages, is undoubtedly interesting. In this regard a pioneering report on synthesis of free α-amino-phosphonic acids starting from phosphorous acid in boiling acetic anhydride followed by acid hydrolysis is remarkable [20]. Herein, we propose a modification of the approach described in ref. [20] in order to preserve the protective group at the nitrogen atom of α-amino-phosphonic acid. Aldehydes containing substituent isosteric to the corresponding natural amino acid were investigated as the carbonyl components (Scheme 1).

Previously we elaborated the optimal conditions of *N*-protected α-amino-phosphoryl compounds preparation using alkyl carbamates as agent for amidoalkylation of hydrophosphoryl compounds, more efficient as compared with amides [6–9].

In the present work interaction of phosphorous acid with the corresponding aldehydes and methyl or ethyl carbamates as amide component was performed in a

Scheme 1.



I–VII

Alk = Me, Et; R = Me, *i*-Pr, *i*-Bu, Ph, *p*-Cl-C_6H_4.

mixture of acetic anhydride and acetyl chloride upon cooling. Those reaction conditions allowed preservation of the protective function at the nitrogen atom to obtain *N*-alkyloxycarbonyl-α-aminophosphonic acids **I–VII** in good yields. The proposed approach is promising for peptide synthesis.

EXPERIMENTAL

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded with a Bruker DPX-200 Fourier spectrometer referenced to internal TMS or external 85% H_3PO_4. Melting points were determined with a Boetius PHMK instrument or using open capillary method. TLC analysis was carried out on Silufol plates, Merck glass plates coated with silica gel UV-254 (0.2 mm) eluting with chloroform–isopropanol (7–3%) mixture, or on Alufol plates (Kavalier), developing with iodine vapor, UV light, or ninhydrin solution for amino acid analysis.

Methyl carbamate, ethyl carbamate, acetic anhydride, acetic acid, acetyl chloride, and phosphorous acid were purchased from Alfa Aesar. Benzaldehyde, acetaldehyde, and isobutyric and isovaleric aldehydes were purchased from Acros Organics.

***N*-Alkyloxycarbonyl-α-aminophosphonic acids (I–VII) (general procedure).** Crystalline phosphorous acid (5 mmol) was added to 5–8 mL of a mixture of acetic anhydride and acetyl chloride, (1–3) : 1 upon stirring. Then 6.5 mmol of the appropriate aldehyde was added dropwise at 5–10°C. The reaction progress was monitored with ^{31}P NMR. After the reaction was complete, the mixture was poured into 20–25 mL of icy water, and volatile compounds were evaporated in vacuum.

Acids **I–IV** prepared from aliphatic aldehydes were isolated as follows. The oily residue was partitioned between 20–25 mL of water and 10 mL of chloroform. The aqueous layer was separated, washed with diethyl ether (2 × 10 mL), and evaporated in vacuum. Pale yellowish oily residue was treated with benzylamine or cyclohexylamine (10 mmol) in an aqueous alcohol solution, and the corresponding phosphonic acid salts **I–IV** were crystallized from ethanol–diethyl ether mixture [1 : (3–5)].

Acids **V–VII** prepared from aromatic aldehydes were isolated as follows. The oily residue was partitioned between 20–25 mL of ethyl acetate and 10 mL of water. The organic layer was separated and evaporated. The residue was partitioned between 10 mL of chloroform and 25–35 mL of saturated aqueous $NaHCO_3$ solution. Then the aqueous layer was separated, extracted with 5–7 mL of diethyl ether, acidified to pH ~ 1, and extracted with chloroform or ethyl acetate (3 × 15 mL). The organic layer was separated, dried over magnesium or sodium sulfate, and evaporated. The residue was crystallized from diethyl ether.

1-(*N*-Methyloxycarbonyl)aminoethylphosphonic acid (Ia). Yield 67%, oily substance. ^{1}H NMR spectrum (MeOH-d_4), δ, ppm: 1.33 d.d (3H, CH_3, $^3J_{PH}$ 16.1, $^3J_{HH}$ 7.3 Hz), 3.64 s (3H, CH_3O), 3.94 m (1H, PCHN). ^{13}C NMR spectrum (MeOH-d_4), δ_C, ppm: 16.1, 45.5 d ($^1J_{PC}$ 157.0 Hz), 52.8, 159.0 d ($^3J_{PC}$ 5.1 Hz). ^{31}P NMR spectrum (MeOH-d_4): δ_P 24.9 ppm.

Bis(cyclohexylammonium) 1-(*N*-methyloxycarbonyl)aminoethylphosphonate (Ib). Yield 73%, mp 136–138°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.10–1.35 m (13H, $\underline{CH_3}CH$, 10CH, cyclohexyl), 1.45–1.95 m (10H, cyclohexyl), 3.03 m (2H, 2CHN), 3.54 s (3H, CH_3O), 3.63 m (1H, PCHN). ^{31}P NMR spectrum (D_2O): δ_P 20.5 ppm. Found, %: C 50.21, 50.15; H 9.68, 9.57; N 10.82, 10.77. $C_4H_{10}NO_5P{\cdot}2C_6H_{11}NH_2$. Calculated, %: C 50.38; H 9.51. N 11.02

Bis(benzylammonium) 1-(*N*-methyloxycarbonyl)-aminoethylphosphonate (Ic). Yield 81%, mp 86–89°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.10 d.d (3H, CH_3, $^3J_{PH}$ 15.2, $^3J_{HH}$ 7.3 Hz), 3.46 s (3H, CH_3O), 3.55 m (1H, PCHN), 4.01 br.s (4H, $2CH_2N$), 7.30 br.s (10H, 2Ph). ^{31}P NMR spectrum (D_2O): δ_P 20.4 ppm. Found, %: C 54.21, 54.05; H 7.18, 7.27; N 10.42, 10.37. $C_4H_{10}NO_5P{\cdot}2C_6H_5CH_2NH_2$. Calculated, %: C 54.40; H 7.10; N 10.57

1-(*N*-Ethyloxycarbonyl)aminoethylphosphonic acid (IIa). Yield 75%, oil. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.10 t (3H, CH_3), 1.20 d.d (3H, CH_3, $^3J_{PH}$ 16.6, $^3J_{HH}$ 7.3 Hz), 3.83 m (1H, PCHN), 3.98 q (2H, CH_2O, $^3J_{HH}$ 7.0 Hz). ^{31}P NMR spectrum (D_2O): δ_P 24.7 ppm.

Bis(cyclohexylammonium) 1-(*N*-ethyloxycarbonyl)aminoethylphosphonate (IIb). Yield 83%, mp 132–133°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.00–1.37 m (16H, $\underline{CH_3}CH_2$, $\underline{CH_3}CH$, 10CH, cyclohexyl), 1.45–1.97 m (10H, cyclohexyl), 3.03 m (2H, 2CHN), 3.46 m (1H, PCHN), 3.98 q (2H, CH_2O, $^3J_{HH}$ 7.0 Hz). ^{31}P NMR spectrum (D_2O): δ_P 18.5 ppm. Found, %: C 51.40, 51.33; H 9.90, 10.05; N 10.54, 10.47. $C_5H_{12}NO_5P{\cdot}2C_6H_{11}NH_2$. Calculated, %: C 51.63; H 9.69; N 10.62.

Bis(benzylammonium) 1-(*N*-ethyloxycarbonyl) aminoethylphosphonate (IIc). Yield 76%, mp 91–92°C.

^{1}H NMR spectrum (D_2O), δ, ppm: 1.05–1.35 m (6H, $\underline{CH_3}CH_2$, $\underline{CH_3}CH$), 3.44 m (1H, PCHN), 3.98 q (2H, CH_2O, $^3J_{HH}$ 7.0 Hz), 4.07 br.s (4H, $2CH_2N$), 7.25–7.50 m (10H, 2Ph). Found, %: C 55.19, 55.31; H 7.47, 7.53; N 10.32, 10.40. $C_5H_{12}NO_5P{\cdot}2C_6H_5CH_2NH_2$. Calculated, %: C 55.47; H 7.35; N 10.21.

1-(*N*-Ethyloxycarbonyl)amino-2-methypropylphosphonic acid (IIIa). Yield 64%, oil. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.87 d (6H, $2CH_3$, $^3J_{HH}$ 6.4 Hz), 1.13 t (3H, CH_3, $^3J_{HH}$ 7.1 Hz), 2.05 m (1H, CH), 3.87 m (1H, PCHN), 3.97 q (2H, CH_2O, $^3J_{HH}$ 7.1 Hz), 5.90 d (1H, NH, $^3J_{HH}$ 8.3 Hz). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 br.s (6H, $2CH_3$), 1.13 t (3H, CH_3, $^3J_{HH}$ 6.9 Hz), 2.19 m (1H, CH), 3.91 m (1H, PCHN), 4.13 m (2H, CH_2O), 5.65 d (1H, NH, $^3J_{HH}$ 7.3 Hz), 8.90–9.80 m (2H, 2POH). ^{31}P NMR spectrum ($CDCl_3$): δ_P 26.3 ppm. ^{31}P NMR spectrum (DMSO-d_6): δ_P 22.7 ppm.

Bis(benzylammonium) 1-(*N*-ethyloxycarbonyl) amino-2-methylpropylphosphonate (IIIb). Yield 70%, mp 108–109°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90–1.30 m (6H, $\underline{CH_3}CH_2$, $\underline{CH_3}CH$), 3.44 m (1H, PCHN), 3.65–4.05 m (6H, CH_2O, $2CH_2N$), 6.26 br.s (1H, NH), 7.15–7.50 m (10H, 2Ph). ^{1}H NMR spectrum (D_2O), δ, ppm: 0.79 d (6H, $2CH_3$, $^3J_{HH}$ 6.9 Hz), 1.13 t (3H, CH_3, $^3J_{HH}$ 6.9 Hz), 2.02 m (1H, CH), 3.34 d.d (1H, PCHN, $^3J_{PH}$ 18.1, $^3J_{HH}$ 3.5 Hz), 3.96 m (2H, CH_2O), 4.03 br.s (4H, $2CH_2N$), 7.28–7.43 m (10H, 2Ph). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.7, 17.4, 43.7, 45.4 d ($^1J_{PC}$ 146.4 Hz), 59.5, 122.3, 127.3, 128.1, 128.3, 130.1, 138.8, 155.9 d (C=O, $^3J_{PC}$ 9.9 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 13.8, 16.9, 21.1 d ($^3J_{PC}$ 11.3 Hz), 29.4, 43.3, 44.7, 55.7 d ($^1J_{PC}$ 140.2 Hz), 61.7, 126.6, 126.8, 128.5, 128.8, 129.1, 134.2, 159.2 d ($^3J_{PC}$ 11.1 Hz). ^{31}P NMR spectrum (D_2O): δ_P 18.8 ppm. ^{31}P NMR spectrum (DMSO-d_6): δ_P 17.5 ppm. Found, %: C 57.15, 57.03; H 7.95, 8.03; N 9.72, 9.57. $C_7H_{16}NO_5P{\cdot}2C_6H_5CH_2NH_2$. Calculated, %: C 57.39; H 7.80; N 9.56.

1-(*N*-Ethyloxycarbonyl)amino-3-methylbutylphosphonic acid (IVa). Yield 71%, oil. ^{1}H NMR spectrum ($CDCl_3$ + drop of TFA), δ, ppm: 0.91 br.s (6H, $2CH_3$), 1.23 t (3H, CH_3, $^3J_{HH}$ 7.0 Hz), 1.50–1.75 m (2H, CH_2), 1.90–2.05 m (1H, CH), 3.74 m (1H, PCHN), 4.12 m (2H, CH_2O), 5.60 m (1H, NH), 9.20–10.20 m (2H, 2POH). ^{31}P NMR spectrum ($CDCl_3$ + drop of TFA): δ_P 27.4 ppm.

Bis(benzylammonium) 1-(*N*-ethyloxycarbonyl)-amino-3-methylbutylphosphonate (IVb). Yield 67%, mp 142–143°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d (6H, $2CH_3$, $^3J_{HH}$ 5.9 Hz), 1.10 t (3H, CH_3, $^3J_{HH}$ 7.1 Hz), 1.43 m (2H, CH_2), 1.60 m (1H, CH), 3.50 m (1H, PCHN), 3.81 br.s (4H, $2CH_2N$), 3.92 m (2H, CH_2O), 6.05 m (1H, NH), 7.25–7.45 m (10H, 2Ph). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 13.9, 20.7, 23.1, 24.5 d ($^3J_{PC}$ 11.7 Hz), 43.1, 48.8 d ($^1J_{PC}$ 143.5 Hz), 61.6, 128.7, 129.0, 129.1, 133.1, 158.4 d (C=O, $^3J_{PC}$ 5.3 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 17.9 ppm. Found, %: C 57.95, 57.88; H 8.16, 8.23; N 9.32, 9.36. $C_8H_{18}NO_5P{\cdot}2C_6H_5CH_2NH_2$. Calculated, %: C 58.27; H 8. 00; N 9.27.

α-(*N*-Methyloxycarbonyl)aminobenzylphosphonic acid (V). Yield 92%, mp 220–221°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.51 s (3H, CH_3O), 4.81 d.d (1H, PCHN, $^2J_{PH}$ 22.5, $^3J_{HH}$ 9.8 Hz), 7.20–7.40 m (5H, Ph), 7.84 d (1H, NH, $^3J_{HH}$ 9.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 51.7, 53.8 d ($^1J_{PC}$ 148.9 Hz), 126.9, 127.5, 127.8, 128.0, 128.1, 137.9, 156.5 d (C=O, $^3J_{PC}$ 9.5 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 17.9 ppm. Found, %: C 44.33, 44.08; H 5.10, 5.20; N 5.77, 5.76. $C_9H_{12}NO_5P$. Calculated, %: C 44.09; H 4.93; N 5.71.

α-(*N*-Ethyloxycarbonyl)aminobenzylphosphonic acid (VI). Yield 87%, mp 133–135°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.14 t (3H, CH_3, $^3J_{HH}$ 7.0 Hz), 3.97 q (2H, CH_2O, $^3J_{HH}$ 7.0 Hz), 4.82 d.d (1H, PCHN, $^2J_{PH}$ 22.0, $^3J_{HH}$ 9.8 Hz), 7.10–7.45 m (5H, Ph), 7.71 d.d (1H, NH, $^3J_{PH}$ 2.9, $^3J_{HH}$ 9.8 Hz). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.09 t (3H, CH_3, $^3J_{HH}$ 7.0 Hz), 3.97 q (2H, CH_2O, $^3J_{HH}$ 7.0 Hz), 4.86 m (1H, CHN), 7.30 m (5H, Ph). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.7, 53.7 d ($^1J_{PC}$ 148.6 Hz), 60.2, 126.9 d ($^2J_{PC}$ 2.2 Hz), 127.9, 128.0, 128.2, 129.0, 137.9, 156.1 d (C=O, $^3J_{PC}$ 9.5 Hz). ^{31}P NMR spectrum (DMSO-d_6): δ_P 18.0 ppm. ^{31}P NMR spectrum (D_2O): δ_P 18.2 ppm. Found, %: C 46.08, 46.15; H 5.52, 5.65; N 5.47, 5.58. $C_{10}H_{14}NO_5P$. Calculated, %: C 46.34; H 5.44; N 5.40.

α-(*N*-Ethyloxycarbonyl)amino-*p*-chlorobenzylphosphonic acid (VII). Yield 81%, mp 122°C. ^{1}H NMR spectrum ($CDCl_3$ + drop of TFA), δ, ppm: 1.12 t (3H, CH_3, $^3J_{HH}$ 7.0 Hz), 4.05 q (2H, CH_2O, $^3J_{HH}$ 7.0 Hz), 5.08 m (1H, CHN), 6.00 m (1H, NH), 7.05–7.55 m (5H, Ph), 10.6–10.8 br.s (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.12 t (3H, CH_3, $^3J_{HH}$ 6.9 Hz), 3.97 q (2H, CH_2O, $^3J_{HH}$ 6.9 Hz), 4.84 d.d (1H, PCHN, $^2J_{PH}$ 22.5, $^3J_{HH}$ 9.8 Hz), 6.30–6.60 br.s (POH), 7.30–7.45 m (4H, C_6H_4), 7.79 d ($^3J_{HH}$ 9.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.7, 53.2 d ($^1J_{PC}$

148.6 Hz), 60.4, 127.9, 129.9, 130.0, 131.7, 137.1, 156.1 d (C=O, $^{3}J_{PC}$ 8.8 Hz). ^{31}P NMR spectrum ($CDCl_3$ + drop of TFA): δ_P 27.0 ppm. ^{31}P NMR spectrum (DMSO-d_6): δ_P 17.6 ppm. Found, %: C 41.03, 41.15; H 4.50, 4.53; N 4.97, 4.88. $C_{10}H_{13}ClNO_5P$. Calculated, %: C 40.90; H 4.46; N 4.77.

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