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*****New Phosphorus-Containing Amino Acids and Their Analogs**********as Promising Bioactive Substances*****

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Abstract

The convenient methods for the synthesis of organophosphorus analogs of glycine, *β*-alanine, *γ*-aminobutyric acid, sarcosine, and proline bearing three-, four- and five-coordinate phosphorus moieties have been developed from readily available synthons under mild reaction conditions. Thus, the aminomethylation of trivalent phosphorus acid esters using the esters of *N*-chloromethyl-*N*-alkoxycarbonylamino acids leads to new phosphorus-containing amino acids in high yields, which represent promising biologically active substances, effective extracting agents, and water-soluble multidentate ligands.

**Key words:** trivalent phosphorus acid esters, aminomethylation, phosphorus-containing amino acids, bioactive substances.

**Introduction**

Functionalized phosphorus-containing amino acids of various structures include structurally similar groups P(O)OH and C(O)OH and therefore are capable of actively interfering with various biochemical processes and exhibiting a broad spectrum of biological activity. These compounds include hydrolytically stable P–C bonds and display antibacterial, antiviral, herbicidal and antitumor properties. Thus, the well-known plant growth regulators glyphosate **A**, glyphosine **B**, and glufosinate **C**, the organophosphorus derivatives of glycine and *α*-aminobutyric acid (Fig. 1), are produced on an industrial scale and are widely used for various purposes [1, 2].

**Figure 1.** Organophosphorus plant growth regulators **A**–**C**.

These compounds exhibit high herbicidal effect and do not accumulate in the environment, easily decomposing under the influence of soil bacteria into biogenic amino acids and phosphorous acid. Moreover, organophosphorus amino acids contain several polarized phosphoryl and carbonyl groups and are promising extracting agents and multidentate chelating ligands [1, 2]. Therefore, a further expansion of this class of organophosphorus compounds seems to be highly interesting. This work is devoted to the synthesis of new representatives containing three-, four- and five-coordinate phosphorus substituents.

**Results and discussion**

As initial synthons, we used readily available *N*-chloromethyl derivatives of *N*-alkoxycarbonylamino acids as well as alkyl and trimethylsilyl esters of trivalent phosphorus acids, which we recently successfully used for the synthesis of a number of promising phosphorus-containing amines, azaheterocycles, amino acids, and peptides [3–5]. Thus, bis(trimethylsiloxy)phosphine readily reacted with electrophilic *N*-chloromethylamides in the presence of triethylamine to form phosphonites **1**, which were easily converted into stable sodium salts of phosphorus-containing glycine, *β*-alanine and *γ*-aminobutyric acid **2** (Scheme 1). The electrophilic esters of *N*-chloromethyl-*N*-alkoxycarbonylamino acids were successfully used by us for the synthesis of new types of functionalized *N*-acylated amino acids, including the fragments of phosphonic and phosphinic acids along with the hydrolysis-stable PCH2N moieties. Thus, the interaction of *N*-chloromethylamides with phosphites and methylphosphonite proceeded smoothly according to the Arbuzov reaction scheme in dichloromethane under mild conditions and led to functionalized phosphonates **3**–**5** and phosphinates **6**–**8**. Phosphonates **4** containing trimethylsilyl groups reacted with dilute solutions of sodium methylate in methanol to form white crystals of water-soluble sodium salts of phosphonic acids **9**, and when treated with methanol excess, phosphonic acids **10**, including the fragments of glycine, *β*-alanine, and *γ*-aminobutyric acid, were formed (Scheme 2). Hydrospirophosphorane **D**, containing the nucleophilic tautomer **E**, was readily aminomethylated with less electrophilic aminals, including sarcosine and proline units, upon heating to 100 °C to form new types of phosphorus-containing amino acids with five-coordinate phosphorus **11**, **12**

**Scheme 1.** Synthesis of organophosphorus amino acids with three-coordinate phosphorus **1**, **2**.

**Scheme 2.** Synthesis of organophosphorus amino acids with four-coordinate phosphorus **3**–**8**.

**Scheme 3.** Synthesis of organophosphorus derivatives of sarcosine and proline with spirophosphoranyl moieties **11**, **12**.

(Scheme 3). The compositions and structures of compounds **1**–**12** were confirmed by elemental analysis and NMR spectroscopy (for the corresponding data, see the Electronic supplementary information (ESI)). Some of the compounds obtained contain amide units NC(O) and are mixtures of two conformers that differ by the NMR signals, which is typical for the stereochemistry of *N-*substituted amides of carboxylic acids. The ratio of the conformers is determined by a complex superposition of the spatial and electronic properties of the substituents at the amide fragments [6, 7].

**Experimental section**

All reactions were carried out under a dry argon atmosphere in anhydrous solvents.

**Phosphonites 1.** A solution of *N*-chloromethyl-*N*-(ethoxycarbonyl)amino acid alkyl ester (65 mmol) in dichloromethane (35 mL) was added dropwise to a stirred solution of bis(trimethylsiloxy)phosphine (90 mmol) in CH2Cl2 (30 mL) at 10 °C. The reaction mixture was stirred at 20 °C for 1 h. Then triethylamine (70 mmol) was added, and the resulting mixture was stirred for another 2 h. The solvent was removed under vacuum, and the residue obtained was treated with pentane (150 mL) and filtered. The filtrate was evaporated to dryness, and the resulting residue was distilled to give phosphonites **1**.

**Sodium salts of amino acids 2, 9.** A solution of phosphonite **1** (40 mmol) or phosphonate **4** (20 mmol) in diethyl ether (30 mL) was added to a stirred solution of sodium methylate (40 mmol) in methanol (70 mL) at 10 °C. The reaction mixture was heated to reflux, and the solvent was distilled off. The residue obtained was kept under vacuum (1 Torr) for 1 h to give compounds **2**, **9** as white crystals.

**Phosphonates 3–5 and phosphinates 6–8.** A solution of *N*-(chloromethyl)amide (35 mmol) in CH2Cl2 (40 mL) was added dropwise to a stirred solution of tri-coordinate phosphorus acid ester (40 mmol) in CH2Cl2 (35 mL) at 10 °C. The reaction mixture was stirred at room temperature for 1 h and then heated to reflux. The solvent was distilled off, and the residue obtained was distilled to give compounds **3**–**8**.

**Amino acids 10.** A solution of phosphonate **4** (40 mmol) in diethyl ether (30 mL) was added upon stirring to methanol (50 mL) at 10 °C. The reaction mixture was heated to reflux, the solvent was distilled off, and the residue obtained was kept under vacuum (1 Torr) for 1 h to give acids **10** as viscous oils or crystals.

**Methyl esters of *N*-(spirophosphoranylmethyl)sarcosine or proline 11, 12.** A mixture of spirophosphorane **D** (100 mmol) and the corresponding aminal (110 mmol) was heated at 100 °C for 2 h. The resulting mixture was distilled under vacuum to give phosphoranes **11**, **12**.

**Conclusions**

Therefore, the convenient methods for obtaining new organophosphorus amino acids with three-, four- and five-coordinate phosphorus substituents, which contain bioactive moieties of glycine, *β*-alanine, *γ*-aminobutyric acid, sarcosine, and proline, were developed. The compounds obtained are of great interest as promising biologically active substances, effective extracting agents, and multidentate ligands.

Electronic supplementary information

Electronic supplementary information (ESI) available online: the detailed experimental section. For ESI, see DOI: 10.32931/io2501a.

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