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LETTERS TO THE EDITOR

Dedicated to the 110th anniversary of M.I. Kabachnik's birth

Synthesis of 2-Amino-5-hydroxy-5-phosphonovaleric Acid

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Abstract—The synthesis of a new analog of 2-amino-5-phosphonovaleric acid (AP5), namely 2-amino-5-hydroxy-5-phosphonovaleric acid, by successive Michael addition of acetamidomalonic ester to acrolein and Abramov's phosphorylation of the aldehydes formed *in situ* was developed.

Keywords: AP acids, NMDA receptor antagonists, HO-AP5, 4-acetamido-4,4-bis(ethyloxycarbonyl)butyraldehyde

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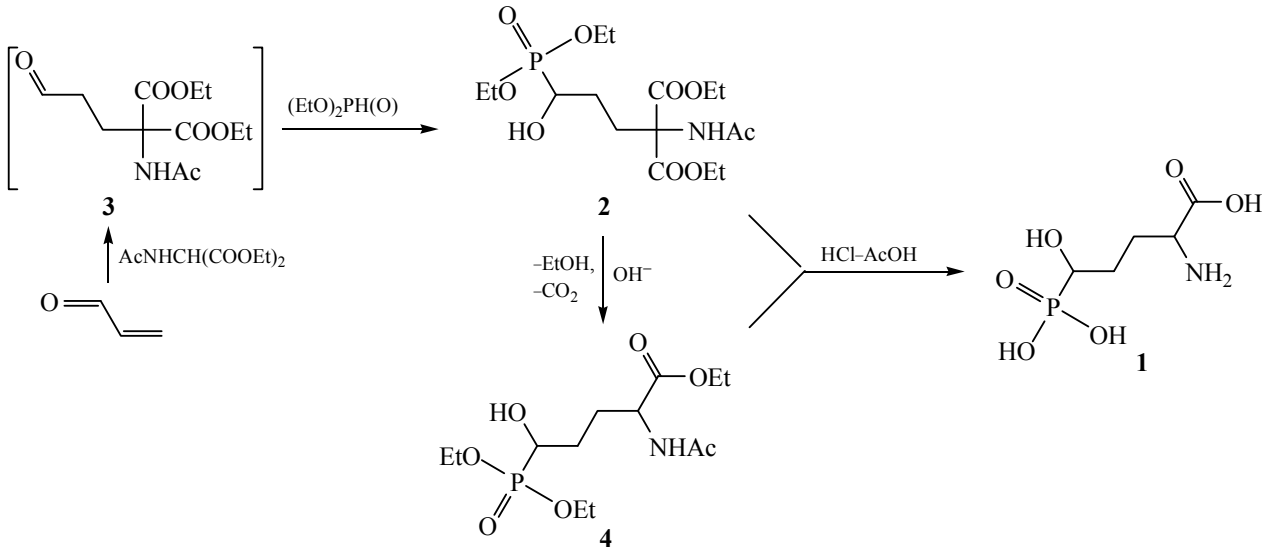
Phosphonic aminocarboxylic acids, which are analogs of monoaminodicarboxylic acids, have a pronounced physiological activity as ligands of glutamate receptors that govern the processes of transmission and processing of information in the central nervous system important for the prevention and treatment of Alzheimer's, Huntington's, Parkinson's and other neurodegenerative and psychoneurological diseases, as well as for learning and memory processes [1, 2]. Among these amino acids 2-amino-5-phosphonovaleric acid (AP5) is an exceptionally potent antagonist of *N*-methyl-D-aspartate (NMDA) receptors [1, 2], one of the subtypes of glutamate receptors. The presence of an intramolecular hydrogen bond underlies the characteristic properties of phosphonic aminocarboxylic acids [3, 4]. In this regard, analogs of AP acids containing keto- or hydroxy-functions in the hydrocarbon chain are of interest [3–5]. However, today analogs of AP5 containing α-hydroxyphosphoryl function are not reported. A probable problem in the synthesis of α-hydroxyphosphonic aminocarboxylic acids may be the lability of these compounds, which are the Abramov reaction products, the reversible addition of hydrophosphorylic compounds to the carbonyl function [6]. This can impede the preparation of α-hydroxyphosphonic aminocarboxylic acids, for example, in the acid hydrolysis stage [3–5].

The aim of this work was the synthesis of 2-amino-5-hydroxy-5-phosphonovaleric acid (HO-AP5) **1**, a potential antagonist of NMDA receptors, an analog of 2-amino-5-phosphonovaleric acid (AP5). The proposed method of one-pot synthesis of α-hydroxyphosphonate **2** containing a protected amino acid function involves the Michael and Abramov addition reactions.

The key intermediate, 4-acetamido-4,4-bis(ethyloxycarbonyl)butyraldehyde **3**, formed by the addition of acetamidomalonic ester to acrolein by Michael reaction, was used in further transformations without isolation from the reaction mixture, since it is a poorly stable compound and has been described as arylhydrazone or other stable derivatives [6–8]. α-Hydroxyphosphonate **2**, the product of the addition of diethyl phosphite to aldehyde **3** by the Abramov reaction, was isolated by chromatography on silica gel after removal of the unreacted diethyl phosphite from the reaction mixture. As a by-product, phosphonate **4** containing one ester function was isolated. It was formed as a result of partial hydrolysis and decarboxylation of the malonic fragment during the work up of the reaction mixture. Unlike phosphonate **2**, compound **4** is a mixture of two diastereomers, which is due to the appearance of a second asymmetric center at the carbon of the aminocarbon fragment. This fact is manifested in the ^{13}C and ^{31}P NMR spectra of phosphonate **4** (Scheme 1).

The hydrolysis of phosphonate **2** in hydrochloric acid resulted in a partial loss of the α-hydroxy-

Scheme 1.



phosphonic moiety with a phosphorus–carbon bond destruction. A positive result was obtained by acid hydrolysis in a mixture of hydrochloric and acetic acids [5]. The hydrolysis of both phosphonates **2** and **4** followed by chromatography on the cation exchanger gave 2-amino-5-hydroxy-5-phosphonovaleric acid (HO-AP5) **1**. It is interesting to note that the spectral data obtained at various pH do not allow to observe the existence of diastereomeric forms of the free amino acid **1**.

In summary, the synthesis of 2-amino-5-hydroxy-5-phosphonovaleric acid, a new analog of AP5 potential NMDA receptor antagonist, was developed.

Diethyl 4,4-bis(ethyloxycarbonyl)-4-acetamido-1-hydroxybutylphosphonate (2). To slurry of 10.8 g (0.05 mol) of acetamidomalonic ester in 20 mL of toluene was added 10 mL of anhydrous methanol containing 0.02 mol of sodium methylate. Next, 4.0 mL (0.06 mol) of freshly distilled acrolein in 10 mL of anhydrous toluene was slowly added dropwise with stirring to the mixture cooled to 5–10°C. The resulting mixture was stirred at room temperature for 5 h. The reaction progress was monitored by TLC until complete consumption of acetamidomalonic ester (R_f ~ 0.4–0.5, chloroform : acetone = 4 : 1). Diethyl phosphite (7.6 g, 0.06 mol) was added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature, then at ~50°C for 4–5 h until the reaction was complete. The reaction progress was monitored by ^{31}P NMR using the ratio of the signal intensities of α-hydroxyphosphonate **2** (δ_P 25.5 ppm) and diethyl phosphite (δ_P 8.5 ppm). The reaction mixture was concentrated in a vacuum, the residue was partitioned between chloroform and water (150 : 30 mL). The organic phase was washed with saturated $NaHCO_3$ solution (2×20 mL), 10% sodium hydroxide solution (1×20 mL), water (2×20 mL), and dried with sodium sulfate. The organic phase was evaporated in a vacuum, the residue was chromatographed on silica gel [eluents: chloroform–toluene (1 : 1), chloroform, chloroform–isopropanol (3–5%)]. Yield 6.6 g (32.1%), an oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (6H, CH_3, $^3J_{HH}$ = 7.0 Hz), 1.30 t (6H, CH_3, $^3J_{HH}$ = 7.0 Hz), 1.42–1.68 m (2H, CH_2), 2.02 s (3H, Ac), 2.32–2.52 m (1H, CH_2), 2.53–2.73 m (1H, CH_2), 3.71–3.85 m (1H, CH), 4.11 q (2H, CH_2O, $^3J_{HH}$ = 7.0 Hz), 4.23 q (2H, CH_2O, $^3J_{HH}$ = 7.0 Hz), 6.84 br. s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.90, 16.40 d ($^3J_{PC}$ = 5.4 Hz), 22.93, 25.90 d ($^2J_{PC}$ = 1.54 Hz), 28.98 d ($^3J_{PC}$ = 14.2 Hz), 62.51 d ($^2J_{PC}$ = 3.5 Hz), 62.61 [C(O)O<u>C</u>], 62.72 d ($^2J_{PC}$ = 3.45 Hz), 66.18 d (CN, $^4J_{PC}$ = 1.5 Hz), 67.17 d ($^1J_{PC}$ = 162.6 Hz), 167.84 [C(O)O], 167.98 [C(O)O], 169.23 [<u>C</u>(O)CH_3]. ^{31}P NMR spectrum ($CDCl_3$): δ_P 25.57 ppm. Mass spectrum (LCMS), *m*/*z*: 412.4 $[M + H]^+$ (calculated for $C_{16}H_{30}NO_9P$: 411.4). Found P, %: 7.65, 7.70. $C_{16}H_{30}NO_9P$. Calculated P, %: 7.53.

Gradually increasing the content of isopropanol in the eluent from 5 to 10%, 2.9 g (17.1%) of **4-ethyloxycarbonyl-4-acetamido-1-hydroxybutylphosphonic acid diethyl ester 4** were isolated as a mixture of two diastereomers (~ 55 : 45). ^{1}H NMR spectrum ($CDCl_3$),

δ, ppm: 1.24 t (3H, CH_3, $^3J_{HH}$ = 7.0 Hz), 1.29 t (6H, CH_3, $^3J_{HH}$ = 7.0 Hz), 1.67–1.85 m (2H, CH_2), 1.87–2.10 m (2H, CH_2), 2.00 s (3H, Ac), 3.77–3.92 m (1H, CHO), 4.02–4.24 m (6H, CH_2O), 4.47–4.65 m (1H, CHN), 6.63 br. d (1H, NH, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (the spectral data for the minor isomer are indicated by asterisk): 14.01, 16.33 d ($^3J_{PC}$ = 5.8 Hz), 22.78* [$\underline{C}H_3C(O)$], 22.84 [$\underline{C}H_3C(O)$], 27.07 d ($^2J_{PC}$ = 1.9 Hz), 27.17* d ($^2J_{PC}$ = 1.9 Hz), 28.12* d ($^3J_{PC}$ = 14.6 Hz), 28.77 d ($^3J_{PC}$ = 14.6 Hz), 51.91 (CHN), 61.28* [C(O)O$\underline{C}$], 61.33 [C(O)O$\underline{C}$], 62.62 d ($^2J_{PC}$ = 7.3 Hz), 66.73* d ($^1J_{PC}$ = 163.3 Hz), 67.17 d ($^1J_{PC}$ = 163.3 Hz), 170.4 [$\underline{C}(O)CH_3$], 172.26 [C(O)O], 172.41 [C(O)O]. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 25.58, 25.77*. Mass spectrum (LCMS), *m*/*z*: 340.3 $[M + H]^+$ (calculated for $C_{13}H_{26}NO_7P$: 339.3). Found P, %: 8.96, 8.82. $C_{13}H_{26}NO_7P$. Calculated P, %: 9.13.

2-Amino-5-hydroxy-5-phosphonovaleric acid (1). Hydrolysis of 4–5 mmol of phosphonate **2** or **4** in 10–14 mL of a mixture of concentrated hydrochloric and acetic acids (1 : 1) was carried out for 13–15 h. The reaction mixture was evaporated in a vacuum, the residue was co-evaporated with water and chromatographed on the cation exchanger eluting with 1 N HCl. Positive ninhydrin fractions were combined and evaporated in a vacuum, the residue was treated in an aqueous alcohol with excess of propylene oxide and crystallized from the alcohol. Yield 63–71%, mp 221–223°C (decomp.). ^1H NMR spectrum (D_2O), δ, ppm: 1.50–2.25 m (4H, CH_2), 3.65 br. t (1H, CHN), 3.97 m (1H, CHO). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 26.22 d ($^2J_{PC}$ = 4.6 Hz), 26.40 d ($^3J_{PC}$ = 6.1 Hz), 52.35 d (CN, $^4J_{PC}$ = 4.6 Hz), 66.34 d (CHOH, $^1J_{PC}$ = 161.8 Hz), 171.38 (C=O). ^{31}P NMR spectrum (D_2O): δ_P 24.1 ppm. Mass spectrum (LCMS), *m*/*z*: 214.1 $[M + H]^+$ (calculated for $C_5H_{12}NO_6P$: 213.1). Found, %: C 27.92, 28.07; H 5.84, 5.90; N 6.33, 6.22; P 14.31, 14.23. $C_5H_{12}NO_6P$. Calculated, %: C 28.18; H 5.68; N 6.57; P 14.53.

^1H, ^{31}P, ^{13}C, ^{13}C Dept NMR spectra were recorded on a Bruker DPX-200 spectrometer. Melting points were determined on a heating block in an open capillaries. For column chromatography silica gel L60/200 (Alfa Aesar) was used, chromatographic analysis was carried out on an Agilent 1100 LC/MSD system equipped with DAD, ELSD and a single-quadrupole mass-selective detector in electrospray ionization mode.

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CONFLICT OF INTERESTS

No conflict of interests was declared by the author.

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