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Synthesis of 11-Amino-9,10-dihydro-9,10-(ethano)anthracen-12-ylphosphonic Acid

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Abstract—Synthesis of a new representative of β-aminophosphonic acids and related esters, namely, 11-amino-9,10-dihydro-9,10-(ethano)anthracen-12-ylphosphonic acid and the respective bis(2-chloroethyl)-phosphonate was carried out.

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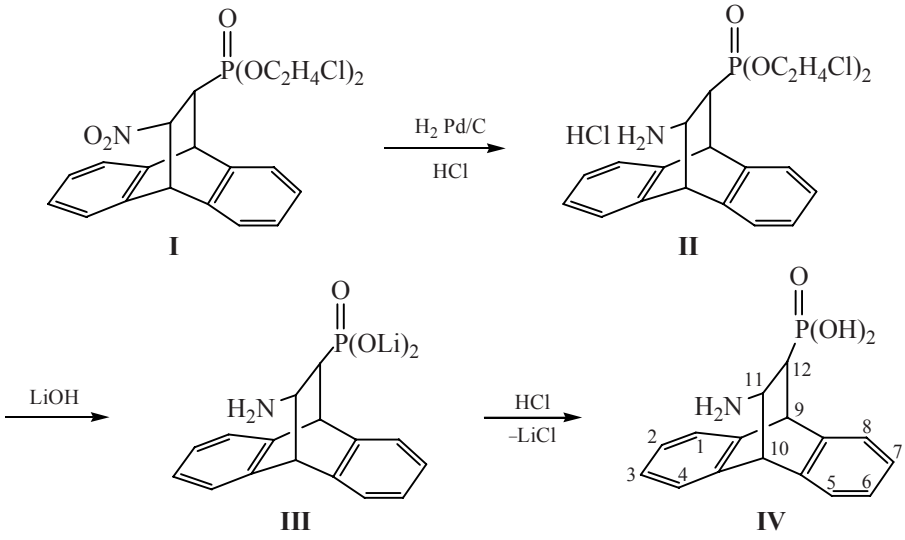
Aminoalkylphosphonates are known to be contained in the plant and animal organisms, fulfilling in them vitally important functions. In most cases the biological activity of aminophosphonic acids is connected with the fact that they compete with the carboxylic analogs for the active centers of enzymes and for cellular receptors and thus specify the execution by them of the functions of growth regulators and enzymes inhibitors, and, therefore, they participate in the metabolic processes of the organism [1, 2]. Furthermore, some of aminophosphonic acids manifest bactericidal, fungicidal, immunotropic activity and play the role of natural antibiotics [3, 4].

In the series of aminoalkylphosphonic acids and related esters a specific position belongs to carbocyclic specimen possessing valuable biological properties. They exhibit the properties of defoliants (*p*-aminophenylphosphonic acid), inhibitors of the cells of leukemia (α-aminocyclopentylphosphonic acid) [3, 4], the antibacterial and antihistaminic means (β-aminocyclopentylphosphonic acid) [5, 6].

This work is the continuation of our studies on the synthesis of cyclic β-aminophosphonic acids [7, 8].

The initial 9,10-dihydro-9,10-(11-nitroethano)-anthracen-12-ylphosphonate (**I**) was prepared by a diene condensation of bis(2-chloroethyl) 2-nitroethenylphosphonate with anthracene [9].

The ethanoanthracene **I** hydrogenation was carried out in methanol as a solvent on acidic palladium on



carbon catalyst at 20°C. The process led to the reduction of the nitro group to the respective amine hydrochloride (**II**) in 81% yield (Table 1). For the preparation of β-aminophosphonic acid the hydrochloride **II** was subjected to alkaline hydrolysis by reflux for 24 h with aqueous solution of LiOH analogously to the procedure in [10]. Thus dilithium salt (**III**) was obtained (yield 88%, mp >300°C), which after acidification to pH~7 afforded 11-amino-9,10-dihydro-9,10-(ethano)anthracen-12-ylphosphonate (**IV**) in 68% yield.

In the ^{31}P NMR spectra of compounds **II–IV** the signals of phosphorus nuclei appear at 30–32 ppm attesting the steric uniformity of the obtained compounds.

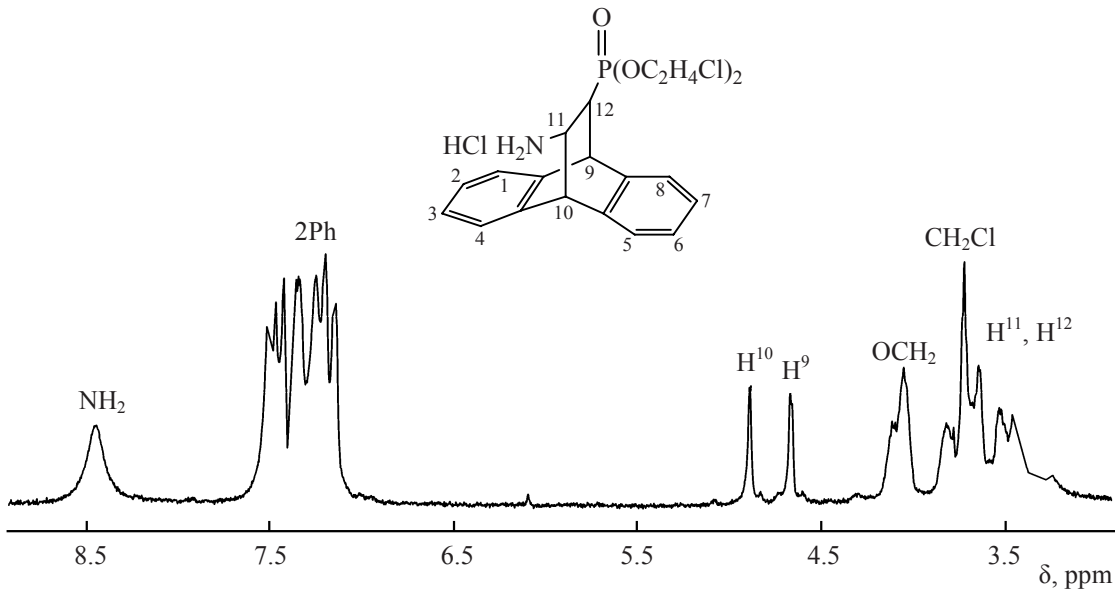
The ^{1}H NMR spectra of the synthesized compounds **II–IV** contain the signals of protons of all structural fragments (Table 1). Aromatic protons H^{1-8} resonate in the range 6.9–7.6 ppm as a broad multiplet, the basic protons $H^{9,10}$ appear as signals in the range 4.60–4.90 ppm. The bridgehead protons $H^{11,12}$ give signals at higher field, in the region of 3.55–3.80 ppm.

According to published data [11, 12], β-aminophosphonic acids like their carboxylic analogs have zwitter-ionic structure. In the spectrum of free aminocycloalkylphosphonic acid **IV** the signal of NH_3^+ group appears at 2.0–2.7 ppm. For the aminophosphonic and aminocarboxylic acids the NH_3^+ signal was registered in the range 1.73–2.6 ppm [10–12]. It is noteworthy that in the spectra of aminoacids the signal of NH_3^+ group can disappear due to the proton exchange with deuterium. In our case the zwitter-ionic structure is confirmed by the downfield shift of the signal of NH_3^+ group protons in the spectrum of ester **II** hydrochloride to 8.4 ppm (see figure). Similar position of NH_3^+ group in the aminophosphonic and aminocarboxylic acid esters hydrochlorides (7.45–7.80 ppm) was reported in [13, 14].

In the IR spectrum of the obtained β-aminophosphonic acid **IV** there are characteristic absorption bands belonging to the groups P=O (1150–1200 cm^{-1}) and P–O$^-$ (1060–1090 cm^{-1}), and a broad band of absorption of NH_3^+ group at 3100–3400 cm^{-1} (overlapped by the band of stretching vibrations of C–H bonds), and at 1560–1660 cm^{-1} (characteristic of bending vibrations of NH_3^+ [10,12]). Thus, the data of IR and ^{1}H NMR spectra allow the assignment of the form of bipolar ion to compound **IV**.

EXPERIMENTAL

The ^{1}H, ^{31}P NMR spectra were registered on a Bruker AC-200 instrument (200 MHz), solvent methanol-d_4 (compound **II**) and dimethylsulfoxide-d_6 (compounds **III,IV**). The proton chemical shifts (δ) were measured relative to external reference (HMDS) with ±0.5 Hz accuracy, ^{31}P shifts relative to the external 85% phosphoric acid. The IR spectra were



^{1}H NMR spectra of bis(2-chloroethyl)-11-amino-9,10-dihydro-9,10-athanoanthracen-12-ylphosphonate hydrochloride (**II**) in CD_3OD.

registered on an Infra-LYM FT-02 spectrometer (in mineral oil).

The initial 9,10-dihydro-9,10-(11-nitroethano)-anthracen-12-ylphosphonate was synthesized according to procedure in [9].

Bis(2-chloroethyl) 11-amino-9,10-dihydro-9,10-ethanoanthracen-12-ylphosphonate hydrochloride (II). To a suspension of 0.6 g of 10% acidic palladium on carbon catalyst in 20 ml of methanol saturated with hydrogen at stirring under the hydrogen flow was poured a solution of 0.5 g of nitroethanoanthracene **I** in 10 ml of methanol. The hydrogenation was carried out to complete consumption of the calculated volume of hydrogen (~120 ml). The catalyst was filtered off, washed with hot methanol, the filtrate was evaporated, and bis(2-chloroethyl) 11-amino-9,10-dihydro-9,10-ethanoanthracen-12-ylphosphonate hydrochloride **II** was isolated with the yield 0.41 g (81%), mp 138–140°C (from methanol). The ^{1}H NMR spectrum (CD_3OD), δ, ppm: 4.70 m (1H, C^9H), 4.90 m (1H, $C^{10}H$), 3.55–3.80 m (2H, $C^{11}H$, $C^{12}H$), 7.00–7.60 m (8H, $C^{1–8}H$), 3.70 m (4H, $2CH_2Cl$), 4.20 m (4H, 2 OCH_2). The ^{31}P NMR spectrum (CD_3OD), δ_P, ppm: 31.00. Found, %: C 51.92, 51.95; H 4.94, 4.97; N 3.13, 3.15; P 6.60, 6.64. $C_{20}H_{23}Cl_3NO_3P$. Calculated, %: C 51.89; H 4.97; N 3.03; P 6.70.

11-Amino-9,10-dihydro-9,10-ethanoanthracen-12-ylphosphonic acid dilithium salt (III). To a solution of 0.5 of hydrochloride **II** in 10 ml of distilled water was added 0.24 g of lithium hydroxide (the hydrochloride to lithium hydroxide molar ratio 1:10). The reaction mixture was refluxed for 24 h, and the crystals precipitated were filtered off and dried. 0.24 g (88%) of compound **III** was obtained, mp >300ºC. The ^{1}H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 4.75 m (1H, C^9H), 4.95 m (1H, $C^{10}H$), 3.62–3.80 m (2H, $C^{11}H$, $C^{12}H$), 6.90–7.50 m (8H, $C^{1–8}H$). The ^{31}P NMR spectrum [$(CD_3)_2SO$], δ_P, ppm: 32.00. Found, %: N 4.48, 4.46. $C_{16}H_{14}Li_2NO_3P$. Calculated, %: N 4.47.

11-Amino-9,10-dihydro-9,10-ethanoanthracen-12-ylphosphonic acid (IV). 0.26 g of dilithium salt **III** was dissolved in 15 ml of hot water and acidified with 10% hydrochloric acid to pH 7. The solution was evaporated, and the dry residue was extracted with ether–ethanol mixture (1:1) (5 ml × 5). The extracts were evaporated, and 0.16 g (68%) of amino-phosphonic acid **IV** was obtained, R_f 0.22. At the prolonged keeping compound **IV** partially crystallizes. The ^{1}H NMR spectrum [$(CD_3)_2SO$], δ, ppm: 4.60 m (1H, C^9H), 4.80 m (1H, $C^{10}H$), 3.55–3.70 m (2H, $C^{11}H$, $C^{12}H$), 7.00–7.50 m (8H, $C^{1–8}H$). The ^{31}P NMR spectrum [$(CD_3)_2SO$], δ_P, ppm: 30.00. Found, %: C 63.83, 63.85; H 5.30, 5.33; N 4.61, 4.64; P 10.25, 10.29. $C_{16}H_{16}NO_3P$. Calculated, %: C 63.79; H 5.32; N 4.65; P 10.30.

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