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Synthesis of Tetraethyl (2-Benzyl-3-oxoisoindolyl-1,1-diyl)-bisphosphonate and Its Properties

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Abstract—The reaction of *o*-phthalyl chloride with sodium diethylphosphite affords a cyclic bisphosphonate, 3,3-bis(diethylphosphono)-1(3*H*)-isobenzofuranone. The reaction of 1(3*H*)-isobenzofuranone with potassium carbonate proceeds through the ring opening and elimination of one phosphonate group to give acyclic α-keto-phosphonate. At the same time, the reaction of bisphosphonate with the concentrated hydrochloric acid does not lead to the ring opening but gives bisphosphonic acid in a good yield. 3,3-Bis(diethylphosphono)-1(3*H*)-isobenzofuranone reacts with benzylamine in the presence of triethylamine with the replacement of endocyclic oxygen atom by benzylamino group, which leads to the formation of the corresponding bisphos-phonate phthalimide, the first representative of a new type of bisphosphonates and phosphorus heterocycles.

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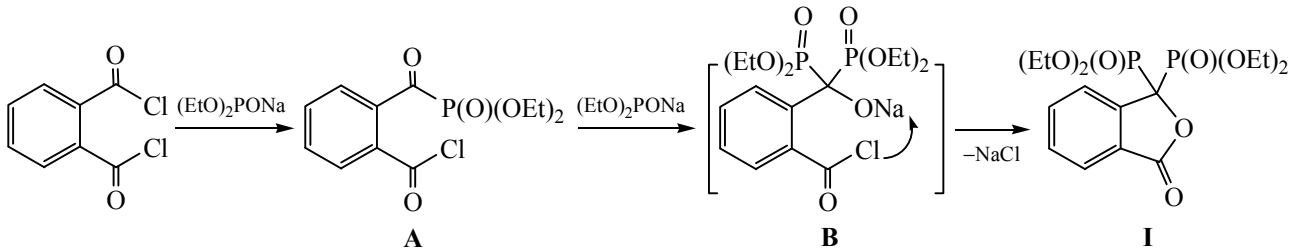
Synthesis of new types of bisphosphonates is of great interest for synthetic chemists [1–3] due to the high biological activity [4, 5]. Some of them are important drugs used in medical practice. On the basis of these compounds the anticancer drugs, antibiotics, and the medicines for osteoporosis treatment were created [5]. For example, pamidronate (ABP), etidronate (HTBP) and chlorodronate (ClMBP) are used as commercial products [1].

In this study we developed a method for the synthesis of bisphosphonates starting from phthaloyl dichloride. Note that the studies on the *o*-phthaloyl dichloride phosphorylation are absent in the literature.

The reaction of *o*-phthaloyl dichloride with sodium diethyl phosphite occurs as 1,1-diphosphorylation accompanied by the intramolecular cyclization involving the second C(O)Cl-group and resulting in 3,3-bis-(diethylphosphono)-1(3*H*)-isobenzofuranone **I**. The reaction apparently proceeds through the formation of ketophosphonate **A**, which reacts with the second molecule of sodium diethylphosphite at the C=O group. The intramolecular cyclization of intermediate **B** gives rise to isobenzofuranone **I**.



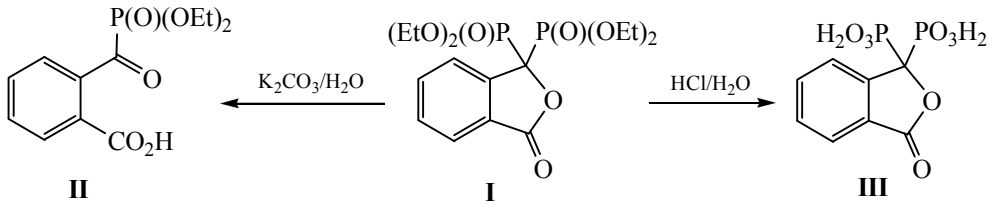
A **B** **I**

The structure of compound **I** was confirmed by the IR spectra, ^{1}H, ^{31}P, and ^{13}C NMR, mass spectra, elemental analysis, and chemical transformations [6]. A characteristic feature of the IR spectra of compound **I** is a significant shift of the band of stretching vibrations of double C=O bond to the region of 1800 cm^{-1}, which confirms the presence of endocyclic C=O group in C(O)O-fragment and is consistent with the cyclic structure of compound **I**. Unlike the acyclic analogs, the signals of compound **I** in the ^{31}P NMR spectra are

shifted downfield by 10–15 ppm to 10.11 ppm. In the ^{13}C NMR spectrum of bisphosphonate **I** the signal of the carbon atom between the two phosphorus atoms is observed as a triplet at 83.26 ppm ($^{1}J_{PC}$ 155.9 Hz), which confirms the presence of 1,1-bisphosphonate fragment and is consistent with the published data for similar compounds [7, 8]. According to the ^{1}H and ^{13}C NMR spectra, the ethoxy groups at the phosphorus atom are not equivalent because of their different positions with respect to the benzene ring. The computer simulation of compound **I** molecule performed using ChemBio3D Ultra 11.0 is consistent with the nonequivalence of ethoxy groups, which are directed upwards and away from the aromatic ring, respectively (Fig. 2). This is also confirmed by the X-ray diffraction analysis of compound **I**, which we shall publish later [6].

The chemical properties of bisphosphonate **I** also confirm its structure. A characteristic feature of bisphosphonate **I** is its instability to hydrolysis in an alkaline medium. Compound **I** is easily hydrolyzed with dilute alkali at room temperature to give α-ketophosphonate **II** and 1-hydroxy-1,1-bisphosphonate **III**, as indicated by the presence of the signals at 16.73 and 1.19 ppm, respectively, in the ^{31}P NMR spectrum. The reflux of the reaction mixture with potassium carbonate leads to the elimination of one diethylphosphonate group and to the formation of acyclic 1-ketophosphonate **II** in good yield.

At the same time, this ring is stable in an aqueous medium in the presence of acid. The boiling of bisphosphonate **I** with the concentrated hydrochloric acid does not lead to the ring opening and gives in good yield bisphosphonic acid **III** obtained earlier by another method [6].



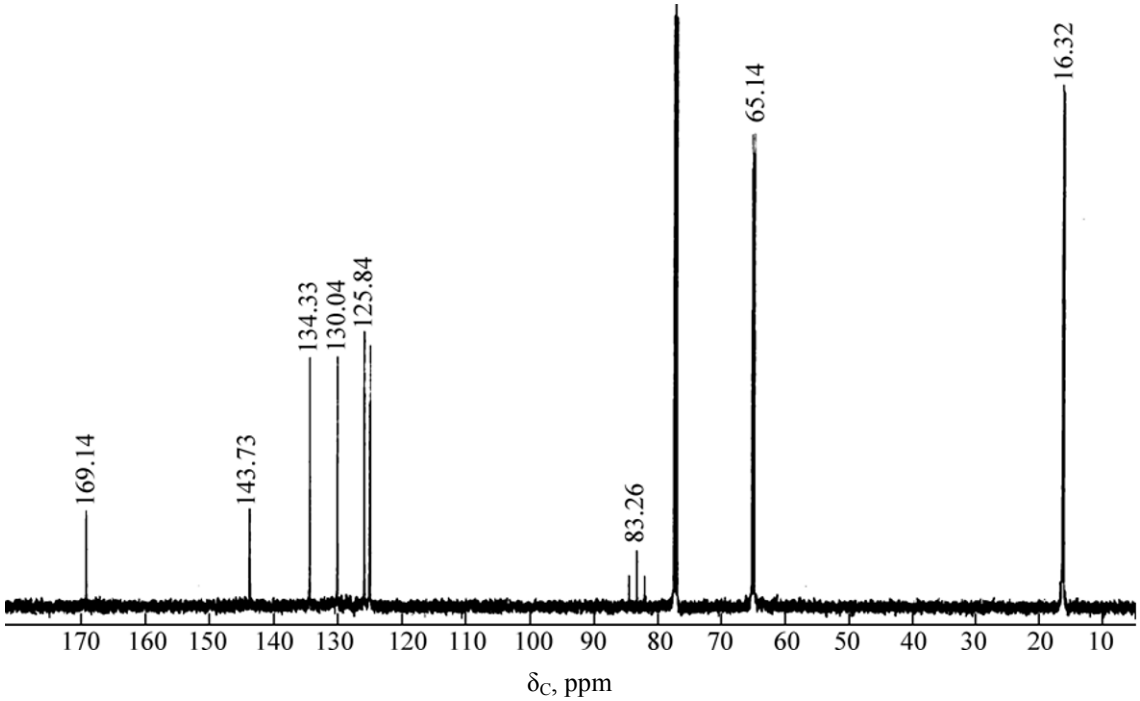
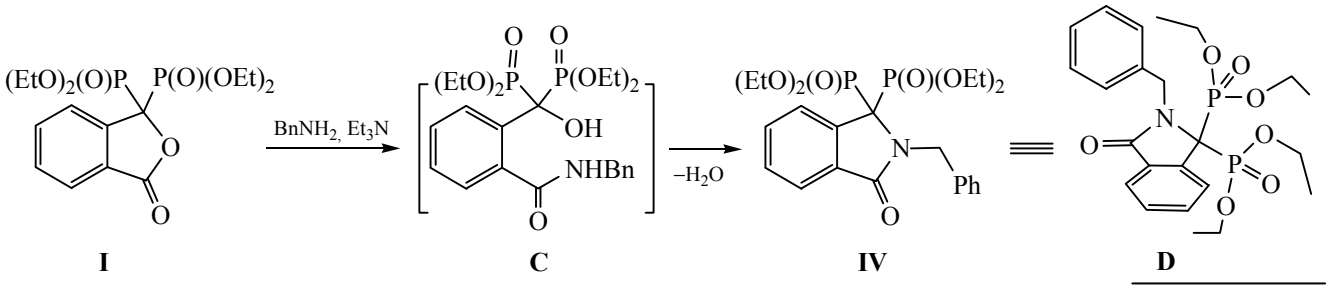


Fig. 1. The ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of diethyl [1-(diethoxyphosphoryl)-1,3-dihydro-3-oxo-1-isobenzofuran-1-yl]-phosphonate **I**.



The reaction of bisphosphonate **I** with benzylamine in the presence of triethylamine with azeotropic distilling off water proceeds with retention of 1,1-bisphosphonate group and leads to the formation of the corresponding phthalimide **IV**.

The reaction of bisphosphonate **I** with benzylamine probably proceeds as a nucleophilic substitution at the C=O group with a ring opening, through the formation of an intermediate compound **C** of 1-hydroxybisphosphonate structure. The monitoring of the reaction process with the ^{31}P NMR spectrum allows detecting the signal at 18.09 ppm, which can be attributed to the intermediate **C**. Subsequently, this intermediate undergoes intramolecular cyclization with the formation of phthalimide **IV**.

The spectroscopic characteristics of compound **IV** are similar to those of compound **I**. In particular, signal in the ^{31}P NMR spectrum is also shifted downfield (δ_P 6 ppm), and phosphonic groups are magnetically nonequivalent. In the ^{1}H and ^{13}C NMR spectra of compound **IV** besides a singlet of CH_2Ph group there are several signals of ethoxy groups at phosphorus atom (CH_3 and CH_2O), which suggests the presence of stable rotamers due to the hindered rotation of the phenyl group around the C–N bond. The ^{13}C NMR spectrum of compound **IV** contains the signals of CH_3- and CH_2O-groups, the singlet of CH_2Ph-group at 43.16 ppm, a doublet of doublets of the α-carbon atom from the PC-group ($^{1}J_{PC}$ 150 Hz), but not a triplet as in the case of compound **I**, indicating some nonequivalence of $(EtO)_2P(O)$ groups, probably due to the

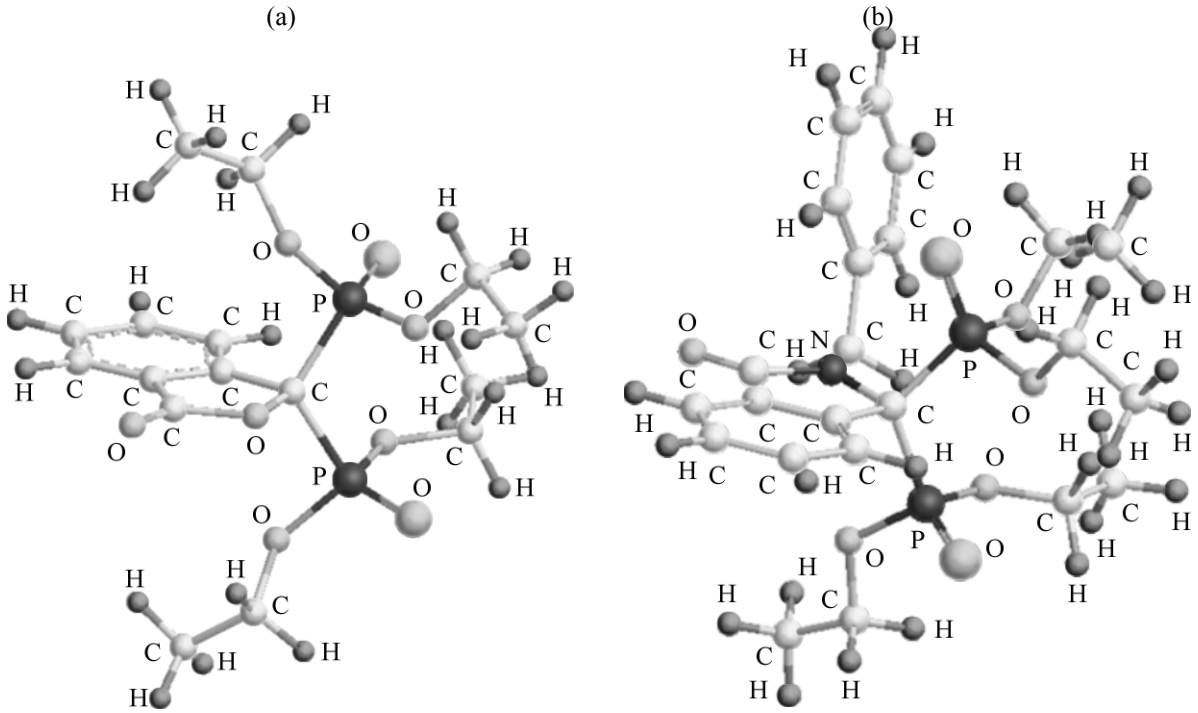


Fig. 2. Models of molecules of (a) 3,3-bis(diethylphosphono)-1(3*H*)-isobenzofuranone **I** and (b) tetraethyl (2-benzyl-3-oxoisoindolyl-1,1-diyl)bisphosphonate **IV** drawn with the help of the program ChemBio 3D Ultra11.0.

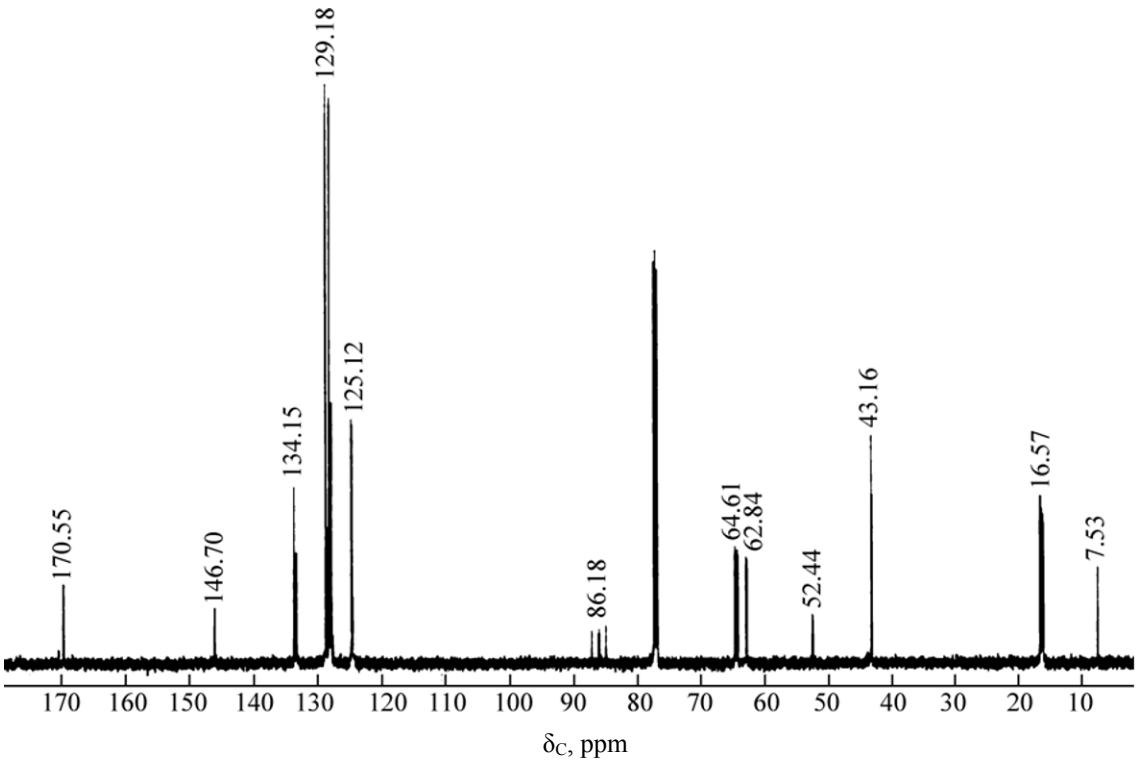
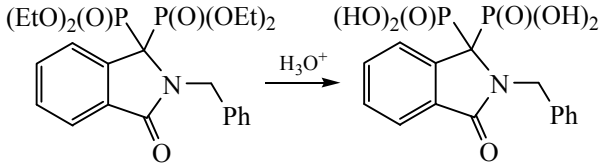


Fig. 3. The ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of tetraethyl (2-benzyl-3-oxoisoindolyl-1,1-diyl)bisphosphonate **IV**.

influence of the benzyl group. There is also a singlet at 170.55 ppm belonging to the carbon of C=O group, and the signals of aromatic carbons (Fig. 3).

Bisphosphonate **IV** is easily hydrolyzed with hydrochloric acid to bisphosphonic acid **VI**. As in the case of bisphosphonate **I**, the reaction proceeds with the retention of the cyclic structure.



IV **V**

The signals of ^{31}P nuclei in the ^{31}P NMR spectrum are shifted downfield to the region of 8 ppm. Two phosphorus atoms are magnetically nonequivalent (δ_P 8.44 and 8.32 ppm). In the ^1H NMR spectrum of compound **V** the proton signals of CH_3, $(EtO)_2P(O)$-, and CH_2N-groups are split, which suggests the presence of stable rotamers due to the hindered rotation around the C–N bond. Unlike the starting **IV**, in the ^{13}C NMR spectrum of compound **V** the signal of α-carbon atom between the two phosphorus atoms appears as a clear triplet at 86.63 ppm with the coupling constant $^1J_{PC}$ 139.59 Hz.

In conclusion, we note that the developed method of phosphorylation of vicinal dicarboxylic acid chlorides may be interesting as a simple approach to the synthesis of phosphonate-containing CO-NH fragment and of PCH(OH)P-pyrophosphate mimetics having wide application in biomedical research and pharmacologic practice.

EXPERIMENTAL

Melting points are uncorrected. The NMR spectra were recorded on a Varian VXR-300 spectrometer at 300 (^1H) and 126.16 MHz (^{31}P) with TMS (^1H) as internal and 85% H_3PO_4 in D_2O (^{31}P) as external references. The IR spectra were obtained on a Vertex 70 IR Fourier spectrometer from KBr pellets or in CCl_4 solution. MS APCI spectra were measured on an Agilent 1100/DAD/MSD VL G1965a instrument. The freshly distilled solvents were used. The reagents were purchased from Merck and used without purification.

Tetraethyl 3-oxo-1,3-dihydroisobenzofuran-1,1-diylbis(phosphonate) (I). To 1.0 g (0.044 mol) of sodium in 40 ml of dry ether was added dropwise 4.7 ml (0.035 mol) of diethylphosphite under cooling. The mixture was stirred for 2–3 h at room temperature until the sodium dissolution. The reaction mixture was

decanted from the residual sodium, and thereto was added dropwise 2.9 ml (0.02 mol) of *o*-phthaloyl dichloride with the stirring and cooling to –40°C. The stirring was continued for 1–2 h, after which the reaction mixture was heated to room temperature and then was refluxed for 1–2 h to complete the reaction. Then a small amount of hexane was added to the mixture for sodium chloride coagulation. Sodium chloride was filtered off, and the residue was washed twice with ethyl acetate. The filtrate was evaporated under reduced pressure, the residue was crystallized from ethyl acetate–hexane mixture (1:2) and dried in a vacuum. Yield 3.20 g (40%). Bisphosphonate **I** was purified by sublimation in a vacuum at 0.1 mm Hg at 100–120°C, mp 90–91°C. IR spectrum (CCl_4), ν, cm^{-1}: 2988.57, 1781.74, 1262.43, 1022.40. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 1.08 t (6H, CH_3, J_{PH} 7), 1.27 t (6H, CH_3, J_{PH} 7), 3.91 m (2H, OCH_2), 4,02 m (2H, OCH_2), 4.26 m (4H, OCH_2), 7.55 d.d (1H, H^5, J_{HH} 6, J_{HH} 8,), 7.69 d.d (1H, H^6, J_{HH} 6, J_{HH} 8), 7.88 d (2H, H^4, H^7, J_{HH} 6). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J,* Hz): 16.09 (CH_3), 16.32 (CH_3), 64.82 (OCH_2), 65.14 (OCH_2), 83.26 t (PC, J_{PC} 155.9), 124.85 d (C^9, J_{PC} 3), 124.95 (C^7), 125.84 (C^4), 130.04 (C^5), 134.33 (C^6), 143.73 (C^8), 169.14 c (C=O). ^{31}P NMR spectrum ($CDCl_3$): δ_P 10.28 ppm. Mass spectrum (APCI), *m*/*z*: 407 [*M* + 1] (calculated *M* 406). Found, %: C 47.30; H 5.85; P 14.92. $C_{16}H_{24}O_8P_2$. Calculated, %: C 47.30; H 5.95; P 15.25.

2-(Diethoxyphosphorylcarbonyl)benzoic acid (II). A mixture of 0.20 g (0.05 mol) of bisphosphonate **I** and 0.2 g (0.015 mol) of K_2CO_3 in 2 ml of water was boiled for 0.5 h until the end of carbon dioxide release. The solution was cooled, acidified with dilute sulfuric acid to pH 2–3 under cooling with ice water. The solution was filtered from the precipitated *o*-phthalic acid and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. Yield 0.12 g, mp 181–185°C. ^1H NMR spectrum [$(CD_3)_2CO$], δ, ppm (*J,* Hz): 1.21 t (6H, CH_3), 3.97 d. q (4H, OCH_2, J_{PH} 7, J_{HH} 7), 6.64 s (1H, CO_2H), 7.63 t (1H, H^5, J_{HH} 6), 7.69 d.d (1H, J_{HH} 6), 7.76 d (2H, H^4, H^7, J_{HH} 6). ^{31}P NMR spectrum ($CDCl_3$): δ_P 1.19 ppm.

3-Oxo-1,3-dihydroisobenzofuran-1,1-diyldiphosphonic acid (III). A mixture of 0.20 g (0.0005 mol) of bisphosphonate **I** and 1 ml of concentrated hydrochloric acid was refluxed for 3–4 h till the end of ethyl chloride release, adding 1 ml of acid every hour. The obtained solution was cooled, evaporated in a vacuum, and dried by azeotropic distilling off water. The residue was crystallized from ethyl acetate and dried. Yield 0.12 g (82.9%), mp > 260°C. ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm (*J*, Hz): 7.57 d.d (1H, H^5, J_{HH} 7), 7.75 d.d (1H, J_{HH} 6), 7.80 d (2H, H^4, H^7, J_{HH} 7). ^{31}P NMR spectrum ($CDCl_3$): δ_P 8.02 ppm [7].

Tetraethyl (2-benzyl-3-oxoisoindolyl-1,1-diyl)bisphosphonate (IV). A mixture of 1.2 g (0.003 mol) of bisphosphonate **I**, 0.4 ml (0.0035 mol) of benzylamine, and 0.4 ml (0.004 mol) of triethylamine in 12 ml of toluene was boiled with simultaneous water removal for 3–4 h. The reaction mixture was evaporated, and the residue was crystallized from anhydrous diethyl ether. Yield 0.6 g (41.0%), mp 170–172°C. IR spectrum (KBr), ν, cm^{-1}: 2984.27, 1764.34, 1259.33, 1232.87, 1064.61. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 0.87 t (J_{HH} 7), 1.06 t (J_{HH} 7), 1.14 t (J_{HH} 7) (intensities ratio 2:2:3) (12H, CH_3), 3.50 m (2H, OCH_2), 3.69 m (2H, OCH_2), 3.95 m (2H, OCH_2), 4.06 m, 4.08, 4.11 (intensities ratio 3:2:2, 2H, CH_2O), 7.31 m (3H, C_6H_5N), 7.47 d.d (1H, J_{HH} 6, J_{HH} 7), 7.50 m (2H, C_6H_5N), 7.62 d.d (1H, H^6, J_{HH} 6, J_{HH} 7), 7.83 d (1H, H^7, J_{PH} 7), 7.86 d (1H, H^4, J_{HH} 6). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J,* Hz): 16.3 (CH_3), 16.6 (CH_3), 43.2 (CH_2N), 62.8 (OCH_2, *J* 7), 64.6 d (OCH_2, *J* 7), 86.1 d.d (CP_2, *J* 147, *J* 150), 125.14, 128.3, 128.67, 128.76, 129.2, 133.8, 134.14 (C^{Ar}), 170.58 (C=O). ^{31}P NMR spectrum ($CDCl_3$): δ_P 6.36 ppm. Found P, %: 12.45. $C_{23}H_{31}NO_7P_2$. Calculated P, %: 12.50.

2-Benzyl-3-oxoisoindoline-1,1-diylbisphosphonic acid (V). A mixture of 1.20 g (0.003 mol) of bisphosphonate **I** and 12 ml of concentrated hydrochloric acid was refluxed for 3 h, then 8 ml of the acid was added and the mixture was refluxed for 1 h to the end of ethyl chloride release. The solution was evaporated under reduced pressure, and the residue was dried in a vacuum and crystallized from 95% ethanol. Yield 0.80 g (87%), mp 240–242°C. IR spectrum (KBr), ν, cm^{-1}: 3033.11, 1778.33, 1289.33, 1199.82, 956.46. ^1H NMR spectrum [$(CD_3)_2SO$], δ, ppm (*J,* Hz): 4.00 s (2H, CH_2N), 7.40–7.56 m (7H, H^5, H^6, C_6H_5), 7.74 d (1H, H^7, J_{HH} 6), 7.78 d (1H, H^4, J_{HH} 8). ^{13}C NMR spectrum [$(CD_3)_2SO$], δ_C, ppm (*J,* Hz): 42.78 (CH_2N), 86.63 t (PC, J_{PC} 139.59), 124.67, 125.45, 125.63, 128.43, 128.82, 129.07, 129.35, 133.41, 134.60, 148.86 (C^{Ar}), 171.41 (C=O). ^{31}P NMR spectrum (D_2O), δ_P, ppm: 8.44, 8.32. Found, %: N 3.68; P 16.16. $C_{15}H_{15}NO_7P_2$. Calculated, %: N 3.65; P 16.16.

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