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RESEARCH ARTICLE

Synthesis of new 1-hydroxy-1,1-bisphosphonic acids

Anastasiia O. Kolodiazhna*, Dmytro V. Prysiazhnuk, Serhiy Yu. Sheiko

V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the NAS of Ukraine, Kyiv, Ukraine

Abstract: A synthetic method for the preparation of 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids, commonly known as dronic acids, has been developed. These compounds were obtained through the formation of the corresponding silyl derivatives at key stages of the synthesis. The developed method provides a simple and convenient approach for the preparation of hydroxybisphosphonates. The resulting compounds are promising substances with potential biological activity.

Keywords: bisphosphonic acids; dronic acids; Arbuzov reaction; hydroxybisphosphonates.

Introduction

1-Hydroxy-1,1-bisphosphonic acids, also known as dronic acids, are a class of bisphosphonic acids characterized by a stable P-C-P fragment and occupy an important place in medicinal chemistry due to their strong affinity for bone mineral and resistance to enzymatic hydrolysis. Their structural similarity to pyrophosphate provides the ability to regulate bone metabolism, making these compounds indispensable in the treatment of osteoporosis, Paget's disease, and oncological lesions of the skeletal system.

Drugs containing the hydroxybisphosphonic fragment are widely used in pharmacology and medicine. For example, well-known pharmaceuticals such as Alendronic acid (Alendra), Ibandronic acid (Bondronat), Zoledronic acid (Zometa), and Risedronic acid (Atelvia) are successfully and extensively applied in clinical practice for the treatment of conditions such as postmenopausal osteoporosis, skeletal damage in patients with breast cancer and metastatic bone lesions, complications following surgical interventions and radiation therapy, and malignancy-associated hypercalcemia (Figure 1) [1, 2, 3, 4]. In addition, the antiproliferative activity of dronic acids against the causative agents of parasitic infections such as malaria, leishmaniasis, and trypanosomiasis has recently been actively investigated [5, 6, 7]. Beyond their clinical applications, dronic acids also serve as valuable synthetic intermediates, offering opportunities for the development of new derivatives with a wide spectrum of biological activities [8, 9] (Figure 1). Therefore, the development of efficient and selective methods for their synthesis remains a relevant and important challenge in modern chemistry and pharmaceutical science.

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* Corresponding author. Tel.: +380-50-870-4187;
e-mail: nastya_k11@ukr.net (A.O. Kolodiazhna)
ORCID: 0000-0002-7990-7830

Results and Discussion

In most cases, hydroxybisphosphonic acids are obtained using the so-called Merk method – the condensation of carbonyl compounds with orthophosphoric acid in the presence of phosphorus trichloride, followed by hydrolysis [5, 6, 7]. However, this method has certain drawbacks, such as harsh reaction conditions and rather low selectivity when complex substrates are used. Another approach employed for the synthesis of bisphosphonates is the phosphorylation of carbonyl compounds (a modification of the Arbuzov/Pudovik reaction), in which carbonyl compounds react with alkyl phosphites and phosphorus sources (PCl_3, $POCl_3$) [10]. Yet this method also has disadvantages,

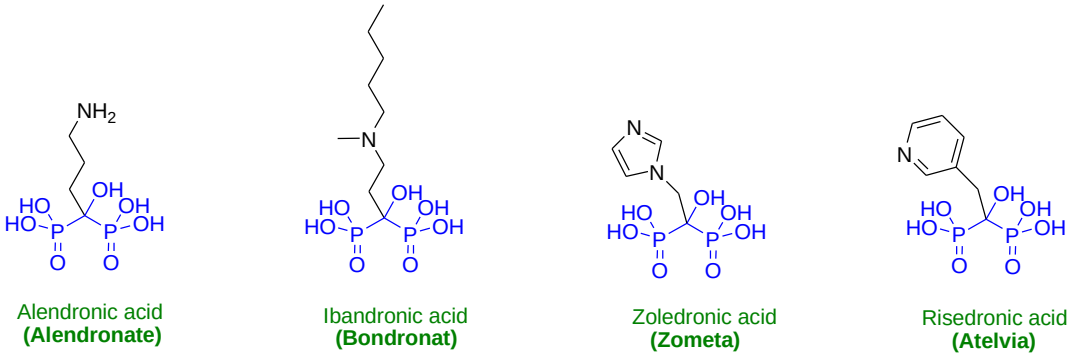

Figure 1. Examples of pharmaceutical preparations based on 1-hydroxy-1,1-bisphosphonic acids.

including the need for aggressive reagents and the occurrence of side reactions. In our work, we obtained a series of 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids using the method described by Marc Lecouvey in 2001 [11] (Figure 2).

This method involves the reaction of acyl chlorides with tris(trimethylsilyl) phosphite, resulting in the formation of pentatrimethylsilyl derivatives of bisphosphonic acids as intermediate products. Previously, this approach had been used for the synthesis of dronic acids [5, 11].

In most cases, during the synthesis of hydroxybisphosphonic acids, the pentasilylated intermediates are not isolated from the reaction mixture but are directly subjected to the subsequent hydrolysis step. In our work, however, we chose to isolate, purify, and characterize all the intermediate tetrakis(trimethylsilyl)alkyl and tetrakis(trimethylsilyl)cycloalkyl derivatives of bisphosphonic acids. These compounds also represent important precursors for organic and organophosphorus synthesis. Notably, these substances have not been previously isolated or described.

For this purpose, we selected readily available alkylcarboxylic and cycloalkylcarboxylic acids. In the first stage of the synthesis, the alkylcarboxylic and cycloalkylcarboxylic acids were converted into the corresponding acid chlorides **1(a-g)** by treatment with thionyl chloride in the presence of dimethylformamide (DMF) as a catalyst. The reaction was carried out at 30 °C for 1 hour. After evaporation of the reaction mixture, the obtained acid chlorides were dissolved in dry dichloromethane and, upon cooling to 0 °C, tris(trimethylsilyl) phosphite was added (Figure 3). The reaction mixture was then stirred at room temperature for 3 hours. After completion, dichloromethane was evaporated. To remove the excess tris(trimethylsilyl) phosphite and by-products, the resulting viscous oily residue was kept under high vacuum (0.01 mm Hg) at 100-120 °C with vigorous stirring, during which volatile components were collected in a liquid nitrogen trap.

As a result, tetrakis(trimethylsilyl)alkyl and tetrakis(trimethylsilyl)cycloalkylalkyl derivatives of bisphosphonic acids were obtained as viscous liquids and characterized using available physical methods (Figure 4 and 5). It should also be noted that the pentasilyl derivatives of bisphosphonic acids are sensitive to moisture; therefore, they must be stored under an inert gas atmosphere.

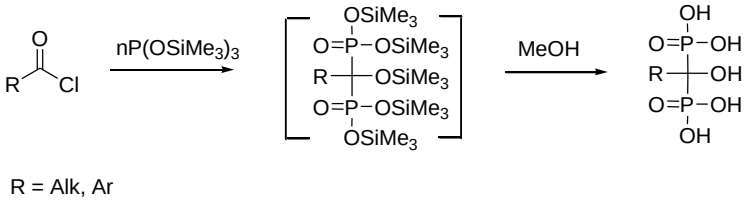

Figure 2. Lecouvey method for obtaining 1-hydroxy-1,1-bisphosphonic acids.

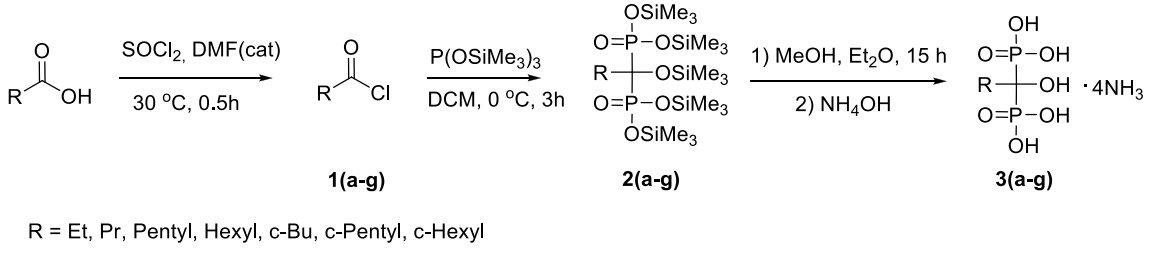

Figure 3. Synthesis of 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids.

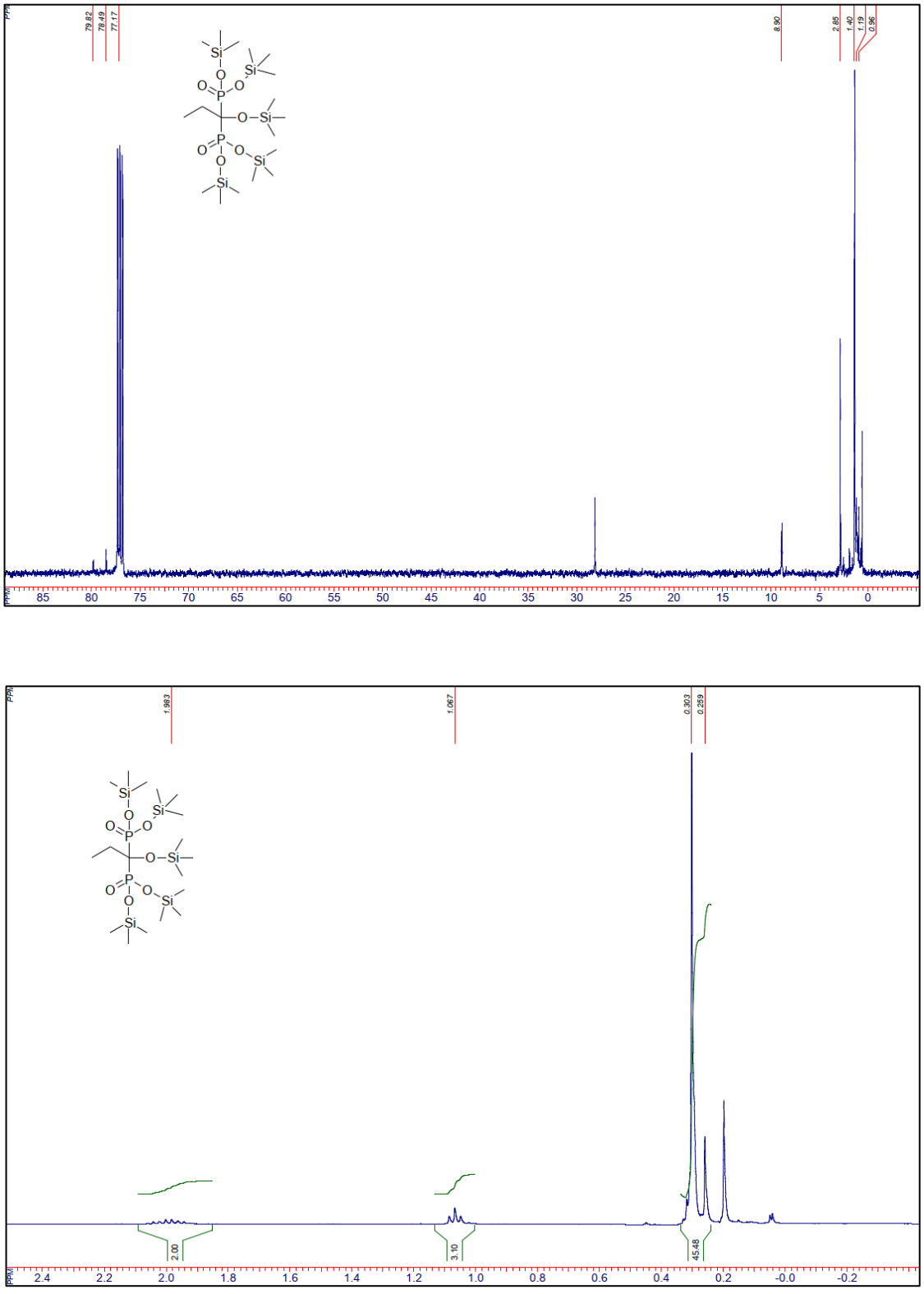

Figure 4. ^{1}H and ^{13}C NMR spectra of tetrakis(trimethylsilyl)ethyl(trimethyloxy) bisphosphonate.

At the next stage of our experiment, all the obtained tetrakis(trimethylsilyl)alkyl and tetrakis(trimethylsilyl)-cycloalkyl derivatives of bisphosphonic acids were subjected to hydrolysis using a solution of 5 equivalents of methanol in dry diethyl ether. The reaction proceeded at room temperature over 12 hours.

After evaporation of the solvents, the residues yielded 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids, which were converted into their ammonium salt forms by treatment with an aqueous ammonia solution. In all cases, the yields were quantitative, and the bisphosphonic acids were obtained with a chemical

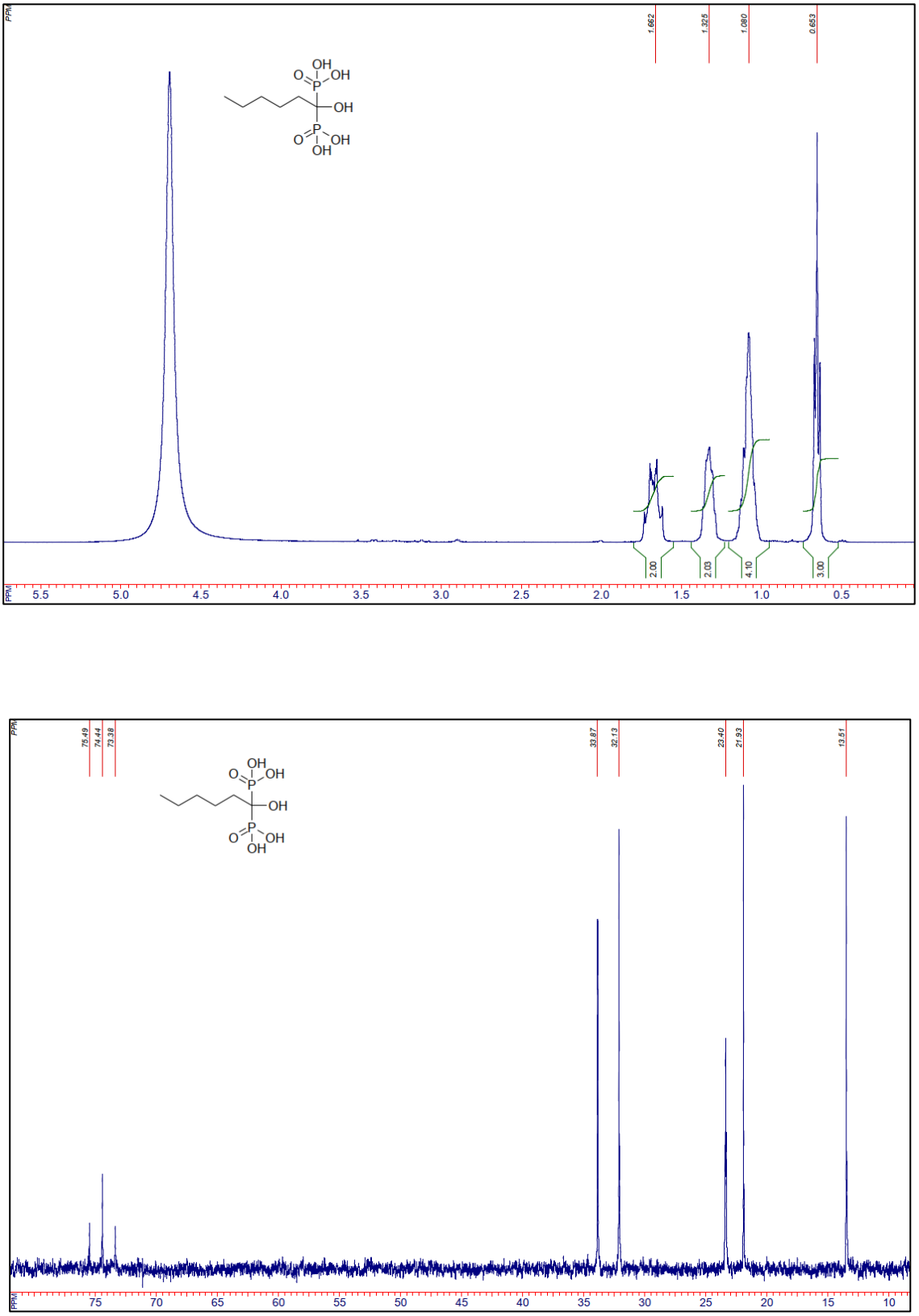

Figure 5. ^{1}H and ^{13}C NMR spectra of hexyldronic acid.

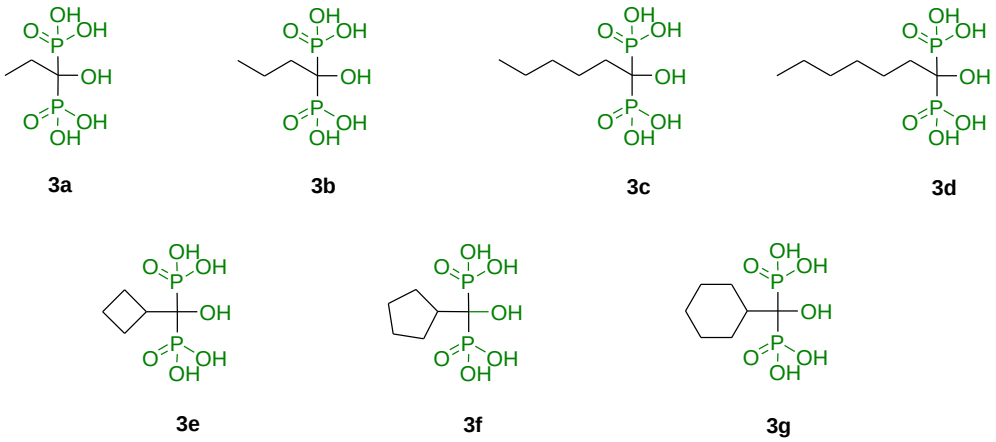

Figure 6. The obtained 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids.

purity of no less than 90%, as confirmed by available physical methods such as ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, as well as LCMS analysis (Figure 5).

Thus, for the first time, tetrakis(trimethylsilyl)alkyl and tetrakis(trimethylsilyl)-[cycloalkyl(trimethoxy)methyl] derivatives of bisphospho-nic acids **2a-g** were obtained and characterized, along with the corresponding 1-hydroxy-alkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids **3a-g**. Some of these compounds (**3a-c**) had been described previously, while the remaining ones (**3d-g**) were characterized for the first time (Figure 6).

Conclusions

Thus, in this work, we obtained and characterized tetrakis(trimethylsilyl)[alkyl(trimethoxy)methyl] and tetrakis(trimethylsilyl)[cycloalkyl(trimethoxy)methyl] derivatives of bisphosphonic acids, as well as 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids.

To achieve this goal, we carried out the bisphosphorylation reaction of the corresponding acid chlorides of carboxylic acids. All obtained tetrakis(trimethylsilyl)-[alkyl(trimethoxy)methyl] and tetrakis(trimethylsilyl)-[cycloalkyl(trimethoxy)methyl] derivatives of bisphosphonic acids, along with the 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bis-phosphonic acids, were characterized using all available physicochemical methods.

All the silylated derivatives and compounds **3d–g** were synthesized for the first time with high chemical yields. Thus, pentasilyl bisphosphonates and 1-hydroxy-1,1-bisphosphonic acids were obtained – promising compounds with potential biological activity and valuable building blocks for the synthesis of new pharmaceuticals and physiologically active substances.

Experimental section

All solvents were purified according to standard procedures. All starting materials were obtained from Enamine LTD or other commercial sources. Melting points were measured using an MPA 100 OptiMelt automated melting point system.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on an "Avance III" 500 MHz spectrometer ("Bruker," Germany) at ambient temperature. Chemical shift values (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. Signal multiplicities are denoted as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad signal), and q (quartet). Coupling constants (J) are given in hertz (Hz). All reagents and solvents were used without special purification. All reactions were carried out in glassware dried over flame or in a drying oven. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on silica gel 60F254 plates ("Merck," Germany), and the products were visualized using anisaldehyde. The purity of all compounds was determined by TLC and NMR analysis.

Synthesis

*General procedure for the synthesis of tetrakis(trimethylsilyl)[alkyl(trimethoxy)methyl] bisphosphonates and tetrakis(trimethylsilyl)[cycloalkyl(trimethoxy)-methyl] bisphosphonates **2a-g**.*

To a pure alkylcarboxylic or cycloalkylcarboxylic acid (0.017 mol, 1 eq.) were added a few drops of DMF (catalyst), and the mixture was cooled while thionyl chloride (0.019 mol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at 40 °C for 30 minutes (until gas evolution ceased). After completion, the reaction mixture was evaporated, and the resulting acid chloride of the alkylcarboxylic or cycloalkylcarboxylic acid was used in the next step without further purification.

At the next stage, the obtained acid chlorides (0.017 mol, 1 eq.) were dissolved in dry methylene chloride (70 mL), cooled to 0 °C, and tris(trimethylsilyl) phosphite (17.6 mL, 0.527 mol, 3.1 eq.) was added dropwise. The reaction mixture was stirred overnight at room temperature. Upon completion, the reaction mixture was evaporated and kept under high vacuum (0.05 mm Hg) at 100-110 ºC to remove volatile impurities.

The residue consisted of tetrakis(trimethylsilyl)[alkyl-(trimethoxy)methyl] bisphosphonates and tetrakis(trimethylsilyl)[cycloalkyl(trimethoxy)methyl] bisphosphonates as clear colorless oils.

*Tetrakis(trimethylsilyl)[ethyl(trimethoxy)methyl] bisphosphonate **2a**.*

Colorless oil. Yield 65%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 2.06-1.92 (m, 2H), 1.09-1.05 (m, 3H), 0.30 (s, 36H, $Si(OMe_3)_{12}$), 0.20 (s, 9H). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 2.43. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 79.81, 78.50, 77.19 (t, J = 164.67, Hz) 8.86, 2.83, 1.36, 1.16, 0.59.

*Tetrakis(trimethylsilyl)[propyl(trimethoxy)methyl] bisphosphonate **2b**.*

Colorless oil. Yield 75%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.91-1.80 (2H, m, CH_2), 1.59-1.50 (2H, m, CH_2), 0.86 (3H, t, J = 7.5, CH_3), 0.28 (36H, s, $Si(OMe_3)_{12}$), 0.16 (9H, s, $Si(OMe_3)_3$). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 2.33. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 79.58, 78.25, 76.92 (t, J = 166.25, Hz), 37.74, 17.09, 14.59, 1.30, 0.59.

*Tetrakis(trimethylsilyl)[hexyl(trimethoxy)methyl] bisphosphonate **2c**.*

Colorless oil. Yield 77%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.96-1.94 (2H, m, CH_2), 1.64-1.52 (2H, m, CH_2), 1.35-1.21 (4H, m, CH_2-CH_2), 0.89 (3H, t, J = 9, CH_3), 0.30 (36H, s, $Si(OMe_3)_{12}$), 0.19 (9H, s, $Si(OMe_3)_3$). Спектр ЯМР ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 2.35. NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 79.59, 78.26, 76.93 (t, J = 166.25, Hz), 35.64, 32.63, 23.55, 22.36, 14.07, 1.40, 0.91.

*Tetrakis(trimethylsilyl)[heptyl(trimethoxy)methyl] bisphosphonate **2d**.*

Colorless oil. Yield 85%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.95-1.81 (2H, m, CH_2), 1.62-1.53 (2H, m, CH_2), 1.32-1.25 (6H, m, $(CH_2)_3$), 0.89 (3H, t, J = 8.5, CH_3), 0.31 (36H, s, $Si(OMe_3)_{12}$), 0.20 (9H, s, $Si(OMe_3)_3$). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 2.38. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 79.57, 78.24, 76.91 (t, J = 166.25, Hz), 34.17, 31.33, 28.77, 24.82, 22.47, 13.97, 0.78, 0.5.

*Tetrakis(trimethylsilyl)[cyclobutyl(trimethoxy)methyl] bisphosphonate **2e**.*

Colorless oil. Yield 67%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 3.72 (1H, m, CH), 2.35-1.74 (6H, m, $(CH_2)_3$), 0.22 (42H, s, $Si(OMe_3)_{15}$). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 3.33. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 79.57, 78.24, 76.91 (t, J = 166.25, Hz), 24.2, 24.14, 17.83, 0.88, 0.54.

*Tetrakis(trimethylsilyl)[cyclopentyl(trimethoxy)methyl] bisphosphonate **2f**.*

Colorless oil. Yield 65%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 2.5 (1H, m, CH), 1.87-1.48 (8H, m,$(CH_2)_4$), 0.24 (42H, s, $Si(OMe_3)_{15}$). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 2.86NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 78.47, 77.17, 75.87 (t, J = 162.5, Hz), 28.52, 26.01, 25.40, 0.88.

*Tetrakis(trimethylsilyl)[cyclohexyl(trimethoxy)methyl] bisphosphonate **2g**.*

Colorless oil. Yield 65%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 3.01-2.94 (1H, m, CH), 2.08-1.64 (10H, m, $(CH_2)_5$), 0.45-0.28 (42H, s, $Si(OMe_3)_{15}$). NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 2.09. NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 78.70, 77.38, 76.06 (t, J = 165, Hz), 27.62, 25.65, 25.38.

*General procedure for the synthesis of 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids **3a-g**.*

Tetrakis(trimethylsilyl)[alkyl(trimethoxy)methyl] bisphosphonates and tetrakis(trimethylsilyl)[cycloalkyl(trimethoxy)methyl] bisphosphonates **2a-g** (0.01 mol, 1 eq.) were dissolved in dry dimethyl ether, and methanol (0.1 mol, 10 eq.) was added. The reaction mixture was stirred at room temperature overnight. Upon completion, the solvent was evaporated, and the residue was converted into the ammonium salt form by treatment of the aqueous solution of the bisphosphonic acid with an excess of aqueous ammonia. The water was then evaporated, and the resulting white or slightly yellow precipitate was purified by washing with a 1:1 mixture of isopropanol and chloroform. As a result, the ammonium salts of 1-hydroxyalkyl-1,1-bisphosphonic and 1-hydroxycycloalkyl-1,1-bisphosphonic acids **3a-g** were obtained.

*1-Hydroxypropyl-1,1-bisphosphonic acid ammonium salt **3a**.*

White solid. Yield 90%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.85-1.72 (2H, m, CH2), 0.89 (3H, t, J = 9,5 Hz, CH_3). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 18.91. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 75.67, 74.61, 73.55 (t, J = 132.5 Hz), 26.64, 8.45.

*1-Hydroxybutyl-1,1-bisphosphonic acid ammonium salt **3b**.*

White solid. Yield 91%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.82-1.70 (2H, m, CH_2), 1.47-1.38 (2H, m, CH_2), 0.78 (3H, t, J = 9 Hz, CH_3). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 18.90. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 75.22, 74.24, 73.26 (t, J = 156,6 Hz), 35.93, 17.09, 14.13.

*1-Hydroxyhexyl-1,1-bisphosphonic acid ammonium salt **3c**.*

White solid. Yield 87%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.73-1.62 (2H, m, CH_2), 1.37-1.29 (2H, m, CH_2), 1.13-1.03 (4H, m, $(CH_2)_2$), 0.65 (3H, t, J = 8.5 Hz, CH_3). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 18.01. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 75.49, 74.43, 73.38 (t, J = 132.5 Hz), 33.87, 32.13, 23.4, 21.93, 13.52.

1-Hydroxyheptyl-1,1-bisphosphonic acid ammonium salt ***3d***.

White solid. Yield 82%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 1.86-1.75 (2H, m, CH_2), 1.47-1.40 (2H, m, CH_2), 1.35-1.15 (6H, m, $(CH_2)_3$), 0.75 (3H, t, J = 9 Hz, CH_3). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 18.7. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 75.51, 74.45, 73.39 (t, J = 168.96 Hz), 33.85, 31.08, 29.53, 23.66, 22.12, 13.47.

1-Hydroxycyclobutyl-1,1-bisphosphonic acid ammonium salt ***3e***.

White solid. Yield 70%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 2.94-2.84 (1H, m, CH), 1.95-1.43 (6H, m, $(CH_2)_3$). NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 17.74. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 75.9, 74.84, 73.78 (t, J = 132.5 Hz), 38.27, 23.68, 17.96.

1-Hydroxycyclopentyl-1,1-bisphosphonic acid ammonium salt ***3f***.

White solid. Yield 65^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 2.29-2.17 (1H, m, CH), 1.65-1.59 (2H, m, CH_2), 1.48-1.27 (6H, m, $(CH_2)_3$), NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 18.64. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 76.56, 75.52, 74.48 (t, J = 130 Hz), 43.29, 27.39, 24.5

1-Hydroxycyclohexyl-1,1-bisphosphonic acid ammonium salt ***3g***.

White solid. Yield 68%. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 ºC) δ 2.75-2.69 (1H, m, CH), 1.76-1.36 (10H, m, $(CH_2)_5$NMR ^{31}P (160 MHz, $CDCl_3$, 25 ºC) δ 19.74. NMR ^{13}C (125.7 MHz, $CDCl_3$, 25 ºC) δ 77.63, 76.68, 75.73 (t, J = 118.87 Hz), 44.29, 27.77, 27.23, 26.43, 25.79, 24.91.

Notes

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The authors declare no conflict of interest.

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Синтез нових 1-гідрокси-1,1-бісфосфонових кислот

А.О. Колодяжна, Д.В. Присяжнюк, С.Ю. Шейко.

Інститут біоорганічної хімії та нафтохімії ім. В.П. Кухаря НАН України, Київ, Україна

Резюме: Розроблено синтетичний метод отримання 1-гідроксиалкіл-1,1-бісфосфонової та 1-гідроксициклоалкіл-1,1-бісфосфонової кислот, широко відомих як дронові кислоти. Ці сполуки були отримані шляхом утворення відповідних силільових похідних на ключових стадіях синтезу. Розроблений нами метод забезпечує простий та зручний підхід до отримання гідроксибісфосфонатів. Отримані сполуки є перспективними речовинами з потенційною біологічною активністю.

Ключові слова: бісфосфонові кислоти; дронові кислоти; реакція Арбузова; гідроксибісфосфонати.