ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 9, pp. 1792–1799. © Pleiades Publishing, Ltd., 2018.
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Dedicated to the 110th anniversary of M.I. Kabachnik's birth

The First 1-Hydroxypropylidenebisphosphonic Acid with 1,8-Naphthyridinone Substituent: Synthesis and Structure

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Received June 28, 2018

Abstract—1-Hydroxy-3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propylidenebisphosphonic acid has been synthesized. The structure of the acid and its precursors synthesized for the first time, 3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propionic acid and the corresponding methyl ester, in the solid state and in the DMSO solution has been elucidated by means of vibrational (IR and Raman) and multinuclear (^{1}H, ^{13}C, and ^{31}P) NMR spectroscopy.

Keywords: 1-hydroxy-3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-maphthyridin-1-yl)propylidenebisphosphonic acid, 3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-maphthyridin-1-yl)propionic acid, methyl 3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propionate

DOI: 10.1134/S1070363218090050

Bisphosphonates, especially nitrogen-containing ones, form an important class of pharmacologically active molecules which have been widely applied in different fields of medicine [1–5]. Over three recent decades, a series of inventions related to bisphosphonic acids and their derivatives have been made, mainly owing to the medicinal applications of these compounds. The most prominent studies in this field since 1970-ies have been performed in groups of H. Fleisch (Switzerland), E. Breuer (Israel), F.H. Ebetino (USA), Ch.E. McKenna, (USA), R.G.G. Russell (Great Britain), P. Kafarski (Poland), M.I. Kabachnik (Russia), and N.M. Dyatlova (Russia).

The presence of the P–C–P bonds in the bisphosphonates makes them resistant to enzymatic hydrolysis, and the nitrogen-containing group in the alkylene linker between the bisphosphonate moieties enhances the pharmacological activity of the compounds in the treatment of bone diseases. The most active bisphosphonates are these containing one or two nitrogen atoms in the heteroaromatic fragment linked to the geminal bisphosphonate moiety [1, 6, 7]. Bisphosphonates have been applied to the treatment of kidney, bone, and neurological diseases and cancer and also as anti-inflammatory drugs [1, 5]. Certain bisphosphonates have exhibited herbicide [5, 8] and antibacterial [9] properties.

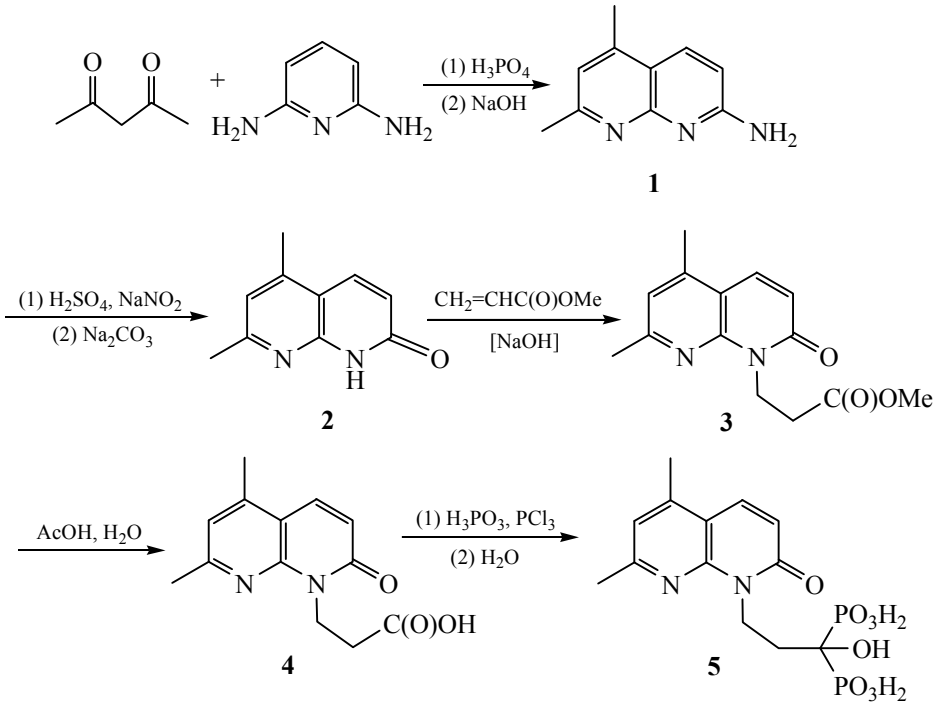
Bisphosphonates exhibit strong affinity to metal cations and are prone to hydrogen bonding [10]. They have been successfully used as new ligands for the formation of complexes with radioactive metals, which can be used in magnetic resonance tomography and radiotherapy [11] or as chelating agents for the treatment of intoxication with metals [12].

Derivatives of 1,8-naphthyridine have been widely used in biochemistry and medicine. The 1,8-naphthyridine scaffold is found in many natural species exhibiting a range of biological activity [13]. The coordination chemistry of 1,8-naphthyridine derivatives has been rapidly developing owing to the variety of applications of these compounds and their complexes [13]. Such complexes with the cations of majority of metals including lanthanides have been studied to date [13, 14]. Derivatives of 1,8-naphthyridine have been recognized for the prominent ability to form hydrogen bonds [15].

In view of the above mentioned, it can be expected that the molecules containing both 1,8-naphthyridine and bisphosphonate moieties will combine the biological activity and coordination affinity to metal cations.

This study aimed to synthesize a new bisphosphonic acid containing 1,8-naphthyridine substituent. Structure of the acid in the solid state and in solutions was investigated by means of vibrational (IR and Raman) and multinuclear (^{1}H, ^{13}C, and ^{31}P) NMR spectroscopy in comparison with its derivatives containing a neutral [C(O)OMe] or acidic [C(O)OH] group as well as with 5,7-dimethyl-1,8-naphtyridin-2(1*H*)-one. To the best of our knowledge, the target acid is the first example of 1-hydroxyalkylidenebisphosphonic acid with a 1,8-naphthyridine substituent.

Synthesis of 1-hydroxy-3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propylidenebisphosphonic acid was performed according to the following scheme.



1 **2** **3** **4** **5**

The starting compound, 2-amino-5,7-dimethyl-1,8-naphthyridine **1**, was prepared via the condensation of pentane-2,4-dione with 2,6-diaminopyridine. The *in situ* diazotization of aminonaphthyridine **1** with nitrosylsulfuric acid at room temperature followed by hydrolysis at 0°C afforded high yield of 5,7-dimethyl-1,8-naphthyridin-2(1*H*)-one **2**, whose structure was confirmed basing on the data of IR as well as ^{1}H and ^{13}C NMR spectroscopy. In particular, the ν(C=O) vibration was observed at 1667 cm^{-1} [16], and the stretching vibration of solvated N–H bond were observed as a broad band with a maximum at 3100 cm^{-1} (Table 1). The ^{13}C NMR signal assigned to the C=O group of 1,8-naphthyridinone heterocycle was observed at 163.3 ppm (Table 2).

Naphthyridinone **2** added at the C=C bond of methyl acrylate at heating in the presence of NaOH, thus affording methyl 3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propionate **3** in a high yield (90%). It should be noted that to the best of our knowledge this reaction is the first successful example of the aza-Michael reaction of naphthyridinone **2**, which significantly extends the range of the preparative use of this available heterocyclic reactant. Hydrolysis of ester **3** in refluxing aqueous solution of AcOH gave the corresponding 3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propionic acid **4** in close to quantitative yield. IR spectra of the solutions of ester **3** and acid **4** contained the absorption band of the heterocycle C=O bond at 1659 cm^{-1}. The ν(C=O) band of ester **3** was observed at 1734 cm^{-1} in the IR spectrum, whereas the same vibrations in the spectrum of acid **4** appeared at 1713 cm^{-1} (Table 1). The lower frequency of the ν(C=O) vibration of acid **4** was due to the formation of the H-bonds (as in the case of

Table 1. Data of vibrational spectra (cm^{-1}) of compounds **2**–**5** in solid state and in DMSO solution

Compound no.	Solvent	ν(C=O)$_{cycle}$		Naphthyridine rings		ν(C=O), ν(CO$_2$)[b]	ν(PO$_3$H$_2$), ν(PO$_3$H)[c]	ν(OH), ν(NH)
		IR	Raman[a]	IR	Raman[a]	IR	IR	IR
2	DMSO	1667	–	1614, 1597	–			3100
	KBr	1652, 1640	1645	1609, 1594, 1536, 1433,	1615, 1506, 1590, 1445, 1311			2950
3	DMSO	1659	–	1610, 1588, 1550, 1440	–	1734		
	KBr	1664, 1650	1664, 1648	1610, 1588, 1545, 1438	1611, 1589, 1552, 1296	1730		
4	DMSO	1659	–	1610, 1588, 1545, 1439	–	1713		2920, 2550
	KBr	1641,1660	1635	1588, 1545, 1433	1596, 1589, 1578, 1548, 1301	1740, 1580, 1400		3000, 2670
5	DMSO	1659	–	1610, 1586, 1547, 1447	–		1196, 1010[d], 956	2740, 2250
	KBr	1671, 1635	1659,1632	1535, 1468	1571, 1542, 1431, 1274		1193, 1016, 978, 1110, 1076, 1041, 944	3310,2700, 2350, 2000

[a] Raman spectra of the solutions were not recorded. [b] Symmetric and asymmetric vibrations of deprotonated CO_2^- group were observed in the IR spectrum upon formation of the betaine structure (zwitter ion) of acid **4** in solid state. [c] Deprotonated $(PO_3H)^-$ group appeared in the zwitter ionic structure of acid **5**. [d] In the spectrum of the solution in DMF.

carboxylic acids); the bands of ν(O–H) in the spectrum of acid **4** were also typical of the associated carboxylic acids [16].

The ^{1}H NMR spectra of compounds **3** and **4** contained, besides the signals typical of the dimethyl-substituted 1,8-naphthyridine fragment, fairly distant (by ~2 ppm) triplets assigned to the CH_2 protons of the ethylidene bridge separating the heterocyclic system and the terminal ester (**3**) or carboxylic (**4**) substituents. The singlet signals corresponding to the carbon atoms of these methylene groups were observed on the ^{13}C NMR spectra of compounds **3** and **4**. These spectra were also remarkable by a very marginal (within the experimental accuracy) deviation of the positions of the observed carbon signals of heterocyclic fragment of compounds **3** and **4** (Table 2), in combination with the IR spectroscopy data (Table 1) evidencing the molecular structure of acid **4** in the solution.

Table 2. Selected ^{13}C NMR spectroscopy data for compounds **2**–**5** in DMSO

Compound no.	δ_C, ppm		
	C^{8a}	C^7	C^2
2	150.04	160.00	163.28
3	149.08	159.48	162.05
4	149.08	159.53	162.06
5	148.81	159.54	162.36

A method of transformation of terminal amino-substituted carboxylic acids into the corresponding nitrogen-containing 1-hydroxyalkylidenebisphosphonic acids via simultaneous action of H_3PO_3 and PCl_3 has been widely used earlier by M.I. Kabachnik et al. [17]. In this study we successfully extended this approach to the case of acid **4**, which was converted into the target 1-hydroxy-3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propylidenebisphosphonic acid **5** under similar conditions; the product was isolated in the yield of 35%.[1] It should be noted that the use of cheaper and available 85% H_3PO_4 at the last phosphorylation stage instead of H_3PO_3 earlier exploited with 3-aminopropionic acids containing the nitrogen atom in the piperidine or morpholine cycle

[1] About 26% of unreacted acid **4** could be isolated from the reaction mixture.

[18], failed in our case: the ^{31}P NMR spectrum of the aqueous phase after the reaction showed only traces of acid **5**. Compound **5** was isolated as white fine-crystalline substance stable in air and exhibiting high decomposition temperature; its structure and composition were confirmed by elemental analysis and the data of IR and NMR spectroscopy. In particular, the presence of two geminal phosphonic substituents in the molecule of acid **5** was evidenced by the presence of triplet splitting of carbon atoms of the $CH_2C(OH)\cdot[P(O)(OH)_2]_2$ moiety with the corresponding spin-spin coupling constants J_{CP}. The positions of the signals of the carbon nuclei of the heterocyclic part of the molecule were practically identical to those in the spectrum of compounds **2**–**4** (Table 2) evidencing the molecular structure of acid **5**. The IR spectrum confirmed the existence of acid **5** in its neutral form in the solution (Table 1): the bands of the naphthyridine scaffold were similar to those of ester **3** and acid **4**, whereas the bands of the phosphonic groups corresponded to the ν(P=O) and ν[P–$(OH)_2$] vibrations [20].

IR spectra of the solid specimens of compounds **2**–**5** significantly differed from their solutions spectra. Therefore, we recorded the Raman spectra of the solid specimens and performed quantum-chemical simulation of the frequencies of the normal vibrations of molecules of compounds **3** and **4**.

The band of endocyclic C=O group was shifted to lower frequency and split in the IR spectrum of solid naphthyridine **2**: its maximum was observed at 1640 cm^{-1}, and the shoulder was found at 1652 cm^{-1}; a sufficiently strong band was observed in the Raman spectrum at 1645 cm^{-1} due to the contribution from the ν(C=C) mode (see the simulation below). The decrease in the frequency of the ν(C=O) band was due to the formation of the C=O···H–N hydrogen bond, this interaction was in line with the presence of a broad ν(NH) band at 2950 cm^{-1} (Table 1).

Quantum–chemical analysis of molecule **3** revealed that the frequency of the vibration of the ester C=O group equaled 1739 cm^{-1}. The vibration of the endocyclic C=O bond was combined with the C=C bond vibration, with the corresponding frequencies 1669 [mainly ν(C=O)] 1617 cm^{-1} and [mainly ν(C=C)]. The frequencies of the vibrations involving nitrogen atoms were 1580, 1546, 1429, 1360, and 1320 cm^{-1}.

The bands of the endocycle C=O bond vibration as well as the stretching and nonplanar bending vibrations of the CH groups in the IR and Raman spectra of solid ester **3** were split, the bands of the ester C=O and double bonds of the naphthyridine cycle remained unchanged (Table 1). That was likely due to the interaction of the C=O and C–H groups, since the vibrations of the *gauche*- and *anti*-conformers of ester **3** were practically identical according to the simulation.

The simulation of acid **4** revealed that the energy minimum corresponded to the structure with intramolecular N···H–O hydrogen bond, ν(C=O) was 1784 cm^{-1}. Frequencies of the ν(C=O) and ν(C=C) vibrations of the cycle (1677, 1623 cm^{-1}) and of the vibrations of the naphthyridine cycle involving nitrogen atoms (1582, 1551, 1429, 1360, and 1315 cm^{-1}) for acid **4** and ester **3** were close, i. e. the formation of the hydrogen bond practically did not affect the frequencies of these vibrations.

The IR spectrum of solid acid **4** contained the bands at 1580 and 1400 cm^{-1} probably corresponding to the asymmetric and symmetric stretching vibrations of the deprotonated CO_2^- group [16] and suggesting the formation of the betaine structure with the proton transfer to the nitrogen atom. At the same time, the frequencies of the naphthyridine cycle remained practically unchanged, probably due to the formation of a strong ionic N–$H^+\cdots{}^-$OOC bonding. Hence, the simulated molecular structure with the hydrogen bonding was not formed in the crystal, but a proton transfer to the nitrogen atom occurred with the formation of a ionic H-bond. Moreover, a low-frequency component of ν(C=O) appeared in the IR and Raman spectra at about 1640 cm^{-1}, i. e. a form of the molecule with the endocyclic C=O group involved in the H-bond formation exists. High-frequency part of the spectrum contained broad bands with maxima at 2920 and 2670 cm^{-1} assignable to theν(OH) and ν(NH) vibrations, respectively [16]. Hence, solid specimen of acid **4** contained zwitter ions with the N^+–H···O^- hydrogen bond and the molecules with the hydrogen bonding between the COOH and naphthyridine C=O groups, in contrast to the solution in DMSO where the dimers similar to the carboxylic acid ones were formed. It should be noted that the existence of polymorphic forms differing in the hydrogen bonding type is characteristic of the majority of amino-carboxylic acids [20].

In the case of acid **5**, the IR spectrum of the solid specimen was the most different from the spectrum of the solution: the number of the bands in the range of phosphonic groups modes was increased, and the

bands of the naphthyridine cycle vibrations including the ν(C=O) one were changed (Table 1). The shift of the strongest Raman band in the spectrum of acid **5** (1274 cm^{-1}) in comparison with the spectra of acid **4** and ester **3** (1301 and 1296 cm^{-1}) was also remarkable. Since the frequencies of the changed bands corresponded to the vibrations with predominant contribution from the unsubstituted nitrogen atom of the naphthyridine scaffold (simulation data), it might be suggested that the changes were due to its protonation. In view of this, the appearance of additional bands in the range of phosphonic groups vibrations could be attributed to the deprotonation of one of them. We therefore believe that acid **5** exists in the form of zwitter ion in solid state. The more significant change in the frequency of the naphthyridine moiety vibrations in the zwitter ion of acid **5** in comparison to that of acid **4** (Table 1), could be due to different basicity of the phosphonate and carbonate ions as well as to the formation of strong hydrogen bonds between the bisphosphonate groups. Intermolecular hydrogen bonds of this type have been observed in structurally similar bisphosphonic acids [5, 21]. Since both phosphonic groups (PO_3H_2 and PO_3H^-) were involved in strong intermolecular H-bonds, there was no sufficiently strong acceptor to form a hydrogen bond with the betaine proton in the crystal of acid **5**, in contrast to that of acid **4**. The C=O and $N–H^+$ groups were evidently involved in weaker interactions. Hence, acid **5** exists in the form of zwitter ion in the solid state, like majority of bisphosphonic acids with nitrogen-containing substituents [5].

A similar feature (the existence of a molecular form in the solution and of a zwitter ion in the solid state) have been revealed in our study of bis(3-aminophenyl) phosphinic acid [22]. At the same time, 1-hydroxybisphosphonic acid with 1*H*-pyrazolo[3,4-*b*]-pyridine substituent exists in the molecular form both in the solution and in the solid state [21]. These examples illustrate the need for experimental study of the ampholytes structure in the solid state and in solutions.

In summary, we synthesized the first bisphosphonic acid with 1,8-naphthyridinone substituent **5**. The acid **5** and its precursor (acid **4**) were shown to exist in the molecular form in the solution in DMSO; in the solid state, acid **5** existed in the form of betaine whereas acid **4**, like aminobenzoic acids, was a mixture of neutral and zwitter ionic polymorphs. We expect that the bisphosphonic acid **5** and carboxylic acid **4** would exhibit a range of biological activity and coordination affinity towards metal cations.

EXPERIMENTAL

Organic solvents ("pure" or "chemically pure" grade) were dried and purified via conventional procedures. Deuterated dimethylsulfoxide (DMSO-d_6) from Acros was used as received.

^1H, ^{13}C, and ^{31}P NMR spectra of 0.1 M. solutions in DMSO-d_6 were recorded using a Bruker AV-400 instrument [400.13 (^1H), 100.61 (^{13}C), and 161.98 (^{31}P) MHz] with internal (residual protons of non-deuterated solvent for ^1H NMR and carbon atoms of the deuterated solvent for ^{13}C NMR) or external (85% H_3PO_4 for ^{31}P NMR) reference. The signals in the ^1H and ^{13}C NMR spectra were assigned using COSY, HMQC, and HMBC two-dimensional heteronuclear correlation spectra. IR spectra were recorded using a Bruker Tensor 37 spectrometer (solid state: KBr pellets, 4000–400 cm^{-1}; solutions: 0.05 M. in DMSO-d_6 and DMF, 4000–900 cm^{-1}, CaF_2 cell, optical path length 0.062 mm]. Raman spectra (3500–100 cm^{-1}) were recorded using a Jobin-Yvon LabRAM 300 spectrometer equipped with a microscope and laser CCD detector. The spectra were excited with a 632.8 nm line of the He–Ne laser, the power not exceeding 2 mW. Melting points were measured in capillaries using a short Anschütz thermometer in special heating block. Elemental analysis was performed in the Laboratory of Microanalysis, Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

Methyl acrylate (Acros, 99%) and phosphorus(III) chloride (Acros, 98%) were freshly distilled before the reaction. Phosphorous acid (Acros, 98%) was used as received. Column chromatography was performed on 130–270 mesh, 60 Å silica gel (Aldrich) for column chromatography.

2-Amino-5,7-dimethyl-1,8-naphthyridine **1** was synthesized as described elsewhere [23].

5,7-Dimethyl-1,8-naphthyridine-2(1*H*)-one (2). 3.2 g (46.4 mmol) of $NaNO_2$ was added in small portions to a stirred solution of 6.74 g (38.9 mmol) of aminonaphthyridine **1** in 50 mL of 96% H_2SO_4 at ~20°C. The mixture was then stirred during 5 min and poured onto 200 g of crushed ice. After 10 min, the reaction mixture was alkalinized with saturated aqueous solution of Na_2CO_3 to pH 9.0, then acidified with

glacial AcOH to pH 5.0, and stored ~12 h at 0°C. The formed precipitate was separated, washed with water (2×50 mL) and acetone (50 mL), and recrystallized from ethanol. Yield 5.75 g (85%), mp 252–253°C (mp 250–251°C [24]). IR spectrum, ν, cm^{-1}: 485, 547, 732, 792, 838, 856, 909, 929, 1195, 1240, 1310, 1433, 1502, 1536, 1594, 1609, 1640, 1652, 2950. Raman spectrum, ν, cm^{-1}: 127, 479, 668, 797, 1311, 1391, 1445, 1506, 1590, 1615, 1645, 2927, 3056. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.46 s (3H, CH_3^7), 2.49 s (3H, CH_3^5), 6.48 d (1H, H^3, $^3J_{HH}$ = 9.6), 6.98 s (1H, H^6), 8.01 d (1H, H^4, $^3J_{HH}$ = 9.6), 11.95 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.0 (CH_3^5), 24.5 (CH_3^7), 111.4 (C^{4a}), 120.0 (C^6), 121.7 (C^3), 136.3 (C^4), 146.3 (C^5), 150.0 (C^{8a}), 160.0 (C^7), 163.3 (C=O). Found, %: C 68.96; H 5.71; N 16.17. $C_{10}H_{10}N_2O$. Calculated, %: C 68.95; H 5.79; N 16.08.

Methyl 3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propionate (3). 5.75 g (33 mmol) of naphthyridinone **2** and then 0.1 g (2.5 mmol) of finely ground NaOH were added by portions to a stirred solution of 4.75 g (55.2 mmol) of methyl acrylate in 50 mL of anhydrous DMF under argon. The mixture was heated at 100°C during 4 h, then 4.75 g (55.2 mmol) of methyl acrylate was added, and the mixture was heated during 4 h at the same temperature. The solvent was removed in a vacuum, the residue was dissolved in 60 mL of benzene and filtered through 6.0 g of silica gel, the carrier was washed with benzene (2×20 mL). The organic filtrates were combined and concentrated to half of the volume; 50 mL of cyclohexane was added, and the mixture was kept during ~12 h at 20°C. The precipitate was separated, washed with hexane (2×25 mL), and dried in a vacuum (~12 mmHg) during 2 h at 70°C. Yield 7.7 g (90%), mp 102.0–102.5°C (benzene–cyclohexane). IR spectrum, ν, cm^{-1}: 488, 620, 791, 833, 860, 908, 1149, 1159, 1188, 1199, 1248, 1317, 1374, 1438, 1545, 1588, 1610, 1650, 1664, 1730. Raman spectrum, ν, cm^{-1}: 447, 488, 546, 631, 871, 976, 1128, 1190, 1250, 1263, 1296, 1334, 1375, 1552, 1589, 1611, 1648, 1664, 2929, 3088. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 s (6H, CH_3^5 + CH_3^7), 2.63 t (2H, $C\underline{H}_2CH_2N$, $^3J_{HH}$ = 7.4), 3.56 s (3H, CH_3O), 4.62 t (2H, CH_2N, $^3J_{HH}$ = 7.4), 6.61 d (1H, H^3, $^3J_{HH}$ = 9.6), 7.06 s (1H, H^6), 8.04 d (1H, H^4, $^3J_{HH}$ = 9.7). ^{13}C NMR spectrum, δ_C, ppm: 18.2 (CH_3^5), 25.0 (CH_3^7), 32.7 (CH_2N), 36.9 ($\underline{C}H_2CH_2N$), 51.9 (CH_3O). 112.3 (C^{4a}), 120.1 (C^6), 120.7 (C^3), 135.1 (C^4), 147.1 (C^5), 149.1 (C^{8a}), 159.5 (C^7), 162.1 (C^2), 171.9 [$\underline{C}$(O)OMe]. Found, %: C 64.69; H 6.19; N 10.73. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.60; H 6.20; N 10.76.

3-(5,7-Dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propionic acid (4). A solution of 3.7 g (14.2 mmol) of ester **3** in a mixture of 100 mL of distilled water and 25 mL of glacial AcOH was refluxed during 7 h, and then kept during ~12 h at room temperature. The precipitate was separated, washed with diethyl ether (2×15 mL), and dried in a vacuum (~12 mmHg) during 1 h at 100°C. Yield 3.33 g (95%), mp 182–183°C (MeCN). IR spectrum, ν, cm^{-1}: 488, 599, 792, 830, 857, 1152, 1204, 1330, 1379, 1400, 1433, 1488, 1545, 1580, 1588, 1641, 1660, 1740, 2670, 3000. Raman spectrum, ν, cm^{-1}: 456, 547, 626, 978, 1129, 1193, 1249, 1301, 1353, 1375, 1548, 1578, 1589, 1596, 1635, 2930, 3076. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 s (6H, CH_3^5 + CH_3^7), 2.55 t (2H, $C\underline{H}_2COOH$, $^3J_{HH}$ = 7.5), 4.58 t (2H, CH_2N, $^3J_{HH}$ = 7.6), 6.60 d (1H, H^3, $^3J_{HH}$ = 9.6), 7.05 s (1H, H^6), 8.03 d (1H, H^4, $^3J_{HH}$ = 9.5), 12.35 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 18.2 (CH_3^5), 25.0 (CH_3^7), 32.7 (CH_2N), 36.9 ($\underline{C}H_2CH_2N$), 112.3 (C^{4a}), 120.1 (C^6), 120.7 (C^3), 135.1 (C^4), 147.0 (C^5), 149.1 (C^{8a}), 159.5 (C^7), 162.1 (C^2), 173.0 (COOH). Found, %: C 63.51; H 5.78; N 11.43. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.40; H 5.73; N 11.38.

1-Hydroxy-3-(5,7-dimethyl-2-oxo-1,2-dihydro-1,8-naphthyridin-1-yl)propylidenebisphosphonic acid (5). A solution of 5.5 g (40 mmol) of PCl_3 in 5 mL of PhCl was added dropwise under argon at stirring to a mixture of 4.92 g (20 mmol) of acid **4**, 3.3 g (40 mmol) H_3PO_3, and 15 mL of PhCl heated at 100°C. The mixture was heated during 4 h at the same temperature and then cooled down to ambient. The solvent was decanted off, the residue was kept in a vacuum (~12 mmHg) during 0.5 h at 25ºC, then 30 mL of water was added, and the mixture was heated on a boiling water bath during 30 min. After cooling to ambient, the aqueous layer was decanted[2] and kept during 14 days at 0°C. The powder precipitate was separated, recrystallized from 70% AcOH, washed with ice water and acetone (10 mL each), and dried in a vacuum (~12 mmHg) during 3 h at 145°C. Yield 2.0 g (35%, with respect to reacted acid **4**), decomp. >240°C. IR spectrum, ν, cm^{-1}: 424, 480, 511, 628, 780, 847, 881, 916, 944, 978, 1016, 1041, 1076, 1110, 1193, 1230, 1248, 1271, 1371, 1468, 1535, 1635, 1671, 2000, 2350, 2700, 3310. Raman spectrum, ν, cm^{-1}: 286, 448, 483,

[2] 1.3 g (25.5%) of unreacted acid **4** was isolated from the tar residue via recrystallization from 20% AcOH.

612, 817, 1110, 1206, 1232, 1250, 1274, 1380, 1431, 1542, 1571, 1632, 1659, 2931, 3073. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 t. t (2H, $\underline{C}H_2CH_2N$, $^{3}J_{HH}$ = 7.0, $^{3}J_{HP}$ = 14.6), 2.51 s (3H, CH_3^7), 2.54 s (3H, CH_3^5), 4.67 t (2H, CH_2N, $^{3}J_{HH}$ = 6.7), 6.63 d (1H, H^3, $^{3}J_{HH}$ = 9.5), 6.93 br. s (5H, OH), 7.07 s (1H, H^6), 8.05 d (1H, H^4, $^{3}J_{HH}$ = 9.5). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 18.2 s (CH_3^5), 24.6 (CH_3^7), 32.6 s (CH_2N), 36.5 t ($\underline{C}H_2CH_2N$, $^{2}J_{CP}$ = 7.7), 72.1 t [C(OH), $^{1}J_{CP}$ = 147.1], 112.6 s (C^{4a}), 120.3 s (C^6), 120.7 s (C^3), 135.2 s (C^4), 147.4 s (C^5), 148.8 s (C^{8a}), 159.5 s (C^7), 162.4 (C=O). ^{31}P NMR spectrum: δ_P 19.1 ppm. Found, %: C 39.62; H 4.59; N 6.99; P 15.54. $C_{13}H_{18}N_2O_8P_2$. Calculated, %: C 39.81; H 4.63; N 7.14; P 15.79.

Quantum-chemical simulation of the frequency and geometry of the normal vibrations at the RIJCOSX [25] TPSS [26] D3 [27] Def2-TZVP [28] theory level was performed using ORCA software [29].

Spectral studies were performed at the Center of Study of Molecular Structure, Institute of Organo-elemental Compounds, Russian Academy of Sciences.

CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

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