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Synthesis of Novel Aminophosphonic Acids with Hydantoin Structure

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ABSTRACT: *The novel α-aminophosphonic acids with hydantoin structure have been synthesized reacting 5,5-dimetylhydantoin with formaldehyde and phosphorus trichloride, or via Kabachnik–Fields reaction. Their structures were proved by means of IR, ^{1}H,$^{13}C\{^{1}H\}$, and ^{31}P NMR spectroscopy.* Heteroatom Chem 20:87–90, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20515

INRODUCTION

Phosphorus-containing compounds play a key role in living organisms as carriers of genetic information, energy transfer, and structural compounds [1]. Among these phosphorus-containing compounds, aminophosphonates are the most attractive substances that have found applications as antibacterial agents [2], enzyme inhibitors [3], antitimor [4], anti-HIV [5], antifungal [6], antiviral [7] agents, and herbicides [8]. They also show complexing properties, which are advantageous for selective ionophores or membrane carrier design [9]. Hence, the synthesis of novel derivatives of α-aminophosphonic acid is currently of high importance [10–12]. It is known that hydantoins, substituted at C-5, are important medicines [13–16]. The discovery that 5-ethyl-5-phenylhydantoin is active as an anticonvulsant resulted in the preparation and testing of a numerous of 5,5-disubstituted hydantoins [17–19]. However, there are no data in the literature for the preparation of aminophosphonic acids bearing hydantoin moiety. We describe herein their synthesis reacting phosphorus trichloride/dimethyl-*H*-phosphonate with formaldehyde and 5,5-dimetylhydantoins.

RESULTS AND DISSCUSION

The novel aminophosphonic acids bearing hydantoin moiety have been synthesized by two different methods. For the synthesis of [(5,5-dimethyl-2,4-dioxoimidazolidine-1,3-diyl)dimethyl]diphosphonic acid (**2**), we used Engelmann and Pikl's procedure [20]. As a starting compound were used 5,5-dimetylhydantoin (**1**), phosphorus trichloride, and formaldehyde, in the molar ratio 1:2:2 (see Scheme 1).

The interaction between (**1**) and formaldehyde involves the formation of bis-hydroxymethylhydantoin (**1b**), which further reacts with phosphorus trichloride. The subsequent hydrolysis resulted in the formation of [(5,5-dimethyl-2,4-dioxoimidazolidine-1,3-diyl)dimethyl]diphosphonic acid (**2**) (Scheme 1).

Dimethyl[(5,5-dimethyl-2,4-dioxoimidazolidin-3-yl)aminomethyl]phosphonate (**4**) and dimethyl[(3-[(dimethoxy-phosphoryl)methyl]amino-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl) methyl]phosphonate (**4′**) were obtained in a good yield from 3-amino-5,5-dimethylimidazolidine-2,4-dione (**3**) via Kabachnik–Fields reaction [21,22] (Scheme 1).

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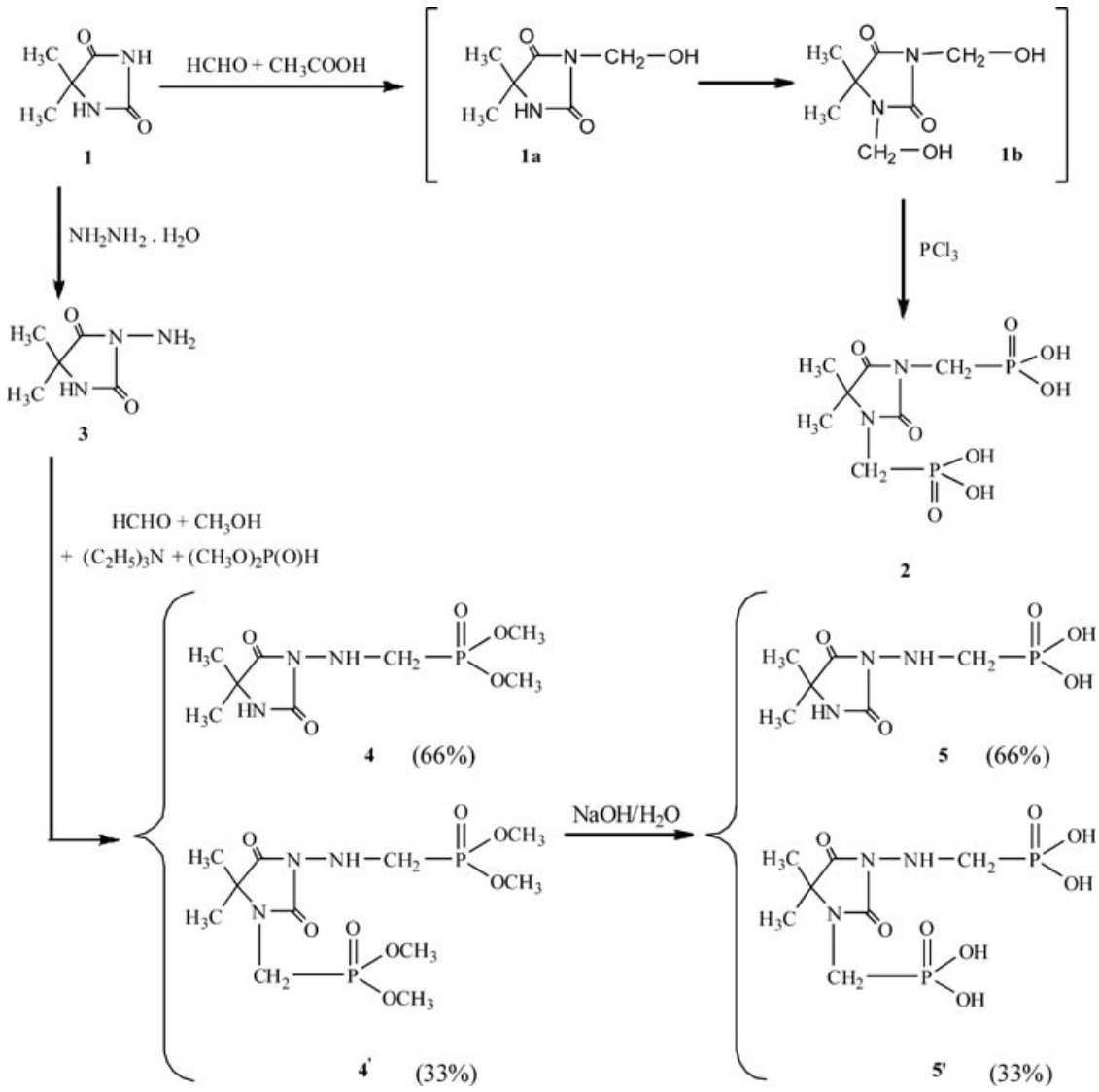

SCHEME 1 Pathways to aminophosphonic acids.

Treatment of (**4**) and (**4′**) with aqueous NaOH furnished [(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-amino]methylphosphonic acid (**5**) and (5,5-dimethyl-2,4-dioxo-3-[(phosphonomethyl)amino]imidazolidin-1-ylmethyl)phosphonic acid (**5′**), respectively.

In the ^{1}Õ NMR spectrum of (**2**), there are two doublets that can be assigned to P-CH_2(see Experimental section). In the ^{1}Õ NMR spectrum of (**4′**), there are doublets that can be assigned to the two different P-CH_2-NH and to the P-OCH_3. In the ^{13}C $\{^{1}H\}$ NMR spectrum of /**2**/, there are two doublets that are characteristic for the carbon atom connected to phosphorus (P-CH_2). The doublets in the ^{13}C $\{^{1}H\}$ NMR spectrum of (**4′**) at 40.8 ppm can be assigned to the carbon atoms connected to phosphorus and confirm the structure.

Infrared (IR) spectroscopy study confirms the structure of the abovementioned compounds. In the IR spectra of all newly synthesized aminophosphonic acids contain characteristic bands attributed to the P=O (about 1250 cm^{-1}), P—O—H (about 1150 cm^{-1}), P-CH_2 (about 1150–1050 cm^{-1} and about 850–750 cm^{-1}), and P—O—C (about 1050 cm^{-1}) vibrations that are used in the structural characterization of this type of compounds.

The signals in the ^{31}P NMR spectra of (**2**) at 18.90 and 19.20 ppm are triplets with $^{2}J_{PH}$ = 11.2 Hz and $^{2}J_{PH}$ = 12.5 Hz, respectively. ^{31}P{H}NMR spectrum

of compounds **4** and **4′** showed multiplets at 22.02 and 29.07 ppm.

EXPERIMENTAL

Instruments and Reagents

5,5-Dimetylhydantoin, phosphorus trichloride, dimethyl-*H*-phosphonate, paraformaldehyde, and solvents were purchased from Fluka (Taufkirchen, Germany) and Merck (Whitehouse Station, NJ), and used without further purification.

The IR spectra were recorded in KBr pellets with a Perkin–Elmer Model 1600 Series FTIR instrument. The purity of the products was checked by TLC on precoated plates of Silica gel 60 F254 (Merck), using as mobile phase a 3:1:1 mixture of *n*-BuOH, AcOH, and H_2O. Spots on thermal lens spectrometry chromatograms were detected by chlorine/*o*-tolidine reaction. The ^1H, ^{13}C, and ^{31}P NMR spectra were obtained with a Bruker DRX 400 spectrometer at 400.13, 100.61, and 161.97 MHz, respectively. ^{13}C NMR spectra were fully ^1H decoupled. Chemical shifts δ are reported in ppm, and coupling constants J are reported in Hz.

*[(5,5-Dimethyl-2,4-dioxoimidazolidine-1,3-diyl)dimethyl]diphosphonic acid (**2**)*

5,5-Dimethylhydantoin (0.0059 mol) and paraformaldehyde (0.36 g, 0.0119 mol) were placed under argon in a four-necked round-bottomed flask equipped with a magnetic stirrer, reflux condenser, thermometer, dropping funnel, and argon inert. Under vigorous stirring, glacial acetic acid of 5.95 mL was added dropwise. A white suspension formed. The reaction mixture was refluxed (~115°C) for 12.5 h, after which it became a clear solution. Then the temperature was lowered to 20°C and 1.04 mL (1.63 g, 0.0119 mol) phosphorus trichloride was added dropwise. During and after the addition, hydrogen chloride evolved. The reaction mixture was refluxed (~118°C). After 6 h refluxing, 6.80 mL of water (distilled) was added. After 4 h refluxing, the reaction mixture was concentrated under reduced pressure.

The solvent was discarded, and the residual product was dissolved in a large excess of methanol. After filtration, the filtrate was evaporated to give a residue, which was purified by precipitation in methanol/ethyl acetate and collected by filtration. The purification step was repeated several times to give the title compound.

Yellow oil, 68.0% yield, $R_f = 0.42$; IR (KBr, cm^{-1}): 2984, 1772 ($^2C=O$), 1725 ($^4C=O$), 1446, 1390, 1165 (P=O), 1002 (P–O–H). ^1H NMR (400.13 MHz, CD_3OD), δ: 1.58 (s, 6H, C$\underline{H}_3$), 3.5 (d, 2H, $^2J_{PH} = 11.5$ Hz, P-C$\underline{H}_2$), 4.1 (d, 2H, $^2J_{PH} = 12.0$ Hz, P-C$\underline{H}_2$). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD), δ in ppm: 22.9 C$\underline{H}_3$, 42.5 (d, $^1J_{PC} = 152.0$ Hz, P-$\underline{C}H_2$), 48.0 (d, $^1J_{PC} = 154.0$ Hz, P-$\underline{C}H_2$), 62.1 –C–, 158.8 $^2C=O$, 179.0 $^4C=O$. ^{31}P NMR (161.97 MHz, CD_3OD), δ in ppm: 18.90 (t, $^2J_{PH} = 11.2$ Hz), 19.20 (t, $^2J_{PH} = 12.5$ Hz).

*3-Amino-5,5-Dimethylimidazolidine-2,4-Dione (**3**)*

This compound was prepared according to procedure described by us [23].

White solid, 90.0% yield; $R_f = 0.58$; IR (KBr, cm^{-1}): 3214, 2980, 1770 ($^2C=O$), 1730 ($^4C=O$). ^1H NMR (400.13 MHz, D_2O), δ: 1.6 (s, 6H, C$\underline{H}_2$), 4.8 (s, 2H, N$\underline{H}$), 6.7 (s, 1H, N$\underline{H}$). $^{13}C\{^1H\}$ NMR (100.61 MHz, D_2O), δ: 24.0 C$\underline{H}_3$, 62.0 –C–, 154.0 $^2C=O$, 174.0 $^4C=O$.

*Dimethyl[(5,5-dimethyl-2,4-dioxoimidazolidin-3-yl)aminomethyl]phosphonate (**4**) and Dimethyl[(3-[(dimethoxyphosphoryl)-methyl]amino-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl)methyl]phosphonate (**4′**)*

Paraformaldehyde (0.40 g, 0.0129 mol), methanol (20.20 mL), and triethylamine (0.14 mL) were put into a three-necked flask equipped with a condenser, magnetic stirrer, thermometer, dropping funnel, and argon inert. The reaction mixture was heated to reflux temperature and held there for 45 min, after which it became a clear solution. 3-Amino-5,5-dimethylimidazolidine-2,4-dione (0.0083 mol) and triethylamine (1.70 mL) were added to this solution. The suspension was heated at 65–70°C and after 3.5 h it became a clear solution. Dimethyl hydrogen phosphonate of 0.883 mL (1.059 g, 0.0094 mol) was added to this solution for approximately 10 min. This reaction mixture was heated at 65–70°C and held there for 3.5 h, after which it was cooled to room temperature and concentrated under reduced pressure. The solvent was discarded, and the residual product was dissolved in a large excess of methanol. After filtration, the filtrate was evaporated to give a residue, which was purified by precipitation in methanol/ethyl acetate and collected by filtration. The purification step was repeated several times to give the title compounds.

Yellow oil, 67.0% yield, $R_f = 0.40$; IR (KBr, cm^{-1}): 3219, 2969, 1760 ($^2C=O$), 1720 ($^4C=O$), 1306, 1245 (P=O), 1170, 1020 (P–O–C). ^1H NMR (400.13 MHz, CD_3OD), δ: 1.70 (s, 6H, C$\underline{H}_3$), 3.21 (d, 2H, $^2J_{PH} = 14.2$ Hz, P-C$\underline{H}_2$-NH), 3.45 (d, 2H, $^2J_{PH} = 13.8$

Hz, P-C$\underline{H}_2$-N), 3.64 (d, 6H, $^3J_{PH} = 12.5$ Hz, O-C$\underline{H}_3$), 3.66 (d, 6H, $^3J_{PH} = 12.5$ Hz, O-C$\underline{H}_3$), 6.8 (s, 1H, N$\underline{H}$), 6.9 (s, 1H, N$\underline{H}$). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD), δ: 22.9 $\underline{C}H_3$, 40.8 (d, $^1J_{PC} = 148.0$ Hz, P-$\underline{C}H_2$), 44.0 (d, $^1J_{PC} = 150.0$ Hz, P-$\underline{C}H_2$), 52.9 (d, $^2J_{PC} = 11.5$ Hz, O-$\underline{C}H_3$), 63.2 —C—, 156.0 ^{2}C=O, 172.0 ^{4}C=O. ^{31}P NMR (161.97 MHz, CD_3OD), δ: 22.02 and 29.07.

*[(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)amino]methylphosphonic acid (**5**) and (5,5-Dimethyl-2,4-dioxo-3-[(phosphonomethyl)amino]imidazolidin-1-ylmethyl)-phosphonic acid (**5′**)*

Dimethyl[(5,5-dimethyl-2,4-dioxoimidazolidin-3-yl)-aminomethyl] phosphonate (**4**) and Dimethyl[(3-[(dimethoxyphosphoryl)methyl]amino-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl) methyl]phosphonate (**4′**) (0.0016 mol), NaOH (0.16 mol) in 25.2 mL of H_2O were placed in a three-necked round-bottom flask equipped with a magnetic stirrer, reflux condenser, and thermometer. The reaction mixture was heated at 120°C for 8.30 h. Subsequently, the reaction mixture was treated with Dowex 50WX8-200 to exchange the sodium cautions by hydrogen ion exchange. The crude mixture was purified by crystallization from water. Yellow oil, 56.0% yield, $R_f = 0.45$; IR (KBr, cm^{-1}): 1765 (^{2}C=O),. 1714 (^{4}C=O), 1306, 1240 (P=O), 1190, 1120 (P—O—H). ^{1}H NMR (400.13 MHz, CD_3OD), δ: 1.79 (s, 6H, C$\underline{H}_3$), 3.35 (d, 2H, $^2J_{PH} = 14.0$ Hz, P-C$\underline{H}_2$-NH), 3.50 (d, 2H, $^2J_{PH} = 13.5$ Hz, P-C$\underline{H}_2$-N). $^{13}C\{^1H\}$ NMR (100.61 MHz, CD_3OD), δ: 24.0 $\underline{C}H_3$; 42.1 (d, $^1J_{PC} = 152.0$ Hz, P-$\underline{C}H_2$), 44.5 (d, $^1J_{PC} = 155.0$ Hz, P-$\underline{C}H_2$), 65.2 —C—, 158.0 ^{2}C=O, 175.0 ^{4}C=O. ^{31}P NMR (161.97 MHz, CD_3OD), δ: 23.41 and 25.17.

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