ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 9, pp. 1593–1595. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © A.A. Prishchenko, M.V. Livantsov, O.P. Novikova, L.I. Livantsova, I.S. Ershov, V.S. Petrosyan, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 9, pp. 1559–1561.

LETTERS TO THE EDITOR

Synthesis of *N*,*N*-Disubstituted Aminomethylenediphosphonates and Their Derivatives

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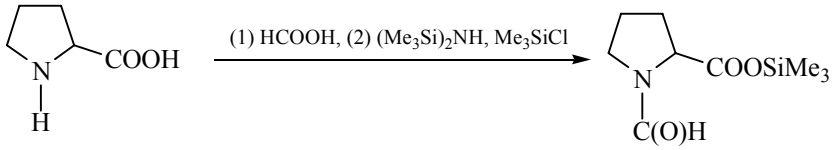
Received June 4, 2012

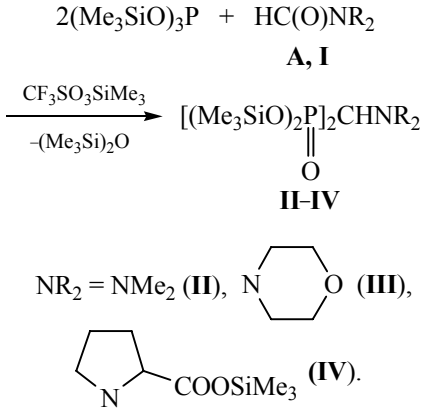
DOI: 10.1134/S1070363212090265

The substituted aminomethylene-containing organophosphorus compounds are analogs of amino acids and natural pyrophosphates and are of interest as promising ligands and biologically active substances with diverse properties [1]. Previously some of the compounds of this type have been synthesized using various formamide derivatives like dialkylformamide dialkylacetals and ethoxymethylene imines [2]. Aiming to synthesize the new types of *N*,*N*-disubstituted aminomethylenediphosphonates we studied the reaction of tris(trimethylsilyl)phosphite directly with the most available *N*,*N*-disubstituted formamides **A** [3]. Formylproline *N*-trimethylsilyl ether **I** we obtained specifically through the proline formylation followed by the treating with bis(trimethylsilyl)amine and trimethylchlorosilane as the silylating reagents at heating to 130°C.

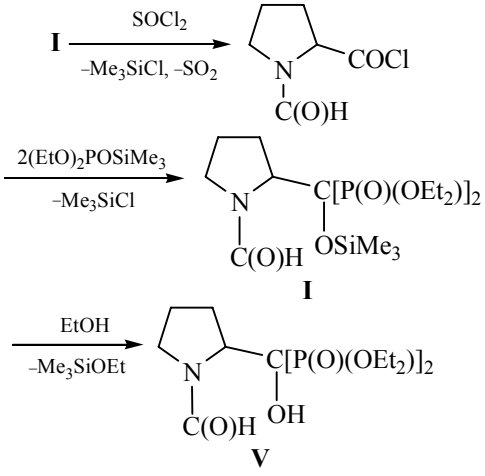


I

Formamides **A** were found to react readily with an excess of tris(trimethylsilyl)phosphite in methylene chloride in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst to give diphosphonates **II**–**IV** in high yields.

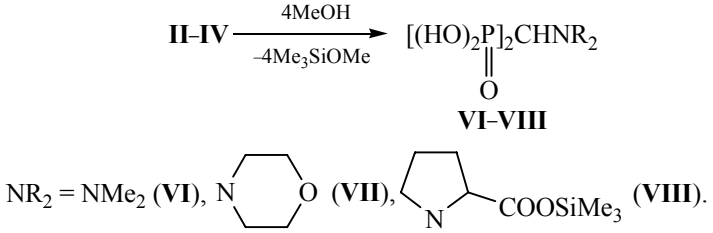


The structural analogue of aminomethylenediphosphonate **IV,** hydroxymethylenediphosphonate **V**, formed in a high yield by the sequential treatment of formamide **I** with thionyl chloride, an excess of diethyl(trimethylsilyl)phosphate, and ethanol [4].



V

The reactions of diphosphonates **II–IV** with an excess of methanol under mild conditions result in aminomethylenediphosphonic acids **VI–VIII** in high yields. They are white hygroscopic crystalline substances.



Aminomethylenediphosphonic acids **VI** and **VII** obtained previously were described as crystal hydrates [5].

The NMR spectra of compounds **I–VIII** contain the characteristic signals of $P_2C^1HNC^2H_n(C^3H_m)$, $\{C^3H_2C^4H_2C^5H_2C^2H[C^6(P_2)]\}NC^1H(P_2)$ fragments whose parameters are listed below. According to the NMR spectra, compounds **I**, **IV**, and **VIII** are mixtures of two stereoisomers, the ratio of which was determined by the ^1H and ^{31}P NMR. The predominant isomer data are given the first. Two diastereotopic diethoxyphosphoryl groups of **V** differ in the NMR spectra, and in the ^{31}P NMR spectrum they are observed as a characteristic AB-system.

Trimethylsilyl ether of *N*-formylproline (I). A mixture of 20 g of proline and 50 g of formic acid was heated with stirring on a boiling water bath for 5 h. Then the solvent was distilled off in a vacuum of 7 mm Hg. To the residue was added 56 g of bis(trimethylsilyl)amine and 8 g of trimethylchlorosilane. The mixture was refluxed to complete sublimation of ammonium chloride. The residue was distilled. Yield 72% (27 g), bp 133°C (2 mm Hg). The first isomer, content 60%. ^1H NMR spectrum, δ, ppm: 7.91 s (C^1H), 4.08 d.d (C^2H, $^3J_{HHA}$ 8.4, $^3J_{HHB}$ 3.6 Hz), 3.25–3.35 m (C^3H_2), 1.5–2.0 m (C^4H_2, C^5H_2,), –0.06 s (Me_3Si). ^{13}C NMR spectrum, δ_C, ppm: 160.18 (C^1), 57.17 (C^2), 45.90 (C^3), 23.63 (C^4), 29.03 (C^5), 171.43 (C^6). The second isomer. ^1H NMR spectrum, δ, ppm: 7.86 s (C^1H), 3.99 d.d (C^2H, $^3J_{HHA}$ 8.4, $^3J_{HHB}$ 4 Hz), 3.08–3.19 m (C^3H_2), 1.5–2.0 m (C^4H_2, C^5H_2), –0.06 s (Me_3Si). ^{13}C NMR spectrum, δ_C, ppm: 161.21 (C^1), 59.27 (C^2), 43.43 (C^3), 22.43 (C^4), 29.31 (C^5), 171.82 (C^6). Found, %: C 49.97; H 7.82. $C_9H_{17}NO_3Si$. Calculated, %: C 50.20; H 7.96.

Tetra(trimethylsilyl) dimethylaminomethylenediphosphonate (II). To a solution of 15 g of tris(trimethylsilyl)phosphate and 1.5 g of dimethylformamide in 8 ml of methylene chloride was added with stirring 3 ml of trimethylsilyl trifluoromethanesulfonate. The mixture was kept at 20°C for 24. After removing the solvent 3 ml of hexane was added to the residue at cooling to 5°C. The solvent was decanted from the mixture, and the white crystals were kept in a vacuum of 0.5 mm Hg. Yield 87% (8.8 g), mp 42°C. ^1H NMR spectrum, δ, ppm: 3.05 t (C^1H, $^2J_{PH}$ 24.4 Hz), 2.40 s ($2C^2H_3N$), –0.08 s (Me_3Si). ^{13}C NMR spectrum, δ_C, ppm: 62.77 t (C^1, $^1J_{PC}$ 147.7 Hz), 43.53 t (C^2, $^3J_{PC}$ 4.3 Hz), 0.48 (Me_3Si). ^{31}P NMR spectrum: δ_P –2.87 ppm. Found, %: C 35.26; H 8.49. $C_{15}H_{43}NO_6 \cdot P_2Si_4$. Calculated, %: C 35.48; H 8.53.

Diphosphonates **III** and **IV** were obtained similarly.

Tetra(trimethylsilyl) *N*-morpholinomethylenediphosphonate (III). Yield 85%, viscous oil. ^1H NMR spectrum, δ, ppm: 2.76 t (C^1H, $^2J_{PH}$ 25.6 Hz), 2.7–2.8 m ($2C^2H_2$), 3.3–3.4 m ($2C^3H_2$), 0.07 s ($4Me_3Si$). ^{13}C NMR spectrum, δ_C, ppm: 63.82 t (C^1, $^1J_{PC}$ 148.9 Hz), 51.33 t (C^2, $^3J_{PC}$ 4.4 Hz), 67.11 s (C^3), 0.75 s (Me_3Si). ^{31}P NMR spectrum: δ_P –0.62 ppm. Found, %: C 36.94; H 8.16. $C_{17}H_{45}NO_7P_2Si_4$. Calculated, %: C 37.14; H 8.25.

Tetra(trimethylsilyl) *N*-(*O*-trimethylsilylprolino)-methylenediphosphonate (IV). Yield 89%, viscous oil. The first isomer, content 60%. ^1H NMR spectrum, δ, ppm: 3.42 br.t (C^1H, $^2J_{PH}$ 26.2 Hz), 3.6–3.8 m (C^2H), 2.6–2.8 m (C^3H_2), 1.3–1.7 m (C^4H_2, C^5H_2), –0.17 s ($4Me_3Si$). ^{13}C NMR spectrum, δ_C, ppm: 58.41 t (C^1, $^1J_{PC}$ 155.7 Hz), 63.8–64.5 m (C^2), 48.9–49.6 m (C^3), 22.97 (C^4), 27.98 (C^5), 171.82 (C^6), 0.43 (Me_3Si). ^{31}P NMR spectrum: δ_P –0.42 ppm. The second isomer. ^1H NMR spectrum, δ, ppm: 3.42 br.t (C^1H, $^2J_{PH}$ 26.2 Hz), 3.6–3.8 m (C^2H), 2.6–2.8 m (C^3H_2), 1.3–1.7 m (C^4H_2, C^5H_2), –0.17 s (4 Me_3Si). ^{13}C NMR spectrum, δ_C, ppm: 58.16 t (C^1, $^1J_{PC}$ 156.5 Hz), 63.8–64.5 m (C^2), 48.9–49.6 m (C^3), 22.97 (C^4), 27.98 (C^5), 171.54 (C^6), 0.43 (Me_3Si). ^{31}P NMR spectrum: δ_P 3.16 ppm. Found, %: C 38.72; H 8.14. $C_{21}H_{53}NO_8P_2Si_5$. Calculated, %: C 38.96; H 8.22.

Tetraethyl (*N*-formylpyrrolidin-2-yl)hydroxymethylenediphosphonate (V). To a solution of 6.1 g of ether

I in 10 ml of methylene chloride was added with the stirring at cooling to 5°C a solution of 3.6 g of thionyl chloride in 5 ml of methylene chloride. The mixture was heated to reflux, and the solvent was removed. The residue was kept in a vacuum of 1 mm Hg for 0.5 h. Then it was dissolved in 15 ml of methylene chloride. To the obtained solution cooled to 5°C was added a solution of 18 g of diethyl(trimethylsilyl)phosphite in 15 ml of methylene chloride under stirring. After removing the solvent, to the residue was added 30 ml of ethanol. The mixture was heated to 40°C. Trimethyl (ethoxy)silane and ethanol were distilled off. The residue was dissolved in 15 ml of diethyl ether and mixed with 10 ml of hexane and 10 ml of water. The formed oily substance was kept in a vacuum of 1 mm Hg for 0.5 h. Yield 91% (10.3 g), viscous oil. ^{1}H NMR spectrum, δ, ppm: 7.84 s (C^1H), 3.6–4.0 m (C^2H, $4CH_2OP$), 3.15–3.65 m (C^3H_2), 1.3–1.6 m (C^4H_2), 1.9–2.3 m (C^5H_2), 0.9–1.0 ($4CH_3$). ^{13}C NMR spectrum, δ_C, ppm: 77.90 t (C^6H, $^2J_{PC}$ 154.9 Hz), 164.22 (C^1), 62.7–64.3 m (C^2, CH_2OP), 48.50 s (C^3), 24.18 s (C^4), 27.71 s (C^5), 15.9–16.2 m (Me). ^{31}P NMR spectrum, δ_P, ppm: 15.87 and 16.22 (AB-system, $^2J_{PP}$ 28.7 Hz). Found, %: C 41.71; H 7.22. $C_{14}H_{29}NO_8P_2$. CAlculated, %: C 41.90; H 7.28.

Dimethylaminomethylenediphosphonic acid (VI). To 30 ml of methanol was added 8.8 g of diphosphonate **II** with the stirring and cooling to 10°C. The mixture was heated to reflux, and the solvent was removed. The white crystals were kept in a vacuum of 1 mm Hg for 1 h. Yield 97% (3.7 g), mp 212°C. ^{1}H NMR spectrum, δ, ppm: 3.05 t (C^1H, $^2J_{PH}$ 18.4 Hz), 2.57 s ($2C^2H_3$). ^{13}C NMR spectrum, δ_C, ppm: 62.24 t (C^1, $^1J_{PC}$ 115.8 Hz), 43.67 (C^2). ^{31}P NMR spectrum: δ_P 6.29 ppm. Found, %: C 16.23; H 4.92. $C_3H_{11}NO_6P_2$. Calculated, %: C 16.45; H 5.06.

Acids **VIII** and **VIII** were obtained similarly.

***N*-Morpholinomethylenediphosphonic acid (VII).** Yield 96%, mp 202°C. ^{1}H NMR spectrum, δ, ppm: 3.08 t (C^1H, $^2J_{PH}$ 17.6 Hz), 2.54 s ($2C^2H_2$), 3.2–3.3 m (C^3H_2). ^{13}C NMR spectrum, δ_C, ppm: 62.99 t (C^1, $^1J_{PC}$ 111 Hz), 51.74 (C^2), 64.07 (C^3). ^{31}P NMR spectrum: δ_P 6.22 ppm. Found, %: C 22.83; H 4.92. $C_5H_{13}NO_7P_2$. Calculated, %: C 23.00; H 5.02.

***N*-Prolinomethylenediphosphonic acid (VIII).** Yield 95%, mp 187°C. The first isomer, content 55%. ^{1}H NMR spectrum, δ, ppm: 4.29 t (C^1H, $^2J_{PH}$ 20 Hz), 5.1–5.2 m (C^2H), 3.95–4.05 m (C^3H_2), 2.0–2.5 m (C^4H_2, C^5H_2). ^{13}C NMR spectrum, δ_C, ppm: 58.31 t (C^1, $^1J_{PC}$ 127.7 Hz), 67.54 t (C^2, $^3J_{PC}$ 5.6 Hz), 54.09 (C^3), 22.84 (C^4), 28.06 (C^5), 170.20 (C^6). ^{31}P NMR spectrum: δ_P 7.04 ppm. The second isomer. ^{1}H NMR spectrum, δ, ppm: 4.32 t (C^1H, $^2J_{PH}$ 20 Hz), 5.1–5.2 m (C^2H), 4.1–4.2 m (C^3H_2), 2.0–2.5 m (C^4H_2, C^5H_2). ^{13}C NMR spectrum, δ, ppm: 58.39 t (C^1, $^1J_{PC}$ 128.5 Hz), 67.21 t (C^2, $^3J_{PC}$ 5.4 Hz), 54.21 (C^3), 22.64 (C^4), 27.78 (C^5), 168.97 (C^6). ^{31}P NMR spectrum: δ_P 7.89 ppm. Found, %: C 24.69; H 4.42. $C_6H_{13}NO_8P_2$. Calculated, %: C 24.93; H 4.53.

The NMR spectra were obtained on a Bruker Avance 400 spectrometer using $CDCl_3$ (**I**–**V**), a mixture of D_2O and C_5D_5N (**VI**, **VII**) or CD_3OD (**VIII**) as the solvents and TMS (^{1}H, ^{13}C) or 85% H_3PO_4 in D_2O (^{31}P) as the reference.

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research (grants no. 11-03-00402, 12-03-00003).

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