ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 10, pp. 2418–2421. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © A.A. Prishchenko, M.V. Livantsov, O.P. Novikova, L.I. Livantsova, G.M. Averochkin, V.S. Petrosyan, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 10, pp. 1747–1749.

LETTERS TO THE EDITOR

Acylation of Aminomethylene Diphosphonic Acids Tetraethyl Esters and Their Analogs

A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, G. M. Averochkin, and V. S. Petrosyan

Lomonosov Moscow State University, Vorob'evy gory, Moscow, 119991 Russia
e-mail: aprishchenko@yandex.ru

Received May 7, 2015

Keywords: phosphorus-substituted amides of carboxylic acids, aminomethylene diphosphonic acids tetraethyl esters, acylation

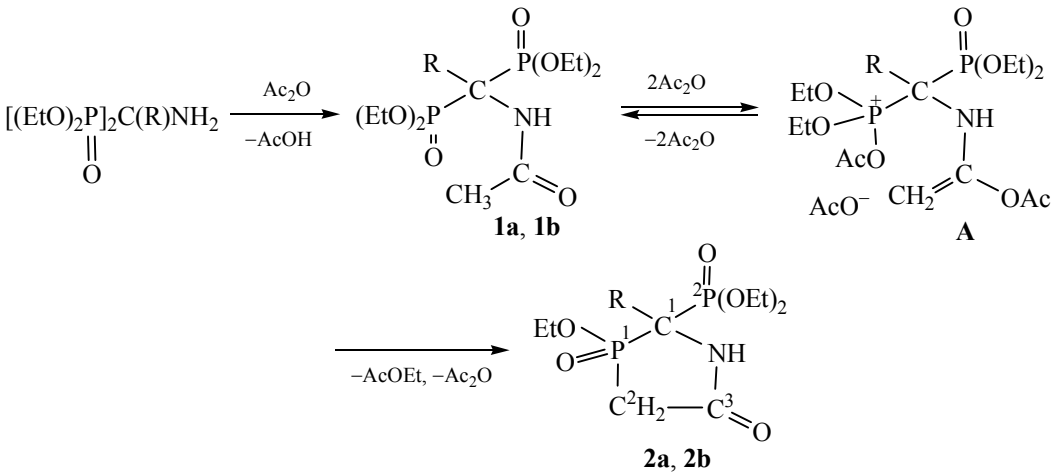
DOI: 10.1134/S1070363215100333

Phosphorus-substituted amides of carboxylic acids containing PCH_2N fragment are interesting as effective ligands and promising biologically active compounds [1]. Recently, we have synthesized tetraethyl esters of aminomethylene diphosphonic acids containing unsubstituted amino group based on accessible hydrochlorides of substituted ethoxyimines [2]. In the present work the acylation of tetraethyl esters of aminomethylene diphosphonic acids and their analogs was investigated.

It was found that the reaction of diphosphonates with an excess of acetic anhydride at reflux unexpectedly led to the formation of cyclic products, 2-phosphorus-substituted 1,3-azaphospholidin-5-ones **2a** and **2b** along with ordinary diphosphorus-substituted acetamides **1a** and **1b**. Such direction of the reaction was undoubtedly connected with the ability of acetic anhydride to add to the phosphoryl group at heating and acylate acetamide fragment of diphosphonates **1** with the formation of intermediates **A** including quasi-phosphonium center and *N*,*O*-ketene acetal fragment; their further transformation proceeded with the formation of a new P–C bond (Scheme 1).

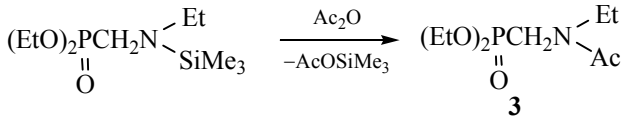
It should be noted that the acylation of both mono- and bis(trimethylsilyl)aminomethylphosphonates under the same conditions led to the sole formation of

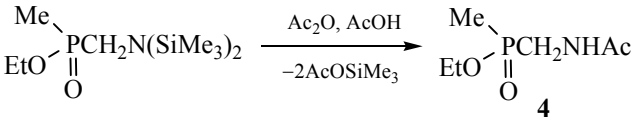
Scheme 1.



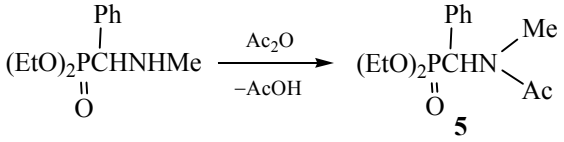
R = Me (**a**), Ph (**b**).

ordinary phosphorus-substituted acetamides **3** and **4** (cf. [3]).





The reaction of diethyl (methylaminophenylmethyl) phosphonate with acetic anhydride proceeded similarly to give phosphorus-substituted acetamide **5** we earlier obtained under mild conditions [4, 5].



Therefore the presence of the second phosphoryl group in diphosphonates **1a** and **2b** most probably facilitated the formation of intermediates **A** and their further cyclization.

The structure of the prepared compounds was confirmed by NMR spectroscopy data. Compounds **1–5** containing *N*-methylacetamide fragment and asymmetric atoms were the mixtures of two stereoisomers.

The obtained compounds are the promising polydentate ligands for the preparation of new mono- and diphosphorus-containing coordination complexes including derivatives of various metals.

***O*,*O*,*O*,*O*-Tetraethyl-*N*-acetyl-1-aminoethylidene diphosphonate (1a) and 2-methyl-2-diethoxyphosphoryl-1,3-azaphospholidine-3,5-dione (2a)**. Acetic anhydride (20 g) was added to a solution of tetraethyl 1-aminoethylidenediphosphonate in 10 mL of methylene chloride at stirring and cooling to 10°C. The mixture was gradually heated with distilling off the volatile compounds till the beginning of boiling of acetic anhydride. An excess of acetic anhydride was distilled off at 7 mmHg, the residue was subjected to distillation. As a result, a mixture of compounds **1a** and **2a** (4.7 g) was obtained in a ratio of 30 : 70 (^{31}P NMR). Yield 85%, bp 173°C (2 mmHg). **Compound 1a.** The first isomer, content 95%. ^{1}H NMR spectrum, δ, ppm: 0.95–1.06 m (12H, CH_3), 1.54 t (3H, CH_3, $^{3}J_{PH}$ 16.4 Hz), 1.64 s (3H, CH_3CO), 3.65–4.05 m (8H, CH_2O), 7.30 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 15.80–16.20 m (CH_3), 23.82 (CH_3CO), 56.11 t (PC, $^{1}J_{PC}$ 146.1 Hz), 63.25–68.35 m (CH_2O), 169.22 t (C=O, $^{3}J_{PC}$ 4.0 Hz). ^{31}P NMR spectrum: δ_P 19.81 ppm. The second isomer, content 5%. ^{31}P NMR spectrum: δ_P 16.79 ppm. **Compound 2a.** The first isomer, content 60%. ^{1}H NMR spectrum, δ, ppm: 0.95–1.06 m (9H, CH_3), 1.29 t (3H, CH_3, $^{3}J_{PH}$ 16.8 Hz), 2.05–2.20 m (2H, C^2H_2), 3.65–4.05 m (6H, CH_2O), 6.12 t (1H, NH, $^{3}J_{PH}$ 6.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.85–16.20 m (CH_3), 18.27 d (CH_3, $^{2}J_{PC}$ 4.8 Hz), 31.80–34.55 m (C^2), 60.50 d.d (C^1, $^{1}J_{P^1C}$ 99.8, $^{1}J_{P^2C}$ 160.4 Hz), 63.20–63.85 m (CH_2O), 160.37 d.d (C^3, $^{2}J_{P^1C}$ 15.2, $^{3}J_{P^2C}$ 24.8 Hz). ^{31}P NMR spectrum, δ_P, ppm: 18.10 d (P^2, $^{2}J_{PP}$ 19.9 Hz), 42.20 d (P^1, $^{2}J_{PP}$ 19.9 Hz). The second isomer, content 40%. ^{1}H NMR spectrum, δ, ppm: 0.95–1.06 m (9H, CH_3), 1.24 t (3H, CH_3, $^{3}J_{PH}$ 16.4 Hz), 2.05–2.20 m (2H, C^2H_2), 3.65–4.05 m (6H, CH_2O), 6.13 t (1H, NH, $^{3}J_{PH}$ 6.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.85–16.20 m (CH_3), 17.85 d (CH_3, $^{2}J_{PC}$ 4.0 Hz), 31.80–34.55 m (C^2), 61.07 d.d (C^1, $^{1}J_{P^1C}$ 102.1, $^{1}J_{P^2C}$ 155.6 Hz), 63.20–63.85 m (CH_2O), 160.65 d.d (C^3, $^{2}J_{P^1C}$ 13.5, $^{3}J_{P^2C}$ 23.2 Hz). ^{31}P NMR spectrum, δ_P, ppm: 17.45 d (P^2, $^{2}J_{PP}$ 27.7 Hz), 40.92 d (P^1, $^{2}J_{PP}$ 27.7 Hz).

Compounds **1b**, **2b**, and **3–5** were obtained similarly.

***O*,*O*,*O*,*O*-Tetraethyl *N*-acetyl-1-aminobenzylidenediphosphonate (1b) and 2-phenyl-2-diethoxyphosphoryl-1,3-azaphospholidine-3,5-dione (2b)** (15 : 85). Yield 78%, bp 148°C (0.3 mmHg). **Compound 1b.** The first isomer, content 97%. ^{1}H NMR spectrum, δ, ppm: 1.05–1.25 m (9H, CH_3), 1.80 s (3H, CH_3CO), 3.80–4.05 m (6H, CH_2O), 7.05–7.76 m (5H, C_6H_5), 8.25–8.28 m (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 15.85–16.15 m (CH_3), 20.65 s (CH_3CO), 62.90–65.85 m (CH_2O), 69.07 t (PC, $^{1}J_{PC}$ 157.2 Hz), 126.5–133.85 m (Ph), 166.37 br.s (C=O). ^{31}P NMR spectrum: δ_P 21.74 ppm. The second isomer, content 3%. ^{31}P NMR spectrum: δ_P 20.89 ppm. **Compound 2b**. The first isomer, content 65%. ^{1}H NMR spectrum, δ, ppm:

1.05–1.25 m (12H, CH_3), 2.40–2.55 m (2H, CH_2), 3.80–4.05 m (8H, CH_2O), 7.05–7.76 m (5H, C_6H_5), 8.25–8.28 m (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 15.85–16.10 m (CH_3), 35.05–38.50 m (C^2), 62.90–65.85 m (CH_2O), 69.15 d.d (C^1, $^1J_{P^1C}$ 101.4, $^1J_{P^2C}$ 145.3 Hz), 126.55–133.85 m (Ph), 161.68 d.d (C^3, $^2J_{P^1C}$ 11.2, $^3J_{P^2C}$ 21.6 Hz). ^{31}P NMR spectrum, δ_P, ppm: 13.08 d (P^2, $^2J_{PP}$ 27.4 Hz), 37.18 d (P^1, $^2J_{PP}$ 27.4 Hz). The second isomer, content 35%. ^1H NMR spectrum, δ, ppm: 1.05–1.25 m (9H, CH_3), 2.40–2.55 m (2H, C^2H_2), 3.80–4.05 m (6H, CH_2O), 7.05–7.76 m (5H, C_6H_5), 8.25–8.28 m (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 15.85–16.10 m (CH_3), 35.05–38.50 m (C^2), 62.90–65.85 m (CH_2O), 68.96 d.d (C^1, $^1J_{P^1C}$ 102.1, $^1J_{P^2C}$ 146.0 Hz), 126.55–133.85 m (Ph), 160.76 d.d (C^3, $^2J_{P^1C}$ 13.6, $^3J_{P^2C}$ 23.1 Hz). ^{31}P NMR spectrum, δ_P, ppm: 14.67 d (P^2, $^2J_{PP}$ 15.9 Hz), 38.78 d (P^1, $^2J_{PP}$ 15.9 Hz).

***O*,*O*-Diethyl (*N*-acetyl-*N*-ethylaminomethyl)phosphonate (3).** Yield 85%, bp 133°C (0.5 mmHg). The first isomer, content 75%. ^1H NMR spectrum, δ, ppm: 0.69 t (3H, CH_3, $^3J_{HH}$ 7.2 Hz), 0.79 t (6H, CH_3, $^3J_{HH}$ 6.8 Hz), 1.60 s (3H, CH_3CO), 3.02 t (2H, CH_2N, $^3J_{HH}$ 7.2 Hz), 3.31 d (2H, PCH_2, $^2J_{PH}$ 11.6 Hz), 3.50–3.75 m (4H, CH_2O). ^{13}C NMR spectrum, δ_C, ppm: 12.19 (CH_3), 15.40 d (CH_3, $^3J_{PC}$ 6.2 Hz), 19.86 (CH_3CO), 38.81 d (PC, $^1J_{PC}$ 156.4 Hz), 42.87 (CH_2N), 61.21 d (CH_2O, $^2J_{PC}$ 6.2 Hz), 168.92 br.s (C=O). ^{31}P NMR spectrum: δ_P 22.37 ppm. The second isomer, content 25%. ^1H NMR spectrum, δ, ppm: 0.58 t (3H, CH_3, $^3J_{HH}$ 7.2 Hz), 0.82 t (6H, CH_3, $^3J_{HH}$ 7.2 Hz), 1.63 s (3H, CH_3CO), 3.03 t (2H, CH_2N, $^3J_{HH}$ 7.2 Hz), 3.17 d (2H, PCH_2, $^2J_{PH}$ 10.0 Hz), 3.50–3.75 m (4H, CH_2O). ^{13}C NMR spectrum, δ_C, ppm: 11.08 (CH_3), 15.52 d (CH_3, $^3J_{PC}$ 5.5 Hz), 20.86 (CH_3CO), 40.65 (CH_2N), 43.34 d (PC, $^1J_{PC}$ 159.0 Hz), 61.53 d (CH_2O, $^2J_{PC}$ 7.0 Hz), 169.33 br.s (C=O). ^{31}P NMR spectrum: δ_P 21.14 ppm. Found, %: C 45.52; H 8.42. $C_9H_{20}NO_4P$. Calculated, %: C 45.57; H 8.50.

***O*-Ethyl (methyl)(*N*-acetylaminomethyl)phosphinate (4)**. Yield 83%, bp 157°C (1 mmHg). The first isomer, content 65%. ^1H NMR spectrum, δ, ppm: 0.71 t (3H, CH_3, $^3J_{HH}$ 7.2 Hz), 0.90 d (3H, CH_3P, $^2J_{PH}$ 14.0 Hz), 1.89 s (CH_3CO), 2.87–3.96 m (2H, PCH_2), 3.45–3.55 m (2H, CH_2O), 7.78 d (1H, NH, $^3J_{PH}$ 6.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 11.86 d (CH_3P, $^1J_{PC}$ 92.3 Hz), 15.60 (CH_3), 25.32 (CH_3CO), 37.17 d (PCH_2, $^1J_{PC}$ 103.3 Hz), 59.70 d (CH_2O, $^2J_{PC}$ 6.6 Hz), 171.80 (C=O). ^{31}P NMR spectrum: δ_P 49.86 ppm. The second isomer, content 35%. ^1H NMR spectrum, δ, ppm: 0.95 d (3H, CH_3P, $^2J_{PH}$ 14.4 Hz), 0.73 t (3H, CH_3, $^3J_{HH}$ 6.8 Hz), 1.40 s (3H, CH_3CO), 2.87–3.96 m (2H, PCH_2), 3.45–3.55 m (2H, CH_2O), 7.78 d (1H, NH, $^3J_{PH}$ 5.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.43 d (CH_3P, $^1J_{PC}$ 91.2 Hz), 15.55 (CH_3), 21.44 (CH_3CO), 42.74 d (PCH_2, $^1J_{PC}$ 102.6 Hz), 59.92 d (CH_2O, $^2J_{PC}$ 6.6 Hz), 169.45 d (C=O, $^3J_{PC}$ 2.9 Hz). ^{31}P NMR spectrum: δ_P 47.76 ppm. Found, %: C 40.03; H 7.72. $C_6H_{14}NO_3P$. Calculated, %: C 40.23; H 7.88.

***O*,*O*-Diethyl [(*N*-acetyl-*N*-methylamino)(phenyl)-methyl]phosphinate (5)**. Yield 88%, bp 198°C (2 mmHg). The first isomer, content 80%.^1H NMR spectrum, δ, ppm: 0.71 t (3H, CH_3, $^3J_{HH}$ 6.8 Hz), 0.87 t (3H, CH_3, $^3J_{HH}$ 7.2 Hz), 1.68 s (3H, CH_3CO), 2.60 s (3H, CH_3N), 3.50–3.85 m (4H, CH_2O), 5.99 d (1H, PCH, $^2J_{PH}$ 22.8 Hz), 6.85–7.35 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 15.36 d (CH_3, $^3J_{PC}$ 5.5 Hz), 15.62 d (CH_3, $^3J_{PC}$ 5.5 Hz), 20.88 (CH_3CO), 32.35 (CH_3N), 51.63 d (PCH, $^1J_{PC}$ 157.5 Hz), 61.51 d (CH_2O, $^2J_{PC}$ 1.5 Hz), 61.69 br.s (CH_2O), 127.42 (C^p), 127.83 (C^m), 128.87 d (C^o, $^3J_{PC}$ 8.8 Hz), 132.93 d (C^{ipso}, $^2J_{PC}$ 4.8 Hz), 169.88 (C=O, $^3J_{PC}$ 5.2 Hz). ^{31}P NMR spectrum: δ_P 20.57 ppm. The second isomer, content 20%. ^1H NMR spectrum, δ, ppm: 0.71 t (3H, CH_3, $^3J_{HH}$ 6.8 Hz), 0.87 t (3H, CH_3, $^3J_{HH}$ 7.2 Hz), 1.85 s (3H, CH_3CO), 2.53 s (3H, CH_3N), 4.83 d (1H, PCH, $^2J_{PH}$ 23.6 Hz), 3.50–3.85 m (4H, CH_2O), 6.85–7.35 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 15.36 d (CH_3, $^3J_{PC}$ 5.5 Hz), 15.62 d (CH_3, $^3J_{PC}$ 5.5 Hz), 20.00 (CH_3CO), 29.79 (CH_3N), 58.52 d (PCH, $^1J_{PC}$ 157.5 Hz), 61.51 d (CH_2O), 61.69 br.s (CH_2O), 127.42 (C^p), 128.01 (C^m), 128.24 d (C^o, $^3J_{PC}$ 8.1 Hz), 132.52 d (C^{ipso}, $^2J_{PC}$ 4.4 Hz), 171.58 (C=O). ^{31}P NMR spectrum: δ_P 20.07 ppm. Physicochemical characteristics of phosphonate **5** matched the data described by us earlier [4, 5].

NMR spectra ($CDCl_3$) were obtained on a Bruker Avance 400 spectrometer using TMS (^1H and ^{13}C) or 85% solution of H_3PO_4 in D_2O (^{31}P NMR) as a reference.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grants nos. 14-03-00001 and 15-03-00002).

REFERENCES

1. Kukhar, V.P., and Hudson, H.R., *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*, New York: Wiley, 2000.
2. Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., Averochkin, G.M., and Petrosyan, V.S., *Heteratom. Chem*., 2015, vol. 26. DOI: 10.1002/hc.21274.
3. Prishchenko, A.A., Livantsov, M.V., Kustrya, D.N., Novikova, O.P., Grigoriev, E.V., and Goncharova, Zh.Yu., *Russ. J. Gen. Chem*., 1997, vol. 67, no. 11, p. 1803.
4. Prishchenko, A.A., Novikova, O.P., Livantsov, M.V., Kustrya, D.N., and Grigoriev, E.V., *Russ. J. Gen. Chem*., 1998, vol. 68, no. 3, p. 481.
5. Prishchenko, A.A., Novikova, O.P., Livantsov, M.V., Livantsova, L.I., Koval, Ya.N., and Grigoriev, E.V., *Russ. J. Gen. Chem*., 2003, vol. 73, no. 12, p. 1947. DOI: 10.1023/B:RUGC.0000025161.93030.b9.