ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 11, pp. 2150–2153. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.A. Prishchenko, M.V. Livantsov, O.P. Novikova, L.I. Livantsova, E.R. Milyaeva, 2008, published in Zhurnal Obshchei Khimii, 2008, Vol. 78, No. 11, pp. 1914–1917.

LETTERS TO THE EDITOR

Synthesis of 2-Pyridylethylphosphinates Containing 2,6-Di-*tert*-butyl-4-methylphenol Fragments

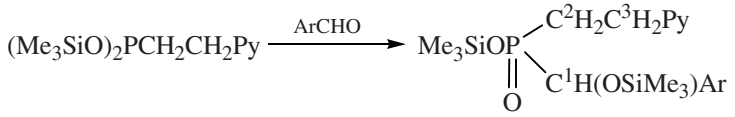
A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, and E. R. Milyaeva

Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia
e-mail: aprishchenko@yandex.ru

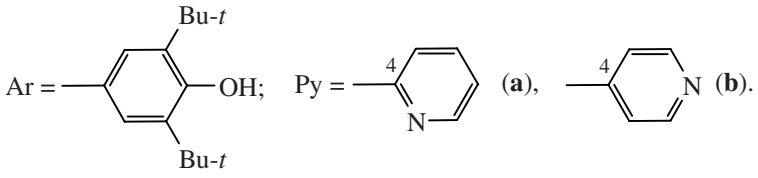
Received April 8, 2008

DOI: 10.1134/S1070363208110297

Various functionalized hydroxyalkylphosphonic acids and their derivatives are effective complexones and biologically active substances [1, 2]. Pyridine-containing derivatives of phosphonic and phosphinic acids are of special interest in this compounds series, and some of them are widely used in medicine [3]. In this work the new 2-pyridylethylphosphinates and diphosphinates were prepared that contain fragments of bulky phenol along with hydroxymethyl groups and pyridine fragments and are promising complexones and antioxidants. As initial compounds we used accessible 2-pyridylethylphosphonites **A** that were successfully applied earlier to the synthesis of organophosphorous analogs of amino acids, containing amino and carboxy groups [3, 4]. Thus, phosphonites **A** readily added to the carbonyl group of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde in methylene chloride medium to form phosphinates (**I**) in high yield.

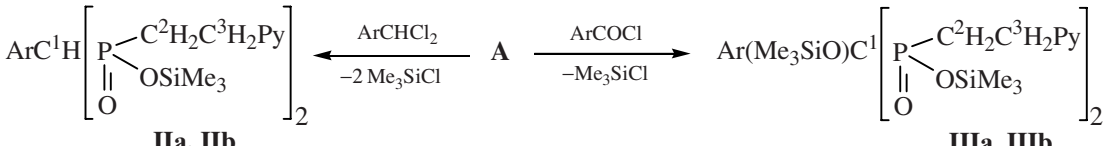


A **Ia, Ib**

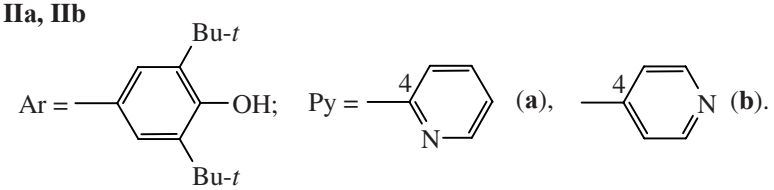


Under the same conditions phosphonites **A** react smoothly with 3,5-di-*tert*-butyl-4-hydroxybenzalchloride and 3,5-di-*tert*-butyl-4-hydroxybenzoyl chloride to give substituted methylenebisphosphinates (**II, III**) in high yield (cf. [5, 6]).

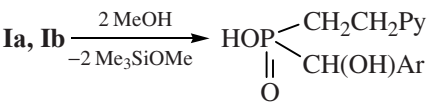
We emphasize that under mild conditions the pyridine-containing fragments and spatially screened phenol groups remain intact in the initial compounds and target products and do not undergo the possible side reactions (cf. [5, 6]). Reactions of phosphinates **I**



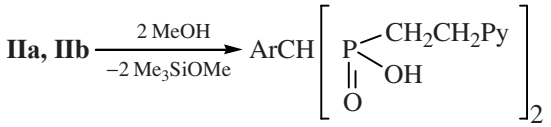
IIa, IIb **IIIa, IIIb**



and bisphosphonates **II** and **III** with methanol excess afford pyridine-substituted mono- and diphos-phonic acids (**IV–VI**) which are white hygroscopic crystals.

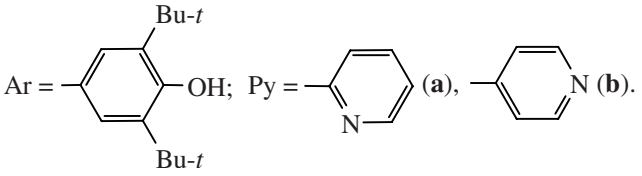


IVa, IVb



Va, Vb

VIa, VIb



In the NMR spectra of compounds **I–IV** characteristic signals of $PC^1H(OX)$ fragments, methylenediphosphorous-containing PC^1P fragments, and also signals of substituted aromatic fragments were observed. These signals are partially superimposed in the ^1H and ^{13}C NMR spectra and appear as multiplets. According to the NMR spectra compounds **I–III** are mixtures of two stereoisomers whose ratio was determined from ^{31}P NMR. Data on the prevailing isomer are given first.

Trimethylsilyl [2-(pyrid-2-yl)ethyl][3,5-di-*tert*-butyl-4-hydroxyphenyl(trimethylsiloxy)-methyl]phosphinate (Ia). To a solution of 4 g of bis(trimethylsilyl) 2-(pyrid-2-yl)ethylphosphonite in 20 ml of methylene chloride was added a solution of 2.4 g of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde in 15 ml of methylene chloride at the cooling to 0°C while stirring. The mixture was stirred for 0.5 h and then was heated to boiling. The solvent was removed and 5 ml of hexane was added to the residue. After cooling the mixture to 0°C hexane was decanted and residue was kept under a vacuum (0.5 mm Hg) for 1 h. Yield 5 g (89%), viscous oily liquid. The first isomer content 55%. ^1H NMR spectrum, δ, ppm: 4.78 d (C^1H, $^2J_{PH}$ 5 Hz). ^{13}C NMR spectrum, δ, ppm: 74.64 d (C^1, $^1J_{PC}$ 120 Hz), 26.22 d (C^2, $^1J_{PC}$ 90 Hz), 29.22 s (C^3), 160.73 d (C^4, $^3J_{PC}$ 15 Hz). ^{31}P NMR spectrum, δ, ppm: 41.84 s. The second isomer, ^1H NMR spectrum, δ, ppm: 4.58 d (C^1H, $^2J_{PH}$ 8 Hz). ^{13}C NMR spectrum, δ, pm: 73.93 d (C^1, $^1J_{PC}$ 117 Hz), 26.17 d (C^2, $^1J_{PC}$ 91 Hz), 29.46 s (C^3), 159.28 d (C^4, $^3J_{PC}$ 13 Hz). ^{31}P NMR spectrum, δ, ppm: 39.94 s. Found, %: C 60.98; H 8.72. $C_{28}H_{48}NO_4PSi_2$. Calculated, %: C 61.17; H 8.80.

Compounds **Ib, II**, and **III** were prepared similarly.

Trimethylsilyl [2-(pyrid-4-yl)ethyl][3,5-di-*tert*-butyl-4-hydroxyphenyl(trimethylsiloxy)methyl]phosphinate (Ib). Yield 91%, viscous oily liquid. The first isomer content 55%. ^1H NMR spectrum, δ, ppm: 4.85 d (C^1H, $^2J_{PH}$ 5 Hz). ^{13}C NMR spectrum, δ, ppm: 74.78 d (C^1, $^1J_{PC}$ 120 Hz), 27.71 d (C^2, $^1J_{PC}$ 90 Hz), 27.39 d (C^3, $^1J_{PC}$ 3 Hz), 150.72 d (C^4, $^3J_{PC}$ 14 Hz). ^{31}P NMR spectrum, δ, ppm: 40.80 s. The second isomer, ^1H NMR spectrum, δ, ppm: 4.66 d (C^1H, $^2J_{PH}$ 8 Hz). ^{13}C NMR spectrum, δ, ppm: 74.10 d (C^1, $^1J_{PC}$ 118 Hz), 27.22 d (C^2, $^1J_{PC}$ 89 Hz), 27.21 d (C^3, $^1J_{PC}$ 3 Hz), 150.78 d (C^4, $^3J_{PC}$ 15 Hz). ^{31}P NMR spectrum, d, pm: 38.90 s. Found, %: C 60.95; H 8.69. $C_{28}H_{48}NO_4PSi_2$. Calculated, %: C 61.17; H 8.80.

Bis(trimethylsilyl) (3,5-di-*tert*-butyl-4-hydroxyphenyl)methylenebis[2-(pyrid-2-ylethyl)phosphinate] (IIa). Yield 90%, bp 82°C. The first isomer (content 75%): ^1H NMR spectrum, δ, ppm: 3.42 t (C^1H, $^2J_{PH}$ 16 Hz). ^{13}C NMR spectrum, δ, ppm: 49.80 t (C^1, $^1J_{PC}$ 81 Hz), 27.47 d (C^2, $^1J_{PC}$ 97 Hz), 29.18 s (C^3), 160.31 d (C^4, $^3J_{PC}$ 18 Hz). ^{31}P NMR spectrum, δ, ppm: 37.94 s. The second isomer, ^1H NMR spectrum, δ, ppm: 3.38 t (C^1H, $^2J_{PH}$ 18 Hz). ^{13}C NMR spectrum, δ, ppm: 52.34 t (C^1, $^1J_{PC}$ 80 Hz), 29.25 d (C^2, $^1J_{PC}$ 106 Hz), 29.14 s (C^3), 160.35 d (C^4, $^3J_{PC}$ 18 Hz). ^{31}P NMR spectrum, δ, ppm: 39.23 s. Found, %: C 59.74; H 7.96. $C_{35}H_{56}N_2O_5P_2Si_2$. Calculated, %: C 59.80; H 8.03.

Bis(trimethylsilyl) (3,5-di-*tert*-butyl-4-hydroxyphenyl)methylenebis[2-(pyrid-4-ylethyl)phosphinate] (IIb). Yield 88%, bp 102°C. The first isomer content 75%, ^1H NMR spectrum, δ, ppm: 3.41 t (C^1H, $^2J_{PH}$ 17 Hz). ^{13}C NMR spectrum, δ, ppm: 49.82 t (C^1, $^1J_{PC}$ 80 Hz), 28.42 d (C^2, $^1J_{PC}$ 84 Hz), 28.88 s (C^3), 147.00 d (C^4, $^3J_{PC}$ 17 Hz). ^{31}P NMR spectrum, δ, ppm: 36.32 s. The second isomer, ^1H NMR spectrum, δ, ppm: 3.26 t (C^1H, $^2J_{PH}$ 18 Hz). ^{13}C NMR spectrum, δ, ppm: 52.40 t (C^1, $^1J_{PC}$ 78 Hz), 28.91 d (C^2, $^1J_{PC}$ 82 Hz), 28.00 s (C^3), 147.22 d (C^4, $^3J_{PC}$ 16 Hz). ^{31}P NMR spectrum, δ, ppm: 36.56 s. Found, %: C 59.66; H 7.91. $C_{35}H_{56}N_2O_5P_2Si_2$. Calculated, %: C 59.80; H 8.03.

Bis(trimethylsilyl) (3,5-di-*tert*-butyl-4-hydroxyphenyl)trimethylsiloxymethylenebis[2-(pyrid-2-yl)phosphinate] (IIIa). Yield 91%, bp 75°C. The first isomer content 70%. ^{1}H NMR spectrum, δ, ppm: 5.28 br.s (OH). ^{13}C NMR spectrum, δ, ppm: 82.91 t (C^1, $^1J_{PC}$ 98 Hz), 27.30 d (C^2, $^1J_{PC}$ 101 Hz), 28.87 s (C^3), 160.37 d (C^4, $^3J_{PC}$ 16 Hz). ^{31}P NMR spectrum, δ, ppm: 39.46 s. The second isomer, ^{1}H NMR spectrum, δ, ppm: 4.74 br.s (OH). ^{13}C NMR spectrum, δ, ppm: 83.12 t (C^1, $^1J_{PC}$ 96 Hz), 27.39 d (C^2, $^1J_{PC}$ 103 Hz), 29.10 s (C^3), 160.28 d (C^4, $^3J_{PC}$ 18 Hz). ^{31}P NMR spectrum, δ, ppm: 39.17 s. Found, %: C 57.52; H 8.12. $C_{38}H_{64}N_2O_6P_2Si_3$. Calculated, %: C 57.69; H 8.15.

Bis(trimethylsilyl) (3,5-di-*tert*-butyl-4-hydroxyphenyl)trimethylsiloxymethylenebis[2-(pyrid-4-yl)phosphinate] (IIIb). Yield 93%, bp 85°C. The first isomer content 70%. ^{1}H NMR spectrum, δ, ppm: 5.88 br.s (OH). ^{13}C NMR spectrum, δ, ppm: 82.65 t (C^1, $^1J_{PC}$ 96 Hz), 28.08 d (C^2, $^1J_{PC}$ 94 Hz), 29.56 s (C^3), 150.16 d (C^4, $^3J_{PC}$ 16 Hz). ^{31}P NMR spectrum, δ, ppm: 38.14 s. The second isomer, ^{1}H NMR spectrum, δ, ppm: 5.94 br.s (OH). ^{13}C NMR spectrum, δ, ppm: 82.58 t (C^1, $^1J_{PC}$ 96 Hz), 28.21 d (C^2, $^1J_{PC}$ 92 Hz), 29.46 s (C^3), 150.49 d (C^4, $^3J_{PC}$ 18 Hz). ^{31}P NMR spectrum, δ, ppm: 38.38 s. Found, %: C 57.55; H 8.07. $C_{38}H_{64}N_2O_6P_2Si_3$. Calculated, %: C 57.69; H 8.15.

2-(Pyrid-2-yl)ethyl[3,5-di-*tert*-butyl-4-hydroxyphenyl(hydroxy)methyl]phosphinic acid (IVa). To 30 ml of methanol was added 5 g of phosphinate **Ia** at cooling to 10°C while stirring. The mixture was heated to boiling, the solvent was removed, and the residue was kept under a vacuum (1 mm Hg) for 1 h. Yield 3.6 g (98%), bp 139°C. ^{1}H NMR spectrum, δ, ppm: 4.70 d (C^{1}H, $^2J_{PH}$ 8 Hz). ^{13}C NMR spectrum, δ, ppm: 71.86 d (C^1, $^1J_{PC}$ 112 Hz), 24.92 d (C^2, $^1J_{PC}$ 85 Hz), 28.04 s (C^3), 159.27 d (C^4, $^3J_{PC}$ 14 Hz). ^{31}P NMR spectrum, δ, ppm: 42.85 s. Found, %: C 64.97; H 8.02. $C_{22}H_{32}NO_4P$. Calculated, %: C 65.17; H 7.95.

Acids **IVb, V**, and **VI** were prepared similarly.

2-(Pyrid-4-yl)ethyl[3,5-di-*tert*-butyl-4-hydroxyphenyl(hydroxy)methyl]phosphinic acid (IVb). Yield 97%, bp 152°C. ^{1}H NMR spectrum, δ, ppm: 5.50 d (C^{1}H, $^2J_{PH}$ 8 Hz). ^{13}C NMR spectrum, δ, ppm: 72.66 d (C^1, $^1J_{PC}$ 110 Hz), 27.42 d (C^2, $^1J_{PC}$ 78 Hz), 27.76 d (C^3, $^2J_{PC}$ 3 Hz), 149.36 d (C^4, $^3J_{PC}$ 14 Hz). ^{31}P NMR spectrum, δ, ppm: 44.0 s. Found, %: C 64.92; H 7.99. $C_{22}H_{32}NO_4P$. Calculated, %: C 65.17; H 7.95.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)methylenebis[2-(pyrid-2-yl)ethylphosphinic] acid (Va). Yield 96%, bp 105°C. ^{1}H NMR spectrum, δ, ppm: 3.77 t (C^{1}H, $^2J_{PH}$ 19 Hz). ^{13}C NMR spectrum, δ, ppm: 50.99 t (C^1, $^1J_{PC}$ 77 Hz), 29.50 d (C^2, $^1J_{PC}$ 93 Hz), 27.49 s (C^3), 158.62 d (C^4, $^3J_{PC}$ 15 Hz). ^{31}P NMR spectrum, δ, ppm: 37.62 s. Found, %: C 62.12; H 7.26. $C_{29}H_{40}N_2O_5P_2$. Calculated, %: C 62.36; H 7.22.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)methylenebis[2-(pyrid-4-yl)ethylphosphinic] acid (Vb). Yield 97%, bp 110°C. ^{1}H NMR spectrum, δ, ppm: 3.84 t (C^{1}H, $^2J_{PH}$ 18 Hz). ^{13}C NMR spectrum, δ, ppm: 50.03 t (C^1, $^1J_{PC}$ 78 Hz), 28.37 d (C^2, $^1J_{PC}$ 74 Hz), 28.64 s (C^3), 162.68 d (C^4, $^3J_{PC}$ 15 Hz). ^{31}P NMR spectrum, δ, ppm: 39.10 s. Found, %: C 62.23; H 7.28. $C_{29}H_{40}N_2O_5P_2$. Calculated, %: C 62.36; H 7.22.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)hydroxymethylenebis[2-(pyrid-2-yl)ethylphosphinic] acid (VIa). Yield 97%, bp 119°C. ^{1}H NMR spectrum, δ, ppm: 2.1–2.3 m (CH_2P), 3.1–3.3 m (CH_2Py). ^{13}C NMR spectrum, δ, ppm: 78.72 t (C^1, $^1J_{PC}$ 91 Hz), 26.67 d (C^2, $^1J_{PC}$ 96 Hz), 27.19 s (C^3), 158.37 d (C^4, $^3J_{PC}$ 14 Hz). ^{31}P NMR spectrum, δ, ppm: 39.80 s. Found, %: C 60.49; H 7.08. $C_{29}H_{40}N_2O_6P_2$. Calculated, %: C 60.62; H 7.02.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)hydroxymethylenebis[2-(pyrid-4-yl)ethylphosphinic] acid (VIb). Yield 97%, bp 152°C. ^{1}H NMR spectrum, δ, ppm: 2.1–2.2 m (CH_2P), 3.1-3.2 m (CH_2Py). ^{13}C NMR spectrum, δ, ppm: 77.02 t (C^1, $^1J_{PC}$ 102 Hz), 27.40 d (C^2, $^1J_{PC}$ 96 Hz), 28.36 s (C^3), 159.72 d (C^4, $^3J_{PC}$ 17 Hz). ^{31}P NMR spectrum, δ, ppm: 43.13 s. Found, %: C 60.47; H 6.98. $C_{29}H_{40}N_2O_6P_2$. Calculated, %: C 60.62; H 7.02.

The NMR spectra were obtained on a Bruker Avance-400 instrument using $CDCl_3$ (**I–IV**) or $(CD_3)_2SO$ (**V–VII**) as solvents and TMS (^{1}H, ^{13}C) and 85% H_3PO_4 in D_2O solution (^{31}P) as references.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grant No. 08-03-00282).

REFERENCES

1. Kolodyazhnyi, O.I., *Usp. Khim.*, 2006, vol. 75, no. 3, p. 254; Matkovskaya, T.A., Popov, K.I., and Yur'eva, E.A.,

Bisfosfonaty. Svojstva, stroenie i primenenie v meditsine (Biophosphinates: Properties, Structure and Medical Application), Moscow: Khimiya, 2001, p. 224.

2. Ebetino, F.H., *Phosphorus, Sulfur, Silicon, Relat. Elem*., 1999, vols. 144–146, p. 9.
3. Prishchenko, A.A., Livantsov, M.V., Livantsova, L.I., Novikova, O.P., and Grigoryev, E.V., *Zh. Obshch. Khim*., 1996, vol. 66, no. 12, p. 2055.
4. Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., Shpakovskii, D.B., and Milayeva, E.R., *Zh. Obshch. Khim*., 2006, vol. 76, no. 11, p. 1834. Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., Maryashkin, A.V., and Milayeva, E.R., *Zh. Obshch. Khim*., 2007, vol. 77, no. 8, p. 1397.