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LETTERS TO THE EDITOR

Synthesis of Isoprenyl Bis(phosphonates)

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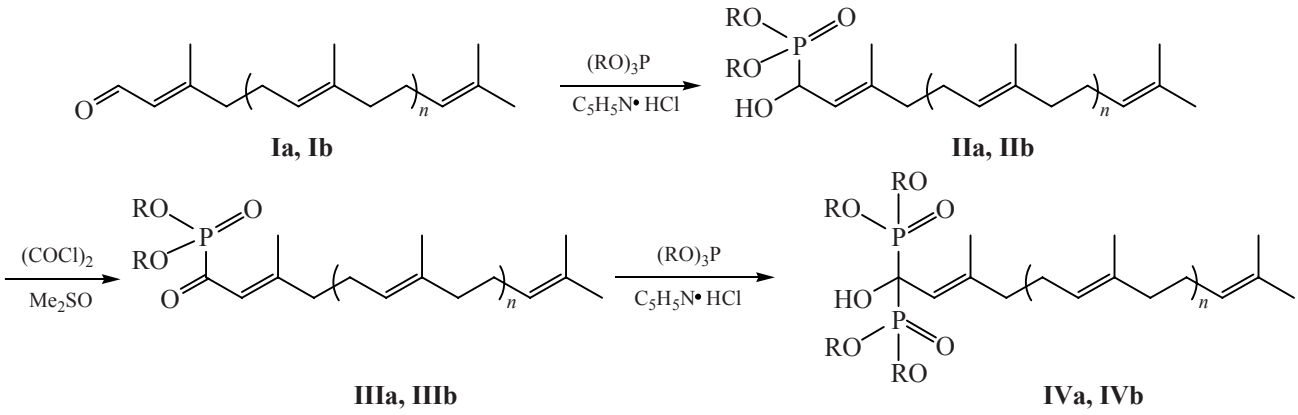
We developed a method of synthesis of isoprenyl bis(phosphonates) that are potential biologically active compounds [1]. The key moment of this method is the use of the trialkylphosphite–pyridine hydrochloride, a highly reactive pair of reagents, in the reaction with carbonyl compounds **I** and **III**, leading to hydroxyphosphonates formation in a high yield. This reagent was not used previously in reactions of this type [2, 3]. We applied the Swern method to the oxidation of the unsaturated hydroxyphosphonates **II**. In this case the method was found to be very convenient, and the reaction proceeded regioselectively only at the OH group not affecing the multiple C=C bonds as it was observed with other oxidants. As a result, ketophosphonates **III** were obtained in a high yield and were transformed further into isoprenyl bis-phosphonates **IV**.



Ia, Ib **IIa, IIb** **IIIa, IIIb** **IVa, IVb**

n = 0, R = Et (**a**); *n* = 1, R = Me (**b**).

Diethyl (2*E*)-1-hydroxy-3,7-dimethyl-2,6-octadienylphosphonate (IIa). To a solution of 3 mmol of trimethylphosphite and 2.5 mmol of geranial **Ia** in 3 ml of methylene chloride was added 3 mmol of pyridine hydrochloride at 0°C, and this mixture was kept for 2 h at room temperature. Then the undissolved precipitate was filtered off, the solvent was removed, and the residue was distilled in a vacuum. Yield 80%, bp 135°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 t (CH_3, J_{HH} 7 Hz), 1.29 t (CH_3, J_{HH} 7 Hz), 1.61 s (3H, CH_3), 1.69 s (3H, CH_3), 2.1 (4H, CH_2), 4.12 m (4H, OCH_2), 4.52 d. d (1H, J_{HH} 9 Hz, J_{HP} 9 Hz), 5.12 br. (1H, CH=C), 5.36 br. (1H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 24.19. Found, %: P 10.69. $C_{14}H_{27}O_4P$. Calculated, %: P 10.67.

Dimethyl [(2*E*,6*E*)-1-hydroxy-3,7,11-trimethyl-2,6,10-dodecatrienylphosphonate (IIb). Yield 90%, oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.59 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.69 d (3H, CH_3CH, J_{HH} 1.5 Hz), 1.71 (3H, CH_3CH, J_{HH} 1.5 Hz), 2.09 m (6H, CH_2), 2.25 m (2H, CH_2), 3.78 d (3H, CH_3O, J_{HP}

10 Hz), 3.8 d (3H, CH_3O, J_{HP} 10 Hz), 4.5 br. (1H, OH), 4.7 t (1H, PCH, J_{HP} 10 Hz), 5.09 br. (1H, CH=C), 5.35 br. (2H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 26.05. Found, %: P 9.39. $C_{17}H_{31}O_4P$. Calculated, %: P 9.37.

Diethyl (2*E*)-3,7-dimethyl-1-oxo-2,6-octadienylphosphonate (IIIa). To a solution of 0.5 ml of oxalyl chloride in 10 ml of anhydrous methylene chloride were added 0.9 ml of dimethyl sulfoxide in 2 ml of methylene chloride and a solution of 1.4 g of hydroxyphosphonate **IIa** in 4 ml of methylene chloride at –60ºC. After 15 min to the reaction mixture was added 3.5 ml of triethylamine at –50°C. The mixture was stirred for 5 min and heated to room temperature. Then 35 ml of ice water was added. The water layer was separated and extracted with 2×10 ml of methylene chloride. Organic layers were dried with magnesium sulfate. Then the solvent was removed and the residue was distilled in a vacuum. Yield 70%, bp 115°C (0.08 mm Hg). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 m (3H, CH_3), 1.24 s (3H, CH_3C=), 1.29 s (3H, CH_3C=), 1.31 t (6H, CH_3CH_2O, J_{HH} 7 Hz), 1.6 m (2H, CH_2), 2.0 m (2H, CH_2), 2.29 m (2H, CH_2), 4.1 m (4H, CH_2O), 5.33 m (=CH–C=O). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 1.2. Found, %: P 10.76. $C_{14}H_{25}O_4P$. Calculated, %: P 10.74.

Dimethyl (2*E*,6*E*)-3,7,11-trimethyl-1-oxo-2,6,10-dodecatrienylphosphonate (IIIb). Yield 60%, bp 145°C (0.1 mm Hg). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.6 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.69 d (3H, CH_3C=, *J* 1.5 Hz), 1.71 (3H, CH_3C=, *J* 1.5 Hz), 2.1 m (6H, CH_2), 2.25 m (2H, CH_2), 3.75 d (3H, CH_3O, J_{HP} 10 Hz), 3.8 d (3H, CH_3O, J_{HP} 10 Hz), 5.1 br. (1H, CH=C), 5.5 br. (2H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 0.98. Found, %: C 62.38; H 8.89; P 9.45. $C_{17}H_{29}O_4P$. Calculated, %: C 62.18; H 8.90; P 9.43.

1,1-Bis(diethylphosphono)(2*E*)1-hydroxy-3,7-dimethyl-2,6-octadiene (IVa). To a solution of 3 mmol of triethylphosphite and 2.5 mmol of oxophosphonate **IIIa** in 3 ml of methylene chloride was added 3 mmol of pyridine hydrochloride at 0°C, and the mixture was kept for 24 h at room temperature. Then the precipitate was filtered off and the solvent was removed. The residue was purified by column chromatography. Yield 65%, oil. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 t (6H, *J* 7 Hz), 1.28 t (6H, *J* 7 Hz), 1.63 s (3H), 1.8 d (3H), 2.0 m (4H, CH_2), 4.21 m (8H, OCH_2), 4.8 m (1H, CH=), 5.1 t (1H, CH=, J_{HH} 7 Hz). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 23.3. Found, %: C 50.45; H 8.41; P 14.50. $C_{18}H_{36}O_7P_2$. Calculated, %: C 50.70; H 8.51; P 14.53.

1,1-Bis(diethylphosphono)-1-hydroxy-(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatriene (IVb). Yield 60% (eluent hexane–ethyl acetate 3:1). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.6 s (3H, CH_3), 1.69 s (3H, CH_3), 1.8 d. d (3H, J_{HP} 8 Hz, J_{HH} 7 Hz), 2.0 m (4H, CH_2), 3.75 d (3H, CH_3O, J_{HP} 10 Hz), 3.8 d (3H, CH_3O, J_{HP} 10 Hz), 4.8 m (2H, CH=), 5.1 m (1H, CH=). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 23. Found, %: P 14.60. $C_{18}H_{34}O_7P_2$. Calculated, %: P 14.60.

The NMR spectra were registered on a Varian-300 instrument relative to internal TMS (^1H and ^{13}C) and to external 85% H_3PO_4 in D_2O (^{31}P).

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