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LETTERS
TO THE EDITOR

Synthesis and Some Properties of Dialkyl 1-Hydroxy-3-(alkylamino)-2,2-dimethylpropylphosphonates

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It is known that dialkyl hydrogen phosphites **I** react with aldehydes in the presence of basic catalysts [1]. With trialkylamines as catalysts the process is carried out at prolonged heating of reaction mixture at 80°C.

We found for the first time that in 3-(alkylamino)-substituted aldehydes **II** the secondary amino group exhibits catalytic properties and the reaction between the compounds **I** and **II** proceeds under mild conditions without an additional catalyst. Thus, dropwise addition of the aldehyde **II** to dialkyl hydrogen phosphite **I** causes increase in temperature to 40–50°C. For the completion of the process the reaction mixture was stirred at 25°C for 24 h. After removing of volatile compounds in a high vacuum the dialkyl [1-hydroxy-3-(alkylamino)-2,2-dimethylpropyl]phosphonates **III** were identified as the crude products because they decompose at an attempt of distillation.

$$\underset{\mathbf{I}}{(R^1O)_2PHO} + \underset{\mathbf{II}}{R^2NHCH_2CMe_2CHO}$$

$$\longrightarrow \underset{\mathbf{III}}{(R^1O)_2P(O)CH(OH)CMe_2CH_2CHR^2},$$

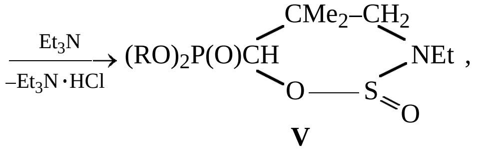
I, R^1 = Me (**a**), Et (**b**). **II**, R^2 = Me (**a**), Et (**b**). **III**, R^1 = R^2 = Me (**a**), Et (**c**); R^1 = Me, R^2 = Et (**b**).

The structure of the products **III** besides the elemental analysis and ^1H and ^{31}P NMR spectra was confirmed by their acylation with acetyl chloride and thionyl chloride. At 1:1 reagent ratio *N*-acetylation of phosphonate **III** took place. It was confirmed by the location of the proton signal of CH-fragment in ^1H NMR spectrum at δ 3.96 ppm while in acetoxy derivatives at δ 5.21–5.40 ppm. In the case of thionyl chloride *O,N*-acetylation takes place with the formation of a new heterocyclic compound with the exophosphoryl group, 6-(dimethoxyphosphoryl)-5,5-dimethyl-2-oxo-3-ethylperhydro-1,2,3-oxathiazine **IV**.

$$\mathbf{IIIb} + AcCl$$

$$\xrightarrow[-Et_3N\cdot HCl]{Et_3N} \underset{\mathbf{IV}}{(MeO)_2P(O)CH(OH)CMe_2CH_2N(Ac)Et},$$

IIIb, IIIc + $SOCl_2$



V

V, R = Me (**a**), Et (**b**).

Reaction of dimethyl hydrogen phosphite (Ia) with 3-(methylamino)-2,2-dimethylpropanal (IIa). Compound **Ia**, 1.95 g was added dropwise with stirring under the dry nitrogen flow to 2.04 g of aldehyde **IIa**. The temperature of reaction mixture rose to 44°C. After stirring for a day at room temperature and removing volatile products off in a high vacuum 3.6 g (88%) of crude dimethyl 1-hydroxy-3-(methylamino)-2,2-dimethylpropylphosphonate **IIIa** was obtained, n_D^{20} 1.4558. ^1H NMR spectrum (acetone-d_6), δ, ppm: 0.93 s (6H, CMe_2); 2.35 s (3H, NMe_2); 2.45 d, 2.95 d (2H, CH_2N, $^2J_{HH}$ 13 Hz); 3.56 d, 3.65 d (6H, 2POMe,

$^3J_{PH}$ 10 Hz); 3.75 d (1H, PCH, $^3J_{PH}$ 13 Hz); 5.63 (broad) (2H, OH, NH). ^{31}P NMR spectrum, δ_P, ppm: 27.2. Found, %: N 6.31; P 13.83. $C_8H_{20}NO_4P$. Calculated, %: N 6.22;P 13.78.

Dimethyl 1-hydroxy-3-(ethylamino)-2,2-dimethylpropylphosphonate (IIIb). Crude compound **IIIb**, 15.52 g (89%) was prepared from 17.3 g of dimethyl hydrogen phosphite and 8.5 g of 3-(ethylamino)-2,2-dimethylpropanal **IIb**, n_D^{20} 1.4532. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.83 s, 1.00s (6H, CMe_2); 0.99 t (3H, NCH_2Me, $^3J_{HH}$ 7.5 Hz); 2.38 d, 3.05 d (2H, NCH_2, $^2J_{HH}$ 13 Hz); 3.58 d, 3.70 d (6H, 2POMe, $^3J_{PH}$ 10 Hz); 2.57 q (2H, NC*H*$_2$Me, $^3J_{HH}$ 7.5 Hz); 3.75 d (1H, PCH_2, $^2J_{PH}$ 13 Hz); 4.80 (broadened) (2H, OH, NH). Found, %: N 5.89; P 13.00. $C_9H_{22}NO_4P$. Calculated, %: N 5.86; P 12.98.

Diethyl 1-hydroxy-3-(ethylamino)-2,2-dimethylpropylphosphonate (IIIc). Crude compound **IIIc**, 11.91 g (89.5%), n_D^{20} 1.4570, was prepared from 6.9 g of diethyl hydrogen phosphite and 6.4 g of the aldehyde **IIb**. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.86 s, 0.99 s (6H, CMe_2); 1.00 t (3H, NCH$_2$*Me*, $^3J_{HH}$ 7.5 Hz); 1.18 t (6H, 2OCH$_2$*Me*, $^3J_{HH}$ 7.5 Hz); 2.56 q (2H, NC*H*$_2$Me, $^3J_{HH}$ 7.5 Hz); 2.37 d and 3.07 d (2H, NCH_2, $^2J_{HH}$ 13 Hz); 3.5 d (1H, PCH, $^2J_{PH}$ 9 Hz); 4.00 d.q (4H, $2OCH_2$, $^3J_{HH}$ 7.5 Hz, $^3J_{PH}$ 15 Hz); 4.77 br.s (2H, OH, NH). Found, %: N 5.25; P 11.66. $C_{11}H_{26}NO_4P$. Calculated, %: N 5.24; P 11.61.

Reaction of compound IIIb with acetyl chloride. To a mixture of 10 g of phosphonate **IIIb**, 4.24 g of triethylamine and 60 ml of dry benzene a solution of 3.30 g of acetyl chloride in 20 ml of benzene was added dropwise with stirring and cooling to –10°C under dry argon. After the addition was complete reaction mixture was allowed to reach room temperature and stirred for 12 h. The crystals obtained were filtered off, washed with CCl_2 and dried. The yield of dimethyl 3-(acetylethylamino)-1-hydroxy-2,2-dimethylpropylphosphonate **IV** 15.9 g (38%), mp 90°C (from CCl_4). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.00 s, 1.03 s (6H, CNe_2); 1.07 t (3H, NCH$_2$*Me*, $^3J_{HH}$ 7.5 Hz); 2.06 s (3H, MeCO); 2.30 d.d (1H, C*H*^{1}CH^2, $^2J_{HH}$ 15 Hz, $^4J_{PH}$ 6 Hz); 3.65 d (1H, CH^{1}C*H*^{2}, $^2J_{HH}$ 15 Hz); 3.0–3.6 m (2H, NC*H*$_2$Me); 3.73 d and 3.81 d (6H, 2POMe, $^3J_{HH}$ 10 Hz); 3.96 d (1H, PCH, $^2J_{PH}$ 15 Hz); 5.88 br.s (1H, OH). Found, %: N 4.90; P 11.15. $C_{11}H_{24}NO_5P$. Calculated, %: N 4.98; P 11.03.

Reaction of compound (IIIb) with thionyl chloride. To a mixture of 18.86 g of phosphonate **IIIb**, 15.96 g of triethylamine, and 150 ml of dry benzene a solution of 9.4 g of thionyl chloride in 30 ml of benzene was added dropwise under dry argon with strirring and cooling to –5°C. After the addition was complete the reaction mixture was allowed to reach room temperature and stirred for 12 h. Obtained crystals were filtered off, the volatile compoments were removed, and the residue was distilled in a vacuum to give 10 g (45%) of 6-(dimethoxyphosphoryl)-5,5-dimethyl-2-oxo-3-ethylperhydro-1,2,3-oxathiazine, bp 122°C (0.03 mm Hg), n_D^{20} 1.4800. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.87 s, 1.08 s (6H, CMe_2); 0.90 t (3H, NCH$_2$*Me*, $^3J_{HH}$ 7 Hz); 2.01 d.d (1H, C*H*^{1}CH^2, $^2J_{HH}$ 13 Hz, $^4J_{PH}$ 7.5 Hz); 3.04 d (1H, CH^{1}C*H*^{2}, $^2J_{HH}$ 13 Hz); 2.45 d.q and 2.79 d.q (2H, NH^{1}H^{2}Me, $^2J_{H^1H^2}$ 14 Hz, $^3J_{H^1H}$ = $^3J_{H^2H}$ 7 Hz); 3.54 d and 3.59 d (6H, 2POMe, $^3J_{HH}$ 11 Hz); 4.60 d (1H, PCH, $^2J_{PH}$ 14 Hz). ^{31}P NMR spectrum, δ_P, ppm: 19.11. Found, %: N 4.90; P 10.90. $C_9H_{20}NO_6PS$. Calculated, %: N 4.91; P 10.88.

6-(Diethoxyphosphoryl)-5,5-dimethyl-2-oxo-3-ethylperhydro-1,2,3-oxathiazine (Vb). Reaction of 18.87 g of compound **IIIc** with 9.6 g of thionyl chloride gave 12.13 g of thiazine **Vb**, bp 130°C (0.03 mm Hg), n_D^{20} 1.4810. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.99 s, 1.15 s (6H, CMe_2); 1.05 t (3H, NCH$_2$*Me*, $^3J_{HH}$ 7 Hz); 1.22 t (6H, OCH$_2$*Me*, $^3J_{HH}$ 7.5 Hz); 2.15 d.d (1H, C*H*^{1}H^2, $^2J_{HH}$ 14 Hz, $^4J_{PH}$ 7.0 Hz); 3.10 d (1H, CH^1*H*^{2}, $^2J_{HH}$ 14 Hz); 2.60 d.q and 2.88 d.q (2H, NH^{1}H^{2}Me, $^2J_{H^1H^2}$ 14 Hz, $^3J_{H^1H}$ = $^3J_{H^2H}$ 7 Hz), 3.0 d.t and 3.05 d.t (4H, POC*H*$_2$Me, $^3J_{HH}$ = $^3J_{PH}$ 7.5 Hz); 4.62 d (1H, PCH, $^2J_{PH}$ 13 Hz); 4.01 m (4H, $POCH_2$). ^{31}P NMR spectrum, δ_P, ppm: 19.15. Found, %: N 4.50; P 9.92. $C_{10}H_{22}NO_6PS$. Calculated, %: N 4.44; P 9.84.

^{1}H NMR spectra were taken on a Tesla BS-567A spectrometer (100 MHz). ^{31}P NMR spectra were measured on a RYa-2303 spectrometer (21 MHz) against external 85% phosphoric acid.

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