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Synthesis and Properties of *O,O*-Dialkyl [1-Hydroxy-3-(dialkylamino)-2,2-dimethylpropyl]phosphonates

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Abstract—*O,O*-Dialkyl [1-hydroxy-3-(dialkylamino)-2,2-dimethylpropyl]phosphonates were prepared for the first time. By means of NMR ^{1}H, IR spectroscopy and quantum-chemical calculations the presence in them of various H-bonds was established. In the crystalline state P=O···HO intermolecular hydrogen bonds favor the formation of cyclic dimer associates $D_{P=O}$. In the liquid state and concentrated solutions P=O···HO and N···HO intermolecular hydrogen bonds cause the formation of cyclic dimer associates $D_{P=O}$ and D_N, and intramolecular hydrogen bonds provide the existence of different conformations of the monomer form MN, the most stable among them with the non-strained six-membered ···NCCCOH··· ring.

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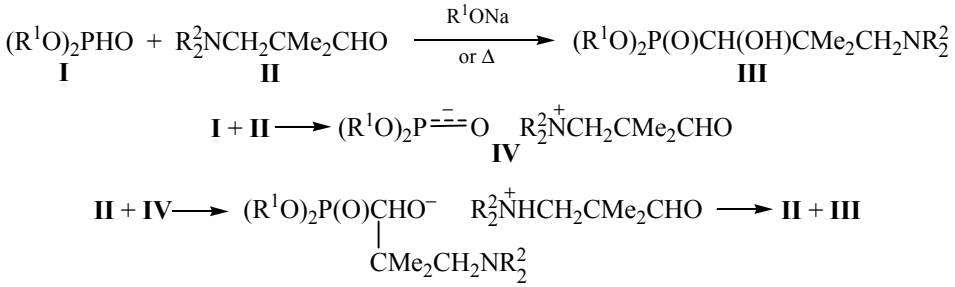
Organic derivatives of P(IV) phosphorus acids functionalized in various positions occupy an important place in organic chemistry. Among them aminoalkylphosphoryl compounds are distinguished by structural variety, availability, and broad spectrum of useful applied properties [1–2]. Their structural variety is determined by broad possibility of variation of the nature of substituents at P(IV) and N(III), different mutual location of the phosphoryl and amino groups, and the location of the additional characteristic group, for example, of the hydroxy group with respect to both the phosphoryl and the amino groups. Though the first representatives of hydroxyl-substituted aminoalkylphosphonates were prepared more than 40 years ago [3], they were insufficiently studied. Moreover, some types of them, for example, 1-hydroxy-3-(dialkylamino)-alkylphosphonates, compounds with competing functional groups, were not yet described, though their positional analogs, 3-hydroxy-1-aminoalkylphosphonates, were already prepared [4].

The aim of this work was the synthesis and NMR, IR, and quantum-chemical studies of the structure of *O,O*-dialkyl [1-hydroxy-2,3-dimethyl-3-(dialkylamino) propyl]phosphonates **III**.

Compounds **III** were synthesized by the reaction of dialkyl hydrogen phosphites **I** with 3-(dialkylamino)-substituted aldehydes **II**. At the addition of ethanol solution of sodium alcoholate or the insignificant amount of sodium to the mixture of compounds **I** and



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

II the exothermic reaction takes place. After neutralization the reaction mixture with the acetic acid compounds **III** were isolated pure by vacuum distillation. The synthesis of compounds **III** may be also carried out by heating the mixture of compounds **I** and **II** at 80°C. Due to the presence of tertiary amino group in starting aldehydes the nucleophilic catalysis takes place.

In the course of solving structural problems phosphonates **V** containing amino group in the position 2 with respect to the phosphoryl group, compounds **VI** con-taining amino group in the aromatic ring, and also thiophosphonate **VII** were synthesized for comparison. Two analogs of compound **VI** were prepared before [5–6].

$$(MeO)_2PHO + Et_2NCMe_2CHO \longrightarrow (MeO)_2P(O)CH(OH)CMe_2NEt_2$$
V

$$(MeO)_2PHO + 4\text{-}Me_2NC_6H_4CHO \longrightarrow (MeO)_2P(O)CH(OH)C_6H_4NMe_2\text{-}4$$
VI

$$(PrO)_2P(S)H + Me_2NCH_2CMe_2CHO \longrightarrow (PrO)_2P(S)CH(OH)CMe_2CH_2NMe_2$$
VII

The composition of the products **III-VII** was confirmed by elemental analysis, and their structure, by the ^1H, ^{13}C, and ^{31}P NMR spectra. ^1H and ^{13}C NMR spectral characteristics of these substances are compiled in Table 1.

^{31}P NMR spectra of compounds **V–VI** contain a singlet at δ_P 27–28 ppm, and for compounds **VII** a singlet at δ_P 92 ppm was observed. It confirms that the nearest surrounding of phosphorus atoms is $O_2P(O)C$ and $O_2P(S)C$ respectively. Note the form and location of the signal of the hydroxy proton in compounds **III**. It is strongly broadened and shifted downfield to δ 7.10–8.52 ppm. In functionalized 1-hydroxyalkyl-phosphonates lacking an amino group this signal is narrow, and its chemical shift is located in the range 4.8–5.5 ppm [7, 8]. In 2-amino-1-hydroxyalkyl-phosphonate **V** and in compounds **VI** containing the amino group in the rigid aromatic fragment it is also located upfield at δ 4.13 and 4.35 ppm respectively. Besides, methyl and methylene group protons and carbon atoms of methyl groups in CMe_2CH_2N fragment are magnetically nonequivalent and have different $^4J_{HH}$, $^3J_{PH}$, and $^3J_{PC}$ values (Table 1) indicatibg their definite orientation with respect to the phosphorus atom and the CH proton. Starting from these data it was possible to suggest the formation of cyclic structure with a strong hydrogen bond between the hydroxy and the dialkylamino groups in compounds **III**.

Indirect chemical confirmation of this suggestion is the upfield shift of the hydroxy proton at the conversion of compounds **III** to quaternary ammonium salts **VIII**.

$$\mathbf{III} + R^3Hlg \longrightarrow (R^1O)_2P(O)CH(OH)CMe_2CH_2\overset{+}{N}R^2_2R^3\ \ Hlg^-$$
VIII

VIII, $R^1 = R^2 = Me$, $R^3 = Bn$, Hlg = Br (**a**); $R^1 = R^2 = R^3 = Me$, Hlg = I (**b**); $R^1 = Et$, $R^2 = R^3 = Me$, Hlg = I (**c**).

It follows from the comparison of ^1H and ^{13}C NMR spectra of starting amine **IIIc** and its salt **VIIIc** that the main changes in the ^1H NMR spectra occur in the location of the hydroxy protons and in the signals of hydrogen atoms at the carbon atoms directly bound with the quaternary nitrogen. In the ^{13}C NMR spectra changes are observed in the range characteristic of the signals of the above-mentioned carbon atoms. For example, the hydroxy proton singlet is shifted upfield from δ 7.5 ppm to δ 5.05 ppm, namely, to the range where it is observed in the case of 1-hydroxyalkyl-phosphonates having no amino group, in 2-amino-1-hydroxyalkylphosphonate **V**, and in compound **VI** containing amino group in the aromatic fragment. The quaternization of N(III) is proved by the downfield shift of signals of protons of the methylene and methyl groups directly bound to the nitrogen (δ, ppm): 2.15 d → 3.15 d, 3.15 d → 3.84 m, and 2.25 s → 3.59 s. Signals of carbon atoms in these groups are also shifted downfield (δ_C, ppm): 68.68 d → 74.10 d (CH_2N^+), 46.87 s → 56.5 s (NMe_3).

Proton-acceptor ability of thionophosphoryl group is significantly lower as compared to the phosphoryl

Table 1. Characteristics of ^{1}H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) of $(R^{1}{}^{9}CH_2{}^{8}O)_2P(X)CH(OH)YN(CH_2{}^{6}R^{7})_2$

R^1	R^2	X	Y	NMR ^nE	Solvent	C^1 $^2J_{PH}$ $^4J_{HH}$ $^1J_{PC}$	C^2 $^2J_{PC}$	C^3 $^4J_{PH}$ $^2J_{HH}$ $^3J_{PC}$	$C^{4,5}$ $^4J_{HH}$ $^3J_{PC}$	C^6 $^3J_{HH}$	C^7 $^3J_{HH}$	C^8 $^3J_{PH}$ $^3J_{HH}$ $^2J_{PC}$	$C^{9,10}$ $^3J_{HH}$ $^3J_{PC}$	OH
H	H	O	$^{4,5}CMe_2{}^{3}CH_2$	^{1}H	Acetone-d_6	3.79 12.5 2.0	–	2.15, 3.23 – 14.0	0.95, 1.20 2.0	2.40	–	3.74, 3.82 14.2 –	–	7.25
					$CDCl_3$	3.95 12.7 2.0	–	2.15, 3.23 3.0 12.7	1.00, 1.20 2.0	2.38	–	3.81, 3.90 12.9 –	–	7.56
H	Me	O	$^{2}{}^{4,5}CMe_2{}^{3}CH_2$	^{1}H	$CDCl_3$	3.79 7.8 0.6	–	2.32, 2.81 5.4 13.75	0.99, 1.03 0.6	2.57 7.2	0.90 7.2	3.62, 3.73 10.2 –	–	8.56
					CCl_4	3.32 16.5 0.9	–	1.96, 2.85 0.9 13.8	0.64, 0.85 0.9	2.42 7.5	0.75 7.5	3.50, 3.35 9.9 –	–	7.40
				^{13}C	$CDCl_3$	78.2 – 161.1	36.54 8.66	66.57 – 10.35	23.40, 26.50 0.6, 19.1	47.61	10.98	54.20, 54.04 7.13	–	–
Me	H	O	$^{4,5}CMe_2{}^{3}CH_2$	^{1}H	Acetone-d_6	3.45 8.75 1.5	–	1.99, 3.09 – 13.75	0.83, 1.08 1.5	2.25	–	3.92, 4.04 7.5 7.5	1.19 7.5	7.10
				^{13}C	$CDCl_3$	76.70 – 158.7	36.11 3.98	68.68 – 6.0	23.04, 25.53 11.5	46.87	–	59.97, 62.12 – 6.6, 7.5	15.7, 15.8 13.5	–
Me	Me	O	$^{4,5}CMe_2{}^{3}CH_2$	^{1}H	Acetone-d_6	3.55 8.75 0.6	–	2.18, 2.98 2.3 13.75	0.75, 1.00 0.6	2.60 6.5	0.8 6.5	4.00, 4.08 7.5 7.5	1.2 7.5	7.18
H	Me	O	$^{4,5}CMe_2$	^{1}H	Acetone-d_6	3.80 7.8 –	–	–	1.05, 1.15 –	2.5 7.0	0.95 7.0	3.60, 3.68 10.0 –	–	4.13
$^{10}{}^{9}CH_3CH_2$	H	S	$^{4,5}CMe_2{}^{3}CH_2$	^{1}H	Acetone-d_6	3.82 7.8 –		2.13, 2.22 – 13.75	1.0, 1.3 –	2.5 –	–	4.0–4.5 m	1.78 m; 1.05, 1.37, 7.0	7.48
H	H	O	$^{3}C_6H_4$	^{1}H	Acetone-d_6	4.95 9.5 –	–	7.5–6.6 m	–	2.5	–	3.79, 3.75 10.0 –	–	4.35

one. Therefore we expected that formation of N···OH hydrogen bond will take place instead of P=S···HO bond. Actually, the signal of the hydroxy group hydrogen in thionophosphonate **IV** has downfield location (δ 7.48 ppm) similarly to compound **III**.

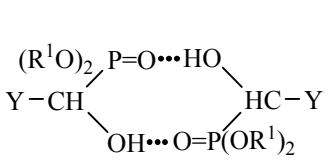
Note also that compounds **III-VI** under study contain the competing proton-acceptor groups (R_2N > P=O > P–) demonstrating different trend to the formation of various intermolecular and intramolecular hydrogen bonds, particularly to the formation of the

non-strained six-membered ···NCCCOH··· and the strained five-membered ···O=PCOH··· and ···O–COH··· cycles. That is why we have carried out investigation of hydrogen bonds in compounds **III** by means of the IR spectroscopy and quantum-chemical methods.

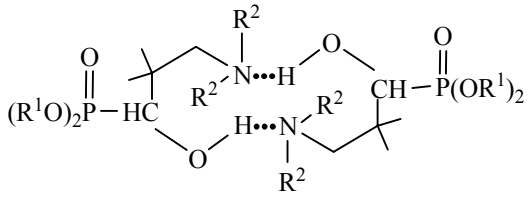
IR spectra of compound **IIIa** agree with the assumed structural formula. They contain a broad strong absorption band at 3000–3500 cm^{-1} [ν(OH)], a series of peaks at ~2700–3100 cm^{-1}, ~1300–1500 cm^{-1} [δ(CH_3), CH_2, CH, ω, τ(CH_2)], comparatively high absorption maximum at ~1245 cm^{-1} [ν(PO)]; a very intense doublet at 1070–1045 cm^{-1} [ν(C–OH), ν(PO–C)], the bands of middle intensity at 835, 766 cm^{-1} [ν(P–O), ν(P–C)], and a series of comparatively weak bands in the range 400–700 cm^{-1} (deformational vibrations of molecular skeleton) [9, 10].

Experiments with phase variation, heating and cooling (+75 to –160°C) of the liquid film and solutions ($c = 2\times10^{-3}$ M, t = +50 to –15°C), using differential spectroscopy and expansion methods showed that the molecules of compound **IIIa** are conformationally non-uniform and form different types of hydrogen bonds. It is confirmed by the variation of the intensities in the series of doublets (2828/2815, 2881/2763 etc.), simplifying the spectral picture in crystal and the diluted solutions, and variability of the observed ν(OH).

Experiments with the variation of medium, phase, and temperature showed a clear ν(OH) peak at ~3300 cm^{-1}, broad bands at ~3150 cm^{-1}, and flattened diffuse absorption, a wing, at ~2730 cm^{-1}. Differential spectrograms showed that the band at ~3150 cm^{-1} is two-component [ν(OH) 3200 cm^{-1} and ν(OH) 3100 cm^{-1}]. The band at 3300 cm^{-1} is dominant in liquid phase, and its intensity increases during the cooling of condensed phase and the increase in concentration of solutions. It becomes a single one in the crystalline state. The absorption band at ~2780 cm^{-1} clearly seen in the differential spectra is revealed as a long-wave slope of the ν(CH) absorption in the concentrated solutions and accompanies the growth in intensity of the band at 3300 cm^{-1} on cooling. Absorption bands with maxima at ~3300 and ~2730 cm^{-1} disappear in diluted solutions. At the same time absorption bands of free hydroxy groups are not observed either in liquids or in concentrated or diluted solutions. From the above-mentioned and the reported data [10–13] it follows that they must be attributed to the dimeric associates OH···O=P ($D_{P=O}$) and OH···NR^2_2 (D_N) with intermolecular hydrogen bonds.



$D_{P=O}$ (Y = $CMe_2CH_2NR^2_2$)



D_N

Free hydroxy group in 1-hydroxyalkylphosphoryl compounds as well as the phenol one absorbs at ~3610 cm^{-1} [9, 10]. Shifts Δν(OH) in CCl_4 for the OH···O=P and OH···N hydrogen bonds in the PhOH···O=P and PhOH···NEt_3 dimers are ~300 and 800 cm^{-1} respectively resulting in the bands shifts to ~3300 and 2730 cm^{-1} [9]. Hence, absorption band at ~3300 cm^{-1} must be attributed to the OH···O=P hydrogen bridge, and the band at ~2730 cm^{-1}, to the OH···N one.

Absorption band ν(OH) at ~3100 cm^{-1} decreases while cooling of liquid phase and becomes the only one in the diluted solution (c < 0.1 M). Absorption band at ~3200 cm^{-1} is observed in differential spectra (c = 2 M) on heating. These data permit to attribute the bands at ~3100 and 3200 cm^{-1} to intramolecular hydrogen bonds. Though both the amine N(III) and phosphoryl oxygen possess expressed proton-acceptor properties [10–13], the first fragment is the stronger electron-donor group than the second one (I_1 ~8 eV [14] and 10.5 eV [10] in tertiary amines and alkyl phosphonates respectively).

Formation of non-strained six-membered ring stabilizes the intramolecular hydrogen bond, and the formaition of the strained five-membered one destabilizes it [10]. According to these two factors the interaction with N(III) in compound **IIIa** proves to be more effective than the interaction with P=O and P–O in the competition for the formation of intramolecular hydrogen bond. Therefore this bond is formed by means of the OH···NR_2 bridge. At the same time note

that the conditions of interaction of the lone electron pair of nitrogen with the hydroxy group proton are less favorable here than at the formation of linear intermolecular hydrogen bonds.

This fact explains the smaller shift of the absorption band of intramolecular hydrogen bonds (3600 – 3100 = 500 cm^{-1}) as compared to intermolecular ones (3600 – 2730 = 870 cm^{-1}). The appearance of two bands (~3200 and ~3100 cm^{-1}) attributed above to the OH···N intramolecular hydrogen bond must be connected with the conformational nonuniformity of intramolecular hydrogen bonds of the ring.

It is confirmed also by the doublet of characteristic peaks of the NMe_2 group: 2828/2815 and 2871/2763 cm^{-1}.

IR spectra of some other representatives of the group of compounds **III** under discussion were also studied. For example, compounds **IIIb** and **IIIc** differ from compound **IIIa** only in the nature of substituents. Compound **IIIc** contains EtO group at the P(IV) atom instead of MeO groups, and in compound **IIIb** NEt_2 group is present instead of NMe_2 one. It could be expected that these differences can hardly bring significant variations in the properties of molecules under discussion. Really, spectrograms of liquid samples and the solution of compound **IIIb** in CCl_4 repeat all the characteristic specific features of compound **IIIa**.

In all the wavelength range 400–4000 cm^{-1} the spectrograms are much alike. The spectrum of compound **IIIc** differs from the spectrum of substance **IIIa** mainly by the appearance of a strong band at 980 cm^{-1} characteristic of EtOP(O) fragment. In the case of compound **IIIb** main difference is observed in the range of ν(CH) and δ(CH) absorption according to the difference in the alkyl substituents at nitrogen. In the spectra of diluted solutions of compounds **IIIb, IIIc** absorption band at 3320 cm^{-1} disappears as well as in the spectra of compound **IIIa**. Only the bands forming the base in the spectrum of condensed phase remains. Short-wave part of the absorption band with the maximum at ~3100 cm^{-1} is the same as in the spectrum of phosphonate **IIIa**. Hence, the main conclusions concerning the structure and hydrogen bonds of molecule in the case of compound **IIIa** correspond also to substances **IIIb, IIIc**.

On the basis of the IR studies of compound **IIIa** a conclusion about its conformational non-uniformity was made above. This fact was confirmed by quantum-chemical calculations using the density functional method on the DFT/PBE/TZ2P [15,16] and B3LYP/6-31G** [15] levels.

According to the calculated data molecules of the compound **IIIa** have significant number of stable conformations (we have localized 18) resulting from the rotational isomerism of methoxy groups and the internal rotation about C–P, C–O, C–C, and C–N groups. In Tables 2 and 3 the results of calculation of four stable conformers **IIIaa, IIIac, IIIad** are listed. Spatial arrangement of these substances is presented in Fig. 1.

PBE/TZ2P and B3LYP/6-31G** calculations gave close values of free energies and the geometrical parameters of conformers (Table 2). Relative values of total and free energies of three conformers **IIIaa**, **IIIac**, and **IIIad** with the intramolecular hydrogen bonds via the N, O=P, and O-P fragments calculated by means of B3LYP/6-31G** method are 0.00, 6.23, 6.77 and 0.00, 3.88, and 4.62 kcal mol^{-1} respectively. Thus they are close to the values obtained by the PBE/TZ2P method (Table 2). ν(OH) Frequencies of compound **IIIa** calculated by means of B3LYP/6-31G** method exceed the values [for conformers **IIIaa, IIIac**, **IIIad** ν(OH) are equal to 3284, 3756, and 3794 cm^{-1}, their intensities being 706, 35, and 64] obtained by means of the PBE/TZ2P method (Table 2), but both methods in the same manner indicate the spectral difference of the obtained conformers.

In the Table 2 the differences in total and free energies (ΔE, ΔG) of conformers calculated by means of PBE/TZ2P method are listed. They include the difference in conformational energies proper, and the difference in the H-bonding energy. Hence, the correlation is absent between ΔE values and the parameters characterizing H-coordination, among them the frequencies of the OH-vibrations. At the same time such parameters of intramolecular hydrogen bond as the frequency and the intensity of ν(OH) bond vibrations, interatomic distance I_{OH}, and the charges on oxygen and hydrogen atoms of the OH group vary proportionally decreasing in the series of conformers **IIIaa**, **IIIab**, **IIIac**, **IIIad**.

According to theoretical data all four stable conformations of molecules of compounds **IIIa** are characterized by intramolecular coordination of hydroxy group to one of the proton-acceptor groups like nitrogen (**IIIaa** and **IIIab**), phosphoryl (**IIIac**), and ester (**IIIad**) oxygen. Local minimum point related to hydroxy group free from intramolecular coordination was not found at all.

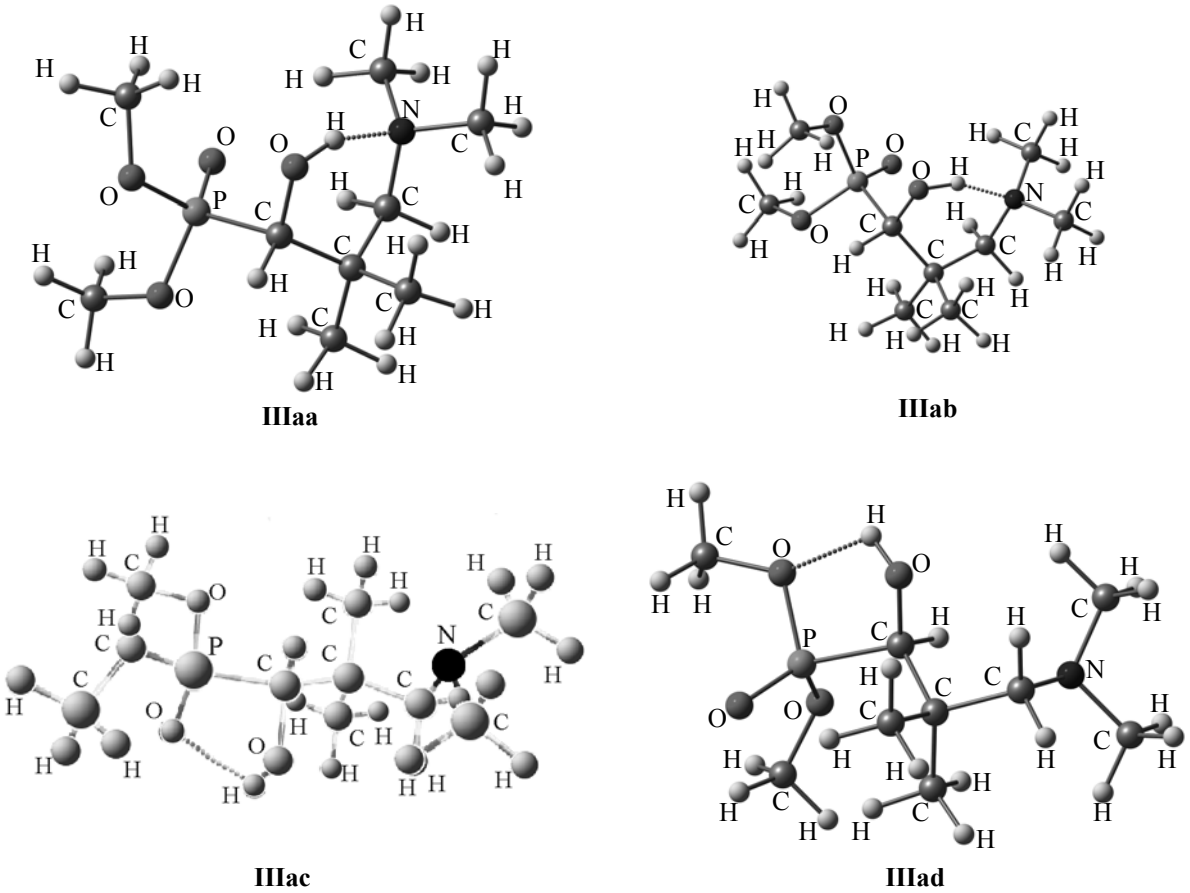


Fig. 1. Models of most stable conformers of compound **IIIa.**

Let us carry out more detailed consideration of geometrical parameters of stable conformations. Structures **IIIaa** and **IIIab** differ significantly in the orientation of methoxy groups. Structure **IIIaa** is characterized by the *gauche*, *gauche* conformation in the C–O–P–O chains of atoms, and the structure **IIIab** by the *gauche, trans* one which is less stable. Note that conformation of methoxy groups in P(IV) derivatives was considered previously [18]. Similarly to the case of simpler compounds having no intramolecular hydrogen bonds **IIIab** conformation with the transoid orientation of one of methoxy groups with respect to the P=O bond is less stable. Hydrogen bond parameters of the conformers **IIIaa** and **IIIab** are close. Conformation **IIIac** is characterized by the *gauche,gauche* orientation of methoxy groups with respect to the P=O bond, but the conformer **IIIad** with intramolecular coordination through the ester oxygen

Table 2. Relative values of total and free energy of conformers **IIIa–IIId** (ΔE, ΔG, kcal mol^{-1})[a]

Conformation	X	ΔE	ΔG	$l_{H\cdots X}$	l_{OH}	l_{CO}	Q_O	Q_H	δ_H	ν(OH)	I	$\nu^1(OH)_{exp}$
IIIaa	N	0.00	0.00	1.732	1.013	1.425	–0.218	0.091	9.11	2954	122	~3100
IIIab	N	1.66	1.96	1.727	1.014	1.418	–0.218	0.091	9.35	2946	148	~3200
IIIac	O=P	5.80	2.72	2.287	0.980	1.445	–0.187	0.141	2.27	3578	51	3562[b]
IIIad	O–P	6.44	3.58	2.147	0.975	1.432	–0.193	0.141	1.74	3660	67	3600[b]

[a] X is the place of coordination, $I_H\cdots_X$, I_{OH}, and I_{CO} are the bond lengths (Å); Q_O, Q_H are the charges on oxygen and hydrogen of the OH group; δ_H is the chemical shift, ppm; ν(OH) are the frequencies, cm^{-1}; I is a relative ν(OH) intensities. DFT/PBE/TZ2P method.

[b] For hydroxyalkylphosphinates having no amino group.

Table 3. Place of intramolecular coordination of the OH groups (X) and torsion angles (deg) of internal rotation (DFT/PBE/TZ2P and DFT/B3LYP/6-31G**)

Conformation	X	COPO	COPO	OPCO	PCOH	OPCC	PCCC	CCCN	CCNC	CCNC
IIIaa	N	–50	–36	74	–92	–52	64	52	96	–142
IIIaa[a]	N	–53	–38	72	–90	–54	61	53	96	–140
IIIab	N	–39	–178	88	–88	–93	65	49	96	–139
IIIac	P=O	31	52	–45	48	80	–171	–59	124	–109
IIIac[a]	P=O	35	56	–52	56	73	–175	–57	120	–112
IIIad	P–O	–44	–6	–84	–46	39	172	–57	123	–111
IIIad[a]	P–O	–42	–1	–83	–47	40	174	–57	118	–113

[a] DFT/B3LYP/6-31G** method.

has less stable *gauche,cis*-structure which cannot take place without the intramolecular hydrogen bond [14].

Structures **IIIaa** and **IIIab** have *gauche,gauche,-gauche* conformation in the O=P–C–C–C–N chain of atoms, and the conformers **IIIac** and **IIIad** are characterized by *gauche,trans,gauche* and *gauche,trans,-gauche* conformations respectively. Conformations **IIIaa–IIIad** differ from one another by the value of PC–OH torsion angle (Table 3) which is determined by the maximum degree of interaction between the hydroxy proton and the acceptors. The torsion angle CCCN of four conformations under consideration is mainly *gauche* with respect to the C–C bond. Transoid configurations are less stable.

In the conformers **IIIaa** and **IIIab** the hydroxy group is included in the non-strained six-membered ···NCCCOH··· cycle with the CO–HN and OH···NC torsion angles close to zero (–14°, 7°) providing the possibility of the maximum H-interaction. In the conformers **IIIac** and **IIIad** the hydroxy group is included in the composition of the five-membered ring impeding the maximum approach and optimal OH bonding with proton acceptors like the phosphoryl and the ester oxygen atoms (Fig. 2).

As it was shown above the resonance signal of the hydroxy proton in compound **VI** (4.35 ppm) unlike compounds **III** is observed near the upfield range where it appears in 2-aminoalkyl-1-hydroxyphosphonate **V** (4.13 ppm) and hydroxyalkylphosphoryl compounds having no amino group (4.8–5.54 ppm). Therefore we expected that the difference observed in the ^{1}H NMR spectra of compounds **III** and **VI** will be revealed also in the IR spectra.

Really, in the case of compound **VI** the picture differs significantly as compared to the spectra of compounds **III**. Aromatic fragment containing NMe_2

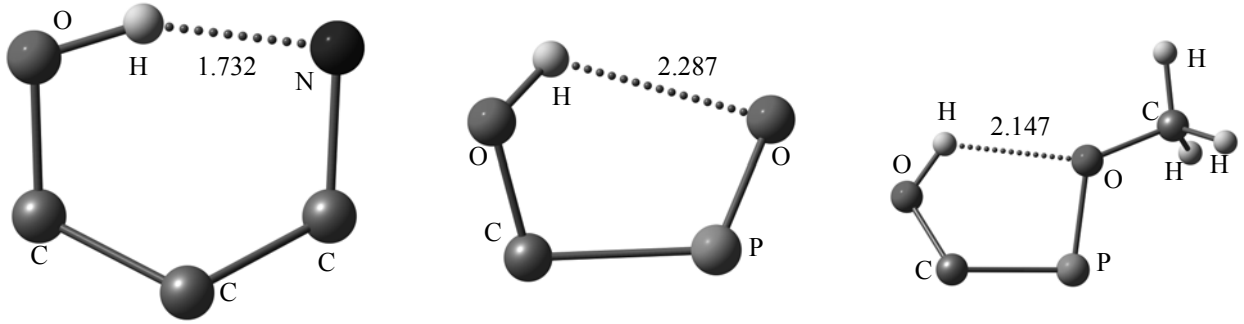
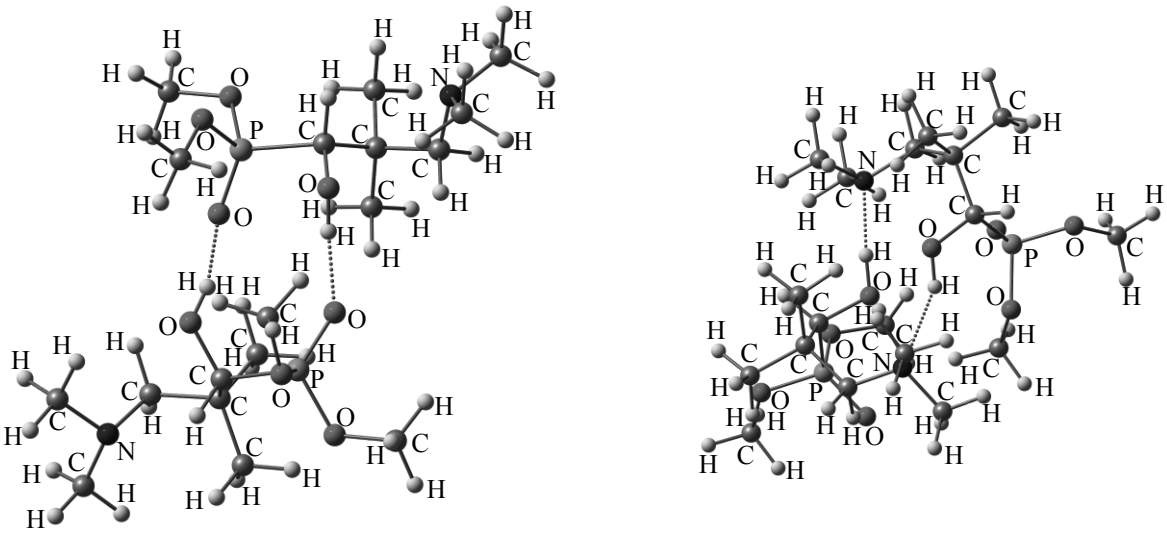


Fig. 2. Three types of coordination of H-interaction in the conformers of compounds **IIIaa, IIIac,** and **IIIad.**

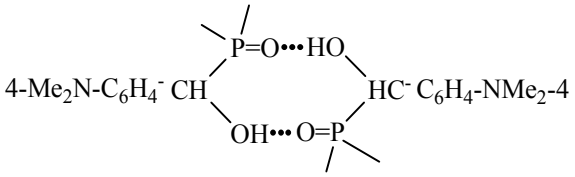


$D_{P=O}$ D_N

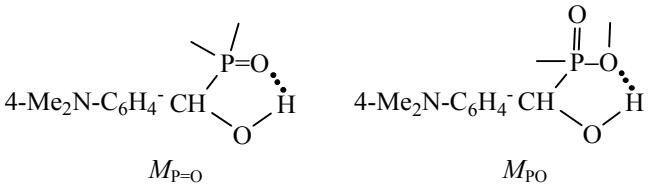
Fig. 3. Models of $D_{P=O}$ (OH···O=P) and D_N(OH···N) dimers of compound **IIIa**.

group in the position 4 makes the molecule more rigid, and the formation of intramolecular hydrogen bond between the hydroxy group and the tricoordinate nitrogen atom does not take place. Besides, n_N,π-orbital interaction decreases the electron-acceptor properties of N(III) and its ability to form hydrogen bonds [10].

In the spectrum of compound **VI** recorded from the mull in mineral oil the absorption bands of benzene fragment at ~3000 cm^{-1} [ν(CH)], ~1614, 1527, 1449 cm^{-1} [ν(C=C)] are revealed. In the range of the hydroxy group only one strong symmetric band with maximum at 3277 cm^{-1} is registered. It is much like the band observed for the crystalline compound **IIIa**. Evidently it is an analog of the absorption band of compounds **III** and **V** attributed to the cyclic H-phosphodimers $D_{P=O}$.



In the spectrum of diluted solution (c = 1 M) of compound **VI** in carbon tetrachloride another picture as compared to the spectra of compounds **III** is observed. In this case there is no signs of association by the N(III) atom (~3100-~2800 cm^{-1}), but the absorption band of H-cyclodimer by P=O remains. It shifts from 3277 cm^{-1} in crystal to 3305 cm^{-1} in solution and its intensity significantly decreases. Under further dilution it disappears, but new peaks appear at 3603 and 3562 cm^{-1} which were absent in the spectra of compounds **III**. Considering the data on 1-hydroxyalkylphosphonates having no amino group [11] these absorption bands can be attributed as follows. The band at ~3277 cm^{-1} in crystal and at 3305 cm^{-1} in solution must be related to ν(OH) of cyclic H-phosphodimers $D_{P=O}$ prevailing in the condensed state as well as in sufficiently concentrated solutions. New ν(OH) absorption bands with the high-frequency maxima relate to monomeric forms with the intramolecular hydrogen bond, particularly, the band at 3562 cm^{-1} to $M_{P=O}$, and the band at 3603 cm^{-1}, to M_{P-O} [11].



$M_{P=O}$ M_{PO}

According to DFT/PBE/TZ2P calculations dimeric structure ($D_{P=O}$) of compound **IIIa** is significantly more preferable than the OH···N dimer D_N. The difference is 12 and 16 kcal mol^{-1} according to evaluations by the total and free energy respectively due to the sterical hindrances in the dimer D_N (Fig.3). According to the calculations the bond vibrations of two OH groups in the dimers give two close

frequencies ν(OH) of the symmetric and antisymmetric OH vibrations which for $D_{P=O}$ are 3288 and 3269 cm^{-1} and the intensities 1844 and 25 respectively.

Hence, theoretical studies lead to conclusions analogous to the experimental data about the prevalence of the $D_{P=O}$ dimeric form with intermolecular hydrogen bond via the phosphoryl oxygen OH···O=P, but the preference of the M_N monomeric form with the OH···N hydrogen bond. Calculations reproduce experimentally observed shifts of ν(OH) and δ_H in H-complexes of different composition and coordination.

EXPERIMENTAL

IR spectroscopic studies were carried out on a Fourier Vector 22 spectrometer (Bruker) with the resolution of 4 cm^{-1}. Spectra of liquid products were recorded from thin films pressed between KBr plates. Crystalline substances were dispersed in mineral oil, and the solutions in CCl_4 and $CHCl_3$ were placed in the cells of various thickness. Temperature studies were carried out in special cryostate. OPUS complex of programs (Brucker) was used.

Molecular and electronic structure of compounds **III** and also the vibrational spectra of conformers were calculated by the density functional method (DFT) with the non-empiric Perdew-Burke-Ernzerhof functional (PBE/TZ2P) [15] and the three-component basis with two sets of polarizational TZ2P functions. The optimization of geometry and calculations of the vibration frequencies were carried out according to the PRIRODA program [16]. Atomic charges were evaluated by the spatial integration method according to Hirshfeld [17].

^1H NMR spectra were taken on a Tesla BS-567A spectrometer (100 MHz) with respect to $CDCl_3$, acetone-d_6, and acetonitrile-d_3. ^{31}P NMR spectra were recorded on a Spectrospin WH-80 (32.31 MHz) spectrometer with respect to the external 85% phosphoric acid. ^{13}C NMR spectra were taken on a Varian Unity 300 (75.43 MHz) with respect to internal $CDCl_3$ and acetone-d_6.

***O,O*-Dimethyl [1-hydroxy-3-(dimethylamino)-2,2-dimethylpropyl]phosphonate (IIIa)**. *a.* To a mixture of 6.27 g of dimethyl hydrogen phosphite **Ia** and 7.4 g of 3-(dimethylamino)-2,2-dimethylpropanal **IIa** small piece of sodium was added under nitrogen. The temperature of the reaction mixture increased to 76°C. After stirring the reaction mixture for 6 h and subsequent keeping for 3 days it was neutralized with the ether solution of acetic acid. Then solvent and volatile products were removed under the reduced pressure, and the reaction mixture was distilled in a vacuum to give 10.39 g (76%) of compound **IIIa**, bp 82–83°C (0.06 mm Hg), n_D^{20} 1.4587.

b. To a mixture of 6.82 g of dimethyl hydrogen phosphite **Ia** and 8 g of 3-(dimethylamino)-2,2-dimethylpropanal **IIa** a solution of sodium methylate in methanol was added dropwise under nitrogen until the end of temperature growth (62°C). After stirring for 5 h at 25°C the reaction mixture was neutralized with the ether solution of acetic acid. Solvent and volatile products were removed under the reduced pressure, and the residue was distilled in a high vacuum to give 11.56 g (78%) of compound **IIIa**, bp 82–83°C (0.06 mm Hg), n_D^{20} 1.4589.

c. A mixture of 2.2 g of dimethyl hydrogen phosphite **Ia** and 2.58 g of 3-(dimethylamino)-2,2-dimethylpropanal **IIa** was kept at 80°C for 3 h. After removing volatile substances the residue was distilled in a vacuum to give 3.65 g (76.5%) of compound **IIIa**, bp 82–83°C (0.06 mm Hg), n_D^{20} 1.4584. ^{31}P NMR spectrum, δ_P, ppm: 27. Found, %: N 5.72, P 12.81. $C_9H_{22}NO_4P$. Calculated, %: N 5.85, P 12.95.

***O,O*-Dimethyl [1-hydroxy-3-(diethylamino)-2,3-dimethylpropyl]phosphonate (IIIb)**. This compound was prepared from 1.85 g of dimethyl hydrogen phosphite **Ia** and 2.62 g of 3-(diethylamino)-2,2-dimethylpropanal **IIb** according to the procedure *b*. Yield 3.21 g (72.3%), bp 92–94°C (0.045 mm Hg), n_D^{20} 1.4596. ^{31}P NMR spectrum, δ_P, ppm: 27. Found, %: N 5.31, P 11.43. $C_{11}H_{26}NO_4P$. Calculated, %: N 5.24, P 11.60.

***O,O*-Diethyl [1-hydroxy-3-(dimethylamino)-2,2-dimethylpropyl]phosphonate (IIIc).** This compound was prepared from 5 g of diethyl hydrogen phosphite **Ib** and 4.67 g of 3-(dimethylamino)-2,2-dimethylpropanal **IIa** according to the procedure *b,* yield 7.44 g (77%) bp 87–88°C (0.05 mm Hg), n_D^{20} 1.4532. ^{31}P NMR spectrum, δ_P, ppm: 27. Found, %: N 5.41, P 11.33. $C_{11}H_{26}NO_4P$. Calculated, %: N 5.24, P 11.60.

***O,O*-Diethyl {1-hydroxy-3(diethylamino)-2,2-dimethylpropyl]phosphonate (IIId).** This compound was prepared from 2.1 g of diethyl hydrogen phosphite **Ib** and 2.4 g of 3-(diethylamino)-2,2-dimethylpropanal **IIb** according to the procedure *b*. Yield 3.28 g (73%), bp 95–96°C (0.07 mm Hg), n_D^{20} 1.4512. ^{31}P NMR spectrum, δ_P, ppm: 27. Found, %: N 4.79, P 10.35. $C_{13}H_{30}NO_4P$. Calculated, %: N 4.74, P 10.49.

***O,O*-Dimethyl [1-hydroxy-2-(diethylamino)-2-methylpropyl]phosphonate (V).** This compound was prepared from 6.65 g of dimethyl hydrogen phosphite **Ia** and 8.65 g of 2-(diethylamino)-3-methylpropanal according to the procedure *b*. Yield 10.25 g (67%), bp 94–96°C (0.065 mm Hg), n_D^{20} 1.4593. ^{31}P NMR spectrum, δ_P, ppm: 28. Found, %: N 5.69, P 12.38. $C_{10}H_{22}NO_4P$. Calculated, %: N 5.53, P 12.25.

***O,O*-Dipropyl [1-hydroxy-3-(dimethylamino)-2,2-dimethylpropyl]thionophpsphonate (VII).** This compound was prepared from 5 g of dimethylthiophosphorous acid **VI** and 3.54 g of 3-(dimethylamino)-2,2-propanal **IIa**. Yield 6.75 g (79%), bp 95–96°C (0.07 mm Hg), n_D^{20} 1.4769. ^{31}P NMR spectrum, δ_P, ppm: 92. Found, %: N 4.75; P 10.25. $C_{13}H_{32}NO_3PS$. Calculated, %: N 4.50; P 9.97.

***O,O*-Dimethyl {1-hydroxy-[4-(diphenylamino)-phenyl]methyl}phosphonate (IX)**. This substance was prepared from 12.05 g of dimethyl hydrogen phosphite **Ia** and 16.32 g of 3-(dimethylamino)-benzaldehyde in 45 ml of anhydrous benzene. Yield 20.14 g (71%), mp 105–106°C (from benzene). ^{31}P NMR spectrum δ_P, ppm: 28. Found, %: N 5.52, P 12.03. $C_{11}H_{18}NO_4P$. Calculated, %: N 5.4, P 11.97.

Synthesis of [3-hydroxy-2,2-dimethyl-3-(diethoxyphosphoryl)propyl]trimethylammonium iodide (VIIIc). To a solution of 7 g of *O,O*-diethyl [1-hydroxy-3-(dimethylamino)-2,2-dimethylpropyl]phosphonate **IIIc** in 25 ml of anhydrous acetonitrile 4.43 g of methyl iodide was added dropwise with stirring at room temperature under the dry nitrogen flow. After stirring for 8 h at room temperature and 3 h at 40°C the volatile products were removed under a high vacuum. The residue was washed with ether, and after several days the crystalline product was formed. Yield 10.11 g (94%), mp 123–124°C. ^{1}H NMR spectrum (CCl_4–acetone-d_6), δ, ppm: 5.05 s (1H, OH), 4.03 q, 4.11 q (4H, $^3J_{PH}$ = $^3J_{HH}$ = 7 Hz, $POCH_2$), 3.84 m (N^+CH_2, CH), 3.59 s (9H, N^+Me_3), 1.35 s, 1.51 s (6H, CMe_2), 1.35 t (6H, $^3J_{HH}$ 7 Hz, CH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 71.93 d ($^1J_{PC}$ 160.5 Hz, CH), 74.1 d ($^3J_{PC}$ 6.1 Hz, CH_3N^+), 62.37 d, 63.79 d ($^2J_{PC}$ 7.5 Hz, OCH_2), 56.5 s (N^+Me_3), 40.79 d ($^2J_{PC}$ 5.6 Hz, CMe_2), 25.06 s, 26.15 d ($^3J_{PC}$ 0.00, 8.02 Hz, CMe_2), 16.49 d, 16.47 d ($^3J_{PC}$ 12 Hz, CH_2Me). ^{31}P NMR spectrum δ_P, ppm: 24. Found, %: N 3.51; P 7.69. $C_{12}H_{29}NO_4PI$. Calculated, %: N 3.42; P 7.58.

[3-Hydroxy-2,2-dimethyl-3-(dimethoxyphosphoryl)propyl]trimethylammonium iodide (VIIIb). This compound was prepared from 2 g of *O,O*-dimethyl [1-hydroxy-3-(dimethylamino)-2,2-dimethylpropyl]phosphonate **IIIa** and 1.43 g of methyl iodide. Yield 3.15 g (91%). ^{31}P NMR spectrum, δ_P, ppm: 24. Found, %: N 3.85, P 8.69. $C_{12}H_{29}NO_4PI$. Calculated, %: N 3.67, P 8.13.

Benzyl[3-hydroxy-2,2-dimethyl-3-(dimethoxyphosphoryl)propyl]dimethylammonium bromide (VIIIa). This compound was prepared from 4.85 g of *O,O*-dimethyl [1-hydroxy-3-(dimethylamino)-2,2-dimethylpropyl]phosphonate **IIIa** and 3.82 g of benzyl bromide, yield 7.66 g (92%), mp 134–135°C (from acetone). ^{1}H NMR spectrum (acetonitrile-d_3), δ, ppm: 7.58 s (5H, Ph), 4.65 s (1H, OH), 3.98 d (1H, $^2J_{PH}$ 11.25 Hz, PCH), 3.6–3.85 m (10H, $2POCH_3$, CH_2N, NCH_2Ph), 3.11 d (6H, $^2J_{PH}$ 3 Hz, NMe_2), 1.3 s., 1.4 s (6H, CMe_2). ^{31}P NMR spectrum, δ_P, ppm: 26. Found, %: N 3.75, P 8.02. $C_{16}H_{29}NO_4PBr$. Calculated, %: N 3.41, P 7.56.

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