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Original Russian Text © A.O. Kolodyazhnaya, O.O. Kolodyazhnaya, O.I. Kolodyazhnyi, 2010, published in Zhurnal Obshchei Khimii, 2010, Vol. 80, No. 4, pp. 549–562.

An Efficient Method for the Phosphonation of C=X Compounds[1]

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Abstract—Reaction of trialkyl phosphites with C=X electrophiles (aldehydes, ketones, ketophosphonates, aldimines, ketimines, isocyanates, isothiocyanates, and activated olefins) in the presence of amines and anilines hydrohalides was studied. We found that pyridine hydrohalides effectively activate the reaction of tralkyl phosphites with various C=X electrophiles: aldehydes, ketones, ketophosphonates, aldimines, ketimines, isocyanates, isothiocyanates, and activated olefins. Particularly high activity showed pyridine hydroiodide. This reaction is a convenient method of synthesis of hydroxyphosphonates, aminophosphonates, carbamoylphosphonates, carbamoylthiophosphonates, and methylenebisphosphonates.

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Intensive development of the chemistry and biology of functionalized phosphonic acids led in the last decade to the development of highly effective routes for the preparation of such compounds [1–4]. There are several methods for the synthesis of α-functionalized phosphonates, which in most cases are based on the reaction of dialkyl phosphites with aldehydes (Abramov reaction) in the presence of acids or bases [5, 6], the reaction of dialkyl phosphites with aldehydes and amines or imines (Kabachnik–Fields reaction) [7, 8], the reaction of dialkyl phosphites with activated alkenes in the presence of Brønsted bases or Lewis acids (Pudovik reaction) [9, 10]. Less commonly the reactions of triakyl phosphites with aldehydes or alkyl imines in the presence of Lewis acids are used [7, 11]. The disadvantage of these methods consists in insufficient activity of reacting compounds, and phosphonation of not activated ketones or ketenimines either proceeds difficultly or cannot be reached at all. In addition, in the presence of a base the reaction is accompanied by phosphonate–phosphate rearrangement [12], and by reverse processes such as Abramov retro-reaction [13].

We developed a convenient and general method of phosphonation of various unsaturated C=X electrophiles. We found that reaction couple trialkyl phosphite–pyridinium iodide is very active and easily phosphonates various C=X electrophiles, where X = O, S, NR, and CR_2 (Scheme 1).

The reaction was carried out without a solvent or in methylene chloride at room temperature. The activity of the reaction couple is due to high acidity of pyridinium iodide: it easily protonated betaine intermediate **A** with the formation of alkoxyphosphonium iodide **B**, which then through the Arbuzov type raction is converted into phosphonate **C** (Scheme 2).

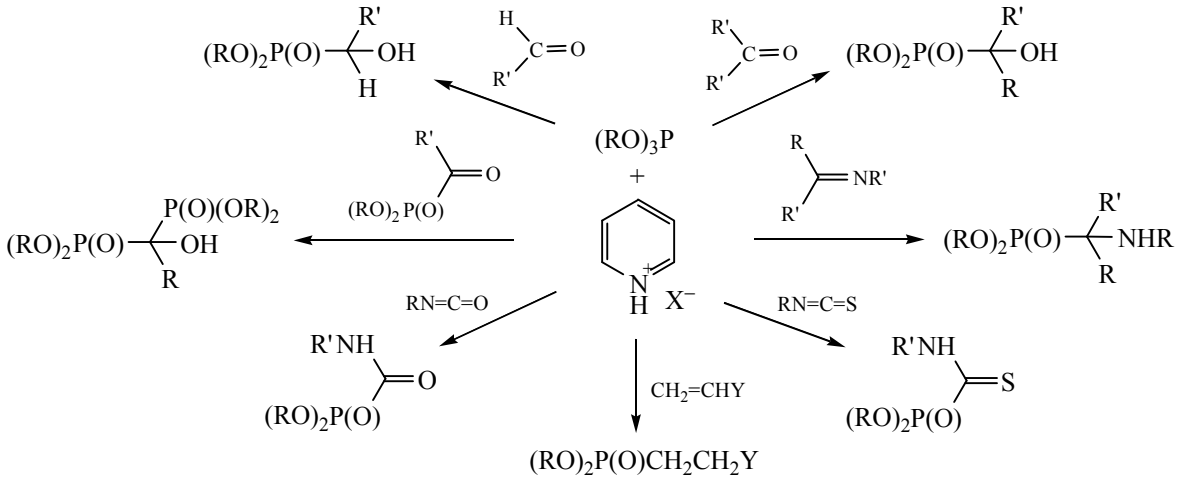
As shown by our studies, the reaction course is affected by the acidity of the proton donor and the nature of the halogen ion. The acidity of the organic base hydrohalide should not be too high or too low; it should be optimal, that is, such as that of pyridinium halides. We investigated hydrohalides of various amines and anilines and found that aniline and dimethylaniline hydrohalides, owing to a high mobility of the proton, dealkylate trialkyl phosphites turning them into dialkyl phosphites, while triethylamine and diisopropylethylamine hydrohalides due to low mobility of the proton are not active in this reaction.

$$(AlkO)_3P + [C_6N_5NR_2H]^+X^- \rightarrow (AlkO)_2P(O)H + AlkX + C_6H_5NR_2,$$

X = Cl, Br, I; Alk = Me, Et; R = H, Me.

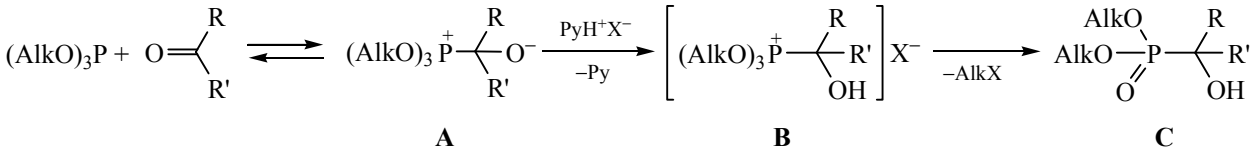
[1] This work is a part of the master's thesis of the student O.O. Kolodyazhnaya at the National Technical University of Ukraine (KPI).

Scheme 1.



X = Cl, Br, I; R, R' = Alk, Ar; Y = NO_2, CN.

Scheme 2.



X = Cl, Br, I; Alk = Me, Et; R, R' = Alk, Ar.

Replacing the pyridinium iodide by pyridinium chloride significantly slows down this reaction, which is especially notable in the case of the reaction with ketones (Table 1). This is explainable by easier dealkylation of the intermediate alkoxyphosphonium salt **B** by iodide ion than bromide or chloride ion, just as it happens in the decay of an intermediate in the Arbuzov reaction. Probably dealkylation of alkoxyphosphonium salt defines the rate of this reaction.

Thus, pyridinium iodide most actively initiated the reaction. Note that the pyridinium bromide or chloride also are active and able to initiate the reaction of trialkyl phosphite with C=X electrophiles.

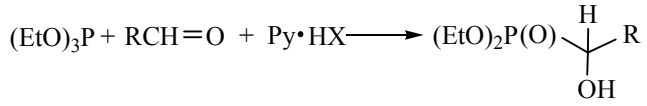
Reaction of trialkyl phosphites with aldehydes in the presence of pyridine halides proceeds very actively, with high rate and with heat release, and leads to the corresponding hydroxyphosphonates **I–IX** in high yield (Table 2). For the preparation of hydroxyphosphonates **I–IX** the best is to use pyridinium bromide, which results in less vigorous reaction than with pyridinium iodide, although actually in both cases were achieved high yields of compounds. The reaction

Table 1. The effect of the nature of proton donor on the reaction of triethylphosphite with cyclohexanone

Proton donor	$PhNH_3^+Cl^-$	$PhNHMe_2^+Cl^-$	PyH^+Cl^-	PyH^+Br^-	PyH^+I^-	$Et_3NH^+Cl^-$	*i*-$Pr_2EtNH^+Cl^-$
pK_a [14, 15]	4.6	5.1	5.3	5.3	5.3	10.64	11.0±0.2
Time, h	24	24	12	12	6	24	24
Temperature, °C	25	25	35	35	25	25	25
Yield, %	~0[a]	~0[a]	50	70	90	5	10

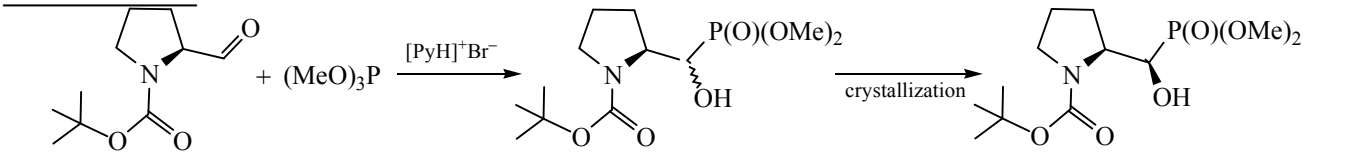
[a] To the end of the given time the reaction mixture contained a mixture of diethylphosphite and triethylphosphite.

was carried out in methylene chloride or without a solvent, at cooling.



I–IX

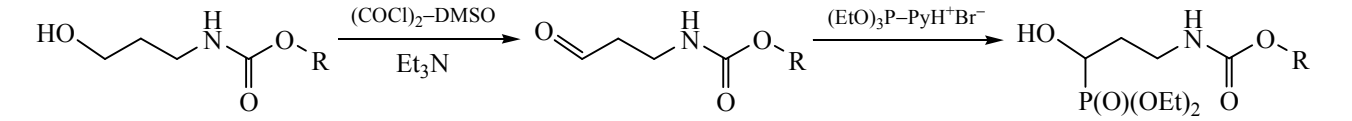
Reaction of trimethyl phosphite with chiral aldehyde (*S*)-*N*-Boc-prolinal in the presence of pyridinium bromide proceeds diastereoselectively, giving a mixture of the hydroxyphosphonate **III** (*S,R*)- and (*S,S*)-diastereomers in 4:1 ratio, as revealed by the analysis of the reaction mixture using $^{31}P–\{^1H\}$ NMR spectroscopy (the signals δ_P 26.9 and 26.3 ppm). By the crystallization of the diastereomeric mixture from hexane we succeeded to isolate (*S,R*)-hydroxylphosphonate **III**, whose configuration was established using chiral Mosher's acid along the known procedure [17]. Previously only racemic compound **III** has been described [16].



(*S,S*) + (*S,R*)-**III** (*S,R*)-**III**

The structures of products **I–IX** were proved by the NMR analysis of purified samples. In the ^1H NMR spectra of the compounds a broad signal of OH proton was detected in a weak field and a doublet of the proton of PCH groups. In the ^{13}C NMR spectra there is a signal of the P–C carbon as a doublet with large $^1J_{PC}$ coupling constant in the region of 50–60 ppm.

Using the method we developed a series of hydroxyphosphonates has been synthesized, which are interesting as C–P analogs of natural compounds. For example, we synthesized phosphonate derivatives of γ-aminopropanol **I** and **II**, which are potential biologically active substances [18]. To perform the synthesis, 3-aminopropanol was protected at the NH group by conversion to chlorocarbonate or by acylation with Boc_2O (Boc is *t*-butoxycarbonyl) that gave amides **Xa** and **Xb**. These compounds were oxidized by the Swern method [19] to aldehydes **XIa, XIb**, which were purified by a vacuum distillation; the aldehydes were obtained in good yield. Finally, these aldehydes were phosphonated by the action of $(RO)_3P–[PyH]^+Br^–$. The final compounds, hydroxyphosphonates **I** and **II** were obtained in almost quantitative yields.



Xa, Xb **XIa, XIb** **I, II**

R = MeOCO (**a**), R = Boc = *t*-BuOC(O) (**b**).

The synthesized α-hydroxy-γ-aminopropanols **I** and **II** were used as starting compounds for the synthesis of new analogs of lysophosphatidic acid [20]. This acid is an intercellular signal phospholipid that induces a number of important biological effects [21]. Replacing carbon for the oxygen atom in the phosphate group gives hydrolytically stable phosphonate that can be an inhibitor of the processes in which lysophosphatidic acid participates. By a reaction of the hydroxyphosphonate **I** with oleoyl chloride and triethylamine at 80°C in THF we prepared oleinate **XII**, which was purified by the column chromatography. The structure of this compound was proved by ^{31}P and ^1H NMR spectroscopy.

The reaction couple trialkyl phosphite–pyridinium iodide relatively easily phosphonates ketones, which under the condition of Abramov reaction are phosphonated difficultly or not at all. Commonly dialkyl phosphite sodium salts are used, and therefore reaction is accompanied by side processes like phosphonate–phosphate rearrangement. All our methods can be used for the phosphonation in high yields of not only simple ketones **Ia**, but also of complex ketones of natural origin.

Table 2. Conditions of the reaction $(R^1O)_3P + R^2R^3C{=}X + [PyH]^+I^- \rightarrow (R^1O)_2P(O)C(XH)R^2R^3$

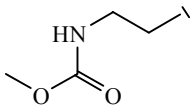
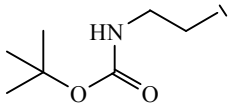
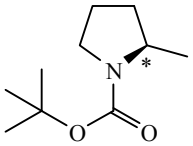
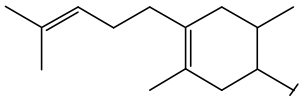
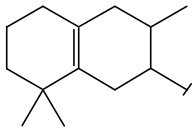
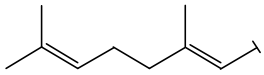
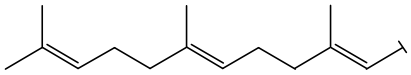
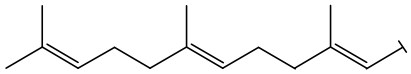
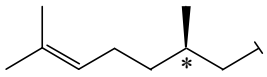
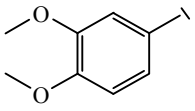
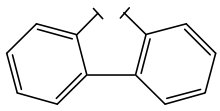
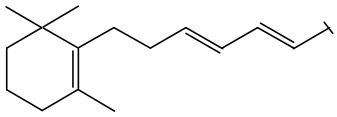
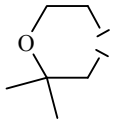
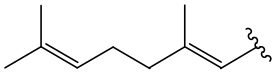
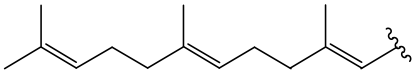
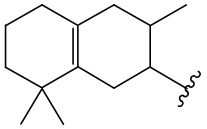
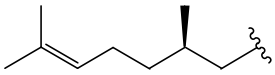
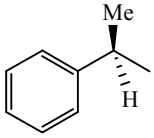
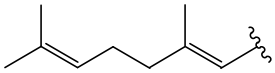
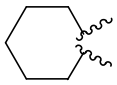
Comp. no.	R^1	R^2	R^3	X	Temperature, °C	Time, h	Yield, %[a]
I	Et		H	O	20	2	95
II	Et		H	O	20	2	90
III	Me		H	O	20	2	90
IV	Et		H	O	20	4	90
V	Et		H	O	20	4	90
VI	Et		H	O	20	2	90
VII	Me		H	O	20	2	90
VIII	Et		H	O	20	2	90
IX	Et		H	O	20	2	90
XIII	Et	Ph	Me	O	40	5	80
XIV	Et	3-$F_3CC_6H_4$	Me	O	25	6	80
XV	Et	4-*t*-BuC_6H_4	Me	O	25	24	70
XVI	Me	Ph	CH_2Cl	O	30	12	70
XVII	Et		Et	O	25	24	80
XVIII	Et			O	25	24	65
XIX	Et		Me	O	25	24	

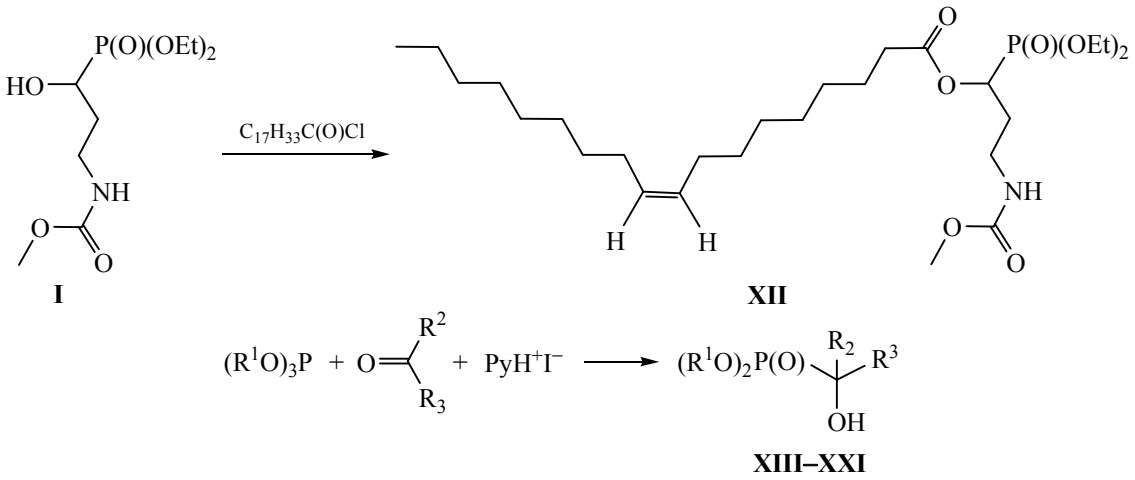
Table 2. (Contd.)

Comp. no.	R^1	R^2	R^3	X	Temperature, °C	Time, h	Yield, %[a]
XX	Et			O	25	12	
XXI	Et			O	25	12	
XXVII	Et	Me	$(EtO)_2P(O)$	O	20	10	70
XXVIII	Et		$(EtO)_2P(O)$	O	20	10	70
XXIX	Et		$(EtO)_2P(O)$	O	20	10	70
XXX	Et		$(EtO)_2P(O)$	O	20	10	70
XXXI	Et		$(EtO)_2P(O)$	O	20	12	90
XXXII	Et	Ph	H	NBn	30	12	70
XXXIII	Et	Ph	H		30	10	70
XXXIV	Et		H	Ph	30	12	60
XXXV	Et		Ph	40	12	50	
XXXVI	Et	Ph	H	$CHNO_2$	25	6	70
XXXVII	Et	Ph	H	$CHNO_2$	25	6	65

[a] Yields of purified products are reported.

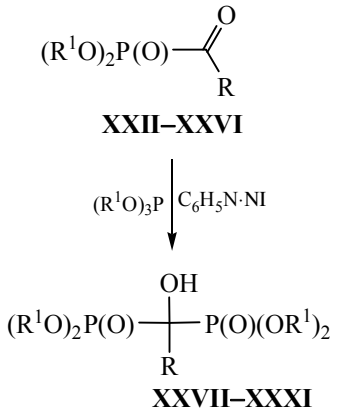
The reaction was carried out in methylene chloride as a solvent, at room temperature or at gentle heating. The structure of final products **XIII–XXI** was proved by NMR spectroscopy. In the spectra of proton magnetic resonance a broad signal of OH proton appeared in a weak field. In the ^{13}C NMR spectra a signal of PC carbon nucleus is observed in the region of 50–60 ppm as a doublet with a large $^1J_{PC}$ coupling constant (Table 2).

The reaction couple $(RO)_3P$–$[PyH]^+I^-$ phosphonated ketophosphonates with the formation of 1-hydroxy-1,1-bisphosphonates. High biological activity of 1-hydroxy-1,1-bisphosphonoalkanes is well known [22].

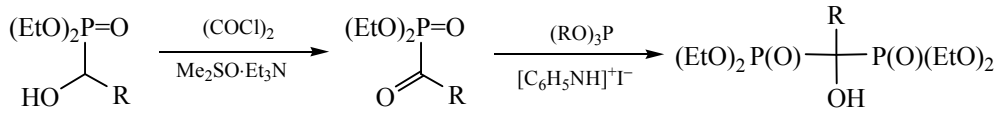


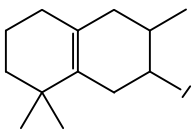
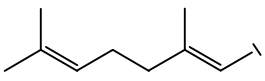
On the basis of 1-hydroxy-1,1-bisphosphonates some highly effective drugs have been produced: etidronate, alendronate, risedronate, zoledronate and others; various methods for their synthesis were developed [23–25]. We developed another convenient pathway for the synthesis of hydroxybisphosphonates.

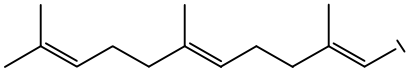
The reaction was carried out in methylene chloride as a solvent, at room temperature. The reaction was completed within few hours affording in a good yield hydroxybisphosphonates **XXVII–XXXI** (Table 2).



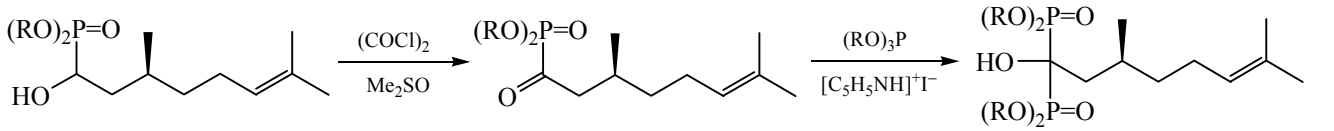
We applied this method to the synthesis of bisphosphonates **XXVIII–XXX**, the derivatives of terpenes such as farnesol, geraniol, citronellol, and others [26]. The initial ketophosphonates were obtained by oxidation of unsaturated hydroxyphosphonates **VI, VIII** by the Swern method with a complex of oxalyl chloride with dimethylsulfoxide. The method in this case is very useful, since the reaction proceeds regioselectively and only at the OH group, without affecting the multiple C=C bond, as used to occur with other oxidants. By this method the ketophosphonates **XXIII–XXV** were obtained in high yields and were introduced in the next stage in the reaction with $(EtO)_3P$–$[PyH]^+Br^-$ and converted into isoprenylbisphosphonates **XXVIII–XXX**. The bisphosphonates were purified by chromatography on silica gel. The structure of bisphosphonates **XXVIII–XXX** was confirmed by the data of NMR spectroscopy.



R =  (**V, XXIII, XXVIII**);  (**VI, XXIV, XXIX**);

 (**VIII, XXV, XXX**).

A similar scheme was applied to obtain chiral bisphosphonates **XXXI** based on (+)-(R)-citronellal. By reaction of citronellal with the reagent $(EtO)_3P$–$[PyH]^+Br^-$ hydroxyphosphonate **IX** was quantitatively obtained and purified by distillation in a vacuum. Then the hydroxyphosphonate was oxidized by the Swern method, and with the yield 70% the chiral ketophosphonate **XXV** was obtained, which was purified by distillation in a vacuum. In the last stage of the synthesis the ketophosphonate by the reaction with $(EtO)_3P$–$[PyH]^+I^-$ was in a high yield transformed into bisphosphonate **XXXI**.

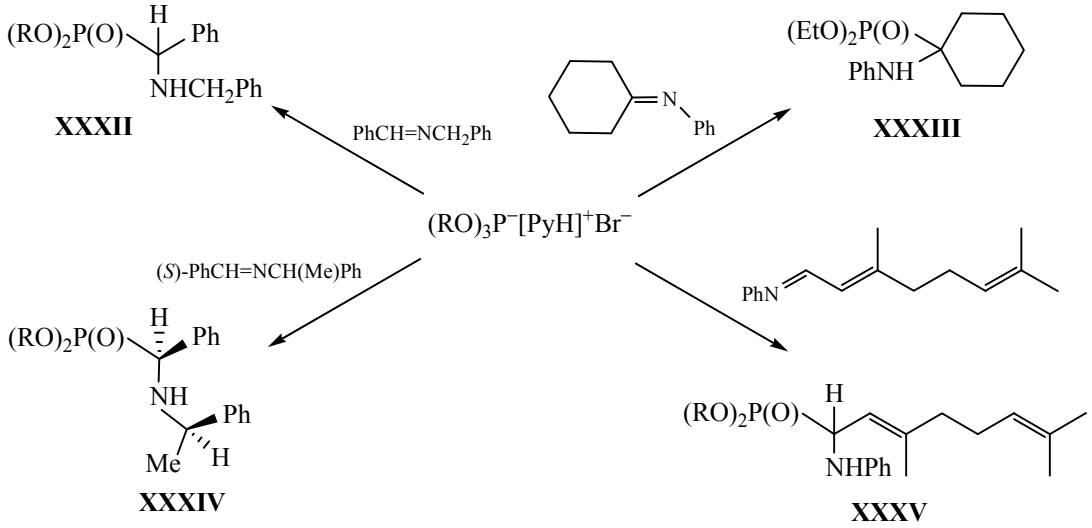


IX **XXV** (*S*)-**XXXI**

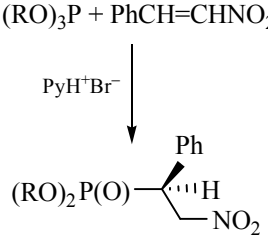
Compound **XXXI** was purified by column chromatography and obtained in analytically and spectroscopically pure form. As in the previous case, an interesting feature of the chiral compounds is the presence of diastereotopic phosphonic groups affecting their NMR spectra. A special feature of the ^{31}P NMR spectrum is the presence of two signals of diastereotopic phosphonic groups. The presence of a chiral center in the molecule makes the ethoxy groups also diastereotopic as seen in ^1H NMR spectrum.

The reaction of $(EtO)_3P$–$[PyH]^+I^-$ with imines leads to the formation of the respective aminophosphonates **XXXII–XXXV** under relatively mild conditions (Table 2). Thus, the reaction of $(EtO)_3P$–$[PyH]^+I^-$ with benzylbenzaldimine proceeds at room temperature with the formation of *N*-benzyl-substituted aminophosphonic acid, namely, much easier than the reaction of the same imine with diethylphosphite, which requires heating at 140°C for several hours. Reaction of $(EtO)_3P$–$[PyH]^+I^-$ with a chiral (*S*)-1-methylbenzylbenzaldimine also occurs at room temperature and leads to the formation of (*S,S*)-diastereomer of *N*-benzyl-substituted aminophosphonic acid diester with 80% *de*. It was noted that initially a mixture formed of (*S,S*)- and (*S,R*)-diastereomers of *N*-benzyl-substituted aminophosphonic acid diester in the 3:1 ratio. Upon heating to 130–140°C the ratio of diastereomers changed in favor of the (*S,S*)-diastereoisomer and became equal to 9:1. In contrast to this reaction, addition of diethyl phosphite to (*S*)-1-methylbenzylbenzaldimine proceeds with predominant formation of (*S,R*)-diastereoisomer [27]. We succeeded also to involve into the reaction with $(EtO)_3P$–$[PyH]^+I^-$ some ketimines which do not enter into the Kabachnik–Fields reaction under normal condition [28], as exemplified by the phosphonation of cyclohexenylidenaniline with the formation of compound **XXXIII**.

Scheme 3.



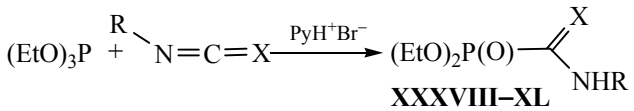
Triethyl phosphite and trimenthyl phosphite in the presence of pyridinium bromide phosphonylated nitrostyrene with the formation of β-nitro-α-phenylethylphosphonates **XXXVI, XXXVII** [29, 30]. The reaction proceeded readily with heat evolution. Moreover, the reaction of nitrostyrene with trimenthyl phosphite proceeded stereoselectively with the formation of optically active phosphonate **XXXVII**, which was isolated and purified by crystallization from acetonitrile. Previously compound **XXXVII** we obtained by the reaction of nitrostyrene with dimenthylphosphite [30]. Physicochemical characteristics of the compounds obtained by the two methods coincided.



XXXVI, XXXVII

R = Et, (1*R*,2*S*,5*R*)-Mentyl.

The the couple $(EtO)_3P$–$[PyH]^+Br^-$ reacts readily with isocyanates and isothiocyanates transforming them in very high yields into respective carbamoylphosphonates **XXXVI** or carbamoylthiophosphonates **XXXVII, XXXVIII**. The reaction was carried out in a methylene chloride solution at cooling. The reaction products were purified by a vacuum distillation. Their structure and purity were proved by ^1H, ^{13}C, and ^{31}P NMR spectra, as well as by elemental analysis. Carbamoylphosphonates attract attention due to their high biological activity and, therefore, they were intensively studied [31–36]. Earlier carbamoylphosphonates were synthesized by the reaction of alkylthiocarbonylphosphonates with ammonia [31, 32]. They also were prepared by the Arbuzov reaction of dialkylcarbamoyl chlorides with trialkyl phosphites [34, 35]. Thiocarbamoylphosphonates were prepared by a reaction of trialkyl phosphonothioformates with ammonia or amines [37]. Our method is simpler and gives higher yields of products compared with the previously described methods.



XXXVIII–XL

R = Pr, X =O (**XXXIV**); R = CH_2=$CHCH_2$, X = S (**XXXV**); R = Ph, X = S (**XXXVI**).

Thus, we developed a convenient general method for the synthesis of phosphonic acids with the use of the reaction couple $(RO)_3P$–$[PyH]^+X^-$. The use of pyridinium halides allows to activate the reaction of trialkyl phosphites with C=X electrophiles, thus providing ready phosphonation of aldehydes, ketones, aldimines and ketimines, ketophosphonates, and compounds containing activated multiple C=C bond, with the formation of functionalized phosphonates. The advantage of this method in comparison with existing ones is a high activity of the reagents, absence of rearrangements and isomerizations (of the type of phosphonate-phosphate rearrangement), and of reverse processes (such as Abramov retro-reaction).

EXPERIMENTAL

The NMR spectra were recorded on a Varian VXR-300 spectrometer at 300 (^1H) and 126.16 (^{31}P) MHz with internal reference TMS (^1H) and external reference 85% H_3PO_4 in D_2O (^{31}P). All chemical shifts are expressed in the δ scale (ppm).

The melting points were not corrected. For column chromatography was used silica gel Merck 60, eluent a mixture of hexane with ethyl acetate. Experiments were carried out in an inert atmosphere (Ar). For reactions were used anhydrous solvents: THF freshly distilled over sodium in the presence of benzophenone, methylene chloride distilled over P_4O_{10}. Other reagents were purchased from Merck and Acros, and were used without purification.

The general method of the synthesis of hydroxyphosphonates I–IX. To 0.01 mol of triethyl phosphite and 0.01 mol of aldehyde in 3 ml of methylene chloride at 0°C was added 0.011 mol of pyridinium bromide, and the mixture was left at room temperature during the time specified in Table 1. Then the reaction mixture was filtered, the filtrate was evaporated in a vacuum of water-jet pump and then kept in a vacuum of 0.01 mm Hg at 80°C for 1 h. The product was either purified by distillation in a vacuum, or recrystallized, or used without special treatment when was spectroscopically pure. Yields are listed in Table 2.

Diethyl 3-(metoxycarbonylamino)-1-hydroxypropylphosphonate (I). Yield 90%. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 t (6H, CH_3, *J* 7), 1.87 m (2H, CH_2), 3.35 m (2H, CH_2), 3.62 s (3H , CH_3O), 4.05 m (1H, PCH), 4.15 m (4H, OCH_2), 5.88 br (1H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm:

25.24. Found, %: N 5.22; P 11.56. $C_9H_{20}NO_6P$. Calculated, %: N 5.20; P 11.50.

Diethyl 1-hydroxy-3-tert-butoxycarbonylamino)-propylphosphonate (II). Yield 95%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.34 t (6H, CH_3, *J* 7), s 1.44 [9H, $(CH_3)_3C$], 1.89 m (2H, CH_2), 3.23 m (1H, NCH_2), 3.46 m (1H, NCH_2), 3.96 m (1H, PCH), 4.18 m (OCH_2), 5.1 br (1H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 25.7. Found, %: N 4.55; P 9.91. $C_{12}H_{26}NO_6P$. Calculated, %: N 4.50; P 9.95.

Dimethyl (*S*,*R*)-2-*N*-Boc-pyrrolidine(hydroxy-methyl)phosphonate (III). To 0.01 mol of trimethyl-phosphite at –10°C was added 0.01 mol of *N*-Boc-prolinal and 0.01 mol of pyridine bromide. The mixture was stirred at –10°C for 5 h, then at 0°C for 2 h and at room temperature for 1 h. The reaction mixture was diluted with diethyl ether, filtered, the filtrate was evaporated. Hydroxyphosphonate **III** was obtained with the yield 95% as a mixture of (*S*,*R*)- and (*S*,*S*)-diastereomers in 4:1 ratio. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.9 and 26.3 [16]. The product was recrystallized from cooled to –20°C chloroform–hexane mixture and then several times from hexane, resulting in pure (*S*,*R*)-diastereomer, mp 79°C, $[\alpha]_D$ –60 (*c* 2, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.42 s [9H, $(CH_3)_3C$], 1.8–2.3 m (4H, CH_2), 3.2 m (1H, PCH), 3.7–3.8 m (2H, CH_2N), 3.7 d (6H, CH_3O, *J* 10), 4.1 m (1H, NCH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 6.9.

Diethyl hydroxy[6-methyl-4-(4-methylpentene-3-enyl)cyclohexyl-3-ene-1-yl]methylphosphonate (IV). Yield 80%. Purified by column chromatography on silica gel. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.99 d (3H, CH_3, *J* 6), 1.33 t (6H, CH_3CH_2, *J* 7), 1.6 s (3H, CH_3), 1.87 s (3H, CH_3), 1.91–2.22 m (10H, CH_2 + CH), 3.51 br (OH), 4.17 m (5H, OCH_2 + PCH, *J* 7, *J* 8), 6.28 s (1H, CH=C), 5.32 m (2H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.6. Found, %: C 62.68; H 9.65; P 8.88. $C_{18}H_{33}O_4P$. Calculated, %: C 62.77; H 9.66; P 8.99.

Diethyl hydroxy(3,8,8-trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)methylphosphonate (V). Yield 80%, bp 190°C (0.1 mm Hg), mp 107–110°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.957 d (3H, CH_3C, *J* 6), 0.975 s (6H, CH_3), 1.34 t (6H, CH_3CH_2O, *J* 7), 1.43 m (2H, CH_2), 1.6 m (4H, CH_2), 1.8 m (2H, CH_2), 1.9 m (1H, CH), 2.0 m (1H, CH), 2.19 m (2H, CH_2), 2.91 m (1H, OH), 4.2 m (5H, CH_2O+PCH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 25.63. Found, %: C 62.53; H 9.64; P 9.10. $C_{18}H_{33}O_4P$. Calculated, %: C 62.77; H 9.66; P 8.99.

Diethyl (2*E*)-1-hydroxy-3,7-dimethyl-2,6-octadienylphosphonate (VI). Yield 80%, bp 135°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 t (CH_3, J_{HH} 7), 1.29 t (CH_3, J_{HH} 7), 1.61 s (3H, CH_3), 1.69 s (3H, CH_3), 2.1 br (4H, CH_2), 4.12 m (4H, OCH_2), 4.52 d.d (1H, J_{HH} 9, J_{HP} 9), 5.12 br (1H, CH=C), 5.36 br (1H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ_P, 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 (VII). Yield 90%, oil. Purified by column chromatography on silica gel. ^{1}H NMR spectrum ($CDCl_3$),. δ, ppm (*J*, Hz): 1.59 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.69 d (3H, CH_3CH, J_{HH} 1.5), 1.71 d (3H, CH_3CH, J_{HH} 1.5), 2.09 m (6H, CH_2), 2.25 m (2H, CH_2), 3,78 d (3H, CH_3O, J_{HP} 10), 3.8 d (3H, CH_3O, J_{HP} 10), 4.5 br (1H, OH), 4.7 m (1H, PCH, J_{HP} 10), 5.09 br (1H, CH=C), 5.35 br (2H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.05 [36].

Diethyl (2*E*,6*E*)-1-hydroxy-3,7,11-trimethyl-2,6,10-dodecatrienylphosphonate (VIII). Yield 88%, oil. Purified by column chromatography on silica gel. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 t (CH_3, J_{HH} 7), 1.29 t (CH_3, J_{HH} 7), 1.58 s (3H, CH_3C=), 1.65 s (3H, CH_3C=), 1.68 d (3H, CH_3CH, J_{HH} 1.5), 1.70 (3H, CH_3CH, J_{HH} 1.5), 2.1 m (6H, CH_2), 2.2 m (2H, CH_2), 4.1 m (4H, OCH_2), 4.5 br (1H, OH), 4.7 m (1H PCH, J_{HP} 10), 5.1 br (1H, CH=C), 5.3 br (2H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 25.00. Found, % C 63.78; H 9.86; P 8.34. $C_{19}H_{35}O_4P$. Calculated, %: C 63.66; H 9.84; P 8.64.

Diethyl (6*E*)-1-hydroxy-3,7-dimethyl-6-octenylphosphonate (IX). Yield 80%, bp 145–150°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.96 d (3H, CH_3, *J* 7), 1.29 t (3H, CH_3CH_2, *J* 7), 1.30 t (3H, CH_3CH_2, *J* 7), 1.58 s (3H, CH_3C=), 1.65 s (3H, CH_3C=), 1.83 m (2H, CH_2), 1.96 m (2H, CH_2), 3.8$_2$ m (1H, PCH), 4.09 m (4H, OCH_2), 5.07 m (1H, CH=C, *J* 7), 5.7 br (1H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.5. Found, %: P 10.69. $C_{14}H_{29}O_4P$. Calculated, %: P 10.59.

***N*-Methoxycarbonyl-3-aminopropanol (Xa)**. To 0.1 mol of 3-aminopropanol and 0.1 mol of triethylamine in 100 ml of diethyl ether was added dropwise 0.1 mol of methyl chlorocarbonate, the mixture was cooled to 0°C at stirring. Then stirring was continued

for 1 h at room temperature. The precipitate formed was filtered off, the solution was evaporated, and the residue was distilled in a vacuum. Yield 75%, bp 80°C (10 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.7 t (2H, CH_2, *J* 7) 3.33 m (5H, NH + CH_2), 3.67 s (3H, CH_3), 6.34 br (1H, OH). Found, %: C 45.18; H 8.12; N 11.32. $C_5H_{11}NO_3$. Calculated, %: C 45.10; H 8.33; N 10.52.

***N*-Methoxycarbonyl-3-aminopropanal (XIa)**. In a flask 40 ml of anhydrous dichloromethane and 1.7 ml of oxalyl chloride was placed. The solution was cooled with stirring, and at –50 to –60°C was added dropwise 2.9 ml of dimethyl sulfoxide in 10 ml of dichloromethane. Then 5 min later, 2.9 g of alcohol **Xa** was added dropwise over 10 min maintaining the temperature at –50 to –60°C. After 15 minutes, 11.5 ml of triethylamine was added dropwise, maintaining the temperature below –50°C. The stirring was continued for 5 min, then the mixture was heated to room temperature and poured into 70–80 ml of water with ice. The water layer was separated and extracted with 2 × 30 ml of dichloromethane. The organic layers were combined, washed with 2 × 10 ml of saturated solution of sodium chloride, and dried over magnesium sulfate. The solution was filtered and evaporated, the residue after evaporation was extracted with hexane. Then, this extract was evaporated and the residue was distilled in a vacuum. Yield 60%, bp 100°C (10 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.71 t (2H, CH_2, *J* 7), 3.46 m (2H, NCH_2), 3.63 s (3H, OCH_3), 5.49 br (1H, NH), 9.79 s (1H, CH=O). Found, %: C 45.80; H 6.92; N 10.68. $C_5H_9NO_3$. Calculated, %: C 45.80; H 6.92; N 10.68.

***N*-Boc-3-aminopropanol (Xb)**. In a flask was placed 2.0 g of 3-aminopropanol and a solution of 7 g of 97% aqueous di-*tert*-butyl dicarbonate in 20 ml of THF was added dropwise at stirring and cooling to 0°C. The reaction mixture was stirred for 10 min at 0°C and then 14 h at room temperature, and boiled for 3 h with a reflux condenser. The solvent was then removed under reduced pressure; the residue was washed with saturated aqueous solution of sodium hydrogen carbonate. The aqueous phase was extracted with diethyl ether, the extract was dried over anhydrous sodium sulfate, filtered, evaporated and the residue after evaporation was distilled in a vacuum. Yield 80%, bp 90°C (0.1 mm Hg). Colorless viscous liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.4 s [9H, $(CH_3)_3C$], 1.7 t (2H, CH_2, *J* 7), 3.33 m (5H, NH+CH_2), 6.4 br (1H, OH). Found, %: C 54.55; H 9.67; N 8.11. $C_8H_{17}NO_3$. Calculated, %: C 54.84; H 9.78; N 7.99.

***N*-Boc-aminopropanal (XIb)**. Prepared analogously to compound **XIa**. Yield 60%, bp 75–80°C (0.1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.41 s [9H, $(CH_3)_3C$], 2.7 t (2H, CH_2, *J* 7), 3.45 m (2H, CH_2N), 5.05 br (1H, NH), 9.8 s (1H, CH=O). Found, %: C 55.1; H 8.65. $C_8H_{15}NO_3$. Calculated, %: C 55.47; H 8.73.

1-(Dietoxyphosphinyl)-3-[(*N*-metoxycarbonyl-amino)-propoxy-(9*Z*)-octadecenoate (XII). To 0.005 mol of hydroxyphosphonate **II** and 0.0075 mol of triethylamine in 5 ml of THF at cooling to 0°C was added 0.005 mol of oleoyl chloride. The mixture was left for 2 h at room temperature. Then triethylamine hydrochloride was filtered off, the solvent was evaporated, and the residue was subjected to chromatography on a column with silica gel. Eluent hexane–ethyl acetate, 6:1. The purified product is a colorless viscous oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 t (3H, CH_3, *J* 7), 1.3 m (20H, CH_2), 2.0–2.3 m (4H, CH_2), 2.45 m (4H, CH_2C=), 3.3 m (2H, CH_2N), 3.6 s (3H, CH_3O), 4.05 m (4H, OCH_2), 5.2 m (CH=C); 5.4 m (1H, PCH), 5.5 m (NH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 29.3. Found, %: N 2.62; P 5.80. $C_{27}H_{52}NO_7P$. Calculated, %: N 2.62; P 5.80.

General method of the synthesis of hydroxyphosphonates XIII–XXI. A mixture of 0.01 mol of ketone, 0.01 mol of trialkyl phosphate, and 0.01 mol of pyridinium iodide in 3 ml of methylene chloride was stirred for the period specified in Table 2. Then the solvent was evaporated and the residue was dissolved in 5 ml of ether, filtered, the solvent was evaporated, the product was purified by crystallization from a solvent or distilled in a vacuum. Yields are listed in Table. 2.

Diethyl 1-hydroxy-1-phenylethylphosphonate (XIII). Recrystallized from a mixture of hexane–ether or acetonitrile. Yield 70%, mp 75°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.2 m (3H, CH_3, *J* 7), 1.82 d (3H, *J* 16.5), 4.07 m (4H, OCH_2), 7.6 m (5H, C_6H_5). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 27. Found, %: P 11.99. $C_{12}H_{19}O_4P$. Calculated, %: P 11.99 [1, 28].

Diethyl 1-hydroxy-1-(3-trifluoromethylphenyl)-ethylphosphonate (XIV). Prepared according to the general scheme. Yield 80%, purified by crystallization from hexane, mp 125–128°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.24 t (6H, CH_3, *J* 7), 1.83 d

(3H, CH_3SP, *J* 15.6), 4.04 m (2H, OCH_2), 4.12 m (2H, OCH_2), 4.66 br (1H, NH), 7.44–7.9 m (4H, C6H4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.17 s (CH_3), 26.33 s (CH_3), 63.5 q (OCH_2, *J* 94), 73.5 d (PC, *J* 161), 127 q (CF_3, *J* 271), 123.1, 123.88, 128.16, 130.01, 130.27, 143.00 (C_6H_4). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –57.67. ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 25.3 d, *J* 8. Found, %: P 9.49. $C_{13}H_{18}F_3O_4P$. Calculated, %: P 9.55.

Diethyl 1-hydroxy-1-(4-*tert*-butylphenyl)ethylphosphonate (XV). Yield 80%, mp 84–86°C (hexane). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.15 t (3H, CH_3) 1.17 t (3H, CH_3) 1.24 s [9H, $(CH_3)_3C$], 1.8 d (CH_3, *J* 14.5), 3.93 m (2H, OCH_2), 4.07 m (2H, OCH_2), 7.3–7.5 m (4H, C_6H_4). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.0. Found, %: P 9.65. $C_{16}H_{27}O_4P$. Calculated, %: P 9.85.

Dimethyl 1-hydroxy-2-chloro-1-phenylethylphosphonate (XVI). Yield 70%, mp 152–155°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.60, d (3H, OCH_3, *J* 12), 3.81 d (3H, OCH_3, *J* 12), 4.11 d (1H, CHCl, *J* 3), 4.26 d (1H, CHCl, *J* 3), 7.36–7.4 m (5H, C_6H_5), 4.32 s (1H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 25. Found, %: Cl 13.42; P 11.65. $C_{10}H_{14}ClO_4P$. Calculated, %: Cl 13.40; P 11.70.

Diethyl [1-(3,4-dimethoxyphenyl)-1-hydroxypropyl]phosphonate (XVII). Prepared similarly. The product was purified by chromatography on a column with silica gel (ethyl acetate–hexane, 1:1). R_f 0.33, yield 60%. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.77 t (3H, CH_3, *J* 7.2), 1.15 t (3H, CH_3CH_2O, *J* 7), 1.27 t (3H, CH_3CH_2O, *J* 7), 2.13 d.q (1H, *J* 7, *J* 8), 2.24 d.q (1H, *J* 7, *J* 8), 3.87 s, 3.89 s (3H, CH_3O), 4.1 m (4H, CH_2O), 6.9–7.5 m (3H, C_6H_3). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 24.3. Found, %: P 9.32. $C_{15}H_{25}O_6P$. Calculated, %: P 9.32.

Diethyl (9-Hydroxy-9*H*-fluorene-9-yl)phosphonate (XVIII). Yield 60%, mp 150–152°C (acetonitrile). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.08 t (6H, CH_3, *J* 7) 3.94 d.q (4H, OCH_2, *J* 7, *J* 8), 7.34 t (2H, CH, *J* 7.5), 7.42 t (2H, CH, *J* 7.5), 7.67 d (2H, CH, *J* 7.2), 7.87 d (2H, CH, *J* 7.2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.17 (CH_3), 63.47 (CH_2), 80.6 d (PC, J_{PC} 160), 119.9 s, 126.3 s, 127.6 s, 129.5 s, 140.8 s, 143 s (C_6H_5). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 20.34. Found, %: C 64.15; H 6.02; P 9.73. $C_{17}H_{19}O_4P$. Calculated, %: C 64.15; H 6.02; P 9.73.

Diethyl (2*E*,4*E*)-1-hydroxy-1,5-dimethyl-7-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2,4-heptadienylphosphonate (XIX). The product was purified by column chromatography on silica gel (eluent ethyl acetate–hexane, 1:1), R_f 0.3 (hexane–ethyl acetate, 2:1). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.8 m (3H, CH_3), 0.9 m (3H, CH_3), 1.32 t (6H, CH_3CH_2), 1.5 s (3H, CH_3), 1.6 s (3H, CH_3), 1.4–1.9 m (13H, CH_2), 2.25 d (3H, CH_3), 4.17 d.q (4H, CH_2O, *J* 7, *J* 8), 5.7 d.d (1H, *J* 4.5, *J* 16), 5.9 d.d (1H, CH=C, *J* 10.5, *J* 13.5), 6.65 d.d.d (1H, CH=C, *J* 4.5, *J* 10.5, *J* 15). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 24.5. Found, %: C 66.00; H 9.55; P 7.41. $C_{22}H_{39}O_4P$. Calculated, %: C 66.30; H 9.86; P 7.77.

Diethyl 1-hydroxycyclohexylphosphonate (XX). A mixture of 1 g of cyclohexanol, 2.25 g of triethyl phosphite and 1.6 g of pyridinium bromide was dissolved in 3 ml of methylene chloride and was stirred for 6 h at 40°C. Then the solvent was evaporated and the residue was dissolved in 5 ml of ether, the solution was filtered, evaporated, and the residue was distilled in a vacuum. Yield 80%, bp 120°C (0.1 mm Hg). The product was recrystallized from hexane cooled to 0°C. Prisms, mp 61–63°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.3 t (6H, CH_3CH_2, *J* 7.2), 1.52 m (2H, CH_2), 1.66 m (4H, CH_2), 1.87 m (4H, CH_2), 3.6 br (1H, OH), 4.16 d.q (4H, OCH_2, *J* 7, *J* 8). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.93. Found, %: C 50.62; H 8.91; P 13.09. $C_{10}H_{21}O_4P$. Calculated, %: C 50.84; H 8.96; P 13.11.

Diethyl 4-hydroxy-2,2-dimethyltetrahydro(2*H*)-pyran-4-ylphosphonate (XXI). The product was purified by vacuum distillation or by crystallization from hexane cooled to 0°C. Yield 80%, bp 130–135°C (0.08 mm Hg), mp 72–75°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 [3H, $(CH_3)_2C$], 1.43 s [3H, $(CH_3)_2C$], 1.64–1.9 m (4H, CH_2) , 3.65 m (2H, CH_2O), 3.95 br (1H, OH), 3.65 m (1H, CH_2), 4.05 m (1H, CH_2), 4.15 d.q (4H, CH_3CH_2O, *J* 7, *J* 8). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.45 s (CH_3CH_2), 24.29 s (CH_2), 31.09 s (CH_3), 32.61 s (CH_3), 39.87 s (CH_2), 56.1 d ($PCCH_2$, *J* 12.5), 62.8 d (OCH_2, *J* 8.5), 63.0 d (CH_2, *J* 7.5), 70 d (PC, *J* 183.5), 70.57 s (CMe_2). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 23.6. Found, %: P 11.63. $C_{11}H_{23}O_5P$. Calculated, %: P 11.63.

Diethyl (6*E*)-3,7-dimethyl-1-oxo-6-octenylphosphonate (XXIII). To a solution of 0.5 ml of oxalyl chloride in 10 ml of anhydrous dichloromethane at –60°C was added 0.9 ml of DMSO in 2 ml of dichloromethane and then a solution of 1.4 ml of

hydroxyphosphonate **IX** in 4 ml of dichloromethane was added at the same temperature. After 15 min, 3.5 ml of triethylamine was added at –50°C. The mixture was stirred for 5 min, heated to room temperature, and poured into 35 ml of ice water. The water layer was separated and extracted with 2 × 10 ml of dichloromethane. The solution was dried over magnesium sulfate, then the solvent was evaporated, and the residue was distilled in a vacuum. Yield 70%, bp 115°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 m (3H, CH_3), 0.91 d (CH_3CH, *J* 7), 1.37 t (CH_3CH_2, *J* 7), 1.58 s (3H, CH_3C =), 1.66 s (3H, CH_3C =), 1.97 m (2H, CH_2), 2.14 m (2H, CH_2), 2.6–2.8 m (2H, CH_2C=O), 4.21 m (4H, OCH_2), 6.06 t (2H, CH=C, *J* 6.5). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: –1.96. Found, %: P 10.76. $C_{14}H_{27}O_4P$. Calculated, %: P 10.67.

Diethyl (2*E*)-3,7-dimethyl-1-oxo-2,6-octadienylphosphonate (XXIV). Prepared similarly to compound **XXVIII**. Yield 70%, bp 115°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 m (3H, CH_3), 1.24 s (3H, CH_3C=), 1.29 s (3H, CH_3C=), 1.31 m (6H, CH_3CH_2O, J_{HH} 7), 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_P, 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 (XXV). Yield 60%, bp 145°C (0.1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.6 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.69 d (3H, CH_3C=, *J* 1.5), 1.71 d (3H, CH_3C=, *J* 1.5), 2.1 m (6H, CH_2), 2.25 m (2H, CH_2), 3,75 d (3H, CH_3O, J_{HP} 10), 3.8 d (3H, CH_3O, J_{HP} 10), , 5.1 br (1H, CH=C), 5.5 br (2H, CH=C). ^{31}P NMR spectrum ($CDCl_3$), δ_P, 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.

Diethyl [(1,2,3,4,5,6,7,8-octahydro-3,8,8-trimethyl-2-naphthyl)carbonyl] phosphonate (XXVI). Yield 60%, bp 150°C (0.1 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 d (CH_3, *J* 6.5), 1.36 t (CH_3, *J* 7.2), 1.58 s [3H, $(CH_3)_2C$], 1.67 s [3H, $(CH_3)_2C$], 1.93 m (2H, CH_2), 2.04 m (2H, CH_2), 2.31 m (1H, CH), 3.01 m (1H, CHC=O), 4.2 m (OCH_2). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: –2.54. Found, %: C 63.35; H 9.09; P 9.15. $C_{18}H_{31}O_4P$. Calculated, %: C 63.14; H 9.13; P 9.05.

The general method for the synthesis of bisphosphonohydroxyalkanes (XXVII–XXXI). A mixture of 0.01 mol of a ketophosphonate, 0.01 mol of trialkyl phosphate, and 0.01 mol of pyridinium iodide in 3 ml of methylene chloride was stirred for the time specified in Table 2. Then the solvent was evaporated and the residue was dissolved in 5 ml of ether (or THF), the solution was filtered, evaporated, and the residue was purified by column chromatography or distilled in a vacuum. Yields are listed in Table 2.

1,1-Bis(dietoxyphosphoryl)-1-hydroxyetane (ethyl etidronate) (XXVII). Compound was purified by distillation in a vacuum. Yield 65%, bp 160°C (0.08 mm Hg), which corresponds to the data of the previously described compound [37]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1,32 t (12H, CH_3CH_2, *J* 7), 1.56 t (3H, CH_3CP, *J* 16), 4.16 m (8H, OCH_2) 4 br (1H, OH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 20.3. Found, %: C 37.62; H 7.55. $C_{10}H_{24}O_7P_2$. Calculated, %: C 37.74; H 7.60.

1,1-Bis(dietoxyphosphoryl)-(2*E*)-1-hydroxy-3,7-dimethyl-2,6-octadiene (XXVIII). The product was purified by column chromatography on silica gel, yield 65%, oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27 t (6H, CH_3, *J* 7), 1.28 t (6H, CH_3, *J* 7), 1.6 s (3H, CH_3), 1.63 s (3H, CH_3), 1.8 d (3H, CH_3 , J_{HH} 8), 2.0 m (4H, CH_2), 4.21 m (8H, OCH_2), 4.8 m (1H, CH=), 5.1 m (1H, CH=, J_{HH} 7). ^{31}P NMR spectrum ($CDCl_3$), δ_P, 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(dietoxyphosphoryl)-1-hydroxy-(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatriene (XXIX). Purified by column chromatography (eluent hexane–ethyl acetate, 3:1). Yield 60%. ^{1}H NMR spectrum ($CDCl_3$), ppm (*J*, Hz): 1.6 s (3H, CH_3), 1.69 s (3H, CH_3), 1.8 d.d (3H, J_{HP} 8, J_{HH} 7), 2.0 m (4H, CH_2), 3,75 d (3H, CH_3O, J_{HP} 10), 3.8 d (3H, CH_3O, J_{HP} 10), 4.8 m (2H, CH=), 5.1 m (1H, CH=). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 23. Found, %: P 14.60. $C_{18}H_{34}O_7P_2$. Calculated, %: P 14.60.

Bis(diethylphosphoryl)hydroxy(3,5,5-trimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthyl)methane (XXX). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 23. Found, %: P 14.60. $C_{22}H_{42}O_7P_2$. Calculated, %: P 12.89.

1,1-Bis(dietoxyphosphoryl)-(6*E*)-1-hydroxy-3,7-dimethyl-6-octene (XXXI). The product was purified by chromatography on silica gel column. Yield 65%, oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.02 d (3H, *J* 4), 1.34 m (12H, CH_3CH_2), 1.59 s (3H, CH_3C=),

1.66 s (3H, CH_3C=), 2.0 m (4H, CH_2), 4.23 m (8H, OCH_2), 5.1 m (CHC=, *J* 7). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 20.6. Found, %: C 50.45; H 8.41; P 14.50. $C_{18}H_{38}O_7P_2$. Calculated, %: C 50.46; H 8.94; P 14.46.

Diethyl phenyl(benzylamino)methylphosphonate (XXXII). To the cooled to 0°C solution of 0.01 mol of trialkyl phosphite and 0.01 mol of Schiff base in 3 ml of methylene chloride was added at stirring 0.01 mol of pyridinium bromide. The mixture was stirred at 0°C for 30 min, then heated to room temperature and left at stirring for 12 h, then filtered, the solvent was evaporated, and the residue was dissolved in hexane, filtered, again evaporated, and distilled in a vacuum. Yield 70%, bp 150°C (0.08 mm Hg). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 24 [38].

Dimethyl phenyl[(1-methylbenzyl)amino]methylphosphonate (XXXIII). Prepared similarly to compound **XXX**. Yield 70%, mp 60°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.4 d (3H, CH_3, *J* 7), 3.51 m (1H, NH), 3.79 d (3H, CH_3, *J* 11.8), 3.83 d (3H, CH_3, *J* 10.1), 5.2 d (1H, PCH, *J* 24), 6.8–7.28 m (5H, C_6H_5), 7.3 d (2H, *J* 8.5), 7.5 d (2H, C_6H_5, *J* 8.5) . ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16 d (CH_3), 56.1 q (OCH_3, $^2J_{PC}$ 7.0), 56.2 d (OCH_3, $^2J_{PC}$ 6.8), 57.2 d (CH, $^1J_{PC}$ 150), 114.3 s (CH), 120.0 s (CH), 128.2 d (CH, $^3J_{PC}$ 5.8), 128.4 d (CH, $^3J_{PC}$ 3.1), 130.1 s (CH), 131.2 s, 140.0 s, 146.6 d ($^2J_{PC}$ 14.5) . ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 24, which corresponds to the previously described compound [27].

Diethyl (2*E*)-1-phenylamino-3,7-dimethylocta-2,6-dienylphosphonate (XXXIV). Purified by column chromatography on silica gel. Oil, yield 50%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27–1.17 m (6H, CH_3), 1.49 s (3H, CH_3), 1.54 s (3H, CH_3), 1.61 s (3H, CH_3), 1.72–1.71 m (2H), 2.06–1.97 m (2H), 4.15–3.97 m (4H, CH_2), 4.38 d.d (1H, PCH, $^2J_{PH}$ 20.7, $^3J_{HH}$ 9.4), 4.95–5.12 m (2H, C=CH), 7.13–6.54 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.4, 16.5, 17.1, 17.7, 25.6, 26.2, 39.6, 50.6 d (CP, $^1J_{PC}$ 158.5), 62.8 d (OCH_2CH_3, $^2J_{PC}$ 7.3), 63.1 d (OCH_2CH_3, $^2J_{PC}$ 6.6), 113.9, 118.4, 119.9, 123.6, 129.1, 131.8, 141.6, 146.8 (C_6H_5). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 28.4. Found, %: N 3.72; P 8.48. $C_{20}H_{32}NO_3P$. Calculated, %: N 3.83; P 8.48.

Diethyl 1-phenylaminocyclohexylphosphonate (XXXV). Synthesized like compound **XXXII**. Yield 60%, mp 100°C (published: 93–95°C) [39]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.07 t (6H, OCH_2Me, J_{HH} 7.0), 1.33–1.46 m (C_6H_4), 1.59–2.10 m (6H), 3.86–3.93 m (4H, OCH_2CH_3), 5.38 br (1H, NH), 6.63 t (1H, ArH, *J* 7.1), 6.86 d (2H, ArH, *J* 8.1), 6.99 m (2H, ArH, *J* 8.1). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 31. Found, %: N 4.56; P 9.85. $C_{16}H_{26}NO_3P$. Calculated, %: N 4.50; P 9.95.

Diethyl 2-nitro-1-phenylethylphosphonate (XXXVI). To a solution of 0.01 mol of triethyl phosphite and 0.01 mol of nitrostyrene in 3 ml of methylene chloride cooled to 0°C was added at stirring 0.01 mol of pyridinium bromide. Stirring at 0°C was continued for 30 min, then the mixture was heated to room temperature and stirred for 6 h. Certain amount of precipitate formed and was filtered off, from the filtrate the solvent was evaporated, and the residue was recrystallized from acetonitrile. Yield 70%, mp 65°C (hexane). Found, %: P 10.78. $C_{12}H_{18}NO_5P$. Calculated, %: P 10.78 [29].

Dimenthyl (2-nitro-1-phenyl)ethylphosphonate (XXXVII). Prepared similarly. Yield 65%, mp. 140°C, $[\alpha]_D$ –68 (*c* 1, C_6H_6). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 19.6, which corresponds to the previously described compound [30].

Diethyl (propylamino)carbonylphosphonate (XXXVIII). A mixture of 0.01 mol of triethyl phosphite, 0.01 mol propyl isocyanate, and 0.01 mol of pyridinium bromide was left standing for 2 h. After 2 h the reaction mixture was diluted with ether and filtered. The solvent was evaporated, the residue was distilled in a vacuum. Yield 90%, bp 100–110°C (0.08 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 t (3H, CH_3, *J* 7.5), 1.3 t (6H, CH_3CH_2O, *J* 7), 1.51 m (2H, $CH_3CH_2CH_2$), 3.2 q (4H, NCH_2, *J* 7), 4.15 m (4H, CH_2O), 7.34 m (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 11.2 d (*C*CC, *J* 8), 16.15 d (CH_3CO, *J* 15), 22.6 s (C*C*CN), 40.98 s (CN), 64.15 d (OC, *J* 8), 165 d (PC, J_{PC} 221). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: –0.71. Found, %: N 6.28; P 13.88. $C_8H_{18}NO_4P$. Calculated, %: N 6.28; P 13.88.

Diethyl (allylamino)thiocarbonylphosphonate (XXXIX). Prepared like compound **XXXV**. Yield 80%, bp 120°C (0.08 mm Hg). Yellowish liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 t (6H, CH_3CH_2), 4.08–4.3 m (6H, OCH_2+NCH_2), 5.27 d.d (1H, C=CH_2, *J* 6, *J* 1), 5.31 d.d (1H, C=CH_2, *J* 12.5, *J* 1), 5.91 d.d.t (1H, CH_2CH=C, *J* 17, *J* 10.2, *J* 6), 9.27 br (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.24 d (CCO, *J* 10), 42.4 d (CN, *J* 9), 63 d (POC, *J* 6), 119 s (C=CH), 130.7 s (CH_2=C), 193 d

(PC, *J* 155). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: –1.7. Found, %: N 5.88; P 13.37. $C_8H_{16}NO_3PS$. Calculated, %: N 5.90; P 13.05.

Diethyl phenylaminothiocarbonylphosphonate (XL). Yield 90%, bp 160°C (0.1 mm Hg), yellow liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 t (6H, CH_3, *J* 7), 4.27 d.q (CH_2, *J* 7, *J* 8), 7.28–7.96 m (5H, C_6H_5), 10.86 br (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 15.7 d (CH_3C, *J* 7), 61.3 d (CH_2O, *J* 5), 123.9 s, 127.1 s, 131 s, 140.1 s (C_6H_5), 154.5 d (PC, *J* 90). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: –2.07. Found, %: N 5.11; P 11.30. $C_{11}H_{16}NO_3PS$. Calculated, %: N 5.13; P 11.33.

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