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ω-Haloalkylphosphoryl Compounds: Synthesis and Properties

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Abstract—A general method of the synthesis of ω-haloalkylphosphoryl compounds was developed, a series of compounds of phosphonic and phosphine oxide type were synthesized. The ability of some ω-haloalkylphosphonates to undergo intramolecular cyclization into the corresponding 1,2-oxaphospholane and 1,2-oxaphosphorine was investigated depending on the solvent polarity, the presence of halogen ions in the solution, and temperature. Tetrahydrofuran was chosen as one of the most suitable solvents for the alkylation of CH acids with ω-haloalkylphosphoryl compounds.

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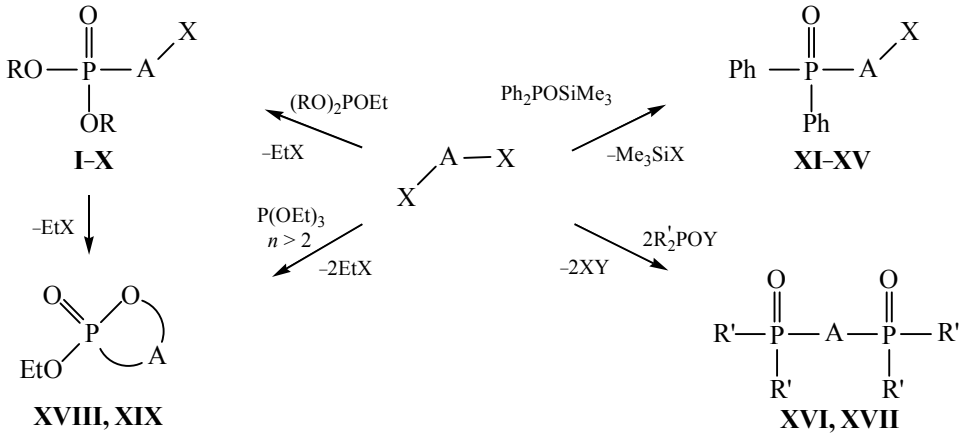
Phosphorylation of organic compounds is a usual method of constructing a molecule of potential physiologically active structural isostere of a natural molecule. Direct phosphorylation is sometimes difficult for various electronic or steric reasons. An alternative way to solve this problem may be a synthesis of some intermediate compounds containing phosphoryl moiety and capable to functionalize the substrate molecule, for example, the synthesis of ω-haloalkylphosphoryl compounds.

In this regard, the search of a convenient method of synthesis of ω-haloalkylphosphoryl compounds as alkylating agents for the introduction of phosphorus fragment into molecules of various compounds containing diverse nucleophilic "coupling sites" is relevant. Moreover, the problem of synthesis of ω-haloalkylphosphoryl compounds is defined by the interest to some physiologically active compounds, the phosphonic analogs of glutamic and aspartic acids, which are ligands in the glutamate receptors that are involved in the transmission and processing information by the central nervous system [1–4]. 2-Amino-5-phosphonovaleric (AR5), 2-amino-7-phosphonoheptanoic (AR7), and 4-(3-phosphonopropyl)-piperazine-2-carboxylic (CPP) acids are selective antagonists of *N*-methyl-D-aspartate receptors and possess antiepileptic, anti-ischemic, and other useful properties [2–6]. The synthesis of these compounds and a number of structural analogs of natural amino acids is based on the use of ω-haloalkylphosphonates as the key intermediates.

The synthetic approaches to the ω-haloalkylphosphoryl compounds have been considered in the pioneering work by Kosolapov dedicated to the synthesis of diethyl 2-bromoethylphosphonic acid by the reaction of triethyl phosphite with 1,2-dibromoethane at a 4-fold excess of the latter [7]. However, he reported that this procedure does not allow synthesizing its analog, the diethyl ester of 3-bromopropylphosphonic acid. The hydrolysis with hydrobromic acid of the residue in the reaction mixture after removal of the unreacted 1,3-dibromopropane gave 3-bromopropylphosphonic acid [8]. On the basis of further research, we can explain now this fact by the formation of cyclic product, 1,2-oxaphospholane. The hydrolysis of the latter with hydrobromic acid also leads to 3-bromopropylphosphonic acid. Pudovik and coworkers [9] were first who observed the formation of cyclic 1,2-oxaphosphoryl compounds, isolated and characterized them. However, these studies did not lead to a method of synthesis of ω-haloalkylphosphoryl compounds.

More recent publications on the synthesis of ω-haloalkylphosphonates resulted from the interest in the ω-phosphonic acid analogs of monoaminodicarboxylic acids [10–13]. In [10] a method was described of the synthesis of 2-amino-5-phosphonovaleric acid (AR5) using diethyl 3-bromopropylphosphonate, which was obtained by heating triethyl phosphite with 20-fold excess of 1,3-dibromopropane. But the subsequent alkylation of acetamidomalonic ester in toluene or diethyl carbonate resulted only in 25% yield of the

Scheme 1.



X = Br, Cl; R = Et, Ph; Y = Et, $SiMe_3$; R' = EtO, Ph; A = $(CH_2)_n$, n = 2–6; *o*-$CH_2C_6H_4CH_2$, *p*-$CH_2C_6H_4CH_2$; $CH_2CH{=}CHCH_2$; $CH_2CH_2OCH_2CH_2$.

desired product, due to the secondary processes [10]. Later on a method was suggested for the synthesis of diethyl 3-bromopropylphosphonate from 3-bromopropyl alcohol with pre-protection of the alcohol group and the subsequent phosphorylation, removal of tetrahydropyranyl protection, and bromination [11].

We report here on a simple and general method of the synthesis of ω-haloalkylphosphoryl compounds by gradual adding the corresponding ester of trivalent phosphorus to the α,ω-dihaloalkane pre-heated to the boiling point [12, 13]. In this case, a sufficiently large excess of α,ω-dihalide with respect to the phosphoric component appears under the conditions similar to those required for the formation of phosphorus–carbon bond, while the side reactions are minimized. Therefore, the ω-haloalkylphosphoryl compounds of phosphonic (**IX**) and phosphine oxide (**XI–XV**) series were synthesized with good or satisfactory yields (Scheme 1).

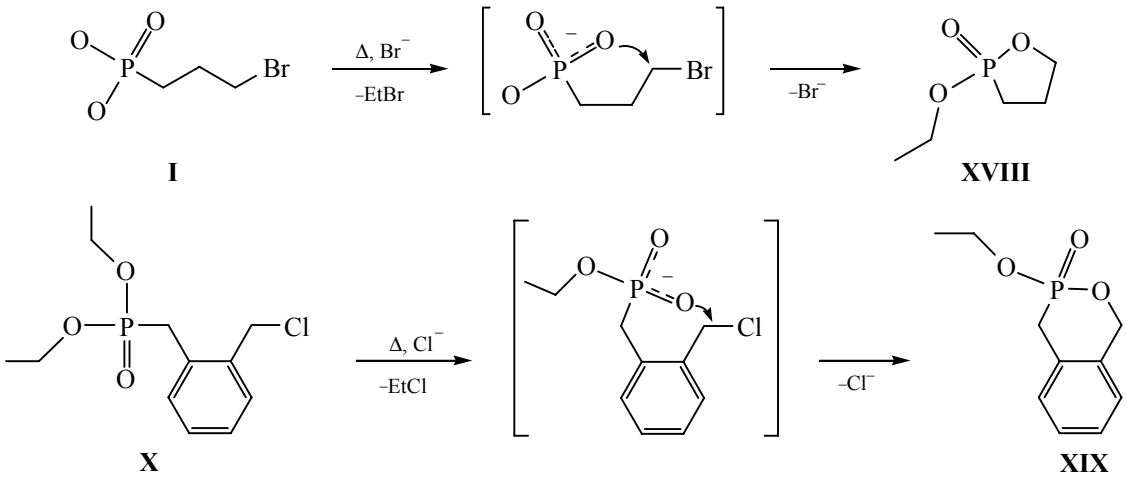
The expected by-products in the reaction of trivalent phosphorus with α,ω-dihaloalkanes are α,ω-alkylene-bisphosphorylated compounds **XVI, XVII** (Scheme 1). The procedure with the gradual addition of phosphoric components to the pre-heated dihalides creates a large excess of the latter over the trivalent phosphorus compound at the moment of the addition and provides a rapid transformation of this reagent into the target ω-haloalkylphosphoryl compound. Therefore, the reaction conditions (temperature, solvent, or the absence of the latter) must comply with the reactivity of dihalide and phosphorus components to provide their interaction according to the Arbuzov reaction. This technique minimizes the formation of the products of bis-phosphorylation, which were detected at the synthesis of ω-halophosphoryl compounds of phosphonic and phosphine oxide types. In some cases, the α,ω-alkylenebisphosphoryl compounds **XVI, XVII** were isolated and characterized.

Further investigation of the conditions of the synthesis of phosphorus-containing target phosphonic halides of **I–IX** type, as well as their use as alkylating agents [13], showed, however, that in addition to the products of bis-phosphorylation, the formation of by-products of cyclic structure **XVIII, XIX** (Scheme 1) was possible depending on the reaction conditions. This is consistent with the results of [9]. We succeeded to show that these substances were five- and six-membered cyclic compounds formed by intramolecular cyclization of the ω-haloalkylphosphonates containing a halogen atom in the third or fourth position with respect to the phosphoryl fragment. The driving force is likely to be the energy gain in the formation of five- and six-membered rings.

Our study showed that ω-haloalkylphosphonates, 3-bromopropylphosphonate **I** and *o*-chloromethylbenzylphosphonate **X** in particular, fairly easily underwent intramolecular cyclization to give 2-oxo-2-ethoxy-1,2-oxaphospholane **XVIII** [9] and 2-oxo-2-ethoxy-4,5-benzo-1,2-oxaphosphorinane **XIX**, respectively, which were isolated and characterized.

The ability of 3-bromopropylphosphonate **I** to undergo intramolecular cyclization into 1,2-oxaphospholane **XVIII** was greater compared with the other ω-haloalkylphosphonates that led to a marked reduction

Scheme 2.



in the yield of desired products in alkylation reactions of CH acids, for example, reduced the overall yield of 2-amino-5-phosphonovaleric acid (AR5) [10]. We investigated the properties of 3-bromopropylphosphonate **I** in various solvents, as well as under different conditions of alkylation. This allowed us the development of a more efficient use of this alkylating agent. We did not study the 4-brombutylphosphonate **III**, which apparently was capable of cyclization to form similar six-membered 1,2-oxaphosphorine.

Our study showed that 3-bromopropylphosphonate **I** undergoes cyclization with the release of ethyl bromide and the formation of 1,2-oxaphospholane **XVIII** when heated in a polar solvents like dimethylformamide. In the less polar but rather high boiling solvents, for example, in toluene, this process is much slower.

In addition, we found that the chemical shift of diethyl 3-bromopropylphosphonate **I** in the ^{31}P NMR spectrum increased with increasing solvent polarity. In turn, in ^{1}H and ^{13}C NMR spectra we registered a downfield shift of the signals of proton in $BrCH_2$ fragment and C^3–Br carbon, respectively, as a function of solvent polarity (Table 1).

Table 1. Chemical shifts (ppm) in the ^{1}H, ^{13}C, and ^{31}P NMR spectra of diethyl 3-bromopropylphosphonate I, depending on the solvent

δ, ppm	C_6D_6	$CDCl_3$	$(CD_3)_2S(O)$
δ_P	30.3	31.1	31.4
δ_H, CH_2Br, t	3.00	3.48	3.60
δ_C, C^3Br, d ($^3J_{PC}$ Hz)	–	26.1 (4.1)	26.9[a] (4.1)

[a] Solvent CD_3CN.

These data can be attributed to the fact that with the increasing solvent polarity the C^3–Br bond polarization increases creating more favorable conditions for the attack of the electrophilic C^3 carbon atom in 3-bromopropylphosphonate **I** by the oxygen of the phosphoryl group with the subsequent formation of the energy favorable five-membered 1,2-oxaphospholane ring.

Perhaps, under the conditions of alkylation of CH acids the attacking center is the negatively charged oxygen atom at the phosphorus atom that forms as a result of the dealkylation of P–O–C ester fragment formed in the process of alkylation with the halide ion (Scheme 2).

The modeling of the alkylation conditions confirmed that in the process of cyclization a very significant factor is the presence in the solution of a halide ion. Study of the behavior of 3-bromopropylphosphonate **I** in various solvents revealed the great influence of the halide ion (sodium chloride or bromide) on the process of cyclization of bromide **I** to form 1,2-oxaphospholane **XVIII**. Probably the halide ion dealkylates the ester P–O–C bond "provoking" the attack of the charged oxygen atom on the most electrophilic third carbon atom (C^3–Br) of the bromide **I** with the subsequent formation of the ester oxygen–carbon bond in the thermodynamically favorable five-membered ring. The study showed that the effect of halide ions is more pronounced with increasing temperature and solvent polarity (see below the procedure of isolation of the cyclic product).

A similar process of intramolecular cyclization to form six-membered ring **XIX** was found in *o*-chloromethylbenzylphosphonate **X** (Scheme 2), both at the synthesis of the latter, and as a result of alkylation with it of acetamidomalonic ester in dimethylformamide. The greatest tendency to cyclization in the series of ω-haloalkylphosphonates exhibited 3-bromopropylphosphonate **I** and *o*-chloromethylbenzylphosphonate **X** in solutions of dimethylformamide in the presence of sodium halides. The presence of the halide ions in the solutions was due to our attempt to simulate the conditions of alkylation of CH acids with ω-haloalkylphosphonates [13].

In order to compare with diethyl ester **I** we synthesized diphenyl 3-bromopropylphosphonate **VI**, which was not capable to suffer the dealkylation of the ester P–OPh group, and therefore, as expected, turned out to be a stable compound. This allows us to recommend the bromide **VI** as an alternative agent in similar alkylation reactions.

Our research on a number of solvents containing halide ions showed that the highest stability of bromide **I**, as well as chloride **X**, to the process of formation of the corresponding cyclic 1,2-oxaphosphoryl compounds **XVIII** and **XIX**, respectively, was found at the use of tetrahydrofuran. Therefore, we recommend the tetrahydrofuran as a medium for the alkylation of CH acids with ω-haloalkylphosphonates as the most suitable solvent, which allows efficient use of alkylating properties of ω-haloalkylphosphonates and minimize or eliminate completely the process of secondary cyclization.

The considered method makes it possible to synthesize a variety of ω-haloalkylphosphoryl compounds with diverse modifications of both the hydrocarbon chain, and the phosphorus fragment of the molecule. The method is of the general nature, the developed synthesis procedure was used to obtain a number of ω-haloalkylphosphine oxides effective as alkylating agents, which might be used in the synthesis of potential complexing compounds [14].

The synthesis of ω-haloalkylphosphine oxides was performed in accordance with the same procedure, by adding the phosphoric component to the boiling α,ω-dihaloalkane. As a phosphoric component trimethylsilyl diphenylphosphinite $Ph_2POSiMe_3$ was used (Scheme 1) obtained preliminary by the reaction of diphenylphosphinic acid with hexamethyldisilazane. The use of the appropriate ethyl ester is less effective because of a slightly lower yield of the target phosphine oxide, as well as due to the easier synthesis of the initial phosphoric component $Ph_2POSiMe_3$.

The cyclization of target compounds similar to that observed for the series of phosphonic compounds is impossible in this case, so the only byproduct of the synthesis is the product of bis-phosphorylation, α,ω-alkylenebisphosphine oxide, whose formation was detected by TLC on Silufol, the R_f of bis-phosphine oxides was 0.10–0.15 (chloroform:acetone = 4: 1), while for the target ω-haloalkylphosphine oxides the R_f value was about 0.50 under the same conditions. The ^{31}P NMR method also revealed the formation of alkylenebisphosphine oxides (5 to 15%), however, these compounds usually were not isolated in the individual form.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were taken on a Bruker DPX-200 and a Bruker CXP-300 Fourier spectrometers with internal reference TMS and external reference 85% H_3PO_4. The melting points of compounds were determined on a Boëtius PHMK device or in a block in an open capillary. The solvents were carefully dried before use. The TLC analysis of individual compounds and the reaction mixtures was performed on Silufol, Alufol (Kavalier) (neutral alumina on aluminum foil), and Merck glass plates with a UV-254 silica gel layer thickness of 0.2 mm (eluent chloroform–acetone, 5–10:1.)

Hexamethyldisilazane, α,ω-dihaloalkanes, and triethyl phosphite were provided by Reakor (Alfa Aesar).

Synthesis of ω-haloalkylphosphoryl compounds consisted in a slow addition of the corresponding ester of trivalent phosphorus to the α,ω-dihaloalkane preheated to the boiling point. Below are some examples of the synthesis of ω-haloalkylphosphonates and phosphine oxides.

Diethyl 3-bromopropylphosphonate (I). To 3.30 g (0.15 mol) of freshly distilled 1,3-dibromopropane, pre-heated to boiling, was added slowly dropwise with stirring 8.3 g (0.05 mol) of triethyl phosphite within 0.5 h. By a vacuum distillation the unreacted excess (~19 g) of 1,3-dibromopropane and 10.0 g (76%) of bromide **I**, bp 77–80ºC (0.05 mm Hg) were isolated. ^1H NMR spectrum ($CDCl_3$, δ, ppm): 1.34 t (6H, $2CH_3$), 1.90 m (2H, CH_2P), 2.14 m (2H, CH_2), 3.48 t (2H, CH_2Br), 4.10 d.q (4H, $2CH_2OP$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 16.5 d (CH_3, $^3J_{PC}$ 5.4 Hz),

24.4 d (CH_2P, $^1J_{PC}$ 142.4 Hz), 26.1 d (CH_2Br, $^3J_{PC}$ 4.1 Hz), 33.5 d (CH_2C, $^2J_{PC}$ 19.0 Hz), 61.6 d (CH_2OP, $^2J_{PC}$ 5.4 Hz). ^{13}C NMR spectrum (CD_3CN, δ, ppm): 16.7 d (CH_3, $^3J_{PC}$ 5.4 Hz), 24.5 d (CH_2P, $^1J_{PC}$ 141.1 Hz), 26.9 d (CH_2Br, $^3J_{PC}$ 4.1 Hz), 34.8 d (CH_2C, $^2J_{PC}$ 19.0 Hz), 62.0 d (CH_2OP, $^2J_{PC}$ 6.8 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 31.0. Found, %: C 32.6, 32.8; H 6.0, 6.1; Br 29.9, 30.1; P 11.7, 11.8. $C_7H_{16}BrO_3P$. Calculated, %: C 32.5; H 6.2; Br 30.2; P 12.0.

At a ratio of reagents 1:1 the yield of bromide **I** is 55%, with a 5:1 excess of 1,3-dibromopropane the yield of **I** reaches 80%.

The synthesis of diethyl 2-bromethylphosphonate in accordance with this procedure is relatively less effective because of the lower boiling point of a mixture of 1,2-dibromoethane and triethyl phosphite, which is insufficient for complete proceeding of the reaction according to the scheme of Arbuzov rearrangement within 0.5 h. The increase in the yield is observed with the increase in the 1,2-dibromoethane excess and the total time of boiling the mixture.

Diethyl 3-chloropropylphosphonate (II). To 24.0 g (0.15 mol) of boiling 1-bromo-3-chloropropane while stirring was slowly added dropwise 8.3 g (0.05 mol) of triethyl phosphite within 1.5 h. By vacuum distillation the excess (~15 g) of 1-bromo-3-chloropropane was isolated, and by the distillation of the residue in a high vacuum 7.2 g (67.0%) of chloride **II** was isolated containing an impurity (5–10%) of bromide **I**. This sample can be used in all subsequent transformations. The repeated distillation provided 5.5 g (51.2%) of pure chloride **II** (Table 1).

Diethyl 4-bromobutylphosphonate (III). To 43.2 g (0.20 mol) of freshly distilled 1,4-dibromopropane, pre-heated to boiling, was added slowly dropwise 8.3 g (0.05 mol) of triethyl phosphite while stirring within 0.5 h. By vacuum distillation the unreacted excess (~19 g) of 1,4-dibromopropane and 10.1 g (70%) of bromide **III** were isolated. The ^1H NMR spectrum ($CDCl_3$, δ, ppm): 1.33 t (6H, $2CH_3$), 1.85 m (4H, $2CH_2$), 2.05 m (2H, CH_2), 3.43 t (2H, CH_2Br), 4.10 d.q (4H, $2CH_2OP$). The ^{13}C NMR spectrum (CD_3OD + CCl_4, δ, ppm): 15.1 d (CH_3, $^3J_{PC}$ 5.6 Hz), 19.8 d (CH_2, $^3J_{PC}$ 5.4 Hz), 23.3 d (CH_2P, $^1J_{PC}$ 141.2 Hz), 31.5 (CH_2), 31.7 d (CH_2, $^2J_{PC}$ 17.4 Hz), 60.0 d (CH_2OP, $^2J_{PC}$ 6.3 Hz). The ^{31}P NMR spectrum (CD_3OD + CCl_4, δ, ppm): 31.7.

Diethyl 5-bromopentylphosphonate **IV** and 6-bromohexylphosphonate **V** were synthesized similarly. The constants and analytical data of the ω-haloalkylphosphonates **I**–**V** are listed in Table 1. Below we list the ^1H, ^{13}C and ^{31}P NMR parameters of bromoalkylphosphonates **IV** and **V**.

Diethyl 5-bromopentylphosphonate (IV). ^1H NMR spectrum ($CDCl_3$, δ, ppm): 1.30 t (6H, $2CH_3$), 1.56 m (2H, CH_2), 1.65 m (2H, CH_2), 1.82 m (4H, $2CH_2$), 3.38 t (2H, CH_2Br), 4.08 d.q. (4H, $2CH_2OR$). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.6 d (CH_3, $^3J_{PC}$ 5.2 Hz), 20.8 d (CH_2, $^3J_{PC}$ 4.8 Hz), 24.5 d (CH_2R, $^1J_{PC}$ 141.0 Hz), 31.5 (CH_2), 28.0 d (CH_2 , $^2J_{PC}$ 16.3 Hz), 31.3 (CH_2), 32.4 (CH_2), 60.4 d (CH_2OR, $^2J_{PC}$ 6.3 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 32.4.

Diethyl 6-bromohexylphosphonate (V). ^1H NMR spectrum (CD_3OD + CCl_4, δ, ppm): 1.31 t (6H, $2CH_3$), 1.80 m (8H, $4CH_2$), 1.90 m (2H, CH_2), 3.35 t (2H, CH_2Br), 4.10 d.q (4H, $2CH_2OR$). ^{13}C NMR spectrum (CD_3OD + CCl_4, δ, ppm): 15.7 d (CH_3, $^3J_{PC}$ 5.4 Hz), 21.5 d (CH_2, $^3J_{PC}$ 4.5 Hz), 24.7 d (CH_2R, $^1J_{PC}$ 140.8 Hz), 26.8 (CH_2), 31.5 (CH_2), 28.8 d (CH_2, $^2J_{PC}$ 16.2 Hz), 31.6 (CH_2), 32.8 (CH_2), 60.5 d (CH_2OR, $^2J_{PC}$ 6.2 Hz). ^{31}P NMR spectrum (CD_3OD + CCl_4, δ, ppm): 32.8.

Diphenyl 3-bromopropylphosphonate (VI). To 157.1 g (0.78 mol) of boiling 1,3-dibromopropane was added slowly dropwise within 1.5 h 38.0 g (0.14 mol) of diphenyl ethyl phosphite, and the mixture was further stirred at reflux for 3 h. Then 1,3-dibromopropane excess (~120 g) was distilled off in vacuo, and the residue was distilled in a high vacuum. After a double vacuum distillation 32.2 g (62.5%) of the desired bromide **VI**, bp 175–180ºC (0.1 mm Hg) was isolated. Oil, n_D^{20} 1.5590. ^1H NMR spectrum ($CDCl_3$, δ, ppm): 2.15–2.45 m (4H, CH_2P + CH_2C), 3.52 t (2H, CH_2Br), 7.17 m (6H, arom.), 7.30 m (4H, arom.). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 24.6 d (CH_2R, $^1J_{PC}$ 142.4 Hz), 25.7 d (CH_2Br, $^3J_{PC}$ 4.1 Hz), 33.1 d (CH_2C, $^2J_{PC}$ 20.4 Hz), 120.4, 120.5, 125.2, 129.8 (2C), 150.1 d ($^2J_{PC}$ 9.5 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 24.5. Found, %: C 50.52, 50.55; H 4.58, 4.63; Br 22.50, 22.71; P 8.77, 8.80. $C_{15}H_{16}BrO_3P$. Calculated, %: C 50.73; H 4.54; Br 22.50; P 8.72.

Diethyl 3-oxa-5-bromopentylphosphonate (VII). To 41.1 g (0.27 mol) of freshly distilled β,β'-dibromodiethyl ether [bp 90–94ºC (11 mm Hg)] heated to 160–170ºC was slowly added dropwise 12.0 ml (0.07 mol) of triethyl phosphite within an hour. The reaction mixture was evacuated and 1.25 g of unreacted β,β'-dibromodiethyl ether was distilled off, the residue was distilled in a high vacuum. 10.8 g (53.4%).

Table 2. Yields and physicochemical characteristics of ω-haloalkylphosphonates $XAP(O)(OEt)_2$ (**I–V**)

Comp. no.	X	A	Yield, %	bp, °C (mm Hg)	d_4^{20}	n_D^{20}	MR_D, found	MR_D, calculated
I	Br	$(CH_2)_3$	76	77–80 (0.05)	1.3478	1.4616	52.69	52.90
II	Cl	$(CH_2)_3$	67(51[a])	82–84 (0.07)	1.1782	1.4585	49.79	50.03
III	Br	$(CH_2)_4$	70	86–88 (0.08)	1.2990	1.4611	57.80	57.50
IV	Br	$(CH_2)_5$	74	112–115 (0.08)	1.2826	1.4625	61.60	62.09
V	Br	$(CH_2)_6$	72	130–133 (0.10)	1.2659	1.4652	65.80	66.69

[a] Redistillation.

Table 3. Data of elemental analyses of compounds **I–V**

Comp. no.	Found, %				Formula	Calculated, %			
	C	H	P	Hlg		C	H	P	Hlg
I	32.7 32.3	6.1 6.2	11.9 11.7	29.6 29.9	$C_7H_{16}BrO_3P$	32.5	6.2	12.0	30.2
II	39.0 38.9	7.9 8.0	14.7 14.8	16.1 16.2	$C_7H_{16}ClO_3P$	39.2	7.5	14.4	16.5
III	35.4 35.3	6.3 6.5	11.0 11.2	29.0 29.2	$C_8H_{18}BrO_3P$	35.2	6.6	11.3	29.3
IV	38.0 37.9	6.8 6.9	10.4 10.5	27.4 27.7	$C_9H_{20}BrO_3P$	37.7	7.0	10.8	27.8
V	40.1 39.8	7.0 7.2	10.2 10.4	26.3 26.4	$C_{10}H_{22}BrO_3P$	39.9	7.4	10.3	26.5

of compound **VII** was isolated, bp 135–138ºC (0.1 mm Hg), n_D^{20} 1.4630. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.34 t (6H, $2CH_3$), 2.13 d.t (2H, CH_2P, $^2J_{PH}$ 20.0 Hz), 3.46 t (2H, CH_2Br), 3.71 t (2H, CH_2OC), 3.75 d.t (2H, CH_2OC, $^3J_{PH}$ 2.0 Hz), 4.09 d.q (4H, $2CH_2OP$, $^3J_{PH}$ 2.0 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 28.6. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.2 d (CH_3, $^3J_{PC}$ 5.6 Hz), 25.7 d (CH_2P, $^1J_{PC}$ 139.5 Hz), 29.2 (CH_2Br), 60.3 d (CH_2OP, $^2J_{PC}$ 5.8 Hz), 63.7 ($O\underline{C}H_2CH_2Br$), 69.5 ($\underline{C}H_2CH_2P$). Found, %: C 32.97, 33.18; H 6.30, 6.37; Br 27.90, 27.77; P 10.73, 10.80. $C_8H_{18}BrO_4P$. Calculated, %: C 33.24; H 6.28; Br 27.64; P 10.71.

Below are examples of modification of the general method of synthesis, for example, the use of solvents in the reaction of phosphite with α,ω-alkylene-dihalides, and chromatographic separation of the reaction products.

Diethyl 4-bromo-2-butenylphosphonate (VIII). To a stirred solution of 4.21 g (0.10 mol) g of 1,4-dibromo-2-butene in 20 ml of boiling benzene or toluene was added dropwise 6.8 ml (0.04 mol) of triethyl phosphite within 1.0–1.5 h. The reaction mixture was stirred for additional 0.5 hour at reflux, cooled, and evaporated in vacuo, and the residue was chromatographed on silica gel, eluent hexane, chloroform–hexane mixture, 1:1. The yield of bromide **VIII** 8.2 g (76%), n_D^{20} 1.4800. The TLC (chloroform–acetone, 5:1), R_f 0.5 (Silufol). ^{1}H NMR spectrum ($CDCl_3$), 1.30 t (6H, CH_3), 2.63 d.d (2H, CH_2P, $^2J_{PH}$ 24Hz), 3.96 d.d (2H, CH_2), 4.08 d.q (4H, CH_2O), 5.82 m (2H, 2CH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 26.6 (*E*-isomer, 95%), 26.3 (*Z*-isomer, 5%). Found, %: C 35.26, 35.00; H 5.70, 6.18, Br 29.13, 29.48, P 11.55, 11.70. $C_8H_{16}BrO_3P$. Calculated, %: C 35.44; H 5.95, Br 29.48, P 11.43. Using chloroform as eluent, 0.4 g of **bis-phosphorylation compound, 1,4-bis(diethoxyphosphinyl)-2-butene XVI**, oil was isolated. The TLC (chloroform–acetone, 5:1), R_f 0.1 (Silufol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (12H, CH_3), 2.65 d.d (4H, CH_2P, $^2J_{PH}$ 22.5 Hz), 4.10 d.q (8H, CH_2O), 5.60 m (2H, 2CH). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 27.3 (*E*-isomer, ~95%), 27.5 (*Z*-isomer, ~5%).

Diethyl *p*-chloromethylbenzylphosphonate (IX). To a boiling solution–melt of 5.3 g (0.03 mol) of *p*-xylylene dichloride in 3 ml of anhydrous benzene or toluene was slowly added dropwise 1.7 ml (0.01mol) of triethyl phosphite within 1.0–1.5 h, and the reaction mixture was stirred at reflux for additional 0.5 h. TLC analysis (chloroform–acetone, 5:1) of the reaction mixture showed the presence of unreacted initial dichloride (R_f 0.95–1.0), *p*-xylylenediphosphonate (R_f ~0.2), and target chloride **IX** (R_f 0.65–0.70). The reaction mixture was evaporated in a vacuum and the residue was chromatographed on 75 ml column with silica gel of "Silpearle" grade, using as eluents chloroform–hexane (1:1), chloroform. 3.3 g of *p*-xylylendichloride was isolated, then using as eluent a mixture of chloroform and 3% of isopropanol *p*-chloromethylbenzylphosphonate **IX** was isolated. Yield 2.3 g (85.2%), oil, n_D^{20} 1.5055. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.22 t (6H, $2CH_3$), 3.15 d (2H, CH_2P, $^2J_{PH}$ 22.0 Hz), 4.00 d.q (4H, CH_2O), 4.53 s (2H, CH_2Cl), 7.28 m (4H, C_6H_4). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 26.6. Found, %: C 51.87, 51.83; H 6.71, 6.67; Cl 12.90, 13.01; P 11.27, 11.08. $C_{12}H_{18}ClO_3P$. Calculated, %: C 52.09; H 6.56; Cl 12.81; P 11.19. The by-product *p*-xylylenebisphosphonate was not isolated.

Diethyl *o*-chloromethylbenzylphosphonate (X). To a boiling solution of 30.0 g (0.17 mol) of *o*-xylylene dichloride in 30 ml of anhydrous toluene was slowly added dropwise 10.3 ml (0.06 mol) of triethyl phosphite within 1 h. The reaction mixture was further refluxed with stirring for 10 min and evaporated in vacuo, the residue was chromatographed on 240 ml column with the "Silpearle" silica gel. With eluent hexane–chloroform (3:1) 4.15 g of unreacted *o*-xylylene dichloride was isolated, then eluting with a mixture of hexane–chloroform (1:1) gave 8.2 g (53.0%) of ***o*-chloromethylbenzylphosphonate X**, oil, n_D^{20} 1.5165, R_f 0.7 (chloroform–acetone, 4:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.20 t (6H, $2CH_3$), 3.30 d (2H, CH_2P, $^2J_{PH}$ 21.2 Hz), 4.00 d.q (4H, CH_2O), 4.80 s (2H, CH_2Cl), 7.30 m (4H, arom.). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 16.0 d (CH_3, $^3J_{PC}$ 6.2 Hz), 30.2 d (CH_2P, $^1J_{PC}$ 138.0 Hz), 44.2 d (CH_2Cl), 61.8 d (CH_2O, $^2J_{PC}$ 7.0 Hz), 127.1 d ($^4J_{PC}$ 3.3 Hz), 128.5 d ($^4J_{PC}$ 3.3 Hz), 130.1 d ($^5J_{PC}$ 2.9 Hz), 130.5 d ($^2J_{PC}$ 9.5 Hz), 131.2 d ($^3J_{PC}$ 5.5 Hz), 136.0 d ($^3J_{PC}$ 6.2 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 26.1. Found, %: C 52.15, 52.23; H 6.51, 6.49; Cl 12.67, 12.77; P 11.05, 11.12. $C_{12}H_{18}ClO_3P$. Calculated, %: C 52.09; H 6.56; Cl 12.81; P 11.19.

Further chromatography with eluent hexane–chloroform, 1:1, furnished 2.7 g (21.3%) of **2-oxo-2-ethoxy-4,5-benzo-1,2-oxaphosphorine XIX**, oil, n_D^{20} 1.5375. R_f 0.33 (chloroform–acetone, 4:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.28 t (3H, CH_3), 3.17 d (1H, one of CH_2R, $^2J_{PH}$ 16.0 Hz), 3.20 d (1H, the second of CH_2R, $^2J_{PH}$ 18.0 Hz), 4.12 m (2H, $POCH_2$), 5.24 d (1H, one of $ROCH_2C$ (arom.), $^3J_{PH}$ 10.0 Hz), 5.26 d (1H, the second of $ROCH_2C$ (arom.), $^3J_{PH}$ 16.0 Hz), 7.05–7.25 m (4H, arom.). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.8 d (CH_3, $^3J_{PC}$ 5.5 Hz), 25.7 d (CH_2R, $^1J_{PC}$ 129.5 Hz), 61.5 d (CH_2OR, $^3J_{PC}$ 6.6 Hz), 69.2 d (CH_2OR, $^3J_{PC}$ 6.6 Hz) , 124.8, 126.6, 127.6 ($^4J_{PC}$ 1.5 Hz), 129.1 ($^3J_{PC}$ 7.7 Hz), 130.0 ($^2J_{PC}$ 14.3 Hz), 132.0 ($^3J_{PC}$ 11.0 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 23.8. Found, %: C 56.50, 56.43; H 6.13, 6.19; P 14.62, 14.55. $C_{10}H_{13}O_3P$. Calculated, %: C 56.61; H 6.18; P 14.60.

The subsequent chromatography with a mixture chloroform–isopropanol, 19:1, as eluent provided the bis-phosphorylated product as an oil. Yield 1.2 g (5.3%), of **tetraethyl *o*-xylylenediphosphonate XVII**, oil, n_D^{20} 1.5052. The substance crystallizes on standing after about 1–2 days, mp 53–55ºC (in bulk). R_f 0.15 (chloroform–acetone, 4:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.20 t (12H, $4CH_3$), 3.12 d (4H, $2CH_2R$, $^2J_{PH}$ 21.5 Hz), 4.00 d.q (4H, CH_2O), 7.40 m (4H, arom.). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 27.0. Found, %: C 50.60, 50.65; H 7.53, 7.49; P 16.32, 16.37. $C_{16}H_{28}O_6P_2$. Calculated, %: C 50.79; H 7.46; P 16.37.

Synthesis of ω-haloalkylphosphine oxides. As a component of trivalent phosphorus trimethylsilyl diphenylphosphinite was used obtained by boiling diphenylphosphinic acid with 1.0–1.5 equivalents of hexamethyldisilazane followed by distillation in a vacuum. The target ester has bp 107–110°C (0.3 mm Hg). Using diphenylsilylphosphinite *in situ*, namely, using the resulting mixture (after the cessation of ammonia release) without additional vacuum distillation was markedly less effective. Attempts to use ethyl diphenylphosphinite was also rather unsuccessful, as showed the lower yield of the target reaction products.

2-Bromoethyldiphenylphosphine oxide (XI). To 62.5 ml (0.72 mol) of boiling dibromoethane at stirring was slowly added dropwise 34.4 g (0.13 mol) of freshly distilled trimethylsilyl diphenylphosphinite within 1 h in a weak stream of argon. Using a top-down condenser the continuously formed bromotrimethylsilane was distilled off. The reaction mixture

was stirred under the same conditions for 0.5 h after the addition of all calculated amount of silyl phosphinite continuously removing bromotrimethylsilane from the reaction mixture. After the release of 14 ml (~85%) of bromotrimethylsilane, the reaction mixture was evacuated and the 1,2-dibromoethane excess was distilled off. After the removal from the reaction mixture of 39 ml (~75%) of unreacted 1,2-dibromoethane, the residue was dissolved in 150 ml of chloroform and washed with saturated sodium carbonate solution (3×50 ml) until complete removal of diphenylphosphinic acid, the byproduct of the reaction (R_f 0.15–0.30 with chloroform–acetone, 4:1; gray spot in iodine vapor stretching along the front). The organic phase was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The oily crystallizing residue was chromatographed on silica gel, eluent chloroform, chloroform–isopropanol (5%). After the evaporation of the eluate and the crystal-lization of the residue 6.16 g (42.7%) of the desired bromide **XI** was isolated, mp 119–121ºC (ether). R_f 0.50, chloroform–acetone, 4:1. ^{1}H NMR spectrum (CD_3OD + CCl_4, δ, ppm): 2.32 m (2H, CH_2P), 3.52 d.t (2H, CH_2Br), 7.47 m (6H, arom), 7.75 m (4H, arom.). ^{13}C NMR spectrum (CD_3CN, δ, ppm): 25.3 (CH_2Br), 34.8 d (CH_2P, $^1J_{PC}$ 63.7 Hz), 129.7, 129.9, 131.0, 131.4, 132.8, 133.8 (PC_{arom}, $^1J_{PC}$ 101.2 Hz). ^{31}P NMR spectrum (CD_3OD + CCl_4, δ, ppm): 31.2.

3-Bromopropyldiphenylphosphine oxide (XII). To 117.8 g (0.58 mol) of freshly distilled 1,3-dibromopropane, pre-heated to boiling, was slowly added dropwise while stirring within an hour in a weak stream of argon 55.4 g (0.20 mol) of freshly distilled trimethylsilyl diphenylphosphinite with continuous distilling off the formed in the reaction bromotrimethylsilane. After adding the whole amount of the phosphinite the reaction mixture was stirred under the same conditions for 0.5 h. After removal of 23 g (~86%) of bromotrimethylsilane the mixture was evacuated and the excess of 1,3-dibromopropane was distilled off. After the removal from the reaction mixture of 63 g (~81%) of unreacted 1,3-dibromopropane, the residue was dissolved in 150 ml of chloroform and washed with saturated sodium carbonate solution until the complete removal of diphenylphosphinic acid, the reaction byproduct [R_f 0.15–0.30 (in iodine vapor gray spot stretched along the front), chloroform–acetone, 4:1]. The chloroform solution was washed with water and evaporated in vacuo. The residue was chromatographed on silica gel, eluent chloroform, chloroform–isopropanol (3%). After evaporation of the eluate and crystallization 34.3 g (53.1%) of the desired bromide **XII** was isolated, mp 94–96ºC (ether), R_f 0.50 (chloroform–acetone, 4:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 2.18 m (2H, CH_2P), 2.43 m (2H, CH_2C), 3.46 t (2H, CH_2Br), 7.48 m (6H, arom.), 7.80 m (4H, arom.). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 32.3. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 24.9 d (CH_2Br, $^3J_{PC}$ 2.7 Hz), 28.4 d (CH_2P, $^1J_{PC}$ 71.9 Hz), 34.2 d (CH_2C, $^2J_{PC}$ 16.3 Hz), 128.5, 128.8, 130.5, 130.7, 131.8, 132.6 ($^1J_{PC}$ 101.2 Hz). ^{13}C NMR spectrum (CD_3CN, δ, ppm): 26.0 (CH_2Br), 28.4 d (CH_2P, $^1J_{PC}$ 71.9 Hz), 35.1 d (CH_2C, $^2J_{PC}$ 16.3 Hz), 129.2, 129.5, 131.0, 131.3, 132.3, 134.2 ($^1J_{PC}$ 97.7 Hz). Found, %: C 55.62, 55.55; H 5.08, 5.13; Br 24.53, 24.73; P 9.47, 9.40. $C_{15}H_{16}BrOP$. Calculated, %: C 55.75; H 4.99; Br 24.72; P 9.58.

Attempted isolation of the product by distillation in a high vacuum was accompanied with a visible dehydrobromination, however, the produced corresponding to 1-propenylphosphine oxide was not isolated individually.

4-Bromobutyldiphenylphosphine oxide (XIII). Yield 61.2%, mp 86–87ºC (ether), R_f 0.55 (chloroform–acetone, 4:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.88 m (2H, CH_2P), 1.98 m (2H, CH_2C), 2.30 m (2H, CH_2C), 3.38 t (2H, CH_2Br), 7.50 m (6H, arom), 7.80 m (4H, arom). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 32.6. Found, %: C 56.92, 57.10; H 5.48, 5.33; Br 23.63, 23.77; P 8.90, 9.05. $C_{16}H_{18}BrOP$. Calculated, %: C 57.03; H 5.43; Br 23.70; P 9.18.

5-Bromopentyldiphenylphosphine oxide (XIV). Yield 54.1%, mp 72–73ºC (ether), R_f 0.55 (chloroform–acetone, 4:1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.68 m (4H, CH_2R), 1.86 m (2H, CH_2C), 2.30 m (2H, CH_2C), 3.35 t (2H, CH_2Br), 7.42 m (6H, arom.), 71.68 m (4H, CH_2P), 1.86 m (2H, CH_2C), 2.30 m (2H, CH_2C), 3.35 t (2H, CH_2Br), 7.42 m (6H, arom), 7.73 m (4H, arom). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 32.5. Found, %: C 58.12, 58.20; H 5.68, 5.81; Br 22.64, 22.83; P 8.92, 8.85. $C_{17}H_{20}BrOP$. Calculated, %: C 58.14; H 5.74; Br 22.75; P 8.82.

6-Bromohexyldiphenylphosphine oxide (XV). Yield 51.3%, mp 65–67ºC (ether), R_f 0.34 (chloroform–acetone, 10: 1). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.40 m (4H, CH_2P), 1.64 m (2H, CH_2C), 1.90 m (2H, CH_2C), 2.28 m (2H, CH_2C), 3.33 t (2H, CH_2Br), 7.52 m (6H, arom.), 7.85 m (4H, arom.). ^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 32.1. Found, %: C 59.30,

59.42; H 6.02, 5.91; Br 22.05, 21.77; P 8.51, 8.30. $C_{18}H_{22}BrOP$. Calculated, %: C 59.19; H 6.07; Br 21.88; P 8.48.

Study of the propensity of 3-bromopropylphosphonate I and *o*-chloromethylbenzylphosphonate X to intramolecular cyclization. The experiments with heating a mixture of 1,3-dibromopropane and triethyl phosphite at different reagent ratios (from 1:3 to 1:5) in the absence of a solvent largely confirmed the data of the earlier study [9], where by vacuum distillation a cyclic compound, 1,2-oxaphospholane (40 to 60%) was isolated and the desired product was obtained in a yield not exceeding 11–23%, depending on experimental conditions. Besides, in the still remained an unreacted substance, apparently of polymeric nature. The ethyl bromide liberated in the reaction was collected in a cooled (dry ice/chloroform) trap. Note that the amount of ethyl bromide exceeded one equivalent, even at a fivefold excess of 1,3-dibromopropane with respect to triethyl phosphite, which may indicate the initial formation of 3-bromopropylphosphonate **I** with the release of the first molecule of ethyl bromide and the subsequent process of cyclization with the formation of a second molecule of ethyl bromide as a byproduct.

In addition, the investigation of the ability of 3-bromopropylphosphonate **I** and *o*-chloromethylbenzylphosphonate **X** to undergo the intramolecular cyclization was carried out under conditions simulating the conditions of the alkylation of CH acids, that is, at reflux with stirring in various solvents in the presence of one equivalent of sodium chloride or bromide. The examples below of the experiments with DMF and THF show the opposite results.

Example 1. A mixture of 3-bromopropylphosphonate **I** (2.6 g, 0.01 mol) and sodium bromide (1.0 g, 0.01 mol) in 7 ml of DMF was refluxed with stirring for 5 h. The reaction mixture was evaporated and the residue was partitioned between chloroform and water (30/30 ml). The organic phase was separated, dried over sodium sulfate, and evaporated in vacuo, and the residue was distilled. 1.2 g (80%) of 2-oxo-2-ethoxy-1,2-oxaphospholane **XVIII** was isolated, bp 85–89°C (0.02 mm Hg), n_D^{20} 1.4540. Published: bp 72–74°C (0.01 mm Hg), n_D^{20} 1.4520. [9]. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.32 t (3H, CH_3), 1.85 m (2H, CH_2R), 2.26 m (2H, CH_2C), 4.15 m (4H, $OC\underline{H}_2CH_3$ + $OC\underline{H}_2CH_2$). ^{31}P NMR spectrum (CD_3OD + CCl_4, δ, ppm): 35.1.

Example 2. A mixture of diethyl ether–chloromethylbenzylphosphonate **X** (2.8 g, 0.01 mol) and sodium chloride (0.6 g, 0.01 mol) in 10 ml of boiling dimethylformamide was stirred for 5 h. The reaction mixture was evaporated and the residue was partitioned between chloroform and water (30/30 ml). The organic phase was separated, dried over sodium sulfate, and evaporated in vacuo, and the residue was chromatographed on silica gel eluting with hexane–chloroform, 1:1, mixture). 0.7 g (25.0%) of *o*-chloromethylbenzylphosphonate **X** was isolated, oil, n_D^{20} 1.5160 . R_f 0.7 (chloroform–acetone, 4:1) and 1.3 g (61.3%) of 2-oxo-2-ethoxy-4,5-benzo-1,2-oxaphosphorine **XIX**, oil, n_D^{20} 1.5380. R_f 0.35 (chloroform–acetone, 4:1). ^{1}H and ^{31}P NMR spectral characteristics of compounds **XI** and **XII** are close to the described above in the synthesis of *o*-chloromethylbenzylphosphonate **X**.

A similar attempt (with the same loads of the parent compounds) of isolation of the products by vacuum distillation gives mainly the cyclic product, 1.5 g (73%) of 1,2-oxaphosphorine **XIX**. This result suggests that the cyclization process takes place under conditions of vacuum distillation, that is, under conditions of continuous removal of the ethyl chloride byproduct from the reaction sphere, which promotes the formation of cyclic 1,2-oxaphosphorine **XIX**.

In the experiment with 3-bromopropylphosphonate **I** in THF the formation of cyclic 1,2-oxaphospholane **XVIII** was not detected, however, after stirring a mixture of *o*-chloromethylbenzylphosphonate **X** (0.01 mol) with sodium chloride (0.01 mol) in 10 ml of boiling tetrahydrofuran for 5 h 0.17 g (8%) of 2-oxo-2-ethoxy-4,5-benzo-1,2-oxaphosphorine **XIX** was isolated (the treatment of the reaction mixture was carried out as in *Example 2*, the product was isolated by chromatography on silica gel). The research results allow us recommending tetrahydrofuran as an appropriate solvent in the reactions of the CH acids alkylation with ω-haloalkylphosphonates.

Thus, this paper describes a general method of the synthesis of ω-haloalkylphosphoryl compounds, and a number of compounds of phosphonic and phosphine oxide types were synthesized. We investigated the ability of ω-haloalkylphosphonates containing a halogen atom in the 3 or 4 position with respect to the phosphoryl moiety to undergo the intramolecular cyclization into the corresponding 1,2-oxaphospholane and 1,2-oxaphosphorine depending on several factors

(temperature, polarity of the solvent, the presence of halide ions in solution). Tetrahydrofuran is recommended the most suitable solvent for the alkylation of CH acids with ω-haloalkylphosphoryl compounds.

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