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Polyfluoroalloxy Phosphonic and Phosphinic Acid Derivatives: I. 1-Hydroxy-2,2,2-Trichloroethylphosphinates

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Abstract—Polyfluoroalkyl esters of 1-hydroxy-2,2,2-trichloroethylphosphonic and aryl(alkyl-)phosphinic acids exhibited antienzyme activity towards esterases of animal and microbial origin. A good correlation is observed between high antiesterase activity of the target compounds and their physicochemical parameters, characterizing their structure.

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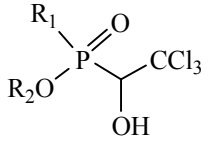
Over past two decades many researchers have shown interest in the methods of synthesis and detection of biological activity of phosphonic (i.e., containing at least one phosphorus-carbon bond) acids and their derivatives, which can be regarded as analogs of natural phosphates. A special group of organophosphorus compounds (OPC) possessing physiological activity, are 1-hydroxyphosphonates. Chemical and biological properties of 1-hydroxyphosphonates, first synthesized more than half a century ago, in terms of their practical application are very interesting. The reactivity of the hydroxy group and the enzymatic stability of the phosphorus-carbon bond allow the suggestion of a high probability that such compounds would possess biological activity. Dimethyl (1-hydroxy-2,2,2-trichloroethyl)phosphonate was a unique compound that had found in the last century the use both as an effective insecticide (*trichlorfon*), and in ophthalmology, as a myotic for reducing intraocular pressure in glaucoma (synonym c*hloroftalm*). Today, due to the relatively high chronic (but not acute!) toxicity trichlorfon is not produced or used in domestic practice. Chloroftalm is also excluded from the medicines list. However, in recent years there are reports in the literature indicating attempts to use the OPC, irreversible cholinesterase inhibitors, for the treatment of Alzheimer's decease[1]. An example of such a drug is *metrifonat* (a synonym for *trichlorfon*!), developed by Bayer AG. All this makes the synthesis of esters of 1-hydroxyalkylphosphone and -phosphinic acids an actual task, for the problem of reducing toxicity of these substances is far from being solved.

We have developed a synthesis of polyfluoroalkyl esters of (1-hydroxy-2,2,2-trichloroethyl)alkyl- and phenylphosphinic acids **I** (Tables 1, 3).



Ia–Iw

It is known that the activity of cholinesterase inhibitor depends on the electrophilic phosphorylating ability of the inhibitor, the propensity to hydrophobic adsorption on the enzyme's surface and on the complementarity of the inhibitor's molecule to the "hydrophobic site–esterase center" system [2]. Such patterns of the expression of anticholinesterase activity were derived on the basis of the structures of "traditional" inhibitors. The main idea of our investigation was to obtain new compounds with more effective than *trichlorfon* antiesterase action while maintaining low *in vivo* toxicity, which would greatly reduce the effective drug concentration. This can be achieved in the following ways. Firstly, it is important to preserve the structural skeleton of 1-hydroxyphosphonates with possible dehydrochlorination in an organism that causes their transformation into dialkyldichlorovinylphosphates (structural analogs of *dichlorvos*). Secondly, it is necessary to introduce additional phosphorus-carbon bond providing the enzymatic stability of the target compounds *in vivo*.

Table 1. Yields, melting or boiling points of 1-hydroxy-2,2,2-trichloroethylphosphinates and -phosphonates **I**

Comp. no.	R_1	R_2	Yield, %	mp or bp, °C (*p*, mm Hg)	Found, %[a]		Formula	Calculated, %	
					C	H		C	H
Ia	C_6H_5	$CH_2CF_2CF_2H$	95	109	32.3	2.35	$C_{11}H_{10}Cl_3F_4O_3P$	32.7	2.50
Ib	C_6H_5	$CH_2(CF_2CF_2)_3H$	96	98	29.5	1.74	$C_{15}H_{10}Cl_3F_{12}O_3P$	29.9	1.67
Ic	C_6H_5	$CH_2C_3F_7$	97	101	30.1	2.00	$C_{12}H_9Cl_3F_7O_3P$	30.6	1.92
Id	C_6H_5	C_3H_7	88	oil	39.3	4.11	$C_{11}H_{14}Cl_3O_3P$	39.8	4.26
Ie	C_6H_5	C_2H_5	89	oil	37.9	3.73	$C_{10}H_{12}Cl_3O_3P$	37.8	3.81
If	CCl_3	CH_3	80	85	13.5	1.39	$C_4H_5Cl_6O_3P$	13.9	1.46
Ig[b]	CH_3	$CH_2(CF_2CF_2)_4H$	91	180 (2)	22.3	1.40	$C_{12}H_8Cl_3F_{16}O_3P$	22.5	1.26
Ih	OC_2H_5	C_2H_5	68	112 (1)	25.1	4.15	$C_6H_{12}Cl_3O_4P$	25.2	4.24
Ii	OC_6H_{13}	C_6H_{13}	77	178 (1)	42.4	7.22	$C_{14}H_{28}Cl_3O_4P$	42.3	7.10

[a] Here and hereinafter the data of elemental analysis for phosphorus and halogens are not shown because of the distortion of the results due to the joint presence in a molecule of these elements. [b] For **Ig**: n_D^{20} 1.3312, d_4^{20} 1.8390

Thirdly, the increased lipophilicity of alkoxyl radicals due to introducing into them fluorine atoms contributes to a more solid fixation of the OPC on hydrophobic areas of the enzyme's surface.

Esters of 1-hydroxy-2,2,2-trichloroethylphosphonic acid were first obtained by the Abramov reaction from chloral hydrate and partial esters of trivalent phosphorus acids [3,4]. We prepared polyfluoroalkyl esters of (1-hydroxy-2,2,2-trichloroethyl)alkyl- and phenylphosphinic acids **I** by the reaction of the appropriate complete alkyl- and arylphosphonites with chloral hydrate:

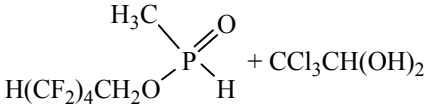
$$R_1P(OR_2)_2 + CCl_3CH(OH)_2 \rightarrow \mathbf{I} + R_2OH.$$

Physicochemical parameters of the obtained compounds are given in Table 1.

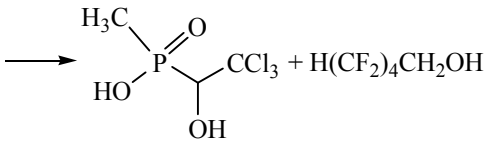
As a result of the reaction two types of products were obtained: esters **I** and a small amount of crystalline alkyl- or aryl-1-hydroxy-2,2,2-trichloroethylphosphinic acids: $R_1P(O)(OH)CH(OH)CCl_3$ [**II**, $R_1 = CH_3$ (**a**), C_2H_5 (**b**), C_6H_5 (**c**)].

Phosphonites $R_1P(OR_2)_2$ were synthesized by conventional reaction of alkyl and phenylphosphonic acid dichlorides with the corresponding alcohols [7]. However, it is necessary to emphasize that phenylphosphonites with polyfluoroalkoxyl radicals were prepared without using hydrogen chloride acceptor. Parameters of the starting phosphonites are presented in Table 3.

Target compounds **Ia–Ii** are viscous liquids, slowly crystallizing on standing. Esters **Ik–Iw** were isolated from the reaction mixture by vacuum fractional distillation after the solvent removal, the individuality of the products was proved by GLC. Phosphonates and phosphinates **Ij–Iv** are colorless, transparent liquids, distilled in a vacuum without decomposition. The formation of crystalline products **II** may be due to the reaction of chloral hydrate with the traces of acidic phosphonites present in the starting material. To prove the latter assumption an independent synthesis was carried out. The reaction of chloral hydrate with incomplete phosphonite **III** in anhydrous benzene led to a colorless crystalline substance, whose parameters fully coincided with the properties of compound **IIa**:



III



Derivatograms of the obtained esters **I** showed their thermal stability up to 150–180°C. When heating above specified temperatures, the cleavage of alkoxyl radicals happens.

Table 2. Antiesterase activity of 1-hydroxy-2,2,2-trichloroethylpolyfluoroalkyl phosphinates and phosphonates **I**, and their physicochemical characteristics

Comp. no.	R_1	R_2	Enzyme inhibition constants, k_{II}, $l\ mol^{-1}\ min$		log*P*	q^P	*V*, Å^3
			BCHE	EBs			
Ia	C_6H_5	$CH_2CF_2CF_2H$	6.50×10^6	3.40×10^5	3.08	0.159	829
Ib	C_6H_5	$CH_2(CF_2CF_2)_3H$	3.50×10^7	4.20×10^5	6.41	0.159	1097
Ic	C_6H_5	$CH_2C_3F_7$	4.30×10^6	1.80×10^5	4.63	0.159	899
Id	C_6H_5	C_3H_7	6.20×10^6	3.30×10^5	2.80	0.159	804
Ie	C_6H_5	C_2H_5	2.20×10^6	2.70×10^5	2.33	0.159	729
If	CCl_3	CH_3	1.10×10^3	3.10×10^5	4.06	0.198	652
Ig	CH_3	$CH_2(CF_2CF_2)_4H$	5.10×10^3	1.31×10^5	7.35	0.148	1118
Ih	OC_2H_5	C_2H_5	2.75×10^3	4.06×10^2	3.86	0.267	682
Ii	OC_6H_{13}	C_6H_{13}	4.20×10^3	1.80×10^7	7.17	0.267	1102
Ij	CH_3[a]	$CH_2(CF_2CF_2)_2H$	2.50×10^6	5.00×10^5	4.01	0.148	841
Ik	CH_3	$CH_2(CF_2CF_2)_3H$	6.20×10^6	3.88×10^6	5.68	0.148	990
Il	C_2H_5	$CH_2(CF_2CF_2)_2H$	6.07×10^6	1.37×10^7	4.35	0.151	903
Im	CH_3	$CH_2CF_2CF_2H$	1.80×10^6	3.45×10^6	2.34	0.148	703
In	C_6H_5	$CH_2(CF_2CF_2)_2H$	3.20×10^7	4.70×10^5	4.74	0.159	955
Io	CH_3	C_8H_{17}	1.55×10^3	–	4.04	0.148	931
Ip	C_6H_5	CH_2CF_3	2.20×10^6	2.90×10^5	2.96	0.159	768
Iq	C_6H_5	C_4H_9	4.20×10^6	1.70×10^5	3.19	0.159	851
Ir	OC_4H_9	C_4H_9	1.16×10^4	1.13×10^3	5.59	0.267	879
Is	*iso*-OC_4H_9	*iso*-C_4H_9	1.16×10^4	1.13×10^3	5.60	0.267	904
It	$(ClCH_2)_2CHO$	$(ClCH_2)_2CH$	2.58×10^4	1.35×10^4	6.13	0.267	940
Iu	$OCH_2CF_2CF_2H$	$CH_2CF_2CF_2H$	4.07×10^7	1.80×10^7	5.35	0.267	890
Iv	*iso*-OC_3H_7	*iso*-C_3H_7	8.21×10^3	–	4.68	0.267	770
Iw	OCH_3	CH_3	4.00×10^3	3.20×10^5	3.17	0.266	576
IIa	CH_3	OH	5.10×10^3	1.31×10^5	2.64	0.173	467

[a] Compounds **Ik-Iw** were described earlier [6, 7].

^{19}F NMR spectra of compounds **Ia, Ib, Ig** contain a doublet signal of CF_2 group in ω-position to the phosphorus atom (*J* 51.4 Hz). In the ^{1}H NMR spectra a multiplet splitting of the CH_2O signal is observed caused by the coupling with the phosphorus and fluorine atoms of the difluoromethylene group, (*J* 7.7 Hz). In addition, there is a signal of the OH group and the doublet signal corresponding to trichloroethyl group, (*J* 11.6 Hz). Chemical shifts in the ^{31}P spectra are located in the δ_P 31.2–36.5 ppm area characteristic of phosphinates of such structure, and 14–16 ppm (for phosphonates **Ih, Ii** and **Ir–Iw**). The IR spectra of **I** feature OH group signal in the 3200–3350 cm^{-1} region.

Antiesterase activity data for 1-hydroxy-2,2,2-trichloroethylphosphonates and -phosphinates **I** (Table 2) show that all the compounds demonstrated high *in vitro* inhibitory ability towards butyrylcholinesterase (BCHE, KF 3.1.1.8) from horse blood serum and esterase isolated from a strain of Gram-positive soil bacterium *Bacillus subtilis* (EBs).

The vast majority of the studies dealing with the structure and properties of esterases concern the esterases of animal origin, which play a central role in the universal and biologically important process of nerve impulse transmission. BCHE is a reserve enzyme that compensates the lack of acetylcholine-

Table 3. Yields, melting or boiling points, n_D^{20}, d_4^{20} ,elemental analyses of phosphonites $R_1P(OR_2)_2$

R_1	R_2	Yield, %	mp or bp, °C (p, mm Hg)	n_D^{20}	d_4^{20}	Found, %		Formula	Calculated, %	
						C	H		C	H
CH_3	$CH_2(CF_2CF_2)_4H$	74	158 (1)	1.3365	1.7638	24.9	0.96	$C_{18}H_9F_{32}O_2P$	25.1	1.00
C_6H_5	$CH_2CF_2CF_2H$	95	139 (12)	1.4306	1.4258	38.0	2.91	$C_{12}H_{11}F_8O_2P$	38.9	3.00
C_6H_5	$CH_2(CF_2CF_2)_3H$	92	175 (8)	1.4178	1.7039	30.9	1.52	$C_{20}H_{11}F_{24}O_2P$	31.2	1.44
C_6H_5	$CH_2C_3F_7$	93	106 (9)	1.4150	1.5304	33.3	1.84	$C_{14}H_9F_{14}O_2P$	33.2	1.79
C_6H_5	C_2H_5	65	103 (8)	1.5130	1.0260	61.0	7.50	$C_{10}H_{15}O_2P$	60.6	7.63
C_6H_5	C_3H_7	69	121 (9)	1.5065	0.9972	63.6	8.54	$C_{12}H_{19}O_2P$	63.7	8.46

esterase under extreme conditions. According to some assumptions, BCHE cleaves the remnants of organic macromolecules accumulated during life activity. It is possible that BCHE participates in the process of xenobiotics detoxification. Plant and microbial esterases have been studied to a lesser extent. It is known that filamentous fungi produce esterases characterized by low sensitivity to the action of the OPCs and carbamates. Microbial esterases were also determined in the producents of various bacterial genera [8].

Studying the biological activity of the target compounds revealed that the replacement of alkoxy groups with polyfluoroalkoxy ones has amplified their antiesterase activity 100–1000 times compared with trichlorfon **Ih**. To evaluate the level of biological activity *in vitro* it was assumed that the limiting stage of the inhibition process is the reaction of pseudo-first order. The true enzyme inhibition constant k_{II} is defined by the formula:

$$k_{II} = \ln (v_0/v_\tau)/\tau[\mathrm{In}], \quad (1)$$

where v_0 and v_τ are the rates of enzymatic hydrolysis before and after contact with the enzyme inhibitor with the incubation time (τ) from 1 to 10 min; [In] is the inhibitor's concentration (10^{-4} M).

To determine the factor contributing to increased biological activity, we used the method of multivariate regression analysis (Gancia model) of structure–inhibitory activity relationship of the studied compounds towards BCHE and EBs.

The choice of parameters to create an adequate mathematical model of the structure–biological activity relationships is quite diverse, herewith the correlation parameters should reflect the nature of the interaction of the compound with biological target as accurate as possible.

The most common system of the constants characterizing the inductive and resonance effects of substituents at the phosphorus atom is deservedly Kabachnik's system of correlation constants, but it often does not allow an unambiguous solution of the problem of the orthogonalization of the inductive and resonance effects of the substituents. Therefore in this paper the values of the electron density at the phosphorus atom were calculated using quantum-chemical method (see below).

It is known that hydrophobic interactions play an essential role in the inhibition of esterases [9]. To evaluate the hydrophobicity of compounds **I** we used lipophilicity parameter log P characterizing the equilibrium distribution of substance in the lipid-water system.

The role of steric factor in the interaction of inhibitors with esterases appears as early as in the first stage of the enzyme phosphorylation. That is why, accounting for the structural features of esterases [10], we used the volume of inhibitor molecule **V** as a parameter characterizing the steric factor.

The values of electron density on the phosphorus atom, the molecular volume V, and lipophilicity parameter log P of the target compounds were calculated using the software package HyperChem™ Release 7.52 for Windows Molecular Modeling System, after geometrical optimization of the structure by Fletcher-Reeves method. Parameters of correlation equations describing the features of inhibition of various esterases by compounds **I** are given in Table 4. Note the high correlation coefficients and large number of degrees of freedom (5–20) in all cases.

Analysis of the correlation dependences reveals a certain patterns of interaction of 1-hydroxy-2,2,2-trichloroalkyl- and -phenylphosphinates with esterases of animal and microbial origin. Firstly, the constant

Table 4. Parameters of correlation equations $\log k_{II} = a_0 + a_1 \log P + a_2(\log P)^2 + a_3 q^P + a_4 V$ [Eqs. (2)–(9)]

Enzyme	Eq. no.	Inhibitor	a_0	a_1	a_2	a_3	a_4	r	s	n
BCHE	2	**Ia–Iw, IIa**	–0.0102	0.265	–0.129	–5.15	0.00949	0.969	0.70	24
	3	**Ia–Ig, Ij–Iq, IIa**	0.00047	–0.176	–0.083	–0.767	0.00976	0.976	0.58	16
	4	**Ia–Iw, IIa**	–0.0044	–2.40	–0.019	–	0.0206	0.966	0.39	8
	5	**Ia–Iw, IIa**	–0.0027	1.71	–0.159	–	–	0.962	0.41	8
EBs	6	**Ia–Iw, IIa**	0.0190	0.442	–0.104	–0.975	0.00690	0.964	0.72	22
	7	**Ia–Ig, Ij–Iq, IIa**	0.00441	0.872	–0.119	10.8	0.00313	0.993	0.29	15
	8	**Ia–Iw, IIa**	0.00234	–12.7	0.438	–	0.0691	0.962	0.43	7
	9	**Ia–Iw, IIa**	0.00711	1.16	–0.051	–	–	0.925	0.59	7

term (a_0) in all equations is close to zero, that confirms the adequacy of the obtained mathematical models to the experiment. Indeed, with the vanishing of all members of the correlations (2)–(9), which becomes possible in the absence of inhibitor, the enzyme inhibition constant should be equal to 1. Taking into consideration the inhibitor's concentration this case is realized with equal values of v_0 and v_τ, [Eq. (1)], that is precisely the case of the absence of inhibition of the enzyme. Secondly, the most significant role in the obtained correlations plays the lipophilicity parameter log P. However, the optimal value of this parameter for BCHE and EBs inhibitors are different. If we equate to zero the first derivatives of functions (4) and (9) (Table 4), the values of log P_{opt} are 5.4 and 11.4, respectively. This points to a greater sensitivity of EBs to inhibitors with hydrophobic fragments.

The study of the properties of 1-hydroxy-2,2,2-trichloroethylalkyl- and -phenylphosphinates revealed that their anticholinesterase activity significantly exceeds that of the known compounds of similar structure. This permits a hundreds of times reduction of effective drug concentration. High inhibitory activity of the target products towards esterases from a *Bacillus subtilis* strain combined with their low toxicity will allow to increase the range of antimicrobial agents.

EXPERIMENTAL

Antiesterase activity assessment was conducted by the method based on a comparison of the enzymatic hydrolysis of chromogenic substrate indophenylacetate [4].

The individuality of the obtained compounds was established by GLC (on a LKhM-8MD instrument, stationary phase XE-60 10% on Chezasorb or SE-30 5% on Inerton, detector katharometer, carrier gas helium, 40 ml min^{-1}) for liquid products and by TLC (on Silufol UV 254 plates, eluent acetone-hexane, 1:4) for the solids.

^{1}H NMR spectra were recorded on a Perkin-Elmer R-12(100 MHz, HMDS as internal standard) and a Bruker 200 (200 MHz, with residual solvent protons as internal reference) instruments in DMSO-d_6 or acetone-d_6. ^{31}P and ^{19}F NMR spectra were recorded on the custom-built device designed in St. Petersburg STI (operating frequency 16.2 and 37.6 MHz, external standard 85% H_3PO_4 and trifluoroacetic acid, respectively). IR spectra of compounds **Ia–Ii** were recorded from films, **Ij–Iv** and **IIa–IIc,** from mulls in mineral oil using an IKS-29 instrument. A Paulik-Paulik-Erdey derivatograph, model OD-2, was used for thermal analysis. Elemental analyses were performed on a Hewlett Packard B-185 analyzer.

Di-(1,1,9-Trihydrohexadecafluorononyl)methylphosphonite. To a mixture of 8.6 g of 1,1,9-trihydrohexadecafluorononanole and 1.6 g of pyridine dissolved in 30 ml of dry diethyl ether, 1.2 g of methylphosphonic acid dichloride was added dropwise under inert atmosphere. Dichloride addition rate was maintained at such a level, that the temperature of the reaction mixture did not exceed 5°C. After adding methyl dichlorophosphite the reaction mixture was stirred at room temperature for further 2 h. The resulting precipitate composed of pyridine hydrochloride was filtered off and washed with ether. After distilling off the solvent from the combined filtrates the fractional distillation gave 6.7 g (74%) of the target compound.

Di-(1,1,3-Trihydrotetrafluoropropyl)phenylphosphonite. To 7.0 g of 1,1,3-trihydrotetrafluoropropanole 4.75 g of phenylphosphonic acid dichloride

was added dropwise with stirring, maintaining the temperature of the reaction mixture within 20–25°C. Simultaneously, hydrogen chloride was removed from the reaction mixture by bubbling dry air through it. After adding of phenyl dichlorophosphite the reaction mixture was stirred for further 5 h with removal of hydrogen chloride. The fractional distillation afforded 9.3 g (95%) of the target phosphonite. Other phenylphosphonites were obtained analogously (Table 3).

Synthesis of the other alkyl- and phenylphosphonites were described elsewhere [2, 7]. Dichlorides of alkyl- and phenylphosphonic acids were prepared accoding to the procedure from [11].

(1,1,5-Trihydrooctafluoropentyl)methylphosphonite (III). In a 4-neck flask equipped with a stirrer, a reflux condenser, and a dropping funnel 32.5 g of 1,1,5-trihydrooctafluoropentanol was placed and cooled to 0°C. Methylphosphonic acid dichloride, 8.2 g, was added dropwise at such a rate that the temperature within the flask did not rise above 3°C. Reaction mixture was kept at room temperature for further 0.5 h, then hydrogen chloride was removed by bubbling dry air through the reaction mixture for 5 h. The residue was subjected to fractional distillation that gave 13 g (63%) of **III,** bp 124°C (17 mm Hg).

(1,1,9-Trihydrohexadecafluorononyl)-(1-hydroxy-2,2,2-trichloroethyl)methyl phosphinate (Ig). To a solution of 4.14 g of chloral hydrate in 60 ml of anhydrous benzene 22.7 g of di-(1,1,9-trihydrohexadecafluorononyl)methylphosphonite was added dropwise with stirring under inert atmosphere. The reaction mixture was stirred for 10 h at a temperature not exceeding 40°C. The precipitate formed during the reaction was filtered off, washed with benzene, and dried. This product was identified as (1-hydroxy-2,2,2-trichloroethyl)methylphosphonic acid **IIa** (mp 159°C). Filtrates were combined, the solvent distilled off. The fractional distillation afforded 14.6 g of the target ester **Ig**. Compounds **Ih, Ii** were obtained in the same way.

(1,1,3-Trihydrotetrafluoropropyl)-(1-hydroxy-2,2,2-trichloroethyl)phenyl phosphinate (Ia). To a solution of 5 g of chloral hydrate in 70 ml of anhydrous benzene 1.11 g of di-(1,1,3-trihydrotetrafluoropropyl)phenylphosphonite was added dropwise with stirring under inert atmosphere. The mixture was stirred for 12 h at 30–40°C. The solvent was distilled off in a vacuum, and the residue that crystallized after standing for 2 h, was washed with diethyl ether and dried giving 11.5 g of **Ia**. Compounds **Ib–If** were obtained in a similar way.

(1-Hydroxy-2,2,2-trichloroethyl)methylphosphonic acid (IIa). To a solution of 2.5 g of chloral hydrate in 30 ml of anhydrous benzene 4.4 g of (1,1,5-trihydrooctafluoropentyl)methylphosphonite was added dropwise with stirring. The reaction mixture was kept under stirring for 8 h at 40°C. The precipitate formed during the reaction was filtered off, washed with benzene, and dried, giving 3.1 g of the product that was identified as (1-hydroxy-2,2,2-trichloroethyl)methylphosphonic acid **IIa** (mp 159°C). Compounds **IIb, IIc** were obtained similarly (mp, °C: **IIb** 160, **IIc** 148).

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