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Synthesis and Some Properties of 4-Phosphorylated Derivatives of 5-Mercapto-1,3-oxazoles

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Abstract—Various approaches to the synthesis of new derivatives of diethyl 5-mercapto-2-R-1,3-oxazole-4-ylphosphonates were considered. The behavior of these compounds in the presence of mineral acids and alkalis resulting in the synthesis of previously unknown 5-mercapto-2-R-1,3-oxazole-4-ylphosphonic acids was studied.

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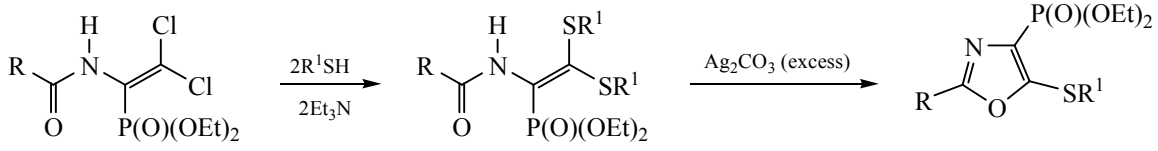
Among the derivatives of 5-mercaptooxazole effective drugs for the treatment of heart diseases [1] and inhibitors of fatty acid hydrolase (FAAN) have been found [2]. Some 1,3-oxazole-4-ylphosphonic acids are fructose-1,6-bisphosphatase antagonists [3]. Therefore, the development of the methods of the synthesis of 4-phosphorylated 5-mercaptooxazoles and their further modification is a promising way to the search for biologically active preparations.

From literary sources we know two basic approaches to the synthesis of 5-mercaptooxazole derivatives. One of them is the interaction of fairly accessible 1-functionalized 2,2-dichloroenamides of general formula Cl_2C=C(EWG)NHCOR (EWG = CN, COOAlk, SO_2Ar, etc.) with thiols in the presence of triethylamine followed by the treatment of the products obtained with silver carbonate excess [4]. By the second method, these reagents are treated initially with an excess of sodium hydrogen sulfide and then with an alkyl halide, which leads to substituted 5-alkylthiooxazoles [5]. However, such transformations are poorly studied with respect to 1-phosphorylated 2,2-dichloroenamides. Therefore, the task of the work was the involvement into these reactions of diethyl 1-acylamino-2,2-dichloroethenylphosphonates to produce 4-phosphorylated derivatives of 5-mercapto-1,3-oxazole and investigation of some chemical properties of these compounds.

It turned out that each of the known methods have their advantages and disadvantages, so we consider them in more detail.

The method of using silver carbonate made it possible to synthesize 5-arylthiooxazoles **IIIa–IIIg** (Scheme 1). However, a drawback of this approach is a rather complicated interaction of 1-phosphorylated 2,2-dichloroenamides **Ia–Ic** with thiols in an alkaline

Scheme 1.



Ia–Ic **IIa–IIg** **IIIa–IIIg**

R = Me (**Ia, IIa–IIc, IIIa–IIIc**); Ph (**Ib, IId, IIe, IIId, IIIe**); 4-MeC_6H_4 (**Ic, IIf, IIg, IIIf, IIIg**); R^1 = Ph (**IIa, IIIa**); 4-MeC_6H_4 (**IIb, IId, IIf, IIIb, IIId, IIIf**); 4-ClC_6H_4 (**IIc, IIe, IIg, IIIc, IIIe, IIIg**).

Table 1. Yields, constants, and elemental analysis data of the synthesized compounds

Comp. no.	R	R^1	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
					N	P	S		N	P	S
IIa	Me	Ph	71	52–53[a]	3.01	7.18	7.19	$C_{20}H_{24}NO_4PS_2$	3.20	7.08	14.66
IIb	Me	4-MeC_6H_4	69	123–125 (MeCN)	2.89	6.78	6.81	$C_{22}H_{28}NO_4PS_2$	3.01	6.65	13.78
IIc	Me	4-ClC_6H_4	64	Oil[a]	2.67	6.23	6.28	$C_{20}H_{22}Cl_2NO_4PS_2$	2.77	6.12	12.66
IId	Ph	4-MeC_6H_4	70	141–143 (MeCN)	2.49	5.99	5.95	$C_{27}H_{30}NO_4PS_2$	2.65	5.87	12.15
IIe	Ph	4-ClC_6H_4	61	174–175 (MeCN)[b]	2.21	5.43	5.48	$C_{26}H_{26}Cl_2NO_4PS_2$	2.40	5.32	11.01
IIf	4-MeC_6H_4	4-MeC_6H_4	69	134–135 (MeCN)	2.48	5.86	5.89	$C_{28}H_{32}NO_4PS_2$	2.59	5.72	11.84
IIg	4-MeC_6H_4	4-ClC_6H_4	64	173–174 (MeCN)	2.29	5.32	5.31	$C_{27}H_{28}Cl_2NO_4PS_2$	2.35	5.19	10.75
IIIa	Me	Ph	83	Oil[a]	4.11	9.58	9.58	$C_{14}H_{18}NO_4PS$	4.28	9.46	9.80
IIIb	Me	4-MeC_6H_4	78	Oil (petroleum ether, 70–100)	3.98	9.26	9.19	$C_{15}H_{20}NO_4PS$	4.10	9.07	9.39
IIIc	Me	4-ClC_6H_4	91	Oil (petroleum ether, 60–95)	3.67	8.67	8.73	$C_{14}H_{17}ClNO_4PS$	3.87	8.56	8.86
IIId	Ph	4-MeC_6H_4	78	46–48 (petroleum ether, 70–100)	3.36	7.86	7.81	$C_{20}H_{22}NO_4PS$	3.47	7.68	7.95
IIIe	Ph	4-ClC_6H_4	85	52–54 (petroleum ether, 70–100)[b]	3.19	7.49	7.48	$C_{19}H_{19}ClNO_4PS$	3.30	7.31	7.57
IIIf	4-MeC_6H_4	4-MeC_6H_4	79	55–56 (petroleum ether, 70–100)	3.28	7.51	7.59	$C_{21}H_{24}NO_4PS$	3.36	7.42	7.68
IIIg	4-MeC_6H_4	4-ClC_6H_4	92	83–84 (petroleum ether, 70–100)	3.01	7.24	7.15	$C_{20}H_{21}ClNO_4PS$	3.20	7.07	7.32
Va	Me	Et	79	Oil[a]	4.89	11.23	11.26	$C_{10}H_{18}NO_4PS$	5.02	11.09	11.48
Vb	4-MeC_6H_4	Et	73	Oil[a]	3.79	8.88	8.89	$C_{16}H_{22}NO_4PS$	3.94	8.72	9.02
VIIIa	Me	Ph	63	131–132 (H_2O–EtOH)	4.52	10.51	10.50	$C_{12}H_{14}NO_4PS$	4.68	10.35	10.71
VIIIc	Me	4-ClC_6H_4	71	158–160 (H_2O–EtOH)	4.01	9.40	9.42	$C_{12}H_{13}ClNO_4PS$	4.20	9.28	9.61
VIIId	Ph	4-MeC_6H_4	69	125–126 (H_2O–EtOH)	3.67	8.50	8.39	$C_{18}H_{18}NO_4PS$	3.73	8.25	8.54
VIIIe	Ph	4-ClC_6H_4	77	167–168 (EtOH)	3.41	7.99	7.99	$C_{17}H_{15}ClNO_4PS$	3.54	7.83	8.10
VIIIf	4-MeC_6H_4	4-MeC_6H_4	85	133–134 (EtOH)	3.49	8.11	8.13	$C_{19}H_{20}NO_4PS$	3.60	7.95	8.23
VIIIg	4-MeC_6H_4	4-ClC_6H_4	73	178–179 (EtOH)	3.34	7.73	7.73	$C_{18}H_{17}ClNO_4PS$	3.42	7.56	7.82
IXb	4-MeC_6H_4	Et	76	120–121 (H_2O–EtOH)	4.04	9.61	9.61	$C_{14}H_{18}NO_4PS$	4.28	9.46	9.80
Xa	Me	Ph	76[c]	179–181 (H_2O–EtOH)	5.01	11.59	11.58	$C_{10}H_{10}NO_4PS$	5.16	11.42	11.82
Xb	Me	4-MeC_6H_4	85[c]	188–189 (H_2O–EtOH)	4.79	10.01	10.98	$C_{11}H_{12}NO_4PS$	4.91	10.86	11.24
Xc	Me	4-ClC_6H_4	88[c]	189–190 (H_2O–EtOH)	4.46	10.30	10.30	$C_{10}H_9ClNO_4PS$	4.58	10.13	10.49
Xd	Ph	4-MeC_6H_4	85[c]	164–168 (EtOH)	3.89	9.07	9.08	$C_{16}H_{14}NO_4PS$	4.03	8.92	9.23
Xe	Ph	4-ClC_6H_4	79[c]	204–205 (EtOH)	3.42	7.98	7.98	$C_{17}H_{15}ClNO_4PS$	3.54	7.83	8.10
Xf	4-MeC_6H_4	4-MeC_6H_4	82[c]	195–196 (EtOH)	3.69	8.72	8.73	$C_{17}H_{16}NO_4PS$	3.88	8.57	8.87
Xg	4-MeC_6H_4	4-ClC_6H_4	84[c]	209–210 (EtOH)	3.58	8.28	8.29	$C_{16}H_{13}ClNO_4PS$	3.67	8.11	8.40
XIb	4-MeC_6H_4	Et	62[c]	155–157 (EtOH)	4.51	10.53	10.52	$C_{12}H_{14}NO_4PS$	4.68	10.35	10.71
XII	Me	4-MeC_6H_4	56	191–192 (EtOH)	4.30	10.01	10.03	$C_{13}H_{16}NO_4PS$	4.47	9.89	10.23

[a] Obtained by column chromatography. [b] Consistent with published data [4]. [c] Yield by method *a*.

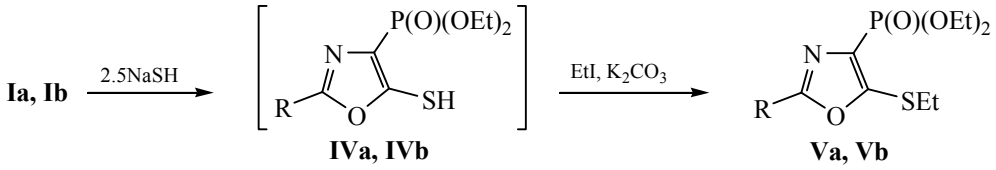
medium. Along with the title compounds **IIa–IIg**, which are formed with average yields of 61–71% (Table 1), we isolated also the thiophenol disulfides. The products of substitution **IIa–IIg** are white crystalline substances or viscous transparent oils, which can be stored for long periods without change.

^{1}H NMR spectra of compounds **II** indicate the nonequivalence of the thiophenol fragments, as their signals are recorded separately (Table 1). The signals of the NH group protons appear as broadened singlets in the region of 7.17–8.30 ppm. In the ^{31}P NMR spectra the signals of phosphorus nuclei are in the region of 10.1–11.7 ppm. The IR spectra of compounds **II** include a strong narrow absorption band of C=O groups at 1619–1689 cm^{-1}, that of P=O group at 1227–1247 cm^{-1}, and of P–O–C group at 1014–1090 cm^{-1} as a strong broad band.

Boiling compounds **IIa–IIg** in anhydrous dioxane with an excess of freshly prepared silver carbonate affords in high yield (78–92%) 4-phosphorylated oxazoles **IIIa–IIIg** . This process can be traced spectrally. Thus, the IR spectra of compounds **III**, in contrast to precursors **II**, do not contain the absorption bands at 1619–1689 cm^{-1} (C=O) and at 3157–3210 cm^{-1} (NH). In the ^{31}P NMR spectra the signals of the phosphorus nuclei of compounds **III** are in the region of 6–8.5 ppm. ^{1}H NMR spectra contain the signals of aliphatic and aromatic protons with the respective ratios of integral intensities.

The second method is more convenient for the synthesis of 5-alkylthiooxazole derivatives (Scheme 2), because it allows avoiding handling of alkylmercaptanes. Thus, the processing dichloroenamides **Ia**, **Ib** with an excess of sodium hydrogen sulfide resulted in 5-mercaptooxazoles **IVa**, **IVb**, respectively, which without further purification were alkylated with ethyl iodide in the presence of potassium carbonate. Compound **Va, Vb** were isolated in 73–79% yields.

Scheme 2.

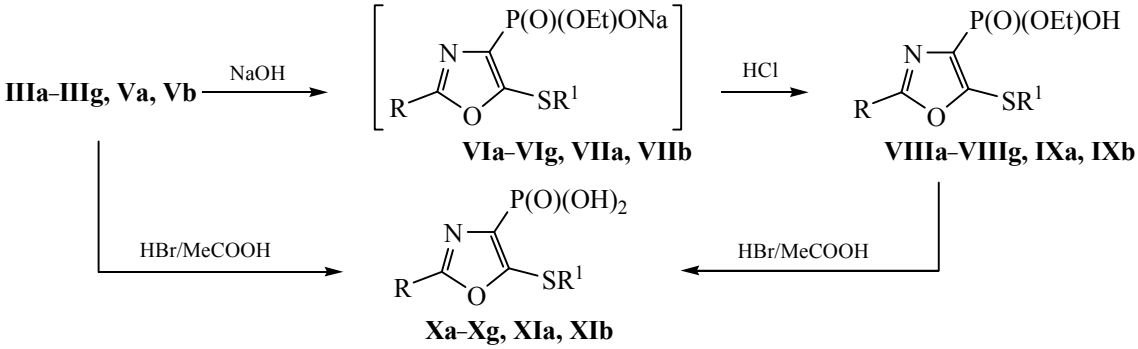


R = Me (**IVa, Va**); 4-MeC_6H_4 (**IVb, Vb**).

The 4-phosphorylated derivatives of 5-mercaptooxazole **IIIa–IIIg, Va, Vb** are white crystalline substances or transparent odorless oils, stable at room temperature for a long time.

In order to expand the range of biologically active substances we studied the hydrolysis of the phosphonic acids esters **IIIa–IIIg, Va, Vb** (Scheme 3). Treating these compounds with an excess of sodium hydroxide

Scheme 3.



R = Me (**IIIa–IIIc, VIa–VIc, VIIa, VIIIa–VIIIc, IXa, Xa–Xc, XIa**); Ph (**IIId, IIIe, VId, VIe, VIId, VIIe, VIIId, VIIIe, Xd, Xe**); 4-MeC_6H_4 (**IIIf, IIIg, VIf, VIg, VIIb, VIIIf, VIIIg, IXb, Xf, Xg, XIb**); R^1 = Ph (**IIIa, VIa, VIIIa, Xa**); 4-MeC_6H_4 (**IIIb, IIId, IIIf, VIb, VId, VIf, VIIIb, VIIId, VIIIf, Xb, Xd, Xf**); 4-ClC_6H_4 (**IIIc, IIIe, IIIg, VIIc, VIIe, VIIg, VIIIc, VIIIe, VIIIg, Xc, Xe, Xg); Et (Va, Vb, VIIa, VIIb, IXa, IXb, XIa, XIb**).

Table 2. Spectral data of synthesized compounds

Comp. no.	IR spectrum, ν, cm^{-1} [a]	^1H NMR spectrum, δ, ppm[b]	δ_P, mmp[b]	$[M + 1]^+$
IIa	1233 (P=O), 1119 (P–O–C), 962 (P–O–C–C)	1.32 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.13 s (3H, CH_3), 4.19 m (4H, OCH_2), 7.06–7.53 m (11H, C_6H_5, NH)	11.8	438
IIb	3157 (N–H), 1619 (C=O), 1227 (P=O), 1017 (P–O–C), 976 (P–O–C–C)	1.33 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.09 s (3H, CH_3), 2.32 s (6H, CH_3), 4.20 m (4H, OCH_2), 6.94–7.03 m (8H, C_6H_4), 7.17 br.s (1H, NH)	10.6	466
IIc	3208 (N–H), 1689 (C=O), 1247 (P=O), 1014 (P–O–C), 975 (P–O–C–C)	1.33 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.09 s (3H, CH_3), 4.21 m (4H, OCH_2), 7.02–7.21 m (8H, C_6H_4), 8.30 br.s (1H, NH)	10.1	507
IId	3210 (N–H), 1661 (C=O), 1228 (P=O), 1025 (P–O–C), 960 (P–O–C–C)	1.33 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.30 s (3H, CH_3), 2.33 s (3H, CH_3), 4.22 m (4H, OCH_2), 6.96–7.84 m (13H, C_6H_5, C_6H_4), 7.91 br.s (1H, NH)	11.2	528
IIe	3188 (N–H), 1664 (C=O), 1237 (P=O), 1027 (P–O–C), 963 (P–O–C–C)	1.33 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 4.21 m (4H, OCH_2), 7.03–7.88 m (13H, C_6H_5, C_6H_4), 7.97 br.s (1H, NH)	10.5	569
IIf	3190 (N–H), 1655 (C=O), 1234 (P=O), 1090 (P–O–C), 1025 (P–O–C–C)	1.32 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.30 s (3H, CH_3), 2.33 s (3H, CH_3), 2.40 s (3H, CH_3), 4.18 m (4H, OCH_2), 6.96–7.79 m (12H, C_6H_4), 7.86 br.s (1H, NH)	10.8	542
IIg	3185 (N–H), 1659 (C=O), 1238 (P=O), 1232 (P–O–C), 973 (P–O–C–C)	1.31 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.42 s (3H, CH_3), 4.20 m (4H, OCH_2), 7.03–7.77 m (12H, $3C_6H_4$), 7.98 s (1H, NH)	10.6	583
IIIa	1261 (P=O), 1021 (P–O–C), 969 (P–O–C–C)	1.31 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.41 s (3H, CH_3), 4.16 m (4H, $O\underline{CH_2}$), 7.26–7.40 m (5H, C_6H_5)	8.2	328
IIIb	1245 (P=O), 1024 (P–O–C), 976 (P–O–C–C)	1.35 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.33 s (3H, CH_3), 2.43 s (3H, CH_3), 4.21 m (4H, OCH_2), 7.13–7.37 m (4H, C_6H_4)	8.4	342
IIIc	1269 (P=O), 1020 (P–O–C), 971 (P–O–C–C)	1.03 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.14 s (3H, CH_3), 3.90 m (4H, OCH_2), 6.98–7.08 m (4H, C_6H_4)	6.7	362
IIId	1222 (P=O), 1014 (P–O–C), 967 (P–O–C–C)	1.41 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.38 s (3H, CH_3), 4.28 m (4H, OCH_2), 7.13–7.98 m (9H, C_6H_5, C_6H_4)	7.2	404
IIIe	1271 (P=O), 1028 (P–O–C), 974 (P–O–C–C)	1.38 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 3.27 m (4H, OCH_2), 6.31–7.16 m (9H, C_6H_5, C_6H_4)	6.6	424
IIIf	1298 (P=O), 1021 (P–O–C), 977 (P–O–C–C)	1.39 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.35 s (3H, CH_3), 2.40 s (3H, CH_3), 4.28 m (4H, $O\underline{CH_2}$), 7.15–7.89 m (8H, C_6H_4)	8.5	418
IIIg	1298 (P=O), 1017 (P–O–C), 977 (P–O–C–C)	1.38 t (6H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.40 s (3H, CH_3), 4.26 m (4H, OCH_2), 7.25–7.90 m (8H, $2C_6H_4$)	7.8	438
Va	–	1.33 m (9H, $OCH_2\underline{CH_3}$, $SCH_2\underline{CH_3}$), 2.47 s (3H, CH_3), 2.98 q (2H, SCH_2, $^3J_{HH}$ 7.2 Hz), 4.17 m (4H, OCH_2)	8.3	280
Vb	–	1.37 m (9H, $OCH_2\underline{CH_3}$, $SCH_2\underline{CH_3}$), 2.39 s (3H, CH_3), 3.09 q (2H, SCH_2, $^3J_{HH}$ 7.2 Hz), 4.22 m (4H, OCH_2), 7.24–7.91 m (4H, C_6H_4)	9.2	358
VIa	1247 (P=O)	1.08 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.34 s (3H, CH_3), 3.77 m (2H, OCH_2), 7.30 m (5H, C_6H_5)	2.3	–
VIb	1231 (P=O)	1.07 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.20 s (3H, CH_3), 2.30 s (3H, CH_3), 3.76 m (2H, OCH_2), 7.12–7.22 m (4H, C_6H_4)	2.9	–
VId	–	1.05 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.26 s (3H, CH_3), 3.76 m (2H, OCH_2), 7.15–7.92 m (9H, C_6H_5, C_6H_4)	–3.1	–
VIIa	–	1.16 m (6H, $OCH_2\underline{CH_3}$, $SCH_2\underline{CH_3}$), 2.34 s (3H, CH_3), 2.84 q (2H, SCH_2, $^3J_{HH}$ 7.2 Hz), 3.78 m (2H, OCH_2)	1.8	–

Table 2. (Contd.)

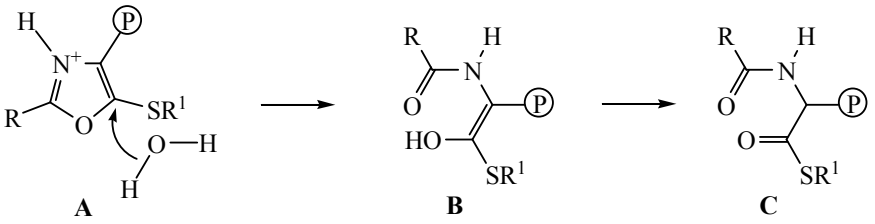
Comp. no.	IR spectrum, ν, cm^{-1} [a]	^1H NMR spectrum, δ, ppm[b]	δ_P, mmp[b]	$[M + 1]^+$
VIIIa	1256 (P=O), 1020 (P–O–C), 960 (P–O–C–C)	1.14 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.41 s (3H, CH_3), 3.89 m (2H, OCH_2), 7.34 m (5H, C_6H_5)	3.0	300
VIIIc	1285 (P=O), 1013 (P–O–C), 948 (P–O–C–C)	1.35 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.46 s (3H, CH_3), 4.21 m (2H, OCH_2), 7.27–7.39 m (4H, C_6H_4)	1.6	334
VIIId	1249 (P=O), 1019 (P–O–C), 957 (P–O–C–C)	1.21 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.28 s (3H, CH_3), 4.00 m (2H, OCH_2), 7.21–7.90 m (9H, C_6H_5, C_6H_4)	2.2	376
VIIIe	1242 (P=O), 1037 (P–O–C), 963 (P–O–C–C)	1.21 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 4.01 m (2H, OCH_2), 7.46–7.93 m (9H, C_6H_5, C_6H_4)	2.4	396
VIIIf	1241 (P=O), 1037 (P–O–C), 956 (P–O–C–C)	1.22 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.28 s (3H, CH_3), 2.36 s (3H, CH_3), 4.01 m (2H, OCH_2), 7.22–7.80 m (8H, $2C_6H_4$)	2.9	390
VIIIg	1241 (P=O), 1040 (P–O–C), 960 (P–O–C–C)	1.21 t (3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$ 7.0 Hz), 2.37 s (3H, CH_3), 4.02 m (2H, OCH_2), 7.35–7.82 m (8H, $2C_6H_4$)	2.4	410
IXb	–	1.24–1.30 m (6H, $SCH_2\underline{CH_3}$, $OCH_2\underline{CH_3}$), 2.39 s (3H, CH_3), 3.11 m (2H, SCH_2), 4.00 m (2H, OCH_2), 7.38–7.88 m (4H, C_6H_4)	4.9	328
Xa	1237 (P=O)	2.43 s (3H, CH_3), 7.31–7.36 m (5H, C_6H_5)	1.1	272
Xb	1239 (P=O)	2.28 s (3H, CH_3), 2.40 s (3H, CH_3), 7.17–7.28 m (4H, C_6H_4)	1.3	286
Xc	1239 (P=O)	2.42 s (3H, CH_3), 7.34–7.43 m (4H, C_6H_4)	0.8	307
Xd	1209 (P=O)	2.29 s (3H, CH_3), 7.21–7.90 m (9H, C_6H_5, C_6H_4)	2.8	348
Xe	1204 (P=O)	7.45–7.93 m (9H, C_6H_5, C_6H_4)	0.5	369
Xf	1240 (P=O)	2.28 s (3H, CH_3), 2.36 s (3H, CH_3), 7.21–7.80 m (8H, C_6H_4)	1.0	362
Xg	1240 (P=O)	2.37 s (3H, CH_3), 7.35–7.83 m (8H, C_6H_4)	0.6	383
XIb	1222 (P=O)	1.29 t (3H, $SCH_2\underline{CH_3}$, $^3J_{HH}$ 7.2 Hz), 2.39 s (3H, CH_3), 3.07 q (2H, SCH_2, $^3J_{HH}$ 7.2 Hz), 7.38–7.87 m (4H, C_6H_4)	3.2	300
XII	3309 (N–H), 1678 (C=O), 1212 (P=O)	2.00 s (3H, CH_3), 2.34 s (3H, CH_3), 4.87 d.d (1H, CHP, $^2J_{HP}$ 22.5, $^3J_{HH}$ 6.0 Hz), 7.24–7.26 m (4H, C_6H_4), 8.80 br.s (1H, NH)	9.5	304

[a] IR spectra of compounds **IIc; IIIa–IIIc, Va, Vb** are recorded from the dichloromethane solution, of other compounds, from KBr tablets.
[b] Solvent for compounds **IIb–IIg, IIIa–IIIg, Va, Vb** $CDCl_3$, for **VIa, VIb** and **VIIa**, D_2O, for **VId, VIIIa–VIIId, IXb, Xb–Xg, XIb**, DMSO-d_6.

in ethanol at 20–25ºC provides a saponification of one ethoxy group with the formation of ethyl sodium phosphonates **VIa–VIg**, **VIIa**, and **VIIb**, respectively. Compounds **VIa**, **VIb**, **VId**, and **VIIa** were isolated and identified by ^1H, 31P NMR, and IR spectra. They are white hygroscopic crystalline substances. In their ^{31}P NMR spectra the signals of the phosphorus nuclei are in the region of –3.1 to 2.9 ppm.

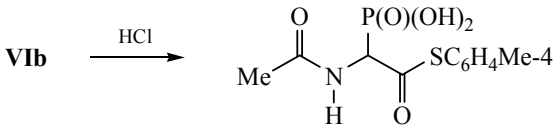
Acidification of aqueous solutions of salts **VIa, VIc–VIg, VIIb** with concentrated hydrochloric acid leads to free monosubstituted phosphonic esters, acids **VIIIa, VIIIc–VIIIg, IXb**. In the ^{31}P NMR spectra of these compounds the signals of the phosphorus nuclei are recorded at 6.1–4.9 ppm. In the ^1H NMR spectra of compounds **VIIIa, VIIIc–VIIIg, IXb** there are signals of aromatic and aliphatic protons with the corresponding ratios of the integral intensities.

It should be noted that compounds **VIIIa, VIIIc–VIIIg, IXb** are formed with the average yields 63–85%. One of the minor products are phosphonoglycine thio-derivatives, which was documented by means of gas chromatography–mass spectra of the reaction mixtures. This process can be represented by the scheme, which involves protonation of oxazole ring **A**, ring opening **A→B**, and prototropic transformation **B→C**:



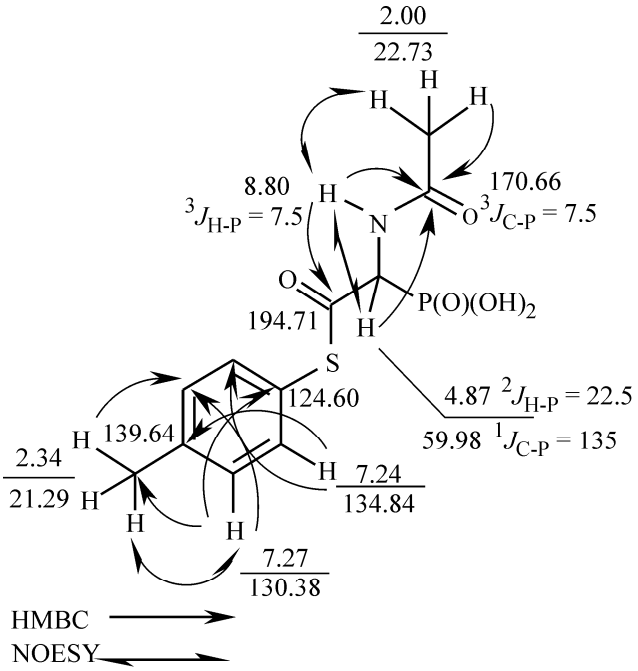
A **B** **C**

At the hydrolysis of compound **VIb** was isolated phosphonoglycine **XII** only, in 56% yield:



XII

Compound **VIIIb** was not detected even in trace amounts. The hydrolysis of compound **VIIa** was carried out similarly without isolation of compound **IXa**. It proceeds with oxazole ring opening, however the compounds of type **B** were not isolated due to their subsequent destruction. Such extreme behavior of compounds **VIb** and **VIIa** at the hydrolysis can be ascribed to the influence of electron-donating methyl group in the position 2, as well as of electron-donating 4-methylphenylsulfanyl or ethylsulfanyl group in the 5 position of oxazole cycle, which contributes to the ease of its protonation and cleavage.



The main correlations (arrows), assignment of signals (ppm), and coupling constants (Hz) in ^{1}H and ^{13}C NMR spectra of compound **XII**.

In the ^{1}H NMR spectrum of phosphonic acid **XII** there is a characteristic one-proton signal of the N–CH–P group at δ 4.87 ppm as a doublet of doublets ($^{2}J_{HP}$ 22.5 Hz, $^{3}J_{HP}$ 8.8 Hz). In the ^{31}P NMR spectrum the signal of phosphorus nucleus is also a doublet of doublets at δ 9.49 ppm ($^{2}J_{HP}$ 22.5 Hz, $^{3}J_{HP}$ 6.0 Hz). In the IR spectrum the NH vibrations occur as a narrow band at ν 3309 cm^{-1}, C=O group vibrations, as a double band at ν 1678 cm^{-1}, and P=O, at ν 1212 cm^{-1} as a band of moderate intensity.

The structure of compound **XII** was proved unambiguously by the comprehensive NMR analysis (NOESY, COSY, HSQC, HMBC). Figure shows the assignment of the ^{1}H and ^{13}C signals, and Table 3 lists a full set of the found correlations. Based on the correlations in the NOESYspectrum 2.34 ppm C$\underline{H}_3$C$_6$H$_4$ ↔ 7.27 ppm 3,5–$\underline{H}$ (C$_6$H$_4$), in HMBC spectrum 7.27 ppm 3,5-$\underline{H}$ (C$_6$H$_4$) → 124.60 ppm 1-$\underline{C}$ (C$_6$H$_4$), 7.24 ppm 2,6-$\underline{H}$ (C$_6$H$_4$) → 139.64 ppm 4-$\underline{C}$ (C$_6$H$_4$) all the signals of the 4-CH$_3$C$_6$H$_4$S fragment of the molecule can be assigned. The signals NOESY 2.00 ppm C$\underline{H}_3$C(O) ↔ 8.80 ppm N$\underline{H}$, HMBC 2.00 ppm C$\underline{H}_3$C(O) → 170.66 ppm CH$_3\underline{C}$(O), 8.80 ppm N$\underline{H}$ → 170.66 ppm CH$_3\underline{C}$(O) confirm the presence of a CH$_3$C·(O)NH fragment. In the NHCH[P(O)(OH)$_2$]C(O)S fragment it is easy to assign the ^{1}H and ^{13}C signals, which are split due to coupling with the phosphorus atom. The cross-peaks in the two-dimensional experiments NOESY 8.80 ppm N$\underline{H}$ ↔ 4.87 ppm C$\underline{H}$[P(O)(OH)$_2$], HMBC 8.80 ppm N$\underline{H}$ → 194.71 ppm $\underline{C}$(O)S complement the information on the chemical shifts of this fragment in the compound **XII**. The assignment made on the basis of the ^{1}H, ^{13}C, and ^{31}P NMR spectra, as well as of the constants J_{HP} and J_{CP} fully confirm the structure of compound **XII**.

The most appropriate reagent for the complete hydrolysis of the diethoxyphosphoryl group in our case was the saturated solution of hydrogen bromide in water-free acetic acid [6, 7]. The hydrolysis of esters

IIIa–IIIg, Va, Vb, as well as hemiesters **VIIIa, VIIIc–VIIIg and IXb** was carried out at room temperature over 24 h. The phosphonic acids **Xa–Xg, XIb** are formed in a high yield (62–88%). However, we failed to isolate analytically pure compound **XIa**. Compounds **Xa–Xg, XIb** are white crystalline substances that are stored for long periods without change. In the ^{31}P NMR spectra of these compounds signals of the phosphorus nuclei fall to the range of 0.5–3.2 ppm.

Thus, in the course of the work different approaches to the synthesis of ethyl esthers of 2-methyl(aryl)-5-ethyl(aryl) thio-1,3-oxazole-4-ylphosphonic acids were studied and their alkaline and acid hydrolysis was investigated, which led to the formation of 5-mercapto-1,3-oxazole-4-ylphosphonic acid or the corresponding monoethyl esters. The possibility of splitting the 4-phosphorylated 5-mercapto-1,3-oxazoles under the action of acidic reagents, which leads to the formation of phosphonoglycine thio-derivatives was demonstrated.

EXPERIMENTAL

IR spectra of the compounds were recorded on a Vertex 70 spectrometer from KBr tablets. NMR spectra were obtained on a Bruker AVANCE DRX-500 instrument: ^{1}H (500 MHz), ^{31}P (202 MHz), ^{13}C (125 MHz), from solutions in DMSO-d_6 or $CDCl_3$. Chemical shifts are given relative to TMS (internal reference) or 85% phosphoric acid (external reference). Melting points were determined on a Fisher Johns instrument. The LC-MS spectra were recorded using liquid chromatography–mass spectrometric system for HPLC of Agilent 1100 Series, equipped with a diode matrix with a mass selective detector Agilent LC MSD SL with fast switching of the positive/negative ionization modes. The LC-MS analysis parameters are as follows: column Zorbax SB-C18 1.8 mm 4.6×15mm (PN 821 975 932), solvents: A, acetonitrile–water (95:5), 0.1% trifluoroacetic acid, B, 0.1% aqueous trifluoroacetic acid, eluent flow 3 ml min^{-1}, injection volume 1 ml, UV detectors 215, 254, 285 nm, the ionization method is chemical ionization at atmospheric pressure (APCI), scan range *m*/*z* 80–1000. The reaction progress monitoring was carried out by TLC.

Diethyl 1-acylamino-2,2-bis(arylthio)ethenylphosphonates (IIa–IIg). To a solution of 0.01 mol of a compound **Ia–Ic** in 50 ml of anhydrous acetonitrile was added 0.022 mol of the corresponding thiophenol and 0.025 mol of triethylamine, and the mixture was kept for 8 h at 20–25°C. The precipitate formed was filtered off, the solvent was removed in vacuo, the residue was washed with water, dried, and purified by crystallization. In the case of compounds **II**a and **IIc** the residue was treated with 30 ml of water, extracted with chloroform (3×25ml), the extract was dried over $CaCl_2$ and purified by column chromatography (eluent dichloromethane–methanol, 95:5). Compound **IIa** solidified in 2 weeks.

Diethyl 2-methyl(aryl)-5-arylthio-1,3-oxazol-4-ylphosphonates (IIIa–IIIg). To a solution of 0.01 mol of a compound **IIa–IIg** in 50 ml of anhydrous dioxane was added 0.04 mol of freshly prepared silver carbonate, the suspension was refluxed for 8 h, the precipitate was filtered off, the solvent was removed in vacuo, and the residue was purified by crystallization. Compounds **IIIa–IIIc** were reprecipitated from petroleum ether.

Diethyl 2-methyl(4-methylphenyl)-5-mercapto-1,3-oxazole-4-ylphosphonates (IVa, IVb). To a solution of 0.01 mol of a compound **Ia, Ib** in 40 ml of anhydrous methanol under argon was added 0.025 mol of sodium hydrogen sulfide. The solution was stirred for 48 h at 20–25°C, the precipitate was filtered off,

Table 3. A list of the correlations in the COSY, NOESY, HSQC, HMBC spectra of compound **XII**

^{1}H, δ	^{1}H, δ		^{13}C, δ_C	
	COSY	NOESY	HSQC	HMBC
2.00	–	8.80	22.73	170.66
8.80	4.87	2.00, 4.87	–	170.66
4.87	8.80	8.80	59.98	170.66, 194.71
7.24	7.27	7.27	134.84	134.84, 139.64,
7.27	2.34, 7.24	2.34, 7.24	130.38	130.38, 124.60, 21.29
2.34	7.27	7.27	21.29	139.64, 130.38

the solvent was removed in a vacuum, to the residue was added 30 ml of water, the product was extracted with diethyl ether (3×25 ml). The extract was dried over $MgSO_4$, the solvent was removed in vacuo, and compound **IVa, IVb** was used without purification for further transformations.

Diethyl 2-methyl(4-methylphenyl)-5-ethylthio-1,3-oxazole-4-ylphosponates (Va, Vb). To a solution of 0.01 mol of one of compound **IVa, IVb** in 30 ml of anhydrous tetrahydrofuran was added 0.02 mol of anhydrous potassium carbonate and 0.015 mol of ethyl iodide. The mixture was stirred for 24 h at 20–25°C, the precipitate was filtered off, the solvent was removed in a vacuum, and compound **Va, Vb** was purified by column chromatography (eluent dichloromethane:methanol, 95:5).

Sodium monoethyl 2-methyl(aryl)-5-ethyl(aryl)-thio-1,3-oxazole-4-ylphosphonates (VIa–VIg, VIIa, VIIb). To a solution of 0.01 mol of compound **IIIa–IIIg, Va, Vb** in 30 ml of ethanol was added a solution of 0.03 mol of sodium hydroxide in 50 ml of ethanol. The mixture was stirred for 8 h at 20–25°C, the solvent was removed in a vacuum, and compound **VIa–VIg, VIIa, VIIb**) was used for further transformation without purification.

Monoethyl 2-methyl(aryl)-5-ethyl(aryl)thio-1,3-oxazol-4-ylphosphonates (VIIIa, VIIIc–VIIIg, IXb). To a solution of 0.01 mol of a compound **VIa, VIc–VIg, VIIb** in 15 ml of water was added conc. hydrochloric acid to pH ~1–2, the mixture was kept for 12 h at 20–25°C, the precipitate was filtered off, dried, and oxazole **VIIIa, VIIIc–VIIIg, IXb** was purified by recrystallisation.

2-Methyl(aryl)-5-ethyl(aryl) thio-1,3-oxazol-4-ylphosphonic acids (Xa–Xg, XIa, XIb). *a*. A solution of 0.01 mole of compound **IIIa–IIIg, Va, Vb** in 15 ml of anhydrous acetic acid saturated with hydrogen bromide was kept for 24 h at 20–25°C. The solvent was then removed in vacuo, the residue was treated with water, filtered, dried, and analysed without further purification.

b. A solution of 0.01 mol of a compound **VIIa, VIIc–VIIg, IXb** in 15 ml of anhydrous acetic acid saturated with hydrogen bromide was kept for 24 h at 20–25°C. The solvent was then removed in vacuo, the residue was treated with water, filtered, dried, and analyzed without further purification. The compounds **Xa, Xc–Xg, XIb** yield was 82–86%.

Mixed samples of compounds **Xa, Xc–Xg, XIb** obtained by the methods *a* or *b*, did not show melting point depression, and their IR and ^1H NMR spectra were identical.

{1-Acetamido-2-[(4-methylphenyl)sulfanyl]-2-oxo-ethyl}phosphonic acid (XII). To a solution of 0.01 mol of the monosodium salt **VIb** in 10 ml of water was added conc. hydrochloric acid to pH ~1–2. The mixture was kept for 24 h at 5–10°C, the precipitate was filtered off, dried, and then dispersed in 10 ml of dichloromethane. The mixture was boiled for 2 min, cooled, the precipitate was filtered off, dried in a vacuum, and analyzed without further purification.

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