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Synthesis of New 4-Phosphorylated Derivatives of 5-Amino-1,3-oxazole

K. M. Kondratyuk, A. V. Golovchenko, T. V. Osadchuk, and V. S. Brovarets

Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02094 Ukraine
e-mail: brovarets@bpci.kiev.ua

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Abstract—The *N*-1,1,1,2-Tetrachloroethylamides were found to react with diethyl amidophosphites via the Arbuzov reaction to afford *N*-substituted amides of ethyl 1-acylamino-2,2,2-trichloroethylphosphonic acids. A convenient method for the synthesis of new 4-phosphorylated 5-amino-1,3-oxazoles on their basis was developed.

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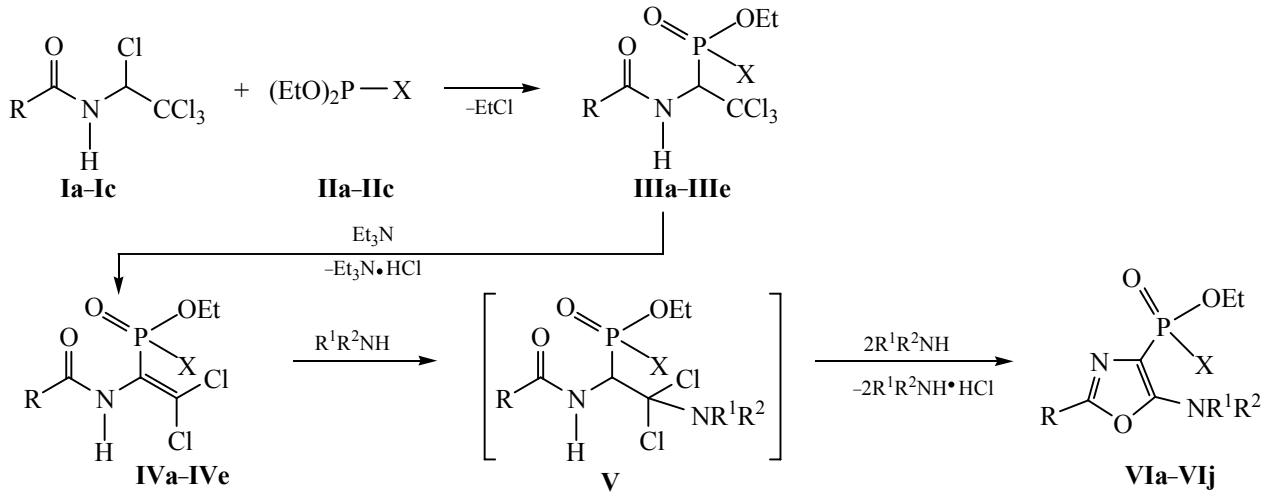
Among the derivatives of 5-aminooxazole containing a dialkoxyphosphoryl group in the 4 position there are substances possessing significant insecticidal and acaricidal activity [1], as well as antiblastic properties [2]. In order to expand the spectrum of biological activity of the substances we attempted to synthesize new 4-phosphorylated derivatives of 1,3-oxazole (Scheme 1, Table 1). We first involved the amidophosphites **II** into the reaction with 1,2,2,2-tetrachloroethylamides **I**. The reaction proceeds via the Arbuzov rearrangement to give the target products in high yields (63–80%). However, it is complicated by side reactions, whose occurrence is evidenced by the formation of a small amount of the precipitate of hydrochloride of the amine present in the amidophosphite composition. According to the ^{31}P NMR spectra (Table 2), compounds **III** were obtained as diastereomers mixtures in the ratio unchanged after the recrystallization from cyclohexane or benzene.

The ^{1}H NMR spectra of compounds **III** also contain a double set of proton signals of all groups.

Scheme 1.



R = Me (**Ia**, **IIIa**–**VIa**, **VIb**), Ph (**Ib**, **IIIb**, **IVb**, **VIc**, **VId**), 4-MeC_6H_4 (**Ic**, **IIIc**–**IIIe**, **IVc**–**IVe**, **VIe**–**VIj**); X = $N(CH_2)_5$ (**IIa**, **IIIa**–**IIIc**, **IVa**–**IVc**, **VIa**–**VIf**), $N(CH_2)_4O$ (**IIb**, **IIId**, **IVd**, **IVg**, **IVh**), $NHCH_2Ph$ (**IIc**, **IIIe**, **IVe**, **VIi**, **VIj**); R^1R^2N = $(CH_2)_5N$ (**VIa**, **VIc**, **VIe**, **VIg**, **VIi**), $O(CH_2)_4N$ (**VIb**, **VId**, **VIf**, **VIh**, **VIj**).

Table 1. Yields, melting points, and elemental analyses of synthesized compounds **III, IV, IX, XII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %		Formula	Calculated, %	
			N	P		N	P
IIIa	80	147–149 (C_6H_6–hexane, 1:1)	7.54	8.51	$C_{11}H_{20}Cl_3N_2O_3P$	7.66	8.47
IIIb	69	126–127 (C_6H_6–hexane, 1:1)	6.40	7.03	$C_{16}H_{22}Cl_3N_2O_3P$	6.55	7.24
IIIe	63	148–150 (C_6H_6–hexane, 1:1)	5.88	6.82	$C_{19}H_{22}Cl_3N_2O_3P$[a]	6.04	6.68
IVa	99	104–105 (C_6H_6)	8.23	9.23	$C_{11}H_{19}Cl_2N_2O_3P$[b]	8.51	9.41
IVb	98	183–184 (C_6H_6)	6.94	7.77	$C_{16}H_{21}Cl_2N_2O_3P$[c]	7.16	7.92
IVc	94	176–178 (C_6H_6)	6.76	7.81	$C_{17}H_{23}Cl_2N_2O_3P$[d]	6.91	7.64
IVd	97	169–170 (2-propanol)	6.65	7.54	$C_{16}H_{21}Cl_2N_2O_4P$[e]	6.88	7.61
IVe	96	147–149 (2-propanol)	6.34	7.36	$C_{19}H_{21}Cl_2N_2O_3P$[f]	6.56	7.25
VIa	49	Oil (hexane)	12.04	9.23	$C_{16}H_{28}N_3O_3P$	12.31	9.07
VIb	61	Oil (hexane)	11.96	9.11	$C_{15}H_{26}N_3O_4P$	12.24	9.02
VIc	73	65–67 (hexane)	10.23	7.82	$C_{21}H_{30}N_3O_3P$	10.42	7.68
VId	67	Oil (hexane)	10.11	7.59	$C_{20}H_{28}N_3O_4P$	10.36	7.64
VIe	58	99–100 (petroleum ether)	9.88	7.38	$C_{22}H_{32}N_3O_3P$	10.07	7.42
VIf	66	115–116 (petroleum ether)	9.76	7.46	$C_{21}H_{30}N_3O_4P$	10.02	7.38
VIg	53	85–86 (petroleum ether)	9.87	7.48	$C_{21}H_{30}N_3O_4P$	10.02	7.38
VIh	64	105–106 (petroleum ether)	9.64	7.46	$C_{20}H_{28}N_3O_5P$	9.97	7.35
VIi	60	129–131 (2-propanol)	9.34	7.24	$C_{24}H_{30}N_3O_3P$	9.56	7.05
VIj	61	141–142 (2-propanol)	9.31	7.14	$C_{23}H_{28}N_3O_4P$	9.52	7.02
XIa	70	71–72 (hexane)	7.51	8.61	$C_{18}H_{25}N_2O_4P$	7.69	8.50
XIb	72	82–83 (hexane)	7.22	8.38	$C_{19}H_{27}N_2O_4P$	7.40	8.19
XIIa	71	121–122 (acetone–water, 2:1)	7.78	8.79	$C_{17}H_{23}N_2O_4P$	8.00	8.84
XIIb	70	131–133 (acetone–water, 2:1)	7.74	8.83	$C_{17}H_{23}N_2O_4P$	8.00	8.84

[a] Found, Cl, %: 22.88. Calculated, Cl, %: 22.94. [b] Found, Cl, %: 21.42. Calculated, Cl, %: 21.54. [c] Found, Cl, %: 18.20. Calculated, Cl, %: 18.12. [d] Found, Cl, %: 17.58. Calculated, Cl, %: 17.50. [e] Found, Cl, %: 17.56. Calculated, Cl, %: 17.41. [f] Found, Cl, %: 16.44. Calculated, Cl, %: 16.60

Thus, the proton groups RCHNH appear as two doublets of doublets at δ 5.09–5.78 ppm (for compound **IIIb**: $^2J_{HP}$ 17.4, $^3J_{HH}$ 9.0 Hz) owing to the spin-spin coupling with the phosphorus nucleus and with the proton of the amide group. The proton of the amide group appears as two doublets of doublets at δ 8.79 and 9.26 ppm (for compound **IIIb**: $^3J_{HH}$ 9.0, $^3J_{HP}$ 1.88 Hz) due to the spin-spin coupling with the methine proton and with the phosphorus nucleus. In the case of compound **IIIe** the signal of $PNHCH_2Ph$ is observed at 5.45–5.75 ppm as a complex multiplet, as well as the signal of methylene groups, as a complex multiplet at 4.14 ppm. In the IR spectra of compounds **IIIa**–**IIIe** there are intensive absorption bands of C=O group at 1648–1682 cm^{-1} and P=O group at 1229–1237 cm^{-1}. Compounds **IIIa**–**IIIe** are stable substances that can be stored at room temperature for a long time, but their treatment with an excess of triethylamine in tetrahydrofuran leads to eliminating hydrogen chloride to form the *N*-substituted amides of ethyl 1-acylamino-2,2-dichloroethenylphosphonates **IV**.

The method we suggested for the synthesis of such compounds expands and to a certain extent simplifies

Table 2. Spectral data of compounds synthesized

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm	^{1}H NMR spectrum (DMSO-d_6), δ_P, ppm
IIIa	1229 (P=O), 1682 (C=O), 3255 (N–H)	17.6 m ($^2J_{HP}$ 17.1 Hz), 19.2 m ($^2J_{HP}$ 17.1 Hz) (1:0.75)[a]	1.27 m (3H, $\underline{CH_3}CH_2O$), 1.44 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.00 s, 2.02 s (3H, CH_3), 2.97 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 4.00 m (2H, $CH_3\underline{CH_2}O$), 5.09 m (1H, CH, $^2J_{HP}$ 17.1, $^3J_{HH}$ 9.9 Hz), 8.88–9.00 m (1H, NH, $^3J_{HH}$ 9.9, $^3J_{HP}$ 1.9 Hz)
IIIb	1237 (P=O), 1666 (C=O), 3170 (N–H)	17.6 m ($^2J_{HP}$ 17.4 Hz), 19.4 m ($^2J_{HP}$ 17.4 Hz) (1:0.8)[a]	1.18 t, 1.30 t (3H, $\underline{CH_3}CH_2O$), 1.41 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 3.02 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 4.00 m (2H, $CH_3\underline{CH_2}O$), 5.41 m (1H, CH, $^2J_{HP}$ 17.6, $^3J_{HH}$ 9.0 Hz), 7.50–7.93 m (5H, C_6H_5), 9.14, 9.26 m (1H, NH, $^3J_{HH}$ 9.0, $^3J_{HP}$ 1.9 Hz)
IIIe	1220 (P=O), 1648 (C=O), 3193 (N–H)	19.9 m, 20.5 m (1:0.5)[a]	1.17 m (3H, $\underline{CH_3}CH_2O$), 2.37 m (3H, CH_3), 3.99, 4.14 m (4H, $CH_3\underline{CH_2}O$, $\underline{CH_2}C_6H_5$), 5.45–5.75 m (2H, CH, $\underline{NH}CH_2C_6H_5$), 7.30–7.84 m (5H, C_6H_5), 8.75, 9.85 m (1H, NH)
IVa	1228 (P=O), 1673 (C=O), 3125 (N–H)	12.2	1.18 t (3H, $\underline{CH_3}CH_2O$), 1.44 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 1.92 s (3H, CH_3), 3.00 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.95 m (2H, $CH_3\underline{CH_2}O$), 9.36 s (1H, NH)
IVb	1219 (P=O), 1666 (C=O), 3119 (N–H)	12.3	1.18 t (3H, $\underline{CH_3}CH_2O$), 1.45 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 3.05 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.96 m (2H, $CH_3\underline{CH_2}O$), 7.51–7.89 m (5H, C_6H_5), 9.88 s (1H, NH)
IVc	1216 (P=O), 1663 (C=O), 3218 (N–H)	12.6	1.17 t (3H, $\underline{CH_3}CH_2O$), 1.44 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.37 s (3H, $\underline{CH_3}C_6H_4$), 3.04 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.95 m (2H, $CH_3\underline{CH_2}O$), 7.32–7.80 m (4H, C_6H_4), 9.80 s (1H, NH)
IVd	1232 (P=O), 1658 (C=O), 3205 (N–H)	11.8	1.21 t (3H, $\underline{CH_3}CH_2O$), 2.39 s (3H, $\underline{CH_3}C_6H_4$), 3.10 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$)], 3.53 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$)], 4.02 m (2H, $CH_3\underline{CH_2}O$), 7.29–7.79 m (4H, C_6H_4), 9.76 s (1H, NH)
IVe	1288 (P=O), 1648 (C=O), 3189 (N–H)	14.2 d ($^2J_{HP}$ 12.7 Hz)	1.14 m (3H, $\underline{CH_3}CH_2O$), 2.37 s (3H, CH_3), 3.97, 4.09 m (4H, $2CH_3\underline{CH_2}O$, $\underline{CH_2}C_6H_5$), 5.57 m (1H, $\underline{NH}CH_2C_6H_5$, $^2J_{HP}$ 12.7 Hz), 7.32–7.81 m (9H, C_6H_5, C_6H_4), 9.81 s (1H, NH)
VIa[b]	–	17.4	1.35 t (3H, $\underline{CH_3}CH_2O$), 1.50 m [6H, $(\underline{CH_2})_3(CH_2)_2NP$], 1.62 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.29 s (3H, CH_3), 3.13 m [4H, $(CH_2)_3(\underline{CH_2})_2NP$], 3.45 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 4.09 m (2H, $CH_3\underline{CH_2}O$)
VIb[b]	–	16.0	1.35 t (3H, $\underline{CH_3}CH_2O$), 1.53 m [6H, $(\underline{CH_2})_3(CH_2)_2NP$], 2.32 s (3H, CH_3), 3.13 m [4H, $(CH_2)_3(\underline{CH_2})_2NP$], 3.49 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$], 3.79 m [4H, $\underline{O}(\underline{CH_2})_2(CH_2)_2N$], 4.10 m (2H, $CH_3\underline{CH_2}O$)
VIc	1222 (P=O)	17.4	1.27 t (3H, $\underline{CH_3}CH_2O$), 1.48–1.60 m [12H, $(\underline{CH_2})_3(CH_2)_2NP$, $(\underline{CH_2})_3(CH_2)_2N$], 3.09 m [4H, $(CH_2)_3(\underline{CH_2})_2NP$], 3.55 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.97 m (2H, $CH_3\underline{CH_2}O$), 7.45–7.84 m (5H, C_6H_5)
VId[b]	–	17.2	1.37 t (3H, $\underline{CH_3}CH_2O$), 1.59 m [6H, $(\underline{CH_2})_3(CH_2)_2NP$], 3.21 m [4H, $(CH_2)_3(\underline{CH_2})_2NP$], 3.64, 3.82 m [8H, $O(\underline{CH_2})_2(\underline{CH_2})_2N$], 4.15 m (2H, $CH_3\underline{CH_2}O$), 7.39–7.86 m (5H, C_6H_5)
VIe	1227 (P=O)	12.9	1.27 t (3H, $\underline{CH_3}CH_2O$), 1.47–1.60 m [12H, $(\underline{CH_2})_3(CH_2)_2NP$, $(\underline{CH_2})_3(CH_2)_2N$], 2.34 s (3H, $\underline{CH_3}C_6H_4$), 3.08 m [4H, $(CH_2)_3(\underline{CH_2})_2NP$], 3.53 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.95 m (2H, $CH_3\underline{CH_2}O$), 7.30–7.71 m (4H, $CH_3C_6H_4$)
VIf	1230 (P=O)	16.6	1.27 t (3H, $\underline{CH_3}CH_2O$), 1.48 m [6H, $(\underline{CH_2})_3(CH_2)_2NP$], 2.35 s (3H, $\underline{CH_3}C_6H_4$), 3.09 m [4H, $(CH_2)_3(\underline{CH_2})_2NP$], 3.57 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$], 3.72 m [4H, $O(\underline{CH_2})_2(CH_2)_2N$], 3.95 m (2H, $CH_3\underline{CH_2}O$), 7.31–7.73 m (4H, $CH_3C_6H_4$)
VIg	1226 (P=O)	17.4	1.27 t (3H, $\underline{CH_3}CH_2O$), 1.60 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.35 s (3H, $\underline{CH_3}C_6H_4$), 3.10 m [4H, $O(CH_2)_2(\underline{CH_2})_2NP$], 3.55 m [8H $(CH_2)_3(\underline{CH_2})_2N$, $O(CH_2)_2(\underline{CH_2})_2NP$], 4.00 m (2H, $CH_3\underline{CH_2}O$), 7.21–7.74 m (4H, $CH_3C_6H_4$)

Table 2. (Contd.)

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm	^1H NMR spectrum (DMSO-d_6), δ_P, ppm
VIh[b]	1232 (P=O)	17.1	1.38 t (3H, $\underline{CH_3}CH_2O$), 2.39 s (3H, $\underline{CH_3}C_6H_4$), 3.26 m [4H, $O(CH_2)_2(\underline{CH_2})_2NP$], 3.64 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$], 3.73 m [4H, $O(\underline{CH_2})_2(CH_2)_2NP$], 3.84 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$], 4.09 m (2H, $CH_3\underline{CH_2}O$), 7.23–7.74 m (4H, $CH_3C_6H_4$)
VIi	1257 (P=O), 3142 (N–H)	17.4 d ($^2J_{HP}$ 12.6 Hz)	1.21 t (3H, $\underline{CH_3}CH_2O$), 1.57 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.34 s (3H, $\underline{CH_3}C_6H_4$), 3.53 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.95, 4.06 m (4H, $2CH_3\underline{CH_2}O$, $\underline{CH_2}C_6H_5$), 5.46 m [1H, $\underline{NH}CH_2C_6H_5$, ($^2J_{HP}$ 12.6 Hz)], 7.19–7.73 m (5H, C_6H_5, 4H, C_6H_4)
VIj[b]	1261 (P=O), 3202 (N–H)	20.1 d ($^2J_{HP}$ 12.7 Hz)	1.34 t (3H, $\underline{CH_3}CH_2O$), 2.40 s (3H, $\underline{CH_3}C_6H_4$), 3.41 m (1H, $\underline{NH}CH_2C_6H_5$, $^2J_{HP}$ 12.7 Hz), 3.65–3.71 m [4H, $O(CH_2)_2(\underline{CH_2})_2N$], 3.84 m [4H, $O(\underline{CH_2})_2(CH_2)_2N$], 4.11, 4.28 m (4H, $2CH_3\underline{CH_2}O$, $\underline{CH_2}C_6H_5$), 7.22–7.76 m (5H, C_6H_5, 4H, C_6H_4)
XIa	1291 (P=O)	13.6	1.27 t (6H, $2\underline{CH_3}CH_2O$), 1.61 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 3.59 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 4.05 m (4H, $2CH_3\underline{CH_2}O$), 7.47–7.84 m (5H, C_6H_5)
XIb	1282 (P=O)	13.8	1.37 t (6H, $2\underline{CH_3}CH_2O$), 1.68 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.38 s (3H, $\underline{CH_3}C_6H_4$), 3.60 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.18 m (4H, $2CH_3\underline{CH_2}O$), 7.21–7.77 m (4H, C_6H_4)
XIIa	1280 (P=O), 3421 (O–H)	9.6	1.23 t (3H, $\underline{CH_3}CH_2O$), 1.61 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 3.58 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.96 m (2H, $2CH_3\underline{CH_2}O$), 7.48–7.84 m (5H, C_6H_5)
XIIb	1248 (P=O), 3417 (O–H)	10.3	1.23 t (3H, $\underline{CH_3}CH_2O$), 1.59 m [6H, $(\underline{CH_2})_3(CH_2)_2N$], 2.36 s (3H, $\underline{CH_3}C_6H_4$), 3.54 m [4H, $(CH_2)_3(\underline{CH_2})_2N$], 3.95 m (2H, $2CH_3\underline{CH_2}O$), 7.30–7.71 m (4H, C_6H_4)

[a] The integral intensity ratio of signals indicated in parentheses corresponds to diastereomers ratio. [b] The spectrum was recorded in $CDCl_3$.

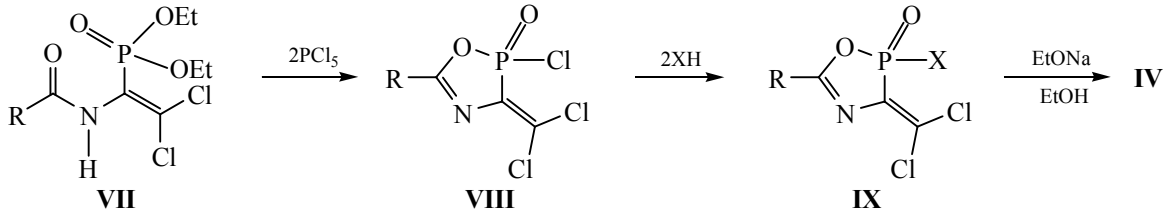
the known method [3], which involves the use of less accessible azlactones of 1-acylamino-2,2-dichloroethenylphosphonic monochlorides **VIII** (Scheme 2).

Due to the fact that in the course of the reaction **III** → **IV** an optically active center on the carbon atom disappears, the NMR spectra of compounds **IV** are greatly simplified. Thus, in the ^{31}P NMR spectra of compounds **IVa**–**IVd** there are single signals of the phosphorus nuclei at 11.82–12.60 ppm, in the case of compound **IVe** a doublet at 14.17 ppm ($^2J_{HP}$ 12.7 Hz). The ^1H NMR spectra of these compounds contain the signals of aromatic and aliphatic protons with the appropriate integral intensity ratios (Table 2). In the IR spectra of compounds **IVa**–**IVe** there are absorption bands of C=O groups at 1648–1673 cm^{-1} and P=O group at 1216–1288 cm^{-1}.

The treatment of compounds **IV** with an excess of piperidine or morpholine in anhydrous methanol leads to the cyclization to form *N*-substituted amides of ethyl [2-aryl(methyl)-5-morpholino(piperidino)-1,3-oxazol-4-yl]phosphonates **VI**. The participation of acylamino moiety of compounds **IV** in the formation of oxazole cycle is confirmed by the IR spectra, which do not contain the absorption bands in the range of 1648–1673 cm^{-1} (C=O), as well as at 3119–3218 cm^{-1} (N–H) **VIa**–**VIh**). In addition, a comparison of the signals of the methyl group in the ^1H NMR spectrum of compound **IVa** (δ 1.92 ppm) and the cyclization product **VIa** (δ 2.29 ppm) also indicates that the methyl group is in the position 2 of the oxazole ring [4, 5].

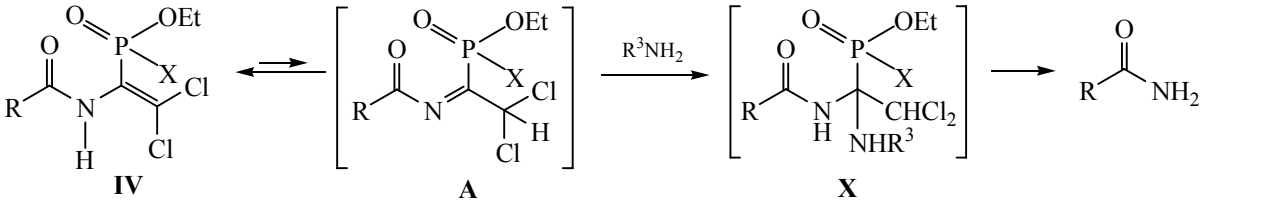
In the ^{31}P NMR spectra of oxazoles **VIa**–**VIh** there are singlet signals of phosphorus nuclei in the range of

Scheme 2.



VII **VIII** **IX**

Scheme 3.



12.89–17.40 ppm, while for compounds **VIi**, **VIj** a doublet signal at 17.40–20.07 ppm ($^2J_{HP}$ 12.6–12.7 Hz) is observed.

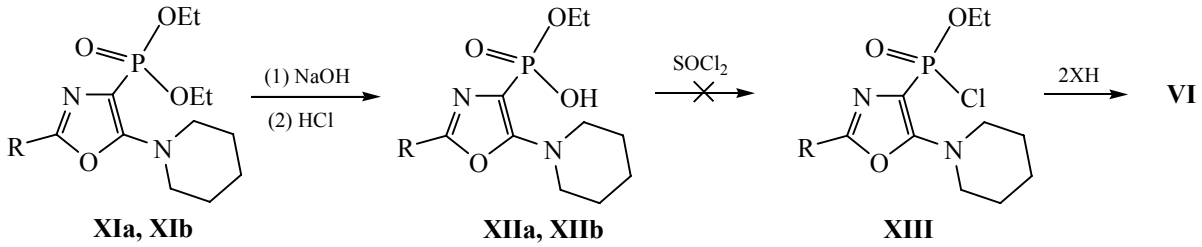
It should be noted that the reaction of compounds **IV** with primary amines (methylamine, benzylamine) proceeds difficultly, the oxazoles **VI** are formed in low yields (~10–20%, according to the ^{1}H and ^{31}P NMR spectra of the reaction mixture). We failed to isolate and purify them by recrystallization. The main reaction products, which were isolated and characterized, are the carboxylic acids amides. This difference in the effect of highly basic primary and secondary amines may be due to the steric effects. The reactions with methylamine and benzylamine proceed as shown in Scheme 3 to form the intermediates **X** due to the possibility of the presence of at least small amounts of *N*-acyliminium tautomers **A**, and it is consistent with the Pearson's hard-soft acid–base (HSAB) principle. However, piperidine and morpholine, which are also relatively strong nucleophiles, cannot yield the adducts **X** owing to the steric hindrances. So they attack the electrophilic center of dichloromethylene group of compounds **IV** to form the intermediate compounds **V** (Scheme 3), which transform into the substituted oxazoles **VI**.

This difference in the action of primary and secondary amines is not observed in the case of diethyl 1-acylamino-2,2-dichlorethenylphosphonates **VII**, the analogs of compounds **IV**: in both cases an attack occurs on the dichloromethylene groups [5] connected with diethoxyphosphoryl group, which obviously is a stronger acceptor compared with amidoethoxyphosphoryl group [6–8].

Finally, we tested an alternative way to obtain compounds **VI** using chlorides of ethyl 1,3-oxazol-4-yl-phosphonates **XIII** synthesized by reactions **XI** → **XII** → **XIII** (Scheme 4). The first stage of this process was the alkaline hydrolysis of diethylphosphonates **XI** [5] followed by acidification with dilute hydrochloric acid. Compounds **XII** are colorless crystalline substances, which are insoluble in water, hexane, benzene, poorly soluble in dichloroethane and chloroform. However, the attempt to convert them into the acid chlorides **XIII** was unsuccessful because they are not stable in the strongly acidic medium, whose action is probably accompanied by the splitting of the oxazole ring [9].

The synthesized compounds **VI** and **XII** were tested as the furin enzyme inhibitors. The compounds **VI** containing a nitrogen substituent at the phosphorus atom inhibit furin in the experiment up to 44.3–64.1%. At the same time oxazoles **XII**, which contain hydroxy group instead of the nitrogen substituent at the phosphorus atom, are negatively charged and do not practically inhibit furin (Table 3). Since furin is an important pharmacological target for the synthesis of inhibitors to create the modern drugs on their basis [15–18], the data suggest the desirability of further research in this area.

Scheme 4.



EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian VXR-300 (300 MHz) instrument in DMSO-d_6 or $CDCl_3$ solution with internal reference TMS. The ^{31}P NMR spectra were registered on a Varian Gemini 200 spectrometer (80.95 MHz) with external reference 85% phosphoric acid. The IR spectra were recorded on a Vertex 70 spectrometer from pellets with KBr. The melting points were determined on a Fisher Johns instrument. The reaction progress was monitored by TLC.

Furin (2000 units/ml, New England BioLabs) and fluorogenic substrate Boc-Arg-Val-Arg-AMC (Bachem) were used.

Diethyl amidophosphites IIa–IIc. To a solution of 0.1 mol of the corresponding amine and 0.1 mol of triethylamine in 50 ml of anhydrous diethyl ether with stirring and cooling to 0°C was added dropwise a solution of 0.1 mol of diethylchlorophosphite in 50 ml of anhydrous diethyl ether within 2 h, then the reaction mixture was kept at room temperature for 12 h. Triethylamine hydrochloride was filtered off, the solvent was distilled off at an atmospheric pressure, and the residue was fractionated in a vacuum in an argon atmosphere.

Compound IIa. Yield 63%, bp 89–90°C (10 mm Hg) {74°C (10 mm Hg) [11], 85°C (1 mm Hg) [12]}. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (6H, 2$\underline{CH_3}CH_2O$), 1.44–1.59 m [6H, ($\underline{CH_2}$)$_3$(CH_2)$_2$N], 3.07 m [4H, (CH_2)$_3$($\underline{CH_2}$)$_2$N], 3.72 m (4H, 2$CH_3\underline{CH_2}O$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 143.0 ppm.

Compound IIb. Yield 61%, bp 84–86°C (10 mm Hg) {92–94°C (0.1 mm Hg) [13], 111–113°C (17 mm Hg) [14]}. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 t (6H, 2$\underline{CH_3}CH_2O$), 3.13 m [4H, O(CH_2)$_2$($\underline{CH_2}$)$_2$N], 3.60 m [4H, O($\underline{CH_2}$)$_2$(CH_2)$_2$N)], 3.76 m (4H, 2$CH_3\underline{CH_2}O$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 142.4 ppm.

Compound IIc. Yield 57%, bp 101–103°C (0.5 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 t (6H, 2$\underline{CH_3}CH_2O$), 2.87 m (1H, NH), 3.78 m (4H, 2$CH_3\underline{CH_2}O$), 4.13 m (2H, $\underline{CH_2}C_6H_5$), 7.25–7.32 m (5H, C_6H_5). ^{31}P NMR spectrum ($CDCl_3$): δ_P 138.3 d (*J* 13 Hz) ppm.

***N*-Substituted amides of ethyl 1-acylamino-2,2,2-trichloroethylphosphonates (IIIa–IIIe).** To a solution of 0.05 mol of compound **I** [10] in 50 ml of anhydrous benzene was added with stirring 0.0575 mol of the corresponding diethylamidophosphite **II** in small portions at 20–l30°C. The mixture was kept for 4 h at 80–85°C. The resulting precipitate was filtered off and the filtrate was concentrated in a vacuum to half volume, and 20 ml of hexane was added. The precipitated oily product solidified in 10–15 h. It was filtered off, washed with hexane, and dried in air. The obtained compounds **IIIa–IIIe** were used without further purification. For the analysis compounds **IIIa**, **IIIb,** and **IIId** were reprecipitated from benzene with hexane.

Table 3. Furin inhibition with compounds **VI, XII**

Comp. no.	Fluoroscience intensity, rel. units	Furin inhibition, %
VIc	5.16	61.1
VIg	7.25	45.4
VIh	4.77	64.1
VIi	5.79	56.4
VIj	7.39	44.3
XIIb	12.94	2.6
–	13.28	–

***N*-Substituted amides of ethyl 1-acylamino-2,2-dichloroethenylphosphonates (IVa–IVe).** To a solution of 0.03 mol of the corresponding compound **IIIa–IIId** in 20 ml of anhydrous tetrahydrofuran was added 0.15 mol of anhydrous triethylamine. The mixture was stirred at 20–25°C for 120 h. Then triethylamine hydrochloride was filtered off, the solvent was removed in a vacuum, and the target compound **IVa–IVg** was recrystallized from a suitable solvent.

***N*-Substituted amides of ethyl carboxylates (VIa–VId).** To a solution of 0.01 mol of the corresponding compound **IVa–IVg** in 20 ml of anhydrous methanol was added 0.035 mol of morpholine or piperidine. The mixture was stirred for12–14 h at 20–25°C. The solvent was removed in a vacuum; the oily residue was treated with hexane. In the case of compounds **VIc**, **VIe–VIj** the oil solidified; it was filtered off and purified by the recrystallization from a suitable solvent.

Compounds **VIa**, **VIb**, **VId** were reprecipitated from hexane as oils.

Diethyl 2-aryl-5-piperidino-1,3-oxazol-4-ylphosphonates **XIa**, **XIb** were obtained by the method described in [5].

Monoethyl esters of 2-aryl-5-piperidino-1,3-oxazol-4-ylphosphonic acid (XIIa, XIIb). To a solution of 0.01 mol of compound **XI** in 10 ml of ethanol at 20–25°C was added a solution of 0.06 mol of NaOH in 20 ml of ethanol. The mixture was kept for 5 h. The solvent was removed in a vacuum. The residue was dissolved in 10 ml of water and cautiously acidified with dilute (1:5) hydrochloric acid at 5–10°C. The precipitate was filtered off, and the product was purified by the recrystalization from a suitable solvent.

The treatment of compounds **XII** with thionyl chloride in benzene under cooling led to the tarring of the reaction mixture, and the target products could not be identified.

Furin activity determination. An aliquot of furin corresponding to the cleavage of 250–300 pmol/h of 7-amino-4-methylcoumarin from the substrate was incubated with Boc-Arg-Val-Arg-Arg-AMC (final concentration 100 mmol l^{-1}) in a buffer at pH 7.2 (100 mmol of Hepes, 1 mmol of $CaCl_2$, 0.5% Triton X-100, and 1 mmol of β-mercaptoethanol) for 1 h at 37°C in 150 ml of sample. Amount of the released 7-amino-4-methylcoumarin was measured on a Signe-4M (Latvia) spectrofluorimeter (excitation 380 nm, emission 460 nm).

The study of the ability of the compounds to inhibit furin was performed in the same buffer at pH 7.2. An aliquot of the enzyme was kept with 10 ml of the test compound in DMSO solution (initial concentration 2.10 mol l^{-1}) for 30 min at 20–25°C. The substrate was then added to a final concentration of 100 μmol l^{-1}, and the mixture was kept for 1 h (final concentration of the tested compounds in the incubation medium 667 μmol l^{-1}).

The substrate cleavage was stopped by adding fluorogenic EDTA solution. The amount of released AMC was determined as described above. The inhibition efficiency was calculated by the formula $(F_0 - F)/F_0$, where F is the fluorescence in the presence of the sample, F_0 is the fluorescence in the absence of the test compound. At the same time furin activity determined in the buffer in the absence of the test compounds was taken as 100%. Measurements processing and plotting were performed using an Origin 7.0 and 8.0 software (OriginLab). An experimental error did not exceed 10% relative to the measured value.

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