ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 4, pp. 643–651. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © K.M. Kondratyuk, E.I. Lukashuk, A.V. Golovchenko, E.B. Rusanov, V.S. Brovarets, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 4, pp. 556–565.

Reaction of Diethyl 1-Acylamino-2,2-dichloroethenylphosphonates with Amino Acids Esters

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Received February 8, 2011

Abstract—Reactions of available diethyl 1-acylamino-2,2-dichloroethenylphosphonates with amino acids esters were studied, which in the case of esters of proline, nipecotic and isonipecotic acids resulted in N-substituted derivatives of 5-amino-4-diethoxyphosphoryloxazol in high yields. Their behavior in the acidic and alkaline media was investigated by the example of methyl *N*-(4-diethoxyphosphoryl-2-R-oxazol-5-yl)isonipecotinate.

DOI: 10.1134/S1070363212040056

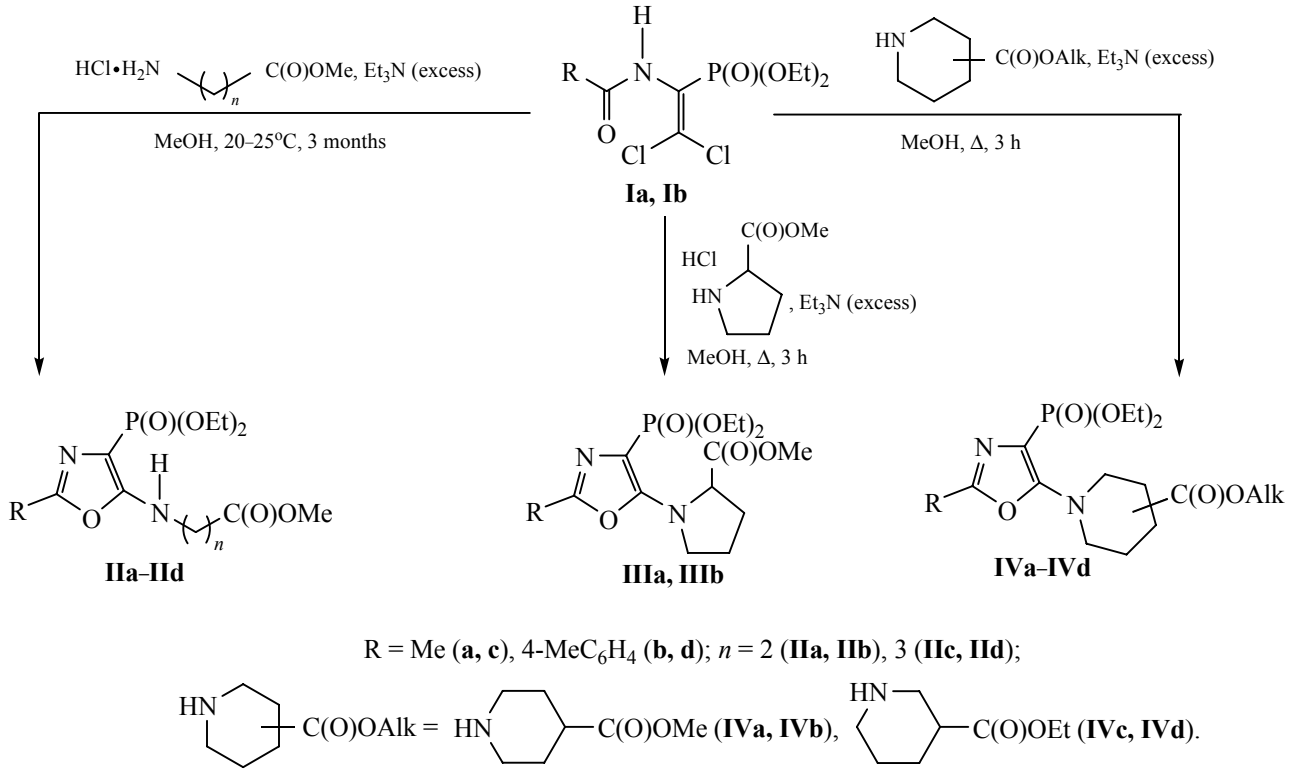
The study of reactions of the available 1-acylamino-2,2-dichlorethenylphosphonates **I** with amines (Scheme 1), which usually give rise to 4-phosphorylated derivatives of 5-aminooxazol [1–3], was continued. In order to expand the limits of the reaction, we examined for the first time some amino acids (glycine, β-alanine, γ-aminobutyric acid, proline, nipecotic, and isonipecotic acids), as well as their esters as the amino function.

The use of amino acids in this reaction as the amine function causes some difficulties. Thus, the reaction of reagent **I** with glycine, β-alanine, or γ-aminobutyric acid in the presence of a base at 20–25°C in a medium of the polar protic and aprotic solvents (water, methanol, ethanol, 2-propanol, acetonitrile, acetone) do not yield oxazols in the amount sufficient to isolation and identification. The TLC analysis and mass spectra of the reaction mixture indicates that the reaction process is complicated. Similar results were obtained in the reaction of **I** with glycine methyl ester in the presence of potassium carbonate or triethylamine.

In the case of methyl esters of β-alanine and γ-aminobutyric acid the oxazols are formed, but there are some differences depending on the structure of the starting dichloroenamide **I**. The reaction with the compound **Ia** at room temperature over 3 months gives rise to products **IIa** and **IIc** in good yields (71–79%). When reagent **Ib** was used, the yields of the target products **IIb** and **IId** decreased. We failed to isolate these compounds in analytically pure state. They are significantly contaminated by the incidentally formed *p*-toluamide that can be due to the nucleophilic attack of amino esters mainly on the α-carbon atom of enamide **I** [4, 5]. This can be avoided, when an amino acid with a secondary amino group (proline, nipecotic and isonipecotic acid) are used. Due to the steric hindrances, they do not give the products of the attack on the α-carbon atom (even a trace of the corresponding amides were not found in the reaction mixture by the mass spectrometry). However, the reaction proceeds extremely slowly at 20–25°C (over several months). The heating leads to the formation of a complex mixture of substances, from which the target oxazols were not isolated.

The use of the esters of these acids in the oxazol cyclization gave the best results: 5-amino-4-diethoxyphosphoryl-1,3-oxazol derivatives **III**–**IV** were formed in high yields (79–93%). It should be noted that the heating accelerates the formation of oxazol rings without significantly reducing the yield. The initial reactants are consumed completely within 3 h in boiling methanol. The isolation of oxazols **III**–**IV** should be performed very carefully. For example, washing out the organic extract from the triethylamine excess and amino acids esters should be done with

Scheme 1.



R = Me (**a, c**), 4-MeC_6H_4 (**b, d**); *n* = 2 (**IIa, IIb**), 3 (**IIc, IId**);

HN—C(O)OAlk = HN—C(O)OMe (**IVa, IVb**), HN—C(O)OEt (**IVc, IVd**).

diluted acetic acid, but not hydrochloric acid, as in the latter case a partial splitting of the oxazol ring occurs. In addition, it is important to remove acetic acid completely, since its traces also lead to the destruction of the oxazol ring at purifying the reaction products.

From the foregoing it can be concluded that a key role in the direction of the oxazol ring formation is the nature of the amino substrate. For example, amino acids and their esters containing the primary amino groups form oxazols in low yields or do not lead at all to their formation, except for oxazols containing alkyl substituents in a 2 position. However, the amino acids esters containing a secondary amino group give good results in the cyclization regardless of the starting dichloroenamine **I** structure that can be used for the preparative production of the *N*-(4-diethoxyphosphoryl-2-R-oxazol-5-yl)-substituted amino acids derivatives and the search among them the for biologically active compounds [6, 7].

Compounds **II**–**IV** are stable oily substances soluble in almost all organic solvents and partially soluble in water. They are stored at room temperature for a long time without changing.

The yields, physicochemical constants, and elemental analysis data are given in Table 1.

The ^{31}P NMR spectra of compounds **II**–**IV** contain the signal at 12.14–13.69 ppm. In the ^{1}H NMR spectra there are all the signals of aromatic and aliphatic protons with the appropriate ratios of integrated intensities (Table 2). The IR spectra contain the absorption bands of C=O group in the range of 1727–1745 cm^{-1}, as well as the bands of moderate or high intensity at ν 1603–1680 and 1576–1646 cm^{-1}, which correspond to the 4-phosphorylated 5-aminooxazol derivatives [2]. The band of moderate intensity of the P=O bond lies in the region of 1195–1250 cm^{-1}. The characteristic absorption bands of the P–O–C fragment are manifested at ν 1024–1026 and 967–977 cm^{-1}.

The mass spectra of compounds **II**–**IV** are not always informative, as they contain an additional peak with *m*/*z* $[M + 19]^+$ corresponding to the product of the oxazol ring cleavage.

Further transformations of the oxazol derivatives were studied by the example of compounds **IVa** and **IVb**. Owing to the stability of the oxazol ring in an alkaline medium, the stepwise hydrolysis of the ester and diethoxyphosphoryl groups was carried out under the action of sodium hydroxide. Thus, the use of 1 equivalent of NaOH followed by the acidification with acetic acid leads only to the ester group

Table 1. Yields, physicochemical constants, and elemental analysis data of compounds **II**–**X**

Comp. no	Yield, %	mp, °C (solvent for purification)	Found, %		Formula	Calculated, %	
			N	P		N	P
IIa	79	Oil (hexane)	8.54	9.86	$C_{12}H_{21}N_2O_6P$	8.75	9.67
IIc	71	Oil (hexane)	8.09	9.44	$C_{13}H_{23}N_2O_6P$	8.38	9.27
IIIa	88	Oil (petroleum ether)	7.89	9.17	$C_{14}H_{23}N_2O_6P$	8.09	8.94
IIIb	87	Oil (petroleum ether)	6.46	7.55	$C_{20}H_{27}N_2O_6P$	6.63	7.33
IVa	88	Oil (hexane)	7.59	8.81	$C_{15}H_{25}N_2O_6P$	7.77	8.60
IVb	79	Oil (hexane)	6.30	7.33	$C_{21}H_{29}N_2O_6P$	6.42	7.10
IVc	85	Oil (hexane)	7.29	8.43	$C_{16}H_{27}N_2O_6P$	7.48	8.27
IVd	93	Oil (hexane)	5.98	7.02	$C_{22}H_{31}N_2O_6P$	6.22	6.88
Va	38	62–70[a]	8.01	9.14	$C_{14}H_{23}N_2O_6P$	8.09	8.94
Vb	46	162–163[a]	6.55	7.60	$C_{20}H_{27}N_2O_6P$	6.63	7.33
VIb	50	133–134 (2-propanol)	6.97	8.12	$C_{18}H_{23}N_2O_6P$	7.10	7.85
VIIa	95	131–132[b]	7.51	8.72	$C_{14}H_{25}N_2O_7P$	7.69	8.50
VIIb	66	137–138[b]	6.18	7.21	$C_{20}H_{29}N_2O_7P$	6.36	7.03
VIIIa	93	99–100 (petroleum ether)	7.21	8.33	$C_{15}H_{27}N_2O_7P$	7.40	8.19
VIIIb	92	45–60 (petroleum ether)	5.89	7.03	$C_{21}H_{31}N_2O_7P$	6.16	6.82
Xb	79	106–107[b]	7.05	8.24	$C_{16}H_{21}N_2O_7P$	7.29	8.06

[a] Without additional purification. [b] After washing with acetone.

Table 2. Spectral data of compounds **II**–**X**

Comp. no	IR spectrum, ν, cm^{-1} [a]	^1H and ^{13}C NMR spectra, δ, ppm [b]	^{31}P NMR spectrum, δ_P, ppm[b]	Mass spectrum, m/z, $[M+1]^+$
IIa	3406 (N–H), 1736 (C=O), 1678, 1641, 1599 (oxazol), 1249 (P=O), 1026 (P–O–C), 977 (P–O–C–C)	1.32 t (6H, $\underline{C}H_3CH_2O$), 2.34 s (3H, CH_3), 2.62 m (2H, CH_2), 3.57 m (2H, CH_2), 3.71 s (3H, CH_3O), 3.98–4.17 m (4H, $CH_3\underline{C}H_2O$), 6.09 br.m (1H, NH)	13.19	321
IIb[c]	–	1.34 t (6H, $\underline{C}H_3CH_2O$), 2.38 s (3H, CH_3), 2.68 m (2H, CH_2), 3.65–3.74 m (5H, CH_2, CH_3O), 4.12 (4H, $CH_3\underline{C}H_2O$), 6.29 br.t (1H, NH), 7.23 d, 7.79 d (4H, C_6H_4, $^3J_{HH}$ 8.0 Hz)	13.01	397
IIc	3356 (N–H), 1734 (C=O), 1678, 1628, 1588 (oxazol), 1195 (P=O), 1025 (P–O–C), 972 (P–O–C–C)	1.32 t (6H, $\underline{C}H_3CH_2O$), 1.92 m (2H, CH_2), 2.34 s (3H, CH_3), 2.41 m (2H, CH_2), 3.33 m (2H, CH_2), 3.69 s (3H, CH_3O), 4.10 m (4H, $CH_3\underline{C}H_2O$), 6.18 br.s (1H, NH)	13.52	335
IId[c]	–	1.35 t (6H, $\underline{C}H_3CH_2O$), 1.99 m (2H, CH_2), 2.39 s (3H, CH_3), 2.46 m (2H, CH_2), 3.46 m (2H, CH_2), 3.69 s (3H, CH_3O), 4.13 m (4H, $CH_3\underline{C}H_2O$), 6.15 br.t (1H, NH), 7.22 d and 7.79 d (4H, C_6H_4, $^3J_{HH}$ 8.0 Hz)	13.69	411
IIIa	1745 (C=O), 1633, 1588 (oxazol), 1214 (P=O), 1026 (P–O–C), 967 (P–O–C–C)	1.32 m (6H, $\underline{C}H_3CH_2O$), 1.97 m (2H, CH_2), 2.06–2.31 m (5H, CH_3, CH_2), 3.68–3.83 m (5H, CH_2, CH_3O), 4.12 m (4H, $2CH_3\underline{C}H_2O$), 4.86 m (1H, CH)	12.89	347
IIIb	1744 (C=O), 1607, 1583 (oxazol), 1214 (P=O), 1025 (P–O–C), 969 (P–O–C–C)	1.36 m (6H, $2\underline{C}H_3CH_2O$), 2.05 m (2H, CH_2), 2.15–2.41 m (5H, CH_2, CH_3), 3.75 s (3H, CH_3O), 3.80–3.95 m (2H, CH_2), 4.20 m (4H, $CH_3\underline{C}H_2O$), 4.92 m (1H, CH), 7.25 d and 7.74 d (4H, C_6H_4, $^3J_{HH}$ 7.6 Hz)	12.80	423

Table 2. (Contd.)

Comp. no	IR spectrum, ν, cm^{-1} [a]	^1H and ^{13}C NMR spectra, δ, ppm [b]	^{31}P NMR spectrum, δ_P, ppm[b]	Mass spectrum, *m/z*, $[M + 1]^+$
IVa	1732 (C=O), 1627, 1580 (oxazol), 1231 (P=O), 1026 (P–O–C), 969 (P–O–C–C)	1.33 t (6H, $\underline{CH_3}CH_2O$), 1.78 m (2H, CH_2), 1.94 m (2H, CH_2), 2.30 s (3H, CH_3), 2.48 m (1H, CH), 3.10 m (2H, CH_2), 3.68 s (3H, CH_3O), 3.96 m (2H, CH_2), 4.10 m (4H, $CH_3\underline{CH_2}O$)	12.47	361
IVb	1732 (C=O), 1604, 1576 (oxazol), 1235 (P=O), 1025 (P–O–C), 970 (P–O–C–C)	1.36 t (6H, $\underline{CH_3}CH_2O$), 1.88 m (2H, CH_2), 2.03 m (2H, CH_2), 2.37 s (3H, CH_3), 2.54 m (1H, CH), 3.22 m (2H, CH_2), 3.70 s (3H, CH_3O), 4.11 m (2H, CH_2), 4.18 m (4H, $CH_3\underline{CH_2}O$), 7.20 d, 7.78 d (4H, C_6H_4, $^3J_{HH}$ 8.0 Hz)	12.57	437
IVc	1727 (C=O), 1680, 1646 (oxazol), 1250 (P=O), 1024 (P–O–C), 977 (P–O–C–C)	1.25 t (3H, $\underline{CH_3}CH_2O$), 1.34 t (6H, $\underline{CH_3}CH_2O$), 1.65 m (2H, CH_2), 1.78 m and 2.08 m (2H, CH_2), 2.32 s (3H, CH_3), 2.62 m (1H, CH), 3.08 m and 3.21 m (2H, CH_2), 3.88 m and 4.01 m (2H, CH_2), 4.13 m (6H, $CH_3\underline{CH_2}O$)	12.37	375
IVd	1727 (C=O), 1603, 1577 (oxazol), 1242 (P=O), 1026 (P–O–C), 968 (P–O–C–C)	1.27 t (3H, $\underline{CH_3}CH_2O$), 1.38 t (6H, $\underline{CH_3}CH_2O$), 1.72 m (2H, CH_2), 1.84 m and 2.13 m (2H, CH_2), 2.39 s (3H, CH_3), 2.70 m (1H, CH), 3.20 m and 3.34 m (2H, CH_2), 4.02 m and 4.18 m (8H, $CH_3\underline{CH_2}O$, CH_2), 7.21 d and 7.80 d (4H, C_6H_4, $^3J_{HH}$ 8.0 Hz)	12.14	451
Va	1712 (C=O), 1630, 1582 (oxazol), 1174 (P=O), 1026 (P–O–C), 972 (P–O–C–C)	1.34 t (6H, $\underline{CH_3}CH_2O$), 1.84 m (2H, CH_2), 1.98 m (2H, CH_2), 2.32 s (3H, CH_3), 2.50 m (1H, CH), 3.11 m (2H, CH_2), 3.93 m (2H, CH_2), 4.13 m (4H, $CH_3\underline{CH_2}O$)[d]	12.34	347
Vb	1715 (C=O), 1609, 1584 (oxazol), 1194 (P=O), 1014 (P–O–C), 961 (P–O–C–C)	1.37 t (6H, $\underline{CH_3}CH_2O$), 1.92 m (2H, CH_2), 2.06 m (2H, CH_2), 2.38 s (3H, CH_3), 2.55 m (1H, CH), 3.23 m (2H, CH_2), 4.07 m (2H, CH_2), 4.20 m (4H, $CH_3\underline{CH_2}O$), 7.21 d and 7.78 d (4H, C_6H_4)[d]; δ_C: 14.9 ($CH_2\underline{C}H_3$), 19.9 (CH_3), 26.3 [$(\underline{C}H_2)_2CH$], 38.6 (CH), 46.5 [$N(CH_2)_2$], 60.9 (OCH_2), 101.0 d (CP, $^1J_{CP}$ 252 Hz), 123.3, 124.6, 129.1, 139.2 (C_6H_4), 150.6, 160.4 (oxazol), 175.3 (COOH)	12.47	423
VIb	1720 (C=O), 1613[e] (oxazol), 1239 (P=O), 1040 (P–O–C), 957 (P–O–C–C)	1.23 t (3H, $\underline{CH_3}CH_2O$), 1.63 m (2H, CH_2), 1.90 m (2H, CH_2), 2.35 s (3H, CH_3), 3.15 m (2H, CH_2), 3.78 m (1H, CH), 3.95 m (2H, $CH_3\underline{CH_2}O$), 4.03 m (2H, CH_2), 7.29 d, 7.73 d (4H, C_6H_4)[d]	8.50	395
VIIa	3411 (N–H), 1713 (C=O), 1681 (C=O), 1646 (C=O), 1206 (P=O), 1024 (P–O–C), 957 (P–O–C–C)	1.22 m (6H, $\underline{CH_3}CH_2O$), 1.31–1.70 m (2H, CH_2), 1.83 m (2H, CH_2), 1.91 s (3H, CH_3); 2.80 m, 3.15 m, 3.44 m, 3.88 m, 4.21 m (5H, CH_2, CH), 4.04 m (4H, $CH_3\underline{CH_2}O$), 5.46 m (1H, CHP), 8.45 m (1H, NH)[d]; δ_C: 14.6 ($CH_2\underline{C}H_3$), 21.1 (CH_3); 26.0, 26.5, 38.7, 40.6, 44.5 (CH_2, $\underline{C}HCO$), 46.0 d (CHP, $^1J_{CP}$ 150 Hz), 62.5 ($O\underline{C}H_2CH_3$); 163.5, 169.2, 176.0 (CON, CONH, COO)	17.71, 17.74	
VIIb	3337 (N–H), 1722 (C=O), 1631[e] (2C=O), 1232 (P=O), 1022 (P–O–C), 978 (P–O–C–C)	1.30 m (6H, $\underline{CH_3}CH_2O$), 1.73 m and 2.00 m (4H, CH_2), 2.40 s (3H, CH_3); 2.57 m, 3.03 m, 3.32 m (3H, CH_2, CH), 3.99–4.36 m (6H, $CH_3\underline{CH_2}O$, CH_2), 4.77 br.m (1H, NH), 5.80 m (1H, CHP), 7.21–7.79 m (4H, C_6H_4)[d]; δ_C: 14.7 ($CH_2\underline{C}H_3$); 19.9 (CH_3); 25.9, 26.5, 38.7, 40.6, 44.4 (CH_2, $\underline{C}HCO$), 46.7 d (CHP, $^1J_{CP}$ 150 Hz), 62.6 ($O\underline{C}H_2CH_3$); 126.4, 128.3, 129.5, 141.7 (C_6H_4); 163.3, 165.9, 176.3 (CON, CONH, COO)	16.48, 16.92	441
VIIIa	3310 (N–H), 1734 (C=O), 1677 (C=O), 1631 (C=O), 1255 (P=O), 1026 (P–O–C), 980 (P–O–C–C)	1.31 m (6H, $\underline{CH_3}CH_2O$), 1.68 m (2H, CH_2), 1.97 m (2H, CH_2), 1.82–2.06 m (5H, CH_3, CH_2), 2.50–3.31 m (3H, CH_2, CH), 3.68 s (3H, CH_3O), 3.95–4.42 m (6H, $CH_3\underline{CH_2}O$, CH_2), 5.53 m (1H, CHP), 6.68 m (1H, NH); δ_C: 14.7 ($CH_2\underline{C}H_3$), 21.4 (CH_3); 26.0, 26.5, 39.0, 40.5, 44.4 (CH_2, $\underline{C}HCO$), 46.2 d (CHP, $^1J_{CP}$ 148 Hz), 50.4 (OCH_3), 62.2 ($O\underline{C}H_2CH_3$); 163.2, 168.4, 173.6 (CON, CONH, COO)	16.73, 16.74	379

Table 2. (Contd.)

Comp. no	IR spectrum, ν, cm^{-1} [a]	^1H and ^{13}C NMR spectra, δ, ppm [b]	^{31}P NMR spectrum, δ_P, ppm[b]	Mass spectrum, m/z, $[M+1]^+$
VIIIb	3413 (N–H), 1732 (C=O), 1645[e] (2C=O), 1247 (P=O), 1022 (P–O–C), 978 (P–O–C–C)	1.31 m (6H, $\underline{CH_3}CH_2O$); 1.72 m, 2.02 m (4H, CH_2), 2.40 s (3H, CH_3), 2.50–4.45 m (9H, $CH_3\underline{CH_2}O$, CH_2, CH), 3.69 s (3H, CH_3O), 5.74 m (1H, CHP), 7.24 d and 7.73 d (4H, C_6H_4, $^3J_{HH}$ 7.1 Hz), 7.31 m (1H, NH); δ_C: 14.7 ($CH_2\underline{C}H_3$), 19.9 (CH_3); 26.0, 26.5, 39.0, 40.6, 44.4 (CH_2, $\underline{C}HCO$), 46.6 d (CHP, $^1J_{CP}$ 148 Hz), 50.4 (OCH_3), 62.3 ($O\underline{C}H_2CH_3$); 126.3, 128.3, 129.6, 141.6 (C_6H_4); 163.4, 165.6, 173.6 (CON, CONH, COO)	16.62	455
Xb	2500–3500 (N–H), (O–H), 1716 (C=O), 1613 (2C=O), 1190 (P=O)	1.71 m (2H, CH_2), 2.07 m (2H, CH_2), 2.31 s (3H, CH_3), 2.65 m (1H, CH), 2.98 m (2H, CH_2), 3.33 m (2H, CH_2), 4.81 d (1H, CHP, $^2J_{HP}$ 21.3 Hz), 7.28 d and 7.67 d (4H, C_6H_4, $^3J_{HH}$ 8.1 Hz)	9.29	385

[a] IR spectra of compounds **IIa**, **IIc**, **IIIa**, **IIIb**, **IVa**–**IVd**, **Va**, **VIIa**, **VIIIb** were recorded in CH_2Cl_2, of compounds **Vb**, **VIb**, **VIIb**, **VIIIa**, from KBr pellets. [b] $CDCl_3$ (**IIa**–**IId**, **IIIa**, **IIIb**, **IVa**–**IVd**, **Va**, **Vb**, **VIIb**, **VIIIa**, **VIIIb**); DMSO-d_6 (**VIb**, **VIIa**); D_2O (**Xb**). [c] The spectra of compounds **IIb** and **IId** are extracted from a spectrum of the mixture. [d] In the ^1H NMR spectrum the OH proton was not observed. [e] A broad band with a shoulder.

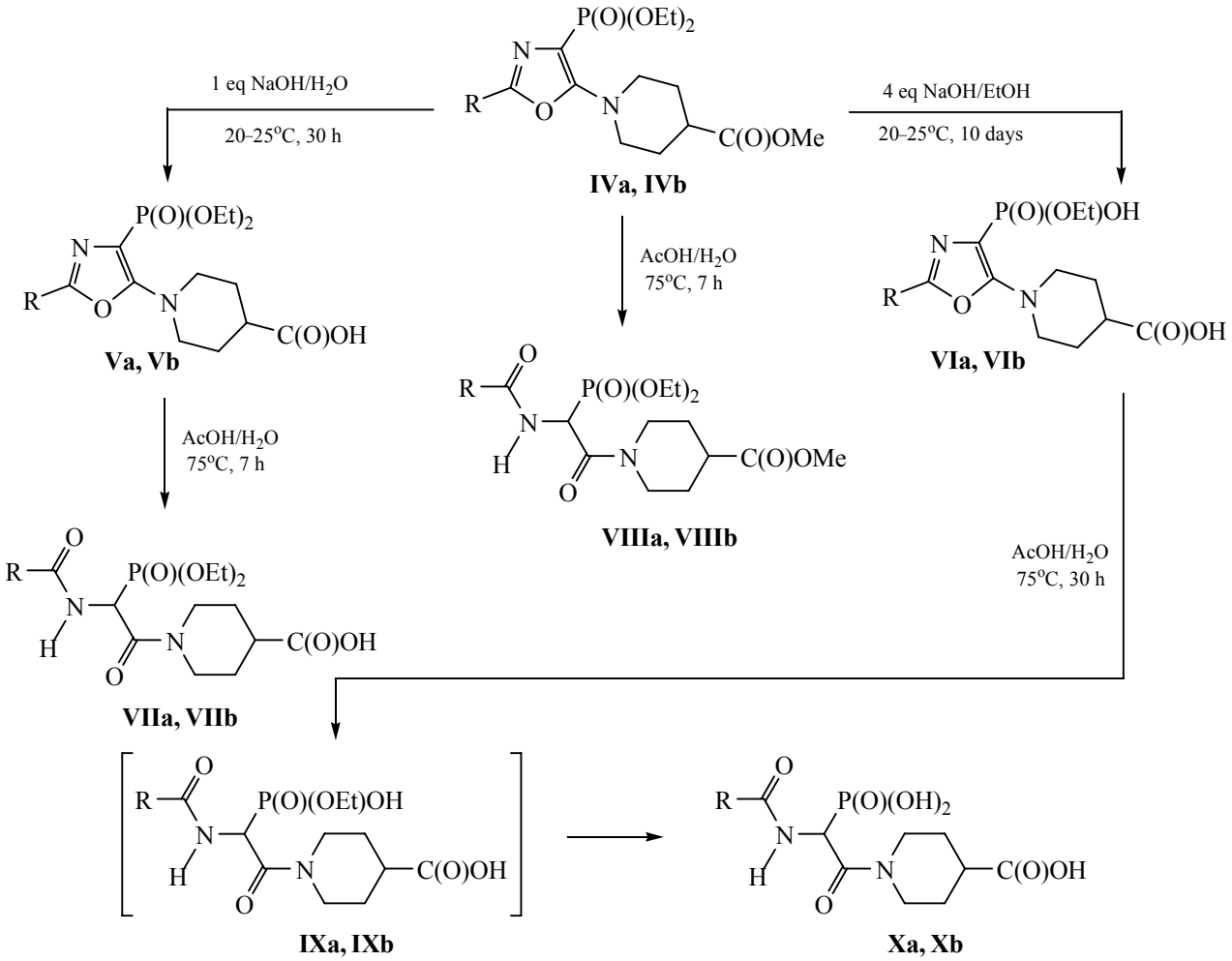
hydrolysis to form compounds **Va** and **Vb**, which is clearly seen in the ^1H and ^{31}P NMR spectra (Table 2). The treatment of compounds **IVa** and **IVb** with a four-fold excess of an alcoholic solution of sodium hydroxide over 10 days at room temperature causes deeper saponification to give sodium salts **VI**. Only acid **VIb** was isolated in a free state by the gentle acidification with 10% hydrochloric acid. The isolation of acid **VIa** is difficult, since the acidifying even with a very dilute (1%) hydrochloric acid causes the opening of the oxazol ring to form compound **IXa** [8, 9] and the products of deeper hydrolysis. The cleavage of amino oxazols with an alcoholic solution of hydrogen chloride leads to the formation of a complex mixture of substances. One of the identified compounds is the isonipecotinate hydrochloride. A similar pattern was observed when using glacial acetic acid.

This prompted us to investigate the behavior of oxazols **IV**–**VI** under milder conditions. Thus, compounds **IV** and **V** were easily decomposed by the heating in an aqueous acetic acid to form the phosphorylated pseudopeptides **VII** and **VIII**. We monitored the dynamics of the cyclic products transformation into acyclic compounds at 75°C in an acetic acid–water mixture (5:1) by the example of **VIb** using the ^{31}P NMR spectroscopy. The results presented in Table 3 show that after 7 h under the experimental conditions a complete transformation occurs of the oxazol rings into the acyclic product **VIIIb**.

A more complicated picture is observed under the action of acetic acid on oxazols **VI**. Thus, the reaction of compounds **IV** and **V** under similar conditions results not only in the oxazol ring opening, but in the partial hydrolysis of phosphoryl group to form a mixture of phosphonic acids **IX** and **X**, which was proved by the mass spectrometry. For example, in the case of the ring opening of oxazol **VIa** there are two signals with m/z 337 and 309 corresponding to the acids **IXa** and **Xa**, respectively. For compound **VIb** we also examined the hydrolysis dynamics at 75°C in an acetic acid–water mixture (5:1). The experimental results are presented in Table 4. The oxazol ring opening occurs rapidly enough, the resulting diastereomers mixture of compound **IXb** (δ_P 9.76 and 9.96 ppm, 3:2) is gradually transformed into product **Xb** (δ_P 9.29 ppm). The diastereomers ratio of **IXb** in the reaction mixture does not change, and the complete conversion **IXb** → **Xb** occurs within 30 h. Note that the attempts to isolate compound **IXb** in a pure form were unsuccessful. When changing the reaction conditions (time, temperature, solvent), the oxazol ring opening does not occur or a mixture of compounds **IXb** and **Xb** is formed, which we failed to separate by the conventional methods. The ease of the oxazol ring opening and hydrolysis of phosphoryl ethyl fragment of **VI** indicates the effect of a strong acidic P(OH) group (pK_a ~ 1.67 in H_2O [10]) on the process. Thus, in a DMSO solution at 75°C, even in the absence of acetic acid, the transformation of the oxazol ring of compound **VI** is completed in ~ 1.5 h. Under the same conditions compounds **IV** and **V** are stable.

The structure of compounds shown in scheme 2 is proved by the spectral data (Table 2). Thus, the

Scheme 2.



R = Me (**a**), 4-MeC_6H_4 (**b**).

presence of PCHNH moiety in the cleavage products **VII**, **VIII**, and **X** is consistent with the signals assignment in the ^{1}H NMR spectra in the range of 5.46–5.80 (CH) and 4.77–8.45 ppm (NH) [11–13]. In the IR spectra of these compounds the intensive absorption bands were found of C=O and P=O groups at 1613–1734 and 1190–1247 cm^{-1}, respectively.

The structure of one of the cleavage products **VIIIa** was proved by the XRD analysis. The general view of the **VIIIa** molecule and its main geometrical parameters are shown in the figure. The bond lengths in the compound studied are close to the values in the related compounds containing a similar $(MeO)_2P(=O)CH\cdot(NRCOPh)COOMe$ moiety [14]. The P–C bond in the compound investigated by us is slightly shortened (P–C 1.859, P=O 1.463, P–O_{av} 1.575 Å). In general, the geometry of the fragment is common enough for this type compounds.

The N^1N^2 nitrogen atoms have a planar trigonal environment, and the sum of bond angles of these atoms is 360°, while the C^2N^1 and C^3N^2 bonds are significantly shortened [to 1.333(4) and 1.333(4) Å, respectively] compared with the standard value of the single C–N bond (1.45 Å). It indicates the effective conjugation of the unshared electron pair of the nitrogen atom with the π-system of carbonyl groups. The piperidine ring has a regular geometry and is in a *chair* conformation. No other special features was found in the structure of the molecule of compound **VI**.

The previous studies of the antiradical activity of the synthesized compounds, which were performed in the Zaporizhia National University, showed that oxazols

Table 3. Dynamics of **IVb → VIIIb** transformation at 75°C in an acetic acid–water mixture (5:1)

Reaction time, h	Molar ratio, %	
	IVb	**VIIIb**
0	100	0
0.5	84	16
1.0	75	25
2.0	23	77
3.5	7	93
5.0	3	97
7.0	0	100

Table 4. Dynamics of **VIb → IXb → Xb** transformation at 75°C in an acetic acid–water mixture (5:1)

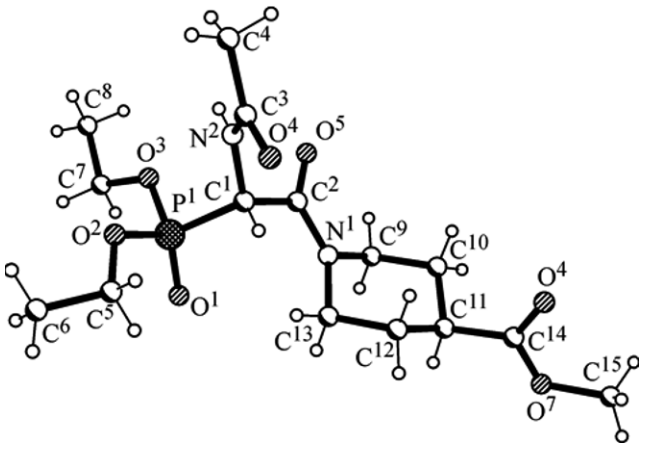
Reaction time, h	Molar ratio, %		
	VIb	**IXb**	**Xb**
0	100	0	0
0.5	18	60	22
1.0	0	85	15
2.0	0	70	30
3.0	0	60	40
4.5	0	45	55
8.0	0	30	70
10.0	0	25	75
30.0	0	0	100

IV have a significant effect on the reaction rate of adrenalin autoxidation, which is associated with the inhibition of reactive oxygen species [15]. The results of the acute toxicity determination of compound **IVa** show that this class of substances is nontoxic (LD_{50} 1.200 mg kg^{-1}) [16], which makes these compounds promising to the search for bioregulators among them.

EXPERIMENTAL

The NMR spectra were obtained on a Bruker Avance DRX-500 and Varian Unityplus-400 instruments [^{1}H (500 MHz and 400 MHz), ^{31}P (202 MHz), ^{13}C (125 MHz)] in a solution of DMSO-d_6, $CDCl_3$ or D_2O relative to internal TMS or external 85% phosphoric acid. The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets or dichloromethane solution. The melting points were determined on a Fisher Johns instrument. The chromato-mass spectra were recorded on an Agilent 1100 Series high performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MSD SL mass selective detector allowing a fast switching the ionization modes positive/negative. The chromato-mass spectral analysis parameters: column Zorbax SB-C18 1.8 μm, 4.6×15 mm (PN 821975-932); solvents: A, acetonitrile–water mixture (95:5), 0.1% trifluoroacetic acid, B, 0.1% aqueous trifluoroacetic acid; eluent flow 3 ml min^{-1}, injection volume 1 μl, UV detectors 215, 254, 285 nm; the ionization method is atmospheric-pressure chemical ionization (APCI), scanning range *m*/*z* 80–1000. The reaction progress was monitored by the TLC method.

The X-ray diffraction study on a single-crystal of **VIIIa** of 0.10×0.12×0.40 mm size was performed at –100°C on a Bruker Smart Apex II diffractometer (λMoK_α-radiation, graphite monochromator, θ_{max} 26.48°, sphere segment $-10 \le h \le 10$, $-10 \le k \le 12$, $-15 \le l \le 14$). 14 302 reflections were collected, of which 3991 were independent (*R*-factor 0.0476). The crystals of compound **VIIIa** are triclinic, $C_{15}H_{27}N_2O_7P$, *M* 378.36, space group *P*–1, *a* 8.6163(3), *b* 10.0939(4), *c* 12.5698(6) Å, α 66.521(2), β 75.917(3), γ 81.608(2)°; *V* 971.10(7) Å^3, *Z* 2, d_{calc} 1.294, μ 0.178 mm^{-1}, *F*(000) 404. The structure was solved by the direct method and refined by a least-squares method in a full-matrix anisotropic approximation using a SHELXS97 and SHELXL97 software [17, 18]. The correction for extinction was done using a SADABS software by a multiscanning method (T_{min}/T_{max} = 0.595083). The



General view of the molecule of **VIIIa**. Some bonds lengths (Å) and bond angles (deg): P^1–O^1 1.454(2), P^1–O^2 1.562(3), P^1–O^3 1.565(2), P^1–C^1 1.815(3), C^1–C^2 1.530(4), C^1–N^2 1.443(3), C^2–N^1 1.333(4), N^2–C^3 1.333(4); $O^1P^1C^1$ 114.13(13), $O^2P^1C^1$ 105.36(14), $O^3P^1C^1$ 101.50(12), $N^2C^1C^2$ 111.5(2), $N^2C^1P^1$ 110.40(19), $C^2C^1P^1$ 110.49(19).

hydrogen atoms were located geometrically. In the refinement 2443 reflections with $I > 2\sigma(I)$ were used (231 refined parameter), the number of reflections per a parameter is 10.57, the used weight scheme is $\omega = 1/[\sigma^2(Fo^2) + (0.0727P)^2 + 0.404P]$, where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximal (average) shift to the error in a last cycle is 0.016(0.002). The final divergence factors are $R_1(F)$ 0.0627, $wR_2(F^2)$ 0.1532 for the reflections with $I > 2\sigma(I)$, $R_1(F)$ 0.1085, $wR_2(F^2)$ 0.1775, GOF 1.115 for all independent reflections. The residual electron density of the difference Fourier series after the last refinement cycle is 0.61 and –0.42 *e* Å^{-3}. A complete set of the X-ray diffraction data for compound **VIIIa** was deposited in the Cambridge Structural Database (CCDC 798674).

Methyl esters of *N*-[4-(diethoxyphosphoryl)-2-methyl-(4-methylphenyl)-1,3-oxazol-5-yl]-β-alanine and γ-aminobutyric acid (IIa–IId). To a solution of 0.01 mol of compound **I** in 50 ml of methanol was added 0.011 mol of the corresponding amino acid methyl ester hydrochloride and 0.055 mol of triethylamine. The mixture was kept at 20–25°C for 80–100 days (^{31}P NMR and TLC control). The reaction mixture was evaporated at a reduced pressure to dryness, the residue was dissolved in 100 ml of ethyl acetate, washed succesively with water, 20% aqueous acetic acid solution, water, and concentrated aqueous solution of potassium carbonate, dried over anhydrous magnesium sulfate. The solvent was removed at a reduced pressure to dryness. The residue was treated with the boiling hexane (3×50 ml) with decanting. The combined hexane extracts were evaporated to dryness at a reduced pressure. The products are colorless or light yellow viscous oils. Only compounds **IIa** and **IIb** were isolated individually, compounds **IIc** and **IId** were contaminated with *p*-toluamide.

Methyl esters of *N*-[4-(diethoxyphosphoryl)-2-methyl-(4-methylphenyl)-1,3-oxazol-5-yl]proline (IIIa, IIIb). To a solution of 0.01 mol of compound **I** in 50 ml of methanol was added 0.011 mol of proline methyl ester hydrochloride and 0.066 mol of triethylamine. The mixture was boiled for 3 h (TLC control). The reaction mixture was evaporated at a reduced pressure to dryness, the residue was triturated in 100 ml of ethyl acetate, washed in succession with water, 20% acetic acid aqueous solution, water, and concentrated aqueous solution of potassium carbonate, dried over anhydrous magnesium sulfate, the solvent was removed at a reduced pressure to dryness. The oil was treated with boiling petroleum ether (3×50 ml) with decanting. The combined ether extracts were evaporated to dryness at a reduced pressure. The products are colorless or light yellow viscous oils.

Methyl *N*-[4-(diethoxyphosphoryl)-2-methyl-(4-methylphenyl)-1,3-oxazol-5-yl]isonipecotinates (IVa, IVb) were obtained similarly to compounds **III** from enamides **I** and methyl isonipecotinate.

Ethyl *N*-[4-(diethoxyphosphoryl)-2-methyl-(4-methylphenyl)-1,3-oxazol-5-yl]nipecotinates (IVc, IVd) were obtained similarly to compounds **III** from enamides **I** and ethyl nipecotinate.

1-[4-(Diethoxyphosphoryl)-2-methyl-(4-methylhenyl)-1,3-oxazol-5-yl]piperidin-4-ylcarboxylic acids (Va, Vb). To a solution of 0.01 mol of compound **IV** in 5 ml of ethanol was added a solution of 0.01 mol of sodium hydroxide in 100 ml of water. The mixture was stirred for 24–30 h at 20–25°C (TLC control). To the mixture 20 ml of ethyl acetate was added, the aqueous layer was separated, acidified with 10 ml of 20% aqueous acetic acid solution. The product was extracted with ethyl acetate (4×25 ml). The combined extracts were washed with 25 ml of the saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated at a reduced pressure at the temperature below 20°C to dryness, and then kept for several hours in a vacuum at 1 mm Hg for a more complete removal of acetic acid traces. Compounds **Va** and **Vb** were analyzed without further purification and used for further syntheses.

1-[4-Hydroxy(ethoxy)phosphoryl-2-methyl-(4-methylphenyl)-1,3-oxazol-5-yl]piperidin-4-carboxylic acids (VIa, VIb). To a solution of 0.01 mol of compound **IV** in 5 ml of anhydrous ethanol was added a solution of 0.05 mol of sodium hydroxide in 100 ml of anhydrous ethanol. The mixture was stirred at 20–25°C for 10 days (^{31}P NMR monitoring). The reaction mixture was evaporated to dryness at a reduced pressure at the temperature not exceeding 30ºC. The residue was triturated in anhydrous dioxane, the precipitate was filtered off, washed on a filter with a small amount of anhydrous dioxane, and then dissolved in a minimal amount of ice water, the solution was carefully acidified with 10% aqueous hydrochloric acid solution to pH ~ 1–2 with cooling, extracted with ethyl acetate (3×25 ml). The combined extracts were washed with brine, dried with magnesium sulfate, the solvent was removed in a vacuum at the temperature above 20°C. Compound

VIb was purified by the recrystallization from 2-propanol. Compound **VIa** we failed to isolate in an analytically pure form owing to its degradation.

1-[2-Acylamino-2-(diethoxyphoshoryl)acetyl]-piperidin-4-ylcarboxylic acids (VIIa, VIIb). A solution of 0.01 mol of compound **V** in 50 ml of an acetic acid–water mixture (5:1) was heated for 7 h at 75°C in a water bath. The reaction mixture was evaporated at a reduced pressure to dryness. The residue was rapidly triturated in anhydrous acetone, the precipitate was filtered off, dried in a vacuum at 75°C. Compounds **VII** were analyzed without further purification.

Methyl 1-[2-acylamino-2-(diethoxyphoshoryl)-acetyl]piperidin-4-ylcarboxylates (VIIIa, VIIIb). A solution of 0.01 mol of compound **IV** was heated in 50 ml of an acetic acid–water mixture (5:1) for 7 h at 75ºC in a water bath. The reaction mixture was evaporated at a reduced pressure to dryness. The precipitated oil was treated with boiling petroleum ether (3×50 ml) with decanting. The combined ether extracts were evaporated to dryness at a reduced pressure. The products are pale yellow viscous oils. Compound **VIIIa** crystallizes after 3 days, and compound **VIIIb**, after 3 months.

1-{2-(Dihydroxyphosphoryl)-2-[(4-methylphenyl)-formamido]acetyl}piperidin-4-ylcarboxylic acid (Xb). A solution of 0.01 mol of acid **VIb** in 50 ml of an acetic acid–water mixture (5:1) was heated for 30 h at 75°C in a water bath. The reaction mixture was evaporated at a reduced pressure to dryness. The residue was rapidly triturated in anhydrous acetone with filtration, dried in a vacuum at 75°C. The product is white hygroscopic powder, which melts in air.

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