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Synthesis of Phosphorylated Derivatives of Furoylglycine and Furoyl-β-alanine

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Abstract—Chloromethylfuroyl chlorides react with alkyl glycinates and β-alanates to form the corresponding chloromethylfuroyl amides. The compounds obtained are phosphorylated with triethyl phosphite under the conditions of the Arbuzov reaction to give (diethoxyphosphorylmethylfuroyl amides. Alkaline hydrolysis of these compounds proceeds only at the carboxy group leading to (diethoxyphosphorylmethyl)furoylglycine and furoyl-β-alanine. Selectivity of hydrolysis does not depend on the position of carboxamide and diethoxyphosphorylmethyl groups in the furan ring.

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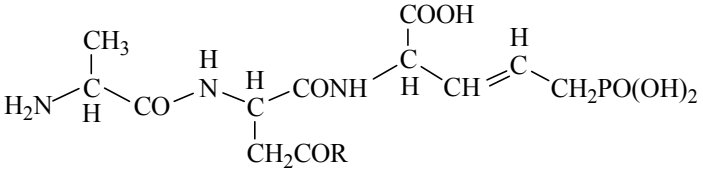
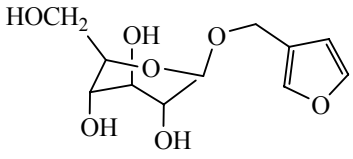
Phosphonates bound with the peptide chain form a noticeable group of natural and synthetic antibiotics of the varied action [1]. Plumbecines A and B (**I**) can serve an example of such substances.



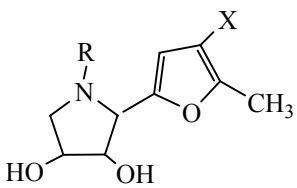
I, R = OH (A), NH_2 (B).

On the other hand it is known that biosynthesis of cellulose *in vivo* is regulated by (3-furyl)methyl-β-glucoside (**II**) [2].



II

Large group of 2-(2-furyl)-3,4-bis(hydroxy)pyrrolidines (**III**) [3 4] exhibits the inhibiting activity in relation to β-galactosidase and α-L-fucosidase.



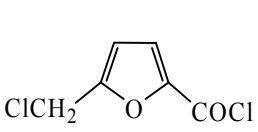
III

R = CH_2OH, COOR, COOH, CONR, $CONH_2$.

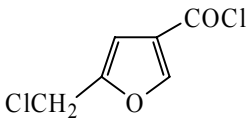
Consequently the combination of organophosphorus substituent, of the furan ring, and of a group permitting the use of the compounds of such structure for modification of natural objects presents great interest from the point of view of search for new biologically active substances. The aim of this work is the synthesis of furan derivatives whose structure permits to introduce them in polypeptide chain.

One of the possible ways of solving this problem is the synthesis of phosphorylated derivatives of furoyl-amino acids. The first step on this pathway consists in the acylation of the amino acids with chloromethylfuroyl chlorides **IV**–**IX**.

To avoid problems connected with racemization alkyl glycinates and β-alanates were chosen as substrates. The set of the acylating agents used permitted obtaining all possible relative location of the carboxy and the chloromethyl groups in the furan ring.



IV



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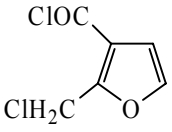
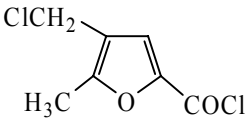
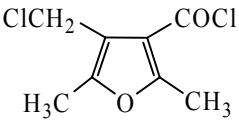


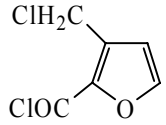
VI



VII

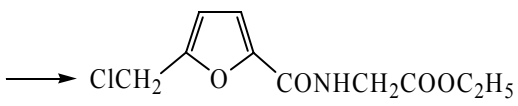


VIII



IX

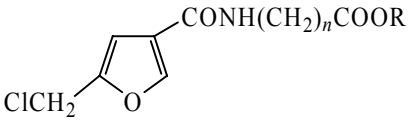
The acylation of the glycine and alanine esters with the acid chlorides **IV–VII** was carried out in methylene chloride in the presence of triethylamine at 10–15°C. Under these conditions the chloromethyl group does not take part in the reaction. In the course of the process a slight heat evolution was observed. It was impossible to establish any definite dependence of the yield of the target product on the structure of the acylating agent. By an example of the acid chloride **IV** and ethyl glycinate the reaction scheme may be described as follows.



Xa

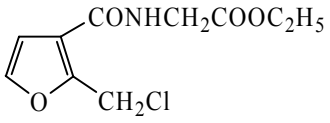
Amides **Xb, XIIa, XIIb**, **XII**, **XIIIa, XIIIb** were prepared analogously.

Xb

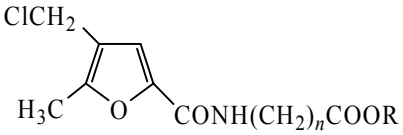


XIa (n = 1, R = C_2H_5)

XIb (n = 2, R = CH_3)



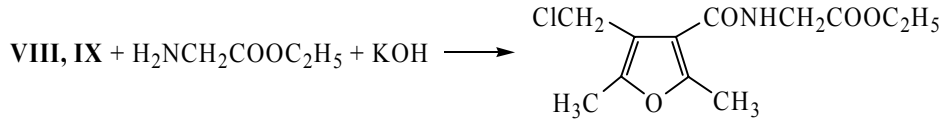
XII



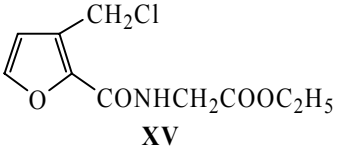
XIIIa (n = 1, R = C_2H_5)

XIIIb (n = 2, R = CH_3)

In the course of acylation of ethyl glycinate with the acid chlorides **VIII, IX** under the above-described conditions complex mixtures of products were formed. Unlike that the reaction performed under the Schotten-Baumann conditions in aqueous acetone at 0°C at a gradual addition of the acylating agent and alkali proceeds selectively to give the target amides **XIV, XV**.



XIV



XV

Table 1. Yields and parameters of ^{1}H NMR spectra of the esters of furoylglycine and furoyl-β-alanine

Comp. no.	Yield, %	mp, °C	δ, ppm
Xa	42	82–83	1.243 t (CH_3-ethyl, J_{HH} 7 Hz), 4.143 d (CH_2N, J_{HH} 5.2 Hz), 4.188 q (CH_2OOC, J_{HH} 7 Hz), 4.500 s (CH_2Cl), 6.407 d (H^4-furan, J_{HH} 3.2 Hz), 7.003 d (H^3-furan, J_{HH} 3.2 Hz), 7.066 br.s (NH)
Xb	59	glass-like mass	2.590 t (CH_2COO, J_{HH} 6.6 Hz), 3.609–3.640 m (CH_3OOC and NCH_2), 4.505 s (CH_2Cl), 6.398 d (H^4-furan, J_{HH} 4 Hz), 6.970 br.s (H^3-furan and NH)
XIa	36	62–63	1.271 t (CH_3-ethyl, J_{HH} 7 Hz), 4.180 q (CH_2OOC, J_{HH} 7 Hz), 4.207 d (CH_2N, J_{HH} 6.4 Hz), 4.527 s (CH_2Cl), 6.628 s (H^4-furan), 6.760 br.s (NH), 7.921 s (H^2-furan)
XIb	19	syrup	2.614 t (CH_2COO, J_{HH} 7 Hz), 3.646 d.t (CH_2N, J_{HH} 6.4 Hz, J_{HH} 7 Hz), 3.704 s (CH_3OOC),4.542 s (CH_2Cl), 6.536 br.s (NH), 6.583 s (H^4-furan), 7.052 s (H^2-furan)
XII	50	syrup	1.254 t (CH_3-ethyl, J_{HH} 7.6 Hz), 4.111 d (CH_2N, J_{HH} 5.2 Hz), 4.189 q (CH_2OOC, J_{HH} 7.6 Hz), 4.870 s (CH_2Cl), 6.581 s (H^4-furan), 6.838 br.s (NH), 7.350 s (H^5-furan)
XIIIa	74	79–80	1.305 t (CH_3-ethyl, J_{HH} 7 Hz), 2.305 s (CH_3-furan), 4.182 d (CH_2N, J_{HH} 6.4 Hz), 4.249 q (CH_2OOC, J_{HH} 7 Hz), 4.409 s (CH_2Cl), 6.744 br.s (NH), 7.091 s (H^3-furan)
XIIIb	31	syrup	2.294 s (CH_3-furan), 2.584 t (CH_2OOC, J_{HH} 6.4 Hz), 3.624 m (CH_2N), 3.665 s (CH_3OOC), 4.358 s (CH_2Cl), 6.670 br.s (NH), 6.998 s (H^3-furan)
XIV	39	113	1.304 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.280 s (CH_3^5-furan), 2.473 s (CH_3^2-furan), 4.198 d (CH_2N, J_{HH} 4.4 Hz), 4.243 q (CH_2OOC, J_{HH} 7 Hz), 4.651 s (CH_2Cl), 6.665 br.s (NH)
XV	68	69	1.294 t (CH_3-ethyl, J_{HH} 7 Hz), 4.166 d (CH_2N, J_{HH} 5.2 Hz), 4.242 q (CH_2OOC, J_{HH} 7 Hz), 4.919 s (CH_2Cl), 6.629 d (H^4-furan, J_{HH} 1.6 Hz), 6.880 br.s (NH), 7.386 d (H^5-furan, J_{HH} 1.6 Hz)

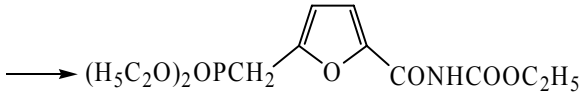
Yields of the obtained amides and characteristics of their ^{1}H NMR spectra are presented in Table 1.

In the second stage of the synthesis the phosphorylation of obtained chloromethyl derivatives of furoylglycine and furoyl-β-alanine with triethyl-phosphite under the Arbuzov reaction conditions was carried out. Surprisingly we found no reported data on the introduction of N-monosubstituted amides of halo-gen-containing acids in the Arbuzov reaction. It seems that the results given below is the first example of phos-phorylation of N-monosubstituted chloromethylamides with trialkyl phosphites.

The phosphorylation of chloromethylfurans was carried out with the excess of triethyl phosphite to provide the complete conversion of furan because the liberating ethyl chloride can also take part in the Arbuzov reaction and consume phosphite.

Liberation of methyl chloride begins at 120–150°C, and the criterion of completeness of the reaction is the increase in temperature of the reaction mixture to 180–190°C and the disappearance of triethyl phosphite. The mixture obtained was kept in a vacuum (1 mm Hg) at 50–60°C for 1 h to remove the traces of volatile products. The reaction proceeded according to the scheme presented below.

Xa + $P(OC_2H_5)_3$



XVIa

Total reaction time as a rule was 40–45 min. The phosphonates obtained are very viscous syrups insoluble in water and soluble in common organic solvents. No exchange of radicals between the phosphoryl and carboxy groups was observed in the case of methyl β-alanates. The transamidation between the phosphoryl and carboxamide groups was also absent. The conditions of the phosphorylation of alkyl chloromethylfuroylglycinates and furoyl-β-alanate are listed in Table 2, and spectral characteristics of the products obtained, in Table 3.

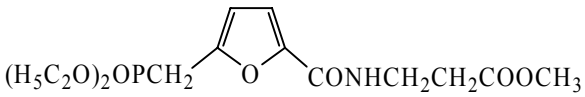
Analysis of the phosphorylation conditions of chloromethylfuroylglycine and furoyl-β-alanine shows that the reaction conditions and the yields of the products do not significantly depend on the location of chloromethyl group in the furan ring. Amount of by-products is insignificant, they are volatile and are

Table 2. Conditions of phosphorylation of chloromethylamides

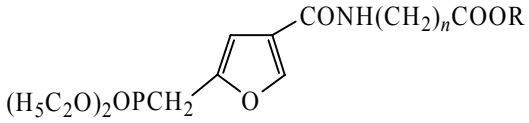
Comp. no.	Substrate:phosphate molar ratio	Temperature, °C		Reaction time, min	Yield, %
		beginning of the reaction	completing of the reaction		
Xa	1:2.17	130	190	40	87
Xb	1:2.11	128	196	45	99
XIa	1:4.37	128	190	60	86
XIb	1:5.64	125	200	45	70
XII	1:1.48	110	182	30	86
XIIIa	1:2.52	120	189	65	91
XIIIb	1:1.87	123	190	60	93
XIV	1:2.24	125	185	40	94
XV	1:1.68	105	190	40	87

Table 3. Spectral characteristics of phosphonates **XVI–XXI**

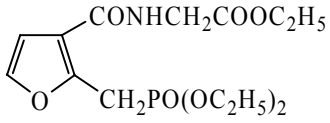
Comp. no.	^{1}H NMR spectrum, δ, ppm	^{31}P NMR spectrum, δ_P, ppm
XVIa	1.259 s (CH_3-ethyl, J_{HH} 7 Hz), 3.227 d (CH_2P, J_{HH} 21.2 Hz), 4.060 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 14.8 Hz), 4.131 d (CH_2N, J_{HH} 4.8 Hz), 4.165 q (CH_2OOC, J_{HH} 7 Hz), 6.330 br.s (H^4-furan), 6.940 s (NH), 7.029 br.s (H^3-furan)	21.159
XVIb	1.229 s (CH_3-ethyl, J_{HH} 7.2 Hz), 2.592 t (CH_2COO, J_{HH} 7.2 Hz), 3.188 d (CH_2P, J_{HH} 21.2 Hz), 3.599 d. t (CH_2N, J_{HH} 5.6, 7.2 Hz), 3. 632 s (CH_3OOC), 4.024 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.4 Hz), 6.283 s (H^4-furan), 6.959 s (H^3-furan)	20.888
XVIIa	1.248 t (CH_3-ethyl, J_{HH} 7.2 Hz), 3.179 d (CH_2P, J_{HP} 20.8 Hz), 4.022–4.077 m (CH_2OP and CH_2N), 4.172 q (CH_2OOC, J_{HH} 7.2 Hz), 6.515 s (H^4-furan), 7.872 s (H^2-furan)	21.710
XVIIb	1.288 m (CH_3-ethyl, J_{HH} 7.2 Hz), 2.606 t (CH_2COO, J_{HH} 7 Hz), 3.205 d (CH_2P, J_{HP} 20.8 Hz), 3.628 d. t (CH_2N, J_{HH} 5.6, 7 Hz), 3.694 s (CH_3OOC), 4.080 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 15.2 Hz), 6.459 s (H^4-furan), 6.566 br.s (NH), 7.830 s (H^2-furan)	21.719
XVIII	1.221 m (CH_3-ethyl, J_{HH} 7.6 Hz), 3.566 d (CH_2P, J_{HP} 20.8 Hz), 4.056 m (CH_2OP and CH_2N), 4.123 q (CH_2OOC, J_{HH} 7.6 Hz), 6.606 br.s (H^4-furan), 7.257 s (H^5-furan), 8.216 br.s (NH)	23.072
XIXa	1.158 m (CH_3-ethyl), 2.174 s (CH_3-furan), 2.739 d (CH_2P, J_{HH} 20.8 Hz), 3.935 m (CH_2OP), 4.035 q (CH_2OOC, J_{HH} 7 Hz), 4.103 d (CH_2N, J_{HH} 7.2 Hz), 6.909 br.s (H^3-furan and NH)	25.089
XIXb	1.255 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.271 d (CH_3-furan, J_{HP} 3.2 Hz), 2.538 t (CH_2COO, J_{HH} 6.0 Hz), 2.890 d (CH_2P, J_{HP} 20.4 Hz), 3.641 d.t (CH_2N, J_{HH} 5.6, 6.0 Hz), 3.688 s (CH_3OOC), 6.803 br.s (NH), 6.961 s (H^3-furan)	25.290
XX	1.230 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.114 d (CH_2^5, J_{HP} 2 Hz), 2.326 s (CH_3^2), 3.002 d (CH_2P, J_{HP} 20 Hz), 4.003–4.057 m (CH_2OP + CH_2N), 4.103 q (CH_2OOC, J_{HH} 7.2 Hz), 8.744 br.s (NH)	28.199
XXI	1.215 m (CH_3-ethyl, J_{HH} 6.9, 7.2 Hz), 3.562 d (CH_2P, J_{HP} 22 Hz), 4.086 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.4 Hz), 4.165 d (CH_2N, J_{HH} 6.0 Hz), 4.233 q (CH_2OOC, J_{HH} 6.9 Hz), 6.614 s (H^4-furan), 7.226 br.s (NH), 7.389 s (H^5-furan)	24.868



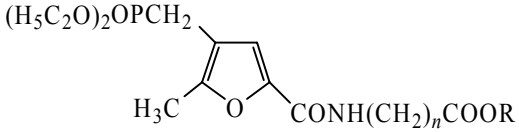
XVIb



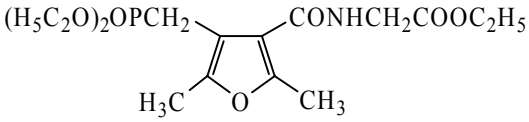
XVIIa (n = 1, R = C_2H_5)
XVIIb (n = 2, R = CH_3)



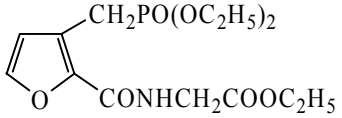
XVIII



XIXa (n = 1, R = C_2H_5)
XIXb (n = 2, R = CH_3)



XX



XXI

easily removed from the reaction mixture in a vacuum. The phosphonates obtained are thermally stable.

Hence, the presence of CO–NH fragment in the molecule does not prevent the proceeding of the Arbuzov reaction. It is interesting that chemical shift values of phosphorus atom in this set of compounds is primarily determined by the location of the phosphorus-containing group in the furan ring. The effect of carboxamide group is significantly smaller. For example, in compounds **XVIa, XVIb** having diethoxyphosphorylmethyl group in the α-position of the furan ring δ_P is ~21 ppm. In this case the effect of carboxamide group on the electron density on the Cα atom is the highest [5]. In the compounds **XVIIa, XVIIb** the transfer of the carboxamide group effect from the position 3 to the position 5 of the ring is significantly smaller, but the upfield shift of the signal of phosphorus atom is only ~0.7 ppm. The transfer of the effect of the substituent in the direction 3→2 of the furan ring is significantly more effective, than in the above-described case, but the upfield shift of the signal of phosphorous atom in the phosphonate **XVIII** is 2 ppm against the products **XVIa, XVIb** and ~1 ppm in relation to the compounds **XVIIa, XVIIb**. It may be suggested that in this case main contribution is made by the sterical factors driving the substituent from the conjugation with the ring and decreasing the transfer of the effect of substituted furan ring through the methylene bridge.

In the series of β-substituted phosphonates **XIX–XXI** the following picture is observed. The chemical shift of phosphorus in products **XIXa, XIXb** has the mean value ~25.1 ppm, and the effect of carboxamide group in this compounds is the smallest. It can be compared to that in the phosphonates **XVIIIa, XVIIIb**. Hence, the alteration in the location of diethoxyphosphorylmethyl group in the ring is accompanied by the upfield shift of the signal by ~3 ppm. In the phosphonate **XXI** the effect of the carboxamide group without the sterical factors would be stronger, but the downfield shift of signal against the compound **XIX** is almost insignificant. It is only 0.2–0.3 ppm. Hence, the electronic and sterical effects have an opposite direction and practically compensate one another. The comparison of phosphonate **XX** with the other members of this series shows that the chemical shift of phosphorus undergoes the upfield shift by 3 ppm. In this case the transfer of the effect of substituent in the furan ring in the direction 3→4 is comparable to 2→3, and is higher than in the direction 4→2.

At the same time the molecule of phosphonate **XX** is the most sterically loaded, and this strong increase in the electron density on phosphorus may be related only to the effect of steric factors.

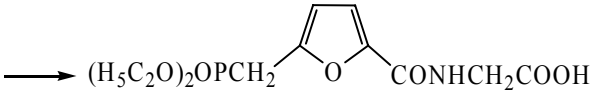
For comparison, the chemical shift of phosphorus in 2-diethoxyphosphorylmethylfurans with the alkyl substituents in the ring is ~23.4 ppm, while in their 3-substituted analogs it is ~26.2 ppm [6, 7]. The

difference in chemical shifts is ~2.8 ppm. Hence, the effect of the furan ring in the case of 2- and 3-phosphorylmethylated furans occurs to be approximately equal for the substances carrying the substituents capable of conjugation with the heteroaromatic ring as well as for the compounds in which the conjugation with the substituent is absent.

Synthesized phosphorylated derivatives of furoylglycine and furoyl-β-alanine can be used as modifiers of peptides only if they have an active functional group. An evident step in this direction is their hydrolysis with the formation of free hydroxy group. A selective hydrolysis of phosphonocarboxylic acid ester was described in [8]. We decided to use analogous procedure for the acylaminoesters **XVI–XXI**.

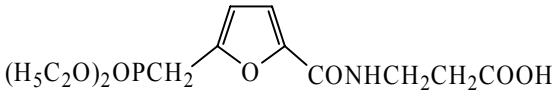
The hydrolysis of compounds under study was carried out with potassium hydroxide in aqueous methanol at 65°C and the KOH:ester molar ratio 1.5. The criterion of completion of the process was establishing of constant pH value in the reaction mixture. It turned out that under the chosen conditions the hydrolysis of the acylaminoesters proceeded selectively at the carboxy group. A significant hydrolysis or the radical exchange on phosphorus was not found. By an example of the phosphonate **XVIa** the reaction scheme may be presented as follows.

XVIa + KOH

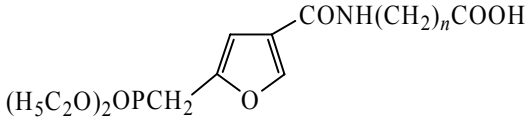


XXIIa

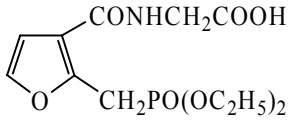
Compounds **XXIIb–XXVII** were obtained analogously.



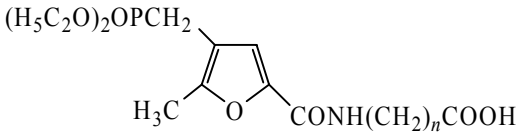
XXIIb



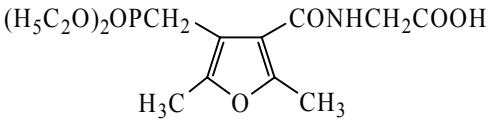
XXIIIa (n = 1)
XXIIIb (n = 2)



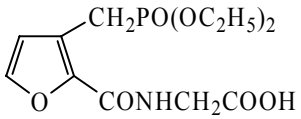
XXIV



XXVa (n = 1)
XXVb (n = 2)



XXVI



XXVII

Reaction times, yields of the products, and spectral characteristics of the acids obtained are presented in Table 4.

The acids obtained as a rule are glass-like solids comparatively well soluble in water. Their isolation from reaction mixture was carried out by removing the solvent, dissolution of potassium salts in the minimum amount of water, acidifying to pH 2, and extraction with 5:1 mixture of methylene chloride and acetone. Only the phosphonates **XXVa** and **XXVI** readily formed crystals.

The character of variations in ^{31}P chemical shifts of the compounds obtained was similar to the pattern described for their esters.

Analysis of the ^{1}H NMR spectra of chloromethylfurans **XI–XV**, of esters **XVI–XXI,** and of acids **XXII–XXVII** shows that their amide group protons take part in the exchange interactions, but the intensity of this process is different. In the majority of cases clear NH–CH coupling constant is observed varying in the range 4.4–7.2 Hz (most frequently 5.2–6.4 Hz). In the case of β-alanine derivatives **XXIIb**,

Table 4. Yields and spectral characteristics of phosphorylated derivatives of furoylglycine and furoyl-β-alanine

Comp. no.	Reaction time, h	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm	^{31}P NMR spectrum, δ_P, ppm
XXIIa	8	48	glass-like mass	1.255 t (CH_3-ethyl, J_{HH} 6.8 Hz), 3.297 d (CH_2P, J_{HP} 21.2 Hz), 4.067 m (CH_2OP, J_{HH} 6.8 Hz, J_{HP} 14.4 Hz), 4.154 d (CH_2N, J_{HH} 4.8 Hz), 6.295 br.s (H^4-furan), 7.045 br.s (H^3-furan), 7.304 br.s (NH), 9.205 br.s (COOH)	21.520
XXIIb	8	75	glass-like mass	1.218 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.581 br.s (CH_2COO), 3.233 d (CH_2P, J_{HP} 20.8 Hz), 3.601–3.696 br.s (CH_2N), 4.035 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.4 Hz), 6.286 s (H^4-furan), 6.993 s (H^3-furan), 7.286 br.s (NH), 8.673 br.s (COOH)	21.301
XXIIIa	8	69	glass-like mass	1.274 t (CH_3-ethyl, J_{HH} 7 Hz), 3.242 d (CH_2P, J_{HP} 21.6 Hz), 4.096 m (CH_2OP and CH_2N), 6.735 s (H^4-furan), 7.355 br.s (NH), 7.928 s (H^2-furan), 8.630 br.s (COOH)	22.077
XXIIIb	6	62	glass-like mass	1.272 m (CH_3-ethyl), 2.643 br.s (CH_2COO), 3.224 d (CH_2P, J_{HP} 20.4 Hz), 3.623 br.s (CH_2N), 4.085 m (CH_2OP), 6.296 br.s (NH), 6.809 s (H^4-furan), 7.257 br.s (COOH), 7.892 s (H^2-furan)	22.826
XXIV[a]	8	76	glass-like mass	1.135–1.228 m (CH_3-ethyl, J_{HH} 7.2 Hz), 3.420 br.s (CH_2P), 3.615 s and 3.756 s (CH_2N), 3.946 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.8 Hz), 6.980 s (H^4-furan), 7.624 s (H^5-furan), 8.616 br.s (NH), 12.655 s (COOH)	21.986
XXVa	8	72	151–152	1.270 t (CH_3-ethyl, J_{HH} 7 Hz), 2.292 d (CH_3-furan, J_{HP} 1.8 Hz), 2.880 d (CH_2P, J_{HP} 20.8 Hz), 4.068 m (CH_2OP, J_{HH} 7 Hz, J_{HP} 14.8 Hz), 4.167 d (CH_2N, J_{HH} 4.4 Hz), 7.030 br.s (NH), 7.119 s (H^3-furan), 7.340 br.s (COOH)	25.055
XXVb	8	57	glass-like mass	1.249 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.252 d (CH_3-furan, J_{HP} 2.4 Hz), 2.601 t (CH_2COO, J_{HH} 5.4 Hz), 2.851 d (CH_2P, J_{HP} 20.4 Hz), 3.631 d.t (CH_2N, J_{HH} 5.4, 6.4 Hz), 4.037 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.4 Hz), 7.010 s (H^3-furan), 7.062 t (NH, J_{HH} 6.4 Hz), 8.925 br.s (COOH)	25.588
XXVI	8	60	96–98	1.286 t (CH_3-ethyl, J_{HH} 7.2 Hz), 2.170 d (CH_3^5-furan, J_{HP} 2.4 Hz), 2.391 s (CH_3^2-furan), 3.055 d (CH_2P, J_{HP} 19.6 Hz), 4.084 m (CH_2OP, J_{HH} 7.2 Hz, J_{HP} 14.0 Hz), 4.130 d (CH_2N, J_{HH} 4.4 Hz), 8.392 br.s (NH), 8.596 br.s (COOH)	28.011
XXVII	7	83	glass-like mass	1.256 t (CH_3-ethyl, J_{HH} 7.6 Hz), 3.572 d (CH_2P, J_{HP} 22.4 Hz), 4.086 m (CH_2OP, J_{HH} 7.6 Hz, J_{HP} 15.2 Hz), 4.147 d (CH_2N, J_{HH} 5.6 Hz), 6.570 s (H^4-furan), 7.107 br.s (NH), 7.367 s (H^5-furan), 9.671 s (COOH)	25.387

[a] Spectrum was taken in DMSO-d_6.

XXIIIb the exchange becomes faster. Signals of the NH, NCH_2, and CH_2COO protons broaden and loose their precise structure. In the case of the acid **XXIV** the process still more intensifies and includes the protons of NH and $CH_2PO(OR)_2$ groups. In the last case instead of the doublet with J_{HP} ~20 Hz only the strongly broadened signal is observed. In this case strong intramolecular interactions can probably take place with the formation of two conformers taking part in the fast exchange because the signals of protons of CH_2N group give two singlets with the difference in chemical shifts 0.141 ppm. It is interesting to note that

in the acid **XXVII** with the reversed location of substituents in the furan ring only the exchange of moderate intensity in the NH–CH_2 fragment takes place (J_{HH} 5.6 Hz).

Another limiting case is observed for the acid **XXVb**. In this case the exchange intensity becomes so weak that the signal of NH proton becomes a clearly expressed triplet, J_{HH} in the NH–CH_2 fragment being equal to 6.4 Hz.

Hence, in the course of the study a series of (diethoxyphosphorylmethyl)furoylglycines and furoyl-β-alanines was synthesized including all possible cases of relative location of the phosphorylmethyl and carboxamide groups in the furan ring. The presence of a free carboxy group permits to use these substances as modifiers of the biologically valuable molecules, for example, peptides, with the purpose of introduction of groups carrying two pharmacophoric fragments, the furan ring and the phosphonate function.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker DPX-400 spectrometer (400.13 MHz), and ^{31}P NMR spectra, on a Bruker AC-200 device (80.014 MHz ^{31}P) in deuterochoroform or DMSO-d_6.

Chloromethylfuroyl chlorides **VI–IX** were prepared according to the procedure [8].

Acylation of alkyl glycinate and β-alanates hydrochlorides with chloromethylfuroyl chlorides *(general procedure). a. Reaction in the presence of triethylamine*. The amino acid ester hydrochloride, 11 mmol, was suspended in 50 ml of methylene chloride, 23 mmol of triethylamine was added in one portion, and the reaction mixture was stirred for 20 min. After that the reaction mixture was cooled to 10°C, and at this temperature a solution of 10 mmol of acid chloride in 10 ml of methylene chloride was added dropwise under the intense stirring. The reaction mixture was stirred for 3 h at 10–15°C and left overnight. On the next day it was washed with 10% hydrochloric acid, with 5% sodium hydrogen carbonate solution, then with water, and dried over calcium chloride. The solvent was removed at a reduced pressure, and the residue was kept in a vacuum (1 mm) for 1 h at room temperature. Yields and ^{1}H NMR spectra of the compounds **X-XIII** prepared by this method are listed in Table 1.

b. Reaction under the Schotten–Baumann conditions. Amino acid ester hydrochloride, 22 mmol, was suspended in 50 ml of acetone at 0–2°C, and the solutions of potassium hydroxide (5% in water, 42 mmol) and of the acid chloride (20 mmol in 10 ml of acetone) were added dropwise under the intense stirring from two dropping funnels at a rate providing pH of the reaction mixture within the range 8–9 units. After the complete addition of reagents the mixture obtained was kept for 2 h at 5–10°C, warmed to room temperature, diluted with 20 ml of water, and acetone was removed at a reduced pressure. The residue was extracted with methylene chloride, washed with diluted hydrochloric acid, then with water, and dried over sodium sulfate. The solvent was removed at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at room temperature. Yields of the compound **XIV, XV** prepared by this method and the parameters of their ^{1}H NMR spectra are listed in Table 1.

Phosphorylation of the (chloromethylfuroyl) glycine and furoyl-β-alanine esters *(general procedure)*. A mixture of the compound to be phosphorylated and the triethyl phosphite was heated with stirring. The reaction began with the liberation of ethyl chloride bubbles at a temperature listed in Table 2, and further heating caused boiling of the reaction mixture. This temperature increased gradually to the value presented in Table 2 when the vapor formation stopped, and the triethyl phosphite was not found in the reaction mixture. The mixture obtained was cooled, dissolved in chloroform, and placed in a flask for vacuum distillation. The solvent was removed at a reduced pressure, and the residue was kept in a vacuum (1 mm Hg) for 1 h at 50–60°C. The substrate-phosphite molar ratio, temperature limits of the reaction, time of phosphorylation, and yields of phosphonates are listed in Table 2, and the characteristics of the products, in Table 3.

Hydrolysis of (diethoxyphosphorylmethyl)furoylglycinates and furoyl-β-alanates *(general procedure)*. To a solution of 20 mmol of phosphonate in 50 ml of methanol a solution of 30 mmol of KOH in 3 ml of water was added in one portion with stirring. The mixture obtained was refluxed with stirring for 6–8 h, and methanol was distilled off at a reduced pressure. The residue was dissolved in a minimum amount of water and acidified with hydrochloric acid to pH 2. The mixture obtained was saturated with potassium chloride and extracted with 5:1 methylene chloride–acetone mixture. The extract was dried over sodium sulfate, evaporated at reduced pressure, and the

residue was kept in a vacuum at room temperature and the residual pressure 1 mm. Reaction times, yields of the products, and their spectral parameters are listed in Table 4.

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