Brief Communications

Phosphorylthioureas and phosphorylureas containing amino acid fragments

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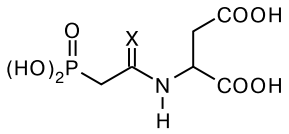
A series of (dialkoxyphosphoryl)thioureas and their 1,3,2-oxazaphosphinane analogs containing fragments of glycine, alanine, β-alanine, L-aspartic and L-glutamic acids, as well as phosphorylureas derived from glycine and β-alanine were synthesized in the search for potential biologically active compounds (including possible inhibitors of aspartate transcarbamoylase).

Key words: phosphoryl isothiocyanates, phosphoryl isocyanates, amino acid esters, esters of phosphorylthiocarbamoylamino acid, esters of phosphorylcarbamoylamino acids, 1,3,2-oxazaphosphinanes.

Earlier,[1] we have described synthesis of structural analogs of PALA[2,3] (**1**), an active carcinolytic, *viz.*, phosphorylureas (**2**) that contain an L-aspartic acid fragment, including 2-oxo-1,3,2-oxazaphosphinane derivatives (**2**, RR′ = $HN(CH_2)_3O$) in which the oxazaphosphinane ring can play «transport» role delivering a pharmacophore group into a cell through cell membranes[4] (similarly to the antitumor agent cyclophosphamide).

It is also known that ThioPALA (**3**) is twice as active as PALA due to higher lipophilicity.[5] It was thus of interest to synthesize thiourea derivatives with L-aspartic acid fragment analogous to compounds **2** including compounds that contain 1,3,2-oxazaphosphinane ring. Phosphorylthiourea and phosphorylurea derivatives that contain other amino acid fragments can also be of definite interest as potential biologically active compounds.



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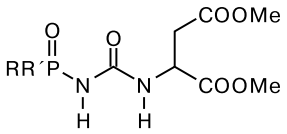

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X = O (**1**); S (**3**).

The reactions of the known[6] phosphoryl isothiocyanates **4** and **5** with amino acid esters **6** afford phosphorylthioureas **7**, **8** (Scheme 1, Table 1), the reaction proceeded smoothly at room temperature in benzene.

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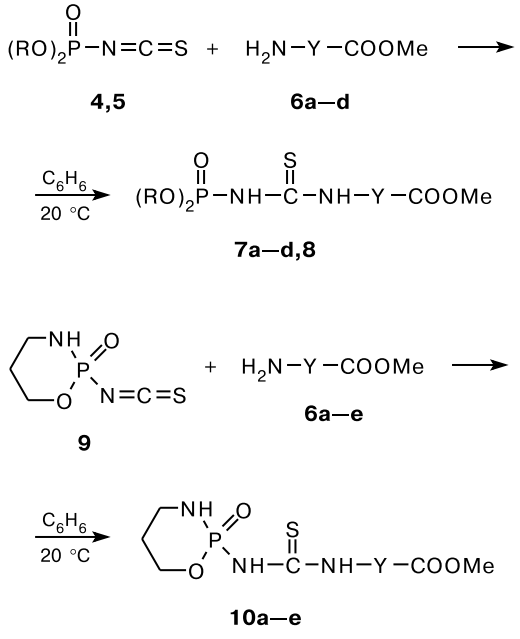
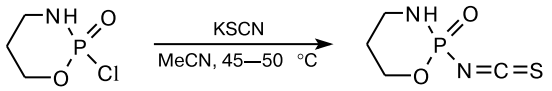
Scheme 1



R = Et (**4, 7**); R = Bu (**5, 8**); **6**, **7**, **10:** Y = CH(CH_2COOMe) (**a**), CH_2 (**b**), CH_2CH_2 (**c**), CH(CH_2CH_2COOMe) (**d**), CH(Me) (**e**). Y = CH(CH_2COOMe) (**8**)

Esters **6** react with 2-isothiocyano-2-oxo-1,3,2λ^5-oxazaphosphinane (**9**) under the same conditions resulting in phosphorylthioureas **10**, which contain a cyclic fragment (see Scheme 1, Table 1). It is worth noting that isothiocyanate **9**, as well as compounds **4**, **5**, was obtained by the reaction of the corresponding acid chloride, 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane[7] (**11**), with KSCN in MeCN, but in this case longer heating (15—18 h) at 45—50 °C and two equivalents of KSCN were required (Scheme 2).

Scheme 2



11 **9**

After removal of inorganic salts, compound **9**, as judged by the ^{31}P NMR spectral data, was free from any admixtures, it was used in further reactions without additional purification.

Besides phosphorylthioureas **7b,c**, phosphorylureas **12a,b** were obtained (analogous L-aspartic and L-glutamic acids derivatives have been described by us earlier[1]), which

Table 1. Yields, melting points and elemental analysis data for the obtained compounds

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula
			C	H	N	P	
7a[a]	70	Oil	36.99 37.10	5.94 5.94	7.68 7.86	8.61 8.69	$C_{11}H_{21}N_2O_7PS$
7b	44	84—85	33.88 33.88	6.09 6.03	9.84 9.88	10.88 10.90	$C_8H_{17}N_2O_5PS$
7c	66	Oil	36.25 36.24	6.47 6.42	9.26 9.39	—	$C_9H_{19}N_2O_5PS$
7d	60	Oil	38.94 38.92	6.32 6.26	7.51 7.56	—	$C_{12}H_{23}N_2O_7PS$
8[b]	20	Oil	43.66 43.68	7.19 7.10	6.57 6.74	7.31 7.51	$C_{15}H_{29}N_2O_7PS$
10a	71	[c]	35.41 35.40	5.18 5.35	12.04 12.38	—	$C_{10}H_{18}N_3O_6PS$
			33.82 33.73	4.96 5.05	11.49 11.57	—	$C_{10}H_{18}N_3O_6PS \cdot 0.2CHCl_3$
10b	78	123—124	31.51 31.46	5.37 5.28	15.77 15.72	—	$C_7H_{14}N_3O_4PS$
10c	76	[c]	33.94 34.16	5.61 5.73	14.98 14.94	10.89 11.01	$C_8H_{16}N_3O_4PS$
10d	81	[c]	37.49 37.39	5.77 5.70	11.81 11.89	—	$C_{11}H_{20}N_3O_6PS$
10e	70	[c]	34.18 34.16	5.79 5.73	14.71 14.94	—	$C_8H_{16}N_3O_4PS$
			32.21 32.28	5.17 5.35	13.69 13.77	—	$C_8H_{16}N_3O_4PS \cdot 0.2CHCl_3$
12a	54	101—102	35.84 35.82	6.51 6.39	10.49 10.45	11.51 11.55	$C_8H_{17}N_2O_6P$
12b	70	98—99	— —	— —	9.56 9.90	11.03 11.00	$C_9H_{19}N_2O_6P$

[a] Found (%): S, 8.93, calculated (%): S, 9.00.
[b] Found (%): S, 7.71, calculated (%): S, 7.77.
[c] Amorphous compound without definite melting point.

allows a comparison of the biological activities of these classes of compounds. Synthesis of ureas **12a,b** was carried out by the described procedure[1] using reaction of diethoxyphosphoryl isocyanate (**13**) with amino acids esters **6** (Scheme 3, see Table 1).

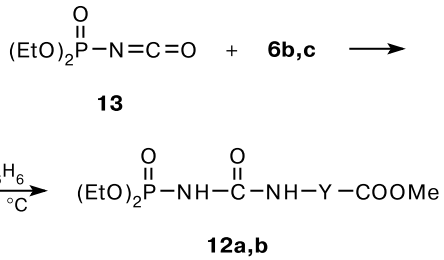
The composition and structures of the obtained compounds were confirmed by data from elemental analysis (see Table 1), and the $^{31}P\{^1H\}$ and ^1H NMR spectra (Table 2). Diastereomeric anisochronous effect was observed in the NMR spectra of compounds **10a,d,e**, which contain two chiral centres in the molecules. Compounds **10a,e** formed stable solvates with 0.2 molecule of $CHCl_3$. Data on the biological evaluation of the synthesized compounds will be published elsewhere.

Table 2. $^{31}P\{^1H\}$ and ^1H NMR spectra for the obtained compounds in $CDCl_3$

Compound	^{31}P NMR, δ	^1H NMR, δ, J/Hz
7a	−4.5	1.35 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.0); 3.03 (AB-system, 1 H, H_B, $NHC\underline{H}_2C(O)$, $^3J_{H,H_B}$ = 4.7, $^2J_{H_A,H_B}$ = 17.2); 3.09 (AB-system, 1 H, H_A, $NHC\underline{H}_2C(O)$, $^3J_{H,H_A}$ = 4.4, $^2J_{H_A,H_B}$ = 17.2); 3.68, 3.75 (both s, 3 H each, $C\underline{H}_3O$); 4.11—4.26 (m, 4 H, $CH_3C\underline{H}_2O$); 5.38 (dt, 1 H, $NHC\underline{H}CH_2$, $^3J_{H,H}$ = 4.4, $^3J_{H,H}$ = 5.3); 7.23 (d, 1 H, $N\underline{H}P$, $^2J_{H,P}$ = 9.8); 9.38 (d, 1 H, $N\underline{H}CH$, $^3J_{H,H}$ = 7.6)
7b	−4.04	1.41 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.1); 3.81 (s, 3 H, $C\underline{H}_3O$); 4.18—4.29 (m, 4 H, $CH_3C\underline{H}_2O$); 4.43 (d, 2 H, $NHC\underline{H}_2$, $^3J_{H,H}$ = 5.0); 7.66 (d, 1 H, $N\underline{H}P$, $^2J_{H,P}$ = 6.6); 9.34 (br.s, 1 H, $N\underline{H}CH_2$)
7c	−4.55	1.35 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 6.6); 2.70 (t, 2 H, $C\underline{H}_2C(O)$, $^3J_{H,H}$ = 6.3); 3.70 (s, 3 H, $C\underline{H}_3O$); 3.91 (dt, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{H,H}$ = 6.2, $^3J_{H,H}$ = 6.1); 4.10—4.20 (m, 4 H, $CH_3C\underline{H}_2O$); 6.57 (d, 1 H, $N\underline{H}P$, $^2J_{H,P}$ = 7.1); 9.15 (br.s, 1 H, $N\underline{H}CH_2$)
7d	−4.26	1.35, 1.36 (both t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 6.7); 2.10—2.36 (m, 2 H, $C\underline{H}_2C(O)$); 2.39—2.47 (m, 2 H, $CHC\underline{H}_2$); 3.65, 3.74 (both s, 3 H each, $C\underline{H}_3O$); 4.13—4.23 (m, 4 H, $C\underline{H}_2O$); 5.04, 5.06 (both t, 1 H, $C\underline{H}CH_2$, $^3J_{H,H}$ = 7.3); 7.16 (br.s, 1 H, $N\underline{H}P$); 9.21 (d, 1 H, $N\underline{H}CH$, $^3J_{H,H}$ = 7.2)
8	−2.11	0.87, 0.88 (both t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.4); 1.30—1.40 (m, 4 H, $C\underline{H}_2CH_3$); 1.59—1.67 (m, 4 H, $CH_2C\underline{H}_2CH_2$); 2.99 (AB-system, 1 H, H_B, $NHC\underline{H}_2C(O)$, $^3J_{H,H_B}$ = 4.5, $^2J_{H_A,H_B}$ = 17.2); 3.06 (AB-system, 1 H, HA, $NHC\underline{H}_2C(O)$, $^3J_{H,H_A}$ = 4.3, $^2J_{H_A,H_B}$ = 17.2); 3.64, 3,72 (both s, 3 H each, $C\underline{H}_3O$); 3.95—4.16 (m, 4 H, $C\underline{H}_2O$); 5.36 (dt, 1 H, $NHC\underline{H}CH_2$, $^3J_{H,H}$ = 4.6, $^3J_{H,H}$ = 7.9); 7.52 (br.s, 1 H, $N\underline{H}P_2$); 9.39 (d, 1 H, $N\underline{H}CH$, $^3J_{H,H}$ = 7.6)
9	−13.69[a]	—
10a	−1.54, −1.57	1.81—1.89[b], 2.15—2.35 (both m, 1 H + 1 H, $CH_2C\underline{H}_2CH_2$); 2.94—3.09 (m, 2 H, $C\underline{H}_2NHP$); 3.20—3.40 (m, 2 H $C\underline{H}_2OP$); 3.67, 3.68 (both s, 3 H, $C\underline{H}_3O$); 3.73, 3.74 (both s, 3 H, $C\underline{H}_3O$); 4.03—4.15 (br., 1 H, $CH_2N\underline{H}P$); 4.33—4.43 (m, 2 H, $C\underline{H}_2CH$); 5.36 (dt, 1 H, $NHC\underline{H}CH_2$, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 8.0); 7.79 (d, 1 H, $N\underline{H}P$, $^2J_{H,P}$ = 9.1); 9.53 (br.s, 1 H, $N\underline{H}CH$)
10b	−0.68	1.77—1.84, 2.02—2.13 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 3.32—3.39 (m, 2 H, $C\underline{H}_2NHP$); 3.75 (s, 3 H, $C\underline{H}_3O$); 4.09 (br.s, 1 H, $CH_2N\underline{H}P$); 4.29 (AB-system, 1 H, HB, $NHC\underline{H}_2C(O)$, $^3J_{H,H_B}$ = 5.1, $^2J_{H_A,H_B}$ = 18.0); 4.39 (AB-system, 1 H, HA, $NHC\underline{H}_2C(O)$, $^3J_{H,H_A}$ = 5.2, $^2J_{H_A,H_B}$ = 18.0); 4.26—4.46 (m, 2 H, $C\underline{H}_2OP$); 8.34 (d, 1 H, $C(S)N\underline{H}P$, $^2J_{H,P}$ = 9.5); 8.92 (t, 1 H, $C(S)N\underline{H}CH_2$, $^3J_{H,H}$ = 5.0)
10c	−1.06	1.81—1.89, 2.00—2.08 (both m, 1 H each, $^3J_{H,H}$ = 4.6, $CH_2C\underline{H}_2CH_2$); 2.64 (ABCD-system, 1 H, H_B, $CH_2C\underline{H}_2C(O)$, $^3J_{H_B,H_C}$ = 6.5, $^3J_{H_B,H_D}$ = 2.5, $^2J_{H_A,H_B}$ = 17.0); 2.71 (ABCD-system, 1 H, H_A, $CH_2C\underline{H}_2C(O)$, $^3J_{H_A,H_C}$ = 6.4, $^3J_{H_B,H_D}$ = 2.4, $^2J_{H_A,H_B}$ = 17.0); 3.68 (s, 3 H, $C\underline{H}_3O$); 3.28—3.42 (m, 2 H, $C\underline{H}_2NHP$); 3.83 (AB-system, 1 H, HB, $C(S)NHC\underline{H}_2$, $^3J_{H,H_B}$ = 2.1, $^2J_{H_A,H_B}$ = 6.4); 3.86 (AB-system, 1 H, HA, $C(S)NHC\underline{H}_2$, $^3J_{H,H_B}$ = 2.2, $^2J_{H_A,H_B}$ = 6.4); 3.90 (br.s, 1 H, $CH_2N\underline{H}P$); 4.33—4.45 (m, 2 H, $C\underline{H}_2OP$); 8.12 (d, 1 H, $PN\underline{H}C(S)$, $^2J_{H,P}$ = 9.4); 8.88 (t, 1 H, $C(S)N\underline{H}CH_2$, $^3J_{H,H}$ = 5.6)
10d	−0.36, −0.47	1.78—1.90, 2.27—2.36 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 2.00—2.15 (m, 2 H, $C\underline{H}_2C(O)$); 3.30—3.46 (m, 2 H, $C\underline{H}_2NHP$); 3.65 (s, 3 H, $CH_2COOC\underline{H}_3$); 3.730, 3.736 (s, 3 H, $CHCOOC\underline{H}_3$); 4.02 (br.s, 1 H, $CH_2N\underline{H}P$); 4.35—4.48 (m, 2 H, $C\underline{H}_2OP$); 5.03 (dt, 1 H, $NHC\underline{H}CH_2$, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 5.3); 8.04 (br.s, 1 H, $PN\underline{H}C(S)$); 9.00—9.05, 9.07—9.14 (both m, 1 H, $N\underline{H}CH$)
10e	0.21, 0.36	1.48 (d, 3 H, $CHC\underline{H}_3$, $^3J_{H,H}$ = 7.3); 1.77—1.90, 1.97—2.12 (both m, 1 H each, $CH_2C\underline{H}_2CH_2$); 3.23—3.48 (m, 2 H, $C\underline{H}_2NHP$); 3.72, 3.73 (both s, 3 H, $OC\underline{H}_3$); 4.04 (br.d, 1 H, $CH_2N\underline{H}P$, $^2J_{H,P}$ = 31.0); 4.31—4.48 (m, 2 H, $C\underline{H}_2OP$); 4.90 (dq, 1 H, $NHC\underline{H}CH_3$, $^3J_{H,H}$ = 7.3, $^3J_{H,H}$ = 6.0); 7.75 (br.s, 1 H, $PN\underline{H}C(S)$); 8.99 (dd, 1 H, $N\underline{H}CH$, $^3J_{H,H}$ = 7.0, $^2J_{H,P}$ = 54.0)
12a	−0.99	1.38 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.0); 3.76 (s, 3 H, $C\underline{H}_3O$); 4.01 (d, 2 H, $NHC\underline{H}_2$, $^3J_{H,H}$ = 5.7); 4.15—4.26 (m, 4 H, $CH_3C\underline{H}_2O$); 7.18 (s, 1 H, $N\underline{H}P$); 7.90 (s, 1 H, $N\underline{H}CH_2$)
12b	−0.8	1.41 (t, 6 H, $CH_2C\underline{H}_3$, $^3J_{H,H}$ = 7.0); 2.63 (t, 2 H, $C\underline{H}_2C(O)$, $^3J_{H,H}$ = 6.4); 3.57 (dt, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{H,H}$ = 6.4, $^3J_{H,H}$ = 6.2); 3.76 (s, 3 H, $C\underline{H}_3O$); 4.17—4.27 (m, 4 H, $CH_3C\underline{H}_2O$); 6.22 (d, 1 H, $N\underline{H}P$, $^2J_{H,P}$ = 5.6); 7.20 (br.s, 1 H, $N\underline{H}CH_2$)

[a] In MeCN.
[b] In CD_3CN.

Scheme 3



12: Y = CH_2 (**a**), CH_2CH_2 (**b**).

Experimental

NMR spectra were recorded on Bruker Avance-400 (^{1}H 400.13 MHz; ^{31}P 161.98 MHz) and Bruker Avance-300 (^{1}H 300.13 MHz; ^{31}P 121.50 MHz) spectrometers in $CDCl_3$, the signals for the residual protons of the deuterated solvents were used as the internal standard (^{1}H), 85% H_3PO_4 in $CDCl_3$ was used as the external standard (^{31}P).

Phosphoryl isothiocyanates **4**, **5** were synthesized by the described method,[6] 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane **11** was obtained by the known method.[7] Phosphoryl isocyanate **13** (Aldrich) was distilled *in vacuo* before reaction. KSCN that was used for the reactions was dried azeotropically with C_6H_6 and then *in vacuo* over P_2O_5. Amino acid esters were obtained by the known method,[8] they were isolated from hydrochlorides by treatment with a solution of NH_3 in $CHCl_3$ (see Ref. 9).

In some cases, the isolation of compounds was carried out using column chromatography on SiO_2 (130—270 mesh, Aldrich) at a ratio compound : SiO_2 1 : 16 (w/w), gradient elution with a mixture $CHCl_3$—MeOH from 100 : 1 to 10 : 1 or hexane—Me_2CO from 100 : 1 to 3 : 2. Fractions were analyzed by TLC on SiO_2 in the solvent systems $CHCl_3$—MeOH (10 : 1) or hexane—Me_2CO (3 : 2).

Dimethyl *N*-[*N*-(diethoxyphosphoryl)thiocarbamoyl]-L-aspartate (7a). A solution of ester **6a** (1.06 g, 6.7 mmol) in C_6H_6 (3 mL) was added dropwise with stirring to a solution of isothiocyanate **4** (1.27 g, 6.5 mmol) in anhydrous C_6H_6 (11 mL) (slight heating occurred). The course of the reaction was monitored by ^{31}P NMR spectroscopy by following disappearance of the signal of **4** (δ −18.4). After 5 h at room temperature, the solution was concentrated *in vacuo*, and the residue (1.68 g) was chromatographed on SiO_2 in a hexane—acetone solvent system. Compound **7a** was obtained in the form of a viscous yellowish oil (1.60 g, 70%) (see Tables 1 and 2).

***N*-[*N*-(Diethoxyphosphoryl)thiocarbamoyl]glycine methyl ester (7b)** was obtained analogously by the reaction of **4** (1.04 g, 5.3 mmol) in C_6H_6 (8 mL) with ester **6b** (0.475 g, 5.4 mmol) in C_6H_6 (1.5 mL). After 16 h, the product was filtered off and chromatographed in a hexane—acetone solvent system. Product **7b** was isolated (0.55 g, 44%) as a white solid (see Tables 1 and 2).

***N*-[*N*-(Diethoxyphosphoryl)thiocarbamoyl]-β-alanine methyl ester (7c)** was obtained under the same conditions from compound **4** (0.80 g, 4.0 mmol) in C_6H_6 (4.5 mL) and ester **6c** (0.43 g, 4.1 mmol) in C_6H_6 (2.0 mL); removal of the solvent *in vacuo* and chromatography in a $CHCl_3$—MeOH solvent system yielded **7c** (0.79 g, 66%) (see Tables 1 and 2).

Dimethyl *N*-[*N*-(diethoxyphosphoryl)thiocarbamoyl]-L-glutamate (7d) was obtained similarly by the reaction of **4** (0.80 g, 4.0 mmol) in C_6H_6 (4.5 mL) with ester **6d** (0.72 g, 4.1 mmol); after chromatographic purification in a $CHCl_3$—MeOH solvent system, product **7d** was obtained (0.90 g, 60%) (see Tables 1 and 2).

Dimethyl *N*-[*N*-(dibutoxyphosphoryl)thiocarbamoyl]-L-aspartate (8) was obtained similarly from isothiocyanate **5** (1.15 g, 4.5 mmol) in acetone (5.5 mL) and ester **6a** (0.75 g, 4.6 mmol) in acetone (1.5 mL); after chromatographic purification in a hexane—acetone solvent system, thiourea **8** was obtained (0.40 g, 20%) (see Tables 1 and 2).

2-Isothiocyano-2-oxo-1,3,2λ^3-oxazaphosphinane (9). Chloride **11** (^{31}P NMR , δ 10.32) (0.23 g, 1.5 mmol) was added to a solution of KSCN (0.29 g, 3.0 mmol) in MeCN (5 mL), the reaction mixture was stirred at 45—50 °C for 17 h (^{31}P NMR monitoring). The mixture was filtered, the precipitate was washed with MeCN; the filtrate was concentrated to dryness *in vacuo*, the residue was extracted with C_6H_6 (5×5 mL), the extracts were concentrated *in vacuo* (1 Torr). Isothiocyanate **9** was obtained (0.23 g, 87%) (^{31}P NMR, δ −13.69). The product was used in the following reactions without additional purification.

Dimethyl *N*-[*N*-(2-oxo-1,3,2λ^3-oxazaphosphinan-2-yl)thiocarbamoyl]-L-aspartate (10a). Ester **6a** (0.74 g, (4.6 mmol) in C_6H_6 (3 mL) was added dropwise with stirring to a solution of isothiocyanate **9** (0.82 g, 4.6 mmol) in C_6H_6 (10 mL) (slight self-heating from 22 to 27 °C occurred), and the reaction mixture was kept for 16 h. The mixture was concentrated *in vacuo*, the residue (1.47 g) was purified by chromatography in a $CHCl_3$—MeOH solvent system. Compound **10a** was isolated (1.11 g, 72%) (solid foam) in the form of a stable solvate with 0.2 molecule of $CHCl_3$ (See Table 1), the presence of the latter was confirmed by the ^{1}H NMR spectrum in CD_3CN. To remove the solvate $CHCl_3$, compound was dissolved in anhydrous MeOH, the solution was concentrated to dryness *in vacuo*, and the residue was dried over P_2O_5 (see Tables 1 and 2).

***N*-[*N*-(2-Oxo-1,3,2λ^3-oxazaphosphinan-2-yl)thiocarbamoyl]-glycine methyl ester (10b)** was obtained similarly from isothiocyanate **9** (0.80 g, 4.5 mmol) and ester **6b** (0.45 g, 5.0 mmol) in C_6H_6 (13 mL). Fine crystals that precipitated were filtered off, the product was purified by precipitation with anhydrous ether from a solition in $CHCl_3$. Compound **10b** was isolated (0.94 g, 78%) (see Tables 1 and 2).

***N*-[*N*-(2-Oxo-1,3,2λ^3-oxazaphosphinane-2-yl)thiocarbamoyl]-β-alanine methyl ester (10c)** was obtained similarly from **9** (0.81 g, 4.55 mmol) and ester **6c** (0.52 g, 5.0 mmol) in C_6H_6 (14 mL). After removal of C_6H_6 and chromatographic purification using a $CHCl_3$—MeOH solvent system, compound **10c** was isolated (0.97 g, 76%) as a solid foam (see Tables 1 and 2).

Dimethyl *N*-[*N*-(2-oxo-1,3,2λ^3-oxazaphosphinan-2-yl)thiocarbamoyl]-L-glutamate (10d) was obtained under the same conditions from **9** (0.60 g, 3.37 mmol) and ester **6d** (0.61 g, 3.50 mmol) in C_6H_6 (10 mL). After chromatographic purification in a $CHCl_3$—MeOH solvent system, the isolated product was dissolved in anhydrous MeOH, the solution was concentrated *in vacuo*, the residue was dried over P_2O_5. Compound **10d** was obtained (0.97 g, 81%) (see Tables 1 and 2) as solid foam.

***N*-[*N*-(2-Oxo-1,3,2λ^3-oxazaphosphinane-2-yl)thiocarbamoyl]-alanine methyl ester (10e)** was obtained similarly from **9 (0**.87 g, 4.88 mmol) and ester **6e** (0.57 g, 5.50 mmol) in C_6H_6 (14 mL). The product was chromatographed in a $CHCl_3$—MeOH solvent

system and isolated in the form of a solvate (0.96 g, 70%) with 0.2 molecule of $CHCl_3$ (see Table 1). To remove the solvate $CHCl_3$, compound was dissolved in anhydrous MeOH, the solution was concentrated to dryness *in vacuo*, and the residue was dried *in vacuo* over P_2O_5 (see Tables 1 and 2).

***N*-[*N*-(Diethoxyphosphoryl)carbamoyl]glycine methyl ester (12a).** Ester **6b** (0.53 g, 5.8 mmol) was added dropwise with stirring to a solution of isocyanate **13** (1.00 g, 5.6 mmol) in C_6H_6 (8 mL) (self-heating by 5 °C occurred). After 16 h at room temperature, the gel-like mixture was diluted with ether, the residue was filtered off and washed with ether. Solid product **12a** was obtained (0.80 g, 54%) (see Tables 1 and 2).

***N*-[*N*-(Diethoxyphosphoryl)carbamoyl]-β-alanine methyl ester (12b)** was obtained similarly from isocyanate **13** (0.59 g, 3.3 mmol) in C_6H_6 (4.5 mL) and ester **6c** (0.35 g, 3.4 mmol) in C_6H_6 (1.5 mL), the precipitate was filtered off and washed with ether. Solid compound **12b** was isolated (0.59 g, 70%) (see Tables 1 and 2).

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