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Reaction of Diethyl 5-Hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonate with Acyl Isothiocyanates

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Abstract—The reactions of diethyl 5-hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonate with acetyl, benzoyl, and ethoxycarbonyl isothiocyanates result in the previously unknown (1,3,4-thiadiazol-2-yl)-substituted aminomethylphosphonic acids.

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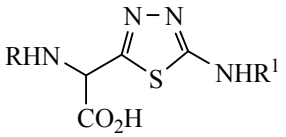
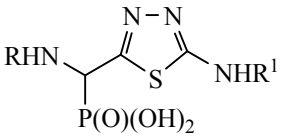
The 2-amino-5-aminomethyl-1,3,4-thiadiazole derivatives obtained from the corresponding 1,4-disubstituted thiosemicarbazides (XNHNHCSNHY) exhibit anticonvulsant [1, 2], antimicrobial [3], antineurodegenerative [4], anti-inflammatory [5, 6], antiviral [7, 8] activity and are also the selective $K_v1.5$ receptor blockers [9] and the CCR1 receptor antagonists [10]. The biological activity of the compounds is known to depend significantly on the nature of substituents in the molecule. Therefore, the development of the synthesis methods for new compounds containing diverse functional groups is of considerable interest for the biological testing and obtaining the promising drugs. The glycine derivatives containing 5-amino-1,3,4-thiadiazol-2-yl substituents [11–13] were well studied, but the corresponding carboxylic acids **I** were not obtained individually because of their decarboxylation. However, α-aminophosphonic acids as the α-amino acids analogs are of particular interest because they differ by the chemical behavior from their counterparts. They also have a certain biological activity [14–18].



I



II

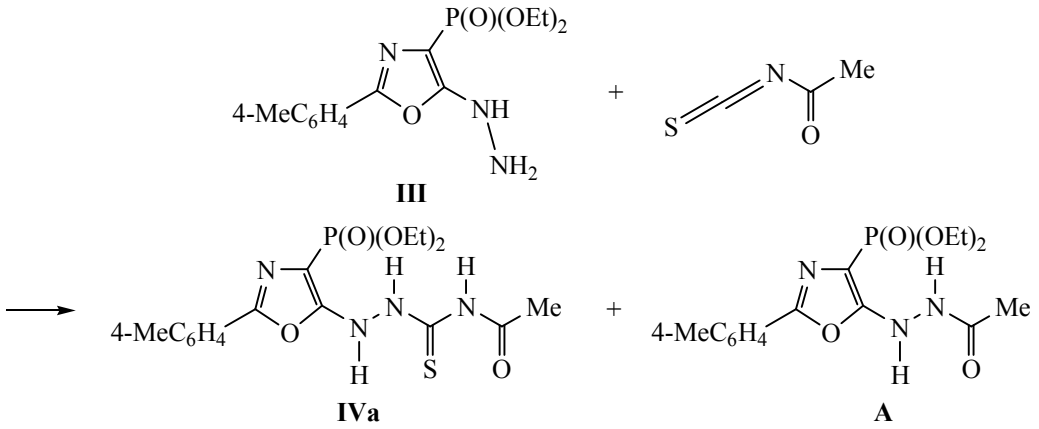
This work continues the study of the phosphorylated derivatives of 1,3,4-thiadiazoles [12, 13] in order to synthesize new substituted (1,3,4-thiadiazole)-methylphosphonic acids **II**. As a model compound the easily accessible diethyl 5-hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-yl-phosphonate **III** was chosen (Schemes 1, 2) obtained by a method [19] modified by us, starting from 4-methylbenzamide and chloral, in an overall yield of 55%.

The reaction of compound **III** with acetyl isothiocyanate in diethyl ether gives a mixture of two substances: thiosemicarbazide **IVa**, an adduct of acetyl isothiocyanate to the hydrazo group, and the acetyl derivative **A** resulting from the substitution of the isothiocyanate group with the hydrazine moiety (Scheme 1). This is confirmed by the GC–MS studies that indicate the presence of two *m*/*z* values of the protonated cation-radicals $[M + 1]^+$: 427 (**IVa**) and 368 (**A**). The composition of the mixture depends strongly on the reaction temperature. At –15°C the adduct **IVa** is produced in an yield of 15% and at 20°C, in 65% yield. The formation of a mixture of compounds **IVa** and **A** was confirmed also by the ^1H and ^{31}P NMR spectral data.

In contrast, the reaction of hydrazine **III** with benzoyl or ethoxycarbonyl isothiocyanate in diethyl ether at 20°C results in the 1,4-disubstituted thiosemicarbazides **IVb** or **IVc** in yields of 89–90% (Scheme 2).

In the ^1H NMR spectra of thiosemicarbazides **IVb** and **IVc** there is no broadened two-protons signal at δ 4.01 ppm corresponding to the primary amino group of the starting hydrazinooxazole. It clearly points to the

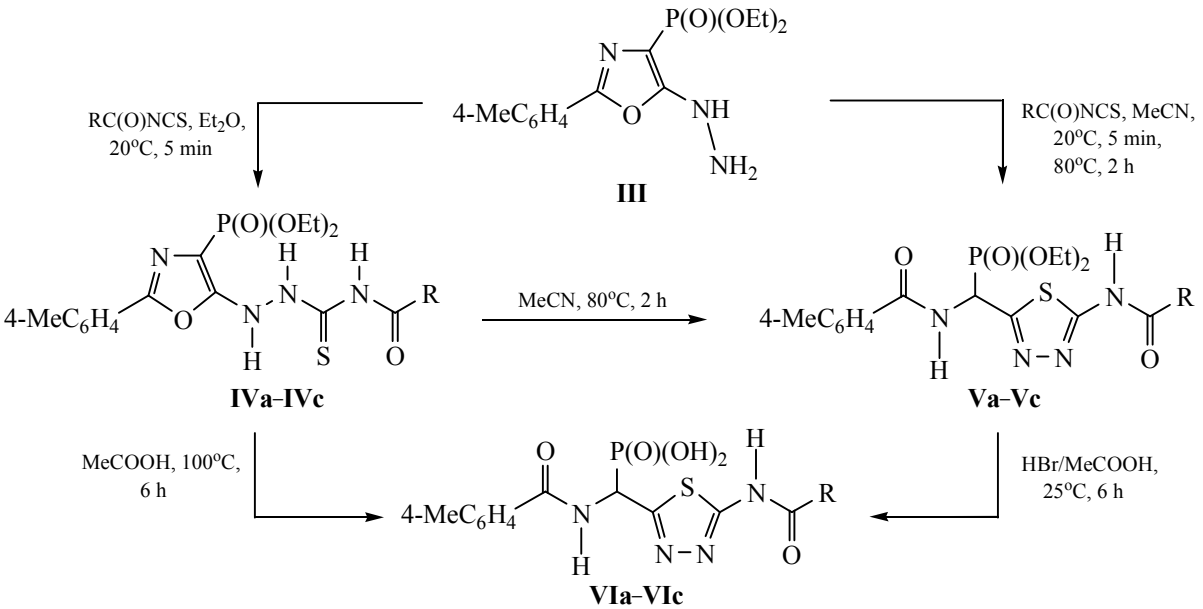
Scheme 1.



reaction with the isothiocyanates. The broad one-proton signal of the NHNHCS fragment of compounds **IVb** and **IVc** is shifted downfield. Also two broad one-proton signals of NHCSNH moiety appear in the weak field. The IR spectra of compounds **IVb** and **IVc** contain strong absorption bands at ν 1173 and 1197 cm^{-1} belonging to the multiple C=S bond. The GC–MS spectra contain the peaks with *m*/*z* values corresponding to the protonated cation-radical $[M + 1]^{+\cdot}$ of the adducts formed.

Compounds **IVb** and **IVc** were isolated in the analytically pure form. They are white, stable crystals, which are insoluble in water, hexane, and readily soluble in diethyl ether. They are readily soluble also in all other organic solvents and in water in the presence of bases. Compounds **IVa**–**IVc** are stable in air only in the crystalline state at 20–25°C and in solution or in suspension in the presence of bases (triethylamine, sodium bicarbonate) under the air-free conditions. However, even at 20–25°C in a solution and in a suspension in diethyl ether in the absence of a base they transform gradually into the new phosphorus-containing functional derivatives of 2-amino-1,3,4-thiadiazole **Va**–**Vc**. This can be due to the instability of the 1,3-oxazole ring in an acidic

Scheme 2.



R = Me (**a**), Ph (**b**), OEt (**c**).

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

Comp. no.	Yield, %	mp, °C [a]	Found, %			Formula	Calculated, %		
			N	P	S		N	P	S
III	93	119–120	12.85	9.40	–	$C_{14}H_{20}N_3O_4P$	12.92	9.52	–
IVa	64 [b]	–	–	–	–	$C_{17}H_{23}N_4O_5PS$	13.14	7.26	7.52
IVb	90	129–130	11.36	6.17	6.66	$C_{22}H_{25}N_4O_5PS$	11.47	6.34	6.56
IVc	89	124–125	12.03	6.70	7.17	$C_{18}H_{25}N_4O_6PS$	12.27	6.79	7.03
Va	99 [c, d]	183–184	12.98	7.19	7.62	$C_{17}H_{23}N_4O_5PS$	13.14	7.26	7.52
Vb	99 [d]	199–200	11.35	6.19	6.63	$C_{22}H_{25}N_4O_5PS$	11.47	6.34	6.56
Vc	99 [d]	174–175	12.11	6.68	7.16	$C_{18}H_{25}N_4O_6PS$	12.27	6.79	7.03
VIa	92 [d]	234–235	14.99	8.25	8.75	$C_{13}H_{15}N_4O_5PS$	15.13	8.36	8.66
VIb	99 [d]	>250 decomp.	12.88	7.01	7.51	$C_{18}H_{17}N_4O_5PS$	12.96	7.16	7.42
VIc	99 [d]	>210 decomp.	13.90	7.67	8.12	$C_{14}H_{17}N_4O_6PS$	13.99	7.74	8.01

[a] After washing with water (**III, VIa–VIc**), diethyl ether (**IVb, IVc**), and acetonitrile (**Va–Vc**). [b] Content in a mixture in the isolated crystalline product according to the GC–MS data. [c] With respect to **IVa** content in the mixture. [d] Yield by the *a* method.

environment created by the acidic proton in the thiosemicarbazide molecule [11–13]. The complete conversion **IVa–IVc** → **Va–Vc** can be performed by boiling the reaction mixture in acetonitrile for 2 h. The spectral data indicate the occurrence of the recyclization and not only the opening of the 1,3-oxazole ring without the formation of the 1,3,4-thiadiazole ring. Thus, the signals of the ^{31}P nuclei in the spectra of **Va–Vc** are shifted from δ_P 10.6 ppm to 17.0–17.6 ppm. In the ^1H NMR spectra there are the characteristic signals of CHP group at δ 6.14–6.22 ppm as a doublet of doublets. The IR spectra contain no absorption bands of the multiple C=S bond, as well as the bands at ν 1583–1619 cm^{-1} belonging to the oxazole ring [20]. The GC–MS spectra of compounds **IVa–IVc** and **Va–Vc** contain the same *m*/*z* value, but different R_f values.

The presence of compound **A** in the mixture did not affect the quantitative recyclization of thiosemicarbazide **IVa**. In this case, the acetyl derivative **Va** was isolated in an analytically pure form due to the significant difference in the solubility.

We attempted to carry out the one-pot synthesis of thiadiazoles **Va–Vc** starting from hydrazinooxazole **III** and the corresponding acyl isothiocyanates without isolating the intermediate thiosemicarbazides **IVa–IVc**. The reactants were mixed in acetonitrile at 20°C, kept at this temperature for 5 min, and then the reaction mixture was boiled for 2 h. The melting points and spectral characteristics of compounds **Va–Vc** obtained by the different methods were the same (Tables 1, 2).

Taking into account the polyfunctionality of the obtained compounds **IV** and **V**, we studied their behavior in the presence of the acids. The reaction of the thiadiazole derivatives **Va–Vc** with the saturated solution of hydrogen bromide in glacial acetic acid at 20°C for 6 h leads to the regioselective hydrolysis to form the previously unknown phosphonic acids **VIa–VIc**. When compounds **Va–Vc** were boiled for 1 min in a mixture of glacial acetic acid and concentrated hydrochloric acid (10:1), the acids **VIa–VIc** also form, but in lower yields. Compounds **VIb** and **VIc** were also obtained by the heating thiosemicarbazides **IVb** and **IVc** for 6 h in glacial acetic acid. In addition, compound **VIb** was obtained by keeping the solution of thiosemicarbazide **IVb** in concentrated sulfuric acid for 6 h at 20°C. The transformation **IV** → **VI** includes not only the oxazole ring recyclization, but also the diethoxyphosphoryl group hydrolysis.

The structure of the phosphonic acids **VIa–VIc** was proved by the spectral data. Thus, in the ^1H NMR spectra the signals of two ethoxyphosphoryl groups are absent. The GC–MS spectra contain peaks with *m*/*z* values corresponding to the cation-radical $[M + 1]^{+\cdot}$ of the corresponding protonated acids. The ^{31}P NMR spectra contain signals at 12.7–12.8 ppm.

Thus, we studied the reaction of diethyl 5-hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-ylphos-

Table 2. Spectra data of the obtained compounds [a]

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	δ_H, ppm	δ_C, ppm	δ_P, ppm	m/z, $[M+1]^{+\cdot}$ (R_f)
III	3344 (N–H), 1667, 1600 (oxaz.), 1218 (P=O), 1026 (P–OC), 968 (PO–CC)	1.33 t (6H, 2C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ 7.0 Hz), 2.36 s (3H, CH$_3$), 4.01 br.s (2H, NH$_2$), 4.05–4.19 m (4H, 2CH$_3$C<u>H</u>$_2$O), 7.06 br.s (1H, NH), 7.20 and 7.82 two d (4H, C$_6$H$_4$, $^3J_{HH}$ 8.0 Hz)	14.6 (OCH$_2$<u>C</u>H$_3$), 19.8 (CH$_3$), 61.1 (O<u>C</u>H$_2$CH$_3$), 98 d (CP, $^1J_{CP}$ 254.0 Hz), 123.2 124.8, 128.4 139.2, 153.1 (oxaz. O<u>C</u>N), 163.8 (oxaz. O<u>C</u>CP)	12.4	326
IVa[b]	–	–	–	10.6	427 (0.54)
IVb	3245 (N–H), 1675 (C=O), 1612, 1583 (oxaz.), 1215 (P=O), 1173 (C=S), 1025 (P–OC), 973 (PO–CC)	1.37 t (6H, 2C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ 7.0 Hz), 2.38 s (3H, CH$_3$), 4.13–4.30 m (4H, 2CH$_3$· C<u>H</u>$_2$O), 7.22 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 7.55 t (2H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 7.67 t (1H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 7.84 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 7.91 d (2H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 8.57 br.s (1H, NH), 9.22 br.s (1H, NH), 12.21 br.s (1H, NH)	14.6 (OCH$_2$<u>C</u>H$_3$), 19.9 (CH$_3$), 61.5 (O<u>C</u>H$_2$CH$_3$), 62.0 (O<u>C</u>H$_2$CH$_3$), 103.0 d (CP, $^1J_{CP}$ 249.0 Hz), 122.9, 125.2, 126.8, 128.3, 130.3, 133.0, 139.7, 154.7 (oxaz. O<u>C</u>N), 159.8, (oxaz. O<u>C</u>CP), 165.8 (C=O), 180.3 (C=S)	10.6	489 (0.64)
IVc	3262 (N–H), 1712 (C=O), 1619 (oxaz.), 1231 (P=O), 1197 (C=S) 1045 (P–OC), 967 (PO–CC)	1.33–1.39 m (9H, 3C<u>H</u>$_3$CH$_2$O), 2.38 s (3H, CH$_3$), 4.13–4.34 m (6H, 3CH$_3$C<u>H</u>$_2$O), 7.22 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 7.83 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 8.34 br.s (1H, NH), 8.39 br.s (1H, NH), 11.20 br.s (1H, NH)	12.5 (OCH$_2$<u>C</u>H$_3$), 14.6 (OCH$_2$<u>C</u>H$_3$), 19.9 (CH$_3$), 61.5 (O<u>C</u>H$_2$CH$_3$), 62.0 (O<u>C</u>H$_2$CH$_3$), 101.0 d (CP, $^1J_{CP}$ 250.0 Hz), 122.9, 125.2, 128.4, 139.7, 151.6, 154.6 (oxaz. O<u>C</u>N), 160.2 (oxaz. O<u>C</u>CP), 179.9 (C=S)	10.6	457 (0.60)
Va	3255 (N–H), 1704 (C=O), 1640 (C=O), 1237 (P=O), 1018 (P–OC), 975 (PO–CC)	1.15–1.24 m (6H, 2C<u>H</u>$_3$CH$_2$O), 2.18 s (3H, CH$_3$), 2.36 s (3H, CH$_3$), 4.00–4.19 m (4H, 2CH$_3$C<u>H</u>$_2$O), 6.17 d.d (1H, CHP, $^3J_{HH}$ 9.0, $^2J_{HP}$ 21.0 Hz), 7.30 and 7.85 two d (4H, C$_6$H$_4$, $^3J_{HH}$ 8.0 Hz), 12.56 br.s (1H, <u>NH</u>CH)	15.0 (OCH$_2$<u>C</u>H$_3$), 19.9 (CH$_3$), 21.3 (CH$_3$), 46.0 d (CP, $^1J_{CP}$ 159.0 Hz), 62.2 (O<u>C</u>H$_2$CH$_3$), 127.4, 128.3, 130.0, 141.5, 158.5, 159.7, 166.1, 168.5	17.0	427 (0.44)
Vb	3226 (N–H), 1671[c] (2C=O), 1236 (P=O), 1028 (P–OC), 982 (PO–CC)	1.22 t (6H, 2C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ 6.6 Hz), 2.36 s (3H, CH$_3$), 4.12 m (4H, 2CH$_3$C<u>H</u>$_2$O), 6.22 d.d (1H, CHP, $^3J_{HH}$ 9.0, $^2J_{HP}$ 21.7 Hz), 7.30 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 7.56 t (2H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 7.66 t (1H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 7.86 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 8.12 d (2H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 9.56 d (1H, <u>NH</u>CH, $^3J_{HH}$ 9 Hz), 13.09 br.s (1H, NH)	15.0 (OCH$_2$<u>C</u>H$_3$), 19.9 (CH$_3$), 46.0 d (CP, $^1J_{CP}$ 159.0 Hz), 62.3 (O<u>C</u>H$_2$CH$_3$), 127.4, 127.9, 128.2, 128.4, 130.0, 131.0, 132.6, 141.5, 159.0, 160.6, 165.0, 166.2	17.9	489 (0.54)
Vc	3239 (N–H), 1726 (C=O), 1665 (C=O), 1239 (P=O), 1053 (P–OC), 981 (PO–CC)	1.20 t (6H, 2C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ 7.0 Hz), 1.25 t (3H, C<u>H</u>$_3$CH$_2$O), 2.36 s (3H, CH$_3$), 4.10 m (4H, 2CH$_3$C<u>H</u>$_2$O), 4.23 κ (2H, CH$_3$C<u>H</u>$_2$O), 6.14 d.d (1H, CHP, $^3J_{HH}$ 9.0, $^2J_{HP}$ 22.0 Hz), 7.29 and 7.83 two d (4H, C$_6$H$_4$, $^3J_{HH}$ 8.0 Hz), 9.48 d (1H, <u>NH</u>CH, $^3J_{HH}$ 9.0 Hz), 12.19 br.s (1H, NH)	13.1 (OCH$_2$<u>C</u>H$_3$), 15.1 (OCH$_2$<u>C</u>H$_3$), 19.9 (CH$_3$), 46.0 d (CHP, $^1J_{CP}$ 160.0 Hz), 61.4 (O<u>C</u>H$_2$CH$_3$), 62.2 (O<u>C</u>H$_2$CH$_3$), 127.4, 128.3, 129.9, 141.5, 153.6, 158.5, 162.0, 166.1	17.0	457 (0.51)
VIa	3500–2500 (N–H, O–H$_{as}$), 1697 (C=O), 1646 (C=O), 1208 (P=O)	2.17 s (3H, CH$_3$), 2.35 s (3H, CH$_3$), 5.88 d.d (1H, CHP, $^3J_{HH}$ 8.8, $^2J_{HP}$ 21.0 Hz), 7.28 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.6 Hz), 7.83 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.6 Hz), 8.89 d (1H, <u>NH</u>CH, $^3J_{HH}$ 8.8 Hz), 12.47 br.s (1H, NH)[d]	19.9 (CH$_3$), 21.2 (CH$_3$), 47.6 d (CP, $^1J_{CP}$ 150.0 Hz), 127.3, 128.3, 130.3, 141.3, 159.2, 160.2, 165.9, 168.4	12.8	371
VIb	3500–2500 (N–H, O–H$_{as}$), 1680[c] (2C=O), 1275 (P=O)	2.36 s (3H, CH$_3$), 5.94 d.d (1H, CHP, $^3J_{HH}$ 9.0, $^2J_{HP}$ 21.0 Hz), 7.29 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 7.56 t (2H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 7.66 t (1H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 7.85 d (2H, C$_6$H$_4$, $^3J_{HH}$ 7.8 Hz), 8.11 d (2H, C$_6$H$_5$, $^3J_{HH}$ 7.6 Hz), 8.94 d (1H, <u>NH</u>CH, $^3J_{HH}$ 9 Hz)[d,e]	19.9 (CH$_3$), 47.7 d (CHP, $^1J_{CP}$ 150.0 Hz), 127.9, 128.2, 130.4, 131.1, 132.5, 141.2, 160.3, 160.8, 165.0, 166.0	12.8	433
VIc	3500–2500 (N–H, O–H$_{as}$), 1728 (C=O), 1651 (C=O), 1242 (P=O)	1.25 t (3H, C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ 7.0 Hz), 2.36 s (3H, CH$_3$), 4.21 κ (2H, CH$_3$C<u>H</u>$_2$O), 5.85 d.d (1H, CHP $^3J_{HH}$ 9.0, $^2J_{HP}$ 21.0 Hz), 7.28 and 7.83 two d (4H, C$_6$H$_4$, $^3J_{HH}$ 8.0 Hz), 8.90 d (1H, <u>NH</u>CH, $^3J_{HH}$ 9.0 Hz)[d]	13.1 (OCH$_2$<u>C</u>H$_3$), 19.9 (CH$_3$), 47.7 d (CHP, $^1J_{CP}$ 150.0 Hz), 61.3 (O<u>C</u>H$_2$CH$_3$), 127.3, 128.3, 130.3, 141.2, 153.6, 160.3, 161.6, 165.9	12.7	401

[a] $CDCl_3$ (**III, IVa–IVc**), DMSO-d_6 (**Va–Vc, VIa–VIc**). [b] The signals were extracted from the spectra of a mixture. [c] Shoulder. [d] The signal of OH was not detected. [e] The signal of NH was not detected.

phonate **III** with acetyl, benzoyl and ethoxycarbonyl isothiocyanates. It was found that the qualitative and quantitative composition of the products was affected by the nature of acyl isothiocyanate and the solvent as well as the temperature and the reaction time. The conditions of the stability of thiosemicarbazides **IV** were studied. Also we examined the acid-catalyzed regioselective hydrolysis of diethoxyphosphoryl group of the thiadiazole derivatives **V**, which results in the new aminomethylphosphonic acids **VI**. The convenient preparative methods for the synthesis of the above compounds were developed. The possibility of the different approaches to their preparation was shown.

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. The NMR spectra were obtained on a Bruker Avance DRX-500 instrument [^{1}H (500 MHz), ^{31}P (202 MHz), and ^{13}C (125 MHz)] using DMSO-d_6 or $CDCl_3$ as the solvents relative to internal TMS or external 85% phosphoric acid. The melting points were determined on a Fisher Johns instrument. The GC–MS spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode array with an Agilent LC\MSD SL mass selective detector with the quick changeover ionization positive/negative mode. The GC–MS (APCI) parameters are as follows: Zorbax SB-C18 column (1.8 mm, 4.6 × 15 mm, PN 821975-932); acetonitrile–water (95:5) + 0.1% of trifluoroacetic acid (solvent A), 0.1% aqueous trifluoroacetic acid (solvent B); the eluent flow is 3 ml min^{-1}; the injection volume is 1 μm; the UV detectors are for 215, 254, 285 nm; the scanning range is *m*/*z* 80–1000 . The reaction progress was monitored by the TLC.

Diethyl 5-hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonate (III). To 25 ml (500 mmol) of hydrazine hydrate was slowly added a solution of 20 g (49.7 mmol) of diethyl 1-(4-methylphenylcarbonylamino)-2,2,2-trichloroethenylphosphonate [20] in 100 ml of dioxane in an argon atmosphere with vigorous stirring and cooling with ice water to 10°C. The reaction mixture was stirred at 20–25°C for 1 h and allowed to stand for 12 h. The solvent was evaporated to dryness under reduced pressure at a temperature not exceeding 50°C. The residue was triturated with 200 ml of water. The crystalline precipitate was filtered off, washed on a filter with water until neutral reaction of the washings and dried in air. The product, white crystalline powder, was used for further transformations without the additional purification.

Diethyl 5-[1-(4-acyl)thiosemicarbazido]-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonates (IVa–IVc). To a suspension of 2 g (6.15 mmol) of hydrazinooxazole **III** in 50 ml of diethyl ether at 20°C was added in one portion 6.77 mmol of the appropriate acyl isothiocyanate. The reaction mixture was stirred for 5 min. The resulting precipitate was filtered off, washed on a filter with diethyl ether (2 × 10 ml) and dried in air. Compound **IVa** cannot be isolated in an analytically pure form. It contains 35% of diethyl 5-(2-acetylhydrazino)-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonate **A**, which, however, does not prevent its further use.

Diethyl (5-acylamino-1,3,4-thiadiazol-2-yl)[(4-methylbenzoyl)amino]methylphosphonates (Va–Vc). *a*. A solution of 3 mmol of the appropriate thiosemicarbazide **IVa–IVc** in 10 ml of acetonitrile was refluxed for 2 h. Then the reaction mixture was cooled to room temperature. The resulting precipitate was filtered off, washed with a small amount of acetonitrile. After drying, the analytically pure products were obtained.

b. To a solution of 2 g (6.15 mmol) of hydrazinooxazole **III** in 20 ml of acetonitrile at 20°C was added in one portion 6.77 mmol of the appropriate acyl isothiocyanate. The reaction mixture was stirred for 5 min at 20°C, then boiled for 2 h and cooled to room temperature. Then the precipitate was filtered off and recrystallized from acetonitrile. The yields of the obtained compounds are 64 (**Va**), 93 (**Vb**), and 88% (**Vb**).

The IR, NMR, and GC–MS spectra of compounds **Va–Vc** obtained by two methods are identical. The mixed samples showed no melting point depression.

(5-Acylamino-1,3,4-thiadiazol-2-yl)-[(4-methylbenzoyl)amino]methylphosphonic acids (VIa–VIc). *a*. To 3 mmol of the appropriate thiadiazole **Va–Vc** at 20–25°C was added 10 ml of glacial acetic acid saturated with the hydrogen bromide. The resulting mixture was maintained at 20–25°C for 6 h and then evaporated to dryness under the reduced pressure at 35°C. The residue was triturated in a minimal amount of water, filtered off, and dried to give the analytically pure products.

b. To a solution of 3 mmol of the corresponding thiadiazole **Va–Vc** in 10 ml of glacial acetic acid was

added 1 ml of the concentrated hydrochloric acid. The mixture was stirred for 1 min at 100°C and then evaporated to dryness under the reduced pressure. The residue was triturated with a minimal amount of water, filtered off, washed on a filter with water and crystallized. The yields of the obtained compounds are 64 (**VIa**, crystallized from water), 93 (**VIb**, from MeCOOH), and 88% (**VIc**, from water).

c. A solution of 3 mmol of the appropriate thiosemicarbazide **IVb** or **IVc** in 10 ml of glacial acetic acid was kept at 100°C for 6 h. Then the reaction mixture was evaporated under the reduced pressure to dryness. The residue was triturated with a minimal amount of water, filtered off, and recrystallized. The yields of the obtained compounds are 92 (**VIb**, from MeCOOH) and 82% (**VIc**, from water).

d. A solution of 1 mmol of thiosemicarbazide **IVb** in 5 ml of the concentrated sulfuric acid was heated at 20°C for 6 h. Then the mixture was poured into 20 g of the crushed ice. The precipitate was filtered off, washed on a filter with water until the neutral reaction. After drying, the analytically pure product was obtained in 92% yield. The IR, NMR, and GC–MS spectra of compounds **VIa**–**VIc** obtained by four methods were identical.

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