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Synthesis of C-Heteryl-Substituted Aminomethylphosphonic Acids Derivatives

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Abstract—The available diethyl 5-hydrazino-2-*p*-tolyl-1,3-oxazol-1-ylphosphonate was readily acylated with chlorides of carboxylic acids of heterocyclic series. On heating in acetic acid it underwent the oxazole ring cleavage, recyclization and diethylation that was used to prepar the substituted 2-*p*-toluylaminomethylphosphonic acids containing a series of 2-heteryl-1,3,4-oxadiazol-5-yl residues in the α-position relative to the phosponyl group.

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Aminophosphonic acids as analogs of natural aminocarboxylic acids are of great interest due to their use or possible use in various fields of medicine and agriculture. They are analogs of antibiotics, inhibitor of different enzymes, antiviral preparations, and also precursors for synthesis of phosphonopeptides [1]. Aminoalkylphosphonic acids containing heterocyclic residues in the α-position to phosphonic group are less studied, but approaches to their synthesis and they properties are very interesting [2]. The C-heteryl-substituted aminomethylphosphonates and the corresponding aminomethylphosphonic acids containing furan [3–5], thiophene [2, 4, 5], pyrrole [2, 5], imidazole [6], pyridine [7, 8], and also 1,3,4-oxa- and 1,3,4-thiadiazole fragments [9–11] are known.

This work concerns the synthesis of 1,3,4-oxadiazol-2-yl-(amino)methylphosphonic acids containing additional heterocyclic fragments in the azole ring. To this end we used the known transformation **I→II** [11], and then oxazole substrate **II** was treated with chlorides of carboxylic acids of heterocyclic series in the presence of *N,N*-dimethylaniline. As a result the new oxazole substrates **IIIa–IIIf** formed. On heating in acetic acid the latter undergo recyclization and ester bonds rupture that led to the formation of the corresponding phosphonic acids **IVa–IVf,** substrates of 1,3,4-oxadiazole series containing in this azole ring the additional furan, thiophene, 5-phenyl-1,2-oxazole, coumarin, chromone, and 6-methylchromone fragments (Table 1).

To incorporate the other heterocyclic substituents into the desired position of the oxadiazole ring we used precursors **IIIe**, **IIIf** containing chromone system. The heating of their alcohol solutions with excess of hydrazine-hydrate results in two recyclization to give not only 1,3,4-oxadiazole fragment, but pyrazole ring too. From the two possible transformations **III→V→VII** and **III→VI→VII** some preference is given to the second. The subsequent heating of substrates **VII** in acetic acid results in phosphonic acids **VIIIa** and **VIIIb**. The structures of compounds represented on the scheme are reliably proved by the spectral data (Table 2). Thus, the presence of PCHNH fragment in the recyclization products **IV**, **VII**, and **VIII** is in agreement with the assignment of signals at δ_H 5.73–6.15 and 8.67–9.55 ppm in the ^{1}H NMR spectra [9–11]. The chromone ring opening **III→VII** is attested by the disappearance of an absorption bands at 1705–1709 cm^{-1} in the IR spectrum and also by the presence of singlet signals of N–H fragment of the pyrazole ring at δ_H 10.03–10.15 ppm and of OH-group of aryl ring at δ_H 13.42–13.51 ppm in the ^{1}H NMR spectra of compounds **VII**.

In conclusion we note that compounds **IV**, **VII,** and **VIII** are promising for the testing as bioregulators of different actions (cf. [1, 8, 12–15]).

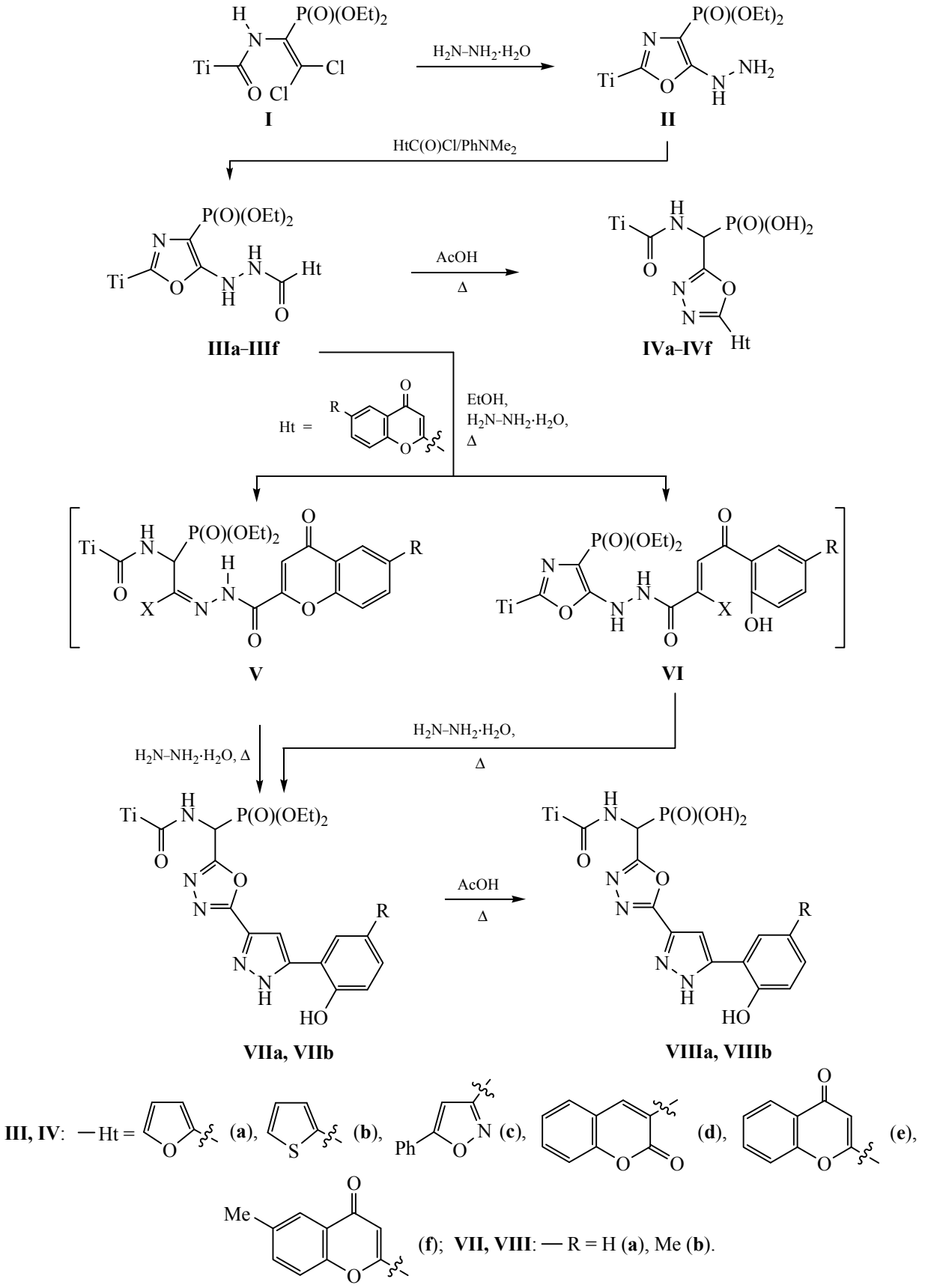
H2N–NH2·H2O
HtC(O)Cl/PhNMe2
AcOH
Δ
EtOH,
H2N–NH2·H2O,
Δ
H2N–NH2·H2O, Δ
H2N–NH2·H2O,
Δ
AcOH
Δ
I
II
IIIa–IIIf
IVa–IVf
V
VI
VIIa, VIIb
VIIIa, VIIIb
III, IV: —Ht = (a), (b), (c), (d), (e), (f); VII, VIII: — R = H (a), Me (b).

Table 1. Yields, constants, and elemental analysis data for compounds **III**, **IV**, **VII**, and **VIII**

Comp. no.	Yield, %	Melting point, °C	Found, %		Formula	Calculated, %	
			N	P		N	P
IIIa	72	171–173 (EtOH)	10.02	7.39	$C_{19}H_{22}N_3O_6P$	10.13	7.43
IIIb	81	160–162 (EtOH)	9.65	7.11	$C_{19}H_{22}N_3O_5PS$	9.73	7.08
IIIc	87	172–173 (EtOH)	11.29	6.24	$C_{24}H_{25}N_4O_6P$	11.37	6.32
IIId	91	170–172 (EtOH)	8.45	6.23	$C_{24}H_{24}N_3O_7P$	8.54	6.21
IIIe	53	168–170 (EtOH)	8.45	6.23	$C_{24}H_{24}N_3O_7P$	8.49	6.19
IIIf	59	183–185 (EtOH)	8.22	6.06	$C_{25}H_{26}N_3O_7P$	8.31	6.01
IVa	69	229–231 (AcOH)	11.57	8.53	$C_{15}H_{14}N_3O_6P$	11.52	8.47
IVb	47	228–230 (AcOH)	11.08	8.17	$C_{15}H_{14}N_3O_5PS$	11.10	8.19
IVc	77	230–231 (AcOH)	12.72	7.03	$C_{20}H_{17}N_4O_6P$	12.84	7.01
IVd	86	163–165 (AcOH)	9.52	7.02	$C_{20}H_{16}N_3O_7P$	9.59	6.97
IVe	72	181–183 (AcOH)	9.52	7.02	$C_{20}H_{16}N_3O_7P$	9.61	6.99
IVf	74	183–185 (AcOH)	9.23	6.80	$C_{21}H_{18}N_3O_7P$	9.32	6.73
VIIa	63	223–225 (EtOH)	13.69	6.06	$C_{24}H_{26}N_5O_6P$	13.78	6.09
VIIb	71	225–227 (EtOH)	13.33	5.89	$C_{25}H_{28}N_5O_6P$	13.46	5.81
VIIIa	71	254–256 (AcOH)	15.38	6.80	$C_{20}H_{18}N_5O_6P$	15.49	6.72
VIIIb	76	255–257 (AcOH)	14.92	6.60	$C_{21}H_{18}N_5O_6P$	15.04	6.51

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. The ^1H and ^{31}P NMR spectra were obtained on a Varian VXR-300 instrument at 300 and 81 MHz respectively in DMSO-d_6 relative to TMS. The melting points were measured on a Fisher-Johns instrument.

***O,O*-Diethyl 5-(2-acylhydrazino)-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonates (IIIa–IIIf).** To a solution of 0.01 mol of **II** in 10 ml of anhydrous acetonitrile were added 0.011 mol of *N,N*-dimethylaniline and 0.0105 mol of a chloride of the corresponding heterocyclic acid. The mixture was heated to boiling and kept for 12 h at 20–25°C. The solvent was removed in a vacuum, and the oily residue was worked up with water to crystallize. The precipitate was filtered off, dried, and recrystallized from a suitable solvent.

5-Heteryl-1,3,4-oxadiazol-2-yl(4-methylbenzoylamino)methylphosponic acids (IVa–IVf). A mixture of 0.01 mol of **IIIa–IIIf** in 3 ml of the glacial acetic acid was refluxed for 6 h and kept for 12 h at 20–25°C. The precipitate was filtered off, washed with ethanol and water, dried over P_2O_5 in a vacuum desiccator and recrystallized from a suitable solvent.

***O,O*-Diethyl {5-[5-(2-hydroxyphenyl)-1*H*-pyrazol-3-yl]-1,3,4-oxa-diazol-2-yl}[(4-methylbenzoyl)amino]-methylphosphonate (VIIa).** A mixture of 0.01 mol of **IIIe** and 0.05 mol of hydrazine hydrate in 5 ml of ethanol was refluxed for 2 h and kept for 12 h at 20–25°C. The precipitate was filtered off, washed with ethanol and water, dried, and recrystallized.

***O,O*-Diethyl {5-[5-(2-hydroxy-5-methylphenyl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazol-2-yl}[(4-methylbenzoyl)amino]methylphosphonate (VIIb)** was prepared similarly from hydrazide **IIIe**.

{5-[5-(2-Hydroxyphenyl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazol-2-yl}[(4-methylbenzoyl)-amino]methylphosphonate (VIIIa). A solution of 0.01 mol of **VIIa** in 10 ml of acetic acid was refluxed for 6 h. The mixture was kept for 12 h at 20–25°C. The precipitate was filtered off, washed with ethanol and water, dried, and recrystallized.

{5-[5-(2-Hydroxy-5-methylphenyl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazol-2-yl}[(4-methyl-benzoyl)amino]-methylphosphonate (VIIIb) was prepared similarly from **VIIb**.

Table 2. The spectral data for compounds **IV**, **VII**, **VIII**

Comp. no.	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)	^{31}P NMR spectrum, δ, ppm (DMSO-d_6)	IR spectrum (KBr), ν, cm^{-1}
IIIa	1.29 t (6H, 2CH_3), 2.35 s (3H,CH_3), 4.09 m (4H, CH_2O), 6.62–7.84 m (7H, C_6H_4, 3H furan), 8.39 s (1H, NH), 10.65 s (1H, NH)	12.22	1225 (P=O), 1659 (C=O), 2981–3261 (NH as.)
IIIb	1.29 t (6H, 2CH_3), 2.35 s (3H,CH_3), 4.09 m (4H, 2 CH_2O), 7.17–7.90 m (7H, C_6H_4, 2H, thiophen), 8.47 s (1H, NH), 10.80 s (1H, NH)	12.11	1219 (P=O), 1641 (C=O), 2986–3320 (NH as.)
IIIc	1.30 t (6H, 2CH_3), 2.35 s (3H,CH_3), 4.10 m (4H, CH_2O), 7.25–7.96 m (9H, C_6H_4, C_6H_5), 8.65 s (1H, NH), 11.14 s (1H, NH)	12.04	1240 (P=O), 1693 (C=O), 2983–3275 (NH as.)
IIId	1.28 t (6H, 2CH_3), 2.35 s (3H,CH_3), 4.07 m (4H, 2 CH_2O), 7.25–7.95 m (8H, C_6H_4, 4H, coumarin), 8.63 br.s (1H, NH), 8.89 s (1H, C^4–H, coumarin), 10.45 s (1H, NH)	12.20	1238 (P=O), 1683 (C=O), 1716 (C=O), 2911–3322 (NH as.)
IIIe	1.31 t (6H, 2CH_3), 2.36 s (3H,CH_3), 4.11 m (4H, 2 CH_2O), 6.89 s (1H, C^3–H, chromone), 7.23–8.08 m (8H, C_6H_4, 4H, chromone), 8.74 s (1H, NH), 11.45 s (1H, NH)	12.30	1240 (P=O), 1640 (C=O), 1705 (C=O), 2987–3207 (NH as.)
IIIf	1.30 t (6H, 2CH_3), 2.35 s (3H,CH_3), 2.48 s (3H,CH_3), 4.11 m (4H, 2OCH_2), 6.86 s (1H, C^3–H, chromone), 7.25–7.85 m (7H, C_6H_4, 3H, chromone), 8.73 s (1H, NH), 11.42 s (1H, NH)	12.10	1236 (P=O), 1638 (C=O), 1709 (C=O), 2986–3235 (NH as.)
IVa	2.39 s (3H,CH_3), 4.84 br.s (OH+H_2O), 5.73 d.d (1H, CH, $^3J_{HH}$ 8.7 Hz, $^2J_{HP}$ 21.6 Hz), 6.72–7.97 m (7H, C_6H_4, 3H, furan), 8.77 d.d (1H, NH, $^3J_{HH}$ 8.9 Hz, $^3J_{HP}$ 3.3 Hz)	12.20	1222 (P=O), 1642[a] (C=O), 2608–3260 (NH, OH as.)
IVb	2.38 s (3H, CH_3), 5.0 br.s (OH+H_2O), 5.76 d.d (1H, CH, $^3J_{HH}$ 8.4 Hz, $^2J_{HP}$ 21.9 Hz), 7.25–7.90 m (7H, C_6H_4, 3H, thiophen), 8.81 d.d (1H, NH $^3J_{HH}$ 8.4 Hz, $^3J_{HP}$ 3.3 Hz)	11.73	1212 (P=O), 1643 (C=O), 2671–3262 (NH, OH as.)
IVc	2.38 s (3H, CH_3), 5.85 d.d (1H, CH, $^3J_{HH}$ 8.6 Hz, $^2J_{HP}$ 21.6 Hz), 7.26–8.02 m (9H, C_6H_4, C_6H_5), 8.95 d.d (1H, NH, $^3J_{HH}$ 8.6 Hz, $^3J_{HP}$ 3.8 Hz)	8.50	1225 (P=O), 1644 (C=O), 2914–3257 (NH, OH as.)
IVd	2.38 s (3H, CH_3), 5.80 d.d (1H, CH, $^3J_{HH}$ 8.7 Hz, $^2J_{HP}$ 21.3 Hz), 7.26–7.94 m (8H, C_6H_4, 4H, coumarin), 8.77 d.d (1H, NH, $^3J_{HH}$ 8.7 Hz, $^3J_{HP}$ 3.6 Hz), 8.84 s (1H, C^4–H, coumarin)	11.70	1240[a] (P=O), 1626[a] (C=O), 1747[a] (C=O), 2689–3250 (NH, OH as.)
IVe	2.38 s (3H, CH_3), 3.95 br.s (OH+H_2O), 5.79 d.d (1H, CH, $^3J_{HH}$ 8.5 Hz, $^2J_{HP}$ 21.2 Hz), 6.90 s (1H, C^3–H, chromone), 7.29–8.00 m (8H, C_6H_4, 4H, chromone), 8.75 d.d (1H, NH, $^3J_{HH}$ 8.7 Hz, $^3J_{HP}$ 3.2 Hz)	12.01	1299 (P=O), 1632 (C=O), 1702 (C=O), 2990–3215 (NH, OH as.)
IVf	2.39 s (3H, CH_3), 2.48 s (3H, CH_3), 3.90 br.s (OH+H_2O), 5.82 d.d (1H, CH, $^3J_{HH}$ 8.6 Hz, $^2J_{HP}$ 21.9 Hz), 7.08 s (1H, C^3–H, chromone), 7.25–7.87 m (7H, C_6H_4, 3H, chromone), 8.88 d.d (1H, NH, $^3J_{HH}$ 8.6 Hz, $^3J_{HP}$ 3.3 Hz)	11.98	1236 (P=O), 1638 (C=O), 1697 (C=O), 2987–3197 (NH, OH as.)
VIIa	1.24 t (6H, 2CH_3), 2.37 s (3H, CH_3), 4.18 m (4H, 2CH_2O), 6.17 d.d (1H, CH, $^3J_{HH}$ 8.9 Hz, $^2J_{HP}$ 21.0 Hz), 6.90–7.85 m (9H, 2C_6H_4, C^4–H, pyrazole), 9.63 d.d (1H, NH, $^3J_{HH}$ 8.9 Hz, $^3J_{HP}$ 3.7 Hz), 10.15 s (1H, NH), 13.42 s (1H, OH)	10.66	1239[a] (P=O), 1651 (C=O), 2990–3298 (NH, OH as.)
VIIb	1.27 t (6H, 2CH_3), 2.27 s (3H, CH_3), 2.40 s (3H, CH_3), 4.19 m (4H, 2CH_2O), 6.15 d.d (1H, CH, $^3J_{HH}$ 9.0 Hz, $^2J_{HP}$ 22.2 Hz), 6.88–7.88 m (7H, C_6H_4, C_6H_3), 7.51 s (1H, C^4–H, pyrazole), 9.55 d.d (1H, NH, $^3J_{HH}$ 9.0 Hz, $^3J_{HP}$ 3.8 Hz), 10.03 s (1H, NH), 13.51 s (1H, OH)	11.39	1256[a] (P=O), 1650 (C=O), 2982–3253 (NH, OH as.)
VIIIa	2.36 s (3H, CH_3), 3.90 br.s (OH+H_2O), 5.80 d.d (1H, CH, $^3J_{HH}$ 8.9 Hz, $^2J_{HP}$ 22.0 Hz), 6.92–7.87 m (9H, 2C_6H_4, C^4–H, pyrazole), 8.95 d.d (1H, NH, $^3J_{HH}$ 8.9 Hz), 10.40 s (1H, NH)	11.34	1189[a] (P=O), 1648[a] (C=O), 2900–3224 (NH, OH as.)
VIIIb	2.28 s (3H, CH_3), 2.39 s (3H, CH_3), 4.0 br.s (OH+H_2O), 5.73 d.d (1H, CH, $^3J_{HH}$ 8.8 Hz, $^2J_{HP}$ 21.9 Hz), 6.87–7.86 m (7H, C_6H_4, C_6H_3), 7.52 s (1H, C^4–H, pyrazole), 8.67 d.d (1H, NH, $^3J_{HH}$ 8.8 Hz, $^3J_{HP}$ 4.0 Hz), 9.98 s (1H, NH)	11.35	1189[a] (P=O), 1648[a] (C=O), 2977–3203 (NH, OH as.)

[a] Band with arm.

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