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Transformations of Acylation Products of Functionally 4-Substituted 2-Alkyl(aryl)-5-hydrazino-1,3-oxazoles into 1,3,4-Oxadiazole Derivatives

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Abstract — Acylation products of 2-aryl-5-hydrazino-4-X-1,3-oxazoles [X = C(O)OAlk, $P(O)(OAlk)_2$], when heated in acetic acid or ethanol, undergo recyclization and transform into the derivatives of 1,3,4-oxadiazol-2-ylglycine or its phosphonyl analog. A similar rearrangement also occurs in the reactions of 2-alkyl(aryl)-5-hydrazino-1,3-oxazole-4-carbonitriles with carboxylic acid chlorides in pyridine, but it is accompanied by additional cyclization involving the amide residue and nitrile group, yielding 2-(5-amino-1,3-oxazol-4-yl)-1,3,4-oxadiazole derivatives.

A systematic study of the reactions of β,β-disubstituted enamides **I**–**III** with hydrazine hydrate, initiated recently [1–3] and continued in this work, showed that the possible applications of this polycondensation are fairly wide, and it is indispensable for preparative synthesis of 5-hydrazino-1,3-oxazole derivatives **IV**–**VI** containing in 4-position various electron-withdrawing groups: C(O)OAlk, $P(O)(OAlk)_2$, and C≡N. The ^{1}H NMR and IR spectra of these products are consistent with their suggested structures (Table 1). Transformations **I** → **IV**, **II** → **V**, and **III** → **VI** are similar to the extensively studied cyclocondensations of enamides **I**–**III** with primary and secondary amines (see references in [4]). Therefore, there is no doubt that compounds **IV**–**VI** are, indeed, the 5-hydrazino-1,3-oxazole derivatives differently reacting with carboxylic acid chlorides in the presence of bases. The reaction pathway essentially depends on the structure of electron-withdrawing substituents in 4-position of the heteroring and on the acylation conditions. In particular, acylation of the hydrazino group in alkyl esters of 2-aryl-5-hydrazino-1,3-oxazole-4-carboxylic acids **IV** and their phosphonyl analogs **V** in acetonitrile in the presence of an equimolar amount of triethylamine mainly occurs at the nitrogen atom more remote from the oxazole ring. The reaction yields β-acylation products **VII** and **VIII** containing the HtNHNHCO fragment, as indicated by the ^{1}H NMR spectra (Table 1).

At the same time, 2-aryl-5-hydrazino-1,3-oxazole-4-carbonitriles **VI** structurally related to **IV** and **V** react with carboxylic acid chlorides in the presence of triethylamine quite differently, yielding mainly the α-acylation products $HtN(COR^2)NH_2$ whose structure was unambiguously proved by spectral and chemical methods [2]. The acylation pathway of substrates **VI** changes if the acylation with carboxylic acid chlorides is performed in pyridine. The β-acylation products **IX** formed in the first step are difficult to isolate pure, because they readily undergo further transformations (see scheme). However, we were able to isolate one of these compounds (X = CN, $R^1 = R^2$ = 4-$CH_3C_6H_4$) and to record its ^{1}H NMR spectrum. The spectrum contained two broadened singlets at 10.43 and 10.93 ppm, assignable to two different N–H protons in the HtNHNHCO group.

The structural similarity of β-acylation products **VII**–**IX** was proved not only by spectroscopy, but also by the fact that, in contrast to the isomeric α-acylation products, compounds **VII**–**IX** after approoriate treatment transformed into 1,3,4-oxadiazole derivatives. In particular, substrates **VII** and **VIII**, when heated in acetic acid or ethanol, recyclize (see scheme) into the corresponding derivatives of 1,3,4-oxadiazol-2-ylglycine (**X**) or its phosphonyl analog (**XI**) (Table 2). The presence of the CHNH and PCHNH groups in **X** and **XI** is confirmed by the ^{1}H NMR spectra in the regions of 6.1–6.4 and 9.6–9.8 ppm (Table 1). The signals were reliably assigned by comparison of the ^{1}H NMR spectra of compounds **X** and those of the related 1,3,4-oxadiazole derivatives **C** (see below) whose structure was proved by single crystal X-ray diffraction [2].

It should be noted that compounds **VII** do not transform into **X** even upon prolonged heating when acetic acid or ethanol as solvent is replaced by

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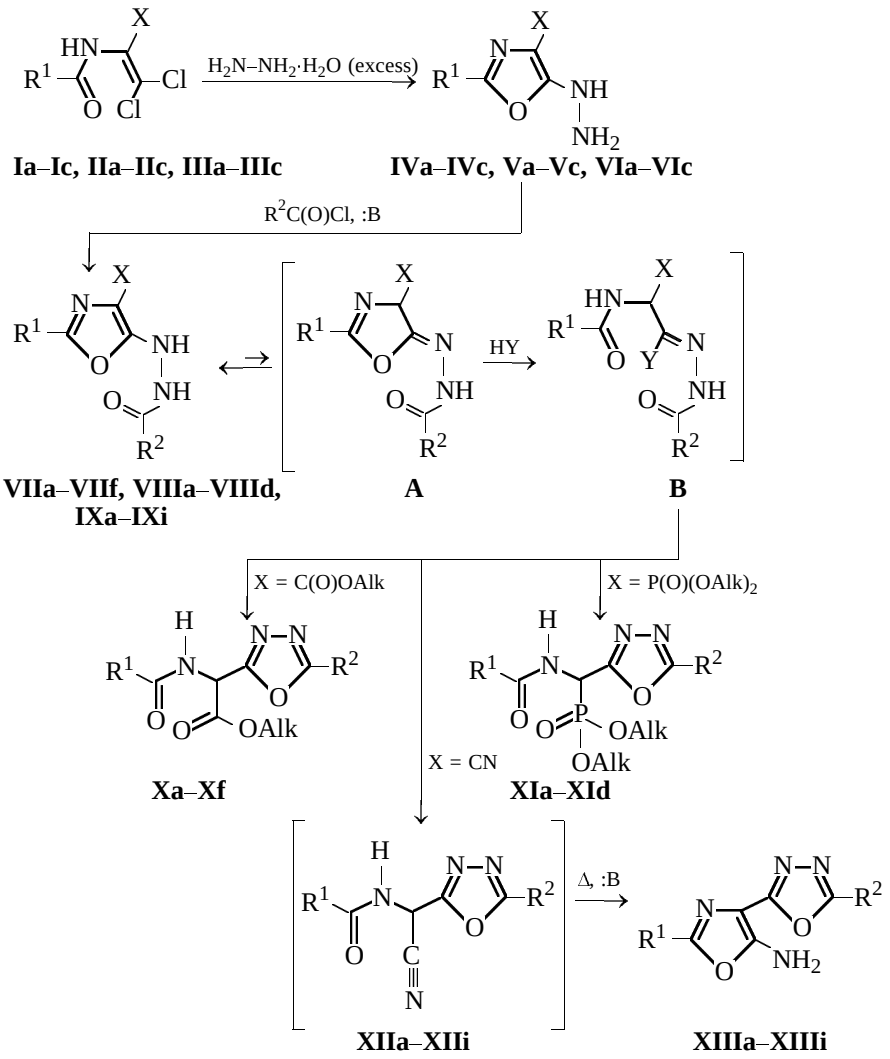
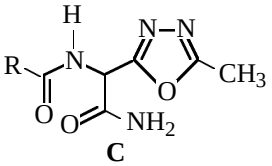


I, II, IV, V, $R^1 = C_6H_5$, Alk = CH_3 (**a**); R^1 = 4-$CH_3C_6H_4$, Alk = CH_3 (**b**); $R^1 = C_6H_5$, Alk = C_2H_5 (**c**). **III, VI,** $R^1 = C_6H_5$ (**a**), 4-$CH_3C_6H_4$ (**b**), CH_3 (**c**). **VII, X,** $R^1 = R^2 = C_6H_5$, Alk = CH_3 (**a**); R^1 = 4-$CH_3C_6H_4$, Alk = CH_3, $R^2 = C_6H_5$ (**b**); $R^1 = R^2 = C_6H_5$, Alk = C_2H_5 (**c**); $R^1 = C_6H_5$, Alk = CH_3, R^2 = 4-$CH_3C_6H_4$ (**d**); $R^1 = C_6H_5$, Alk = C_2H_5, R^2 = 4-$CH_3C_6H_4$ (**e**); $R^1 = R^2$ = 4-$CH_3C_6H_4$, Alk = CH_3 (**f**). **VIII, XI,** $R^1 = R^2 = C_6H_5$, Alk = CH_3 (**a**); $R^1 = R^2$ = 4-$CH_3C_6H_4$, Alk = CH_3 (**b**); $R^1 = C_6H_5$, Alk = C_2H_5, R^2 = 4-$CH_3C_6H_4$ (**c**); $R^1 = C_6H_5$, Alk = CH_3, R^2 = 4-$CH_3C_6H_4$ (**d**). **IX, XII, XIII,** $R^1 = R^2 = C_6H_5$ (**a**); R^1 = 4-$CH_3C_6H_4$, $R^2 = C_6H_5$ (**b**); $R^1 = CH_3$, $R^2 = C_6H_5$ (**c**); $R^1 = C_6H_5$, R^2 = 4-$CH_3C_6H_4$ (**d**); $R^1 = C_6H_5$; $R^2 = CH_3$ (**e**); $R^1 = R^2$ = 4-$CH_3C_6H_4$ (**f**); R^1 = 4-$CH_3C_6H_4$, $R^2 = CH_3$ (**g**); $R^1 = CH_3$, R^2 = 4-$CH_3C_6H_4$ (**h**); $R^1 = R^2 = CH_3$ (**i**). X = AlkOC(O) (**I, IV, VII**), $(AlkO)_2P(O)$ (**II, V, VIII**), N≡C (**III, VI, IX**).



C

dioxane. This fact suggests important role not only of prototropic tautomers **A**, but also of acyclic products **B** formed by cleavage of 5-imino-2-oxazoline moiety with ethanol, acetic acid, or other compounds with a labile hydrogen atom. Further cyclization **B** → **X** or **XI** resembles the previously found transformation of *N*,*N*'-diacyl derivatives of hydrazine into 1,3,4-oxadiazole derivatives [5]. Recyclization **IX** → **B** → **XII** occurs similarly but is complicated by additional intramolecular reaction of the cyano group and amide residue. Cyclization **XII** → **XIII** is a particular case of well-known transformations of some α-acylamino nitriles into 5-amino-1,3-oxazole derivatives, which are formed in the presence of bases or acids [6]. The disappearance of the C≡N bond and formation of a primary amino group in the series of successive reactions

Table 1. Spectroscopic data for compounds **IV, V, VII**–**XI**, and **XIII**

Comp. no	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
IVa	1680 (C=O), 3360 (NH)	3.75 s (3H, OCH_3), 4.70 br.s (2H, NH_2), 7.40–7.88 m (5H, C_6H_5), 8.09 br.s (1H, NH)
IVb	1680 (OC=O), 3340 (NH)	2.34 s (3H, CH_3), 3.71 s (3H, OCH_3), 4.80 br.s (2H, NH_2), 7.31–7.73 m (4H, C_6H_4), 8.27 br.s (1H, NH)
IVc	1660 (OC=O), 3220 (NH)	1.31 t (3H, CH_3), 4.22 q (2H, OCH_2), 4.74 br.s (2H, NH_2), 7.40–7.95 m (5H, C_6H_5), 8.09 br.s (1H, NH)
Va	1240(P=O), 3280 (NH)	3.69 d (6H, $2OCH_3$, $^3J_{HP}$ 12.1), 4.80 br.s (2H, NH_2), 7.48–7.84 m (6H, NH)
VIIa	1640 (NC=O), 1680 (OC=O), 3480 (NH)	3.82 s (3H, OCH_3), 7.43–7.95 m (10H, $2C_6H_5$), 9.28 s (1H, NH), 10.87 s (1H, NH)
VIIc	1645 (NC=O), 1680 (OC=O), 3370 (NH)	1.36 t (3H, CH_3), 7.32 q (2H, OCH_2), 7.43–7.96 m (10H, $2C_6H_5$), 9.17 s (1H, NH), 10.86 s (1H, NH)
VIId	1640 (NC=O), 1670 (OC=O), 3390 (NH)	2.41 s (3H, CH_3), 3.81 s (3H, OCH_3), 7.33–7.86 m (9H, C_6H_5, C_6H_4), 9.21 s (1H, NH), 10.77 s (1H, NH)
VIIe	1620 (NC=O), 1680 (OC=O), 3420 (NH)	1.35 t (3H, CH_3), 2.41 s (3H, CH_3), 4.32 q (2H, OCH_2), 7.36–7.93 m (9H, C_6H_5, C_6H_4), 9.10 s (1H, NH), 10.76 s (1H, NH)
VIIf	1630 (NC=O), 1680 (OC=O), 3410 (NH)	–
VIIIb	1220 (P=O), 1680 (NC=O), 3220 (NH)	2.35 s (3H, CH_3), 2.40 s (3H, CH_3), 3.72 m (6H, $2OCH_3$), 7.23–7.83 m (8H, $2C_6H_4$), 8.43 s (1H, NH), 10.64 s (1H, NH)
IXf	1660 (NC=O), 2200 (C≡N), 3200 (NH)	2.37 s (6H, $2CH_3$), 7.32–7.81 m (8H, $2C_6H_4$), 10.43 br.s (1H, NH), 10.93 br.s (1H, NH)
Xa	1650 (NC=O), 1750 (OC=O), 3250 (NH)	3.81 s (3H, OCH_3), 6.20 d (1H, CH, $^3J_{HH}$ 7.5), 7.46–8.07 m (10H, $2C_6H_5$), 9.69 d (1H, NH, $^3J_{HH}$ 7.5)
Xb	1650 (NC=O), 1770 (OC=O), 3225 (NH)	2.39 s (3H, CH_3), 3.81 s (3H, OCH_3), 6.15 d (1H, CH, $^3J_{HH}$ 7.5), 7.26–8.03 m (9H, C_6H_5), 9.54 d (1H, NH, $^3J_{HH}$ 7.5)
Xc	1645 (NC=O), 1745 (OC=O), 3270 (NH)	1.28 s (3H, CH_3), 4.27 q (2H, OCH_2), 6.13 d (1H, CH, $^3J_{HH}$ 7.5), 7.46–8.09 m (10H, $2C_6H_5$), 9.65 d (1H, NH, $^3J_{HH}$ 7.5)
Xd	1650 (NC=O), 1750 (OC=O), 3260 (NH)	2.42 s (3H, CH_3), 3.81 s (3H, OCH_3), 6.18 d (1H, CH_3, $^3J_{HH}$ 7.5), 7.38–7.95 m (9H, C_6H_5, C_6H_4), 9.64 d (1H, NH, $^3J_{HH}$ 7.5)
Xe	1645 (NC=O), 1750 (OC=O), 3250 (NH)	1.27 t (3H, CH_3), 2.42 s (3H, CH_3), 4.26 q (2H, OCH_2), 6.10 d (1H, CH, $^3J_{HH}$ 7.5), 7.38–7.97 m (9H, C_6H_5, C_6H_4), 9.62 d (1H, NH, $^3J_{HH}$ 7.5)
Xf	1645 (NC=O), 1760 (OC=O), 3250 (NH)	2.42 s (6H, $2CH_3$), 3.80 s (3H, OCH_3), 6.13 d (1H, CH, $^3J_{HH}$ 7.5), 7.26–7.91 m (8H, $2C_6H_4$), 6.34 d (1H, NH, $^3J_{HH}$ 7.5)
XIa	1240 (P=O), 1680 (OC=O), 3230 (NH)	3.86 m (6H, $2OCH_3$), 6.70 d.d (1H, CH, $^3J_{HH}$ 8.7, $^2J_{HP}$ 21.6), 7.45–8.04 m (10H, $2C_6H_5$), 9.59 d (1H, NH, $^3J_{HH}$ 8.7)
XIb	1240 (P=O), 1670 (OC=O), 3230 (NH)	2.41 s (3H, CH_3), 2.42 s (3H, CH_3), 3.84 m (6H, $2OCH_3$), 6.21 d.d (1H, NCHP, $^3J_{HH}$ 8.7, $^2J_{HP}$ 21.6), 7.25–7.91 m (8H, $2C_6H_4$), 9.43 d (1H, NH, $^3J_{HH}$ 8.7)
XIc	1240 (P=O), 1680 (OC=O), 3220 (NH)	1.27 m (6H, $2CH_3$), 2.42 s (3H, CH_3), 4.18 m (4H, $2CH_2$), 6.09 d.d (1H, NCHP, $^3J_{HH}$ 8.6, $^2J_{HP}$ 21.8), 7.38–7.96 m (9H, C_6H_4, C_6H_5), 9.57 d (1H, NH, $^3J_{HH}$ 8.6)
XId	1235 (P=O), 1685 (OC=O), 3220 (NH)	2.42 s (3H, CH_3), 3.84 m (6H, $2OCH_3$), 6.21 d.d (1H, NCHP, $^3J_{HH}$ 8.7, $^2J_{HP}$ 21.6), 7.37–7.97 m (9H, C_6H_5, C_6H_4), 9.53 d (1H, NH, $^3J_{HH}$ 8.7)
XIIIa	3280, 3410 (NH_2)	7.43–8.14 m (12H, $2C_6H_5$, NH_2)
XIIIb	3280, 3410 (NH_2)	2.36 s (3H, CH_3), 7.34–8.10 m (11H, C_6H_5, C_6H_4, NH_2)
XIIIc	3290, 3380 (NH_2)	2.33 s (3H, CH_3), 7.14 br.s (2H, NH_2), 7.59–8.07 m (5H, C_6H_5)
XIIId[a]	3280, 3420 (NH_2)	2.40 s (3H, CH_3), 7.40–8.01 m (11H, C_6H_5, C_6H_4, NH_2)

Table 1. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
XIIIe	3280, 3420 (NH_2)	2.54 s (3H, CH_3), 7.34 br.s (2H, NH_2), 7.49–7.82 m (5H, C_6H_5)
XIIIf[b]	3280, 3420 (NH_2)	2.39 s (3H, CH_3), 2.43 s (3H, CH_3), 7.28–8.00 m (10H, $2C_6H_4$, NH_2)
XIIIg	3280, 3390 (NH_2)	2.37 s (3H, CH_3), 2.53 s (3H, CH_3), 7.15 br.s (2H, NH_2), 7.28–7.70 m (4H, C_6H_4)
XIIIh[c]	3280, 3410 (NH_2)	2.34 s (3H, CH_3), 2.41 s (3H, CH_3), 6.97 br.s (2H, NH_2), 7.37–7.93 m (4H, C_6H_4)
XIIIi	3280, 3440 (NH_2)	2.31 s (3H, CH_3), 2.49 s (3H, CH_3), 6.76 br.s (2H, NH_2)

[a] ^{13}C NMR spectrum of **XIIId** (DMSO-d_6), δ_C, ppm (Ht = 2-R^1-5-amino-1,3-oxazol-4-yl and Ht′ = 5-R^2-1,3,4-oxadiazol-2-yl): 21.13 (CH^3), 98.27 (C^4_{Ht}), 120.83–141.47 (C_{Ar}), 150.18 (C^2_{Ht}), 156.89 (C^5_{Ht}), 159.83 ($C^2_{Ht'}$), 161.75 ($C^5_{Ht'}$). [b] Mass spectrum, *m/z*: 332 $[M]^+$, 318, 199, 169, 144, 117, 90, 65. [c] ^{13}C NMR spectrum of **XIIIh** [$(CD_3)_2SO$], δ_C, ppm: 13.05 (Ht–CH_3), 21.03 ($C_6H_4CH_3$), 96.25 (C^4_{Ht}), 120.89–141.31 (C_{Ar}), 150.34 (C^2_{Ht}), 156.42 (C^5_{Ht}), 159.93 ($C^2_{Ht'}$), 161.35 ($C^5_{Ht'}$).

Table 2. Constants, yields, and elemental analyses of **IV, V, VII**–**XI**, and **XIII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H (P)	N		C	H (P)	N
IVa	85	190–191 (methanol)	57.04	5.06	18.37	$C_{11}H_{11}N_3O_3$	56.65	4.75	18.02
IVb	88	195–196 (methanol)	58.43	5.53	17.19	$C_{12}H_{13}N_3O_3$	58.29	5.30	17.00
IVc	73	119–120 (ethanol)	58.51	5.41	16.85	$C_{12}H_{13}N_3O_3$	58.29	5.30	17.00
Va	84	104–105 (benzene)	–	(10.84)	14.67	$C_{11}H_{14}N_3O_4P$	–	(10.94)	14.84
Vb	87	120–121 (aqueous ethanol)	–	(10.12)	13.86	$C_{12}H_{16}N_3O_4P$	–	(10.42)	14.14
Vc	90	78–80 (benzene)	–	(9.91)	13.45	$C_{13}H_{18}N_3O_4P$	–	(9.95)	13.50
VIIa	66	146–147 (benzene)	64.33	4.61	12.31	$C_{18}H_{15}N_3O_4$	64.09	4.48	12.46
VIIb	71	194–195 (methanol)	65.08	5.11	11.90	$C_{19}H_{17}N_3O_4$	64.95	4.88	11.96
VIIc	78	170–172 (ethanol)	65.09	5.06	11.78	$C_{19}H_{17}N_3O_4$	64.95	4.88	11.96
VIId	62	127–129 (benzene)	65.14	5.02	12.16	$C_{19}H_{17}N_3O_4$	64.95	4.88	11.96
VIIe	73	153–154 (benzene)	65.91	5.37	11.67	$C_{20}H_{19}N_3O_4$	65.74	5.24	11.50
VIIf	81	187–189 (methanol)	65.89	5.12	11.37	$C_{20}H_{19}N_3O_4$	65.74	5.24	11.50
VIIIa	65	134–136[a]	56.04	4.89	10.67	$C_{18}H_{18}N_3O_5P$	55.82	4.68	10.85
VIIIb	79	158–159[a]	–	(7.61)	10.25	$C_{20}H_{22}N_3O_5P$	–	(7.46)	10.12
VIIIc	75	150–152[a]	–	(7.15)	10.01	$C_{21}H_{24}N_3O_5P$	–	(7.21)	9.79
VIIId	82	155–157[a]	–	(7.91)	10.56	$C_{19}H_{20}N_3O_5P$	–	(7.72)	10.47
IXf	35	>260[b]	68.83	4.98	16.69	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86
Xa	61	136–137 (ethanol)	64.27	4.63	12.54	$C_{18}H_{15}N_3O_4$	64.09	4.48	12.46
Xb	67	126–127 (ethanol)	65.12	5.03	12.07	$C_{19}H_{17}N_3O_4$	64.95	4.48	11.96
Xc	63	115–116 (ethanol)	65.16	5.12	12.15	$C_{19}H_{17}N_3O_4$	64.95	4.88	11.96
Xd	69	119–120 (ethanol)	65.09	5.07	12.09	$C_{19}H_{17}N_3O_4$	64.95	4.88	11.96
Xe	64	132–133 (ethanol)	65.89	5.41	11.38	$C_{20}H_{19}N_3O_4$	65.74	5.24	11.50
Xf	71	133–134 (ethanol)	65.83	5.38	11.41	$C_{20}H_{19}N_3O_4$	65.74	5.24	11.50
XIa	73	150–151 (benzene–hexane)	55.98	4.79	10.91	$C_{18}H_{18}N_3O_5P$	5.82	4.68	10.85
XIb	69	158–159 (aqueous ethanol)	–	(7.31)	10.25	$C_{20}H_{22}N_3O_5P$	–	(7.46)	10.12
XIc	77	140–142 (aqueous ethanol)	–	(7.08)	10.03	$C_{21}H_{24}N_3O_5P$	–	(7.21)	9.79

Table 2. (Contd.)

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H (P)	N		C	H (P)	N
XId	63	147–148 (benzene–hexane)	–	(7.91)	10.63	$C_{19}H_{20}N_3O_5P$	–	(7.22)	10.47
XIIIa	86	231–232 (DMF–acetonitrile)	67.32	4.15	18.27	$C_{17}H_{12}N_4O_2$	67.10	3.98	18.41
XIIIb	89	238–239 (DMF–acetonitrile)	68.11	4.58	17.51	$C_{18}H_{14}N_2O_2$	67.92	4.43	17.60
XIIIc	62	182–184 (ethanol)	59.83	4.33	22.97	$C_{12}H_{10}N_2O_2$	59.50	4.16	23.13
XIIId	81	241–242 (DMF–acetonitrile)	68.07	4.67	17.73	$C_{18}H_{14}N_4O_2$	67.92	4.43	17.60
XIIIe	65	227–228 (acetonitrile)	58.89	4.29	23.37	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13
XIIIf	89	253–254 (DMF–acetonitrile)	68.91	4.97	16.65	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86
XIIIg	63	193–194 (ethanol)	60.81	4.89	21.98	$C_{12}H_{10}N_4O_2$	60.93	4.72	21.86
XIIIh	65	251–253 (acetonitrile)	61.16	5.01	21.63	$C_{13}H_{12}N_4O_2$	60.93	4.72	21.86
XIIIi	52	146–147 (aqueous ethanol)	46.81	4.62	31.46	$C_7H_8N_4O_2$	46.67	4.48	31.10

[a] Compounds **VIIIa**–**VIIId** are unstable, and therefore they were not recrystallized. [b] After washing with ethanol.

IX → **XII** → **XIII** can be traced by ^{1}H NMR and IR spectroscopy (Table 1). Furthermore, the structure of one of the simplest representatives of compounds **XIII** ($R^1 = R^2 = CH_3$) in the form of the dihydrate was determined by single crystal X-ray diffraction (figure, Table 3). Owing to the symmetry conditions in the crystal, the molecule is ideally planar (all the nonhydrogen atoms occupy special positions on plane *m*). The N^4 atom has a trigonal planar configuration: The sum of the bond angles at this atom is 360.0° within the experimental error. Owing to very efficient $n(N^4)$–$\pi(C^3{=}C^4)$ conjugation, the N^4–C^4 bond [1.320(3) Å] is appreciably shortened compared to a single N_{sp^2}–C_{sp^2} bond (typical length 1.43–1.45 Å [7, 8]). The short distance $N^2 \cdots N^4$ suggests formation of an intramolecular hydrogen bond $N^2 \cdots H^{41}$–N^4 [$N^2 \cdots N^4$ 3.064(3), $N^2 \cdots H^{41}$ 2.51(3) Å, $\angle N^2H^{41}N^4$ 121(2)°] closing a six-membered ring.

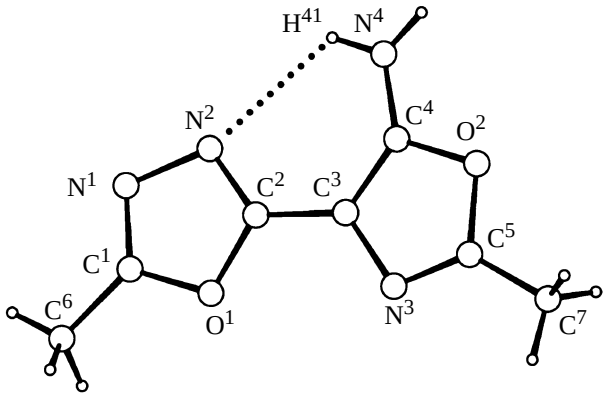
Thus, there is no doubt that heating of accessible substrates **VI** with carboxylic acid chlorides in pyridines involves succesive, quite regioselective transformations **VI** → **IX** → **XII** → **XIII**, allowing one-pot synthesis of previously unknown 2-(5-amino-1,3-oxazol-4-yl)-1,3,4-oxadiazole derivatives in high yield.

Of no less importance are also the preparative syntheses of glycine (**X**) and aminomethylphosphonic acid (**XI**) derivatives containing a 1,3,5-oxadiazole ring at the asymmetric center. Such transformations of α-amino carboxylic [9–18] and α-amino phosphonic [19–24] acids containing residues of other nitrogen heterocycles instead of the 1,3,4-oxadiazole fragment are widely used in the search for bioactive agents. In this connection, further modification of compounds **X** and **XI** is of doubtless interest; this will be the subject of further studies.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer (KBr pellets). The ^{1}H and ^{13}C NMR spectra were measured on a Varian VXR-300 spectrometer at 300 and 75 MHz, respectively (solvent DMSO-d_6, reference TMS). The mass spectrum of **XIIIf** was taken with a Varian MAT-311A device.

The single crystal X-ray diffraction study of **XIIIi**·$2H_2O$ (crystal size 0.25 × 0.31 × 0.43 mm) was performed at room temperature with an



General view of the molecule of **XIIIi** in the crystal of **XIIIi**·$2H_2O$ (water molecules are not shown).

Table 3. Selected bond lengths (*d*, Å) and bond angles (ω, deg) in **XIIIi**·$2H_2O$

Bond	*d*	Angle	ω
O^1–C^1	1.364(2)	$C^1O^1C^2$	102.9(1)
O^1–C^2	1.359(3)	$C^4O^2C^5$	104.8(2)
N^1–C^1	1.281(3)	$N^2N^1C^1$	107.0(2)
N^1–N^2	1.415(3)	$N^1N^2C^2$	105.3(2)
N^2–C^2	1.294(3)	$C^3N^3C^5$	104.9(2)
O^2–C^4	1.365(3)	$O^1C^1N^1$	112.1(2)
O^2–C^5	1.383(3)	$O^1C^2N^2$	112.7(2)
N^3–C^3	1.406(3)	$N^3C^3C^4$	109.0(2)
N^3–C^5	1.282(3)	$O^2C^4C^3$	107.7(2)
N^4–C^4	1.320(3)	$O^2C^5N^3$	113.5(2)
C^2–C^3	1.434(3)		
C^3–C^4	1.355(3)		

Enraf-Nonius CAD-4 automatic four-circle diffractometer (CuK_α radiation, λ 1.54178 Å, scanning rate ratio 2θ/ω 1.2, θ_{max} 70°, sphere segment $0 \le h \le 7$, $0 \le k \le 7$, $-30 \le l \le 30$). A total of 2268 reflections were measured; 1046 of them were unique (R_{int} 0.015). The crystals are rhombic; *a* 6.627(1), *b* 6.274(2), *c* 24.834(6) Å; *V* 1032.6(4) $Å^3$, *M* 216.2, *Z* 4, d_{calc} 1.39 g cm^{-3}, μ 9.43 cm^{-1}, *F*(000) 457.6, space group *Pmna* (no. 53). The structure was solved by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation using the CRYSTALS program package [25]. In the refinement, we used 800 reflections with $I > 3\sigma(I)$ (111 refined parameters, 7.2 reflections per parameter); all the hydrogen atoms were revealed by the differential electron density synthesis and refined positionally with fixed thermal parameters. We used the Chebyshev scheme [26] with five parameters: 3.89, 4.66, 4.09, 1.27, and 0.78. The final divergence factors were *R* 0.040 and R_W 0.043; *GOF* 1.129. The residual electron density from the differential Fourier series is 0.24 and –0.32 e $Å^{-3}$. The absorption in the crystal was taken into account by azimuthal scanning [27].

Alkyl 2-aryl-5-hydrazino-1,3-oxazole-4-carboxylates IVa–IVc. To a solution of 0.01 mol of **Ia** or **Ib** in 30 ml of methanol, we added 0.035 mol of hydrazine hydrate. The mixture was allowed to stand for 24 h at 20–25°C. The precipitate of **IVa** or **IVb** was filtered off, washed with water, dried, and recrystallized from appropriate solvent. Compound **IVc** was prepared similarly using ethanol instead of methanol.

Dialkyl 2-aryl-5-hydrazino-1,3-oxazol-4-ylphosphonates Va–Vc. To a solution of 0.01 mol of **IIa–IIc** in 30 ml of THF, we added 0.035 mol of hydrazine hydrate. The mixture was allowed to stand for 24 h at 20–25°C. The precipitate was filtered off, washed with a minimal amount of water, and mixed with the substance obtained from the THF filtrate. For analysis, the product was dried and recrystallized from appropriate solvent. Compound **Va** was prepared previously [28].

2-Aryl(methyl)-5-hydrazino-1,3-oxazole-4-carbonitriles VIa–VIc was prepared by the published procedure [1, 2].

Alkyl 2-aryl-5-(2-acylhydrazino)-1,3-oxazole-4-carboxylates VIIa–VIIf. To a solution of 0.01 mol of **IVa–IVc** in 15 ml of anhydrous acetonitrile, we added 0.025 mol of anhydrous triethylamine and then 0.0105 mol of appropriate acyl chloride. The mixture was allowed to stand for 24 h at 20–25°C, after which 50 ml of water was added, and the precipitate was filtered off, dried, and recrystallized from appropriate solvent.

Dialkyl 2-aryl-5-(2-acylhydrazino)-1,3-oxazol-4-ylphosphonates VIIIa–VIIId. To a solution of 0.01 mol of **Va–Vc** in 10 ml of anhydrous acetonitrile, we added 0.025 mol of anhydrous triethylamine and 0.0105 mol of appropriate acyl chloride. The mixture was allowed to stand for 24 h at 20–25°C, and the precipitate was filtered off, washed with water, combined with the product obtained from the filtrate, and used for further transformations without additional purification.

2-*p*-Tolyl-5-(2-*p*-toluylhydrazino)-1,3-oxazole-4-carbonitrile IXf. To a solution of 0.01 mol of **IVb** in 20 ml of anhydrous pyridine, we added 0.0105 mol of *p*-toluyl chloride. The mixture was allowed to stand for 24 h at 20–25°C; 70 ml of water was added, and the precipitate was filtered off and washed with ethanol.

Alkyl 5-aryl-1,3,4-oxadiazol-2-yl(acylamino)acetic acids Xa–Xf. A solution of 0.01 mol of **VIIa–VIIf** in 15 ml of glacial acetic acid was heated for 8 h at 110–120°C. The solvent was vacuum-evaporated, and the oily residue was treated with water for crystallization. The precipitate was filtered off and recrystallized from appropriate solvent.

Dialkyl 5-aryl-1,3,4-oxadiazol-2-yl(acylamino)-methylphosphonates XIa–XId. A solution of 0.01 mol of **VIIIa–VIIId** in 10 ml of 80% ethanol was heated for 30 min. The precipitate was filtered off and recrystallized from appropriate solvent.

2-[5-Amino-2-aryl(methyl)-1,3-oxazol-4-yl]-5-aryl(methyl)-1,3,4-oxadiazoles XIIIa–XIIIi. *a*. To

a solution of 0.01 mol of **VIa**–**VIc** in 20 ml of anhydrous pyridine, we added 0.0105 mol of appropriate acyl chloride. The mixture was heated for 8 h at 110–120°C. The solvent was removed in a vacuum, and the oily residue was treated with water for crystallization. The precipitate was filtered off, dried, and recrystallized from appropriate solvent. In the synthesis of **XIIIi**, the oily residue was dissolved in water, and crystals of **XIIIi**·$2H_2O$ formed in 48 h. A crystal of this product was selected for an X-ray diffraction study. For analysis, the solvate was dried in a vacuum desiccator over P_2O_5.

b. A mixture of 0.01 mol of **VIa** or **VIb** with 4 g of benzoic anhydride was heated for 8 h at 130°C and then allowed to stand for 12 h at 20–25°C, after which 15 ml of acetonitrile was added, and the mixture was heated to reflux. The precipitate was filtered off and recrystallized from dimethylformamide–acetonitrile, 1 : 1. Yields: **XIIIa** 76% and **XIIIb** 83%. Mixing of the samples of **XIIIa** prepared by procedures **a** and **b** gave no depression of the melting point. The ^{1}H NMR spectra of these samples, and also of the two samples of **XIIIb** prepared by procedures **a** and **b**, were identical.

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