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SYNTHESIS AND SOME PROPERTIES OF 5-ALKYLAMINO-2-(PHTHALIMIDOALKYL)-1,3-OXAZOLE-4-CARBONITRILES

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5-Alkylamino-1,3-oxazole-4-carbonitriles containing a 2-phthalimidoethyl or 3-phthalimidopropyl substituent at position 2 of the oxazole ring were synthesized. In the reaction of 5-(morpholin-4-yl)-2-(2-phthalimidoethy)l-1,3-oxazole-4-carbonitrile with hydrazine hydrate, 2-(2-aminoethyl)-5-(morpholin-4-yl)-1,3-oxazole-4-carbonitrile is formed. In the case of the 3-phthalimidopropyl analog, the recyclization product 3-amino-2-(morpholin-4-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole is formed.

Keywords: 5-alkylamino-2-(phthalimidoalkyl)-1,3-oxazole-4-carbonitriles, 2-(2-aminoethyl)-5-(morpholin-4-yl)-1,3-oxazole-4-carbonitrile, 2-(morpholin-4-ylcarbonyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole-3-amine, recyclization.

The intensive development of the chemistry of functional derivatives of 1,3-oxazole in the last 20 years is due to searches for effective biologically active substances. The role of 1,3-oxazole derivatives in life processes has proven much more significant than previously supposed, in that numerous derivatives of the oxazole series have been isolated from natural materials [1-4]. Moreover a large number of the synthesized oxazole derivatives exhibit high cytostatic, antimicrobial, immunostimulating, analgesic, and other types of biological activity [5]. For this reason functionalization of the oxazole ring is one of the most important directions in the synthesis of prospective novel compounds in the search for bioactive products.

The aim of the present work was to synthesize 2-phthalimidoalkyl-substituted oxazoles for the production of the corresponding amines after removal of the phthalimide protecting group. For this purpose we used the known method for the synthesis of substituted 5-aminooxazoles from the amides of carboxylic acids and chloral [6]. In this condensation we used for the first time the amides of phthalimidoalkylcarboxylic acids [7]. The choice of a phthalimide protecting group was not incidental since it is resistant to thionyl chloride and to the aqueous-alkaline solution of potassium cyanide used at various stages of the reactions in the chain of transformations shown in the scheme for the production of compounds **5**. It is also important that the 5-aminooxazole fragment is stable to the action of hydrazine hydrate under the conditions for the removal of the phthalimide group.

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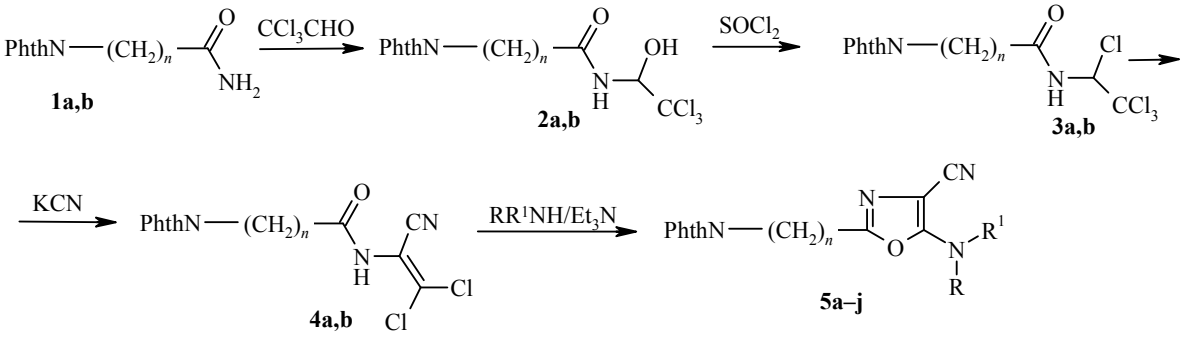
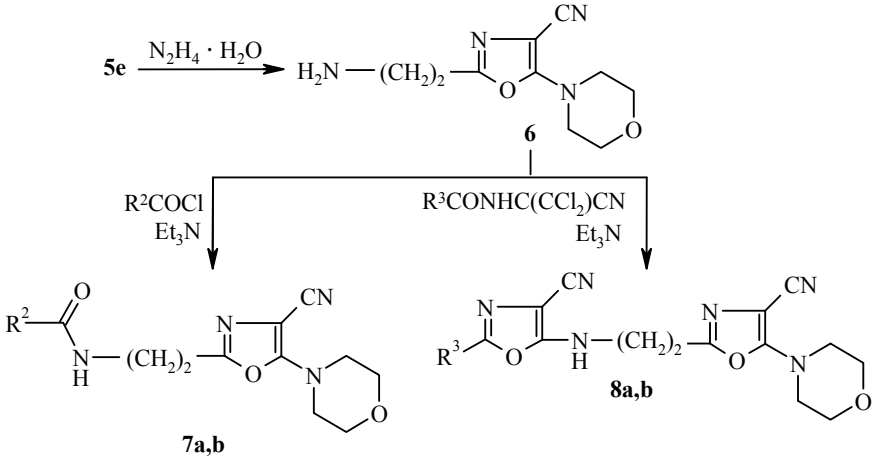
We established that phthalimidopropionamide (**1a)** and phthalimidobutyramide (**1b)** react readily with chloral and give high yields of the corresponding hydroxymethyl derivatives **2a**,**b** (Table 1). In the reaction of the latter with thionyl chloride, compounds **3a**,**b** are formed, and their treatment with an aqueous solution of potassium cyanide in acetone leads to good yields of 3,3-dichloro-2-phthalimidoacylaminoacrylonitriles **4a**,**b**. By analogy with the already known heterocyclization [8, 9], the acrylonitriles **4a**,**b** were used for the production of the substituted alkylaminooxazoles **5a-j**.



1a–4a, **5a–e** n = 2; **1b–4b**, **5f–j** n = 3;
5a,f R = H, R^1 = $PhCH_2$; **b,g** R = H, R^1 = $Ph(CH_2)_2$; **c,h** R+R^1 = –$(CH_2)_5$–;
d,i R+R^1 = –$(CH_2)_2N(Me)(CH_2)_2$–; **e,j** R+R^1 = –$(CH_2)_2O(CH_2)_2$–

In the case of compounds **5e**,**j,** a substantial difference was found in the chemical behavior of the 2-aminoethyl- and 2-aminopropyloxazoles formed after the removal of the phthalimide protection. When compound **5e** is boiled with a small excess of hydrazine hydrate, 2-(2-aminoethyl)-5-(morpholin-4-yl)-1,3-oxazole-4-carbonitrile (**6)** is formed with a moderate yield. Its structure was confirmed by spectral and mass-spectrometric methods (Tables 2, 3) and also by conversion into the corresponding amides **7a**,**b** and dioxazolyl-substituted ethylamines **8a**,**b**.



7a R^2 = Ph, **b** R^2 = 4-MeC_6H_4; **8a** R^3 = Me, **b** R^3 = Ph

In the case of the hydrazinolysis of 2-(3-phthalimidopropyl)-1,3-oxazole-4-carbonitrile **5j,** the amine **9** is evidently formed initially. On account of the favorable disposition of the aminopropyl fragment in relation to the oxazole ring, this compound is susceptible to intramolecular attack from the primary amino group at the C-2 atom of the oxazole. Here cleavage of the oxazole ring and simultaneous formation of the pyrrolidine fragment of compound **10** are observed. A similar transformation was observed earlier for derivatives of 2-(3-amino-propyl)-4,5-diphenyl-1,3-oxazole [10, 11]. In the intermediate **10**, which contains a nucleophilic amidine fragment, attack then occurs at the nitrile group, leading to the formation of the amine **11**.

TABLE 1. Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, ºC*	Yield, %
		C	H	N	Cl		
2a	$C_{13}H_{11}Cl_3N_2O_4$	42.85 / 42.71	3.14 / 3.03	7.52 / 7.66	29.18 / 29.09	140-142	75
2b	$C_{14}H_{13}Cl_3N_2O_4$	44.39 / 44.29	3.57 / 3.45	7.41 / 7.38	28.10 / 28.02	150-152	82
3a	$C_{13}H_{10}Cl_4N_2O_3$	40.57 / 40.66	2.65 / 2.62	7.33 / 7.29	36.99 / 36.93	180-182	64
3b	$C_{14}H_{12}Cl_4N_2O_3$	42.12 / 42.24	2.89 / 3.04	7.13 / 7.04	35.68 / 35.62	145-147	68
4a	$C_{14}H_9Cl_2N_3O_3$	49.76 / 49.73	2.52 / 2.68	12.44 / 12.43	20.99 / 20.97	177-179	85
4b	$C_{15}H_{11}Cl_2N_3O_3$	51.17 / 51.16	3.27 / 3.15	11.85 / 11.93	20.03 / 20.13	193-195	88
5a	$C_{21}H_{16}N_4O_3$	67.79 / 67.73	4.30 / 4.33	15.09 / 15.05	—	118-120	75
5b	$C_{22}H_{18}N_4O_3$	68.34 / 68.38	4.75 / 4.70	14.60 / 14.50	—	122-124	78
5c	$C_{19}H_{18}N_4O_3$	65.00 / 65.13	5.11 / 5.18	16.03 / 15.99	—	105-107	75
5d	$C_{19}H_{19}N_5O_3$	62.31 / 62.46	5.22 / 5.24	19.05 / 19.17	—	107-109	74
5e	$C_{18}H_{16}N_4O_4$	61.24 / 61.36	4.63 / 4.58	16.05 / 15.90	—	151-153	80
5f	$C_{22}H_{18}N_4O_3$	68.24 / 68.38	4.71 / 4.70	14.57 / 14.50	—	114-115	80
5g	$C_{23}H_{20}N_4O_3$	68.97 / 68.99	5.20 / 5.03	14.11 / 13.99	—	106-108	81
5h	$C_{20}H_{20}N_4O_3$	65.84 / 65.92	5.41 / 5.53	15.47 / 15.37	—	Oil	87
5i	$C_{20}H_{21}N_5O_3$	63.33 / 63.31	5.69 / 5.58	18.45 / 18.46	—	105-106	77
5j	$C_{19}H_{18}N_4O_4$	62.38 / 62.29	4.85 / 4.95	15.27 / 15.29	—	106-108	85
6	$C_{10}H_{14}N_4O_2$	54.15 / 54.04	6.21 / 6.35	25.34 / 25.21	—	Oil	52
7a	$C_{17}H_{18}N_4O_3$	62.64 / 62.57	5.68 / 5.56	17.09 / 17.17	—	119-121	77
7b	$C_{18}H_{20}N_4O_3$	63.40 / 63.52	5.84 / 5.92	16.39 / 16.46	—	147-149	68
8a	$C_{15}H_{16}N_6O_3$	54.69 / 54.87	4.83 / 4.91	25.67 / 25.60	—	Oil	43
8b	$C_{20}H_{18}N_6O_3$	61.44 / 61.53	4.66 / 4.65	21.59 / 21.53	—	200-203 (decomp.)	38
11	$C_{11}H_{16}N_4O_2$	55.83 / 55.92	6.69 / 6.83	23.88 / 23.71	—	231-233	65
12a	$C_{18}H_{20}N_4O_3$	63.59 / 63.52	5.96 / 5.92	16.31 / 16.46	—	161-163	32
12b	$C_{19}H_{22}N_4O_3$	64.45 / 64.39	6.46 / 6.26	15.95 / 15.81	—	187-189	30

*Solvent: EtOH (compounds **2a**,**b**), PhMe (compounds **3a**,**b**, **4a**,**b**), EtOH–H_2O, 1:1 (compounds **5a**-**g**,**i**,**j**, **11**), 2-PrOH (compounds **7a**,**b**, **8b**, **12a**,**b**).

Compound **11** undergoes acylation by carboxylic acid chlorides with the formation of the amides **12a**, **b** just as readily as compound **6**, indicating the presence of an amino function in the starting compound **11**.

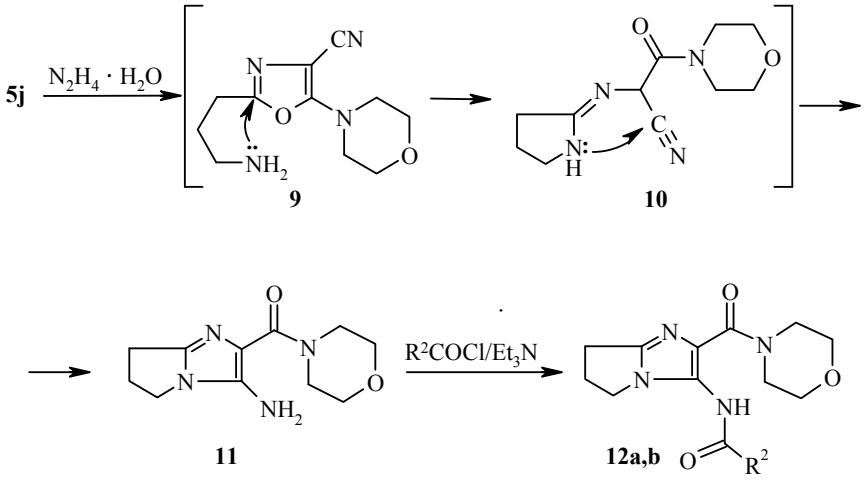
TABLE 2. ^{1}H NMR Spectra of Compounds Synthesized

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2a	2.66 (2H, t, *J* = 6.5, CH_2); 3.74-3.88 (2H, m, NCH_2); 5.73 (1H, dd, *J* = 5.9, *J* = 8.9, CH); 7.69 (1H, d, *J* = 5.9, OH); 7.77-7.91 (4H, m, H Ar); 8.89 (1H, d, *J* = 8.9, NH)
2b	1.83-1.88 (2H, m, CH_2); 2.28 (2H, t, *J* = 7.8, CH_2); 3.61 (2H, t, *J* = 7.0, NCH_2); 5.73 (1H, dd, *J* = 5.5, *J* = 9.0, CH); 7.65 (1H, d, *J* = 5.5, OH); 7.79-7.93 (4H, m, H Ar); 8.69 (1H, d, *J* = 9.0, NH)
3a	2.74-2.92 (2H, m, CH_2); 3.93-4.21 (2H, m, NCH_2); 6.54 (1H, d, *J* = 9.5, CH); 6.83 (1H, d, *J* = 9.5, NH); 7.68-7.80 (2H, m, H Ar); 7.80-7.95 (2H, m, H Ar)
3b	1.98-2.16 (2H, m, CH_2); 2.38 (2H, t, *J* = 6.5, CH_2); 3.88-3.72 (2H, m, NCH_2); 6.59 (1H, d, *J* = 10.0, CH); 7.54 (1H, d, *J* = 10.0, NH); 7.71-7.79 (2H, m, H Ar); 7.82-7.92 (2H, m, H Ar)
4a	2,74-2.91 (2H, m, CH_2); 3,94-4.17 (2H, m, NCH_2); 7.73-7.80 (2H, m, H Ar); 7.80-7.86 (2H, m, H Ar)
4b	2.03-2.16 (2H, m, CH_2); 2.41 (2H, t, *J* = 6.0, CH_2); 3.83 (2H, t, *J* = 5.5, NCH_2); 7.73-7.82 (2H, m, H Ar); 7.82-7.95 (4H, m, H Ar); 8.14 (1H, br. s, NH)
5a	2.93 (2H, t, *J* = 5.8, CH_2); 3.86 (2H, t, *J* = 5.8, NCH_2); 4.38 (2H, d, *J* = 5.5, CH_2); 7.22-7.41 (5H, m, H Ar); 7.79-7.94 (4H, m, H Ar); 8.68 (1H, br. t, *J* = 5.0, NH)
5b	2.81 (2H, t, *J* = 6.4, CH_2); 2.91 (2H, t, *J* = 5.7, CH_2); 3.35-3.43 (2H, m, CH_2); 3.86 (2H, t, *J* = 5.7, NCH_2); 7.13-7.36 (5H, m, H Ar); 7.76-7.94 (4H, m, H Ar); 8.24 (1H, br. t, *J* = 5.5, NH)
5c	1.38-1.67 (6H, m, 3CH_2 piperidine); 2.95 (2H, t, *J* = 6.0, CH_2); 3.25-3.41 (4H, m, 2CH_2 piperidine); 3.87 (2H, t, *J* = 6.0, NCH_2); 7.72-7.97 (4H, m, H Ar)
5d	2.25 (3H, c, CH_3); 2.39-2.48 (4H, m, 2CH_2); 2.97 (2H, t, *J* = 6.5, CH_2); 3.31-3.42 (4H, m, 2CH_2); 3.88 (2H, t, *J* = 6.5, NCH_2); 7.72-7.96 (4H, m, H Ar)
5e	2.98 (2H, t, *J* = 6.0, CH_2); 3.30-3.39 (4H, m, 2CH_2 morpholine); 3.61-3.70 (4H, m, 2CH_2 morpholine); 3.89 (2H, t, *J* = 6.0, NCH_2); 7.78-7.96 (4H, m, H Ar)
5f	1.87-2.04 (2H, m, CH_2); 2.64 (2H, t, *J* = 7.0, CH_2); 3.66 (2H, t, *J* = 6.3, NCH_2); 4.40 (2H, d, *J* = 5.5, CH_2); 7.19-7.43 (5H, m, H Ar); 7.73-7.92 (4H, m, H Ar); 8.61 (1H, br. t, *J* = 5.0, NH)
5g	1.91-2.02 (2H, m, CH_2); 2.62 (2H, t, *J* = 7.3, CH_2); 2.82 (2H, t, *J* = 7.3, CH_2); 3.40 (2H, t, *J* = 6.0, CH_2); 3.66 (2H, t, *J* = 6.5, NCH_2); 7.15-7.34 (5H, m, H Ar); 7.76-7.89 (4H, m, H Ar); 8.15 (1H, t, *J* = 5.5, NH)
5h	1.49-1.65 (6H, m, 3CH_2 piperidine); 1.94-2.06 (2H, m, CH_2); 2.66 (2H, t, *J* = 6.8, CH_2); 3.31-3.40 (4H, m, 2CH_2 piperidine); 3.67 (2H, t, *J* = 6.3, NCH_2); 7.77-7.88 (4H, m, H Ar)
5i	1.93-2.06 (2H, m, CH_2); 2.25 (3H, c, CH_3); 2.38-2.49 (4H, m, 2CH_2); 2.67 (2H, t, *J* = 7.0, CH_2); 3.31-3.44 (4H, m, 2CH_2); 3.67 (2H, t, *J* = 6.3, NCH_2); 7.77-7.90 (4H, m, H Ar)
5j	1.95-2.08 (2H, m, CH_2); 2.70 (2H, t, *J* = 7.0, CH_2); 3.35-3.44 (4H, m, 2CH_2 morpholine); 3.63-3.77 (6H, m, NCH_2, 2CH_2 morpholine); 7.77-7.92 (4H, m, H Ar)
6	2.65 (2H, t, *J* = 7.0, CH_2); 2.83 (2H, t, *J* = 7.0, NCH_2); 3.35-3.55 (4H, m, 2CH_2 morpholine); 3.64-3.86 (4H, m, 2CH_2 morpholine)
7a	2.89 (2H, t, *J* = 6.2, CH_2); 3.39 (4H, m, 2CH_2 morpholine); 3.57 (2H, m, NCH_2); 3.68 (4H, m, 2CH_2 morpholine); 7.40-7.63 (3H, m, H Ar); 7.75-7.92 (2H, m, H Ar); 8.63 (1H, t, *J* = 5.5, NH)
7b	2.35 (3H, c, CH_3); 2.88 (2H, t, *J* = 5.8, CH_2); 3.38-3.45 (4H, m, 2CH_2 morpholine); 3.51-3.59 (2H, m, NCH_2); 3.63-3.73 (4H, m, 2CH_2 morpholine); 7.27 (2H, d, *J* = 7.0, H Ar); 7.73 (2H, d, *J* = 7.0, H Ar); 8.56 (1H, t, *J* = 5.0, NH)
8a	2.25 (3H, s, CH_3); 2.91 (2H, t, *J* = 6.0, CH_2); 3.39-3.48 (4H, m, 2CH_2 morpholine); 3.52-3.60 (2H, m, NCH_2); 3.67-3.76 (4H, m, 2CH_2 morpholine); 8.18 (1H, br. t, *J* = 5.0, NH)

TABLE 2 (continued)

1	2
8b	2.97 (2H, t, *J* = 4.0, CH_2); 3.29-3.43 (4H, m, $2CH_2$ morpholine); 3.60-3.75 (6H, m, NCH_2, $2CH_2$ morpholine); 7.42-7.59 (3H, m, H Ar); 7.71-7.85 (2H, m, H Ar); 8.60 (1H, br. s, NH)
11	2.39-2.48 (2H, m, CH_2); 2.61 (2H, t, *J* = 7.0, CH_2); 3.50-3.64 (4H, m, $2CH_2$ morpholine); 3.74 (2H, t, *J* = 7.0, NCH_2); 3.78-4.12 (4H, m, $2CH_2$ morpholine); 6.60 (2H, br. s, NH_2)
12a	2.50 (2H, m, CH_2); 2.80 (2H, t, *J* = 6.0, CH_2); 3.55-3.69 (8H, m, $4CH_2$ morpholine); 4.09 (2H, t, *J* = 5.0, NCH_2); 7.49-7.72 (3H, m, H Ar); 7.91-8.03 (2H, m, H Ar); 10.84 (1H, s, NH)
12b	2.30-2.44 (5H, m, CH_3, CH_2); 2.77 (2H, t, *J* = 6.0, CH_2); 3.48-3.71 (8H, m, $4CH_2$ morpholine); 4.06 (2H, t, *J* = 5.0, NCH_2); 7.35 (2H, d, *J* = 6.0, H Ar); 7.85 (2H, d, *J* = 6.0, H Ar); 10.77 (1H, s, NH)

Such an unexpected result of the transformation of compound **5j** with the formation of the recyclization product **11** required substantial spectral and chemical evidence. The NMR spectra of compounds **6** and **11** differ significantly. Thus, in the ^{1}H NMR spectra of the amines **6** and **11,** the signals of the NCH_2 methylene protons in the latter are shifted appreciably downfield relative to compound **6** (Table 2). The ^{13}C NMR spectrum of the amine **6** contains signals at 85.0 (oxazole C-4) and 116.5 ppm (CN), while the spectrum of compound **11** contains only one signal in the region of 70-120 ppm at 115.6 ppm (C–NH_2), which could be assigned erroneously to the nitrile. However, this does not agree with the data from the IR spectrum of compound **11**, in which there is no signal for the nitrile group in the region of 2100-2300 cm^{-1} (Table 3).



12a R^2 = Ph, **b** R^2 = 4-MeC_6H_4

Significant evidence for the structure of the obtained compounds is obtained by comparison of the spectral characteristics of the amides **7** and **12**. Thus, the signal for the proton of the amide group of compounds **7a**,**b** in the ^{1}H NMR spectra is a triplet, while that of compounds **12a**,**b** is a singlet (Table 2). The chemical shifts and the multiplicity of the amide protons indicate the presence of the C(O)NHCH_2 fragment in compounds **7a**,**b** and of the C(O)NHC fragment in compounds **12a**,**b**, where C is an sp^2-hybridized carbon atom. In the ^{13}C NMR spectra of compound **7a** there is a signal for the carbon of a nitrile group at 116.5 ppm, but it is not observed in the spectrum of compound **12a**.

TABLE 3. IR and Mass Spectra of Compounds **2-8**, **11**, and **12**

Compound	IR spectrum, ν, cm $^{-1}$			*m/z* $[M+H]^+$
	C=O	CN	NH	
2a	1640, 1709 sh	—	3056–3515	365
2b	1666, 1713 sh	—	3111–3529	379
3a	1652, 1715 sh	—	3106–3358	383
3b	1667, 1717 sh	—	3214–3378	397
4a	1670, 1704 sh	2232	3176–3335	338
4b	1669, 1699 sh	2234	3089–3347	352
5a	1657*, 1716 sh	2213	3091–3316	373
5b	1645*, 1710 sh	2209	3027–3305	387
5c	1642*, 1721 sh	2231	—	351
5d	1632*, 1716 sh	2210	—	366
5e	1636*, 1713 sh	2206	—	353
5f	1652*, 1718 sh	2218	3066–3466	387
5g	1652*, 1708 sh	2212	3057–3472	401
5h	1645*, 1711 sh	2214	—	365
5i	1636*, 1703 sh	2215	—	380
5j	1624*, 1715 sh	2217	—	367
6	1636*	2213	3072	223
7a	1631 sh*^{2}	2209	3061–3385	327
7b	1633 sh*^{2}	2214	3129–3456	341
8a	1638 sh*	2216 sh	3087–3324	329
8b	1656 sh*	2218 sh	3114–3298	391
11	1622	—	3327, 3429	237
12a	1625, 1676	—	3025–3215	341
12b	1623, 1673	—	3027–3345	355

* The band corresponds to the 5-amino-1,3-oxazole fragment [8].

*^{2} Superimposition of the absorption bands of the 5-amino-1,3-oxazole fragment and the amide C=O group.

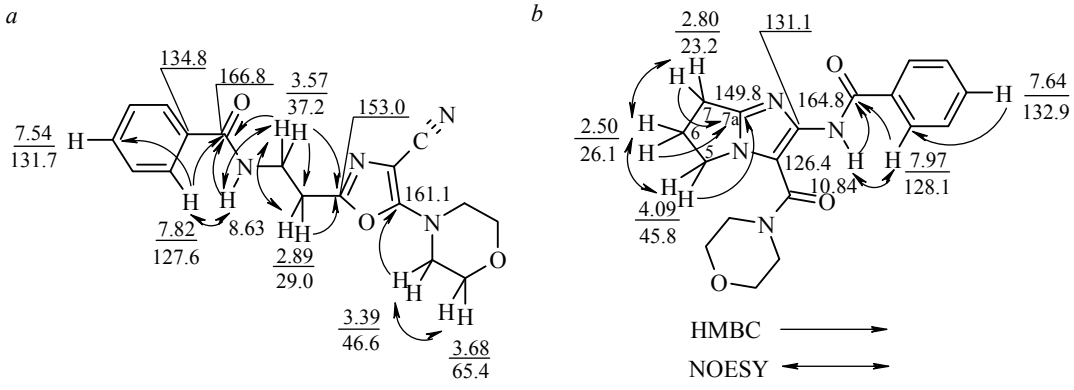


Fig. 1. The main correlations and assignment of the signals in the ^{1}H and ^{13}C spectra of compounds **7a** (*a*) and **12a** (*b*).

TABLE 4. Correlations in the COSY, NOESY, HSQC, and HMBC Spectra of Compounds **7a** and **12a**

^{1}H, δ, ppm	^{1}H, δ, ppm		^{13}C, δ, ppm	
	COSY	NOESY	HSQC	HMBC
Compound **7a**				
7.54	7.47	7.47	131.7	127.6
7.47	7.54, 7.82	7.54, 7.82	128.8	128.8, 134.8
7.82	7.47	7.47, 8.63	127.6	127.6, 131.7, 166.8
8.63	3.57	3.57, 7.82	—	166.8
3.57	2.89, 8.63	2.89, 8.63	37.2	166.8, 28.0, 153.0
2.89	3.57	3.57	28.0	37.2, 153.0
3.39	3.68	3.68	46.6	46.6, 65.4, 161.1
3.68	3.39	3.39	65.4	46.6, 65.4
Compound **12a**				
7.64	7.57	7.57	132.9	128.1
7.57	7.64, 7.97	7.64, 7.97	129.9	129.9, 133.5
7.97	7.57	7.57, 10.84	128.1	128.1, 132.9, 164.8
10.84	—	7.97	—	164.8
3.61	—	—	66.9	66.9
2.80	2.50	2.50	23.2	26.1, 149.8
2.50	2.80, 4.09	2.80, 4.09	26.1	23.2, 149.8
4.09	2.50	2.50	45.8	149.8

Complex NMR analysis (NOESY, COSY, HSQC, HMBC) was also used for compounds **7a** and **12a** (Fig. 1, Table 4). The formation of a pyrrolidine ring through the aminopropyl fragment in compound **12a** is indicated by HMBC correlations of 7-C$\underline{H}_2$ with C-7a, 6-C$\underline{H}_2$ with C-7a, and 5-C$\underline{H}_2$ with C-7a. It should be mentioned that it was not possible to find correlations for C-2 and C-3 in the HMBC spectra, and they were therefore assigned according to the residual principle. The discovery of the aminoethyl fragment in the side chain of the heterocycle **7a** is confirmed by NOESY correlations of CON$\underline{H}$ with NC$\underline{H}_2$, and NC$\underline{H}_2$ with C$\underline{H}_2$C and by HMBC correlation of NCH$_2$ with C=O, NC$\underline{H}_2$ with C-2, and NC$\underline{H}_2$ with C$\underline{H}_2$C.

EXPERIMENTAL

The IR spectra were recorded in KBr pellets (compounds **2a**,**b**-**4a**,**b**, **5a-g**,**i**,**j**, **7a**,**b**, **8b**, **11**, **12a**,**b**) and $CHCl_3$ (compounds **5h**, **6**, **8a**) on a Vertex 70 spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 solution (compounds **2a**,**b**, **5a-j**, **6**, **7a**,**b**, **8a**,**b**, **11**, **12a**,**b**) and $CDCl_3$ solution (compounds **3a**,**b**, **4a**,**b**) on a Bruker Avance DRX-500 instrument (500 and 125 MHz respectively) with TMS as internal standard. The COSY, NOESY, HSQC, and HMBC spectra were measured by the standard procedure with gradient isolation of the signal. For the NOESY spectra τ_{mix} = 500 ms, while for the HMBC spectra τ_{mix} = 125 ms. The measurement temperature was 20°C. The chromato-mass spectra were recorded on a Agilent 1100 Series high-performance liquid chromatograph with a diode matrix and an Agilent LC/MSD SL mass-selective detector. Parameters of chromato-mass analysis: Zorbax SB-C18 1.8 μ, 4.6×15 mm column; solvents A – acetonitrile–water, 95:5, 0.1% trifluoroacetic acid, B – 0.1% aqueous trifluoroacetic acid; eluent flow rate – 3 ml/min; injection volume – 1 μl; UV detectors – 215, 254, 285 nm; ionization method – chemical ionization at atmospheric pressure (APCI). The melting points were measured on a Fisher–Johns apparatus.

The amides **1a**,**b** were synthesized by the known method [7].

2,2,2-Trichloro-1-(3-phthalimidoalkanoylamino)ethanols 2a,b (General Method). A mixture of the amide **1a** or **1b** (0.5 mol) and chloral hydrate (182 g, 1.1 mol) was heated on an oil bath (95-100°C) for 5 h. The reaction mixture was cooled, washed thoroughly with water, and purified by recrystallization.

1,2,2,2-Tetrachloro-1-(3-phthalimidoalkanoylamino)ethanes 3a,b (General Method). Thionyl chloride (0.8 ml, 11 mmol) was added with stirring to a suspension of compound **2a** or **2b** (5 mmol) in dry toluene (50 ml). The mixture was boiled with stirring for 2 h. The solvent was removed under reduced pressure, and the residue was purified by recrystallization.

3,3-Dichloro-2-(3-phthalimidoalkanoylamino)acrylonitriles 4a,b. Compound **3a** or **3b** (5 mmol) was added with stirring in portions to a suspension of KCN (0.715 g, 11 mmol) in acetone (15 ml) cooled to -15°C. Water (3 ml) was then added dropwise to the reaction mixture. The suspension was stirred at -5°C for 1 h, after which the temperature of the mixture was brought to room temperature. A portion of water (50 ml) was added to the reaction mixture, and the precipitate was filtered off, washed with water, and purified by recrystallization.

5-Alkylamino-2-(2-phthalimidoethyl)-1,3-oxazole-4-carbonitriles 5a-e (General Method). Triethylamine (1.5 ml, 11 mmol) and then corresponding amine (5 mmol) were added to a suspension of compound **4a** (1.685 g, 5 mmol) in acetonitrile (20 ml) with stirring and cooling to 0°C. The mixture was stirred for 12 h, the acetonitrile was removed at reduced pressure, and the residue was dissolved in 15 ml of CH_2Cl_2. The extract was washed with water (4×5 ml), dried with Na_2SO_4, evaporated, and the residue was purified by recrystallization.

5-Alkylamino-2-(3-phthalimidopropyl)-1,3-oxazole-4-carbonitriles 5f-j (General Method). The compounds were obtained similarly to the oxazoles **5a-e** from compound **4b**. Compound **5h** was obtained in the form of an oil, which was analyzed without further purification.

2-(2-Aminoethyl)-5-(morpholin-4-yl)-1,3-oxazole-4-carbonitrile (6). Hydrazine hydrate (0.25 ml, 5.2 mmol) was added to a suspension of compound **5e** (1.76 g, 5 mmol) in ethanol (15 ml). The mixture was boiled for 6 h and cooled, and then ethanol was removed at reduced pressure. The residue was suspended in a 4% aqueous solution of HCl and filtered off, and a 25% aqueous solution of NaOH was added to the mother solution to pH ~ 10. The solution was extracted with CH_2CH_2 (5×5 ml) and dried with Na_2SO_4, and the solvent was removed at reduced pressure. A yellow oil was obtained and was used for further transformations without additional purification. ^{13}C NMR spectrum, δ, ppm: 31.0 ($N\underline{C}H_2CH_2$); 39.0 ($NCH_2\underline{C}H_2$); 46.5 (NCH_2 morpholine); 65.5 (OCH_2 morpholine); 85.0 (C-4 oxazole); 116.5 (CN); 153.6 (C-2 oxazole); 161.0 (C-5 oxazole).

N-{2-[4-Cyano-5-(morpholin-4-yl)-1,3-oxazol-2-yl]ethyl}benzamides 7a,b. Triethylamine (0.515 g, 5.1 mmol) and then corresponding acid chloride (5.1 mmol) were added with stirring and cooling to a solution of compound **6** (1.11 g, 5 mmol) in 10 ml of CH_2Cl_2. The mixture was stirred for 6 h, the solvent was removed at reduced pressure, and the residue was washed with water and purified by recrystallization. ^{13}C NMR spectrum, δ, ppm: 28.0; 37.2; 46.6; 65.4; 85.2 (C-4 oxazole); 116.5 (CN); 127.6; 128.8; 131.7; 134.8; 153.0; 161.1; 166.8 (C=O).

2-{2-[(4-Cyano-2-methyl-1,3-oxazol-5-yl)amino]ethyl}-5-(morpholin-4-yl)-1,3-oxazole-4-carbonitrile (8a). Triethylamine (1.5 ml, 11 mmol) and then a solution of compound **6** (1.11 g, 5 mmol) in acetonitrile (10 ml) were added with stirring and cooling (10-15°C) drop by drop to a solution of 2-acetylamino-3,3-dichloroacrylonitrile [8] (0.895 g, 5 mmol) in acetonitrile (10 ml). The mixture was stirred for 12 h, and the solvent was removed under reduced pressure. The residue was dissolved in 10 ml of CH_2Cl_2 and washed with a 5% aqueous citric acid solution (10 ml). A yellow oil was obtained and was analyzed without further purification.

5-({2-[4-Cyano-5-(morpholin-4-yl)-1,3-oxazol-2-yl]ethyl}amino)-2-phenyl-1,3-oxazole-4-carbonitrile (8b) was obtained similarly to compound **8a** from 2-benzoylamino-3,3-dichloroacrylonitrile [12] in the form of a solid substance, which was purified by recrystallization.

2-(Morpholin-4-ylcarbonyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole-3-amine (11) was obtained similarly to compound **6** from the oxazole **5j**. ^{13}C NMR spectrum, δ, ppm: 22.7 ($NCH_2\underline{C}H_2CH_2$); 26.3 ($NCH_2CH_2\underline{C}H_2$); 42.3 ($NCH_2$ morpholine); 67.1 (OCH_2 morpholine); 115.6 (C–NH_2); 144.8; 144.9; 164.4 (C=0).

***N*-[2-(Morpholin-4-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazol-3-yl]benzamides 12a,b** were obtained similarly to the amides **7a,b** from compound **11**. ^{13}C NMR spectrum, δ, ppm: 23.2; 26.1; 45.8; 66.9; 126.4; 128.1; 129.9; 131.1 (C–NHCO); 132.9; 133.5; 149.8; 163.4 (C=0); 164.8 (C=0).

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