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SYNTHESIZE 1,3,5-SUBSTITUTED ISOXAZOLES AT EXCESSIVE BENZOYLATION OF β-AMINOPROPIOAMIDOXIMES IN PYRIDINE

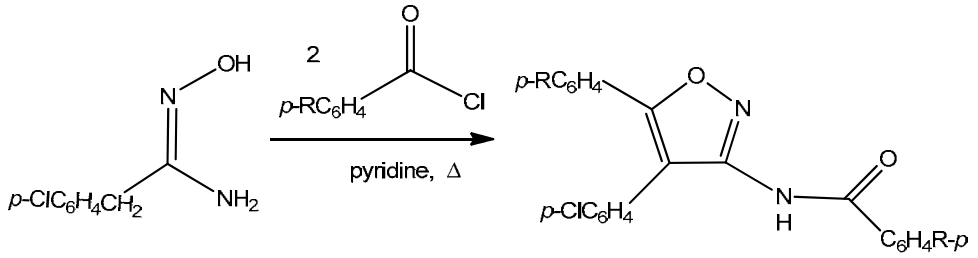
Abstract. Excessive acylation of β-aminopropioamidoximes (β-amino group: piperidin-1-yl, morpholin-1-yl, benzimidazol-1-yl, 4-phenylpiperazin-1-yl, thiomorpholin-1-yl) was carried out with a doubling excess of benzoyl chloride in pyridine at the boiling point of the solvent for 4–8 h. The isolated products are: N,O-dibenzoyl-β-aminopropioamidoxime dihydrochlorides in the case of еркуу ашкые amidoximes, respectively. Chloride hydrate of 2-amino-1-aza-7-phenylaminospiro(4.5)decane-2-ene-10-ammonium and benzoic acid were the isolated products at using as starting amidoxime β-(4-phenylpiperazin-1-yl)propioamidoxime and hydrochloride of O-benzoyl-β-(thiomorpholin-1-yl)propioamidoxime at using of β-(thiomorpholin-1-yl)propioamidoxime as substrate. The formation of 2-amino-1-aza-7-phenylaminospiro(4.5)decane-2-ene-10-ammonium chloride monohydrate can be represented as the initial formation of O-benzoyl-β-aminopropioamidoxime hydrochloride, its dehydration to 1,2,4-oxadiazole, and the subsequent passing of the Boulton-Katritazky rearrangement to form a spiropyrazolinium compound and benzoic acid.

Key words: β-Aminopropioamidoximes, excessive acylation in pyridine, the Boulton-Katritzky rearrangement, benzoyl chloride, IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy.

Introduction. Previously, in the series of products of monoacylation of β-aminopropioamidoximes where among the bases and hydrochlorides of O-aroyl-β-aminopropioamidoximes, and in the array of products of their dehydration – 5-substituted phenyl-3-(β-aminoethyl)-1,2,4-oxadiazoles the compounds possessing with high biological activity were found.

The list of practically useful of β-aminopropioamidoxime derivatives includes such as properties antiarrhythmic, local anesthetic and antitubercular [1, 2]. To modify β-aminopropioamidoximes in potentially biologically active derivatives containing a 3,4,5-substituted isoxazole heterocycle, the conditions for their interaction with a double excess of acylating agents were searched. It is known that the reaction of amidoxime 4-chlorophenylacetic acid with aromatic acid chlorides with a double molar excess of acid chlorides in pyridine leads to the formation of N-[4-(4-chlorophenyl) -5-phenylisoxazol-3-yl]benzamide (scheme 1) [3].

Structural analogs of isoxazole exhibit various types of biological activity and are used for a long time in pharmaceutics. Sulfamethoxazole is widely known as part of the synergistic sulfonamide bacteriostatic antibiotic biseptol; cyclose-



Scheme 1

rine as an antibiotic agent with anti-tuberculosis, antibacterial activity, and also used in the treatment of leprosy. Biseptol and cycloserine are included in the WHO Model List of Essential Medicines [4]. The antibiotic Co-trimaxazole (sulfamethoxazole and trimethoprim), sulfisoxazole (or sulfafurazole) is used as an agent against a wide range of gram-positive and gram-negative microorganisms [5]. Oxacillin is an antimicrobial drug [6].

EXPERIMENTAL PART

IR spectra were recorded on a NICOLET 5700 FT-IR device in KBr tablets. NMR spectra (^{1}H and ^{13}C) are recorded on a NMR Avance III 500 MHz Bruker (Germany) device with an internal HMDS standard as solutions of compounds **6**–**11** in DMSO-d_6. Chemical shifts are determined with respect to solvent signals (2,51 ppm for ^{1}H nuclei and 40,0 ppm for ^{13}C nuclei). The melting points was determined in glass capillaries on a TPL device. The purity of the products and the course of the reaction were monitored by TLC on Sorbfil plates (ZAO Sorbopolymer) with a sorbent-loaded silica gel layer CTX-1A with 5–17 μm grain and UV-254 UV indicator. The solvents used in the synthesis and recrystallization of the compounds and for elution in the TLC method (ethanol, i-PrOH, benzene) were prepared by standard procedures [11]. The solvent ratio ethanol : benzene in the eluent for TLC amounted to 3 : 1.

The two-step synthesis of the starting β-aminopropioamidoximes [β-amino group: piperidin-1-yl (**1**) and morpholin-1-yl (**2**)], we proposed to carry out in one reactor according to the "one-pot" method [12, 13]. β-Aminopropioamidoximes **3**–**5** [β-amino group: benzimidazol-1-yl (**3**); 4-phenylpiperazin-1-yl (**4**); thiomorpholin-1-yl (**5**)] were obtained by a two-step synthesis with isolation of β-aminopropionitriles and subsequent reaction of nitriles with hydroxylamine in absolute ethanol [14, 15].

*N,O-Dibenzoyl-β-(piperidin-1-yl)propioamidoxime dihydrochloride (**6**).* To 1000 mg (53 mmol) of β-(piperidin-1-yl)propioamidoxime (**1**) in 45 ml of pyridine 1,39 ml (106,0 mmol) of benzoyl chloride was added dropwise; then the reaction mixture was kept at room temperature for 2 h with stirring. After that the reaction mixture with TLC control was stirred at 115 °C for 4 h. The solvent was distilled off in a vacuum of a water jet pump; the residue was recrystallized from

i-PrOH. The yield of colorless crystals of N,O-dibenzoyl-β-(piperidin-1-yl)-propioamidoxime dihydrochloride (**6**) amounted to 1300 mg (89%); m.p. 155 °C (i-PrOH); R_f 0,24. Found: C 58,62; H 5,46; Cl 15,30; N 9,07. $C_{22}H_{27}Cl_2N_3O_3$. Calculated: C 58,41; H 6,02; Cl 15,67; N 9,29.

*N,O-Dibenzoyl-β-(morpholin-1-yl)propioamidoxime dihydrochloride (**7**).* To 300 mg (17 mmol) of β-(morpholin-1-yl)propioamidoxime (**2**) in 15 ml of pyridine, 0,4 ml (34 mmol) of benzoyl chloride was added dropwise; then the reaction mixture was kept at room temperature for 2 h with stirring. After that the reaction mixture was stirred at 115 °C for 6 h with TLC control. The solvent was distilled off under an oil pump vacuum; the residue was recrystallized from i-PrOH. The yield of a fine white powder of N,O-dibenzoyl-β-(morpholin-1-yl)propioamidoxime dihydrochloride (**7**) was 190 mg (7,5 mmol) (43%); m.p. 110 °C (i-PrOH); R_f 0,40. Found: C 55,78; H 5,20; Cl 15,24; N 9,03. $C_{21}H_{25}C_{l2}N_3O_4$. Calculated: C 55,51; H 5,55; Cl 15,61; N 9,25.

*N,O-Dibenzoyl-β-(benzimidazol-1-yl)propioamidoxime dihydrochloride (**8**).* To a suspension of 1000 mg (49 mmol) of β-(benzimidazol-1-yl)propioamidoxime (**3**) in 45 ml of pyridine at room temperature 1,39 ml (98 mmol) of benzoyl chloride was added dropwise; then the reaction mixture was kept at room temperature for 2 h with stirring. After that the reaction mixture was heated at 115 °C for 6 h. The end of the reaction is fixed by the presence on the plate for TLC of a single spot of product **8** with R_f 0,69. Pyridine was evaporated in a vacuum of a water jet pump; The precipitate was recrystallized from EtOH. Yield of colorless crystals of N,O-dibenzoyl-β-(benzimidazol-1-yl)propioamidoxime dihydrochloride (**8**) was 370 mg (27%); m.p. 180 °C (EtOH); R_f 0,69. Found: C 59,14; H 4,96; Cl 14,55; N 11,50. $C_{24}H_{22}Cl_2N_4O_3$. Calculated: C 59,39; H 4,57; Cl 14,61; N 11,54.

*Chloride of 2-amino-1-aza-7-phenylaminospiro(4.5)decane-2-ene-10-ammonium (**9**) and benzoic acid (**10**).* To 1000 mg (40 mmol) of β-(4-phenylpiperazin-1-yl)propioamidoxime (**4**) in 45 ml of pyridine 0,93 ml (80 mmol) of benzoyl chloride was added dropwise; then the reaction mixture was kept at room temperature for 2 h with stirring. After that the reaction mixture with TLC control was stirred at 115 °C for 4 h. The solvent was distilled off in a vacuum of a water jet pump; the residue was sublimed in a vacuum of oil pump at 50 °C and 2 mm Hg. At first 420 mg (43%) of a white precipitate of benzoic acid (**10**) with R_f 0,76 was collected on a cooled part of the sublimation apparatus; m.p. 121 °C (EtOH) [colorless needles, m.p. 122 °C (EtOH)] [16]. Found: C 68,95; H 5,22. $C_7H_6O_2$. Calculated: C 68,85; H 4,95. Then the residue in the distillation flask was recrystallized. Yield of light yellow powder of chloride of 2-amino-1-aza-7-phenylaminospiro(4.5)decane-2-ene-10-ammonium (**9**) was 440 mg (39%); m.p. 270 °C (i-PrOH); R_f 0,08. Found: C 54,94; H 7,82; Cl 11,97; N 19,48. $C_{13}H_{21}ClN_4O$. Calculated: C 54,83; H 7,43; Cl 12,45; N 19,67.

*O-Benzoyl-β-(thioporpholin-1-yl)propioamidoxime hydrochloride (**11**).* To 1000 mg (26 mmol) of β-(thiomorpholin-1-yl)propioamidoxime (**5**) in 10 ml of pyridine, with stirring 0,61 ml (52 mmol) of benzoyl chloride was added; then the reaction mixture was kept at room temperature for 2 h with stirring. After that the

reaction mixture was stirred at 115 °C for 8 h and monitored by TLC. The solvent was distilled off in a vacuum of a water jet pump; the precipitate was recrystallized from i-PrOH. Yield of O-benzoyl-β-(thioforolin-1-yl)propioamidoxime hydrochloride (**11**) was 510 mg (52%), m.p. 119 °C (i-PrOH); R_f 0,80. [m.p. 120 °C (i-PrOH); R_f 0,79] [15]. Found: C 50,72; H 6,26; Cl 11,02; N 13,06. $C_{14}H_{20}ClN_3O_2S$. Calculated: C 50,98; H 6,11; Cl 10,75; N 12,74.

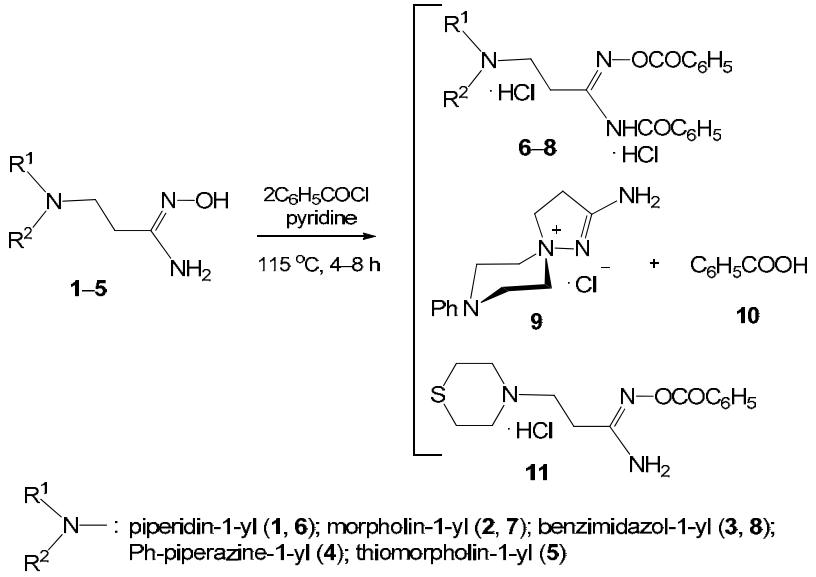
RESULTS AND DISCUSSION

We have not previously studied the acylation of β-aminopropioamidoximes under rigid conditions – with an excess of the acylating agent, in a polar solvent, at the boiling point of the solvent. The preparation of isoxazoles based on β-aminopropioamidoximes by the method [3] would allow us to investigate the little-known question of the excessive acylation of a multifunctional amidoxime group and, in the case of isolating new isoxazole derivatives, to study their biological activity.

When analyzing reaction products based on physicochemical and spectral data (elemental analysis, m.p., R_f, IR spectra and ^{1}H and ^{13}C NMR spectra) (table 1–3), it was found that in the case of amidoximes **1**–**3** products **6**–**8** were isolated in the form dihydrochloride of double acylation products on oxygen and nitrogen atoms of the amidoxime group. In the acylation of β-(4-phenylpiperazin-1-yl)propioamidoxime (**4**), a spiropyrazolinium compound **9** and benzoic acid (**10**) were obtained; O-benzoyl-(β-thiomorpholin-1-yl)propioamidoxime hydrochloride (**11**) was a single product in the reaction of amidoxime **5** (table 1, scheme 2):

Table 1 – Physico-chemical characteristics of the reaction products of β-aminopropioamidoximes with two equivalents of benzoyl chloride **6**–**11**

Compound	Gross formula	Found, % / Calculated, %				Reaction time, h	Mp, °C	R_f	Output, %
		C	H	Cl	N				
6	$C_{22}H_{27}Cl_2N_3O_3$	58,62 / 58,41	5,46 / 6,02	15,30 / 15,67	9,07 / 9,29	4	155	0,24	89
7	$C_{21}H_{25}Cl_2N_3O_4$	55,78 / 55,51	5,20 / 5,55	15,24 / 15,61	9,03 / 9,25	6	110	0,40	43
8	$C_{24}H_{22}Cl_2N_4O_3$	59,14 / 59,39	4,96 / 4,57	14,55 / 14,61	11,50 / 11,54	6	180	0,69	44
9	$C_{13}H_{19}ClN_4$	58,59 / 58,53	7,68 / 7,18	13,49 / 13,29	21,35 / 21,00	4	270 (decomp.)	0,08	39
10	$C_7H_6O_2$	68,76 / 68,85	5,26 / 4,95	–	–	4	121	0,76	43
11	$C_{14}H_{20}ClN_3O_2S$	50,72 / 50,98	6,26 / 6,11	11,02 / 10,75	13,06 / 12,74	8	120	0,80	52



Scheme 2

The products of N,O-dibenzoylation of β-aminopropioamidoximes (**6**–**8**) have not been synthesized before. Obviously, the probable subsequent intramolecular splitting off of the water molecule involving protons of the α-methylene group and the carbonyl oxygen atom of the ester group could lead to isoxazoles.

IR spectral characteristics of compounds **6**–**8**: the band of valence bond vibration $\nu_{C=O}$ is in the range of 1686–1731 cm^{-1}; the stretching vibrations of the $\nu_{C=N}$ bonds are manifested in the region of 1638–1686 cm^{-1}; the valence bond vibration bands $\nu_{C=C}$ are present in the region of 1584–1620 cm^{-1}; in the region 1264–1293 cm^{-1} there are bands of stretching vibrations of the bonds ν_{C-O}; the stretching vibrations of the $\nu_{N(+)-H}$ ammonium bonds – in the region of 2464–2835 cm^{-1} (table 2).

Table 2 – Infrared spectra of the products of acylation of β-aminopropioamidoximes (**6**–**11**) by two equivalents of benzoyl chloride in pyridine

Compound	Valence vibrations of bonds, ν, cm-1						
	$\nu_{C=N}$	$\nu_{C=O}$	$\nu_{C=C}$	ν_{Csp3-H}	ν_{Csp2-H}	ν_{C-O}	$\nu_{N(+)-H}$ (ν_{N-H})
6	1641	1727	1600	2958	3202–3375	1267	2562–2700 (3376)
7	1638	1731	1620	2930	3200–3375	1264	2464–2700 (3375)
8	1650	1730	1601	3063	3250–3416	1246	2500–2680 (3429)
9	1644	–	1600	2846	3116–3220	–	(3300; 3415)
10	–	1675	1600	–	3067; 3235; 3414	1289	3414 (ν_{O-H})
11	1640	1714	1611	2907	–	1268	2553; 2582; 2640 (3416; 3488)

In ^{1}H NMR spectra of N,O-dibenzoylation products **6**–**8**, in contrast to the literature data [1], the α-CH_2 group signal is retained, which has a triplet structure from the spin-spin interaction with the β-CH_2 group (table 3). Signals of α- and β-methylene groups are in the regions δ 2,73–3,50 ppm. and δ 3,10–4,85 ppm, respectively.

The intensity of multiplet signals of aromatic protons in the range of δ 7–8 ppm indicates the presence in the molecules of compounds **6**, **7** ten $C_{sp2}H$ protons, and in the molecule of compound **8** – fifteen $C_{sp2}H$ protons.

In addition, in the area of δ 6,85–7,50 ppm in the spectra of ^{1}H NMR compounds **6**–**8** there is a signal of ammonium protons of the $N(+)H_2CO_6H_5$ group, and in the range of δ 10,55–12,90 ppm – the signal of the ammonium N(+)H proton coordinated on the nitrogen atom of the β-amino group.

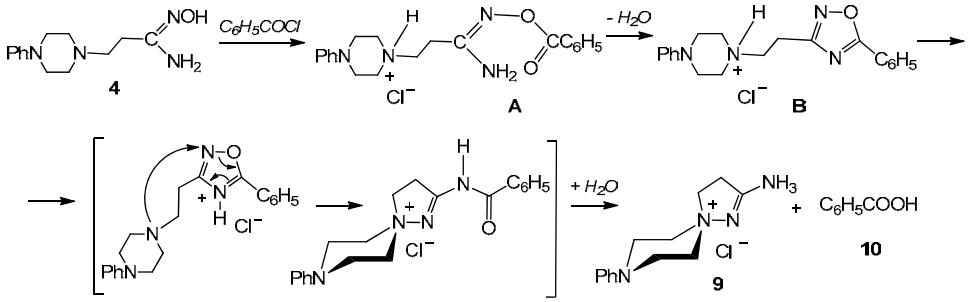
Table 3 – ^{1}H and ^{13}C NMR spectra of compounds **6**–**11**, solutions in DMSO-d_6, δ, ppm*

Compound	Chemical shifts, δ, ppm (J, Hz)	
6	1,39; 1,68; 1,79 [6H, m, –N$(CH_2)_2(\underline{CH_2})_3$]; 2,74 (2H, t, *J* = 6,0, α–CH_2); 2,90 [4H, m, –N(+)$(\underline{CH_2})_2(CH_2)_3$]; 3,30 (2H, t, *J* = 6,0; β–CH_2); 6,87 [2H, s, N(+)H_2]; 7,51; 7,65; 8,11 (10H, m, C_6H_5); 10,74 [1H, s, N(+)H]	21,82; 22,72; 22,83; 25,87; 52,44; 53,11; 129,01; 129,71; 129,83; 129,88; 133,49; 156,80; 163,88
7	2,76 (2H, t, *J* = 7,0, α–CH_2); 3,15 [4H, m, -N$(CH_2)_2(\underline{CH_2})_2(CH_2)_2$O]; 3,67 (2H, t, *J* = 7,0, β–CH_2); 3,94 [4H, m, -N(+)$(\underline{CH_2})_2(CH_2)_2$O]; 6,85 [2H, s, N(+)$H_2$]; 7,49–8,12 (10H, m, C_6H_5); 11,65 [1H, s, N(+)H]	25,55; 25,60; 31,43; 31,45; 51,46; 53,12; 62,08; 62,43; 63,24; 63,65; 129,01; 129,84; 129,88; 133,48; 156,61; 163,86; 169,02; 169,10
8	3,40 (2H, t, *J* = 7,0, α–CH_2); 4,74 (2H, t, *J* = 7,0, β–CH_2); 7,48; 7,51; 7,60; 7,65; 7,94; 7,96; 8,04; 8,06; 9,00 [17H, m, $C_{sp2–H}$ and N(+)H_2]; 12,95 [1H, s, N(+)H]	26,35; 43,00; 123,73; 124,61; 124,79; 128,25; 129,00; 129,71; 130,01; 131,27; 133,27; 133,79; 143,54; 167,75; 168,57; 175,57
9	3,19 (2H, t, *J* = 6,0, β–CH_2); 3,44 [2H, m, half-width 12,5 mm, PhN$(CH_2)_2$ (axial)]; 3,56 [4H, m, N(+)$(CH_2)_2$]; 3,78 [2H, m, half-width 11 mm, PhN$(CH_2)_2$, (equatorial)]; 3,98 (2H, t, *J* = 6,0, α–CH_2); 6,86; 7,02; 7,27 (5H, m, C_6H_5); 7,53 (2H, s, NH_2)	31,57; 44,57; 61,42; 62,91; 116,32; 120,38; 129,58; 149,94; 169,11
10	7,50; 7,63; 7,95 (5H, m, C_6H_5); 12,95 (1H, s, COOH)	129,02; 129,72; 131,24; 133,31; 167,76
11	2,76 (2H, t, *J* = 7,0, α–CH_2); 3,39 (2H, t, *J* = 7,0, β–CH_2); 3,35 (4H, m, S$(CH_2)_2$]; 3,70 [4H, m, N(+)$(CH_2)_2$]; 6,86 (2H, s, NH_2); 7,51; 7,64; 8,12 (5H, m, C_6H_5); 11,37 [1H, s, N(+)H]	24,25; 25,61; 53,43; 53,68; 129,00; 129,83; 133,48; 148,56; 156,67; 163,88

*The assignment of the multiplet signals of the protons of the methylene groups of the thiomorpholine heterocycle, having the intensity of two protons which adjacent to the N(+)$(CH_2)_2$ nitrogen atom of compound **9**, to equatorial and axial is made on the basis of a half-width comparison of the signal. The half-width of the axial signals of the protons is greater than the half-width of the equatorial signals.

In the ^{13}C NMR spectra of compounds **6–8**, the carbon signals of the C=N functional groups are found at δ 156,80 (**6**); 156,61 (**7**); 168,57 (**8**), respectively, and C=O at 163,88 (**6**), 163,86 (**7**) , 175,57 (**8**), respectively.

The formation of 2-amino-1-aza-7-phenylaminospiro(4.5)decane-2-ene-10-ammonium chloride monohydrate (**9**) can be represented as the initial formation of O-benzoyl-β-aminopropioamidoxime hydrochloride (**A**), its dehydration to 1,2,4-oxadiazole (**B**) and the subsequent proton transfer and nucleophilic attack steps, also involving hydrolysis with the formation of spirocompound **9** and benzoic acid (**10**) (scheme 3).



Scheme 3

Such course of the acylation reaction under severe conditions – when the reagents are heated at the boiling point of the polar solvent of pyridine is possible.

Formation of analogous structures under milder conditions – at room temperature in ethanol in the preparation of 5-substituted phenyl-3-[(β-thiomorpholin-1-yl)ethyl]-1,2,4-oxadiazoles hydrochlorides and recrystallization from isopropanol of 5-substituted phenyl-3-[β-(4-phenylpiperazin-1-yl)ethyl]-1,2,4-oxadiazoles was detected by us earlier [7, 8].

In the IR spectrum of the chloride hydrate of the spiropyrazolinium compound **9**, there are bands of characteristic valence vibrations of the bonds $\nu_{C=N}$ and $\nu_{C=C}$ at 1644 and 1600 cm^{-1}, respectively. In the ^1H NMR spectrum of the spiropyrazolinium compound **9**, the triplet signals of α-CH_2 and β-CH_2 groups with an intensity of two protons are at δ 3,19 and 3,98 ppm; the signal of the amino group of pyrazolinium ring with an intensity of two protons is present at δ 7,53 ppm.

The carbon atom signal of the C=N bond of the compound **9** in the ^{13}C NMR spectrum is observed at δ 169,11 ppm. Benzoic acid **10** was isolated during the treatment of the reaction mixture described in the experimental part. Its physicochemical and spectral characteristics correspond to tabular data.

β-(Thiomorpholin-1-yl)propioamidoxime (**5**) reacts with two equivalents of benzoyl chloride in boiling pyridine with a regiospecific formation of the monoacylation product at the oxygen atom of the amidoxime group, O-benzoyl-β-(thiomorpholin-1-yl)propioamidoxime hydrochloride (**11**). Compound **11** obtained by monoacylation of β-(thiomorpholin-1-yl)propioamidoxime (**5**) at room temperature in chloroform was described by us earlier [9].

Conclusion. Thus, the interaction of β-aminopropioamidoximes with a double excess of benzoyl chloride in boiling pyridine instead of the expected isoxazoles yielded a set of acylation products: N,O-diacylated β-aminopropioamidoxime dihydrochlorides, spiropyrazolinium compound hydrochloride, and O-acylation hydrochloride. The ambiguous direction of the reaction was obviously connected with the electronic influence of the β-aminoheterocyclic substituent and the possibility of thermodynamically light rearrangements of the initially formed products [10].

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REFERENCES

[1] Kayukova L.A. Chemistry of azometines of 2-substituted cyclohehanons, β-aminopropioamidoximes and α-chloro-α-isonitrosoketones; their anti-tuberculosis, anti-arithmic, local-anaesthetic and other properties: Author's Abstract of a Doctoral Dissertation in Chemical Sciences. Almaty: JSC «A.B. Bekturov Institute of Chemical Sciences», 2005. 53 p.

[2] Kayukova L.A., Praliev K.D., Akhelova A.L., Kemel'bekov U.S., Pichkhadze G.M., Mukhamedzhanova G.S., Kadyrova D.M., Nasyrova S.R. Local anesthetic activity of new amidoxime derivatives // Pharmaceutical Chemistry Journal. 2011. Vol. 45, N 8. P. 468-471. (Russian Original: Vol. 45, N 8. P. 30-32).

[3] Vakhitov T.R., Veretennikov E.A., Shtabova O.V. Formation of an isoxazole ring from phenylacetic acid amidoximes // Chemistry of Heterocyclic Compounds. 2007. Vol. 43, N 1. P. 118-119. (Russian Original: Vol. 43, N 1. P. 134-135).

[4] WHO Model list of Essential Medicines 18th edition. April 2013.

[5] Mashkovskii M.D. Medications. M.: Publishing Ltd New Wave, 2002. Vol. II. P. 282. (Russian).

[6] Greenwood D. Antimicrobial Drugs. Chronicle of a twentieth century medical triumph. London: Oxford University Press US, 2008. 429 p.

[7] Kayukova L.A., Orazbaeva M.A., Gapparova G.I., Beketov K.M., Espenbetov A.A., Faskhutdinov M.F., Tashkhodjaev B.T. Rapid acid hydrolysis of 5-aryl-3-(β-thiomorpholinoethyl)-1,2,4-oxadiazoles // Chem. Heterocycl. Compd. 2010. Vol. 46. P. 879-886. [Russian Original: 2010. Vol. 46. P. 1086-1096.]

[8] Beketov K.M., Kayukova L.A., Praliyev K.D., Baitursunova G.F. Variety of Boulton-Katritzky rearrangement on the sample of 3-β-(4-phenylpiperazin-1-yl)-5-phenyl-1,2,4-oxadiazole // Chemical Journal of Kazakhstan. 2011. N 4. P. 14–19. (Russian).

[9] Kayukova L.A., Orazbaeva M.A. Synthesis of β-(thiomorpholin-1-yl) propionitrile and amidoxime; preparation of O-aroyl-β-(thiomorpholin-1-yl) propioamidoximes as potential antituberculous agents // Bulletin of NAS RK. Series of Chemistry and Technology Sciences. 2007. N 5. P. 37-42.

[10] Kayukova, L.A., Imanbekov K.I., Praliyev K.D. Evaluation of thermodynamic stability of 5-aryl-3-[β-(thiomorpholin-1-yl) and β-(4-phenylpyperazin-1-yl)]ethyl-1,2,4-oxadiazoles and spiropyrazolinium compounds in Boulton-Katritzky rearrangement // Chemical Journal of Kazakhstan. 2014. N 2. P. 208–212. (Russian).

[11] Gordon A.J., Ford R.A. The Chemist's Companion. A Handbook of Practical Data, Techniques, and References. M.: Mir, 1976. P. 442-443.

[12] Innovation Patent of the Republic of Kazakhstan № 28057 / Kayukova L.A., Praliyev K.D., Dusembaeva G.T. A process for the preparation of β-(morpholin-1-yl)propioamidoxime. // Publ. 25.12.2013. Byul. Izobret. of the Republic of Kazakhstan. N 12; https://gosreestr.kazpatent.kz (Russian).

[13] Innovation Patent of the Republic of Kazakhstan № 28453 / Kayukova L.A., Praliyev K.D., Dusembaeva G.T., Uzakova A.B. A process for the preparation of β-(piperidin-1-yl)pro-

pioamidoxime // Publ. 15.05.2014. Byul. Izobret. of the Republic of Kazakhstan. N 5; https://gosreestr.kazpatent.kz Russian

[14] Akhelova A.L. β-Aminopropioamidoximes as N,O-nucleophiles in the reactions with acylchlorides, α-halogenketones and propargyl haloids; biological properties of the products: Author's Abstract of a Candidate Dissertation in Chemical Sciences. Almaty: JSC «A.B. Bekturov Institute of Chemical Sciences», 2005. 25 p. (Russian).

[15] Orazbaeva M.A. Products of O-aroylation, propargylation and heterocyclization of β-aminopropioamidoximes; their antitubercular properties: Author's Abstract of a Candidate Dissertation in Chemical Sciences. Almaty: JSC «A.B. Bekturov Institute of Chemical Sciences», 2008. 25 p. (Russian).

[16] Rabinovich V.A., Khavin Z.Ya. Brief Chemical Reference Book, 2nd. Ed., Revised and Updated. L.: Chemistry Publishers, 1978. P. 131. (Russian).

Резюме

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β-АМИНОПРОПИОАМИДОКСИМДЕРДІ ПИРИДИНДЕ АРТЫҚ БЕНЗОИЛИРЛЕУ КЕЗІНДЕ 1,3,5-ОРЫНБАСҚАН ИЗОКСАЗОЛДАРДЫ СИНТЕЗДЕУ

β-Аминопропиоамидоксимдердің шамадан тыс ацелирленуі (β-аминотоп: пиперидин-1, морфолин-1, бензимидазол-1, 4-фенилпиперазин-1, тиоморфолин-1) еріткіштің қайнау нүктесінде 4–8 сағат ішінде пиридиннің бензоил хлоридінің қос тотығымен көбеюімен жүзеге асырылды. Пиперидин, морфолин және безимидазол амидоксимі жағдайында N, O-дибензоил-β-аминопропиоамидоксим дихидрохлоридтері ерекше өнім болып табылады; тиісінше, хлоридті гидрат спиропиразолин қосылысының және бензой қышқылы және O-бензоил-β-(тиоморфолин-1-ил)пропиоамидоксим гидрохлоридтеріне субстраттар ретінде β-(4-фенилпипиразин-1-ил)пропиоамидоксим және β-(тиоморфолин-1 -ил)пропиоамидоксимдер пайдаланылады.

Түйін сөздер: β-Аминопропиоамидоксимдер, пиридиннің артық ациляциясы, бензойл хлориді, ИК-спектроскопия, ^{1}H и ^{13}C ЯМР спектроскопиясы.

Резюме

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СИНТЕЗ 1,3,5-ЗАМЕЩЕННЫХ ИЗОКСАЗОЛОВ ПРИ ИЗБЫТОЧНОМ БЕНЗОИЛИРОВАНИИ β-АМИНОПРОПИОАМИДОКСИМОВ В ПИРИДИНЕ

Избыточное ацилирование β-аминопропиоамидоксимов (β-аминогруппа: пиперидин-1-ил, морфолин-1-ил, бензимидазол-1-ил, 4-фенилпиперазин-1-ил, тиоморфолин-1-ил) проведено при двукратном избытке бензоилхлорида в пиридине при температуре кипения растворителя в течение 4–8 ч. Выделенными продуктами являются дигидрохлориды N,O-дибензоил-β-аминопропиоамидоксимов в случае пиперидинового, морфолинового и безимидазольного амидоксима; гидрат хлорида спиропиразолиниевого соединения и бензойная кислота и гидрохлорид O-бензоил-β-(тиоморфолин-1-ил)пропиоамидоксима при использовании в качестве субстратов β-(4-фенилпипиразин-1-ил)пропиоамидоксима и β-(тиоморфолин-1-ил)пропиоамидоксима, соответственно.

Ключевые слова: β-Аминопропиоамидоксимы, избыточное ацилирование в пиридине, хлористый бензоил, ИК-спектроскопия, спектроскопия ^{1}H и ^{13}C ЯМР.