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SYNTHESIS OF SOME HALOGEN- AND NITRO-SUBSTITUTED NICOTINIC ACIDS AND THEIR FRAGMENTATION UNDER ELECTRON IMPACT

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Features of electrophilic and nucleophilic substitution under chlorination and nitration reactions conditions have been investigated for 6-hydroxy- and 6-methyl-substituted derivatives of 3-cyano-4-methyl-2(1H)-pyridones. The polychloro- and nitro-substituted 3-cyano-4-methylpyridines obtained were used as synthons in the synthesis of some polyhalo- and nitro-substituted nicotinic acids and their amides. The fragmentation pathways of the synthesized compounds under electron impact have been studied.

Keywords: halo and nitro derivatives, nicotinic acids, fragmentation under electron impact.

Substituted nicotinic acids and their functional derivatives attract the attention of investigators as potential physiologically active substances belonging to a group in which compounds are known possessing a broad spectrum of pharmacological [1-3], and also pesticidal [4, 5] activity. However there is no information in the literature on nicotinic acids containing 3-4 identical or different substituents in the pyridine ring.

In the present work the synthesis is described of new polysubstituted derivatives of nicotinic acid starting from 3-cyano-4-methyl-2(1H)-pyridones **1a,b,** containing methyl or hydroxyl groups in position 6 of the ring, by the conversions given in the scheme. Electrophilic substitution of the hydrogen atom in position 5 of the ring of compounds **1a,b** and also nucleophilic substitution of the 2-OH group and the 6-OH of the enolic form of pyridones **1** by a chlorine atom and a nitro group depends on the substituent in position 6, and also on the type of chlorinating or nitrating agent. Thus 6-methylpyridine **1a** on chlorination with an excess of SO_2Cl_2 in CCl_4 forms the product of electrophilic substitution, the 5-chloro derivative **2a**, in 94% yield. Nitration with nitric acid also proceeds selectively at the same position, leading to the 5-nitro derivative **2b**. Treatment with an excess of $POCl_3$ at ~105°C leads to substitution of the 2-OH group of the enolic form of pyridone **1a** by an atom of chlorine, with aromatization of the ring and the formation of 2-chloro-3-cyano-4,6-dimethylpyridine (**3a**). The 5-chloro and 5-nitro derivatives **2a,b** react analogously with $POCl_3$ and lead to the 2,5-dichloro- and 2-chloro-5-nitro-substituted products **3c,d** respectively (in the case of nitro compound **2b** chlorination was conducted at 180°C). 2,6-Dichloro-3-cyanopyridine **3b** is formed from 3-cyano-6-hydroxy-4-methyl-2(1H)-pyridone (**1b**) with $POCl_3$ (**1b** : $POCl_3$, 1:2) after 6 h at 120°C.

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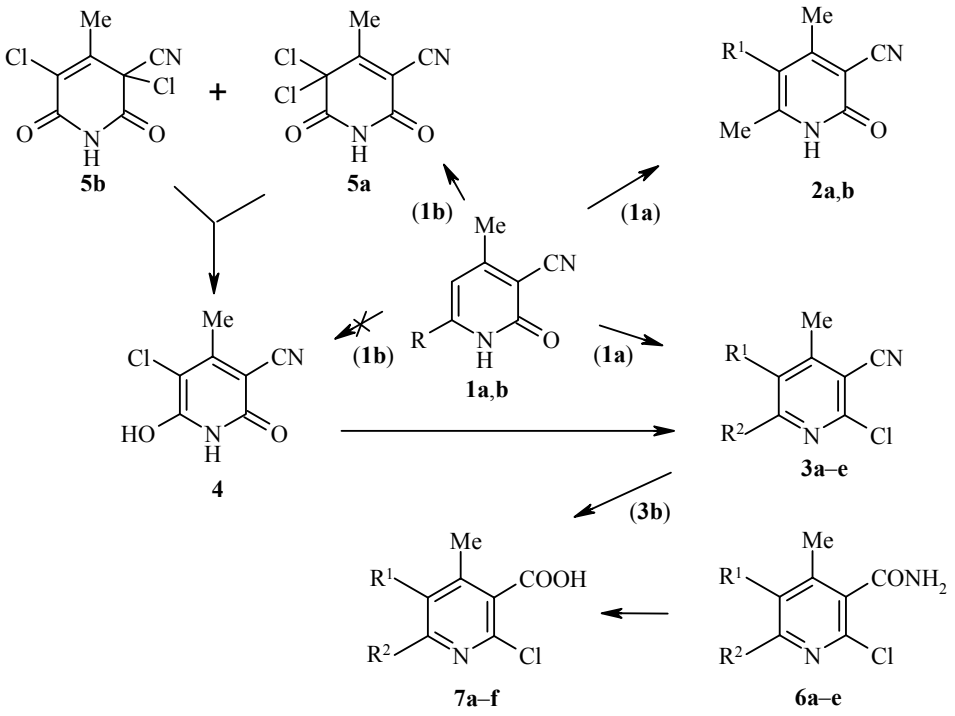

1 a R = CH_3, **b** R = OH; **2 a** R^1 = Cl, **b** R^1 = NO_2; **3**, **6**, **7 a** R^1 = H, R^2 = Me; **b** R^1 = H, R^2 = Cl; **c** R^1 = Cl, R^2 = CH_3; **d** R^1 = NO_2, R^2 = Me; **e** R^1 = Cl, R^2 = Cl; **f** R^1 = NO_2, R^2 = Cl

The behavior of pyridone **1b**, in position 6 of which an OH group possessing a *+M* effect is found in place of a methyl group possessing a marked *+I* effect, differs markedly in the reactions described above. Its chlorination with sulfuryl chloride or the direct action of chlorine does not lead to the desired 5-chloro-6-hydroxypyridone **4**, but is completed by the formation of a mixture of isomeric dichlorides **5a** and **5b** (varying the reaction conditions affects only the ratio of isomers), which is in agreement with the data of [6]. Reduction of this mixture with zinc dust in a protic solvent proceeds smoothly with the formation only of 5-chloro-3-cyano-6-hydroxy-4-methyl-2(1H)-pyridone (**4**). On treating the latter with an excess of $POCl_3$ the trichloro-substituted pyridine derivative **3e** is formed.

Attempts to nitrate pyridone **1b**, in spite of a wide variation of the conditions (HNO_3 of various concentrations, mixtures of it with AcOH, Ac_2O, and H_2SO_4, and also HNO_2 and isoamyl nitrate [7]), were unsuccessful. Even at reduced temperature (-9±1°C) the reaction was accompanied by resinification, destruction of the 2-pyridone ring, and the formation of a complex mixture of colored resinous products, which it was not possible to identify.

Acid hydrolysis of halogen-substituted cyanopyridines **3a-e** with aqueous 80% sulfuric acid solution leads smoothly and in maximum yield to the corresponding amides of nicotinic acid **6a-e**. Subsequent diazotization of these difficultly hydrolyzable amides **6a-e** with nitrous acid by the known method of Bouveault [8] led to the target substituted acids **7a-e**. The halonitro-substituted acid **7f** was successfully obtained only by the nitration of nitrile **3b** with a mixture of conc. HNO_3 and H_2SO_4 at ~100°C. It transpired that hydrolysis of the cyano group to carboxyl occurs simultaneously with the introduction of the nitro group.

All the synthesized compounds were amorphous or white finely crystalline powders. The aromatic nitriles **3a-e** (mp 67-110°C) were readily soluble in the usual organic solvents. Amides **6a-e** and acids **7a-e** were high-melting substances, soluble with difficulty or not at all in the usual organic solvents, soluble in some highly polar solvents, except for of DMF and DMSO. The characteristics of the synthesized compounds are given in Tables 1 and 2.

TABLE 1. Characteristics of Compounds **2a,b**, **3a-e**, **6a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Mass spectrum, *m/z* (I_{rel})	Yield, %
		C	H	Cl	N			
2a	$C_8H_7ClN_2O$	52.84 / 52.61	3.69 / 3.87	19.53 / 19.41	15.40 / 15.34	260-261	$[M]^+$ 182 (100); 154 (39); 119 (29); 92 (8)	94
2b	$C_8H_7N_3O_3$	50.01 / 49.74	3.72 / 3.66		21.94 / 21.76	265-266	$[M]^+$ 193 (68); 176 (100); 148 (21); 119 (53); 92 (28)	54
3a	$C_8H_7ClN_2$	57.94 / 57.66	4.32 / 4.24	21.58 / 21.28	17.01 / 16.82	95-96	$[M]^+$ 166 (100); 130 (21); 131 104 (13); 132 77 (7)	95
3b	$C_7H_4Cl_2N_2$	44.78 / 44.95	2.04 / 2.16	37.72 / 37.91	14.75 / 14.98	107-108	$[M]^+$ 186 (60); 151 (100); 125 (41); 105 (32)	98
3c	$C_8H_6Cl_2N_2$	47.68 / 47.96	3.18 / 3.01	35.44 / 35.26	13.60 / 13.96	67-68	$[M]^+$ 200 (100); 164 (15); 129 (21); 102 (11)	76
3d	$C_8H_6ClN_3O_2$	45.12 / 45.40	2.77 / 2.86	16.61 / 16.75	19.50 / 19.86	90-91	$[M]^+$ 21 (59); 194 (100); 165 (32); 139 (69); 130 (45); 102 (23)	61
3e	$C_7H_3Cl_3N_2$	38.14 / 37.96	1.24 / 1.37	47.94 / 48.02	12.49 / 12.65	110-111	$[M]^+$ 184 (89); 168 (100); 140 (33); 104 (13); 78 (30)	69
6a	$C_8H_9ClN_2O$	51.95 / 52.04	5.04 / 4.92	19.28 / 19.20	15.01 / 15.18	154-155	$[M]^+$ 184 (89); 140 (33); 104 (13); 78 (30)	89
6b	$C_7H_6Cl_2N_2O$	40.79 / 41.00	2.84 / 2.96	34.65 / 34.58	13.49 / 13.66	170-171	$[M]^+$ 204 (74); 188 (100); 160 (23); 124 (24); 99 (14)	93
6c	$C_8H_8Cl_2N_2O$	43.61 / 43.86	3.64 / 3.69	32.51 / 32.36	12.87 / 12.79	146-147	$[M]^+$ 218 (86); 202 (100); 183 (12); 174 (38); 147 (26); 133 (9)	91
6d	$C_8H_8ClN_3O_3$	42.00 / 41.84	3.46 / 3.52	15.68 / 15.44	18.26 / 18.30	188-189	$[M]^+$ 229 (29); 213 (21); 196 (16); 168 (24); 140 (100)	47
6e	$C_7H_5Cl_3N_2O$	35.31 / 35.10	2.13 / 2.11	44.67 / 44.41	11.73 / 11.70	167-168	$[M]^+$ 238 (41); 222 (100); 194 (14); 187 (18); 159 (28); 133 (9)	69

* Solvents for crystallization: acetone (compound **2a**), EtOH (compounds **2b**, **6a-e**), cyclohexane (compounds **3a,b,d**), hexane (compound **3c**).

The dissociation constants pK_a of the substituted nicotinic acids **7a-f** were within the range 2.55-2.79 (Table 2), which enables them to be assigned to the strong acids, exceeding the strength of nicotinic acid by two orders of magnitude.

There were broadened absorption bands in the IR spectra of the synthesized acids for the carboxyl OH group at 3200-3600 with maxima at 3430-3448 cm^{-1} (see Table 2). Medium and strong sharp absorption bands for the C=C and C=N bonds of the conjugated pyridine ring were found at 1539-1603 cm^{-1}. At 1715-1734 cm^{-1} there was an absorption band for the C=O group, which is characteristic of strong acids existing as dimers [9]. In the spectra of the acids containing a nitro group there were also intense bands at 1540-1545 and 1339-1348 cm^{-1} which may be interpreted as being characteristic for NO_2.

It is not expedient to give and discuss the ^1H NMR spectra of the synthesized compounds because they were not very informative.

TABLE 2. Characteristics of the Synthesized Compounds **7a-f**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	p*K*a	Yield, %
		C	H	Cl	N			
7a	$C_8H_8ClNO_2$	51.55 / 51.77	4.50 / 4.34	19.2 / 19.1	7.42 / 7.54	139-140	2.79	60
7b	$C_7H_5Cl_2NO_2$	40.66 / 40.81	2.31 / 2.45	34.3 / 34.4	6.83 / 6.79	119-120	2.64	88
7c	$C_8H_7Cl_2NO_2$	47.21 / 47.07	2.43 / 2.31	32.4 / 32.5	6.35 / 6.42	159-160	2.72	96
7d	$C_8H_7ClN_2O_4$	41.79 / 41.67	3.21 / 3.06	15.3 / 15.4	12.28 / 2.15	170-171	2.57	76
7e	$C_7H_4Cl_3NO_2$	34.78 / 34.95	1.52 / 1.68	44.3 / 44.2	5.73 / 5.82	150-151	2.64	75
7f	$C_7H_4Cl_2N_2O_4$	33.35 / 33.49	1.52 / 1.61	28.2 / 28.3	11.25 / 11.16	168-169	2.55	60

* Solvents for crystallization: EtOAc (compounds **7a,b,e**) and EtOH (compounds **7c,d,f**).

Study of the behavior of the synthesized acids under the action of electron impact showed that their molecular ions $[M]^+$ were characterized by enhanced stability and relative intensity (54-100%), while the directions of their primary fragmentation were fairly diverse. It is known [10] that as a result of the primary fragmentation of M^+ of nicotinic acid under electron impact there is loss of COOH, hydroxyl, or a H_2O molecule. This turned out to be characteristic also for the substituted nicotinic acids **7a-e**, in the mass spectra of which peaks for $[M\text{-}H_2O]^+$ ions were detected with a relative intensity (I_{rel}) of 10-46%. Elimination of the COOH group and the formation of highly stable $[M\text{-}COOH]^+$ ions also takes place (I_{rel} 18-100%). In addition ejection of a molecule of CO_2 was observed in the mass spectra of acids **7a-e**, as indicated by the presence of peaks for $[M\text{-}CO_2]^+$ ions (I_{rel} 21-31%).

We note that the 5-nitro-substituted acid **7f** loses an NO_2 group in the initial stage of decomposition and elimination of CO_2 is a characteristic only for the secondary processes of fragmentation. The formation of $[M\text{-}HCl]^+$ fragments (I_{rel} 20-100%) is characteristic of the primary fragmentation processes of the molecular ions of all the halogen-substituted nicotinic acids with the exception of compounds **7d,f** containing a 5-nitro group. The latter probably split off a chlorine atom in the later stages of fragmentation.

In the fragment ions from electron impact of the majority of the 2-chloronicotinic acids being discussed, it is probable that migration of the hydroxyl group occurs to the position where the positive charge is localized, i.e. to carbon atom 2, which corresponds to the fragmentation pathway of *o*-nitrobenzoic acids [11], with subsequent elimination of CO.

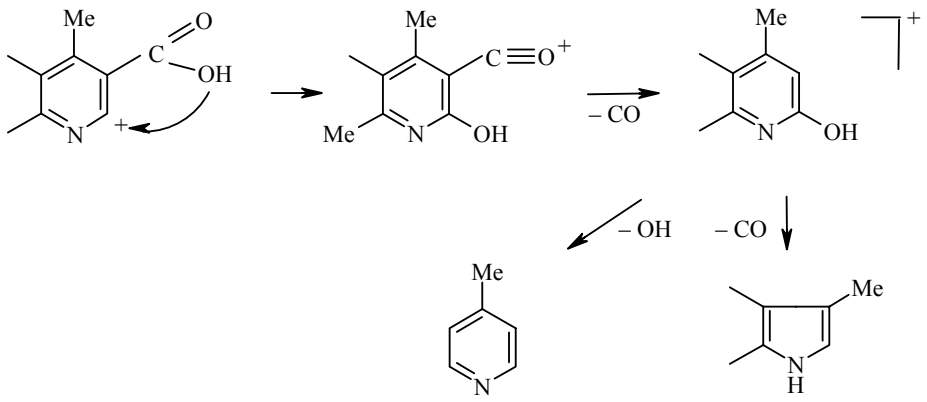

TABLE 3. Spectral Characteristics of Compounds **7a-f**

Compound	Mass spectrum: molecular and characteristic ions, *m/z* (I_{rel}, % of maximal)	IR spectrum, ν_{max}, cm^{-1}				Yield, %
		OH	C=O	C=C, C=N	NO_2	
7a	$[M]^+$ 185 (93); $[M–OH]^+$ 168 (20); $[M–H_2O]^+$ 167 (10); $[M–HCl]^+$ 149 (100); $[168-CO]^+$ 140 (12); $[149–CH_3, –CH_2]^+$ 120 (25); $[149–CO]^+$ 105 (17)	3600, 3300 (3443)	1725	1603	—	60
7b	$[M]^+$ 205(100); $[M–OH]^+$ 188 (68); $[M–H_2O]^+$ 187 (44); $[M–HCl]^+$ 168 (41); $[M–CO_2]^+$ 161 (31); $[M–COOH]^+$ 160 (19); $[169–CO]^+$ 141 (33)	3600, 3000 (3430)	1717	1570 1539	—	88
7c	$[M]^+$ 219 (100); $[M–HOH]^+$ 201 (32); $[M–HCl]^+$ 183 (75); $[M–COOH]^+$ 174 (18); $[183–Cl]^+$ 148 (81); $[183–COOH]^+$ 138 (15); $[148–CO]^+$ 120 (22)	3600, 3300 (3431)	1734	1576	—	96
7d	$[M]^+$ 230(64); $[M–OH]^+$ 213 (52); $[M–OH,–H_2O]^+$ 195 (11); $[M–NO_2]^+$ 184 (13); $[213–Cl,–CN]^+$ 142 (27); $[184–CO_2]^+$ 140 (33); $[140–Cl]^+$ 105 (44)	3600, 3200 (3430)	1726	1589	1540 1348	76
7e	$[M]^+$ 239 (100); $[M–OH]^+$ 222 (28); $[M–H_2O]^+$ 221 (35); $[M–HCl]^+$ 203 (20); $[M–CO_2]^+$ 192 (10); $[M–COOH]^+$ 194 (12); $[203–Cl]^+$ 168 (55); $[203–COOH]^+$ 158 (16); $[168–CO_2]^+$ 124 (19)	3600 2200 (3448)	1718	1545	—	75
7f	$[M]^+$ 250 (54); $[M–OH]^+$ 233 (49); $[M–OH,–H_2O]^+$ 205 (100); $[M–NO_2,–Cl]^+$ 169 (45); $[M–CO_2,–NO_2]^+$ 160 (68); $[169–CO]^+$ 141 (28); $[169–Cl]^+$ 134 (28); $[141–OH]^+$ 124 (28)	3600 3200 (3430)	1715	1576	1545 1389	60

In the later stages of fragmentation, elimination of a hydroxyl group or one further CO fragment is possible with the formation of more stable five-membered heterocyclic ions with a relative intensity of 17-33%.

The features of the electrophilic and nucleophilic substitution in 6-oxo- and 6-methyl-substituted 3-cyano-4-methyl-2(1H)-pyridones have been studied. Accessible routes have been developed for the synthesis of polysubstituted nicotinic acids, which are potentially biologically active substances.

EXPERIMENTAL

The IR spectra were recorded on a Bruker IFS-45 spectrometer with an analyzing Aspekt-1000 computer for compounds in KBr disks. The mass spectra were recorded on an LKB-2091 chromato-mass spectrometer with direct insertion of samples into the ion source (energy of ionizing electrons 70 eV). The elemental analysis of the synthesized compounds was carried out on a Carlo Erba model 1106 analyzer. The dissociation constants of acids **7a-f** were determined on a type I130.2M.1 ionomer. The homogeneity of the synthesized compounds was confirmed by TLC on Silufol UV-vis plates, solvent was hexane–acetone, 1:1, visualizing with iodine vapor.

The solvents used were purified and dried by known methods [14].

The initial 3-cyano-4,6-dimethyl-2(1H)-pyridone **1a** and 3-cyano-6-hydroxy-4-methyl-2(1H)-pyridone **1b** were obtained and purified as described previously in [12, 13]. The synthesis of mixtures of isomeric nitriles **5a** and **5b** and their reduction to 5-chloro-3-cyano-6-hydroxy-4-methyl-2(1H)-pyridone **4** was carried out analogously to [6]. Their physicochemical characteristics are given in the cited work.

5-Chloro-3-cyano-4,6-dimethyl-2(1H)-pyridone (2a). A mixture of cyanopyridone **1a** (5 g, 33.7 mmol) and sulfuryl chloride (18.25 g, 135.2 mmol) in dry CCl_4 (50 ml) was boiled under reflux for 6 h. After cooling, the precipitated solid was filtered off, washed with CCl_4, and dried. Product **2a** (5.8 g) was obtained as a white, finely crystalline powder.

3-Cyano-4,6-dimethyl-5-nitro-2(1H)-pyridone (2b). A solution of HNO_3 (d = 1.51 g/cm^3, 2.1 ml) in Ac_2O (1.8 ml) was added slowly with stirring to a suspension of cyanopyridone **1a** (3.48 g, 18 mmol) in Ac_2O (12 ml) at 0±1°C. The reaction mixture was maintained at 5°C for 0.5 h, then at 20°C for 0.5 h, and poured onto ice. The precipitated solid was filtered off, washed with ice water (3 × 50 ml), and dried in vacuum. Product **2b** (2.5 g) was obtained as a white powder.

2-Chloro-4,6-dimethylnicotinic Acid Nitrile (3a). A mixture of cyanopyridone **1a** (5.0 g, 33.7 mmol) and $POCl_3$ (5.17 g, 33.7 mmol) was heated in a sealed ampule at 120°C for 5.5-6.0 h. The ampule was opened and the contents were poured onto crushed ice (30 g). The resulting solid was filtered off, washed with ice water (3 × 50 ml), and dried under reduced pressure. Nitrile **3a** (5.35 g) was obtained as a white, finely crystalline powder.

Nitriles **3b-e** were obtained analogously from compounds **1b**, **2a,b**, and **4** respectively.

2,6-Dichloro-4-methylnicotinic Acid Amide (6b). A mixture of nitrile **3b** (1 g, 5.35 mmol) and 80% H_2SO_4 (15 ml) was stirred at 98±2°C for 6 h. The cooled reaction mixture was poured onto crushed ice (30 g), and aqueous ammonia solution added to pH ~5. The resulting solid was filtered off, washed thoroughly with water, and dried in a vacuum desiccator. Amide **6b** (1 g) was obtained as a white, finely crystalline powder.

Amides **6a,c-e** were obtained analogously, but at a hydrolysis time of 10 h.

2,6-Dichloro-4-methylnicotinic Acid (7b). A mixture of amide **6b** (5 g, 24 mmol) and conc. H_2SO_4 (d = 1.84 g/cm^3, 21.4 ml) was heated slowly until complete solution of the amide. A solution of $NaNO_2$ (3.9 g, 56.5 mmol) in water (20 ml) was slowly added dropwise to the cooled solution at ~0°C. The reaction mixture was kept for 40-60 min at 20-25°C, then poured onto crushed ice (50 g). The solid which separated was filtered off, and purified by reprecipitation from 10% NaOH solution by acidifying with 10% HCl solution. The solid was washed with water, dried at 20°C, and the crystallohydrate of **7b** (4.8 g) was obtained; mp 108-110°C. After additional drying in vacuum at 80°C for 1.5 h, the anhydrous **7b** acid (4.4 g) was obtained as a white powder.

Substituted nicotinic acids **7a,c-d** were obtained analogously from amides **6a,c-d** respectively.

2,6-Dichloro-4-methyl-5-nitronicotinic Acid (7f). A solution of nitrile **3b** (1 g, 5.35 mmol) in a mixture of HNO_3 (d = 1.51 g/cm^3, 7 ml) and H_2SO_4 (d = 1.84 g/cm^3, 7 ml) was heated at ~100°C for 10 h. The mixture was cooled to 0°C and added dropwise to ice (30 g) powdered and cooled to -40°C. The precipitated solid was filtered off, washed with water, reprecipitated from saturated $NaHCO_3$ solution, washed with water to pH 7, and dried. Acid **7f** (0.81 g, 60%) was obtained as a white, finely crystalline powder.

REFERENCES

1. A. I. Mikhalev, V. K. Kudryashova, and M. E. Konshin, *Khim.-farm. Zh.*, No. 5, 7 (1973).
2. Australian Patent 4593111975; *Ref. Zh. Khim.*, 12 O92P (1980).
3. V. P. Chesnokov, M. E. Konshin, V. S. Zalesov, and V. K. Kudryashova, *Khim.-farm. Zh.*, No. 11, 7 (1973).
4. A. D. Gutman, US Patent 4251263; *Ref. Zh. Khim.*, 17 O339P (1973).
5. A. D. Gutman, US Patent 4327218; *Ref. Zh. Khim.*, 4 O431P (1983).
6. L.V. Dyadyuchenko, V. D. Strelkov, and V. N. Zaplishnii, *Khim. Geterotsikl. Soedin.*, 1641 (1999).
7. I. Guben, in: *Methods of Organic Chemistry* [in Russian], Vol. IV, Goskhimizdat, Moscow (1949), Book 1, p. 251.
8. K. V. Vatsuro and G. L. Mishchenko, in: *Named Reactions in Organic Chemistry* [in Russian], Khimiya, Moscow (1976), p. 84.

9. K. Nakanishi, in: *Infrared Spectra and Structure of Organic Compounds* [Russian translation], Mir, Moscow (1965), p. 53.
10. O. N. Porter, *Mass-spectrometry of Heterocyclic Compounds*, New York (1984).
11. B. P. Terentiev, in: *Mass-spectrometry in Organic Chemistry* [in Russian], Vyssh. shkola, Moscow (1979), p. 120.
12. H. Jahine, H. A. Zaher, F. A. Sayed, and M. Sayed, *J. Prakt. Chem.*, 316 (1974).
13. R. C. Elderfield (editor), *Heterocyclic Compounds*, Vol. 1, Wiley, New York (1950).
14. A. Weissberger, E. Proskauer, J. A. Riddick, and E. E. Toops, *Organic Solvents* [Russian translation], Izd. Inostr. Lit., Moscow (1958).