ISSN 1070-4272, Russian Journal of Applied Chemistry, 2010, Vol. 83, No. 6, pp. 1027–1031. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © E.V. Vlasova, A.A. Aleksandrov, M.M. El'chaninov, 2010, published in Zhurnal Prikladnoi Khimii, 2010, Vol. 83, No. 6, pp. 974–977.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Properties of 1-Methyl-2-phenyl-5-(2-furyl)- and 1-Methyl-2-phenyl-5-(2-thienyl)imidazoles

E. V. Vlasova, A. A. Aleksandrov, and M. M. El'chaninov

South-Russian State Technical University (Novocherkassk Polytechnic Institute), Novocherkassk, Rostov oblast, Russia

Received June 23, 2009

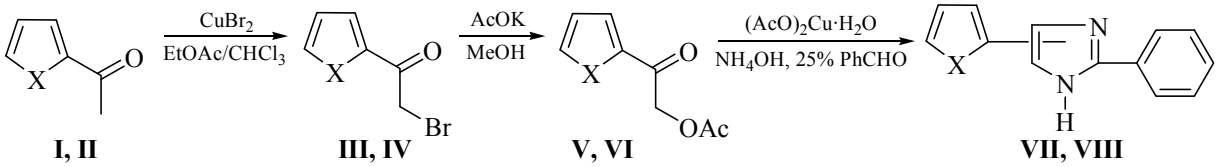
Abstract—2-Phenyl-5-(2-furyl)- and 2-phenyl-5-(2-thienyl)imidazoles were synthesized by condensation of 2-furoylmethyl and 2-thenoylmethyl acetates with benzaldehyde under the conditions of Weidenhagen reaction. The products were converted to *N*-methyl derivatives in the KOH–acetone system. The electrophilic substitution reactions of the products (acylation, bromination, nitration, sulfonation, hydroxymethylation) were studied.

DOI: 10.1134/S1070427210060194

Polycyclic fluorophores are widely used today in designing fluorescent dyes. For example, derivatives of naphthoylbenzimidazole [1], oxazole [2], and oxadiazole [3] find growing application. The electronic structure and spectral properties of fused 2-hetarylimidazoles were studied previously [4].

This paper deals with the synthesis of 2-phenyl-4(5)-(2'-furyl)imidazole **VII** and 2-phenyl-4(5)-(2'-thienyl)imidazole **VIII** and with electrophilic substitution reactions of these compounds, performed to prepare potential luminophores.

4(5)-(2'-furyl)imidazole was prepared previously from furoyl chloride, diazomethane, and potassium acetate, with the subsequent condensation of the resulting 2-furoylmethyl acetate with formalin under the conditions of Weidenhagen reaction [5]. We were able to synthesize compounds **VII** and **VIII** by the similar reaction but without using dangerously explosive diazomethane:



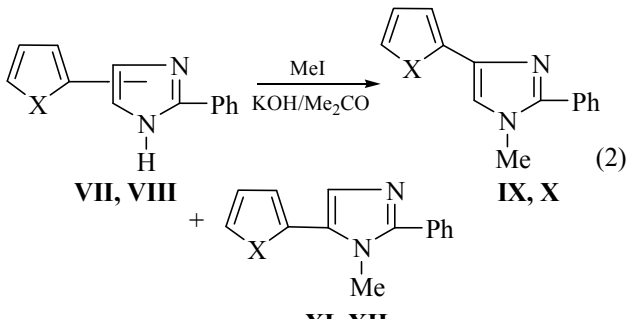
(1)

I, II **III, IV** **V, VI** **VII, VIII**

X = O (**I, III, V, VII**), S (**II, IV, VI, VIII**).

We were able to methylate 2-phenyl-4(5)-(2'-hetaryl) imidazoles **VII** and **VIII** in almost quantitative yield with an equivalent amount of methyl iodide in the KOH–acetone system [6], which, in contrast to the reaction in alcoholic alkaline solutions, considerably accelerates the reaction and virtually fully excludes quaternization. Because of the asymmetric structure of the imidazole anions, two isomers (4- and 5-) were obtained in each case **IX–XII**.

According to the ^{1}H NMR spectrum, the isomer ratio in the mixture is 1 : 2, with isomers **XI** and **XII** pre-



(2)

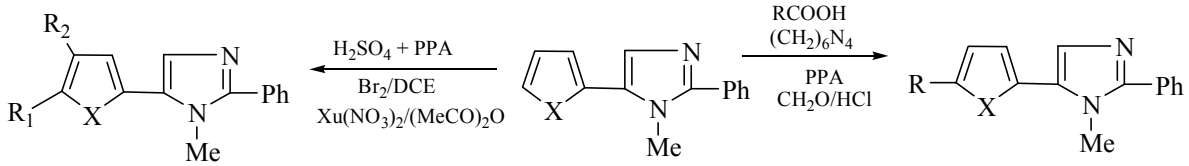
VII, VIII **IX, X**

+

XI, XII

X = O (**VII, IX, XI**), S (**VIII, X, XII**).

vailing. By fractional crystallization, previously unknown imidazoles **XI** and **XII** were isolated in the spectroscopically pure form and were subjected to the action of electrophilic agents [carboxylic acids in polyphosphoric acid (PPA), acetyl nitrate, mixtures of sulfuric and polyphosphoric acids, hexamethylenediamine and polyphosphoric acid, formalin in the presence of catalytic amounts of HCl, bromine in dichloroethane (DCE)]:



(3)

XXI–XXVI **XI, XII** **XIII–XX**

X = O, R = CH (**XIII**), COMe (**XIV**), COPh (**XV**), CH_2OH (**XVI**); X = S, R = CHO (**XVII**), COMe (**XVIII**), COPh (**XIX**), CH_2OH (**XX**); X = O, R_1 = Br, R_2 = H (**XXI**), R_1 = NO_2, R_2 = H (**XXII**), X = S, R_1 = SO_3H, R_2 = H (**XXIII**), R_1 = Br, R_2 = H (**XXIV**), R_1 = H, R_2 = Br (**XXV**), R_1 = NO_2, R_2 = H (**XXVI**).

Compounds **XI** and **XII** readily react with carboxylic acids and hexamethylenetetramine in polyphosphoric acid to form derivatives with 5'-formyl or 5'-acyl substituents in the hetaryl ring (**XIII–XV**, **XVII–XIX**). Alcoholic solutions of these compounds show strong fluorescence under UV irradiation, which gives grounds to believe that these compounds exhibit photoluminescence properties. Hydroxymethylation of **XI** and **XII** in boiling formalin upon addition of a drop of concentrated hydrochloric acid occurs fairly smoothly, in contrast to 2-(2-hetaryl)imidazoles inert in the process [7]. The reaction gives compounds **XVI** and **XX** in 58 and 64% yields, respectively. These results indicate that the electron-withdrawing effect exerted on the hetaryl rings by 5-imidazolyl substituent is weaker, compared to the previously studied 2-hetarylimidazoles [7, 8].

It is known that furan, because of its acidophobic properties, is best sulfonated with such a mild agent as adduct of sulfuric anhydride with pyridine. Taking this fact into account, we first attempted to apply this method to hetarylimidazoles **XI** and **XII**. We found that sulfonation with pyridine–sulfur trioxide in refluxing dichloroethane did not give positive results. Therefore, these compounds were sulfonated with sulfuric acid (d = 1.84) in PPA at 80–100°C. We failed to isolate and identify the sulfonic acid derived from 5-(2-furyl)imidazole **XI** because of its very high solubility in water. Sulfonic acid **XXIII** was isolated in 86% yield. It apparently exists in the betaine form, as indicated by the absence of the sulfonic acid proton signal in the ^{1}H NMR spectrum recorded in DMSO-d_6 and by the presence of such signal in the spectrum recorded in trifluoroacetic acid.

Bromination of **XI** in dichloroethane at 80°C yields monobromide **XXIV**, whereas for the thiophene analog **XII** it is not so selective and yields, according to ^{1}H NMR spectrum, a mixture of monobromo derivatives **XXIV** and **XXV**. Unfortunately, we failed to separate these isomers because of their similar chromatographic mobility. However, their identification in the ^{1}H NMR spectra involves no problems, because each isomer has certain specific features. In addition, for more accurate signal assignment, we prepared compounds **XXIV** and **XXV** by independent synthesis following scheme (1) from 5-bromo-2-acetylfuran or -thiophene.

Nitration of 1-methyl-2-phenyl-5-(2-furyl)imidazole **XI** and 1-methyl-2-phenyl-5-(2-thienyl)imidazole **XII** with acetyl nitrate at 0–10°C is accompanied by the formation of an intractable mixture of nitro derivatives. With the aim to perform a selective reaction under mild conditions, we used the procedure reported previously [9] for nitration of 2-thiophenecarbaldehyde with a complex of copper nitrate and acetic anhydride. The most favorable conditions for the mononitration were found at the molar ratio of **XI** or **XII** and nitrating agent of 1 : 1.2. As a result, we obtained 5'-nitro derivatives **XXII** and **XXVI**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz), with the residual protons of the deuterated solvent ($CDCl_3$ 7.26 ppm and DMSO-d_6 2.45 ppm) and TMS as internal references. Elemental analysis was performed with a Perkin–Elmer 2400 analyzer. The melting point was

Yield and properties of compounds **IX–XXVI**

Comp. no.	Yield, %	mp, °C	Formula[a]	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
IX	25	52–60	$C_{14}H_{12}N_2O$	3.77 s (3H, CH_3), 6.42-6.44 m (1H, H-4'), 6.49 d (1H, H-3', *J* 3.3), 7.26 s (1H, imide), 7.35 d (1H, H-5', *J* 1.8), 7.41–7.46 m (3H, arom.), 7.62 d (2H, arom., *J* 7.7)
X	28	42–43	$C_{14}H_{12}N_2S$	3.74 s (3H, CH_3), 7.01–7.05 m (1H, H-4'), 7.18 s (1H, imide), 7.24 d (1H, H-3', *J* 4.0), 7.30 d (1H, H-5', *J* 5.0), 7.41–7.46 m (3H, arom.), 7.62 d (2H, arom., *J* 7.7)
XI	62	40–41	$C_{14}H_{12}N_2O$	3.71 s (3H, CH_3), 6.42-6.44 m (1H, H-4'), 6.67 d (1H, H-3', *J* 3.3), 7.18 s (1H, imide), 7.37 d (1H, H-5', *J* 1.8), 7.41–7.46 m (3H, arom.), 7.62 d (2H, arom., *J* 7.7)
XII	56	55–56	$C_{14}H_{12}N_2S$	3.73 s (3H, CH_3), 7.01–7.05 m (1H, H-4'), 7.18 s (1H, imide), 7.26 d (1H, H-3', *J* 3.9), 7.32 d (1H, H-5', *J* 4.9), 7.41–7.46 m (3H, arom.), 7.66 d (2H, arom., *J* 7.8)
XIII	41	120–121	$C_{15}H_{12}N_2O_2$	3.93 s (3H, CH_3), 6.72 d (1H, H-3', *J* 3.6), 7.35 d (1H, H-4', *J* 4.6), 3.72 s (1H, imide), 7.50–7.56 m (3H, arom.), 7.68 d (2H, arom., *J* 7.2), 9.65 s (1H, CHO)
XIV	35	130–132	$C_{16}H_{14}N_2O_2$	2.52 s (3H, CH_3), 3.78 s (3H, NCH_3), 6.85 d (1H, H-3', *J* 3.6), 7.45 d (1H, H-4', *J* 3.6), 7.30 s (1H, imide), 7.47 t (3H, arom., *J* 7.1), 7.64 d (2H, arom., *J* 7.2)
XV	58	115–117	$C_{21}H_{16}N_2O_2$	3.93 s (3H, CH_3), 6.71 d (1H, H-3',*J* 3.7), 7.33 d (1H, H-4', *J* 3.7), 7.47 s (1H, imide) 7.48–7.54 m (3H, arom.),7.64 d (2H, arom., *J* 7.2), 7.64–7.67 m (3H, arom.), 7.97 d (2H, arom., *J* 7.2)
XVI	44	143–144	$C_{15}H_{14}N_2O_2$	2.18c (1H, OH), 3.74c (3H, CH_3), 4.73c (2H, CH_2), 6.50 d (1H, H-4', *J* 3.5), 6.70 d (1H, H-3',*J* 3.5), 7.22 s (1H, imide), 7.42–7.45 m (3H, arom.), 7.63 d (2H, arom., *J* 7.8)
XVII	57	79–80	$C_{15}H_{12}N_2OS$	3.78 s (3H, CH_3), 7.35 s (1H, imide), 7.44 d (1H, H-3', *J* 4.0), 7.49 t (3H, arom., *J* 6.70), 7.66 d (2H, arom., *J* 7.2), 7.70 d (1H, H-4', *J* 4.0), 9.86 s (1H, CHO)
XVIII	45	86–87	$C_{16}H_{14}N_2OS$	2.55 s (3H, CH_3), 7.30c (1H, imide), 7.36 d (1H, H-3', *J* 4.0), 7.47 t (3H, arom., *J* 7.0), 7.64 d (2H, arom., *J* 7.2), 7.66 d (1H, H-4', *J* 4.0)
XIX	64	123–124	$C_{21}H_{16}N_2OS$	3.77 s (3H, CH_3), 7.34 s (1H, imide), 7.41 d (1H, H-3', *J* 4.0), 7.49 t (4H, arom., *J* 6.7), 7.50 d (1H, arom., *J* 7.2), 7.56 d (1H, arom., *J* 7.2), 7.61 d (1H, H-4', *J* 4.0) 7.66 d (2H, arom., *J* 7.7), 7.87 d (2H, arom., *J* 7.0)
XX	77	157–158	$C_{15}H_{14}N_2OS$	2.20 s (1H,OH), 3.74 s (3H, CH_3), 4.90 s (2H, CH_2), 7.30 s (1H, imide), 7.32 d (1H, H-4', *J* 3.9), 7.34 d (1H, H-3', *J* 3.9), 7.45 t (3H, arom., *J* 7.0), 7.63 d (2H, arom., *J* 7.2)
XXI	56	112–113	$C_{14}H_{11}BrN_2O$	3.75 s (3H, CH_3), 6.40 d (1H, H-4', *J* 3.5), 6.65 d (1H, H-3', *J* 3.5), 7.18 s (1H, imide), 7.42–7.45 m (3H, arom.), 7.63 d (2H, arom., *J* 7.7)
XXII	20	91–93	$C_{14}H_{11}N_3O_3$	3.80 s (3H, CH_3), 6.92 d (1H, H-3', *J* 3.8), 7.42 d (1H, H-4', *J* 3.8), 7.48–7.51 m (3H, arom.), 7.47 s (1H, imide), 7.64 d (2H, arom., *J* 7.7)
XXIII	75	307–308	$C_{14}H_{12}N_2O_3S_2$	3.82 s (3H, CH_3), 7.15 d (1H, H-3', *J* 3.7), 7.35 d (1H, H-4', *J* 3.7), 7.67 t (3H, arom., *J* 7.0), 7.83 d (2H, arom., *J* 7.8), 8.12 s (1H, imide)
XIV	33	89–90	$C_{14}H_{11}BrN_2S$	3.74 s (3H, CH_3), 7.30 s (1H, imide.), 7.15 d (1H, H-4', *J* 4.0), 7.35 d (1H, H-3', *J* 4.0), 7.48 t (3H, arom., *J* 6.9), 7.63 d (2H, arom., *J* 7.2)
XV	31	95–97	$C_{14}H_{11}BrN_2S$	3.76 s (3H, CH_3), 7.05 d (1H, H-5', *J* 1.3), 7.28 d (1H, H-3', *J* 1.3), 7.32 s (1H, imide), 7.49 t (3H, arom., *J* 6.9), 7.63 d (2H, arom., *J* 7.2)
XVI	66	132–133	$C_{14}H_{11}BrN_3O_2S$	3.69 s (3H, CH_3), 7.31 d (1H, H-3', *J* 4.2), 7.48–7.51 m (3H, arom.), 7.68 s (1H, imide), 7.70 (2H, arom., *J* 7.7), 8.01 d (1H, H-4', *J* 4.2)

[a] The results of elemental analysis for the C, H, and N content agree with the calculated values within ±0.34%. The ^{1}H NMR spectrum of **XXIII** was recorded in DMSO-d_6.

determined by the capillary method with a PTP device. The yield and properties of the compounds are given in the table.

2-Phenyl-4(5)-(2'-hetaryl)imidazoles VII and VIII. To a solution of 6.86 g (0.07 mol) of potassium acetate in 100 ml of methanol, we added 0.05 mol of 2-bromoacetylfuran (-thiophene) **III** or **IV**. The mixture was refluxed for 2 h under stirring with a magnetic stirrer. The KBr precipitate was filtered off, and the filtrate was added to a solution containing 100 g (0.5 mol) of copper acetate in 1200 ml of 25% ammonia solution and 5.3 g (0.05 mol) of benzaldehyde. The mixture was refluxed for 1.5 h, after which the copper salt was separated, suspended in 100 ml of water, and decomposed by passing hydrogen sulfide for 0.5 h. The resulting solution was acidified with concentrated HCl, and CuS was separated. Then the filtrate was alkalized with 25% ammonia solution. The precipitate of **VII** and **VIII** was filtered off and crystallized from alcohol; mp 160–162°C (**VII**), 173–175°C (**VIII**).

1-Methyl-2-phenyl-4(5)-(2'-hetaryl)imidazoles IX–XII. Isomer mixture. To a mixture of 0.01 mol of **VII** or **VIII**, 0.62 g (0.011 mol) of powdered KOH, and 10 ml of acetone, we added dropwise with vigorous stirring at 3–5°C 0.68 g (0.011 mol) of methyl iodide, avoiding warm-up of the reaction mixture over 8°C. The mixture was stirred at this temperature for 1 h and poured into 100 ml of water, and the precipitated product was filtered off. By fractional crystallization from hexane we isolated and identified compounds **XI** and **XII**. Compounds **IX** and **X** were not isolated pure.

1-Methyl-2-phenyl-5-(5'-acyl-2'-hetaryl)imidazoles XIV, XV, XVIII, and XIX. General procedure. A mixture of 0.005 mol of **XI** or **XII** and 0.01–0.015 mol of appropriate acylating agent (acetic acid, benzoic acid) in 10 g of polyphosphoric acid was stirred for 2–4 h at 90–100°C. Then the mixture was cooled by dilution with 50 ml of cold water and carefully neutralized with a 25% NH_4OH solution. The precipitated product was extracted with methylene chloride (3 × 15 ml), the extract was dried over $CaCl_2$, the solvent was evaporated, and the residue was passed through a column packed with alumina, 15 cm long and 1 cm in diameter. The eluent was methylene chloride.

1-Methyl-2-phenyl-5-(5'-formyl-2'-hetaryl)imidazoles XIII and XVII. A mixture of 0.005 mol of **XI** or **XII** and 1.4 g (0.01 mol) of hexamethylenetetramine in 15 g of polyphosphoric acid was stirred at 70–80°C for 1–3 h. Then the mixture was diluted with 50 ml of water. The reaction product was isolated in the same way as acyl derivatives **XIV** and **XV**.

1-Methyl-2-phenyl-5-(5'-hydroxymethyl-2'-hetaryl)imidazoles XVI–XX. To a mixture of 0.005 mol of **XI** or **XII** with 70 ml of formalin, we added a drop of concentrated HCl and refluxed for 2 h. Then the mixture was poured into 100 ml of cold water and neutralized with a 25% NH_4OH solution to pH 7–8. The precipitate was filtered off and thoroughly washed with cold water. The product was crystallized from alcohol.

1-Methyl-2-phenyl-5-(5'-sulfo-2'-thienyl)imidazole XXIII. A mixture of 1.2 g (0.005 mol) of **XII**, 0.98 g (0.01 mol) of sulfuric acid (d = 1.84), and 20 g of polyphosphoric acid was heated at 100–110°C for 2 h. Then the mixture was cooled and diluted with 50 ml of water, and the precipitate of sulfonic acid **XXIII** was filtered off. The product was crystallized from water.

1-Methyl-2-phenyl-5-(5'-bromo-2'-furyl)imidazole XXI. To a stirred solution of 1.12 g (0.005 mol) of **XI** in 10 ml of dichloroethane, we added dropwise at 0°C 1.6 g (0.01 mol) of bromine. The mixture was stirred for 0.5 h at 0°C and poured into 25 ml of a 25% ammonia solution. The organic layer was washed with water (2 × 25 ml), dried for 10 min over anhydrous sodium sulfate, and chromatographed on a column (h = 20 cm, d = 2.5 cm) packed with 70 ml of aluminum oxide (eluent chloroform).

1-Methyl-2-phenyl-5-[4'(5')-bromo-2'-thienyl]-imidazoles XXIV and XXV. Isomer mixture. To a solution of 1.12 g (0.005 mol) of **XII** in 20 ml of dichloroethane, we gradually added at room temperature a solution of 0.8 g (0.005 mol) of bromine in 10 ml of dichloroethane. After adding the whole amount of bromine, the mixture was refluxed for 30 min. The precipitate of hydrobromides **XXIV** and **XXV** was separated, converted to the base by treatment with an ammonia solution, and chromatographed as in the previous experiment.

1-Methyl-2-phenyl-5-(5'-nitro-2'-hetaryl)imidazoles XXII–XXVI. To prepare the nitrating mixture, a 100-ml Erlenmeyer flask was charged with 16.5 g (0.07 mol) of $Cu(NO_3)_2 \cdot 3H_2O$, and 40 ml of acetic anhydride was added in small portions with strong cooling, avoiding warm-up of the mixture over 30–40°C. After the exothermic reaction was complete, the

mixture was allowed to stand at room temperature for 24 h, after which the copper(II) acetate precipitate was filtered off. The resulting mixture was stored for no more than 10 days at 5–10°C.

To a solution of 0.005 mol of **XI** and **XII** in 5 ml of freshly distilled acetic anhydride, 1.4 ml of the nitrating mixture was added in small portions with vigorous stirring at room temperature. The reaction time was 30–40 min. Then 25 ml of cold water was added, and the mixture was neutralized with a 25% ammonia solution. The precipitate was filtered off, thoroughly washed with water, and chromatographed on a column packed with aluminum oxide (eluent methylene chloride). The product was crystallized from alcohol.

CONCLUSIONS

(1) A procedure was developed for preparing 2-phenyl-4(5)-(2'-hetaryl)imidazoles by condensation of 2-furoylmethyl and 2-thenoylmethyl acetates with benzaldehyde under the conditions of Weidenhagen reaction without using dangerously explosive diazomethane.

(2) The 1-methyl-2-phenyl-5-(2'-furyl)imidazoles and 1-methyl-2-phenyl-5-(2'-thienyl)imidazoles studied, in contrast to the related 1-methyl-2-(2'-hetaryl)-imidazoles, are more reactive toward electrophilic agents.

(3) Electrophilic substitution in 1-methyl-2-phenyl-5-(2'-hetaryl)imidazole molecules occurs exclusively in the hetaryl ring.

REFERENCES

1. Krasovitskii, B.M., Pereyaslava, D.G., and Yushko, E.T., in *Monokristally, stsintillyatory i organicheskie lyuminofory* (Single Crystals, Scintillators, and Organic Luminophores), Kharkov: Vses. Nauchno-Issled. Inst. Monokristallov, Stsintillyatsionnykh Materialov i Osobo Chistykh Khimicheskikh Veshchestv, 1968, issue 4, pp. 105–115.
2. Doroshenko, A.O., Patesenker, L.D., and Baumer, V.N., *Mol. Eng*., 1994, no. 3, p. 343.
3. Krasovitskii, B.M. and Afanasiadi, L.M., in *Preparativnaya khimiya lyuminoforov* (Preparative Chemistry of Luminophores), Kharkov: Folio, 1997, p. 206.
4. Roshal', A.D., Luk'yanov, B.S., and El'chaninov, M.M., *Zh. Fiz. Khim*., 2003, vol. 77, no. 10, pp. 1899–1905.
5. Schubert, H., Hagen, E. and Lehman, G., *J. Pr. Chem*., 1962, vol. 17, pp. 173–179.
6. Kirugava, Y., *Synthesis*, 1981, no. 2, pp. 124–127.
7. Stoyanov, V.M., El'chaninov, M.M., and Pozharskii, A.F., *Khim. Geterotsikl. Soedin*., 1991, no. 10, pp. 1414–1418.
8. Stoyanov, V.M., El'chaninov, M.M., Simonov, A.M., and Pozharskii, A.F., *Khim. Geterotsikl. Soedin*., 1989, no. 10, pp. 1396–1400.
9. Churkin, Yu.D. and Savin, V.I., *Khim. Geterotsikl. Soedin*., 1968, no. 2, pp. 369–370.