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CHEMISTRY

Synthesis and Properties of a New Family of Phosphorus- and Nitrogen-Containing Ionenes

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Abstract—Polyquaternization reactions of bis[2-(4-pyridyl)ethyl]phenylethylphosphine oxide and tris[2-(4-pyridyl)ethyl]phosphine oxide with 1,4-dibromobutane were implemented for the first time to give linear (water-soluble) and cross-linked (limitedly water swelling), respectively, representatives of new phosphorus- and nitrogen-containing ionenes. The synthesized linear ionenes react with heparin and polyacrylic acid yielding water-insoluble polyelectrolyte complexes.

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Ionenes, i.e., heterochain polymers containing positively charged quaternary nitrogen atoms in the backbone, attract persistent interest of researchers as an important class of polycations [1–5]. They are used in the production of pharmaceutical drugs (in particular, to purify alendronic acid used for bone tissue therapy, including sarcoma treatment [4]), as cross-linking agents [1], elastomers [3], and radical reaction initiators [1]. Compounds possessing clear-cut thixotropic [2], biocidal [5], and antimicrobial [6] properties were found among ionenes.

The traditional method of ionene synthesis is based on atom-economical reaction of tertiary aliphatic and aromatic amines with dihaloalkanes [1, 3, 5]. The same method was used to synthesize ionenes based on bispyridines [3] and bisazoles [7]. The latter are able to form interpolymer polyelectrolyte complexes with synthetic (polyacrylic acid) and natural (heparin) polyanions, which, in particular, indicates a potential antiheparin activity of azole-containing ionenes [7].

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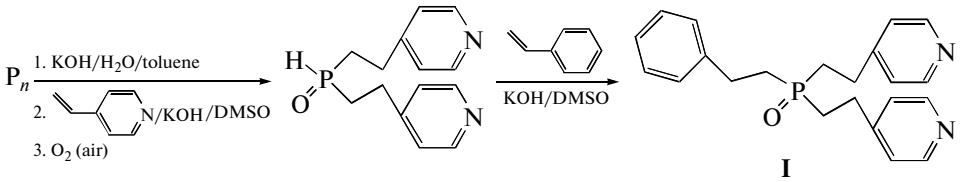
It is noteworthy that pyridinium polycations containing phosphoryl groups have not been reported in the literature, although it is known, for example, that tris(2-organylpyridiniumethyl)phosphine oxide trihalides exhibit pronounced antibacterial properties [8]. In addition, neutral polypyridylphosphine oxides are precursors for the design of antibacterial drugs [8] and serve as building blocks for organic and organometallic synthesis [8–10].

This communication describes the first study of reactions of bis[2-(4-pyridyl)ethyl]phenylethylphosphine oxide (**I**) and tris[2-(4-pyridyl)ethyl]phosphine oxide (**II**) with 1,4-dibromobutane giving linear (water-soluble) and cross-linked (limitedly water swelling), respectively, phosphorus- and nitrogen-containing polycations with the goal to synthesize a new class of phosphorus- and nitrogen-containing ionenes.

Bispyridylphosphine oxide (**I**) was synthesized here for the first time in 52% yield by the reaction of bis[2-(4-pyridyl)ethyl]phosphine oxide with styrene in the KOH–DMSO system. The initial bis[2-(4-pyridyl)ethyl]phosphine oxide was prepared by an original method [11, 12] comprising the generation of phosphine from red phosphorus and aqueous potassium hydroxide, the addition of phosphine to 4-vinylpyridine, and oxidation of the resulting bis[2-(4-pyridyl)ethyl]phosphine in air to the corresponding secondary phosphine oxide (Scheme 1).



Scheme 1. Synthesis of bis[2-(4-pyridyl)ethyl]phenylethylphosphine oxide.

Experiments showed that bispyridylphosphine oxide (**I**) readily (60°C, 24 h, ethanol, 1 : 1 molar ratio of the reactants) reacts with 1,4-dibromobutane to give linear ionene type polymers (**III**) in 38–51% yields. Two samples of these ionenes were prepared (**IIIa, IIIb**), their yields (Table 1) and the viscosity of their aqueous solutions (Fig. 1) depending on the reactant concentrations in ethanol.

The obtained ionenes **IIIa** and **IIIb** are light pink-colored powders decomposing above 280°C. The IR spectra of ionenes **IIIa** and **IIIb** contain characteristic absorption bands of the phosphine oxide P=O group centered at 1166 cm^{-1} and for the pyridinium ring at 1516, 1599, and 1637 cm^{-1}.

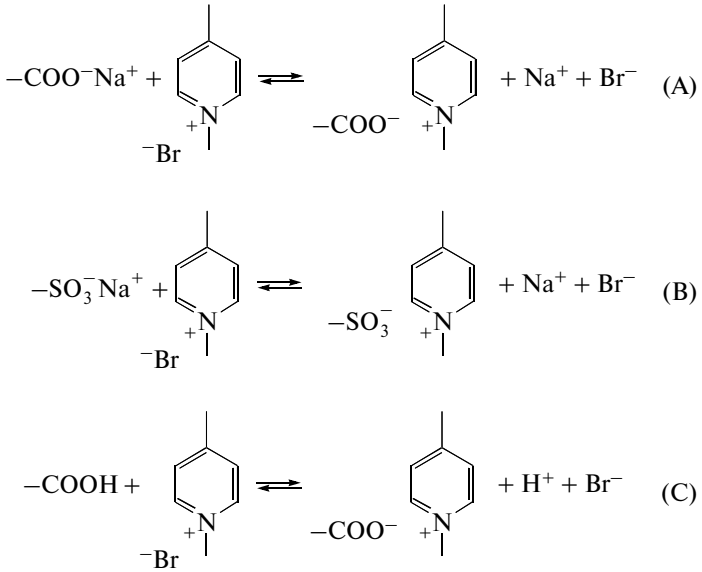
The data of ^1H NMR spectra confirm the structure of ionenes **IIIa** and **IIIb** (δ, ppm, D_2O): 8.71 d and 8.65 d (pyridine ring protons, $^3J_{HH} = 6$ Hz), 8.03–7.96 m (phenyl ring protons), 4.54, 3.27, 2.51, and 2.07 m (methylene protons).

The ^{31}P NMR (δ_P, D_2O) spectra of ionenes **IIIa** and **IIIb** exhibit a broadened signal at 55–56 ppm (characteristic of tertiary tris(organylpyridinium-ethyl)phosphine oxides [8]).

The elemental analysis data of ionenes **IIIa** and **IIIb** are also consistent with the presented structure (Table 1).

In aqueous solutions, linear ionenes (**IIIa, IIIb**) behave as typical polyelectrolytes for which the polyelectrolyte swelling in water occurs with dilution (Fig. 1, curves *a* and *b*). Ionene **IIIa** obtained at lower concentration of co-monomers in ethanol (Table 1, run 1) is characterized by somewhat higher viscosity of aqueous solutions (Fig. 1, curve *a*) than **IIIb** (Fig. 1, curve *b*). Apparently, polyquaternization is heterogeneous in more concentrated reaction mixtures and homogeneous in dilute ones, which promotes the formation of high-molecular-mass polycations.

Since the physiological activity of ionenes is largely determined by their ability to form interpolymer complexes with negatively charged polyelectrolytes [7], we studied the reactions of ionene **IIIa** with polyacrylic acid and heparin. These reactions can be schematically depicted as the interaction of positively charged pyridine moieties and negatively charged carboxy groups for sodium polyacrylate or sulfo and carboxy groups for heparin (Scheme 2).



Scheme 2. Polyelectrolyte reactions of ionenes with sodium polyacrylate (A) and heparin (B, C).

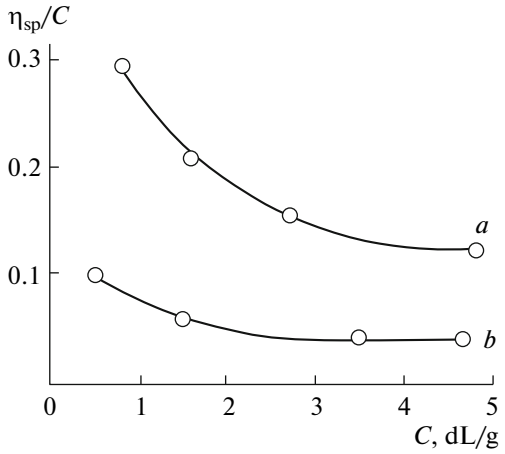


Fig. 1. Reduced viscosity (20°C) of aqueous solutions of ionenes (*a*) **IIIa** and (*b*) **IIIb** vs. concentration.

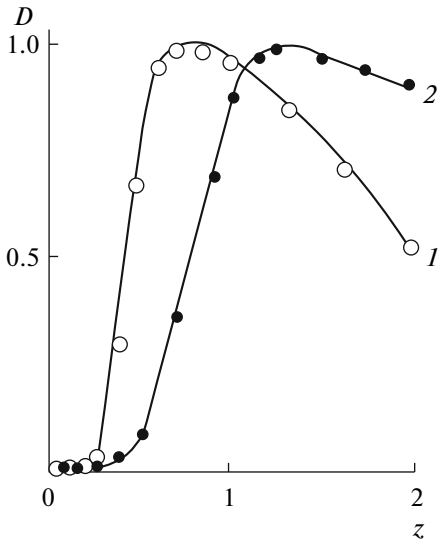
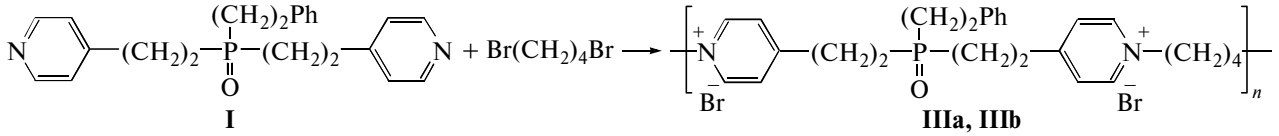


Fig. 2. Turbidimetric titration curves of solutions of (*1*) sodium polyacrylate at pH 9.5 and (*2*) heparin at pH 5.0 with an ionene solution (sample **IIIa**, Table 1). The concentration of solutions of sodium polyacrylate, heparin, and ionene is 0.0015 base-mol/L. *D* is the absorbance referred to unity; z = [ionene] : [sodium polyacrylate] (heparin).

Mixing of aqueous solutions of ionene **IIIa** and heparin or polyacrylic acid (as the sodium salt, pH 9.5) was found to result in the formation of insoluble stoichiometric polyelectrolyte complex, as confirmed by the results of turbidimetric titration of aqueous solutions of sodium polyacrylate (pH 9.5) or heparin with an aqueous solution of ionene **IIIa** (Fig. 2). In both cases, precipitation of insoluble stoichiometric polyelectrolyte complex was already noticed at the ionene/sodium polyacrylate or heparin ratio (z) of more than 0.3; the maximum precipitation corresponded to $z = 0.7–0.8$ in the case of flexible-chain polyacrylate polyanion and $z = 1.2–1.3$ in the case of rigid-chain heparin polyanion. In this case, z reflects the ratio of the ionene and the polyanion calculated in relation to the contents of positively charged (for ionene) and negatively charged groups (COO^- for sodium polyacrylate or SO_3^- and COO^- for heparin) in the reactants. When there is excess of the polycation ($z > 1$) in the reaction mixture, the stoichiometric polyelectrolyte complex with polyacrylic acid is dissolved only partly, whereas the complex with heparin remains insoluble even with a fourfold excess of ionene (Fig. 2). This distinguishes the phosphorus- and nitrogen-containing ionenes **IIIa** and **IIIb** from known ionenes based on aliphatic amines and azoles, because in the latter cases, water-soluble non-stoichiometric polyelectrolyte complexes are formed, no matter whether the blocking polyelectrolyte (ionene) or the lyophilizing polyelectrolyte (sodium polyacrylate or heparin) is taken in excess [7, 13]. Probably, the difference is due to higher hydrophobicity of phosphorus- and nitrogen-containing ionenes caused by the presence of phenyl side groups in the molecule. As a consequence,

Table 1. Reaction of bispyridylphosphine oxide (**I**) with 1,4-dibromobutane (60°C, 24 h)

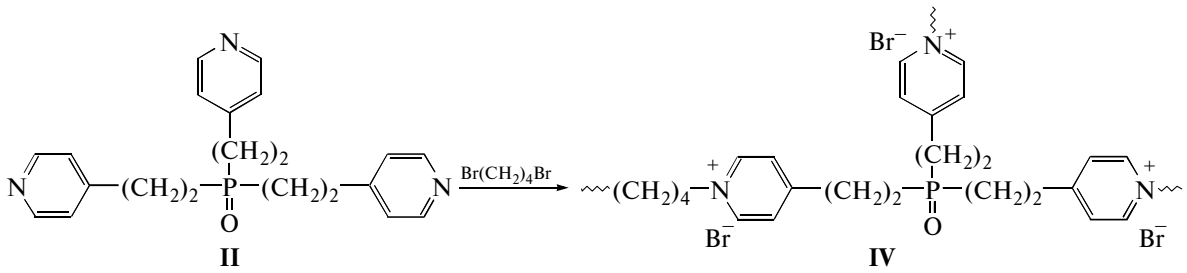


I

Pyridylphosphine oxide **I**, mmol	1,4-Dibromobutane, mmol	EtOH, mL	Ionene (yield), %	Elemental analysis* (found), %				
				C	H	Br	N	P
0.6	0.6	2.2	**IIIa** (38)	54.68	6.54	27.52	5.13	4.60
0.6	0.6	1.0	**IIIb** (51)	55.03	6.32	29.57	5.04	4.43

*Calculated for $C_{26}H_{33}Br_2N_2OP$, %: C, 53.81; H, 5.73; Br, 27.54; N, 4.83; P, 5.34.

Table 2. Reaction of trispyridylphosphine oxide (**II**) with 1,4-dibromobutane*



Run	Pyridylphosphine oxide **II**, mmol	1,4-Dibromobutane, mmol	Ionene** (yield), %	Elemental analysis*** (found), %				
				C	H	Br	N	P
1	0.6	0.6	**IVa** (34)	45.33	5.56	38.15	5.76	4.24
2	0.6	0.9	**IVb** (29)	43.94	5.46	40.57	5.47	4.05
3****	0.5	0.75	**IVc** (43)	45.21	5.52	39.70	5.58	4.17
4	0.6	1.2	**IVd** (35)	43.53	5.31	41.18	4.67	3.61

* The reaction was carried out at 60°C for 24 h in ethanol (1 mL).
** Swelling ratio in H_2O: 2.3, 1.8, 3.9, and 12.8 for **IVa**, **IVb**, **IVc**, and **IVd**, respectively.
*** For $C_{25}H_{32}Br_3N_3OP$, anal. calcd. (%): C, 47.05; H, 5.26; Br, 36.14; N, 6.10; P, 4.49.
**** A mixture of EtOH (0.5 mL) and DMF (1 mL) was used as the solvent.

the insoluble complex is formed even at a relatively large excess ($z \geq 0.3$) of the lyophilizing agent (polyanion) and there is no region of existence of a non-stoichiometric polyelectrolyte complex with an excess of blocking agent (polycation).

The results indicate that ionenes of type **III** can bind heparin into polyelectrolyte complex, which is, moreover, water-insoluble (Scheme 2). Owing to this feature, the ionenes we synthesized could be used in the future to neutralize the anticoagulating action of heparin and to control in this way blood coagulation properties [7, 14].

Tris(pyridyl)phosphine oxide (**II**) (prepared beforehand from red phosphorus and 4-vinylpyridine [15]) reacts with 1,4-dibromobutane on heating (60°C, 24 h) in ethanol to give phosphorus- and nitrogen-containing ionenes **IV**, which are insoluble in organic solvents and in water and evidently have a three-dimensional network structure. The structure proposed for ionenes **IV** was also confirmed by elemental analysis data (Table 2). The yields (29–43%) and the swelling ratios in water (1.8–12.8) of ionenes **IVa**–**IVd** depend little on the initial reactant ratio (Table 2) and the solvent nature (Table 2, no. 3).

Ionenes **IVa**–**IVd** are hygroscopic light pink powders. The IR spectra of **IVa**–**IVd** exhibit characteristic absorption bands of the phosphine oxide P=O group centered at 1166 cm^{-1} and for the pyridinium ring at 1516, 1599, and 1637 cm^{-1}.

Thus, polyquaternization of bis[2-(4-pyridyl)ethyl]-phenylethyl- and tris[2-(4-pyridyl)ethyl]phosphine oxides with dibromobutane gave linear (water-soluble) and cross-linked (limitedly water swelling) phosphorus- and nitrogen-containing polycations (ionenes). The ability of linear ionenes to be involved in reactions with negatively charged polyelectrolytes (in particular, heparin and polyacrylic acid) to give water-insoluble polyelectrolyte complexes gives hope for subsequent application of these compounds as heparin antagonists. The synthesized cross-linked ionenes are promising ion exchange resins and sorbents [3] and can also be used as polymer hydrogels in medicine and agriculture [3].

Synthesis of bis[2-(4-pyridyl)ethyl]phenylethylphosphine oxide (I). Styrene (1.38 g, 13.3 mmol) was added dropwise at 56–58°C over a period of 0.5 h to a mixture of bis[2-(4-pyridyl)ethyl]phosphine oxide (2.3 g, 8.8 mmol), KOH (0.67 g, 12.0 mmol), DMSO (20 mL), water (0.18 mL), and hydroquinone (0.01 g). The reaction mixture was heated (56–58°C) for additional 8 h, cooled, diluted with water, extracted with chloroform, and dried with potassium carbonate. Chloroform and DMSO were evaporated and the residue was dried in vacuum to give 1.65 g (52% yield) of bis[2-(4-pyridyl)ethyl]phenylethylphosphine oxide (**I**), white crystals, $T_m = 192$°C (from ethyl acetate).

For $C_{22}H_{25}N_2OP$ anal. calcd. (%): C, 72.51; H, 6.91; N, 7.69; P, 8.50.

Found (%): C, 72.34; H, 6.79; N, 7.74; P, 8.65.

^{1}H NMR, δ, ppm ($CDCl_3$): 1.82 (m, 4H, CH_2P), 1.93 (m, 2H, CH_2P), 2.74 (m, 6H, CH_2CH_2P), 6.91

(d, 4H, Py, CH=C, $^3J_{HH}$ = 5.5 Hz), 7.01–7.13 (m, 5H, Ph), 8.34 (d, 4H, Py, CH=N, $^3J_{HH}$ = 5.5 Hz). ^{13}C NMR, δ, ppm ($CDCl_3$): 26.67 (CH_2Py, $^2J_{CP}$ = 2.2 Hz), 27.45 (CH_2Ph, $^2J_{CP}$ = 3.0 Hz), 28.82 (d, PyCH_2CH_2P, $^1J_{CP}$ = 63.4 Hz), 29.86 (d, PhCH_2CH_2P, $^1J_{CP}$ 62.9 Hz), 122.97 (CH=C, Py), 126.44 (C^p), 127.70 (C^m), 128.52 (C^o), 139.94 (d, C^i, $^3J_{CP}$ = 12.1 Hz), 149.18 (d, CH=C, Py, $^3J_{CP}$ = 13.3 Hz), 149.75 (CH=N). ^{31}P NMR, δ_P, ppm ($CDCl_3$): 45.7. IR (KBr, cm^{-1}): 1165 (P=O).

Synthesis of ionenes IIIa and IIIb. A solution of bis[2-(4-pyridyl)ethyl]phenylethylphosphine oxide (**I**) (0.21 g, 0.6 mmol) and 1,4-dibromobutane (0.13 g, 0.6 mmol) in 2.2 mL of ethanol for ionene **IIIa** and in 1.0 mL of ethanol for ionene **IIIb** was heated in a sealed ampoule under argon (60°C, 24 h). The reaction mixture was precipitated with acetone (25 mL), and the ionene precipitate formed was washed with acetone (3 × 25 mL) and dried in vacuum to a constant weight to give 0.13 g of ionene **IIIa** (38% yield) and 0.17 g of ionene **IIIb** (51% yield) as light pink powders, mp (dec.) 280–290°C.The data of IR and ^{1}H and ^{31}P NMR spectra and elemental analysis of ionenes **IIIa** and **IIIb** are given above.

General procedure for the synthesis of ionenes IVa–IVd. A solution of tris[2-(4-pyridyl)ethyl]phenylethylphosphine oxide (**II**) and 1,4-dibromobutane in 1 mL of ethanol was heated in a sealed ampoule under argon (60°C, 24 h) (for reactant ratios, see Table 2). The product was precipitated with acetone (25 mL) and the ionene precipitate was washed with acetone (3 × 25 mL) and dried in vacuum to a constant weight to give ionenes **IVa**–**IVd** in 34, 29, 43, and 35% yields, respectively, as light pink powders insoluble in organic solvents and swelling in water, mp (dec.) 280–290°C. The data of IR spectra and elemental analysis are given above.

Bis[2-(4-pyridyl)ethyl]phosphine oxide and tris[2-(4-pyridyl)ethyl]phosphine oxide (**II**) were prepared and purified according to procedures reported in [11] and [15], respectively. 1,4-Dibromobutane (Merck) was used as the quaternization agent. IR spectra were measured on a Specord IR-75 instrument. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker 400DPX spectrometer (400.13, 100.62, and 161.98 MHz, respectively) using HMDS as an internal standard and 85% H_3PO_4 as an external standard. The viscosity of aqueous solutions of polymers was determined on an Ubbelohde viscometer at 20°C. The swelling ratio of the cross-linked ionenes in water was determined by gravimetric method and calculated by the formula

$$K_{sw} = \frac{M_h - M_p}{M_p},$$

where M_h is the swollen hydrogel mass and M_p is the dry polymer mass.

The interpolymer reactions of the ionenes were studied using commercial heparin, Spofa (Czechia) (30% content of acid groups and acid number of 81.3 mg/g) and non-fractionated polyacrylic acid sample with MM 170000. The formation of interpolymer complexes was studied by turbidimetric titration using a KFK-2 photocolorimeter.

REFERENCES

1. Bicak, N. and Tunca, U., *Polym. Bull.*, 2000, vol. 43, pp. 477–483.
2. Misawa, Y., Koumura, N., Matsumoto, H., Tamaoki, N., and Yoshida, M., *Macromolecules*, 2008, vol. 41, no. 22, pp. 8841–8846.
3. Williams, S.R. and Long, T.E., *Prog. Polym. Sci.,* 2009, vol. 34, no. 8, pp. 762–782.
4. Svidritskii, E.P., Tszin, M.Sh., Il'in, V.I., Dyn'kov, D.I., Pirogov, A.V., and Shpigun, O.A., *Vestn. Mosk. Univ., Ser. 2: Khim.*, 2010, vol. 51, no. 1, pp. 53—61.
5. Mattheis, C., Zheng, M., and Agarwal, S., *Macromol. Biosci.*, 2012, vol. 12, no. 3, pp. 341–349.
6. Carmona-Ribeiro, A.M. and de Melo Carrasco, L.D., *Int. J. Mol. Sci.*, 2013, vol. 14, no. 5, pp. 9906–9946.
7. Kizhnyaev, V.N., Krakhotkina, E.A., Petrova, T.L., Kazantseva, M.V., Pokatilov, F.A., and Verkhozina, O.N., *Vysokomol. Soedin., Ser. B*, 2011, vol. 53, no. 3, pp. 494–501.
8. Gusarova, N.K., Kuznetsova, E.E., Arbuzova, S.N., Shaikhudinova, S.I., Malysheva, S.F., Kozlova, G.V., Zorina, E.F., and Trofimov, B.A., *Khim.-Farm. Zh.*, 1994, no. 9, pp. 37–39.
9. Trofimov, B.A., Andriyankova, L.V., Shaikhudinova, S.I., Kazantseva, T.I., Mal'kina, A.G., Zhivet'ev, S.A., and Afonin, A.V., *Synthesis,* 2002, no. 7, pp. 853–855.
10. Saucedo, A.S.A., Hagenbach, A., and Abram, U., *Inorg. Chem. Commun.,* 2009, vol. 12, pp. 128–130.
11. Gusarova, N.K., Trofimov, B.A., Malysheva, S.F., Shaikhudinova, S.I., Belogorlova, N.A., Arbuzova, S.N., Nepomnyashchikh, K.V., and Dmitriev, V.I., *Zh. Org. Khim.*, 1997, vol. 67, no. 1, pp. 70–76.
12. Gusarova, N.K., Arbuzova, S.N., and Trofimov, B.A., *Pure Appl. Chem.,* 2012, vol. 84, no. 3, pp. 439–459.
13. Gulyaeva, Zh.G., Zansokhova, M.F., Zezin, A.B., and Kabanov, V.A., *Vysokomol. Soedin. Ser. B*, 1985, vol. 27, no. 6, pp. 426–429.
14. Efimov, V.S., Men'shova, G.I., and Gulyaeva, Zh.G., *Farmakol. Toksikol.*, 1978, vol. 41, no. 4, pp. 409–413.
15. Gusarova, N.K., Trofimov, B.A., Malysheva, S.F., Arbuzova, S.N., Shaikhudinova, S.I., Dmitriev, V.I., Polubentsev, A.V., and Albanov, A.I., *Zh. Org. Khim.*, 1993, vol. 63, no. 1, pp. 53–59.

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