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Phosphorylation of 1,4-Bis(hydroxymethyl)benzene with Trivalent Phosphorus Derivatives

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Abstract — Phosphorylation of 1,4-bis(hydroxymethyl)benzene with complete phosphorous acid amides and phenyl phosphorodichloridite is studied. Some phosphorus-containing linear systems, the phosphamacrocycle precursors, are synthesized. The possibility of synthesis of phosphamacrocyclic systems based on 1,4-bis(hydroxymethyl)benzene is considered; it was shown that this compound does not tend to form macrocycles.
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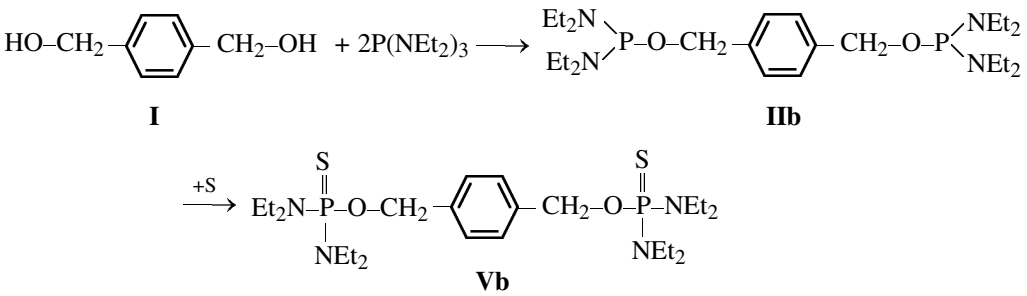
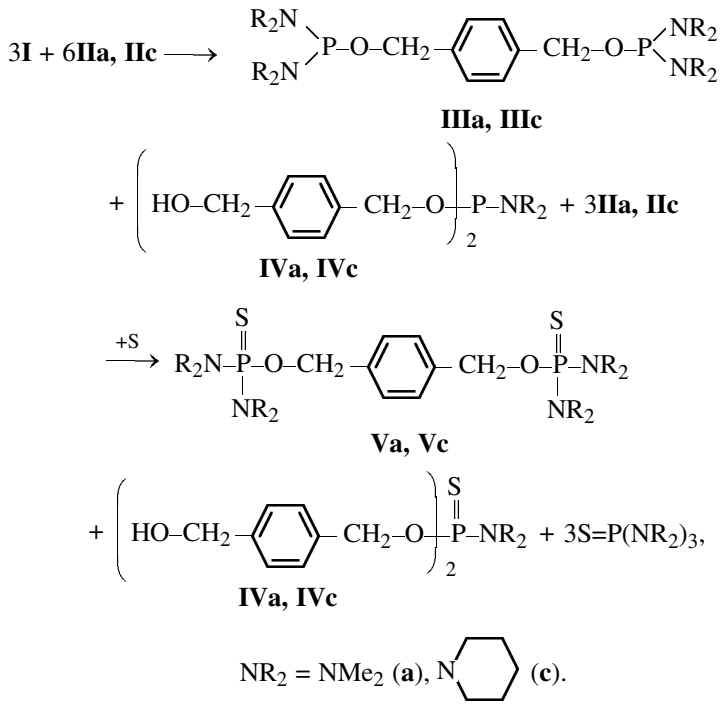
Previously we prepared a series of phosphamacrocyclic compounds based on aromatic diols and phosphorous acid amides using methodologies of molecular assembling, direct cyclophosphorylation, and dismutation of aromatic diol tetraalkylphosphorodiamidites [1–6]. In this work we studied phosphorylation of alkylaromatic diols with both complete phosphorous acid amides and phosphorochloridites and examined the possibility of using such systems for constructing macrocycles. The first attempt of bringing alkylaromatic diols into phosphorylation was reported in [7]. As an object of our study we chose the simplest aromatic glycol, 1,4-bis(hydroxymethyl)benzene **I**.

We started our work with carrying out phosphorylation of diol **I** with different phosphorylating reagents. The reaction with complete phosphorous acid amides **IIa**–**IIc** at the reactant ratio of 1 : 2 was performed at room temperature, unlike the phosphorylation of benzyl alcohol with hexaethylphosphorous triamide **IIb** on heating [8]. We used acetonitrile and 1,4-dioxane as solvents. With **IIb**, the reaction followed the scheme:



After two days, in the ^{31}P NMR spectrum of the reaction mixture in acetonitrile we found only one signal, a singlet at δ_P 135.4 ppm, characteristic of esters of phosphorous acid diamides with aliphatic substituents. It should be noted that bisphosphorylated product **IIIb** did not undergo dismutation in acetonitrile solution even in the course of three weeks, in contrast to the related diamido esters derived from aromatic systems [5, 6].

The reaction of diol **I** with hexamethylphosphorous triamide **IIa** or phosphorous tripiperidide **IIc**, both in acetonitrile and in dioxane, yielded two products. For example, the ^{31}P NMR spectrum of the reaction mixture from the synthesis of **IIIa** contained signals at δ_P 148.1 (amido diester), 137.5 (diamido ester), and 122.2 ppm (phosphorous acid triamide). The signal with chemical shift δ_P 148.1 ppm is the strongest.



Presumably, products **IV** are formed concurrently with bisphosphorylated derivatives **III**.

The time of complete phosphorylation and the ^{31}P chemical shifts of the compounds prepared are listed in the table.

Such a difference in the phosphorylation pathways with compounds **IIa**, **IIc**, and **IIb** may be due to the difference in the activity of the leaving groups. To confirm this assumption, we changed the phosphorylation temperature. The reaction of **I** with **IIb** was carried out at 70°C. We found that, under these conditions, compound **IIb** behaved in the same manner as did **IIa** at room temperature.

Both in dioxane and in acetonitrile, two products were formed, namely, phosphorous acid diamido ester **IIIb** and amido diester with chemical shifts δ_P 135.1 and 147.9 ppm, respectively. When diol **I** was phosphorylated with **IIa** with cooling to 5°C, the reaction was initially slower than at room temperature and yielded only one product, phosphorous acid diamido ester **IIIa**. However, with the reaction progress, accumulation of **IVa** was observed, and the further reaction course was similar to that at room temperature. That is, on the whole, the reaction is slower, but the general trend remains the same. Thus, the activity of complete phosphorous acid amides **IIa** and **IIb** in the reactions with diol **I** depends on the reaction temperature.

To confirm our assumptions about the structure of the products, we performed sulfurization of the reaction mixtures. The ^{31}P NMR spectrum of the reaction mixture after sulfurization contained two signals at δ_P 76–79 ppm, characteristic of the phosphorothioic acid mono- and diamides. The products **Va**–**Vc**, **VIa**, and **VIc** were isolated by column chromatography.

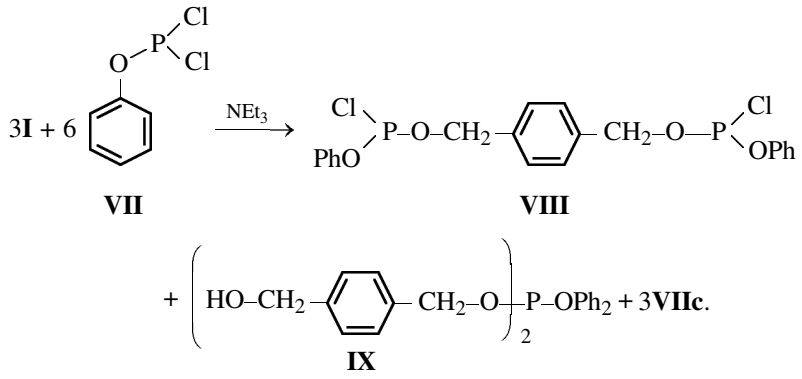
Time of complete phosphorylation of 1,4-bis(hydroxymethyl)benzene **I** and the ^{31}P NMR data for compounds **IIIa**–**IIIc, IVa**, and **IVc**

Comp. no.	R	1,4-Dioxane (days)	Acetonitrile (days)	^{31}P NMR spectrum, δ_P, ppm (ratio of integral intensities of signals)
IIIa, IVa	NMe_2	2	2	148.1, 137.5 (8 : 5)
IIIb	NEt_2	4	2	135.4
IIIc, IVc	N	5	2	145.6, 130.6 (1 : 2)

Compounds **Va**–**Vc** are low-melting solids. All the compounds were characterized by physicochemical methods such as TLC and ^{1}H and ^{31}P NMR spectroscopy, and compound **Vb** was additionally examined by single crystal X-ray diffraction [7].

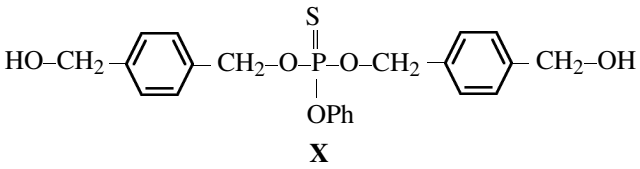
Compound **VIa** was isolated by column chromatography as oily substance in a considerably lower yield than the corresponding phosphorodiamidothioates **Va**–**Vc**. We failed to isolate compound **VIc** pure because of similar chromatographic mobilities of the products formed.

In the phosphorylation of diol **I** with phenyl phosphorodichloridite **VII** in the presence of triethylamine, we observed the same pattern as in the case of amides **IIa** and **IIc**.



The ^{31}P NMR spectrum of the reaction mixture, recorded 30 min after the start of the reaction, contained signals at δ_P 178.5, 157.1, and 135.4 ppm, corresponding to the starting dichloride **VII**, chloride **VIII**, and phosphorous acid triester **IX**, respectively.

After sulfurization of the reaction mixture, we isolated by column chromatography product **X** as individual compound in 5% yield; in the ^{31}P NMR spectrum, it gave a signal with the chemical shift δ_P 63.8 ppm.



The structure and purity of **X** were confirmed by physicochemical methods (TLC; ^{1}H and ^{31}P NMR spectroscopy) and elemental analysis.

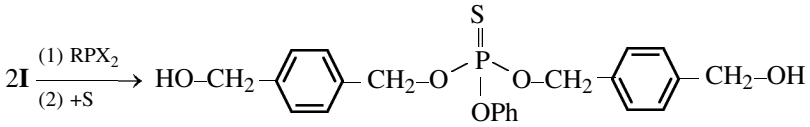
With the aim to prepare compounds **VI** and **X**, we performed their synthesis at a 2 : 1 ratio of the starting diol and phosphorylating reagent in acetonitrile in the case of **IIb** and in dioxane in the presence of triethylamine in the case of **VII**.

Compounds **VIa** and **X** were isolated by column chromatography. The purposeful synthesis gave the target compounds in four times higher yields.

From diol **I**, we prepared oligomeric systems containing fragments of resorcinol **XI** and 2,7-dihydroxynaphthalene **XII**. These syntheses were carried out by the schemes suggested earlier for the similar structures derived from aromatic diols [1, 2, 9].

The first procedure involved the addition of diol **I** to bisphosphorylated resorcinol **XIII** or 2,7-dihydroxynaphthalene **XIV**.

The synthesis was performed in acetonitrile, because the rate of the phosphorylation of compounds **XI** and **XII** in this solvent is much higher than that in



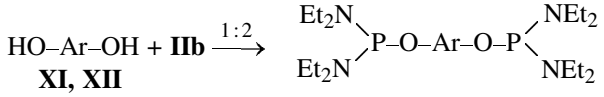
VIa, X

RPX_2 = **IIa, VII**; R = NMe (**VIa**), OPh (**X**).

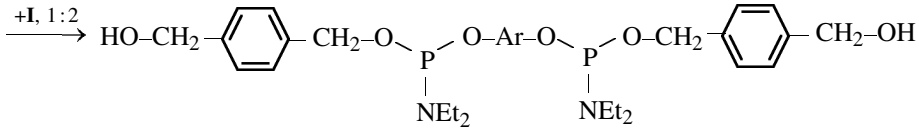
other polar solvents [9, 10]. To the synthesized diamido esters **XIII** and **XIV**, we added two molar equivalents of diol **I**. Five days after adding 1,4-bis(hydroxymethyl)benzene **I** to the reaction mixture containing **XIV**, an oily substance readily soluble in methylene chloride and dioxane separated out. Its ^{31}P NMR spectrum contained a signal at δ_P 140.7 ppm, characteristic of phosphorous acid amido diester with aromatic substituents. The solution over the oil showed a signal at δ_P 145.5 ppm in the ^{31}P NMR spectrum. In the experiment with **XI**, no precipitate formed, and the ^{31}P NMR spectrum of the reaction mixture contained the signals at δ_P 145.5 and 141.4 ppm in 1 : 3 ratio.

After sulfurization of the reaction mixtures in methylene chloride, the ^{31}P NMR spectra of the reaction solutions contained the signals at δ_P 72.5 ppm and 66–67 ppm in both cases. The compounds were isolated by column chromatography. The ^1H NMR spectra showed that, in the case of the resorcinol derivative, the product with δ_P 72.5 ppm was linear phosphoramidothioate **XIX**, and that with δ_P 66 ppm was cyclic bis(phosphoramidothioate) **XXI** described previously [1, 2]. The yield of **XIX** was as low as 8%. We failed to isolate pure the acyclic derivative of 2,7-dihydroxynaphthalene **XX**.

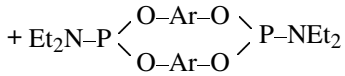
The low yield of the desired oligomers **XIX** and **XX** is probably due to the competing dismutation of bis(phosphorodiamidites) **XIII** and **XIV** [5, 6]. In our case, dismutation is more favorable than phosphorylation of diol **I** with diamido esters **XIII** and **XIV**, especially in the case of bisphosphorylated derivative of 2,7-dihydroxynaphthalene **XIV**. The second assumed pathway of the reaction involves phosphorylation of 2,7-dihydroxynaphthalene **XII** with bis(phosphorodiamidite) **IIIb**. Here dismutation as a compet-



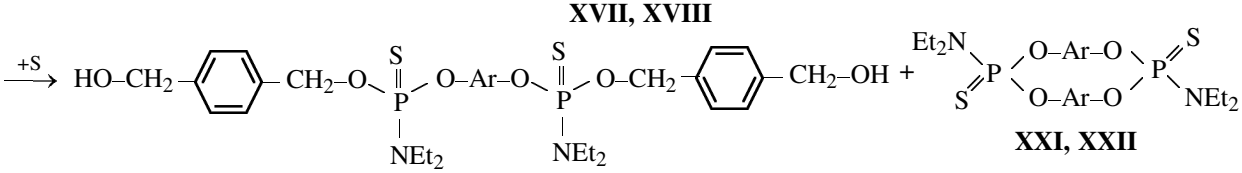
XI, XII **XIII, XIV**



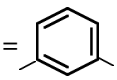
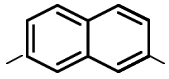
XV, XVI

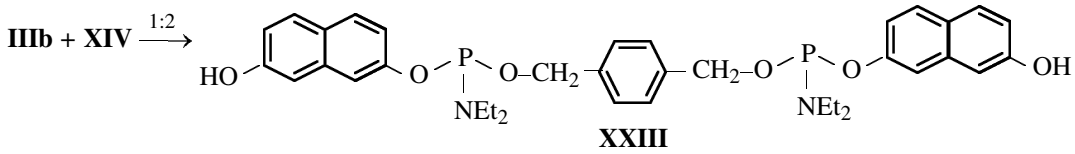


XVII, XVIII



XIX, XX **XXI, XXII**

Ar =  (**XI, XIII, XV, XVII, XIX, XXI**);  (**XII, XIV, XVI, XVIII, XX, XXII**).



XXIII

ing process will be absent, because compound **IIIb** is resistant to dismutation.

After the bisphosphorylation of diol **I** in dioxane, a solution of 2,7-dihydroxynaphthalene in dioxane was added to the reaction mixture in a stoichiometric amount. A day later, a glassy precipitate insoluble in organic solvents formed. According to the TLC data, the solution over the precipitate contained naphthalenic diol **XII** only. The same pattern was observed when a mixture of bisphosphite **IIIb** and naphthalenic diol **XII** in 1:2.5 or 1:3 ratio was used. Thus, changing the synthesis scheme did not lead to the desired increase in the yield of linear oligomers derived from diol **I**.

The second part of our study concerned finding the conditions for preparing macrocyclic systems from phosphorus-containing 1,4-bis(hydroxymethyl)benzene derivatives **VIIa**, **X**, and **XIX**.

We expected that the use of 1,4-bis(hydroxymethyl)benzene **I** as a building block in the synthesis of a macrocyclic system would lead to the formation of bulkier configurations than with rigid aromatic diols.

Recently we showed that direct cyclophosphorylation of diol **I** with **IIb** yielded oligomeric structures with the number of units from 3 to 6 [7]. The same results were obtained with 1,4-bis(hydroxymethyl)-benzene **I** itself and with other diols taken for molecular assembling. As diol **I** cannot be directly used for cyclophosphorylation, we used its phosphorus-containing analogs **VIa**, **X**, and **XIX**. However, regardless of the nature of the phosphorylating agent (complete phosphorous acid amides and dichlorides) and the synthesis conditions (lowering temperature, decreasing concentrations, varying a solvent), a viscous gelatinous substance insoluble in dioxane, acetonitrile, and acetone but swelling in DMF separated out.

Thus, our results show that 1,4-bis(hydroxymethyl)-benzene **I** is readily phosphorylated with trivalent phosphorus reagents, forming linear structures; no tendency to the formation of cyclic structures was observed.

EXPERIMENTAL

All the syntheses were carried out in anhydrous solvents in a dry nitrogen atmosphere. The ^{1}H NMR spectra were measured on a Bruker AC-200 spectrometer operating at 250 MHz (internal reference TMS); the ^{31}P NMR spectra were recorded on a Bruker WP-80SY apparatus operating at 32.4 MHz (external reference 85% H_3PO_4).

Adsorption chromatography was performed on a column packed with silica gel L 100/250; TLC was performed on Silufol plates with the followings eluting systems: hexane–dioxane, 5:1 (A); hexane–dioxane, 3:1 (B); benzene–dioxane, 5:1 (C); chloroform (D); and ethyl acetate (E). The substance spots were developed by iodine vapor and by calcination. Hexaalkylphosphorous triamides **IIa** and **IIb** [10], phosphorous acid tripiperidide **IIc** [11], and phenyl phosphorodichloridite **VII** [12] were prepared by published procedures.

1,4-Bis(diaminothiophosphoryloxy)xylenes (Va–Vc). To 1 mol of **IIa**–**IIc**, a solution of 0.5 mol of 1,4-bis(hydroxymethyl)benzene **I** in 100 ml of dioxane was added at room temperature with stirring. After 48 h, 1 mol of sulfur was added to the reaction mixture, and the mixture was allowed to stand for an additional 3 days. Then the solution was filtered, the solvent was removed in a vacuum, and the residue was purified by column chromatography. The products were eluted by the followings systems: hexane–dioxane, 7:1 (**IVa**, **IVc**); hexane–dioxane, 10:1 (**IVb**). The compounds prepared were dried in a vacuum for 2 h (1 mm Hg, 70°C).

1,4-Bis(tetramethyldiaminothiophosphoryloxy)-xylene (Va), yield 20%, mp 140–142°C, R_f 0.49 (A). ^{1}H NMR spectrum, δ, ppm, ($CDCl_3$): 2.58 d (24H, CH_3, $^3J_{PH}$ 12.1 Hz), 5.00 d (4H, CH_2, $^3J_{PH}$ 8.3 Hz), 7.36 s (4H, Ar). ^{31}P NMR spectrum, δ_P, ppm (1,4-dioxane): 81.7. Found, %: C 43.55; H 7.40; N 12.59; P 14.28. $C_{16}H_{32}N_4O_2P_2S_2$. Calculated, %: C 43.82; H 7.36; N, 12.78; P 14.13.

1,4-Bis(tetraethyldiaminothiophosphoryloxy)-xylene (Vb), yield 73%, mp 132–133°C, R_f 0.65 (A), 0.68 (D). ^{1}H NMR spectrum, δ, ppm ($CDCl_3$): 1.07 t (24H, CH_3, $^3J_{HH}$ 7.6 Hz), 3.11 m (16H, CH_2N, $^3J_{PH}$ 4.7 Hz), 4.96 d (4H, CH_2O, $^3J_{PH}$ 8.2 Hz), 7.34 s (4H, Ar). ^{31}P NMR spectrum, δ_P, ppm (1,4-dioxane): 79.4.

1,4-Bis(dipiperidylthiophosphoryloxy)xylene (Vc), yield 32%, oily substance, R_f 0.60 (B). ^{1}H NMR

spectrum, δ, ppm ($CDCl_3$): 1.55 t (24H, CH_2, $^3J_{HH}$ 6.1 Hz), 3.07 m (16H, CH_2N, $^3J_{PH}$ 4.7 Hz), 4.98 d (4H, CH_2O, $^3J_{PH}$ 9.2 Hz), 7.37 s (4H, Ar). ^{31}P NMR spectrum, δ_P, ppm (1,4-dioxane): 76.8.

***O,O'*-Bis[(4-(hydroxymethyl)benzyl] dimethylphosphoramidothioate (IVa).** To a solution of 0.247 g of **IIa** in 5 ml of dry benzene, a solution of 0.345 g of diol **I** in 10 ml of anhydrous acetonitrile was added at room temperature with stirring. Then, 2 days later, 0.032 g of sulfur was added to the solution, and the mixture was allowed to stand for an additional 2 days. The solvent was removed in a vacuum, and the residue was purified on a chromatographic column; the product was eluted with ethyl acetate. The resulting substance was dried in a vacuum for 2 h (1 mm Hg, 70°C) to yield 0.072 g (20%) of **IVa** as oily substance, R_f 0.38 (C), 0.75 (E). ^1H NMR spectrum, δ, ppm [$(CD_3)_2CO$]: 2.69 d (6H, CH_3, $^3J_{PH}$ 11.9 Hz), 3.34 br.s (2H, OH), 4.63 s (4H, CH_2OH), 4.98 d (4H, CH_2O, $^3J_{PH}$ 9.2 Hz), 7.37 s (8H, Ar). ^{31}P NMR spectrum, δ_P, ppm (1,4-dioxane): 77.4.

***O,O'*-Bis[4-(hydroxymethyl)benzyl] *O''*-phenyl phosphorothioate (X).** To a solution of 0.276 g of diol **I** in 15 ml of dry dioxane, a mixture of 0.195 g of phenyl phosphorodichloridite and 0.253 g of triethylamine in 10 ml of dioxane was slowly added at 5–7°C with stirring. After addition of the whole amount of the dichloride, cooling of the reaction mixture was stopped, and the reaction mixture was allowed to stand for 3 h at room temperature. Then triethylammonium chloride was filtered off, the solvent was removed in a vacuum, and the residue was dissolved in a minimal amount of methylene chloride; the solution was filtered, diluted with methylene chloride, and 0.032 g of sulfur was added. The reaction mixture was allowed to stand for 3 days at room temperature. Then the solvent was evaporated, and the residue was purified by column chromatography, eluent benzene–dioxane, 10 : 1. The product was dried in a vacuum for 2 h (1 mm Hg, 70°C); yield 0.086 g (20%), mp 121–123°C, R_f 0.95 (C). ^1H NMR spectrum, δ, ppm [$(CD_3)_2CO$]: 4.64 d (4H, CH_2O, $^3J_{PH}$ 14 Hz), 4.67 s (4H, CH_2OH), 5.23 br.s (2H, OH), 7.27–7.42 m (13H, Ar). ^{31}P NMR spectrum, δ_P, ppm: 63.8. Found, %: C 61.31; H 5.40; P 7.23. $C_{22}H_{23}O_5PS$. Calculated, %: C 61.39; H 5.39; P 7.20.

1,3-Bis[(4-hydroxymethylbenzyl)(diethylamino)thiophosphoryloxy]benzene (XIX). To a solution of 0.494 g of **IIb** in 10 ml of acetonitrile, a solution of 0.11 g of resorcinol **XI** in 6 ml of acetonitrile was added at room temperature, and the reaction mixture was vigorously stirred for 1 h. Then 0.345 g of diol **I** in 10 ml of acetonitrile was added. The reaction mixture was allowed to stand for 5 days at room temperature, after which 0.064 g of sulfur was added. Two days later, the solvent was removed in a vacuum, and the residue was purified by column chromatography, eluent benzene–dioxane, 7 : 1. The product was dried in a vacuum for 2 h (1 mm Hg, 70°C). Yield 0.052 g (8%); oil, R_f 0.67 (C), 0.89 (E). ^1H NMR spectrum, δ, ppm [$(CD_3)_2CO$]: 1.10 t (12H, CH_3, $^3J_{HH}$ 6.9 Hz), 3.35 m (8H, CH_2, $^3J_{PH}$ 14.3 Hz), 4.19 br.s (2H, OH), 4.63 s (4H, CH_2OH), 5.07 d.d (4H, CH_2O, $^3J_{PH}$ 8.8, 8.4 Hz), 7.06 d (2H, CH, $^3J_{HH}$ 8.4 Hz), 7.32 s (1H, CH), 7.37 t (1H, CH, $^3J_{PH}$ 8.4 Hz), 7.39 s (8H, CHBzl). ^{31}P NMR spectrum, δ_P, ppm (CH_3CN): 72.5.

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REFERENCES

1. Nifant'ev, E.E., Rasadkina, E.N., and Yankovich, I.V., *Zh. Obshch. Khim.,* 1997, vol. 67, no. 11, p. 1812.
2. Nifant'ev, E.E., Rasadkina, E.N., Yankovich, I.V., Vasyanina, L.K., Stash, A.I., and Bel'skii, V.K., *Zh. Obshch. Khim.,* 1999, vol. 69, no. 1, p. 36.
3. Nifant'ev, E.E., Rasadkina, E.N., and Evdokimenkova, Yu.B., *Zh. Obshch. Khim.,* 2001, vol. 71, no. 3, p. 401.
4. Nifant'ev, E.E., Suvorkin, C.V., Rasadkina, E.N., Selyutina, O.V., and Shishin, A.V., *Zh. Obshch. Khim.,* 2002, vol. 72, no. 8, p. 1263.
5. Rasadkina, E.N., Slitikov, P.V., Vasyanina, L.K., and Nifantyev, E.E., *Phosphorus, Sulfur, Silicon,* 2005, vol. 180, no. 2, p. 513.
6. Nifant'ev, E.E., Rasadkina, E.N., and Slitikov, P.V., *Zh. Obshch. Khim.,* 2006, vol. 76, no. 2, p. 196.
7. Rasadkina, E.N., Slitikov, P.V., Stash, A.I., and Nifant'ev, E.E., *Izv. Ross. Akad. Nauk, Ser. Khim.,* 2005, no. 2, p. 440.
8. Nifant'ev, E.E., Predvoditelev, D.A., and Shin, V.A., *Zh. Vses. Khim. O–va. im. D.I. Mendeleeva,* 1978, vol. 23, no. 4, p. 220.
9. Rasadkina, E.N., Slitikov, P.V., Evdokimenkova, Yu.B., and Nifant'ev, E.E., *Zh. Obshch. Khim.,* 2003, vol. 73, no. 8, p. 1279.
10. Noth, H., and Vetter, H.J., *Chem. Ber.,* 1965, vol. 98, no. 9, p. 1981.
11. Burgada, R., *Ann. Chem.,* 1963, vol. 8, nos. 5–6, p. 351.
12. Tolkmith, H., *J. Org. Chem.,* 1958, vol. 23, no. 10, p. 1682.