Reactions of 2-(4,5-dihydro-3-furyl)-1,3-diphenyl-1,3-diaza-2λ^3-phospholidine and 4,5-dihydro-3-furylphosphonous diamides with nitrile imines

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Reactions of 2-(4,5-dihydro-3-furyl)-1,3-diphenyl-1,3-diaza-2λ^3-phospholidine (**1**) with nitrile imines are multistep processes involving cleavage of one P—N bond of the diazaphospholidine ring to form substituted 5-(2-chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-1,4-dihydro-1,2,4λ^5-diazaphosphorines **4** as final products. Analogs of phospholidine **1**, namely, 4,5-dihydro-3-furylphosphonous dipiperidide and dimorpholide, react with *C,N*-diphenylnitrile imine with retention of both P—N bonds to give 5-(2-hydroxyethyl)-1,2,4-diazaphosphorinium chlorides.

Key words: 2-(4,5-dihydro-3-furyl)-1,3-diphenyl-1,3-diaza-2λ^3-phospholidine, 4,5-dihydro-3-furylphosphonous diamides, nitrile imines, substituted 5-(2-chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-1,4-dihydro-1,2,4λ^5-diazaphosphorines, 5-(2-hydroxyethyl)-1,2,4-diazaphosphorinium chlorides.

Recently,[1] we found that the reaction of 2-(4,5-dihydro-3-furyl)-1,3-diphenyl-1,3-diaza-2λ^3-phospholidine (**1**) with *C,N*-diphenylnitrile imine (Huisgen 1,3-dipole) is a multistep process involving opening of both rings of the starting organophosphorus compound to give a 1,2,4-diazaphosphorine ring. The final product was 5-(2-chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-1,3-diphenyl-1,4-dihydro-1,2,4λ^5-diazaphosphorine.

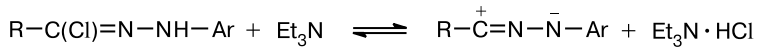
It is known[2] that in reactions of phosphorus(III) derivatives with nitrile imines, the structures of final products are often determined by the nature of the substituent at the carbenium atom of the 1,3-dipole. Taking this into account, we studied here reactions of diazaphospholidine **1** with nitrile imines containing donating (R = Me), weakly withdrawing (R = *p*-$NO_2C_6H_4$), and strong withdrawing substituents (R = EtOC(O)) at the aforementioned C atom. For comparison, we also investigated reactions of *C,N*-diphenylnitrile imine with 4,5-dihydro-3-furylphosphonous dimorpholide (**2**) and dipiperidide (**3**). These are analogs of diazaphospholidine **1**, in which the N—P—N fragment is no part of the same ring. Reactions were carried out under mild conditions (THF or benzene, 20 °C); nitrile imines were generated *in situ* from the corresponding hydrazonoyl chlorides under the action of triethylamine.

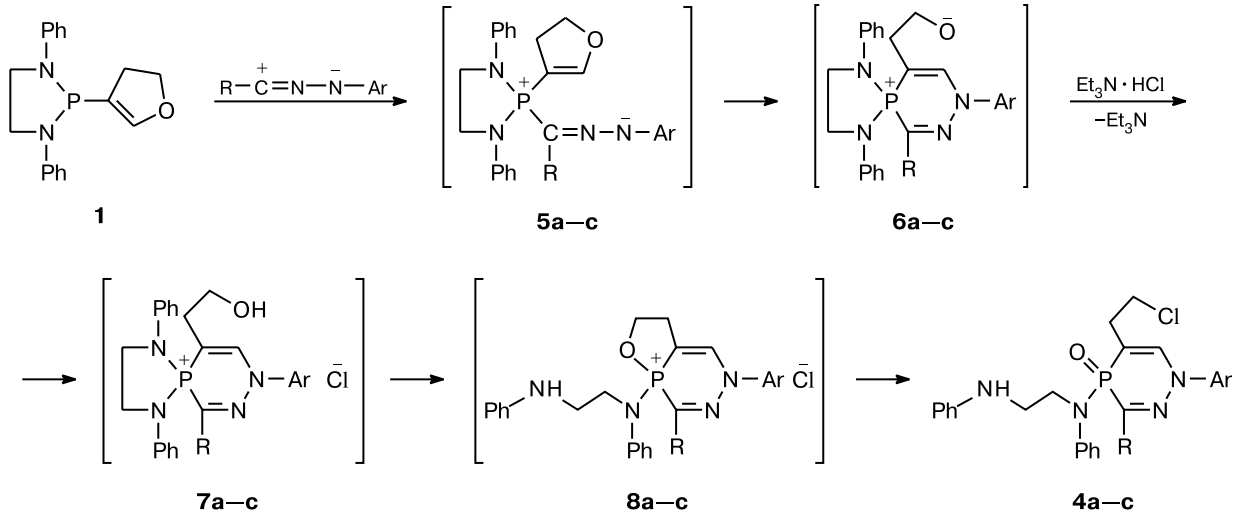
It was found that in the reactions of diazaphospholidine **1** with nitrile imines, the nature of substituent R does not affect the reaction pathway and the structure of the products. As in the previously studied reactions with *C,N*-diphenylnitrile imine,[1] substituted 5-(2-chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-1,4-dihydro-1,2,4λ^5-diazaphosphorines (**4a—c**) were obtained as final products. Apparently, the reaction pathway (Scheme 1) starts with the formation of a bipolar ion (**5a—c**) followed by its intramolecular cyclization (proceeding as nucleophilic vinylic substitution) into a cyclic intermediate (**6a—c**) with the betaine fragment P^+CCCO^-. This intermediate is protonated by triethylamine hydrochloride present in the reaction medium to form a spirocyclic phosphonium salt (**7a—c**). Then the alcohol hydroxyl interacts with quaternized P atom, which results in opening of the diazaphospholidine ring to give phosphonium salt (**8a—c**). The multistep process ends in opening of the oxaphospholane ring as the result of a nucleophilic attack of a chloride ion on the C atom bound to the O atom. This step is similar to dealkylation of alkoxyphosphonium salts at the second step of the Arbuzov reaction.

In contrast to the reactions with phospholidine **1**, reactions of (4,5-dihydro)-3-furylphosphonous dimorpholide and dipiperidide (**2** and **3**) with *C,N*-diphenylnitrile imine yield phosphonium salts **9a,b** (Scheme 2), which are structurally analogous to intermediates **7a—c** in Scheme 1. Subsequent transformations of salts **9a,b** into 5-(2-chloroethyl)-1,2,4λ^5-diazaphosphorines (see

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1590—1593, July, 2005.

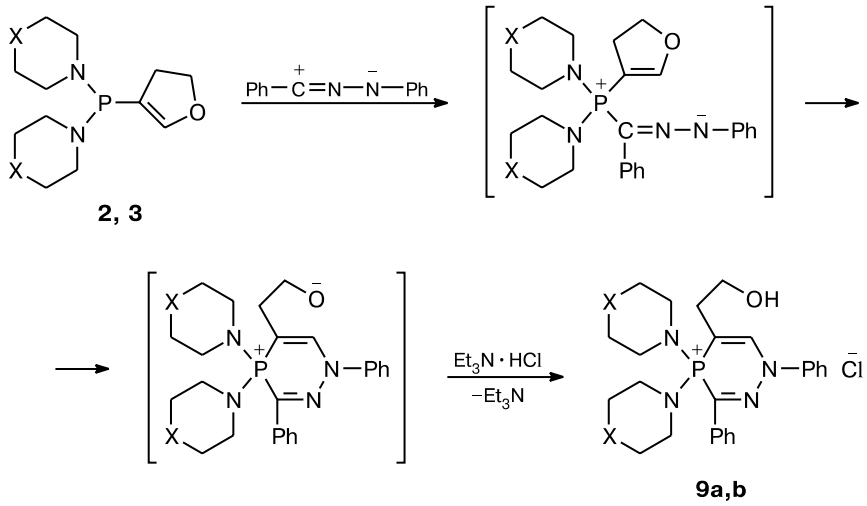
Scheme 1





4—8	R	Ar
a	Me	*p*-$NO_2C_6H_4$
b	*p*-$NO_2C_6H_4$	Ph
c	C(O)OEt	*p*-BrC_6H_4

Scheme 2



X = O (**2**, **9a**), CH_2 (**3**, **9b**)

Scheme 1) do not occur, probably, for two reasons. First, if the N—P—N fragment is present in the ring (diazaphospholidine **1** as the starting reagent) or out the ring (dimorpholide **2** and dipiperidide **3** as the starting reagents), various spatial conditions arise for closure of the oxaphospholane ring in intermediate **8a**—**c**. Second, simultaneous (with the closure of this ring) opening of the diazaphospholidine ring (diazaphospholidine **1** as the starting reagent) is preferred to a possible replacement of morpholine or piperidine (dimorpholide **2** and dipi-

peridide **3** as the starting reagents) because the phenylamino group is less basic than and thus is a superior leaving group compared to morpholine or piperidine.

It should be noted that 4,4-diamido-5-(2-hydroxyethyl)-1,3-diphenyl-1,4-dihydro-1,2,4λ^5-diazaphosphorinium chlorides **9a,b** are obtained by the reactions of (4,5-dihydro)-3-furylphosphonous dimorpholide (**2**) and dipiperidide (**3**) with *C*,*N*-diphenylnitrile imine both in the presence and in the absence of triethylamine. In the latter case, dehydrochlorination of *N*-phenylbenzhydrazonoyl chloride occurs under the action of the starting (4,5-dihydro)-3-furylphosphonous diamides **2** and **3**. Earlier, we demonstrated in a number of papers (see the review[2]) that phosphorus(III) acid amides exhibit such an ability toward hydrazonoyl halides.

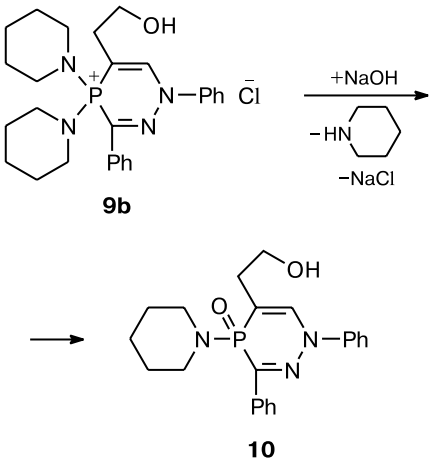
Substituted 1,4-dihydro-1,2,4λ^5-diazaphosphorines **4a—c** are colorless crystalline substances; these are well soluble in THF, acetone, chloroform, and benzene but are poorly soluble in hexane and diethyl ether. The spectroscopic characteristics of compounds **4a—c** fully agree with those for an analogous diazaphosphorine (R = Ar = Ph), whose structure was unambiguously confirmed[1] by X-ray diffraction analysis. For instance, their ^{31}P NMR spectra show a chemical shift at δ_P −2.8 to −6.5. The IR spectra contain absorption bands of NH (3320—3345 cm^{-1}) and P=O groups (1197—1228 cm^{-1}). The ^{1}H NMR spectra contain a doublet for the alkenyl proton at the C(6) atom (δ 7.37—7.52, $^3J_{P,H}$ = 23.5—23.9 Hz). The methylene protons of all four groups (=CH_2, CH_2Cl, $PNCH_2$, and $NHCH_2$) are anisochronous and manifest themselves as pairs of multiplets.

The ^{31}P chemical shifts of phosphonium salts **9a,b** appear at δ_P 11.0 (**9a**) and 11.7 (**9b**). The ^{1}H NMR spectra show signals for the protons of the OH group (δ 6.03 (**9a**) and 5.99 (**9b**)). The position of the doublet for the alkenyl proton at the C(6) atom of the heterocycle in compounds **9a,b** is substantially shifted downfield compared to compounds **4a—c** (δ 9.07 (**9a**) and 9.08 (**9b**)) and the spin-spin coupling constant $^3J_{P,H}$ is higher (26.8 (**9a**) and 26.3 Hz (**9b**)), which indicates the quaternized state of the P atom. Signals for the protons of the other groups are also slightly shifted downfield.

Salt **9a** was isolated in an analytically pure form as a colorless crystalline substance that is stable without access for atmospheric moisture for a long period of time. Salt **9b** was not isolated in the individual state; it was characterized by spectroscopic data and hydrolyzed to substituted diazaphosphorine **10** containing a phosphoryl group and one piperidine substituent at the P atom (Scheme 3).

Compound **10** is a colorless crystalline substance; its ^{31}P NMR spectrum shows a signal at δ_P −1.0 characteristic of such compounds (*cf.* compounds **4a—c**). The ^{1}H NMR spectrum contains signals for the protons of the

Scheme 3



OH group (δ 6.03) and the alkenyl proton at the C(6) atom of the heterocycle (δ 7.77, $^3J_{P,H}$ = 23.2 Hz).

Thus, regardless of the nature of the substituent at the carbenium atom of nitrile imines, these dipoles react with 2-(4,5-dihydro-3-furyl)-1,3-diphenyl-1,3-diaza-2λ^3-phospholidine **1** to give 1,2,4-diazaphosphorine ring with opening of both (diazaphospholidine and dihydrofuran) rings in the starting organophosphorus compound. In the reactions of (4,5-dihydro-3-furyl)phosphonous diamides **2** and **3** with *C*,*N*-diphenylnitrile imine, the closure of the 1,2,4-diazaphosphorine ring is accompanied by opening of the dihydrofuran ring; however, both P—N bonds are retained. The 1,2,4-diazaphosphorinium chlorides **9a,b** obtained in this case confirm the proposed formation mechanism for final products **4a—c** in the reactions of nitrile imines with phospholidine **1**.

Experimental

IR were recorded on an IKS-29 instrument (pellets with KBr). ^{1}H NMR spectra were recorded on a Bruker AM-500 instrument (500.1 MHz; internal stabilization relative to the ^{2}H resonance line). ^{31}P NMR spectra were recorded on a Bruker AS-200 instrument (84.1 MHz); chemical shifts were measured with reference to 85% H_3PO_4.

2-(4,5-Dihydro-3-furyl)-1,3-diphenyl-1,3-diaza-2λ^3-phospholidine (**1**) was prepared from *N*,*N*′-diphenylethylenediamine and 3-dichlorophosphino-4,5-dihydrofuran as described earlier.[1] *N*-Phenylbenzhydrazonoyl chloride (m.p. 130—131 °C), *N*-phenyl-*p*-nitrobenzhydrazonoyl chloride (m.p. 158—159 °C), *N*-*p*-nitrophenylethanehydrazonoyl chloride (m.p. 137—138 °C), and *p*-bromophenylhydrazone ethoxycarbonylformyl chloride (m.p. 164—165 °C) were prepared according to known procedures.[3] Diethyl ether, THF, and triethylamine were dried over NaOH and then distilled over metallic sodium. Benzene was dried by azeotropic removal of water and then distilled

over metallic sodium. The preparation of diazaphospholidine **1** and (4,5-dihydro-3-furyl)phosphonous dimorpholide and dipiperidide **2** and **3** and their reactions with nitrile imines were carried out in an atmosphere of argon; dried solvents and triethylamine were used.

(4,5-Dihydro-3-furyl)phosphonous diamides 2 and 3. A solution of 3-dichlorophosphino-4,5-dihydrofuran[4] (0.025 mol) in ether (20 mL) was added dropwise at −10 °C to a stirred solution of morpholine or piperidine (0.1 mol) in ether (100 mL). The reaction mixture was stirred at −10 °C for 0.5 h and at 20 °C for 0.5 h. Amine hydrochloride was filtered off and washed with ether (50 mL). The solvent was removed under reduced pressure and the solid residue was recrystallized from hexane.

(4,5-Dihydro-3-furyl)phosphonous dimorpholide (2). The yield was 70%, m.p. 62—64 °C. Found (%): C, 52.71; H, 7.89; P, 11.12. $C_{12}H_{21}N_2O_3P$. Calculated (%): C, 52.93; H, 7.77; P, 11.38. ^{1}H NMR ($CDCl_3$), δ: 2.57 (m, 2 H, $=CCH_2$); 3.13 (m, 8 H, 4 NCH_2); 3.65 (m, 8 H, 4 OCH_2-morpholine); 4.40 (m, 2 H, OCH_2-furan); 6.26 (m, 1 H, =CH). ^{31}P NMR ($CDCl_3$), δ: 80.8.

(4,5-Dihydro-3-furyl)phosphonous dipiperidide (3). The yield was 63%, m.p. 38—40 °C. Found (%): C, 62.46; H, 9.17; P, 11.42. $C_{14}H_{25}N_2OP$. Calculated (%): C, 62.66; H, 9.39; P, 11.54. ^{1}H NMR ($CDCl_3$), δ: 1.47 (m, 12 H, 6 CH_2-piperidine); 2.56 (m, 2 H, $=CCH_2$); 3.02 (m, 8 H, 4 NCH_2); 4.37 (m, 2 H, OCH_2); 6.20 (m, 1 H, =CH). ^{31}P NMR ($CDCl_3$), δ: 82.0.

Substituted 5-(2-chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-1,4-dihydro-1,2,4λ^5-diazaphosphorines (4a—c). A solution of 1,3-diaza-2λ^3-phospholidine **1** (0.005 mol), the corresponding hydrazonoyl chloride (0.005 mol), and triethylamine (2 mL) in THF (20 mL) was kept under argon at 20 °C for 24 h. An insignificant amount (≤15%) of triethylamine hydrochloride was filtered off. The filtrate was concentrated under reduced pressure and the crystalline residue was triturated in diethyl ether (5 mL), filtered off, and recrystallized from benzene—diethyl ether (1 : 1).

5-(2-Chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-3-methyl-1-(*p*-nitrophenyl)-1,4-dihydro-1,2,4λ^5-diazaphosphorine (4a). The yield was 55%, m.p. 163—165 °C. Found (%): C, 59.81; H, 5.02; P, 6.05. $C_{26}H_{27}ClN_5O_3P$. Calculated (%): C, 59.60; H, 5.19; P, 5.91. IR, ν/cm^{-1}: 3345 (NH); 1210 (P=O). ^{1}H NMR ($CDCl_3$), δ: 2.45 (d, 3 H, Me, $^3J_{P,H}$ = 7.5 Hz); 2.55, 3.08 (both m, 1 H each, $=CCH_2$); 3.20, 3.26 (both m, 1 H each, $C\underline{H}_2NHPh$); 3.78, 3.88 (both m, 1 H each, CH_2Cl); 3.75, 4.00 (both m, 1 H each, CH_2NP); 4.10 (s, 1 H, NH); 7.42 (d, 1 H, =CH, $^3J_{P,H}$ = 23.9 Hz); 6.55—8.20 (m, 14 H, Ar). ^{31}P NMR ($CHCl_3$), δ: −4.0.

5-(2-Chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-3-(*p*-nitrophenyl)-1-phenyl-1,4-dihydro-1,2,4λ^5-diazaphosphorine (8b). The yield was 80%, m.p. 149—152 °C. Found (%): C, 63.37; H, 4.77; P, 5.19. $C_{31}H_{29}ClN_5O_3P$. Calculated (%): C, 63.54; H, 4.99; P, 5.29. IR, ν/cm^{-1}: 3330 (NH); 1197 (P=O). ^{1}H NMR ($CDCl_3$), δ: 2.65, 3.25 (both m, 1 H each, $=CCH_2$); 3.07, 3.20 (both m, 1 H each, $C\underline{H}_2NHPh$); 3.82, 3.92 (both m, 1 H each, CH_2Cl); 3.55, 4.08 (both m, 1 H each, CH_2NP); 4.20 (s, 1 H, NH); 7.52 (d, 1 H, =CH, $^3J_{P,H}$ = 23.7 Hz); 6.48—8.34 (m, 19 H, Ar). ^{31}P NMR ($CHCl_3$), δ: −2.8.

1-(*p*-Bromophenyl)-5-(2-chloroethyl)-4-(*N,N′*-diphenylethylenediamino)-3-ethoxycarbonyl-1,4-dihydro-1,2,4λ^5-diazaphosphorine (4c). The yield was 72%, m.p. 118—120 °C. Found (%): C, 54.76; H, 4.57; P, 5.18. $C_{28}H_{29}BrClN_4O_3P$. Calculated (%): C, 54.60; H, 4.75; P, 5.03. IR, ν/cm^{-1}: 3320 (NH); 1725 (C=O), 1228 (P=O). ^{1}H NMR ($CDCl_3$), δ: 1.43 (t, 3 H, Me); 2.52, 3.23 (both m, 1 H each, $=CCH_2$); 3.12, 3.26 (both m, 1 H each, $C\underline{H}_2NHPh$); 3.76, 3.86 (both m, 1 H each, CH_2Cl); 3.67, 4.28 (both m, 1 H each, CH_2NP); 4.45, 4.51 (both m, 1 H each, CH_2O); 4.64 (s, 1 H, NH); 7.37 (d, 1 H, =CH, $^3J_{P,H}$ = 23.5 Hz); 6.54—7.48 (m, 14 H, Ar). ^{31}P NMR ($CHCl_3$), δ: −6.5.

4,4-Diamino-5-(2-hydroxyethyl)-1,3-diphenyl-1,4-dihydro-1,2,4λ^5-diazaphosphorinium chlorides 9a,b. A solution of (4,5-dihydro-3-furyl)phosphonous dimorpholide or dipiperidide **3a,b** (0.005 mol) in benzene (10 mL) was added at 20 °C to a solution of *N*-phenylbenzhydrazonoyl chloride (0.005 mol) in benzene (20 mL). A crystalline (for dimorpholide) or viscous oily precipitate (for dipiperidide) formed rapidly. Phosphonium salt **9a** was filtered off and washed with benzene; salt **9b** was washed with benzene and dried *in vacuo*.

5-(2-Hydroxyethyl)-4,4-dimorpholino-1,3-diphenyl-1,4-dihydro-1,2,4λ^5-diazaphosphorinium chloride (9a). The yield was 95%, m.p. 160—163 °C (acetone—hexane, 2 : 1). Found (%): C, 59.86; H, 6.31; P, 6.22. $C_{25}H_{32}ClN_4O_3P$. Calculated (%): C, 59.70; H, 6.41; P, 6.16. ^{1}H NMR ($CDCl_3$), δ: 2.88 (m, 2 H, $=CCH_2$); 3.24 (m, 8 H, CH_2N); 3.56, 3.64 (both m, 4 H each, CH_2O-morpholine); 4.06 (m, 2 H, $\underline{CH}_2OH$); 6.03 (s, 1 H, OH); 7.35—7.85 (m, 10 H, Ph); 9.07 (d, 1 H, =CH, $^3J_{P,H}$ = 26.8 Hz). ^{31}P NMR ($CHCl_3$), δ: 11.0.

5-(2-Hydroxyethyl)-1,3-diphenyl-4,4-dipiperidino-1,4-dihydro-1,2,4λ^5-diazaphosphorinium chloride (9b). The yield was 85%, a semicrystalline substance. ^{1}H NMR ($CDCl_3$), δ: 1.53 (m, 12 H, CH_2-piperidine); 2.82 (m, 2 H, $=CCH_2$); 3.09 (m, 8 H, CH_2N); 4.05 (m, 2 H, $\underline{CH}_2OH$); 5.99 (s, 1 H, OH); 7.40—7.85 (m, 10 H, Ph); 9.08 (d, 1 H, =CH, $^3J_{P,H}$ = 26.3 Hz). ^{31}P NMR ($CHCl_3$), δ: 11.7.

5-(2-Hydroxyethyl)-4-oxo-1,3-diphenyl-4-piperidino-1,4-dihydro-1,2,4λ^5-diazaphosphorine (10). A solution of (4,5-dihydro-3-furyl)phosphonous dipiperidide **3** (0.005 mol) in benzene (10 mL) was added at 20 °C to a solution of *N*-phenylbenzhydrazonoyl chloride (0.005 mol) in benzene (20 mL). A viscous oily precipitate formed. The solvent was removed under reduced pressure. The semicrystalline residue was dissolved in methanol (20 mL) and a solution of sodium hydroxide (0.005 mol) in methanol (10 mL) was added. The reaction mixture was kept at 20 °C for two days and the solvent was removed under reduced pressure. The residue was extracted with benzene (30 mL) and the benzene was removed *in vacuo*. The precipitate was triturated in ether (15 mL) and recrystallized from acetone—hexane (1 : 1). The yield was 40%, m.p. 165—167 °C. Found (%):C, 66.70; H, 6.73; P, 7.88. $C_{22}H_{26}N_3O_2P$. Calculated (%): C, 66.82; H, 6.63; P, 7.83. IR, ν/cm^{-1}: 3300 (OH); 1278 (P=O). ^{1}H NMR ($CDCl_3$), δ: 1.30 (m, 2 H, $CH_2\underline{CH}_2CH_2$); 1.42 (m, 4 H, $\underline{CH}_2CH_2\underline{CH}_2$); 2.46, 2.74 (both m, 1 H each, $=CCH_2$); 2.86, 2.93 (both m, 1 H each, CH_2N); 3.66, 3.92 (both m, 1 H each, CH_2O); 4.74 (s, 1 H, OH); 7.77 (d, 1 H, =CH, $^3J_{P,H}$ = 23.2 Hz); 7.28—8.12 (m, 10 H, Ph). ^{31}P NMR ($CHCl_3$), δ: −1.0.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-32905).

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Received September 24, 2004