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Reactions of *p*-Hydroxyphenylphosphine and Functionally Substituted Bis(hydroxymethyl)phosphines with Heterocumulenes

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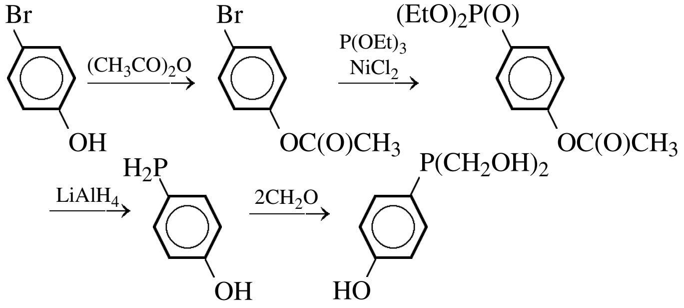
Abstract—Reactions of *p*-hydroxyphenylphosphine, bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine, and bis(hydroxymethyl)(5-allyl-2-ethoxybenzyl)phosphine with nitrogen-containing heterocumulenes were studied. The competitive reactivity of the phenol, phosphine, and hydroxymethyl groups in these reactions was examined.

Primary and secondary phosphines readily react with various nitrogen-containing heterocumulenes (carbodiimides, isocyanates, isothiocyanates), attacking the C=N bond and yielding functionally substituted phosphines with amidine, carbamoyl, and thiocarbamoyl groups [1–3]. Several examples of addition of bis(hydroxymethyl)organylphosphines to aryl isocyanates, to give the corresponding bis(urethanomethyl)organylphosphines, have been reported. However, the reaction is accompanied by substantial polymerization of the starting isocyanates [4]. These experiments were performed with the phosphines and bis(hydroxymethyl)phosphine that contained no additional functional groups. There is only one reported example of the reaction of a functionally substituted secondary phosphine, (2-mercaptoethyl)phenylphosphine, with phenyl isothiocyanate; the addition occurs via secondary phosphino group only [1].

In view of these facts, we studied in this work the reaction of nitrogen-containing heterocumulenes with *p*-hydroxyphenylphosphine and bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine. These reactions could be a route to new polyfunctional phosphines and their derivatives. Our goal was to compare the reactivity of the P–H and O–H groups in reactions with heterocumulenes.

p-Hydroxyphenylphosphine **I** used in this work was prepared by the scheme based on the reaction of *p*-bromophenyl acetate with triethyl phosphite in the presence of nickel(II) chloride [5]:

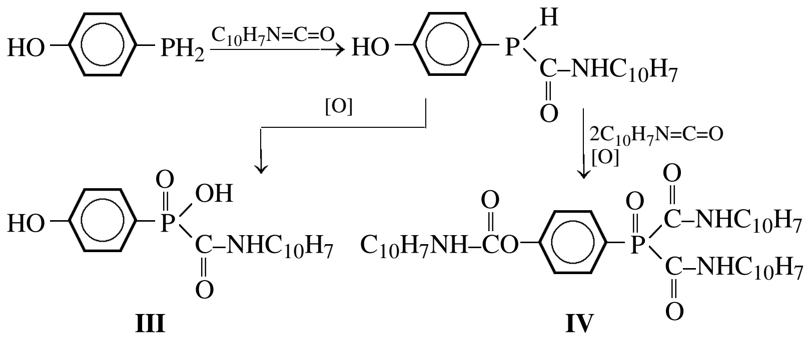


I **II**

Phosphine **I** is a low-melting crystalline substance; it was isolated by distillation and characterized by ^{31}P and ^{1}H NMR spectroscopy.

Bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine **II** was prepared by reaction of **I** with 2 equiv of paraform at 100–120°C without of a solvent. Compound **II** is a thermally unstable noncrystallizing viscous liquid. Its ^{31}P NMR spectrum consisted of a single signal, δ_P –23 ppm, which allowed us to use this compound in further reactions without additional purification.

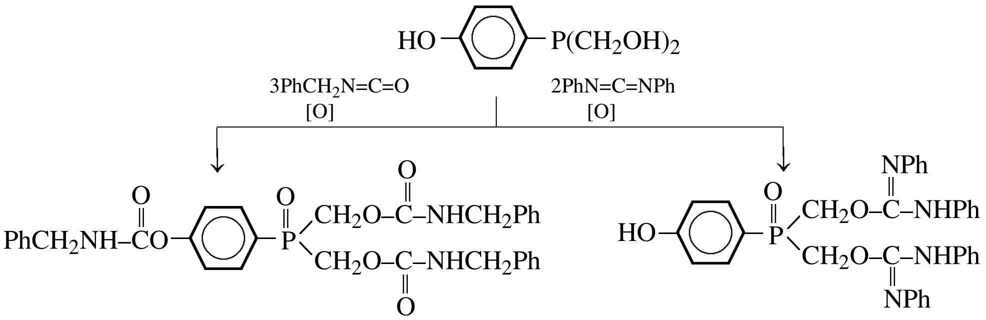
First, we studied addition of **I** to isocyanates. We found that the reaction of **I** with 1 equiv of 1-naphthyl isocyanate yields more than one product. The ^{31}P NMR spectrum of the reaction mixture consists of three signals: that of the starting primary phosphine, δ_P 127.3 ppm; a strong signal of a secondary phosphine (probably, the product of addition of one isocyanate molecule at the phosphino group), δ_P −47.68 ppm; and a signal of a tertiary phosphine (probably, the product of addition of two or three heterocumulene molecules), δ_P 1.9 ppm. The ratio of the integral intensities of these signals was 2 : 3 : 1. The reaction is accompanied by formation of a small amount of a high-melting crystalline precipitate. The ^{31}P NMR spectrum of this precipitate contains a signal with δ_P 14.43 ppm. The ^{31}P NMR data in combination with analytical data allow us to identify this substance as (*N*-naphthylcarbamoyl)(4-hydroxyphenyl)phosphinic acid **III**; it is presumably formed by oxidation of the initially formed monoadduct. On adding two more equivalents of the isocyanate to the reaction mixture, the signals of the primary and secondary phosphines (δ_P −127.3 and −47.68 ppm) disappear, and only the signal of the tertiary phosphine (δ_P 1.9 ppm) remains in the spectrum. Further heating of the reaction mixture at 60°C for several hours caused no changes in the ^{31}P NMR spectrum. We failed to isolate the phosphine pure. However, storage of the reaction mixture at 4–7°C resulted in precipitation of a small amount of a crystalline substance; its IR spectrum contained absorption bands of the N–H (3284 cm^{-1}) and C=O (1636 cm^{-1}) bonds of the carbamoyl moiety and of the P=O group (1220 cm^{-1}). The ^{31}P NMR spectrum of this product consisted of a single signal at 58 ppm, and the ^{1}H NMR spectrum contained only a complex multiplet of aromatic ring protons at 6.76–8.3 ppm. The OH signal at 9–10 ppm was absent. The analytical data correspond to the 1 : 3 (phosphine : naphthyl isocyanate) addition product. These results allow us to identify this compound as di(*N*-naphthylcarbamoyl)(4-naphthylurethanophenyl)phosphine oxide **IV**, product of oxidation of the initially formed tertiary phosphine.



Our results suggest that the first reaction step is addition of one isocyanate molecule to the phosphino group.

As the OH group in **I** is fairly reactive toward isocyanates, in the experiments with bis(hydroxymethyl)(*p*-hydroxyphenyl)phoshine **II** we took 3 equiv of heterocumulenes. We found that the reaction products are readily oxidized with traces of oxygen, and only the oxides were detected in the ^{31}P NMR spectra. With naphthyl isocyanate, polymerization prevailed, and we failed to isolate phosphorus-containing products pure. With benzyl isocyanate, we obtained a crystalline precipitate; its ^{31}P NMR spectrum contained a signal with δ_P 33.7 ppm. The IR spectrum of this compound contained absorption bands of the P=O (1250 cm^{-1}) and C=O (1630 cm^{-1}) groups, and also broad N–H stretching bands (3320 cm^{-1}). The ^{1}H NMR spectrum contains no OH signals (9–10 ppm), and the ratio of the integral intensities corresponds to the presence of three benzylurethane fragments. The analytical data also confirm this composition. Thus, the isolated reaction product can be identified as di(benzylurethanomethyl)(4-benzylurethanophenyl)phosphine oxide **V**.

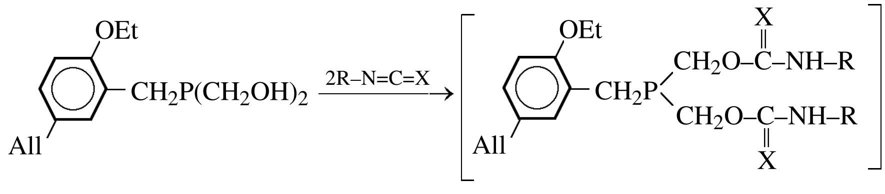
A study of the reaction of **II** with diphenylcarbodiimide showed that the hydroxyphenyl group is less reactive than the hydroxymethyl group. The IR spectrum of the crystalline precipitate isolated from the reaction mixture contained the absorption bands of the P=O group (1245 cm^{-1}), C=N bonds in the isourea



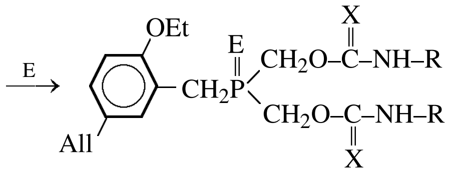
V **VI**

moiety (1600 cm^{-1}), and N–H bonds (3280 cm^{-1}). The ^{31}P NMR spectrum contained a signal with δ_P 34.32 ppm, and the ^1H NMR spectrum contained, along with a complex multiplet of aromatic protons and a broad singlet originating from superposition of the signals of the methylene and amine protons, also a narrow singlet at 9.15 ppm belonging to the phenol proton. The ratio of the signal intensities and analytical data suggest the presence of two *N,N'*-diphenylisourea fragments in the molecule. These data allow the product to be identified as bis(1,3-diphenylisoureomethyl)(4'-hydroxyphenyl)phosphine oxide **VI**, an oxidation product of the initially formed adduct of phosphine **II** with two carbodiimide molecules. Thus, only hydroxymethyl groups of **II** participate in the reaction with carbodiimide.

Taking into account the fact that the reactions of bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine **II** with heterocumulenes were accompanied by fast oxidation of trivalent phosphorus compounds, we performed the reactions of isocyanates with a sterically hindered substrate, (hydroxymethyl)(5-allyl-3-ethoxybenzyl)phosphine [6]. Its reaction with benzyl isocyanate, as monitored by ^{31}P NMR spectrocsopy, is complete in 3–4 h. The ^{31}P NMR spectrum of the reaction mixture contains a signal with δ_P –24 ppm, apparently corresponding to adduct **VII**:



VII, VIII



VIIA, VIIIA

R = Bn (**VII, VIIA**), Ph (**VIII, VIIIA**); X = O (**VII, VIIA**), S (**VIII, VIIIA**); E = S (**VIIA**), O (**VIIIA**).

An attempt to isolate pure **VII** by precipitation from hexane failed; only oxidation and decomposition products were obtained. Therefore, the mixture containing phosphine **VI**, after removing the solvent, was treated with a solution of elemental sulfur in benzene. The residue after removing excess sulfur and solvents was a viscous substance which, according to the ^1H NMR, ^{31}P NMR, and IR spectra, was identified as 5-allyl-2-ethoxybenzyldi(benzylurethanomethyl)phosphine sulfide **VIIA**. The IR spectrum of **VIIA** contained stretching bands of the N–H (3256 cm^{-1}), C=O (1728 cm^{-1}), and C=C (1596 cm^{-1}) bonds. The ^{31}P NMR spectrum consisted of a single signal with δ_P 42.47 ppm; the ^1H NMR spectra was also consistent with the suggested structure. The ratio of the integral intensities of the signals corresponded to the presence of one 5-allyl-2-ethoxybenzyl and two benzylurethanomethyl fragments in the molecule.

The ^{31}P NMR monitoring of the reaction of phenyl isothiocyanate with bis(hydroxymethyl)(2-ethoxy-5-allylbenzyl)phosphine showed that the signal of the starting phosphine (δ_P 21 ppm) gradually disappeared, and signals with δ_P 26.9 and 44 ppm appeared. These signals can be tentatively assigned to oxides of the starting compound and initial reaction products, which could not be separated by reprecipitation. Oxidation of the product mixture with aqueous H_2O_2 yielded a solid high-melting precipitate. Its IR spectrum contained stretching bands of the P=O group (1220 cm^{-1}), C=C bonds in aromatic fragments (1600 cm^{-1}), and N–H bonds (3200 cm^{-1}). The ^{31}P NMR spectrum consisted of a single signal with δ_P 38.39 ppm, and the ^1H NMR spectrum suggested the presence of two phenylthiocarbamatomethyl fragments. Based on the spectral ana analytical data, the product was identified as bis(phenylthiocarbamatomethyl)(5-allyl-2-ethoxybenzyl)phosphine oxide **VIIIA**.

Thus, our results show that bis(hydroxymethyl)organylphosphines readily add across the C=N bonds of not only isocyanates but also other nitrogen-containing heterocumulenes: isothiocyanates and carbodiimides. The phenolic group, if present in the starting phosphine molecule, is less reactive toward heterocumulenes.

EXPERIMENTAL

The IR spectra (mulls in mineral oil) were recorded on a Specord M-80 spectrometer. The ^{31}P NMR spectra were taken on Bruker CXP-100 (36.5 MHz) and Bruker MSL-400 (161 MHz) spectrometers, and the ^1H NMR spectra, on a Bruker WM-250 spectrometer (250 MHz). Bis(hydroxymethyl)(5-allyl-2-ethoxybenzyl)phosphine was prepared according to [6] from 5-allyl-2-ethoxybenzylphosphine.

All manipulations with phosphines were performed in an inert atmosphere.

***p*-Hydroxyphenylphosphine I.** Five drops of concentrated H_2SO_4 were added to a mixture of 90.42 g of *p*-bromophenol and 58.69 g of acetic anhydride. The mixture was heated for 3 h on a water bath, cooled, and poured with stirring into ice-cold water. A clotted precipitate formed (mp 21.5°C), which, after decanting the liquid, was dissolved in toluene. The aqueous phase was neutralized to weakly alkaline reaction by adding sodium carbonate and extracted with toluene; the combined organic layers were dried over calcium chloride. The low-boiling components were distilled off, and the residue was fractionated. Yield of *p*-bromophenyl acetate 74.5 g (67%), bp 114°C (10 mm). ^1H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 2.16 s [3H, OC(O)CH_3], 6.97 d (2H, *o*-BrC_6H_4, $^3J_{HH}$ 9), 7.47 d (2H, *m*-BrC_6H_4, $^3J_{HH}$ 9).

Triethyl phosphite (57.52 g) was added dropwise with stirring over a period of 2 h in a weak Ar flow to a mixture of 74.5 g of *p*-bromophenyl acetate and 1.73 g of nickel(II) chloride, heated to 170°C; the released ethyl bromide was distilled off. Fractionation of the reaction mixture yielded 27.99 g (29.66%) of diethyl *p*-acetoxyphenylphosphonate, bp 154°C (0.1 mm). ^{31}P NMR spectrum: δ_P 17 ppm.

A solution of 12.24 g of diethyl *p*-acetoxyphenylphosphonate in 60 ml of diethyl ether was added at stirring and cooling with ice to a suspension of 3.2 g (50% excess) of $LiAlH_4$ in 156 ml of diethyl ether. The mixture was stirred for 6 h and decomposed, at cooling with ice, with 6.07 ml of water and 29.33 ml of 18% HCl. The organic layer was separated and dried overnight over magnesium sulfate. The solvent was removed, and the residue was vacuum-distilled. Yield of *p*-hydroxyphenylphosphine **I** 2.46 g (43%), bp 137°C (0.08 mm); colorless liquid crystallizing at room temperature. ^1H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 4.27 d (2H, PH_2, $^1J_{PH}$ 199.6), 5.08 br.s (1H, OH), 6.86 d (2H, OC_6H_4-*o*, $^3J_{HH}$ 7.7), 7.58 d.d (2H, OC_6H_4-*m*, $^3J_{HH}$ 7.7, $^3J_{PH}$ 6.37). ^{31}P NMR spectrum: δ_P –126.28 ppm ($^1J_{PH}$ 198 Hz).

Bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine II. Paraform (0.39 g) was added to 0.82 g of *p*-hydroxyphenylphosphine; the mixture was heated on a water bath to homogenization, after which it was cooled. ^{31}P NMR spectrum: δ_P –23 ppm.

(*N*-Naphthylcarbamoyl)(4-hydroxyphenyl)phosphinic acid III and di(*N*-naphthylcarbamoyl)(4-naphthylurethanophenyl)phosphine oxide IV. A solution of 0.29 g of naphthyl isocyanate in 3 ml of THF was added to a solution of 0.22 g of *p*-hydroxyphenylphosphine **I** in 5 ml of THF. The mixture was refluxed for 30 min; the precipitate was filtered off. Yield of **III** 0.2 g (38%), mp >260°C. ^{31}P NMR spectrum (DMF): δ_P 14.43 ppm. Found, %: C 62.28; H 4.31; N 4.24; P 9.74. $C_{17}H_{14}NO_4P$. Calculated, %: C 62.38; H 4.28; N 4.28; P 9.48.

An additional 0.58-g portion of naphthyl isocyanate in 3 ml of THF was added to the filtrate; the mixture was refluxed for 4 h. On standing, a precipitate formed, which was filtered off and washed with diethyl ether. Yield of **IV** 0.02 g (2%), mp 276°C. IR spectrum (mull in mineral oil), ν, cm^{-1}: 678, 770 (CH_{ar}), 1212 (P=O), 1556, 1636 (CO), 3284 (NH). ^1H

NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 6.76–8.3 m (25H, C_6H_4 + $C_{10}H_7$). ^{31}P NMR spectrum (DMF): δ_P 58 ppm. Found, %: C 74.05; H 4.76; N 7.24; P 4.74. $C_{39}H_{28}N_3O_4P$. Calculated, %: C 73.93; H 4.42; N 6.64; P 4.89.

Di(benzylurethanomethyl)(4-benzylurethanophenyl)phosphine oxide V. A solution of 0.25 g of benzyl isocyanate in 3 ml of THF was added to a solution of 0.12 g of bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine in 5 ml of THF. The mixture was refluxed for 6 h, the solvent was removed in a vacuum, and the residue was crystallized from diethyl ether. Yield of **V** 0.06 g (16%), mp 128–130°C. IR spectrum (mull in mineral oil), ν, cm^{-1}: 1250 (P=O), 1580 (C=C$_{ar}$), 1630 (C=O), 3320 (NH). ^{1}H NMR spectrum (DMF-d_7), δ, ppm (*J*, Hz): 4.1–4.5 m (PCH_2O), 4.35 s (NCH_2Ph) (total intensity 10H), 6.5–7.8 m (22H, C_6H_5 + C_6H_4 + NH). ^{31}P NMR spectrum (DMF): δ_P 33.7 ppm. Found, %: C 63.17; H 5.10; N 7.02; P 6.48. $C_{32}H_{32}N_3O_7P$. Calculated, %: C 63.89; H 5.32; N 6.98; P 6.15.

Bis(1,3-diphenylisoureomethyl)(4'-hydroxyphenyl)phosphine oxide VI. A solution of 0.25 g of diphenylcarbodiimide in 3 ml of THF was added to a solution of 0.08 g of bis(hydroxymethyl)(*p*-hydroxyphenyl)phosphine in 5 ml of THF. The mixture was refluxed for 6 h, the solvent was evaporated, and the residue was crystallized from diethyl ether. Yield of **VI** 0.13 g (39%), mp 146–150°C. IR spectrum (mull in mineral oil), ν, cm^{-1}: 1245 (P=O), 1600 (C=N), 3280 (NH). ^{1}H NMR spectrum (DMF-d_7), δ, ppm (*J*, Hz): 4.2 br.s (6H, PCH_2O + NH), 6.55–7.87 m (24H, C_6H_4 + C_6H_5), 9.15 s (1H, OH). ^{31}P NMR spectrum (DMF): δ_P 34.32 ppm. Found, %: C 70.73; H 5.85; N 9.45; P 7.70. $C_{34}H_{30}N_4O_3P$. Calculated, %: C 71.20; H 5.23; N 9.77 P 8.30.

Bis(benzylurethanomethyl)(5-allyl-2-ethoxybenzyl)phosphine sulfide VIIA. Paraform (0.41 g) was added to 1.43 g of 5-allyl-2-ethoxybenzylphosphine. The mixture was heated to homogenization, after which it was dissolved in 3 ml of THF, and a solution of 1.83 g of benzyl isocyanate in 3 ml of THF was added. The mixture was refluxed for 4 h. After cooling, 5 ml of hexane was added; the emulsion obtained after mixing was allowed to separate in two layers. The upper layer was separated and evaporated in a vacuum; a solution of 0.12 g of sulfur in benzene was added to the residue. The mixture was heated for 4 h, the solvent was removed, the residue was dissolved in acetonitrile, and the precipitate of excess sulfur was filtered off. The filtrate was evaporated in a vacuum (0.1 mm); the liquid oily residue was bis(benzylurethanomethyl)(5-allyl-2-ethoxybenzyl)phosphine sulfide **VIIA**. Yield 0.04 g (19%). IR spectrum (film from $CHCl_3$), ν, cm^{-1}: 1536 (NH), 1596 (C=C$_{ar}$), 1728 (CO), 3256 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.26 t (3H, CH_3CH_2O, $^3J_{HH}$ 6), 3.0–3.5 m (4H, PCH_2Ar + $NCH_2CH{=}CH_2$), 3.55–4.8 m (12H, PCH_2O + OCH_2CH_3 + NCH_2Ph + NH), 4.9–5.15 m (2H, $CH_2{=}CH$), 5.7–6.0 m (1H, $CH_2{=}CH$), 6.5–7.6 m (13H, C_6H_5 + C_6H_3). ^{31}P NMR spectrum (CH_3CN): δ_P 42.47 ppm.

Bis(phenylthiocarbamatomethyl)(2-ethoxy-5-allylbenzyl)phosphine oxide VIIIA. Paraform (0.62 g) was added to 2.15 g of 5-allyl-2-ethoxybenzylphosphine. The mixture was heated to homogenization and dissolved in 3 ml of THF; a solution of 2.71 g of phenyl isothiocyanate in 3 ml of THF was added. The mixture was stirred for 6 h, and 5 ml of hexane was added. After mixing, an emulsion formed, which was allowed to separate. The lower layer was evaporated in a vacuum, the residue was dissolved in acetone, and a mixture of 0.5 g of 30% H_2O_2 and 2 ml of acetone was added. The precipitate that formed after standing for 24 h was filtered off. Yield of **VIIIA** 0.02 g (6%), mp 187°C. IR spectrum (mull in mineral oil), ν, cm^{-1}: 688 (CH$_{ar}$), 1220 (P=O), 1376, 1552 (NH), 1600 (C=C$_{ar}$), 3050–3200 (NH). ^{1}H NMR spectrum (DMF-d_7), δ, ppm (*J*, Hz): 1.42 t (3H, CH_3CH_2O, $^3J_{HH}$ 6), 3.1–3.5 m (4H, PCH_2Ar + $NCH_2CH{=}CH_2$), 3.6–4.75 m (6H, PCH_2O + OCH_2CH_3), 4.85–5.1 m (2H, $CH_2{=}CH$), 5.8–6.1 m (1H, $CH_2{=}CH$), 6.5–7.6 m (13H, C_6H_5 + C_6H_3). ^{31}P NMR spectrum (DMF): δ_P 38.39 ppm. Found, %: C 60.73; H 5.85; N 5.45; P 5.70. $C_{27}H_{31}N_2O_4PS_2$. Calculated, %: C 59.77; H 5.71; N 5.17; P 5.71.

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