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Monosaccharide Phenylphosphonites

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Abstract — Synthesis and chemical properties of the first carbohydrate phenylphosphonites are described.
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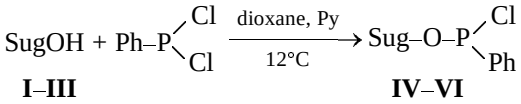
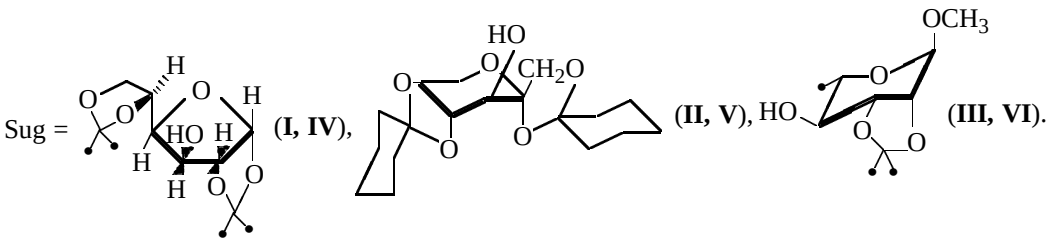
Previously in our laboratory we obtained and studied hydrophosphoryl derivatives of protected monosaccharides containing P–C [1, 2] and P–OAlk [3–5] bonds. With alkyl phosphites as examples, we showed that these compounds readily form complexes with some of transition metals. Proceeding with these studies, we prepared the first monosaccharide phenylphosphonites and examined their chemical properties.

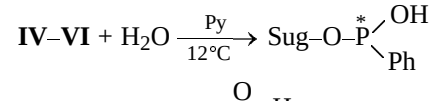
The desired compounds were prepared by a two-step procedure involving in the first step the reaction of a carbohydrate with an equimolar amount of phenylphosphonous dichloride. As a carbohydrate matrix we used 1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose **I**, 1,2:4,5-di-*O*-cyclohexylidene-α-*D*-fructopyranose **II**, and 1-*O*-methyl-2,3-*O*-isopropylidene-α-*L*-rhamnopyranozide (**III**):

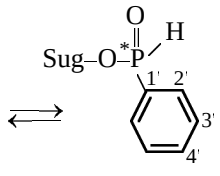


I–III **IV–VI**



To perform this reaction, a solution of 1 equiv of monosaccharide and 2.5 equiv of pyridine in dioxane was added to 1.1 equiv of phenylphosphonous dichloride. The rate of dropwise addition of the carbohydrate to the phosphorylating agent is very significant. To avoid formation of by-products and to increase the phosphonous monochloride yield, the addition should be performed over a period of 20 to 30 min. The reaction progress was monitored by ^{31}P NMR spectroscopy. The ^{31}P spectrum of the reaction mixture contained singlets at 168–174 ppm corresponding to monochlorides **IV**–**VI**. In the second step, monochlorides **IV**–**VI** obtained, which are extremely labile, were hydrolyzed without additional purification to the corresponding hydrophosphoryl compounds **VII**–**IX**:



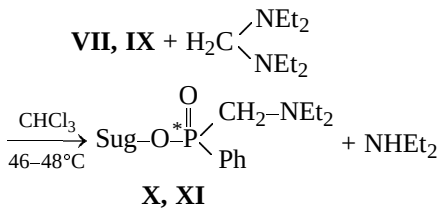


VII–IX

Their ^{31}P NMR spectra contained doublets with chemical shifts of 25–26 ppm, $^{1}J_{PH}$ 570–600 Hz. It

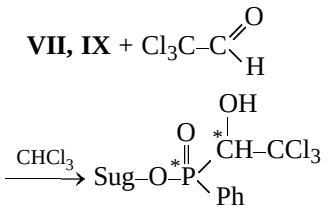
should be noted that phosphorylation with phenylphosphonous dichloride gives rise to chirality of the P atom, and therefore the final synthesis products **VII**–**IX** were obtained as mixtures of two diastereomers. The structures of **VII**–**IX** were proved by ^{13}C and ^{31}P NMR spectroscopy.

Phenylphosphonites **VII** and **IX** were brought into electrophilic Kabachnik–Fields and Abramov reactions, and previously unknown carbohydrate-substituted phosphinates were prepared. In the Kabachnik–Fields reaction we used bis(diethylamino)methane as an electrophilic reagent:



X, XI

Bis(diethylamino)methane was taken in an excess (2.5 equiv per 1 equiv of the sugar) at a glycerol bath temperature of 46–47°C. Compounds **X** and **XI** were formed each as two diastereomers in approximately equal amounts. In the Abramov reaction we used chloral. The reaction occurred more readily than the Kabachnik–Fields aminomethylation:



XII, XIII

The reaction was performed at equimolar reactant ratio with slight cooling (15°C in the bath). Compounds **XII** and **XIII** were formed each as four isomers. It is interesting that in the reaction with rhamnose virtually a single diastereomer of **XIII** was obtained. Thus, it is principally possible to prepare in a satisfactory yield monosaccharide hydrophosphoryl derivatives which can be used in reactions with electrophiles. This result opens prospects for the design of complicated carbohydrate–phosphorus structures which are interesting as bioregulators and the ligands for coordination catalysts.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (50.32 MHz). The ^{31}P NMR spectra were measured on a Bruker WP-80SY spectrometer (32.4 MHz, external reference 85% orthophosphoric acid). Column chromatography was performed with silica gel L 100/160. TLC analysis was performed on Silufol UV-254 plates using the following systems: benzene–dioxane 7:1 (A), hexane–dioxane 3:1 (B), hexane–dioxane 5:1 (C), hexane–dioxane 5:2 (D), hexane–dioxane 10:1 (E), and hexane–dioxane–triethylamine 28:2:1 (F). The chromatograms were developed with iodine vapor or by calcination.

In all the syntheses we used anhydrous solvents and performed the reactions under dry oxygen-free argon.

1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose 3-*O*-phenylphosphonite VII. A solution of 1.06 g of monosaccharide **I** and 0.81 g of pyridine in 5 ml of dioxane was slowly (over a period of 20–30 min) added dropwise with cooling (bath temperature 12°C) to a solution of 0.80 g of phenylphosphonous dichloride in 3 ml of dioxane. The mixture was stirred for 30 min at room temperature, then again cooled, and 0.08 g of water dissolved in 3 ml of dioxane was slowly added. The mixture was then stirred for 30 min at room temperature, the pyridinium chloride precipitate was filtered off, the filtrate was evaporated, and the residue was passed through a column packed with silica gel (elution with system A). Yield 0.67 g (43%); white powder-like substance, mp 115–117°C, R_f 0.51 (E). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.9–26.5 all s [$C(CH_3)_2$], 67.0, 67.4 both s (C^6), 72.4 s (C^5), 74.0, 74.6 both s (C^3), 81.1, 83.4 s (C^4), 83.5, 84.9 both s (C^2), 104.8, 105.0 both s (C^1), 108.9, 111.3 and 109.2, 112.2 all s [$C(CH_3)_2$], 128.4, 128.7 both s ($C^{3'}$), 130.6 s ($C^{2'}$), 131.3 s ($C^{4'}$), 131.9 d ($C^{1'}$, $^1J_{PC}$ 153.0 Hz). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 28.2 d ($^1J_{PH}$ 578.0 Hz), 26.5 d ($^1J_{PH}$ 577.3 Hz). Found, %: C 56.15; H 6.66; P 7.98. $C_{18}H_{25}O_7P$. Calculated, %: C 56.25; H 6.56; P 8.06.

1,2:4,5-Di-*O*-cyclohexylidene-α-*D*-fructopyranose 3-*O*-phenylphosphonite VIII. A solution of 0.71 g of monosaccharide **II** and 0.41 g of pyridine in 5 ml of dioxane was slowly (over a period of 20–30 min) added dropwise with cooling (bath temperature 12°C) to a solution of 0.41 g of phenylphosphonous dichloride in 3 ml of dioxane. Then the mixture was stirred for 30 min at room temperature, cooled again, and 0.04 g of water dissolved in 2 ml of dioxane was added. Then the mixture was stirred for 30 min and left overnight. The resulting mixture was filtered to remove pyridinium chloride precipitate and evaporated; by-products were removed by precipitation with hexane. The solution in hexane was left for 12 h for complete precipitation of the by-products. The solvent was then evaporated and the residue was

passed through a column packed with silica gel (elution with system E). For better purification, the product was dissolved in a small amount of hexane (ca. 2 ml) and left for 12 h, then the solution was filtered and evaporated. Yield 0.31 g (32%); colorless oily substance, R_f 0.15 (E). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 23.35–23.77, 34.93–37.75 (cyclohexylidene protecting group); 60.6, 60.7 both s (C^6), 71.5, 71.7 both s (C^1), 72.9 d (C^4, $^3J_{PC}$ 5.2 Hz), 73.9, 74.0 both s (C^5), 74.7 d (C^3, $^2J_{PC}$ < 2.0 Hz), 103.0, 103.1 both d (C^2, $^3J_{PC}$ 5.5, $^3J_{PC}$ 4.7 Hz), 110.0, 112.7, and 110.5, 112.8 all s (C_{quat}), 128.3, 128.5 both d ($C^{2'}$, $^2J_{PC}$ 6.0 Hz); 130.3 s ($C^{3'}$), 130.5, 130.8 both s ($C^{4'}$), 132.0 d ($C^{1'}$, $^1J_{PC}$ 92.6 Hz). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 27.2, 27.6 d ($^1J_{PH}$ 598.5 Hz). Found, %: C 62.17; H 7.03; P 6.54. $C_{24}H_{33}O_7P$. Calculated, %: C 62.06; H 7.16; P 6.67.

2,3-*O*-Isopropylidene-α-*L*-methylrhamnopyranoside 4-*O*-phenylphosphonite (IX). A solution of 0.65 g of monosaccharide **III** and 0.59 g of pyridine in 5 ml of dioxane was slowly (over a period of 20–30 min) added dropwise with cooling (bath temperature 12°C) to a solution of 0.59 g of phenylphosphonous dichloride in 3 ml of dioxane. The mixture was stirred for 30 ml at room temperature and cooled again, and 0.06 g of water dissolved in 2 ml of dioxane was added. The stirring was continued for 30 min, and the mixture was left overnight. Pyridinium chloride was filtered off, and the residue was separated on a column (system B). Yield 0.28 g (27%); colorless oily substance, R_f 0.32 (C). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.2 s (C^6), 26.5–28.7 all s [$C(CH_3)_2$], 54.8 s (OCH_3), 63.9, 64.0 both s (C^5), 75.9, 76.0 both s (C^2), 78.3, 78.6 both s (C^3), 79.1 d (C^4, $^2J_{PC}$ 7.2 Hz), 97.7 s (C^1), 109.5, 110.0 both s [$C(CH_3)_2$], 128.5, 128.8 both d ($C^{2'}$, $^2J_{PC}$ 7.1, $^2J_{PC}$ 7.0 Hz), 130.5, 130.8 both s ($C^{3'}$), 131.0, 131.3 both s ($C^{4'}$), 132.2 d ($C^{1'}$, $^1J_{PC}$ 93.4 Hz). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 26.6, 27.1 both d, $^1J_{PH}$ 572.3 Hz. Found, %: C 56.25; P 8.93. $C_{16}H_{23}O_6P$. Calculated, %: C 56.14; P 9.05.

1,2:5,6-*O*-Diisopropylidene-α-*D*-glucofuranose 3-*O*-[(diethylaminomethyl)phenylphosphinate] X. A solution of 0.72 g of bis(diethylamino)methane in 2 ml of chloroform was added dropwise to 0.75 g of **VII** in 3 ml of chloroform. The reaction mixture was heated for 5 h at a glycerol bath temperature of 45–47°C. Then the solvent was evaporated and the mixture was separated on a column using system C. Yield 0.39 g (42%); oily substance, R_f 0.15 (C). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.9 c (NCH_2CH_3), 24.5–26.3 all s [$C(CH_3)_2$], 47.8, 47.9 both d (NCH_2CH_3, $^3J_{PC}$ 12.8, $^3J_{PC}$ 13.0 Hz), 51.2, 51.6 both d (P–CH_2, $^1J_{PC}$ 115.6, $^1J_{PC}$ 122.0 Hz), 66.8, 67.0 both s (C^6), 71.4, 71,6 both s (C^5), 71.9, 72.3 both s (C^3), 80.1, 80.3 both d (C^4, $^3J_{PC}$ 7.5, $^3J_{PC}$ 5.5 Hz), 83.1 d (C^2, $^3J_{PC}$ 8.2 Hz), 104.4, 104.5 both s (C^1), 108.6, 111.4 and 108.6, 111.5 all s [$C(CH_3)_2$], 127.7, 127.9 both d ($C^{2'}$, $^2J_{PC}$ 11.4, $^2J_{PC}$ 12.4 Hz), 128.9, 129.0 both s ($C^{3'}$), 131.4, 131.6 both d ($C^{1'}$, $^1J_{PC}$ 72.5, $^1J_{PC}$ 72.4 Hz), 131.5, 131.8 both s ($C^{4'}$). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 40.2, 42.7 both s. Found, %: C 58.96; H 7.59; P 6.74. $C_{23}H_{36}NO_7P$. Calculated, %: C 58.84; H 7.73; P 6.60.

2,3-*O*-Isopropylidene-α-L-methylrhamnopyranoside 4-*O*-[(diethylaminomethyl)phenylphosphinate] XI. A solution of 0.60 g of bis(diethylamino)methane in 2 ml of chloroform was added dropwise to 0.55 g of **IX** in 3 ml of chloroform. The mixture was heated for 5 h at a glycerol bath temperature of 44–46°C. Then the solvent was evaporated and the mixture was separated on a column using system F. Yield 0.34 g (49%); colorless oily substance, R_f 0.26 (F). ^{13}C NMR spectrum (C_6D_6), δ, ppm: 12.3, 12.4 both s (NCH_2CH_3), 18.6 s (C^6), 49.1, 49.3 both d (NCH_2CH_3, $^3J_{PC}$ 9.3, $^3J_{PC}$ 8.9 Hz), 53.7 d (P–CH_2, $^1J_{PC}$ 113.7 Hz), 55.0 s (OCH_3), 65.3, 65.6 both d (C^5, $^3J_{PC}$ 3.4, $^3J_{PC}$ 2.9 Hz), 77.1, 77.2 both s (C^2), 77.6, 77.7 both s (C^3), 86.8 s (C^4), 98.7 s (C^1), 98.7, 109.8 and 98.7, 110.3 all s [$C(CH_3)_2$], 128.2, 128.8 both s ($C^{2'}$), 132.3, 132.5 both s ($C^{3'}$), 133.6, 133.9 both s ($C^{4'}$), 133.8 d ($C^{1'}$, $^1J_{PC}$ 71.9 Hz). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 40.15 s. Found, %: C 59.10; H 8.09; P 7.11. $C_{21}H_{34}NO_6P$. Calculated, %: C 59.00; H 8.02; P 7.25.

1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose 3-*O*-[(1'-hydroxy-2',2',2'-trichloroethyl)phenylphosphinate] XII. A solution of 0.31 g of freshly distilled chloral in 2 ml of chloroform was added dropwise at 15°C (water bath) to 0.73 g of **VII** in 3 ml of chloroform. The mixture was stirred for 1 h, after which the solvent was evaporated and the system was separated on a column using system A. Yield 0.38 g (38%); colorless amorphous substance, mp 73–76°C, R_f 0.20 (A). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.0–26.6 [$C(CH_3)_2$], 66.8–67.8 (C^6), 71.8–72.8 (C^5), 78.4–79.8 (CHOH), 80.3–81.1 (C^4), 83.5–85.0 (C^2), 97.5–97.8 (CCl_3), 105.0–105.1 (C^1), 109.1–112.4 [$C(CH_3)_2$], 125.3–133.8 (Ph). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 37.0, 34.5, 35.1, 32.6 all s. Found, %: C 45.25; H 5.03; P 5.65. $C_{20}H_{26}Cl_3O_8P$. Calculated, %: C 45.17; H 4.93; P 5.82.

2,3-*O*-Isopropylidene-α-*L*-methylrhamnopyranoside 4-*O*-[(1'-hydroxy-2',2',2'-trichloroethyl)-phenylphosphinate] XIII. A solution of 0.29 g of

freshly distilled chloral in 2 ml of chloroform was added dropwise at 15°C (water bath) to 0.62 g of **IX** in 3 ml of chloroform. The mixture was stirred for 1 h. The solvent was evaporated, and the mixture was separated on a column using system D. Yield 0.46 g (52%); colorless amorphous substance, mp 149–150°C, R_f 0.35 (D). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.2 s (C^6), 26.5–28.7 all s [$C(CH_3)_2$], 54.8 s (OCH_3), 64.1 d (C^5, $^3J_{PC}$ 3.2 Hz), 78.8 s (C^3), 80.0 s (C^4), 81.6 d (CHOH, $^1J_{PC}$ 113.2 Hz), 97.4 s (C^1), 97.8 d (CCl_3, $^2J_{PC}$ 7.3 Hz), 109.1, 110.1 both s [$C(CH_3)_2$], 127.6 d ($C^{2'}$, $^2J_{PC}$ 13.8 Hz), 132.6 s ($C^{3'}$), 133.3 d ($C^{1'}$, $^1J_{PC}$ 46.8 Hz), 133.5 s ($C^{4'}$). ^{31}P NMR spectrum ($CHCl_3$), δ_P, ppm: 33.0, 34.0 all s. Found, %: C 44.02; H 5.00; P 6.20. $C_{18}H_{24}Cl_3O_7P$. Calculated, %: C 44.15; H 4.94; P 6.32.

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