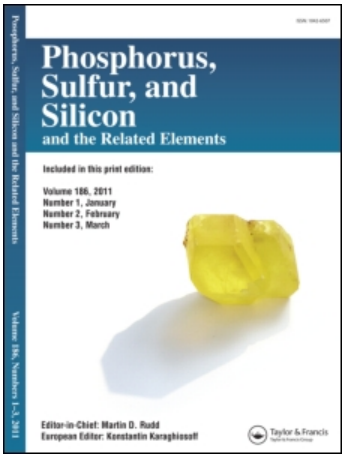

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New Type of Hypophosphites

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New Type of Hypophosphites

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*Optimal conditions were found for the synthesis of hypophosphoric acid esters with the cyclic systems of cyclohexanol and 1,2;5,6-*O*-diisopropylidene-α-*D*-glycofuranose as an example. It was shown that these hypophosphoric acid esters have high reactivity and are candidates for processes resulting in the formation of P—C bonds. The structure of the products was reliably supported by spectral methods.*

Keywords 1,2;5,6-*O*-Diisopropylidene-α-*D*-glycofuranose hypophosphite; cyclohexyl hypophosphite; hydrophosphoryl compounds; hypophosphites; phosphorus–carbon bond; phosphorylation

INTRODUCTION

Hypophosphoric acid esters (hypophosphites) are the least understood hydrophosphoryl compounds. A few of the simplest alkyl hypophosphites[1] and a nucleoside hypophosphite[2] have been obtained to date. All these compounds are unstable; they decompose spontaneously under short storage. At the same time, some reactions of freshly prepared hypophosphites produced difficultly available compounds.[3–6] In this context, our object was to evaluate the possibility of expanding the scope of work on compounds in whose molecules the hypophosphite function is bound to the alicyclic framework. The main objects of study were hypophosphites of cyclohexanol and 1,2;5,6-*O*-diisopropylidene-α-*D*-glycofuranose.

The above esters were synthesized by the reaction of the corresponding alcohols with triethylammonium salt of hypophosphoric acid **1** in the

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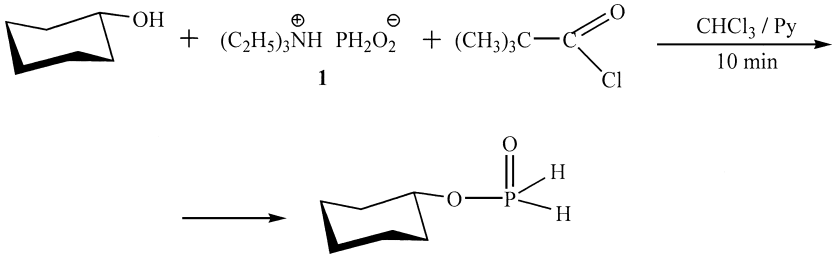
presence of pivaloyl chloride (2, 2-dimethylpropanoic acid chloride). The reaction probably involves the transformation of hypophosphorous acid into pivaloyl hypophosphite, which acts as a phosphorylating agent.

RESULTS AND DISCUSSION

Cyclohexyl hypophosphite (**2**) was synthesized according to Scheme 1:

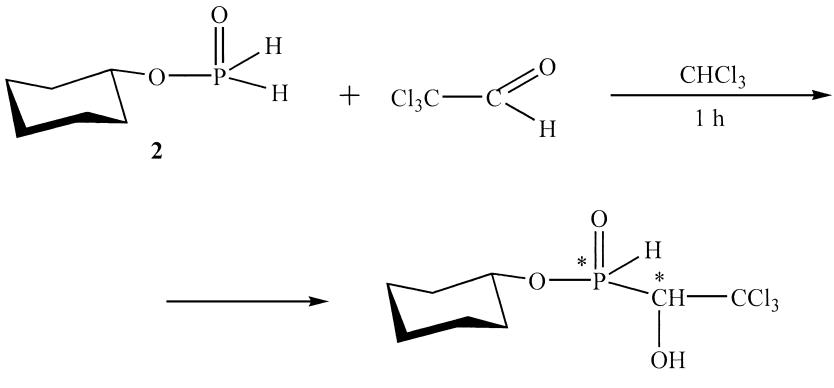


SCHEME 1 Synthesis of Cyclohexyl Hypophosphite (**2**).

Reaction conditions were selected to obtain the target product **2** with a good yield.

Compound **2** was isolated in the individual form by high-vacuum sublimation. Its structure was supported by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy (see Experiment). The obtained hypophosphite **2** is an unstable compound; it spontaneously disproportionates when stored under an inert atmosphere but can exist in solution for a relatively long time.

The obtained cyclohexyl hypophosphite was introduced into the Abramov reaction with chloral to give phosphonite (Scheme 2):

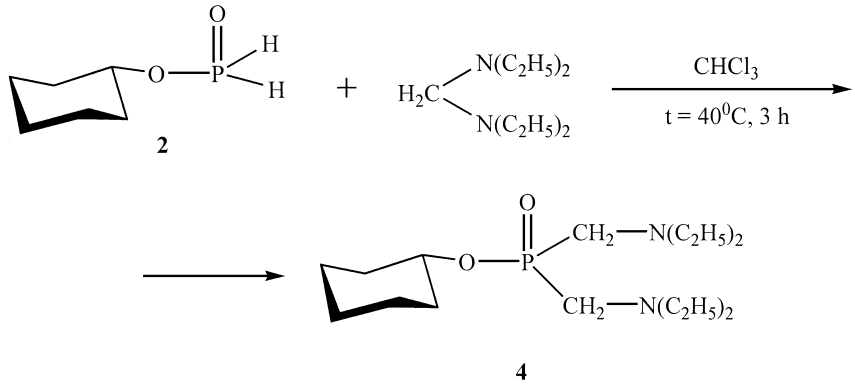


SCHEME 2 Abramov's reaction with Cyclohexyl Hypophosphite (**2**).

Compound **3** is obtained as two diastereomers, as is evidenced by the ^{31}P NMR spectrum of the reaction mixture, which show two doublets with chemical shifts of 26.3 and 20.7 ppm and coupling constants of 593.04 and 586.33 Hz, respectively.

We isolated one of the isomers in the pure form. Its ^{31}P NMR spectrum showed a doublet with a chemical shift of 26.3 ppm and a coupling constant of 593.04 Hz.

Next, we attempted to obtain a compound with two P–C bonds, i.e., a phosphinic acid derivative from cyclohexyl hypophosphite. This task was implemented by mixing cyclohexyl hypophosphite with bis(diethylamino)methane. Note that the reaction of 1 equivalent of compound **2** with 2.5 equivalents of bis(diethylamino)methane gives two products with mono- and disubstituted phosphorus atoms in a proportion of 1:5, as is evidenced by the ^{31}P NMR spectrum which shows a doublet with a chemical shift of 34.5 ppm and a coupling constant of 550.25 Hz, as well as a singlet with a chemical shift of 51.1 ppm. The reaction was shifted toward the formation of the phosphinic acid derivative only under heating for several hours (Scheme 3).



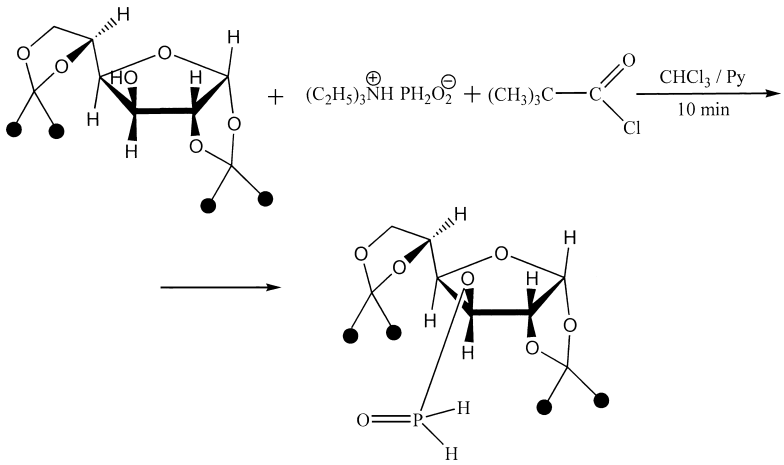
SCHEME 3 Kabachnik-Fields' reaction with Cyclohexyl Hypophosphite (**2**).

The structure of compound **4** was supported by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and by elemental analysis.

Next, glucofuranose hypophosphite **5** was synthesized analogously to product **2** (Scheme 4).

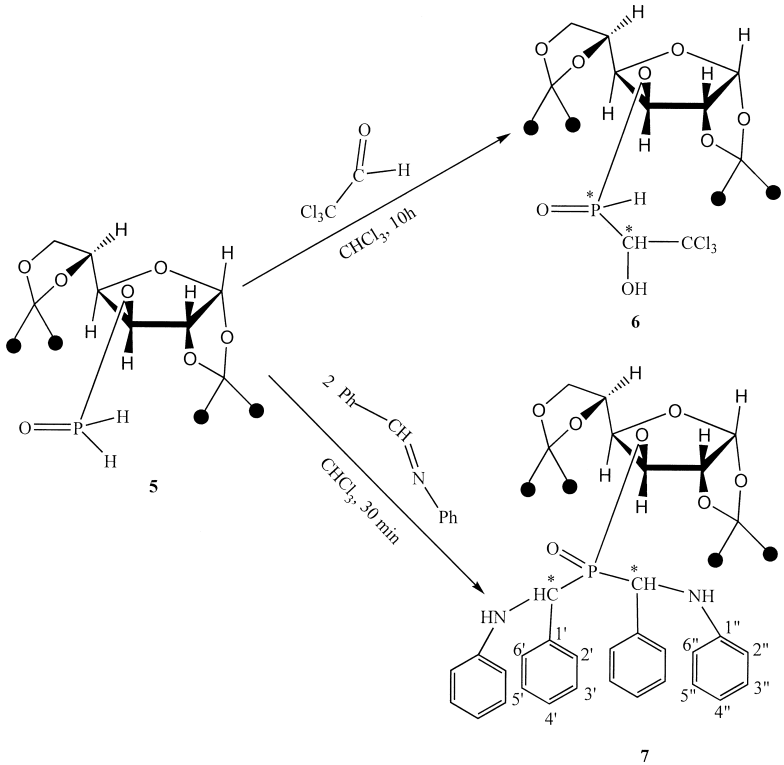
Hypophosphite **5** is a very labile compound, which decomposes by 77% in 30–40 min. Therefore, syntheses with hypophosphite **5** were performed without isolating it from the reaction mixture.

To synthesize new phosphorus derivatives of glucose, hydrophosphoryl compound **5** was introduced into the Abramov and Kabachnik–Fields reactions (Scheme 5).



5

SCHEME 4 Synthesis of 3-O-Hypophosphite-1,2;5,6-O-diisopropylidene-α-D-glucofuranose (**5**).



5 **6** **7**

SCHEME 5 Electrophil reactions with 3-O-Hypophosphite-1,2;5,6-O-diisopropylidene-α-D-glucofuranose (**5**).

It is interesting that phosphinate was not formed even when an excess of chloral was used; the single reaction product was always phosphonite **6**, which was isolated as an individual compound and whose structure was supported by spectral methods. Compound **6** is formed as two stereoisomers, with one being predominant; therefore, it was isolated in the pure form by column chromatography.

Hypophosphite **5** exhibits high reactivity in the reaction with benzalaniline and forms phosphinate **7**, in spite of spatial hindrance.

Compound **7** was isolated in the individual form and characterized by spectral methods, as well as by elemental analysis (see Experiment).

The performed study of the synthesis and properties of cyclohexanol and 1,2;5,6-*O*-diisopropylidene-α-*D*-glycofuranose hypophosphites showed that these compounds are candidates for processes resulting in the formation of P—C bonds.

EXPERIMENT

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz). ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (50.32 MHz). ^{31}P NMR spectra were recorded on a Bruker WP-80SY instrument (32.4 MHz) against 85% H_3PO_4. Adsorption column chromatography was performed on silica gel L 100/160 and neutral alumina oxide (Brockman activity II). Thin layer chromatography was carried out on Silufol UV-254 plates using benzene–dioxane, 3:1 (A) and hexane-dioxane, 1:1 (B) systems as eluants; detection was achieved using iodine vapor or calcinations.

All syntheses were performed in dry chloroform under dry oxygen-free argon. The target hypophosphorous acid derivatives were used without isolation.

General Procedure for the Synthesis of 1–7

Triethylammonium Hypophosphite (1)

Hypophosphoric acid was synthesized according to the known procedure[7] from 10.00 g (0.0961 mol) of KPH_2O_2. Triethylamine (9.73 g, 0.0961 mol) was dropped to an aqueous solution of freshly prepared hypophosphorous acid under stirring and cooling in an ice bath, and the mixture was left for 12 h. Next, water was evaporated under vacuum to a volume of about 5–7 ml. The resulting oily product was 4–5 times evacuated with dry benzene (10 ml) to remove residual water. The colorless oil was filtered and dried over P_2O_5 under vacuum for 3 h. Yield, 9.00 g (56%); the compound is soluble in acetonitrile, acetone, dioxane, benzene, and chloroform. ^{1}H NMR ($CDCl_3$): δ 1.03 (t 9H, CH_3), 2.81

(q, 6H, CH_2, $^3J_{HH} = 7.7$ Hz), 6.82 (d, 2H, PH_2, $^1J_{PH} = 504.28$ Hz), 11.01 (sb, 1H, NH), 14.75 (1H, OH in exchange with N). ^{31}P NMR (without solvent): δ 0.12 (t, $^1J_{PH} = 504.28$ Hz).

Cyclohexyl Hypophosphite (2)

A solution of 0.87 g (0.0087 mol, 1.5 equiv.) of cyclohexanole in 3 ml of chloroform and 0.92 g (0.0116 mol, 2 equiv.) of pyridine were added to 0.98 g (0.0058 mol, 1 equiv.) of triethylammonium hypophosphite. 2,2-Dimethylpropanoic acid chloride (1.05 g, 0.0087 mol, 1.5 equiv.) in 3 ml of chloroform were slowly dropped to the obtained mixture under stirring and cooling. The mixture was stirred for 7–10 min and used for syntheses without further purification. To purify the product, the solvent was removed under vacuum without heating; an inert gas was bubbled through a capillary. Next, the mixture was treated with hexane and filtered. The solvent was removed from the filtrate under vacuum without heating. The resulting colorless oil was sublimated under high vacuum (10^{-4} mm Hg) at a glycerol bath temperature of 80–90°C. Colorless amorphous substance was obtained with a yield of 0.44 g (34%); d.p. 95–100°C; R_f 0.3 (B). ^{1}NMR ($CDCl_3$): δ 1.20 (m, 2H, $^4CH_2$), 1.50 (m, 2H, $^3CH_2$), 1.62 (m, 2H, $^2CH_2$), 1.82 (m, 1H, CHOP), 7.08 (d, 2H, PH_2, $^1J_{PH} = 563.52$ Hz). ^{31}P NMR ($CHCl_3$): δ 11.99 (t, $^1J_{PH} = 563.52$ Hz, $^3J_{PH} = 9.85$ Hz).

Cyclohexyl Ester of 1-Hydroxy-2,2,2-trichloroethylphosphonous Acid (3)

Freshly distilled chloral (1.28 g, 0.0087 mol) in 3 ml of chloroform was slowly dropped to a solution of 1.29 g (0.0087 mol) of cyclohexyl hypophosphite in chloroform. The mixture was stirred for 1 h, and the solvent was removed in vacuum. By-products were removed by precipitation with hexane. The filtrate was purified by column chromatography with system B as eluent. The isolated diastereomers were separated by fractional crystallization from hexane. Yield, 1.03 g (40%); m.p. 148–152°C; R_f 0.56 (B). ^{1}NMR (DMSO-d_6): δ 1.28 (m, 2H, $^4CH_2$), 1.49 (m, 2H, $^3CH_2$), 1.68 (m, 2H, $^2CH_2$), 1.88 (m, 1H, CHOP), 4.43 (dd, 1H, C<u>H</u>OH, $^3J_{HH} = 2.92$ Hz, $^2J_{PH} = 8.77$ Hz), 7.05 (dd, 1H, PH, $^1J_{PH} = 593.04$ Hz, $^3J_{HH} = 2.92$ Hz), 8.09 (sb, 1H, OH). ^{31}P NMR ($CHCl_3$): δ 25.19 (d, $^1J_{PH} = 593.04$ Hz). Anal. calcd. for $C_8H_{14}Cl_3O_3P$: C, 32.51; H, 4.77; P, 10.48. Found: C, 32.99; H, 4.81; P, 10.67.

Cyclohexyl Ester of Bis(diethylaminomethylene)phosphinic Acid (4)

A solution of 2.04 g (0.0138 mol) bis(diethylamino)methane in 3 ml of chloroform was dropped to a solution of 0.81 g (0.0055 mol) cyclohexyl

hypophosphite in chloroform. The mixture was stirred for 1 h and next heated at a glycerol bath temperature of 40°C for 3 h. The solvent was distilled off. By-products were removed by precipitation with hexane. The resulting mixture was purified by column chromatography using system B as eluent and alumina oxide as stationary phase. Yellow oily substance was obtained with a yield of 1.40 g (80%); R_f 0.4 (B). ^{13}C NMR ($CDCl_3$): δ 9.45–10.96 (s, 4C, CH_3), 23.33 (s, C(5)), 24.88 (s, C(3)), 27.20 (s, C(4)), 33.85 (s, 2C, C(2), C(6)), 47.77 (d, 4C, N-CH_2, $^3J_{PC} = 8.02$ Hz), 50.12 (d, 2C, P(CH_2)$_2$, $^1J_{PC} = 109.60$ Hz), 73.63 (d, C(1), $^2J_{PC} = 7.60$ Hz). ^{31}P NMR (without solvent): δ 51.49 (s). Anal. calcd. For $C_{16}H_{35}N_2O_2P$: C, 60.35; H, 11.08; N, 8.80; P, 9.73. Found: C, 59.95; H, 11.01; N, 8.62; P, 9.63.

3-O-*Hypophosphite-1,2;5,6*-O-*diisopropylidene*-α-D-*glucofuranose (5)*

A solution of 1.25 g (0.0048 mol, 1.5 equiv.) of 1,2;5,6-*O*-diisopropylidene-α-*D*-glucofuranose in 3 ml of chloroform and 0.51 g (0.0064 mol, 2 equiv.) of pyridine were added to 0.54 g (0.0032 mol, 1 equiv.) of triethylammonium hypophosphite. 2,2-Dimethylpropanoic acid chloride (0.58 g, 0.0048 mol, 1.5 equiv.) in 3 ml of chloroform was slowly dropped to the obtained mixture under stirring and cooling. The mixture was stirred for 7–10 min and used for the next syntheses without further purification. Rf 0.62 (A). ^{31}P NMR ($CHCl_3$): δ 17.64 (t, $^1J_{PH} = 575.17$ Hz).

3-O-(1′-hydroxy-2′,2′,2′-trichloroethylphosphinite)-1,2; 5,6-diisopropylidene-α-*D*-glucofuranose (6)

Freshly distilled chloral (1.17 g, 0.0080 mol) in 3 ml of chloroform was added to a solution of 0.99 g (0.0379 mol) of 3-*O*-hypophosphinite-1,2;5,6-diisopropylidene-α-*D*-glucofuranose. The reaction mixture was stirred for 10 h. The solvent was removed under vacuum, and the mixture was chromatographed on a column using system A as eluent. Colorless oily liquid crystallized when stored. Yield of 0.55 g (40%), m.p. 90–92°C. Rf 0.62 (A). ^{13}C NMR ($CDCl_3$) δ 26.03–26.95 (s, 4C, CH_3), 67.64 (s, C(6)), 72.85 (s, C(5)), 74.67 (d, CHOH, $^1J_{CP} = 12.2$ Hz), 81.02 (s, C(4)), 83.65 (d, C(3), $^2J_{PC} = 2.52$ Hz), 84.96 (s, C(2)), 106.24 (s, C(1)), 109.30 and 111.58 (s, $\underline{C}(CH_3)_2$), 112.54 (d, CCl_3, $^2J_{PC} = 6.00$ Hz). ^{31}P NMR ($CHCl_3$): δ 30.1 (d, $^1J_{PH} = 608.45$ Hz). Analuse calculated for $C_{14}H_{22}Cl_3O_8P$: C, 36.90; H, 4.87; P, 6.80. Found: C, 35.44; H, 4.67; P, 6.69.

3-O-[bis-α-(N-phenylaminobenzyl)-phosphinate]-1,2:5,6-diisopropylidene-α-*D*-glucofuranose (7)

Benzalaniline (0.54 g, 0.0032 mol) in 3 ml of chloroform was added to a solution of 0.99 (0.0032 mol) g of 3-*O*-hypophosphinite-1,2;5,6-diisopropylidene-α-*D*-glucofuranose. The reaction mixture was stirred for 30 min. The solvent was next removed under vacuum, and the mixture was chromatographed on a column using benzene as eluent. Yellowish scummy substance was obtained with a yield of 0.26 g (12%), m.p. 98–100°C. Rf 0.68 (benzene-dioxane, 5:1) ^{13}C NMR ($CDCl_3$): δ 25.34–27.24 (4C, CH_3), 52.61–57.14 (CH-Ph), 67.30–67.68 (C(6), 72.29–72.53 (C(5)), 73.12 (C(3)), 79.26–80.08 (C(4)), 83.50–83.83 (C(2)), 104.59–104.87 (C(1)), 109.36–112.03 ($\underline{C}(CH_3)_2$), 113.84–114.45 (C(2″)), 118.83–119.34 (C(4″)), 127.48–129.37 (C(2′), C(3′), C(3″)), 133.80–136.08 (C(1′)), 145.31–146.67 (C(1″)). ^{31}P NMR ($CHCl_3$): δ 45.33 and 45.80 (s). Anal. calcd for: $C_{38}H_{43}N_2O_7P$ C, 68.05; H, 6.46; N, 4.18; P, 4.62. Found: C, 68.11; H, 6.54; N, 4.03; P, 4.39.

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