Carbohydrate Research, 111 (1982) 67–73
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

1,2-*O*-ALKYLIDENE-3(5,6)-THIO-α-D-GLUCOFURANOSE 3,5,6-THIOPHOSPHITES

EDUARD E. NIFANTYEV, MICHAIL P. KOROTEEV, SERGEY A. LYSENKO, SVETLANA A. RUMYANTSEVA, AND NIKOLAY K. KOCHETKOV

Department of Chemistry, V. I. Lenin Moscow State Pedagogical Institute, and N. D. Zelinsky Institute of Organic Chemistry of the Academy of Sciences of the U.S.S.R., Moscow (U.S.S.R.)

(Received March 9th, 1982; accepted for publication, May 24th, 1982)

ABSTRACT

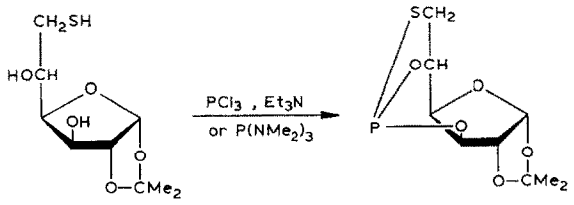
The first representatives of sugar bicyclothiophosphites have been synthesised and their structures confirmed by chemical and spectral (^{13}C- and ^{31}P-n.m.r.) data. Chlorination of the sugar bicyclothiophosphites has been studied and new representatives of cyclic thiolo- and thioxo-chlorophosphates of hexofuranoses have been obtained.

INTRODUCTION

Bicyclophosphites of glucofuranose, possessing a strained structure, are characterised by remarkable chemical features[1–4]. We now report on the synthesis and transformations of bicyclothiophosphites of 1,2-*O*-alkylidene-D-glucofuranose derivatives containing a sulphur atom in each of the three possible positions of the bicyclophosphite system*.

RESULTS AND DISCUSSION

The reaction of 1,2-*O*-isopropylidene-6-thio-α-D-glucofuranose (**1**) with phosphorus trichloride in the presence of triethylamine afforded 55% of the 3,5,6-bicyclothiophosphite (**2**).



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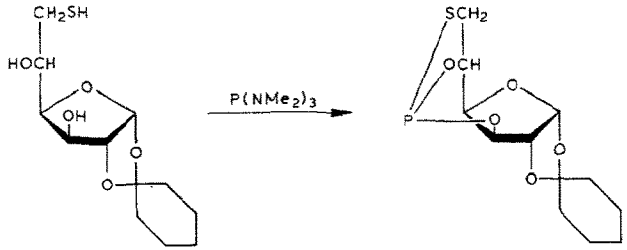
*Preliminary data are reported in refs. 5 and 6.

Although aliphatic thiols are reported to be poorly phosphorylated by triamidophosphites, because of sulphur-transfer processes[7], **1** reacted with hexamethylphosphorous triamide to give 90% of **2**. Similarly, hexamethylphosphorous triamide reacted with 1,2-*O*-cyclohexylidene-6-thio-α-D-glucofuranose (**3**) to give 1,2-*O*-cyclohexylidene-6-thio-α-D-glucofuranose 3,5,6-thiophosphite (**4**).



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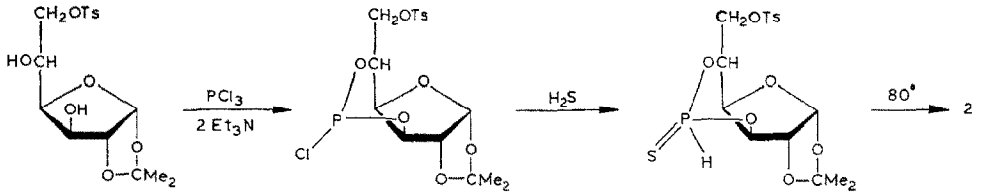
Another approach to the synthesis of sugar bicyclothiophosphites involved the 3,5-thioxophosphite (**7**) of 1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulphonyl-α-D-glucofuranose, which was synthesised by the sequence **5**→**6**→**7**. When a solution of **7** in 1,4-dioxane was kept at 80° for 2 h, **2** was formed. The cyclisation **7**→**2** is related to a rare type of reaction that is the converse of the Michaelis–Becker synthesis. Alkylation of the ambident anion at the sulphur atom is governed by stereochemical factors[4].



5 6 7

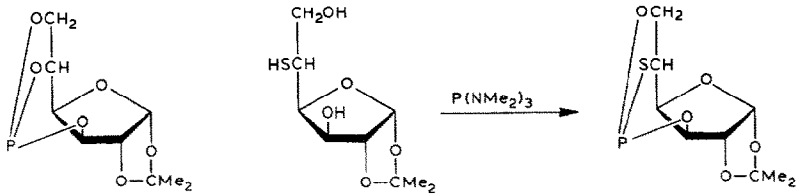
The homogeneity of the above bicyclothiophosphites was shown by t.l.c. and ^{31}P-n.m.r. data, and their structures follow from the results of alcoholysis (see below) and from the ^{13}C-n.m.r. data. Thus, the ^{13}C-n.m.r. spectrum of **2** is similar to that of 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-phosphite (**8**) (see Table I). As expected, the most significant difference in the spectra of **2** and **8** involves the chemical shift of the signal for C-6 (32.3 and 67.0 p.p.m., respectively). A substantial change in the chemical shift was observed also for the phosphorus signal (151 and 117 p.p.m., respectively). There was no C–P spin-coupling of C-1 and C-2 for **2** and **8**, but coupling was observed for C-3,4,5,6 which are involved in the bicyclophosphite system, and this indicates unequivocally the presence of a 3,5,6-bicyclothiophosphite fragment. The C–P coupling constants for C-3 and C-5 of **2** and **8** are the same. Some difference is observed for the C-4–P and C-6–P constants, which is due probably to the steric effect of the sulphur atom.

TABLE I

^{31}P- AND ^{13}C-CHEMICAL SHIFTS (P.P.M.) AND ^{13}C–^{31}P SPIN-COUPLING CONSTANTS (Hz)

Compound	*C-1*		*C-2*		*C-3*		*C-4*		*C-5*		*C-6*		*P*
	δ	J	*δ*	J	*δ*	J	*δ*	J	*δ*	J	*δ*	J	*δ*
2	105.0	—	84.0	—	76.5	2.7	80.4	7.9	71.9	4.1	32.6	5.1	151
8	106.1	—	84.2	—	73.3	2.6	77.7	4.4	71.4	4.5	67.0	6.0	117
10	106.3	—	85.1	—	75.6	8.6	76.9	4.4	37.6	2.4	45.7	5.7	158
14	105.9	—	84.8	—	41.6	2.5	77.7	5.5	77.1	4.5	61.2	5.9	159
19	105.3	—	83.6	4.9	84.8	8.3	78.9	8.0	45.8	5.6	43.5	2.7	12.7
21	105.5	—	82.7	8.0	84.4	10.1	76.7	6.0	77.1	5.9	45.6	9.2	71.3

Phosphorylation of 1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (**9**) by hexamethylphosphorous triamide in pyridine at 100° for 2 h followed by chromatography on silica gel afforded 60% of 1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose 3,5,6-thiophosphite (**10**). The structure of **10** was established by ^{13}C- and ^{31}P-n.m.r. spectroscopy. The data are given in Table I, which shows only a small difference in the chemical shift for the phosphorus resonances of the 5-bicyclothiophosphite **10** and the 6-bicyclothiophosphite **2** (158 and 151 p.p.m., respectively). The chemical shifts of the signals for C-1,2,3,4 for **10** and **2** were also similar. Substantial differences in the chemical shifts were observed for the signals for C-5 (37.6 p.p.m. for **10** and 71.9 p.p.m. for **2**), and C-6 (45.7 p.p.m. for **10** and 32.3 p.p.m. for **2**). As with **2**, the splitting of the phosphorus signal in **10** was observed for C-3,4,5,6 which are involved in the bicyclophosphite system. This is the first representative of sugar bicyclophosphites having a sulphur atom simultaneously involved in phosphorinane and phospholane rings.

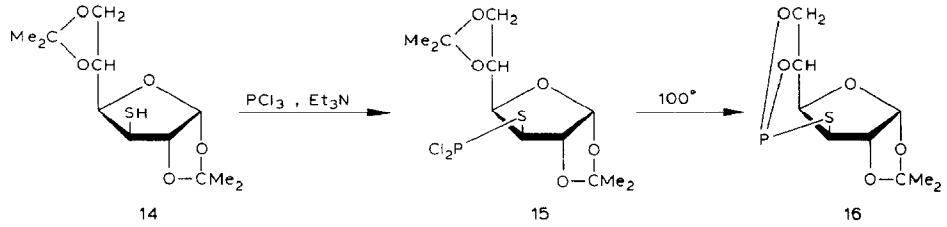


8 9 10

The phosphorylation of 1,2-*O*-isopropylidene-3-thio-α-D-glucofuranose (**11**) was complicated by the ready oxidation of **11** to the disulphide and its marked tendency to desulphuration. Thus, treatment of **11** with hexamethylphosphorous triamide afforded the product of desulphuration, 3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose 5,6-dimethylphosphoramidate.

Desulphuration could be avoided by generation of the bicyclophosphite system *via* intramolecular phosphorylation. Since thio sugars and their derivatives are not

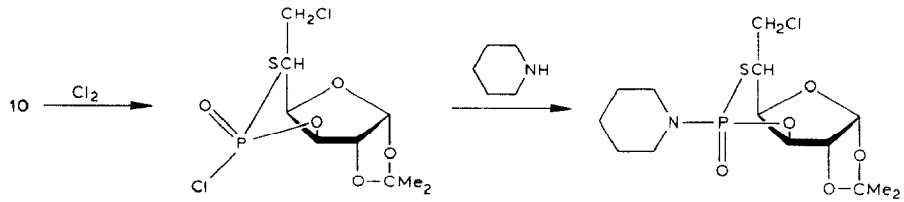
readily accessible, the oxygen analogues were used as the model compounds. Thus, treatment of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**) with phosphorus trichloride in the presence of 1 mol of triethylamine in 1,4-dioxane afforded the 3-dichlorophosphite **13** which, at 80°, was converted into the 3,5,6-phosphite **8**.



14 15 16

Optimum conditions for this new reaction were found, and then applied to 1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose (**14**). Thus, treatment of **14** with phosphorus trichloride in 1,4-dioxane in the presence of 1 mol of triethylamine gave the 3-dichlorophosphite **15**, which was readily converted into 1,2-*O*-isopropylidene-3-thio-α-D-glucofuranose 3,5,6-thiophosphite (**16**). The structure of **16** was confirmed by ^{13}C- and ^{31}P-n.m.r. data (see Table I), elemental analysis, and chemical transformations. The most substantial differences in the chemical shifts of the resonances of **16** and **10** involve C-3 (41.6 and 75.6 p.p.m., respectively) and C-5 (71.1 and 37.6 p.p.m. respectively), and C–P coupling was observed only for C-3,4,5,6.

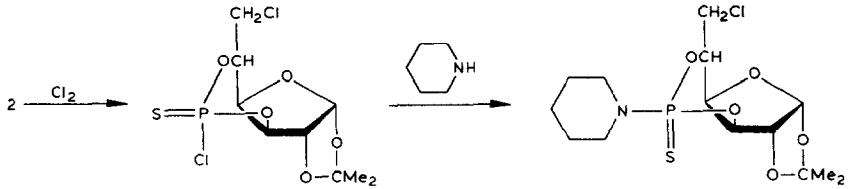
Methanolysis of the bicyclothiophosphites gave trimethyl phosphite and the corresponding thio sugar; thus, **16** gave **11**. As expected, bicyclothiophosphites reacted with chlorine. Thus, with chlorine in dichloromethane at −10 to 0°, **10** was converted into 6-chloro-6-deoxy-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose 3,5-phosphorochloridothioate (**18**). Two isomers of **18** were formed in the ratio 1.2:1 with ^{31}P resonances at 7.8 and 7.3 p.p.m. The isomers could not be separated, probably because of their lability (see ref. 1). Treatment of the mixture of isomers with piperidine gave two isomers of 6-chloro-6-deoxy-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose 3,5-phosphoropiperididothioate (**19**).



18 19

The interaction of the bicyclothiophosphite **2** with chlorine occurred less readily than with **10** and scission of the C-6–S-6 bond occurred to give 6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 3,5-phosphorochloridothioate (**20**), which

had a ^{31}P resonance at 32.9 p.p.m., characteristic of thioxo compounds. Compound **20** had comparatively high reactivity and treatment with piperidine gave 6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 3,5-phosphoropiperididothioate (**21**). The presence of a six-membered 2-thioxo-1,3,2-dioxaphosphorinane ring in **21** was confirmed by the ^{31}P-n.m.r. data (see Table I). In the reaction **2**→**20**, cleavage of the P–S bond occurs, and not the P–O bond as is usual in the Arbuzov reaction. Steric factors may control this reaction, with chlorine attacking C-6 which is sterically more accessible than C-5 or C-3. Such differences in the reactivity of the primary and secondary carbons in sugar derivatives are well known. Also, phosphorinanes are known to be more stable than phospholanes and phosphepanes, which may also contribute to the selective reaction at C-6.



20 21

EXPERIMENTAL

Reactions were carried out under dry N_2 Column chromatography was performed on silica gel L 100/25 μm (Czechoslovakia) with hexane containing 0→25% of 1,4-dioxane T.l.c. was performed on Silufol UV-254 (Czechoslovakia) with *A*, benzene–1,4-dioxane (3:1); *B*, hexane–1,4-dioxane (3:1); and detection with iodine vapour N.m.r. spectra were measured with a Bruker WH-90 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) Optical rotations were measured with a Perkin–Elmer 141 polarimeter.

1,2-O-Isopropylidene-6-thio-α-D-glucofuranose 3,5,6-thiophosphite (**2**). — (*a*) To a mixture of **1** (4.7 g) and triethylamine (6.1 g) in ether (50 mL) was added phosphorus trichloride (2.7 g) dropwise with stirring at 0°. The mixture was stirred for 2 h at room temperature, filtered, and concentrated, and the residue was subjected to column chromatography (solvent *A*), to yield **2** (2.8 g, 55%), m.p. 147°, $[\alpha]_D^{20}$ −4.5° (*c* 1, benzene), R_F 0.9 (solvent *A*), 0.86 (solvent *B*).

Anal. Calc. for $C_9H_{13}O_5PS$: C, 40.91; H, 4.96; P, 11.72; S, 12.13. Found: C, 40.19; H, 4.64; P, 11.39; S, 12.05.

(*b*) To a solution of **1** (2 g) in pyridine (20 mL) was added hexamethylphosphorous triamide (1.2 g), the mixture was heated for 2 h at 80–100° until no more amine was evolved, and then concentrated, and the residue was subjected to column chromatography (solvent *A*), to yield **2** (2.03 g, 91%), m.p. 147°, $[\alpha]_D^{20}$ −4.5° (*c* 1, benzene).

(*c*) To a mixture of **5** (3.7 g) and triethylamine (2.1 g) in 1,4-dioxane (50 mL)

was added phosphorus trichloride (1.4 g) dropwise with stirring at 10°. The mixture was stirred for 1 h at 30° and then filtered, and hydrogen sulphide was passed through the filtrate for 2 h. The mixture was then kept at 80° for 2 h and concentrated, and the residue was subjected to column chromatography (solvent *A*), to yield **2** (1.1 g, 42%), m.p. 145–146°, $[\alpha]_D^{20}$ −4.5° (*c* 1, benzene).

1,2-O-Cyclohexylidene-6-thio-α-D-glucofuranose 3,5,6-thiophosphite (**4**). — Treatment of **3** (2.8 g) with hexamethylphosphorous triamide (1.7 g), as described above, afforded **4** (2.57 g, 85.6%), m.p. 125°, $[\alpha]_D^{20}$ −3° (*c* 1, benzene), R_F 0.9 (solvent *A*), 0.8 (solvent *B*).

Anal. Calc. for $C_{12}H_{17}O_5PS$: C, 44.07; H, 5.52; P, 10.19; S, 10.51. Found: C, 43.89; H, 5.44; P, 9.99; S, 10.34.

1,2-O-Isopropylidene-5-thio-α-D-glucofuranose 3,5,6-thiophosphite (**10**). — Treatment of a solution of **9** (0.25 g) in pyridine (2 mL) with hexamethylphosphorous triamide (0.18 g), as described above, afforded **10** (0.17 g, 60%), m.p. 97–98°, $[\alpha]_D^{20}$ −2.5° (*c* 1, benzene), R_F 0.5 (solvent *B*).

Anal. Calc. for $C_9H_{13}O_5PS$: C, 40.91; H, 4.96; P, 11.71; S, 12.13. Found: C, 40.24; H, 4.72; P, 11.98; S, 12.01.

1,2-O-Isopropylidene-α-D-glucofuranose 3,5,6-phosphite (**8**) — To a solution of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (5.2 g) and triethylamine (2.1 g) in 1,4-dioxane (20 mL) was added at 10° with stirring a solution of phosphorus trichloride (2.7 g) in the same solvent (80 mL). The mixture was heated to room temperature, filtered, and kept at 100° for 3 h. The solvent was evaporated and the residue was subjected to column chromatography (benzene–1,4-dioxane system), to give **8** (2.2 g, 44.8%), m.p. 155–156°, $[\alpha]_D^{20}$ −45° (*c* 0.15, 1,4-dioxane), R_F 0.85 (solvent *A*); ^{31}P resonance, 117 p.p.m.; lit. m.p. 155–156°.

1,2-O-Isopropylidene-3-thio-α-D-glucofuranose 3,5,6-thiophosphite (**16**). — Using the procedure described above, **14** (1.3 g), triethylamine (0.7 mL), and phosphorus trichloride (0.45 mL) were allowed to react in 1,4-dioxane (60 mL), to afford **16** (0.8 g, 55%), $[\alpha]_D^{20}$ −2.5° (*c* 1, benzene), R_F 0.9 (solvent *B*).

Anal. Calc. for $C_9H_{13}O_5PS$: C, 40.91; H, 4.96; P, 11.72; S, 12.13. Found: C, 40.69; H, 4.76; P, 11.92; S, 12.30.

6-Chloro-6-deoxy-1,2-O-isopropylidene-5-thio-α-D-glucofuranose 3,5-phosphoropiperididothioate (**19**). — Dry chlorine was passed for 30 min at −10° into a solution of **10** (0.23 g) in dichloromethane (5 mL) until the solution turned green. The mixture was stirred for 30 min and then concentrated to dryness *in vacuo*, and to a solution of the residue in dichloromethane (5 mL) at −10° was added piperidine (0.18 g). The mixture was stored for 1 h at 20°, filtered, and concentrated, to give, after column chromatography (solvent *A*), syrupy **19** (0.17 g, 54%), R_F 0.37 (solvent *A*).

Anal. Calc. for $C_{14}H_{23}ClNO_5PS$: C, 43.80; H, 5.75; N, 3.65; P, 8.07; S, 8.35. Found: C, 43.58; H, 5.58; N, 3.70; P, 8.20, S, 8.46.

6-Chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose 3,5-phosphoropiperididothioate (**21**). — Using the procedure described above, a solution of **20** (0.7 g)

in dichloromethane (15 mL) was treated with piperidine (0.6 g) at 40°, to afford syrupy **21** (0.5 g, 55%), R_F 0.41 (solvent *A*).

Anal. Calc. for $C_{14}H_{23}ClNO_5PS$: C, 43.80; H, 5.75; N, 3.65; P, 8.07; S, 8.35. Found: C, 43.71; H, 5.49; N, 3.54; P, 7.93; S, 8.38.

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