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Note

Efficient synthesis of *S*- and *Se*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl) thiophosphates and selenophosphates

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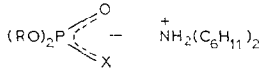
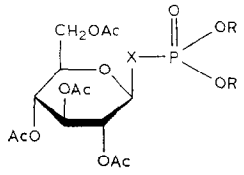
Chmielewski and BeMiller[1] described a series of *O,O*-di-*tert*-butyl *S*-α- and -β-D-glucopyranosyl thiophosphates and *S*-α- and -β-D-galactopyranosyl thiophosphates and found that these products were thermally unstable, decomposed during chromatography, and were rather impure. The authors were not able to prepare the free acids. Following our earlier work[2–7], we now describe an efficient preparation of the relatively stable di-*tert*-butyl esters of *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) thiophosphate (**3**) and *Se*-(2,3,4,6-*O*-acetyl-β-D-glucopyranosyl) selenophosphate (**4**) in high yield, and their quantitative conversion into the free acids.



1 X = S, R = ^{t}Bu

2 X = Se, R = ^{t}Bu



3 X = S, R = ^{t}Bu

4 X = Se, R = ^{t}Bu

5 X = S, R = H

6 X = Se, R = H

O,O-Di-*tert*-butyl phosphorothioate (**1**) and *O,O*-di-*tert*-butyl phosphoroselenoate (**2**) are more reactive towards glycosyl halides than are simple *O,O*-dialkyl phosphorothioates and phosphoroselenoates. Hence, glycosylation could be performed under mild conditions, and the reaction of the salts **1** and **2** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide in dichloromethane at room temperature gave **3** and **4**, respectively, in quantitative yield.

A low reaction temperature is required in order to avoid decomposition of the thermally unstable products **3** and **4**. When the foregoing reactions were performed in

boiling benzene, partly dealkylated, acidic products were formed, which promoted further decomposition. This fact explains the low yields and instability of the di-*tert*-butyl esters prepared by Chmielewski and BeMiller[1]. Because of their thermal instability, the *O,O*-di-*tert*-butyl β-D-glycosyl phosphorothioates and phosphoroselenoates were best purified by fractional precipitation. The purity of the products was confirmed by the results of elemental analysis, ^{31}P- and ^{1}H-n.m.r. spectroscopy, and i.r. spectroscopy. Compounds **3** and **4** were stable on storage at 0–5°, but decomposed slowly at ambient temperature.

The dealkylation of **3** and **4** to give the respective free acids **5** and **6** was effected with boiling toluene for 5 min or with catalytic amounts of trifluoroacetic acid in benzene at ambient temperature. In each dealkylation, the yield of *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)phosphorothioic acid (**5**), characterised as the cyclohexylammonium salt **7**, was quantitative. However, the yield of *Se*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)phosphoroselenoic acid (**6**) was somewhat lower, which accords with the known instability of many phosphoroselenium compounds.

EXPERIMENTAL

Melting points (Kofler) are uncorrected. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian 60 MHz instrument. ^{31}P-N.m.r. spectra were recorded for solutions in $CHCl_3$ (external 85% H_3PO_4) with Jeol 24-MHz FT and Bruker 36.43 MHz instruments. Optical rotations were determined on solutions in $CHCl_3$ with a Polamat polarimeter. Analyses were performed at the Microanalytical Laboratories of the Centre of Molecular and Macromolecular Studies (Lodz) and at the Microanalytical Laboratories of the Medical Academy (Lodz).

The yields of the products were determined on the basis of ^{31}P-n.m.r. spectroscopy; yields of the isolated products are given in brackets.

Dicyclohexylammonium O,O-*di*-tert-*butyl phosphorothioate* (**1**). — The procedure of Zwierzak and Gramze[8] was modified as follows. A mixture of equimolar amounts of di-*tert*-butyl phosphite (18.4 g), dicyclohexylamine (18.1 g), and sulphur (3.2 g) was stirred for 24 h at ambient temperature. The precipitate was collected, and crystallised from benzene to give **1** (75%) as colorless crystals, m.p. 190–191° (dec.). ^{31}P-N.m.r. data: +40 p.p.m.

Anal. Calc. for $C_{20}H_{42}NO_3PS$: C, 58.92; H, 10.41; N, 3.44; P, 7.60. Found: C, 59.29; H, 10.47; N, 3.39; P, 7.54.

Dicyclohexylammonium O,O-*di*-tert-*butyl phosphoroselenoate* (**2**). — A mixture of equimolar amounts of di-*tert*-butyl phosphite (18.4 g), dicyclohexylamine (18.1 g), and selenium (7.9 g) in benzene (100 mL) was boiled under reflux for 10 h. Unreacted selenium was separated from the hot mixture. The product (**2**) precipitated on cooling, and crystallisation from benzene gave colorless needles (70%), m.p. 179–180° (dec.) with darkening at 160°. ^{31}P-N.m.r. data: +21.7 p.p.m. ($J_{P,Se}$ 726 Hz).

Anal. Calc. for $C_{20}H_{42}NO_3PSe$: C, 52.84; H, 9.33; N, 3.08; P, 6.81. Found: C, 53.18; H, 8.87; N, 3.30; P, 6.41.

O,O-*Di*-tert-*butyl* S-(*2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl*) *thiophosphate* (**3**). — A solution of equimolar amounts of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.411 g) and **1** (0.407 g) in CH_2Cl_2 was kept at ambient temperature for 4 days. The precipitate of dicyclohexylammonium bromide (0.256 g, 98%) was removed, the filtrate was concentrated *in vacuo*, and the residue was recrystallised from ether–light petroleum, to give **3** (0.42 g, 75%), m.p. 95–96°. The yield determined by ^{31}P-n.m.r. spectroscopy was quantitative. A second recrystallisation gave **3** as colorless needles, m.p. 97–98.5° (dec.); lit.[1] m.p. 98–100°. ^{31}P-N.m.r. data: +11.8 p.p.m. (d, $^3J_{P,H}$ 11.6 Hz). The ^{1}H-n.m.r. data were consistent with those given by Chmielewski and BeMiller[1].

Anal. Calc. for $C_{22}H_{37}O_{12}PS$: C, 47.47; H, 6.71; P, 5.56; S, 5.76. Found: C, 47.50; H, 6.60; P, 5.48; S, 5.81.

O,O-*Di*-tert-*butyl* Se-(*2,3,4,6-tetra*-O-*acetyl*-β-D-*glucopyranosyl*) *selenophosphate* (**4**). — A solution of equimolar amounts of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.411 g) and **4** (0.454 g) in CH_2Cl_2 was kept at ambient temperature for 4 days. The precipitate of dicyclohexylammonium bromide was removed, the filtrate was concentrated *in vacuo*, and the residue was crystallised from ether–light petroleum, to give **4** (0.41 g, 68%), m.p. 99–100°. The yield determined by ^{31}P-n.m.r. spectroscopy was 95%. A second recrystallisation gave **4** as colorless needles, m.p. 102–103°, $[\alpha]_{578}^{16}$ +6° (*c* 1.7); ν_{max}^{KBr} 1225 (P=O) and 1750 cm^{-1} (C=O). N.m.r. data: ^{31}P, +2.7 p.p.m. (d, $^3J_{P,H}$ 9.4, $J_{P,Se}$ 426 Hz); ^{1}H, δ 1.55 (s, 18 H, 2 ^{t}Bu), 2.1, 2.06, 2.02, 1.98 (4 s, 12 H, 4 OAc), 5.2–5.1 (m, 4 H, H-1,2,3,4), 4.25–4.05 (m, 2 H, H-6,6′), and 3.8–3.6 p.p.m. (m, 1 H, H-5).

Anal. Calc. for $C_{22}H_{37}O_{12}PSe$: C, 43.78; H, 6.19; P, 5.13. Found: C, 43.71; H, 5.94; P, 5.31.

S-(*2,3,4,6-Tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*phosphorothioic acid* (**5**) *and its cyclohexylammonium salt* (**7**). — (*a*) A solution of **3** (0.556 g) in toluene (20 mL) was boiled under reflux for 5 min, and then concentrated *in vacuo* to give syrupy **5** which showed no ^{1}H-n.m.r. signals for ^{t}Bu. N.m.r. data: ^{31}P, +22.8 p.p.m.; ^{1}H, +10.5 p.p.m. (bs, 2 H, 2 OH). To a solution of **5** in acetone (20 mL) was added cyclohexylamine (1 mmol). The solvent was removed *in vacuo* and the residue was crystallised from methanol–ether, to give **7** (0.4 g, 72%), m.p. 154–155°, $[\alpha]_{578}^{20}$ +3.5° (*c* 1).

Anal. Calc. for $C_{20}H_{34}NO_{12}PS$: C, 44.19; H, 6.32; N, 2.58; P, 5.70; S, 5.90. Found: C, 43.94; H, 6.29; N, 2.48; P, 5.48; S, 5.95.

The di-cyclohexylammonium salt, m.p. 135–136°, was formed on addition of 2 mmol of cyclohexylamine to **5**.

Anal. Calc. for $C_{26}H_{46}N_2O_{12}PS$: C, 48.6; H, 7.15; N, 4.36; P, 4.82; S, 4.98. Found: C, 47.5; H, 7.45; N, 4.03; P, 4.52; S, 5.20.

(*b*) To a solution of **3** (0.556 g) in benzene (20 mL) was added CF_3COOH (0.2 mL), and the mixture was kept at ambient temperature for 24 h. The solvent was

removed *in vacuo*, and the oily residue **5** was transformed into **7** as described in (*a*). The yield was quantitative, as judged by ^{31}P-n.m.r. spectroscopy.

Se-(*2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl*)*phosphoroselenoic acid* (**6**) *and its cyclohexylammonium salt* (**8**). — The salt **8** was obtained from **4** as described in (*a*) and (*b*). The yield was quantitative, as judged by ^{31}P-n.m.r. spectroscopy. The yield of **8** isolated was 68–70%, and crystallisation from methanol–ether gave material having m.p. 140–142°, $[\alpha]_{578}^{19}$ +11° (*c* 1.8).

Anal. Calc. for $C_{20}H_{34}NO_{12}PSe$: C, 40.68; H, 5.82; N, 2.37; P, 5.24. Found: C, 40.60; H, 5.98; N, 2.30; P, 4.89.

N.m.r. data for **6**: ^{31}P, +14.4 p.p.m.; ^{1}H, 10 p.p.m. (bs 2 H, OH); no signals for ^{t}Bu.

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