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ADDITION REACTIONS OF GLYCOSID-4-ULOSES AND RELATED COMPOUNDS WITH SOME PHOSPHORUS COMPOUNDS

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ABSTRACT

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (**2**) was treated with methyl phenylphosphinate in the presence of triethylamine, to give mainly methyl 6-deoxy-2,3-*O*-isopropylidene-4-*C*-[(methoxy)phenylphosphinyl]-α-L-talopyranoside. Treatment of compound **2** with dimethyl and diethyl phosphonate under the same reaction conditions also afforded adducts having the L-*talo* configuration. The reaction of (6-*S*)-tetrahydro-6-methoxypyran-3-one with dimethyl phosphonate and methyl phenylphosphinate, respectively, gave the corresponding adducts in good yields. The reaction of methyl 2,3-*O*-isopropylidene-α,β-L-*erythro*-pentopyranosid-4-ulose and 2,3,5-tri-*O*-benzyl-*aldehydo*-L-*threo*-pentos-4-ulose 1-(dimethyl acetal) with methyl and phenyl phenylphosphinate also gave the corresponding adducts. These results suggest that the substituents on the sugar skeleton play an important role in the addition of phosphorus compounds.

INTRODUCTION

For the chemical modification of carbohydrates, we have synthesized sugars having a phosphorus atom as the ring hetero-atom[1,2], the addition of phosphorus compounds to C=C and C=N double bonds of sugars being utilized. Glyculoses have often been used as intermediates for the preparation of sugar derivatives, *e.g.*, amino sugars[3]. On the other hand, reactions of ketones with phosphorus compounds having a P–H bond have been widely investigated[4]. Even in the field of carbohydrates, the reaction of glyculoses with dialkyl phosphonates has been reported (by Paulsen and Greve[5]).

From the viewpoint of comparatively ready preparation, glycosid-4-uloses seemed to be good starting-materials. In order to synthesize sugars bearing a phosphorus–carbon bond at C-4, addition reactions of glycosid- and glycos-4-uloses with

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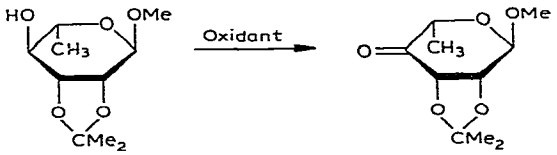
some kind of phosphorus compound were attempted under the Abramov reaction-conditions[6]. We now describe the preparation of 4-phosphinyl and 4-phosphonyl derivatives of sugars, and the effect of substituents on the sugar skeleton on the addition of phosphorus compounds.

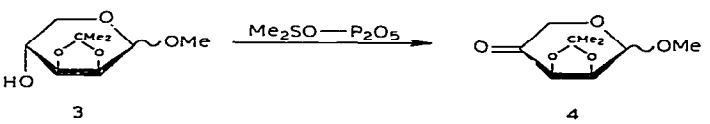
RESULTS AND DISCUSSION

Oxidation of methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**1**) by several convenient methods was examined. Oxidation of compound **1** with chromium trioxide–pyridine[7], dimethyl sulfoxide–phosphorus pentaoxide[8], and the Jones reagent[9] gave the corresponding glycosidulose, namely, methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (**2**), in 38, 75, and 68% yield, respectively. Photoreaction of the pyruvic ester[10] of compound **1** gave glycosidulose **2** in 72% yield.



1 2

Attempted oxidation of the partially protected sugar **1** with chromium trioxide–dipyridine complex[11] did not proceed, and treatment of compound **1** with Me_2SO–trifluoroacetic anhydride[12] gave a complex mixture (t.l.c. analysis). Oxidation with Me_2SO–phosphorus pentaoxide seemed to be the best method for preparation of **2**, judging from the high yield, and the simple handling involved. Methyl 2,3-*O*-isopropylidene-α,β-L-*erythro*-pentopyranosid-4-ulose (**4**) was also prepared quantitatively by oxidation of methyl 2,3-*O*-isopropylidene-α,β-D-lyxopyranoside (**3**) with Me_2SO–phosphorus pentaoxide.



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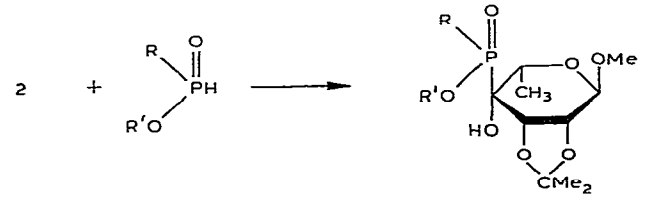
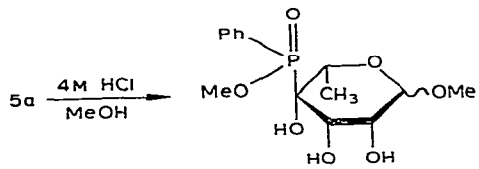


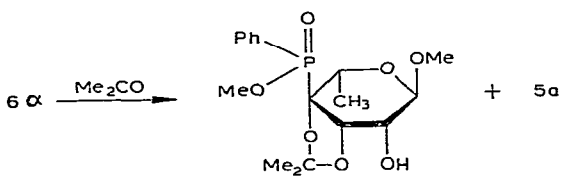
5a R = Ph, R′ = Me
5b R = OMe, R′ = Me
5c R = OEt, R′ = Et

Reaction of glycosidulose **2** with methyl phenylphosphinate in the presence of triethylamine for 10 h at 70–80° afforded the 1 : 1 adduct, namely, methyl 6-deoxy-2,3-*O*-isopropylidene-4-*C*-[(methoxy)phenylphosphinyl]-α-L-talopyranoside (**5a**), which was recrystallized from methanol to give the pure product in 45% yield.

Compound **5a** was hydrolyzed overnight at 50° with 4M hydrochloric acid in methanol, giving methyl 6-deoxy-4-*C*-[(methoxy)phenylphosphinyl]-α-L-talopyranoside (**6α**) and its β anomer (**6β**) in 72 and 8% yield, respectively. Treatment of compound **6α** with acetone in the presence of copper(II) sulfate for a week at room temperature gave a quantitative yield of a 1 : 1 mixture of methyl 6-deoxy-3,4-*O*-isopropylidene-4-*C*-[(methoxy)phenylphosphinyl]-α-L-talopyranoside (**7**) and compound **5a**. Repeated recrystallization of the mixture from ethyl acetate gave compound **7** (having a lower melting point than **5a**).



6α, 6β



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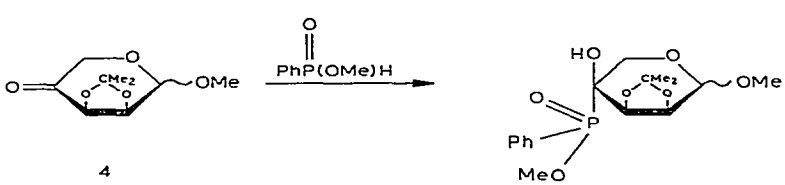
Reaction of compound **2** with dimethyl phosphonate, followed by recrystallization from ethyl acetate, gave methyl 6-deoxy-2,3-*O*-isopropylidene-4-*C*-(dimethoxyphosphinyl)-α-L-talopyranoside (**5b**) in 45% yield. The same procedure gave compound **5c** in 45% yield from compound **2** and diethyl phosphonate[13].

Reaction of glycosidulose **4** with methyl phenylphosphinate in the presence of triethylamine gave a 1 : 1 mixture of adducts in 90% yield. The major adduct (ratio of major to minor adduct, 4 : 1) was determined to be methyl 2,3-*O*-isopropylidene-4-*C*-[(methoxy)phenylphosphinyl]-β-L-ribopyranoside (**8**). The minor adduct is presumably, the α anomer.



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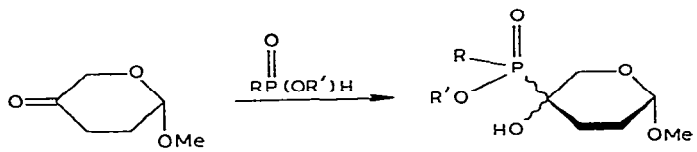
8

(6-*S*)-Tetrahydro-6-methoxypyran-3-one (**9**) with methyl phenylphosphinate and dimethyl phosphonate, respectively, in the presence of triethylamine, gave the corresponding, syrupy, 1 : 1 adducts (**10a** and **10b**) in quantitative yield. From carbon tetrachloride, compound **10a** gave crystals (m.p. 137°) in 58% yield. Compound **10b**, which contained the enantiomers in 1 : 1 ratio, also gave crystals (m.p. 79–81°), in 22% yield, from carbon tetrachloride–cyclohexane.



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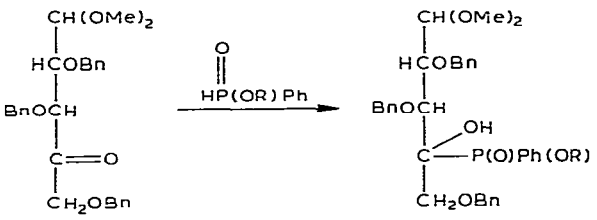
10a R = Ph, R' = Me
10b R = OMe, R' = Me

Reaction of 2,3,5-tri-*O*-benzyl-*aldehydo*-L-*threo*-pentos-4-ulose 1-(dimethyl acetal) (**11**) with methyl and phenyl phenylphosphinate also gave the corresponding adducts, **12a** and **12b**, in 92 and 64% yield, respectively, but the isomer ratios were not determinable by n.m.r. spectroscopy. The reaction of 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranos-5-ulose with methyl phenylphosphinate gave 1 : 1 adducts in the ratio[14] of ~1 : 1. Acyclic and exocyclic ketones showed almost no stereospecific, phosphorus addition.



11

12a R = Me
12b R = Ph

These results showed that the reaction of glycosuloses and other ketones with phosphonates and phosphinates having a P–H bond gives 1 : 1 adducts in good yields; hence, the reaction seems to provide a good method for preparing sugar derivatives containing a phosphorus–carbon bond. The stereospecificity and reaction rate of addition of phosphorus compounds were controlled mainly by substituents adjacent to the carbonyl group, as well as by the conformation (steric-approach control[15]).

EXPERIMENTAL

Materials. — Methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**1**) was prepared according to the Percivals's method[16]. Methyl 2,3-*O*-isopropylidene-α,β-D-

lyxopyranoside (**3**) was prepared by Kent and Ward's method[17]; b.p. 59–60°/0.01 mmHg (lit.[17] b.p. 65°/0.02 mmHg). (6-*S*)-Tetrahydro-6-methoxypyran-3-one (**9**) was prepared from 2-furanmethanol[2]. 2,3,5-Tri-*O*-benzyl-*aldehydo*-D-xylose 1-(dimethyl acetal) was prepared from the diethyl dithioacetal derivative of D-xylose[18].

Measurements. — Melting and boiling points are uncorrected. I.r. spectra were recorded with an A-3 spectrophotometer (Japan Spectroscopic Co., Ltd.). Optical rotations were determined with a DIP-4 polarimeter (Japan Spectroscopic Co., Ltd.). ^{1}H-N.m.r. spectra were recorded with Hitachi–Perkin–Elmer R-20 (60 MHz) and Hitachi R-24 (60 MHz) n.m.r. spectrometers. Mass spectra were recorded with a Hitachi RMU 7MG GC-MS spectrometer. Reactions were monitored by t.l.c., using sulfuric acid or cobalt chloride, or both, as the indicator.

Oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (**1**) *with dimethyl sulfoxide–phosphorus pentaoxide*[8]. — To a solution of compound **1** (4 g) in anhydrous dimethyl sulfoxide (16 mL) and pyridine (4 mL) was added phosphorus pentaoxide (10 g) at room temperature with stirring. Addition of water (50 mL) to the reaction mixture, followed by extraction with chloroform, gave a crude oil which was distilled (b.p. 70°/0.1 mmHg), giving pure compound **2** (2.98 g, 75% yield).

Oxidation of compound **1** *with the Jones reagent*[9]. — A mixture of chromium trioxide (13.4 g) and sulfuric acid (11 mL) was diluted with enough water to give 100 mL of the Jones reagent. To a solution of compound **1** (2.0 g) in acetone (200 mL) was added the Jones reagent (3.0 mL) at −70°. The mixture was kept for 1 h at 5°, an additional 1.0 mL of the Jones reagent was added, and the solution was kept for 4 days at 5°. Neutralization of the acid with potassium carbonate, followed by dehydration with magnesium sulfate, and evaporation, gave syrupy material, which was purified by chromatography on silica gel to afford 1.37 g of compound **2** (68% yield).

Photoreaction of the pyruvic ester of compound **1**. — Treatment of compound **1** (3.3 g) with a solution of pyruvoyl chloride[19] (2.5 g) in anhydrous benzene (75 mL) containing pyridine (2.6 g) gave 4.32 g of the pyruvate (98% yield); ^{1}H-n.m.r. (CCl_4): δ 1.09 (d, 3 H, J 7.0 Hz, Me-5), 1.26 and 1.52 (s, 6 H, C-Me), 2.40 (s, 3 H, Ac), 3.32 (s, 3 H, OMe-1), and 3.6–4.9 (m, 5 H, H-1–5).

Irradiation[10] for 3 days of the pyruvate (1.0 g) in benzene (350 mL) under nitrogen by a 250-W low-pressure, mercury lamp equipped with a Pyrex filter, followed by evaporation *in vacuo*, gave compound **2** (0.48 g, 63%), together with recovered **1** (0.09 g).

Preparation of compound **4**. — Compound **3** (2.0 g) was oxidized with dimethyl sulfoxide (20 mL) and 2.0 g of phosphorus pentaoxide for 3 days at room temperature, giving compound **4** in almost quantitative yield.

Preparation of compound **11**. — 2,3,5-Tri-*O*-benzyl-*aldehydo*-D-xylose 1-(dimethyl acetal) was oxidized with dimethyl sulfoxide–acetic anhydride, to afford compound **11** in 98% yield.

Reaction of compound **2** *with methyl phenylphosphinate.* — A mixture of compound **2** (2 g), methyl phenylphosphinate (1.5 g), and triethylamine (1 mL) was heated for 10 h at 70–80°, to give a crystalline product. A solution of this in chloro-

form was successively washed with a saturated solution of sodium hydrogencarbonate, and water, dehydrated, and evaporated *in vacuo*, to give crystals; recrystallization from methanol gave compound **5a** (1.55 g, 45% yield), m.p. 179–180°, $[\alpha]_D^{20}$ −82.3° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 3320 (OH) and 1210 cm^{-1} (P=O); ^{1}H-n.m.r. ($CDCl_3$): δ 1.04 (d, 3 H, *J* 7.0 Hz, Me-5), 1.36 (s, 3 H, C-Me), 1.52 (s, 3 H, C-Me), 3.33 (s, 3 H, OMe-1), 3.65 (d, 3 H, J_{POCH} 11.0 Hz, POMe), 4.0–5.0 (m, 5 H, H-1–3,5, OH), and 7.30–8.10 (m, 5 H, Ph); *m/e* (%), 45 (65), 51 (28), 59 (54), 71 (85), 77 (91), 85 (59), 87 (48), 99 (24), 115 (23), 141 (36), 155 (85), 156 (100), 157 (85), 184 (25), 212 (18), 255 (16), 352 (2), and 372 (M^+, 1).

Anal. Calc. for $C_{17}H_{25}O_7P$: C, 54.84; H, 6.76. Found: C, 54.70; H, 6.86.

Preparation of compounds **5b** *and* **5c**. — In a similar way, compounds **5b** and **5c** were separately prepared from compound **2** in 45% yield.

Compound **5b**: m.p. 134–135° (recrystallized from ethyl acetate), $[\alpha]_D^{17}$ −38.2° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 3340 (OH) and 1230 cm^{-1} (P=O); ^{1}H-n.m.r. ($CDCl_3$): δ 1.40 (s, 3 H, Me), 1.45 (d, 3 H, *J* 6.7 Hz, Me-5), 1.59 (s, 3 H, Me), 3.40 (s, 3 H, OMe-1), 3.83 (d, 6 H, *J* 11.0 Hz, POMe), and 4.0–5.0 (m, 5 H, H-1–3,5, OH); *m/e* 326 (M^+).

Anal. Calc. for $C_{12}H_{23}O_8P$: C, 43.80; H, 7.24. Found: C, 44.17; H, 7.10.

Compound **5c**: m.p. 125–126° (recrystallized from ethyl acetate), $[\alpha]_D^{17}$ −40.6° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 3300 (OH) and 1220 cm^{-1} (P=O); ^{1}H-n.m.r. ($CDCl_3$): δ 1.30 (t, 6 H, *J* 7.1 Hz, CH_2*Me*), 1.40 (s, 3 H, Me), 1.68 (s, 3 H, Me), 1.72 (d, 3 H, *J* 6.0 Hz, Me-5), 3.39 (s, 3 H, OMe-1), 3.98–5.2 (m, 9 H, $POCH_2$, H-1–3,5, OH); *m/e* 354 (M^+).

Anal. Calc. for $C_{14}H_{27}O_8P$: C, 47.45; H, 7.68. Found: C, 47.15; H, 7.69.

Reaction of compound **4** *with methyl phenylphosphinate*. — Treatment of compound **4** (0.5 g) with methyl phenylphosphinate (1 mL) in the presence of triethylamine (2 mL) for 2 days at 40° gave compounds **8** (0.8 g) in 90% yield (anomeric ratio, $\beta:\alpha$ = 4:1). Recrystallization of the product from carbon tetrachloride gave pure compound **8**β (45%), m.p. 197°, $[\alpha]_D^{20.5}$ +72.1° (*c* 0.77, $CHCl_3$); ν_{max}^{KBr} 3430 (OH) and 1200 cm^{-1} (P=O); ^{1}H-n.m.r. ($CDCl_3$): δ 1.40 (s, 3 H, Me), 1.58 (s, 3 H, Me), 3.35 (s, 3 H, OMe-1), 3.75 (d, 3 H, *J* 10.5 Hz, POMe), 2.8–5.0 (m, 6 H, H-1–3, CH_2, OH), and 7.3–8.1 (m, 5 H, Ph); *m/e* 358 (M^+).

Anal. Calc. for $C_{16}H_{23}O_7P$: C, 53.63; H, 6.47. Found: C, 53.23; H, 6.59.

Reaction of compound **9** *with methyl phenylphosphinate*. — Treatment of compound **9** (1.5 g) with methyl phenylphosphinate (2 g) in the presence of triethylamine (4 mL) for 1 day at room temperature afforded adduct **10a** (2.0 g) in 72% yield. Recrystallization from carbon tetrachloride gave pure compound **10a**, m.p. 137°, $[\alpha]_D^{25.5}$ −0.26° (*c* 1.2, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.3–2.4 (m, 4 H, H-2,2,3,3), 3.38 (s, 3 H, OMe-1), 3.70 (d, 3 H, J_{POCH} 10.5 Hz, POMe), 3.0–4.7 (m, 4 H, H-1,5,5, OH), and 7.3–8.1 (m, 5 H, Ph); *m/e* 284 (M^+).

Anal. Calc. for $C_{13}H_{19}O_5P$: C, 54.54; H, 6.69. Found: C, 54.45; H, 6.64.

Preparation of compound **10b**. — Treatment of compound **9** (0.5 g) with dimethyl phosphonate (1 mL) as described for **10a** gave adduct **10b** in quantitative yield; m.p. 79–81° (recrystallized from carbon tetrachloride–cyclohexane), $[\alpha]_D^{25.5}$ −0.5° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.0–2.5 (m, 4 H, H-2,2,3,3), 3.45 (s, 3 H,

OMe-1), 3.83 (d, 6 H, J_{POCH} 10.5 Hz, POMe), 4.33 (s, 1 H, OH), and 2.9–4.9 (m, 3 H, H-1,5,5); *m/e* 240 (M^+).

Anal. Calc. for $C_8H_{17}O_6P$: C, 40.00; H, 7.13. Found: C, 39.53; H, 7.02.

Compound **11** was treated similarly with methyl and with phenyl phenylphosphinate, to give compounds **12a** and **12b** in 64 and 92% yield, respectively.

Hydrolysis of compound **5a**. — Hydrolysis of compound **5a** was performed with 4M hydrochloric acid in methanol (30 mL) overnight at 50°. Neutralization of the acid with silver carbonate, followed by filtration and evaporation, afforded methyl 6-deoxy-4-*C*-[(methoxy)phenylphosphinyl]-α- and -β-L-talopyranoside (**6α** and **6β**, ratio of α:β anomer = 9:1). Isolation of the α anomer by t.l.c. (silica gel; eluant, ethyl acetate) gave 0.51 g (72% yield) of pure compound **6α**, $[\alpha]_D^{19}$ −94.4° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 3400 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 1.28 (d, 3 H, *J* 7.0 Hz, Me-5), 3.18 (s, 3 H, OMe-1), 3.80 (d, 3 H, J_{POCH} 10.5 Hz, POMe), 3.5–5.0 (m, 7 H, H-1–3,5, OH-2–4), and 7.4–8.1 (m, 5 H, Ph); *m/e* 332 (M^+).

Synthesis of methyl 6-deoxy-3,4-O-isopropylidene-4-C-[(methoxy)phenylphosphinyl]-α-L-talopyranoside (**7**). — Treatment of compound **6α** (0.5 g) with acetone (50 mL) in the presence of anhydrous copper(II) sulfate (10 g) with stirring for 1 week at room temperature, followed by the usual processing, gave a mixture of compounds **7** and **5a** in quantitative yield (ratio of compound **7** to **5a**, 1:1). Repeated recrystallization from ethyl acetate gave compound **7**, m.p. 166–167°, $[\alpha]_D^{17}$ −127.5° (*c* 1.0, $CHCl_3$); ν_{max}^{KBr} 3400 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 1.08 (d, 3 H, *J* 7.0 Hz, Me-5), 1.10 (s, 3 H, C-Me), 1.45 (s, 3 H, C-Me), 3.40 (s, 3 H, OMe-1), 3.68 (d, J_{POCH} 10.5 Hz, POMe), 3.5–5.0 (m, 5 H, H-1–3,5, OH), and 7.3–8.1 (m, 5 H, Ph); *m/e* (%), 41 (30), 43 (26), 51 (23), 59 (32), 77 (38), 85 (39), 87 (33), 99 (22), 128 (30), 142 (35), 156 (100), 163 (26), 197 (38), 265 (19), 283 (15), 328 (7), 358 (5), and 372 (M^+, 2).

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