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SUGARS CONTAINING A CARBON–PHOSPHORUS BOND
PART V. 5-DEOXY-5-(ETHYLPHOSPHINYL)-D-RIBOPYRANOSE

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ABSTRACT

The Michaelis–Arbuzov reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**) with diethyl ethylphosphonite gave methyl 5-deoxy-5-(ethoxyethylphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) which, on treatment with sodium dihydrobis(2-methoxyethoxy)aluminate, afforded methyl 5-deoxy-5-(ethylphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**9**). Hydrolysis of **9** with hydrochloric acid yielded a mixture of the anomeric 5-deoxy-5-(ethylphosphinyl)-D-ribopyranoses (**10**). The hygroscopic, syrupy mixture **10** was converted into a syrup consisting of the two 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-(ethylphosphinyl)-D-ribopyranoses (**11**).

INTRODUCTION

There has been a great deal of activity in recent years in connection with syntheses of sugar analogs having nitrogen or sulfur in the hemiacetal ring[1]. Concerning sugar analogs having phosphorus in the ring, however, only a few reports have been published[2–4]. The present paper reports the synthesis of 5-deoxy-5-(ethylphosphinyl)-D-ribopyranose (**10**).

RESULTS

As the starting material, methyl 2,3-*O*-isopropylidene-5-*O*-(methylsulfonyl)-β-D-ribofuranose[5] (**1**) was used. In an attempt to obtain methyl 5-deoxy-2,3-*O*-isopropylidene-5-(methylphosphino)-β-D-ribofuranoside (**2**), the Becker reaction of **1** with methylphosphide in hexamethylphosphoric triamide (HMPA) was performed, but the product obtained was methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranoside (**3**) (29% yield). The structure of **3** was established by a study of the proton magnetic resonance (p.m.r.) spectrum and by comparison with compound **3** obtained by treatment of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside[6] (**4**) with sodium methoxide in methanol.

The Michaelis–Arbuzov reaction of **4** with diethyl ethylphosphonite or diethyl

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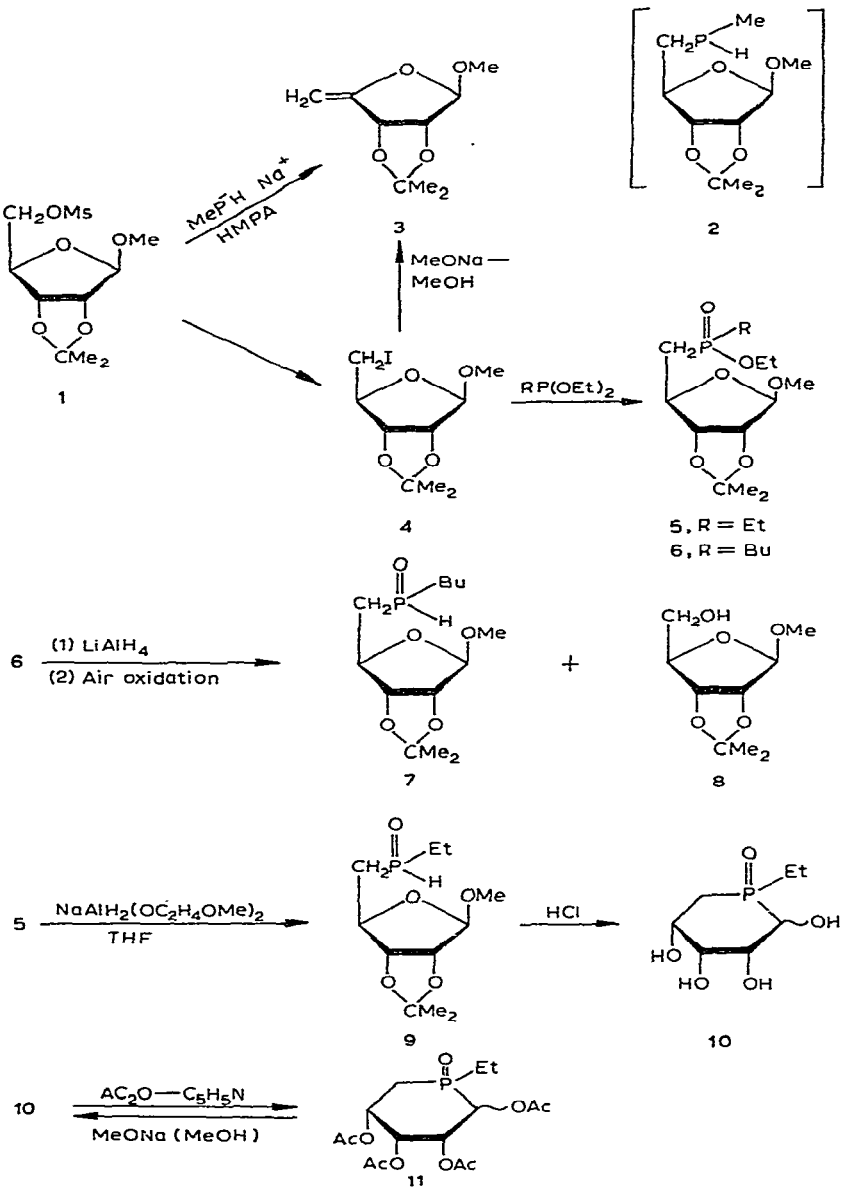
butylphosphonite gave methyl 5-deoxy-5-(ethoxyethylphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) or methyl 5-deoxy-5-(butylethoxyphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**6**), respectively, in 80% yield. Reduction of **6** with lithium aluminum hydride, followed by oxidation with air, afforded only a small proportion of crystalline methyl 5-(butylphosphinyl)-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**7**), although methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**8**) was obtained in 24% yield. However, reduction of **5** with sodium



dihydrobis(2-methoxyethoxy)aluminate (SDMA) gave, in 30% yield, crystalline methyl 5-deoxy-5-(ethylphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**9**). The structure of **9** was determined by study of its p.m.r. and infrared (i.r.) spectra, and by elemental analysis. The p.m.r. spectrum (chloroform-*d*) showed a characteristic *J* (P–H) value[7] of 460 Hz at τ 3.0 (one-proton multiplet, disappearing upon addition of D_2O). The i.r. spectrum (KBr) showed absorption due to a P–H group at 2310 cm^{-1} and due to a P=O group at 1280 cm^{-1}.

Hydrolysis of **9** with 0.25–0.5M hydrochloric acid for 2 h under reflux afforded, almost quantitatively, a hygroscopic syrup of the two 5-deoxy-5-(ethylphosphinyl)-D-ribopyranoses (**10**), $[\alpha]_D^{14}$ −6.9° (*c* 1.0, methanol). In the p.m.r. (Me_2SO-d_6) and i.r. spectra, the characteristic absorptions caused by a P–H group completely disappeared. Acetylation of **10** with acetic anhydride–pyridine gave, almost quantitatively, 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-(ethylphosphinyl)-D-ribopyranose (**11**), $[\alpha]_D^{14}$ −24° (*c* 2.3, chloroform). The p.m.r. spectrum (chloroform-*d*) thereof showed that **11** had four acetyl groups. Treatment of **11** with sodium methoxide in methanol regenerated **10** in almost quantitative yield. Hence, **10** was identified as being 5-deoxy-5-(ethylphosphinyl)-D-ribopyranose, a sugar having phosphorus in the hemiacetal ring.

Compound **10** was fairly stable; mutarotation was not observed during 24 h, and attempted methyl glycosidation of **10** with a strong-acid ion-exchange resin in methanol during 35 h under reflux gave no detectable amount of methyl glycoside, **10** being recovered unchanged.

EXPERIMENTAL

General. — The i.r. spectra were recorded with a Hitachi–Perkin–Elmer 337 spectrophotometer, and the n.m.r. spectra (at 60 MHz) with a Hitachi–Perkin–Elmer R-20 spectrometer, with tetramethylsilane as the internal reference standard. Optical rotations (sodium D line) were measured with a Hitachi PO–B polarimeter by use of a 0.5-dm cell. Thin-layer chromatography (t.l.c.) was conducted on layers of silica G-10 (Nakarai Chemicals, Ltd., Japan); the compounds were detected by spraying the plates with 1:19 (v/v) sulfuric acid–ethanol and then heating them. Periodical monitoring by t.l.c. permitted determination of reaction conditions suitable for the preparative reactions.

Materials. — Methyl 2,3-*O*-isopropylidene-5-*O*-(methylsulfonyl)-β-D-ribofuranoside (**1**) was prepared by the method of Kissman and Baker[5]; m.p. 82.5–83.0°. Methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**) was prepared by the method of Levene and Stiller[6]; $b_{0.5}$ 85–92°. The diethyl ethylphosphonite (b_{38} 58–60°), diethyl butylphosphonite (b_{12} 68–70°), and dimethyl methylphosphonate (b_{10} 63°) were prepared in the usual ways.

Reaction of methyl 2,3-O-isopropylidene-5-O-(methylsulfonyl)-β-D-ribofuranoside (**1**) *with sodium methylphosphide.* — Into a solution of sodium (0.2 g) in hexamethylphosphoric triamide (HMPA) (20 ml) was passed methylphosphine[8] (produced by

reduction of dimethyl methylphosphonate with lithium aluminum hydride in 1,2-dimethoxyethane under a nitrogen atmosphere at 0° until the solution became yellow). To this solution was added **1** (1.5 g) in HMPA (10 ml) at 0°; the solution was kept for 24 h in a refrigerator, and then the HMPA was distilled off *in vacuo*. The residue was extracted with chloroform, and the extract was washed with water, dried (sodium sulfate), and evaporated to a syrup. This was chromatographed on a column of silica gel, with 2:1 chloroform–ethyl acetate; evaporation of the eluate gave a syrup (0.4 g, 29%) of methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranoside (**3**), b_8 53–60°.

Compound **3** was also obtained (in 88% yield) by reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (1.0 g) with sodium methoxide (0.6g of sodium in 12 ml of methanol) in a sealed tube for 4 h at 124–130°. P.m.r. data (CCl_4): τ 5.01 (1 H, s, H-1), 5.10 (1 H, t, H-3), 5.65 (1 H, d, H-2), 5.55, 5.78 (2 H, d, H_2C=C), 6.67 (3 H, s, OCH_3), 8.62, and 8.72 (6 H, s, CMe_2).

Methyl 5-deoxy-5-(ethoxyethylphosphinyl)-2,3-O-isopropylidene-β-D-ribofuranoside (**5**). — A solution of **4** (7.0 g) in diethyl ethylphosphonite (15 ml) was heated under a stream of nitrogen for 40 h at 150–170°. During the reaction, diethyl ethylphosphonite (0.5–1 ml) was added every 2 h. The excess of the phosphonite was distilled off *in vacuo*, the residue was dissolved in chloroform, and the solution was washed with water, dried (sodium sulfate), and evaporated *in vacuo*. Distillation gave syrupy **5** (5.5 g, 80%), $b_{0,01}$ 103–110°, $[\alpha]_D^{24}$ −35° (*c* 2.1, chloroform); p.m.r. data (CCl_4): τ 5.17 (1 H, s, H-1), 5.27–5.60 (2 H, H-2, H-3), 5.65–6.35 (4 H, m. $OPCH_2$), 6.68 (3 H, s, OCH_3), 7.85–9.15 (10 H, PC_2H_5, POC_2H_5, H-5, H-5′), 8.57, and 8.71 (6 H, s, CMe_2).

Methyl 5-deoxy-5-(butylethoxyphosphinyl)-2,3-O-isopropylidene-β-D-ribofuranoside (**6**). — Compound **4** (5.0 g) was treated with diethyl butylphosphonite as just described, to give a syrup (4.3 g, 80%) of **6**, $b_{0.01}$ 48–53°, $[\alpha]_D^{14}$ −48° (*c* 2.4, chloroform), p.m.r. data (CCl_4): τ 5.14 (1 H, s, H-1), 5.25–5.60 (2 H, H-2, H-3), 5.63–6.20 (3 H, $OPCH_2$, H-4), 6.63 (3 H, s, OCH_3), 7.35–9.20 (14 H, m, POC_2H_5, PC_4H_9, H-5, H-5′), 8.53, and 8.68 (6 H, s, CMe_2).

Reduction of **6** *with lithium aluminum hydride* — A solution of compound **6** (5.0 g) in ether (100 ml) was cooled to −10°, a suspension of lithium aluminum-hydride (2 g) in ether (100 ml) was added, and the mixture was stirred for 30 min at 0° under a nitrogen atmosphere. The excess of hydride was decomposed with water-saturated ether, and the ether layer was washed with aqueous sodium carbonate solution dried (sodium sulfate), and evaporated *in vacuo*; the residual syrup was dissolved in isopropyl alcohol (100 ml), and a stream of air was passed through the solution at room temperature. The solution was evaporated *in vacuo*, the resulting syrup was dissolved in ether, and the solution was washed with water (washing *A*), dried (sodium sulfate), evaporated *in vacuo*, and the residual syrup chromatographed on a column of silica gel with 1:1 ethyl acetate–petroleum ether to give methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**8**) (0.8 g, 24%).

The aqueous layer (*A*) was evaporated *in vacuo* to give a very small amount of

7, m.p. 102.5–103.5°, p.m.r. data ($CDCl_3$): τ 3.01 (1 H, d, J (P–H) 450 Hz, PH), 5.04 (1 H, s, H-1), 5.15–5.56 (3H, H-1, H-2, H-3), 6.62 (3H, s, OCH_3), 7.75–9.25 (11 H, PC_4H_9, H-5, H-5'), 8.52, and 8.67 (6 H, s, CMe_2); ν_{max}^{nujol}: 2320 cm^{-1} (PH).

Methyl 5-deoxy-5-(ethylphosphinyl)-2,3-O-isopropylidene-β-D-ribofuranoside (**9**). — To a solution of **5** (2.0 g) in tetrahydrofuran (THF) (150 ml) was added 1.8 g of a 70% solution of sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in benzene at 0° under a nitrogen atmosphere; then, THF (50 ml) containing concentrated hydrochloric acid (0.6 ml) and water (1.2 ml) was added to the mixture. The suspension was filtered, and the filtrate was dried (sodium sulfate), and evaporated, to yield crystals (0.8 g, 47%) of **9**, m.p. 112.5–113° (from 1:1 ethyl acetate–petroleum ether), $[\alpha]_D^{15}$ −29° (*c* 2.5, chloroform), p.m.r. data ($CDCl_3$): τ 2.96 (1 H, d, J (P–H) 460 Hz, PH), 5.01 (1 H, s, H-1), 5.19–5.62 (3 H, H-2, H-3, H-4), 6.63 (3 H, s, OCH_3), 7.58–9.08 (7 H, PC_2H_5, H-5, H-5'), 8.51, and 8.64 (6 H, s, CMe_2); ν_{max}^{KBr}: 2310 (P–H) and 1279 cm^{-1} (P=O).

Anal. Calc. for $C_{11}H_{21}O_5P$: C, 50.00; H, 8.01. Found: C, 49.65; H, 8.32.

5-Deoxy-5-(ethylphosphinyl)-D-ribopyranose (**10**). — A solution of **9** (0.9 g) in 0.25M hydrochloric acid (30 ml) was boiled under reflux in a nitrogen atmosphere for 24 h. The acid was neutralized with Amberlite IRA-410 (OH^-) ion-exchange resin (5.0 g), and the solution was washed with petroleum ether, and evaporated *in vacuo* to give a hygroscopic syrup (0.7 g, 97%) of **10**, $[\alpha]_D^{14}$ −6.9° (*c* 1.0, methanol; no mutarotation in 24 h), p.m.r. data (Me_2SO-d_6): τ 4.25–5.40 (4 H, OH), 5.55–6.95 (4 H, H-1, H-2, H-3, H-4), 7.60–8.66 (4 H, PCH_2, H-5, H-5'), and 8.66–9.25 (3 H, PC_2H_5); p.m.r. data (D_2O): τ 5.78–6.63 (4 H, H-1, H-2, H-3, H-4), 7.48–8.66 (4 H, PCH_2, H-5, H-5'), and 8.66–9.28 (3 H, PC_2H_5).

1,2,3,4-Tetra-O-acetyl-5-deoxy-5-(ethylphosphinyl)-D-ribopyranose (**11**). — Treatment of **10** (0.6 g) with acetic anhydride (16 ml) in pyridine (10 ml) in the usual way gave a syrup (0.95 g, 90%) of **11**, $[\alpha]_D^{16}$ −24° (*c* 2.34, chloroform); p.m.r. data ($CDCl_3$): τ 3.90–4.98 (4 H, H-1, H-2, H-3, H-4), 7.15–8.40 (4 H, PCH_2, H-5, H-5'), 7.80, 7.88, 7.93, 8.00 (12 H, s, $COCH_3$), and 8.40–9.20 (3 H, PC_2H_5).

Deacetylation of **11**. — To a solution of **11** (0.9 g) in methanol (10 ml) was added sodium methoxide solution [from sodium (10 mg) and methanol (5 ml)]. After being stirred for 20 h at 5°, the base was neutralized with Amberlite IRC-50 (H^+) ion-exchange resin, and the solution was evaporated *in vacuo* to give a syrup (0.45 g, 90%) of **10**.

Attempted methyl glycosidation of **10**. — A solution of **10** (0.2 g) in methanol (5 ml) was boiled under reflux with Dowex 50 (H^+) ion-exchange resin (0.5 g) for 35 h, with stirring and the solution was evaporated to give a syrup (0.2 g) of unchanged **10**.

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