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Note

Synthesis of 1,5-anhydroxylitol and 1,5-anhydro-D-arabinitol 2,3,4-tris(phosphates)

Henk Regeling [a], Binne Zwanenburg [a], Gordon J.F. Chittenden [a,*] and Nicola Rehnberg [b]

[a] *Department of Organic Chemistry, NSR Centre for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen (Netherlands)*
[b] *Perstorp Pharma, S-28480 Perstorp (Sweden)*

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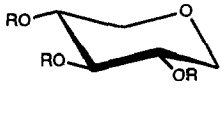
The title tris(phosphates) **1** and **2** were required as mimics for some *myo*-inositol phosphates in pharmacological–biomechanistic studies. Neither compound has been described previously. The synthesis of **1** and **2** by conventional procedures is now presented.

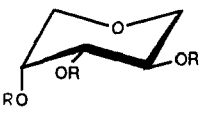
The required parent 1,5-anhydroalditols **3** and **4** were obtained from the corresponding per-*O*-acetylpentopyranosyl bromides **5**[1] and **6**[2] through reduction with lithium aluminium hydride, using a described method[3]. Treatment[4] of a pyridine solution of **3** with an excess of diphenyl phosphorochloridate yielded the pure tris(diphenyl phosphate) ester **7** (74%) after column chromatography. Compound **3** has a *meso* structure, and the resulting **7** was accordingly optically inactive.

Reaction of 1,5-anhydro-D-arabinitol (**4**) with diphenyl phosphorochloridate in a similar manner provided the tris(triester) **8** in only 12% yield after column chromatography. The low yield of **8** was probably due to competitive formation of the cyclic phosphate triester **9**, which would be facilitated by the equatorial–axial arrangement of the C-3 and C-4 hydroxyl groups in compound **4**. In reactions with diphenyl phosphorochloridate, it is known[5] that if two hydroxyl groups are suitably situated on adjacent carbon atoms then an initial monophosphorylated product may undergo attack at the phosphorus atom by the remaining hydroxyl group to give a cyclic triester. No attempts were made to isolate or identify the other products of the reaction, but evidence[5] supporting the alternative formation of compound **9** was provided by the detection (GLC) of significant amounts of phenol in the crude reaction mixture obtained from **4**.

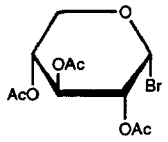
* Corresponding author.



1 R = $PO(OH)_2$
3 R = H
7 R = $PO(OPh)_2$



2 R = $PO(OH)_2$
4 R = H
8 R = $PO(OPh)_2$



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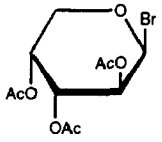

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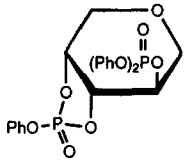

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The *trans*-equatorial disposition of the hydroxyl groups of compound **3** makes cyclic phosphate formation less likely as an alternative pathway in its reaction with diphenyl phosphorochloridate.

Catalytic hydrogenation of compounds **7** and **8** provided the desired **1** and **2**, which were isolated, and characterised as their pentakis(cyclohexylammonium) salts by treatment with cyclohexylamine. The salt obtained from **1** was isolated as a monohydrate, whereas that from **2** recrystallised as a hemi-ethanolate.

The elemental analyses of cyclohexylamine salts of sugar phosphate esters do not always conform with the theoretical values[6]. ^{13}C NMR spectroscopy has been suggested[7] as a method for the accurate determination of the number of cyclohexylammonium cations associated with a given derivative. It was found that inspection of routine (90-MHz) ^1H NMR spectra was also sufficient for this purpose. With the corresponding salts of compounds **1** and **2**, good correlation with the elemental analyses was shown by merely considering the integrals of the signals assigned to the methine and methylene protons of the cyclohexylammonium groups, which occurred at $\delta \pm 3.10$ ppm, and between 1–2 ppm, respectively.

Compounds **1** and **2** may be of further interest for other biochemical applications.

EXPERIMENTAL

Optical rotations were determined with a Perkin–Elmer Model 241 polarimeter. TLC was performed on Kieselgel 60 F_{254} (Merck) with ethyl acetate–light petroleum (1 : 1) and detection was by UV illumination. Column chromatography was performed on Silica Gel 60 (Merck). GLC was conducted with a Hewlett–Packard HP 5890 gas chromatograph as described previously (ref 8). ^1H NMR spectra were

recorded with a Varian EM 2940 (90 MHz) spectrometer on solutions in $CDCl_3$ (internal standard Me_4Si) or D_2O. ^{31}P NMR spectra were recorded with a Bruker AM 400 (161 MHz) spectrometer on solutions in $CDCl_3$ or D_2O (external standard TMP in $CDCl_3$).

1,5-Anhydroxylitol (**3**).—A stirred solution of bromide **5**[1] (10.83 g, 32 mmol) in dry 1,2-dimethoxyethane (30 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (13 g, 0.34 mol) in dry 1,2-dimethoxyethane (200 mL) maintained under N_2 at room temperature. The resulting mixture was processed as described[3], to give **3** (3.34 g, 78%); mp 113.5–115.5°C (MeOH–EtOAc), lit.[9] 116–117°C.

1,5-Anhydro-D-arabinitol (**4**).—Treatment of bromide **6**[2] (29.8 g, 88 mmol) as described above yielded **4** (6.2 g, 53%); mp 95–97°C (EtOH–EtOAc), $[\alpha]_D^{20}$ −98.7° (*c* 1, H_2O); lit.[10] m.p. 96–97°C, $[\alpha]_D$ −98.6°.

1,5-Anhydroxylitol 2,3,4-tris(diphenyl phosphate) (**7**).—A stirred, cooled (0°C) solution of **3** (302 mg, 2.25 mmol) in dry pyridine (3 mL) was treated with diphenyl phosphorochloridate (1.7 mL, 10.4 mmol), stirred at 0°C for 30 min, and then set aside at room temperature for 7 days. The mixture was treated with ice–water (0.5 mL) and, after 10 min, poured into ice-cold, satd aq $NaHCO_3$ (80 mL), and then stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined extracts were washed successively with 2 M HCl, satd aq $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (EtOAc–light petroleum, 1:1) of the residue (1.72 g) gave pure **7** (1.27 g, 74%) as an oil. $^1H \pm$ NMR data ($CDCl_3$): δ 7.19 (m, 30 H, aromatic H), 5.00 (m, 1 H, H-3), 4.70 (m, 2 H, H-2,4), 4.05 (dd, 2 H, H-1*e*,5*e*), 3.63 (dd, 2 H, H-1*a*,5*a*). ^{31}P NMR data ($CDCl_3$): δ -15.27 (s, 1P), -14.70 (s, 2 P).

1,5-Anhydro-D-arabinitol 2,3,4-tris(diphenyl phosphate) (**8**).—Treatment of anhydride **4** (1.0 g, 7.47 mmol) in the above manner yielded pure **8** (0.66 g, 12%), $[\alpha]_D^{20}$ −34° (*c* 3.5, chloroform), as an oil after column chromatography (EtOAc–light petroleum, 1:1). ^1H NMR data ($CDCl_3$): δ 7.17 (m, 30 H, aromatic H), 5.09 (bs, 1 H, H-4), 4.95 (m, 2 H, H-2,3), 3.96 (bd, 1 H, H-5*e*), 3.85 (m, 1 H, H-1*e*), 3.73 (d, 1 H, H-5*a*), 3.57 (m, 1 H, H-1*a*). ^{31}P NMR data ($CDCl_3$): δ −14.83 (s, 1 P), −14.74 (s, 1 P), −14.68 (s, 1 P).

1,5-Anhydroxylitol 2,3,4-tris(phosphate), pentakis(cyclohexylammonium) salt (**1**).—A solution of **7** (623 mg, 0.82 mmol) in EtOH (30 mL) was treated with platinum oxide (100 mg) and the mixture was hydrogenated (1 atm) for 3 h at room temperature. The inorganic material was removed by filtration and washed with EtOH (3 × 10 mL), the combined filtrate and washings were treated with a further amount of platinum oxide (100 mg), and hydrogenation (1 atm) was continued for a further 4 h at room temperature. The inorganic material was again removed by filtration, then washed with EtOH (2 × 10 mL), and the combined filtrate and washings were concentrated in vacuo. A solution of the residue in MeOH (10 mL) was treated with cyclohexylamine (0.53 mL, 4.68 mmol, 6 equiv) and concentrated in vacuo, and the residue triturated with ether. The resulting crystalline material (848 mg, 88%) was recrystallised from MeOH–propan-2-ol to give pure **1** monohy-

drate (376 mg, 52%); mp 187.5–190°C. ^{1}H NMR data (D_2O): δ 4.02 (m, 5 H), 3.34 (t 2 H), 3.09 (m, 5 H, N–CH), 1.93 (m, 10 H, CH_2), 1.75 (m, 10 H, CH_2), 1.59 (m, 5 H, CH_2), 1.29 (m, 20 H, CH_2), 1.13 (m, 5 H, CH_2). ^{31}P NMR data (D_2O): δ 3.08 (s, 2 P), 1.62 (s, 1 P). Anal. Calcd for $C_{35}H_{78}N_5O_{13}P_3 \cdot H_2O$: C, 47.34; H, 9.08; N, 7.89. Found: C, 47.30; H, 8.99; N, 7.57.

*1,5-Anhydro-*D*-arabinitol 2,3,4-tris(phosphate), pentakis(cyclohexylammonium) salt* (**2**).—The tris-ester **8** (659 mg, 0.87 mmol) was reduced catalytically and the mixture processed as described above. The product was recrystallised from MeOH–EtOH to give **2** hemi-ethanolate (560 mg, 79%); mp 184–194°C; $[\alpha]_D^{23}$ −11° (*c* 1, H_2O). ^{1}H NMR data (D_2O): δ 4.37 (m, 1 H), 4.22 (m, 2 H), 3.91 (bd, 1 H), 3.75 (m, 1 H), 3.62 (dd, 1 H), 3.59 (q, 1 H, 0.5 CH_3CH_2), 3.51 (m, 1 H), 3.06 (m, 5 H, N–CH), 1.91 (m, 10 H, CH_2), 1.73 (m, 10 H, CH_2), 1.57 (bd, 5 H, CH_2), 1.27 (m, 20 CH_2), 1.11 (m, 6.5 H, 5 CH_2 and 0.5 CH_3CH_2). ^{31}P NMR data (D_2O): δ 3.36 (s, 1 P), 3.09 (s, 1 P), 2.43 (s, 1 P). Anal. Calcd for $C_{35}H_{78}N_5O_{13}P_3 \cdot 0.5$ CH_3CH_2OH: C, 48.42; H, 9.14; N, 7.84. Found: C, 48.35; H, 9.04; N, 7.68.

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