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Note

Synthesis of some 5-bromo-5-deoxy-aldohexose derivatives

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Although 5-deoxy-5-halo-aldohexose derivatives are important synthetic intermediates, few reports thereon have appeared in the literature. This paper describes the preparation of 3,6-anhydro-5-bromo-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**2**), 3-*O*-benzyl-5-bromo-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**4**), and 3-*O*-benzyl-5-bromo-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**), as well as some of their reactions.

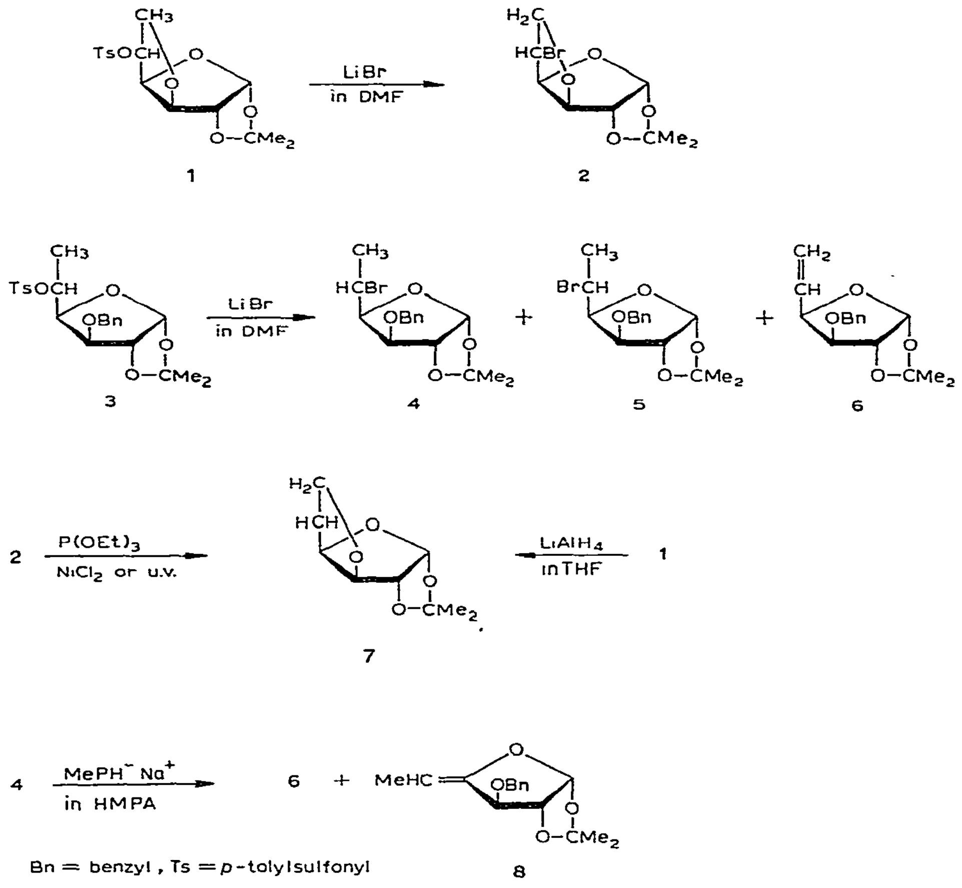
When a solution of 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose[1] (**1**) and lithium bromide in *N*,*N*-dimethylformamide (DMF) was heated, compound **2** was formed in 71% yield; its structure was established by elemental analysis and by a study of its n.m.r. spectrum. The value of the coupling constant $J_{4,5}$ ($\sim$0) seems reasonable as indicating that **2** is an L-*ido* form[2].

When a solution of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**3**) and lithium bromide in DMF was heated, with monitoring of the progress of the reaction by t.l.c. (solvent *B*), it was found that the starting compound (**3**), R_F 0.71, was initially transformed into a product (**4**) having R_F 0.44, and then into two other products (**5**, R_F 0.60, and **6**, R_F 0.48). Separation by column chromatography on silica gel gave **4**, **5**, and **6** in 7.8, 7.2, and 2.2% yields, respectively. The structures of **4** and **5** were established by study of their n.m.r. spectra, and by consideration of the progress of the reaction as monitored by t.l.c. Product **6** was identified as 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose by a study of its n.m.r. spectrum and by comparison with the same compound prepared by a well-known route.

The reaction of **2** with triethyl phosphite by heating in the presence of anhydrous nickel chloride, or by u.v. irradiation, did not give the expected product having a carbon–phosphorus bond, but, instead, gave 3,6-anhydro-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**), the structure of which was determined by its elemental analysis and by a study of its n.m.r. spectrum. Compound **7** was also prepared by reduction of **1** with lithium aluminum hydride in tetrahydrofuran (THF).

The reaction of **4** with sodium methylphosphide in hexamethylphosphoramide (HMPA) gave **6** plus 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*threo*-hex-4-

enofuranose (**8**) in 19 and 51% yields, respectively. The structure of **8** was established by a study of its n.m.r. spectrum.



Bn = benzyl, Ts = *p*-tolylsulfonyl

EXPERIMENTAL

The nuclear magnetic resonance spectra were measured at 60 MHz with a Hitachi–Perkin–Elmer R-20 spectrometer, with tetramethylsilane as the internal reference standard. T.l.c. was performed on a layer of Silica Gel G, with detection of sugars by spraying the plates with a 20% solution of sulfuric acid in methanol and then heating them. Periodical sampling and examination by t.l.c. permitted the determination of the reaction conditions most suitable for the preparative experiments. The solvent systems used for t.l.c. and column chromatography were: (*A*) 1:4 (v/v) ethyl acetate–benzene, (*B*) 1:4 (v/v) ethyl acetate–petroleum ether, and (*C*) 1:6 (v/v) ethyl acetate–petroleum ether.

Materials. — 3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**9**), R_F 0.46 (solvent *A*), was prepared in 82% yield by conventional *p*-toluenesulfonylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[3]. 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**10**), R_F 0.28 (solvent *B*), was prepared in 90% yield by reduction of **9** with lithium aluminum hydride by the method of Wolfrom and Hanessian[4]. Compound **3**, R_F 0.71 (solvent *B*), was prepared in 84% yield by conventional *p*-toluenesulfonylation of **10**.

*3,6-Anhydro-5-bromo-5-deoxy-1,2-*O*-isopropylidene-β-*L*-idofuranose* (**2**). — A solution of **1** (5.5 g) and lithium bromide (3.2 g) in DMF (60 ml) was heated for 4 h at 130°. The solution was then evaporated *in vacuo*. A solution of the residue in chloroform was washed with water, dried (sodium sulfate), and evaporated *in vacuo* to give a solid. Recrystallization from ether–hexane gave colorless needles (3.1 g, 71%) of **2**, m.p. 61–62°, $[\alpha]_D^{26}$ −62.5° (*c* 4.0, carbon tetrachloride), R_F 0.82 (solvent *B*). N.m.r. data (in chloroform-*d*): τ 4.28 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1), 5.13 (1-proton doublet, H-4), 5.32 (1-proton doublet, $J_{3,4}$ 3.7 Hz, H-3), 5.52 (1-proton doublet, H-2), 5.7–5.9 (3-proton multiplets, H-5 and H-6), and 8.57, 8.72 (6-proton singlets, CMe_2).

Anal. Calc. for $C_9H_{13}BrO_4$: C, 40.78; H, 4.94. Found: C, 40.76; H, 5.02.

*3-*O*-Benzyl-5-bromo-5,6-dideoxy-1,2-*O*-isopropylidene-β-*L*-idofuranose* (**4**), *3-*O*-benzyl-5-bromo-5,6-dideoxy-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**5**), *and 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-*D-xylo*-hex-5-enose* (**6**). — A solution of **3** (5.0 g) and lithium bromide (3.2 g) in DMF (250 ml) was heated for 15 h at 120–130°. The solution was treated as just described, and the resulting syrup was separated by use of a column of silica gel (solvent *C*) to give **4**, **6**, and **5** (7.8, 2.2, and 7.2%). Compound **4** had R_F 0.44 (solvent *B*), $[\alpha]_D^{14}$ −37.4° (*c* 4.5, chloroform); n.m.r. data (in chloroform-*d*): τ 2.80 (5-proton singlet, Ph), 4.16 (1-proton doublet, $J_{1,2}$ 3.0 Hz, H-1), 5.4–5.6 (3-proton multiplets, CH_2Ph and H-2), 5.8–6.2 (3-proton multiplets, H-3, H-4, and H-5), 8.54 (3-proton doublet, $J_{5,6}$ 6.0 Hz, 3 H-6), and 8.61, 8.72 (6-proton singlets, CMe_2). Compound **5** had R_F 0.56 (solvent *B*), $[\alpha]_D^{14}$ −51.5° (*c* 4.7, chloroform); n.m.r. data (in chloroform-*d*): τ 2.80 (5-proton singlets, Ph), 4.25 (1-proton doublet, $J_{1,2}$ 3.0 Hz, H-1), 5.53 (2-proton singlet, CH_2Ph), 5.57 (1-proton doublet, H-2), 5.8–6.1 (3-proton multiplets, H-3, H-4, and H-5), 8.34 (3-proton doublet, $J_{4,5}$ 6.0 Hz, 3 H-6), and 8.65, 8.85 (6-proton singlets, CMe_2). Compound **6** had R_F 0.48 (solvent *B*), $[\alpha]_D^{14}$ −43.1° (*c* 2.6, chloroform); n.m.r. data (in chloroform-*d*): τ 2.80 (5-proton singlets, Ph), 4.18 (1-proton doublet, overlapping with H-5, $J_{1,2}$ 4.0 Hz, H-1), 4.1–4.3 (1-proton multiplet, overlapping with H-1, H-5), 4.5–5.0 (2-proton multiplet, 2 H-6), 5.56 (2-proton singlet, overlapping with H-2, CH_2Ph), 6.15 (1-proton doublet, H-3), and 8.53, 8.71 (6-proton singlets, CMe_2). Compound **6** was also prepared, in 82% yield, from **9** by a modification of the method of Jones and Thompson[5].

Reaction of **2** *with triethyl phosphite. — A. By heating in the presence of nickel chloride.* A solution of **2** (0.5 g) in triethyl phosphite (5.0 ml) was heated for 20 h at 120° in the presence of anhydrous nickel chloride under a nitrogen atmosphere, and then evaporated *in vacuo*; fractional distillation gave **7**, b.p. 45–50°/2 torr, R_F 0.5 (solvent *B*), $[\alpha]_D^{20}$ +14.5° (*c* 1.2, chloroform); n.m.r. data (in chloroform-*d*): τ 4.20

(1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1), 5.14 (1-proton multiplet, H-4), 5.49 (1-proton doublet, H-2), 5.81 (1-proton doublet, $J_{3,4}$ 3.0 Hz, H-3), 6.30 (2-proton multiplets, 2 H-6), 8.05 (2-proton multiplets, H-5), and 8.57, 8.75 (6-proton singlets, CMe_2).

Anal. Calc. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.22; H, 7.44.

B. By u.v. irradiation. A solution of **2** (1.0 g) in triethyl phosphite (10 ml) containing acetone was irradiated under nitrogen for 50 h in a quartz tube by means of a high-pressure, mercury u.v. lamp (100 W) at a distance of about 5 cm, and then treated as described in *A*, to give **7**. Compound **7** was also prepared, in 57% yield, by reduction of **3** with lithium aluminum hydride.

Reaction of **4** *with sodium methylphosphide.* — A solution of **4** (2.0 g) in HMPA (20 ml) was added to sodium methylphosphide (0.55 g; prepared from sodium in liquid ammonia and methylphosphine[6] under a nitrogen atmosphere), and the mixture was heated for 10 h at 120°. The solution was evaporated *in vacuo*, and the syrup was separated on a column of silica gel (solvent *C*) to give **6** and **8** (19 and 51%, respectively). Compound **8** had R_F 0.57 (solvent *B*), $[\alpha]_D^{14}$ $-36.0°$ (*c* 2.5, chloroform); n.m.r. data (in chloroform-*d*): τ 2.70 (5-proton singlet, Ph), 3.93 (1-proton doublet, $J_{1,2}$ 2.5 Hz, H-1), 5.28 (1-proton multiplet, H-5), 5.45 (2-proton singlet, overlapping with H-2, CH_2Ph), 5.52 (1-proton doublet, overlapping with CH_2Ph, H-2), 5.80 (1-proton singlet, H-3), 8.30 (3-proton doublet, 3 H-6), and 8.57, 8.65 (6-proton singlets, CMe_2).

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