

Note

Synthesis of some methyl dideoxy-D-hexosides

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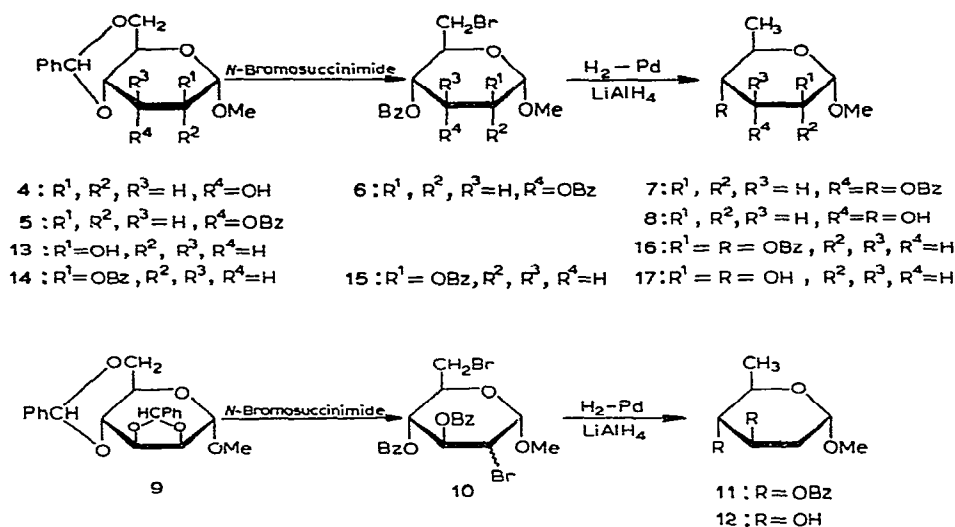
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In connection with other studies, pure methyl glycosides of some dideoxy-D-hexoses were needed as reference compounds. In this paper are described improved syntheses of methyl α -glycopyranosides of 2,6-dideoxy-D-*ribo*-, 2,6-dideoxy-D-*arabino*- and 3,6-dideoxy-D-*arabino*-hexoses. The sequence of high-yield steps used involves the oxidation of 4,6-*O*-benzylidene groups with *N*-bromosuccinimide, as reported by Hanessian¹.

2,6-Dideoxy-D-*ribo*-hexose (known as digitoxose) is important because it occurs as a component of some cardiac glycosides². The first synthesis of this sugar, by Reichstein and Iselin³, was effected through the glycol method. Later, a route by reductive opening with lithium aluminum hydride of the epoxide ring in methyl 2,3-anhydro-4,6-di-*O*-*p*-tolylsulfonyl- α -D-alloside (3) was reported⁴. However, the lithium aluminium hydride reduction of 3, as well as of methyl 2,3-anhydro-4-*O*-benzoyl-6-bromo-6-deoxy- α -D-alloside^{10b} (2) [prepared from methyl 2,3-anhydro-4,6-*O*-benzylidene- α -D-alloside⁵ (1) with *N*-bromosuccinimide], was ascertained to be inadequate for our purposes. The product was considerably contaminated with 3,6-dideoxy derivative (probably because of the flexible conformation of 2 and 3), and difficulty in purification was encountered. As another route, methyl 4,6-*O*-benzylidene 2-deoxy- α -D-*ribo*-hexoside⁶ (4) was benzoylated to give the 3-benzoate (5). Treatment of the benzoate 5 with *N*-bromosuccinimide gave crystalline methyl 3,4-di-*O*-benzoyl-6-bromo-2,6-dideoxy- α -D-*ribo*-hexoside^{10b} (6) in high yield. Catalytic hydrogenolysis of the bromo derivative 6 in the presence of triethylamine gave crystalline methyl 3,4-di-*O*-benzoyl-2,6-dideoxy- α -D-*ribo*-hexoside (7). Debenzoylation of 7 with sodium methoxide gave syrupy methyl 2,6-dideoxy- α -D-*ribo*-hexopyranoside (8), furthermore, treatment of 6 with lithium aluminum hydride also gave 8 in satisfactory yield.

Several reports dealing with the oxidative brominolysis of *O*-benzylidene groups with *N*-bromosuccinimide have been published⁷⁻⁹, and the wide applicability of this



reaction for various synthetic purposes has been documented by Hanessian and Plessas¹⁰. The reagent was evaluated with the dibenzylidene acetal system in methyl 2,3:4,6-di-*O*-benzylidene- α -D-mannoside¹¹ (9). An attempt to perform a selective brominolysis of compound 9 with *N*-bromosuccinimide in carbon tetrachloride proved abortive, since use of an equimolar amount of *N*-bromosuccinimide always left a considerable amount of unreacted 9. With two molar equivalents of reagent, 9 reacted to give the syrupy methyl dibromo derivative (10) in good yield. Catalytic hydrogenolysis of 10 in the presence of triethylamine gave the syrupy methyl dideoxy derivative (11), deduced to be methyl 3,4-di-*O*-benzoyl-2,6-dideoxy- α -D-*arabino*-hexoside by its non-identity with methyl 2,4-di-*O*-benzoyl-3,6-dideoxy- α -D-*arabino*-hexoside (16). Debenzoylation of 11 with sodium methoxide gave syrupy methyl 2,6-dideoxy- α -D-*arabino*-hexoside¹² (12). Compound 12 was also obtained by treating 10 with lithium aluminum hydride. The unsubstituted 2,6-dideoxy-D-*arabino*-hexose was originally found as a component sugar in a cardiac glycoside¹³ and in certain antibiotics¹², and has been named D-canarose or chromose C. Synthesis of this sugar starting from 2-deoxy D-*arabino*-hexose has been reported by Zorbach and Ciaudelli¹⁴.

3,6-Dideoxy-D-*arabino*-hexose (known also as tyvelose)¹⁵ has been synthesized¹⁶ unequivocally by starting from methyl 4,6-*O*-benzylidene-3-deoxy- α -D-*arabino*-hexoside¹⁶ (13). An aryl glycoside of this sugar has been reported recently⁹. Benzoylation of compound 13 gave the 2-benzoate (14), which was treated with *N*-bromosuccinimide to give crystalline methyl 2,4-di-*O*-benzoyl-6-bromo-3,6-dideoxy- α -D-*arabino*-hexoside (15) in high yield. Catalytic hydrogenolysis of 15 in the presence of triethylamine gave syrupy methyl 2,4-di-*O*-benzoyl-3,6-dideoxy- α -D-*arabino*-hexoside (16), which was then deacylated to afford crystalline methyl 3,6-dideoxy- α -D-*arabino*-hexopyranoside (17). The utility of 7, 11, and 16 as precursors for glycosyl halides of the dideoxy sugars is the subject of another paper.

EXPERIMENTAL

General. — Solvents were evaporated under diminished pressure below 40°. Melting points are uncorrected. *N*-Bromosuccinimide and barium carbonate were dried by storing over phosphorus pentoxide under diminished pressure for 24 h. Analytical t.l.c. was performed with Silica Gel GF (E. Merck, Darmstadt, Germany) on microscope slides. Solvent systems were 4:1 (v/v) benzene-ether and 4:1 petroleum ether-ether, and detections were effected with ultraviolet light (short wavelength), and sulfuric acid. Column chromatography was performed on Silica Gel (60–200 mesh, Kanto Chemical Co., Tokyo, Japan) with 1:3 ethyl acetate-petroleum ether. New compounds had i.r. and n.m.r. spectra consistent with the assigned structures.

Methyl 3-O-benzoyl-4,6-O-benzylidene-2-deoxy- α -D-ribo-hexoside (5). — Benzoyl chloride (10 ml) was added to an ice-cold solution of methyl 4,6-*O*-benzylidene-2-deoxy- α -D-ribo-hexoside⁶ (10.0 g) in dry pyridine (200 ml) and the mixture was kept for 24 h at 0°. After decomposition of the excess of reagent with pieces of ice, the mixture was poured onto crushed ice (500 ml). The precipitate was filtered off and recrystallized from ethyl alcohol; yield 11.4 g (82%), m.p. 95–97°, $[\alpha]_D^{20} +192.1^\circ$ (c 3.6, chloroform).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.88; H, 6.02.

Methyl 3,4-di-O-benzoyl-6-bromo-2,6-dideoxy- α -D-ribo-hexoside (6). — Compound **5** (10.0 g) and *N*-bromosuccinimide (5.2 g, 1.1 molar equivalents) were added to a suspension of barium carbonate (10 g) in carbon tetrachloride (200 ml) and the mixture was refluxed for 3 h, cooled, and filtered. The combined filtrate and washings (2 \times 50 ml) were washed with water, dried (sodium sulfate), and evaporated. The resultant syrup was crystallized from ethyl alcohol; yield 10.8 g (89%), m.p. 100–102°, $[\alpha]_D^{20} +172.6^\circ$ (c 1.8, chloroform). [lit.^{10b}, m.p. 95–96].

Anal. Calc. for $C_{21}H_{21}O_6Br$: C, 56.13; H, 4.71; Br, 17.78. Found: C, 56.11; H, 4.77; Br, 17.75.

Methyl 3,4-di-O-benzoyl-2,6-dideoxy- α -D-ribo-hexoside (7). — Compound **6** (8.0 g) was dissolved in methyl alcohol (100 ml) containing triethylamine (5 ml), and palladium black [freshly prepared from palladium chloride (980 mg)] was added to catalyze the hydrogenolysis. The reactant consumed the theoretical amount of hydrogen within 40 min. The mixture was filtered and the filtrate was evaporated to dryness. The resultant, crystalline mass was dissolved in dichloromethane (200 ml), washed successively with cold, m sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water, and dried (sodium sulfate). Evaporation of the solvent gave a syrup, which crystallized as long needles; yield 5.8 g (88%). Recrystallization from ether-petroleum ether afforded **7**, m.p. 83–85°, $[\alpha]_D^{20} +214.6^\circ$ (c 1.6, chloroform).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.17; H, 5.87.

Methyl 2,6-dideoxy- α -D-ribo-hexopyranoside (8). — *A.* The benzoate **7** (5.0 g) was dissolved in methyl alcohol (50 ml) containing sodium methoxide (48 mg). The solution was kept for 4 h at 40°, saturated with carbon dioxide to neutralize the base, and then evaporated. The resultant syrup was suspended in water (50 ml) and

extracted with ether (2×30 ml) to remove methyl benzoate. The aqueous solution was evaporated to a syrup, which was extracted with ethyl acetate (4×50 ml). The combined extract was filtered and evaporated to give a mobile syrup; yield 2.0 g (92%). The syrup, which was homogeneous by t.l.c., was distilled for analysis; b.p. $98-110^\circ$ at 10^{-1} torr, $[\alpha]_D^{20} + 178.4^\circ$ (c 3.7, chloroform).

Anal. Calc. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.94; H, 8.58.

B. The 6-bromo derivative **6** (5.0 g) and lithium aluminum hydride (2.5 g) were dissolved in dry tetrahydrofuran (200 ml) and refluxed for 5 h under protection from moisture. After the solution had cooled and the excess reagent had been decomposed with water, the mixture was neutralized with sulfuric acid and evaporated to dryness. For the complete removal of benzyl alcohol, repeated co-evaporation with water were required. The residue was extracted with ethyl acetate (4×50 ml), and the extract was filtered and evaporated, to give a colorless syrup; yield 940 mg (52%), which was shown by t.l.c. to be identical with the syrupy **8** already described. Acid hydrolysis of **8** according to the directions of Bolliger and Ulrich⁴ gave digitoxose, m.p. $109-111^\circ$, $[\alpha]_D^{20} + 51.3^\circ$ (c 1.2, water at equilibrium) [lit.⁴, m.p. $110-112^\circ$, $[\alpha]_D^{20} + 50.2^\circ$ (water)].

Methyl 3,4-di-O-benzoyl-2,6-dibromo-2,6-dideoxy- α -D-hexoside (10). — Methyl 2,3,4,6-di-*O*-benzylidene- α -D-mannoside¹¹ (18.0 g) and *N*-bromosuccinimide (19.0 g, 2.2 molar equivalents) were added to a suspension of barium carbonate (20 g) in carbon tetrachloride (300 ml) and the mixture was refluxed for 6 h. The precipitate was removed by filtration of the cooled mixture and was washed with carbon tetrachloride (2×50 ml). The combined filtrate and washings were washed with water and dried (sodium sulfate). Evaporation of the solvent gave a syrup that was shown by t.l.c. to contain two components, R_F 0.67 (*ca.* 95%) and 0.28 (trace); yield 22.6 g (88%). After purification by column chromatography, the faster-moving component was shown, by its n.m.r. spectrum, to consist of two components having the following OMe signals (60 MHz): δ 3.50 (*ca.* 55%) and 3.55 (*ca.* 45%); $[\alpha]_D^{20} - 16.1^\circ$ (c 4.9, chloroform).

Anal. Calc. for $C_{21}H_{20}O_6Br_2$: C, 47.74; H, 3.81; Br, 30.25. Found: C, 48.18; H, 3.82; Br, 30.58.

Methyl 3,4-di-O-benzoyl-2,6-dideoxy- α -D-arabino-hexoside (11). — The dibromide **10** (18.0 g) was dissolved in methyl alcohol (200 ml) containing triethylamine (10 ml) and the mixture was hydrogenated with palladium catalyst [freshly prepared from palladium chloride (1.86 g). For complete reduction a further addition of catalyst (2–3 g) was required. After removal of the catalyst, the filtrate was concentrated to a syrup, which was dissolved in dichloromethane (300 ml), washed successively with cold *M* sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water, and dried (sodium sulfate). Evaporation of the solvent afforded a syrup; yield 11.9 g (92%) that gave an unsatisfactory elemental analysis. The syrup had $[\alpha]_D^{20} - 8.1^\circ$ (c 2.9, chloroform); n.m.r. data (60 MHz): δ 1.35 (3-proton doublet, H-6), 1.80–2.45 (2-proton multiplet, H-2), 3.45 (3-proton singlet, OMe), 3.85–5.35 (4-proton multiplet, H-1,3,4,5), and 7.28–8.20 (10-proton multiplet, phenyl).

Methyl 2,6-dideoxy- α -D-arabino-hexopyranoside (12). — *A.* The benzoate **11**

(10.0 g) was treated with sodium methoxide as described for **8** to give **12**; yield 3.4 g (78%). After two distillations (b.p. 85–110° at 10⁻¹ torr), it had $[\alpha]_D^{20} +86.4^\circ$ (*c* 1.6, water) [lit.¹², $[\alpha]_D +87^\circ$ (water)].

Anal. Calc. for C₇H₁₄O₄: C, 51.84; H, 8.70. Found: C, 52.14; H, 8.62.

B. The crude dibromide **10** (10.0 g) was treated with lithium aluminum hydride (10.0 g) in dry tetrahydrofuran (200 ml) for 6 h under reflux. After treating as described for **8**, a colorless syrup was obtained; yield 1.3 g (46%). Acid hydrolysis of **12** with 10mm sulfuric acid gave syrupy 2,6-dideoxy-*D*-arabino-hexose (85%), which was characterized by its crystalline diethyl dithioacetal, m.p. 83–84°, $[\alpha]_D^{20} +10.6^\circ$ (*c* 2.2, chloroform) [lit.¹⁴, m.p. 83–84°, $[\alpha]_D +11.8^\circ$ (dichloromethane)].

Methyl 2-O-benzoyl-4,6-O-benzylidene-3-deoxy- α -D-arabino-hexoside (14). — Compound **13**, prepared from methyl 2,3-anhydro-4,6-*O*-benzylidene- α -*D*-mannoside¹⁷ as modified⁶ for **4**, was benzoylated to give **14** as needles; yield 85%, m.p. 137–139°, $[\alpha]_D^{20} +6.4^\circ$ (*c* 2.3, chloroform), after two recrystallizations from ethyl alcohol.

Anal. Calc. for C₂₁H₂₂O₆: C, 68.09; H, 5.99. Found: C, 68.16; H, 6.02.

Methyl 2,4-di-O-benzoyl-6-bromo-3,6-dideoxy- α -D-arabino-hexoside (15). — The benzylidene acetal **14** (5.0 g) was treated with *N*-bromosuccinimide (2.6 g, 1.1 molar equivalents) and barium carbonate (5 g) in carbon tetrachloride (100 ml) as described for **6**. By similar method of processing, **15** was obtained as plates from ethyl alcohol; yield 5.3 g (88%), m.p. 87–89°, $[\alpha]_D^{20} +12.8^\circ$ (*c* 1.2, chloroform).

Anal. Calc. for C₂₁H₂₁BrO₆: C, 56.13; H, 4.71; Br, 17.78. Found: C, 56.32; H, 4.66; Br, 18.00.

Methyl 2,4-di-O-benzoyl-3,6-dideoxy- α -D-arabino-hexoside (16). — The bromo derivative **15** (5.0 g) was hydrogenated as described for **7**, and **16** was obtained as a colorless syrup; yield 2.6 g (82%). After purification by column chromatography, **16** had $[\alpha]_D^{20} -22.9^\circ$ (*c* 2.4, chloroform). N.m.r. data (60 MHz): δ 1.30 (3-proton doublet, H-6), 2.10–2.40 (2-proton multiplet, H-3), 3.40 (3-proton singlet, OMe), 3.70–5.20 (3-proton multiplet, H-2,4,5), 5.50 (1-proton singlet, H-1), and 7.30–8.20 (10-proton multiplet, phenyl).

Anal. Calc. for C₂₁H₂₂O₆: C, 68.09; H, 5.99. Found: C, 68.35; H, 6.13.

Methyl 3,6-dideoxy- α -D-arabino-hexopyranoside (17). — Debenzoylation of **16** (2.0 g) as described for **8** gave slightly hygroscopic prisms (after recrystallization from acetone–petroleum ether); yield 710 mg (81%), m.p. 82–84°, $[\alpha]_D^{20} +102.7^\circ$ (*c* 1.8, water).

Anal. Calc. for C₇H₁₄O₄: C, 51.84; H, 8.70. Found: C, 52.16; H, 8.57.

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