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Note

Methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside

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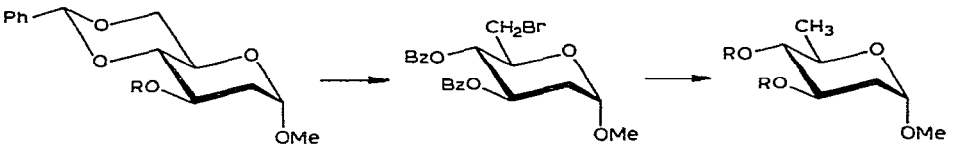
Several groups[1–9] have independently obtained a syrupy compound* believed to be pure methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside† (**1**), in small amounts when elucidating the structures of the antibiotics olivomycin, chromomycin A_3, venturicidin B, chlorothricin, and curamycin, either by direct methanolysis of the antibiotics, or by hydrolysis followed by glycosidation. However, variations in the $[\alpha]_D$ values reported (see Experimental) indicate difficulties in the isolation of homogeneous material; the simultaneous formation of the β anomer having a highly negative specific rotation but very similar chromatographic properties[4,12], as well as the formation of furanosides[12], may be reasoned as possible sources of complication, and make this method impractical for preparative purposes.

The only prior attempt at synthesis of the α anomer (for a synthesis of the anomeric mixture in the L series, see ref. 13) was reported by Haga *et al.*[14] in 1971; its key step involved the reaction of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside with *N*-bromosuccinimide, followed by reductive cleavage of both C–Br bonds and debenzoylation. However, Monneret *et al.*[15] recently found that the bromine atom does not attack the pyranoid ring at C-2, but at C-3 and C-4 (because of equilibrium between intermediary benzoxonium ions), yielding 3,6- and 4,6-dibromodideoxy derivatives, so that the syrupy final product having $[\alpha]_D$ +86.4° (water) is, in fact, a mixture of methyl 3,6-dideoxy-α-D-*arabino*-hexopyranoside and methyl 4,6-dideoxy-α-D-*arabino*-hexopyranoside, instead of **1**.

Uncertainty in the literature, as well as the need for larger quantities of the title compound in connection with methylation studies[16,17], prompted us to synthesize methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (**1**) by an unambiguous route starting from the readily available methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside[18] (**2**). Benzoylation of the free hydroxyl group (yielding **3**) was found

*The trivial names methyl α-D-olivoside, methyl α-D-chromoside C, methyl 2-deoxy-α-D-rhamnoside, methyl α-D-oxamicetoside (ref. 10), methyl α-D-canaroside have been used; for the last-mentioned synonym, see D-canarose[11].
†For the corresponding L enantiomer, see ref. 12.



2 R = H
3 R = Bz

4

5 R = Bz
1 R = H

to improve the course of cleavage of the 1,3-dioxane ring by *N*-bromosuccinimide in carbon tetrachloride (compare refs. 19 and 20). The resulting 6-bromo derivative **4** was then converted into methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**5**) by hydrogenolysis with Raney nickel. The structure of the crystalline derivative **5** was confirmed by ^{1}H-n.m.r. spectroscopy; the 3-proton doublet at δ 1.30 ($J_{5,6}$ 6.3 Hz) and multiplets at δ 1.95 and 2.50 ($J_{2ax,2eq}$ 13.0 Hz, $J_{1,2ax}$ 3.5 Hz, $J_{1,2eq}$ 1.2 Hz) indicate the 2,6-dideoxyglycoside structure, and the high values of $J_{3,4}$ (9.5 Hz), $J_{4,5}$ (9.5 Hz), and $J_{2ax,3}$ (11.5 Hz), together with the $J_{1,2ax}$ value already mentioned, are compatible only with the α-D-*arabino* configuration in the $^4C_1$(D) conformation. A proportion of the β anomer was probably present in **5** as prepared by Ogawa and Matsui[10], and the preparation in ref. 14 is incorrect[21] (compare also, ref. 15). By avoiding any contact with acid, debenzoylation of **5** yielded syrupy methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (**1**), $[\alpha]_D$ +120° (water), uncontaminated by the β anomer*. In view of the $[\alpha]_D$ values given in the literature, compound **1** supposedly prepared in refs. 3,5–8 must have been a mixture containing up to 15% of the β anomer. As expected, the glycoside **1** adopts in chloroform solution the $^4C_1$(D) conformation (see ^{1}H-n.m.r. data in the Experimental section).

EXPERIMENTAL

General methods. — Melting points were measured on a Kofler block and are not corrected. Optical rotations were determined with an Opton Photoelectric Precision Polarimeter 0.005° at 20°. Chromatography was performed on silica gel (Lachema, Brno), 100–160 μm, thin-layer chromatography on silica gel G according to Stahl (Merck, Darmstadt), 10–40 μm, using of 25 × 75 mm plates and a layer 0.2–0.3 mm thick. Components were detected by spraying with 1% cerium(IV) sulfate in 10% sulfuric acid and subsequent charring. The solvents were evaporated under diminished pressure on a rotary evaporator, at a temperature not exceeding 50°. Samples for analysis were dried at 20–50° and 13 Pa. ^{1}H-N.m.r. spectra were measured in chloroform-*d* on a Varian XL-100-15 instrument with tetramethylsilane as the internal standard. Chemical shifts (δ) and coupling constants (Hz) are first-order values. G.l.c. analyses were performed with a Varian–Aerograph 2100 instrument (column 900 × 2 mm, 5% polypropylene sebacate on Chromosorb G, 80–100 mesh, 160°, helium 20 ml/min) fitted with a flame-ionization detector.

*A period of 30 min at 20° is sufficient for attainment of the anomeric equilibrium in 2% methanolic hydrogen chloride[21] (compare also, ref. 12).

Methyl 3-O-benzoyl-4,6-O-benzylidene-2-deoxy-α-D-arabino-hexopyranoside (**3**). — Benzoyl chloride (2.8 ml) was added to a cooled (−20°) solution of 5.0 g of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside[18] (**2**) in 30 ml of pyridine and the mixture was kept for 24 h at room temperature. Water was added and the product (**3**) was isolated by conventional extraction with chloroform. Crystallization from ether gave 6.9 g (96.5%) of **3**, m.p. 150–151.5°, $[\alpha]_D$ −9.9° (*c* 1.0, chloroform).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 67.98; H, 6.01.

Methyl 3,4-di-O-benzoyl-6-bromo-2,6-dideoxy-α-D-arabino-hexopyranoside (**4**). — A suspension containing **3** (10 g), *N*-bromosuccinimide (5.4 g), barium carbonate (10.8 g), and carbon tetrachloride (300 ml) was boiled for 2 h under reflux. The mixture was filtered and the filtrate was evaporated to dryness. The resulting syrup was dissolved in chloroform (150 ml) and the solution was washed with water (3 × 40 ml), dried (magnesium sulfate), filtered through 60 g of alumina, and evaporated to a colorless syrup that crystallized from ether. Recrystallization from the same solvent gave 10.5 g (87%) of **4**, m.p. 110.5–113°, $[\alpha]_D$ +1.7° (*c* 0.7, chloroform).

Anal. Calc. for $C_{21}H_{21}BrO_6$: C, 56.13; H, 4.71; Br, 17.79. Found: C, 56.21; H, 4.84; Br, 17.60.

Methyl 3,4-di-O-benzoyl-2,6-dideoxy-α-D-arabino-hexopyranoside (**5**). — A mixture of the bromide **4** (4.0 g), methanol (120 ml), Raney nickel (20 ml), and of diethylamine (1.0 ml) was hydrogenated at room temperature and atmospheric pressure for 5 h. The reaction course was monitored by t.l.c. with 50:3 benzene–acetone as the developing solvent. Filtration and evaporation afforded a crystalline residue that was partitioned between water and chloroform. Drying, filtration, and evaporation of the combined chloroform extracts gave **5**, which was recrystallized from hexane; yield 2.9 g (88%), m.p. 93–94°, $[\alpha]_D$ −0.5° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.30 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-C), 1.95 (1H, m, $J_{1,2ax}$ 3.5, $J_{2ax,3}$ 11.5, $J_{2ax,2eq}$ 13.0 Hz, H-2ax), 2.50 (1H, m, $J_{1,2eq}$ 1.2, $J_{2eq,3}$ 5.1 Hz, H-2eq), 3.41 (3H, s, CH_3-O), 4.08 (1H, dq, $J_{4,5}$ 9.5 Hz, H-5), 4.85 (1H, dd, H-1), 5.23 (1H, t, H-4), 5.64 (1H, m, $J_{3,4}$ 9.5 Hz, H-3), and 8.10–7.20 (10H, aromatic); lit.[10] m.p. 80–83°, $[\alpha]_D$ −1.7° (chloroform); in the L series[22], m.p. 88–89°, $[\alpha]_D$ +1.1° (chloroform); ^{1}H-n.m.r. data close to ours were described[22].

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.08; H, 6.10.

Methyl 2,6-dideoxy-α-D-arabino-hexopyranoside (**1**). — A drop of M methanolic sodium methoxide was added to a solution of **5** (1.0 g) in 10 ml of methanol and the mixture was kept overnight at 20°. Methanol was evaporated off, the residue dissolved in chloroform (2 ml), and the solution introduced onto a column of silica gel (20 g); methyl benzoate was eluted with benzene, and methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (**1**) with 20:1 benzene–ethanol. Evaporation of the combined fractions gave a syrup that was dissolved in ether and the solution was treated with charcoal. The syrupy glycoside **1** retention time (0.42 g, 95%, 5.47 min) obtained on evaporation of ether was pure enough for further preparations and was not contaminated with the β anomer (retention time 7.79 min). All attempts to crystallize this compound failed. ^{1}H-N.m.r. data: δ 1.30 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-C), 1.66 (1H, m,

$J_{1,2ax}$ 3.5, $J_{2ax,3}$ 11.2, $J_{2ax,2eq}$ 12.7 Hz, H-2ax), 2.13 (1H, m, $J_{1,2eq}$ 1.1, $J_{2eq,3}$ 5.0 Hz, H-2eq), 3.05 (1H, t, $J_{3,4} = J_{4,5}$ 9.0 Hz, H-4), 3.32 (3H, s, CH_3-O), 3.59 (1H, dq, $J_{5,6}$ 6.2 Hz, H-5), 3.86 (1H, m, $J_{2eq,3}$ 5.0 Hz, H-3), and 4.72 (1H, dd, H-1). The data are close to those described by Allgeier for the L enantiomer[12]; for further, incomplete data, see refs. 3, 5, and 7. For analysis, the syrup was distilled at 85° and 2 Pa; $[\alpha]_D$ +120° (*c* 2.0, water) (lit.[3] +87°); $[\alpha]_D$ +147° (*c* 1.3, chloroform) (lit.[8] +126.5°), $[\alpha]_D$ +158° (*c* 1.4, acetone) (lit.[5,7] +133° and +158°, lit.[6] +126° as calculated from $[\alpha]_{578}$ +150°, by using a calibration curve; for the L enantiomer[12] −152.5 ±2°); $[\alpha]_D$ +129° (*c* 1.0, ethanol) (lit.[1,4] +131°).

Anal. Calc. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.89; H, 8.56.

REFERENCES

1 Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, M. M. Shemyakin, and M. G. Brazhnikova, *Tetrahedron Lett.*, (1964) 1323–1328.
2 Yu. A. Berlin, S. E. Esipov, M. N. Kolosov, M. M. Shemyakin, and M. G. Brazhnikova, *Tetrahedron Lett.*, (1964) 3513–3516.
3 M. Miyamoto, Y. Kawamatsu, M. Shinohara, Y. Nakadaira, and K. Nakanishi, *Tetrahedron*, 22 (1966) 2785–2799.
4 Yu. A. Berlin, S. E. Esipov, O. A. Kiseleva, and M. N. Kolosov, *Khim. Prir. Soedin.*, 3 (1967) 331–339.
5 M. Brufani, W. Keller-Schierlein, W. Löffler, I. Mansperger, and H. Zähner, *Helv. Chim. Acta*, 51 (1968) 1293–1304.
6 W. Keller-Schierlein, R. Muntwyler, W. Pache, and H. Zähner, *Helv. Chim. Acta*, 52 (1969) 127–142.
7 H. Zähner and W. Keller, U.S. Pat. 3,636,198; *Chem. Abstr.*, 76 (1972) 152036.
8 R. Muntwyler and W. Keller-Schierlein, *Helv. Chim. Acta*, 55 (1972) 2071–2094.
9 V. Deulofeu, E. G. Gros, and O. L. Galmarini, *An. Quim.*, 70 (1974) 1062–1066.
10 T. Ogawa and M. Matsui, *J. Chem. Soc. Chem. Commun.*, (1975) 992–993.
11 T. Reichstein, *Angew. Chem.*, 74 (1962) 887–894; P. Studer, S. K. Pavanaram, C. R. Gavilanes, H. Linde, and K. Meyer, *Helv. Chim. Acta*, 46 (1963) 23–45; K. Stöckel, W. Stöcklin, and T. Reichstein, *ibid.*, 52 (1969) 1175–1202; Y. Nozaki and K. Akagi, Japan Pat. 7,019,488; *Chem. Abstr.*, 73 (1970) 77558.
12 H. Allgeier, *Helv. Chim. Acta*, 51 (1968) 311–325.
13 F. Sztaricskai, I. Pelyvás, R. Bognár, and G. Bujtás, *Tetrahedron Lett.*, (1975) 1111–1114.
14 M. Haga, M. Chonan, and S. Tejima, *Carbohydr. Res.*, 16 (1971) 486–491.
15 C. Monneret, J.-C. Florent, N. Gladieux, and Q. Khuong-Huu, *Carbohydr. Res.*, 50 (1976) 35–44.
16 K. Kefurt, J. Staněk, Jr, Z. Kefurtová, and J. Jarý, *Collect. Czech. Chem. Commun.*, 40 (1975) 300–312.
17 M. Marek, K. Kefurt, J. Staněk, Jr, and J. Jarý, *Collect. Czech. Chem. Commun.*, 41 (1976) 2596–2606.
18 B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc. C*, (1966) 398–403.
19 S. Hanessian and N. R. Plessas, *J. Org. Chem.*, 34 (1969) 1045–1053.
20 E. G. Gros and E. M. Gruñeiro, *J. Org. Chem.*, 36 (1971) 1166–1169.
21 J. Staněk, Jr., and J. Jarý, unpublished results.
22 K. Bock, J. K. Christiansen, and C. Pedersen, *Carbohydr. Res.*, 20 (1971) 73–81.