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Note

Diastereomers of 2,4:3,5-di-O-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol

TIBOR HORVÁTH, PÁL SOHÁR, AND GIZELLA ÁBRAHÁM
Institute for Drug Research, H-1325 Budapest, POB 82 (Hungary)
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In the acid-catalyzed benzylidenation reaction of sugars and sugar alcohols, both 2-phenyl-1,3-dioxolane and 2-phenyl-1,3-dioxane derivatives can be formed[1–7]. Whereas *cis*- and *trans*-isomers of the dioxolane derivatives are usually formed in nearly equal amounts, only one diastereomer is formed as a rule for 1,3-dioxane derivatives. Baggett *et al.*[8] prepared both the diastereomers of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside and -α-D-galactopyranoside by reaction of the parent diols with benzylidene dibromide in alkaline media. There are few other examples of the preparation of the diastereomers of acetals having 1,3-dioxane rings examples of the preparation of the diastereomers of acetals having 1,3-dioxane rings[9–11]. Apparently, diastereomers of dibenzylidene sugar derivatives containing dioxane rings have not been described, except in a reference to unpublished data[12]. This is not surprising, since, for the formation of 1,3-dioxane derivatives in acidic media, the more-stable diastereomer always preponderates, and usually only this product can be isolated. In principle, however, each of the benzylidene diastereomers can be formed, and we now report such an example.

In the reaction of 1,6-dibromo-1,6-dideoxy-D-mannitol with benzaldehyde in the presence of zinc chloride, by a modification of the method of Bird *et al.*[13], 26.4% of two monobenzylidene derivatives [**1** (m.p. 104°) and **2** (m.p. 161°) in the ratio 6:1] and 15% of two diastereomers [**6** (m.p. 161°) and **7** (m.p. 165°) in the ratio 4:1] of a dibenzylidene derivative were formed simultaneously. Compound **2** was insoluble in benzene and could easily be isolated. The mixture of **6** and **7** was then separated from **1** by fractional crystallisation from ethanol, and **6** and **7** were fractionated by ascending dry-column chromatography[14].

Treatment of the dibenzylidene derivative **6** with sodium azide gave 1,6-diazido-2,4:3,5-di-*O*-benzylidene-1,6-dideoxy-D-mannitol, which, with lithium aluminium

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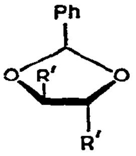

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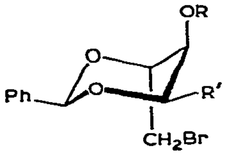
4 R = Ac



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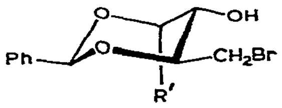
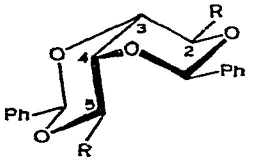
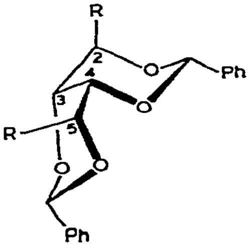


3

R' = CH(OR)–CH_2Br



6 R = CH_2Br
8 R = CH_2N_3
9 R = CH_2NH_2



7 R = CH_2Br

hydride, gave the corresponding 1,6-diamino derivative **9**. Compound **9** was identical with that obtained by Bird *et al.*[13], but its structure was not then confirmed.

The structures of compounds **1**, **2**, **6**, and **7** were established as follows. Neither **1** nor **2** reacted with periodate, thereby excluding 2,5- and 2,3-benzylidene structures. There remain two diastereomeric 2,4-structures (**2** and **3**) and one 3,4-structure (**1**). Compound **2** and its diacetate **5** are known[15,16], and the m.p. and i.r. data of our samples are identical with those described.

Mesylation of **1** and debenzylidenation of the product gave known[17] 1,6-dibromo-1,6-dideoxy-2,5-di-*O*-methanesulphonyl-D-mannitol.

Compounds **6** and **7** could be 2,3:4,5-, 2,4:3,5-, or 2,5:3,4-di-*O*-benzylidene derivatives. The chemical shifts of the n.m.r. signals for the benzylic protons and acetal carbon atoms of **6** are identical[18], as are those for **7**. Therefore the 2,5:3,4-structure is excluded, as are the unsymmetrical diastereomers having 2,3:4,5- and 2,4:3,5-structures. Since the chemical shifts of the signals for the acetal carbon atoms of **6** and **7** (95.0 and 96.1 p.p.m., respectively) are similar to that (94.6 p.p.m.) of **5**, the structure of which is known, but markedly different from that (104.4 p.p.m.) of **4**, which contains a 1,3-dioxolane ring, the symmetrical diastereomers **6** and **7** are shown to be 2,4:3,5-di-*O*-benzylidene derivatives.

EXPERIMENTAL

Melting points are not corrected. T.l.c. was performed on Kieselgel G with *A*, chloroform–ethyl acetate (1:1); *B*, chloroform–hexane (6:4); *C*, benzene–hexane

(7:3); *D*, chloroform–methanol–2M ammonia (3:5:2); *E*, chloroform–propan-2-ol (9.5:0.5); and detection with 0.1M potassium permanganate–2M sulphuric acid (1:1) or with 4-(*p*-nitrobenzyl)pyridine followed by treatment with 4M potassium hydroxide and heating at 105°. Column chromatography was performed on a dry column, by the ascending technique. I.r. spectra were recorded for KBr discs with a Perkin–Elmer 457 spectrometer. ^{1}H-N.m.r. and ^{13}C-n.m.r. spectra were recorded for solutions in $CDCl_3$ or Me_2SO-d_6 at room temperature with JEOL 60-HL and Varian XL-100 FT spectrometers, respectively. Solutions were concentrated in a rotary evaporator under diminished pressure. Organic solutions were dried over anhydrous sodium sulphate. Light petroleum refers to the fraction having b.p. 60–80°. Optical rotations were measured for 1% solutions in $CHCl_3$, unless otherwise specified.

*Benzylidenation of 1,6-dibromo-1,6-dideoxy-*D*-mannitol.* — A mixture of benzaldehyde (200 ml), powdered, anhydrous zinc chloride (75 g), and 1,6-dibromo-1,6-dideoxy-D-mannitol (46.3 g) was shaken until dissolution was nearly complete (2–4 h). The mixture was stored for 1 week, triturated with hexane (1 litre) added in portions, and decanted. A solution of the residual, thick oil in dichloromethane (600 ml) was washed several times with water and saturated, aqueous sodium hydrogen carbonate, and then concentrated to dryness. A mixture of the residue and benzene (400 ml) was stored overnight, to give 2,4-*O*-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**2**; 1.75 g, m.p. 147–148°). Recrystallisation from acetone gave material having m.p. 161–162°, $[\alpha]_D^{20}$ +50° (1,4-dioxane), R_F 0.58 (solvent *A*); lit.[15] m.p. 162–163°.

Compound **2** did not consume sodium periodate, and its i.r. spectrum was identical with that of the authentic material[15]. The 3,5-diacetate (**5**) of **2**, conventionally obtained by using pyridine–acetic anhydride, had m.p. 99–100° (from ethanol), $[\alpha]_D^{20}$ —0.8°, and its i.r. spectrum was identical with that of the previously reported compound[15,16].

The foregoing mother liquor (benzene) was concentrated (to ~100 ml), and hexane (600 ml) was added in portions. The crystalline precipitate (34.9 g) was separated and, when crystallised from ethanol (200 ml), gave a mixture of **6** and **7** (15.0 g, m.p. 138–143°) contaminated with a small proportion of **1**.

The ethanolic mother liquor was diluted portionwise with water (1.3 litres) to give 3,4-*O*-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**1**; 11.2 g, m.p. 101–104°) which, after recrystallisation from benzene–hexane, had m.p. 103–104°, $[\alpha]_D^{20}$ +19°, R_F 0.85 (solvent *A*) and 0.08 (solvent *B*). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 5.90 (s, 1 H, PhC*H*).

Anal. Calc. for $C_{13}H_{16}Br_2O_4$: C, 39.41; H, 4.04; Br. 40.35. Found: C, 39.62; H, 4.22; Br, 40.24.

Compound **1** did not consume sodium periodate, and its 2,5-diacetate (**4**), prepared conventionally by using pyridine–acetic anhydride, had m.p. 52–53° (from ethanol), $[\alpha]_D$ 0°, R_F 0.47 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.97 (s, 1 H, PhC*H*), 2.14 and 2.20 (2s, 6 H, 2 AcO).

Anal. Calc. for $C_{17}H_{20}Br_2O_6$: C, 42.52; H, 4.21; Br, 33.29. Found: C, 42.71; H, 4.18; Br, 33.10.

The 2,5-dimesylate (0.53 g) of **1**, conventionally prepared by using methanesulphonyl chloride and pyridine, was treated with boiling, methanolic 1% hydrochloric acid (25 ml) for 8 h. The solution was concentrated to dryness and the residue was triturated with hot ether to give 1,6-dibromo-1,6-dideoxy-2,5-di-*O*-methanesulphonyl-D-mannitol (0.38 g), which, after recrystallisation from propan-2-ol and then from chloroform, had m.p. 122–123°, $[\alpha]_D^{20}$ −24° (1,4-dioxane), R_F 0.38 (solvent *E*); lit.[17] m.p. 122–123°.

A solution of the mixture of **6** and **7** (15 g) in benzene (160 ml) was mixed with Kieselgel (16 g), and the solvent was evaporated. The residue was stratified with Kieselgel (280 g) in a column (150 cm). Elution with solvent *C* was effected by the ascending technique at 0.3–0.5 atmos. The fractions containing a mixture (7.4 g) of the compounds having R_F 0.35 and 0.48 were rechromatographed. The fractions containing the compound of R_F 0.48 were combined and concentrated to dryness, and the product was crystallised from ethanol to give 2,4:3,5-di-*O*-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**6**, 7.20 g), m.p. 160–161°, $[\alpha]_D^{20}$ +24°, R_F 0.48 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.70 (s, 1 H, PhC*H*).

Anal. Calc. for $C_{20}H_{20}Br_2O_2$: C, 49.61; H, 4.16; Br, 33.01. Found: C, 49.84; H, 4.24; Br, 32.92.

The fractions containing the product of R_F 0.35 were combined and concentrated to dryness, and the residue was recrystallised from ethanol to yield 2,4:3,5-di-*O*-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**7**, 1.75 g), m.p. 165°, $[\alpha]_D^{20}$ +60°, R_F 0.31 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.78 (s, 1 H, PhC*H*).

Anal. Found: C, 49.88; H, 4.28; Br, 33.20.

*1,6-Diazido-2,4:3,5-di-O-benzylidene-1,6-dideoxy-*D*-mannitol* (**8**). — To a solution of **6** (4.84 g) in 2-methoxyethanol (50 ml) was added a solution of sodium azide (2.6 g) in water (5 ml). The mixture was boiled under reflux for 3 h and then concentrated to dryness. The crystalline residue was triturated with water and then with propan-2-ol, and the product (3.7 g, m.p. 143–145°) was recrystallised from ethanol to give **8**, m.p. 144–145°, R_F 0.45 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.95 (s, 1 H, PhC*H*).

Anal. Calc. for $C_{20}H_{20}N_6O_4$: C, 58.81; H, 4.93; N, 20.57. Found: C, 59.10; H, 5.13; N, 20.62.

*1,6-Diamino-2,4:3,5-di-O-benzylidene-1,6-dideoxy-*D*-mannitol* (**9**). — A solution of **8** (2.36 g) in tetrahydrofuran (12 ml) was added dropwise, with stirring and cooling, to a solution of lithium aluminium hydride (2 g) in tetrahydrofuran (120 ml). The mixture was boiled under reflux for 3 h, the excess of reductant was decomposed with aqueous potassium sodium tartrate, and the mixture was filtered, dried, and concentrated to dryness. The crystalline residue was triturated with ether, and the product (1.56 g, m.p. 182–184°) was recrystallised from water to give **9**, m.p. 184–185°, $[\alpha]_D^{20}$ +69°, R_F 0.83 (solvent *D*); lit.[13] m.p. 179–181°, $[\alpha]_D^{20}$ +59.3°. The differences in physical constants may be due to the presence of a mixture of diastereomers in the earlier compound.

Anal. Calc. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.73; N, 7.66. Found: C, 67.18; H, 6.82; N, 7.70.

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