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SYNTHESIS AND CONFORMATIONS OF 2,3:4,5- AND 2,4:3,5-DI-*O*-ISOPROPYLIDENE-D-MANNITOL

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ABSTRACT

The 2,3:4,5- (**8**) and 2,4:3,5-di-*O*-isopropylidene (**10**) derivatives of D-mannitol have been prepared from 1,6-di-*O*-benzoyl-D-mannitol and their structures established by ^{13}C-n.m.r. spectroscopy. The 1,3-dioxane rings in **10** adopt a skew conformation and the sugar carbon chain in **8** is bent around the C-3–C-4 bond, as found by i.r. data and molecular mechanics calculations. Oxidation of **8** with pyridinium dichromate gave 2,3:4,5-di-*O*-isopropylidene-D-mannono-1,6-lactone (**12**).

INTRODUCTION

Selective protection of the hydroxyl groups in D-mannitol by acetalation has received much attention[1]. Thus, acid-catalysed isopropylidenation[2] with acetone–zinc chloride[3–5], acetone-2,2-dimethoxypropane[6], 2,2-dimethoxypropane in methyl sulfoxide[7], or 2-methoxypropene in 1,2-dimethoxyethane[8] or in *N,N*-dimethylformamide[9] yields the 1,2:5,6-di-*O*-isopropylidene derivative **2**. With a limited amount of 2-methoxypropene, the 1,2-*O*-isopropylidene derivative **3** can be obtained[9] and more-forcing conditions provide the 1,2:3,4:5,6-tri-*O*-isopropylidene derivative **4**[2,10]. Selective hydrolysis of **4** gave 1,2:3,4-di-*O*- (**5**)[11] and 3,4-*O*-isopropylidene (**6**)[12–15] derivatives.

2,3:4,5-Di-*O*-isopropylidene-D-mannitol (**8**) is of special interest since, owing to the unique conformation (see below), its derivatives should be amenable to 1,6-ring closure. Both **8**[16] and its L enantiomer[17] have been prepared from D- and L-inositol, and we now report the preparation of **8** from the cheap starting-material D-mannitol. Although this involves the formation of isopropylidene derivatives from *erythro*-diols, such reactions have been reported for D-mannitol[2] and D-ribose diethyl dithioacetal[18]. However, for 1,6-disubstituted derivatives of D-mannitol, 2,3:4,5-, 2,4:3,5-, and 2,5:3,4-diacetals are possible products. Acetalation of 1,6-dichloro-1,6-dideoxy-D-mannitol with trifluoroacetone and sulfuric acid was claimed to give two diastereoisomeric 2,3:4,5-di-*O*-trifluoroisopropylidene derivatives, but the structures were not proved[19].

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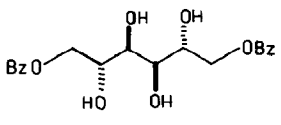
RESULTS AND DISCUSSION

Treatment of 1,6-di-*O*-benzoyl-D-mannitol[20] (**1**) with an excess of 2,2-dimethoxypropane and a trace of toluene-*p*-sulfonic acid gave 72% of an inseparable mixture of the diacetals **9** and **11** and the 3,4-acetal **7** (17%), which was isolated easily by column chromatography. Compound **7** was the main product of acetalation of **1** with acetone–toluene-*p*-sulfonic acid and its spectral characteristics were in accord with those published[14,21,22].

The presence of the two diacetals **9** and **11** in the above mixture was established by the ^{13}C-n.m.r. data (Table I), namely, two sets of signals for the CMe_2 groups and the carbons of the sugar chain. In addition, only two signals for CMe_2 were seen in the 100–110 p.p.m. range, namely, at 109.6 and 101.2 p.p.m. characteristic of a dioxolane ring and a dioxane or a dioxepane ring[23], respectively. A 2,5:3,4-diacetal structure was ruled out, since pure **11**, prepared by benzoylation of **10** (see below), shows no signal for CMe_2 in the range 109–110 p.p.m. and, hence, contained no dioxolane ring. The methyl groups in **9** and **11** are diastereotopic; since the molecules each possess a C_2 axis of symmetry, the acetal rings are equivalent and only two ^{1}H- and ^{13}C-n.m.r. signals are expected and observed for each compound. In addition, the small (2.0 p.p.m.) $\Delta\delta$ value for the ^{13}C resonances of the gem-dimethyl carbons in **9** is characteristic of the dioxolane ring[23]. Thus, the 2,3:4,5- (**9**) and 2,4:3,5-diacetal (**11**) structures comply with the n.m.r. data. Integration of the ^{13}C resonances of the methyl groups gave the ratio of **9** and **11** as 2:1.



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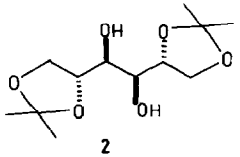

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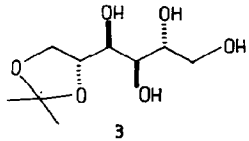

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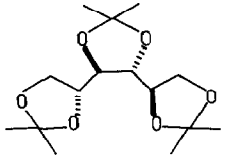

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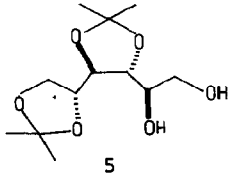

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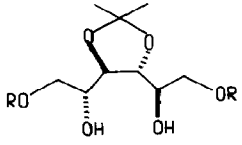

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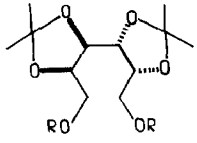

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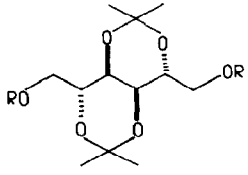

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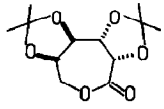

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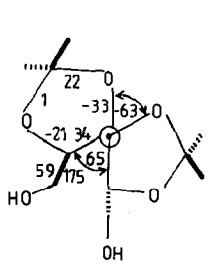
TABLE I

^{13}C-N.M.R. DATA OF THE ISOPROPYLIDENE DERIVATIVES **7–12**

Compound	*CMe$_2$*	*Sugar chain carbons*	*CMe$_2$*	*Δδ CMe$_2$*
7	110.0	67.0 71.8 80.0	26.0	0
8	109.0	61.5 74.7 77.5	25.5 27.4	1.9
9[a]	109.6	64.2 74.7 75.1	25.4 27.4	2.0
10	100.9	62.9 67.7 70.3	23.8 24.8	1.0
11	101.2	64.7 68.2 68.6	23.7 24.5	0.8
12	111.0	65.3 73.6 74.4 75.8 76.3 167.5	23.1 25.5 25.8 26.4	≤3.3

[a]Obtained from a mixture of **9** and **11**.

The small (0.8 and 1.0 p.p.m., respectively) Δδ values for the ^{13}C resonances of the gem-dimethyl carbons of the 1,3-dioxane rings in **11** and **10** indicate non-chair conformations, since a chair conformation requires a Δδ value of ~10 p.p.m.[23]. Thus, a skew conformation (**15**) of the dioxane rings in **10** and **11** is preferred since 1,3-diaxial interactions are avoided thereby.



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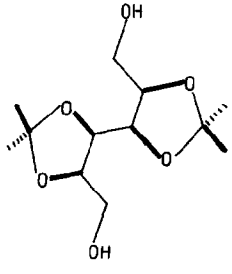

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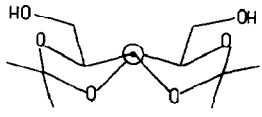

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Treatment of the mixture of dibenzoates **9** and **11** with sodium methoxide in methanol–chloroform followed by chromatography afforded the diacetals **8** (m.p. 93–95°) and **10** (m.p. 134–136°). The ^{13}C-n.m.r. data (Table I) for **8** and **10** corresponded closely to those for **9** and **11**. Their ^{1}H-n.m.r. spectra each contained two singlets for the methyl groups, in accord with the symmetry considerations noted above. The mass spectra of **8** and **10** each contained a characteristic peak at *m/z* 131 (relative intensities, 38% and 56%, respectively) due to the fragmentation of the molecules about the C-3–C-4 bond. There was no peak at *m/z* 101 due to a terminal dioxolane ring.

The i.r. spectra of 10^{-3}M solutions of **8** and **10** in CCl_4 differed considerably (Fig. 1). Whereas that for **10** contains a single band at 3602 cm^{-1}, typical of an intramolecular hydrogen bond in a five-membered ring*, that of **8** contains a weak band at 3638 cm^{-1}, due to the free primary hydroxyl group; a stronger band at 3603 cm^{-1} ($\Delta\nu$ 35), characteristic of an intramolecular hydrogen bond in a five-membered ring; and a much stronger band at 3532 cm^{-1} ($\Delta\nu$ 106), due to a shorter hydrogen bond[24]. The band at 3532 cm^{-1} could reflect the formation of a hydrogen bond between the two CH_2OH groups, since the dioxolane rings force the molecule into a bent conformation and bring the two terminal hydroxyl groups into close proximity.

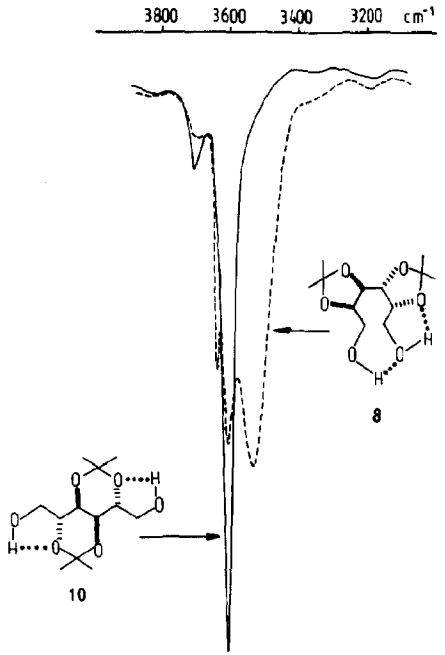

Fig. 1. Infrared spectra of diacetals **8** and **10** in 10^{-3}M CCl_4.

*Alternative hydrogen bonding to give a six-membered ring apparently is disfavoured due to the C–O/C–O dipole interaction.

The structural parameters for the preferred conformation of **8** were found by force field calculations, using the MM2 method[25]. The molecule **8** can adopt two conformations (**13** and **14**) of similar energy. In each conformation, the substituents around the C-3–C-4 bond are staggered and the two dioxolane rings have the $^{3,4}E$ conformations. The calculated steric energy (hydrogen bonding not included) for **8** in the conformation **13** with the C-2–C-3 and C-4–C-5 bonds synclinal (dihedral angle, +65°) is lower by 0.3 kcal mol^{-1} than that of the molecule in the conformation **14** in which the above bonds are antiperiplanar (dihedral angle, +171°). The calculated dihedral angles for the preferred conformation are shown in formula **13**.

The conformation of the diol **8** affects its reactivity. Whereas oxidation of **10** with pyridinium dichromate gives a complex mixtures of products, **8** is smoothly converted into the lactone **12**, presumably *via* rapid formation of the hemiacetal of the intermediate aldehyde. The structure of the lactone **12** was confirmed by the spectral data. The compound had a strong i.r. carbonyl stretching band at 1745 cm^{-1} and no absorption for hydroxyl. There were four signals for methyl groups in both the ^1H- and ^{13}C-n.m.r. spectra. The presence of the two non-equivalent dioxolane rings was also confirmed by the ^{13}C-n.m.r. spectrum (Table I).

EXPERIMENTAL

General. — T.l.c. was performed on Silica Gel GF_{254} (Merck) with dichloromethane–methanol (99:1) and detection by charring with sulfuric acid. Silica gel 100–200 mesh (P.O.Ch., Gliwice) was used for column chromatography. Melting points are uncorrected. Specific rotations were measured with a Polamat polarimeter. I.r. spectra were recorded with a Perkin–Elmer 580 grating spectrophotometer. N.m.r. spectra were recorded with a JEOL FX 90-MHz spectrometer for solutions in $CDCl_3$ (internal Me_4Si). C.d. spectra were recorded with a Jobin-Yvon Mark III dichrograph, u.v. spectra with a Cary 118C spectrophotometer, and mass spectra with a JEOL JMS-D 100 spectrometer.

*1,6-Di-*O*-benzoyl-2,3:4,5-di-*O*-isopropylidene-*D*-mannitol* (**9**) *and 1,6-di-*O*-benzoyl-2,4:3,5-di-*O*-isopropylidene-*D*-mannitol* (**11**). — A mixture of 1,6-di-*O*-benzoyl-D-mannitol[12] (**1**, 4.8 g), 2,2-dimethoxypropane (30 mL), and toluene-*p*-sulfonic acid hydrate (50 mg) was heated for 1 h at 80°, then cooled, and extracted with ether–aqueous Na_2CO_3. Concentration of the ether solution yielded a colorless oil which was subjected to short-column chromatography (dichloromethane) to afford a mixture (4.2 g, 72%) of **9** and **11** as a colorless oil; ν_{max}^{film} 1720, 1272, 1108, and 707 cm^{-1}; $\lambda_{max}^{dioxane}$ 229 nm (ε 24,900). ^1H-N.m.r. data: δ 1.32, 1.37, 1.43, and 1.54 (4 s, 12 H, 2 CMe_2), 4.0–4.6 (m, 8 H), 7.3–7.6 (m, 6 H), 8.0–8.1 (m, 4 H).

Further elution with dichloromethane–ether (9:1) gave 1,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol (**7**; 0.85 g, 17%), m.p. 94–95° (from ether–hexane), $[\alpha]_D^{20}$ +22.5° (*c* 2.5, chloroform); lit.[14] m.p. 94°, $[\alpha]_D^{23}$ +25° (pyridine).

*2,3:4,5-Di-*O*-isopropylidene-*D*-mannitol* (**8**) *and 2,4:3,5-di-*O*-isopropylidene-*D*-mannitol* (**10**). — A solution of the foregoing mixture (4.2 g) of **9** and **11** in

chloroform (100 mL) and methanol (10 mL) was stirred overnight at room temperature with methanolic M MeONa (1 mL), and then concentrated. The residue was washed with light petroleum, and then a solution in dichloromethane was subjected to short-column chromatography. Elution with dichloromethane gave **10** which, after crystallisation from acetone-hexane, gave a product (0.63 g, 27%) having m.p. 134–136°, $[\alpha]_D^{20}$ +22° (*c* 2.5, chloroform); ν_{max}^{KBr} 3300, 1215, and 1025 cm^{-1}. ^{1}H-N.m.r. data: δ 1.33 and 1.40 (2 s, 12 H, 2 CMe_2), 2.1 (bs, 2 H, 2 OH), and 3.7–4.0 (m, 8 H). Mass spectrum: *m/z* 247 (8%), 144 (8), 131 (56), 113 (15), 86 (9), 68 (11), and 59 (100).

Anal. Calc. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 55.01; H, 8.72.

Further elution with dichloromethane–ether (9:1) gave **8** which, after crystallisation from ether–hexane, gave a product (1.33 g, 57%) having m.p. 93–95°, $[\alpha]_D^{20}$ +15° (*c* 2.8, chloroform); lit.[16] m.p. 90–92°, $[\alpha]_D$ +13.4° (chloroform); ν_{max}^{KBr} 3470, 3410, 1212, and 1045 cm^{-1}. ^{1}H-N.m.r. data: δ 1.39 and 1.51 (2 s, 12 H, 2 CMe_2), 3.3 (bs, 2 H, OH), 3.73 (bs, 4 H, 2 CH_2), and 4.31 (s, 4 H, 4 CH). Mass spectrum: *m/z* 247 (27%), 173 (17), 131 (38), 129 (11), 115 (10), 111 (7), 99 (12), 85 (18), 73 (11), 71 (12), 69 (9), and 59 (100).

Anal. Calc. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.96; H, 8.41.

2,3:4,5-Di-O-isopropylidene-D-mannono-1,6-lactone (**12**). — The diacetal **8** (262 mg, 1 mmol) was stirred with pyridinium dichromate (1.13 g, 3 mmol) in dichloromethane (6 mL) for 6 h at room temperature. The mixture was diluted with ether, filtered, and concentrated. Column chromatography (hexane–dichloromethane, 1:1) of the residue and distillation at 130°/10 Pa gave **12** as a colorless syrup (191 mg, 74%), $[\alpha]_D^{25}$ −49.5° (*c* 1.3, chloroform); ν_{max}^{film} 1745 cm^{-1} (lactone); c.d. (MeCN): $\Delta\varepsilon$ −0.23 (246), +0.7 (220). ^{1}H-N.m.r. data: δ 1.39, 1.41, 1.54, and 1.60 (4 s, 12 H, 2 CMe_2), 4.1–5.1 (m, 6 H).

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.51; H, 7.23.

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