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Note

1,2:4,6- and 1,2:3,6-Di-*O*-isopropylidene-D-mannitol*

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In a previous paper[1], it was mentioned that acetalation of D-mannitol according to Horton *et al.*[2], using 2-methoxypropene in *N,N*-dimethylformamide as the reagent, in the presence of *p*-toluenesulfonic acid as the catalyst, led, according to g.l.c. investigations** to the formation of three diacetals **D, E,** and **H** (see Fig. 1). These isomers have now been separated by column chromatography, and their structures elucidated by ^{13}C-n.m.r. investigations using the ring-size-dependent shift of the acetal carbon atoms, established by Buchanan *et al.*[3].

Peak **E**. This isomer was eluted first from the column, and proved to be identical in every respect with 1,2:5,6-di-*O*-isopropylidene-D-mannitol[1,4,5]. In accord

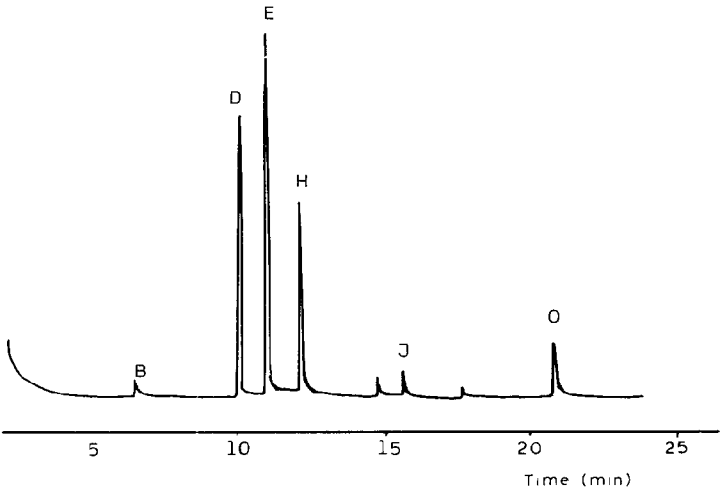

Fig. 1. G.l.c. of the acetylated reaction-mixture obtained from D-mannitol and 2-methoxypropene in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid after 4 h at 0°. (Peaks are lettered as in Fig. 2.)

*The Acetalation of D-Mannitol, Part II. For Part I, see ref. 1.
**For g.l.c. examination, the samples were acetylated with acetic anhydride in pyridine.

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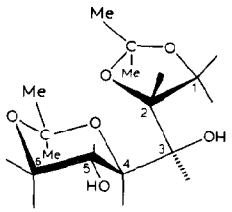
with the literature[3], the ^{13}C-n.m.r. shifts for the two magnetically equivalent acetal carbon atoms appeared at 109.6 p.p.m., and at 109.7 p.p.m. for the diacetate.

Peak **D.** This isomer was eluted second from the column, and could be obtained in crystalline state. Originally[1], the 1,2:3,6-diacetal structure was suggested for the corresponding g.l.c. peak, as it was always present in the different acetalation mixtures, and it was considered to be an intermediate from which the 1,2:3,6:4,5-triacetal (peak **B**) could be formed. According to ^{13}C-n.m.r. investigations, the signals for the two acetal carbon atoms of the isolated compound appeared at 109.7 and 99.1 p.p.m., proving the presence of one dioxolane and one larger (dioxane or dioxepane) ring.

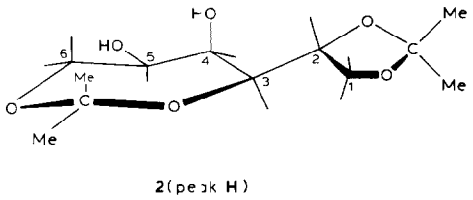
For obtaining further proof of the structure, the isomer was acetylated. The ^{13}C-n.m.r. spectrum of the diacetate so obtained confirmed the presence of these two rings, as the signals for the acetal carbon atoms appeared at 109.1 and 99.9 p.p.m., respectively. On the other hand, the ^{1}H-n.m.r. spectrum of the diacetate excluded the presence of a terminal acetoxyl group, as well as vicinal positions for the acetoxyl groups, and consequently, the two acetal rings must occupy the 1,2 and 4,6 position, respectively, as depicted in formula **1** for the unacetylated dia-



1 (peak D)

cetal. The presence of a dioxane ring is further confirmed by the ^{13}C-chemical shifts of the methyl groups, as one of them appears at 20.0 p.p.m., excluding the presence of a dioxepane ring. In accord with the most probable conformation of this acetylated 1,2:4,6-diacetal, H-4 and H-5 are *trans*-diaxially oriented, as proved by their coupling constant, $J_{4,5}$ 10 Hz.

Peak **H.** This isomer, of unknown structure[1], was eluted last among the different diacetals formed in the reaction. Its ^{13}C-n.m.r. spectrum proved the presence of a dioxolane and a dioxepane ring, as the signals for the corresponding acetal carbon atoms appeared at 109.9 and 102.4 p.p.m., and no methyl signal could be detected below 25.8 p.p.m. These two rings could either be situated separately, in the 1,2:3,6 positions (as suggested originally[1] for peak **D**), or in a fused structure, as, *e.g.*, in the 3,6:4,5-diacetal (suggested originally[1] as a contaminant included in peak **E**). The former arrangement was much the more probable, as the formation of terminal is always faster than that of nonterminal acetal rings[6,7]. The n.m.r. investigations of the diacetate confirmed the 1,2:3,6-di-*O*-isopropylidene structure **2** for the parent diacetal, as neither of the acetoxyl groups was situated in a terminal



2(peak H)

position and the signals of the acetal carbon atoms appeared at 109.7 and 101.9 p.p.m.

CONCLUSIONS

The elucidation of the structure of 1,2:5,6-, 1,2:4,6-, and 1,2:3,6-di-*O*-isopropylidene-D-mannitol, and the identification of their diacetylated derivatives with peaks **E, D,** and **H** in g.l.c. as containing all of the isopropylidene acetals of D-mannitol so far detected (see Fig. 2), made a revision of the earlier explanation of the acetalation reaction of D-mannitol necessary.

When acetone, in the presence of zinc chloride, or 2,2-dimethoxypropane in 1,2-dimethoxyethane in the presence of tin(II) chloride, is used[1], D-mannitol (peak **O**) is converted *via* its 1,2-acetal (**J**) into the 1,2:4,6- (**D**), 1,2:5,6- (**E**), 1,2:4,5-

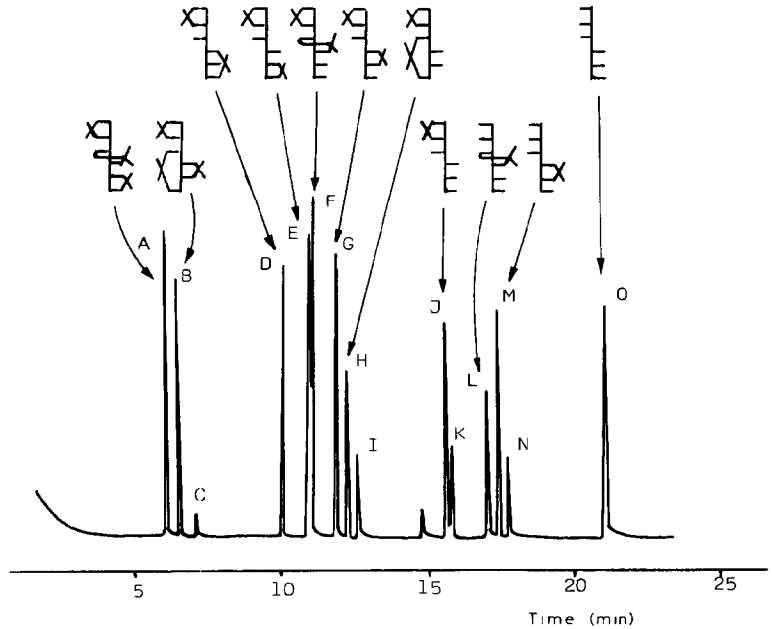


Fig. 2. G.l.c. of a mixture of the different acetylated, isopropylidene acetals of D-mannitol. [**A**, 1,2:3,4:5,6-tri-; **B**, 1,2:3,6:4,5-tri-; **D**, 1,2:4,6-di-; **E**, 1,2:5,6-di-; **F**, 1,2:3,4-di-; **G**, 1,2:4,5-di-; **H**, 1,2:3,6-di-; **J**, 1,2-mono-; **L**, 3,4-mono-; and **M**, 4,5-mono-*O*-isopropylidene-D-mannitol; **O**, D-mannitol; **C**, **I**, **K**, and **N**, unknown structures.]

(G), and 1,2:3,6-diacetal (H). The relatively high proportion of **D** compared to **H** might be due to the fact that **D** cannot be converted into a triacetal and is therefore stable, whereas, on further reaction, **H** gives the 1,2:3,6:4,5-triacetal **B**.

The fact that partial hydrolysis of triacetal **B** in ethanol containing aqueous hydrochloric acid gives, besides the 1,2:4,5-diacetal (**G**), the isomeric 1,2:5,6-diacetal **E*** and traces[1] of the 1,2:3,6-diacetal **D**, can be explained only by assuming a partial rearrangement reaction, the existence of which was denied by Baggett *et al.*[8] on account of their ^{1}H-n.m.r. investigations. This contradiction is probably due to the low concentration of the rearranged isomers, making their detection by ^{1}H-n.m.r. spectroscopy uncertain.

EXPERIMENTAL

General methods. — All evaporations were conducted in a rotary evaporator under diminished pressure. Light petroleum used had b.p. 60–80°. T.l.c. was effected on Kieselgel G with 1:3 carbon tetrachloride–ethyl acetate (*A*). For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (63–200 μm). ^{13}C-N.m.r. (25.16 MHz) and ^{1}H-n.m.r. spectra (100 MHz) were recorded with a Varian XL-100 F.t. spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. G.l.c. was conducted with a Hewlett–Packard 5830 A gas chromatograph, using a glass capillary column (25 m × 0.25 mm) coated with OV-101; temperature, 2°.min^{-1} from 140 to 220°; carrier gas, nitrogen; inlet pressure, 124 kPa; make-up gas, nitrogen (193 kPa).

The acetalation of D-*mannitol with 2-methoxypropene.* — To a stirred and cooled (0°) solution of *p*-toluenesulfonic acid (0.1 g) in *N,N*-dimethylformamide (200 mL) were added Drierite (1 g), dried D-mannitol (9.1 g), and 2-methoxypropene (8 mL). The slurry was stirred at 0°, and, at 1-h intervals, three 2-mL portions of 2-methoxypropene were added. After 1 h, potassium carbonate (2.5 g) was added, and stirring was continued for 1 h at 0°. The slurry was filtered, and a 1-mL aliquot was acetylated with acetic anhydride (0.5 mL)–pyridine (1 mL). G.l.c. analysis of this sample revealed the presence of diacetals **D**, **E**, and **H** in proportions of 29, 44, and 17%, respectively.

The filtrate was evaporated, and the residue was partitioned between dichloromethane and water. The organic solution was washed with water, dried, and evaporated. The syrupy residue (10 g) was separated by chromatography, using a column (1200 × 45 mm), and solvent *A* for elution.

*In the original paper[1], it was presumed that the performance of the g.l.c. column used was not such as to separate the hypothetical 3,6:4,5-diacetal from the 1,2:5,6 isomer, thus giving peaks having identical retention-times. G.l.c.–mass-spectral measurements proved, however, the identity of peak **E** in the samples, obtained on acetonation of D-mannitol, as well as on graded hydrolysis of the 1,2:3,6:4,5-triacetal, with authentic 3,4-di-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol; consequently, a rearrangement must have taken place during the hydrolysis reaction, and the hypothetical 3,6:4,5-diacetal does not exist.

The fractions having R_F 0.65 afforded, on evaporation, a solid residue which was filtered with the aid of ether–light petroleum, to give pure 1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.8 g, 31.4%); m.p. 122–123° (lit.[1] m.p. 120–122°; lit.[4] m.p. 120–121°; lit.[5] m.p. 122°); ^{1}H-n.m.r. data: δ 3.9–4.2 (m, H-1,2,5,6), 3.36 (t, $J_{2,3}$ 7 Hz, H-3,4), 3.07 (d, $J_{H,OH}$ 7 Hz, OH-3,4), and 1.42 (s, 6 H) and 1.34 (s, 6 H, 2 CMe_2); ^{13}C-n.m.r. data: δ 109.6 (acetal-C), 76.1 (C-2,5), 71.2 (C-3,4), 67.0 (C-1,6), 26.9, and 25.3 (acetal-CH_3).

On acetylation with acetic anhydride–pyridine, pure 3,4-di-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol was obtained (peak **E**); m.p. 122–123°, $[\alpha]_D^{20}$ +26.4° (*c* 1, chloroform) {lit.[9] m.p. 123°, $[\alpha]_D^{20}$ +26.7° (*c* 1, chloroform); lit.[10] m.p. 121–122°, $[\alpha]_D^{20}$ +26° (*c* 2.4, dichloromethane)}; ^{1}H-n.m.r. data: δ 5.3 (d, $J_{2,3}$ 6 Hz, H-3,4), 4.1 (ddd, $J_{1,2} = J_{1',2}$ = 6 Hz, H-2,5), 3.7–4.0 (m, H-1,6), 2.1 (s, 6 H, 2 acetyl), and 1.35 (6 H) and 1.30 (6 H, 2 CMe_2); ^{13}C-n.m.r. data: δ 170 (CH_3CO), 109.7 (acetal-C), 74.8 (C-2,5), 71.8 (C-3,4), 66.0 (C-1,6), 26.6 and 25.4 (acetal-CH_3), and 20.8 (CH_3CO).

The fractions having R_F 0.55 afforded, on evaporation, a crystalline residue, which was filtered off with the aid of ether–light petroleum, to give pure 1,2:4,6-di-*O*-isopropylidene-D-mannitol (1.2 g, 9.2%); m.p. 83–85°, $[\alpha]_D^{20}$ −26° (*c* 1, chloroform); ^{1}H-n.m.r. data: δ 3.5–4.2 (m, 10 H, H-1–6 and OH-3,5), 1.45, 1.40, 1.36, and 1.33 (12 H, 2 CMe_2); ^{13}C-n.m.r. data: δ 109.7 and 99.1 (acetal-C), 75.6 (C-2), 74.4 and 71.4 (C-3,4), 67.3 (C-1), 64.5 (C-6), 62.7 (C-5), 28.4, 26.8, 25.6, and 19.7 (acetal-CH_3).

On acetylation with acetic anhydride–pyridine, pure 3,5-diacetate of **1** was obtained (peak **D**); ^{1}H-n.m.r. data: δ 5.22 (dd, $J_{2,3}$ 6, $J_{3,4}$ 3 Hz, H-3), 4.63 (ddd, $J_{4,5}$ 10, $J_{5,6}$ 7.5, 4.3 Hz, H-5), 4.20 and 3.66 (dd, $J_{6,6'}$ 12 Hz, H-6,6'), 3.7–4.1 (m, H-1,2), 2.06 and 2.00 (s, 6 H, 2 acetyl), 1.43, 1.38, 1.35, and 1.32 (12 H, 2 CMe_2); ^{13}C-n.m.r. data: δ 170.5 and 170.2 (CH_3CO), 109.1 and 99.9 (acetal-C), 74.5 (C-2), 70.0 and 69.9 (C-3,4), 66.4 (C-1), 65.0 (C-5), 62.3 (C-6), 27.6, 26.7, 25.6, and 20.0 (acetal-CH_3), and 20.7 (CH_3CO).

The fractions having R_F 0.45 afforded, on evaporation, a crystalline residue, which was filtered off with the aid of ether–light petroleum, to give pure 1,2:3,6-di-*O*-isopropylidene-D-mannitol (1.1 g, 8.4%); m.p. 140–142°, $[\alpha]_D^{20}$ −15.6° (*c* 1, chloroform); ^{1}H-n.m.r. data: δ 3.2–4.3 (m, 10 H, H-1–6' and OH-4,5), and 1.38 (3 H), 1.33 (6 H), and 1.30 (3 H, 2 CMe_2); ^{13}C-n.m.r. data: δ 109.9 and 102.4 (acetal-C), 75.5 (C-2), 73.1, 71.3, and 69.8 (C-3,4,5), 67.7 (C-1), 61.8 (C-6), 28.0, 26.7, 26.0, and 25.8 (acetal-CH_3).

On acetylation with acetic anhydride–pyridine, pure 4,5-diacetate of **2** was obtained (peak **H**); ^{1}H-n.m.r. data: δ 5.42 (d, $J_{4,5}$ 3 Hz, H-4), 4.80 (dt, $J_{5,6}$ 3 and 10 Hz, H-5), 3.7–4.2 (m, 5 H, H-1,2,3,6), 3.32 (dd, $J_{6,6'}$ 12 Hz, H-6'), 2.10 and 1.93 (s, 6 H, 2 acetyl), and 1.36 (6 H), 1.32 (3 H), and 1.28 (3 H, 2 CMe_2); ^{13}C-n.m.r. data: δ 170.5 and 169.7 (CH_3CO), 109.7 and 101.9 (acetal-C), 74.4 (C-2), 71.8, 69.6, and 68.3 (C-3,4,5), 66.4 (C-1), 59.1 (C-6), 27.0, 25.5, 24.7, and 24.7 (acetal-CH_3), and 20.6 (CH_3CO).

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