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THE SYNTHESIS OF 1,2:5,6-DI-*O*-ISOPROPYLIDENE-D-MANNITOL: A COMPARATIVE STUDY

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ABSTRACT

Three different methods of acetonation of D-mannitol using (*a*) acetone and zinc chloride, (*b*), 2,2-dimethoxypropane, 1,2-dimethoxyethane, and tin(II) chloride, and (*c*) 2-methoxypropene, *N,N*-dimethylformamide, and *p*-toluenesulfonic acid were studied in detail and compared, using gas–liquid chromatographic techniques. In each reaction, isomeric diacetals are formed, but method *a* gives the 1,2:5,6-diacetal in the highest yield (63%). Methods *b* and *c* give a more complex mixture of acetals than proposed in the literature, and both methods are less economical than *a*. A new 1,2:3,6:4,5-tri-*O*-isopropylidene-D-mannitol could be separated, and its graded hydrolysis was compared to that of the 1,2:3,4:5,6-triacetal.

INTRODUCTION

For the large-scale preparation of 1,6-di-*O*-mesyl-3,4-di-*O*-methyl-D-mannitol, a compound having outstanding cytostatic activity[1], 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**5**) as the starting material was needed in large quantities. To find the optimal technology for the synthesis of compound **5**, the different methods so far published[2–11] had to be reinvestigated and compared to each other.

RESULTS AND DISCUSSION

Acetalation of D-*mannitol with acetone in the presence of zinc chloride (method* a*).* — In our previous synthesis[1], diacetal **5** was prepared from D-mannitol (**1**) by using acetone and anhydrous zinc chloride, a method first described by Baer[2] and later improved by Tipson and Cohen[3]. The reported yield of 55% could be reproduced, but to optimize the reaction conditions, the reaction was monitored by

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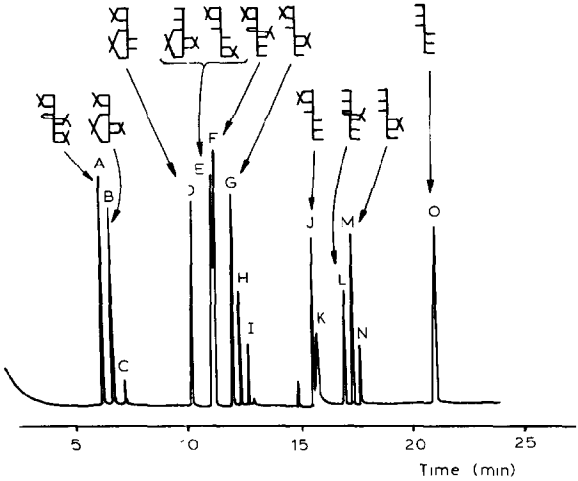


Fig. 1. G.l.c. of a mixture of the different acetylated, isopropylidene acetals of D-mannitol. **A**, 1,2:3,4:5,6-tri- (**9**); **B**, 1,2:3,6:4,5-tri- (**12**); **D**, 1,2:3,6-di- (**6**); **E**, 3,6:4,5-di- (**7**) and 1,2:5,6-di- (**5**); **F**, 1,2:3,4-di- (**10**); **G**, 1,2:4,5-di- (**8**); **J**, 1,2-mono- (**2**); **L**, 3,4-mono- (**11**); **M**, 4,5-mono-*O*-isopropylidene-D-mannitol (**4**); **O**, D-mannitol (**1**); **C, H, I, K,** and **N**, unknown structures.

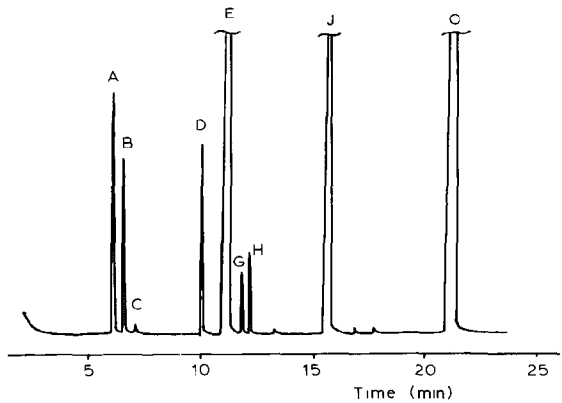


Fig. 2. G.l.c. of the acetylated reaction-mixture obtained from D-mannitol and acetone in the presence of anhydrous zinc chloride after 5 h at 20°. (Peaks are lettered as in Fig. 1.)

g.l.c. During this study, it became clear that the acetonation of D-mannitol under the conditions given is a rather complex reaction yielding a mixture of two triacetals, several diacetals, and a monoacetal (see Fig. 2). For establishing the course of the reaction in detail, it was stopped at different time-intervals, and each run was analyzed, after acetylation, by g.l.c. The peaks obtained were identified by peak-matching (see Fig. 1 for a g.l. chromatogram containing all of the acetals of **1** so far detected), as well as by g.l.c.–m.s. investigations*. From the data obtained (listed

*Details of the peak identification are given in the Experimental part.

TABLE I

RELATIVE INTENSITIES (%) OF G L C PEAKS OBTAINED AFTER ACETYLATION OF THE REACTION MIXTURE OF D-MANNITOL WITH ACETONE IN THE PRESENCE OF ANHYDROUS ZINC CHLORIDE

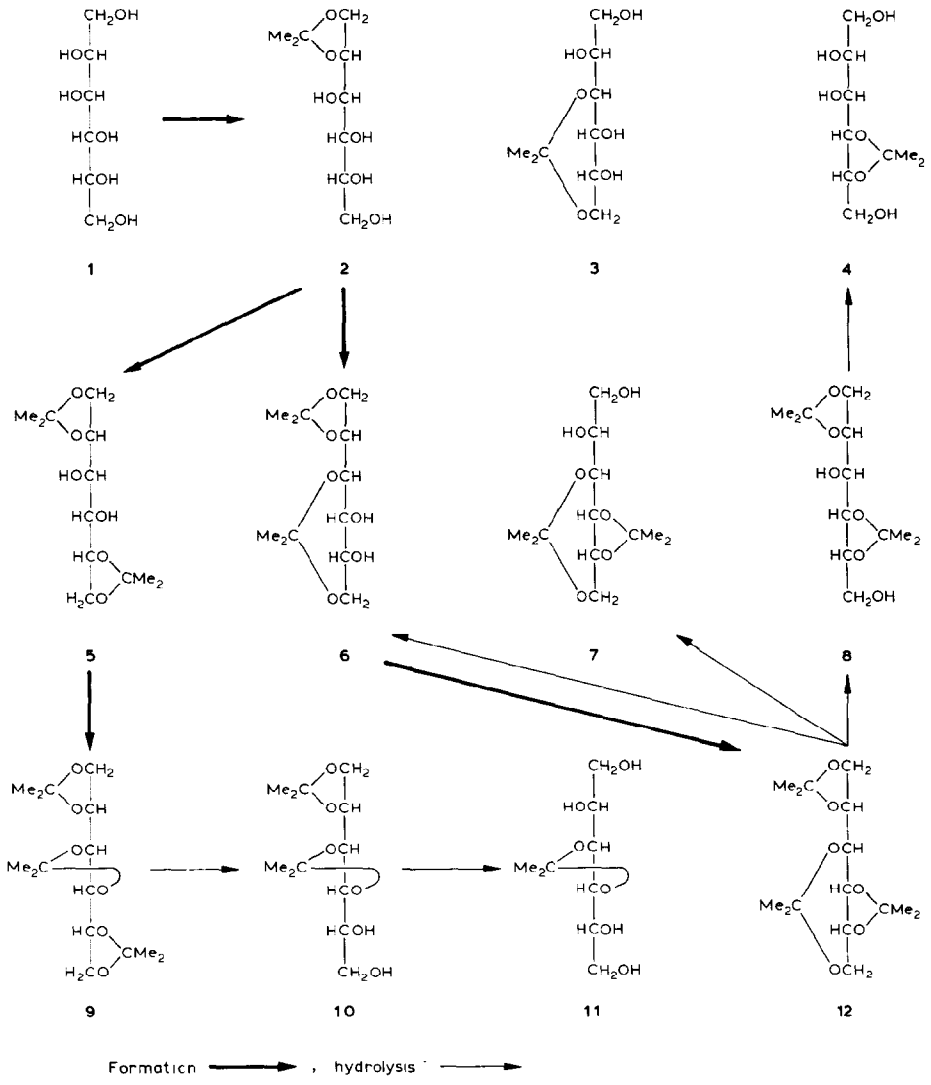
Reaction time	*Peaks*[a]							
	A	**B**	**D**	**E**	**G**	**H**	**J**	**O**
10 min	—	—	—	—	—	—	4.5	93.9
20	—	—	—	1.6	—	—	6.9	91.5
30	—	—	0.4	3.7	—	—	9.9	85.5
1 h	0.2	0.2	1.3	12.6	0.1	0.6	13.6	71.1
2	0.8	0.7	2.1	24.2	0.3	0.9	12.5	58.4
3	1.0	0.8	2.3	31.9	0.7	0.7	11.5	51.0
5	2.5	2.0	3.2	45.7	0.8	1.2	12.4	32.3
16	2.1	1.5	3.8	60.7	1.8	1.4	12.1	15.9
24	8.2	5.0	4.3	63.4	2.3	1.4	11.5	2.9
168	16.0	8.0	3.6	58.0	1.5	0.5	8.0	—

[a]Compounds lettered as in Fig. 1.

in Table I), it may be seen that **1** (peak **O**) is first converted *via* its 1,2-acetal **2** (peak **J**) into the 1,2:5,6-diacetal **5** (peak **E**), but simultaneously two other diacetals, the 1,2:4,5 (**8**, peak **G**) and the 1,2:3,6 isomer (**6**, peak **D**) are also formed in low yield. A third isomer (peak **H**) is also present, but its structure has not yet been established. The conversion of these diacetals into the 1,2:3,4:5,6-triacetal (**9**, peak **A**) and the new 1,2:3,6:4,5-triacetal (**12**, peak **B**) is a much slower process, but, after 24 h, when diacetal **5** is present in the maximal yield of 63.4%, these two isomers are formed in 8.2 and 5% yield, respectively. After 7 days, when equilibrium is reached, triacetals **9** and **12** are present in yields of 16 and 8%, respectively.

It should be noted that the g.l.c. column used, despite its high performance, could not separate the 3,6:4,5-diacetal **7** from the 1,2:5,6 isomer **5**; consequently, both are incorporated in peak **E**, but, as terminal dioxolane rings are formed much faster than nonterminal ones[12,13], the amount of **7** can be neglected in the acetalation reaction, and it is formed only on graded hydrolysis of triacetal **12**.

Acetalation of D-*mannitol with 2,2-dimethoxypropane (method* b*).* — In our first attempts, the method described by Chittenden[8] was reproduced, using 2,2-dimethoxypropane in 1,2-dimethoxyethane as the solvent without any catalyst. A clear solution was, however, obtained only after boiling the reaction mixture for 72 h, instead of the 20–24 h reported. G.l.c. investigation of the acetylated mixture revealed the presence of the two triacetals **9** and **12** in yields of 67 and 13%, respectively, whereas that of the 1,2:5,6-diacetal **5**, which should have been formed as the main component, was only ~8%. This rather unexpected result led us to reinvestigate the course of the reaction. For obtaining more-exact data, the reagents were first purified by distillation, but, in this case, no reaction took place, and all of the starting material could be recovered, even after 72 h of boiling. This suggests that, under neutral conditions, no acetalation takes place, and only impurities in the sol-



vents, probably the peroxides formed from 1,2-dimethoxyethane, can act as catalysts in the absence of added catalyst.

In our further experiments, we reproduced the method, described earlier by Chittenden[7], using tin(II) chloride as the catalyst. The parallel runs were quenched at different time-intervals and each run was analyzed, after acetylation, by g.l.c. (see Table II). A typical chromatogram is shown in Fig. 3. As D-mannitol is highly insoluble in the reaction mixture, the ratio of the 1,2-monoacetal **2** (peak **J**) remains very low, as it is immediately converted into the isomeric diacetals (peaks **D–H**), two of them, the 1,2:5,6 (peak **E**) and the 1,2:3,6 isomer (peak **D**) being the

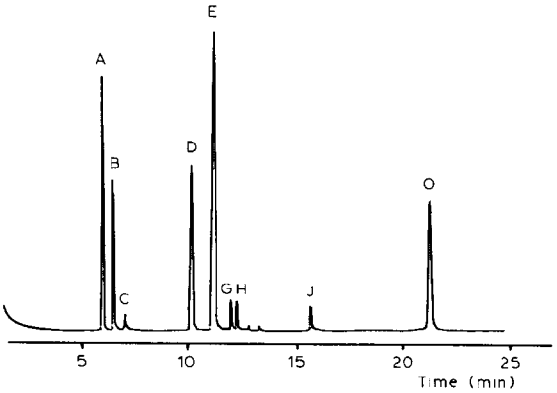


Fig. 3. G.l.c. of the acetylated reaction-mixture obtained from D-mannitol and 2,2-dimethoxypropane in 1,2-dimethoxyethane in the presence of tin(II) chloride after 30 min at 70°. (Peaks are lettered as in Fig. 1.)

TABLE II

RELATIVE INTENSITIES (%) OF G L.C. PEAKS OBTAINED AFTER ACETYLATION OF THE REACTION MIXTURE OF D-MANNITOL WITH 2,2-DIMETHOXYPROPANE IN 1,2-DIMETHOXYETHANE IN THE PRESENCE OF TIN(II) CHLORIDE

Reaction time	*Peaks*[a]								
	A	**B**	**C**	**D**	**E**	**G**	**H**	**J**	**O**
10 min	3.7	2.0	0.3	5.3	12.2	—	0.5	—	75.8
20	7.2	4.0	0.6	8.2	21.1	0.3	0.9	0.1	57.6
30	4.7	3.1	0.6	12.5	30.5	0.7	1.5	0.7	44.6
1 h	10.2	5.9	0.8	12.5	46.3	1.5	1.7	1.7	18.5
2	16.0	6.7	0.4	4.7	55.8	4.3	1.2	5.9	3.2
3	16.0	6.5	0.3	4.8	58.7	4.8	1.2	5.9	0.1
5	29.9	8.0	—	2.8	48.9	5.3	0.8	3.5	—
10	32.5	5.4	—	2.6	46.6	4.6	0.7	5.3	—

[a]Compounds lettered as in Fig. 1.

main components. These two compounds are slowly converted into the isomeric triacetals **9** and **12**, and therefore, the maximum yield of diacetal **5** (58.7%) can be obtained after 3 h, when practically all of the D-mannitol has been consumed (see Table II).

Acetalation of D-*mannitol with 2-methoxypropene (method* c*).* — In the following experiments, 2-methoxypropene in *N,N*-dimethylformamide was used as the reagent in the presence of *p*-toluenesulfonic acid as the catalyst. This method was first applied[10] to D-mannitol in 1974, and was recently developed into a preparative method by Debost, Gelas, and Horton[11], affording diacetal **5** in a yield of 92%.

This reaction differs from methods *a* and *b* in applying only 2.4–2.7 mol.

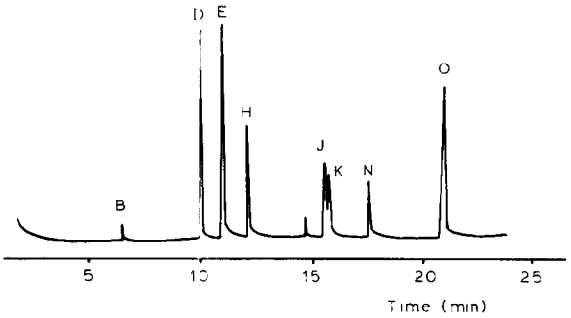


Fig. 4. G.l.c. of the acetylated reaction-mixture obtained from D-mannitol and 2-methoxypropene in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid after 1 h at 0°. (Peaks are lettered as in Fig. 1.)

TABLE III

RELATIVE INTENSITIES (%) OF G L C PEAKS OBTAINED AFTER ACETYLATION OF THE REACTION MIXTURE OF D-MANNITOL WITH 2-METHOXYPROPENE IN *N,N*-DIMETHYLFORMAMIDE IN THE PRESENCE OF *p*-TOLUENESULFONIC ACID

Reaction time	*Peaks*[a]							
	B	**D**	**E**	**H**	**J**	**K**	**N**	**O**
10 min	—	4.2	6.1	1.8	6.0	2.1	1.6	77.5
20	0.1	11.6	17.1	5.5	9.3	3.1	3.2	49.5
30	0.15	13.9	20.6	7.1	9.2	2.9	3.3	41.2
1 h	0.3	17.1	25.5	9.0	8.6	2.6	3.3	31.1
2	0.4	19.8	29.4	10.7	8.7	2.9	3.4	22.2
3	0.5	24.0	35.9	12.3	10.0	2.9	3.7	7.7
5	0.6	23.7	35.7	11.9	10.0	2.8	3.4	9.7

[a]Compounds lettered as in Fig. 1.

equiv. of the reactant. For investigating the course of the reaction, a catalytic amount of *p*-toluenesulfonic acid was added to a mixture of *N,N*-dimethylformamide and 2-methoxypropene in the ratio described in the literature[11], and, from this mixture, aliquots were used, containing the reagent in the molar ratio of 2.8:1, calculated on D-mannitol. The reaction was performed at 0°, and the runs were quenched at different time-intervals by adding pyridine and then acetic anhydride. According to g.l.c. (see Fig. 4), besides several monoacetals (peaks **J, K,** and **N**), three diacetals, the 1,2:5,6 (peak **E**), the 1,2:3,6 (peak **D**), and an isomer of unknown structure (peak **H**), were formed simultaneously in ratios of 2:3:1. The reaction reaches equilibrium after 3 h, and the triacetals are then present only in traces (peak **B**). The optimal yield of diacetal **5** was 36%, far from the 90% claimed in the literature[11] (see Table III).

As the reaction conditions applied differed somewhat from those described in the literature[11] for the preparation of diacetal **5**, the reaction was also repro-

duced under the conditions there given, but the resulting reaction mixture gave (after acetylation, and analysis by g.l.c.) the aforementioned isomers in a distribution resembling that for the analytical reaction run for 2 h. Even in t.l.c. using 1:3 carbon tetrachloride–ethyl acetate, two spots could be detected (R_F 0.55 and 0.60), indicating the presence of at least two isomeric diacetals.

For checking the course of the reaction in the presence of an excess of the reagent, the acetalation was repeated, using D-mannitol and 2-methoxypropene in the molar ratio of 1:15. At 0°, the D-mannitol remained partly undissolved, even after 1 h, but it dissolved in 10 min after warming the reaction mixture to 20°. The reaction was stopped at this stage by adding pyridine, and the mixture was analyzed, after acetylation, by g.l.c. Despite the fact that a very complex mixture of different compounds was present, the proportions of the two isomeric triacetals **9** and **12** could be established (26 and 22%, respectively) and these were in good agreement with the 3:2 ratio for the corresponding isomeric diacetals **5** and **6**, formed in the kinetically controlled reaction.

Determination of the structure of the 1,2:3,6:4,5-triacetal (**12**). —The new triacetal of D-mannitol (peak **B**), which could be separated by column chromatography of the crude mixture obtained *via* method *a*, was investigated by n.m.r. spectroscopy and by its graded hydrolysis. According to ^{13}C-n.m.r. investigations, the new tri-*O*-isopropylidene isomer showed three signals in the region for the acetal carbon atoms, at 109.1, 108.6, and 101.6 p.p.m. As it had been proved by Buchanan *et al.*[14] that the shifts of the corresponding acetal carbon atoms of dioxolane rings always appear in the range of 108.1–112.3 p.p.m., those of dioxane rings between 97.1 and 101.1 p.p.m., and those of dioxepane rings between 100.8 and 102.3 p.p.m., it became obvious that the new triacetal must possess two dioxolane rings and a larger one. As D-mannitol itself has a symmetrical structure, and the two acetal carbon atoms had different shifts, all symmetrical arrangements were ruled out. Accordingly, the triacetal can have only the 1,2:3,6:4,5-tri-*O*-isopropylidene structure **12**, in which one of the dioxolane rings is terminal, and the other is *cis*-fused to the terminal dioxepane ring. The mass spectrum was in agreement with the proposed structure, as the fragment at *m/z* 101, characteristic for the terminal dioxolane ring, appeared with an intensity of 29%. The counterpart fragment, representing the two fused, 7- and 5-membered rings of the "lower" part of the molecule, could not be detected.

It was of interest to study the behavior of triacetal **12** in graded hydrolysis with acid. For this reaction, a solution of hydrochloric acid in ethanol was used[12]. As would be expected, the 3,6-terminal, dioxepane ring was the most susceptible, and consequently, among the isomeric diacetals, the 1,2:4,5-di-*O*-isopropylidene derivative **8** (peak **G**) was formed as the major component, and cleavage of the terminal dioxolane ring, yielding the 3,6:4,5-diacetal **7** (peak **E**), was a less pronounced reaction. Splitting of the nonterminal dioxolane ring is the slowest reaction, and therefore, the 1,2:3,6-diacetal **6** (peak **D**) could only be detected in traces (see Fig. 5). Diacetal **8** is further hydrolyzed, yielding, in almost equal amounts,

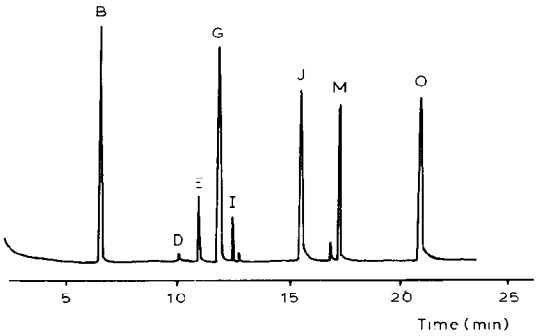


Fig. 5. G.l.c. of the acetylated reaction-mixture obtained from the graded-hydrolysis products of **12** in ethanol containing aqueous hydrochloric acid, after 1 h at 20°. (Peaks are lettered as in Fig. 1.)

TABLE IV

RELATIVE INTENSITIES (%) OF G.L.C. PEAKS OBTAINED AFTER ACETYLATION OF THE GRADED HYDROLYSIS PRODUCTS OF 1,2:3,6:4,5-TRI-*O*-ISOPROPYLIDENE-D-MANNITOL (**12**) IN ETHANOL CONTAINING HYDROCHLORIC ACID, AT 20°

Reaction time (min)	*Peaks*[a]							
	B	**D**	**E**	**G**	**I**	**J**	**M**	**O**
15	55	1	1	19	8	3	4	1
30	42	1	2	23	7	6	9	4
60	12	1	6	20	3	19	17	20

[a]Compounds lettered as in Fig. 1.

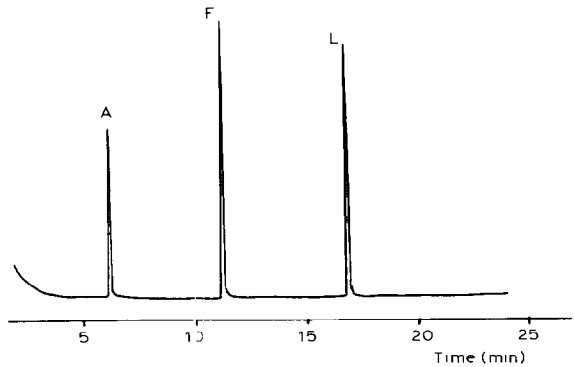


Fig. 6. G.l.c. of the acetylated reaction-mixture obtained from the graded-hydrolysis products of **9** in ethanol containing aqueous hydrochloric acid, after 1 h at 45°. (Peaks are lettered as in Fig. 1.)

the known 1,2-acetal **2** (peak **J**) and the new 4,5-monoacetal **4** (peak **M**), which are further hydrolyzed to **1** (peak **O**).

To compare the rate of the hydrolysis of triacetal **12** (see Table IV) with that of the 1,2:3,4:5.6 isomer **9**, the latter was hydrolyzed under similar conditions (see

TABLE V

RELATIVE INTENSITIES (%) OF G L C. PEAKS OBTAINED AFTER ACETYLATION OF THE GRADED HYDROLYSIS PRODUCTS OF 1,2:3,4:5,6-TRI-*O*-ISOPROPYLIDENE-D-MANNITOL (**9**) IN ETHANOL CONTAINING HYDROCHLORIC ACID, AT 45°

Reaction time (min)	*Peaks*[a]		
	A	**F**	**L**
5	95	5	—
10	71	28	1
15	60	38	2
30	55	39	6
45	26	40	34
60	22	42	36

[a]Compounds lettered as in Fig. 1.

Table V). As the reaction was too slow for study, the temperature was increased to 45°, to give comparable rates. In this case, besides the unchanged starting-material, only two products, namely, the 1,2:3,4-diacetal **10** (peak **F**) and the 3,4-monoacetal **11** (peak **L**), but no D-mannitol, could be detected after 1 h (see Fig. 6). That means that the dioxolane group at C-3,4, being *trans*-disubstituted, is more stable towards hydrolysis than that at C-4,5, which is *cis*-disubstituted.

CONCLUSIONS

From the facts just mentioned, the conclusion may be drawn that acetalation of D-mannitol under relatively mild conditions starts with the formation of the 1,2-acetal **2**, which seems to be the rate-determining step because of the limited solubility of D-mannitol in the various reaction-mixtures. Acetal **2** is converted in a fast reaction into the 1,2:5,6- (**5**) and 1,2:3,6-diacetal (**6**). The latter could also be formed *via* the 3,6-monoacetal **3**, but its presence could not be detected by g.l.c. Diacetals **5** and **6** are finally converted, in a slow reaction, into triacetals **9** and **12**, respectively. The ratios of the different isomers depend on the methods applied, but, for the synthesis of diacetal **5**, the acetone–zinc chloride method (*a*) is recommended, because of its relatively high yield, easy separation of **5**, and cheap reagents.

The other general conclusion that may be drawn from these experiments refers to the relatively easy formation of 1,3-dioxepane rings, a matter that is usually not taken into consideration when acetalation reactions are discussed. Because of the high sensitivity of these rings towards acids, they are probably formed to a lesser degree when acetalations are performed under strongly acidic conditions.

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 *A*, 5:1 benzene–ethyl acetate and (*B*) 1:2 1,2-dichloroethane–ethyl acetate. 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. spectra (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 5830A 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). Mass spectra were recorded with a Hewlett–Packard 5990A gas chromatograph–mass spectrometer, using the same column, at 70 eV electron energy and 3.000 keV multiplier-voltage.

The acetalation of D-*mannitol with acetone in the presence of zinc chloride.* — Anhydrous zinc chloride (5.7 g) was dissolved in dry acetone (35 mL). To each of a series of aliquots (3.6 mL) of this solution was added dried (100°, 24 h) D-mannitol (0.36 g) at 20°, and the stirred reaction-mixture was quenched at 10, 20 and 30 min, and 1, 2, 3, 5, 10, 24, and 168 h, by adding pyridine (5 mL) and, subsequently, acetic anhydride (3 mL). After being kept overnight at room temperature, the mixture was diluted with chloroform, and submitted to g.l.c. analysis. The results obtained are listed in Table I.

The acetalation of D-*mannitol with 2,2-dimethoxypropane in the presence of 1,2-dimethoxyethane and tin(II) chloride.* — In a mixture of 2,2-dimethoxypropane (20 mL) and freshly distilled 1,2-dimethoxyethane (30 mL) was dissolved tin(II) chloride (10 mg). To aliquots (5 mL) of this solution was added D-mannitol (1 g), and the stirred slurry was boiled for 10, 20, and 30 min, and 1, 2, 3, 5, and 10 h. Thereafter, each mixture was cooled, and pyridine (15 mL) and acetic anhydride (10 mL) were added. After being kept overnight at room temperature, the clear solutions were diluted with chloroform, and submitted to g.l.c. analysis. The results obtained are listed in Table II.

No reaction took place in the absence of tin(II) chloride. When ordinary-grade 1,2-dimethoxyethane was used without distillation, the reaction proceeded without the catalyst, but a reaction time of 72 h was needed in order to afford a clear solution, and peaks **A, B, D,** and **E** were present in the proportions of 67, 13, 8, and 7%, respectively.

The acetalation of D-*mannitol with 2-methoxypropene in* N,N-*dimethylformamide in the presence of* p-*toluenesulfonic acid.* — To a stirred and cooled (0°) solution of *p*-toluenesulfonic acid (20 mg) in dry *N,N*-dimethylformamide (40 mL) were added Drierite (0.1 g) and (after 30 min) 2-methoxypropane (1.8 g). Stirring was continued for 15 min at 0°; then, aliquots (4.5 mL) were withdrawn, D-man-

nitol (0.2 g) was added to each, and stirring was continued for 10, 20, and 30 min, and 1, 2, 3, and 5 h at 0°. The reaction was quenched by addition of pyridine (2 mL) and acetic anhydride (1 mL). After being kept overnight at room temperature, each mixture was diluted with chloroform, and submitted to g.l.c. analysis. The results obtained are listed in Table III.

The same reaction was repeated on a preparative scale in the following way. *N,N*-Dimethylformamide (200 mL) was cooled to 0°, and then Drierite (1 g), D-mannitol (9.1 g), 2-methoxypropene (8 mL), and *p*-toluenesulfonic acid (0.1 g) were added. The slurry was stirred at 0° and, at 1-h intervals, three 2-mL portions of 2-methoxypropene were added. A clear solution was not obtained, even after 4 equivalents of 2-methoxypropene had been added; therefore, the reaction was quenched by addition of potassium carbonate (2.5 g). Stirring was continued for 1 h at 0°; thereafter, an aliquot (5 mL) was acetylated with acetic anhydride (1 mL)–pyridine (2 mL), and the product was analyzed by g.l.c. Peaks **D, E, H, J, N,** and **O** were present in proportions of 19.5, 31, 7, 5, 1.2, and 30%, respectively.

When a large excess (15 mol) of 2-methoxypropene was employed and the reaction was quenched after complete dissolution had occurred, g.l.c. analysis revealed a complex mixture in which triacetals **9** and **12** (peaks **A** and **B**) were the preponderant components (26 and 22%, respectively).

Graded hydrolysis of triacetal **12**. — A solution of conc. HCl (0.1 mL) in ethanol (54 mL) was used for the hydrolysis. Triacetal **12** (0.1 g) was dissolved therein, and this solution (5 mL), was kept at 20°. Samples (1 mL) were withdrawn after 15, 30, and 60 min, and each reaction was quenched by adding 1 drop of conc. ammonium hydroxide. Thereafter, pyridine (1 mL) and acetic anhydride (1 mL) were added and, after being kept overnight at room temperature, the samples were submitted to g.l.c. analysis. The results obtained are summarized in Table IV.

Graded hydrolysis of triacetal **9**. — To a solution of triacetal **9** (12 g) in ethanol (540 mL) at 45° was added conc. HCl (0.8 mL). Samples were withdrawn at 5, 10, 15, 30, 45, and 60 min, and, after acetylation, analyzed by g.l.c. The results obtained are listed in Table V.

1,2:5,6-Di- (**5**) *and 1,2:3,6:4,5-tri-*O*-isopropylidene-*D*-mannitol* (**12**). — Anhydrous zinc chloride (570 g) was dissolved, with stirring, in dry acetone (3.5 L). The slightly turbid solution was cooled to 20°, and dry D-mannitol (364 g) was added. Stirring was continued until complete dissolution of the D-mannitol had occurred (20–22 h); then, the reaction mixture was poured into a vigorously stirred (ultra-turax mixer), and extensively cooled, suspension of potassium carbonate (577 g) in water (580 mL). The precipitated salts were filtered off, and washed separately with chloroform (2 L). The acetonic filtrate was made basic with conc. ammonium hydroxide (5 mL), and evaporated, to yield a semisolid residue; this was dissolved in the chloroform solution, and the aqueous layer that separated was discarded. The organic solution was washed with cold water (100 mL), dried*

*According to g.l.c., the following isomers were present: **9** (10%), **12** (6.6%), **6** (1.3%), and **5** (75%).

(sodium sulfate), and evaporated, and the solid residue recrystallized from carbon tetrachloride (300 mL), to give crude diacetal **5** (324 g, 61.8%); m.p. 107–115°, containing (according to g.l.c.) triacetals **9** and **12** as the main impurities (~3%). This material is pure enough for most preparative purposes, but pure **5** may be obtained by a second recrystallization from carbon tetrachloride or dibutyl ether, m.p. 120–122°; lit.[2] m.p. 122°; lit.[3] m.p. 120–121°.

The mother liquor of the crude diacetal **5** was evaporated, and the solid residue was filtered with the aid of light petroleum (300 mL), to yield a second crop of diacetal **5** (20 g, 3.8%) containing, according to g.l.c., ~5% of triacetals **9** and **12**. The filtrate was concentrated to 150 mL, and the concentrate chilled to −50°, whereupon triacetal **9** crystallized out and was filtered off (25.6 g, 4.2%); m.p. 67–69°, R_F 0.35 (*A*). The filtrate was evaporated, and the residue separated by column chromatography using solvent *A* for elution. The fractions containing mainly triacetal **12** (R_F 0.30) were combined, and evaporated, yielding a crude material (20 g) containing isomers **9** and **12** in the ratio of 1:9.

A second column chromatography afforded **12** in 99% purity (7.6 g, 1.25%); m.p. 51–53°, $[\alpha]_D^{20}$ +6.3° (*c* 1, chloroform); ^{13}C-n.m.r. data: δ 109.1, 108.6, 101.6, 75.5, 75.3 (2 C), 68.4, 66.7, 60.5, 28.5, 27.0, 25.9, 25.6, 24.8, and 23.9; ^{1}H-n.m.r. data: δ 4.3–3.3 (m, H-1–6), 1.45 (3 H), 1.38 (6 H), and 1.33 (9 H, *O*-isopropylidene); mass-spectral data: peaks at *m/z* 287 (3% of base peak at *m/z* 59), 229 (5), 171 (5), 169 (3.4), 157 (41), 141 (12), 115 (25), 114 (13), 111 (17), 101 (29), and 85 (17).

*3,6-Di-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*D*-mannitol* (**8** diacetate). — Triacetal **12** (0.5 g) was dissolved in ethanol (25 mL) and M hydrochloric acid was added. The solution was kept for 1.5 h at 20°, and was then made neutral with conc. ammonium hydroxide. The residue obtained on evaporation was purified by column chromatography, using solvent *B* for elution. The fractions having R_F 0.45 were combined and evaporated (unchanged **12** has R_F 0.90; the monoacetals, R_F 0.10). The residue was acetylated with acetic anhydride (0.5 mL) in pyridine (1 mL), to give, after the usual processing, **8** diacetate (0.1 g, 16%), containing, according to g.l.c. ~5% of isomer **7**; ^{13}C-n.m.r. data: δ 170.4, 169.9, 109.4 (2 C), 75.8 (2 C), 75.1, 70.2, 66.4, 62.8, 26.9, 26.5, 25.5 (2 C), 21.0, and 20.7; ^{1}H-n.m.r. data: δ 5.15 (dd, *J* 6 and 2, H-3), 4.4–3.8 (m, H-1,2,4,5,6), 2.12 and 2.10 (acetyl-Me), 1.55 (3 H), and 1.40 (9 H, *O*-isopropylidene); mass-spectral data: peaks at *m/z* 331 (12% of base peak at *m/z* 101), 273 (19), 259 (31), 213 (13), 171 (12.5), 157 (19), 153 (56), 115 (85), 111 (75), and 85 (37).

Identification of the g.l.c. peaks. — Peaks **A, E, F, J, L,** and **O** were identified by peak-matching with authentic samples of acetylated **9, 5, 10, 2, 11,** and **1**, respectively[9,15]. Evidence for the structure of triacetal **12** (peak **B**) is given herein. Its hydrolysis gives diacetals **6, 7,** and **8**, as well as monoacetals **2** and **4**, detected as peaks **D, E, G, J,** and **M**, respectively. On hydrolysis, triacetal **9** (**A**) gives diacetal **10** and monoacetal **11** (peaks **F** and **J**). Diacetal **6** (**D**) is formed, besides the 1,2:5,6 isomer **5** (**E**), as one of the main byproducts in all three acetalation methods; there-

fore, it was regarded as the intermediate of the new triacetal **12**, and its structure was suggested accordingly.

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REFERENCES

1 J. KUSZMANN, *Carbohydr. Res.*, 71 (1979) 123–134.
2 E. BAER, *J. Am. Chem. Soc.*, 67 (1945) 338–339.
3 R. S. TIPSON AND A. COHEN, *Carbohydr. Res.*, 7 (1968) 232–243.
4 G. KOHAN AND G. JUST, *Synthesis*, (1974) 192.
5 E. BAER AND H. O. L. FISCHER, *J. Am. Chem. Soc.*, 61 (1939) 761–765; *J. Biol. Chem.*, 128 (1939) 463–473.
6 A. CARAYON-GENTIL, *Bull. Soc. Chim. Biol.*, 34 (1952) 617–618.
7 G. F. CHITTENDEN, *Carbohydr. Res.*, 84 (1980) 350–352.
8 G. F. CHITTENDEN, *Carbohydr. Res.*, 87 (1980) 219–226.
9 L. VARGHA, *Ber.*, 66 (1933) 1394–1399.
10 M. L. WOLFROM, A. B. DIWADKAR, J. GELAS, AND D. HORTON, *Carbohydr. Res.*, 35 (1974) 87–96.
11 J. L. DEBOST, J. GELAS, AND D. HORTON, *J. Org. Chem.*, 48 (1983) 1381–1382.
12 T. G. BONNER, E. J. BOURNE, R. F. J. COLE, AND D. LEWIS, *Carbohydr. Res.*, 21 (1972) 29–35.
13 J. KUSZMANN, P. SOHÁR, G. HORVÁTH, É. TOMORI, AND M. IDEI, *Carbohydr. Res.*, 79 (1980) 243–253.
14 J. G. BUCHANAN, A. R. EDGAR, D. I. RAWSON, P. SHAHIDI, AND R. H. WIGHTMAN, *Carbohydr. Res.*, 100 (1982) 75–86.
15 L. F. WIGGINS, *J. Chem. Soc.*, (1946) 13–14.