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GAS CHROMATOGRAPHIC AND MASS SPECTROMETRIC ANALYSES OF THE ACID-CATALYSED DEHYDRATION REACTIONS OF D-MANNITOL

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SUMMARY

The reactions of D-mannitol with concentrated hydrochloric acid were studied under different conditions and the structures of the products were determined by means of gas chromatography and mass spectrometry. Complete separations of the reaction mixtures were achieved on a capillary column coated with OV-101. The identities and concentrations of thirteen components were compared with those given in the literature; some compounds were identified in the reaction mixtures for the first time. The dehydration mechanism and the reactions leading to the product distribution (1,4 ⇌ 1,5-anhydro derivative isomerization) are discussed.

INTRODUCTION

Many anhydroalditols, derivatives of tetritols, pentitols and hexitols, have been obtained by acid-catalysed dehydration of alditols under different conditions[1,2]. Tetritols and pentitols are dehydrated exclusively to 1,4-anhydrides. It is interesting, however, that only ribitol gives an almost quantitative yield of 1,4-anhydro-DL-ribitol under mild conditions, L-arabinitol and D-xylitol being resistant to anhydride formation.

When hexitols are subjected to dehydration reactions, the resulting mixtures are much more complicated, products with 1,4-, 2,5- or 1,5-ring systems together with dianhydrohexitols being found, depending on the time of reaction[1,2].

Under more drastic conditions (fuming hydrochloric acid, sealed glass tube, 100°), substitution reactions can occur; xylitol treated with hydrochloric acid gave 1,4-anhydro-5-chloro-5-deoxy-DL-xylitol in a moderate yield[3].

Montgomery and Wiggins[4] studied the reaction of D-mannitol with hydrochloric acid under different conditions and identified anhydro and chlorodeoxy derivatives of D-mannitol. However, the structures of some of the products were not elucidated.

Our previous good results in the separation of alditols and aldononitriles as acetyl derivatives on a capillary column[5] enabled us to study the reaction of hydrochloric acid with D-mannitol by this technique.

EXPERIMENTAL

Reaction 1

D-Mannitol (5 g), crystallized from ethanol–water, was dissolved in 20 ml of concentrated hydrochloric acid (sp.gr. 1.18) and refluxed for 24 h at 100°. A sample of 1 ml of this solution was heated with about 0.2 g of activated charcoal for 5 min at 90° and filtered. The colourless solution was evaporated under vacuum to a syrupy consistency. The evaporation was repeated twice with the addition of 1 ml of ethanol each time. A 0.006-g amount of syrup product was treated with a mixture of 125 μl of dry pyridine and 125 μl of acetic anhydride and heated for 10 min at 100° in a sealed glass tube. The mixture was used directly in gas chromatographic (GC) and mass spectrometric (MS) analyses.

Reaction 2

The above procedure was employed, but with a time of reaction of 78 h.

Reaction 3

Pure D-mannitol (0.2 g) was dissolved in 0.8 ml of concentrated hydrochloric acid and the solution was heated for 78 h at 100° in a sealed glass tube. The product was prepared for analysis as in reaction 1.

The conditions used in these reactions are typical of those for the synthesis of 1,4- and 1,5-anhydro-D-mannitol[6,7].

Gas chromatography and mass spectrometry

The separation of a mixture was carried out with the gas chromatograph attached to an LKB 2091 mass spectrometer, equipped with a 25-m capillary column coated with OV-101 liquid stationary phase. The temperature was programmed from 100° to 200° at 2°/min. The sample volume was 0.2 μl; the splitting ratio was 5:1 and the pre-column inlet splitter temperature was 250°.

The mass spectra were recorded on an LKB 2091 mass spectrometer linked to a PDP-11 mini-computer. The spectrometer was operated at a source temperature of 260°, molecular separator temperature 250°, ionizing voltage 70 V and trap current 100 μA, with scanning from m/e 10 to 680 in 2 sec.

RESULTS AND DISCUSSION

The first two reactions (solutions refluxed at 100° for 24 and 78 h, respectively) gave different compositions of the products.

GC traces (TIC) of samples 1, 2 and 3 are shown in Figs. 1, 2 and 3, respectively. The identities of GC peaks were established for some compounds (mannitol[8] and anhydromannitol[9]) by simple comparison of the mass spectra with those of the standard compounds (Table I). The structures of the other components are discussed below. The mass spectra of peaks A–N are shown in Figs. 4–14.

GC peak B corresponds to the acetyl derivative of 1-chloro- or 2-chloromonodeoxy-D-mannitol. The mass spectrum of this compound (Fig. 5) shows some ions, at m/e 337 ($M-73$), 265 ($M-145$), 235 ($M-73-102$) and 163 (265$-$102), which are not present in the mass spectrum of D-mannitol acetate (Fig. 4). However, these
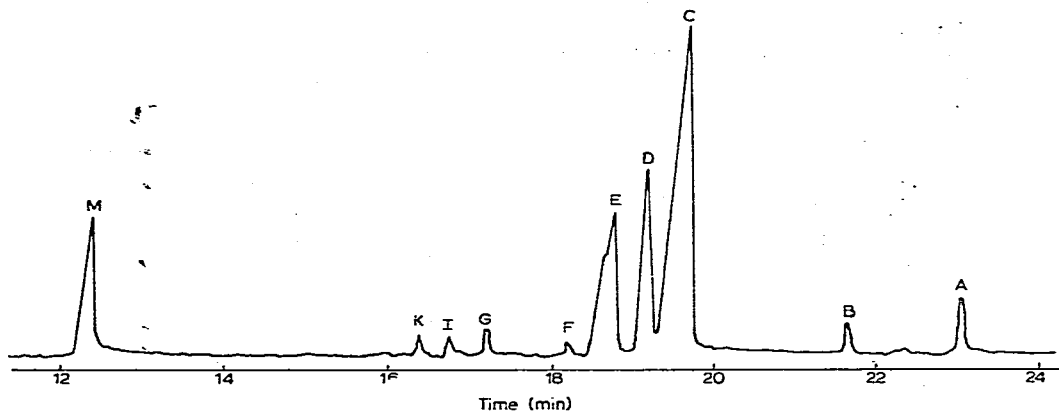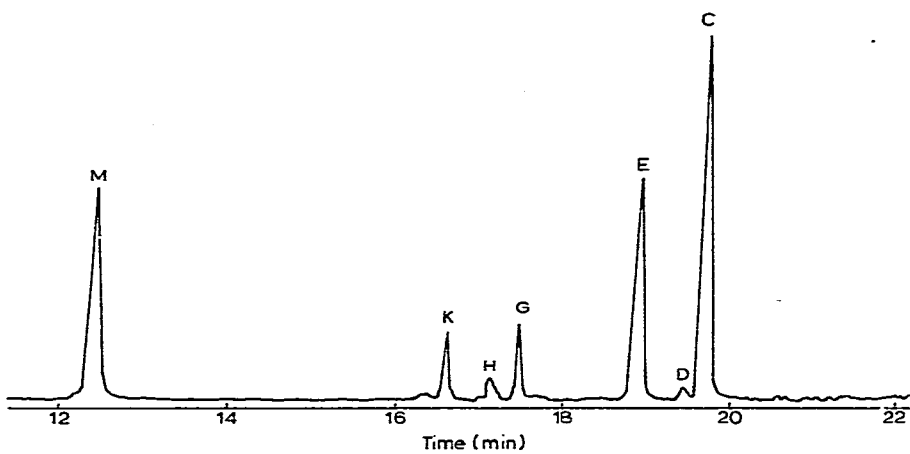
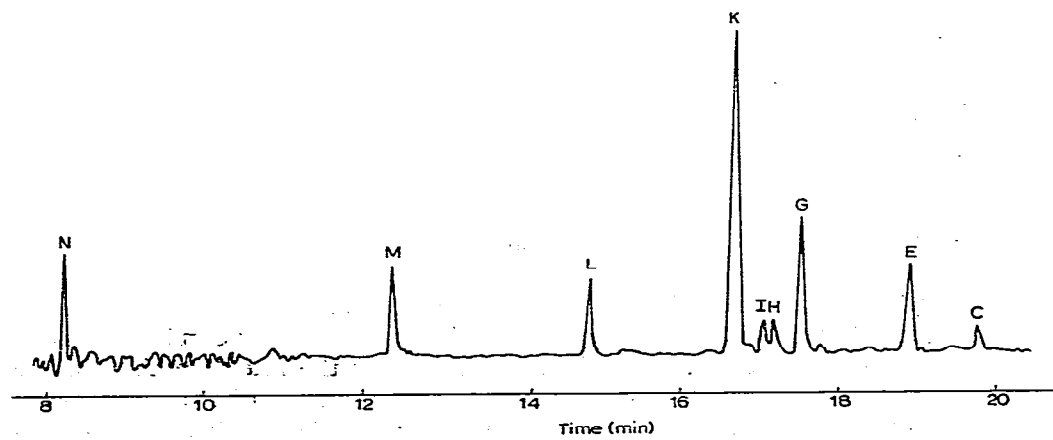Fig. 1. Chromatogram of mixture 1.

Fig. 2. Chromatogram of mixture 2.

Fig. 3. Chromatogram of mixture 3.

TABLE I

COMPOSITIONS OF REACTION MIXTURES 1, 2, AND 3

| GC peak	Acetyl derivative	Yield* in reaction mixtures (%)		
		Mixture 1	Mixture 2	Mixture 3
A	D-Mannitol	3	—	—
B	1- or 2-Chloromonodeoxy-D-mannitol	2	—	—
C	2,5-Anhydro-D-mannitol	46	40	2
D	1,4-Anhydro-D-mannitol	15	1	—
E	1,5-Anhydro-D-mannitol	18	24	7
F	1,5-Anhydro-6-chloro-6-deoxy-D-mannitol	0.5	—	—
G	2,5-Anhydro-1(6)-chloromonodeoxy-D-mannitol	2	5	13
H	Unknown	—	1.5	3
I	Unknown	1	—	2.5
K	1,4-Anhydro-6-chloro-6-deoxy-D-mannitol	1	4	41
L	1,4-Anhydro-6-chloro-2- or -3-chloro-dideoxy-D-mannitol	—	—	12
M	1,4;3,6-Dianhydro-D-mannitol	12	24	8.5
N	1,4;3,6-Dianhydro-2(5)-chloromonodeoxy-D-mannitol	—	—	10

* Calculated from GC peak areas.
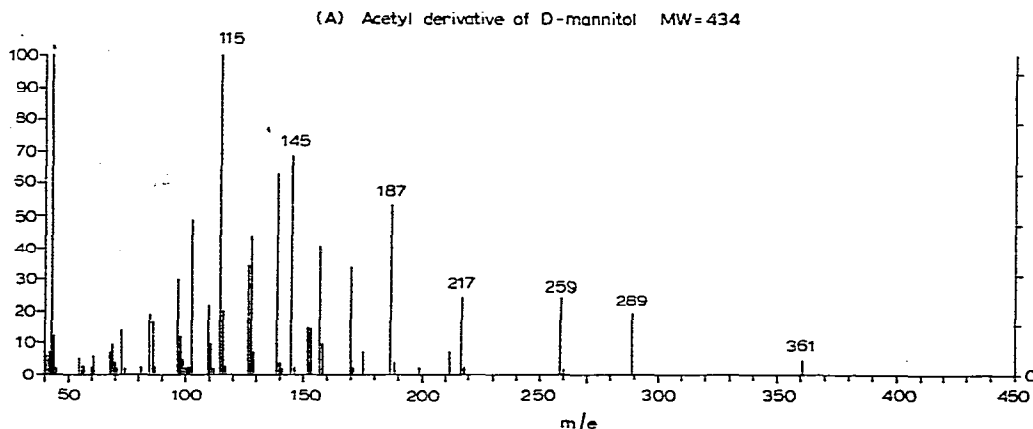
Fig. 4. Mass spectrum of GC peak A.

ions are not sufficient evidence for the assignment of the position of the chlorine atom to carbon atom C_1 or C_2.

GC peak F was identified as 6-chloro-6-deoxy-1,5-anhydro-D-mannitol acetate on the following grounds. The mass spectrum (Fig. 9) of this compound and that of 1,5-anhydro-D-mannitol acetate (Fig. 8) are similar, but the retention time of the former compound is shorter. Hence there is only the possibility of the 6-chloro-1,5-anhydro structure, in which the $-CH_2Cl$ substituent is lost very easily, which makes the two mass spectra similar.
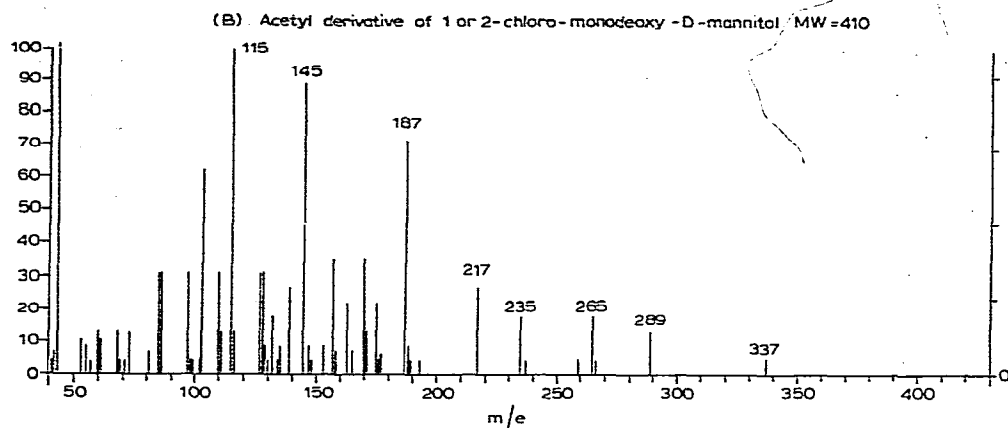
(B) Acetyl derivative of 1 or 2-chloro-monodeoxy-D-mannitol MW=410

Fig. 5. Mass spectrum of GC peak B.

(C) Acetyl derivative of 2,5-anhydro-D-mannitol MW = 332

Fig. 6. Mass spectrum of GC peak C.

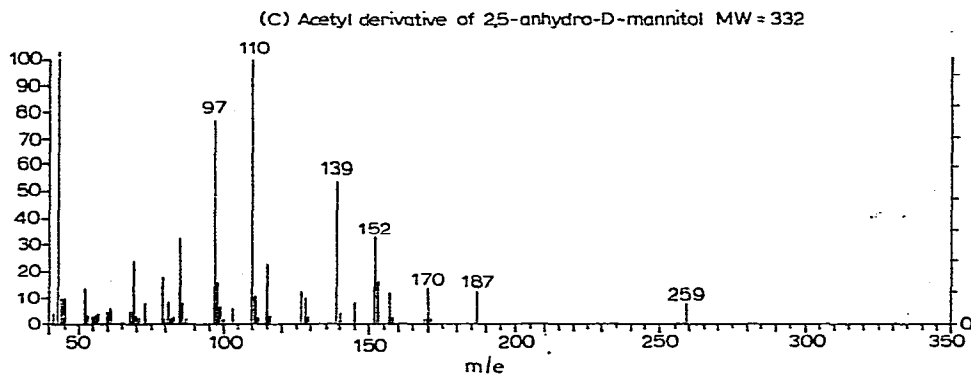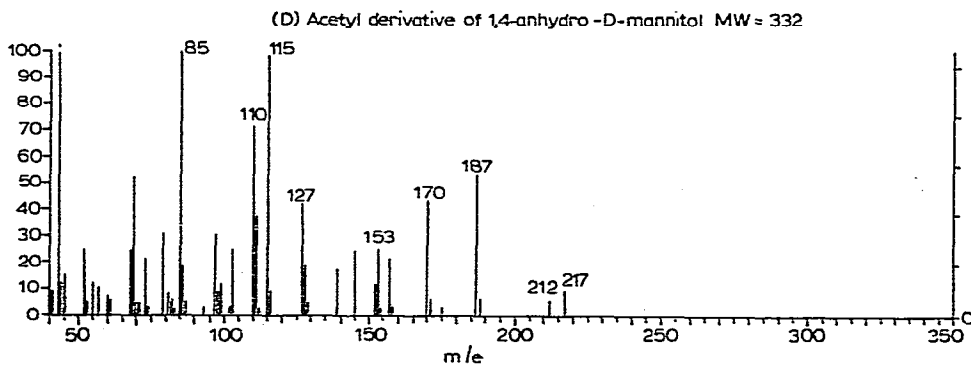(D) Acetyl derivative of 1,4-anhydro-D-mannitol MW = 332

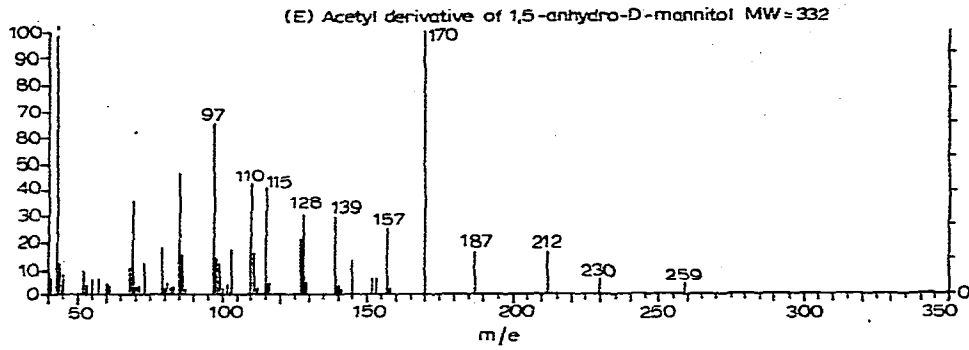Fig. 7. Mass spectrum of GC peak D.
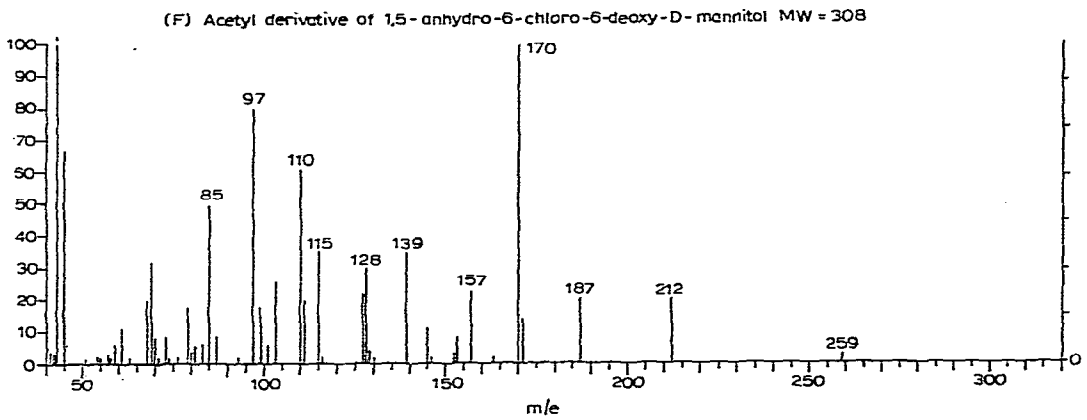
Fig. 8. Mass spectrum of GC peak E.

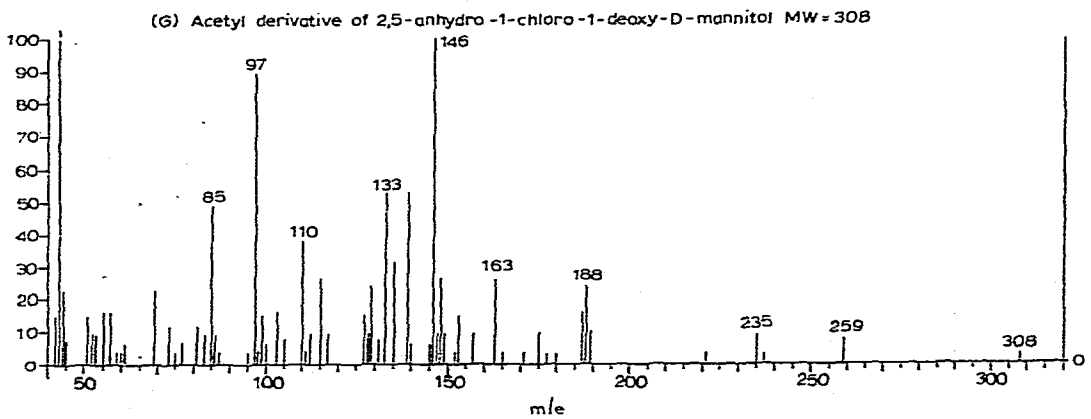Fig. 9. Mass spectrum of GC peak F.
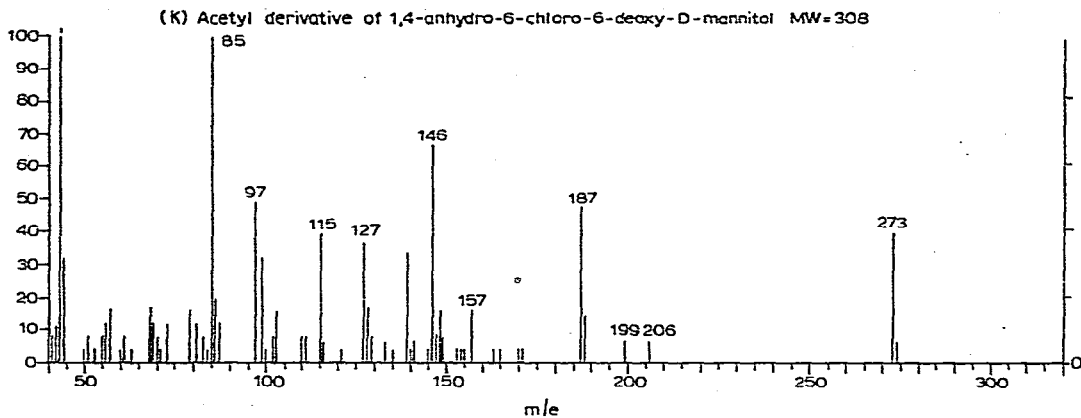

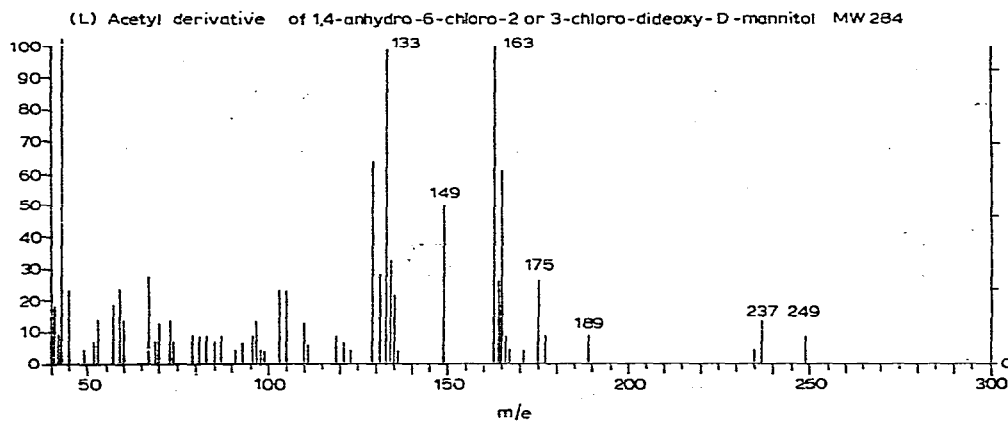Fig. 10. Mass spectrum of GC peak G.

Fig. 11. Mass spectrum of GC peak K.

Fig. 12. Mass spectrum of GC peak L.

Fig. 13. Mass spectrum of GC peak M.

(N) Acetyl derivative of 1,4;3,6 -dianhydro - 2 or 5 chloro -monodeoxy - D- mannitol   MW = 206
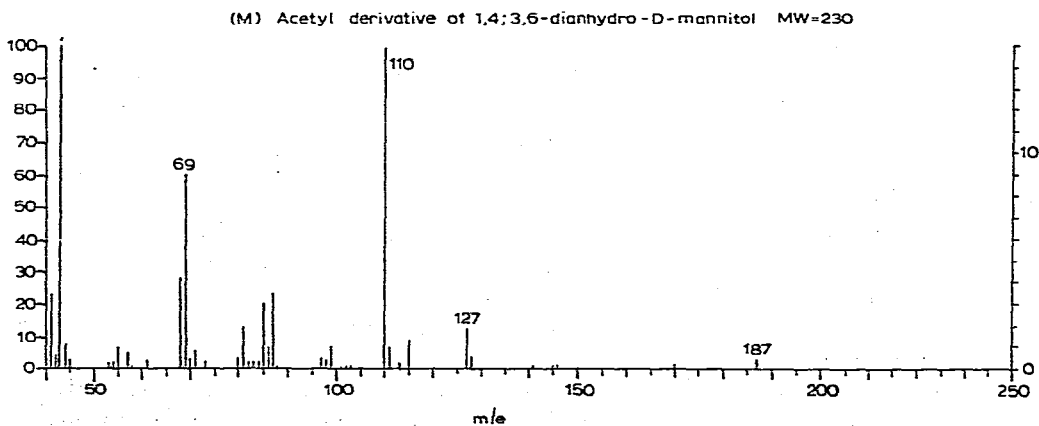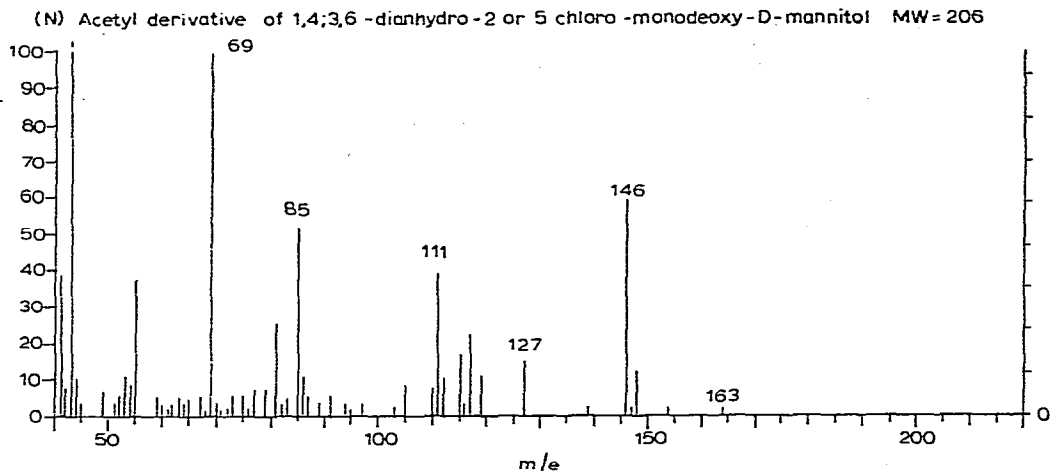

Fig. 14. Mass spectrum of GC peak N.

A product of the substitution of the OH group in the 2,5-anhydro derivative (GC peak G) was also found. Here, the mass spectrum (Fig. 10) is significantly different from that of 2,5-anhydro-D-mannitol acetate (Fig. 6). Evidence that the structure is 1-chloro-1-deoxy-2,5-anhydro-D-mannitol acetate is provided by the ions at m/e 259 (M—CH$_2$Cl) and 235/237 (M—73). This suggests a structure with a 2,5-ring and a –CH$_2$Cl group.

One further chloro compound (GC peak K) is present in the mixture, viz., 6-chloro-1,4-anhydro-D-mannitol acetate (Fig. 11). The useful ions for identifying the structure are those at m/e 273 (M—Cl), 187 (M—CHOAcCH$_2$Cl) and 146/148 (M—2CH$_3$COOH—CH$_2$CO).

The composition of reaction mixture 1 is shown in Table I. The most abundant compounds are 2,5-anhydro-D-mannitol (46%), 1,5-anhydro-D-mannitol (18%), 1,4-anhydro-D-mannitol (15%) and 1,4;3,6-dianhydro-D-mannitol (12%). The concentrations of the chloro derivatives are insignificant.

The product obtained after a longer period of heating (Fig. 2) contains a much higher concentration of dianhydro-D-mannitol acetate. Further, it is of interest to find the complete consumption of D-mannitol, a significant decrease in the 1,4-anhydro-D-mannitol concentration and a slight increase in the concentrations of chloro derivatives (Table I). No compounds other than those in mixture 1 were found.

Drastic conditions (concentrated hydrochloric acid, sealed glass tube) gave mostly chloroanhydro derivatives of D-mannitol (Fig. 3). The evidence for the structures of two new components is discussed below.

GC peak L is 6-chloro-2- or 3-chlorodideoxy-1,4-anhydro-D-mannitol acetate (Fig. 12). Supporting evidence for these structures is the ions at m/e 249 (M—Cl), 235 (M—CH$_2$Cl) and 163/165 (M—CHOAcCH$_2$Cl). The last ion, which is the base peak, corresponds to the structure of the ion of m/e 187 in the mass spectrum of 1,4-anhydro-D-mannitol acetate.

The shortest retention time (GC peak N) was shown to be due to 2(5)-chloro-monodeoxy-1,4;3,6-dianhydro-D-mannitol acetate on the basis of the mass spectrum (Fig. 14), which has a small ion at m/e 163 (M—CH$_3$CO·) and a prominent ion at

m/e 146/148 (M—CH_3COOH). Both fragmentation processes are obvious if it is taken into account that only one acetyl group is present in the molecule.

The major components of mixture 3 are chloroanhydro derivatives (Table I), the anhydro derivatives having almost completely disappeared.

We found that the techniques applied were very successful in studies of reaction mixtures 1, 2 and 3 and the results provide a basis for kinetic studies of the reactions under consideration.

Comparison of the results in Table I permit some conclusions to be drawn. The mechanism of the dehydration reactions of D-mannitol under the conditions used probably involves protonation of the OH group instead of the formation of chloro derivatives[10] because the concentration of chloro compounds is negligible in the mixture 1 and does not increase until the mixtures are heated for a longer period.

The results provide evidence that D-mannitol first undergoes dehydration between C_1 and C_4 but then 1,4-anhydro-D-mannitol is converted into the 1,4;3,6-dianhydro derivative or 1,5-anhydro-D-mannitol. The change in ring size may occur with a ring-opening reaction as an intermediate step[11,12]. The concentration of 2,5-anhydro-D-mannitol is not dependent on the time of reaction, as expected, as the 2,5-ring is more resistent to opening reactions[13].

Montgomery and Wiggins[4] have suggested that the following equilibrium represents the main reaction between D-mannitol and fuming hydrochloric acid

$$HCl + 1,4;3,6\text{-dianhydro-D-mannitol} \rightleftharpoons 1,6\text{-dichloro-1,6-dideoxy-D-mannitol} + H_2O$$
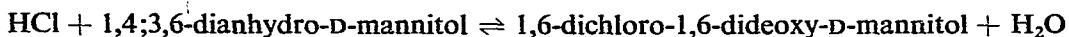
The conditions applied in our experiments (an excess of hydrochloric acid) should favour the formation of the 1,6-dichloro derivative, but the GC results (Table I) did not confirm this. If a dichloro derivative was present in the mixture, its concentration did not exceed 1 %. Also, no trace of 1,6-anhydro-D-mannitol was found in any reaction mixture.

In conclusion, dehydration reactions can be used in the synthesis of an anhydro-D-mannitol only under precisely controlled conditions, because otherwise the reaction mixture becomes very complicated.

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