577. *The Mechanism of the Reaction of Boron Trichloride with Cyclic Acetals of Hexitols.*

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The function of boron trichloride as a reagent for the cleavage of cyclic acetals of hexitols has been studied. It appears that co-ordination of the boron trichloride with an acetal oxygen atom is followed by ring opening to produce an α-chloro-ether group, the presence of which has been proved by reduction to a methoxyl group.

Investigation of the complex between boron trichloride and a tri-*O*-methylenehexitol by analysis and infrared absorption spectra shows that ring opening occurs in the complex with formation of chloroboronate and α-chloro-ether groups.

In a brief report,[1] an account was given of the efficacy of boron trichloride in opening the rings of cyclic acetals of hexitols, in demethylation and deacylation of sugar derivatives, and in degradation of polysaccharides. Invariably, although yields are not quantitative, the major product isolated after treatment of the reaction mixture with aqueous methanol is the unsubstituted polyhydroxy-compound. The attack of the boron trichloride is directed towards oxygen centres in these molecules and more detailed studies have now been made, particularly of the cyclic acetals of hexitols, to discover the nature of the interaction at these sites and of the subsequent heterolysis of the C–O bonds.

Trimethylene derivatives of hexitols, in addition to regenerating mainly the parent hexitol, always give small quantities of the partially degraded derivatives, *e.g.*, 1,3:2,4:5,6-tri-*O*-methylene-D-glucitol gives, in addition to glucitol (61% yield), a detectable amount of 2,4-*O*-methylene-D-glucitol, the surviving ring in which is the most readily formed when glucitol is converted into its methylene derivatives [2] and is the most stable to aqueous acid,[3] to sulphuric acid in acetic anhydride–acetic acid solution (acetolysis),[4] and to acyl trifluoroacetate.[5] This monomethylene derivative alone with boron trichloride is largely converted into glucitol but even under vigorous conditions a residue of unchanged acetal remains. In contrast, the acetal ring in 2,5-*O*-methylene-D-mannitol, which preferentially survives only in the acetolysis of 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol,[6] is completely destroyed by boron trichloride, the monomethylenemannitol being converted in 94% yield into mannitol without a detectable quantity of the acetal remaining. The lability of this ring is also evident in acid-hydrolysis [7] (which preferentially opens the 2,5-ring in the trimethylenemannitol) and is confirmed by treatment of the trimethylene compound with one mol. of boron trichloride instead of the excess normally used; none of the products obtained except a trace of unchanged acetal, contained the 2,5-ring. The explanation that the survival of this ring in acetolysis is due to a preference of the reagent for attack at a methylene group engaged at a primary rather than a secondary carbon atom suggests that the orientation and steric factors which determine this preference are not operative in the case of boron trichloride. Since both boron trichloride and the acetolysis reagent are essentially electrophilic, it is unlikely that polar factors underlie the difference in the mode of attack of the two reagents. Other cyclic acetals of D-mannitol which gave high yields (55—85%) of mannitol with excess of boron trichloride were the tri-*O*-ethylidene, -benzylidene, -isopropylidene, and -cyclohexylidene derivatives. Bis-*O*-(trifluoroisopropylidene)-D-mannitol yielded only a trace of mannitol under the usual

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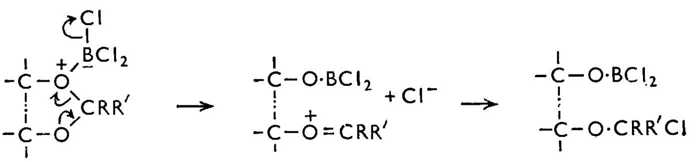
[1] Allen, Bonner, Bourne, and Saville, *Chem. and Ind.*, 1958, 630.
[2] Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 1909.
[3] Bourne and Wiggins, *J.*, 1944, 517.
[4] Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 665.
[5] Bourne, Burdon, and Tatlow, *J.*, 1958, 1274; 1959, 1864.
[6] Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 2215.
[7] Fletcher and Diehl, *J. Amer. Chem. Soc.*, 1952, **74**, 3797.

conditions, but when the reaction was prolonged at higher temperatures more extensive ring opening occurred; the inductive effect of the trifluoromethyl groups in this acetal creates an exceptional resistance to attack by acidic and electrophilic reagents.[8] Other compounds which yield the unsubstituted polyhydric alcohol as the chief product are di-*O*-methylene- and mono- and di-*O*-benzylidene-pentaerythritol and the methyl ethers and carboxylic esters of D-glucitol and D-mannitol. The only exception so far discovered is the 1,6-ditoluene-*p*-sulphonate of 2,4-*O*-methylene-D-glucitol which gave only a very small yield of the hexitol. Under all conditions employed it was established that the parent polyols were not affected and could be recovered unchanged.

The Mechanism of Attack of Boron Trichloride at Oxygen Centres.—In extensive studies of the interaction of excess of boron trichloride with oxygen-containing organic compounds, Gerrard and his co-workers [9] have proposed mechanisms for the fission of C–O–C bonds in aliphatic and cyclic ethers, *i.e.*, in compounds closely resembling the cyclic acetals of polyols. In most ether fissions studied it appeared that the alkyl group with the greater electron-releasing properties is found in the alkyl halide produced, suggesting initial formation of a carbonium ion by alkyl–oxygen fission.

In a complex formed between boron trichloride and a cyclic acetal, the –O–C–O– group provides an effective system for stabilisation of the central carbon when the bond with either oxygen atom undergoes heterolysis to give a carbonium ion. The dichloroboronite group contains the still strongly electrophilic boron atom which can co-ordinate with an oxygen centre of an adjacent acetal ring. This undoubtedly occurs when a 1 : 1 molar ratio of boron trichloride to a triacetal compound is used, with formation of the stable cyclic chloroboronate grouping; the absence of any chlorodeoxy-derivative of a polyol in the products of the reaction of its cyclic acetal with boron trichloride also suggests that this intermediate is formed. The α-chloro-ether group –O·CRR′Cl formed in reaction (1) could, by analogy with the known reactions of α-chloro-ethers, give with excess of boron trichloride either a chlorodeoxypolyol or a dichloroboronite, the latter being accompanied by the product $RR'CCl_2$. With methylene acetals this dichloro-derivative would be dichloromethane, already employed as the solvent; benzylidene derivatives, however, were found to give a product with the properties of benzylidene chloride, indicating formation of a dichloroboronite from an α-chloro-ether substituent.



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Detection of an α-Chloro-ether Group by Replacement of Chlorine.—Since an α-chloromethyl ether group, if formed in the reaction of boron trichloride with a cyclic methylenedioxy-compound, would be subsequently hydrolysed during the treatment with aqueous methanol, the conversion of this group into a less labile derivative by nucleophilic replacement of the chlorine was investigated, *i.e.*, $-O\cdot CH_2Cl \longrightarrow -O\cdot CH_2X$. Two suitable reagents of this type are the acetate ion [10] and the methoxide ion.[11] In both cases, chlorine attached to boron would also be replaced, but the mild hydrolysis of the complex with aqueous methanol should remove the boron and its attached groups leaving the free hydroxyl groups. In the experimental investigation, anhydrous sodium acetate in suspension in chloroform was added to the products obtained by treating tri-*O*-methylene-D-mannitol and -D-glucitol with excess of boron trichloride after removing the excess of

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[8] Stacey, Bourne, Huggard, and Tatlow, Papers read at the 14th Meeting Internat. Union Pure Appl. Chem., 1955, p. 555.

[9] See Gerrard and Lappert, *Chem. Rev.*, 1958, **58**, 1081.

[10] Wedekind, *Ber.*, 1903, **36**, 1383; Clark, Cox, and Mack, *J. Amer. Chem. Soc.*, 1917, **39**, 712.

[11] Strauss and Weber, *Annalen*, 1932, **498**, 127.

the latter under reduced pressure. After treatment with aqueous methanol, the residue was extracted first with chloroform which removes highly substituted hexitols, and then with pyridine which is a solvent both for these derivatives and for hexitols. Examination by paper chromatography showed that both extracts contained a mixture of fast-moving products (*i.e.*, highly substituted hexitols) while the pyridine solution contained in addition unsubstituted hexitol. Trisacetoxymethylhexitol, in which the three rings have been opened, and bisacetoxymethylmethylene- and monoacetoxymethyldimethylene-hexitols in which only partial ring opening has occurred, would provide fast-moving products while the slower-moving derivatives and the hexitol itself could result either from partial hydrolysis of the acetoxymethyl groups or from incomplete replacement of the chlorine. A similar result was obtained by treating the same trimethylenehexitol–boron trichloride reaction products with sodium methoxide in methanol. After removal of the sodium chloride formed and adjustment to pH 8, evaporation left a residue in which paper chromatography showed the presence of fast-moving substances. Slower-moving, less highly substituted derivatives together with the parent hexitol also indicated partial hydrolysis or incomplete formation of the expected unsymmetrical acetal. The reaction mixtures in both cases were too complex for separation of the acetoxymethyl or unsymmetrical acetal derivatives to be attempted. Attention was, therefore, directed to the possibility of replacing the chlorine by hydrogen, giving a methoxyl group in place of the α-chloro-ether. As the methyl ethers of the hexitols are known to be stable and to resist hydrolysis, it was assumed that their isolation and characterisation would present less difficulty.

The reducing agent used was lithium aluminium hydride, to which ether and acetal groups appear to be stable. It was expected that chloroboronates would give the same products as were obtained with sodium borohydride,[12] with the probability that the subsequent hydrolysis removes any borate ester groups, leaving only a methyl ether group in place of each α-chloro-ether group initially present. Initial investigations of the reaction in tetrahydrofuran of lithium aluminium hydride with the boron trichloride–methylenedioxy-complexes were evaluated by paper chromatography. Tri-*O*-methylene-D-mannitol yielded a mixture and it was significant that no hexitol was detected; the omission of the reduction step as indicated above leads to a substantial yield (53%) of the hexitol. More conclusive evidence was obtained with 2,4-*O*-methylene-D-glucitol, the products from which were separated on a Celite column. One fraction contained the unchanged acetal in relatively small amount together with a larger quantity of a product of closely similar constitution which was converted by boron trichloride into D-glucitol in high yield and had a methoxyl content of 11·8% (calc. 15·8% for monomethylglucitol). By the above sequence of reactions, 2,4-*O*-methylene-D-glucitol could afford the 2- and the 4-methyl ether or both—a model indicates that the two ring-oxygen atoms are equally accessible to attack by boron trichloride. In fact chromatography indicated formation of two similar methyl ethers. To overcome this difficulty, 2,5-*O*-methylene-D-mannitol was used for subsequent investigations. The reduction products from this acetal would be either 2-*O*- or 5-*O*-methylmannitol, which are identical. Also, as the acetal is quantitatively converted into mannitol on reaction with excess of boron trichloride and aqueous methanol, the reduction products should contain no unchanged acetal.

Reaction of Lithium Aluminium Hydride with the 2,5-O-*Methylene*-D-*mannitol–Boron Trichloride Complex.*—Treatment of 2,5-*O*-methylenemannitol with excess of boron trichloride followed by lithium aluminium hydride gave two fractions separable on a carbon–Celite column. One fraction yielded mannitol only (1·1% yield) and the other an oil (*E*; yield, 59% calc. as $C_7H_{16}O_6$). Examination of the oil by paper chromatography indicated a single product and a chromotropic acid determination of its acetal content showed a negligible amount (0·1%). The R_m value of the substance *E* was less than that of the monomethylenemannitol but on ionophoresis in a borate buffer it migrated further; both observations suggest the formation of a more stable borate complex than that formed

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[12] Brown and Tierney, *J. Amer. Chem. Soc.*, 1958, **80**, 1552.

by the monomethylene derivative. Treatment with boron trichloride and aqueous methanol yielded only mannitol, confirming that the compound is a mannitol derivative. The position of the single substituent was investigated by periodate oxidation. One mol. (calc. on $C_7H_{16}O_6$) consumed 3 mol. of periodate with the production of 1·02 mol. of formaldehyde and 1·90 mol. of formic acid. The only monomethylhexitol which can give a result of this type is the 2-methyl derivative:

$$HO{\cdot}CH_2{\cdot}CH(OMe){\cdot}[CH(OH)]_3{\cdot}CH_2{\cdot}OH \xrightarrow{3NaIO_4} HO{\cdot}CH_2{\cdot}CH(OMe){\cdot}CHO + CH_2O + 2H{\cdot}CO_2H \quad . \quad (2)$$

Analysis of the substance *E* for carbon and hydrogen agrees with that of a monomethyl ether, but the Zeisel analysis for methoxyl, while indicating a monomethyl ether, gave varying values for the methoxyl content all of which were higher than that calculated for a monomethyl ether. However, the completely acetylated derivative gave carbon, hydrogen, and methoxyl values in accord with those for the penta-acetate of a monomethylhexitol.

While other monomethyl ethers of mannitol are known, the 2-methyl ether has not previously been synthesised. 2-*O*-Methyl-D-mannose, however, had been reported [13] although the evidence for the position of the substituent was known not to be conclusive. This compound was prepared from a sample of methylated D-mannose dibenzyl mercaptal (kindly supplied by Professor Pacsu [13]) by first treating it with mercuric chloride to remove the mercaptal group; the product obtained contained mannose and a faster-moving derivative, and the latter gave an indication of being a 2-methylmannose by its failure to react with triphenyltetrazolium chloride which does not give a positive reaction when there is a substituent adjacent to the reducing group, *i.e.*, at the 2-position in this case.[14] Both products were reduced to the hexitol by potassium borohydride,[15] and paper chromatography then showed that no reducing sugars remained. The monomethylmannitol was separated on a carbon–Celite column and the migration of this compound and of the substance *E* were compared in several solvents. In all cases, including ionophoresis in borate and molybdate buffers, the rates of movement were the same. The penta-acetates were identical (m. p., mixed m. p. and infrared spectra at 5000—666 $cm.^{-1}$). A peak for the pentacetate at 2836 $cm.^{-1}$ was attributed to the carbon–hydrogen stretching frequency of the methoxyl group (anisole and methyl 2-naphthyl ether had peaks at 2837 $cm.^{-1}$). Other workers have shown the spectra of methyl ethers to contain characteristic shoulders on the side of carbon–hydrogen absorption bands in the range 2815—2832 $cm.^{-1}$ which have been correlated with vibration of the methoxyl group: [16] substance *E* gave an absorption peak at 2847 $cm.^{-1}$, *i.e.*, sufficiently close to be acceptable evidence for the presence of the methoxyl group. The failure of the Zeisel method to provide a satisfactory analysis of 2-*O*-methylmannitol while giving a satisfactory result for its penta-acetate is apparently a feature of the hexitol structure, since mannitol and glucitol give apparent methoxyl contents of 11·8% and 12·7% respectively owing to the production of volatile ethyl and vinyl iodide.[17]

Addition Complex of Boron Trichloride and a Cyclic Methylenedioxy-derivative.—The problem remained of whether the cyclic acetal ring is opened by the boron trichloride before, or as a result of, attack of a nucleophilic reagent. A similar uncertainty arises in the reaction of certain non-cyclic acetals and ketals [18] and ethers [19] with a mixture of aluminium chloride and lithium aluminium hydride; reduction occurs readily with the mixed reagent but the compounds are unreactive to lithium aluminium hydride alone. The operative mechanism for the boron trichloride reaction became evident in a study of

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[13] Pacsu and Trister, *J. Amer. Chem. Soc.*, 1941, **63**, 925.

[14] Bell and Dedonder, *J.*, 1954, 2866.

[15] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.

[16] Henbest, Meakins, Nicholls, and Wagland, *J.*, 1957, 1462; Barker, Bourne, Pinkard, and Whiffen, *J.*, 1959, 807.

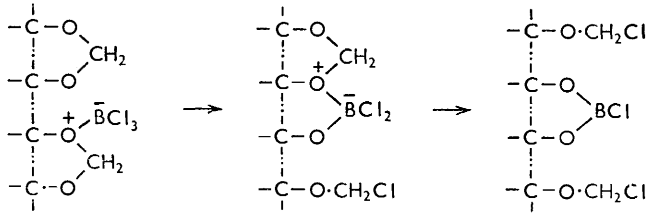
[17] von Rudloff, *Analyt. Chim. Acta*, 1957, **16**, 294.

[18] Eliel and Rerick, *J. Org. Chem.*, 1958, **23**, 1088.

[19] Brown and Somerfield, *Proc. Chem. Soc.*, 1958, 7.

the complex formed between this reagent and 1,3:2,5:4,6-*O*-trimethylene-D-mannitol. Attempts to analyse quantitatively the complex formed by treatment of weighed amounts of the acetal with excess of boron trichloride and evaporation to constant weight under reduced pressure were not wholly successful.

The suspected ring fission during interaction of the boron trichloride and cyclic acetal was confirmed by a comparison of the infrared spectra of the complex with the 1 : 1 addition compound formed by 1,4-dioxan and boron trichloride. This is a very stable compound which regenerates 1,4-dioxan readily on treatment with pyridine or hydroxylic solvents. Decomposition products of dioxan are only obtained on heating. The spectra of dioxan itself and its compound with boron trichloride were recorded and strong absorptions at 789 and 761 cm.$^{-1}$ were found only in the addition compound; these were correlated with the stretching vibration of the boron–chlorine bonds. In boron trichloride alone, the asymmetric stretching vibrations of these bonds give rise to absorption peaks at 995 (due to ^{10}B–Cl) and at 954 cm.$^{-1}$ (due to ^{11}B–Cl).[20] The lower frequency in its compound with dioxan is attributed to the increase in electron density on the boron atom; this decreases the electron-accepting power of the boron, back-co-ordination of the chlorine atoms is therefore less than in pure boron trichloride, and the consequent reduction in the double-bond character of the boron–chlorine bonds in the addition compound leads to absorption at a lower frequency. If ring opening occurs in the boron trichloride–trimethylenemannitol complex, the products would be dichloroboronites or chloroboronates. The spectra of compounds of this type have been reported;[21] absorptions of methyl dichloroboronite at 997 and 960 cm.$^{-1}$ were correlated with the asymmetric boron–chlorine vibration while in methyl chloroboronate strong absorption at 630 cm.$^{-1}$ was assigned to the boron–chlorine vibration. The spectra of the trimethylenemannitol complex showed strong absorption at 663 cm.$^{-1}$ also attributed to boron–chlorine vibration. This frequency is much lower than in the dioxan–boron trichloride compound and if attributed to the same cause would imply that the trimethylenemannitol complex is even more stable than that of dioxan. This is very unlikely and it is more probable that ring opening has occurred with the formation of a chloroboronate group giving an absorption (663 cm.$^{-1}$) close to that of methyl chloroboronate. The evidence is therefore that the following sequence of reactions (3) occurs with boron trichloride–cyclic methylenedioxy-complexes:



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Water converts the complex into the polyhydroxy-derivative, while treatment with lithium aluminium hydride followed by hydrolysis produces a methoxyl group in place of an α-chloro-ether group and hydroxyl groups at all other positions.

EXPERIMENTAL

Materials.—Boron trichloride, b. p. 12·5°/760 mm., was obtained in sealed bottles (B.D.H.). These were cooled in acetone–solid carbon dioxide (*ca.* −80°), the contents were transferred to a distillation flask cooled to −80°, and the boron trichloride was distilled by allowing it to warm to room temperature.[22] Small portions of the distillate also at −80° were rapidly transferred to weighed, stoppered test-tubes, each of which had been drawn out to provide a

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[20] Lindeman and Wilson, *J. Chem. Phys.*, 1956, **24**, 242.

[21] Lehmann, Onak, and Shapiro, *J. Chem. Phys.*, 1959, **30**, 1219.

[22] Dr. W. Gerrard, personal communication.

constriction near the mouth, and cooled to −80°. The tubes were sealed off at the constriction and reweighed.

Dichloromethane was washed with 5% sodium carbonate solution and then water, dried ($CaCl_2$), and stored in the dark over calcium chloride.

Paper Chromatography.—Whatman No. 1 paper was used with the following solvents: (*a*) butan-1-ol saturated with water at 0°; (*b*) acetone–water (4 : 1 v/v); (*c*) butan-1-ol–pyridine–water–saturated aqueous boric acid (6 : 4 : 2 : 1 v/v). The usual spray reagents were employed.[23–26] The positions of the compounds are recorded either as R_F values related to the distance of the solvent front from the base line or as R_X values related to the distance travelled by a standard substance X. Paper ionophoresis was carried out on Whatman No. 3 paper with a borate buffer (pH 9·8).[27]

Reactions of Polyol Derivatives with Boron Trichloride.—1,3:2,4:5,6-Tri-*O*-methylene-D-glucitol (0·81 g.) in dichloromethane (40 ml.) was added during 30 min. to boron trichloride (3·0 g., 6·9 mol.) in dichloromethane (30 ml.) at −80°. After attaining room temperature the flask was connected through a trap at −80° to a water-pump to remove the solvent and excess of boron trichloride. The temperature was finally raised to 40° and a brown glass (1·69 g.) was obtained. Methanol (containing *ca.* 0·05% of water) was added and the solution evaporated; this treatment with methanol was continued until no detectable amount of boron remained (indicated by the absence of a red colour on turmeric paper in warm acid solution). Examination of the residual oil (1·10 g.) by paper chromatography with solvent (*b*) showed the presence of a hexitol, R_{glucitol} (R_g) 1·00, a second product, R_g 1·45 (2,4-*O*-methylene-D-glucitol, R_g 1·36), and a third, R_g 1·90. The oil was refluxed for 30 min. with sodium acetate (6·4 g.) and acetic anhydride (20 ml.), and the product shown to be glucitol hexa-acetate (0·76 g.), m. p. 94—97°, mixed m. p. 95—96°. Chloroform-extraction of the filtrate gave a less pure specimen of glucitol hexa-acetate (0·35 g.), m. p. 92—93°; the total yield corresponded to 61% based on the trimethyleneglucitol. The mother-liquor from the crystallisation of the second crop of hexa-acetate was deacetylated with one drop of 0·2N-sodium methoxide in methanol–chloroform; examination by paper chromatography in solvent (*b*) showed the presence of glucitol, R_g 1·00, and a second compound, R_g 1·27 (2,4-*O*-methylene-D-glucitol, R_g 1·25).

1,3:2,5:4,6-Tri-*O*-methylene-D-mannitol, when similarly treated, gave mannitol (53%) and a second product, R_{mannitol} (R_m) 1·43 (2,5-*O*-methylene-D-mannitol, R_m 1·28; 1,3-*O*-methylene-D-mannitol, R_m 1·40).

1,3:2,5:4,6-Tri-*O*-ethylidene-D-mannitol and its isopropylidene, benzylidene, and cyclohexylidene analogues were converted into mannitol in yields of 67%, 84%, 85%, and 55% respectively. Small amounts of substituted mannitol were also detected.

2,4-*O*-Methylene-D-glucitol gave mainly glucitol (61%). 2,5-*O*-Methylene-D-mannitol gave a 94% yield of mannitol. 1,5,6-Tri-*O*-benzoyl-2,4-*O*-methylene-D-glucitol and mannitol hexa-acetate both gave the parent polyol in substantial yield. Di-*O*-methylenepentaerythritol gave a 76% yield of pentaerythritol and a small amount of a second product; both di-*O*-benzylidene- and mono-*O*-benzylidene-pentaerythritol were converted in 91% yield into pentaerythritol. The pentaerythritol (m. p. and mixed m. p. 258—260°) in each case was left as a residue after chloroform-extraction of the product obtained from the methanol-treatment. The chloroform extract in the case of the benzylidenepentaerythritols contained an oil which on treatment with aqueous sodium hydrogen carbonate yielded benzaldehyde, identified as its 2,4-dinitrophenylhydrazone.

1,2:5,6-Bis-*O*-(trifluoroisopropylidene)-D-mannitol gave only a small amount of mannitol on treatment with boron trichloride, but ring scission appeared to occur to a greater extent when the ketal was kept in contact with the reagent in a sealed tube for 6 days at room temperature. 2,4-*O*-Methylene-1,6-di-*O*-toluene-*p*-sulphonyl-D-glucitol was also resistant to the reagent and only a small yield of the hexitol was obtained. D-Glucitol and D-mannitol were not affected by the reagent and after treatment could be recovered as hexa-acetate in 80—90% yield.

Reaction of 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol (0·48 g.) with boron trichloride (0·26 g.,

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[23] Trevelyan, Procter, and Harrison, *Nature*, 1950, **166**, 444.
[24] Wolfrom and Miller, *Analyt. Chem.*, 1956, **28**, 1037.
[25] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[26] Wallenfels, *Naturwiss.*, 1950, **37**, 491; *Chem. Abs.*, 1951, **45**, 4604.
[27] Foster, *Adv. Carbohydrate Chem.*, 1957, **12**, 81.

1 mol.) gave a product which was separated on a Celite column into D-mannitol (0·1 g.), 1,3:4,6-di-*O*-methylene-D-mannitol (0·05 g.), m. p. and mixed m. p. 200—209° (Found: C, 46·2; H, 6·9. Calc. for $C_8H_{14}O_6$: C, 46·6; H, 6·9%), and an oil (0·09 g.); paper chromatography with solvent (*a*) showed that the last product had R_m 2·66 (1,3-*O*-methylene-D-mannitol, R_m 2·66); with acetic anhydride (0·5 ml.) in pyridine (2 ml.) it gave 2,4,5,6-tetra-*O*-acetyl-1,3-*O*-methylene-D-mannitol (0·04 g.), m. p. 138—140° (lit.,[28] 143—144°) (Found: C, 49·8; H, 6·4. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1%). This derivative was deacetylated with 0·2M-sodium methoxide in methanol, and the periodate uptake of the monomethylenemannitol was determined [29] by addition of standard sodium metaperiodate solution and measurement of the optical density of the solution at 223 mμ: the decrease in periodate concentration corresponded to reaction of 2·03 mol. of periodate (theor. for 1,3-*O*-methylene-D-mannitol 2·00, and for 2,5-*O*-methylene-D-mannitol 1·00).

Successive Treatment of 2,5-O-*Methylene*-D-*mannitol with Boron Trichloride and Lithium Aluminium Hydride.*—The acetal (2·91 g.) was treated with boron trichloride (32 g., 18 mol.) to give, after evaporation, a glass (6·25 g.), whose solution in tetrahydrofuran (100 ml.; dried and distilled over sodium) was added slowly to lithium aluminium hydride (6 g., 15·5 mol.) in ether (200 ml.; dried over sodium). The mixture was refluxed for 1 hr., then cooled in ice, water (150 ml.) was added, and the pH adjusted to 4 by addition of hydrochloric acid. The organic solvents were removed under reduced pressure and the aqueous residue was concentrated. The product was centrifuged and the supernatant liquid was passed down a Biodeminrolit ion-exchange column. The eluate, after freeze-drying, was repeatedly refluxed with methanol, acidified with hydrochloric acid, and evaporated to dryness to remove residual boric acid. The neutral residue was finally extracted with pyridine, and the solution concentrated to give a dark oil (1·98 g.). Paper chromatography with solvent (*c*) showed the presence of mannitol, R_m 1·0, and a second product, R_m 1·4 (2,5-*O*-methylene-D-mannitol, R_m 2·0). The oil was dissolved in a small amount of water and run on to a column prepared from equal amounts of charcoal and Celite. Elution was with water containing ethanol, so that the ethanol content increased continuously from 0 to 10%, and fractions of 25 ml. were collected. Examination by paper chromatography with solvent (*a*) showed that fractions 55—100 contained a product (*E*), R_m 2·6. These fractions were concentrated and the solution was passed through an asbestos filter (Ford's Sterimat) to remove any fine particles of Celite. Evaporation to dryness gave colourless, oily 2-*monomethylmannitol* (1·70 g.) (Found: C, 43·4; H, 8·2; OMe, 26·5. $C_7H_{16}O_6$ requires C, 42·9; H, 8·2; OMe, 15·8%). Examination by paper chromatography with solvent (*a*) and ionophoresis in borate buffer established that the substance *E* was not unchanged 2,5-*O*-dimethylene-D-mannitol, while similar examination of the product of its reaction with boron trichloride indicated this to be mannitol only (m. p. and mixed m. p. 168—168·5°). Confirmation that the substance *E* was not a methylene derivative was obtained by attempted acid-hydrolysis to give formaldehyde; determination of the latter with chromotropic acid indicated less than 0·1% of a formal present.

Periodate oxidation of the substance *E* determined by ultraviolet measurement at 223 mμ of the fall in periodate concentration showed that for one sample (6·84 mg.), 2·94 mol. of periodate were consumed, of 4 mol. initially present, and for a second sample (3·34 mg.), 3·06 mol. from 8 mol. initially present. The products of the periodate oxidation, formaldehyde and formic acid, were also determined. For the former, erythritol which gives 2 mols. of formaldehyde per mol. consumed was used as the standard [30] for the preparation of a calibration curve for the chromotropic acid method of determination of formaldehyde.[31] Two samples of the substance *E* (each *ca.* 3 mg.) gave values of 1·07 and 0·96 mol. of formaldehyde. The formic acid simultaneously produced was determined (1·81—1·90 mol.).

Substance *E* (0·103 g.) was refluxed for 1 hr. with acetic anhydride (2·0 ml.) and sodium acetate (0·1 g.); pouring the mixture into water gave an oil (0·22 g.) which was isolated by chloroform-extraction. This crystallised from ethanol, to give 1,3,4,5,6-*penta*-O-*acetyl*-2-O-*methyl*-D-*mannitol* (0·12 g.), m. p. 102—102·5° unchanged by further crystallisation (Found: C, 50·1; H, 6·4; OMe, 8·0. $C_{17}H_{26}O_{11}$ requires C, 50·3; H, 6·5; OMe, 7·6%), $[\alpha]_D^{22}$ +29·5 (*c* 0·87 in $CHCl_3$).

[28] Fletcher and Diehl, *J. Amer. Chem. Soc.*, 1952, **74**, 3799.
[29] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[30] Hough, Powell, and Woods, *J.*, 1956, 4799.
[31] Mitchell and Percival, *J.*, 1954, 1423.

Synthesis of 2-O-*Methyl*-D-*mannitol.*—2-*O*-Methyl-D-mannose dibenzyl mercaptal (0·65 g.) was demercaptalised by the standard procedure.[13] The oily product was shown by chromatography to contain mannose and a compound moving almost twice as fast as mannose, which was not the unchanged mercaptal. The products were reduced to hexitols with potassium borohydride (0·16 g. in 7·5 ml. of water). By next morning gas evolution had stopped and Amberlite ion-exchange resin IR-120(H) was added to decompose the excess of borohydride. Sodium hydrogen carbonate was added to raise the pH from 2 to 5, the resin was filtered off, and the filtrate and washings were concentrated under reduced pressure, giving a white solid. The residue after removal of boric acid was an oil (0·17 g.). Chromatography in solvent (*a*) showed the presence of a hexitol, R_{mannitol} 0·92, and a second product, R_m 1·84. No reducing sugar was detected by the *p*-anisidine hydrochloride spray. The two products were separated on a charcoal–Celite column by elution, first with water (300 ml.) and then with 2% aqueous ethanol. 10 ml. fractions were collected; paper chromatography with solvent (*a*) showed only mannitol, R_m 1·0, and a product, R_m 1·9. After concentration of the appropriate fractions, filtration through asbestos and evaporation gave an oil (0·09 g.) presumed to be 2-*O*-methylmannitol. Sodium acetate (0·1 g.) and acetic anhydride (2·0 ml.) gave a product which after two crystallisations from aqueous ethanol was 1,3,4,5,6-penta-*O*-acetyl-2-*O*-methyl-D-mannitol (0·06 g.), m. p. 102—102·5°. The mixed m. p. with the penta-acetate of the product *E* described above was 101·5—102·5°. The product *E* and 2-*O*-methyl-D-mannitol showed identical behaviour on paper chromatography and ionophoresis. Infrared spectra (in Nujol) of the penta-acetates over the range 5000—666 cm.$^{-1}$ were identical. A diffraction grating spectrometer (third-order spectrum) was used for the fine spectrum between 3158 and 2727 cm.$^{-1}$, in which the symmetrical C–H stretching frequency of the methoxyl group is located.

Analysis and Examination of the Boron Trichloride–Tri-O-*methylenemannitol Complex.*—The complex was obtained by adding excess of boron trichloride to a known weight of 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol, complete dissolution being allowed to occur in a closed vessel and the excess of boron trichloride then removed under reduced pressure in anhydrous conditions. Determination of the molar ratio, boron trichloride: acetal, was made uncertain by the dependence of the final weight of residue on the extent to which the pressure is reduced; the average value with an oil-pump was 1·8, and with a water-pump 2·3. On analysis of the residue for chlorine no conclusive and reproducible results could be obtained, the values being dependent on the pH of the hydrolysate.

The infrared spectrum of the complex was measured on a sample prepared by distilling boron trichloride (1·99 g.) in a closed system and condensing it on the trimethylenemannitol (0·02 g.); the latter was contained in a narrow tube having a constriction at its upper end and cooled to −80°. The acetal did not dissolve at this low temperature but allowing the mixture to attain room temperature caused complete dissolution. Excess of boron trichloride was removed by evacuation at a water-pump (protected to prevent back-diffusion of moisture). The tube containing the complex (0·06 g.) was sealed off at the constriction. The complex formed by 1,4-dioxan and boron trichloride was prepared by adding dioxan (7·2 g.; distilled from sodium) to dichloromethane (10 ml.), cooling the whole to −80°, then adding boron trichloride (2·3 g., 0·25 mol.). After 15 min., the mixture was allowed to warm to room temperature. After 1 hr., volatile matter was removed at room temperature, first by a water-pump and then at 2 mm. The residue of white crystals (3·74 g.) was recrystallised from dichloromethane–light petroleum (b. p. 60—80°) under anhydrous conditions. The infrared spectra of both complexes were measured in carbon disulphide solution (see above).

The authors are indebted to Dr. R. L. Williams for recording and interpreting the infrared spectra and thank Professor E. J. Bourne, Dr. A. Lovecy, and Mr. C. H. Miller for their interest.

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[*Received, February* 10*th*, 1960.]