370. *Studies of Trifluoroacetic Acid. Part XVII.* Reaction of Acyl Trifluoroacetates with βC-, β-, and α-Acetals of D-Glucitol.†*

By E. J. Bourne, J. Burdon, and J. C. Tatlow.

β- and α-Methylene [1] derivatives of D-glucitol react with equimolecular mixtures of acetic, benzoic, or propionic acid and trifluoroacetic anhydride to give, after mild hydrolysis, D-glucitol derivatives *O*-acylated in the primary positions and with free hydroxyl groups in the secondary positions. With benzylidene and *iso*propylidene derivatives of D-mannitol and D-glucitol, the fully acetylated hexitols are produced.

In Part XIV [2] it was shown that treatment of 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol with an equimolecular mixture of a carboxylic acid and trifluoroacetic anhydride caused rupture of the βT-ring [1] (3 : 5), but not of the βC-ring (2 : 4): Related investigations are now reported for methylene derivatives of D-glucitol containing β- and α-rings. These rings also are broken, and in a similar manner to that described by Ness, Hann, and Hudson,[3] who used a mixture of acetic acid, acetic anhydride, and concentrated sulphuric acid and obtained products with an *O*-acetyl group in the primary position and an *O*-acetoxymethyl group in the secondary position for each ring that was broken. It is now shown that, with an equimolecular mixture of acetic, propionic, or benzoic acid, and trifluoroacetic anhydride, β- and α-methylene rings break to give, after mild hydrolysis which presumably removes trifluoroacetoxymethyl residues, D-glucitol derivatives *O*-acylated in the primary positions and with hydroxyl groups in the secondary positions. The work described here and in Part XIV [2] illustrates a new approach to the synthesis of partly substituted polyhydroxy-compounds.

Treatment of 5 : 6-di-*O*-acetyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol (I) with an equimolecular mixture of acetic acid and trifluoroacetic anhydride (3 mol. each) for 7 hr. at 25° yielded, after mild hydrolysis, a crystalline tri-*O*-acetyl-*O*-methylenehexitol, which was acetylated to give the known 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (II). The same triacetate was obtained by a similar acetolysis and subsequent hydrolysis of 1 : 6-di-*O*-acetyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol (III), which showed that it was 1 : 5 : 6-tri-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (IV), as would be expected from the results described in Part XIV.[2] Thus the 1 : 3-*O*-methylene ring (β) had broken in the expected manner to give a 1-*O*-acetyl group and a free 3-hydroxyl group, leaving the 2 : 4-ring (βC) intact.

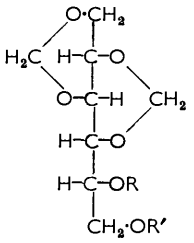
1 : 3-2 : 4-Di-*O*-methylene-D-glucitol (V) was preferentially benzoylated to give a compound (VI) believed to be the 6-benzoate. This afforded the 5-acetate 6-benzoate (VII) on acetylation. Treatment of this diester with benzoic acid and trifluoroacetic anhydride (3 mol. each) for 12 hr. at 25° gave a product which was readily hydrolysed to 5-*O*-acetyl-1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol (VIII), identical with the material prepared previously [2] from 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol. The two independent syntheses of compound (VIII) together show (*a*) that the benzoate groups in (VI) and (VII) were in fact located on position 6; (*b*) that the 1 : 3-*O*-methylene ring of (VII) had been ruptured in the same way as that of (I); and (*c*) that the structure allocated to (VIII) in the earlier work [2] was correct. Tri-*O*-methylene-D-glucitol (IX), prepared by an improved method, which resembled that of Ness, Hann, and Hudson [4] for

* Part XVI, *J.*, 1958, 3945.
† Presented in part at XIVth Internat. Congr. Pure Appl. Chem., Zurich, 1955.

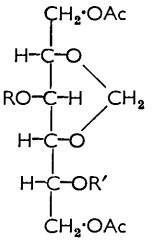
[1] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[2] Bourne, Burdon, and Tatlow, *J.*, 1958, 1274.
[3] Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 665.
[4] *Idem, ibid.*, 1943, **65**, 2215.

the preparation of tri-*O*-methylene-D-mannitol, reacted similarly with benzoic acid–trifluoroacetic anhydride (4·5 mol. each) to give finally the known [2] 1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol (X).

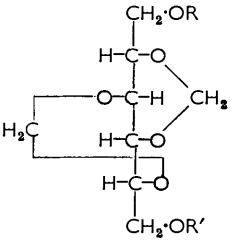
It follows that tri-*O*-methylene-D-glucitol (IX) should react with acetic acid–trifluoroacetic anhydride to give, after mild hydrolysis, 1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (XI) and this was very probably the case, since a syrup was obtained which gave the expected analytical values. This syrup was acetylated to give the known 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (II), and methylation demonstrated the presence of two free hydroxyl groups. However, a direct proof of the structure of this compound (XI) has not been obtained, as attempts to prepare crystalline derivatives failed: for example, attempted esterifications with benzoyl chloride in pyridine and with benzoic acid–trifluoroacetic anhydride, propionylation, tosylation, and nitration gave syrups. Attempted condensation with formaldehyde gave either tri-*O*-methylene-D-



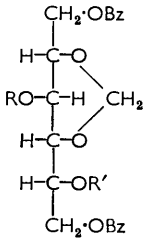
(I) R = R′ = Ac
(V) R = R′ = H
(VI) R = H, R′ = Bz
(VII) R = Ac, R′ = Bz



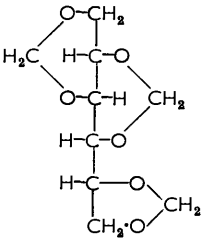
(II) R = R′ = Ac
(IV) R = H, R′ = Ac
(XI) R = R′ = H
(XII) R = R′ = $CF_3 \cdot CO \cdot O \cdot CH_2$
(XIII) R = R′ = $CH_3 \cdot CO \cdot O \cdot CH_2$



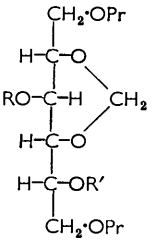
(III) R = R′ = Ac
(XVI) R = R′ = Pr



(VIII) R = H, R′ = Ac
(X) R = R′ = H



(IX)



(XIV) R = R′ = H
(XV) R = R′ = Ac

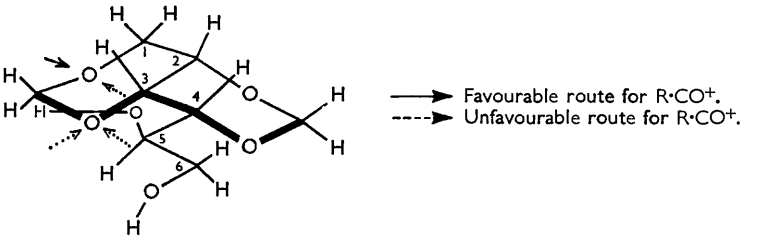
glucitol (IX) or the original syrup (XI). The supposition that the acetate groups were at positions 1 and 6 is supported by the analogous reaction of the triacetal (IX) with propionic acid–trifluoroacetic anhydride (see below) and by the fact that the 1 : 3(β)-ring in the diacetal has already been shown to yield a 1-acetate. Several attempts were made, under rigorously anhydrous conditions, to isolate the intermediate in the formation of the 1 : 6-diacetate (XI); in every case a fluorine-containing syrup was obtained which smelled strongly of trifluoroacetic acid and formaldehyde. It was probably impure 1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-3 : 5-bis-*O*-trifluoroacetoxymethyl-D-glucitol (XII), contaminated with the diacetate (XI) produced by hydrolysis with atmospheric moisture. With a tenfold excess of acetic acid over trifluoroacetic anhydride, tri-*O*-methylene-D-glucitol gave 3 : 5-di-*O*-acetoxymethyl-1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (XIII), identical with the compound obtained by the method of Ness *et al.*[3] (see Part XIV [2] for a discussion of this reaction).

An equimolecular mixture of propionic acid and trifluoroacetic anhydride converted tri-*O*-methylene-D-glucitol (IX) into 2 : 4-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (XIV), as was shown by its hydrolysis to 2 : 4-*O*-methylene-D-glucitol and by the formation

of its 3 : 5-diacetate (XV). The structure of this diacetate was proved by its synthesis by an alternative route, which involved treatment of 2 : 4-3 : 5-di-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (XVI) with acetic acid–trifluoroacetic anhydride, mild hydrolysis of the product, and acetylation (cf. Part XIV [2]).

Thus it has been established that 1 : 3(β)- and 5 : 6(α)-rings in methylene acetals of glucitol can be ruptured under very mild conditions with equimolecular mixtures of trifluoroacetic anhydride and carboxylic acids, leaving ester groups at the primary positions. Under the same conditions, there is no detectable attack on 2 : 4(βC)-methylene rings; it will be recalled that βC-acetals are also the most resistant to hydrolysis with aqueous acid.[1]

It was suggested in Part XIV [2] that the unsymmetric anhydride ($R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$), in its ionic form [$(R{\cdot}CO)^+(O{\cdot}CO{\cdot}CF_3)^-$], is the component of an equimolecular mixture of a carboxylic acid and trifluoroacetic anhydride which is responsible for the fission of methylene acetals. Some direct supporting evidence has now been obtained since with acetyl trifluoroacetate alone there was no indication that either methylene or the more reactive (see below) benzylidene groups were affected. In esterifications with acetyl trifluoroacetate [5] the presence of trifluoroacetic acid has a pronounced effect and seems to favour ionic processes. In a 1 : 3-2 : 4-diacetal of D-glucitol, the acylium ion ($R{\cdot}CO^+$) could form an oxonium complex with each of the oxygen atoms involved in the β-ring, and



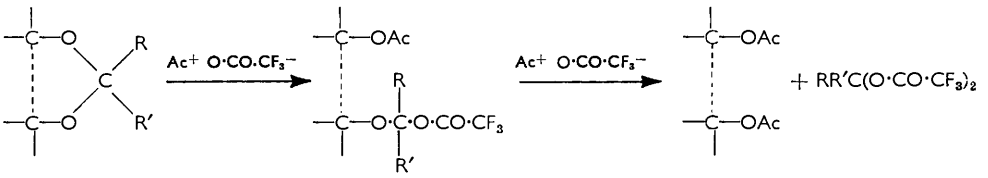
the ion could approach from an axial or an equatorial direction. The most probable conformation of the diacetal is shown in the Figure and it will be seen that an axial approach is improbable at each of the oxygen positions, because of non-bonded interactions analogous to the 1 : 3-diaxial interactions of *cyclo*hexane. Further, the same type of interaction would impede an equatorial approach to the oxygen atom at position 3 so that an equatorial approach to the oxygen atom at position 1 is by far the more probable, to give the 1-ester of the 2 : 4-acetal. With 1 : 3-2 : 4-5 : 6-tri-*O*-methylene-D-glucitol, the 5 : 6(α)-ring is known to be easily the most labile towards acidic reagents,[1,6] so that this will be ruptured first, by attack of the acylium ion at the more accessible oxygen atom at position 6, to give initially the 6-ester of the 1 : 3-2 : 4-diacetal.

Hann, Hudson, and their co-workers [7,8] also showed that a mixture of acetic acid, acetic anhydride, and concentrated sulphuric acid would completely remove a benzylidene acetal ring of any type to give the corresponding diacetate. We have now shown that an equimolecular mixture of acetic acid and trifluoroacetic anhydride reacts in the same way with both benzylidene acetals and *iso*propylidene ketals. For example, 3 : 4-di-*O*-acetyl-1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol, on being treated for 2 hr. at 25°, gave a small yield (21%) of mannitol hexa-acetate. 1 : 3-2 : 5-4 : 6-Tri-*O*-benzylidene-D-mannitol, treated similarly for 24 hr., gave a 39% yield of the same compound together with a 73% yield of benzaldehyde, isolated as its 2 : 4-dinitrophenylhydrazone. The expected benzylidene bistrifluoroacetate could not be isolated. 1 : 3 : 5 : 6-Tetra-*O*-acetyl-2 : 4-*O*-benzylidene-D-glucitol gave D-glucitol hexa-acetate (85%) and benzaldehyde 2 : 4-dinitrophenylhydrazone (74%) under the same conditions, so that even the 2 : 4(βC)-ring was

[5] Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.
[6] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.
[7] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 132, 136, 137, 1614.
[8] Wolfe, Hann, and Hudson, *ibid.*, p. 1493.

ruptured here. {Vargha [9] gave m. p. 87—88° and $[\alpha]_D$ −6·7° (in $CHCl_3$) for 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-benzylidene-D-glucitol, whereas we find m. p. 121° and $[\alpha]_D$ −5·2° (in $CHCl_3$). Our compound gave correct analyses and was deacetylated to the original 2 : 4-*O*-benzylidene-D-glucitol.} In these three experiments there was considerable darkening of the reaction mixtures and it is interesting that acetone, benzaldehyde, D-glucitol, or D-mannitol alone do not darken under these conditions.

The mechanism of the acetolysis of these benzylidene and *iso*propylidene compounds probably follows the same path as that suggested [2] for the methylene acetals as far as the trifluoroacetoxymethyl ether, which is then subjected to further attack by the unsymmetric anhydride, as follows:



(Benzylidene acetals, R = Ph, R′ = H; *iso*propylidene ketals, R = R′ = Me)

The much greater reactivity of the benzylidene and *iso*propylidene compounds than of methylene acetals reflects their known stabilities to acid and may be due to two factors: (i) oxonium-ion formation will be aided by the inductive effect of the methyl groups with *iso*propylidene ketals and by resonance effects for the benzylidene acetals; (ii) the positive ion formed initially on ring scission [2] will be more stable with both *iso*propylidene and benzylidene compounds and will therefore be more likely to combine with a trifluoroacetate ion. From arguments advanced by Ingold [10] for the hydrolysis of acyclic acetals, the latter seems the most likely explanation, although difference in reactivity of different ring types of the same acetal must be due mainly to ring strain and accessibility of the oxygen atoms.

The usefulness of trifluoroacetic anhydride as an esterification catalyst [11] is not seriously limited as a consequence of the reactions described in this paper and in Part XIV; [2] hydroxyl groups in acetals can still be acetylated in reasonable yield (see p. 1870) with a slight excess of an equimolecular mixture of acetic acid and trifluoroacetic anhydride, without much accompanying ring scission. Even under these conditions, however, *iso*propylidene ketals give negligible amounts of ketal acetates. This must mean that with acetals esterification is much faster than ring scission, whereas with *iso*propylidene ketals the rates are comparable. In connection with this, it has been shown [5] that simple alcohols are almost fully esterified in a few minutes. An earlier report [12] that a derivative of 4 : 6-*O*-benzylideneglucose can be esterified in 64% yield with acetic acid–trifluoroacetic anhydride is consistent with these observations.

Experimental

Methylenation of D-*Glucitol.*—A mixture of D-glucitol (50 g.), 40% formaldehyde solution (70 ml.), and concentrated hydrochloric acid (70 ml.) was kept at 100°. The acetal was gradually precipitated and after 1 hr. the solution was cooled and filtered. The solid gave 1 : 3-2 : 4-5 : 6-tri-*O*-methylene-D-glucitol (23 g.), m. p. and mixed m. p. 208—210° (from ethanol), $[\alpha]_D^{16}$ −27·5° (*c* 2·31 in $CHCl_3$). Ness *et al.*[3] gave m. p. 212—216° and $[\alpha]_D^{20}$ −30·8° (in $CHCl_3$).

The original filtrate was neutralised with sodium carbonate and evaporated to dryness *in vacuo*. The residue was extracted exhaustively with boiling chloroform; the extracts

[9] Vargha, *Magyar Kém. Folyóirat*, 1934, **40**, 151.
[10] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 334.
[11] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976.
[12] Bourne, Stacey, Tatlow, and Tatlow, *J.*, 1951, 826.

deposited a crystalline solid which was recrystallised from ethanol, to give 1 : 3-2 : 4-di-*O*-methylene-D-glucitol (6·2 g.), m. p. and mixed m. p. 173—174°, $[\alpha]_D^{17}$ −27·2° (*c* 2·34 in H_2O). Ness *et al.*[3] gave m. p. 174—175° and $[\alpha]_D^{20}$ −29·6° (in H_2O).

1 : 5 : 6-*Tri*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—(*a*) 5 : 6-Di-*O*-acetyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol, prepared from 1 : 3-2 : 4-di-*O*-methylene-D-glucitol and acetic anhydride in pyridine, had m. p. 135—136° and $[\alpha]_D^{17}$ −11·9° (*c* 2·79 in $CHCl_3$). Ness *et al.*[3] gave m. p. 135—136° and $[\alpha]_D^{20}$ −12·8° (in $CHCl_3$). A solution of this diacetate (1·00 g.) in trifluoroacetic anhydride (3 mol.) and acetic acid (3 mol.) was kept at 25° for 7 hr. (constant rotation), then poured into sodium hydrogen carbonate solution, and the precipitate was extracted with chloroform. Evaporation of the dried ($MgSO_4$) extracts left a syrup which crystallised from ethanol to give 1 : 5 : 6-*tri*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol* (0·80 g.), m. p. 125—126°, $[\alpha]_D^{21}$ +2·4° (*c* 2·47 in $CHCl_3$) (Found: C, 48·1; H, 6·0; Ac, 40·7. $C_{13}H_{20}O_9$ requires C, 48·75; H, 6·3; Ac, 40·3%).

(*b*) 1 : 6-Di-*O*-acetyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol, prepared by the method of Hann *et al.*,[13] had m. p. 113—114° and $[\alpha]_D^{21}$ +5·7° (*c* 1·72 in $CHCl_3$). These authors gave m. p. 114° and $[\alpha]_D$ +6·6° (in $CHCl_3$). A solution of this compound (0·40 g.) in trifluoroacetic anhydride (3 mol.) and acetic acid (3 mol.) was kept at 25° for 3 hr. and then treated as in (*a*) to give 1 : 5 : 6-tri-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (0·31 g.), m. p. 125—126° alone and on admixture with the above specimen, $[\alpha]_D^{19}$ +2·2° (*c* 1·04 in $CHCl_3$) (Found: C, 48·2; H, 6·3%).

1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol* *from* 1 : 5 : 6-*Tri*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—The product from (*a*) (0·47 g.), with acetic anhydride in pyridine, gave the tetra-acetate (0·43 g.), m. p. and mixed m. p. 150—151° (aqueous ethanol), $[\alpha]_D^{17}$ −2·1° (*c* 1·34 in $CHCl_3$) (Found: C, 49·3; H, 5·8. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1%). Ness *et al.*[3] gave m. p. 150—151° and $[\alpha]_D^{20}$ −1·5° (in $CHCl_3$).

1 : 5 : 6-*Tri*-O-*acetyl*-2 : 4-O-*methylene*-3-O-*propionyl*-D-*glucitol*.—The product from (*a*) (0·60 g.), trifluoroacetic anhydride (0·66 ml.), and propionic acid (0·23 ml.) were kept at room temperature for 15 hr., and poured into sodium hydrogen carbonate solution. The precipitate gave the 3-*propionate* (0·38 g.), m. p. 139—140° (from aqueous ethanol), $[\alpha]_D^{20}$ +1·0° (*c* 1·00 in $CHCl_3$) (Found: C, 51·0; H, 6·3%; N-alkali uptake, 10·73 ml./g. $C_{16}H_{24}O_{10}$ requires C, 51·1; H, 6·4%; N-alkali uptake, 10·64 ml./g.). The product from (*b*) gave the same propionate.

6-O-*Benzoyl*-1 : 3-2 : 4-*di*-O-*methylene*-D-*glucitol*.—To an ice-cold solution of 1 : 3-2 : 4-di-*O*-methylene-D-glucitol (3·00 g.) in pyridine (200 ml.), benzoyl chloride (1 mol.) was added dropwise, with shaking. After 3 hr. at room temperature, the 6-benzoate (1·41 g.) was isolated in the usual way; it had m. p. 196—197° (from aqueous ethanol) alone and on admixture with the compound obtained by Bourne and Wiggins,[14] and $[\alpha]_D^{19}$ −14·7° (*c* 2·31 in $CHCl_3$) (Found: C, 58·7; H, 5·8. Calc. for $C_{15}H_{18}O_7$: C, 58·1; H, 5·8%). Bourne and Wiggins [14] reported a monobenzoate (prepared by Schotten–Baumann benzoylation) with m. p. 195—197° and $[\alpha]_D$ −15·9° (in $CHCl_3$).

5-O-*Acetyl*-6-O-*benzoyl*-1 : 3-2 : 4-*di*-O-*methylene*-D-*glucitol*.—6-*O*-Benzoyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol (0·60 g.) with acetic anhydride in pyridine gave the 5-*acetate* (0·52 g.), m. p. 101° (from aqueous ethanol), $[\alpha]_D^{18}$ −36·1° (*c* 1·55 in $CHCl_3$) (Found: C, 58·3; H, 5·5%; N-alkali uptake, 5·78 ml./g. $C_{17}H_{20}O_8$ requires C, 57·95; H, 5·7%; N-alkali uptake, 5·68 ml./g.).

5-O-*Acetyl*-1 : 6-*di*-O-*benzoyl*-2 : 4-O-*methylene*-D-*glucitol*.—A solution of 5-*O*-acetyl-6-*O*-benzoyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol (0·20 g.) in benzoic acid (3 mol.) and trifluoroacetic anhydride (3 mol.) was kept at 25° for 12 hr., poured into sodium hydrogen carbonate solution, and extracted with chloroform. The dried ($MgSO_4$) extracts yielded a syrup, which crystallised from ethanol to give 5-*O*-acetyl-1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol (0·16 g.), m. p. and mixed m. p. with the specimen obtained previously [2] 149—150°, $[\alpha]_D^{18}$ +5·9° (*c* 1·54 in $CHCl_3$) (Found: C, 62·0; H, 5·3. Calc. for $C_{23}H_{24}O_9$: C, 62·2; H, 5·4%).

Action of Benzoic Acid–Trifluoroacetic Anhydride on Tri-O-*methylene*-D-*glucitol*.—Tri-*O*-methylene-D-glucitol (0·50 g.) was kept at 25° for 12 hr. in a solution of benzoic acid (4·5 mol.) in trifluoroacetic anhydride (4·5 mol.). The mixture was worked up as before, to give 1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol [2] (0·54 g.), m. p. and mixed m. p. 155—156° (from aqueous ethanol), $[\alpha]_D^{17}$ +16·9° (*c* 1·79 in $CHCl_3$) (Found: C, 62·7; H, 5·3; Bz, 52·2. Calc. for $C_{21}H_{22}O_8$: C, 62·7; H, 5·5; Bz, 52·2%).

Action of Propionic Acid–Trifluoroacetic Anhydride on Tri-O-*methylene*-D-*glucitol*.—A

[13] Hann, Wolfe, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 1898.
[14] Bourne and Wiggins, *J.*, 1944, 517.

solution of tri-*O*-methylene-D-glucitol (2·00 g.) in a mixture of trifluoroacetic anhydride (4·5 mol.) and propionic acid (4·5 mol.) was kept at 25° for 7 hr. Isolation of the product as before gave 2 : 4-O-*methylene*-1 : 6-*di*-O-*propionyl*-D-*glucitol* (2·01 g.) (from ethanol), m. p. 139—141°, $[\alpha]_D^{19}$ −4·8° (*c* 1·42 in $CHCl_3$) (Found: C, 50·9; H, 7·2; C_2H_5·CO, 36·8. $C_{13}H_{22}O_8$ requires C, 51·0; H, 7·2; C_2H_5·CO, 37·25%).

2 : 4-O-*Methylene*-D-*glucitol*.—2 : 4-*O*-Methylene-1 : 6-di-*O*-propionyl-D-glucitol (1·00 g.) was dissolved in dry methanol in which a small piece of sodium had been dissolved. After 24 hr. the methanol was removed by distillation and the residue recrystallised from ethanol, to give 2 : 4-*O*-methylene-D-glucitol (0·57 g.), m. p. and mixed m. p. 163—164°, $[\alpha]_D^{18}$ −9·1° (*c* 1·06 in H_2O) (Found: C, 43·6; H, 7·3. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3%).

2 : 4-3 : 5-*Di*-O-*methylene*-1 : 6-*di*-O-*propionyl*-D-*glucitol*.—2 : 4-3 : 5-Di-*O*-methylene-D-glucitol (1·00 g.), prepared by the method of Hann *et al.*,[13] had m. p. 192—193°, $[\alpha]_D^{19}$ +40·7° (*c* 0·90 in H_2O). With propionic anhydride in pyridine it gave the 1 : 6-*dipropionate* (1·01 g.), m. p. 110—111° (from ethanol), $[\alpha]_D^{19}$ +3·6° (*c* 2·24 in $CHCl_3$) (Found: C, 52·9; H, 6·8; C_2H_5·CO, 35·5. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0; C_2H_5·CO, 35·85%).

3 : 5-*Di*-O-*acetyl*-2 : 4-O-*methylene*-1 : 6-*di*-O-*propionyl*-D-*glucitol*.—(*a*) 2 : 4-*O*-Methylene-1 : 6-di-*O*-propionyl-D-glucitol (0·50 g.) with acetic anhydride in pyridine gave the 3 : 5-*di-acetate* (0·47 g.), m. p. 133—134° (from ethanol), $[\alpha]_D^{19}$ +1·7° (*c* 0·60 in $CHCl_3$) (Found: C, 52·5; H, 6·6. $C_{17}H_{26}O_{10}$ requires C, 52·3; H, 6·7%).

(*b*) A solution of 2 : 4-3 : 5-di-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (0·40 g.) in acetic acid (3 mol.) and trifluoroacetic anhydride (3 mol.) was kept at 25° for 7 hr. and poured into sodium hydrogen carbonate solution. The syrupy product, presumably 5-*O*-acetyl-2 : 4-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol, was isolated by chloroform extraction. With acetic anhydride in pyridine it gave 3 : 5-di-*O*-acetyl-2 : 4-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (0·35 g.), m.p. 133—134° (from ethanol) alone and on admixture with specimen obtained in (*a*), $[\alpha]_D^{18}$ +1·5° (*c* 2·74 in $CHCl_3$).

Action of Acetic Acid–Trifluoroacetic Anhydride on Tri-O-*methylene*-D-*glucitol*.—(i) *Attempted preparation of* 1 : 6-*di*-O-*acetyl*-2 : 4-O-*methylene*-3 : 5-*bis*-O-*trifluoroacetoxymethyl*-D-*glucitol*. A solution of tri-*O*-methylene-D-glucitol (1·00 g.) in trifluoroacetic anhydride (4·5 mol.) and acetic acid (4·5 mol.) was kept at 25° for 7 hr. (constant rotation). Volatile material was removed at 15°/0·005 mm. A fluorine-containing syrup (2·10 g.), which smelled strongly of formaldehyde and trifluoroacetic acid, remained, and was probably impure 1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-3 : 5-bis-*O*-trifluoroacetoxymethyl-D-glucitol, b. p. 186—190°/0·02 mm. (Found: C, 41·5; H, 4·5. Calc. for $C_{17}H_{20}O_{12}F_6$: C, 38·5; H, 3·8%). Repeated attempts to obtain a pure compound failed and in every case the product smelled strongly of formaldehyde and trifluoroacetic acid.

(ii) 1 : 6-*Di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*. Tri-*O*-methylene-D-glucitol (3·00 g.) was treated as in the previous experiment, but, after removal of the volatile products, the residual syrup was refluxed with dry methanol (25 ml.) for 1 hr. Evaporation of the methanol left a syrup which was 1 : 6-*di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol* (3·18 g.), b. p. 167—168°/0·01 mm., $[\alpha]_D^{14}$ −1·5° (*c* 1·96 in acetone) (Found: C, 47·8; H, 6·5; Ac, 30·9. $C_{11}H_{18}O_8$ requires C, 47·5; H, 6·5; Ac, 30·9%). This had still not crystallised after 12 months.

(iii) 3 : 5-*Di*-O-*acetoxymethyl*-1 : 6-*di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*. Tri-*O*-methylene-D-glucitol (1·0 g.) was kept at 60° for 6 hr. in trifluoroacetic anhydride (4·5 mol.) and acetic acid (45 mol.), poured into sodium hydrogen carbonate solution and extracted with chloroform. The product was 3 : 5-di-*O*-acetoxymethyl-1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (1·31 g.), m. p. and mixed m. p. 110—111° (from ethanol), $[\alpha]_D^{14}$ +26·9° (*c* 2·31 in $CHCl_3$). Ness *et al.*[3] gave m. p. 111—112° and $[\alpha]_D$ +29·8° (in $CHCl_3$).

1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol from* 1 : 6-*Di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—The diacetate (0·50 g.) with acetic anhydride in pyridine gave the tetra-acetate (0·54 g.), m. p. and mixed m. p. 150—151° (from aqueous ethanol), $[\alpha]_D^{17}$ −2·0° (*c* 2·03 in $CHCl_3$) (Found: C, 49·8; H, 6·0%).

Methylation of 1 : 6-*Di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—The diacetate (2·00 g.) was refluxed for 24 hr. with methyl iodide (40 ml.) and silver oxide (16·0 g.). The solvent was distilled, the residue was extracted with boiling chloroform, the filtered extracts were evaporated, and the residue was remethylated twice more in the same way. The *dimethyl ether* (1·31 g.) was a syrup, b. p. 158—164°/0·02 mm., $[\alpha]_D^{15}$ +4·2° (*c* 2·17 in $CHCl_3$) (Found: C, 50·6; H, 7·0; Ac, 27·7; OMe, 20·7. $C_{13}H_{22}O_8$ requires C, 51·0; H, 7·2; Ac, 28·1; OMe, 20·3%).

Action of Acetic Acid–Trifluoroacetic Anhydride on 3 : 4-*Di*-O-*acetyl*-1 : 2-5 : 6-*di*-O-iso*propylidene*-D-*mannitol*.—A solution of the compound (0·50 g.) {m. p. 123° and $[\alpha]_D^{17}$ +25·1° (*c* 1·92 in $CHCl_3$); Vargha [15] gave m. p. 123° and $[\alpha]_D$ +26·7° (in $CHCl_3$)} in acetic acid (6 mol.) and trifluoroacetic anhydride (6 mol.) was kept at 25°. After 2 hr. it had become almost black; it was poured into sodium hydrogen carbonate solution and extracted with chloroform. The extracts were dried ($MgSO_4$), decolorised with charcoal, filtered, and evaporated. The residue yielded D-mannitol hexa-acetate (21%), m. p. and mixed m. p. 122°, $[\alpha]_D^{21}$ + 25·0° (*c* 2·32 in $CHCl_3$).

1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*benzylidene*-D-*glucitol*.—2 : 4-*O*-Benzylidene-D-glucitol [16] (1·00 g.) with acetic anhydride in pyridine gave the *tetra-acetate* (1·22 g.), m. p. 121°, $[\alpha]_D^{20}$ −5·2° (*c* 1·49 in $CHCl_3$) (Found: C, 57·6; H, 5·9; Ac, 39·8. $C_{21}H_{26}O_{10}$ requires C, 57·5; H, 6·0; Ac, 39·3%).

De-acetylation of 1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*benzylidene*-D-*glucitol*.—The compound (0·50 g.) was dissolved in dry methanol in which a small piece of sodium had been dissolved. Evaporation of the methanol after 17 hr. left a solid which gave 2 : 4-*O*-benzylidene-D-glucitol (0·28 g.), m. p. and mixed m. p. 175—176° (from aqueous ethanol), $[\alpha]_D^{16}$ +7·9° (*c* 0·76 in ethanol).

Action of Acetic Acid–Trifluoroacetic Anhydride on Benzylidene Acetals.—(a) *Tri*-O-*benzylidene*-D-*mannitol*. (i) A solution of the compound (0·50 g.), prepared by Pette's method [17] {m. p. 212—216°, $[\alpha]_D^{17}$ −15·0° (*c* 2·30 in $CHCl_3$); Pette gave m. p. 224°}, in acetic acid (24 mol.) and trifluoroacetic anhydride (24 mol.) was kept at 25° for 24 hr. Considerable darkening took place. The mixture was poured into sodium hydrogen carbonate solution. The product, isolated by chloroform-extraction, was D-mannitol hexa-acetate (39%), m. p. and mixed m. p. 122—123°, $[\alpha]_D^{17}$ +24·2° (*c* 0·91 in $CHCl_3$).

(ii) The reaction was carried out as in (*a*) but, instead of being poured into sodium hydrogen carbonate solution, the reaction mixture was distilled. The distillate was taken up in chloroform, washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation of the chloroform left a liquid which smelled strongly of benzaldehyde and did not contain fluorine. This was converted into benzaldehyde 2 : 4-dinitrophenylhydrazone (73%), m. p. and mixed m. p. 237°.

(b) 1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*benzylidene*-D-*glucitol*. A solution of this compound (0·50 g.) in acetic acid (8 mol.) and trifluoroacetic anhydride (8 mol.) was treated as in the previous experiment, to give D-glucitol hexa-acetate (85%), m. p. and mixed m. p. 99·5—100°, $[\alpha]_D^{17}$ +8·2° (*c* 5·40 in acetone), and benzaldehyde 2 : 4-dinitrophenylhydrazone (74%), m. p. and mixed m. p. 237°.

Acetylation of Acetals and Ketals with Acetic Acid–Trifluoroacetic Anhydride.—1 : 3-2 : 4-Di-*O*-methylene-D-glucitol, 1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol, and 2 : 4-*O*-benzylidene-D-glucitol were fully acetylated in 68%, 59%, and 64% yield, respectively, by the following method: the acetal (0·50 g.) was dissolved in acetic acid (1·2 mol. per hydroxyl group) and trifluoroacetic anhydride (1·2 mol. per hydroxyl group), and the solution kept at room temperature for about 20 hr. The reaction mixture was taken up in chloroform, washed with sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). Evaporation of the chloroform and recrystallisation of the product from ethanol gave the required acetate. 1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-mannitol gave a yield of less than 10%, and 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucitol no yield of the corresponding acetate by this method.

Non-reactivity of Acetyl Trifluoroacetate with Cyclic Acetals.—When treated with acetyl trifluoroacetate (1 mol.), 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol (0·17 mol., 3 hr. at 25°), tri-*O*-methylene-D-glucitol (0·10 mol., 7 hr. at 25°), tri-*O*-benzylidene-D-mannitol (0·02 mol., 24 hr. at 25°), and 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-benzylidene-D-glucitol (0·06 mol., 24 hr. at 25°) were recovered unchanged (yields 88, 62, 64, and 86%, respectively).

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