[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA 14, MD.]

Behavior of Esters in Liquid Hydrogen Fluoride. Some Glycitol Esters

BY E. J. HEDGLEY[1] AND HEWITT G. FLETCHER, JR.

RECEIVED NOVEMBER 6, 1963

The behavior of esters of ethylene glycol, glyceritol, DL-arabinitol, and three hexitols in liquid hydrogen fluoride has been examined. Deacylation was observed in every case, accompanied (where asymmetric carbon atoms were involved) with Walden inversion. Glycitol anhydrides were not formed. A partially acylated glycitol, 2,3,4,5-tetra-*O*-benzoylgalactitol, is converted by liquid hydrogen fluoride to a mixture of glycitols and anhydroglycitols. Mechanisms which rationalize the observed reactions are proposed.

Earlier studies of the behavior of the esters of polyhydroxycyclohexanes,[2] of polyhydroxytetrahydropyrans,[3] and of polyhydroxytetrahydrofurans[4] in liquid hydrogen fluoride indicated that glycitol esters should, owing to their structural flexibility, readily undergo Walden inversion with concomitant deacylation when dissolved in this reagent. Investigation has now shown this to be true and revealed a simple method for the isomerization of the hexitols.

As expected, the dibenzoate of ethylene glycol and the tribenzoate of glyceritol were both found to be partially debenzoylated on recovery from their solutions in hydrogen fluoride.[5] DL-Arabinitol pentaacetate (**1**)[6] was converted into a mixture of DL-arabinitol, xylitol (**6**), and ribitol (**4**). The hexaacetates of galactitol (**19**), D-glucitol (**7**), and D-mannitol (**11**) were all deacetylated and, in part, isomerized by treatment with hydrogen fluoride; the products found in each case are indicated in Table I.

TABLE I

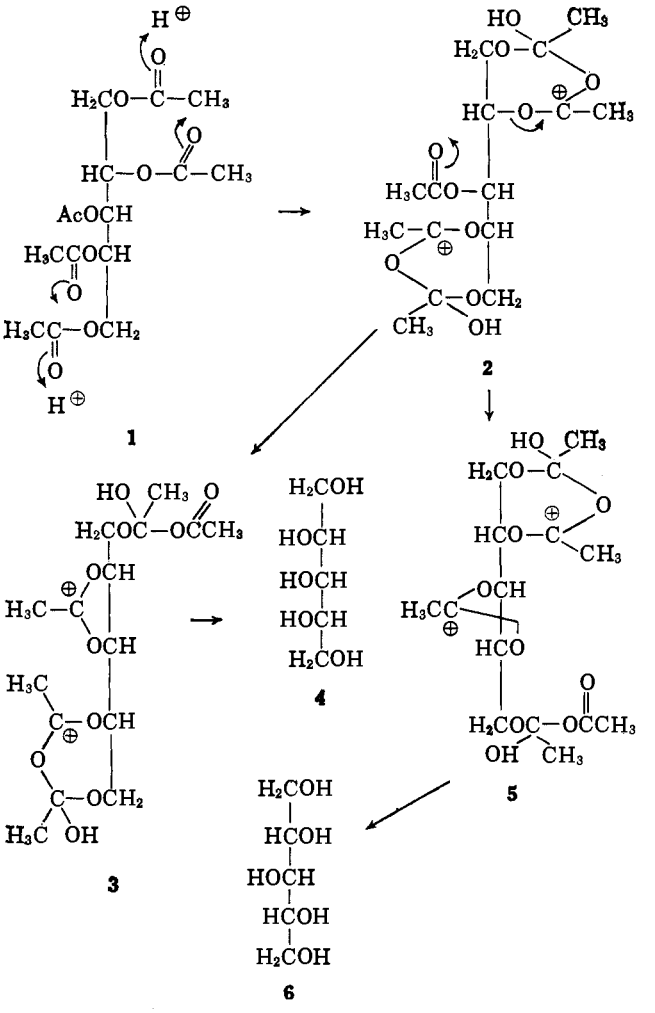
TRANSFORMATION OF HEXITOL HEXAACETATES

Starting material, hexaacetate of	Hexitols detected			
	Galactitol	Glucitol	Iditol	Mannitol
Galactitol	+	+	+	+
D-Glucitol	−	+	+	−
D-Mannitol	+	+	+	+

Discussion

Mechanisms offered earlier[2,3] predict the conversion of DL-arabinitol pentaacetate (**1**) into a mixture of DL-arabinitol, xylitol (**6**), and ribitol (**4**). Attack of acetyl groups on adjacent protonated acetyl groups might give the bicyclic intermediate **2**. In this structure the acetyl group at C-3 could attack C-2 to give **3** which, upon the addition of water, would yield ribitol (**4**); attack of the acetyl group at C-3 on C-4 would convert **2** to **5** which, in turn, would afford xylitol (**6**). The DL-arabinitol may be derived by simple deacetylation, although a more complex origin for at least some of it can be visualized.

Let us now consider the isomerization of the three hexitol hexaacetates. As shown in Table I, D-glucitol hexaacetate (**7**) gave only glucitol and iditol[7] while the hexaacetates of galactitol and D-mannitol gave, in addition to the parent hexitol, three diastereoisomeric hexitols.



In examining first the behavior of D-glucitol hexaacetate (**7**) it is clear that if the bicyclic intermediate **8** (analogous to **2**) were formed, then the nucleophilic attack of the acetyl group at C-4 upon C-5 would result in formation of intermediate **9** and, eventually, iditol (**10**). An alternative reaction pattern in which the acetyl at C-3 attacks at C-2 in **8** would lead to the formation of glucitol which is doubtless also formed by simple deacetylation **7**.[8]

D-Mannitol hexaacetate (**11**) could likewise give the bicyclic intermediate **12** in which attack of the acetyl group at C-3 on C-2 would give **13**, a glucitol (**18**)

(1) Visiting Associate, 1961–1963.

(2) E. J. Hedgley and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **84**, 3726 (1962).

(3) E. J. Hedgley and H. G. Fletcher, Jr., *ibid.*, **85**, 1615 (1963).

(4) E. J. Hedgley and H. G. Fletcher, Jr., *ibid.*, **86**, 1576 (1964).

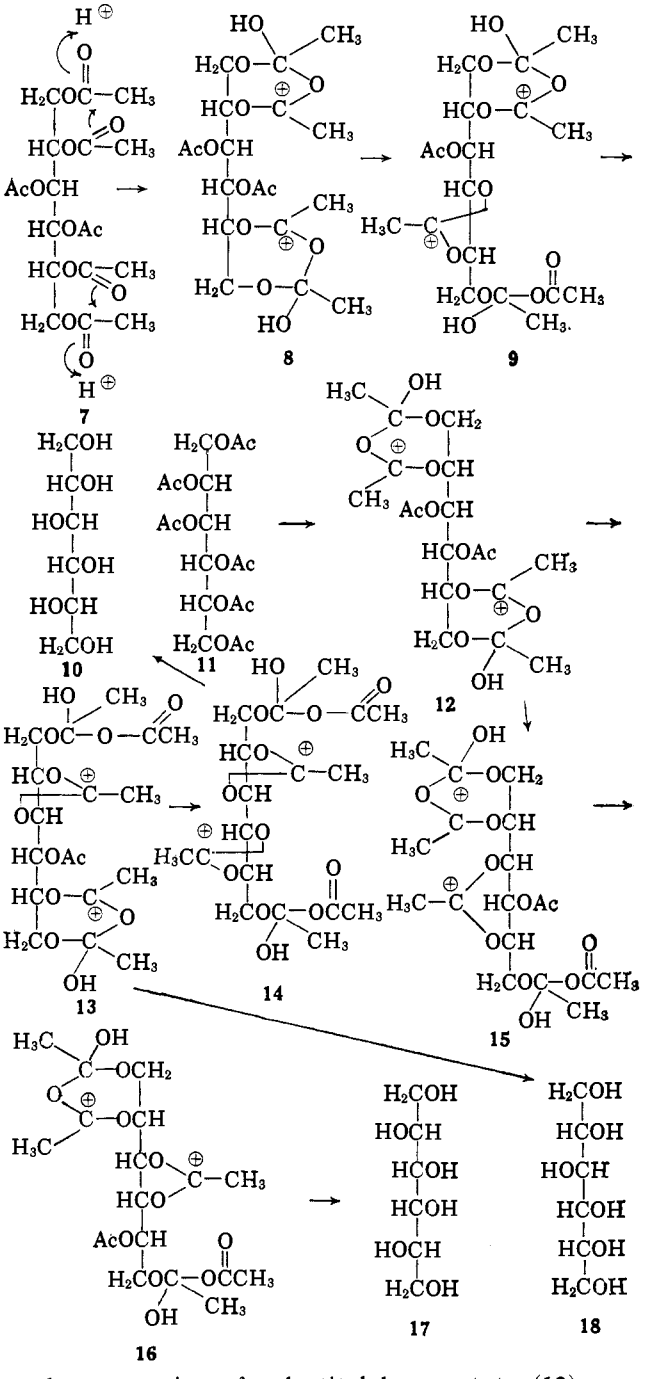
(5) Previous investigations[2,3] have shown that the benzoates of polyhydric alcohols are only partially deacylated in this process, whereas their acetates appear to undergo complete deacylation.

(6) In this and the other cases, only one enantiomorph is depicted.

(7) Inasmuch as all identifications were based on electrophoretic evidence (see Experimental), enantiomorphic designations of products are omitted.

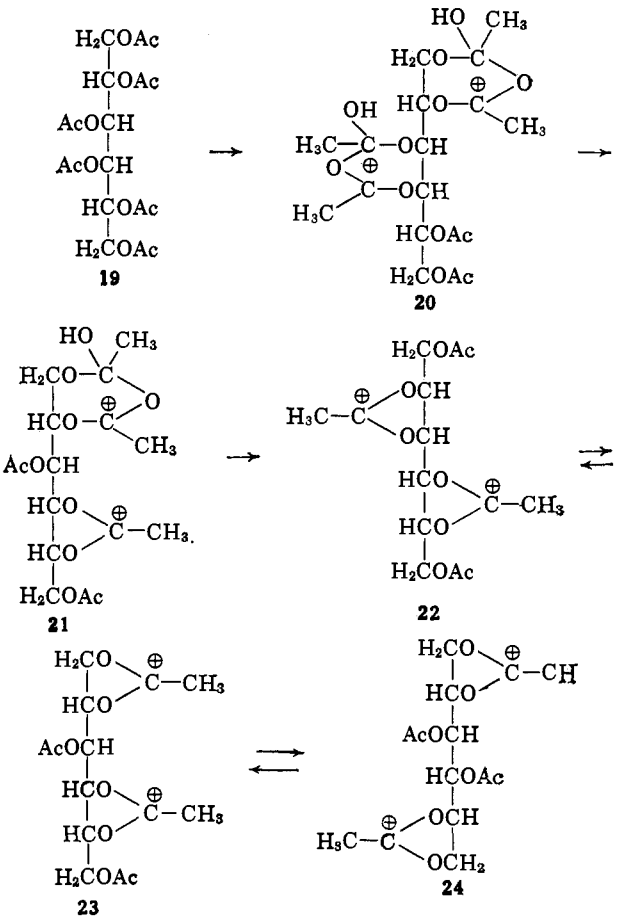
(8) One may also envisage a structure analogous to **8** in which the lower seven-membered ring involves C-4 and C-5 (rather than C-5 and C-6). In such an intermediate, attack by the C-6 acetyl group on C-5 would give the iditol configuration.

derivative; a second inversion in **13**, with the acetyl at C-4 attacking C-5 would give **14**, an iditol (**10**) derivative. If the acetyl group at C-3 in **12** were to attack C-5, structure **15** would result; a further rearrangement, the acetyl at C-4 attacking C-3, to give **16** would lead to the formation of galactitol (**17**).



The conversion of galactitol hexaacetate (**19**) may be regarded as proceeding through **20**; attack of the C-5 acetyl on C-4 with loss of acetic acid would lead to the glucitol derivative **21**. A second inversion would give the mannitol derivative **22**; subsequent inversions give **23** and then the iditol derivative **24**. Since, in principle, the last two conversions (**22** to **23** and **23** to **24**) are reversible, these three structures, representing mannitol, glucitol, and iditol, may conceivably exist in equilibrium with each other.

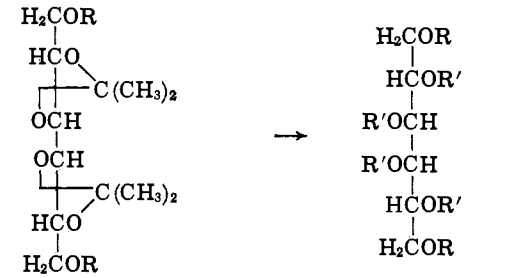
The transformations observed when the hexaacetates of D-glucitol, D-mannitol, and galactitol are treated



with hydrogen fluoride have two noteworthy aspects. The first is the absence of detectable quantities of either talitol or allitol.[9] The second is the complete absence of cyclization reactions that lead to the formation of anhydroglycitols. While the esters of the 1,5-anhydroglycitols do not undergo ring cleavage in hydrogen fluoride,[2] the majority of the esters of the 1,4-anhydroglycitols do suffer such cleavage.[4] That this cleavage is, moreover, reversible, has been postulated in order to explain the formation of the diastereoisomeric 1,4-anhydroglycitols observed. However, in every case the acyclic structure assumed was a *partially* acylated glycitol, bearing a hydroxyl group on that carbon atom which was to become part of the ring. The failure of fully acylated glycitols to give anhydroglycitols when treated with hydrogen fluoride does not then invalidate the earlier hypothesis. We have now synthesized a partially acylated glycitol in order to study this point. Benzylation of the known 2,3;4,5-di-*O*-isopropylidenegalactitol (**25**)[10] readily gave its 1,6-di-*O*-benzyl ether **26**; hydrolysis of **26** afforded crystalline 1,6-di-*O*-benzylgalactitol (**27**) which was converted to its crystalline tetrabenzoate **28**. Hydrogenolysis of **28** gave 2,3,4,5-tetra-*O*-benzoylgalactitol

(9) F. Micheel and R. Böhm [*Tetrahedron Letters*, 107 (1962)] have shown that three 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonylhexopyranoses are converted to a mixture containing *all* the diastereoisomeric 1,1,2,3,4,5,6-hepta-*O*-acetyl-*aldehydo*-hexoses when treated with acetic anhydride–zinc chloride. While these authors suggest that this transformation may proceed through an intermediate similar to one type postulated here, it should be pointed out that their rearrangements were conducted under acetylating conditions while the rearrangements in liquid hydrogen fluoride involve deacetylation. It is, therefore, not surprising that liquid hydrogen fluoride is more stereospecific in its action. *Cf.* ref. 3, footnote 4.

(10) R. M. Hann, W. D. Maclay, and C. S. Hudson, *J. Am. Chem. Soc.*, **61**, 2432 (1939).



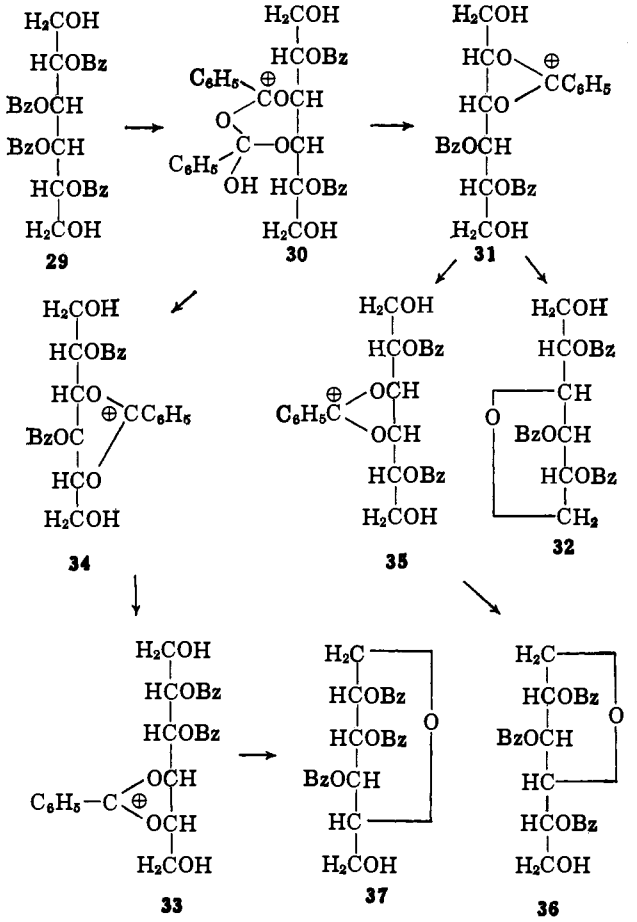
25, R = H
26, R = $-CH_2C_6H_5$

27, R = $-CH_2C_6H_5$, R′ = H
28, R = $-CH_2C_6H_5$, R′ = Bz
29, R = H, R′ = Bz
30, R = Ts, R′ = Bz

(**29**), a partially acylated glycitol of the type required.[11]

Solution of 2,3,4,5-tetra-*O*-benzoylgalactitol (**29**) in liquid hydrogen fluoride and subsequent debenzoylation with sodium methoxide afforded a mixture of periodate-positive substances which were shown to include galactitol, glucitol, and mannitol. Anhydrohexitols were also found and tentatively identified by paper electrophoresis as 1,4-anhydrogalactitol, 1,4-anhydroglucitol, and a third anhydride which appeared to be either 1,5-anhydrogulitol or 1,4-anhydroiditol.

If 2,3,4,5-tetra-*O*-benzoylgalactitol (**29**) is envisaged as forming, initially, the cyclic intermediate **30**, pathways to a variety of transformation products are readily seen. Attack of the C-2 benzoyl on C-3 (with loss of benzoic acid) gives **31**, an intermediate which would give glucitol or, by cyclization, the 1,4-anhydrogalactitol derivative **32**. Rearrangement of **31** to the galactitol derivative **35** would lead to the 1,4-anhydroglucitol derivative **36**; the same anhydride could conceivably arise by the direct cyclization of **30**. The intermediate **30** could also rearrange to the glucitol derivative **34** through attack of the C-5 benzoyl on C-3; subsequent rearrangement to the mannitol derivative **33** and cyclization would give the 1,5-anhydrogulitol derivative **37**.



Experimental[12]

Chromatography and Electrophoresis.—The identification of products was made through paper chromatography and paper electrophoresis using the techniques described in the preceding paper.[4] In every case authentic specimens were run simultaneously with the mixtures arising from the hydrogen fluoride treatment of the glycitol esters.

Behavior of Ethylene Glycol Dibenzoate with Liquid Hydrogen Fluoride.—Ethylene glycol dibenzoate[13] (2.70 g., m.p. 72°) was dissolved in *ca.* 20 ml. of liquid hydrogen fluoride and the solution kept at 18° for 7 hr. After removal of the excess of hydrogen fluoride with a stream of dry air, the residue was neutralized through the addition of saturated aqueous sodium bicarbonate. The oil which separated (and crystallized on standing) was removed by extraction with dichloromethane; after drying the extract with magnesium sulfate it was concentrated to a sirup (1.85 g.) which crystallized readily. The infrared spectrum of the material showed it to be predominantly ethylene glycol dibenzoate, slightly contaminated with deacylated components; recrystallization from aqueous acetone gave crystals which melted at 72° either alone or in admixture with authentic ethylene glycol dibenzoate.

The aqueous solution obtained above was evaporated to dryness and the residue extracted with hot ethanol. Evaporation of the extract gave a liquid (0.36 g.) in which the presence of ethylene glycol was shown by paper chromatography (10% acetone system, periodate–*p*-anisidine reagents).

The Behavior of Tri-*O*-benzoylglyceritol with Liquid Hydrogen Fluoride.—Tri-*O*-benzoylglyceritol (2.0 g., m.p. 72–73°, purified from the commercial product) was dissolved in *ca.* 20 ml. of liquid hydrogen fluoride and the solution kept at 18° for 7 hr. After removal of the major part of the hydrogen fluoride with a stream of dry air, the residue was neutralized with saturated aqueous sodium bicarbonate, a sirup separating at this stage. The mixture was extracted with dichloromethane, the combined extracts were dried with magnesium sulfate, and the solvent was removed to give a sirup (1.41 g.) which could not be induced to crystallize. The infrared spectrum of the sirup showed it to be mainly tri-*O*-benzoylglyceritol, contaminated with deacylated materials.

Evaporation of the aqueous solution to dryness gave a residue which was extracted with boiling ethanol. Concentration of this extract afforded a hygroscopic residue (0.33 g.) in which the presence of glyceritol was demonstrated by paper chromatography (10% acetone, periodate–*p*-anisidine reagents).

Behavior of Penta-*O*-acetyl-DL-arabinitol with Liquid Hydrogen Fluoride.—Penta-*O*-acetyl-DL-arabinitol[14] (70 mg., m.p. 134–136°) was dissolved in *ca.* 15 ml. of liquid hydrogen fluoride and the solution kept at 18° for 18 hr. After the removal of the hydrogen fluoride with a stream of dry air, the residue was treated with saturated aqueous sodium bicarbonate in which it dissolved completely. After deionization by successive passage through columns of Dowex 2-X8 (OH) and Amberlite IR-120 (H), the solution was concentrated to a small volume and examined by paper electrophoresis in arsenite buffer (3 hr., 16 v./cm., 50–60 ma.). Three components detectable with periodate–*p*-anisidine were found; their migration rates corresponded to arabinitol, xylitol, and ribitol. As measured qualitatively by the intensity of the reaction with the spray reagents, arabinitol and xylitol appeared to account for the bulk of the mixture, ribitol constituting only a minor component. In fact, in order for the

(11) 2,3,4,5-Tetra-*O*-benzoylgalactitol (**29**) proved difficult to purify and, since such structures are normally prone to undergo acyl migration, a sample of the preparation was converted to a crystalline ditosylate. This ester gave a theoretical yield of sodium *p*-toluenesulfonate when heated with sodium iodide in 2,4-pentanedione solution, indicating that its structure is, actually, **30** and that acyl migration had not taken place. Further confirmation of the structure of **30** was obtained by an independent synthesis from 2,3;4,5-di-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonylgalactitol.

(12) Melting points are corrected.

(13) H. C. Heim and C. F. Poe, *J. Org. Chem.*, **9**, 299 (1944).

(14) R. A. Raphael, *J. Chem. Soc.*, S44 (1949).

ribitol to be detected, the electrophoretogram had to be almost overloaded with the mixture. However, it may be noted that this pentitol is readily differentiable from arabinitol and xylitol by a subtle but definite color difference in reaction with the spray reagent on electrophoretograms.

Behavior of Three Hexa-*O*-acetylhexitols (7, 11, 23) with Liquid Hydrogen Fluoride.—The hexa-*O*-acetylhexitol (13.02 g.) was dissolved in *ca.* 50 ml. of liquid hydrogen fluoride and the solution held overnight at 18°. The major part of the hydrogen fluoride was removed with a stream of dry air and the residue neutralized with saturated aqueous sodium bicarbonate in which it was readily soluble. The mixture was evaporated to dryness and the residue heated at 100° for 3 hr. with a mixture of 100 ml. of acetic anhydride and 5 g. of anhydrous sodium acetate. After removal of the acetic anhydride and acetic acid (80° bath, water pump), the mixture was neutralized with aqueous sodium bicarbonate and the product extracted with dichloromethane. Moisture was removed from the combined extracts with magnesium sulfate and the solution concentrated *in vacuo* to a sirup. The entire material was deacetylated with sodium methoxide in methanol to give a sirup, 5.8–6.6 g. (theory 5.46 g.). Electrophoresis (basic lead acetate buffer, 6.75 hr., 24 v./cm., 20 ma.) gave a satisfactory separation of the hexitols, detection being achieved with hydrogen peroxide–ammonia spray followed by acetic acid. The products from the three hexitol hexaacetates are indicated in Table I; no quantitative estimation was attempted.

1,6-Di-*O*-benzylgalactitol (27).—A mixture of 13.1 g. of 2,3;4,5-di-*O*-isopropylidenegalactitol,[10] 150 ml. of benzene, 20 ml. of dioxane, and 22.4 g. of powdered potassium hydroxide[15] was heated under reflux while 25.2 g. of benzyl chloride was added over the course of 1 hr. Heating was continued for 4 hr. and the solution was cooled, diluted with acetone, and filtered. After removal of the solvent the product was distilled: b.p. 150–155° (0.1 mm.), 8.0 g., no hydroxyl absorption in the infrared spectrum. The entire product was dissolved in 50% aqueous ethanol and hydrolyzed by heating at gentle reflux for several hours with a suspension of Amberlite IR-120(H). The oily layer which separated over this period was redissolved through the addition of acetone and the resin then removed by filtration. On concentration, the filtrate gave a crystalline residue which was dried by azeotroping with alcohol: 6.6 g., 36%. Recrystallized from ethanol, the 1,6-di-*O*-benzylgalactitol was obtained (with ethanol of crystallization) as lustrous leaflets, m.p. 182–184° (rapid heating) or 176–181° (slow heating).

Anal. Calcd. for $C_{20}H_{26}O_6 \cdot C_2H_5OH$ (408.48): C, 64.68; H, 7.90. Found: C, 64.36; H, 7.55.

2,3,4,6-Tetra-*O*-benzoyl-1,6-di-*O*-benzylgalactitol (28).—1,6-Di-*O*-benzylgalactitol (1.5 g. of the solvated material) was benzoylated with benzoyl chloride in pyridine solution using the conventional procedure. Crystallization from acetone gave 2.89 g. (quantitative) of crude product, m.p. 165–167°; recrystallization from acetone raised the m.p. to 166–168°.

Anal. Calcd. for $C_{48}H_{42}O_{10}$ (778.87): C, 74.02; H, 5.44. Found: C, 74.03; H, 5.45.

2,3,4,5-Tetra-*O*-benzoylgalactitol (29).—2,3,4,6-Tetra-*O*-benzoyl-1,6-di-*O*-benzylgalactitol (2.13 g.) was suspended in 50 ml. of ethyl acetate containing 0.5 g. of 10% palladium-on-charcoal (presaturated with hydrogen). When shaken with hydrogen the suspension failed to absorb the gas; on the addition of a few mg. of palladium chloride, however, absorption took place rapidly, the theoretical amount of hydrogen being consumed in 50 min. After dilution with 100 ml. of ethyl acetate, the suspension was heated to boiling and filtered, the catalyst being washed twice with the same volume of ethyl acetate. Evaporation of the solvent gave a theoretical yield of 2,3,4,5-tetra-*O*-benzoylgalactitol as a pale tan powder, m.p. 179–185°, which proved to be sparingly soluble in a wide range of organic solvents. Treatment of a sample with boiling methanol led to partial deacylation as evidenced by the odor of methyl benzoate. Recrystallization from acetone–water gave a fine powder but failed to change the m.p. of the substance. Between quartz plates (on a Kofler hot stage) the substance softened at 210–220° and melted at 235–240°, suggesting that the alkalinity of the glass capillaries normally used for m.p. determinations causes a lowering of the m.p. through base-catalyzed acyl migration.[16] In our hands, all attempts to purify this substance failed to yield analytically pure material. Debenzoylation of a portion of the crude ester, however, afforded chromatographically homogeneous galactitol.

2,3,4,5-Tetra-*O*-benzoyl-1,6-di-*O*-*p*-tolylsulfonylgalactitol (30).—2,3,4,5-Tetra-*O*-benzoylgalactitol (0.9 g., m.p. 175–180°) was treated with an excess of *p*-toluenesulfonyl chloride in pyridine solution to give, from a mixture of acetone and ethanol, very fine needles, m.p. 148–149°.

Anal. Calcd. for $C_{48}H_{42}O_{14}S_2$ (906.94): C, 63.56; H, 4.67; S, 7.07. Found: C, 63.79; H, 4.56; S, 7.10.

A sample (0.154 g.) of 2,3,4,5-tetra-*O*-benzoyl-1,6-di-*O*-*p*-tolylsulfonylgalactitol was dissolved in 20 ml. of 2,4-pentanedione containing 0.10 g. of sodium iodide and the solution heated at 100° for 3 hr. The precipitate which formed was collected by filtration, washed with acetone, and dried at 70°: 0.058 g., quantitative.

2,3;4,5-Di-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonylgalactitol[10] (0.5 g.) was treated at room temperature with a mixture of 2.6 g. of benzoic acid and 4.4 g. of trifluoroacetic anhydride for 1 hr.[17] to give starting material as well as a second crystalline substance which melted at 149–150° either alone or in admixture with the product from the tosylation of 2,3,4,5-tetra-*O*-benzoylgalactitol.

Behavior of 2,3,4,5-Tetra-*O*-benzoylgalactitol (29) with Liquid Hydrogen Fluoride.—2,3,4,5-Tetra-*O*-benzoylgalactitol (0.60 g.) was dissolved in *ca.* 15 ml. of liquid hydrogen fluoride and the solution stored at 18° for 12 hr. The hydrogen fluoride was then removed with a stream of dry air and the brown residue treated with 10 ml. of saturated aqueous sodium bicarbonate. The water-insoluble sirup was extracted with dichloromethane and the aqueous phase further extracted with this solvent. The aqueous solution contained no periodate-positive material and was discarded. After pooling, the extracts were dried with sodium sulfate and freed of solvent to yield a slightly colored stiff sirup (0.53 g.) which was debenzoylated with sodium methoxide in methanol. The solution was filtered, concentrated to dryness, and the crystalline residue extracted with hot acetone. After concentration, the acetone extract was examined by paper chromatography, revealing the product to be a mixture of periodate-positive components with R_f values corresponding to hexitols and anhydrohexitols. Preparative paper chromatography permitted a ready separation of the two classes of compounds. Examination of the anhydroglycitol mixture by electrophoresis (borate buffer, 2 hr., 13 v./cm., 40 ma.) showed three components: two of these migrated at rates identical with 1,4-anhydroiditol and 1,4-anhydroglucitol; the third migrated at the same rate as 1,4-anhydrogalactitol and 1,5-anhydrogulitol.

Paper electrophoresis of the hexitol mixture in basic lead acetate buffer indicated the presence of glucitol and mannitol, no galactitol being detected.

Acknowledgment.—We are indebted to Mr. Harry W. Diehl for the preparation of 2,3,4,5-tetra-*O*-benzoyl-1,6-di-*O*-*p*-tolylsulfonylgalactitol from 2,3;4,5-di-*O*-isopropylidenegalactitol. Analyses were performed by the Analytical Services Unit of this Laboratory under the direction of Mr. H. G. McCann.

(15) Hooker Chemical Corp., Niagara Falls, N. Y.

(16) It is of interest to note that Y. Hamamura [*Bull. Agr. Chem. Soc. Japan*, **18**, 665 (1942); *Chem. Abstr.*, **45**, 4653 (1951)] described a galactitol tetrabenzoate of m.p. 224° which he considered as possibly having structure **29**; in pyridine solution the substance isomerized to what Hamamura believed might be 1,3,4,6-tetra-*O*-benzoylgalactitol.

(17) The procedure is that of E. J. Bourne, J. Bardon, and J. C. Tatlow, *J. Chem. Soc.*, 1864 (1959).