mechanical slit width of 0.028 mm., corresponding to a spectral width of about 3 cm.$^{-1}$, was maintained for all readings. The infrared cells had a path length of 0.26 mm.

The experimental details were as reported in the earlier paper.[1] For acetonitrile, two sets of experiments, utilizing a nitrile concentration of 0.0117 and of 0.047 g./ml., were performed. For *p*-anisonitrile, a nitrile concentration of 0.010 g./ml. was used for all measurements. Beer's law plots of the nitrile band absorbance were linear up to approximately 0.020 g./ml. for both nitriles.

For acetonitrile, in addition to the nitrile band at 2246 there appeared a second band at 2286 cm.$^{-1}$. Since the literature did not reveal an assignment for this band, we tried to establish whether it was related to the nitrile group. Beer's law plots of this band were linear to a concentration of about 0.050 g./ml. in dimethyl sulfoxide, carbon tetrachloride, or pyridine solvent. The intensity of the band was independent of the concentration of dimethyl sulfoxide in binary mixtures with carbon tetrachloride. From these facts, we infer that this band is not related to the nitrile group.

**Equilibration of *cis*- and *trans*-4-*t*-Butylcyclohexylcarbonitrile.**—Preparation of the nitriles followed the procedures of Rickborn and Jensen.[4] The transformation of the *trans*-4-*t*-butylcyclohexanecarboxylic acid, obtained by fractional crystallization of the mixed isomers from the reduction of 4-*t*-butylbenzoic acid,[19] gave an over-all yield of 30% of the nitrile which was found to contain 1% of the *cis* isomer by gas chromatography.

We were not able to obtain the *cis*-4-*t*-butylcyclohexanecarboxylic acid in pure form, but instead used the partially separated mixture of isomers to prepare the nitrile. The nitrile obtained from the mixture was found to contain 36% of the *cis* nitrile and 64% of the *trans* nitrile.

Samples were equilibrated by placing 0.138 g. of the nitrile in 10 ml. of solvent and adding 0.11 g. of potassium *t*-butoxide. The reaction flasks were sealed with serum bottle caps and placed in a constant temperature bath at 28.0°. Samples were withdrawn with a hypodermic syringe, quenched with water, and extracted into pentane; the pentane solution dried and evaporated to a volume of about 0.5 ml. The samples were analyzed by gas chromatography on a 20% GE XF 1170 on Chromosorb W column (obtained commercially from the F and M Company), at a temperature of 120° and an inlet pressure of 30 p.s.i.g. The injection port of the chromatograph was maintained at 275°.

The data obtained are reported in Table I.

**Lithium Borohydride Reductions.**—Commercial lithium borohydride (96.7%, Metal Hydrides, Inc.) was used without further purification. Dimethyl sulfoxide (Baker AR grade) was fractionally frozen and stored over Molecular Sieves 4-A (The Linde Co.). Reagent grade pyridine was distilled from KOH and stored over Molecular Sieves 4-A. Commercial samples of cyclohexanone and of dihydroisophorone were used without further purification after gas chromatographic analysis had indicated the absence of other ketones. All manipulations of lithium borohydride were carried out under a dry nitrogen atmosphere. Reactions were carried out at room temperature of 24 ± 1°.

(19) H. H. Lau and H. Hart, *J. Am. Chem. Soc.*, **81**, 4897 (1959).

A typical kinetic run of the reduction of cyclohexanone in pyridine solvent was carried out as follows. A sample of lithium borohydride was transferred into a tared 10-ml. volumetric flask and weighed 0.0694 g. The flask was filled to volume with pyridine, and 3.2 ml. of the resulting solution (1.0 mmole of $LiBH_4$) was pipetted into a second 10-ml. volumetric flask and diluted to just below the mark with pyridine. A micropipet was then used to add 0.100 ml. of cyclohexanone to the solution. The reaction mixture was brought to volume exactly and, by means of a hypodermic syringe, an infrared cell was filled with the solution. The well matched reference cell was filled with pyridine beforehand. Infrared readings of the absorbance at 1705, 2240, and 2380 cm.$^{-1}$ were taken at frequent intervals for the first hour of reaction. The infrared cells used had a path length of 0.26 mm. which gave conveniently high absorbances for the dilute solutions.

For the reduction of cyclohexanone in dimethyl sulfoxide solution, higher concentrations of ketone and lithium borohydride were necessary to give an easily measurable rate. A typical run used 0.40 *M* borohydride and an equal initial concentration of ketone. The reaction mixture was kept in a 10-ml. volumetric flask, and samples were withdrawn and diluted to about one-fifth for infrared analyses. In a typical run, analyses were performed at intervals of 5, 160, 300, 480, and 700 min.

For the reductions in dimethyl sulfoxide, the data were plotted according to the integrated second-order, 4:1 stoichiometry, rate expression, $k_2t = (1/3K_0)\ln(K + 3K_0)/4K$, for the concentration of ketone where $K$ is the concentration of ketone at time $t$, $K_0$ is the initial concentration of ketone, which is equal to the initial concentration of borohydride, and $k_2$ is the second-order rate constant. An analogous expression is obtained for the concentration of borohydride.

The usual second-order, 1:1 stoichiometry, integrated rate expression was used for the reductions in pyridine.

As previously reported, we found that a large amount of reduction occurs on attempted quenching of these reaction mixtures with aqueous acid, aqueous base, or aqueous potassium iodate.[5]

The stereochemistry of the reductions of dihydroisophorone was determined by allowing the reduction to proceed to completion as indicated by infrared analysis. The reaction mixture was then poured into dilute HCl and extracted with ether. After drying, the ether was removed and the products were analyzed by gas chromatography on an 8 ft. UCON (water soluble) on firebrick column at 130°. The *cis* and *trans* alcohols, cyclohexanone, dihydroisophorone, and cyclohexanol were all completely resolved on this column.

**Acknowledgments.**—We wish to express our appreciation to the Graduate School of State University of New York at Buffalo for a grant for the purchase of the gas chromatography equipment used in this investigation. This work was supported in part by a grant from the Petroleum Research Fund. Grateful acknowledgment is made to the donors of this fund.

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

# Behavior of Esters in Liquid Hydrogen Fluoride. Walden Inversions and Ring Cleavage in Tetrahydrofuran Derivatives

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

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The behavior of esters of five polyhydroxytetrahydrofurans (1,4-anhydroglycitols) in liquid hydrogen fluoride has been examined. Deacylation was observed in every case, accompanied by Walden inversion, or ring cleavage, or both. Mechanisms are proposed to rationalize the observed reactions.

Recent investigations have shown that esters of polyhydroxycyclohexanes[2] and of polyhydroxytetrahydropyrans[3] readily undergo deacylation, often with concomitant Walden inversion, when treated with liquid hydrogen fluoride. In all cases studied, Walden

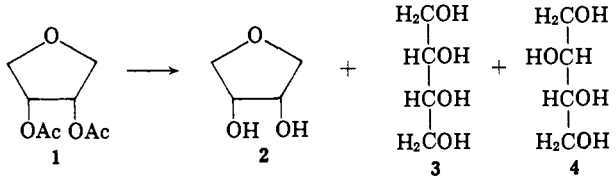
(1) Visiting Associate, 1961-1963.

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

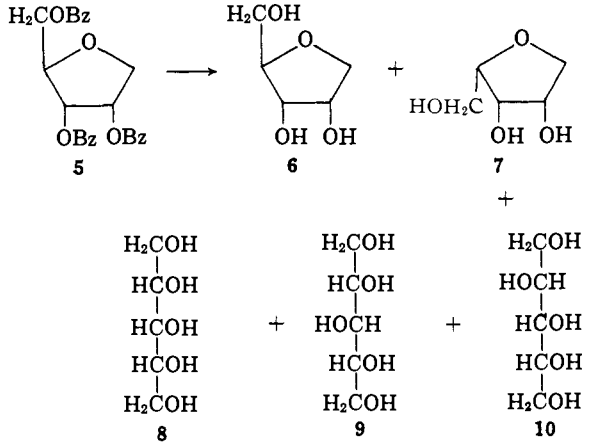
(3) E. J. Hedgley and H. G. Fletcher, Jr., *ibid.*, **85**, 1615 (1963).

inversion was encountered only when the ester contained a *cis–trans* sequence of contiguous acyloxy groups, the actual inversion occurring at the middle carbon atom of such a sequence. A comparatively simple mechanism, consonant with the observed facts, was proposed.[3] We have now extended these studies to the esters of a variety of polyhydroxytetrahydrofurans other than those bearing a hydroxyl group adjacent to the ring oxygen,[4] the 1,4-anhydroglycitols.

One of the simplest 1,4-anhydroglycitols is 1,4-anhydroerythritol (**2**) readily preparable from erythritol (**3**).[5] Like *myo*-inositol,[2] it was unattacked by liquid

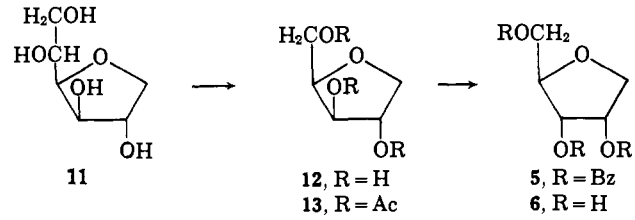



hydrogen fluoride. Its diacetate **1**, on the other hand, was converted into a mixture of 1,4-anhydroerythritol (**2**), erythritol (**3**), and threitol (**4**).[6] Similarly, 1,4-anhydro-D-ribitol (**6**)[7,8] proved to be stable in hydrogen fluoride solution while its tribenzoate **5**[9] afforded a complex mixture which contained 1,4-anhydroribitol (**6**), 1,4-anhydrolyxitol (**7**),[9] an unidentified 1,4-

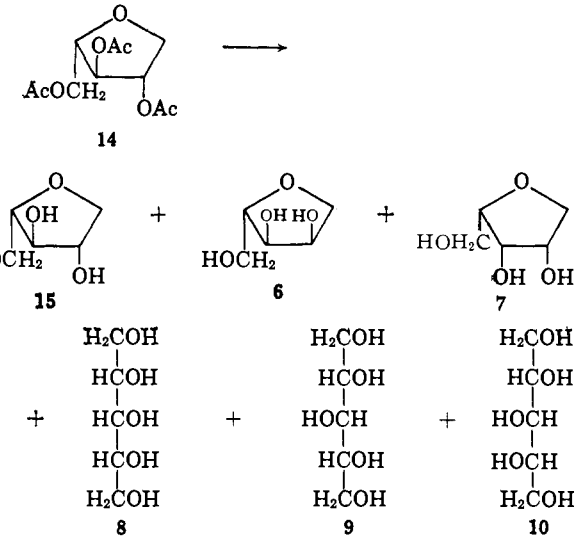



anhydropentitol (possibly 1,4-anhydroarabinitol), ribitol (**8**), xylitol (**9**), and DL-arabinitol (**10**), isolated as its crystalline pentabenzoate.

1,4-Anhydro-D-xylitol (**12**) was prepared from 1,4-anhydro-D-glucitol (**11**)[10,11] by cleavage of the C-5–C-6 bond with periodate and reduction of the aldehyde thus formed. On treatment with hydrogen fluoride, its triacetate **13** gave but one detectable product which was isolated in crystalline form and found to be 1,4-anhydro-D-ribitol (**6**); its identity was confirmed through conversion to its tribenzoate **5**.




Liquid hydrogen fluoride reacted with the triacetate of 1,4-anhydro-L-arabinitol (**14**)[12] to give a complex mixture of anhydropentitols and pentitols; chroma-




tography on a cellulose powder column separated these two groups of products. Paper electrophoresis of the anhydropentitol mixture showed it to consist of 1,4-anhydroarabinitol (**15**), 1,4-anhydroribitol (**6**), and 1,4-anhydrolyxitol (**7**). Paper electrophoresis of the pentitol mixture revealed ribitol (**8**), xylitol (**9**), and arabinitol (**10**).

Treatment of 1,4-anhydro-D-glucitol tetraacetate (**16**)[13,14] with liquid hydrogen fluoride also led to the formation of a complex mixture which was cleanly separable into two fractions by cellulose column chromatography. One fraction consisted of 1,4-anhydrohexitols; paper electrophoresis showed it to contain 1,4-anhydroglucitol (**11**), 1,4-anhydromannitol (**17**),[15,16] and a third anhydrohexitol which was not identified. The other fraction consisted of the hexitols, galactitol (**18**), glucitol (**19**), iditol (**20**), and mannitol (**21**) which were detected by paper electrophoresis. Neither allitol nor altritol was detected.

## Discussion

The hydrogen fluoride-induced Walden inversions in the cyclitol esters[2] and in 1,5-anhydroglycitol esters[3] are explicable in terms of the comparatively

(4) The 2-hydroxytetrahydrofurans include, of course, the furanose forms of the sugars, whose esters readily give acylated glycofuranosyl fluoride, when treated with hydrogen fluoride: *cf.* C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 941 (1960).

(5) F. H. Otey and C. L. Mehltretter, *J. Org. Chem.*, **26**, 1673 (1961).

(6) As with a number of other products encountered in this research, the threitol was identified by paper electrophoresis, and direct evidence as to the form obtained is therefore lacking. However, in view of the fact that **1** is a *meso* substance, the product must have been DL-threitol. For simplicity in this and other cases, the formula for only one enantiomorph is given.

(7) R. Kuhn and G. Wendt, *Chem. Ber.*, **81**, 553 (1948).

(8) F. Weygand and F. Wirth, *ibid.*, **85**, 1000 (1952).

(9) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org Chem.*, **28**, 428 (1963).

(10) S. Soltzberg, R. M. Goepp, Jr., and W. Freudenberg, *J. Am. Chem. Soc.*, **68**, 919 (1946).

(11) R. C. Hockett, M. Conley, M. Yusem, and R. I. Mason, *ibid.*, **68** 922 (1946).

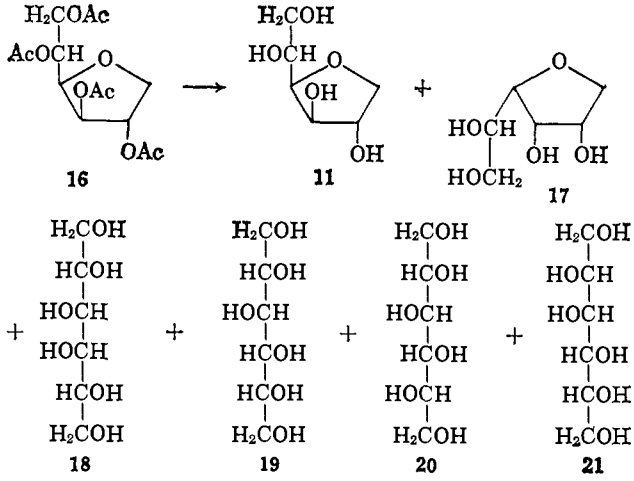
(12) 1,4-Anhydro-L-arabinitol was prepared by R. Barker and H. G. Fletcher, Jr. [*J. Org. Chem.*, **26**, 4605 (1961)], who isolated it as its tri-*p*-nitrobenzoate.

(13) V. G. Bashford and L. F. Wiggins, *J. Chem. Soc.*, 299 (1948).

(14) H. G. Fletcher, Jr., and C. M. Sponable, *J. Am. Chem. Soc.*, **70**, 3943 (1948).

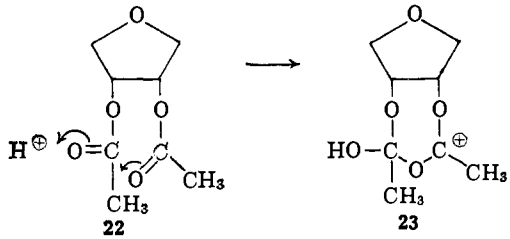
(15) F. Valentin, *Collection Czech. Chem. Commun.*, **8**, 35 (1936).

(16) R. C. Hockett, H. G. Fletcher, Jr., E. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, *J. Am. Chem. Soc.*, **68**, 930 (1946).

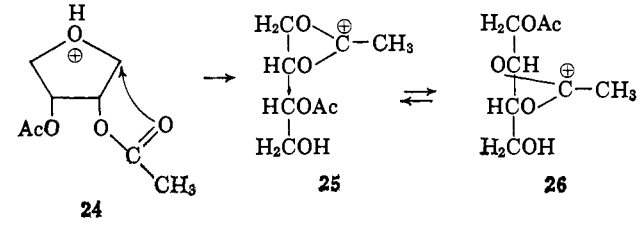


simple mechanism proposed earlier. However, the behavior of the esters of 1,4-anhydroglycitols in hydrogen fluoride stands in marked contrast to that of the two classes of substances previously studied. Despite the fact that these tetrahydrofuran derivatives cannot possess the contiguous *cis–trans*-triacyloxy sequence which was shown to be essential for the six-membered cyclic systems, they not only undergo Walden inversion but usually suffer ring cleavage as well. Methods used for the detection of glycitols are particularly sensitive, but no evidence for the ring cleavage of the esters of the 1,5-anhydroglycitol esters was obtained during the investigation of those compounds.[3] It is apparent that a mechanism, different (at least in some respects) from that previously evoked, is operating here. However, one factor is common to the three classes: when not acylated the substances appear to be completely unaltered by solution in hydrogen fluoride. The acyl groups, then, play an essential part in the transformations observed.

Let us first consider 1,4-anhydroerythritol diacetate (**22**). On the basis of previously developed concepts[2,3] one would expect that protonation of this substance in hydrogen fluoride would cause the two *cis*-acyloxy groups to join in the formation of a seven-membered ring (**23**), preserving the structural and configura-

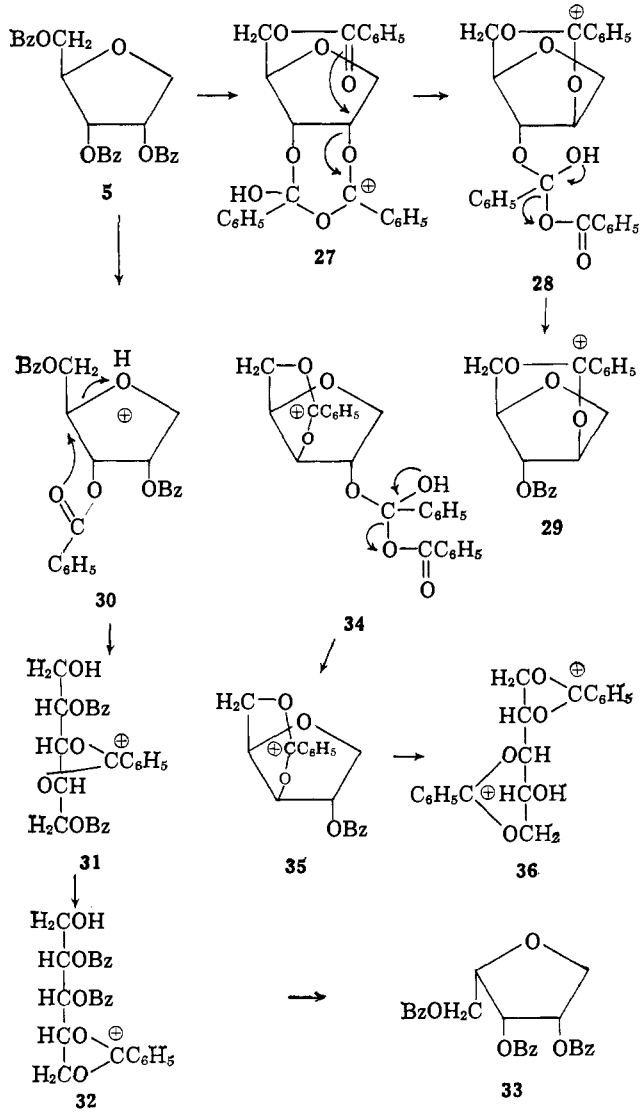


tional integrity of the anhydride since the eventual addition of water would convert **23** to 1,4-anhydroerythritol. To rationalize the observed occurrence of ring cleavage it appears necessary to postulate a second type of reaction, competitive with that which leads to **23**. We suggest that one of the acyloxy groups (it matters not which, since they are equivalent in this case) may attack its adjacent methylene carbon (**24**), the protonated ring oxygen being displaced to give the ionic intermediate **25**. The cyclic ion in **25** could then undergo nucleophilic attack by the acyloxy group at C-3 to give **26**. Addition of water would convert **25** to erythritol and **26** to threitol.



1,4-Anhydro-D-ribitol tribenzoate (**5**) bears a structural resemblance to 1,4-anhydroerythritol diacetate (**24**), but is complicated by the presence of an acyloxymethyl group at C-4.[17] As with the simpler ester **24**, we may postulate an initial union of the *cis*-acyloxy groups to form a seven-membered ring as in **27**. The *trans*-annular attack of the C-5 benzoyl on C-2 in **27** leads to **28** which would lose benzoic acid to form **29**, a derivative of 1,4-anhydro-D-arabinitol.

The formation of 1,4-anhydro-D-lyxitol from 1,4-anhydro-D-ribitol tribenzoate (**5**) would necessitate the inversion of both C-2 and C-3. However, the formation of 1,4-anhydro-L-lyxitol (**7**) requires only inversion at C-4, and a plausible mechanism for such a

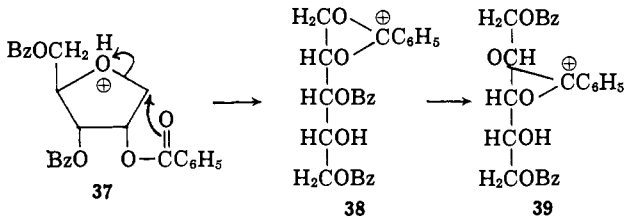


(17) No evidence has been found to indicate that benzoates differ significantly from acetates as regards their behavior in hydrogen fluoride other than the fact that this reagent removes acetyl groups completely but benzoyl groups only partially. *Cf.* the Experimental part of this paper as well as ref. 3, footnote 7.

conversion is provided by that postulated earlier for the ring cleavage of 1,4-anhydroerythritol diacetate (**24** → **25**). Attack of the C-3 benzoyl group on C-4 (**30**) would give a cyclic ion of the L-arabinitol series (**31**) which could then rearrange to the ribitol derivative **32**. Ring closure of **32** through attack of the oxygen at C-1 on C-4 would give 1,4-anhydro-L-lyxitol tribenzoate (**33**). 1,4-Anhydro-D-ribitol can arise either by the simple debenzoylation of **5** or the rearrangement of **29**. Thus the three anhydropentitols observed are accounted for.

The formation of the four pentitols may equally well be rationalized. The intermediate **32** would give ribitol while **31** would give L-arabinitol. In accounting for xylitol, it should be noted that while **27** is depicted with the positive charge localized on the carbon atom contributed originally by the C-2 benzoyloxy group, the bicyclic ion may be written in an alternative form in which the charge is borne by the carbon atom contributed originally by the C-3 benzoyloxy group. Attack of the C-5 benzoyl on C-3 in such an intermediate would give the 1,4-anhydro-D-xylitol derivatives **34** and **35**. Ring cleavage of the latter could give the xylitol derivative **36**. In passing, it may be noted that rearrangement of **35** would lead to 1,4-anhydro-D-ribitol.

The formation of D-arabinitol may be envisaged as occurring through cleavage of **37** to the ribitol derivative **38** and subsequent rearrangement of the latter to

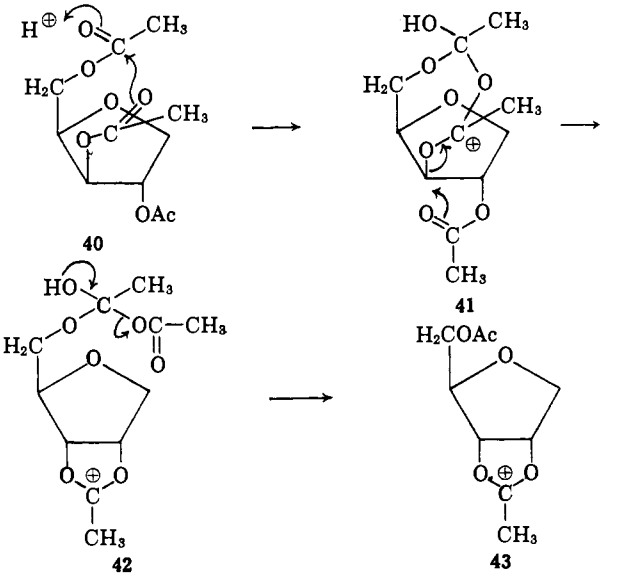


**37** **38** **39**

the D-arabinitol derivative **39**.

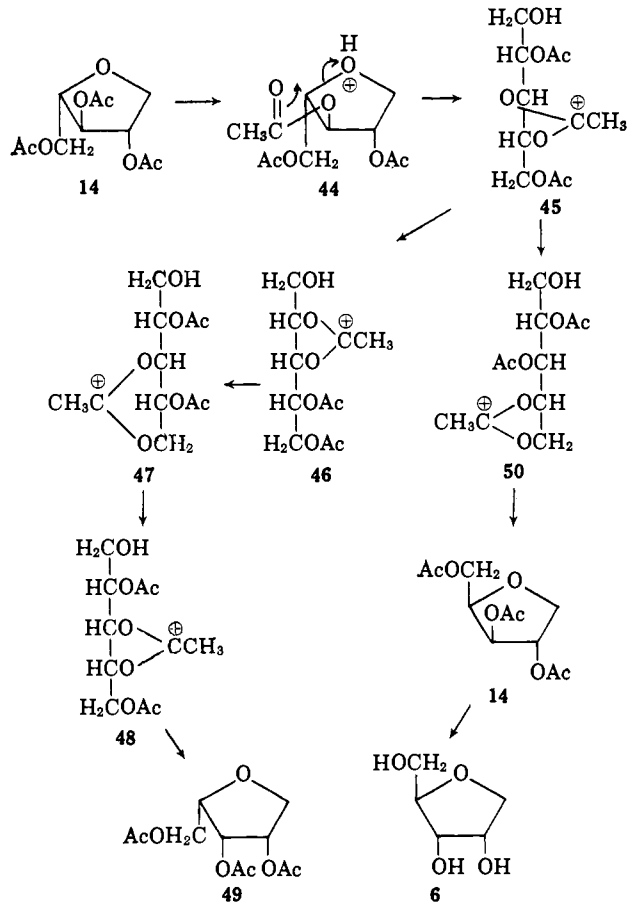
The reaction of 1,4-anhydro-D-xylitol triacetate (**40**) with hydrogen fluoride appears to be a fairly simple one, leading as it does to a high yield of optically pure 1,4-anhydro-D-ribitol (**6**) in complete absence of ring cleavage. Unique among the 1,4-anhydropentitol esters studied, 1,4-anhydro-D-xylitol triacetate (**40**) has acyl groups at C-3 and C-5 which are sterically accessible to each other, suggesting that an intermediate such as **41** may first be formed. Nucleophilic attack at C-3 by the acetoxy group of C-2 would yield **42**, loss of acetic acid then giving the 1,4-anhydro-D-ribitol derivative **43**. Two aspects of this proposed mechanism deserve special comment. First, attack of the C-5 acetyl group on C-4 of **43** would open the ring and lead to further transformations. However, as stated above, no evidence of ring cleavage was obtained and, indeed, we have in no case found it necessary to postulate such an attack by an exocyclic acyl group in order to explain the variety of products formed. Second, the reader will have noted that in principle **43** might rearrange to one or both of the intermediates analogous to the benzoates **29** and **35** previously postulated. Its failure in fact to rearrange may be attributed to the greater stability of the ring structure in **43** than that in **27**.

In seeking an explanation of the products occurring in the reaction of 1,4-anhydro-L-arabinitol triacetate



**40** **41** **42** **43**

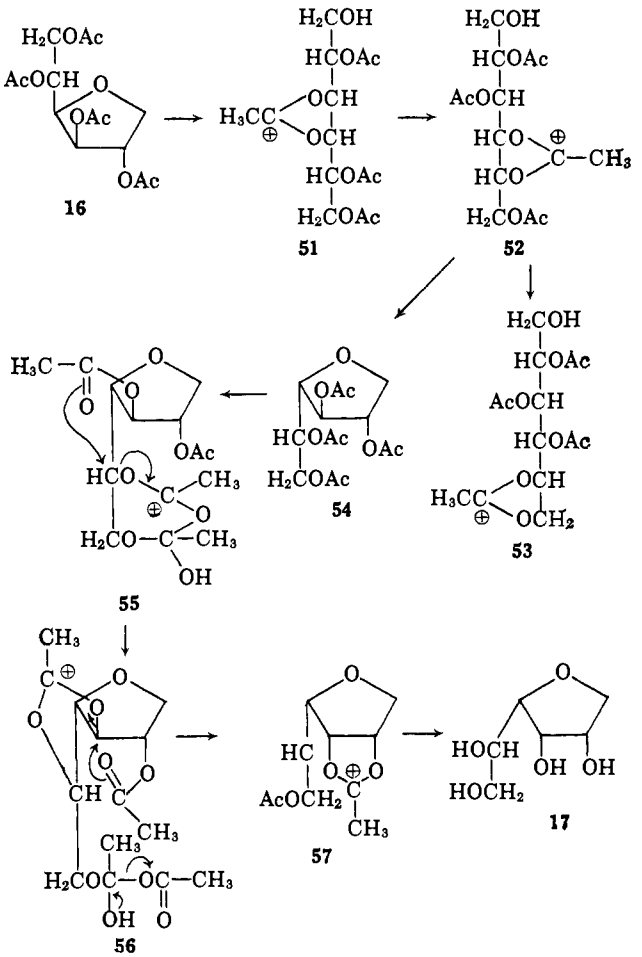
(**44**) with hydrogen fluoride, it appears necessary to assume the formation of the intermediate **47**, a structure made feasible by the flexibility inherent in the open chain pentitol derivatives. This intermediate (**47**) is envisaged to arise by the sequence of ring cleavage and rearrangements **14** → **47** representing essentially no departure from schemes so far postulated. Rearrangement of **47** affords the ribitol derivative **48**, cyclization of which leads to 1,4-anhydro-L-lyxitol tetraacetate (**49**). The intermediate xylitol derivative **45** then may rearrange on the one hand to **46**, a ribitol derivative, or on the other hand to **50**, an L-arabinitol derivative. Cyclization of the latter would lead to



**14** **44** **45** **47** **46** **50** **48** **14** **49** **6**

1,4-anhydro-D-xylitol triacetate (**14**), a substance which, as has been established by experiment, is converted exclusively to 1,4-anhydro-D-ribitol (**6**).

Finally, we come to the behavior of 1,4-anhydro-D-glucitol tetraacetate (**16**) with hydrogen fluoride. It can be seen that, following the now familiar pattern, cleavage by attack of the acetyl of C-3 on C-4 will open the ring to give **51**, a galactitol derivative which rearranges to **52**, a D-glucitol derivative. The latter in turn may rearrange to the L-iditol derivative **53** or, alternatively, cyclize to 1,4-anhydro-D-galactitol tetraacetate (**54**). Union of the acetyl groups of C-5 and C-6 produces **55**, facilitating the attack of the acetyl at C-3 on C-5 to give a cyclic ion (**56**) related to 1,4-anhydro-L-altritol. A final rearrangement involving nucleophilic displacement at C-3 by the acetyl group of C-2 affords the ion **57** which would give 1,4-anhydro-L-mannitol (**17**).



In conclusion, it should be emphasized that these mechanisms, while mutually consistent and in accord with the observed facts, are necessarily speculative at this juncture. They, however, have the merit of suggesting further experiments; some of these experiments are described in the following paper.[18]

## Experimental[19]

**Chromatography and Electrophoresis.**[20]—Paper chromatography was conducted on Whatman No. 1 or No. 31 paper in the descending manner with aqueous acetone ($H_2O$–acetone, 1:9 v./v.) unless otherwise stated. Columns for chromatography (4 × 58 cm.) were prepared from Whatman Standard Grade cellulose powder, packed as a slurry in acetone, and developed with the same solvent used for chromatograms. Eluate was collected in 25-ml. portions.

Paper electrophoresis was conducted on Whatman No. 3 paper in either arsenite,[21] borate, or basic lead acetate buffer solution of composition specified by Frahn and Mills.[22]

Glycitols and anhydroglycitols were detected on chromatograms and those electrophoretograms which had been conducted in arsenite or borate buffers by spraying, first with 0.2% (or less for increased sensitivity) sodium metaperiodate in dilute acetic acid, and then (after 4–5 min.) with 2% *p*-anisidine in dilute acetic acid. With electrophoretograms using arsenite buffer, it was often found advantageous to respray lightly with the periodate reagent after the *p*-anisidine spray had been allowed to dry somewhat. Detection of compounds on electrophoretograms which had been run in basic lead acetate was achieved using the hydrogen peroxide spray recommended by Frahn and Mills.[22] Both 1,4-anhydroarabinitol and 1,4-anhydroxylitol respond feebly to the periodate–*p*-anisidine treatment and the detection of trace quantities of these substances, especially on arsenite electrophoretograms, by this method is difficult. On paper chromatograms (but not on electrophoretograms), these two anhydrides are readily detected through the use of ammoniacal silver nitrate spray (10% w./v.) or, alternatively, by spraying with a saturated aqueous solution of basic lead acetate and then with the hydrogen peroxide reagent as for electrophoretograms run in basic lead acetate buffer.

**2,3-Di-*O*-acetyl-1,4-anhydroerythritol** (1).—1,4-Anhydroerythritol was prepared by a modification of the procedure of Otey and Mehltretter.[5] Erythritol (10 g., m.p. 117–122°) was mixed with 1 g. of Amberlite IR-120(H) and heated at 130–140° (bath) for 1.5 hr. The product was then distilled at 98–104° and 0.04 mm.; 5.78 g., 18%. On redistillation from 1 g. of fresh IR-120-(H), the 1,4-anhydroerythritol was obtained as a colorless, hygroscopic sirup which showed $n^{20}D$ 1.4769[23] and was free of erythritol as demonstrated by paper chromatography.

Freshly distilled 1,4-anhydroerythritol was acetylated with acetic anhydride and anhydrous sodium acetate in conventional fashion to yield a mobile oil of b.p. 66–67° (0.04 mm.). The redistilled product ($n^{20}D$ 1.4465), showing no OH absorption in the infrared region, was used without further purification in subsequent experiments. A sample of the 2,3-di-*O*-acetyl 1,4-anhydroerythritol was deacetylated and then *p*-nitrobenzoylated to give 1,4-anhydro-2,3-di-*O*-*p*-nitrobenzoylerythritol as pale green prisms, m.p. 175–176°. Klosterman and Smith[24] reported m.p. 173–174° for this substance.

*Anal.* Calcd. for $C_5H_{12}O_5$ (188.18): C, 51.06; H, 6.43. Found: C, 51.80; H, 6.65.

**Behavior of 1,4-Anhydroerythritol (2) with Hydrogen Fluoride.**—1,4-Anhydroerythritol (0.28 g., chromatographically free of erythritol) was dissolved in *ca.* 10 ml. of liquid hydrogen fluoride and the solution kept at 18° for 24 hr. The hydrogen fluoride was removed from the colorless solution with a stream of air and the sirupy residue neutralized through the addition of saturated aqueous sodium bicarbonate in which it was completely soluble. Paper chromatography, using 2% aqueous acetone, revealed only 1,4-anhydroethythritol, tetritols being absent.[25] Electrophoresis in borate buffer (2 hr., 15 v./cm., 40 ma.) revealed only a single component, migrating at the same rate as 1,4-anhydroerythritol.[26]

**Behavior of 2,3-Di-*O*-acetyl-1,4-anhydroerythritol** (1) **with Hydrogen Fluoride.**—2,3-Di-*O*-acetyl-1,4-anhydroerythritol (4.30 g.) was dissolved in *ca.* 30 ml. of liquid hydrogen fluoride and the slightly pink solution maintained at 18° for 24 hr. After the hydrogen fluoride had been removed with a stream of air, the residue was neutralized with saturated aqueous sodium bicarbon-

(18) E. J. Hedgley and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **86**, 1583 (1964).

(19) Melting points are corrected.

(20) All identifications based on chromatography or electrophoresis were made through direct comparison with authentic specimens run simultaneously with the unknowns.

(21) With this system, salt bridges of 0.05 *M* sodium tetraborate were used to protect the platinum electrodes.

(22) J. L. Frahn and J. A. Mills, *Australian J. Chem.*, **12**, 65 (1959).

(23) Otey and Mehltretter (ref. 5) reported $n^{25}D$ 1.478; the hygroscopicity of the anhydride renders a precise determination difficult.

(24) H. Klosterman and F. Smith, *J. Am. Chem. Soc.*, **74**, 5336 (1952).

(25) Although threitol and erythritol are not resolved in this solvent system, they are well separated from 1,4-anhydroerythritol.

(26) 1,4-Anhydroerythritol and 1,4-anhydrothreitol are readily separable under these conditions: *cf.* J. S. Brimacombe, A. B. Foster, M. Stacey, and D. H. Whiffen, *Tetrahedron*, **4**, 351 (1958).

ate. The somewhat opalescent solution was evaporated to dryness and the residue extracted with boiling absolute ethanol. Evaporation of the alcoholic extract afforded a hygroscopic sirup (3.11 g.) which showed a feeble ester carbonyl absorption in the infrared region. The sirup was, therefore, treated with sodium methoxide in methanol for 12 hr. and the solution then deionized with Amberlite IR-120(H). The resulting solution was examined by paper chromatography using 2% aqueous acetone. Two components, detectable with the periodate–*p*-anisidine reagent, were observed; one, with the greater $R_f$, corresponded to a 1,4-anhydrotetritol and the other to a tetritol. Evaporation of the methanolic solution gave a hygroscopic sirup (1.46 g. after equilibration with atmospheric moisture) which was chromatographed on a column of cellulose powder using aqueous acetone for elution. Periodate-positive material emerged from the column after 600 ml. of eluate had been collected and was present in the succeeding 175 ml. of collected solvent. A second periodate-positive component (uncontaminated with the first) emerged after a total of 950 ml. had passed through the column and was completely eluted after a further 300 ml. of eluate had been collected.

Evaporation of the eluate containing the second component afforded a hygroscopic sirup (0.52 g.) which was investigated by paper electrophoresis in arsenite buffer (3.5 hr., 5 v./cm., 40 ma.); it consisted of a mixture of erythritol and threitol.

Evaporation of the solvent containing the first component eluted from the column also gave a hygroscopic sirup (0.53 g.). Paper chromatography and electrophoresis (borate buffer, 2 hr., 15 v./cm., 40 ma.) showed this to be a homogeneous specimen of 1,4-anhydroerythritol, no 1,4-anhydrothreitol being detected. Identification was confirmed through the preparation of the di-*p*-nitrobenzoate, pale green prisms from acetone, m.p. 174–176.6°; admixture with an authentic sample caused no depression.

**Behavior of 1,4-Anhydro-D-ribitol (6) with Hydrogen Fluoride.**—1,4-Anhydro-D-ribitol was prepared through the reduction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide with lithium aluminum hydride[8] and purified by chromatography on a cellulose powder column using aqueous acetone.

A sample (65 mg., m.p. 99–102°) of chromatographically pure 1,4-anhydro-D-ribitol was dissolved in *ca.* 15 ml. of liquid hydrogen fluoride and the solution kept at 18° for 7 hr. After removal of the bulk of the hydrogen fluoride the acid in the residue was neutralized by the addition of 1 ml. of saturated aqueous sodium bicarbonate solution. The aqueous solution was evaporated to dryness and the residue extracted with boiling ethanol; after concentration, the ethanolic extract was examined by paper chromatography and electrophoresis (borate buffer, 2 hr., 25 v./cm., 50 ma.; arsenite buffer, 2.75 hr., 17 v./cm., 50 ma.). In each case only a single component, corresponding to 1,4-anhydro-D-ribitol, was detectable using the periodate–*p*-anisidine reagent. Complete evaporation of the ethanolic solution yielded a stiff sirup which crystallized spontaneously after storage for a few days. Upon recrystallization from acetone, the material was obtained as fine needles which showed m.p. 101–102° either alone or in admixture with authentic 1,4-anhydro-D-ribitol.

**Behavior of 1,4-Anhydro-2,3,5-tri-*O*-benzoyl-D-ribitol (5) with Hydrogen Fluoride.**—1,4-Anhydro-2,3,5-tri-*O*-benzoyl-D-ribitol[9] (m.p. 71–72°, 3.93 g.) was dissolved in *ca.* 50 ml. of liquid hydrogen fluoride and the solution stored at 18° for 3 days. After removal of the major part of the hydrogen fluoride with a stream of air, the sirupy residue was neutralized with *ca.* 100 ml. of saturated aqueous sodium bicarbonate. The insoluble sirup which separated was removed by the addition of 100 ml. of dichloromethane, the aqueous solution being extracted with dichloromethane (2 × 50 ml.) and the organic solutions being pooled. Removal of the water from the aqueous phase afforded a dry residue which was extracted with boiling ethanol. After concentration, the ethanolic extract was examined by paper chromatography. No carbohydrate materials could be detected by the periodate–*p*-anisidine reagent and the extract was, therefore, discarded.

The dichloromethane solution obtained above was dried with magnesium sulfate and concentrated, the residual sirup being held at 60° and 0.1 mm. pressure to give a glass (2.99 g.). The infrared absorption spectrum of this glass showed strong absorption at frequencies associated with both hydroxyl and ester carbonyl groups; a test for fluorine[27] in the material was essentially negative. Accordingly, the entire glass was debenzoylated with sodium ethoxide in ethanol to give (after the conventional purification) 1.17 g. of deionized, solvent-free sirup. The product was chromatographed on a cellulose-powder column using aqueous acetone for elution. Two periodate-positive components, free from mutual contamination, were obtained, the first emerging after the collection of 700 ml. of eluate and the second after 1150 ml. of eluate had been collected.

The first component, 0.40 g. of sirup, moved at the rate of a 1,4-anhydropentitol on paper chromatography in 5% aqueous acetone, a system which fails to separate the 1,4-anhydropentitols from one another. Paper electrophoresis in arsenite buffer (4 hr., 15 v./cm., 40 ma.) resolved the mixture into three components; of these, two migrated at rates identical with 1,4-anhydroribitol and 1,4-anhydrolyxitol, respectively. The third component was not identified unequivocally but migrated at a rate not incompatible with 1,4-anhydroarabinitol.

The second component from the cellulose column was obtained as a hygroscopic sirup (0.83 g.) which paper chromatography showed to be a pentitol or mixture of pentitols. On benzoylation with benzoyl chloride in pyridine, the material afforded a crystalline benzoate which was optically inactive in the wave length range of 300–700 mμ ($CH_3CN$, *c* 1.36, *l* 10 cm.). Recrystallization from ethanol gave needles, m.p. 134–135°, undepressed on admixture with authentic DL-arabinitol pentabenzoate.

*Anal.* Calcd. for $C_{40}H_{32}O_{10}$ (672.66): C, 71.42; H, 4.80; $C_6H_5CO$, 78.13. Found: C, 71.13; H, 4.50; $C_6H_5CO$, 77.9.

Debenzoylation of the pentabenzoate gave crystalline, electrophoretically homogeneous[28] DL-arabinitol which was further characterized as its pentaacetate, m.p. 95–96°, indistinguishable by vapor phase chromatography[29] from authentic DL-arabinitol pentaacetate.[30]

The combined mother liquors from the recrystallization of DL-arabinitol pentabenzoate were debenzoylated to leave a sirup which was examined by paper electrophoresis in arsenite and lead acetate buffers (3 hr., 18 v./cm., 60 ma., and 4.5 hr., 39 v./cm., 40 ma., respectively) and shown to contain arabinitol, ribitol, and xylitol.

**1,4-Anhydro-D-xylitol (12) and its Triacetate (13).**—A method which Kjølberg[31] used for shortening the chain length of glycosides was adapted to the synthesis of 1,4-anhydro-D-xylitol. 1,4-Anhydro-D-glucitol[32] (1.64 g., m.p. 113–115°) was dissolved in 20 ml. of water and the solution stirred during the dropwise addition of a solution of 2.15 g. (1 molar equivalent) of sodium metaperiodate in 25 ml. of water. After 3 hr. at room temperature the reaction mixture was concentrated to dryness and the residue extracted with 3 × 25 ml. of hot ethanol. The combined extracts were concentrated to a sirup which was dissolved in 25 ml. of water and the solution treated with 0.25 g. of sodium borohydride. After 12 hr., the solution was decationized, freed of boric acid, and concentrated *in vacuo* to yield crude 1,4-anhydro-D-xylitol as a colorless sirup (1.26 g.). This sirup was acetylated with acetic anhydride and anhydrous sodium acetate and the triacetate distilled: 1.66 g., b.p. 90–98° (0.04 mm.), $[\alpha]^{20}D$ +31.5 ± 1.5° (*c* 0.92 in $CH_2Cl_2$), $n^{20}D$ 1.4537.

*Anal.* Calcd. for $C_{11}H_{16}O_7$ (260.24): C, 50.76; H, 6.20. Found: C, 50.80; H, 6.32.

Catalytic deacetylation of a portion of the triacetate regenerated pure **1,4-anhydro-D-xylitol** as a viscous, very hygroscopic sirup which distilled at 160–170° and 0.02 mm.

*Anal.* Calcd. for $C_5H_{10}O_4$ (134.13): C, 44.78; H, 7.52. Found: C, 44.42; H, 7.61.

A sample (0.041 g.) of 2,3,5-tri-*O*-acetyl-1,4-anhydro-D-xylitol was deacetylated with sodium methoxide in methanol, the solvent removed, and the product dissolved in water to a total volume of 2.5 ml. The resulting solution showed a rotation corresponding to $[\alpha]^{20}D$ −11.2 ± 1.0° (*c* 0.9) for 1,4-anhydro-D-xylitol.

**Behavior of 2,3,5-Tri-*O*-acetyl-1,4-anhydro-D-xylitol (13) with Hydrogen Fluoride.**—2,3,5-Tri-*O*-acetyl-1,4-anhydro-D-xylitol (1.29 g.) was dissolved in *ca.* 20 ml. of hydrogen fluoride and the straw-colored solution stored at 18° for 24 hr. Evaporation of the hydrogen fluoride in the usual way left a brown residue; on

(27) Amadac-F reagent (Burdick & Jackson Laboratories, Muskegon, Mich.) was used after combustion of the sample in an oxygen atmosphere.

(28) Arsenite buffer, 3 hr., 18 v./cm., 60 ma.; lead acetate buffer, 6 hr., 30 v./cm., 35 ma.

(29) Column 2 ft. long, 15% Q.F. 1 on 60–80 mesh Chromosorb A, 40 ml. argon/min., programmed from 150° at 5.6°/min.

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

(31) O. Kjølberg, *Acta Chem. Scand.*, **14**, 1118 (1960).

(32) Kindly provided by Dr. J. W. LeMaistre, Atlas Chemical Industries, Inc.

neutralization with saturated aqueous sodium bicarbonate there was obtained a straw-colored solution containing a trace of colored insoluble matter as fine flecks. The solution was evaporated to dryness and the residue extracted with boiling ethanol. After concentration, the extract was examined by paper chromatography and electrophoresis (arsenite and borate buffers), these techniques revealing a component which migrated at the same rate as 1,4-anhydroribitol. No pentitols or other anhydropentitols were detected. The entire alcoholic extract was concentrated to dryness and the residue acetylated with acetic anhydride and sodium acetate. After the conventional work-up the product was distilled as a colorless, mobile liquid: 1.12 g., b.p. 110–112° (0.06 mm.) The acetate thus made was deacetylated catalytically to give a stiff sirup (0.57 g., 86%) which crystallized promptly on scratching. Recrystallization from ethanol afforded prismatic needles, m.p. 104°; sublimation at 110–140° (bath) and 0.04 mm. gave material of m.p. 101–103° and $[\alpha]^{20}D$ +67.3 ± 1.0° in water (*c* 0.9). A mixture melting point with authentic 1,4-anhydro-D-ribitol was undepressed. Further characterization of the product was made through its tribenzoate which had m.p. 73–74° and $[\alpha]^{20}D$ +106.3 ± 1.0° (chloroform, *c* 0.85); a mixture melting point with authentic 1,4-anhydro-2,3,5-tri-*O*-benzoyl-D-ribitol[9] was undepressed.

**2,3,5-Tri-*O*-acetyl-1,4-anhydro-L-arabinitol** (14).—An improvement on the general procedure of Barker and Fletcher[12] was used for the preparation of 1,4-anhydro-L-arabinitol. 2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose[33] (8.4 g.) was treated in benzene solution with hydrogen chloride as described by Glaudemans and Fletcher[34] for the D-isomer to yield 2,3,5-tri-*O*-benzyl-L-arabinofuranosyl chloride as a clear, colorless sirup which was dried *in vacuo* over sodium hydroxide for 12 hr. (7.7 g.). The chloride was reduced with lithium aluminum hydride in tetrahydrofuran solution in a manner similar to that used by Barker and Fletcher[12] for the analogous bromide. The resulting sirupy 1,4-anhydro-2,3,5,-tri-*O*-benzyl-L-arabinitol (6.95 g.) was hydrogenolyzed in ethanolic solution using hydrogen and 10% palladium-on-charcoal to give 1,4-anhydro-L-arabinitol as a clear sirup (2.10 g.) which paper chromatography showed to be homogeneous and free of arabinitol. Acetylation with acetic anhydride and anhydrous sodium acetate afforded 2,3,5-tri-*O*-acetyl-1,4-anhydro-L-arabinitol as a mobile liquid which was distilled at 106–108° and 0.06 mm.; 4.08 g. (78%), $n^{20}D$ 1.4511, $[\alpha]^{20}D$ +22.6 ± 2.0° ($CHCl_3$, *c* 1.1).

*Anal.* Calcd. for $C_{11}H_{16}O_7$ (260.24): C, 50.76; H, 6.20; $CH_3CO$, 49.62. Found: C, 50.63; H, 6.38; $CH_3CO$, 49.1.

Vapor phase chromatography, using a 6-ft. column packed with 1% S.E. 30 on Gaschrom P at 190° and 25 ml. of nitrogen per min., showed the triacetate to be homogeneous (retention time 25 sec.).

**Behavior of 2,3,5-Tri-*O*-acetyl-1,4-anhydro-L-arabinitol** (14) **with Hydrogen Fluoride.**—2,3,5-Tri-*O*-acetyl-1,4-anhydro-L-arabinitol (1.32 g.) was dissolved in *ca.* 15 ml. of hydrogen fluoride and the solution left at 18° for 24 hr. After removal of the excess of reagent, the colorless residue was neutralized with saturated aqueous sodium bicarbonate solution in which it dissolved completely. The solution was evaporated to dryness and the residue acetylated with acetic anhydride and sodium acetate. After the usual purification, the product (1.43 g.) was obtained as a colorless mobile oil. Catalytic deacetylation, followed by decationization, afforded a colorless, hygroscopic sirup (0.60 g.) which was chromatographed on a cellulose powder column, developed with aqueous acetone. Two fractions giving a positive test when spotted on paper and sprayed with basic lead acetate and then with hydrogen peroxide[22] were eluted. The first of these began to appear after the collection of 550 ml. of eluate and was obtained as 0.48 g. of colorless, hygroscopic sirup. The second fraction began to appear after 1 l. of eluate had been collected and was obtained as 0.11 g. of colorless sirup. On paper chromatography the first fraction was found to move at the rate of a 1,4-anhydropentitol and showed no contamination with pentitols; the second fraction moved at the rate of a pentitol, no anhydropentitols being detected. Paper electrophoresis of the first fraction (arsenite buffer, 3 hr., 15 v./cm., 60 ma.) showed three components having rates of migration identical with 1,4-anhydrolyxitol, 1,4-anhydroribitol, and 1,4-anhydroarabinitol, authentic samples of these substances being run at the same time.

The second fraction was also resolvable into three components when subjected to electrophoresis in arsenite buffer; these were identifiable as arabinitol, ribitol, and xylitol.

**Behavior of 2,3,5,6-Tetra-*O*-acetyl-1,4-anhydro-D-glucitol** (16) **with Hydrogen Fluoride.**—2,3,5,6-Tetra-*O*-acetyl-1,4-anhydroglucitol[14] (3.33 g.) was dissolved in *ca.* 60 ml. of hydrogen fluoride and the solution stored at 18° for 24 hr. After removal of the major part of the hydrogen fluoride with a stream of air, the colorless, sirupy residue dissolved completely in the aqueous sodium bicarbonate solution used to effect neutralization. The aqueous solution was evaporated to dryness and the resulting residue acetylated with acetic anhydride and sodium acetate to give, after the usual purification, 3.16 g. of colorless sirup; on catalytic deacetylation, this material afforded 1.58 g. of colorless sirup.

Paper chromatography resolved the product into two components detectable by periodate–*p*-anisidine, that with the larger $R_f$ being characteristic of the anhydrohexitols while the slower moving component had an $R_f$ characteristic of a hexitol. The two components were cleanly separable on a cellulose column developed with aqueous acetone, 0.76 g. of the sirup affording a first component (0.69 g. of sirup) which emerged after 600 ml. of eluate had been collected and a second component (0.04 g. of sirup) after 1400 ml. of eluate had passed through the column. Paper electrophoresis of the second component (basic lead acetate buffer, 8 hr., 30 v./cm., 35 ma.) resolved the material into four substances identifiable as galactitol, glucitol, iditol, and mannitol; neither allitol nor altritol was detected.

The first component which had emerged from the cellulose column was subjected to paper electrophoresis in borate buffer (2 hr., 30 v./cm., 60 ma.) and resolved into two spots, corresponding to 1,4-anhydroglucitol and 1,4-anhydromannitol. Paper electrophoresis in arsenite or basic lead acetate (2 hr., 18 v./cm., 60 ma., and 3 hr., 30 v./cm., 55 ma., respectively) confirmed the presence of 1,4-anhydroglucitol and of 1,4-anhydromannitol. A third substance was detected in these two systems; this was neither 1,4-anhydroiditol[32] nor 1,4-anhydrogalactitol, but the lack of further key reference compounds prevented unequivocal identification.

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(33) S. Tejima and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 2999 (1963).
(34) C. P. J. Glaudemans and H. G. Fletcher, Jr., *ibid.*, **28**, 3004 (1963).