1,1,4,4-tetraphenylbutane, showed no peak at 6.17 τ for benzhydrylic hydrogen. Mass spectrometry showed the compound to have mol. wt. 364 and to contain two deuterium atoms per molecule.[30]

Methanolysis of 1,4-Difluoro-1,1,4,4-tetraphenylbutane (XIX).—A mixture of 100 mg. (0.25 mmole) of 1,4-difluoro-1,1,4,4-tetraphenylbutane, 5.0 ml. of dioxane and 14 ml. of methanol was heated to boiling. After 5 minutes of boiling, an additional 1.0 ml. of dioxane was added to the suspension and as soon as the last traces of solid had dissolved a solution of 2 drops of concentrated sulfuric acid in 2.0 ml. of methanol was added. The solution was maintained at the reflux temperature for 20 minutes, treated again with concentrated sulfuric acid (1 drop) in methanol (1.0 ml.), and allowed to cool to room temperature. From the light green solution, 63 mg. of colorless needles, m.p. 199–217°, separated after standing overnight at room temperature. Three recrystallizations of this material from toluene gave 30 mg. (27%) of 1,4-dimethoxy-1,1,4,4-tetraphenylbutane, m.p. 233–234° (lit.[14] 230°), which was shown by a mixture melting point determination and infrared and ultraviolet spectral comparisons to be identical with an authentic sample.[14]

2-Chloro-1-fluoro-1,1-diphenylethane (XXI).—Following the procedure described above for the preparation of 1,2-difluoro-1,1-diphenylethane (I), 1.00 g. (4.3 mmoles) of 2-chloro-1,1-diphenylethanol[6] was converted by the action of 0.5 ml. of anhydrous hydrogen fluoride at Dry Ice temperature for 1 minute to 2-chloro-1-fluoro-1,1-diphenylethane. One recrystallization from methanol afforded 0.71 g. (70%) of analytically pure XXI as white crystals, m.p. 52.7–53.2°.

Anal. Calcd. for $C_{14}H_{12}ClF$: C, 71.64; H, 5.16. Found: C, 71.70; H, 5.20.

Heating of XXI at 110° caused an immediate evolution of hydrogen fluoride; 2-chloro-1,1-diphenylethylene, m.p. 41.5–42.5° (from methanol) (lit.[19] m.p. 42°), identified by a mixture melting point determination and infrared spectral comparison with an authentic sample,[19] was formed.

Purified XXI appears to have the same stability characteristics as 1,2-difluoro-1,1-diphenylethane (I).

Acknowledgment.—We are indebted to Dr. Glenn A. Berchtold and Mr. George R. Harvey of M.I.T. for the n.m.r. spectra. This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of the Fund.

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Behavior of Esters in Liquid Hydrogen Fluoride. Walden Inversion in Tetrahydropyran Derivatives

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

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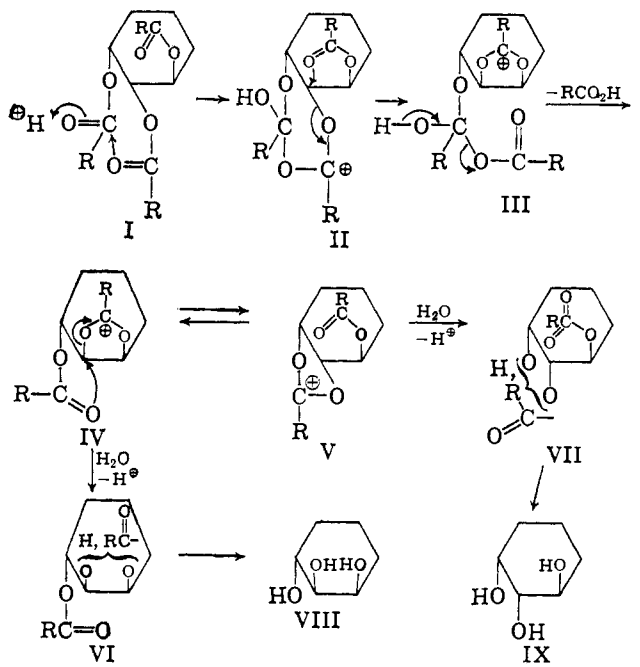
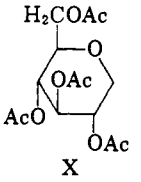
The effect of liquid hydrogen fluoride upon the esters of four polyhydroxytetrahydropyrans (1,5-anhydroglycitols) is predicted on the basis of earlier experience with esters of hexahydroxycyclohexanes. In each case, experiment confirmed prediction, Walden inversion taking place only at the central carbon atom of a contiguous *cis–trans*-triacyloxy sequence.

It has recently been shown[2] that esters of a variety of



polyhydroxycyclohexanes undergo deacylation with Walden inversion when treated with liquid hydrogen fluoride. From the examples studied, the stereochemical feature common to these reactions appears to be the inversion of the configuration of the middle carbon atom of a contiguous *cis–trans* sequence of acyloxy groups. A mechanism, illustrated by the simplified formulas I to IX, was proposed to explain the observed facts. With acetyl groups, complete deacetylation results, the end products being the triol IX, having the configuration of the original ester used (I), and the diastereoisomeric triol VIII.[3,4] In order to explore further the utility of this reaction and to confirm or refute the generalizations offered earlier, we have now turned our attention to the esters of certain hydroxylated tetrahydropyrans, *viz.*, the 1,5-anhydroalditols.

2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol (X)



X

may be considered first. Here, in the absence of a *cis* pair of acyloxy groups, initial ring formation as in II is excluded and thus, barring the intervention of other mechanisms, X should simply be deacetylated by the

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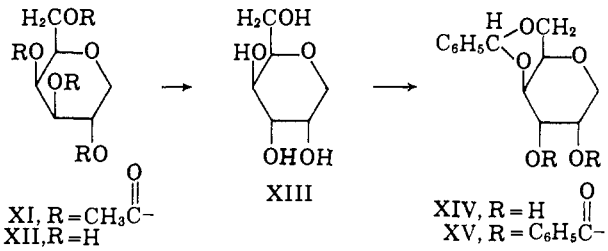
(2) E. J. Hedgley and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **84**, 3726 (1962).

(3) Obviously, substituents other than those shown in formulas I to IX would be required in order to make VIII and IX diastereoisomers.

(4) S. J. Angyal, P. A. J. Gorin and M. Pitman [*Proc. Chem. Soc.*, 337 (1962)] have shown recently that the acetates of some cyclitols as well as the cyclitols themselves undergo partial Walden inversion when refluxed with 95% acetic acid containing 1.5% sulfuric acid. Here the stereochemical requirements for the inversion appear to be the same as those which were found for rearrangements in hydrogen fluoride.[2] However, there is a fundamental difference between the two processes: With anhydrous hydrogen fluoride the mechanism involves an essentially irreversible deacetylation, whereas the rearrangements in the aqueous acetic acid–sulfuric acid system are carried out under conditions which permit re-esterification of deacylated species and the establishment of a true equilibrium. It is not surprising, therefore, that the proportion and nature of the products in the two processes differ. Thus, Angyal, Gorin and Pitman found *epi*-inositol to give a mixture of *epi*-, *allo*- and *neo*-inositols in the proportion of 17:23:60, while we found[2] that *epi*-inositol hexaacetate in hydrogen fluoride gives a mixture of *epi*- and *allo*-inositols only, no trace of the readily recognizable *neo*-inositol being detected.

usual treatment with hydrogen fluoride. Such proved to be the case; under conditions which had readily caused Walden inversions among the cyclitol esters studied earlier,[2] only 1,5-anhydro-D-glucitol was obtained, paper chromatography failing to reveal any other product.

The second compound examined was 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-galactitol (XI). Here, with the requisite *cis–trans* arrangement of acetoxy groups at



XI, R = $CH_3C(=O)$–
XII, R = H

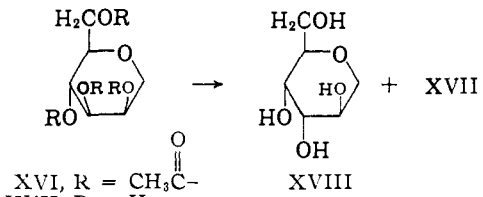
XIII

XIV, R = H
XV, R = $C_6H_5C(=O)$–

C_2–C_3–C_4, one might predict at least some inversion at C_3 to give 1,5-anhydro-D-gulitol (XIII). Treatment of XI with hydrogen fluoride gave a mixture which paper chromatography showed to contain two components. These were separated on a cellulose powder column and one was found to be 1,5-anhydro-D-galactitol (XII). The other component was isolated as a crystalline benzylidene acetal which proved to be identical with 1,5-anhydro-4,6-*O*-benzylidene-D-gulitol (XIV), described originally by Ness and Fletcher.[5] The identity of XIV was confirmed through conversion to its dibenzoate XV.

On the basis of the column chromatographic separation, the yield of the 1,5-anhydro-D-galactitol (XII) was *ca.* 40% while that of the 1,5-anhydro-D-gulitol (XIII) was *ca.* 50%.

The third substrate investigated was 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-mannitol (XVI). The mechanism postulated for rearrangements in hydrogen fluoride

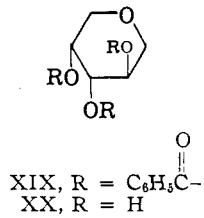


XVI, R = $CH_3C(=O)$–
XVII, R = H

XVIII

predicts the formation of 1,5-anhydro-D-mannitol (XVII) and 1,5-anhydro-D-altritol (XVIII), formed by inversion at C_3, the central carbon atom of the *cis–trans* acyloxy sequence in XVI. Treatment of XVI with liquid hydrogen fluoride was found to produce a two-component mixture, readily and sharply separable on a cellulose powder column. One component proved to be 1,5-anhydro-D-mannitol (XVII); the other (whose identity was confirmed through the preparation of its tetraacetate) was 1,5-anhydro-D-altritol (XVIII), a substance reported several years ago by Zissis and Richtmyer.[6] The 1,5-anhydro-D-mannitol (XVII) predominated (84%) while the yield of 1,5-anhydro-D-altritol (XVIII) was much smaller (16%); paper chromatography failed to detect products other than these two.

The last substance examined was 1,5-anhydro-2,3,4-tri-*O*-benzoyl-D-arabinitol (XIX). Because of the symmetry involved, inversion at C_3 would regenerate 1,5-anhydro-D-arabinitol (XX). The study of the effect of hydrogen fluoride in this simple system therefore provides a control experiment of value only in confirming the absence of side reactions. In fact, 1,5-



XIX, R = $C_6H_5C(=O)$–
XX, R = H

anhydroarabinitol proved to be the only product detectable after treatment of XIX with hydrogen fluoride.[7]

In summarizing, it may be noted that all four of the esters studied behave in liquid hydrogen fluoride in a manner predictable on the basis of earlier experience with esters of the cyclitols.

Experimental[8]

Chromatography.—Paper chromatography, used for the preliminary identification of components in mixtures and to ascertain the homogeneity of purified specimens, was conducted in the descending manner on Whatman No. 1 and 31 paper, useful separations being obtained in 3–7 hr. Chromatography columns were prepared from Whatman Standard Grade cellulose powder, packed as a slurry in acetone. Both paper chromatograms and columns were developed with acetone–water (9:1, v./v.). Components on paper chromatograms were detected with periodate–*p*-anisidine spray or silver nitrate reagent as described earlier.[2]

Behavior of 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol (X) with Hydrogen Fluoride.—2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol (16.3 g., m.p. 73–74°) was dissolved in *ca.* 50 ml. of liquid hydrogen fluoride and the solution stored at 18° for 24 hr. The hydrogen fluoride was then removed as completely as possible with a stream of dry air, the container being warmed slightly to facilitate the process. The colorless, sirupy residue was neutralized with saturated aqueous sodium bicarbonate in which it dissolved completely. Concentration of the neutral solution gave a dry residue which was treated with acetic anhydride (100 ml.) and anhydrous sodium acetate and the mixture boiled under reflux for 3 hr. Worked up in the conventional manner, the product was obtained as a colorless glass (14.8 g.). The whole of this was deacetylated with sodium methoxide to give 9.0 g. of a sirup which crystallized spontaneously; paper chromatography of the material at this point revealed but a single substance, having an R_f identical with that of 1,5-anhydro-D-glucitol.[9] Recrystallization of the crude product from aqueous acetone yielded needles showing $[\alpha]^{20}D$ +62.6 ± 0.3° in water (*c* 1.0) and melting at 140–142° either alone or in admixture with authentic **1,5-anhydro-D-glucitol.**

2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol (XI).—The method which Zervas and Zioudrou[10] described for the catalytic reduction of acetylated glycosyl bromides was applied to 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide. The bromide (16.4 g.) was dissolved in 250 ml. of dry ethyl acetate containing 8 ml. of triethylamine and 1.0 g. of 10% palladium-on-charcoal. The mixture was shaken with hydrogen at room temperature and pressure, the theoretical amount of hydrogen being absorbed in 80 min. The filtered solution was washed with saturated aqueous sodium bicarbonate, dried with magnesium sulfate and concentrated to a slightly colored, viscous sirup (13.3 g.) which crystallized immediately on trituration with petroleum ether. Recrystallized from aqueous ethanol, the product was obtained in two crops (total 11.1 g., 84%) melting at 103–105°; distillation of this at 0.025 mm. and 90–100° (bath) afforded a colorless sirup which crystallized spontaneously; m.p. 103–104°, $[\alpha]^{20}D$ +47.9 ± 1.0° ($CHCl_3$, *c* 1.0).

Anal. Calcd. for $C_{14}H_{20}O_9$ (332.30); C, 50.60; H, 6.07. Found: C, 50.39; H, 5.85.

Fletcher and Hudson[11] described 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-galactitol (XI) as melting at 75–76° and showing $[\alpha]^{20}D$ +49.1° ($CHCl_3$). The sample prepared by those authors

(5) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **75**, 2619 (1953).

(6) E. Zissis and N. K. Richtmyer, *ibid*, **77**, 5154 (1955).

(7) While the acetates studied here as well as those of the cyclitol series described earlier (ref. 2) are fully deacetylated by hydrogen fluoride, the more stable benzoyl groups in XIX survive in part. A similar observation was made earlier (ref. 2) with DL-inositol hexabenzoate.

(8) Melting points are corrected. Reactions with hydrogen fluoride were conducted in polyethylene vessels, the usual precautions to prevent the ingress of moisture being taken.

(9) It was established that the solvent system employed (aqueous acetone) resolved the 1,5-anhydrides of altritol, galactitol, glucitol, gulitol and mannitol and these from the hexitols themselves.

(10) L. Zervas and C. Zioudrou, *J. Chem. Soc.*, 214 (1953).

(11) H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **70**, 310 (1948).

now shows m.p. 103–105°, a value unchanged on admixture with the sample prepared as described above. It is evident that the substance as obtained earlier was a metastable dimorphic form.

Behavior of 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol (XI) with Hydrogen Fluoride.—2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol (8.76 g.) was treated with liquid hydrogen fluoride in the manner described for the D-glucitol analog. In contrast to the D-glucitol analog (and the cyclitol esters previously reported[2]), the D-galactitol derivative gave a darkly colored solution in liquid hydrogen fluoride; after 24 hr. the hydrogen fluoride was removed, the vessel being warmed gently to expel from the dark, mobile residue as much as possible of the dissolved gas. Saturated aqueous sodium bicarbonate solution (200 ml.) was added and then solid sodium bicarbonate until neutralization was complete. The clear, pale amber solution was evaporated to dryness under reduced pressure and the residue dried thoroughly at 90° to give a pulverulent mass which was boiled with a mixture of 80 ml. of acetic anhydride and anhydrous sodium acetate for 4 hr. The solution was concentrated *in vacuo* to a nearly dry solid which was treated with 450 ml. of water and the resulting suspension extracted with 5 × 50 ml. of dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate, dried with magnesium sulfate and concentrated to give a slightly colored glass (8.56 g.) which was immediately dissolved in dry methanol containing a trace of sodium methoxide. The deacetylated product was obtained as a slightly colored, viscous, hygroscopic sirup (4.62 g.); paper chromatography revealed 1,5-anhydro-D-galactitol as well as another component with a greater R_f value. A portion (1.04 g.) of the mixture was chromatographed on a cellulose column (4 × 58 cm.). Periodate-positive material emerged from the column after the collection of 1 l. of eluent, while a second component, uncontaminated with the first, emerged after the collection of a further 450 ml. The first and second components were obtained as colorless glasses of 0.49 g. and 0.39 g., respectively. The second component crystallized on scratching: recrystallized from ethanol–acetone, it was obtained as colorless prisms, $[\alpha]^{20}D$ +78.9 ± 0.5° (H_2O, *c* 1.0), m.p. 114°. A mixed melting point with authentic **1,5-anhydro-D-galactitol (XII)** was undepressed; Fletcher and Hudson[11] reported $[\alpha]^{20}D$ +76.6° (H_2O) and m.p. 114–115° for this substance.

Characterization of the first component was achieved through benzylidenation: 0.49 g. of the glass, as isolated from the column, was treated at room temperature for 24 hr. with methanol (10 ml.), containing 1.3% (w./v.) of hydrogen chloride and benzaldehyde (2 ml.). Saturated aqueous sodium bicarbonate (8 ml.) was then added and the mixture steam distilled. The benzaldehyde-free solution was evaporated to dryness and the residue extracted with acetone. Evaporation of the extract afforded a sirup (0.71 g.) which crystallized readily; recrystallization from water gave needles which showed $[\alpha]^{20}D$ +7.4 ± 0.5° in ethanol (*c* 1.0) and melted partially at 165–166°, and then again at 171–172°. This behavior on melting is characteristic of **1,5-anhydro-4,6-*O*-benzylidene-D-gulitol[5] (XIV)**; a mixed melting point with authentic material was undepressed. Ness and Fletcher[5] reported $[\alpha]^{20}D$ +5.8 ± 0.4° (ethanol) for 1,5-anhydro-4,6-*O*-benzylidene-D-gulitol.

Anal. Calcd. for $C_{13}H_{16}O_5$ (252.26): C, 61.89; H, 6.39. Found: C, 62.14; H, 6.35.

For further characterization, the 1,5-anhydro-4,6-*O*-benzylidene-D-gulitol (XIV) was converted to its dibenzoate XV which was obtained as needles from ethanol–pentane, m.p. 175–178°, $[\alpha]^{20}D$ −2.6 ± 0.5° ($CHCl_3$, *c* 0.3). Ness and Fletcher[5] reported m.p. 177–180° and $[\alpha]^{20}D$ −3.1 ± 0.2° ($CHCl_3$) for **1,5-anhydro-2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-D-gulitol (XV)**; a mixed melting point showed no depression.

Based on the chromatographically pure glasses obtained *via* cellulose column chromatography, the yield of 1,5-anhydro-D-gulitol (XIII) was *ca.* 50% and that of 1,5-anhydro-D-galactitol (XII) *ca.* 40%.

Behavior of 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-mannitol (XVI) with Hydrogen Fluoride.—2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-mannitol[12] (13.28 g.) was dissolved in *ca.* 50 ml. of hydrogen fluoride and the solution kept at 18° for 24 hr. After removal of the excess reagent, the water-soluble residue was neutralized with saturated aqueous sodium bicarbonate and then acetylated as in the first experiment described above. The slightly colored glass (12.57 g.) thus obtained was deacetylated with sodium methoxide to give a stiff sirup (6.63 g.) which crystallized spontaneously. Paper chromatography showed this material to be a mixture of 1,5-anhydro-D-mannitol, together with a second substance having a greater R_f. Resolution of 1.07 g. of the mixture was achieved on a cellulose powder column (4 × 58 cm.), the first component emerging from the column after the collection of 1.1 l. of eluent and the second, uncontaminated with the first, emerging after a total of 1.3 l. had been collected. Pooling and evaporation of the appropriate fractions afforded the first component (0.17 g.) and the second (0.90 g.), both as glasses which crystallized spontaneously. From ethanol solution, the second component deposited prisms, $[\alpha]^{20}D$ −50.4 ± 1.0° (H_2O, *c* 1.0) and m.p. 156–157°. **1,5-Anhydro-D-mannitol (XVII)** shows $[\alpha]^{20}D$ −50.3° (H_2O) and m.p. 156–157°[12]; a mixed melting point was undepressed.

The first component crystallized from ethanol as fine rhombs showing m.p. 129° and $[\alpha]^{20}D$ +26.0° in water (*c* 1.0); its melting point was not depressed on admixture with authentic **1,5-anhydro-D-altritol (XVIII)** for which a rotation of $[\alpha]^{20}D$ +28.4° (H_2O) and an m.p. of 127–129° have been reported.[6]

The product was further characterized through preparation of its tetraacetate, obtained from ethanol–pentane as prisms melting at 103–104° and showing $[\alpha]^{20}D$ −24.4 ± 1.0° ($CHCl_3$, *c* 1.3). A mixed melting point with authentic **2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-altritol** was undepressed; Zissis and Richtmyer[6] recorded $[\alpha]^{20}D$ −22.7° ($CHCl_3$) and m.p. 104–105° for this substance.

Based on the chromatographically pure components resolved on the cellulose column, the yield of 1,5-anhydro-D-mannitol (XVII) was 84% while that of 1,5-anhydro-D-altritol (XVIII) was 16%.

Behavior of 1,5-Anhydro-2,3,4-tri-*O*-benzoyl-D-arabinitol (XIX) with Hydrogen Fluoride.—1,5-Anhydro-2,3,4-tri-*O*-benzoyl-D-arabinitol[13] (0.66 g.) was dissolved in *ca.* 15 ml. of hydrogen fluoride and the solution kept at 18° for 24 hr. The sirupy residue remaining after removal of the hydrogen fluoride was only partly soluble in the aqueous sodium bicarbonate used to effect neutralization, and dichloromethane was used to extract the water-insoluble portion. The aqueous phase was concentrated to dryness and the residue extracted with boiling ethanol. Paper chromatographic examination of the ethanolic extract revealed only **1,5-anhydroarabinitol (XX)**. Debenzoylation of the residue remaining after removal of solvent from the dichloromethane extract was followed by paper chromatography; again, only **1,5-anhydroarabinitol (XX)** could be detected.

Acknowledgment.—We are indebted to Mr. Harry W. Diehl for assistance in some of the preparations and to the Analytical Services Unit of this Laboratory, under the direction of Mr. H. G. McCann, for analyses.

(12) H. G. Fletcher, Jr., and H. W. Diehl, *J. Am. Chem. Soc.*, **74**, 3175 (1952).

(13) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 1672 (1947).