XIV and IV in a pure state in order to determine their optical purities.

A solution of 6 g. of (−)-amine III in 60 ml. of glacial acetic acid was stirred at 10° and 5.28 g. of sodium nitrite was added over a period of 1 hour. After stirring for a further hour at 0–10°, the mixture was allowed to stand at room temperature overnight.

After adding another 0.72 g. of sodium nitrite, the mixture was poured into iced aqueous sodium carbonate and the basic solution was extracted several times with ether. The combined extracts were washed with dilute hydrochloric acid and water before drying over anhydrous magnesium sulfate. Evaporation of the filtered solution yielded *ca.* 8 g. of a sweet smelling orange oil. (A thin layer chromatoplate run on silica gel G in benzene and sprayed with 50% methanol–sulfuric acid showed four spots in two pairs.)

The mixture of acetate and nitrate esters was dissolved in dry ether (70 ml.) and this solution was added dropwise to a stirred slurry of 2.5 g. of lithium aluminum hydride in 100 ml. of dried ether. After stirring for 2 hours at room temperature, the mixture was allowed to stand overnight and then refluxed for 0.5 hours. After the dropwise addition of 10 ml. of water to the cooled mixture, stirring was continued for a further hour. The inorganic salts were removed by filtration on a sinter, where they were triturated with ether. The combined filtrate and washings were dried over anhydrous magnesium sulfate, filtered and the solvent removed through a short column, to yield a pale yellow liquid (*ca.* 5.7 g.).

Infrared spectra indicated that this was a mixture of alcohols and a thin layer chromatoplate on silica gel G in chloroform showed two main spots (identical in migration behavior with the α- and β-alcohols) separated by a diffuse area (corresponding to the rearranged and ring-opened alcohols).

At this stage, a series of preliminary investigations was carried out in order to find a suitable v.p.c. packing for the separation of the α- and β-alcohols in the mixture. These can be reviewed as: analytical columns: (i) 15% Carbowax on firebrick, 162°, good separation of first two components but no separation of α- and β-alcohols; (ii) 3% neopentyl glycol succinate, 112°, partially separated the α-alcohol as a shoulder; (iii) Ucon, 125°, no separation of α- and β-alcohols; (iv) Craig polyester, 94°, partial separation of α- and β-alcohols; (v) 20% LAC 446 on firebrick, 126°, quite good separation of α- and β-alcohols.

The α- and β-alcohols were successfully separated preparatively on a 5-ft. column of 20% LAC 446 on firebrick at a temperature of 126°. By recycling the fractions first collected, pure samples were obtained of both these alcohols.

The α-alcohol showed $[\alpha]^{25}D$ −4.9° (*c* 7.9 in ethanol) whilst a synthetic sample had $[\alpha]^{25}D$ −5.3° (*c* 8.0 in ethanol), indicating that racemization could have occurred only to an extent of 7.5% and this is almost within the experimental error in readings from the polarimeter.[17]

A thin layer chromatoplate of the synthetic and deamination α-alcohols showed them to be identical and in a high state of purity.

(+)-5,5-Dimethylbicyclo[2.1.1.]hexan-2-one.—The pure α-alcohol (70 mg.) was recovered from the ethanolic solution which was used to determine its rotation. The alcohol then was dissolved in 5 ml. of A.R. acetone and the solution cooled in ice whilst 0.2 ml. of 6 *N* chromic acid was added dropwise with stirring. The mixture was allowed to stand for 15 min. at room temperature with occasional shaking. After pouring the mixture into water, it was extracted several times with ether. The combined extracts were washed with aqueous sodium carbonate and then dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 40 mg. of the ketone (infrared spectrum identical with that of previous samples).

Without further purification, this ketone showed $[\alpha]^{25}D$ +73° (*c* 1.67 in ethanol) [optically pure material, $[\alpha]^{25}D$ +120.5° (*c* 1.8 in ethanol)]. The crude ketone therefore shows *ca.* 60% of the expected optical activity. Considering the state of purity of the sample, this confirms the previous result that the α-alcohol from the deamination cannot be far from optical purity.

A sample of pure β-alcohol collected after a second pass through the v.p.c. showed $[\alpha]^{25}D$ −7.5° (*c* 8.7 in ethanol) [optically pure material, $[\alpha]^{25}D$ −7.7° (*c* 10 in ethanol)]. This confirms that no racemization has taken place.

(17) The previously reported (ref. 5) value for the specific rotation of XIV was erroneously given as −3.0°.

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

Behavior of Esters in Liquid Hydrogen Fluoride. Facile Inversions in the Cyclitol Series[1]

BY E. J. HEDGLEY[2] AND HEWITT G. FLETCHER, JR.

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A number of cyclitol esters have been found to undergo rearrangement when dissolved in liquid hydrogen fluoride. In these rearrangements, the configuration of the middle carbon atom of a *cis–trans* sequence is inverted. Mechanisms to rationalize these transformations are proposed and a simple method for the preparation of *muco*-inositol from *myo*-inositol is described.

In earlier work in this Laboratory[3] it has been shown that β-L-arabinopyranose tetrabenzoate and 2,3,4-tri-*O*-benzoyl-β-L-arabinosyl fluoride are readily converted to 3,4-di-*O*-benzoyl-β-L-ribosyl fluoride through the action of liquid hydrogen fluoride at room temperature. Much earlier, Brauns[4] had reported a similar conversion of cellobiose octaacetate to what was probably 3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranosyl fluoride. These Walden inversions, readily carried out with accessible derivatives under mild conditions, are comparatively rare in the carbohydrate field[5] and are obviously of

(1) The nomenclature used here is that of H. G. Fletcher, Jr., L. Anderson and H. A. Lardy [*J. Org. Chem.*, **16**, 1238 (1951)]. The numbering of the carbon atoms in the cyclitol field presents unique difficulties and the reader should be warned that in the system used here (as well as in others) the numbering depends not only on the configuration of the cyclitol but also, at times, on the position of substituents. Thus, for instance, corresponding carbon atoms in *myo*-inositol (I) and *muco*-inositol (III) are assigned different numbers. For a discussion of the nomenclature of the cyclitols as well as an excellent comprehensive review of this field see S. J. Angyal and L. Anderson, *Adv. Carbohydrate Chem.*, **14**, 135 (1959).

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(3) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 945 (1960).

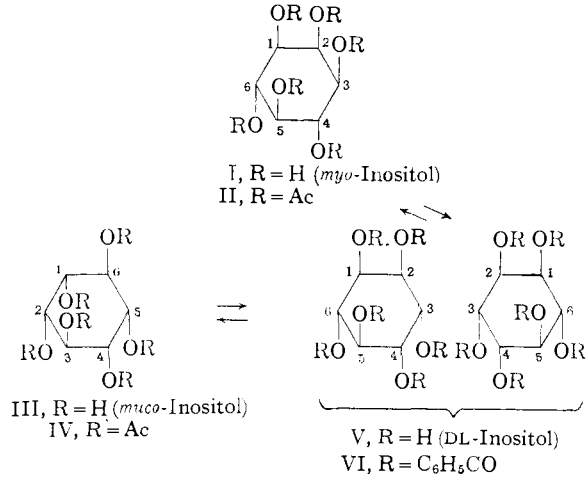
(4) D. H. Brauns, *ibid.*, **48**, 2776 (1926).

(5) The rearrangements which are induced by a mixture of aluminum chloride and phosphorus pentachloride [*cf.* N. K. Richtmyer, *Adv. Carbohydrate Chem.*, **1**, 37 (1945)] present some features which suggest that the mechanism involved may closely resemble the transformations caused by hydrogen fluoride. The racemizations of some sugar derivatives, recently reported by F. Micheel and R. Böhm [*Tetrahedron Letters*, 107 (1962)], have been rationalized by mechanisms similar to some of those proposed here.

potential synthetic utility. One may ask what the limitations of the reaction may be, whether the presence of a fluorine atom in the molecule is essential, and what the mechanism and steric requirements are. In hope of throwing light upon some of these questions we have examined the effect of liquid hydrogen fluoride on esters of some of the inositols and on the esters of some of their mono-*O*-methyl ethers.

myo-Inositol hexaacetate (II), like the sugar esters which had previously been examined, readily dissolved in liquid hydrogen fluoride[6] to give a clear solution which remained colorless after 19 hr. at 18°. Removal of the excess acid afforded a water-soluble product, indicating that partial or complete deacetylation had occurred. Indeed, paper chromatography showed no evidence of partially acetylated materials but revealed three inositols which were identified as *myo*- (I), *muco*- (III) and DL-inositol (V). Preparative chromatography on a cellulose column showed that *muco*-inositol predominated, the DL-inositol being a comparatively minor component. It is thus apparent that Walden inversions caused by liquid hydrogen fluoride are not confined to the acylated aldoses and that the presence of a fluorine atom in the molecule is not essential to the rearrangement. In passing, it may be noted that this rearrangement of *myo*-inositol hexaacetate constitutes a more practical method for the preparation of *muco*-inositol than those which have been reported.[7-9]

DL-Inositol hexabenzoate (VI) was similarly treated with liquid hydrogen fluoride. Here, with the more stable benzoyl groups, deacylation was not complete; after catalytic debenzoylation the presence of *muco*- (III), *myo*- (I) and DL-inositol (V) was demonstrated by paper chromatography. *muco*-Inositol hexaacetate (IV) similarly gave a mixture of *muco*-inositol (III), DL-inositol (V) and a trace of *myo*-inositol (I).



I, R = H (*myo*-Inositol)
II, R = Ac

III, R = H (*muco*-Inositol)
IV, R = Ac

V, R = H (DL-Inositol)
VI, R = C_6H_5CO

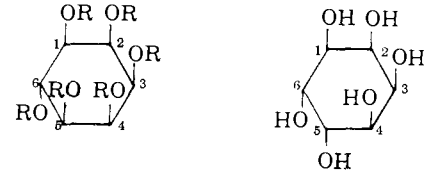
(6) While all ordinary precautions were taken to avoid the ingress of moisture, the possibility of the presence of water in these reactions cannot be excluded.

(7) G. Dangschat and H. O. L. Fischer, *Naturwissenschaften*, **27**, 756 (1939).

(8) M. Nakajima, I. Tomida, N. Kurihara and S. Takei, *Chem. Ber.*, **92**, 173 (1959).

(9) S. J. Angyal and coworkers, unpublished research; see the review by Angyal and Anderson cited in ref. 1.

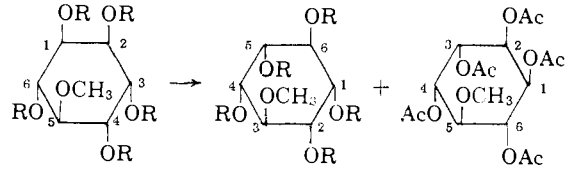
After treatment with liquid hydrogen fluoride *epi*-inositol hexaacetate (VIII) afforded a mixture of *epi*-inositol (VII) and allo-inositol (IX) as shown by paper chromatography.



VII, R = H (*epi*-Inositol) IX (*allo*-Inositol)
VIII, R = Ac

Since methyl ethers should survive the treatment with hydrogen fluoride they should be of use in limiting the possible points of inversion in this type of reaction. For this reason the pentaacetate of (+)-pinitol (X, 5-*O*-methyl-D-inositol) was treated with hydrogen fluoride and the product chromatographed on a cellulose column. Two pure mono-*O*-methylinositols were obtained. One of these was a glass which was indistinguishable chromatographically from 5 - *O* - methyl - D - inositol (X). However, on acetylation, it gave an *optically inactive* mono-*O*-methylinositol pentaacetate with the melting point which Angyal and Gilham[10] reported for 5-*O*-methyl-DL-inositol pentaacetate (XI·XIV). A sample of the substance was deacetylated, demethylated with hydriodic acid and reacetylated to give DL-inositol hexaacetate.

The second mono-*O*-methylinositol, obtained in crystalline form, was optically inactive; it was further characterized as its crystalline pentaacetate. The physical constants obtained clearly indicated that the substance differs from the previously described mono-*O*-methylinositols. On demethylation with hydriodic acid it gave *muco*-inositol (III). The conversion of 5-*O*-methyl-D-inositol to a mono-*O*-methyl-*muco*-inositol could occur by inversion at either carbon 1 or carbon 4 of X. Had inversion occurred at the latter position, the product would have been asymmetric (L-1-*O*-methyl-*muco*-inositol); since the product obtained was optically inactive, inversion had taken place at C_1 and the product is, therefore, 3-*O*-methyl-*muco*-inositol (XII).



X, R = H (5-*O*-methyl-D-inositol)
XI, R = Ac

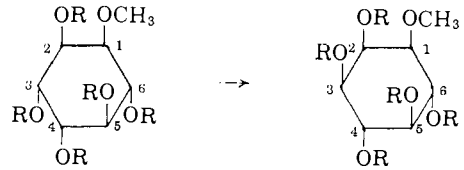
XII, R = H (3-*O*-methyl-*muco*-inositol)
XIII, R = Ac

XIV (5-*O*-methyl-L-inositol pentaacetate)

Attention was now turned to the pentaacetate of (−)-quebrachitol (XV, 1-*O*-methyl-L-inositol). In this case, after the customary neutralization of the residual acid, the aqueous solution was evaporated and the solid residue acetylated. The product, freed of inorganic salts and deacetylated, gave a crystalline, chromatographically homogen-

(10) S. J. Angyal and P. T. Gilham, *J. Chem. Soc.*, 3691 (1957).

eous solid from which a pure mono-*O*-methylinositol was obtained. The material was optically active; its physical constants and those of its pentaacetate clearly identified it as L-1-*O*-methyl-*myo*-inositol (XVII), the known (−)-bornesitol.[11,12]



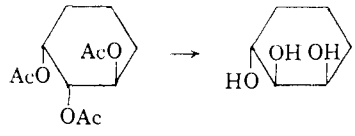
XV, R = H (1-*O*-methyl-L-inositol)
XVI, R = Ac
XVII, R = H (L-1-*O*-methyl-*myo*-inositol)
XVIII, R = Ac

Discussion

Over-all Stereochemical Features.—Conversion of *myo*-inositol (I) to DL-inositol (V) as well as DL-inositol (V) to *muco*-inositol (III) (and the reverse reactions) requires inversions at single carbon atoms only. The direct interconversion of *myo*-inositol (I) to *muco*-inositol (III) must involve two inversions; it is likely, therefore, that DL-inositol derivatives are intermediates in the interconversion of *myo*- and *muco*-inositols. In the *meso* structure of *myo*-inositol (I) carbons 1 and 3 are strictly equivalent, inversion of the former leading to L-inositol while inversion of the latter gives D-inositol. Conversion of DL-inositol (V) to *muco*-inositol (III) may take place by inversion of either carbons 1 or 4 of DL-inositol. However, 5-*O*-methyl-D-inositol (X) gave 3-*O*-methyl-*muco*-inositol (XII), inversion taking place at C_1. The racemization of 5-*O*-methyl-D-inositol (X) requires inversion at *both* C_1 and C_3. No evidence for inversion at C_3 alone (which would have given 5-*O*-methyl-*myo*-inositol) was obtained.

In (−)-quebrachitol (XV), where the hydroxyl at C_1 is blocked with a methyl group, inversion took place at C_3 to give L-1-*O*-methyl-*myo*-inositol (XVII), racemization (requiring inversions at both C_3 and C_1) being impossible because C_1 is blocked.

epi-Inositol (VII) inverts at C_1 or C_5, these positions being equivalent. All of the inversions are summarized in Table I. Consideration of these examples reveals that in each case inversion occurs at the middle carbon atom of a contiguous *cis-trans* arrangement.



Mechanism.—Since *myo*-inositol (I) itself is unaltered by hydrogen fluoride, it is obvious that the acyl groups (acetyl or benzoyl here) play a critical role in the inversions. The stereochemical features of the reactions lead us to propose the mechanism XIX to XXVII.[13]

(11) V. Plouvier, *Compt. rend.*, **241**, 983 (1955); **247**, 2190 (1958).
(12) G. G. Post and L. Anderson, *J. Am. Chem. Soc.*, **84**, 478 (1962).
(13) For simplicity, only one enantiomorph is given for asymmetric structures.

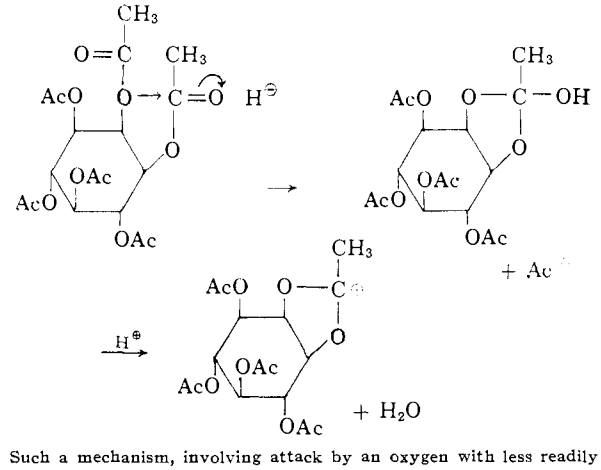
TABLE I

Compound (acetate or benzoate)	Carbon inverted[a]	Product
myo-Inositol (I)	1 (= 3)	DL-Inositol (V)
DL-Inositol (V)	1 or 4	*muco*-Inositol (III)
DL-Inositol (V)	3 or 6	*myo*-Inositol (I)
muco-Inositol (III)	1 (= 5)	DL-Inositol (V)
epi-Inositol (VII)	1 (= 5)	*allo*-Inositol (IX)
5-*O*-Methyl-D-inositol (X)	1	3-*O*-Methyl-*muco*-inositol (XII)
5-*O*-Methyl-D-inositol (X)	1 and 3	5-*O*-Methyl-L-inositol
1-*O*-Methyl-L-inositol (XV)	3	L-1-*O*-Methyl-*myo*-inositol (XVII)

[a] The numbering is that of the starting material.

While extensive protonation of a cyclitol ester in hydrogen fluoride may safely be assumed, all of the acyl groups are not equivalent and so are not, probably, equally protonated. An attack of an ester carbonyl group upon an adjacent, protonated acyl group[14] would lead to a charge-bearing, seven-membered ring as shown in formula XX. Attack on C_3 of this system by the *trans*-acyl group at C_4 would lead to XXI which bears a charged five-membered ring, acetic acid being eliminated to give XXII. With water, such an intermediate, a DL-inositol derivative, would undergo *cis* opening of the five-membered ring, the two carbons of the cyclic ion becoming a normal acetyl group at one or the other of the two positions involved. The product XXIII is a DL-inositol pentaacetate; under the conditions employed it is completely deacetylated.[15] The cyclic ion XXII is susceptible to rearrangement in two different directions by attack of the acetyl groups at C_2 or C_5. In the most probable conformation[16] *trans* diaxial attack by the acetyl group at the former carbon restores the *myo*-inositol configuration, giving an ion (XXIV) which water converts to a *myo*-inositol pentaacetate (XXV); similarly, attack (diequatorial) by the acetyl group at the latter carbon leads to the ion

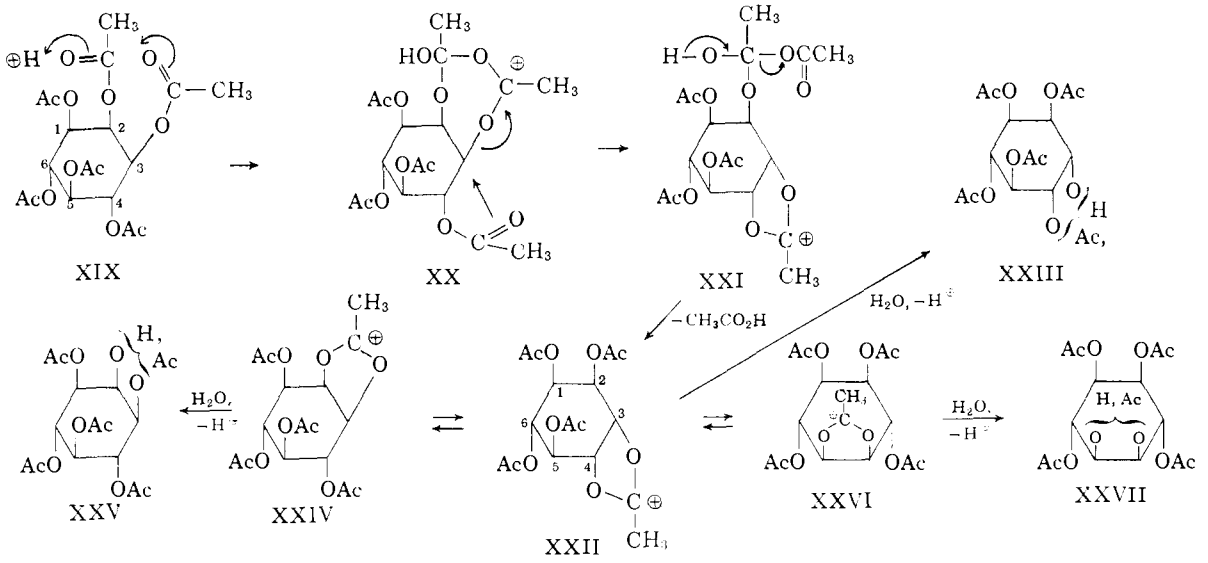
(14) An alternative mechanism for the initial step, leading to a five-membered (rather than a seven-membered) ring was also envisaged

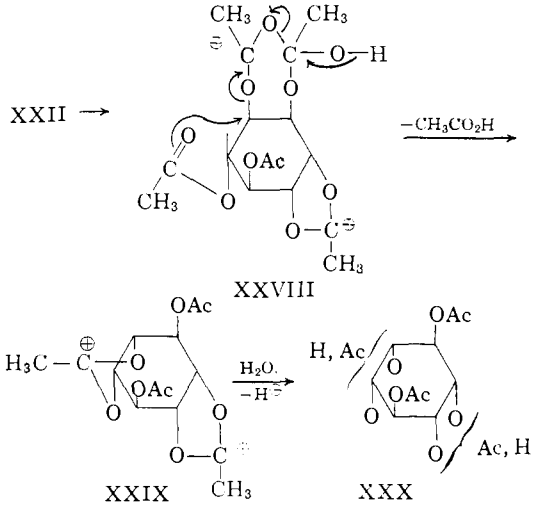


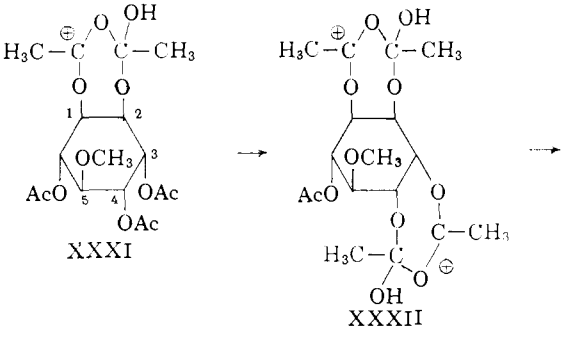
Such a mechanism, involving attack by an oxygen with less readily available electrons than the ester carbonyl oxygen, seems, however, much less plausible.

(15) With acyl groups more stable than acetyl it is possible that one might isolate discrete penta-*O*-acylcyclitols.

(16) For a discussion of the conformations of the inositols see the review of Angyal and Anderson referred to in ref. 1.

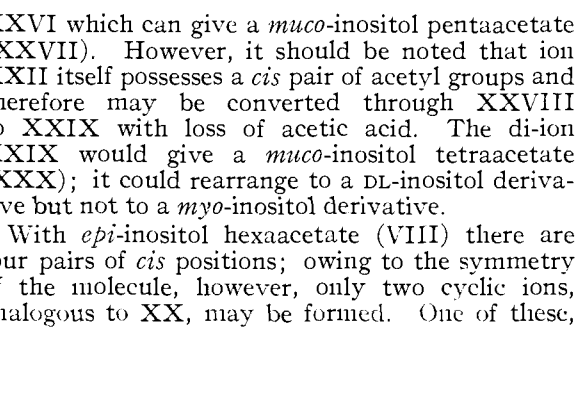


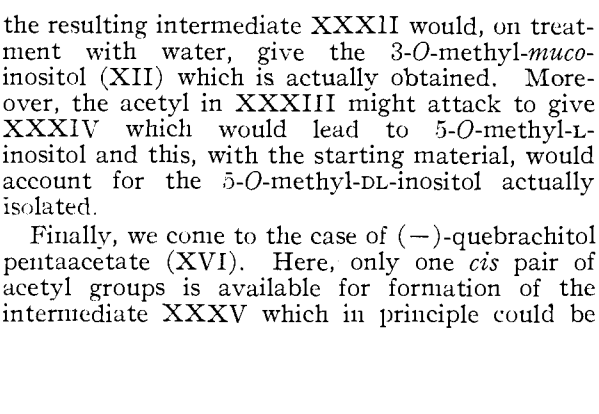




bridging C_2-C_3 (=C_3-C_4) would not lead to an inversion since it would not be flanked by a *trans*-acetoxy group. A cyclic ion bridging C_1-C_2 (=C_4-C_5), on the other hand, would allow attack by the *trans*-acetyl at C_6 with inversion at C_1 (=C_5) to give an *allo*-inositol derivative.

(+)-Pinitol pentaacetate (X) presents a picture related to the others which have been considered. If we assume the initial formation of a seven-membered intermediate bridging C_1-C_2 (XXXI), then subsequent attack by the C_3 acetyl rather than the C_6 acetyl group would seem more probable since the former offers the opportunity for a *trans* diaxial attack. However, if this were the case a *myo*-inositol ether would result and this was not observed. It is suggested, therefore, that a second and rapid interaction of the acetyls at C_3 and C_4 ensues to give XXXII. In this molecule only one type of attack, that by the acetyl at C_6, is possible;

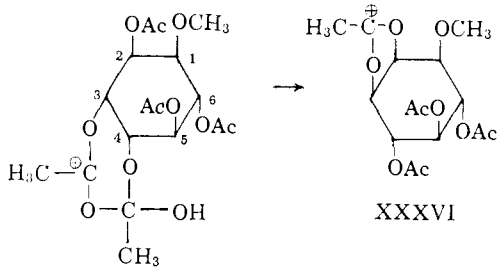




XXVI which can give a *muco*-inositol pentaacetate (XXVII). However, it should be noted that ion XXII itself possesses a *cis* pair of acetyl groups and therefore may be converted through XXVIII to XXIX with loss of acetic acid. The di-ion XXIX would give a *muco*-inositol tetraacetate (XXX); it could rearrange to a DL-inositol derivative but not to a *myo*-inositol derivative.

With *epi*-inositol hexaacetate (VIII) there are four pairs of *cis* positions; owing to the symmetry of the molecule, however, only two cyclic ions, analogous to XX, may be formed. One of these, the resulting intermediate XXXII would, on treatment with water, give the 3-*O*-methyl-*muco*-inositol (XII) which is actually obtained. Moreover, the acetyl in XXXIII might attack to give XXXIV which would lead to 5-*O*-methyl-L-inositol and this, with the starting material, would account for the 5-*O*-methyl-DL-inositol actually isolated.

Finally, we come to the case of (−)-quebrachitol pentaacetate (XVI). Here, only one *cis* pair of acetyl groups is available for formation of the intermediate XXXV which in principle could be



XXXV

XXXVI

attacked by either the acetyl at C_2 or that at C_5. However, one might predict that the acetyl at C_2 would attack, since the normal conformation of this cyclitol would permit a diaxial attack, while a less stable conformation must be invoked to provide a diaxial attack by the acetyl group at C_5. The intermediate XXXVI, therefore, is formed and leads to the L-1-*O*-methyl-*myo*-inositol (XVII) which was the only product actually found.

Let us now return briefly to the aldose derivatives referred to at the beginning of this paper. It is apparent that the mechanisms postulated here for the inositols would predict that 2,3,4-tri-*O*-benzoyl-β-L-arabinosyl fluoride should give a partially benzoylated L-lyxopyranosyl fluoride and that hepta-*O*-acetyl-cellobiosyl fluoride (Brauns' undoubted intermediate) should not be altered. Moreover, Pedersen[17] recently has shown that D-glucose pentaacetate is converted to D-mannose and D-altrose derivatives through the action of hydrogen fluoride. It is obvious, therefore, that while the presence of a fluorine atom in a molecule is not a prerequisite for the rearrangement, it may, nevertheless, play an essential role in some cases.

Experimental[18]

Chromatography.—Paper chromatography was employed for the preliminary identification of components in reaction products and for ascertaining the homogeneity of materials eluted from chromatography columns. Chromatograms were conducted on Whatman No. 1 paper in the descending manner, using an acetone–water (9:1, v./v.) system. As reported by other workers,[19–21] acetone–water systems permit a rapid resolution of cyclitol mixtures and are especially useful for the unsubstituted inositols.

Angyal, McHugh and Gilham[22] reported that *epi*- and *cis*-inositols migrated at the same rate with 4:1 acetone–water and recommended a system of ethyl acetate–acetic acid–water (3:1:1) for the separation of this pair. We have observed, however, that *epi*- and *cis*-inositols are readily separable when 9:1 (v./v.) acetone–water is used. With this system an unequivocal identification of components was usually possible provided a direct comparison was made with authentic materials run on the same paper. The cyclitols were detected either by dipping the chromatograms in 5% aqueous acetone saturated with silver nitrate and then spraying with 0.5% sodium hydroxide in ethanol, or by spraying the chromatograms with 0.06% sodium metaperiodate in dilute acetic acid, followed, after a period of 4–5 min., with a spray containing 2% *p*-anisidine in dilute acetic acid.

Chromatography columns were prepared with Whatman standard grade cellulose powder, wet-packed as a slurry in acetone and developed with the same solvent mixture used for paper chromatograms.

Behavior of Hexa-*O*-acetyl-*myo*-inositol (II) with Hydrogen Fluoride.—Anhydrous hydrogen fluoride[23] was condensed (*ca.* 50 ml.) in an ice-cooled polyethylene bottle containing 6.94 g. of *myo*-inositol hexaacetate (m.p. 216–217°). Gentle swirling of the bottle promoted mixing, the solid dissolving rapidly and completely to give a colorless solution. The container, closed save for a small gas-release vent, was stored for 9 hr. in a Dewar vessel containing water at 18°. The excess of hydrogen fluoride then was evaporated by passing a stream of dry air into the vessel, gentle heat being applied to assist in the removal of the gas from the sirupy residue. Saturated aqueous sodium bicarbonate (150 ml.) was added and then sufficient solid sodium bicarbonate to bring the solution to neutrality. The absence of water-insoluble material indicated extensive, if not complete, deacetylation of the products. Paper chromatographic examination of the solution revealed three components, tentatively identified on the basis of their R_f values as *myo*-inositol (I), DL-inositol (V) and *muco*-inositol (III). Partially acetylated cyclitols were not observed.

The neutral aqueous solution was evaporated to dryness and the residue acetylated with acetic anhydride (100 ml.) and anhydrous sodium acetate (6 g.) under reflux for 3 hr. Worked up in the usual way, the mixed acetates were obtained as a white powder (4.79 g.). A catalytic deacetylation with sodium methoxide in methanol then gave a solid which was freed from traces of sodium ions by dissolution in water and treatment with Amberlite IR-120(H). Evaporation of the filtered solution afforded a cyclitol mixture (2.13 g.); a portion of this (1.55 g., ion-free) was applied to a cellulose powder column (6.5 × 82 cm.) and developed with aqueous acetone, the eluent being collected in 25-ml. fractions. Without prior concentration, each fraction was spotted on filter paper and the spot sprayed with the periodate and *p*-anisidine reagents. The first component of the mixture emerged from the column, free from contamination, after 5.5 l. of eluate had been collected, crystals of the cyclitol depositing from some of the fractions on standing. Pooling and concentration of the appropriate fractions yielded *muco*-inositol (III), m.p. >280° dec.,[24] 1.12 g. (representing 72% of the mixture). The product gave a satisfactory elementary analysis; its identity, as indicated by its behavior on paper chromatography, was confirmed through conversion to hexa-*O*-acetyl-*muco*-inositol, m.p. 179.5–180° either alone or in admixture with authentic material (IV).[25]

After collection of a total of 18.25 l. of eluate, a second component emerged, uncontaminated, from the column. This (0.15 g., representing 7% of the mixture) showed m.p. 252°[26] and did not depress the melting point of authentic DL-inositol; its chromatographic behavior was also identical with DL-inositol.

The third component, *myo*-inositol, was not recovered from the column, the quantity present being either too small or diffused over too many fractions for detection.

Behavior of Hexa-*O*-benzoyl-DL-inositol (VI) with Hydrogen Fluoride.—DL-Inositol hexabenzoate[27] (0.40 g., m.p. 216–217°) was dissolved in 15 ml. of hydrogen fluoride and the solution left at 18° for 4.5 hr. as described above for *myo*-inositol hexaacetate. The sirupy residue, obtained on removal of the hydrogen fluoride, crystallized spontaneously and did not dissolve when triturated with aqueous sodium bicarbonate solution, chromatographic examination of the aqueous solution revealing no trace of cyclitol. The solid, washed thoroughly with water and dried, gave an infrared spectrum indicating the presence of free hydroxyl groups. Benzoyl groups were removed with sodium meth-

(17) C. Pedersen, *Acta Chem. Scand.*, in press. We wish to thank Mr. Pedersen for allowing us to study the manuscript of this paper before publication.

(18) Melting points are corrected. Concentrations for rotations are expressed in g. of substance per 100 ml. of solution.

(19) C. E. Ballou and A. B. Anderson, *J. Am. Chem. Soc.*, **75**, 648 (1953).

(20) L. Anderson, E. S. DeLuca, A. Bieder and G. G. Post, *ibid.*, **79**, 1171 (1957).

(21) G. G. Post and L. Anderson, *ibid.*, **84**, 471 (1962).

(22) S. J. Angyal, D. J. McHugh and P. T. Gilham, *J. Chem. Soc.*, 1432 (1957).

(23) Matheson Co., Inc., E. Rutherford, N. J.

(24) Dangschat and Fischer[2] reported m.p. 285–290° dec.

(25) Nakajima[8] reported m.p. 177–178° for *muco*-inositol hexaacetate.

(26) T. Posternak [*Helv. Chim. Acta*, **31**, 2242 (1948)] reported m.p. 253° for DL-inositol.

(27) H. G. Fletcher, Jr., and G. R. Findlay, *J. Am. Chem. Soc.*, **70**, 4050 (1948).

oxide and a sample of the resulting solution chromatographed on paper. Using the periodate–*p*-anisidine reagents, three components only were detected; by comparison with authentic specimens run simultaneously, these were identified as *muco*-inositol (III), *myo*-inositol (I) and DL-inositol (V).

Behavior of Hexa-*O*-acetyl-*muco*-inositol (IV) with Hydrogen Fluoride.—*muco*-Inositol hexaacetate (m.p. 179–180°) was exposed to liquid hydrogen fluoride under conditions analogous to those used for *myo*-inositol hexaacetate. After removal of the hydrogen fluoride the residue was neutralized with aqueous sodium bicarbonate in which it dissolved readily. The whole was evaporated to dryness and the solid residue extracted with boiling ethanol. Paper chromatography of the extract revealed DL-inositol (V), *muco*-inositol (III) and a trace of *myo*-inositol (I).

Behavior of Hexa-*O*-acetyl-*epi*-inositol (VIII) with Hydrogen Fluoride.—*epi*-Inositol hexaacetate (m.p. 188°), when treated with hydrogen fluoride and the reaction mixture worked up as for *muco*-inositol hexaacetate, gave a mixture of two cyclitols only. Paper chromatography, using either the acetone–water or ethyl acetate–acetic acid–water systems referred to previously, served to identify these as *allo*-inositol (IX) and *epi*-inositol (VII).

Behavior of Penta-*O*-acetyl-5-*O*-methyl-D-inositol (XI, (+)-Pinitol Pentaacetate) with Hydrogen Fluoride.—(+)-Pinitol pentaacetate (8.1 g., m.p. 98.5–98.8°, $[\alpha]^{20}D$ + 6.2 ± 1°, *c* 1.0 and 4.9 in ethanol)[28] was dissolved in 50 ml. of liquid hydrogen fluoride and the solution stored at 0° for 2 hr. and then at 18° for 6 hr. Removal of the hydrogen fluoride with a stream of dry air left a sirupy residue which dissolved completely in the saturated aqueous sodium bicarbonate solution added to effect neutralization. The aqueous solution was evaporated to dryness and the residue extracted with 3 × 150 ml. of boiling ethanol. Ethanol was removed from the combined extracts and the residue, dissolved in 200 ml. of water, deionized with mixed-bed resin (Amberlite IR-120(H) and Dowex-1-X8). Filtered free from resin the solution was evaporated to dryness under reduced pressure (15 mm.) to yield a gummy, hygroscopic material which exhibited no carbonyl absorption in its infrared spectrum. Paper chromatography showed the material to be a mixture of two cyclitols only. An air-equilibrated sample (1.05 g.) was resolved by chromatography on a cellulose powder column (60 × 4.0 cm.), using aqueous acetone. The first component emerged after 1.35 l. of eluate had been collected; the second came through after a total of 1.75 l. of eluate had been collected.

Combination and evaporation of the appropriate fractions afforded the first component as a glass which crystallized readily; recrystallization from acetone containing a little ethanol gave **3-*O*-methyl-*muco*-inositol (XII)** (0.48 g.) as long, flat prisms, m.p. 127.2–128°, devoid of optical activity.

Anal. Calcd. for $C_7H_{14}O_6$ (194.18): C, 43.29; H, 7.27. Found: C, 43.53; H, 7.17.

A sample (0.042 g.) of the 3-*O*-methyl-*muco*-inositol was treated with 3 ml. of freshly distilled, constant boiling hydriodic acid and the solution boiled under reflux for 2.5 hr. The acid was then removed under reduced pressure at 80° to leave a slightly colored oil which, from ethanol, afforded colorless crystals. Recrystallization from aqueous acetone gave ***muco*-inositol (III)** in quantitative yield; the needle-shaped crystals melted >280° with decomposition and the material was identical in chromatographic behavior with an authentic specimen of *muco*-inositol. Acetylation of a sample, using acetic anhydride and sodium acetate, afforded an acetate which melted at 180.4–180.8° and did not depress the melting point of an authentic sample of *muco*-inositol hexaacetate.

(28) D. C. Pease, M. J. Reider and R. C. Elderfield [*J. Org. Chem.*, **5**, 198 (1940)] reported m.p. 98° and $[\alpha]^{25}D$ +8.6° (*c*, 1.97, alcohol); A. B. Anderson [*Ind. Eng. Chem.*, **45**, 593 (1953)] gave m.p. 98–99° and $[\alpha]^{22}D$ +11.3° (*c* 1 in alcohol).

The new ether, 3-*O*-methyl-*muco*-inositol, was further characterized through its pentaacetate which was prepared by conventional acetylation using acetic anhydride and anhydrous sodium acetate. From aqueous ethanol the **penta-*O*-acetyl-3-*O*-methyl-*muco*-inositol (XIII)** was obtained as colorless prisms, m.p. 134.6–134.8°, devoid of optical rotation in chloroform solution (*c* 1.3).

Anal. Calcd. for $C_{17}H_{24}O_{11}$ (404.36): C, 50.49; H, 5.98. Found: C, 50.22; H, 5.96.

The second component as obtained from the column was a colorless glass (0.23 g.), indistinguishable chromatographically from pinitol. Acetylation afforded optically inactive **penta-*O*-acetyl-5-*O*-methyl-DL-inositol (XI·XIV)** as thin, flat prisms, m.p. 124.5–125°. Angyal and Gilham[10] reported m.p. 125° for this substance. To confirm the identity of the substance it was successively deacetylated, demethylated and acetylated to yield DL-inositol hexaacetate as long, flat prisms from ethanol. The material melted at 111.8–112.2° and did not depress the melting point of an authentic sample of DL-inositol hexaacetate. Fletcher and Findlay[27] reported m.p. 111–112° for this substance.

Behavior of Penta-*O*-acetyl-1-*O*-methyl-L-inositol (XVI) with Hydrogen Fluoride.—Penta-*O*-acetyl-1-*O*-methyl-L-inositol (XVI, (−)-quebrachitol pentaacetate; 12.12 g., m.p. 96.4–97.2°, $[\alpha]^{20}D$ −24.0 ± 1.0°, *c* 1.0 in $CHCl_3$[29]) was dissolved in 50 ml. of hydrogen fluoride and the colorless solution maintained, first at 0° for 2.5 hr., and then at 18° for 28 hr. Excess hydrogen fluoride was then removed with a stream of dry air and the residue treated with 150 ml. of saturated sodium bicarbonate in which it dissolved readily. More solid sodium bicarbonate was added to bring the solution to neutrality and the solution was then concentrated to dryness. The pulverulent residue was acetylated by heating under reflux with acetic anhydride (150 ml.) and sodium acetate (5 g.) for 3 hr. The excess acetic anhydride was removed *in vacuo* (15 mm.) at 90° and the residue treated with water (500 ml.). On standing overnight, the precipitated sirup crystallized; the solid was washed thoroughly with water and then dried to constant weight (4.0 g.) at 55°. Dissolved in absolute methanol (150 ml.), the material was deacetylated with a catalytic quantity of sodium methoxide. On evaporation of the methanol, a crystalline, chromatographically homogeneous solid was obtained. Recrystallization from aqueous acetone gave 1.42 g. (24%) of pure L-1-*O*-methyl-*myo*-inositol (XVII, (−)-bornesitol), m.p. 204.2–205°, $[\alpha]^{20}D$ −31 ± 0.5° in water (*c* 1.0). A further 0.3 g. of the same material was recovered from the mother liquors, raising the total yield to 1.72 g. (30%).[30] Post and Anderson[12] found m.p. 205–205.5° and $[\alpha]^{20}D$ −32.6° (H_2O) for (−)-bornesitol.

Acetylation of this substance gave **L-1-*O*-methyl-*myo*-inositol pentaacetate (XVIII)** which crystallized from aqueous ethanol as fine needles, m.p. 140–141°, $[\alpha]^{20}D$ −9.3 ± 0.5° (*c* 1.0 in $CHCl_3$). Plouvier[11] recorded m.p. 142° and 157° and $[\alpha]D$ −11.2° ($CHCl_3$) for this substance.

Demethylation of the L-1-*O*-methyl-*myo*-inositol with hydriodic acid gave *myo*-inositol which was characterized as its hexaacetate (II), obtained from aqueous acetone as feather crystals, m.p. 216.7–217°.

Acknowledgment.—We are indebted to Drs. L. Anderson and S. J. Angyal for samples of authentic cyclitols.

(29) J. A. Goodson [*Biochem. J.*, **16**, 489 (1922)] reported m.p. 94–95° for this substance. A. Contardi [*Ann. chim. applicata*, **14**, 281 (1924); *C. A.*, **19**, 1138 (1925)] gave $[\alpha]^{15}D$ −16.78° (4% in $CHCl_3$) for quebrachitol pentaacetate.

(30) In subsequent experiments, the solubility of mono-*O*-methyl inositol pentaacetates in water was found to be unexpectedly high. It is evident, therefore, that the low yield of (−)-bornesitol reported here was caused by losses incurred in the washing of its pentaacetate with water.