SUGAR EPOXIDES

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1. Introduction

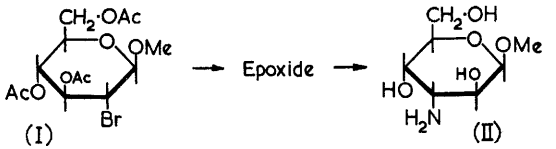
AN ethylene oxide group is easily introduced into a sugar molecule by alkaline hydrolysis of an *O*-arene(or alkane)sulphonyl derivative or deoxyhalogeno-compound which has a vicinal hydroxyl group *trans* to the anionic group. This reaction occurs easily and with few exceptions, and the epoxide is formed nearly quantitatively. The interest in sugar epoxides, as distinct from other anhydro-derivatives, lies in this reactive group. The oxide ring is opened by nucleophilic reagents to give, usually, two products with the *trans*-configuration and a substituent group which is derived from the reagent. This reaction has, therefore, provided a versatile method for the preparation of rare sugars from easily accessible ones and for the selective introduction of groups or atoms, such as *O*-alkyl, amino, and halogen, into sugar molecules. The reaction is easily carried out, but separation and characterisation of the products have often needed prolonged study. It will be appreciated that much impetus has been given to the chemistry of sugar epoxides by the desire to synthesise naturally occurring sugars, and two well-known examples are the synthesis of glucosamine (2-amino-2-deoxy-D-glucose) in 1939 and chondrosamine (2-amino-2-deoxy-D-galactose) in 1946. In the years following 1946 much attention was also given to sugar epoxides as intermediates in the preparation of deoxy-sugars. The syntheses of the sugar components of the cardiac glycosides were successfully achieved, but the chemistry was not so favourable for 2-deoxyribose because of the direction of ring opening.

Although the preparative aspect of the reactions of the sugar epoxides has been most closely studied, there are important features in the field such as different rates of formation of the various oxides and the different proportions in which the products of ring fission are obtained. These have led to a consideration of the influence which other groups in the sugar molecule may have upon the formation and fission of the epoxide ring. In many cases it is possible to assign a particular conformation to the sugar ring with reasonable certainty, and the chemistry of the sugar epoxides has now reached a stage where study of their reactions can reveal much about the intramolecular interactions which operate in the sugar molecule.

2. Formation

2.1. Fischer's Epiglucosamine.—One of the earliest reactions in which a sugar epoxide must have been formed was an attempt to synthesise

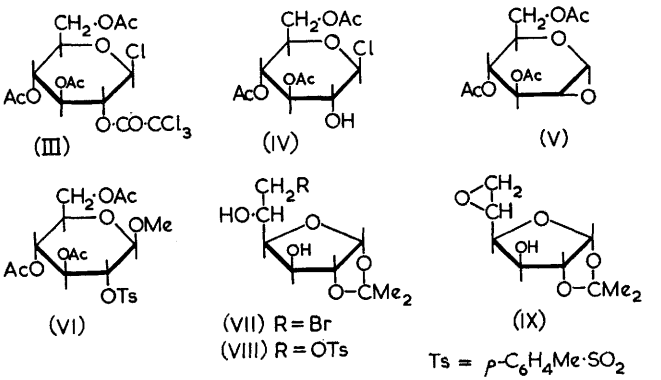
glucosamine from glucal.[1] 3:4:6-Tri-*O*-acetyl-D-glucal 1:2-dibromide was converted into methyl 3:4:6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucoside (I). When this compound (or its chloro-analogue) was treated with ammonia the product was, not 2-amino-2-deoxy-D-glucose or mannose, but a substance which Fischer called methyl epiglucosaminide. This was later[2] shown to be methyl 3-amino-3-deoxy-β-D-altroside (II). Fischer suspected this at the time and suggested that a 2:3-anhydro-ring might have been formed intermediately.



(I) (II)

It can of course be recognised now that the intermediate was methyl 2:3-anhydro-β-D-mannoside, but it was not until 13 years later that the existence of 2:3-anhydrohexosides was established by concurrent work at Birmingham and St. Andrews.

2.2. 1:2-Anhydro-D-glucopyranose and 5:6-Anhydro-D-glucofuranose.—The first example of a sugar epoxide was given by Brigl[3] in 1921. He found that when tetra-*O*-acetyl-β-D-glucose was treated with phosphorus pentachloride, 3:4:6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucosyl chloride (III) was formed. Careful treatment of this compound with ammonia removed only the trichloroacetyl group, forming 3:4:6-tri-*O*-acetyl-β-D-glucosyl chloride (IV) and on further mild treatment with ammonia this was converted into 3:4:6-tri-*O*-acetyl-1:2-anhydro-α-D-glucose (V). This compound is a valuable synthetic intermediate. It reacts with methanol, to give methyl 3:4:6-tri-*O*-acetyl-β-D-glucoside, and the 2-*O*-tosyl derivative (VI) was important in establishing the chemistry of the 2:3-epoxides.



(III) (IV) (V)

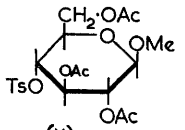
(VI) (VII) R = Br (VIII) R = OTs (IX)

Ts = *p*-$C_6H_4Me·SO_2$

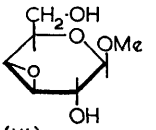
[1] Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509.
[2] Haworth, Lake, and Peat, *J.*, 1939, 271.
[3] Brigl, *Z. physiol. Chem.*, 1921, **116**, 1, 245.

Before considering this aspect, however, it is convenient to mention the conversion of 6-bromo-6-deoxy-1:2-*O*-isopropylidene-α-D-glucofuranose[4] (VII) and 1:2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose[5] (VIII) into 5:6-anhydro-1:2-*O*-isopropylidene-α-D-glucofuranose (IX) since this is a reaction not complicated by Walden inversion.

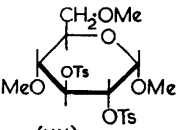
2.3. 2:3- and 3:4-Anhydrides.—In 1930 Helferich and Müller[6] isolated a crystalline methyl anhydro-β-D-hexoside after treating methyl 2:3:6-tri-*O*-acetyl-4-*O*-tosyl-β-D-glucoside (X) with sodium methoxide; this product was shown by Müller[7] to be methyl 3:4-anhydro-β-D-galactoside (XI). In 1933 an anhydro-sugar was obtained from methyl 4:6-di-*O*-methyl-2:3-di-*O*-tosyl-α-D-glucoside (XII), and the alkaline conditions produced also some methyl 4:6-di-*O*-methyl-α-D-altroside[8] (XIII). The following year, Haworth and his co-workers[9] described the formation of a methyl 2:3-anhydro-β-D-hexoside from methyl 3:4:6-tri-*O*-acetyl-2-*O*-tosyl-β-D-glucoside (VI), and they commented that the change of optical rotation to a high negative value on hydrolysis of the anhydride suggested the formation of an altrose derivative.



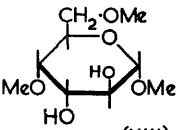
(X)



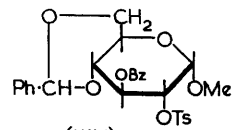
(XI)



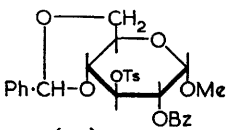
(XII)



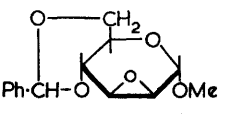
(XIII)



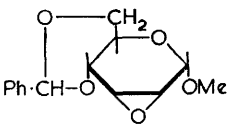
(XIV)



(XV)



(XVI)



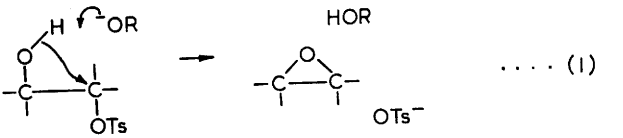
(XVII)

The manner in which these reactions were proceeding was now becoming obvious and Robertson and Griffith[10] made an important contribution by showing that the products obtained from methyl 3-*O*-benzoyl-4:6-*O*-benzylidene-2-*O*-tosyl-α-D-glucoside (XIV) and methyl 2-*O*-benzoyl-4:6-*O*-benzylidene-3-*O*-tosyl-α-D-glucoside (XV) by treatment with sodium

[4] Freudenberg, Toepfer, and Anderson, *Ber.*, 1928, **61**, 1751.
[5] Ohle and Vargha, *Ber.*, 1929, **62**, 2435.
[6] Helferich and Müller, *Ber.*, 1930, **63**, 2142.
[7] Müller, *Ber.*, (*a*) 1934, **67**, 421; (*b*) 1935, **68**, 1094.
[8] Mathers and Robertson, *J.*, 1933, 1076.
[9] Haworth, Hirst, and Panizzon, *J.*, 1934, 154.
[10] Robertson and Griffith, *J.*, 1935, 1193.

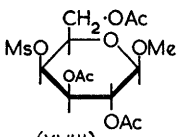
methoxide are methyl 2:3-anhydro-4:6-*O*-benzylidene-α-D-mannoside (XVI) and -α-D-alloside (XVII) respectively.

In all these reactions the formation of an anhydro-ring has been accompanied by inversion of configuration at that carbon atom to which the sulphonyloxy-group is attached. In the alkaline medium the anion of the vicinal *trans*-hydroxyl group can displace the toluene-*p*-sulphonyloxy-anion to form an epoxide and this can be represented as the intramolecular S_N2 process (1):

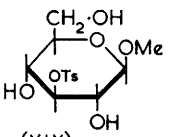


. . . . (1)

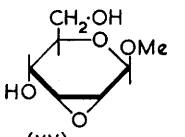
If the vicinal group is *cis*, as in methyl 2:3:6-tri-*O*-acetyl-4-*O*-methanesulphonyl-β-D-galactose (XVIII), then only deacetylation occurs and the methanesulphonyloxy-group is not displaced.[11] An interesting reaction examined by Peat and Wiggins[12] was the treatment of methyl 3-*O*-tosyl-β-D-glucoside (XIX) with mild alkali. Methyl 2:3- (XX) (60%) and methyl 3:4-anhydro-β-D-alloside (XXI) (25%) were formed since the toluene-*p*-sulphonyloxy-group has two neighbouring hydroxyl groups which can cause its displacement. In addition to the two epoxides, some methyl 3:6-anhydro-β-D-glucoside (XXII) [shown later[13] to be the furanoside (XXIII)] was formed. Although at the time, it was considered that this was one of the examples of hydrolysis of a toluene-*p*-sulphonyloxy-group with retention of configuration, the 3:6-anhydride is a secondary product formed, as Ohle and Wilke[14] pointed out, by the anion from the 6-hydroxyl group attacking at position 3 in either (XX) or (XXI).[15]



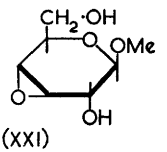
(XVIII)



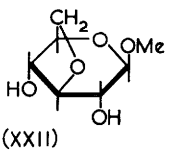
(XIX)



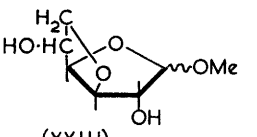
(XX)



(XXI)



(XXII)



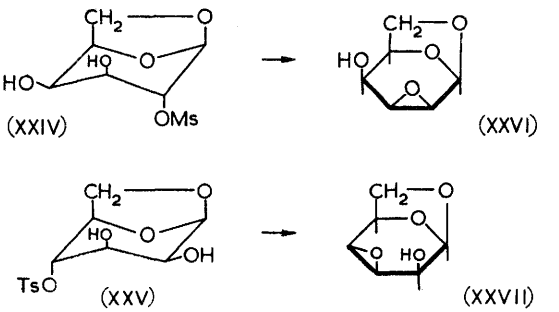
(XXIII)

Ms = $CH_3 \cdot SO_2$

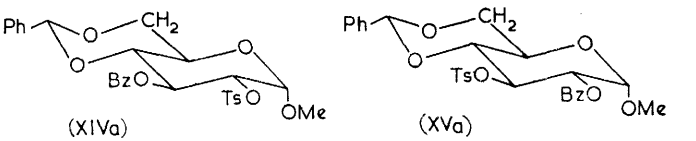
[11] Müller, Moricz, and Verner, *Ber.*, 1939, **72**, 745.
[12] Peat and Wiggins, *J.*, 1938, 1088.
[13] Haworth, Jackson, and Smith, *J.*, 1940, 620.
[14] Ohle and Wilke, *Ber.*, 1938, **71**, 2316.
[15] Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37.

2.4. The Stereochemistry of Epoxide Formation.—The examples given so far illustrate the development of the subject and all appear straightforward; in the light of the accepted views on inversion of configuration at a saturated carbon atom they are what would be expected. This part of carbohydrate chemistry is, unfortunately, completely lacking in quantitative data. In spite of this, however, inspection shows that although the experimental conditions chosen are often excessive some reactions are more difficult to carry out than others. The Haworth ring formulæ admirably show configurational changes but do not help in finding the steric cause of different reactivities or the reason why a reaction follows a particular course. It is not until conformational drawings are made that intramolecular interactions can become apparent and *a posteriori* explanations can be given for such behaviour.

In the base-catalysed formation of an epoxide from a *trans*-1:2-diol mono-*O*-toluene-*p*-sulphonate (reaction 1), the intramolecular S_N2 process in a six-membered ring requires the two groups to be in the diaxial position. The entering and the departing anion, and the carbon atoms to which they are attached, are then co-planar and this permits maximum participation. This condition is found in 1:6-anhydro-2-*O*-methanesulphonyl-β-D-galactose (XXIV) and 1:6-anhydro-4-*O*-tosyl-β-D-mannose (XXV), and they are easily converted into the 2:3-[16] (XXVI) and the 3:4-*talo*-epoxide[17] (XXVII) by mild alkali. The majority of toluene-*p*-sulphonates vicinal to a *trans*-hydroxyl group are, however, in the diequatorial

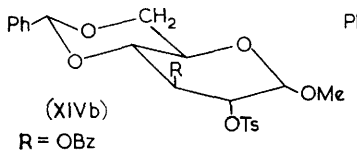


position as, for example, in the 2- (XIVa) and the 3-*O*-tosyl derivative and (XVa) which are smoothly converted into the *manno*- (XVI) and *allo*-epoxide (XVII). The ease with which these compounds react suggests

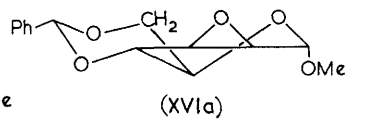


[16] James, Smith, Stacey, and Wiggins, *J.*, 1946, 625.
[17] Hann and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 925, 2435.

structural modification before epoxide formation and, indeed, in the analogous bimolecular ionic elimination from 1:2-dihalides no reaction occurs when both *trans*-substituents are rigidly held in equatorial positions.[18] In a monocyclic system, the diequatorial groups can pass into the diaxial position without much difficulty (conformation $C1 \rightarrow 1C$[19]) but in the bicyclic compounds (XIVa) and (XVa) the *trans*-fused ring containing the 4:6-*O*-benzylidene group confers rigidity on the chair form of the sugar ring and prevents this change. $C_{(2)}$, on the other hand, can move downwards to give the boat form (XIVb) without disturbing the point of ring fusion and the two groups at $C_{(2)}$ and $C_{(3)}$ are now co-planar and in a position to react.[20]



(XIVb)
R = OBz
(OH)



(XVIa)

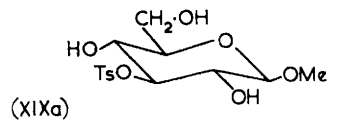
The hexose epoxides must be considered as analogous to 1:2-epoxycyclohexane which has been shown to have the half-chair conformation similar to that in cyclohexane.[21] The *manno*-epoxide (XVI) can therefore be shown as (XVIa).[22] It must then be recognised that the epoxide conformation is halfway in the chair–boat conversion, and $C_{(2)}$ and $C_{(3)}$ in the boat form would have to move again in the reverse direction to become co-planar with $C_{(1)}$ and $C_{(4)}$. For this reason the true boat form may never be reached. It is convenient, however, to formulate this extreme condition since, in its attainment, steric interactions are apparent which explain different activities and permit predictions.

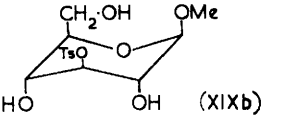
It is of interest to consider here the alkaline hydrolysis of methyl 3-*O*-tosyl-β-D-glucoside[12] (XIX) to see whether conformational analysis can account for the predominance of the 2:3-*allo*-epoxide (XX) [allowing for the formation of the 3:6-anhydride] over the 3:4-*allo*-epoxide (XXI) in the reaction product.

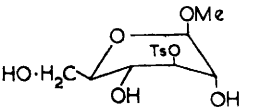
The form (XIXa) is the least hindered (all groups equatorial) and will be the "resting position" of the molecule. Form (XIXb), although it has the desired axial relation between the reacting groups, must be ignored because of its state of extreme hindrance (all groups axial). Forms (XIXc, d, and e) represent three points in the cycle of positions possible in the flexible boat form[23] in which the 2-, 3-, and 4-groups are axial (Reeves's 2B, B3,

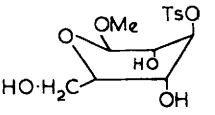
[18] Barton and Rosenfelder, *J.*, 1951, 1048.
[19] Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 215.
[20] Newth, *J.*, 1956, 441.
[21] Ottar, *Acta Chem. Scand.*, 1947, **1**, 283.
[22] Cookson, *Chem. and Ind.*, 1954, 223, 1512.
[23] Reeves, *J. Amer. Chem. Soc.*, 1957, **79**, 2261.

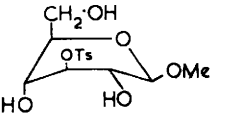
and 1B conformations[24]). Form (XIXd) appears to be able to give equally the 2:3- and the 3:4-epoxide; form (XIXc) will lead to the 2:3-epoxide, and (XIXe) to the 3:4-epoxide. A difference must be found, therefore, between the last two forms and probably lies in the 1:3-interactions $OTs_{(3)}/OMe_{(1)}$ and $OTs_{(3)}/CH_2{\cdot}OH_{(5)}$. In the alkaline reaction medium, the


(XIXa)


(XIXb)

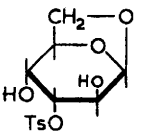

(XIXc)

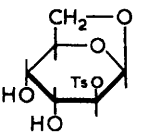

(XIXd)

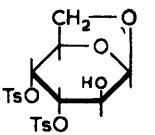

(XIXe)

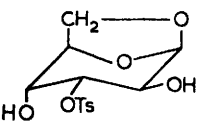
anion of the 5-hydroxymethyl group will cause more hindrance to the departing toluene-*p*-sulphonyloxy-anion than the glycosidic methoxyl group, and so the more favoured form would be (XIXc), leading to the 2:3-epoxide. It would be interesting now to know the composition of the products from the reaction of methyl 6-*O*-methyl-3-*O*-tosyl-β-D-glucoside and methyl 3-*O*-tosyl-β-D-xyloside with alkali.

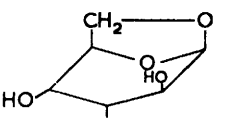
There is a very striking difference in the reactivity of the *O*-tosyl derivatives of 1:6-anhydro-β-D-altrose.[20] It was found that, although 1:6-anhydro-3-*O*-tosyl-β-D-altrose (XXVIII) could be converted into an epoxide, 1:6-anhydro-2-*O*-tosyl-β-D-altrose (XXIX) and the 3:4-di-*O*-tosyl derivative (XXX) were quite resistant to alkaline hydrolysis. This behaviour can be explained when steric interactions are considered. In the


(XXVIII)


(XXIX)


(XXX)


(XXVIIIa)

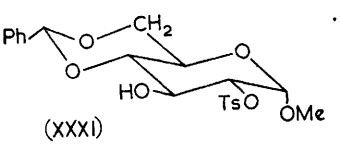

(XXVIIIb)

boat form (XXVIIIb), which is the condition suitable for epoxide formation, there are interactions between $OH_{(2)}$ and $O_{(1)}$, and between $OH_{(2)}$ and $C_{(6)}$. On passing from the chair to the boat conformation there will be steric interaction between vicinal groups when one is axial and the other equatorial (*cis*) since they must move past each other. Thus in (XXVIII

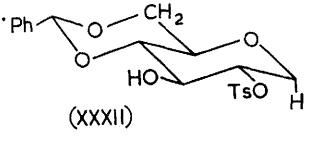
[24] *Idem, ibid.*, 1950, **72**, 1499.

a→b) there will also be a $OTs_{(3)}/OH_{(4)}$ passing interaction. Although the alkaline hydrolysis does not occur with great ease, these combined steric factors are not sufficiently great to prevent reaction. In the ester (XXIX), on the other hand, the interaction $OH_{(3)}/OH_{(4)}$ will be less, but when it is combined with the more severe interactions $OTs_{(2)}/O_{(1)}$ and $OTs_{(2)}/C_{(6)}$ the total hindrance must be sufficiently great to prevent reaction. Similarly, in the diester (XXX) there will be a very severe $OTs_{(3)}/OTs_{(4)}$ passing interaction and with the interactions $OH_{(2)}/O_{(1)}$ and $OH_{(2)}/C_{(6)}$ there is enough hindrance again to prevent reaction or even attainment of the boat form.

More weight is given to the concept of passing interaction when the alkaline hydrolysis of methyl 4:6-*O*-benzylidene-2-*O*-tosyl-α-D-glucoside[10] (XXXI) and 1:5-anhydro-4:6-*O*-benzylidene-2-*O*-tosyl-D-glucitol[25] (XXXII) is considered. The ester (XXXI) requires the temperature of



(XXXI)



(XXXII)

boiling methanol, and compound (XXXII) is hydrolysed easily at 0°. The only difference between the two compounds is the presence or absence of the 1-methoxyl group. If the first postulate that the diaxial condition must be attained by chair–boat transformation is correct, the difference in reactivity must be due entirely to the different passing interactions $OTs_{(2)}/OMe_{(1)}$ and $OTs_{(2)}/H_{(1)}$.

This concept also provides an explanation for the difference in reactivity between methyl 4:6-*O*-benzylidene-2-*O*-tosyl-α- and -β-D-galactoside.[20,26]

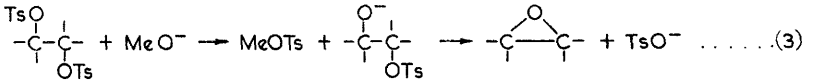
2.5. Epoxides from Di-*O*-sulphonyl Compounds.—In addition to the reactions already described, it is also possible to obtain an epoxide by alkaline hydrolysis of di-*O*-sulphonyl compounds. A well-known example of this is the formation of methyl 2:3-anhydro-4:6-*O*-benzylidene-α-D-alloside (XVII) from methyl 4:6-*O*-benzylidene-2:3-di-*O*-tosyl-α-D-glucoside (XXXIII). This reaction occurs easily with cold sodium methoxide and the anhydro-glycoside (XVII) is formed quantitatively as the sole product.[10,27] The preparative value lies in the ease of formation of the di-*O*-tosyl derivative since only a protecting *O*-benzylidene group need be introduced into the glucoside. The reaction is also of considerable theoretical interest since one of the ester groups must undergo O–S cleavage without difficulty, in contrast to the well-known S_N2 reaction (2) of alkyl sulphonates. This displacement at a sulphur atom, which is very prevalent

[25] Newth, XVIth Int. Congr. Pure Appl. Chem., Paris, 1957.
[26] Wiggins, *J.*, 1944, 522.
[27] Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1727.

in carbohydrate chemistry, has been called S_N2S[28] and must occur in those "isolated" secondary sulphonates which are hydrolysed with difficulty but with retention of configuration.[29] Angyal and Gilham[30] consider that

$$Ar{\cdot}SO_2{\cdot}O{-}R + R'O^- \longrightarrow Ar{\cdot}SO_2O^- + R'OR \quad \ldots\ (2)$$

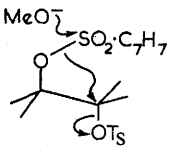
the removal of the first sulphonyl group, which will be the more accessible one, will be facilitated by the inductive effect of the other sulphonyloxy-group (reaction 3).



If this is so, the side reaction (4) should occur, but the presence of the low-boiling dimethyl ether in the reaction product seems to have eluded investigators:

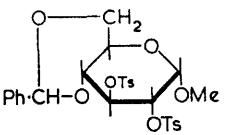
$$TsOMe + MeO^- \longrightarrow Me_2O + TsO^- \quad \ldots\ (4)$$

It is tempting to combine the reaction sequence (3) and postulate the concerted mechanism (5), but when the di-*O*-tosyl compound (XXXIII) is treated with mild alkali for a short time, the *allo*-epoxide (XVII) is formed together with some methyl 4:6-*O*-benzylidene-3-*O*-tosyl-α-D-glucoside.[31] The formation of the mono-*O*-tosyl derivative supports Angyal and Gilham's view and clearly hows the 2-sulphonyl group to be the more accessible.

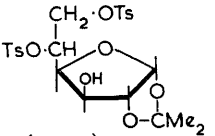


(5)

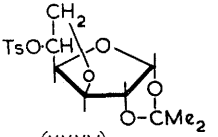
Before the discussion of epoxide formation from 2:3-di-*O*-sulphonyl compounds is continued, the alkaline hydrolysis of 1:2-*O*-isopropylidene-5:6-di-*O*-tosyl-α-D-glucofuranose (XXXIV) should be mentioned. Instead of 5:6-anhydro-1:2-*O*-isopropylidene-α-D-glucofuranose, 3:6-anhydro-1:2-*O*-isopropylidene-5-*O*-tosyl-α-D-gluco-



(XXXIII)



(XXXIV)



(XXXV)

furanose (XXXV) is formed.[32] It is not immediately obvious why the reaction should follow this course and not yield the 5:6-epoxide.

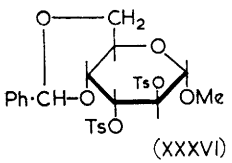
[28] Cope and Shen, *ibid.*, 1956, **78**, 5912.
[29] Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 207.
[30] Angyal and Gilham, *J.*, 1957, 3691.
[31] Honeyman and Morgan, *J.*, 1955, 3660.
[32] Ohle and Thiel, *Ber.*, 1933, **66**, 525.

There are several 2:3-di-*O*-tosyl derivatives and the problem is why should those of glucose and altrose give only one epoxide (*allo*- and *manno*-) whereas those of galactose give mixtures of the *gulo*- and the *talo*-epoxide. The factors which have been discussed in the preceding section must operate here and, although the uncertainty about the exact mode of hydrolysis makes it difficult to be precise, it is valuable to make a preliminary conformational appraisal.

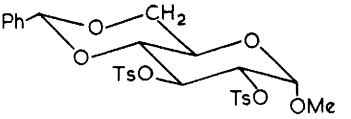
In the following discussion it is assumed that reaction (3) operates. O–S fission may then occur in either diequatorial or diaxial systems but, by the argument already developed, the resulting anion must be in or approaching the diaxial position before epoxide formation. The same factors then should affect this reaction as are believed to influence the reaction of mono-*O*-toluene-*p*-sulphonates; namely, non-bonded interactions by axial substituents and passing interaction of two *cis*-groups on change of conformation. It is, however, the first step in reaction (3) which determines the course of the reaction.

It will of course be recognised that there may be an electronic influence from the acetal character of $C_{(1)}$ but in none of the reactions—epoxide formation or fission—has the Reviewer found any consistent indication that this is so.

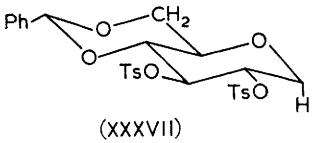
In methyl 4:6-*O*-benzylidene-2:3-di-*O*-tosyl-α-D-altroside (XXXVI) the reacting groups are diaxial and the *manno*-epoxide (XVI) is formed;[33] it is unfortunate that the reaction conditions employed were too severe to give any indication of the ease of reaction. It can be inferred that the 2-toluene-



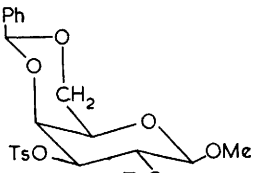
(XXXVI)



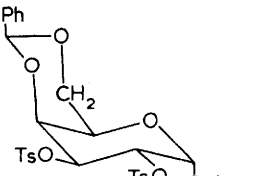
(XXXIIIa)



(XXXVII)



(XXXVIII)



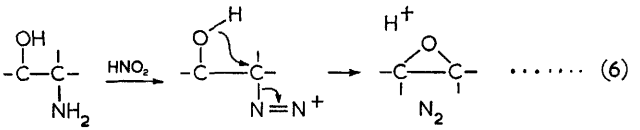
(XXXIX)

p-sulphonyloxy-group is the more accessible since this must provide the anion to displace the 3-group. In compound (XXXIIIa) and 1:5-anhydro-4:6-*O*-benzylidene-2:3-di-*O*-tosyl-D-glucitol (XXXVII), which has been shown to give also the *allo*-epoxide,[25,34] the primary attack must be also at $OTs_{(2)}$. The picture is complicated by the analogous galactose derivatives.

[33] Robertson and Whitehead, *J.*, 1940, 319.
[34] Zissis and Richtmyer, *J. Amer. Chem. Soc.*, 1955, **77**, 5154.

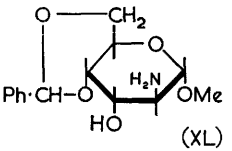
Methyl 4:6-*O*-benzylidene-2:3-di-*O*-tosyl-β-D-galactoside (XXXVIII) gives only the *talo*-epoxide[35] whereas the α-glycoside (XXXIX) gives a mixture of *talo*- and *gulo*-epoxide.[36] In the former, the primary attack must be at $OTs_{(3)}$, and in the latter at both $OTs_{(2)}$ and $OTs_{(3)}$. There does not appear, at present, to be any obvious reason for this behaviour.

2.6. Epoxides from Amino- and Nitrate Derivatives.—Deamination of aminodeoxy-compounds with nitrous acid occurs when there is a hydroxyl *trans* to the amino-group, and an epoxide is formed. The reaction follows the course shown in (6). Methyl 2-amino-4:6-*O*-benzylidene-2-deoxy-α-D-altroside (XL) and methyl 3-amino-4:6-*O*-benzylidene-3-deoxy-α-D-altroside (XLI) are rapidly converted into the epoxides (XVII) and

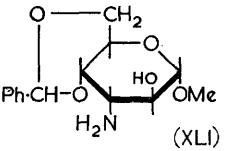


(6)

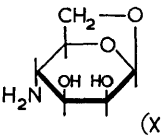
(XVI) by a solution of sodium nitrite in acetic acid.[37] Sugar epoxides are equally easily formed in the same way from 4-amino-1:6-anhydro-4-deoxy-β-D-mannose (XLII) and 6-amino-6-deoxy-1:2-*O*-isopropylidene-α-D-glucofuranose[38] (XLIII).



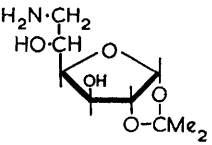
(XL)



(XLI)



(XLII)



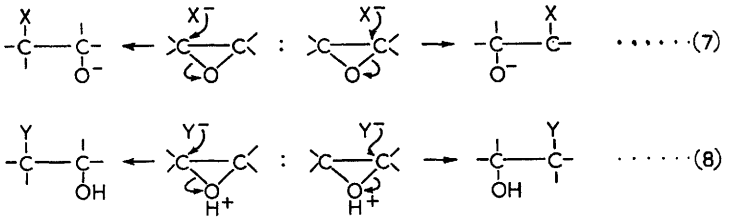
(XLIII)

During his studies on the sugar nitrates, Honeyman has found that certain derivatives yield an epoxide on alkaline hydrolysis. The subject is complex and it can only be pointed out here that the derivatives of methyl 4:6-*O*-alkylidene-α-D-glucoside which yield the 2:3-*allo*-epoxide are the 2:3-dinitrate, 3-nitrate, 2-*O*-tosyl 3-nitrate, and 3-*O*-tosyl 2-nitrate.[39]

[35] Sorkin and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 1, 662.
[36] Gyr and Reichstein, *ibid.*, 1945, **28**, 226.
[37] Wiggins, *Nature*, 1946, **157**, 300.
[38] Bashford and Wiggins, *ibid.*, 1950, **165**, 566.
[39] Ansell and Honeyman, *J.*, 1952, 2778; Honeyman and Morgan, *J.*, 1955, 3660; Honeyman and Stening, *J.*, 1957, 2278.

3. Reactions

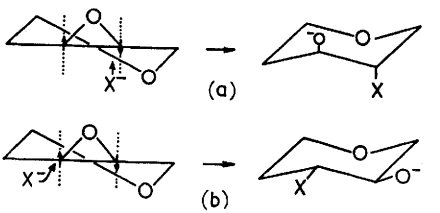
Peat[15] has very clearly described the stereochemistry of ring-opening by nucleophilic reagents (7). It is only necessary to add that with acidic reagents the same reaction occurs but is faster because protonation of the epoxide facilitates the movement of electrons (8). In the early work the reactions were nearly all with alkaline reagents, and the products were



[X may be HO^-, RO^-, NH_3,RS^-, H^-, etc.; Y may be Cl^-, Br^-, $(RO)_2PO^-$, etc.]

sugar derivatives which could be easily characterised. The isolation of both isomers established the constitution of the epoxide, although there appeared to be no reason for the predominance of one isomer over the other. In the last few years epoxide fission has been much discussed and the pattern of reaction is now clear.[22,40,41]

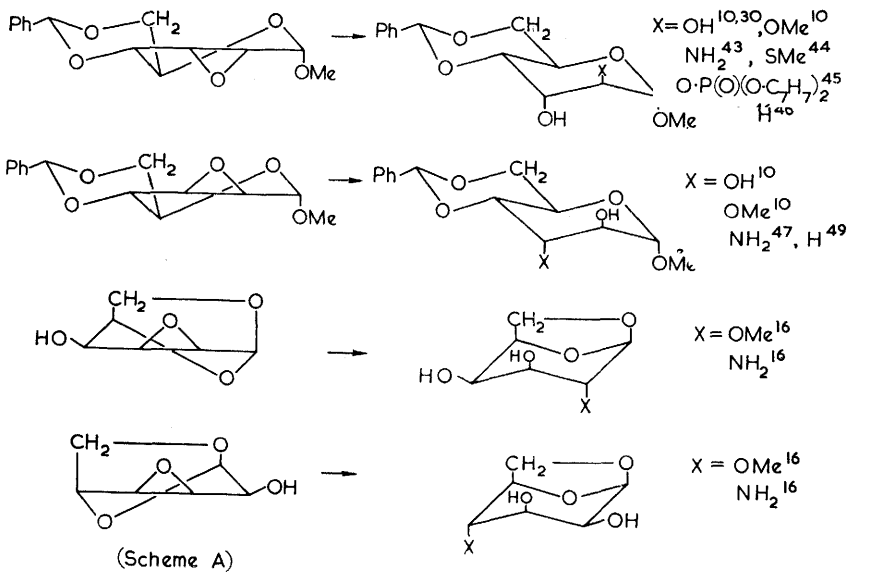
3.1. Ring-opening in Systems with a Rigid Conformation.—Mills[42] first suggested the applicability to sugar epoxides of Fürst and Plattner's rule that steroid epoxides break to give predominantly the axial isomer. The geometry of axial opening is shown at (a) (the small arrows indicate the direction of movement of the oxiran-carbon atoms) and it is obvious that there is a favourable co-planar transition state. Equatorial opening (b) is seen to be a very hindered process.



When the conformation of a sugar epoxide is made rigid by a *trans*-fused 4:6-benzylidene group or a 1:6-anhydro-ring the product of ring scission contains almost exclusively the axial isomer. Thus with nucleophilic reagents, the epoxides shown in the annexed group of formulæ (A)

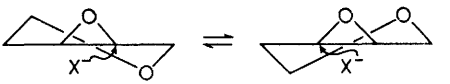
[40] Angyal, *Chem. and Ind.*, 1954, 1230.
[41] Overend, *ibid.*, 1955, 995.
[42] Mills, cited by Newth and Homer, *J.*, 1953, 989.

give predominantly the products indicated. The very small amount of the other isomer which is usually formed shows that equatorial opening can occur to a limited extent.



(Scheme A)

3.2. Ring-opening in Systems with a Flexible Conformation.—The monocyclic sugar epoxides have a flexible conformation and can exist in two forms (9).[22] If it is accepted that axial attack is the rule, either



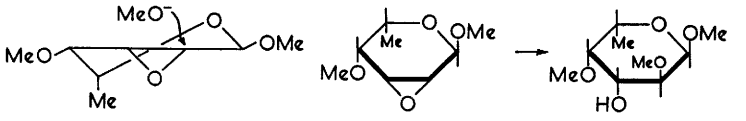
.....(9)

form may react and the products can then change into their most stable conformations.[40] From this point of view, it is unnecessary to postulate "exceptions" to Fürst and Plattner's rule. The predominant isomer will have its origin in the more stable form of the epoxide; the proportion of each isomer will reflect the energy difference between the two conformations of the epoxide. It is not possible to predict at present which conformation will be the more stable.

Charalambous and Percival[48] examined the fission of methyl 2:3- and

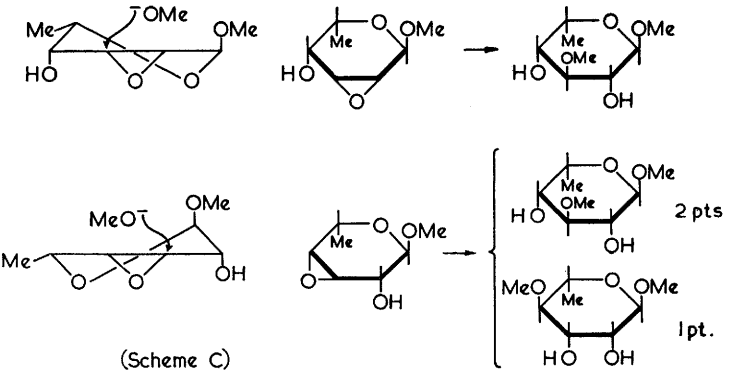
[43] Peat and Wiggins, *J.*, 1938, 1810.
[44] Grob and Prins, *Helv. Chim. Acta*, 1945, **28**, 840; Jeanloz, Prins, and Reichstein, *ibid.*, 1946, **29**, 371.
[45] Harvey, Michalski, and Todd, *J.*, 1951, 2271.
[46] Prins, *J. Amer. Chem. Soc.*, 1948, **70**, 3955.
[47] Myers and Robertson, *ibid.*, 1943, **65**, 8; Wiggins, *J.*, 1947, 18.
[48] Charalambous and Percival, *J.*, 1954, 2443.

3:4-anhydro-6-deoxy-α-L-taloside and their 2- and 4-*O*-methyl derivatives by sodium methoxide. The course of the reactions of the two *O*-methyl derivatives is shown in the following formulæ (B) and the axial opening of the stable conformations of the epoxides (*eq'*: *eq'*: *ax'*) accounts for the products which were isolated. The unmethylated anhydrides, in contrast,



(Scheme B)

gave predominantly the alternative isomers and for comparison the "unstable" (*ax'*: *ax'*: *eq'*) conformations are shown in (C). It is, however, from these two conformations that the products must originate. The only reasonable explanation must involve the free hydroxyl group, and it is suggested that hydrogen-bonding between this and the lactol-oxygen atom makes the conformations in (C) the more stable (cf. 1:6-anhydrides for similar atomic distances).

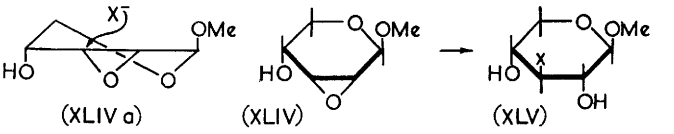


(Scheme C)

This suggested role of the hydroxyl group adequately explains the persistent formation of xylose derivatives (XLV) from methyl 2:3-anhydro-β-D(and L)-ribopyranoside (XLIV).

3.3. Epoxide Migration.—It has been seen that *trans*-opening of an epoxide ring occurs by attack of a nucleophilic reagent on one of the oxiran-carbon atoms from the side opposite to the oxygen atom. This reagent may be within the molecule itself, as in the formation of methyl

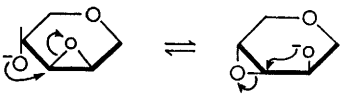
3:6-anhydro-β-D-glucoside (XXII) from (XX) or (XXI).[12] If there is a hydroxyl group adjacent to the epoxide but *trans* to the ring, an intra-



(XLIV a) (XLIV) (XLV)

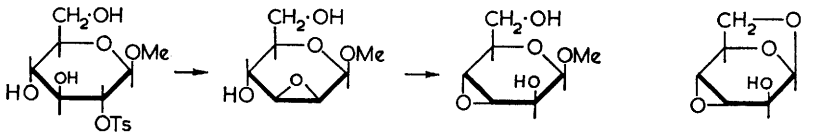
X = OH[49], SMe[50], NH_2[51], Br[52], Cl[53], H[54]

molecular displacement by the hydroxyl anion can also occur with the formation of a second epoxide (Scheme 10). This migration was first



(10)

postulated by Lake and Peat[54] to explain the formation of methyl 3:4-anhydro-β-D-altroside (XLVIII) as well as methyl 2:3-anhydro-β-D-mannoside (XLVII) from methyl 2-*O*-tosyl-β-D-glucoside (XLVI). The reaction was also assumed to occur when 1:6-anhydro-3-*O*-tosyl-β-D-altrose (XXVIII) was found to give, not 1:6-2:3-dianhydro-β-D-mannose, but 1:6-2:3-dianhydro-β-D-altrose[20] (XLIX).



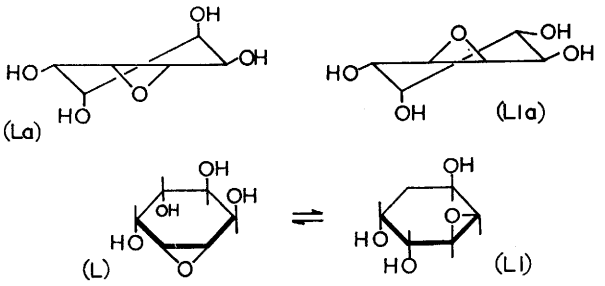
(XLVI) (XLVII) (XLVIII) (XLIX)

Epoxide migration in the inositol series has recently been demonstrated[30] in the conversion of (1*S*)-1:2-anhydroalloinositol (L) into (1*S*)-1:2-anhydroneoinositol (LI) by very mild alkali. At equilibrium, there is present 10% of the compound (L) and 90% of its isomer (LI). The latter is more stable by about 1·3 kcal./mole and in its preferred conformation has only one axial hydroxyl group.

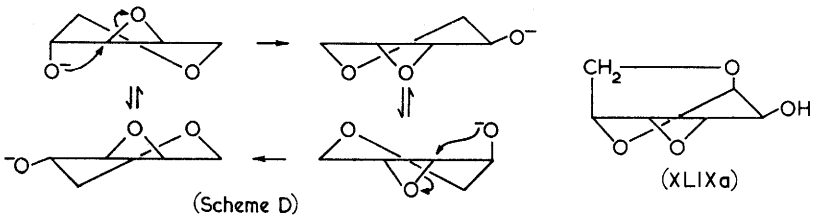
In Scheme (D) it can be seen that it is an obvious requirement that the attacking hydroxyl anion shall be in an axial position; the displaced anion will then be equatorial. For the reverse reaction there must be a conformational shift and axial attack can again occur. It is necessary to consider the non-bonded interactions in all four forms when attempting to predict the

[49] Honeyman, *J.*, 1946, 990.
[50] Mukherjee and Todd, *J.*, 1947, 969.
[51] Baker and Schaub, *J. Org. Chem.*, 1954, **19**, 646.
[52] Kent, Stacey, and Wiggins, *J.*, 1949, 1232.
[53] Allerton and Overend, *J.*, 1951, 1480.
[54] Lake and Peat, *J.*, 1939, 1069.

direction of equilibrium. It is interesting that the conformational shift cannot occur in 1:6-3:4-dianhydro-β-D-altrose (XLIXa) and it is very



doubtful whether its reconversion into 1:6-2:3-dianhydro-β-D-mannose is possible.

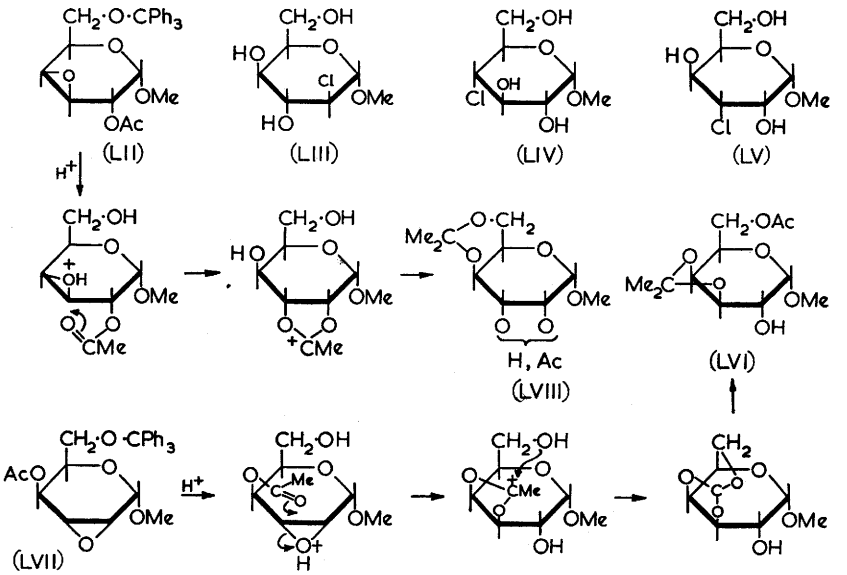


3.4. 3:4-Anhydrogalactose.—In 1935 Oldham and Robertson[55] isolated mono-*O*-isopropylidene derivatives of galactose and gulose from the reaction of the 3:4-anhydro-derivative of methyl α-D-galactoside (LII). This apparently anomalous *cis*- and *trans*-opening of the oxide ring was re-investigated by Labaton and Newth[56] who confirmed the earlier work and examined the action of hydrochloric acid on the anhydro-sugar. It was, however, their assignment of a 3:6-structure to the benzylidene derivative of one of the chlorohydrins believed to be methyl 4-chloro-4-deoxy-α-D-glucoside that stimulated further investigation. Buchanan[57] saw that the syrupy anhydride (LII) could be a mixture of the *gulo*- and *galacto*-epoxides owing to epoxide migration, and that some of the earlier products could be derived from the *gulo*-epoxide. By treating methyl 2:3-anhydro-4:6-*O*-benzylidene-α-D-guloside[35] with hydrochloric acid he showed that "methyl 3:6-*O*-benzylidene-4-chloro-4-deoxy-α-D-glucoside"[56] was methyl 4:6-*O*-benzylidene-2-chloro-2-deoxy-α-D-idoside (LIII), and this confirmed the presence of the *gulo*-epoxide in the mixture designated (LII). There was now an obvious uncertainty about the identity of "methyl 3-chloro-3-deoxy-α-D-guloside". Buchanan re-examined this compound

[55] Oldham and Robertson, *J.*, 1935, 685.
[56] Labaton and Newth, *J.*, 1953, 992.
[57] Buchanan, *J.*, 1958, 995; *Chem. and Ind.*, 1954, 1484.

and observed a very slow consumption of 1 mol. of periodate. It was, therefore, methyl 4-chloro-4-deoxy-α-D-glucoside (LIV). This was confirmed when authentic methyl 3:4-anhydro-α-D-galactoside was treated with hydrochloric acid[58] and one of the chlorohydrins was identical with Labaton and Newth's compound; the other by virtue of its stability to periodate was methyl 3-chloro-3-deoxy-β-D-guloside (LV).

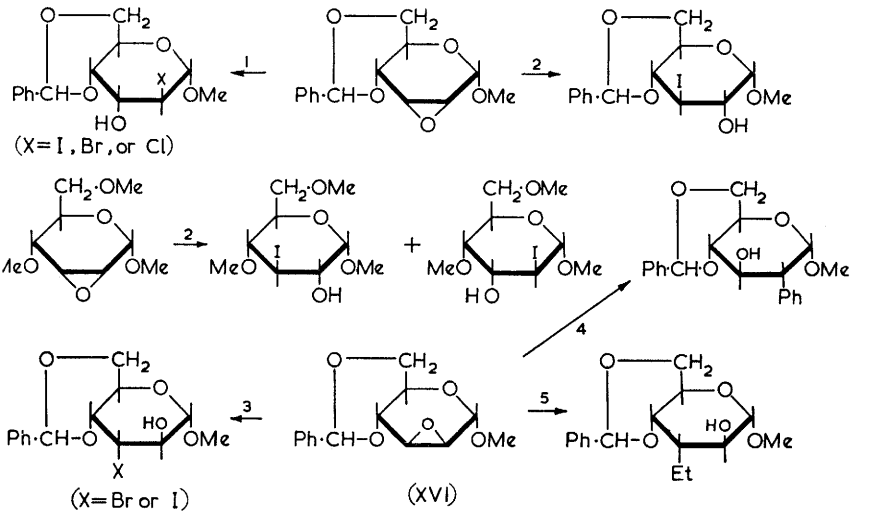
To explain the formation of *O*-acetyl-3:4-*iso*propylidene-α-D-galactoside in the Oldham and Robertson reaction, acid-catalysed *cis*-opening of the epoxide by acetone was suggested.[56] Buchanan[57] showed, however, that this was not the 2-*O*-acetate but the 6-*O*-acetate (LVI), and its formation was explained when he treated pure and authentic methyl 2-*O*-acetyl-3:4-anhydro-6-*O*-trityl-α-D-galactoside (LII) and methyl 4-*O*-acetyl-2:3-anhydro-6-*O*-trityl-α-D-guloside (LVII) with anhydrous hydrogen chloride in acetone.[58] The former was converted into methyl *O*-acetyl-4:6-*O*-isopropylidene-α-D-guloside (LVIII), and the latter into 6-*O*-acetyl-3:4-*O*-isopropylidene-α-D-galactoside (LVI). This was explained by the directive influence of the neighbouring *trans*-*O*-acetyl group on the epoxide fission through the carbonium-type intermediates shown in (LII)→(LVIII) and (LVII)→(LVI).



3.5. Reaction with Grignard Reagents.—The epoxides (XVI) and (XVII) have been very completely examined. With alkyl- and phenyl-magnesium halides the products are the halogenohydrins, and these are also formed with magnesium halides. Diethylmagnesium and diphenylmagnesium give

[58] Buchanan, *J.*, 1958, 2511.

C-ethyl and *C*-phenyl derivatives. The reactions, which are shown in the batch of formulæ below, do not show a consistent pattern and more varied examples are required before the mechanism of reaction can be fully understood.



Reagents: 1, (*a*) MgX_2[62], (ii) EtMgBr[60]; EtMgI, PhMgBr. 2, MgMeI[59]. 3, (*a*) MeMgI[61], EtMgI, PhMgI; (*b*) $MgBr_2$[62], MgI_2 (not $MgCl_2$). 4, $MgPh_2$. 5, $MgEt_2$[63].

[59] Newth, Richards, and Wiggins, *J.*, 1950, 2356.
[60] Richards and Wiggins, *J.*, 1953, 2442.
[61] Richards, *J.*, 1954, 4511.
[62] Richards, Wiggins, and Wise, *J.*, 1956, 496.
[63] Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308.
[64] Richards, *J.*, 1955, 2013.