128. *Preparation and Properties of Some Poly-O-acetylglycosyl Chlorides of the " Unstable " Series.*

By W. Korytnyk and J. A. Mills.

Fully acetylated aldopyranoses of 1 : 2-*trans*-configuration, and acetylated aldoses of this configuration with a free hydroxyl group at the hemiacetal centre, react with aluminium chloride in cold chloroform, giving *O*-acetylglycosyl chlorides of 1 : 2-*trans*-configuration (so-called " unstable" chlorides). The reaction is successful with 4 : 6-*O*-benzylidene- and 4 : 6-*O*-ethylidene-β-D-glucopyranose triacetate, and with β-maltose octa-acetate. The stereospecificity of the reaction, criteria for the structures of the products, and conformational implications for aldopyranoses are discussed.

O-Acetylglycosyl chlorides of 1 : 2-*trans*-configuration are fairly stable. Reported mutarotations of " unstable " chlorides are apparently due to slow reaction with traces of water in solvents.

Tetra-*O*-acetyl-β-D-mannopyranosyl chloride has been obtained in small yield by reaction of β-D-mannopyranose penta-acetate with hydrogen chloride in acetyl chloride. The significance of this finding is also discussed.

In 1953, Dr. J. Gagolski [1] found that reaction of β-D-glucopyranose penta-acetate with anhydrous aluminium chloride in cold chloroform gave a good yield of a product identical with the " β-acetochloroglucose " obtained [2] by reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with " active " silver chloride. A similar observation was made at about the same time by Zemplen, Mester, and Eckhart.[3] Gagolski found that one mole of aluminium chloride ($AlCl_3$) would convert up to three moles of glucose penta-acetate into acetylglucosyl chloride, that α-D-glucopyranose penta-acetate did not react under the same conditions, and that the method showed promise for the preparation of acetylglycosyl chlorides from other acetylated sugars. The more extensive study of the reaction described here has established the main details of procedure, scope, and mechanism. The mechanism deduced fits satisfactorily into the general scheme for replacement

[1] Gagolski, Ph.D. Thesis, Adelaide, 1954.
[2] Schlubach, *Ber.*, 1926, **59**, 840.
[3] Zemplen, Mester, and Eckhart, *Acta Chim. Acad. Sci. Hung.*, 1954, **4**, 73.

reactions in cyclic reducing sugars elaborated by Lemieux and others.[4,5,6] While the work was in progress, the Ottawa group published further papers on closely related topics; our work is in general agreement with theirs, and in several respects complementary to it.

Aluminium chloride or titanium tetrachloride has been used, in refluxing chloroform, to afford "stable" isomers of acetylglycosyl chlorides from acetylated reducing sugars,[7] and titanium chloride is a powerful epimerising agent that will react under such conditions with each of a pair of anomeric sugar acetates. Other workers had also found that under milder conditions these reagents may sometimes act more selectively. With aluminium chloride in cold chloroform, β-maltose octa-acetate afforded an oily chloride different from the crystalline hepta-*O*-acetylmaltosyl chloride obtained by using more vigorous conditions.[8] The same reagent afforded epimeric chlorides from the epimeric penta-acetates of *aldehydo*-D-arabinose methyl hemiacetal.[9] Titanium tetrachloride in chloroform at 40° rapidly converted β-D-glucopyranose penta-acetate into the β-chloride, which slowly rearranged to the α-chloride; the α-penta-acetate was relatively unreactive.[10]

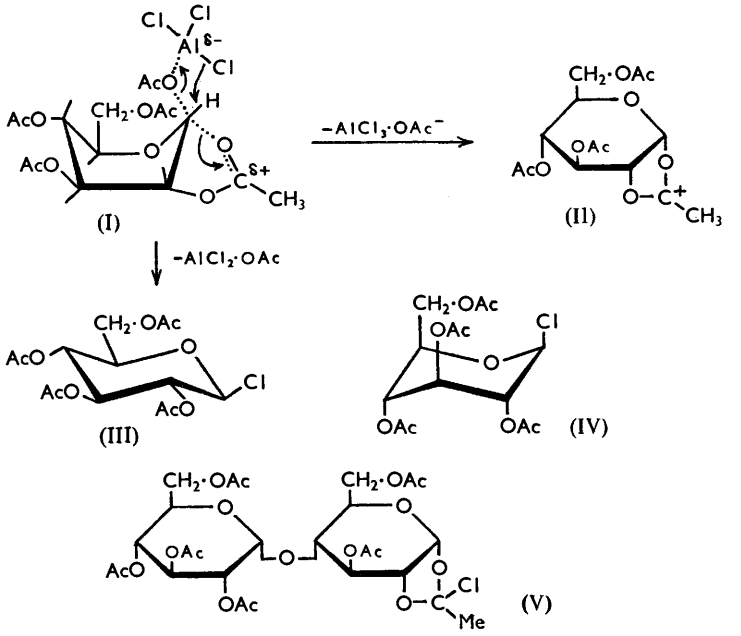
Treatment of a number of anomeric pairs of sugar acetates with aluminium chloride in cold chloroform under standardised conditions has now shown that the reaction has high configurational specificity, but that ring size and conformations of pyranose sugars have little effect. The fully acetylated β-D-forms of glucopyranose, galactopyranose, galactofuranose, and xylopyranose, and α-D-mannopyranose penta-acetate, all reacted readily and gave the acetylglycosyl chloride of the same configuration as the acetate used, whereas the anomeric acetate was in every case recovered unchanged (α-D-xylopyranose tetra-acetate was not available). A quantitative study of the rates for the various sugars would be difficult, and was not attempted.

The reaction constitutes a stereospecific synthesis of acetylglycosyl chlorides of 1 : 2-*trans*-configuration from sugar acetates of 1 : 2-*trans*-configuration, and therefore probably belongs to the class of reaction in which displacement of a group at position 1 depends on participation by the neighbouring 2-acetoxy-group.[4] The following mechanism is suggested: the electrophilic aluminium atom becomes co-ordinated to the ether-oxygen of the 1-acetoxy-group, and the resulting change in polarity, assisted by electron-displacement from the 2-acetoxy-group, causes transfer of the acetoxy-group from position 1 to aluminium. Complete separation of $AlCl_3{\cdot}OAc^-$ to afford the free ion (II) (which might exist in mesomeric forms) is unlikely, although an ion-pair may be transiently formed. More probably, transfer of chlorine from aluminium to position 1 within the reaction complex (I) is practically synchronous with fission of the $C_{(1)}$–acetoxyl bond. The primary products are tetra-*O*-acetyl-β-D-glucopyranosyl chloride, shown in its most stable conformation (III), and aluminium dichloride acetate. The stoicheiometry of the reaction[1] requires the latter to effect replacement in more penta-acetate, but whether it acts directly, or by disproportionation to aluminium trichloride, is not known. Stannic trichloride acetate transfers acetoxy-groups, not chlorine atoms, to β-D-glucopyranose penta-acetate.[10]

The efficiency of participation by groups other than acetate was examined. A 2-benzoyloxy-group, as in β-D-glucopyranose 1 : 3 : 4 : 6-tetra-acetate 2-benzoate, permitted normal displacement of the 1-acetoxy-group by aluminium chloride. When a 1-benzoyloxy-group was also present, in β-D-glucopyranose pentabenzoate, satisfactory reaction could not be effected even with titanium tetrachloride in chloroform. Aluminium chloride did not react in the cold with the 2-toluene-*p*-sulphonate or 2-trichloroacetate of β-D-glycopyranose 1 : 3 : 4 : 6-tetra-acetate, probably because of the weakening of the nucleophilic properties by the strong inductive effects in the toluene-*p*-sulphonyloxy- and

[4] Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 1.
[5] Pacsu, *ibid.*, 1945, **1**, 77.
[6] Frush and Isbell, *J. Res. Nat. Bur. Stand.*, 1941, **27**, 413.
[7] Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207.
[8] Pacsu and Rich, *J. Amer. Chem. Soc.*, 1935, **57**, 587.
[9] Montgomery, Hann, and Hudson, *ibid.*, 1937, **59**, 1124.
[10] Lemieux and Brice, *Canad. J. Chem.*, 1952, **30**, 295.

the trichloroacetoxy-group. The 6-toluene-*p*-sulphonyloxy-group in β-D-glucopyranose 1 : 3 : 4 : 6-tetra-acetate 6-toluene-*p*-sulphonate had no detectable effect on the normal displacement at $C_{(1)}$. 2-Acetamido-1 : 3 : 4 : 6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose

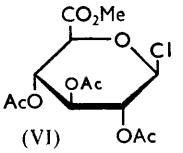


did not react with aluminium chloride. The acetamido-group is known to show neighbouring-group reactivity in carbohydrates,[11,12] and the reaction may have failed through the sparing solubility of the compound, or through inactivation of the aluminium chloride by co-ordination to nitrogen.

" β-Acetochloroglucose " and the other pyranosyl chlorides (except that from mannose) obtained by the aluminium chloride procedure are isomers of the well-known " stable " acetylglycosyl chlorides, and proof was needed that they are true epimers of the " stable " chlorides. The epimeric nature of " stable " and " unstable " chlorides has been assumed by most workers, except for the " exceedingly sensitive " acetylmaltosyl chloride of Freudenberg and Ivers,[13] which it is generally conceded is one of the isomers of the cyclic orthoacetyl chloride (V). The regular formation of methyl orthoacetates from the " unstable " chlorides in the Koenigs–Knorr synthesis of methyl glycosides [5] is not conclusive, as they may be formed directly from orthoacetyl chlorides of type (V), or from 1 : 2-*trans*-acylglycosyl chlorides by neighbouring-group participation. Zemplen *et al.* have now suggested [3] that " β-acetochloroglucose " is also a cyclic orthoacetyl chloride, because their preparation of it from β-D-glucopyranose penta-acetate and aluminium chloride in cold chloroform was analogous to Pacsu and Rich's preparation [8] of an oily acetylmaltosyl chloride, which the latter assumed to be essentially the same as Freudenberg and Ivers's chloride (V). This argument was disproved by our finding that the reaction of β-maltose octa-acetate with aluminium chloride in cold chloroform affords a stable, crystalline compound having properties to be expected of the hitherto unknown hepta-*O*-acetyl-β-maltosyl chloride. Like other chlorides obtained by the aluminium chloride procedure, it differed from Freudenberg and Ivers's chloride in being relatively

[11] Baker and Schaub, *J. Amer. Chem. Soc.*, 1953, **75**, 3864.
[12] Jeanloz, *ibid.*, 1957, **79**, 2591; Tarasiejska and Jeanloz, *ibid.*, p. 4215.
[13] Freudenberg and Ivers, *Ber.*, 1922, **55**, 929.

resistant to hydrolysis when dissolved in moist benzene, which rapidly hydrolysed compound (V).[14] Gagolski [1] seems to have prepared the new maltosyl chloride in impure form, and it presumably was the major component of Pacsu and Rich's oily product.[8]



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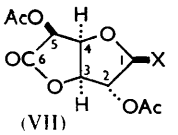


(VII)

Optical rotations of the products of the aluminium chloride procedure are consistent with the true acetylglycosyl chloride structures.[15] Further evidence that the compounds are not orthoacetyl chlorides was found in their reaction with silver acetate in benzene. The orthoacetyl maltosyl chloride (V) reacted readily with silver acetate in cold benzene, giving a maltose octa-acetate different from the known α- and β-octa-acetates.[14] The 1 : 2-*trans*-chloride-acetates from the aluminium chloride reaction were relatively unreactive toward silver acetate in cold benzene, but at the b. p. afforded the sugar acetates of 1 : 2-*trans*-configuration from which they had been prepared. Chlorides of 1 : 2-*cis*-configuration also afforded sugar acetates of 1 : 2-*trans*-configuration at the b. p., but far more slowly. The greater reactivity of the 1 : 2-*trans*-chloride-acetates is due to participation of the 2-acyl group in the displacement at position 1, by way of the ion (II). The rate of reaction with silver acetate in benzene permits discrimination between the three classes of poly-*O*-acetylglycosyl chloride.

The structures and configurations, hitherto doubtful, of some chlorides related to D-glucuronic acid have been clarified by their preparation by the aluminium chloride method. Methyl tetra-*O*-acetyl-β-D-glucopyranuronate of known structure and configuration (see p. 644) afforded, on reaction with aluminium chloride, a chloride with m. p. 150—151° and $[\alpha]_D$ −17° (rotations in chloroform), identical with a compound obtained by Goebel and Babers by treating an acetylated methyl D-glucuronate of unproven structure with hydrogen chloride in acetyl chloride.[16c] The compound is, therefore, methyl 2 : 3 : 4-tri-*O*-acetyl-1-chloro-1-deoxy-β-D-glucopyranuronate (VI); the configuration is confirmed by the optical rotation [15] and by the reconversion of the chloride into the parent tetra-acetate by silver acetate in boiling benzene. Three different incorrect structures have been suggested for this chloride.[16d, 4, 7] Goebel and Babers obtained an isomeric compound with m. p. 99—100° and $[\alpha]_D$ +169°, which is now seen to be the α-anomer of (VI), by refluxing the acetate used for making (VI) with titanium tetrachloride in chloroform.[16d]

The same authors [16b] prepared an acetylglycosyl chloride with m. p. 108—109° and $[\alpha]_D$ +96° by treating acetylated D-glucurone with hydrogen chloride in acetyl chloride. The furanoid structure of D-glucurone [17] and its triacetates [18] seems to be well established, and as the β-triacetate [16a, 18] readily reacted with aluminium chloride in cold chloroform, affording a chloride identical with that described by Goebel and Babers,[16b] their product is probably 2 : 5-di-*O*-acetyl-1-chloro-1-deoxy-β-D-glucofuranurono-6 ⟶ 3-lactone (VII; X = Cl). Chemical evidence consistent with this configuration is found in the formation of a methyl orthoacetate under Koenigs–Knorr conditions,[19] and in the ready regeneration of the β-triacetate (VII; X = OAc) from the chloride by silver acetate in acetic acid. This evidence does not completely exclude an orthoacetyl chloride structure, as the 5-acetoxy-group in the lactone (VII) is close enough to participate in displacements at position 1. Consideration of the optical rotations of the chloride and of the α- and the

[14] Freudenberg, von Hochstetter, and Engels, *Ber.*, 1925, **58**, 666.
[15] Korytnyk, following paper.
[16] Goebel and Babers, *J. Biol. Chem.*, (*a*) 1933, **100**, 743; (*b*) 1933, **101**, 173; (*c*) 1934, **106**, 63; (*d*) 1935, **111**, 347.
[17] Smith, *J.*, 1944, 584.
[18] Tsou and Seligman, *J. Amer. Chem. Soc.*, 1952, **74**, 5605.
[19] Goebel and Babers, *J. Biol. Chem.*, 1935, **110**, 707.

β-triacetate of D-glucurone (+204° and +84°, respectively)[16a] strongly favours the β-configuration for the chloride. If this is correct, it is surprising that reaction with silver acetate or aluminium chloride should occur readily at an *endo*-position in the bicyclic system (VII). Bulky reagents do not attack at *endo*-positions in the related ring system of the 1 : 4-3 : 6-dianhydrohexitols.[20]

β-D-Fructopyranose penta-acetate reacted only slowly with aluminium chloride in chloroform, and refluxing was needed to give a good yield of tetra-*O*-acetyl-β-D-fructopyranosyl chloride, which is also obtained by using more powerful reagents. There was no evidence of the formation of an isomeric chloride. The sluggish reaction is probably due to hindrance to the attachment of aluminium chloride to the 2-acetoxy-group, as the 1-acetoxy-group is favourably placed to participate in the displacement step.

Reducing sugars with a free hydroxyl group at the hemiacetal carbon also give chlorides when treated with aluminium chloride if a neighbouring acyl group is correctly orientated to assist in displacement of the hydroxy-group. β-D-Galactopyranose 2 : 3 : 4 : 6-tetra-acetate reacted in the usual way, affording tetra-*O*-acetyl-β-D-galactopyranosyl chloride, but the α-D-tetra-acetate did not react under these conditions. β-D-Fructopyranose 1 : 3 : 4 : 5-tetra-acetate afforded a fair yield of tetra-*O*-acetyl-β-D-fructopyranosyl chloride in the cold; it is therefore more reactive than the fructose penta-acetate.

The 1 : 2-*trans*-glycosyl chlorides are practically unaffected by short contact with aluminium chloride in chloroform at room temperature, but at higher temperatures epimerisation to the more stable 1 : 2-*cis*-chloride-acetates may occur. Tetra-*O*-acetyl-β-D-glucopyranosyl chloride readily afforded the α-chloride when refluxed with aluminium chloride in chloroform. Tetra-*O*-acetyl-β-D-galactopyranosyl chloride was also transformed under these conditions, but the product had a specific rotation (+177·5°) lower than the accepted value[21] for the α-isomer (+212·3°). Repetition of Skraup and Kremann's preparation of the α-galactosyl chloride showed that their reported rotation is wrong, and the β-chloride is in fact completely transformed into α-chloride by aluminium chloride. 2 : 3 : 4-Tri-*O*-acetyl-6-*O*-toluene-*p*-sulphonyl-β-D-glucopyranosyl chloride and methyl 2 : 3 : 4-tri-*O*-acetyl-1-chloro-1-deoxy-β-D-glucopyranuronate resisted epimerisation by aluminium chloride, and their stability may be due to the larger, more electronegative groups at position 6.

Anhydrous aluminium bromide was allowed to react with β-D-glucopyranose penta-acetate in cold chloroform in the hope that tetra-*O*-acetyl-β-D-glucopyranosyl bromide would be formed, but the only crystalline product isolated was tetra-*O*-acetyl-β-D-glucopyranosyl *chloride*. Since this was formed under conditions identical with those used for reaction of the glucose penta-acetate with aluminium chloride, an extremely rapid exchange of halogen must occur between aluminium bromide and chloroform. There may be a risk of halogen exchange in the preparation of poly-*O*-acetylglycosyl bromides by refluxing acetylated sugars with titanium tetrabromide in chloroform.[22]

All 1 : 2-*trans*-*O*-acetylglycosyl chlorides except methyl 2 : 3 : 4-tri-*O*-acetyl-1-chloro-1-deoxy-β-D-glucopyranuronate showed a slow rotational change when dissolved in nominally "dry" chloroform, and larger, more rapid changes in ordinary chloroform. A detailed study of the behaviour of tetra-*O*-acetyl-β-D-glucopyranosyl chloride in chloroform of varying moisture content showed that the change was negligible in very rigorously dried chloroform, but successive increases in the ratio of water to β-chloride in the solutions caused more extensive and more prolonged changes in rotation. No crystalline material could be isolated from the chloroform solutions after the changes had ceased, and the oils recovered contained ionic chlorine. Contrary to the common belief[4,7] the changes are not true mutarotations indicative of simple anomerisation to the more stable α-chloride, but are due to hydrolysis; and the change of rotation to more positive values, and the

[20] Matheson and Angyal, *J.*, 1952, 1133; Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[21] Skraup and Kremann, *Monatsh.*, 1901, **22**, 375.
[22] Zemplen and Gerecs, *Ber.*, 1934, **67**, 2049.

known course of the hydrolysis of the β-chloride in moist acetic acid,[23] suggest that the primary product is α-D-glucopyranose 2 : 3 : 4 : 6-tetra-acetate. The early observation [24] that the rate of change of rotation of "β-acetochloroglucose" in various solvents increased with the dielectric constant of the solvent is as consistent with hydrolysis by traces of moisture as with the simple anomerisation originally postulated, the rate of each reaction being determined by solvation and ionisation of the chlorine. The "mutarotation" of an acyclic acetylglycosyl chloride in "dry" chloroform was found to be accompanied by hydrolysis. [25] It is likely that all chlorides of 1 : 2-*trans*-configuration would be stable in perfectly dry, non-polar solvents.

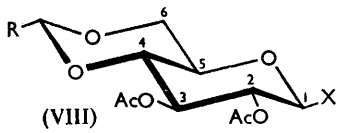
Conditions favourable for rapid hydrolysis of acylglycopyranosyl chlorides by traces of water should be an equatorial orientation (usually β) of the chlorine atom, a solvent with good solvating power for chloride ions, and a neighbouring acyl group capable of participating in the solvolytic displacement of chlorine. Available data for acylated aldohexopyranosyl halides or the related aldoheptopyranosyl halides [4] show that the halide containing equatorial halogen is the thermodynamically less stable of a pair of epimers, and because of its lower stability and the greater accessibility of the halogen atom to solvation the equatorial halide should be more readily hydrolysed, other factors being equal. Participation by the neighbouring acyl group is, however, the most important single factor promoting rapid hydrolysis, because the cyclic ion (II) is highly reactive and, once formed, acts as a scavenger for traces of water.[26] When neighbouring-group participation is ineffective, true epimerisation of halogen without hydrolysis is possible, as with 3 : 4 : 6-tri-*O*-acetyl-β-D-glucopyranosyl chloride, which mutarotates in acetone, affording a solution from which the α-anomer may be isolated.[27] Water is required in this reaction, probably to assist the ionisation of the β-chloride by solvation, because it was found that the β-chloride could be recovered unchanged after four days in scrupulously dried, pure acetone, whereas the same solvent briefly exposed to moist air converted it into the α-chloride. Brigl's speculation on the rôle of water in the mutarotation of this β-chloride [28] is thereby confirmed. The stability of the glucuronosyl chloride (VI) in chloroform (it is also unaffected by aluminium chloride in refluxing chloroform) shows that other factors, probably electronic, may sometimes override the more obvious steric factors.

Lemieux and his colleagues have postulated that a conformational change is required in some pyranose sugars if neighbouring groups are to participate in displacement reactions.[4, 26, 29] For example, tetra-*O*-acetyl-β-D-glucopyranosyl chloride changes from the stable C1 conformation (III) to the alternative 1C chair conformation (IV) to provide the favourable antiparallel arrangement of the chlorine atom and the 2-acetoxy-group. They further postulate that the cyclic ion (II) formed by the displacement at $C_{(1)}$ has a half-chair conformation analogous to that of *cyclo*hexene, and have correlated differences in reactivity of several pyranose sugar acetates of 1 : 2-*trans*-configuration with the arrangement of substituents in the two possible half-chair conformations of the carbonium ions.[30] Our experience with derivatives of 4 : 6-*O*-benzylidene- and 4 : 6-*O*-ethylidene-D-glucose shows that part of this thesis must be modified.

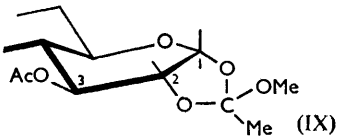
4 : 6-*O*-Benzylidene-β-D-glucopyranose triacetate (VIII; R = Ph, X = OAc) reacted smoothly with aluminium chloride in cold chloroform, affording the corresponding β-chloride (VIII; R = Ph, X = Cl) as a stable, crystalline compound. When refluxed with silver acetate in benzene, this regenerated the β-triacetate. With methanol, in the presence of silver carbonate, quinoline, or collidine, it gave a crystalline compound

[23] Lemieux and Brice, *Canad. J. Chem.*, 1955, **33**, 109.
[24] Schlubach, Stadler, and Wolf, *Ber.*, 1928, **61**, 287.
[25] Wolfrom, Konigsberg, and Moody, *J. Amer. Chem. Soc.*, 1940, **62**, 2343.
[26] Lemieux and Cipera, *Canad. J. Chem.*, 1956, **34**, 906.
[27] Lemieux and Huber, *ibid.*, 1953, **31**, 1040.
[28] Brigl, *Z. physiol. Chem.*, 1921, **116**, 1.
[29] Lemieux, Brice, and Huber, *Canad. J. Chem.*, 1955, **33**, 134.
[30] Lemieux and Brice, *ibid.*, 1956, **34**, 1006.

formulated as the 1 : 2-(methyl orthoacetate) (partial structure IX). Hydrolysis of the methyl orthoacetate with ammonia, followed by methylation (Purdie) and vigorous acidic hydrolysis, afforded 3-*O*-methyl-D-glucose, showing that an alkali-labile group was present at position 3, and alkali-stable, acid-labile substituents at the other positions. Treatment of the methyl orthoacetate with anhydrous acetic acid regenerated the 4 : 6-*O*-benzylidene β-triacetate (VIII; R = Ph, X = OAc) [cf. the analogous behaviour of α-D-glucopyranose 3 : 4 : 6-triacetate 1 : 2-(ethyl orthoacetate) [26]]. A solution of the methyl orthoacetate in 99% acetic acid [26] showed a very rapid increase in optical rotation, followed by a decrease. The product isolated from this solution at the point of maximum rotation seemed to be 4 : 6-*O*-benzylidene-α-D-glucopyranose 2 : 3-diacetate; it was also



(VIII)



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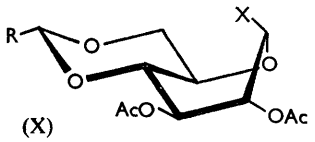

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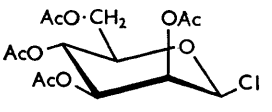

(XI)

obtained by treating the β-chloride (VIII; R = Ph, X = Cl) with silver carbonate and silver nitrate in aqueous acetone. The methoxy-group is therefore more labile to acid than the benzylidene group. This proves that the product was the authentic 1 : 2-(methyl orthoacetate) (IX), and it is virtually certain that the chloride from which it was made is the true glycopyranosyl chloride of β-D-configuration, and that the reaction of aluminium chloride with the β-triacetate has followed the normal course, without affecting the cyclic acetal grouping. The action of aluminium chloride on 4 : 6-*O*-ethylidene-β-D-glucopyranose triacetate (VIII; R = Me, X = OAc) afforded a chloride similar in all respects to the 4 : 6-*O*-benzylidene chloride, and it is therefore (VIII; R = Me, X = Cl).

The rates of formation of these chlorides from the bicyclic systems (VIII), and of the subsequent reactions of the chlorides, were qualitatively similar to rates for the monocyclic pyranose compounds previously studied, even though the *trans*-junction of the rings in (VIII) prevents the pyranose ring from passing into the 1C conformation. Structure (VIII) may, however, pass without undue conformational strain into the boat-form (X), which has the required antiparallel arrangement about positions 1 and 2. Transformation of monocyclic derivatives of β-D-glucopyranose into an analogous boat form during reaction is probable, as the 1C chair form (IV) involves excessive steric strains. Our experiments do not disprove the half-chair conformation for the carbonium ion formed by participation of the 2-acetoxy-group in displacements at position 1, but only one half-chair form is possible from the structure (VIII).

Both epimers of acetylated aldopyranosyl chlorides are now readily available in all cases where the 1 : 2-*trans*-chloride-acetate, obtainable by the aluminium chloride method, contains an equatorial chlorine atom and is therefore the less stable isomer, provided the acetylated sugar is stable enough to permit the use of the more powerful reagents, such as titanium tetrachloride, required for formation of the more stable 1 : 2-*cis*-chloride-acetate (axial). If the pure 1 : 2-*trans*-sugar acetate needed for the aluminium chloride method is not known, it can be made by the action of silver acetate on the chloride or bromide of 1 : 2-*cis*-configuration, which can usually be prepared from a crude mixture of the epimeric acetates. If the 1 : 2-*trans*-compound contains axial chlorine (aldoses of *manno-*, *talo-*, *altro-*, or *ido*-configuration), it will be the stable epimer, and be formed by the action of either aluminium chloride or titanium tetrachloride; in such cases, no general route to the 1 : 2-*cis*-chloride-acetate is available.

Hydrogen chloride in acetyl chloride, used by Goebel and Babers [16b, 16c] in preparing the glucuronosyl chlorides (VI) and (VII), is a neglected reagent. In the two examples cited, it gave the same isomer as was obtained by the aluminium chloride method. Experiments with various sugar acetates, exposed to the action of hydrogen chloride in acetyl chloride under standardised conditions, showed that this apparent similarity between the two reactions is not general. Both the α- and the β-penta-acetate of methyl D-glucopyranuronate afforded about 70% of the β-chloride (VI). Somewhat lower yields (54—62%) of tetra-*O*-acetyl-β-D-glucopyranosyl chloride were obtained from both the α- and the β-penta-acetate of D-glucopyranose; optical rotations of the crude reaction mixture suggested that about 30% of α-chloride was also present. From reactions of the β-octa-acetates of maltose and lactose only the α-chlorides could be isolated, in 65% yield. β-D-Fructopyranose 1 : 3 : 4 : 6-tetra-acetate gave about 76% of tetra-*O*-acetyl-β-D-fructopyranosyl chloride.

β-D-Mannopyranose penta-acetate afforded two products under the the same conditions, tetra-*O*-acetyl-α-D-mannopyranosyl chloride (63% isolated) and a new compound, tetra-*O*-acetyl-β-D-mannopyranosyl chloride (XI) (1% isolated); polarimetry showed that the ratio of α- to β-chloride in the crude mixture was about 83 : 17. α-D-Mannopyranose penta-acetate afforded 76% of crude α-chloride, and no β-chloride (XI) could be isolated. The new chloride (XI) is the first example of an acetylated aldopyranosyl chloride of 1 : 2-*cis*-configuration that definitely contains an equatorial chlorine atom. Lack of material has prevented an exhaustive study of it, but it shows the stability expected of 1 : 2-*cis*-acylglycosyl chlorides. It was recovered unchanged after two months from a solution in chloroform, and reacted slowly with silver acetate in boiling benzene, affording α-D-mannopyranose penta-acetate. Hydrogen chloride in acetyl chloride caused partial epimerisation to the α-chloride. The new chloride has a higher melting point than the α-chloride; the same relation was noted for every other α, β pair of acetylated aldopyranosyl chlorides examined.

The action of hydrogen chloride in acetyl chloride on sugar acetates deserves further study, especially of the course of the reaction with time. The diverse stereochemical results of the reaction when applied under fixed conditions to the acetates listed above may merely be due to different rates of epimerisation of starting material and product for the various sugars. The successful isolation of the new 1 : 2-*cis*-chloride-acetate (XI) from mannose, even though in poor yield, suggests that the reaction should be tried with sugar acetates of *talo*-, *altro*-, and *ido*-configuration. If a mixture of chlorides is obtained, it is possible that enrichment in 1 : 2-*cis*-compound might be achieved by selective destruction of the more reactive 1 : 2-*trans*-isomer, either hydrolytically or by other means.

Experimental

Optical rotations were measured in ordinary chloroform, unless otherwise stated.

Materials.—Anhydrous aluminium chloride was resublimed, and crushed with exclusion of moisture, just before use. Chloroform used for the syntheses was freed from alcohol and distilled over phosphoric oxide. Acetylated sugars were recrystallised from ether and dried in a high vacuum. The majority were known compounds, made by standard methods.

1 : 3 : 4 : 6-*Tetra*-O-*acetyl*-2-O-*benzoyl*-β-D-*glucopyranose* was prepared by benzoylation of β-D-glucopyranose 1 : 3 : 4 : 6-tetra-acetate [27] in pyridine at 0°. It was crystallised twice from alcohol and twice from ether, and obtained as fine needles, m. p. 184—184·5°, $[\alpha]_D$ +45·0° (*c* 0·7) (Found: C, 56·2; H, 5·5. $C_{21}H_{24}O_{11}$ requires C, 55·8; H, 5·3%). 1 : 3 : 4 : 6-*Tetra*-O-*acetyl*-2-O-*toluene*-p-*sulphonyl*-β-D-*glucopyranose* was similarly prepared and obtained as needles (from methanol), m. p. 157—158°, $[\alpha]_D^{23}$ +22·3° (*c* 0·7) (Found: S, 6·5. $C_{21}H_{26}O_{12}S$ requires S, 6·4%).

The original directions for the preparation of methyl tetra-*O*-acetyl-β-D-glucopyranuronate [16c] do not adequately define the ring size or configuration. β-D-Glucopyranose 1 : 2 : 3 : 4-tetra-acetate was oxidised with potassium permanganate,[31] and the oily product

[31] Stacey, *J.*, 1939, 1529.

was esterified with diazomethane. Several recrystallisations of the impure methyl ester from alcohol gave material with m. p. 176—177°, $[\alpha]_D^{22}$ +5·9° (*c* 0·8), which proved to be identical with that obtained according to Goebel and Babers [16c] by methanolysis of D-glucofuranurono-6 ⟶ 3-lactone and acetylation of the oily product (Found: C, 48·2; H, 5·4. Calc. for $C_{15}H_{20}O_{11}$: C, 47·9; H, 5·4%). The permanganate oxidation of β-D-glucopyranose 1 : 2 : 3 : 4-tetra-acetate gave variable yields, and attempts were made to use chromium trioxide in glacial acetic acid, and also liquid nitrogen dioxide, as oxidants, but pure material could not be isolated from the products of such oxidations.

4 : 6-*O*-Benzylidene-β-D-glucopyranose triacetate [32] was prepared by the acetylation of somewhat impure 4 : 6-*O*-benzylidene-D-glucose with acetic anhydride and sodium acetate at 100°. The crude material was recrystallised from ether and obtained as plates, m. p. 198—199°, $[\alpha]_D^{17}$ −52·1° (*c* 0·9); Zervas [32] reported similar constants. Like Zervas, we obtained a small yield of a by-product, which had m. p. 154°, $[\alpha]_D^{17}$ +48·6° (*c* 1), after several recrystallisations from alcohol and ether. This may have been the corresponding α-triacetate contaminated with a compound containing less carbon (Found: C, 56·3; H, 5·5. Calc. for $C_{19}H_{22}O_9$: C, 57·8; H, 5·6%). Lengthy fractional crystallisation did not afford a demonstrably pure compound.

4 : 6-O-*Ethylidene*-β-D-*glucopyranose triacetate* was prepared in a similar way from 4 : 6-*O*-ethylidene-D-glucose.[33] The crude product crystallised when the reaction mixture was diluted with ice and water, and one recrystallisation from methanol afforded material with m. p. 117—119° in 67% yield. Two crystallisations from ether–light petroleum gave the pure compound as needles, m. p. 122—123°, $[\alpha]_D^{23}$ −28·8° (*c* 1) (Found: C, 51·0; H, 6·1. $C_{14}H_{20}O_9$ requires C, 50·6; H, 6·1%). Acetylation of 4 : 6-*O*-ethylidene-D-glucose with acetic anhydride and pyridine at room temperature gave only syrups.

Reactions with Aluminium Chloride.—(a) *Fully acetylated sugars.* β-D-Galactopyranose penta-acetate (5 g.) was dissolved in pure, dry chloroform (25 ml.), crushed aluminium chloride (0·9 g., 0·53 mole) was added, and the mixture was shaken at room temperature for 30 min. Aluminium chloride gradually disappeared and was replaced by a fine white precipitate. The mixture was then filtered directly into a large volume (750 ml.) of dry hexane (cf. Gagolski [1]), and the resulting precipitate was also filtered off. Evaporation of the hexane and chloroform under reduced pressure afforded crystals, from which last traces of solvent were removed in a high vacuum. The crude tetra-*O*-acetyl-β-D-galactopyranosyl chloride was dissolved in ether, and light petroleum (b. p. below 40°) was added to turbidity, the practically pure β-chloride then crystallising in 80% yield. After one more crystallisation it had m. p. 93°, $[\alpha]_D^{20}$ +14·9° (*c* 0·9), and was identical with the compound obtained by Schlubach and Gilbert's method.[34] Use of a large excess of aluminium chloride reduced the yield, whereas a shortened period of reaction, or reduction of aluminium chloride to the theoretical amount, gave a product contaminated with D-galactose penta-acetate.

β-D-Galactofuranose penta-acetate [35] afforded an 88% yield of tetra-*O*-acetyl-β-D-galactofuranosyl chloride [35,36] under the above conditions. The purified product had m. p. 72—73° (somewhat higher than previously reported [36]) and $[\alpha]_D^{23}$ −78·7° (*c* 1).

Tri-*O*-acetyl-β-D-xylopyranosyl chloride [34] was prepared from β-D-xylopyranose tetra-acetate by a more convenient method. The proportion of reagents was the same as in the first example, but shaking was continued for 40 min., and the mixture was then diluted with pure benzene, salts were removed by three extractions with ice-water, and the benzene solution was dried ($CaCl_2$). Solvents were evaporated below 45°, and the crude β-chloride was recrystallised twice from ether–light petroleum. It then had m. p. 112—113°, $[\alpha]_D^{23}$ −141·0° (*c* 1) (yield 90%).

The last procedure was also used to obtain the following chlorides from the appropriate acetylated sugars (β-D-configurations): 2 : 3 : 4-*tri*-O-*acetyl*-6-O-*toluene*-p-*sulphonyl*-β-D-*glucopyranosyl chloride* (40% yield), m. p. 160—161° (from ether), $[\alpha]_D^{22}$ +9·0° (initial) ⟶ +32° (19 hr.) (*c* 0·7) (Found: C, 47·9; H, 4·8; S, 6·7; Cl, 7·3. $C_{19}H_{23}O_{10}SCl$ requires C, 47·7; H, 4·8; S, 6·7; Cl, 7·4%); *methyl* 2 : 3 : 4-*tri*-O-*acetyl*-1-*chloro*-1-*deoxy*-β-D-*glucopyranuronate*

[32] Zervas, *Ber.*, 1931, **64**, 2289.
[33] Hockett, Collins, and Scattergood, *J. Amer. Chem. Soc.*, 1951, **73**, 599.
[34] Schlubach and Gilbert, *Ber.*, 1930, **63**, 2292.
[35] Schlubach and Prochownick, *ibid.*, p. 2298.
[36] Hudson and Johnson, *J. Amer. Chem. Soc.*, 1916, **38**, 1223.

(67% yield), m. p. 149—150°, $[\alpha]_D^{18}$ −16·9° (no change in 24 hr.) (*c* 0·5) (Found: C, 44·5; H, 4·9; Cl, 10·7. $C_{13}H_{17}O_9Cl$ requires C, 44·1; H, 4·9; Cl, 10·0%); and 3 : 4 : 6-*tri*-O-*acetyl*-2-O-*benzoyl*-β-D-*glucopyranosyl chloride* (80% yield), m. p. 124—125° (Found: Cl, 8·0. $C_{19}H_{21}O_9Cl$ requires Cl, 8·3%).

β-D-Fructopyranose penta-acetate gave only traces of organic chloro-compound after 90 minutes' shaking in the cold, and reaction was incomplete after 15 min. at the b. p. After 30 min. at the b. p., a nearly quantitative yield of tetra-*O*-acetyl-β-D-fructopyranosyl chloride was obtained, with m. p. 82—83°, not depressed on admixture with an authentic sample.[37]

(b) *Acetylated sugars with the hemiacetal hydroxyl group free.* When β-D-galactopyranose 2 : 3 : 4 : 6-tetra-acetate [38] was shaken with aluminium chloride in cold chloroform and the mixture was worked up by the above method, tetra-*O*-acetyl-β-D-galactopyranosyl chloride, identical with the product obtained from the penta-acetate, was recovered in 50% yield. β-D-Fructopyranose 1 : 3 : 4 : 5-tetra-acetate [39] was largely converted into tetra-*O*-acetyl-β-D-fructopyranosyl chloride within 80 min. at room temperature, a small part of starting material being unchanged.

(c) *Compounds not reacting significantly.* Treatment of α-D-galactopyranose penta-acetate, α-D-galactofuranose penta-acetate,[36] α-D-galactopyranose 2 : 3 : 4 : 6-tetra-acetate,[36] and 2-acetamido-1 : 3 : 4 : 6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose [40] with aluminium chloride in cold chloroform did not afford detectable quantities of chloro-compounds.

The reagents had no effect at the b. p. on 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-*O*-trichloroacetyl- or 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-*O*-toluene-*p*-sulphonyl-β-D-glucopyranose, and the latter was also unaffected by titanium tetrachloride in refluxing chloroform. In attempts to force reaction, the acetates were refluxed with pure titanium tetrachloride (10 ml. for 0·4 g. of acetate) for 2—3 min., then the solutions were quickly cooled and stirred into ice-water. The former acetate yielded only an unidentified oil, but the latter gave about 5% of 3 : 4 : 6-tri-*O*-acetyl-2-*O*-toluene-*p*-sulphonyl-α-D-glucopyranosyl chloride, obtained as plates (from ether–light petroleum), m. p. 120—122° (not depressed on admixture with authentic material [41]), $[\alpha]_D^{21}$ +134·5° (*c* 0·8).

β-D-Glucopyranose pentabenzoate was prepared by the method of Ness, Fletcher, and Hudson,[42] but its m. p. could not be raised above 161—165°; it had $[\alpha]_D^{16}$ +22·6° (*c* 1·2). It did not react with aluminium chloride. When it was dissolved in a solution of titanium tetrachloride (2·5% v/v) in chloroform, and the mixture was set aside for 30 min. before being worked up by the methods used in experiments with aluminium chloride, a solid of indefinite m. p. was obtained, having $[\alpha]_D^{16}$ +14·2° and containing only 1% of chlorine.

Epimerisations by Aluminium Chloride.—A solution of tetra-*O*-acetyl-β-D-galactopyranosyl chloride (2·5 g.) in pure chloroform (20 ml.) was refluxed for about 15 min. with anhydrous aluminium chloride (0·45 g., 0·5 mol.), then the product was isolated in the usual way, being obtained as fine needles, m. p. 78—79°, $[\alpha]_D^{25}$ +175·1° (*c* 1), in 88% yield. Many crystallisations from light petroleum did not change the m. p., and the rotation changed only to $[\alpha]_D^{25}$ +177·5° (*c* 1). Tetra-*O*-acetyl-α-D-galactopyranosyl chloride, prepared by Skraup and Kremann's method,[21] had identical properties.

Tetra-*O*-acetyl-β-D-galactofuranosyl chloride and tri-*O*-acetyl-6-*O*-toluene-*p*-sulphonyl-β-D-glucopyranosyl chloride did not afford identifiable products when refluxed for 30 and 40 min., respectively, under conditions similar to the above. Methyl tri-*O*-acetyl-1-chloro-1-deoxy-β-D-glucopyranuronate was recovered after being refluxed for 40 min.

Reactions of 1 : 2-trans-*Chloride-acetates with Silver Acetate.*—When a solution of tetra-*O*-acetyl-β-D-glucopyranosyl chloride (0·4 g.) in dry benzene (6 ml.) was refluxed with finely divided silver acetate (0·2 g.), chlorine was still detectable in the solution after 45 min. After 2 hr., the reaction was apparently complete, whereupon the solution was filtered and the benzene was evaporated, leaving an oil that crystallised on addition of ether. The product was β-D-glucopyranose penta-acetate. Tetra-*O*-acetyl-α-D-glucopyranosyl chloride was treated in the same way, but organic chloride was still present after 24 hr. After 48 hr., a high yield of pure β-D-glucopyranose penta-acetate was obtained.

[37] Brauns, *J. Amer. Chem. Soc.*, 1920, **42**, 1846.
[38] Compton and Wolfrom, *ibid.*, 1934, **56**, 1157.
[39] Pacsu and Rich, *ibid.*, 1933, **55**, 3018.
[40] Bergmann and Zervas, *Ber.*, 1931, **64**, 975.
[41] Reynolds, *J.*, 1931, 2626.
[42] Ness, Fletcher, and Hudson, *J. Amer. Chem. Soc.*, 1950, **72**, 2200.

A solution of 2 : 3 : 4-tri-*O*-acetyl-6-*O*-toluene-*p*-sulphonyl-β-D-glucopyranosyl chloride (0·1 g.) in anhydrous acetic acid (1 ml.) was shaken overnight with excess of silver acetate. Filtration and evaporation of the solvent under reduced pressure afforded tetra-*O*-acetyl-6-*O*-toluene-*p*-sulphonyl-β-D-glucopyranose (70%).

Methyl 2 : 3 : 4-tri-*O*-acetyl-1-chloro-1-deoxy-β-D-glucopyranuronate, dissolved in benzene, was unchanged after 3 hours' shaking with a large excess of silver acetate. When the mixture was refluxed for 3 hr., methyl tetra-*O*-acetyl-β-D-glucopyranuronate of high purity was obtained.

Hepta-O-acetyl-β-maltosyl Chloride.—β-Maltose octa-acetate (5 g.), dissolved in chloroform (5 ml.), was shaken with finely divided aluminium chloride (1·2 g.) for 3·5 hr. Solids were crushed under the solution, and shaking was continued for 45 min. The mixture was worked up by the method used for the xylosyl chloride, and the crude product was crystallised once from ether, affording an 81% yield of material with m. p. 123—124°, $[\alpha]_D^{18}$ +54·4° (*c* 0·7). Three further crystallisations afforded pure *hepta-O-acetyl-β-maltosyl chloride*, m. p. 125°, $[\alpha]_D^{18}$ +57·4° (*c* 0·9) (Found: C, 47·6, 47·8; H, 5·4, 5·4; Cl, 4·9, 5·9; CH_3·CO, 47·2. $C_{26}H_{35}O_{17}Cl$ requires C, 47·7; H, 5·4; Cl, 5·4; $7CH_3$·CO, 46·0%). The pure chloride could be stored for long periods in a desiccator. The preparation was reproducible.

The β-maltosyl chloride was unchanged 3 hr. after being dissolved in benzene that had been emulsified with water. β-Maltose octa-acetate was obtained in 68% yield when the chloride (0·2 g.) in benzene (2 ml.) was refluxed with silver acetate (0·1 g.) for 48 hr. Much organic chloride was present after 2 hr., and some after 12 hr., but β-maltose octa-acetate was isolated after 12 hr.

β-Maltosyl chloride (0·5 g.) was added to a mixture of anhydrous methanol (3 ml.) and collidine (0·5 ml.), and the solution was set aside for 16 hr. Fine needles separated. The mixture was cooled in the refrigerator for 2 hr., then the solid (0·44 g.) was collected and washed with light petroleum. It had m. p. 156—160°, rising to 161—162° after several recrystallisations from methanol; $[\alpha]_D^{19}$ was then +93·2° (*c* 0·7) [Found: C, 50·3; H, 6·1; CH_3·CO (by acidic hydrolysis), 46·1. Calc. for $C_{27}H_{38}O_{18}$: C, 49·8; H, 5·9; $7CH_3$·CO, 46·3%]. The constants are similar to those reported by Freudenberg, von Hochstetter, and Engels,[14] and by Pacsu and Rich,[8] and the compound is almost certainly hexa-*O*-acetyl-1 : 2-*O*-(1-methoxyethylidene)-α-maltose.

Derivatives of D-*Glucofuranurono-6* ⟶ *3-lactone.*—1 : 2 : 5-Tri-*O*-acetyl-β-D-glucofuranurono-6 ⟶ 3-lactone was obtained in 87% yield when Tsou and Seligman's procedure [18] was modified by using boron trifluoride in acetic acid (40% w/w) in place of boron trifluoride in ether. A solution of the β-triacetate (1·5 g.) in chloroform (5 ml.) was shaken with aluminium chloride (0·33 g.), and the product was isolated in the usual way. It was recrystallised from ether, and afforded (85% yield) a compound with m. p. 107° and $[\alpha]_D^{31}$ +100° (initial) ⟶ +109° (5 days) (*c* 1), which is considered to be 2 : 5-di-*O*-acetyl-1-chloro-1-deoxy-β-D-glucofuranurono-6 ⟶ 3-lactone. Goebel and Babers [16b] reported m. p. 107·5—108·5°, $[\alpha]_D^{20}$ +95·5° (in $CHCl_3$), for material made by a different method. When a solution of the chloride in anhydrous acetic acid was shaken with silver acetate for 12 hr., the β-triacetate, m. p. 192—193°, was re-formed in 84% yield.

2 : 3-*Di-O-acetyl-4* : 6-*O-benzylidene-β-D-glucopyranosyl Chloride.*—A solution of 4 : 6-*O*-benzylidene-β-D-glucopyranose triacetate (2·06 g.) in chloroform (7 ml.) was shaken with aluminium chloride (0·35 g.) for 40 min. The mixture was filtered into benzene (100 ml.), and a solid product was isolated in the usual way. The odour of benzaldehyde was noticeable. One recrystallisation from ether afforded a 72% yield of material with m. p. 175—179°, and several further crystallisations gave the pure *O-benzylidene chloride* as large, hexagonal plates, m. p. 178—179°, $[\alpha]_D^{24}$ −89·2° (initial) ⟶ −45·7° (9 days) (*c* 1·4) (Found: C, 55·0; H, 5·1; Cl, 9·6. $C_{17}H_{19}O_7Cl$ requires C, 55·1; H, 5·1; Cl, 9·6%). It was unchanged for long periods when stored in a desiccator.

4 : 6-*O*-Benzylidene-β-D-glucopyranose triacetate was obtained in 69% yield by refluxing a solution of the above chloride in benzene with silver acetate for 2 hr. A solution of the chloride (0·5 g.) in acetone (5 ml.) was treated with silver carbonate (0·5 g.) and powdered silver nitrate (0·1 g.), and the mixture was vigorously shaken for 5 min. Filtration, followed by rapid evaporation of acetone under reduced pressure and two crystallisations of the residue from ether, afforded a 32% yield of 2 : 3-*di*-O-*acetyl*-4 : 6-O-*benzylidene*-α-D-*glucopyranose*, needles, m. p. 185—187°, $[\alpha]_D^{23}$ +96·5° (*c* 0·8) (Found: C, 58·4; H, 5·8. $C_{17}H_{20}O_8$ requires C, 58·0; H, 5·7%).

3-O-*Acetyl*-4 : 6-O-*benzylidene*-1 : 2-O-(1-*methoxyethylidene*)-α-D-*glucopyranose*.—This was prepared by three different methods. Suspensions (about 10% w/v) of the 4 : 6-*O*-benzylidene chloride in anhydrous methanol were (*a*) shaken with excess of silver carbonate and anhydrous calcium sulphate at room temperature for 26 hr., (*b*) mixed with 0·1 vol. of anhydrous quinoline, then held at 40° for 4 hr. and set aside at room temperature overnight, or (*c*) mixed with 0·25 vol. of freshly distilled collidine and set aside at room temperature. The solution from (*a*) was filtered and placed in the refrigerator for several days, whereupon it deposited fine needles, m. p. 140—142°. An equal quantity of solid with m. p. 133—135° was obtained by concentrating the mother liquor (total yield, 40%). The solution from (*b*) was concentrated under reduced pressure, the residual oil was dissolved in chloroform, and the solution was extracted in turn with ice-cold hydrochloric acid, ice-cold sodium hydrogen carbonate, and water. Removal of the solvent and dissolution of the residual oil in ether–light petroleum afforded needles, m. p. 138—145°, in 27% yield. The reaction mixture from (*c*) deposited solid within 4 hr. After 21 hr., it was diluted with an equal volume of light petroleum and placed in the refrigerator for 2 hr. The product, when collected and washed with light petroleum, had m. p. 145—147°. Further additions of light petroleum afforded a little more, with m. p. 135—140° (total yield, 87%). When crystallised from ether, the product of each experiment afforded the pure *methyl orthoacetate*, m. p. 148—149°, $[\alpha]_D^{20}$ +36·0° (*c* 0·7) [Found: C, 58·8; H, 6·0; MeO, 8·0; CH_3·CO (by acidic hydrolysis), 23·5. $C_{18}H_{22}O_8$ requires C, 59·0; H, 6·1; MeO, 8·5; $2CH_3$·CO, 23·5%].

The orthoester (380 mg.) was dissolved in methanol (15 ml.) that had been saturated with anhydrous ammonia at 0°, and the mixture was set aside for 7 hr. Methanol and ammonia were removed under reduced pressure, and the residual oil was methylated by being refluxed for 3 hr. with methyl iodide (1 ml.), methanol (1 ml.), and silver oxide (1 g.). The oil recovered by filtration and evaporation of the solution under reduced pressure was further methylated for 3 hr. with methyl iodide (2 ml.) and silver oxide (1 g.). The product recovered at this stage crystallised when mixed with a little ether. A warm ethereal extract of the solid, after being filtered from insoluble matter, deposited 4 : 6-O-*benzylidene*-1 : 2-O-(1-*methoxyethylidene*)-3-O-*methyl*-α-D-*glucopyranose* (48%), long needles, m. p. 130—131°, $[\alpha]_D^{18}$ −63·8° (*c* 0·7) (Found: C, 60·1; H, 6·5; MeO, 17·8. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·6; MeO, 18·3%). The pure methylated orthoester (160 mg.) was suspended in aqueous 2% hydrochloric acid (25 ml.), and the mixture was set aside for one week. The solution was extracted with ether, treated with silver carbonate in the usual way, and then evaporated under reduced pressure, affording a yellow syrup with $[\alpha]_D^{18}$ +53° (*c* 0·4 in water). Only one reducing sugar could be detected in the syrup, and this moved at the same rate as authentic 3-*O*-methyl-D-glucose on paper chromatography in butan-1-ol–ethanol–water (50 : 10 : 40) or butanol–ethanol–ammonia (*d* 0·88)–water (40 : 10 : 1 : 49) and on ionophoresis in 0·05M-borax buffer. Aniline picrate [43] was used to detect the sugars on paper.

Action of Acetic Acid on 3-O-*Acetyl*-4 : 6-O-*benzylidene*-1 : 2-O-(1-*methoxyethylidene*)-α-D-*glucopyranose*.—(*a*) The ester (100 mg.) was dissolved in carefully purified, anhydrous acetic acid (4 ml.) and set aside for 18 hr. Removal of the solvent under reduced pressure afforded a solid with a strong odour of benzaldehyde. A solution of the solid in warm ether deposited crystals (35 mg.), m. p. 200—201°, identified as 4 : 6-*O*-benzylidene-β-D-glucopyranose triacetate.

(*b*) A solution of the ester (95 mg.) in acetic acid (10 ml.) containing 1% of water showed a rapid change in measured rotation from 0·86° (4 min.) to a maximum of 0·93° (18 min.), followed by a slow decline to 0·87° (5 hr.). At the end of 6 hr., the solvent was removed under reduced pressure and the solid obtained crystallised once from chloroform. The product had m. p. 169—170°, and seemed to be essentially a D-glucose diacetate (Found: C, 45·0; H, 6·1. Calc. for $C_{10}H_{16}O_8$: C, 45·5; H, 6·1%). In a separate experiment, a similar mixture was diluted with a ten-fold volume of toluene after 8 min., and the solvents were immediately evaporated in a high vacuum. Recrystallisation of the solid residue from ether afforded needles (59 mg.), m. p. 173—178°. After several recrystallisations, 2 : 3-di-*O*-acetyl-4 : 6-*O*-benzylidene-α-D-glucopyranose was obtained with m. p. 184—186°, identical with the material described above.

Derivatives of 4 : 6-O-*Ethylidene*-D-*glucose*.—A solution of 4 : 6-*O*-ethylidene-β-D-glucopyranose triacetate (2 g.) in chloroform (10 ml.) was shaken with aluminium chloride (0·4 g.)

[43] Frahn and Mills, *Chem. and Ind.*, 1956, 578.

for 45 min. The product was isolated by the method used for tetra-*O*-acetyl-β-D-galactopyranosyl chloride, and was recrystallised from ether–light petroleum. The crude product (76% yield) had m. p. 170—171°, and after two recrystallisations pure 2 : 3-*di*-O-*acetyl*-4 : 6-O-*ethylidene*-β-D-*glucopyranosyl chloride* was obtained as plates, m. p. 173—174° (decomp.), $[\alpha]_D^{21}$ −70·0° (initial) ⟶ +7·3° (25 hr.) (*c* 1) (Found: C, 46·9; H, 5·7; Cl, 11·7. $C_{12}H_{17}O_7Cl$ requires C, 46·6; H, 5·6; Cl, 11·5%). The method gave a similar yield if shaking was continued for 6 hr. In rigorously dried chloroform, the specific rotation of the chloride changed only from −70° to −58° during 13·5 days, and about 60% was then recovered from the solution.

A solution of the *O*-ethylidene chloride (0·5 g.) in acetic anhydride (5 ml.) was shaken with silver acetate (0·26 g.) for 6 hr., then the solvent was evaporated under reduced pressure, and the residue was twice recrystallised from ether. 4 : 6-*O*-Ethylidene-β-D-glucopyranose triacetate, m. p. 121—122°, was obtained in 30% yield.

Treatment of the *O*-ethylidene chloride in acetone with silver carbonate and silver nitrate, under conditions used for the *O*-benzylidene chloride, afforded a substance that crystallised from ether as needles, m. p. 135—136°, $[\alpha]_D^{18}$ +114·5° (*c* 0·9). This is assumed to be 2 : 3-di-*O*-acetyl-4 : 6-*O*-ethylidene-α-D-glucopyranose. A solution of the *O*-ethylidene chloride in apparently dry acetone showed a change in rotation, $[\alpha]_D^{18}$ −55·0° (initial) ⟶ +104·2° (3 days), and at this stage the same substance, m. p. 135°, could be isolated.

Tetra-O-*acetyl*-β-D-*mannopyranosyl Chloride*.—β-D-Mannopyranose penta-acetate (5 g.) was dissolved in freshly distilled acetyl chloride (10 ml.; "AnalaR") contained in a thick-walled long, narrow tube terminating in a standard ground socket. The lower part of the tube was cooled to about −70° and the contents were saturated with dry hydrogen chloride. The tube was quickly closed with a hollow stopper (lubricated with "Apiezon" grease), to which a closed, narrow side-tube had been sealed. The closed tube was removed from the cooling-bath, the tube and stopper were clamped firmly between rubber pads, and the mixture was held at room temperature for 2 days. Pressure was released by heating the side-tube to softening point, and the acetyl chloride was quickly evaporated under reduced pressure. The residual oil was dissolved in benzene, and the solution was extracted successively with ice-water, ice-cold dilute sodium hydrogen carbonate, and ice-water, and dried ($MgSO_4$). Removal of benzene under reduced pressure afforded an oil, $[\alpha]_D^{17}$ +68·7° (*c* 1·5), which partially crystallised. Two kinds of crystal separated from a solution of the oil in ether on dilution with light petroleum, and were separated by selective decantation of the small quantity of lighter form after the mixture was swirled. The main product (3·0 g.) consisted of large crystals with m. p. 78—80°, and after several recrystallisations it afforded tetra-*O*-acetyl-α-D-mannopyranosyl chloride, m. p. 81° and $[\alpha]_D^{20}$ +89·6° (*c* 0·9), constants very close to those reported for this compound by Pacsu.[44] The minor product (70 mg.) was recrystallised several times from ether, and pure *tetra*-O-*acetyl*-β-D-*mannopyranosyl chloride* was obtained as small plates, m. p. 165—166°, $[\alpha]_D^{17}$ −34·1° (unchanged in 24 hr.) (*c* 0·8) (Found: Cl, 9·6. $C_{14}H_{19}O_9Cl$ requires Cl, 9·7%). The chloride was recovered from a solution in purified, anhydrous chloroform after 2 months.

The new mannosyl chloride (200 mg.) was treated with hydrogen chloride in acetyl chloride (2 ml.) under the conditions used in its preparation. The material recovered had $[\alpha]_D^{22}$ +3·8° (*c* 0·8), and crystallisation from ether afforded 43% of starting material with m. p. 164—165°, $[\alpha]_D^{22}$ −33·8° (*c* 1).

A solution of the new chloride (113 mg.) in benzene (1·4 ml.) was refluxed with silver acetate (60 mg.). After 4 hr., considerable quantities of starting material could be recovered, but after 48 hr. the solution did not contain chlorine. Removal of the benzene at this stage gave an oil, $[\alpha]_D$ +39·7° (*c* 0·7), which had an infrared spectrum identical with that of the syrupy α-D-mannopyranose penta-acetate described below, but resisted crystallisation. After a long period, crystals were obtained from it, and identified as α-D-mannopyranose penta-acetate by mixed m. p.

Tetra-*O*-acetyl-α-D-mannopyranosyl chloride was refluxed with silver acetate in benzene in a parallel experiment; the test for organic chloro-compounds was weak after 4 hr., and negative after 6 hr. Evaporation of the benzene afforded a syrup that eventually crystallised from water after it had been distilled at 135° (bath)/10^{-4} mm., and then had m. p. 75—76°, $[\alpha]_D^{22}$ +58·6° (*c* 0·9). Levene and Tipson [45] reported m. p. 74°, $[\alpha]_D$ +56·6° (*c* 1·4), for α-D-mannopyranose penta-acetate.

[44] Pacsu, *Ber.*, 1928, **61**, 1508.
[45] Levene and Tipson, *J. Biol. Chem.*, 1931, **90**, 89.

Action of Hydrogen Chloride on Other Compounds.—The apparatus and procedure described in the preparation of the β-mannosyl chloride were used, and the period of reaction was generally 2 days. Yields are reported for crude products, but in all cases these readily afforded the pure compounds on recrystallisation.

(a) α-D-*Glucopyranose penta-acetate.* Tetra-*O*-acetyl-β-D-glucopyranosyl chloride was obtained in 54% yield. (b) β-D-*Glucopyranose penta-acetate.* The β-chloride was isolated in 62% yield, and the specific rotation of the syrupy mixture initially obtained indicated a ratio of β-chloride to α-chloride of about 69 : 31. (c) α-D-*Mannopyranose penta-acetate.* The reaction period was 4 days, and α-mannosyl chloride was isolated in 76% yield, no β-chloride being detected at any stage. (d) β-D-*Fructopyranose* 1 : 3 : 4 : 5-*tetra-acetate.* Tetra-*O*-acetyl-β-D-fructopyranosyl chloride was obtained in 76% yield. (e) β-*Lactose octa-acetate and* β-*maltose octa-acetate.* Each afforded the corresponding hepta-*O*-acetyl-α-glycosyl chloride in about 65% yield. (f) *Tetra*-O-*acetyl*-α-D-*glucopyranosyl chloride.* The residue initially obtained on evaporation of the benzene had $[\alpha]_D^{17}$ +150° instead of +174°, but at least 73% of pure α-chloride was recovered.

Stability of Tetra-O-*acetyl*-β-D-*glucopyranosyl Chloride in Solution.*—Thoroughly dried apparatus and purified chloroform, freshly distilled over phosphoric oxide, were used. Solutions containing 1, 2, and 4% (w/v) of the β-chloride were prepared with careful exclusion of moisture, and as far as possible all were handled in the same way. The initial specific rotations were very similar (−7° to −8°), and the rotations were also similar after 24 hr. (+2° to +2·5°), but after one week the specific rotations of the respective solutions were +10·8°, +7·5°, and +2·6°, calculated on the starting material.

In another experiment, a 1% solution of β-chloride was prepared by percolating the dried chloroform through activated aluminium oxide directly into the flask containing the chloride. The neck of the flask was sealed in the flame, and the solution was set aside for 24 hr. The specific rotation changed only from −8° to −4°.

Solutions of β-chloride in less thoroughly dried chloroform, for which the rotational changes were much larger, never afforded crystalline material on evaporation, and the syrups obtained always contained easily ionisable chlorine.

The stability of the β-chloride in the presence of tertiary bases was briefly examined. A solution (1%) of the chloride in a mixture of equal volumes of anhydrous ether and anhydrous collidine showed a change in specific rotation from −23° to −17° during 6 days. In a comparable experiment with pyridine in place of collidine, the change was from −18° to −9° in 19 hr., and to +45° in 7 days.

This work was supported by the award of a C.S.I.R.O. Australian Studentship (to W. K.). We thank Professor G. M. Badger for his interest, Dr. H. J. Rodda for determining infrared spectra, and Dr. J. L. Frahn for performing paper ionophoresis. The C.S.I.R.O. Microanalytical Service provided the analyses.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA.
COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION,
ADELAIDE, SOUTH AUSTRALIA.

[*Received, September 19th,* 1958.]